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Julie BROGGI

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Contribution de Catalyseurs Contenant un Carbène *N*-Hétérocyclique pour la Chimie des Nucléosides

THÈSE dirigée par :

Luigi A. AGROFOGLIO	Professeur, Université d'Orléans
Sabine BERTEINA-RABOIN	Maître de Conférence, Université d'Orléans

RAPPORTEURS :

Annie-Claude GAUMONT	Professeur, ENSICAEN
Sylvie POCHET	Directeur de Recherche, Institut Pasteur

JURY:

Roger CONDOM	Professeur, Université de Nice Sophia-Antipolis - Président -
Steven P. NOLAN	Professeur, University of St Andrews
Ulysse ASSELINE	Directeur de Recherche, CNRS

A mes parents,

Pour votre soutien et votre confiance,

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Abbreviations

A

A	Adenine
Ac_2O	Acetic anhydride
AcO	Acetate
AcOH	Acetic acid
ADMET	Acyclic diene metathesis polymerization
AIBN	Azobis*iso*butyronitrile
AIDS	Acquired immune deficiency syndrome
ANP	Acyclic nucleoside phosphonate
ATP	Adenosine triphosphate
AZT	3'-Azido-3'-deoxythymidine

B

B	Base (nucleobase)
Bn	Benzyl
BzCl	Benzoyl chloride

C

C	Cytosine
$C18_6$tren	*tris*(2-Dioctadecylaminoethyl) amine
Cbz	Carboxybenzyl
CC_{50}	Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology
CG	Chromatographie gaz
CM	Cross metathesis
CMV	Cytomegalovirus
CNH	Carbène N-hétérocyclique
COA	Cyclooctane
1,3-COD	1,3-Cyclooctadiene
1,5-COD	1,5-Cyclooctadiene
COE	*cis*-Cyclooctene
Conv	Conversion
Cp*	Pentamethylcyclopentadienyl
CSA	(+)-Camphor-10-sulfonic acid
CuAAC	Cu^I-catalyzed alkyne–azide 1,3-dipolar cycloaddition

D

DAP	2,6-Diaminopurine
DAPy	2,4-Diaminopyrimidine
DFT	Density functional theoretical
5-DHFU	5,6-Dihydro-5-fluorouracil
DIAD	Di*iso*propyl azodicarboxylate
DIEA	Di*iso*propylethylamine
DMAP	4-Dimethylaminopyridine

DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNA	Deoxy-ribonucleic acid
DPPA	Diphenyl phosphoryl azide
dppf	1,1-Bis(diphenylphosphino)ferrocene
dTMP	Thymidine monophosphate

E

Equiv	Equivalent
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol

F

5-FU	5-fluorouracil

G

G	Guanine
GC	Gas chromatography
GMP	Guanosine monophosphate
GTP	Guanosine triphosphate

H

HBV	Hepatitis B virus
HDP	Hexadecyloxypropyl
HIV	Human immunodeficiency virus
HMBC	Hetero-nuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HPMP	3’-Hydroxy-2’-(phosphonomethoxy)propyl
HPMPC	Cidofovir
HPPen	1’-hydroxymethyl-5’-phosphono-pent-2’-en-1’-yl
HRMS	High-resolution mass spectrometry
HSV	Herpes simplex virus
hTK	Human thymidine kinase
hTMPK	Human thymidine monophosphate kinase
hUCK	Human uracil cytosine kinase

I

IAd	*N*,*N*'-di(adamantyl)imidazol-2-ylidene
IC_{50}	Minimum inhibitory concentration required to reduce virus-induced cytopathogenicity by 50%
IMes	*N*,*N*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IMPDH	Inosine monophosphate dehydrogenase
^{i}Pr	*Iso*propyl
IPr	*N*,*N’*-bis(2,6-di*iso*propylphenyl)imidazol-2-ylidene
IR	Infrared

M

*m*CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
MO	Micro-onde
MW	Microwave

N

NaAsc	Sodium ascorbate
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NDP	Nucleoside diphosphate kinase
NHC	*N*-Heterocyclic carbene
NMP	Nucleoside monophosphate kinase
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy

P

PBut	3’-Phosphono-but-2’-en-1’-yl
PCC	Pyridinium chlorochromate
PEth	Phosphonoethenyl
Ph	Phenyl
PMA	2’-(Phosphonomethoxy)alkyl
PME	2’-(Phosphonomethoxy)ethyl
PMEA	Adefovir™
PMEO	6-[2’-(phosphonomethoxy)ethoxy]
PMP	2’-(Phosphonomethoxy)propyl
PMPA	Tenofovir™
PPen	5’-Phosphono-pent-2’-en-1’-yl
PPro	4’-Phosphono-prop-2’-en-1’-yl
PPTS	Pyridine *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid

R

r.t.	Room temperature
RCM	Ring-closing metathesis
RNA	Ribonucleic acid
ROMP	Ring-opening metathesis polymerization
RRM	Ring-rearrangement metathesis

S

SAH	*S-Adenosylhomocysteine hydrolase*
SAR	Structure-antiviral activity relationship
SIMes	*N,N’*-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene

T

T	Thymine
TBAF	*Tetra*-butyl ammonium fluoride
TBDMS	*Tert*-butyl dimethyl silyl
TBDPS	*Tert*-butyl diphenyl silyl
*t*BuOH	*Tert*-butanol
TFA	Trifluoroacetic acid
TH	Transfer hydrogenation
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMPK	Thymidine monophosphate kinase
TMSBr	Bromotrimethylsilane
TMSCl	Trimethylsilyl chloride
TOF	Turnover frequency
TsCl	Tosyl chloride

U

U	Uracil
UMP-CMPK (or UCK)	Uridine-cytosine monophosphate kinase
UV	Ultraviolet

V

VV	Vaccinia virus
vvTMPK	Vaccinia virus thymidine monophosphate kinase

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Introduction

1. GENERALITIES ABOUT NUCLEOSIDES

1.1. Nucleosides Structures

Natural nucleosides are the basic building blocks required for RNA and DNA synthesis and they are, in that sense, essential to life cycles and cell replications. Naturally, they are made according to two pathways: salvage from recycling nucleosides from native RNA or DNA, or by *de novo* synthesis, the primary source. Their central skeleton is constituted of two main parts: the nucleobase and the sugar moiety, linked through a carbon-nitrogen bond. It exist two families of natural nitrogen bases gathered in Figure 1: the purine bases (adenine or A, guanine or G, hypoxanthine and xanthine) and the pyrimidine bases (Cytosine or C, Uracil or U, Thymine or T). The conventional nomenclature adopted for the general structure of nucleosides is depited in Figure 1.

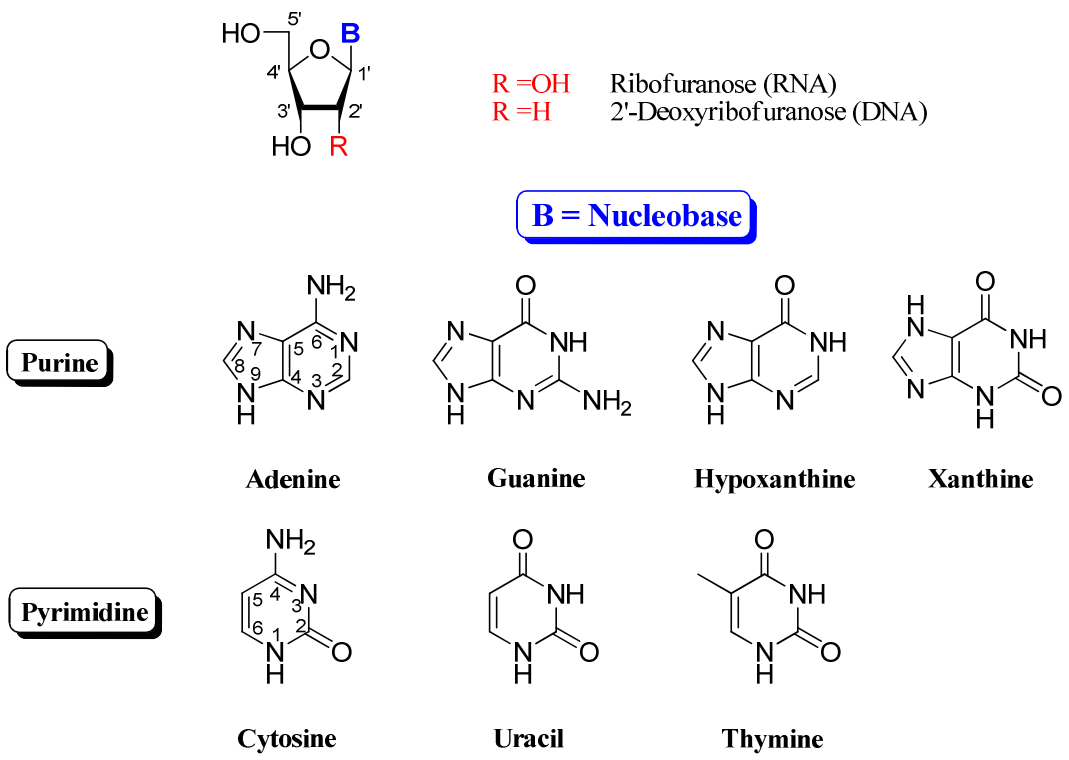


Figure 1. General structures of nucleosides.

A substituent is orientated β if the latter is placed on *cis* of the 4'-hydroxymethyl group in relation to the medium plan of the furanose ring. It is orientated α if it is on *trans* of this function (Figure 2). Finally, two forms of nucleoside enantiomers are admitted, D-nucleosides correspond to the natural configuration and L-nucleosides, the non-natural nucleosides.

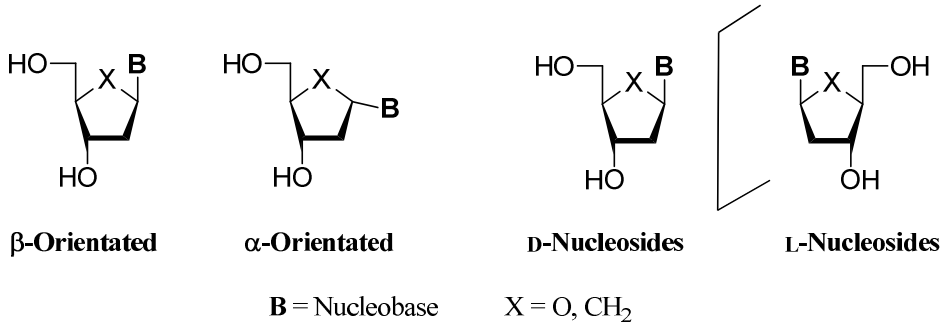


Figure 2. Different nucleoside configurations.

1.2. Nucleosides as Antiviral Therapeutics

In the last decades, synthetically modified nucleosides have played a major role in the treatment of viral infectious diseases that continue to be a major concern wordwilde, such as AIDS, hepatitis, herpes, or influenza.[1] With 40 compounds officially approved by the Food and Drug Administration, nucleoside derivatives are currently the best therapies available to inhibit virus replication (Figure 3). During the course of this Ph.D., we have focused our attention on carbocyclic nucleosides and acyclic nucleoside phosphonates that will be properly introduced in each relevant chapter.

The general mode of action of nucleoside analogs is through inhibition of viral DNA polymerases by acting as competitive inhibitors (blocking the access to the enzyme cavity for natural substrates) and/or DNA chain terminators (blocking the elongation of the forming DNA chain). Nevertheless for this purpose, nucleosides primary require intracellular conversion to their triphosphate forms, so-called nucleotides, to be active as antiviral agents (Figure 4). The phosphate group is attached through an ester bound to the nucleoside. The rate-determining step is often the first phosphorylation step which affords the corresponding 5'-monophosphate.[2]

[1] (a) Elion, G.B.; Furman, P.A.; Fyfe, J.A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H.J. *J. Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5716-5720. (b) Holý, A.; Dvorakova, H. *Nucleos. Nucleot.* **1995**, *14*, 695-702. (c) Agrofoglio, L.A., Challand, S.R. in "*Acyclic, Carbocyclic and L-Nucleosides*", Kluwer Academic Publishers: Dordrecht, Netherlands, **1998**. (d) Simons, C.; Wu, Q.; Htar, T.T. *Curr. Top. Med. Chem.* **2005**, *5*, 1191-1203. (e) Agrofoglio, L.A. *Curr. Org. Chem.*, **2006**, *10*, 333-362. (f) De Clercq, E. *Expert Opin. Ermerging. Drug.* **2008**, *13*, 393-416. (g) Superti, F.; Ammendolia, M.G.; Marchetti, M. *Curr. Med. Chem.* **2008**, *15*, 900-911. (h) Balsano, C.; Alisi, A. *Curr. Med. Chem.* **2008**, *15*, 930-939. (i) Komiotis, D.; Manta, S.; Tsoukala, E.; Tzioumaki, N. *Anti- Infec. Agent. Med. Chem.* **2008**, *7*, 219-244.

[2] Hao, Z.; Cooney, D.A.; Farquhar, D.; Perno, C.F.; Zhang, K.; Masood, R.; Wilson, Y.; Hartman, N.R.; Balzarini, J.; Johns, D.G. *Mol. Pharmacol.* **1990**, *37*, 157-163.

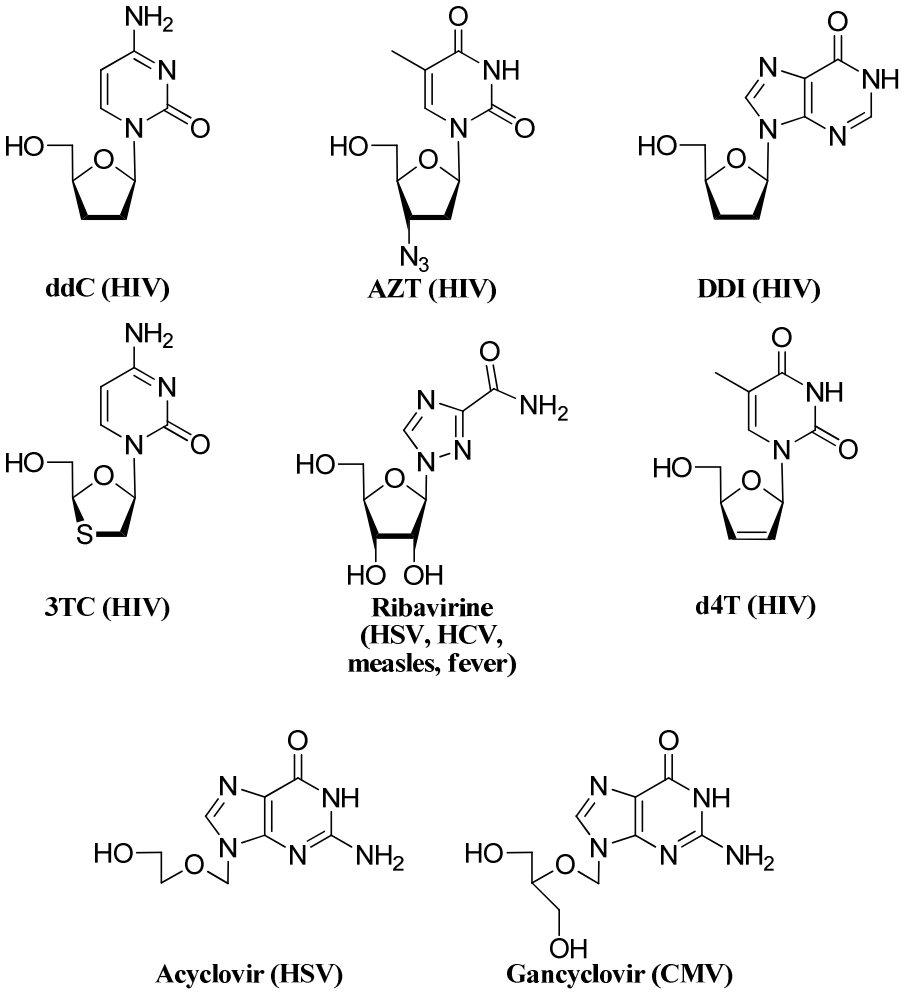


Figure 3. Examples of nucleosides approved by the Food and Drug Administration.

Nucleoside analogues are phosphorylated in three steps involving: first, a deoxyribonucleoside kinase, then a NMP kinase (Nucleoside monophosphate kinase) and finally a NDP kinase (Nucleoside diphosphate kinase).[3] In the family of NMP kinase, human UMP-CMP kinase (Uridine-cytosine monophosphate kinase, UCK or UMP-CMPK, Figure 5) plays a key role in the ribo- and deoxyribo-nucleosides salvage pathways as well as in the anabolic phosphorylation of nucleoside analogues used in antiviral and anticancer therapies.[4] UMP-CMP kinase binds the phosphodonor, usually the adenosine triphosphate (ATP), and the nucleoside monophosphate (phosphoacceptor) at different biding sites.[5] The reaction results from in-line phosphotransfer from the donor to the acceptor. Hence, a nucleoside

[3] (a) Schneider, B.; Xu, Y.W.; Sellam, O.; Sarfati, R.; Janin, J.; Veron, M.; Deville-Bonne, D. *J. Biol. Chem.* **1998**, *273*, 11491-11497. (b) Van Rompay, A.R.; Johansson, M.; Karlsson, A. *Pharmacol. Ther.* **2000**, *87*, 189-198. (c) Eriksson, S.; Munch-Petersen, B.; Johansson, K.; Eklund, H. *Cell. Mol. Life Sci.* **2002**, *59*, 1327-1346.

[4] Pasti, C.; Gallois-Montbrun, S.; Munier-Lehmann, H.; Veron, M.; Gilles, A-.M.; Deville-Bonne, D. *Eur. J. Biochem.* **2003**, *270*, 1784-1790.

[5] Topalis, D.; Kumamoto, H.; Amaya Velasco, M.-F.; Dugue, L.; Haouz, A.; Alexandre, J.A.C.; Gallois-Montbrun, S.; Alzari, P.M.; Pochet, S.; Agrofoglio, L.A.; Deville-Bonne, D. *FEBS J.* **2007**, *274*, 3704-3714.

analogue is called "substrate" if it is recognized by the kinase and binded in the enzyme cavity and, consequently, phosphorylated. The inhibition potency of nucleoside analogues can be limited by either a poor cellular penetration or an inefficient phosphorylation or a weak interaction with the viral DNA polymerase.

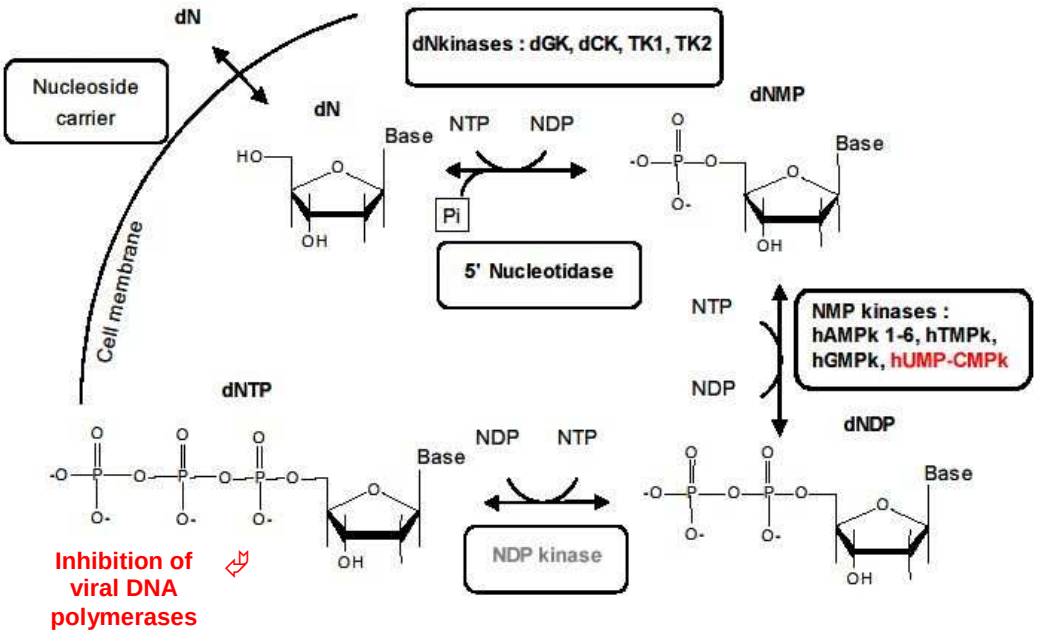


Figure 4. Activation of nucleosides to nucleotides *via* tri-phosphorylation.

As aforementioned, nucleosides have been widely used in antiviral therapies and have already proven to be successful. Nevertheless, the apparition of new viruses or the outbreaks of new strains of mutated viruses highlight the importance in development of more efficient and resistant antiviral therapeutics. Recently, nucleoside analogues have also been identified as potent antiviral agents with convincing activity against poxviruses.[6] The eradication of smallpox was announced by the World Health Organization in 1980 (Figure 6). However, its potential use as a biological weapon on a population hardly tolerant to the previous vaccine makes of new anti-pox agents a priority for anti-terrorism authorities.[7,8] Moreover, the lack of any approved antiviral drug has prompted the development of novel candidate molecules to treat poxvirus infections.

[6] (a) Baker, R.O.; Bray, M.; Huggins, J.W. *Antiviral Res*. **2003**, *57*, 13-23. (b) Neyts, J.; De Clercq, E. *Antiviral Res*. **2003**, *57*, 25-33. (c) De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, *14*, 289-300.

[7] (a) Mahy, B.W.J. *Antiviral Res*. **2003**, *57*, 1-5. (b) Whitley, R.J. *Antiviral Res*. **2003**, *57*, 7-12. (c) Stittelaar, K.J.; Neyts, J.; Naesens, L.; van Amerongen, G.; van Lavieren, R.F.; Holý, A.; De Clercq, E.; Niesters, H.G.M.; Fries, E.; Maas, C.; Mulder, P.G.H.; van der Zeijst, B.A.M.; Osterhaus, A.D.M.E. *Nature* **2006**, *439*, 745-748.

[8] (a) Tseng, C.K. in *"Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats"*; Torrence, P.F., Ed.; Wiley: New York, United States, **2005**, 31-82. (b) Kern, E.R. in *"Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats"*; Torrence, P.F., Ed.; Wiley: New York, United States, **2005**, 331-353. (c) De Clercq, E. in *"Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats"*; Torrence, P.F., Ed.; Wiley: New York, United States, **2005**, 83-114.

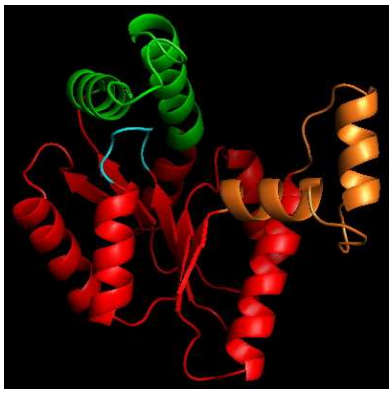


Figure 5. Human UMP-CMP kinase.

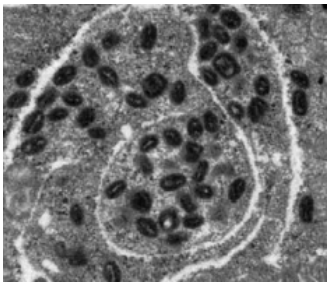


Figure 6. Smallpox virus.

To achieve this goal, pharmacomodulation has become fundamental in the drug discovery process to rapidly generate large collections of nucleosidic structures. However, synthetic routes to obtain these compounds libraries are often slow, expensive, low yielding and involve harsh conditions. Even newly combinatorial chemistry technologies[9] are still dependent on the reliability of the individual reactions. The development of new methodologies and, above all, the design of new tools are highly needed to access efficiently a large variety of compounds. Over the past few years, transition metal-mediated transformations have turned out to be inescapable synthetic procedures in the hand of the chemist. Among all the available homogeneous catalysts, our attention has focused on a class of ancillary ligands that have remarquebly improved the organometallic field these last years, but that have been not so much represented in the nucleoside chemistry: The *N*-heterocyclic carbenes.

2. GENERALITIES ABOUT *N*-HETEROCYCLIC CARBENES (NHC)

Carbenes are electron-deficient two-coordinate carbon compounds that have two non-bonding electrons on that carbon (Figure 7). In the ground state, the two unshared electrons may be either in the same orbital with antiparallel spins (singlet state), or in two different orbitals with parallel spins (triplet state).

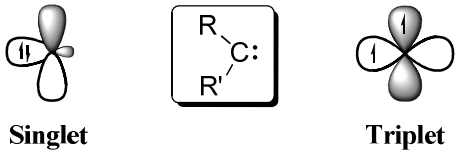


Figure 7. Schematic representation of a carbene and its electronic configurations.

[9] Weber, L. *Drug discov. today: Technologies* **2004,** *1*, 261-267.

The quest for a stable carbene was long considered an unreasonable target, until Wanzlick showed that the stability of carbenes could be dramatically increased by vicinal amino substituents.[10] However, no isolation of a "monomeric" carbene was achieved before 1991 and the X-ray determination of the free imidazol-2-ylidene IAd (*N*,*N*'-di(adamantyl)imidazol-2-ylidene) by Arduengo *et al.*[11] Since this groundbreaking isolation, the development of *N*-heterocyclic carbene (NHC) ligands has blossomed and numerous structures has been reported (Figure 8).

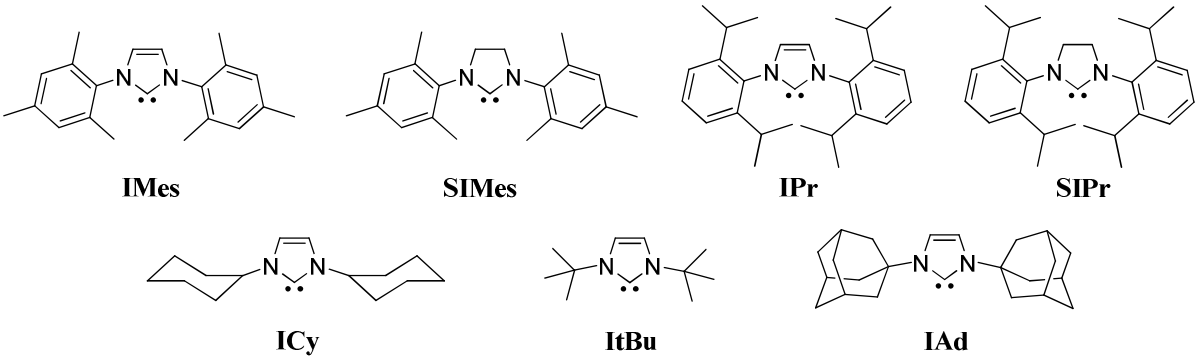


Figure 8. Structures of representative *N*-heterocyclic carbene ligands.

Several synthetic routes can be found in the literature for the preparation of *N*-containing ring systems that can be used as precursors of *N*-heterocyclic carbenes. We will only present the most commonly employed synthetic routes for the formation of symmetrical five-membered ring imidazol-2-ylidene and imidazolidin-2-ylidene, which represent the two classes of NHCs used during this Ph.D. work.

2.1. Synthesis of Symmetrical NHCs

a) Preparation of symmetrical imidazol-2-ylidenes *via* imidazoliums:

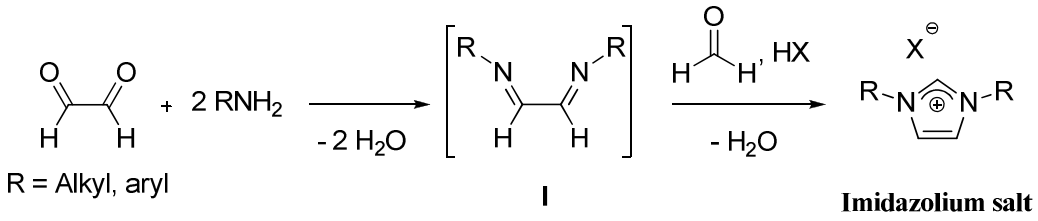
The most straightforward and reliable route to prepare imidazolium salts, which are the immediate precursors of imidazol-2-ylidenes, is the one-pot synthesis described in Scheme 1, using a primary amine, glyoxal and formaldehyde.[12] Under acidic conditions, the reaction proceeds through a coupling between the amine and the glyoxal, forming, upon

[10] (a) Wanzlick, H.W.; Kleiner, H.J. *Angew. Chem.* **1961**, *73*, 493-498. (b) Wanzlick, H.W. *Angew. Chem.* **1962**, *74*, 129-134. (c) Wanzlick, H.W.; Kleiner, H.J. *Chem. Ber.* **1963**, *96*, 3024-3027. (a) Lavallo, V.; Canac, Y.; Präsang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705-5709. (b) Lavallo, V.; Canac, Y.; DeHope, A.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7236-7239.

[11] (a) Arduengo, A.J., III; Harlow, R.L.; Kline, M.A. *J. Am. Chem. Soc.* **1991**, *113*, 361-363. (b) Arduengo, A.J., III *Acc. Chem. Res.* **1999**, *32*, 913-921.

[12] (a) Arduengo, A.J., III Patent: WO 9114678, **1992**. (b) Gridnev, A.A.; Mihaltseva, I.M. *Synth. Commun.* **1994**, *24*, 1547-1555.

dehydration, the corresponding Schiff base **I**. Condensation with formaldehyde leads to the imidazolium salt.



Scheme 1. One-pot synthesis of imidazolium salts.

This very general procedure allows for the synthesis of symmetrically *N,N'*-substituted imidazolium salts with various aryl and alkyl groups such as the commercially available IPr·HCl and IMes·HCl (Figure 9). The reaction of deprotonation of imidazoliums and formation of imidazol-2-ylidenes is usually carried out in the presence of strong bases in ammonia or in non-protic solvents, such as THF or ethers, and requires anhydrous conditions (Scheme 2).

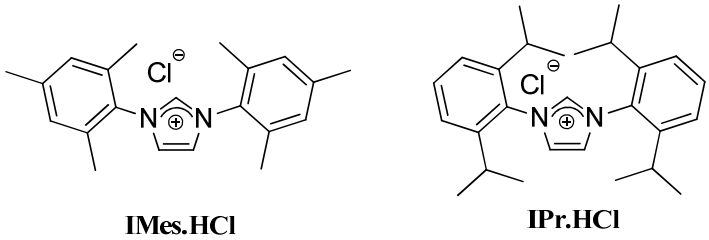
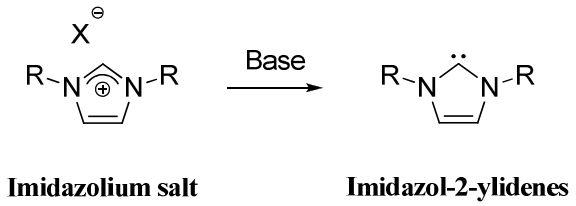


Figure 9. Structure of IPr·HCl and IMes·HCl used as NHC precursors.



Scheme 2. Deprotonation of imidazolium salts.

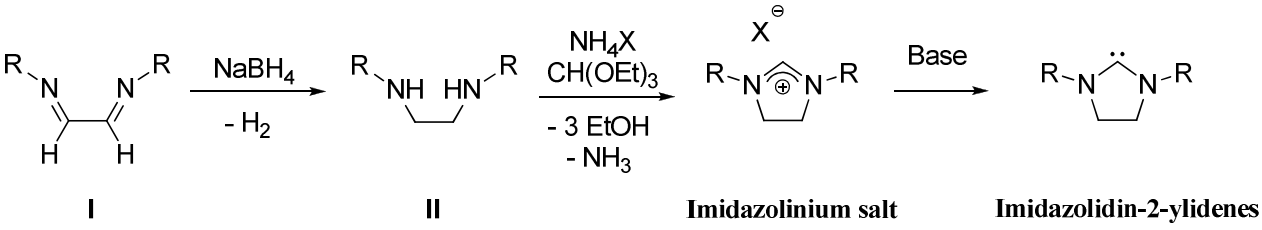
<u>b) Preparation of symmetrical imidazolidin-2-ylidenes *via* imidazoliniums:</u>

Diazabutadienes **I**, obtained as intermediates in the synthesis of imidazol-2-ylidenes (Scheme 1), can be reduced to 1,2-diaminoethane **II** by treatment with sodium borohydride. The reduced diamines further react with triethyl orthoformate under acidic conditions to form imidazolinium salts (Scheme 3).[13,14] This methodology allows for the synthesis of

[13] (a) Arduengo, A.J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523-14534. (b) Jafarpour, L.; Stevens, E.D.; Nolan, S.P. *J. Organomet. Chem.* **2000**, *606*, 49-54. (c) Hintermann, L. *Beilstein J. Org. Chem.* **2007**, *3*:22.

[14] Aidouni, A.; Demonceau, A.; Delaude, L. *Synlett* **2006**, 493-495.

symmetrically *N,N'*-disubstituted imidazolinium salts with various aryl groups. Similarly to their unsaturated counterparts, imidazolinium salts are deprotonated by strong bases. [15]



Scheme 3. Synthesis and deprotonation of imidazolinium salts.

The unexpected stability of the *N*-heterocyclic carbenes (NHCs) prompted several groups to carry out studies in order to better understand these unusual species. The valuable results provided access to numerous transition metal carbene complexes by simple complexation of a stable *N*-heterocyclic carbene ligand acting as a two-electron donor.

2.2. Synthesis of Transition Metal Carbene Complexes

For almost every metal of the periodic table, NHC-containing complexes have been reported, spanning from the alkali metals to borderline metalloid elements such as boron and silicon, without forgetting lanthanides and all transition metals. Without surprise, some metals exhibit an amazing collection of NHC complexes (notably Ni, Ir, Ru, Rh, and Pd), while for others only a handful of compounds have been synthesized to date. There are many ways of synthesizing NHC-containing metal complexes, and the description of every available protocol is beyond the scope of the present introduction.[16] Therefore, we will depict only the most commonly employed procedures for the coordination of a NHC to a metal (Scheme 4):

[15] (a) Hocker, J.; Merten, R. *Chem. Ber.* **1972**, *105*, 1651-1653. (b) Taton, T.A.; Chen. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1011-1013. (c) Herrmann, W.A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G.R.J. *Chem.–Eur. J.* **1996**, *2*, 772-780.

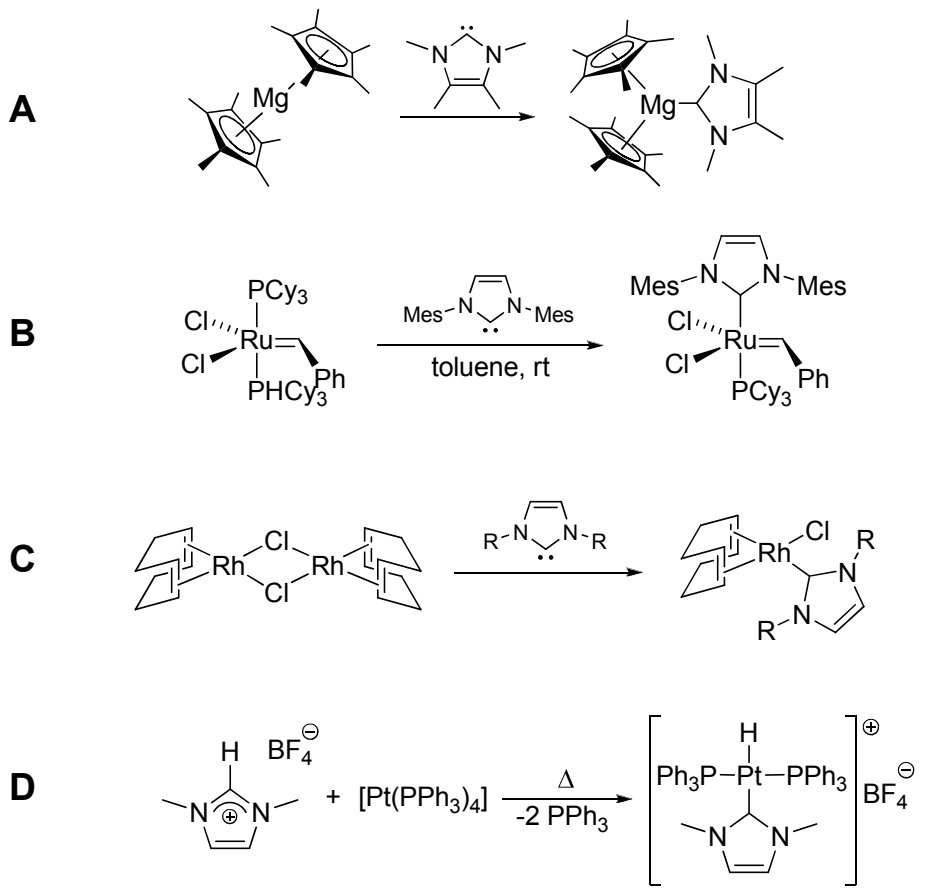
[16] For reviews, see: (a) Herrmann, W.A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162-2187. (b) Weskamp, T.; Böhm, V.P.W.; Herrmann, W.A. *J. Organomet. Chem.* **2000**, *600*, 12-22. (c) Crudden, C.M.; Allen, D.P. *Coord. Chem. Rev.* **2004**, *248*, 2247-2273. (d) Gok, Y.; Cetinkaya, E.; Ozdemir, I.; Cetinkaya, B.; Lappert, M.F. *Acta Chim. Slov.* **2004**, *51*, 437-446. (e) Lappert, M.F. *J. Organomet. Chem.* **2005**, *690*, 5467-5473. (f) Braband, H.; Kückmann, T.I.; Abram, U. *J. Organomet. Chem.* **2005**, *690*, 5421-5429. (g) Scott, N.M.; Nolan, S.P. *Eur. J. Inorg. Chem.* **2005**, 1815-1828. (h) Liddle, S.T.; Edworthy, I.S.; Arnold, P.L. *Chem. Soc. Rev.* **2007**, *36*, 1732-1744. (i) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726-764. (j) Lin, I.J.B.; Vasam, C.S. *Coord. Chem. Rev.* **2007**, *251*, 642-670. (k) Pugh, D.; Danopoulos, A.A. *Coord. Chem. Rev.* **2007**, *251*, 610-641. (l) Kühl, O. *Chem. Soc. Rev.* **2007**, *36*, 592-607. (m) Arnold, P.L.; Pearson, S. *Coord. Chem. Rev.* **2007**, *251*, 596-609.

A - Coordination to an empty site: The reaction of a free NHC with an open shell metallic center able to accommodate an additional ligand in its coordination sphere.

B - Ligand displacement: A NHC binds strongly to a metal, which allows it to displace numerous types of ligands, whether neutral or anionic, including the ubiquitous tertiary phosphines[17] (The most employed method).

C - Splitting of bridged metal-dimers: Bridged metal dimers or polymers that can be broken upon addition of a free NHC.

D - Oxidative addition of imidazolium salts: Zerovalent Group 10 metals, especially platinum and nickel complexes, are prompt to react with imidazolium and 2-haloimidazolium salts to form NHC-complexes by oxidative addition.[18,19]



Scheme 4. Most commonly employed procedures for the coordination of a NHC to a metal.

[17] Huang, J.; Stevens, E.D.; Nolan, S.P.; Petersen, J.L. *J. Am. Chem. Soc.* **1999**, *121*, 2674-2678.

[18] (a) McGuiness, D.S.; Cavell, K.J.; Yates, B.F.; Skelton, B.W.; White, A.H. *J. Am. Chem. Soc.* **2001**, *123*, 8317-8328. (b) McGuiness, D.S.; Cavell, K.J.; Yates, B.F. *Chem. Commun.* **2001**, 355-356. (c) Gründemann, S.; Albrecht, M.; Kovacevic, A.; Faller, J.W.; Crabtree, R.H. *J. Chem. Soc., Dalton Trans.* **2002**, 2163-2167. (d) Fürstner, A.; Seidel, G.; Kremzow, D.; Lehmann, C.W. *Organometallics* **2003**, *22*, 907-909.

[19] Duin, M.A.; Clement, N.D.; Cavell, K.J.; Elsevier, C.J. *Chem. Commun.* **2003**, 400-401.

Of note, most procedures for the synthesis of NHC-metal complexes where a free NHC is used can be also carried out with the corresponding imidazolium salt and a base, which will generate *in situ* the free NHC.[15c,20]

2.3. NHCs in Homogeneous Catalysis

According to various structural studies quantifying steric and electronic effects, the nature and strength of the NHC-metal bond clearly appear to be key information to rational catalyst design.[21,22] Hence, the right combination of electronic and steric factors characterizing NHCs has a major impact on the development of new and improved ligands for catalysis.[23,24] First considered as simple tertiary phosphine mimics,[25] NHCs have rapidly gained great popularity with the increasing experimental evidences that NHC-metal catalysts can surpass their phosphine-based counterparts in both activity and scope.[26,27] In most cases, it is relied to the fact that NHCs are better σ-donors than phosphines,[28] possess in general higher thermal stability and the use of NHC as supporting ligand usually leads to better complex stability.[29] The stabilization of these complexes was explained by the directional distribution of the steric bulk and the electronic properties of carbene ligands. Structural studies have proven that bulkiness of the groups bound to the nitrogen atoms of the NHC ligands and more importantly, the short metal–carbon distances in these complexes, increase the steric congestion around the metal center when compared to tertiary phosphines (Figure 10).[21]

[20] Díez-González, S.; Stevens, E.D.; Scott, N.M.; Petersen, J.L.; Nolan, S.P. *Chem.–Eur. J.* **2008**, *13*, 158-168.

[21] (a) Arduengo, A.J., III; Krafczyk, R. *Chem Z.* **1998**, *32*, 6-14. (b) Trnka, T.M.; Morgan, J.P.; Sanford, M.S.; Wilhelm, T.E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M.W.; Grubbs, R.H. *J. Am. Chem. Soc.* **2003**, *125*, 2546-2558.

[22] (a) Fröhlich, N.; Pidun, U.; Stahl, M.; Frenking, G. *Organometallics* **1997**, *16*, 442-448. (b) Tafipolsky, M.; Scherer, W.; Öfele, K.; Artus, G.; Pedersen, B.; Herrmann, W.A.; McGrady, G.S. *J. Am. Chem. Soc.* **2002**, *124*, 5865-5880.

[23] (a) Clement, N.D.; Cavell, K.J.; Jones, C.; Elseiver, C.J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1277-1279. (b) Schaub, T.; Radius, U. *Chem.–Eur. J.* **2005**, *11*, 5024-5030.

[24] Viciu, M.S.; Navarro, O.; Germaneau, R.F.; Kelly, R.A., III; Sommer, W.; Marion, N.; Stevens, E.D.; Cavallo, L.; Nolan, S.P. *Organometallics* **2004**, *23*, 1629-1635.

[25] Green, J.C.; Scur, R.G.; Arnold, P.L.; Cloke, G.N. *Chem. Commun.* **1997**, 1963-1964.

[26] Herrmann, W.A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290-1309.

[27] Cavallo, L.; Correa, A.; Costabile, C.; Jacobsen, H. *J. Organomet. Chem.* **2005**, *690*, 5407-5413.

[28] (a) Huang, J.; Stevens, E.D.; Nolan, S.P. *Organometallics* **2000**, *19*, 1194-1197. (b) Perrin, L.; Clot, E.; Eisenstein, O.; Loch, J.; Crabtree, R.H. *Inorg. Chem.* **2001**, *40*, 5806-5811. (c) Chianese, A.R.; Li, X.; Jarzen, M.C.; Faller, J.W.; Crabtree R.H. *Organometallics* **2003**, *22*, 1663-1667.

[29] (a) Díez-González, S.; Nolan, S.P. *Coord. Chem. Rev.* **2007**, *251*, 874-883. (b) Scott, N.M.; Clavier, H.; Mahjoor, P.; Stevens, E.D.; Nolan, S.P. *Organometallics* **2008**, *27*, 3181-3186.

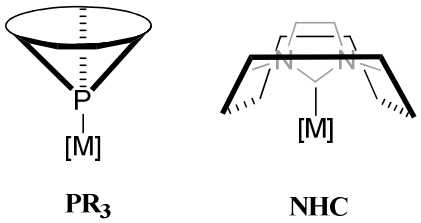


Figure 10. Schematic representation of the steric impact of phosphines and NHCs.

NHCs are now recognized as efficient and versatile tools for both transition metal-mediated reactions[30] and organocatalysis.[31] The outstanding abilities of NHCs in homogeneous catalysis cover a wide range of applications and have been largely reviewed the last ten years.[26,30] NHC-containing transition metal complexes have been reported to efficiently catalyze a number of reactions such as ruthenium-mediated metathesis,[32,33] cycloaddition and hydrosilylation using copper complexes,[34] gold-catalyzed transformations,[35] palladium-mediated cross-coupling reactions,[36] among others. During the course of this Ph.D., we have focused our attention on palladium, ruthenium and copper chemistries that will be properly introduced in each relevant chapter.

3. OBJECTIVES: DEVELOPMENT OF EFFICIENT TOOLS FOR THE NUCLEOSIDE CHEMISTRY

In the field of antiviral therapeutics, several nucleosides are well established as potent inhibitors of virus replication. In spite of this success, numerous problems remain as aforementioned. The chemistry of our group focus on the conception, the synthesis and the discovery of new heterocyclic and nucleoside derivatives for the treatment of various

[30] (a) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181–222. (b) *N-heterocyclic Carbenes in Synthesis*, Nolan, S.P., Ed.; Wiley-VCH: Weinheim, Germany, **2006**. (c) *N-Heterocyclic Carbenes in Transition Metal Catalysis*, Glorius, F., Ed.; Springer-Verlag: Berlin Heidelberg, Germany, **2007**. (d) Clavier, H.; Nolan, S.P. *Annu. Rep. Prog. Chem., Sect B: Org. Chem.* **2007**, *103*, 193-222. (e) Boeda, F.; Nolan, S.P. *Annu. Rep. Prog. Chem., Sect B: Org. Chem.* **2008**, *104*, 184-210.

[31] Marion, N.; Díez-González, S.; Nolan, S.P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988-3000.

[32] (a) Trnka, T.M.; Grubbs, R.H. *Acc. Chem. Res.* **2001**, *34*, 18-29. (b) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55-66. (c) Hoveyda, A.H.; Zhugralin, A.R. *Nature* **2007**, *450*, 243-251.

[33] (a) *Handbook of Metathesis*; Grubbs, R.H., Ed.; Wiley-VCH: Weinheim, Germany, **2003**, vols. 1-3. (b) Despagnet-Ayoub, E.; Ritter, T. *Top. Organomet. Chem.* **2007**, *21*, 193-218. (c) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726-764.

[34] Díez-González, S.; Nolan, S.P. *Synlett*, **2007**, 2158-2167.

[35] (a) Lin, I.J.B.; Vasam, C.S. *Can. J. Chem.* **2005**, *83*, 812-825. (b) Marion, N.; Nolan, S.P. *Chem. Soc. Rev.* **2008**, *37*, 1776-1782.

[36] (a) Hillier, A.C.; Grasa, G.A.; Viciu, M.S.; Lee, H.M.; Yang, C.; Nolan, S.P. *J. Organomet. Chem.* **2002**, *653*, 69-82. (b) Hillier, A.C.; Nolan, S.P. *Platinum Metals Rev.* **2002**, *46*, 50-64. (c) Herrmann, W.A.; Öfele, K.; Preysing, D.V.; Schneider, S.K. *J. Organomet. Chem.* **2003**, *687*, 229-248. (d) Díez-González, S.; Nolan, S.P. *Top. Organomet. Chem.* **2007**, *21*, 47-82. (e) Kantchev, E.A.B.; O'Brien, C.J.; Organ, M.G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768-2813.

infectious diseases. Our tight collaboration with biological laboratories allows for drawing rationally structures and modulations of targeted compounds. Efforts are concentrated as well into the development or/and the improvement of synthetic methodologies of general interest in the field of nucleoside chemistry. In this context, our partnership with Prof. S.P. Nolan aims at developing new useful tools for organometallic reactions that could be further applied to the synthesis of nucleosides. In the laboratory of the Prof. S.P. Nolan, the coordination chemistry of *N*-Heterocyclic carbene (NHC) ligands with transition metals and the catalytic activity of carbene complexes have been explored for many years. A major goal has been the development of straightforward synthetic routes, leading, in few chemical steps and after rapid purification, to the desired well-defined, stable and easy to handle pre-catalyst. NHCs have gained great popularity in organometallic chemistry and homogeneous catalysis since their first isolation in 1991. Nevertheless, their application in nucleoside synthetic procedures has been mainly limited to ruthenium-catalyzed metathesis reactions.[37,38]

The guiding line of this Ph.D. work is thereby based on collaboration between the two laboratories. Combining both research focuses, the main goal consists in developing new NHC-containing late transition-metal catalysts and applying them in the synthesis of various series of nucleoside analogues, potential smallpox inhibitors.

3.1. Cu^{I}-catalyzed Cycloaddition for 1,2,3-Triazolo-Carbanucleoside Synthesis

The purpose of this first project is to develop a simple and optimum tool adapted to the preparation of 1,2,3-triazolo-carbanucleosides *via* Huisgen 1,3-dipolar cycloaddition. Comprehensive study of copper(I)-catalyzed Huisgen cycloaddition has to be run with terminal and internal alkynes in the presence of different copper catalysts. The optimized method will be then used to extend the scope of the reaction to a large variety of racemic or enantioselective carbocyclic nucleosides. The comparison of the biological results of the evaluated compounds should give us interesting structure-activity relationship informations.

[37] (a) Liu, J.; Robin, M.J. *Org. Lett.* **2004**, *6*, 3421-3423. (b) Kazzouli, S.E.; Berteina-Raboin, S.; Agrofoglio, L.A. *Nucleos. Nucleot. Nucl. Acids* **2007**, *26*, 1395-1398.

[38] Examples in metathesis reactions: (a) Gillaizeau, I.; Charamon, S.; Agrofoglio, L.A. *Tetrahedron Lett.* **2001**, *42*, 8817-8819. (b) Moon, H.R.; Kim, H.O.; Lee, K.M.; Chun, M.W.; Kim, J.H.; Jeong, L.S. *Org. Lett.* **2002**, *4*, 3501-3503. (c) Gillaizeau, I.; Lagoja, I.M.; Nolan, S.P.; Aucagne, V.; Rozenski, J.; Herdewijn, P.; Agrofoglio, L.A. *Eur. J. Org. Chem.* **2003**, 666-671. (d) Amblard, F.; Nolan, S.P.; Gillaizeau, I.; Agrofoglio, L.A. *Tetrahedron Lett.* **2003**, *44*, 9177-9180. (e) Agrofoglio, L.A.; Amblard, F.; Nolan, S.P.; Charamon, S.; Gillaizeau, I.; Zevaco, T.A.; Guenot, P. *Tetrahedron* **2004**, *60*, 8397-8404. (f) Amblard, F.; Nolan, S.P.; Agrofoglio, L.A. *Tetrahedron* **2005**, *61*, 7067-7080. (g) Amblard, F.; Nolan, S.P.; Schinazi, R.F.; Agrofoglio, L.A. *Tetrahedron* **2005**, *61*, 537-544. (h) Roy, V.; Mieczkowski, A.; Topalis, D.; Berteina-Raboin, S.; Deville-Bonne, D.; Nolan, S.P.; Agrofoglio, L.A. *Synthesis* **2008**, *13*, 2127-2133. (i) Kumamoto, H.; Topalis, D.; Broggi, J.; Pradère, U.; Roy, V.; Berteina-Raboin, S.; Nolan, S.P.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J.-M.; Agrofoglio, L.A. *Tetrahedron* **2008**, *64*, 3517-3526.

3.2. Acyclic Nucleoside Phosphonates via Ruthenium-mediated Cross-Metathesis

Based on the modification of structural parameters influencing the cellular activation, we would like to aim new pyrimidine acyclic nucleotides possessing enhanced antiviral activities. The objective of this second part is thus to synthesize two new series of acyclic nucleoside phosphonates using a cross-metathesis reaction as key step. At the same time, we will attempt to develop a new original strategy for the preparation of various unsaturated optically active acyclic nucleoside phosphonates bearing a functional group on the *C*-1' position of the side chain. The behaviour in olefin cross-metathesis of a ruthenium complex bearing a NHC will be also studied.

3.3. NHC-containing Complexes in Palladium-catalyzed Reactions

Palladium-catalyzed reactions are certainly the most resourceful methodologies to access variety of appealing pharmacomodulations. Although applications of Pd-assisted reactions have been widely considered, they have been confined to a certain type of bond-forming reactions and limited by the catalysts abilities. In this third part, we focus on the development of new classes of homogeneous and well-defined palladium catalysts bearing a NHC ligand. We will then conduct the evaluation of these NHC-Pd complexes as tools in the catalysis of C-C, C-N and C-O bond formations. To explore and optimize their catalytic capacities, the study will be carried out on simple surrogates before further possible applications to nucleosides. Their catalytic activities will be examined in different cross-coupling reactions and in transfer hydrogenation reactions.

3.4. Collaborations

Within the framework of this Ph.D work for the development of NHC-bearing catalysts for the synthesis of nucleosides, I realized a one year visiting fellowship in the group of Pr. S.P. Nolan at the Institut of Chemical Investigation of Catalunia (ICIQ) - Tarragona - Spain.

Concerning the biological activity and toxicity results, this Ph.D work has been realized in collaboration with the Prs J. Balzarini, J. Neyts, and R. Snoeck from the Rega Institute for Medical Research - Louvain - Belgique, and Dr J.M. Crance and Pr D. Garin from the Centre de Recherche du Service de Santé des Armées - La Tronche - France.

Activation studies of our nucleosidic analogues by human kinases have been realized by the Dr D. Topalis during the course of his Ph.D work in the group of Dr D. Deville-Bonne

from the Institut Jacques Monod - Paris - France. As enhanced antiviral activity is correlated to a high intracellular concentration of the analogue active form (nucleotide), they searched for new pyrimidine nucleotide analogues possessing improved binding and substrate properties towards hUCK and TMPK (Thymidylate monophosphate kinase). If somes of our synthesized compounds appeared to be specific substrates of the vaccinia viral TMPK,[39] they would be incorporated into the forming DNA chain and inhibit the virus replication.

[39] Topalis, D.; Collinet, B.; Gasse, C.; Dugué, L.; Balzarini, J.; Pochet, S.; Deville-Bonne, D. *FEBS J.* **2005**, *272*, 6254-6265.

Chapter I:

Alkyne - azide [3+2] cycloaddition, an efficient tool for 1,2,3-triazolo-carbanucleoside synthesis

1. INTRODUCTION

As mentionned in general introduction, the recent emergence of viral diseases has been a driving force for the development of small nucleoside libraries.[1] Particularly, analogues of nucleosides structurally related to ribavirin have attracted much interest.[40,41] They are presently under development and might surpass the standard ribavirin. First discovered in 1970, ribavirin is a guanosine analogue composed of a ribofuranosyl moiety and [1,2,4]-triazole base with a carboxamide function (Figure 11). This compound can interact with several enzymes but it is mainly a potent inhibitor of the *inosine monophosphate dehydrogenase* (IMPDH).[40,42] The inhibition of this enzyme, required for virus cell replication, prevents the guanosine monophosphate synthesis, blocking the formation of guanosine nucleotide through the *de novo* pathway. Therefore, the ribavirin shows a broad-spectrum of antiviral activity against DNA and RNA viruses, including influenza, hepatitis B/C, polio, measles, canine distemper, hemorrhagic fevers and smallpox.[43] However, ribavirin causes potential dose-dependent haemolytic anaemia as side effect.[44] Hence, modulation on the triazolo moiety would allow for the development of new and safer anti-virus inhibitors.

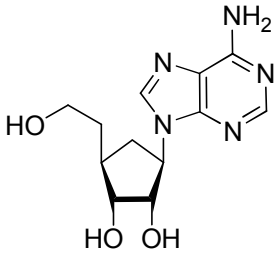
[40] Gish, R.G. *J. Antimicrob. Chemother.* **2006,** *57*, 8-13.

[41] (a) Witkowski, J.T.; Robins, R.K.; Khare, G.P.; Sidwell, R.W. *J. Med. Chem.* **1973**, *16*, 935-937. (b) Markland, W.; McQuaid, T.J.; Jain, J.; Kwong, A.D. *Antimicrob. Agents Ch.* **2000**, *44*, 859-866. (c) Wu, J.Z.; Lin, C-.C.; Hong, Z.J. *Antimicrob. Chemother.* **2003**, *52*, 543-546.

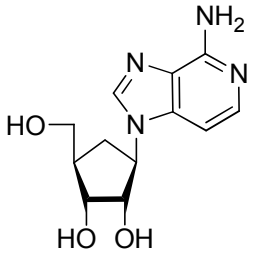
[42] Graci, J.D.; Cameron, C.E. *Rev. Med. Virol.* **2006**, *16*, 37-48.

[43] (a) Sidwell, R.W.; Huffman, J.H.; Khare, G.P.; Allen, L.B.; Witkowski, J.T.; Robins, R.K. *Science* **1972**, *177*, 705-706. (b) *Ribavirin: A Broad Spectrum Antiviral Agent*; Smith, R.A., Kirkpatrick, W., Eds.; Academic Press: New York, United States, **1980**. (c) Wu, J.Z.; Walker, H.; Lau, J.Y.N.; Hong, Z. *Antimicrob. Agents Chemother.* **2003**, *47*, 426-431.

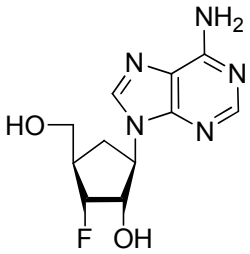
[44] (a) Sulkowski, M.S. *Clin. Infect. Dis.* **2003**, *37*, 315-322. (b) Lindahl, K.; Stahle, L.; Bruchfeld, A. *Hepatology* **2005**, *41*, 275-279. (c) Alvarez, D.; Dieterich, D.T.; Brau, N.; Moorehead, L.; Ball, L.; Sulkowski, M.S. *J. Viral Hepat.* **2006**, *13*, 683-689.



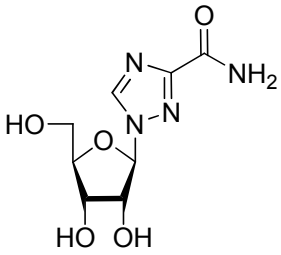
5'-Homoaristeromycin



Carbocyclic 3-deazaadenosine



Carbocyclic 3'-deoxy-3'-α-fluoroadenosine



Ribavirin

Figure 11. Nucleosides with *in vitro* anti-pox activity.

In addition, during the last decade carbanucleosides have also played a major role in the treatment of viral infectious diseases such as AIDS or hepatitis.[45] Carbocyclic analogues of nucleosides are compounds in which the furan ring of the nucleoside has been replaced by a cyclopentane system.[46] This modification makes these compounds more resistant to hydrolases but does not prevent their enzymatic conversion into nucleotide analogues. This synthetically challenging class of compounds has generated interesting and wide range of antiviral nucleosides.[47] Several carbanucleosides have emerged as the most (so far) potent inhibitors of vaccinia virus replication in cell culture.[48] They are targeted at the *S-adenosylhomocysteine* (SAH) *hydrolase*, an enzyme involved in methyl transfer reactions.[49] Thus, the carbocyclic nucleoside 5'-homoaristeromycin,[50] as well as the carbocyclic

[45] (a) Balzarini, J.; De Clercq, E. *Pharmacochemistry Library* **1990**, *14*, 175-194. (b) Marquez, V.E. *Adv. Antivir. Drug Design* **1996**, *2*, 89-146. (c) Schneller, S.W. *Curr. Top. Med. Chem.* **2002**, *2*, 1087-1092. (d) Neyts, J.; De Clercq, E. *Antivir. Res.* **2003**, *57*, 25-33. (e) Baker, R.O.; Bray, M.; Huggins, J.W. *Antivir. Res.* **2003**, *57*, 13-23. (f) De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, *14*, 289-300.

[46] (a) Marquez, V.E.; Lim, M.I. *Med. Res. Rev.* **1986**, *6*, 1-40. (b) Huryn, D.M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768. (c) Agrofoglio, L.A.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.R.; Earl, R.A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10684. (d) Crimmins, M.T. *Tetrahedron* **1998**, *54*, 9229-9272. (e) Agrofoglio, L.A., Challand, S.R. in "*Acyclic, Carbocyclic and L-Nucleosides*", Kluwer Academic Publishers: Dordrecht, Netherlands, **1998**. (f) Ichikawa, E.; Kato K. *Curr. Med. Chem.* **2001**, *8*, 385-423. (g) Ludek, O.R.; Meier, C. *Synthesis* **2006**, 2101-2109.

[47] (a) De Clercq, E. *Nucleos. Nucleot.* **1998**, *17*, 625-634. (b) Hervey, P.S.; Perry, C.M. *Drugs* **2000**, *60*, 447-479. (c) Jeong, L.S.; Jeong, L.A. *Antivir. Chem. Chemoth.* **2004**, *15*, 235-250.

[48] (a) Chu, C.K.; Jin, Y.H.; Baker, R.O.; Huggins, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 9-12. (b) Simons, C.; Wu, Q.; Htar, T.T *Curr. Top. Med. Chem.* **2005**, *5*, 1191-1203. (c) Arumugham, B.; Kim, H-.J.; Prichard, M.N.; Kern, E.R.; Chu, C.K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 285-287.

[49] (a) Wolfe, M.S.; Borchardt, R.T. *J. Med. Chem.* **1991**, *34*, 1521-1530. (b) Mosley, S.L.; Bakke, B.A.; Sadler, J.M.; Sunkara, N.K.; Dorgan, K.M.; Zhou, Z.S.; Seley-Radtke, K.L. *Bioorg. Med. Chem.* **2006**, *14*, 7967-7971.

[50] Yang, M.; Schneller, S.W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 149-151.

analogues of 3-deazaadenosine and 3'-deoxy-3'-α-fluoroadenosine[51] display good activities against vaccinia, cowpox and monkeypox viruses (Figure 11).

Combining both strategies, we and others have reported the synthesis of diverse carbanucleosides bearing a 1,2,3-triazole moiety, presented as ribavirin analogues, with interesting antiviral activities against HIV-1,[52] varicella-zoster virus,[53] or vaccinia virus.[54] The pharmaceutical importance of designing new effective anti-viral agents of this class prompted us to optimize and extend the synthesis of 1,2,3-triazolo-carbanucleosides *via* Huisgen 1,3-dipolar cycloaddition.

1.1. The Copper-catalyzed Huisgen 1,3-Dipolar Cycloaddition or CuAAC

1,3-Dipolar cycloaddition reactions have attracted much interest in the last decades, Rolf Huisgen being the father of the concept.[55] Dipolar cycloadditions generate a large variety of five-membered heterocycles in a rapid, reproducible and efficient manner. The reaction between an azide and a terminal alkyne is one of the most popular Huisgen cycloadditions. The resulting 1,2,3-triazoles have been intensively studied because of their antiviral and antimicrobial activities.[56] Not present in natural products, they are remarkably stable to metabolic transformations, such as oxidation, reduction, and both basic and acidic hydrolysis. Under thermal conditions, this reaction usually affords a mixture of 1,4- and 1,5-disubstituted regioisomers and generally requires elevated temperatures and long reaction times (Scheme 5).[55,57] Good regioselectivity could be observed only for coupling reactions involving highly electron-deficient terminal alkynes. Thanks to the recent discovery of copper(I) as efficient

[51] (a) De Clercq, E.; Montgomery, J.A. *Antivir. Res.* **1983**, *3*, 17-24. (b) De Clercq, E. *Clin. Microbiol. Rev.* **2001**, *14*, 382-397.

[52] Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R.F.; Agrofoglio, L.A. *Bioorg. Med. Chem.* **2003**, *11*, 3633-3639.

[53] Pérez-Castro, I.; Caamaño, O.; Fernández, F.; García, M.D.; López, C.; De Clercq, E. *Org. Biomol. Chem.* **2007**, *5*, 3805-3813.

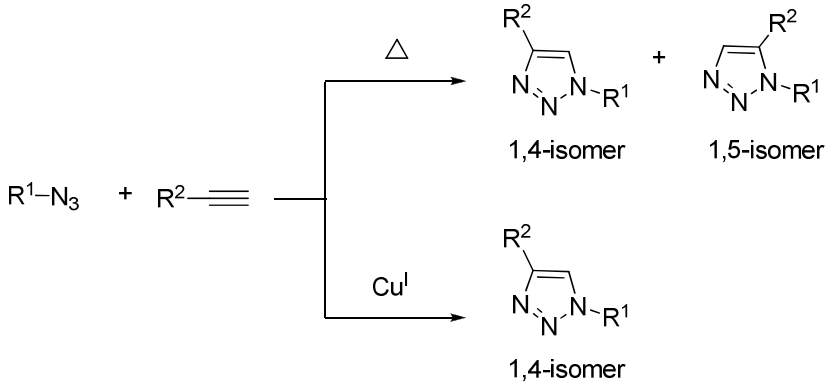
[54] Cho, H.; Bernard, D.L.; Sidwell, R.W.; Kern, E.R.; Chu, C.K. *J. Med. Chem.* **2006**, *49*, 1140-1148.

[55] (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565-598. (b) Huisgen, R. in *"1,3-Dipolar Cycloaddition Chemistry"*, Vol. 1; Padwa, A., Ed.; Wiley: New York, United States, **1984**.

[56] (a) Gilchrist, T.L.; Gymer, G.E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33-85. (b) Finley, K.T. *Triazoles: 1,2,3* in *"The Chemistry of Heterocyclic Compounds"*; Weissberger, A., Taylor, C.E., Eds.; John Wiley & Sons: New York, United States, **1980**, 1-349. (c) Katritzky, A.R.; Zhang, Y.; Singh, S.K. *Heterocyles* **2003**, *60*, 1225-1239. For therapeutic activities, see: (d) Buckle, D.R.; Rockell, C.J.M.; Smith, H.; Spicer, B.A. *J. Med. Chem.* **1986**, *29*, 2262-2267. (e) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.F.; Karlsson, A.; Balzarini, J.; Camarasa, M.J. *J. Med. Chem.* **1994**, *37*, 4185-4194. (f) Chen, M.D.; Lu, S.J.; Yuag, G.P.; Yang, S.Y.; Du, X.L. *Heterocycl. Commun.* **2000**, *6*, 421-426. (g) Genin, M.J.; Allwine, D.A.; Anderson, D.J.; Barbachyn, M.R.; Emmert, D.E.; Garmon, S.A.; Graber, D.R.; Grega, K.C.; Hester, J.B.; Hutchinson, D.K.; Morris, J.; Reischer, R.J.; Ford, C.W.; Zurenko, G.E.; Hamel, J.C.; Schaadt, R.D.; Stapert, D.; Yagi, B.H. *J. Med. Chem.* **2000**, *43*, 953-970.

[57] Wang, Q.; Chittaboina, S.; Barnhill, H.N. *Lett. Org. Chem.* **2005**, *2*, 293-301.

and regiospecific catalyst for this process,[58,59] this transformation represents a general and mild approach for the preparation of the 1,4-regioisomer exclusively (Scheme 5). Primary, secondary, and tertiary substituted azides as well as aromatic azides, in the presence of numerous terminal acetylene and a small amount of catalyst, afford 1,4-disubstituted-1,2,3-triazoles in good yields. Moreover, although the azide and the alkyne are mutually very reactive, individually they are practically inert, which renders the reaction orthogonal to numerous functional groups including unprotected esters, acids, alkenes, alcohols or amines. Electron-deficient alkynes are more reactive whereas an electron-donating substituent will be more efficient on an azide. However, under the copper-catalyzed version the differences of alkynes reactivity are strongly reduced.



Scheme 5. Thermal and copper-catalyzed Huisgen cycloadditions.

Pharmacomodulation has become fundamental in drug discovery as it has played a major role in the research of new treatments for viral infectious diseases. However, the discovery and process optimization of potential agents is often slow, expensive and involve complex synthesis. The concept of “Click Chemistry”, proposed by Sharpless,[60] has emerged as a fast and efficient approach to generate novel compounds utilizing a collection of reliable chemical reactions. To be defined as “click”, a reaction must respond to a set of stringent criteria:

- Wide Scope
- Stereoselectivity
- High purity and yields
- No protecting groups required
- No chromatographic purification
- Insensitivity to oxygen and water

[58] Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, K.B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596-2599.

[59] Tornøe, C.W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.

[60] Kolb, H.C.; Finn, M.G.; Sharpless, K.B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004-2021.

In light of its impressive selectivity, efficiency and versatility, the Huisgen [3+2] cycloaddition fulfills these criteria. The scope of this reaction is very large, since alkyne and azide components can be incorporated into a wide range of substituents.[55] Moreover, this process, in combination with other organic transformations, has allowed for the assembly of a huge variety of complex molecules and thus generated novel structures unknown *hitherto* as pharmacophores.[61]

In the search for new therapeutic agents, nucleosides with a five membered-ring nucleobase are of high potential value.[52,56e,62] Accordingly, this 1,3-dipolar cycloaddition reaction has been used to synthesize novel nucleosidic and carbanucleosidic analogues.[52-54,63,64] In the literature, the construction of triazolo-carbanucleosides was initially explored using the thermal cycloaddition reaction of an azido-carbocycle and an excess of the strong electron-deficient methylpropiolate.[52,53] However, a mixture of 1,4- and 1,5-disubstituted regioisomers was obtained. First attempts of Cu^{I}-catalyzed 1,3-dipolar cycloaddition were limited to electron-deficient or aryl alkynes.[53,54,64c] Although regioselectivity was induced, large amount of copper and base were required[53,54,64] and the final products were sometimes obtained in modest yields along with side products.[53] These drawbacks underlined the necessity for a versatile and efficient procedure adapted to the nucleoside chemistry.

1.2. The Catalyst: Copper(I) species

As shown in Scheme 6, the mechanism proposed for the Cu^{I}-catalyzed alkyne–azide 1,3-dipolar cycloaddition (CuAAC) starts by the formation of Cu^{I} acetylides *via* initial π-complex formation (**I**) then subsequent deprotonation to afford σ-acetylide Cu^{I} complexes (**II**) and (**III**).[65] A mononuclear Cu^{I}-acetylide complex was first proposed to be the active form

[61] (a) Kolb, H.C.; Sharpless, K.B. *Drug Discov. Today* **2003**, *8*, 1128-1137. (b) Tron, G.C.; Pirali, T.; Billington, R.A.; Canonico, P.L.; Sorba, G.; Genazzani, A.A. *Med. Res. Rev.* **2007**, *28*, 278-308.

[62] (a) Alonso, R.; Camarasa, M.J.; Alonso, G.; de las Heras, F.G. *Eur. J. Med. Chem.* **1980**, *15*, 105-109. (b) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De Clercq, E.; Balzarini, J.; Camarasa, M.J. *Antiviral. Chem. Chemother.* **1998**, *9*, 481-489.

[63] (a) San-Felix, A.; Alvarez, R.; Velazquez, S.; De Clercq, E.; Balzarini, J.; Camarasa, M.J. *Nucleos. Nucleot.* **1995**, *14*, 595-598. (b) Yamashita, M.; Mallikarjuna Reddy, P.; Kato, Y.; Krishna Reddy, V.; Suzuki, K.; Oshikawa, T. *Carbohyd. Res.* **2001**, *336*, 257-270. (c) Lazrek, H.B.; Taourirte, M.; Oulih, T.; Barascut, J.L.; Imbach, J.L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. *Nucleos. Nucleot. Nucl. Acids* **2001**, *20*, 1949-1960. (d) Joubert, N.; Schinazi, R.F.; Agrofoglio, L.A. *Tetrahedron* **2005**, *61*, 11744-11750.

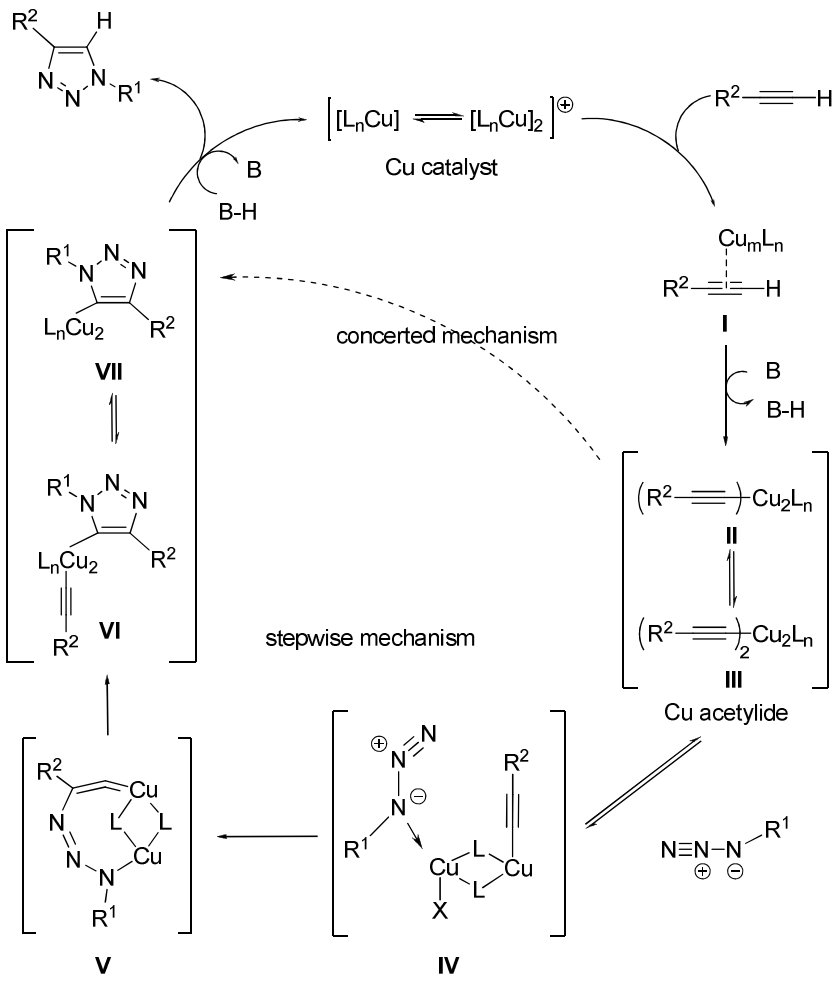
[64] (a) Guezguez, R.; Bougrin, K.; El Akri, K.; Benhida, R. *Tetrahedron Lett.* **2006**, *47*, 4807-4811. (b) El Akri, K.; Bougrin, K.; Balzarini, J.; Farajd, A.; Benhida, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6656-6659. (c) Li, L.; Lin, B.; Yang, Z.; Zhang, L.; Zhang, L. *Tetrahedron Lett.* **2008**, *49*, 4491-4493.

[65] (a) Rodionov, V.O.; Fokin, V.V.; Finn M.G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210-2215. (b) Wu, P.; Fokin, V.V. *Aldrichim. Acta* **2007**, *40*, 7-17.

which reacts with an azide to give a six-membered copper metallacycle intermediate.[66] However, commercially available copper acetylides have so far proven to be ineffective in this reaction. Kinetic studies revealed that the copper catalyzed reaction might proceed through a stepwise catalytic cycle that involves a dynamically exchanging family of Cu^{I}–acetylide complexes.[65a] Density functional theory calculations, performed by Fokin and Sharpless, were consistent with this stepwise mechanism over a concerted one.[66] Although questions about the nature of these complexes still exist, the active Cu^{I}–acetylide species involved in catalysis might contain two metal centers, one (**II**) or two (**III**) alkyne ligands, and other labile ligands. It has not been yet determined if two pathways are operative (requiring one and two alkynes, respectively) or if the preferred catalytic mechanism involves two alkynes. It is envisioned that the azide is activated by the appropriate dinuclear copper(I) complex in the rate-determining step; the resulting dicopper species (**IV**) represents one of many possible structures consistent with density functional theory calculations performed previously.[66] This copper acetylide-azide complex (**IV**) would be generated by azide displacement of one ligand. Recently, the isolation and characterization of a molecular copper(I) triazolide complex[67] could be a direct evidence for the existence of the five-membered triazolyl-copper derivative (**VII**) obtained after ring contraction of the copper metallacycle intermediate (**V**). Proteolysis of this triazolyl-copper derivative (**VII**) releases the triazole compound and regenerates the Cu^{I} species catalyst.

[66] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V.V.; Noodleman, L.; Sharpless, K.B.; Fokin, V.V. *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

[67] Nolte, C.; Mayer, P.; Straub, B.F. *Angew. Chem., Int. Ed.* **2007**, *46*, 2101-2103.



Scheme 6. Proposed outline of species involved in the copper catalytic cycle.[65a]

The commercial availability of easy-to-handle copper(I) complexes makes this cycloaddition reaction highly practical. Moreover, simple copper salts are usually less expensive compared to other late transition metal salts (Pd, Rh, Ru,…). It is established that Cu^{I} can be coordinated by soft donor atoms such as P, S or N to form relatively stable copper(I) complexes.[68] Copper(I) is also capable of bonding to small gaseous molecules such as olefins,[69] alkynes[70] and carbon monoxide[71] to form π complexes. For the cycloaddition

[68] Wilkinson, G. in *"Comprehensive Coordination Chemistry"*, Vol. 5; Pergamon Press: Oxford, **1987**.

[69] (a) van den Hende, J.H.; Baird, W.C. *J. Am. Chem. Soc.* **1963**, *85*, 1009-1010. (b) Baenziger, N.C.; Haight, H.L.; Doyle, J.R. *Inorg. Chem.* **1964**, *3*, 1535-1541. (c) Pasquali, M.; Floriani, C.; Gaetini-Manfredotti, A.; Chiesi-Villa, A. *J. Am. Chem. Soc.* **1978**, *100*, 4918-4919; *Znorg. Chem.* **1979**, *18*, 3535-3542. (d) Thompson, J.S.; Harlow, R.L.; Whiteney, J.F. *J. Am. Chem. Soc.* **1983**, *105*, 3522-3527. (e) Thompson, J.S.; Whiteney, J.F. *Znorg. Chem.* **1984**, *23*, 2813-2819. (f) Munakata, M.; Kitagawa, S.; Kosome, S.; Asahara, A. *Znorg. Chem.* **1986**, *25*, 2622-2627. (g) Masuda, H.; Yamamoto, N.; Taga, T.; Machida, K.; Kitagawa, S.; Munakata, M. *J. Organomet. Chem.* **1987**, *322*, 121-129. (h) Munakata, M.; Kitagawa, S.; Shimono, H.; Emori, T.; Masuda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1798-1799. (i) Masuda, H.; Machida, K.; Munakata, M.; Kitagawa, S.; Shimono, H. *J. Chem. Soc., Dalton Trans.* **1988**, 1907-1910. (j) Munakata, M.; Kitagawa, S.; Shimono, H.; Masuda, H. *Inorg. Chem.* **1991**, *30*, 2600-2609.

[70] (a) Corfield, P.W.R.; Shearer, H.M.M. *Acta Crystallogr.* **1966**, *21*, 957-965. (b) Pasquali, M.; Leoni, P.; Floriani, C.; Gaetani-Manfredotti, A. *Znorg. Chem.* **1982**, *21*, 4324-4328. (c) Thompson, J.S.; Whitney, J.F. *J. Am. Chem. Soc.* **1983**, *105*, 5488-5489. (d) Thompson, J.S. *J. Am. Chem. Soc.* **1984**, *106*, 4057-4059; 8308-8309. (e) Munakata, M.; Kitagawa, S.; Kawada, I.; Maekawa, M.; Shimono, H. *J. Chem. Soc., Dalton Trans.* **1992**, 2225-2230.

reaction, active Cu^{I} catalytic species[72] can be directly formed from addition of a ligand to cuprous salts,[59,73] or prepared by *in situ* reduction of Cu^{II} salts,[57,58] oxidation of Cu^{0} metal,[66] or Cu^{II}/Cu^{0} comproportionation.[57,58,74] Supported, reusable and heterogeneous copper catalysts have also been studied.[75]

a) *In situ* prepared copper(I) complexes:

Several copper(I) salts (CuI, CuBr) and coordination complexes ($[Cu(CH_3CN)_4]PF_6$, $[CuBr(PPh_3)_3]$) have been directly employed as copper(I) sources in the CuAAC.[58] However, Cu^{I} is thermodynamically unstable and can be relatively easily oxidized to catalytically inactive Cu^{II} leading to the formation of undesired side-products.[59,76,77] For instance, Cu^{II} can participate in the oxidative alkyne-alkyne homocoupling first described by Glaser in 1869.[76] Therefore, to prevent these complications when a copper(I) is used directly, the reaction requires additives like a nitrogen base in excess[58,59,78] and/or a Cu^{I} stabilizer ligand,[73,79] and exclusion of oxygen may be necessary. The tetrakis(acetonitrile) copper(I)

[71] (a) Churchill, M.R.; Deboer, B.D.; Rotella, F.J.; Abu Salah, O.M.; Bruce, M.I *Inorg. Chem.* **1975**, *14*, 2051-2056. (b) Gagne, R.R.; Allison, J.L.; Gall, R.S.; Koval, C.A. *J. Am. Chem. Soc.* **1977**, *99*, 7170-7178. (c) Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A. *J. Chem. Soc., Chem. Commun.* **1978**, 921-922. (d) Pasquali, M.; Marchetti, F.; Floriani, C. *Inorg. Chem.* **1978**, *17*, 1684-1688. (e) Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A.; Guastini, C. *J. Chem. Soc., Chem. Commun.* **1979**, 197-199. (f) Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A. *Znorg. Chem.* **1981**, *20*, 3382-3388; *Inorg. Chem.* **1980**, *19*, 1191-1197. (g) Gagne, R.R.; Kreh, R.P.; Dodge, J.A.; Marshand, R.E.; McCool, M. *Inorg. Chem.* **1982**, *21*, 254-261.

[72] Bock, V.D.; Hiemstra, H.; van Maarseveen, J.H. *Eur. J. Org. Chem.* **2006**, 51-68.

[73] Lewis, W.G.; Magallon, F.G.; Fokin, V.V.; Finn, M.G. *J. Am. Chem. Soc.* **2004**, *126*, 9152-9153.

[74] Quader, S.; Boyd, S.E.; Jenkins, I.D.; Houston, T.A. *J. Org. Chem.* **2007**, *72*, 1962-1979.

[75] (a) Durán Pachón, L.; Van Maarseveen, J.H.; Rothenberg, R. *Adv. Synth. Catal.* **2005**, *347*, 811-815. (b) Aucagne, V.; Hänni, K.D.; Leigh, D.A.; Lusby, P.J.; Walker, D.B. *J. Am. Chem. Soc.* **2006**, *128*, 2186-2187. (c) Lipshutz, B.H.; Taft, B.R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235-8238. (d) Chassaing, S.; Kumarraja, M.; Sido, A.S.S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883-886. (e) Chassaing, S.; Sido, A.S.S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. *Chem. Eur. J.* **2008**, *14*, 6713-6721.

[76] For the copper-catalyzed coupling of terminal alkynes (i.e. the Glaser reaction), see: (a) Glaser, C. *Chem. Ber.* **1869**, *2*, 422-429. (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137-171. (c) Siemsen, P.; Livingston, R.C.; Diederich, F. *Angew. Chem., Int. Ed*. **2000**, *39*, 2632-2657.

[77] For the reactions of copper(I) complexes with dioxygen, see: (a) Schindler, S. *Eur. J. Inorg. Chem.* **2000**, 2311-2326. (b) Blackman, A.G.; Tolman, W.B. in *"Structure and Bonding"*, Vol. 97; Meunier, B., Ed.; Springer: Berlin, Germany, **2000**, 179-211.

[78] (a) Fazio, F.; Bryan, M.C.; Blixt, O.; Paulson, J.C.; Wong, C.H. *J. Am. Chem. Soc.* **2002**, *124*, 14397-14402. (b) Dondoni, A.; Giovannini, P.P.; Massi, A. *Org. Lett.* **2004**, *6*, 2929-2932. (c) Li, Z.; Seo, T.S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143-3146. (d) Zhou, Z.; Fahrni, C.J. *J. Am. Chem. Soc.* **2004**, *126*, 8862-8863. (e) Wu, Y.M.; Deng, J.; Fang, X.; Chen, Q.Y. *J. Fluorine Chem.* **2004**, *125*, 1415-1423. (f) Malkoch, M.; Thibault, R.J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T.P.; Hawker, C.J. *J. Am. Chem. Soc.* **2005**, *127*, 14942-14949. (g) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C.J.; Hales, N.J.; Ramsey, R.R.; Gravestock, M.B. *J. Med. Chem.* **2005**, *48*, 499-506. (h) Petchprayoon, C.; Suwanborirux, K.; Miller, R.; Sakata, T.; Marriott, G. *J. Nat. Prod.* **2005**, *68*, 157-161. (i) Yan, Z.Y.; Zhao, Y.B.; Fan, M.J.; Liub, W.M.; Liang, Y.M. *Tetrahedron* **2005**, *61*, 9331-9337. (j) Tanaka, K.; Kageyama, C.; Fukase, K. *Tetrahedron Lett.* **2007**, *48*, 6475-6479.

[79] (a) Meng, J.; Fokin, V.V.; Finn, M.G. *Tetrahedron Lett.* **2005**, *46*, 4543-4546. (b) Rodionov, V.O.; Presolski, S.I.; Gardinier, S.; Lim, Y.-H.; Finn, M.G. *J. Am. Chem. Soc.* **2007**, *129*, 12696-12704. (c) Rodionov, V.O.; Presolski, S.I.; Diaz Diaz, D.; Fokin, V.V.; Finn, M.G. *J. Am. Chem. Soc.* **2007**, *129*, 12705-12712.

hexafluorophosphate[80] $[Cu(CH_3CN)_4]PF_6$ was thus rarely reported as a ligand-free catalyst[81,82] but mainly as a copper source in ligand-assisted Cu^I-catalyzed reactions.[75b,79b,83] Investigations and kinetic studies have shown that bases or nitrogen- or phosphorus-based ligands can stabilize the copper(I) by coordination to the metal center, thus protecting it from oxidation and disproportionation while enhancing its catalytic activity.[83,79a,84] Nevertheless, the cycloaddition were generally run with an organic co-solvent in order to improve the solubility of the additive.[73,85] Although coordination complexes have been particularly effective in organic solvents, cuprous salts have limited solubility. Hence, the tight binding of the additive to the copper ion provides additional electron density and increases the solubility of the catalyst in organic media. Moreover, deprotonation of the initial π-complex to form σ-acetylide Cu^I complexes (Scheme 6) can occur without the addition of a base in water, but in organic solvents, the formation of the Cu^I–acetylide species is unfavourable and a base is required for deprotonation.[66]

b) *In situ* generation of active copper(I) species from copper(II) salts:

In-situ generation of Cu^I from Cu^{II} salts can occur by comproportionation with copper metal or by reduction and it has the advantage of not requiring inert atmospheres due to the instability of the Cu^I oxidation state in the presence of oxygen.[77] Typically, the CuAAC is performed with copper(II) sulfate and sodium ascorbate in a mixture of ^{t}BuOH and water.[58,65,66,86] The ascorbate serves as a water soluble *in situ* reducing agent to generate and maintain necessary concentration of catalytically active copper(I). The mixture Cu^0 copper/ $CuSO_4$ copper sulfate, *in situ* comproportionated to form Cu^I, can also be used as a water soluble *in situ* generated catalyst.[58,87] Experiments showed that the reaction occurs on the surface of the copper particles, rather than *via* Cu^0 atoms or Cu^I/Cu^{II} ions that are leached into

[80] Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90-92.

[81] Aucagne, V.; Leigh, D.A. *Org. Lett.* **2006**, *8*, 4505-4507.

[82] Feng, L.; Zhang, X.; Yu, Z.; Wang, J.; Gu, Z. *Chem. Mater.* **2002**, *14*, 4021-4022.

[83] (a) Chan, T.R.; Hilgraf, R.; Sharpless, K.B.; Fokin, V.V. *Org. Lett.* **2004**, *6*, 2853-2855. (b) Gerard, B.; Ryan, J.; Beeler, A.B.; Porco Jr., J.A. *Tetrahedron* **2006**, *62*, 6405-6411.

[84] (a) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F.G.; Calvo-Asín, J.A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951-1954.

[85] Kolthoff, I.M.; Coetzeem, J. *J. Am. Chem. Soc.* **1957**, *79*, 1852-1858.

[86] (a) Link, A.J.; Vink, M.K.S.; Tirrell, D.A. *J. Am. Chem. Soc.* **2004**, *126*, 10598-10602. (b) Speers, A.E.; Cravatt, B.F. *Chem. Biol.* **2004**, *11*, 535-546.

[87] (a) Deiters, A.; Cropp, T.A.; Mukerji, M.; Chin, J.W.; Anderson, J.C.; Schultz, P.G. *J. Am. Chem. Soc.* **2003**, *125*, 11782-11783. (b) Lee, L.V.; Mitchell, M.L.; Huang, S.-J.; Fokin, V.V.; Sharpless, K.B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588-9589. (c) Appukkuttan, P.; Dehaen, W.; Fokin, V.V.; VanderEycken, E.A. *Org. Lett.* **2004,** *6*, 4223-4225. (d) Zhan, W.-H.; Barnhill, H.N.; Sivakumar, K.; Tian, H.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 1691-1695. (e) Quader, S.; Boyd, S.E.; Jenkins, I.D.; Houston, T.A. *J. Org. Chem.* **2007**, *72*, 1962-1979.

the reaction mixture.[75a] This option is particularly attractive, as copper metal and sulfate copper are inexpensive. Moreover, the reducing agent ascorbate and its oxidation products, which are sometimes not tolerated by the substrate, can thus be avoided.[66] However, reactions are relatively slow and require a significant amount of catalyst. This drawback is increasingly important when large-scale production is considered. Although both methods have a wide scope and tolerate many organic functional groups, the reduction method is generally preferred to the comproportionation limited to special applications, such as biological systems.

c) Well defined NHC-containing copper(I) complexes:

NHC-containing copper(I) complexes have been reported to efficiently catalyze a number of reactions[88] such as olefination[89] or hydrosilylation of carbonyl compounds,[90] cyclopropanation reactions[91] and carboxylation of organoboronic esters.[92] The high ability of the NHC ligands to stabilize Cu^I species renders the complexes insensitive toward heat, oxygen and moisture. The variation of the counteranion as well as the NHC substituent can also have an influence on the catalytic activity.[89,93] For instance, replacing the chloride on the copper center by a bromide can accelerate the reaction. Hence, studies have shown that the presence of this strong σ-donor ligand on the copper center enhances its catalytic activity in the Huisgen cycloaddition.[93] Terminal alkynes were successfully used to afford 1,4-disubstituted-1,2,3-triazoles *via* NHC-Cu^I catalyzed cycloaddition.[93] The [CuBr(SIMes)] (SIMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) showed better catalytic activity when compared with unsaturated NHC ligand or chloro analogues. For the synthesis of a variety of 1,4-disubstituted triazoles, its catalyst loading could be lowered to 0.8 mol% with no loss of activity, ensuring straightforward reaction workups (Scheme 7). No precautions to exclude oxygen were taken in any of these reactions. No copper disproportionation with precipitation of metal copper was observed in aqueous medium which shows the high ability of NHC groups to stabilize Cu^I species. Furthermore, neat reactions

[88] (a) Díez-González, S.; Nolan, S.P. *Synlett* **2007**, 2158-2167. (b) Díez-González, S.; Nolan, S.P. *Aldrichim. Acta* **2008**, *41*, 43-51.

[89] Lebel, H.; Davi, D.; Díez-González, S.; Nolan, S.P. *J. Org. Chem.* **2007**, *72*, 144-149.

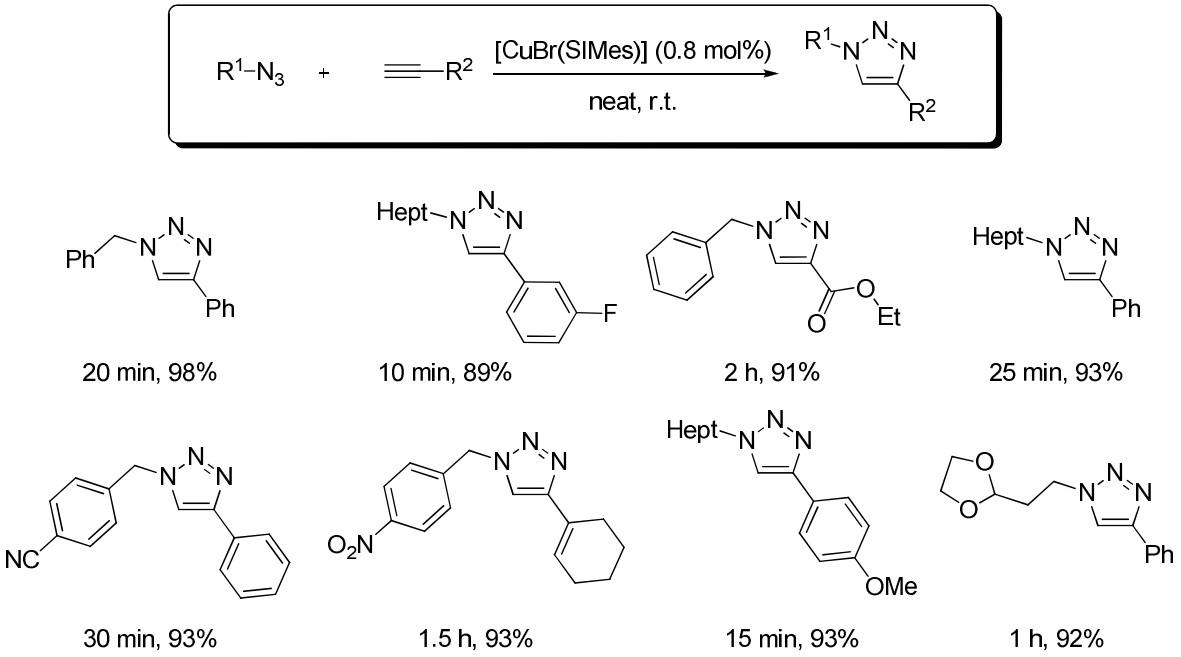
[90] (a) Kaur, H.; Zinn, F.K.; Stevens, E.D.; Nolan, S.P. *Organometallics* **2004**, *23*, 1157-1160. (b) Díez-González, S.; Scott, N.M.; Nolan, S.P. *Organometallics* **2006**, *25*, 2355-2358. (c) Díez-González, S.; Stevens, E.D.; Scott, N.M.; Petersen, J.L.; Nolan, S.P. *Chem. Eur. J.* **2008**, *14*, 158-168.

[91] Fructos, M.R.; Belderrain, T.R.; Nicasio, M.C.; Nolan, S.P.; Kaur, H.; Díaz-Requejo, M.M.; Pérez, P.J. *J. Am. Chem. Soc.* **2004**, *126*, 10846-10847.

[92] Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792-5795.

[93] Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S.P. *Chem. Eur. J.* **2006**, *12*, 7558-7564.

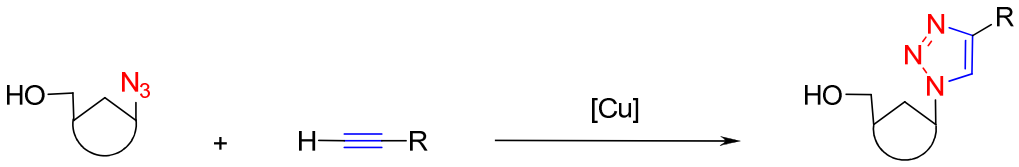
proceeded smoothly at room temperature with no detectable formation of undesirable by-products.



Scheme 7. Solvent-free [CuBr(SIMes)]-catalyzed 1,3-dipolar cycloaddition with terminal alkynes.

2. STUDY OF DIFFERENT COPPER(I) CATALYSTS FOR THE 1,3-DIPOLAR CYCLOADDITION OF (±)-1,4-DISUBSTITUTED-1,2,3-TRIAZOLO-CARBANUCLEOSIDES

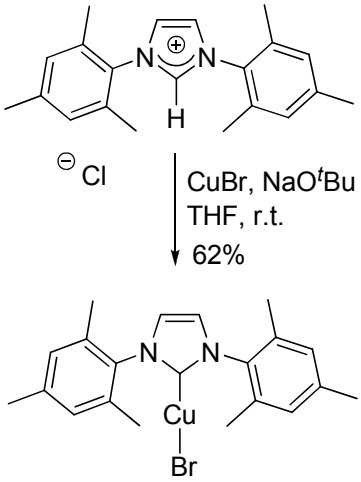
The purpose of this work was to develop a simple and optimum tool adapted to the preparation of 1,2,3-triazolo-carbanucleosides *via* Huisgen 1,3-dipolar cycloaddition (Scheme 8). First, we examined the activity of three different copper(I)-based catalytic systems in the synthesis of (±)-1,4-disubstituted-1,2,3-triazolo carbanucleosides. $[Cu(CH_3CN)_4]PF_6$, [CuBr(IMes)] (IMes = *N*,*N*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and the mixture $Cu^0/CuSO_4$ were chosen for this study. Their catalytic influence was analyzed as a function of the substituent of the alkyne, the solvent or the heating method.



Scheme 8. Preparation of 1,2,3-triazolo-carbanucleosides *via* Huisgen 1,3-dipolar cycloaddition.

2.1. Synthesis of [CuBr(IMes)]

[CuBr(IMes)] was easily prepared by *in situ* deprotonation of the corresponding azolium salt in the presence of a strong base and a copper salt (Scheme 9). The structure of this air- and moisture-stable complex was elucidated by single-crystal diffraction from suitable crystals grown from a dichloromethane/hexane solution. The resulting ball-and-stick drawing is shown in Figure 12. This copper complex crystallize in the orthorhombic space group, *Fdd*2.[94] The observed Cu–C(1) bond length is comparable to known Cu–C bonds in NHC copper complexes.[95]



Scheme 9. Synthesis of [CuBr(IMes)].

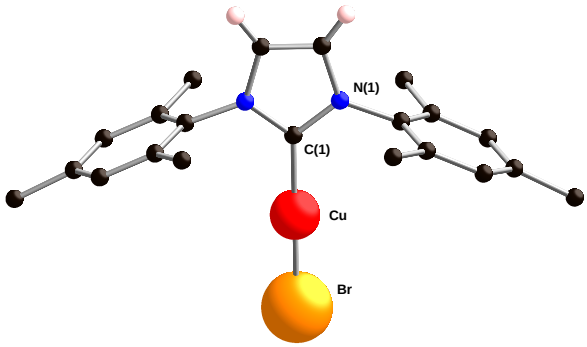


Figure 12. Ball-and-stick drawing for [CuBr(IMes)]. Selected bond lengths (Å): Cu–C(1) = 1.897(6), Cu–Br = 2.2101(7). Selected bond angles (deg): C(1)–Cu–Br = 180.000(1), N(1)–C(1)–N(1) = 105.1(5).

2.2. Preparation of the Key Azido Intermediate

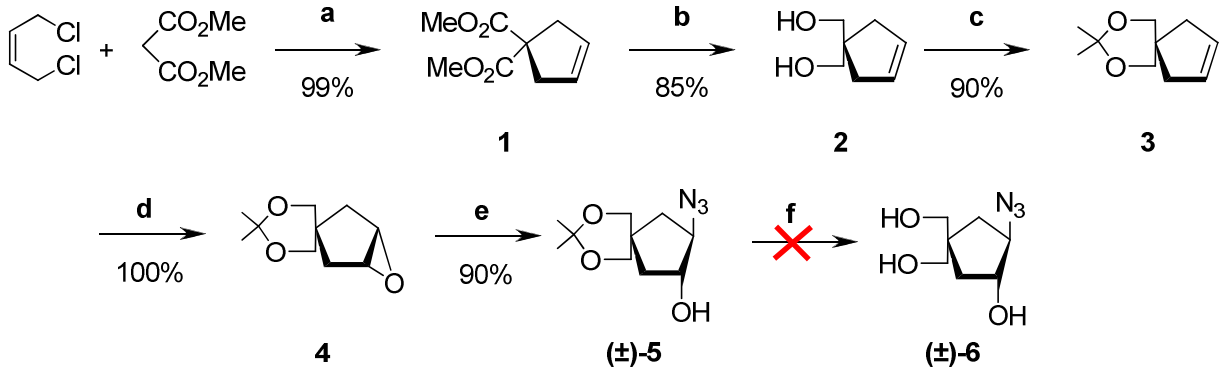
The first synthetic strategy tested for the preparation of the starting azide **(±)-6** is depicted in Scheme 10. Cyclopent-3-ene diester **1** was obtained *via* a malonic synthesis from methyl malonate and *cis*-1,4-dichloro-2-butene.[96] After reduction of the diester **1**, the dialcohol **2** was protected with an *iso*propylidene group. The volatile compound **3** was then stirred for four days in the presence of 3-chloroperoxybenzoic acid (*m*CPBA) to yield the epoxide **4** quantitatively. The protected azido-carbocycle **(±)-5** was obtained after the nucleophilic ring opening of the strained epoxide function group **4** by sodium azide. At that point, this five step procedure afforded azide **(±)-5** with a good overall yield of 68%.

[94] File CCDC 654537 contains the complete crystallographic data for [CuBr(IMes)]. These data can be obtained free of charge from The Cambridge Crystallographic Data center *via* www.ccdc.cam.ac.uk/data–request/cif.

[95] For representative examples, see: (a) Mankad, N.P.; Gray, T.G.; Laitar, D.S.; Sadighi, J.P. *Organometallics* **2004**, *23*, 1191-1193. (b) Díez-González, S.; Kaur, H.; Zinn, F.K.; Stevens, E.D.; Nolan, S.P. *J. Org. Chem.* **2005**, *70*, 4784-4794. (c) Goj, L.A.; Blue, E.D.; Delp, S.A.; Gunnoe, T.B.; Cundari, T.R.; Petersen, J.L. *Organometallics* **2006**, *25*, 4097-4104. See also ref. 90a

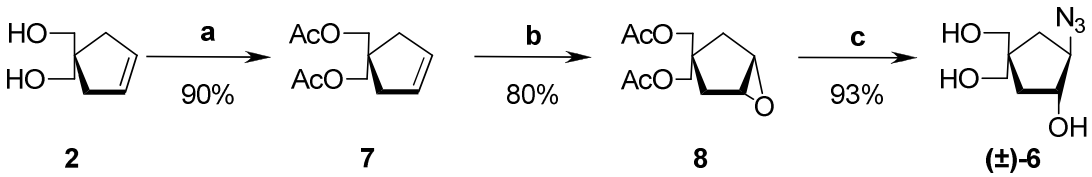
[96] (a) Depres, J.P.; Greene, A.E. *J. Org. Chem.* **1984**, *49*, 928-931. (b) Kang, J.H.; Chung, H.E.; Kim, S.Y.; Kim, Y.; Lee, J.; Lewin, N.E.; Pearce, L.V.; Blumberg, P.M.; Marquez, V.E. *Bioorg. Med. Chem.* **2003**, *11*, 2529-2539.

However, the deprotection of **(±)-5** either by treatment with TFA or by acetic acid with an amberlite resin IR 120H$^+$ was incomplete even after several days of reaction or it lead to the formation of an unknown by-product.



Scheme 10. Reagents and conditions: (a) LiH, DMF, r.t., 3 days; (b) $LiAlH_4$, Et_2O, 0°C, 1 h; (c) 2-Methoxypropene, PTSA, DMF, 0°C to r.t., 16 h; (d) *m*CPBA, CH_2Cl_2, 0°C to r.t., 4 days; (e) NaN_3, MeOH/H_2O 8:2, reflux, 3 days; (f) TFA 60% or acetic acid 50%/Amberlite IR 120H$^+$.

The synthetic approach to azide **(±)-6** was thus revisited and a different protecting group was envisaged for **2** (Scheme 11). The acetylation of **2** afforded the protected cyclopentene **7** in high yields and subsequent oxidation with *m*CPBA generated the epoxide **8**.[97] Finally, the nucleophilic ring opening of **8** with NaN_3 was concomitant with its deacylation. Thus, the desired azidocarbocycle **(±)-6** was isolated in good overall yield after only five steps starting from commercial products. Moreover, column chromatography purification was only required in the last stage of this efficient and multi-gram scale synthesis. This pathway also appeared to be more convenient and efficient than the previous one as the reaction times were considerably reduced (the azidation of **8** occurred in 4 h meanwhile the azidation of **4** required 3 days).



Scheme 11. Reagents and conditions: (a) Ac_2O, pyridine, 0°C to r.t., 3 h; (b) *m*CPBA, CH_2Cl_2, 0°C to r.t., 3 days; (c) NaN_3, MeOH/H_2O 8:2, reflux, 4 h.

[97] Paulsen, H.; Maass, U. *Chem. Ber.* **1981**, *114*, 346-351.

2.3. Activity of Different Copper(I)-based Catalysts for the 1,3-Dipolar Cycloaddition of Azidocarbocycle and Terminal Alkynes

a) Optimization studies:

We first investigated the optimal conditions for the cycloaddition of azide **(±)-6** and phenylacetylene with different catalytic systems (Table 1). Reactions were carried out in a 1/1 mixture water/^{t}BuOH under thermal or microwave heating. No precautions to exclude oxygen were taken in any of these reactions. Microwave heating is known as a powerful technique to promote a variety of chemical reactions.[98] Recently, some examples of microwave-assisted alkyne-azide cycloadditions have been reported to show substantial decrease in reaction times without affecting yield or ease of product purification.[84,99] These results can be rationalized by the proposed polar transition states of this cycloaddition, favorable for a microwave activation.[65-67] In our case, in the absence of copper, total conversion could not be reached after several hours of irradiation and, as expected, two regioisomeric cycloadducts were obtained.[55,100,101] In the presence of $Cu^0/CuSO_4$, the regioselective conversion into triazole carbanucleoside **(±)-9** was complete after only 2 min of microwave irradiation at 125°C. A similar result was obtained when the reaction was carried out thermally under pressure at the same temperature during 20 min. The reaction required 40 min to proceed under thermal heating and 11 h at room temperature. These results might indicate the existence of a specific microwave effect in this copper-catalyzed cycloaddition beyond the pressure and temperature effects. It was also observed that the reaction performed better when the copper(0) was used as a powder. With copper turnings where the particle surface contact is lower, reaction times were longer (1.5 h under microwave irradiation, 6 h under thermal heating). Surprisingly, under the same conditions and with an equal proportion of $CuSO_4$, the reduction method in the presence of sodium ascorbate (NaAsc) slowed the reaction compared to the comproportionated species. For both systems, the catalyst loading was optimized. For $[Cu(CH_3CN)_4]PF_6$, 5 mol% loading was found optimal and led to short reaction times.

[98] For reviews on microwave-assisted reactions see: (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403-10432. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199-9223. (c) *Microwaves in Organic Synthesis*, Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, **2002**. (d) Kappe, C.O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250-6284.

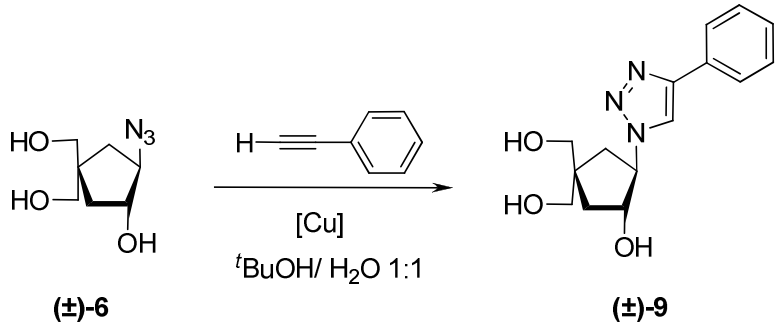
[99] (a) Louërat, F.; Bougrin, K.; Loupy, A.; Ochoa de Retana, A.M.; Pagalday, J.; Palacios, F. *Heterocycles* **1998**, *48*, 161-170. (b) Khanetskyy, B.; Dallinger, D.; Kappe, C.O. *J. Comb.Chem.* **2004**, *6*, 884-892. (c) Rijkers, D.T.S.; Van Esse, G.W.; Merkx, R.; Brouwer, A.J.; Jacobs, H.J.F.; Pieters, R.J.; Liskamp, R.M.J. *Chem. Commun.* **2005**, 4581-4583. (d) Perissutti, E.; Frecentese, F.; Fiorino, F.; Severino, B.; Cirillo, D.; Santagada, V.; Caliendo, G. *J. Heterocyclic Chem.* **2007**, *44*, 815-820. See also reference: 87c.

[100] *Ratio* 1,4-/1,5- = 65:35.

[101] (a) Gothelf, K.V.; Jorgensen, K.A. *Chem. Rev.* **1998**, *98*, 863-909. (b) Mulzer, J. *Org. Synth. Highlights* **1991**, 77-95. (c) Katritzky, A.R.; Singh, S.K. *J. Org. Chem.* **2002,** *67*, 9077-9079.

However, with [CuBr(IMes)] the observed reaction time was surprisingly longer (9 h with 5 mol%). This catalyst loading was kept for the substrate screening in order to obtain comparable results.

Table 1. Optimization studies.[a]



Catalyst	mol%	Heating	Time	Conv (%)[b]
No catalyst	-	MW	10 h	43
$Cu^0/CuSO_4$	80/20	r.t.	11 h	100
$Cu^0/CuSO_4$	80/20	Δ	40 min	100
$Cu^0/CuSO_4$	80/20	MW	2 min	100
$Cu^0/CuSO_4$	80/20	Δ, P	2 min	79
$Cu^0/CuSO_4$	80/20	Δ, P	20 min	100
NaAsc /$CuSO_4$	40/20	MW	15 min	100
$[Cu(CH_3CN)_4]PF_6$	2	MW	2 h	50
$[Cu(CH_3CN)_4]PF_6$	5	MW	15 min	100
$[Cu(CH_3CN)_4]PF_6$	10	MW	10 min	100
$[Cu(CH_3CN)_4]PF_6$	15	MW	5 min	100
$[Cu(CH_3CN)_4]PF_6$	20	MW	3 min	100
[CuBr(IMes)]	2	MW	10 h	100
[CuBr(IMes)]	5	MW	9 h	100
[CuBr(IMes)]	10	MW	7 h	100
[CuBr(IMes)]	15	MW	6.5 h	100
[CuBr(IMes)]	20	MW	6.5 h	100

[a] Reaction conditions: azide **(±)-6** (0.27 mmol), phenylacetylene (1.05 equiv), ^{t}BuOH/H_2O 1:1 (2 mL); Microwave (MW): T = 125°C, Thermal heating under pressure (Δ, P): T = 125°C, Thermal heating (Δ): T = 75°C. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product.

b) Screening of the activity of the Cu^I-based catalysts with different terminal alkynes:

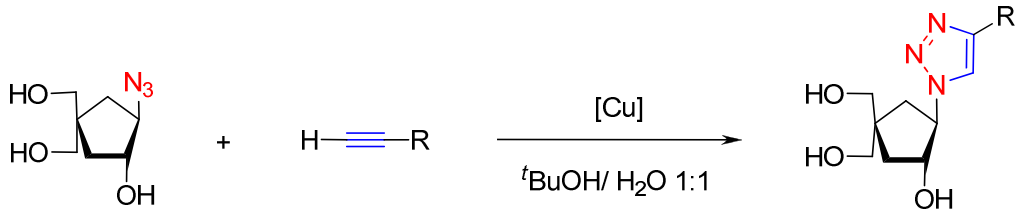
From azide **(±)-6** and aryl, alkyl or functionalized alkynes, various 1,2,3-triazolo carbanucleosides with a 4'-*C*-hydroxymethyl group **(±)-9-12** were successfully prepared. The three catalytic systems were used under thermal (75°C) or microwave (125°C) heating (Table

2). $[Cu(CH_3CN)_4]PF_6$ and [CuBr(IMes)] were found to be slightly soluble in the hot mixture of solvents. Most cycloaddition reactions were completed after short reaction times with no observable formation of by-products. In most examples, microwave irradiation had an evident beneficial effect in terms of reaction time and yield. For example, using classical heating, sluggish reactions with 1-heptyne were observed with any of the three catalytic systems (Table 2, entry 2). However, under microwave irradiation, complete conversion was achieved with $Cu^0/CuSO_4$ or [CuBr(IMes)] after short reaction times (1 h and 2 h respectively). In the case of $[Cu(CH_3CN)_4]PF_6$, microwave irradiation only allowed for a conversion of 79%, however there was no reaction under conventional heating. In a preliminary experiment, we also noticed that the formation **(±)-10** in the presence of $Cu^0/CuSO_4$ using only water as solvent could not be completed after 5 h of microwave irradiation, showing that the *tert*-butanol is essential for this transformation. As it has been previously reported,[55,102] electron-poor alkynes (Table 2, entries 3,4) were more reactive than electron-rich ones (Table 2, entries 1,2). Different isolation techniques were also required according to the substitution of the alkyne moiety. Whereas triazoles with an electron-donating substituent at the 4-position (**(±)-9** and **(±)-10**) were isolated in high yield and purity after a simple extraction in ethyl acetate, triazoles with electron-withdrawing groups (**(±)-11** and **(±)-12**) had to be purified on silica due to their high solubility in water. In the case of triazole **(±)-11**, partial decomposition was observed after prolonged reaction times. For instance, after refluxing for 5 days in the presence of $[Cu(CH_3CN)_4]PF_6$, only 17% of the expected triazole **(±)-11** could be isolated along with 56% of the corresponding 4-(hydroxymethyl)triazole (Table 2, entry 3). This acetate cleavage could be mediated by the copper(I) species present in the reaction mixture.[103] The use of microwave irradiation decreased the reaction time allowing for a higher yield of compound **(±)-11**. Overall, reaction times were reduced using the NHC complex versus the cationic $[Cu(CH_3CN)_4]PF_6$ (Table 2, entries 2,3,4). These results suggest a beneficial stabilizing effect of the NHC-ligand in this cycloaddition and thus a protection of the metal center from oxidation and disproportionation reactions. The poor reactivity of phenylacetylene with [CuBr(IMes)] compared to other catalysts can not be explained at the present time and is currently being investigated. For all entries presented in Table 2, the best results were obtained with $Cu^0/CuSO_4$ as catalyst precursor, regardless of the heating

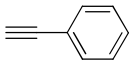
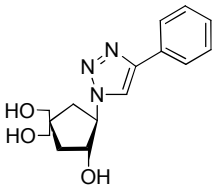
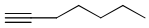
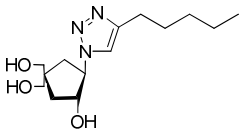
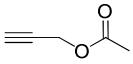
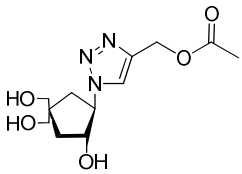
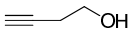
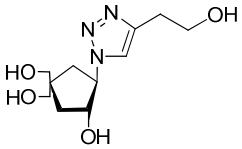
[102] Bastide, J.; Henri-Rousseau, O. in *"The Chemistry of the Carbon Carbon Triple Bond"*; Patai, S., Ed.; Interscience Publishers: London, United Kingdom, **1978**, 447-552.

[103] Trost, B.M.; Ball, Z.T.; Jöge, T.A. *J. Am. Chem. Soc.* **2002**, *124*, 7922-7923.

Table 2. Alkyne screening.[a,b]



(±)-6 **(±)-9-12**

Entry	Alkyne	Triazole		Cu^0 (80 mol%) $CuSO_4$ (20 mol%)	$[Cu(CH_3CN)_4]PF_6$ (5 mol%)	[CuBr(IMes)] (5 mol%)
1		 **(±)-9**	Δ	**40 min**	**13 h**	**5 days**
			conv (%)	100	100	95
			yield (%)	98	99	91
			MW	**2 min**	**15 min**	**9 h**
			conv (%)	100	100	100
			yield (%)	98	98	94
2		 **(±)-10**	Δ	**5 days**	**5 days**	**5 days**
			conv (%)	80	0	51
			yield (%)	75	0	40
			MW	**1 h**	**10 h**	**2 h**
			conv (%)	100	79	100
			yield (%)	98	60	93
3		 **(±)-11**	Δ	**< 1 min**	**5 days**	**2 h**
			conv (%)	100	73	100
			yield (%)	96	17	70
			MW	**< 1 min**	**2 min**	**5 min**
			conv (%)	100	100	100
			yield (%)	95	92	93
4		 **(±)-12**	Δ	**2 min**	**5 days**	**1 h**
			conv (%)	100	75	100
			yield (%)	95	71	96
			MW	**2 min**	**2 h**	**15 min**
			conv (%)	100	100	100
			yield (%)	95	92	96

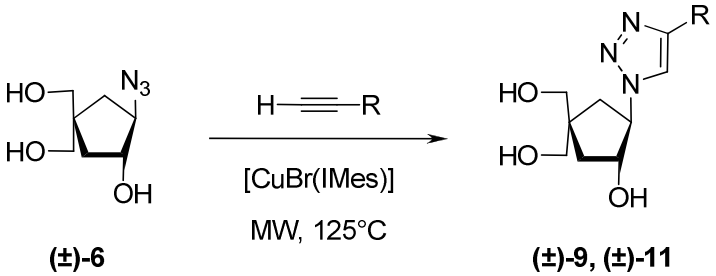
[a] Reaction conditions: azide **(±)-6** (0.27 mmol), alkyne (1.05 equiv), ^{t}BuOH/H_2O 1:1 (2 mL); Microwave (MW): T = 125°C, Thermal heating (Δ): T = 75°C. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product.

method. This system has the advantage of being inexpensive and easily removed from the reaction mixture by simple extraction. Combined with $^{t}BuOH/H_2O$ as solvent mixture and microwave irradiation, it seems to be the most suitable method for the synthesis of triazolo-carbanucleosides. However, this catalytic system would be limited to substrates compatible with aqueous media.

c) Copper(I)-catalyzed cycloaddition in organic solvents:

Alternatively, these cycloaddition reactions could also be carried out in organic solvents in the presence of $[Cu(CH_3CN)_4]PF_6$ or [CuBr(IMes)]. Moreover, sub-stochiometric quantities of copper could be used with these two catalysts. CH_2Cl_2 was chosen as organic solvent and 5% of MeOH was added in order to dissolve the azide **(±)-6** and to enhance the microwave effect. First attempts with phenylacetylene showed that the NHC complex was less efficient in water or in a mixture CH_2Cl_2/MeOH than in $^{t}BuOH/H_2O$ (Table 3). Longer reaction times were required in order to reach good conversions. This tendency was confirmed with the 2-propynyl acetate: 2 h for total conversion in CH_2Cl_2/MeOH (Table 3) *versus* 5 min in $^{t}BuOH/H_2O$ (Table 2, entry 3).

Table 3. Solvent effect for [CuBr(IMes)].[a]



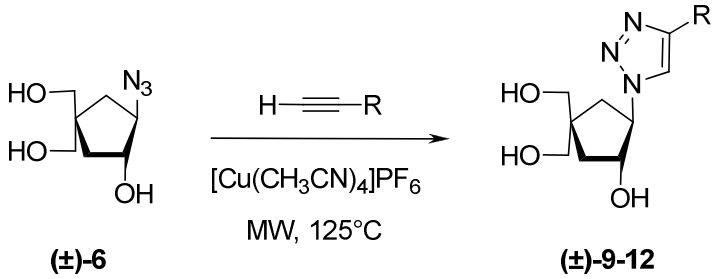
Alkyne	Solvent	Time	Conv (%)[b]
Phenylacetylene	$^{t}BuOH/H_2O$ 1:1	9 h	100
Phenylacetylene	H_2O	10 h	20
Phenylacetylene	CH_2Cl_2/MeOH 95:5	10 h	57
2-Propynyl acetate	CH_2Cl_2/MeOH 95:5	2 h	100

[a] Reaction conditions: azide **(±)-6** (0.27 mmol), alkyne (1.05 equiv), [CuBr(IMes)] (5 mol%), solvent (2 mL), MW: T = 125°C. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product.

In previous studies, Nolan and coworkers reported that NHC-copper complexes were found more efficient in water than in organic solvents.[93] However, all reagents and the catalyst were insoluble in water. In the present case, the solubility of **(±)-6** in water could explain the low conversion in this solvent (20%). The NHC complex was also difficult to

separate from the formed triazoles. Results obtained for the cycloaddition of **(±)-6** and different alkynes in the presence of $[Cu(CH_3CN)_4]PF_6$ under microwave irradiation in $^tBuOH/H_2O$ or $CH_2Cl_2/MeOH$ mixtures are presented in Table 4. $[Cu(CH_3CN)_4]PF_6$ has been used directly without the requirement of any additive or inert atmosphere. Even if similar results were obtained in both cases, it is important to note that the alkyne reactivity switched as the function of the employed solvent. Electron-poor alkynes were more reactive in aqueous media than in organic solvents (Table 4, entries 3 and 4). However, shorter reaction times were required in organic media in the case of triazoles with electron-donating substituents (Table 4, entries 1 and 2).

Table 4. Catalytic activity of $[Cu(CH_3CN)_4]PF_6$ in aqueous and organic media.[a]



		$^tBuOH/H_2O$ 1:1		$CH_2Cl_2/MeOH$ 95:5	
Entry	Triazole	Time	Yield	Time	Yield
1	**9**	15 min	98%	5 min	99%
2	**10**	10 h	60%[b]	2 h	93%
3	**11**	2 min	92%	15 min	93%
4	**12**	2 h	92%	6 h	91%

[a] Reaction conditions: azide **(±)-6** (0.27 mmol), alkyne (1.05 equiv), $[Cu(CH_3CN)_4]PF_6$ (5 mol%), solvent (2 mL); MW: T = 125°C. [b] Conversion = 79%.

d) Regioselectivity of the cycloaddition:

The regioselectivity of the reaction under microwave irradiation was confirmed by using ^1H,^{13}C long range NMR experiments (HMBC). The selective formation of 1,4-disubstituted-[1,2,3]-triazoles was confirmed by the correlations highlighted in Figure 13. Notably, a long range correlation between the $H^{1'}$ of the sugar and the carbon bearing the *1H*-triazole H^5 was observed.

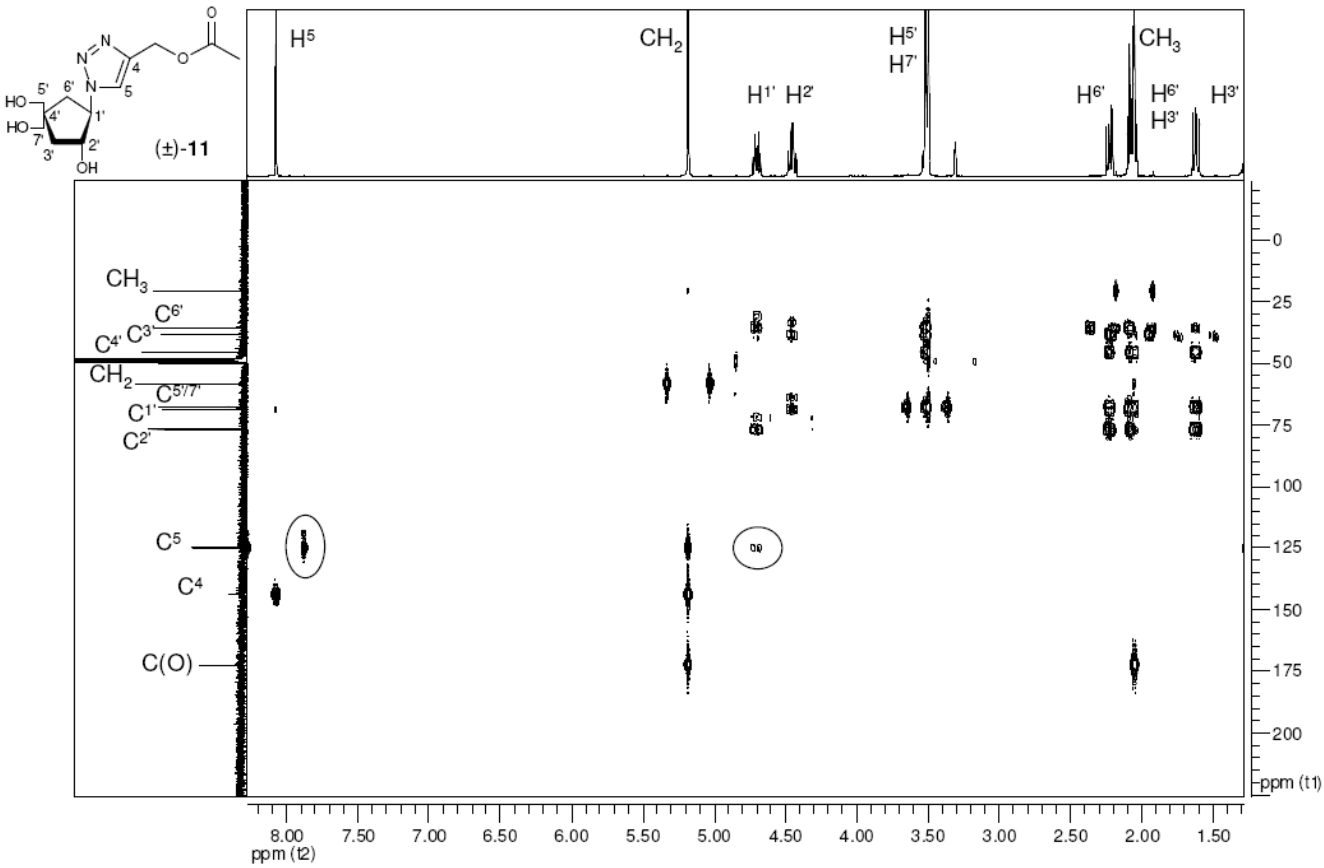


Figure 13. HMBC spectra for **(±)-11**.

2.4. Conclusion

In summary, we have demonstrated the beneficial effect of microwave irradiation in the preparation of (±)-1,4-disubstituted-1,2,3-triazolo-carbanucleosides *via* 1,3-dipolar cycloaddition. Shorter reaction times and higher conversions are hence obtained when compared with thermal heating. The best results were obtained with the inexpensive $Cu^0/CuSO_4$ mixture. The presence of a NHC ligand on the copper center appeared to enhance the catalytic activity when compared to $[Cu(CH_3CN)_4]PF_6$. However, the cationic complex has the additional advantage of being efficient in both aqueous and organic media.

As part of our efforts in drug discovery, this efficient and simple procedure, compiling the beneficial effect of a copper(I)-based catalyst and microwave irradiation, was applied to the enlargement of our series of potential smallpox inhibitor triazolo-carbanucleosides *via* Huisgen 1,3-dipolar cycloaddition.

3. (±)-1,4-DISUBSTITUTED-1,2,3-TRIAZOLO-4'-HYDROXYMETHYL CARBANUCLEOSIDES AS POTENTIAL SMALLPOX INHIBITORS

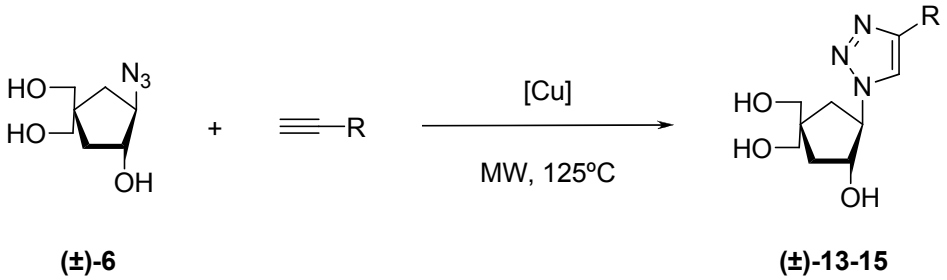
Although several carbocyclic nucleosides are in various stages of development since their identification as potent anti-poxviruses,[45f,48] the lack of approved antiviral drugs along with the existence of side-product effects prompted the development of novel candidate molecules to treat poxvirus infection. Referring to recent interesting results in the literature,[104] this series of triazolo-carbanucleosides was designed with a second 4'-hydroxymethyl group on the carbocycle. Indeed, we speculated that the hydroxyl group of the second 4'-hydroxymethyl moiety could mimic the 3'-hydroxyl group of a ribo-sugar and therefore it might confer to the carbocycle a more pronounced South conformation, an enzyme preferred pseudo-sugar conformation.[104c] From the previous study, where different monosubstituted alkynes were reacted with **(±)-6** in the presence of copper(0)/copper sulfate in a mixture of water and *tert*-butanol, a complete conversion of **(±)-6** into the desired triazole was obtained in short reaction times without the formation of by-products (Table 2). Thus, we applied these optimized conditions to the enlargement of our series of (±)-1,4-disubstituted-1,2,3-triazolo carbanucleosides (Table 5).

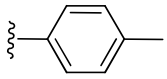
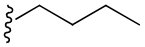
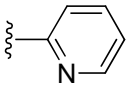
3.1. Synthesis of the (±)-1,4-Disubstituted-1,2,3-Triazolo-Carbanucleosides

In all cases, complete conversion of **(±)-6** into the final triazoles **(±)-13-15** was obtained in short reaction times using the previous conditions (Table 5, method A). The synthesis of **(±)-13-15** could also be conducted in organic solvents (CH_2Cl_2/MeOH) using 10 mol% of $[Cu(CH_3CN)_4]PF_6$ as catalyst (Table 5, method B). As formerly observed, the electron-poor 2-ethynylpyridine (Table 5, entry 3) reacted faster than the electron-rich 4-ethynyltoluene and 1-hexyne (Table 5, entries 1 and 2). Additionally, the deacylation of triazole **(±)-11** in a solution of ammonia afforded the corresponding hydroxymethyl **(±)-16** in excellent yield (Scheme 12).

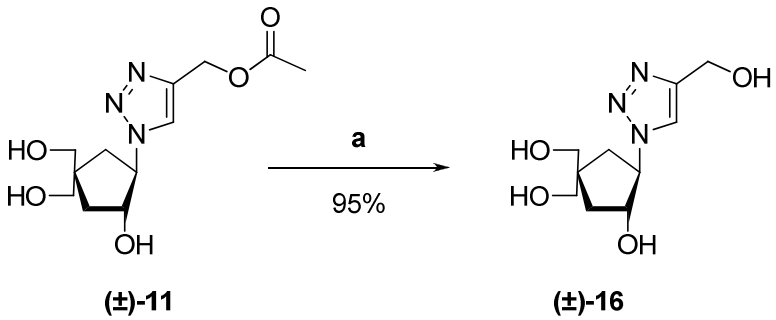
[104] (a) Legraverend, M.; Huel, C.; Bisagni, E. *J. Chem. Res.* **1990**, *4*, 102-103. (b) Hrebabecky, H.; Holý, A. *Collect. Czech. Chem. Commun.* **1994**, *59*, 1654-1664. (c) Hong, J.H. *Nucleos. Nucleot. Nucl.* **2004**, *23*, 625-635. (d) Hrdlicka, P.J.; Andersen, N.K.; Jepsen, J.S.; Hansen, F.G.; Haselmann, K.F.; Nielsend, C.; Wengel, J. *Bioorg. Med. Chem.* **2005**, *13*, 2597-2621.

Table 5. Microwave assisted 1,3-dipolar cycloaddition of azido derivative **(±)-6**.



			Method A		Method B	
Entry	R	Triazole	Time	Yield (%)	Time	Yield (%)
1		**(±)-13**	10 min	94	10 min	99
2		**(±)-14**	1.5 h	95	1.25 h	98
3		**(±)-15**	1 min	78	10 min[a]	60

Method A: azide **(±)-6** (0.27 mmol), alkyne (1.05 equiv), Cu^0 (80 mol%)/$CuSO_4$ (20 mol%), $^tBuOH/H_2O$ 1:1 (2 mL). Method B: azide **(±)-6** (0.27 mmol), alkyne (1.5 equiv), $[Cu(CH_3CN)_4]PF_6$ (10 mol%), CH_2Cl_2/MeOH 95:5 (2 mL). Microwave (MW): T = 125°C.
[a] CH_2Cl_2/MeOH 1:1 (2 mL).

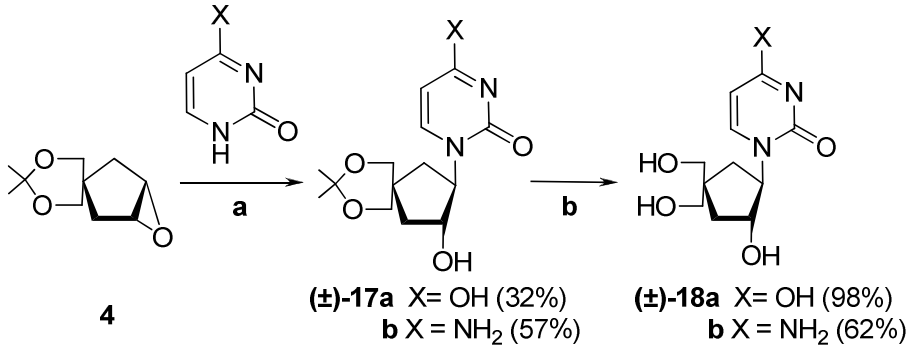


Scheme 12. Reagents and conditions: (a) NH_3 7 N in MeOH, 4°C, overnight.

3.2. Anti-pox Activities

The obtained triazoles **(±)-9-16** were evaluated against vaccinia and cowpox virus cells in order to determine their antiviral activities and cellular toxicities as smallpox inhibitors. To investigate the structure-activity relationships, carbocyclic analogues of the previously presented 4'-hydroxymethyl-1,2,3-triazolo-carbanucleosides, bearing an uracil or a cytosine nucleobase as models were also synthesized for the biological assays (Scheme 13). The ring

opening of epoxide **4** with the potassium salt of the nucleobase[105] afforded the N^1 carbanucleosides **(±)-17a**,**b** regioselectively, which after treatment with a solution of TFA gave the corresponding diols **(±)-18a**,**b**.



Scheme 13. Reagents and conditions: (a) K_2CO_3, DMF, 130°C, 24 h; (b) TFA 60%, r.t., 24 h.

The screening for anti-pox activities is usually carried out on genetically similar surrogates due to the extreme danger of experimenting with the variola virus, the causative agent of smallpox.[7,8] In this work, the IC_{50} (minimum inhibitory concentration required to reduce virus-induced cytopathogenicity by 50%) and CC_{50} (minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology) of the synthesized nucleosidic analogues **(±)-9-16** were measured at concentrations up to 100 mM. Accordingly, none of them inhibited the production of vaccinia virus (Lister strain) or cowpox virus (Brighton strain) in Vero cells. The models bearing natural nucleosidic bases (**(±)-18a** and **(±)-18b**) were also found inactive. This lack of activity could have three different explanations: 1) the triazolo-carbanucleosides do not penetrate the cell membrane; 2) they are not substrates of the kinases and consequently they are not phosphorylated; 3) the nucleotidic analogues (the triphosphorylated forms) are not active.

Thus, in order to determine the origin of this activity deficiency, the phosphorylation of the nucleosidic analogues by human kinases was studied. Our enzyme study indicated that the absence of a 3'-OH function on the sugar moiety hindered the phosphorylation of the nucleoside. Indeed, even though the nucleobase is the recognition site, chelation of such function in the kinase cavity has been shown to be essential for the correct insertion and the subsequent phosphorylation of the nucleoside. We speculated that the hydroxyl group of the second 4'-hydroxymethyl moiety could mimic this 3'-hydroxyl group. However, these compounds were not substrates for the human thymidine kinase (hTK) nor for the human uracil cytosine kinase (hUCK). Despite conferring a pseudo-sugar conformation, the 4',4'-

[105] (a) Brodfuehrer, P.R.; Howell, H.G.; Sapino, C.; Vemishetti, P. *Tetrahedron Lett.* **1994**, *35*, 3243-3246. (b) Ozerov, A.A.; Novikov, M.S.; Brel, A.K. *Chem. Heterocycl. Comp.* **1999**, *35*, 78-83.

dihydroxymethyl group may also impose unfavourable steric effects that decrease recognition by kinases.[104c] These results could explain the lack of activity of the synthesized compounds independently of the nature of the base (triazole or natural nucleosidic base).

3.3. Conclusion

In summary, as part of our smallpox drug discovery program, we have reported the efficient and simple syntheses of racemic 1,4-disubstituted-1,2,3-triazolo-carbanucleosides *via* copper(I)-catalyzed and microwave-assisted Huisgen alkyne-azide cycloaddition. The synthesis and biological assays of this variety of *hitherto* unknown 4'-hydroxymethyl-1,2,3-triazolo-carbanucleosides and their carbocyclic analogues bearing conventional base have been accomplished. Unfortunately, none of the synthesized compounds showed any cytotoxicity or significant antiviral activity on infected vaccinia virus cells.

4. SYNTHESIS OF OPTICALLY ACTIVE D-1,4-DISUBSTITUTED-TRIAZOLO-CARBANUCLEOSIDES *VIA* A KEY D-AZIDO INTERMEDIATE

Natural D-nucleosides and their L-counterparts usually exhibit different antiviral activities and toxicities.[106] Regarding carbocyclic nucleosides, enantiomers with a β-D-configuration exhibited significantly better antiviral effects than their L-analogues as they appeared to be better candidate for enzyme targeting and enzyme activation (phosphorylation). In the search for less toxic and more potent inhibitors of the *SAH hydrolase*, many D-carbocyclic analogues have emerged as effective inhibitors of vaccinia virus.[48,107] Therefore, the enantiospecific syntheses of carbanucleosides are crucial for further exploration of this class of compounds.[108] The synthetic approach deals principally with access to the enantiomerically pure highly oxygenated cyclopentane skeleton. However, the overall availability of optically active derivatives remains limited due to the lack of convenient methodologies for large-scale and stereospecific preparation of key intermediates.

[106] (a) Zemlicka, J. *Pharmacol. Therapeut.* **2000**, *85*, 251-266. (b) Song, G.Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R.W.; Schinazi, R.F.; Chu, C.K. *J. Med. Chem.* **2001,** *44*, 3985-3993. (c) Gumina, G.; Olgen, S.; Chu, C.K. *Antivir. Nucleos.* **2003**, 77-189. (d) Agrofoglio, L.A. *Curr. Org. Chem.* **2006**, *10*, 333-362.

[107] (a) De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84-89. (b) Narayanan, S.R.; Keller, B.T.; Borcherding, D.R.; Scholtz, S.A.; Borchardt, R.T. *J. Med. Chem.* **1988**, *31*, 500-503.

[108] (a) Trost, B.M.; Madsen, R.; Guile, S.D.; Elia, A.E.H.. *Angew. Chem., Int. Ed.* **1996**, *35*, 1569-1572. (b) Crimmins, M.T. *Tetrahedron* **1998**, *54*, 9229-9272. (c) Rodriguez, J.B.; Comin, M.J. *Mini Rev. Med. Chem.* **2003**, *3*, 95-114.

Thus, new synthetic intermediates for enantiomerically pure carbocyclic nucleosides are of significant interest. We report herein the revisited and improved large-scale synthesis of an optically active azido-carbanucleoside as a flexible building block for further synthetic elaboration.[109] This azido-precursor was used in the synthesis of D-(-)-1,4-disubstituted-1,2,3-triazolo-carbanucleosides. In order to complement the previous structure-activity relationship study made for the series of 4',4'-dihydroxymethyl-carbanucleosides, we opted this time for a 2',3'-dihydroxy-4'-hydroxymethyl-carbocyclic part structurally related to the anti-pox ribavirin and carbocyclic 3-deazaadenosine (Figure 14). The biological results of this new series will thus allow a better understanding of the triazole influence on the activity.

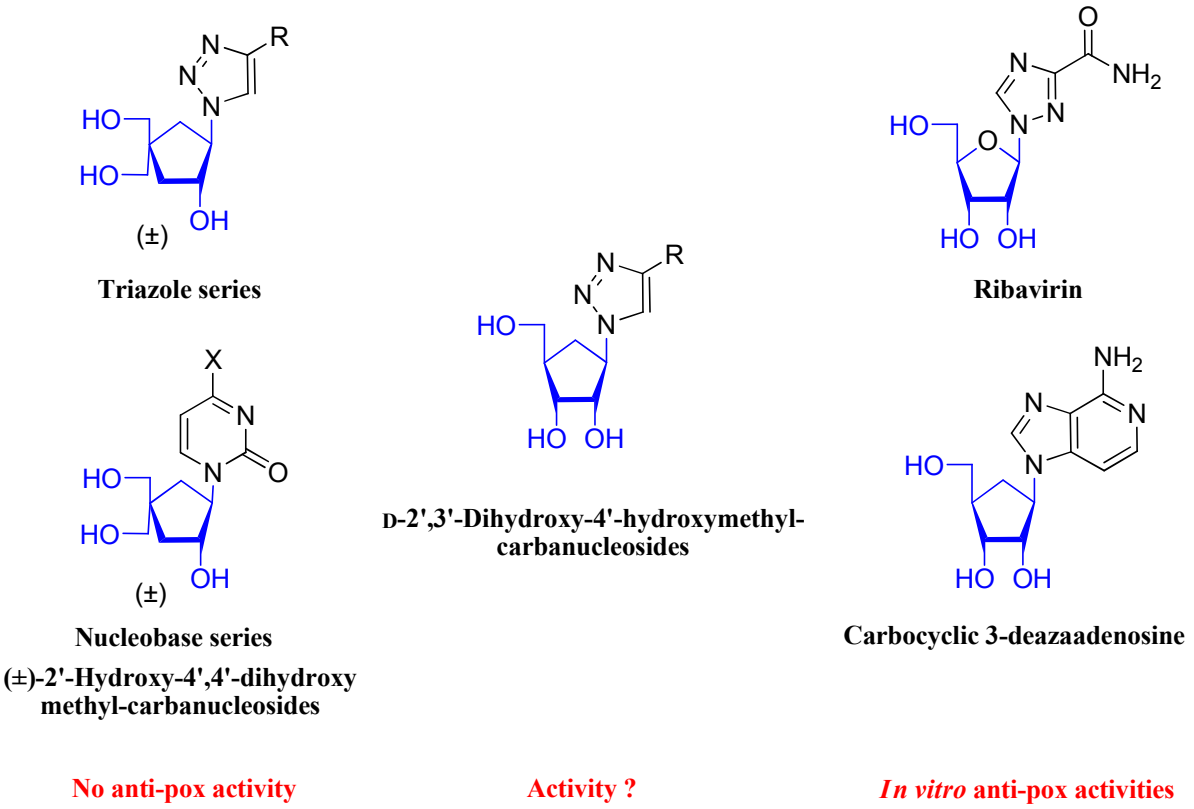


Figure 14. Structure-activity relationship.

4.1. Preparation of the Key Optically Active Azide

To the best of our knowledge, the only synthesis of the D-azidocarbanucleoside **31** was reported in 1988 by Tadano *et al.*; it was used as precursor for carbocyclic nucleoside antibiotics.[110] The synthetic approach used consisted in targeting the optically active carbocyclic skeleton using carbohydrates as starting materials. However, the

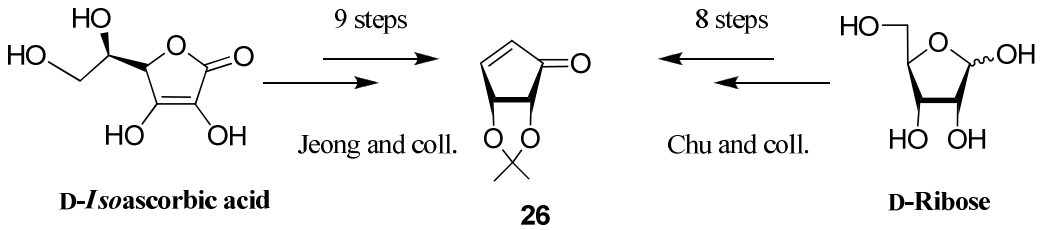
[109] For a comprehensive review about the versatility of organoazides in modern synthetic chemistry, see: Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188-5240.

[110] (a) Tadano, K.; Maeda, H.; Hoshino, M.; Iimura, Y. *Chem. Lett.* **1986**, 1081-1084; *J. Org. Chem.* **1987**, *52*, 1946-1956. (b) Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 1427-1432.

enantioselectivity across numerous steps could not be controlled and tedious purifications by repeated column chromatography were necessary to separate the different epimers. Herein, we present an enantiomerically controlled large-scale synthesis of **31** in 11 steps.

a) Synthesis of the D-2-cyclopentenone **26**:

To access the key optically active azide intermediate **31** (Scheme 16), we selected the D-2-cyclopentenone **26** known as a versatile synthon for the syntheses of various D-carbocyclic nucleosides.[111] The first practical procedures to obtain **26** were reported by Jeong and coll.[112] starting from inexpensive D-*iso*ascorbic acid and then by Chu and coll.[113] from D-ribose (Scheme 14).



Scheme 14. Synthesis of the D-2-cyclopentenone **26** from D-*iso*ascorbic acid or D-ribose.

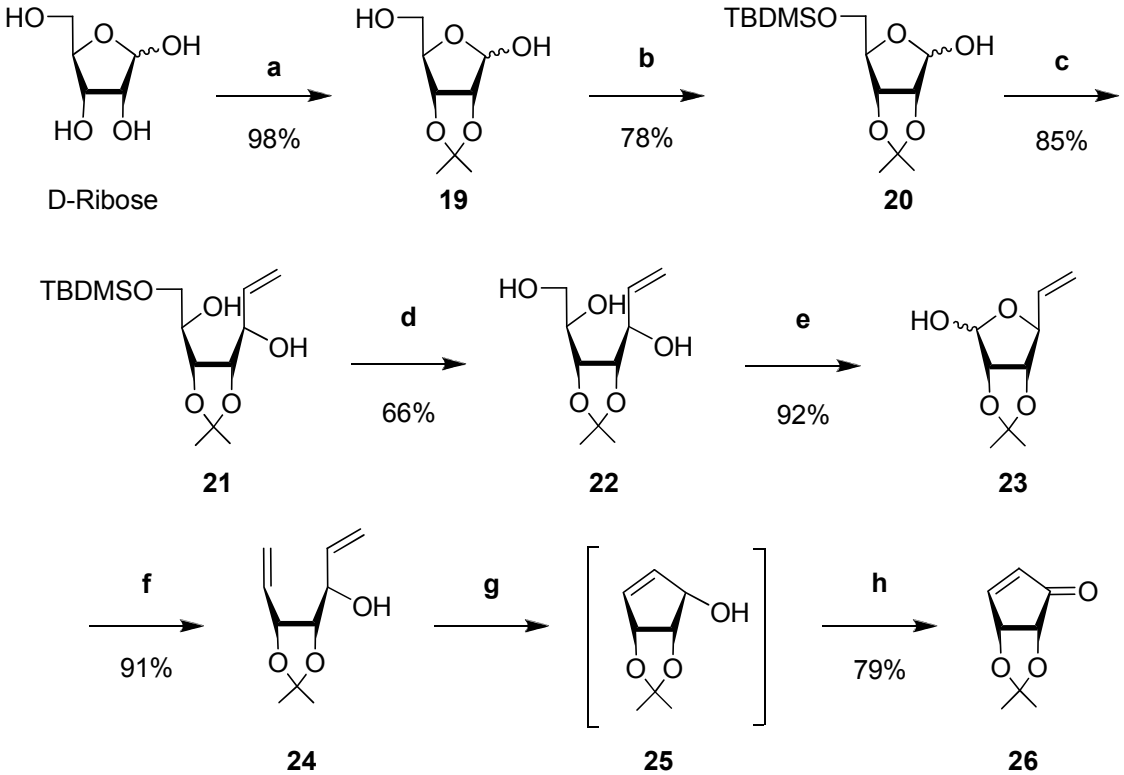
The first method was problematic in large-scale preparation due to the extreme sensitivity of many intermediates as well as difficulties in controlling stereoselective oxidation and reduction steps. Hence in spite of some variations brought to the approach, we chose to follow the second procedure for a milder and larger-scale synthesis of **26** taking advantage of the existing stereogenic centers of D-ribose (Scheme 15). This latter was converted into the *iso*propylidene protected derivative **19** with 2,2-dimethoxypropane in the presence of a catalytic amount of sulfuric acid in 98% yield, followed by silylation of the hydroxyl group using *tert*-butyldimethylsilyl chloride to give lactol **20** in 78% yield. Compound **20** was then reacted with vinylmagnesium bromide to obtain the ring-opened olefin **21** as a single D-stereoisomer. The stereoselectivity of the addition is due to the steric (Cram's rule) as well as the electronic effect (Felkin-Anh model) of the *iso*propylidene group. Indeed, the oxygens present on the aldehyde and the adjacent chiral centre are both chelated with the metal Mg^{2+} which prevents the attack of the Grignard reagent at the hindered α site. To introduce another olefinic moiety, first the deprotection of the silyl group was

[111] (a) Bestmann, H.J.; Roth, D. *Synlett* **1990**, 751-753. (b) Borcherding, D.R.; Scholtz, S.A.; Borchardt, R.T. *J. Org. Chem.* **1987**, *52*, 5457-5461.

[112] Choi, W.J.; Park, J.G.; Yoo, S.J.; Kim, H.O.; Moon, H.R.; Chun, M.W.; Jung, Y.H.; Jeong, L.S. *J. Org. Chem.* **2001**, *66*, 6490-6494.

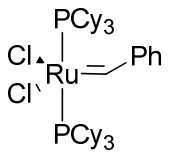
[113] Jin, Y.H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C.K. *J. Org. Chem.* **2003**, *68*, 9012-9018.

accomplished using TBAF, followed by an oxidative cleavage of the vicinal diol with sodium periodate to give the lactol **23** in 92% yield. Lactol **23** was then subjected to a Wittig reaction using methyltriphenylphosphonium bromide to give the diene **24** in 91% yield. Jeong and coll. have reported that the Wittig reaction is greatly affected by the choice of base.[112] The use of DMSO anion as a base allowed the synthesis of the desired diene **24** in good yield without epimerization of the final product. In both Jeong's and Chu's procedures, the ring-closing metathesis (RCM)[114] reaction of the diene **24** was performed using Grubbs' catalyst (Figure 15).[202] In our case, the RCM reaction to afford the D-cyclopentenol **25** was carried out using 1.5 mol% of the Ru-catalyst **58** (Figure 15, Cf. chapter **II.**).[204] Diene **24** was completely converted to **25** within 1 h of reaction at 25°C. However, since the ring-closed cyclopentenol **25** is highly volatile, the desired D-2-cyclopentenone **26** was directly obtained in 79% overall yield from **24** by oxidation of the secondary alcohol under PCC oxidation conditions without isolation of the cyclopentenol **25**.

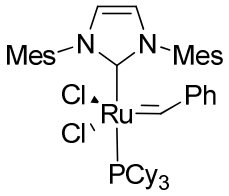


Scheme 15. Reagents and conditions: (a) 2,2-Dimethoxypropane, H_2SO_4, acetone, 0°C to r.t., 1 h; (b) *tert*-Butylchlorodimethylsilane, imidazole, CH_2Cl_2, 0°C to r.t., 1 h; (c) Vinylmagnesium bromide, anhydrous THF, -78 °C to r.t., 1 h; (d) TBAF, THF, r.t., 1 h; (e) $NaIO_4$, H_2O, r.t.,1 h; (f) NaH, DMSO, methyltriphenylphosphonium bromide, THF, 0 °C to reflux, 3 h; (g) [Ru]= **58**, anhydrous CH_2Cl_2, 24 °C, 1 h; (h) Pyridinium chlorochromate, CH_2Cl_2, r.t., 12 h.

[114] For recent reviews on RCM : see references 208 and 214.



Grubbs' catalyst



[Ru]=: **58**

Figure 15. Ruthenium catalysts for the ring-closing metathesis of diene **24**.

b) Synthesis of the D-azidocarbanucleoside **31**:

Compound **26** was then easily converted to unstable *exo*-olefin **27** following Schneller´s method (Scheme 16).[115] This synthetic approach consists in using a vinyl group as a mask of the hydroxymethyl group of carbocyclic nucleosides. The incorporation of a vinyl group onto a cyclopentyl ring by 1,4-enone addition is known to be a high-yielding reaction.[116] Copper(I) bromide-dimethyl sulfide complex induces the formation of an organocuprate derivative *via* transmetallation with vinylmagnesium bromide.[117] This less reactive organocuprate leads to regioselective 1,4-addition of the vinyl group to α,β-unsaturated ketones. On the other hand, addition of TMSCl-HMPA promotes the conjugate addition by trapping the magnesium enolate intermediate with TMSCl.[118] The role of HMPA may be to cleave the dimer frequently engendered by cuprates.[119] Thus, 1,4-addition of vinylmagnesium bromide to **26** cleanly afforded ketone **27** in 82% yield. Freshly opened vinyl magnesium bromide (not chloride!) is essential to successfully carry out this reaction. After stereoselective chelation-controlled reduction of ketone **27** (Felkin-Anh model) and subsequent benzoylation, benzoate **28** was afforded in moderate yield. The silyl ether **29** was obtained in good yield from **28** by i) oxidative glycol cleavage of *exo*-olefin using osmium tetroxide/sodium periodate, ii) sodium borohydride reduction of the resulting aldehyde, iii) protection of primary alcohol and iv) debenzoylation sequence. Finally, we first tried to introduce an azide function by simple tosylation and S_N2 azidation (Scheme 16). However, the overall yield of the desired **31** was

[115] Yang, M.; Ye, W.; Schneller, S.W. *J. Org. Chem.* **2004**, *69*, 3993-3996.

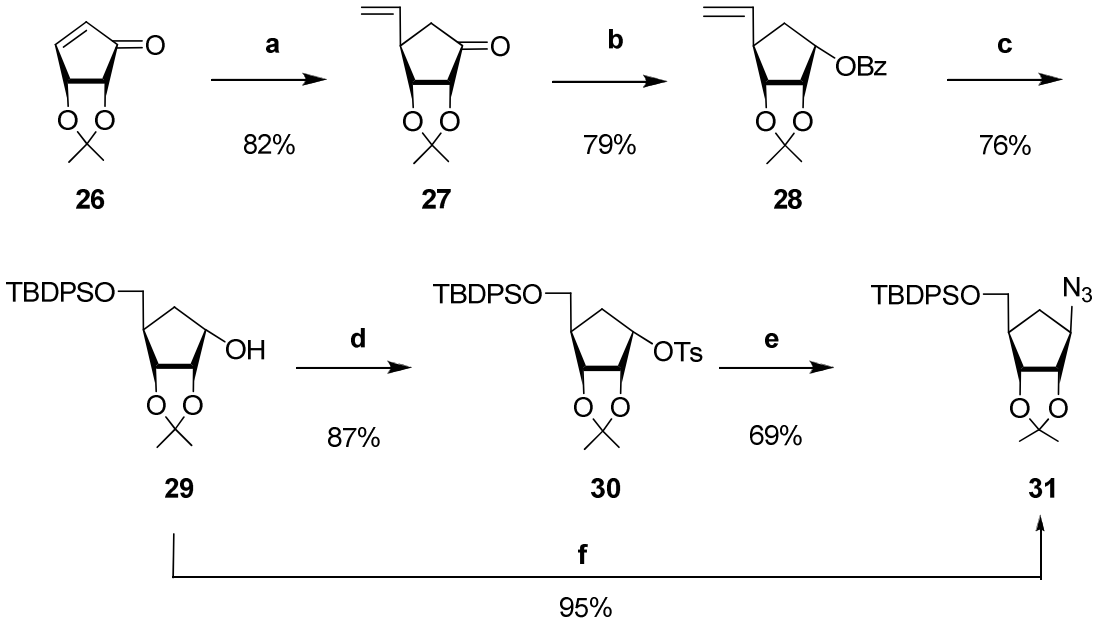
[116] Johnson, C.R.; Chen, Y.F. *J. Org. Chem.* **1991**, *56*, 3344-3351.

[117] (a) Gilman, H.; Jones, R.G.; Woods, L.A. *J. Org. Chem.* **1952**, *17*, 1630-1634. (b) Normant, J.F. *Synthesis* **1972**, 63-80.

[118] (a) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1985**, *26*, 6015-6018; 6019-6022. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047-1050. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029-4032.

[119] (a) Reett, M.T.; Wang, F.; Harms K. *J. Chem. Soc., Chem. Commun.* **1991**, 1309-1311. (b) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3831-3842.

only 60% for two steps. On the other hand, the application of Mitsunobu azidation[120] appeared to be more convenient for the synthesis of **31**. Alcohol **29** was treated with DIAD and DPPA (Figure 16) in the presence of PPh_3. Azide **31** was obtained in 95% yield as the single stereoisomer.



Scheme 16. Reagents and conditions: (a) Vinylmagnesium bromide, $CuBr.Me_2S$, TMSCl, HMPA, THF, -78 °C, 3 h; (b) *(i)* $LiAlH_4$, THF, 0°C to r.t., 2 h; *(ii)* BzCl, DMAP, *i*-Pr_2NEt, CH_3CN, 0°C to r.t., 2 h; (c) *(i)* OsO_4, $NaIO_4$, MeOH/acetone/H_2O, r.t., 30 min; *(ii)* $NaBH_4$, MeOH, -78 °C to r.t., 40 min; *(iii) tert*-Butylchlorodiphenylsilane, imidazole, DMAP, CH_3CN, r.t., 1 h; *(iv)* NaOMe, MeOH, 0°C to r.t., 15 h; (d) TsCl, *i*-Pr_2NEt, DMAP, CH_3CN, 0°C to r.t., 24 h; (e) NaN_3, 18-crown-6, DMF, 140°C, 2 h; (f) DIAD, DPPA, PPh_3, THF, 0°C to r.t., 7 h.

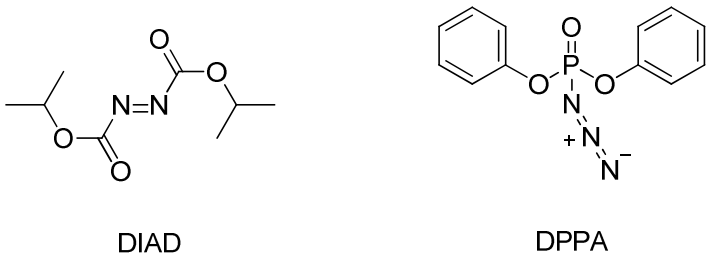


Figure 16. Di*iso*propyl azodicarboxylate (DIAD) and diphenyl phosphoryl azide (DPPA).

The enantioselective addition of azide function with inversion of the configuration was confirmed by NOESY spectroscopy (Figure 17). Unlike the correlation observed between $H^{1'}$ and $H^{2'}$ in the α-cyclopentanol **29**, only correlations between $H^{1'}$ and the two $H^{6'}$ were detected in the β-orientated azido carbocycle **31**.

[120] (a) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Japan* **1967**, *40*, 2380-2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1-28. (c) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140-3152.

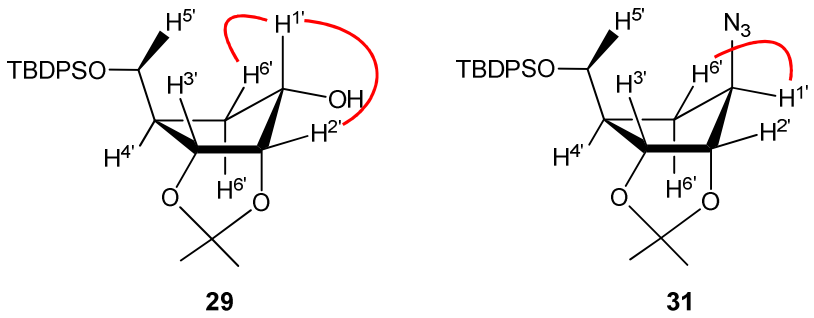


Figure 17. NOESY correlations of **29** and **31**.

4.2. D-Triazolo-Carbanucleosides via 1,3-Dipolar Cycloaddition

a) Synthesis of D-1,4-disubstituted-1,2,3-triazolo-carbanucleosides:

We performed the Huisgen 1,3-dipolar cycloaddition between enantiomerically pure azidocarbocycle **31** and various terminal alkynes under the optimized reaction conditions previously reported for the racemic series. In a mixture water/*tert*-butanol under microwave irradiation, $Cu^0/CuSO_4$-catalyzed reactions were performed with complete conversion of **31** into the desired 1,4-disubstituted triazoles (**32-37**) in extremely short reaction times (<15 min) and with no observable formation of by-products (Table 6). Even, electron-deficient 1-heptyne reacted in few minutes (Table 6, entry 3). Compounds **32-37** were isolated in high yield and purity after a simple extraction in ethyl acetate.

The regioselectivity of the cycloaddition reaction under microwave irradiation was confirmed by using ^1H and ^{13}C long range NMR experiments (HMBC). The selective formation of 1,4-disubstituted-1,2,3-triazoles was confirmed by a long range correlation between the $H^{1'}$ of the sugar and the carbon bearing the *1H*-triazole H^5 (Figure 18).

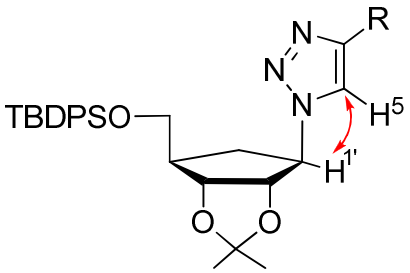
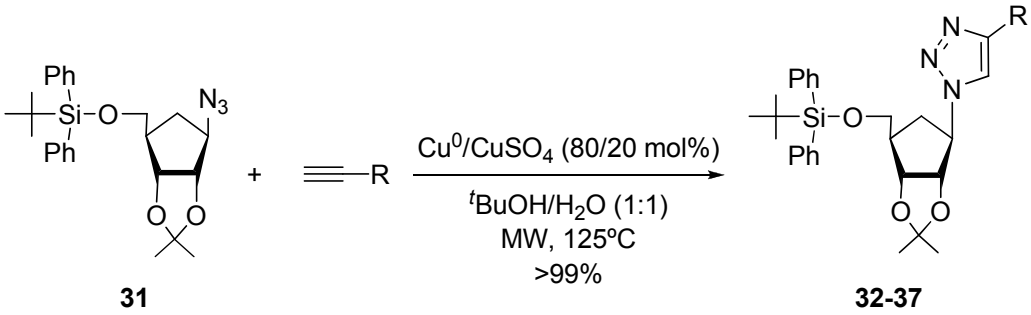
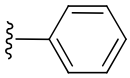
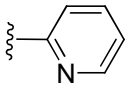
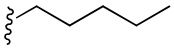
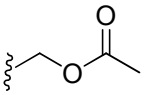
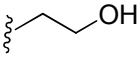
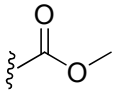


Figure 18. HMBC correlations in the 1,4-disubstituted-1,2,3-triazoles **32-37**.

These results demonstrated that the developed method was also applicable to different azidocarbanucleosidic substrates even if the latter contained protecting groups.

Table 6. Microwave assisted 1,3-dipolar cycloaddition of azido derivative **31**.[a]

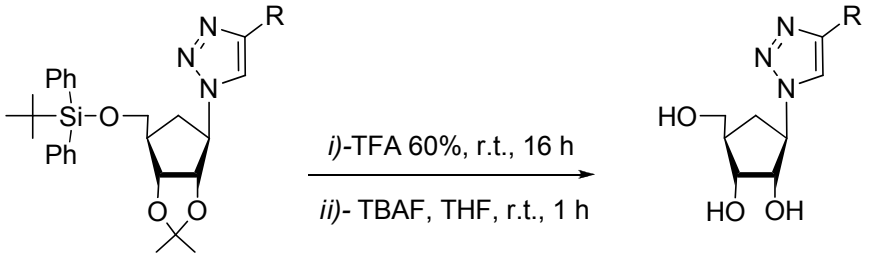


Entry	R	Triazole	Time (min)
1		**32**	5
2		**33**	1
3		**34**	15
4		**35**	1
5		**36**	1
6		**37**	1

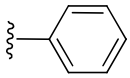
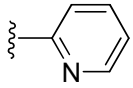
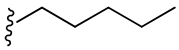
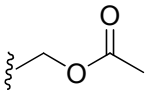
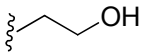
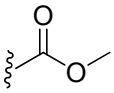
[a] Reaction conditions: azide **31** (0.1 mmol), alkyne (1.05 equiv), Cu^0 (80 mol%)/$CuSO_4$ (20 mol%), $^tBuOH/H_2O$ 1:1 (1 mL), Microwave (MW): T = 125°C.

Finally, deprotection of the *iso*propylidene and the silyloxy groups afforded the final optically active compounds **38-43** in moderate to quantitative yields (Table 7). Of note, we observed that TBAF was not selective when the desilylation step (*ii*-) was achieved before the deprotection of the *iso*propylidene (*i*-) since a mixture of the desilyloxy intermediate and the totally deprotected final compound were obtained. Further treatment of this mixture with TFA 60% afforded only the final compound in good yield. According to NOESY experiments, the β-configuration is conserved during the 1,3-dipolar cycloaddition. As for azide **31**, only correlations between $H^{1'}$ and the two $H^{6'}$ were detected in the β-orientated-triazolo carbanucleosides.

Table 7. Deprotection of 1,4-disubstituted-1,2,3-triazolo-carbanucleosides **38-43**.[a]



32-37 **38-43**

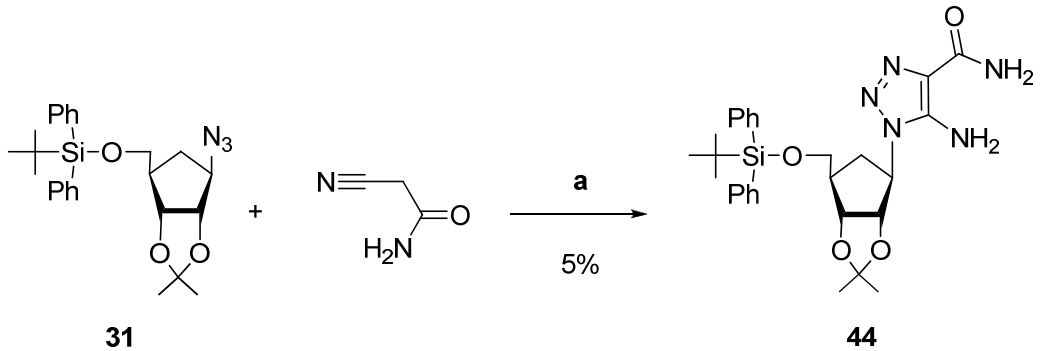
Entry	R	Triazole	Yield (%)
1		**38**	86
2		**39**	98
3		**40**	88
4		**41**	76
5		**42**	80
6		**43**	52

[a] Reaction conditions: *i)*- triazole **32-37** (0.1 mmol), TFA 60% (2 mL), r.t., 16 h; *ii)*- TBAF (1.05 equiv), THF (2 mL), r.t., 1 h.

b) Tentative synthesis of a D-1,4,5-trisubstituted-triazolo-carbanucleoside:

The synthesis of an optically pure 1,4,5-trisubstituted-triazolo-carbanucleoside was also attempted. To achieve the synthesis of **44**, we applied our protocol previously optimized for 1,2,3-triazolo-3'-deoxycarbanucleosides,[63d] inspired by the reported 1,3-dipolar cycloaddition of azides and 2-cyanoacetamide.[121] In spite of reaction times of 48 h in refluxing ethanol, the starting material **31** was almost completely recovered (Scheme 17). Nevertheless, 5% of the expected compound **44** could be isolated and characterized**.**

[121] (a) Ewing, D.F.; Goethals, G.; Mackenzie, G.; Martin, P.; Ronco, G.; Vanbaelinghem, L.; Villa, P. *J. Carbohydr. Chem.* **1999**, 441-450; *Carbohydr. Res.* **1999**, 190-196.



Scheme 17. Reagents and conditions: (a) EtONa, EtOH, reflux, N_2, 48 h.

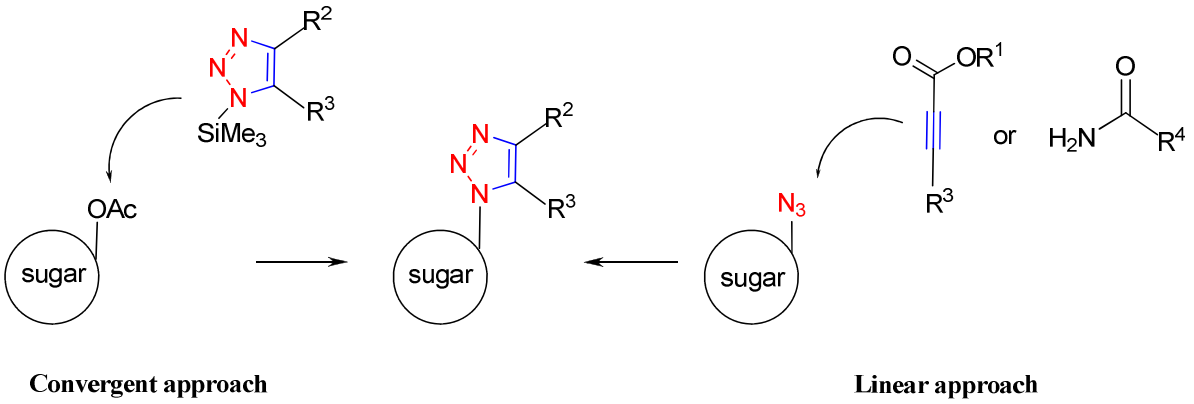
4.3. Conclusion

In summary, we have explored the syntheses of D-configured 1,4-disubstituted-1,2,3-triazolo-carbanucleosides *via* the previously optimized copper(I)-catalyzed microwave-assisted Huisgen alkyne-azide cycloaddition. The preparation of an enantiomerically pure cyclopentane azide derivative was achieved using an optically active enone intermediate, readily obtained by published procedure on multi-gram scale. Final Mitsunobu azidation proved to be a superior method compared to traditional tosylation and S_N2 azidation sequence. The D-azide was then successfully reacted with different terminal alkynes to afford the corresponding D-(-)-1,4-disubstituted-1,2,3-triazolo-carbanucleosides **38-43**, confirming the efficiency of the developed tool with different azidocarbanucleosidic substrates. Despite a carbocyclic 3-deazaadenosine-like carbocycle moiety, none of the synthesized compounds showed any cytotoxicity or significant antiviral activity on infected vaccinia virus cells. They were neither substrates for the human thymidine kinase (hTK) nor for the human uracil cytosine kinase (hUCK). These biological outcomes question the real antiviral effect of 1,4-substituted-1,2,3-triazolo derivatives as smallpox inhibitors.

5. 1,3-DIPOLAR CYCLOADDITION WITH INTERNAL ALKYNES: SYNTHESIS OF 1,4,5-TRISUBSTITUTED-1,2,3-TRIAZOLES

The successful, versatile and efficient tool developed for the preparation of 1,4-disubstituted-1,2,3-triazolo-carbanucleosides prompted us to examine the reactivity of copper(I)-based catalytic systems in the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles *via* Huisgen 1,3-dipolar cycloaddition. Indeed, only a few examples of 1,4,5-trisubstituted-1,2,3-triazolo-nucleosides are reported in the literature. They have been prepared either *via* direct

glycosylation of a suitable trimethylsilyl derivative of 4,5-disubstituted-1,2,3-triazole (convergent approach)[122] or in few steps using linear methodologies[123,124] (Scheme 18).



Scheme 18. Synthesis of 1,4,5-trisubstituted-1,2,3-triazolo-nucleosides *via* convergent or linear approach.

Due to the poor regioselectivity of the glycosylation process, linear strategies based on thermal cyclocondensation between glycosyl azides and activated carboxylates[63a,123,124] or carboxamides[62c,63d,122a,125] derivatives have been the focus of more attention. The carbonylated functions of the glycosylated triazoles could further be converted to amide or nitrile groups *via* classical transformations. Few examples based on 1,3-dipolar cycloaddition with symmetric 1,4-dihalo or 1,4-dihydroxybutyne have been reported.[126] According to azide substrates, reactions with dihalobutynes often gave complex mixtures. This overview of the different strategies to generate 1,4,5-trisubstituted-1,2,3-triazolo-nucleosides clearly underlines the existing limitations and the need for a versatile and efficient methodology. Therefore, it would be an important challenge to extend the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction to a large selection of symmetrical or unsymmetrical internal alkynes (Scheme 19).

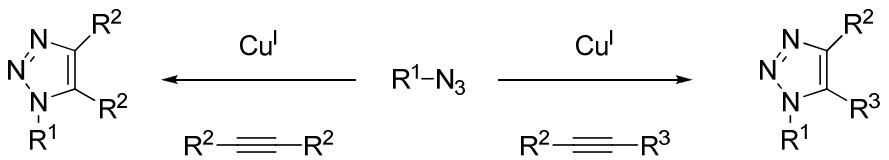
[122] (a) Witkowski, J.T.; Robins, R.K.; Lehmkuhl, F.A. US patent 3948885, **1976**. (b) Meyer, R.B., Jr.; Revankar, G.R.; Cook, P.D.; Ehler, K.W.; Schweizer, M.P.; Robins, R.K. *J. Heterocycl. Chem.* **1980**, *17*, 159-169. (c) Revankar, G.R.; Solan, V.C.; Robins, R.K.; Witkowski, J.T. *Nucleic Acids Symposium Series* **1981**, *9*, 65-68. (d) Shingarova, I.D.; Yartseva, I.V.; Nemeryuk, M.P.; Sedov, A.L.; Safonova, T.S.; Osipov, G.A.; Volodin, Y.Y.; Preobrazhenskaya, M.N *Khim. Geterotsikl+* **1984**, *11*, 1556-1564.

[123] For cycloaddition with acetylene carboxylates : (a) Earl, R.A.; Townsend, L.B. *Can. J. Chem.* **1980**, *58*, 2550-2561. (b) Chretien, F.; Gross, B. *J. Heterocyclic Chem.* **1982**, *19*, 263-267. (c) Al-Masoudi, N.A.; Al-Soud, Y.A. *Nucleos. Nucleot. Nucl.* **2002**, *21*, 361-375. (d) Al-Masoudi, N.; Al-Soud, Y.; Schuppler, T. *J. Carbohyd. Chem.* **2005**, *24*, 237-250.

[124] (a) Schoerkhuber, W.; Zbiral, E. *Liebigs Ann. Chem.* **1980**, *9*, 1455-1469. (b) Stimac, A.; Townsend, L.B.; Kobe, J. *Nucleos. Nucleot*. **1991**, *10*, 727-728. (c) Stimac, A.; Leban, I.; Kobe, J. *Synlett* **1999**, 1069-1073.

[125] Hutzenlaub, W.; Tolman, R.L.; Robins, R.K. *J. Med. Chem*. **1972**, *15*, 879-883.

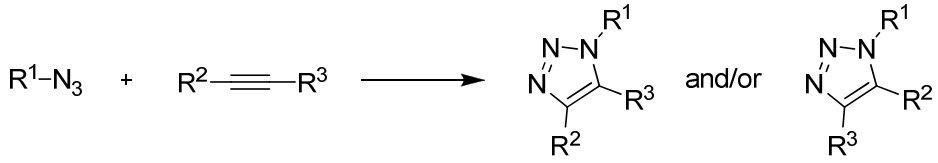
[126] (a) De las Heras, F.G.; Alonso, R.; Alonso, G. *J. Med. Chem.* **1979**, *22*, 496-501. (b) Al-Masoudi, N.A.; Al-Soud, Y.A.; Abdul-Zahra, A. *Heteroatom Chem.* **2004**, *15*, 380-387.



Scheme 19. Expected Cu^I-catalyzed fomation of 1,4,5-trisubstituted-1,2,3-triazoles.

5.1. Background of Late Transition Metal-catalyzed Cycloaddition Reactions

In a general manner, the preparation of 1,4,5-trisubstituted-1,2,3-triazoles is also of significant interest as little is known about the influence of late Transition Metal catalysts on the cycloaddition reaction between azides and internal alkynes. Thus, it is a challenge to find new protocols for the efficient synthesis of these derivatives. A significant drawback is that unsymmetrical acetylenes give regioisomer mixtures of triazoles (Scheme 20).[56a-c] Influenced by the electronic properties of the alkyne, the mixture *ratio* tends to favour the triazole where the electron-withdrawing group occupies the 4-position and the electron-donating group occupies the 5-position.[127]



Scheme 20. [3+2]-Cycloaddition of azide with unsymmetrical internal alkyne.

Initially, traditional methods for producing 1,4,5-trisubstituted-1,2,3-triazoles from azides and disubstituted alkynes could be achieved in the absence of a catalyst. However, the reaction required elevated temperatures[55,128] and the alkyne had at least one electron-withdrawing functional group such as carboxylate.[129,130] First attempts to control regioselectivity were performed by taking advantage of the regiodirecting effect induced by the trimethylsilyl group which exclusively yielded the 1,5-disubstituted-4-trimethylsilyl-triazole (Scheme 21).[128] Even in the presence of an electron-withdrawing second substituent, this latter completely controlled the selectivity by a combination of steric hindrance and the

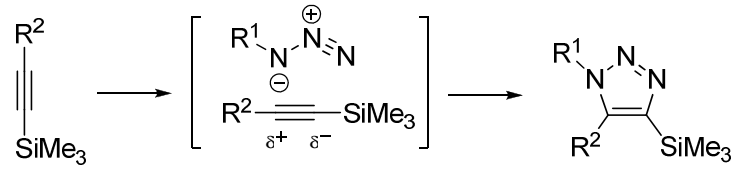
[127] (a) Padwa, A. in *"Comprehensive Organic Synthesis"*, Vol. 4; Trost, B.M., Ed.; Pergamon: Oxford, United Kingdom, **1991**, 1069-1109. (b) Fan, W.-Q.; Katritzky, A.R. in *"Comprehensive Heterocyclic Chemistry II"*, Vol. 4; Katritzky, A.R., Rees, C.W., Scriven, E. F.V., Eds.; Pergamon: Oxford, United Kingdom, **1996**, 101-126.

[128] (a) Hlasta, D.J.; Ackerman, J.H. *J. Org. Chem.* **1994**, *59*, 6184-6189. (b) Coats, S.J.; Link, J.S.; Gauthier, D.; Hlasta, D.J. *Org. Lett.* **2005**, *7*, 1469-1472.

[129] L'Abbè, G. *Ind. Chim. Belg.* **1969**, *34*, 519-530 and references therein.

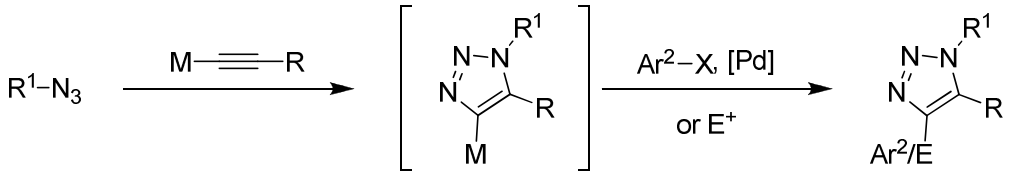
[130] (a) Palacios, F.; Ochoa de Retana, A.; Pagalday, J. *Heterocycles* **1994**, *38*, 95-102. (b) Li, Z.; Seok Seo, T.; Ju, J. *Tetrahedron Lett*. **2004**, *45*, 3143-3146.

ability of silicon to stabilize a partial positive charge on the acetylene *β*-carbon in the transition state.



Scheme 21. Directed 1,3-dipolar cycloaddition.[128]

A different strategy consisting in the formation of 4-metalated-1,5-disubstituted-1,2,3-triazoles has also been investigated and mainly developed by Akimova *et al.* in the late 1960s.[131] As depicted in Scheme 22, the cycloaddition reaction involved an alkyne bearing a metal, such as tin, sodium, lithium or magnesium, attached to the acetylenic carbon atom.[131,132,133,134] The metalated intermediate was then reacted with arylhalides[134] *via* Negishi reaction or trapped with electrophiles[131a,133] resulting in the regioselective formation of 1,4,5-trisubstituted-1,2,3-triazoles.



Scheme 22. Synthesis of 4-metalated-triazoles followed by trapping with electrophiles or by Negishi reaction.

A similar approach was further applied to the insertion of diverse functional groups *via* cross-coupling reactions of 5-halogeno-1,4-disubstituted-1,2,3-triazoles (Scheme 23).[135] 5-Bromo and 5-iodo-1,2,3-triazoles were prepared by cycloaddition from terminal or bromoacetylene using copper salts and an iodide or bromide source.[136] The iodo-intermediate could also be directly trapped by electrophiles *via* a one-pot reaction promoted by copper(I) salt (Scheme 23).[136a] An alternative consisted in introducing aryl groups on the 5-position of

[131] (a) Akimova, G.S.; Chistokletov, V.N.; Petrov, A.A. *Zh. Org. Khim.* **1965**, *1*, 2077-2078. (b) Akimova, G.S.; Chistokletov, V.N.; Petrov, A.A. *Zh. Org. Khim.* **1967**, *3*, 2241-2247. (c) Akimova, G.S.; Chistokletov, V.N.; Petrov, A.A. *Zh. Org. Khim.* **1967**, *3*, 968-974. (d) Akimova, G.S.; Chistokletov, V.N.; Petrov, A.A *Zh. Org. Khim.* **1968**, *4*, 389-394.

[132] (a) Boyer, J.H.; Mack, C.H.; Goebel, N.; Morgan, L.R., Jr. *J. Org. Chem.* **1958**, *23*, 1051-1052. (b) Himbert, G.; Frank, D.; Regitz, M. *Chem. Ber.* **1976**, *109*, 370-394.

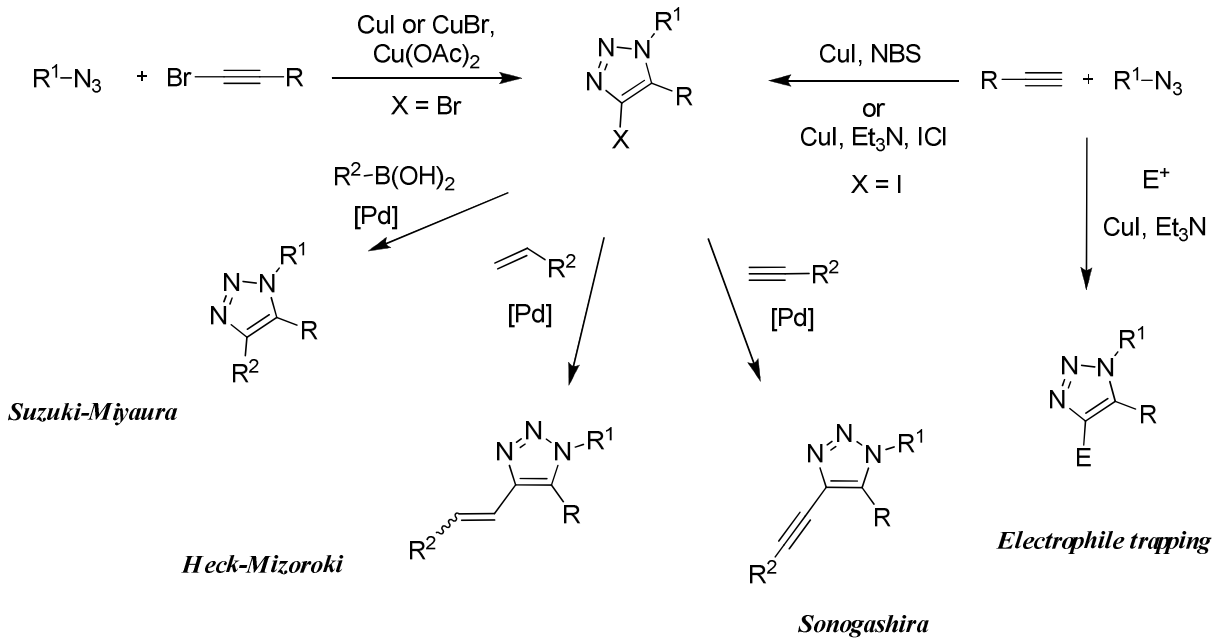
[133] Krasinski, A.; Fokin, V.V.; Sharpless, K.B. *Org. Lett.* **2004**, *6*, 1237-1240.

[134] Kao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2007**, 31-36.

[135] Deng, J.; Wu, Y-.M.; Chen, Q-.Y. *Synthesis* **2005**, 2730-2738.

[136] (a) Wu, Y-.M.; Deng, J.; Li, Y.; Chen, Q-.Y. *Synthesis* **2005**, 1314-1318. (b) Kuijpers, B.H.M.; Dijkmans, G.C.T.; Groothuys, S.; Quaedflieg, P.J.L.M.; Blaauw, R.H.; van Delft, F.L.; Rutjes, F.P.J. T. *Synlett* **2005**, 3059-3062. (c) Li, L.; Zhang, G.; Zhu, A.; Zhang, L. *J. Org. Chem.* **2008**, *73*, 3630-3633.

the existing 1,4-disubstituted-*1H*-1,2,3-triazole ring by Pd-catalyzed arylation.[137] However, these methods display very limited structural diversity for both reactants and substituents. Moreover, yields were generally low and formation of by-products was observed along with unreacted starting materials.



Scheme 23. Synthesis of 4-halogeno-1,2,3-triazoles followed by trapping with electrophiles or by cross-coupling reactions.

Finally, Zhang *et al.* proposed a straightforward way to access 1,4,5-trisubstituted-1,2,3-triazoles by ruthenium-catalyzed cycloaddition between azides and the symmetrical internal diphenlyacetylene in refluxing benzene.[138] The generality of this Ru-catalyzed cycloaddition was then extended to various unsymmetrical disubstituted alkynes by Majireck and Weinreb[139] and more recently by Boren *et al.*[140] Reactions were conducted in dioxane at 60ºC using 2 mol% of [Cp*RuCl(PPh_3)$_2$] (Cp* = pentamethylcyclopentadienyl) or in toluene at room temperature using 2 mol% of [Cp*RuCl(COD)] (COD = 1,5-Cyclooctadiene) (Scheme 24). The trisubstituted triazoles were obtained with virtually exclusive regioselectivity in the case of activated alkynes containing a hydrogen bond donor group (e.g., propargylic alcohols and amines). In the absence of such directing groups, regioselectivity seemed to be governed

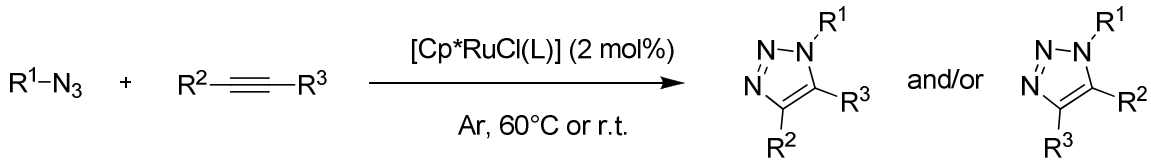
[137] Chuprakov, S.; Chernyak, N.; Dudnik, A.S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333-2336.

[138] Zhang, L.; Chen, X.; Xue, P.; Sun, H.H.Y.; Williams, I.D.; Sharpless, K.B.; Fokin, V.V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998-15999.

[139] Majireck, M.M.; Weinreb, S.M. *J. Org. Chem.* **2006**, *71*, 8680-8683.

[140] Boren, B.C.; Narayan, S.; Rasmussen, L.K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V.V. *J. Am. Chem. Soc.* **2008**, *130*, 8923-8930.

primarily by the electronic (and possibly by steric) properties of the alkyne, as in the thermal version of the cycloaddition reaction.



Scheme 24. [Cp*RuCl(L)]-catalyzed cycloaddition of azides and internal alkynes.

Although the last reaction conditions were improved using lower catalyst loading and temperature in safer solvents, the cycloaddition reactions between azides and internal alkynes are still carried out without a controlled selectivity in non-environmental friendly media and under inert atmosphere. Therefore, milder and simpler protocols responding to the "click" criteria would be of significant importance.

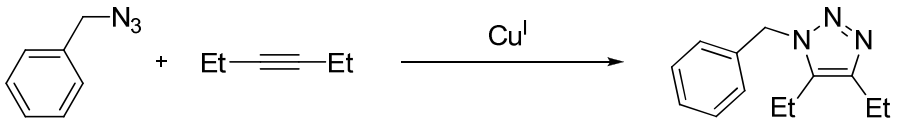
5.2. NHC-Cu^{I}-catalyzed Preparation of 1,4,5-Trisubstituted-1,2,3-triazoles

a) Initial attempts and mechanistic study:

In addition to the successful formation of 1,4-disubstituted-1,2,3-triazoles from terminal alkynes (Scheme 7, pp 35), [CuBr(SIMes)] has allowed notably for the unprecedented copper-catalyzed synthesis of 1,4,5-trisubstituted-derivatives from an internal alkyne.[93] The 1,3-dipolar cycloaddition reaction of benzyl azide with the non-activated 3-hexyne proceeded at 70°C under air atmosphere to afford the 1-benzyl-4,5-diethyl-1,2,3-triazole **45** with 80% conversion (Table 8, entry 1). Optimization studies showed that both, copper salt and NHC ligand are essential for this transformation. When the reaction was carried out with 5 mol% of CuBr, the conversion only reached 34% and no significant formation of triazole **45** (<5%) was observed in the absence of copper. Recently, Candelon *et al*. reported similar copper(I)-catalyzed formation of **45** in presence of 0.5 mol% [CuBr(C18$_6$tren)] (C18$_6$tren = tris(2-dioctadecylaminoethyl) amine) at 60°C in *n*-octane (Table 8, entry 2).[141]

[141] Candelon, N.; Lastécouères, D.; Khadri Diallo, A.; Aranzaes, J.R.; Astruc, D.; Vincent, J.M. *Chem. Commun*. **2008**, 741-743.

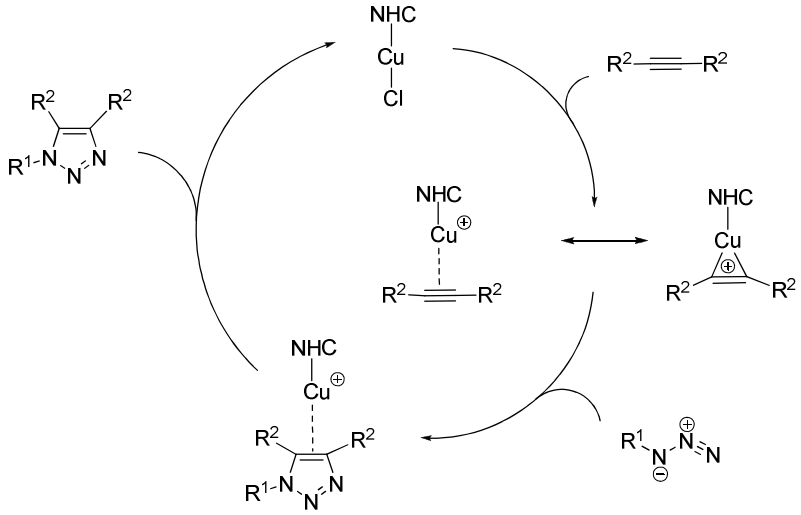
Table 8. Cu^I-catalyzed 1,3-dipolar cycloaddition of benzyl azide and 3-hexyne.



45

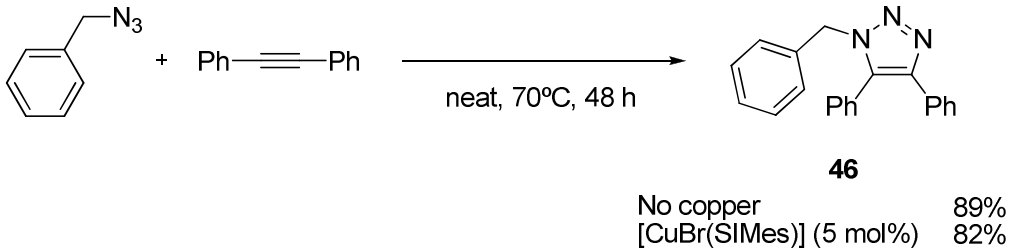
Entry	Reaction conditions	Catalyst	Conversion
1	neat, 70ºC, 48 h	No copper [CuBr] (5 mol%) [CuBr(SIMes)] (5 mol%)	<5% 34% 80%
2	*n*-octane, 60ºC, 24 h	[CuBr(C18$_6$tren)] (0.5 mol%)	85%

Compared to terminal alkynes, the formation of the active σ-acetylide Cu^I complexes, after deprotonation of the initial π-complex, can not be achieved with internal alkynes. Thus, a distinct mechanistic pathway was supported by DFT calculations where the beneficial effect of the NHC allows for the activation of disubstituted alkynes to proceed by the π-alkyne complex (Scheme 25).[93]



Scheme 25. Proposed mechanism for the NHC-copper(I) cycloaddition of internal alkynes.

The NHC-Cu^I-catalyzed cycloaddition of benzyl azide with the more activated diphenylacetylene was also evaluated.[93] Unlike to Zhang *et al.* that have observed a sluggish uncatalyzed reaction in refluxing benzene,[138] the cycloaddition afforded the 1,4,5-trisubstituted-1,2,3-triazole **46** even under copper-free neat conditions (Scheme 26).



Scheme 26. 1,3-dipolar cycloaddition of benzyl azide and diphenylacetylene.

The promising results obtained with 3-hexyne prompted us to optimize the reaction conditions and to extend the scope of the Cu^{I}-catalyzed 1,3-dipolar cycloaddition of disubstituted alkynes and azides. Indeed, to date the only reported examples of copper-catalyzed cycloaddition with internal alkynes involve benzyl azides and 3-hexyne as substrates.[93,141]

b) Experimental work:

- Optimization

We initiated the study using benzyl azide and 3-hexyne as standard substrates. First, the activity of a second NHC-copper(I) complex [CuCl(IPr)][90a,142] (IPr = *N,N'*-bis(2,6-di*iso*propylphenyl)imidazol-2-ylidene) was compared to the previous results under the same reaction conditions (Table 9, entries 1-3). The reaction conversion decreased to 20% using [CuCl(IPr)] (entry 2). However, we chose to keep this catalyst for the following experiments in order to gauge any improvement of the conversion of **45**. Two equivalents of 3-hexyne were used because of its volatility at this temperature.

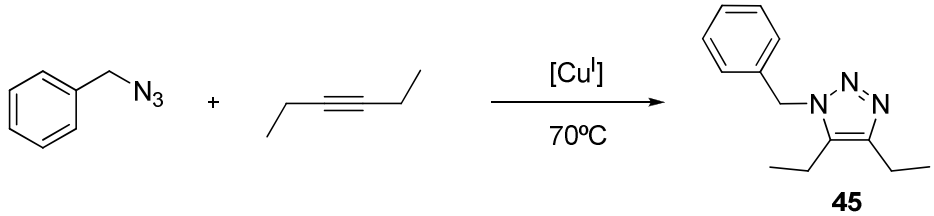
Inert atmosphere did not have any effect on the conversion, excluding an oxygen inhibition of the Cu^{I} catalytic species (entry 3). Under microwave irradiation, the cycloaddition failed under neat conditions (entry 4), while on water, 75% of **45** was obtained after 1 h of microwave irradiation at 70°C (entry 5). Of note, only 1.05 equivalents of alkyne were necessary in the sealed vial of the microwave reactor. Unfortunately, this enhancement was not due to a copper-catalyzed process as the microwave-assisted reaction performed even better under copper free conditions (86%) (entry 6).

Additives like Brønsted bases[72] and acids[64a-b] have been reported to enhance the catalyst activity of the 1,3-dipolar cycloaddition. As mentioned above, Cu^{I}-mediated Huisgen reaction can proceed more rapidly and efficiently in the presence of an excess of base preventing degradation of Cu^{I} and accelerating the formation of the Cu^{I}-acetylide intermediates (Scheme

[142] Jurkauskas, V.; Sadighi, J.P.; Buchwald, S.L. *Org. Lett.* **2003**, *5*, 2417-2420.

6).[59,78] Di*iso*propylethylamine (DIEA) or triethylamine are the most commonly used base additives. Silica gel[143] and acetic acid (AcOH) have also shown an acid catalytic role on the activation of the reaction.[64b] In our case, adding Et_3N (entry 7) or AcOH (entry 8) only induced an important decrease of the conversion certainly due to a decomposition of the catalyst under these conditions. SiO_2 did not have any effect on the catalytic activity either (entry 9).

Table 9. Optimization studies.[a]

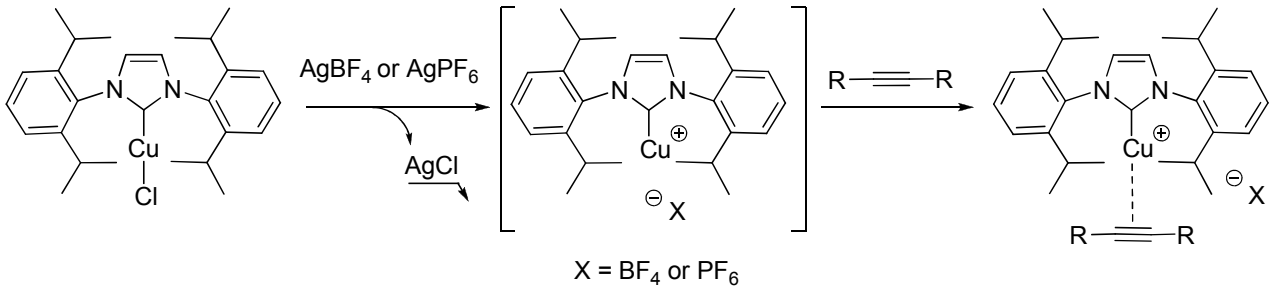


Entry	Catalyst (5 mol%)	Additives	Solvent	Time	Conversion (%)[d]
1	[CuBr(SIMes)]	-	neat	48 h	80
2	[CuCl(IPr)]	-	neat	48 h	20
3	[CuCl(IPr)]	-	neat, Ar	48 h	17
4	[CuCl(IPr)]	-	neat, MW[b]	10 h	0
5	[CuCl(IPr)]	-	H_2O, MW[b]	1 h	75
6	-	-	H_2O, MW[b]	1 h	86
7	[CuCl(IPr)]	NEt_3	neat	48 h	7
8	[CuCl(IPr)]	AcOH	neat	48 h	0
9	[CuCl(IPr)]	SiO_2[c]	neat	48 h	22

[a] Reaction conditions: benzyl azide (1 mmol), 3-hexyne (2 equiv), [CuX(NHC)] (5 mol%), Additives (1.1 equiv), T = 70°C. [b] Reaction conditions under microwave irradiation (MW): benzyl azide (1 mmol), 3-hexyne (1.05 equiv), [CuCl(IPr)] (5 mol%), H_2O (1 mL), T = 70°C. [c] 100 mg of SiO_2. [d] Conversions are average of two runs and were determined by ^1H NMR of the crude products.

[143] Recent reports on silica gel catalysis effects on several organic reactions: (a) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal. A-Chem.* **2006**, *249*, 98-102. (b) Wang, L.; Jing, H.; Bu, X.; Chang, T.; Jin, L.; Liang, Y. *Catal. Commun.* **2006**, *8*, 80-82. (c) Bandgar, B.P.; Patil, A.V. *Tetrahedron Lett.* **2007**, *48*, 173-176.

In an attempt to promote the formation of the proposed π-activated alkyne (Scheme 25), silver salts were employed as chloride abstractor agents to generate the corresponding cationic species more prone to π-coordinate the alkyne (Scheme 27).[144]



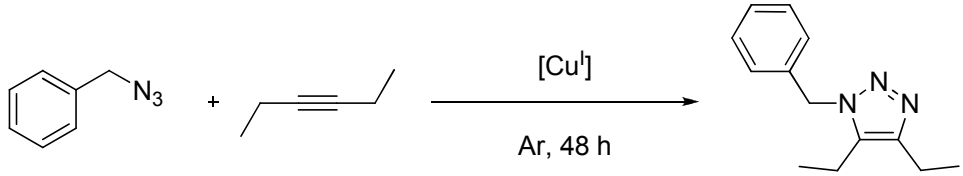
Scheme 27. Envisioned formation of the cationic complex $[Cu(IPr)]^+$ *via* silver salt abstraction of chloride.

The activity of the hypothetic cationic $[Cu(IPr)]^+$ generated by halide abstraction by $AgBF_4$ or $AgPF_6$ was studied in the cycloaddition reaction between benzyl azide and 3-hexyne (Table 10). Both coordinating and non coordinating solvents were tested. With $AgBF_4$, the minimum of solvent necessary to dissolve the catalyst was used in order to have conditions as close to those of the optimized neat system. With $AgPF_6$, the reaction mixture concentration was set at 1M.

In all cases, the precipitation of the silver chloride was observed pointing to the formation of the cationic complex. Nevertheless, this latter was either inactive or unstable. Indeed, the addition of silver salts led to the deactivation of the reaction. Traces of triazole **45** were only observed in the neat condition case (Table 10, entry 2). However, the conversion was identical to the one obtained in the absence of catalyst or additive (Table 9, entry 1). The cycloaddition reaction failed even in the presence of the cationic of the more active [CuCl(SIMes)] (Table 10, entries 9-10).

[144] (a) Liston, D.J.; Lee, Y.J.; Scheidt, W.R.; Reed, C.A. *J. Am. Chem. Soc.* **1989**, *111*, 6643-6648. (b) Albano, V.G.; Di Serio, M.; Monari, M.; Orabona, I.; Panunzi, A.; Ruffo, F. *Inorg. Chem.* **2002**, *41*, 2672-2677.

Table 10. Study of the cationic complex $[Cu(IPr)]^+$ activity.[a]



46

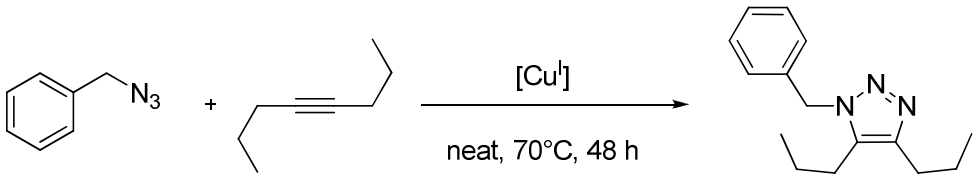
Entry	Catalyst (5 mol%)	Additives	Solvent	TºC	Conversion (%)[b]
1	[CuCl(IPr)]	$AgBF_4$	neat	r.t.	0
2	[CuCl(IPr)]	$AgBF_4$	neat	70ºC	7
3	[CuCl(IPr)]	$AgBF_4$	THF	r.t.	0
4	[CuCl(IPr)]	$AgBF_4$	THF	70ºC	0
5	[CuCl(IPr)]	$AgBF_4$	CH_2Cl_2	r.t.	0
6	[CuCl(IPr)]	$AgBF_4$	CH_2Cl_2	70ºC	0
7	[CuCl(IPr)]	$AgPF_6$	MeCN	70ºC	0
8	[CuCl(IPr)]	$AgPF_6$	THF	70ºC	0
9	[CuCl(SIMes)]	$AgPF_6$	MeCN	70ºC	0
10	[CuCl(SIMes)]	$AgPF_6$	THF	70ºC	0

[a] Reaction conditions using $AgBF_4$: benzyl azide (1 mmol), 3-hexyne (2 equiv), [CuCl(IPr)] (5 mol%), $AgBF_4$ (5 mol%), CH_2Cl_2 (0.2 mL) or THF (0.4 mL), Ar, Absence of light, 48 h. Reaction conditions using $AgPF_6$: benzyl azide (1 mmol), 3-hexyne (2 equiv), [CuCl(NHC)] (5 mol%), $AgPF_6$ (5 mol%), solvent (1 mL), Ar, 48 h. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product.

- Substrates screening

Since the optimization studies did not allow any improvements, the previous reaction conditions used with [CuX(NHC)] (5 mol%, neat, 70ºC) were applied to the synthesis of novel 1,4,5-trisubstituted-1,2,3-triazoles from diverse symmetrical internal alkynes. First, we investigated the reactivity of similar alkyl acetylene, hoping to have the same copper effect (Table 11). Compared to the results obtained with the 3-hexyne, the cycloaddition reaction between benzyl azide and 4-octyne did not proceed very well after 48 h at 70°C (entries 1 and 2), confirming the lower reactivity of electron-rich and bulky alkynes.[55] Unexpectedly, the conversion rate was not influenced by the presence of Cu^I complexes even with our best catalyst [CuBr(SIMes)] (entry 3).

Table 11. 1,3-dipolar cycloaddition of benzyl azide and 4-octyne.[a]



Entry	Catalyst (5 mol%)	Conversion (%)[b]
1	-	14
2	[CuCl(IPr)]	17
3	[CuBr(SIMes)]	8

[a] Reaction conditions: benzyl azide (1 mmol), 4-octyne (1.05 equiv), [CuX(NHC)] (5 mol%), T = 70°C. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product.

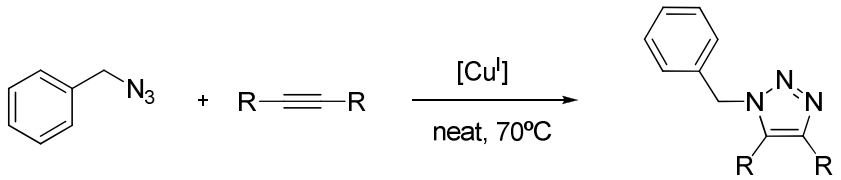
Then, we submitted symmetrical disubstituted alkynes bearing more electron-withdrawing groups to the [3+2] cycloaddition conditions (Table 12). In all cases, the observed conversions were identical after 24 hours with or without [CuCl(IPr)]. However, the copper(I) catalyst allowed for slightly faster conversions over 6 days (>10%). Of note, degradation of the final 4,5-dichloro-triazole product was observed in the media after few days at 70°C (entries 3-4). Once again, the reaction was slowed when using a hindered alkyne (entries 5-6).

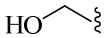
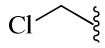
- Cu^{I}-effect on the regioselectivity

Even though NHC-Cu^{I}-catalyst had a weak effect on the conversion rate, we decided to examine the regioselectivity that could be induced by these catalysts on the cycloaddition reaction from unsymmetrical alkynes. 1-Phenyl-1-butyne was tested first in the [3+2] cycloaddition with the benzyl azide (Table 13). After 48 h at 70°C, the conversion was again equivalent with or without [CuCl(IPr)] (entries 1-2). The regioselectivity, in favour of the bulkier phenyl in 4-position (60%), was also identical in both entries and the *ratio* was found similar to the one reported for this type of phenyl alkyl triazole in presence of [Cp*RuCl(PPh$_3$)$_2$].[139] This result suggests that the metallic complex might activate the alkyne and thus accelerate the cycloaddition reaction but does not have an influence on the regioselectivity. We then expected that the encumbrance induced by the bulky IAd ligand in [(IAd)CuCl] (IAd = *N*,*N'*-di(adamantyl)imidazol-2-ylidene) could have an influence on the selectivity. Besides slowing the reaction, this catalyst did not have any effect on the

regioselectivity of the reaction (entry 3). Under microwave irradiation, the cycloaddition did not proceed at all in water (entries 4-5).

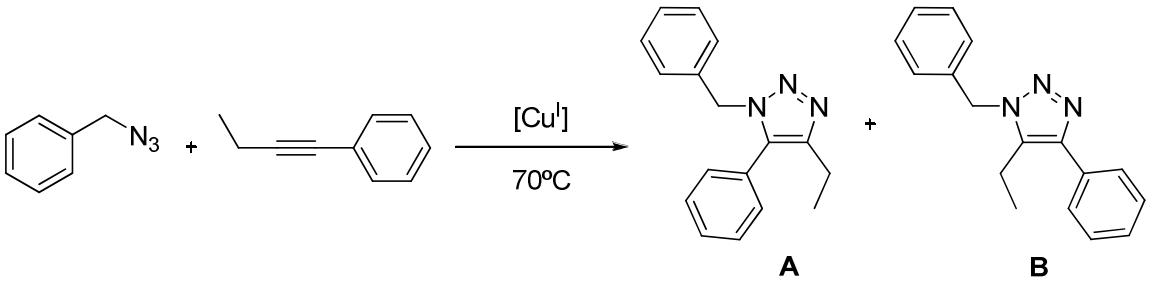
Table 12. 1,3-dipolar cycloaddition of benzyl azide and different symmetrical internal alkynes.[a]



Entry	R	Catalyst (5 mol%)	Time	Conversion (%)[b]
1		-	24 h 6 days	47 88
2		[CuCl(IPr)]	24 h 6 days	66 100
3		-	24 h 6 days	61 63[c]
4		[CuCl(IPr)]	24 h 6 days	61 71[c]
5		-	24 h 6 days	11 42
6		[CuCl(IPr)]	24 h 6 days	8 56

[a] Reaction conditions: benzyl azide (1 mmol), alkyne (1.05 equiv), [CuCl(IPr)] (5 mol%), T = 70°C. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product. [c] Degradation observed after several days at 70ºC.

Table 13. 1,3-dipolar cycloaddition of benzyl azide and the 1-phenyl-1-butyne.[a]

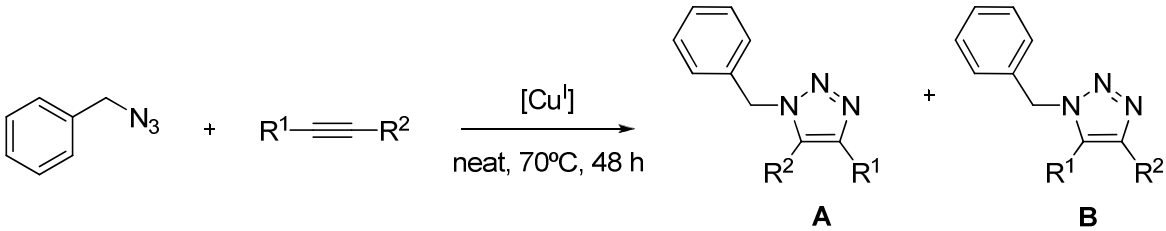


Entry	Catalyst (5 mol%)	Solvent	Time	Conversion (%)[c]	Regioselectivity **A**/**B**[c]
1	-	neat	48 h	24	40/60
2	[CuCl(IPr)]	neat	48 h	21	40/60
3	[CuCl(IAd)]	neat	48 h	10	40/60
4	[CuCl(IPr)]	H_2O, MW[b]	1 h	0	-
5	-	H_2O, MW[b]	1 h	0	-

[a] Reaction conditions: benzyl azide (1 mmol), 1-phenyl-1-butyne (1.05 equiv), [CuCl(NHC)] (5 mol%), T = 70°C, 48 h. [b] Reaction conditions under microwave irradiation (MW): benzyl azide (1 mmol), 1-phenyl-1-butyne (1.05 equiv), [CuCl(IPr)] (5 mol%), H_2O (1 mL), T = 70°C. [c] Conversions and regioselectivities are average of two runs and were determined by ^{1}H NMR of the crude product.

Unfortunately, the same trend was observed with other unsymmetrical disubstituted alkynes (Table 14). The NHC-copper(I) catalysts did not have any influence on the conversion rate or on the regioselectivity of the 1,3-dipolar cycloaddition. Even, [CuBr(SIMes)] showed poorer results than [CuCl(IPr)] (entries 7,10).

Table 14. 1,3-dipolar cycloaddition of benzyl azide and unsymmetrical internal alkynes.[a]



Entry	R^1	R^2	Catalyst (5 mol%)	Conversion (%)[b]	Regioselectivity **A**/**B**[b]
1	$HOCH_2$-	-Ph	-	54	40/60
2			[CuCl(IPr)]	49	40/60
3	$HOCH_2$-	$-CH_3$	-	22	40/60
4			[CuCl(IPr)]	30	40/60
5	$HO(CH_2)_2$-	-Et	-	33	40/60
6			[CuCl(IPr)]	33	40/60
7			[CuBr(SIMes)]	9	40/60
8	Pr-	-Et	-	20	nd
9			[CuCl(IPr)]	17	nd
10			[CuBr(SIMes)]	6	nd

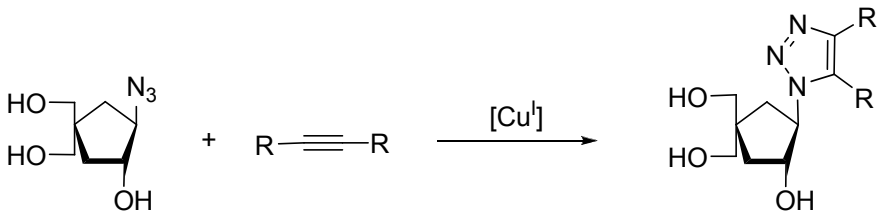
[a] Reaction conditions: benzyl azide (1 mmol), alkyne (1.05 equiv), [CuX(NHC)] (5 mol%), T = 70°C, 48 h. [b] Conversions and regioselectivities are average of two runs and were determined by ^{1}H NMR of the crude product. nd = not determined.

5.3. Reactivity of Azido-nucleosidic Analogues

Although the former results were disappointing, the good performance obtained with terminal alkynes prompted us to test the reactivity of the azidocarbanucleoside **(±)-6** with internal alkynes (Table 15). Moreover, contrary to benzyl azide that is an easy substrate for cycloadditions, the reaction between less activated azides like **(±)-6** and internal alkynes could be influenced by copper(I) complexes. Thus, we first tested the [CuBr(IMes)] with the previously optimized conditions for azide **(±)-6**. Of note, the physical properties of azide **(±)-6**

did not allow neat conditions. Unfortunately, no reaction of **(±)-6** with diphenylacetylene was observed (entry 1). We then applied different reaction conditions (catalyst, solvent and heating method) with a more reactive alkyne (entries 2-7). Once again, no conversion was detected with or without catalyst. Finally, the 1,4,5-trisubstituted-1,2,3-triazolo-carbnucleoside **(±)-47c** was successfully obtained in good yield in only one hour of microwave irradiation (entries 8-9). However, this reaction between the azide **(±)-6** and the strongly electron-deficient dimethyl acetylenedicarboxylate proceeded also under copper-free conditions at this temperature. Completion could be reached by using 1.1 equivalent of dimethyl acetylenedicarboxylate.

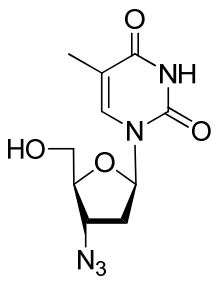
Table 15. Synthesis of 1,4,5-trisubstituted-1,2,3-triazolo-carbnucleosides.[a]



(±)-6 **(±)-47a-c**

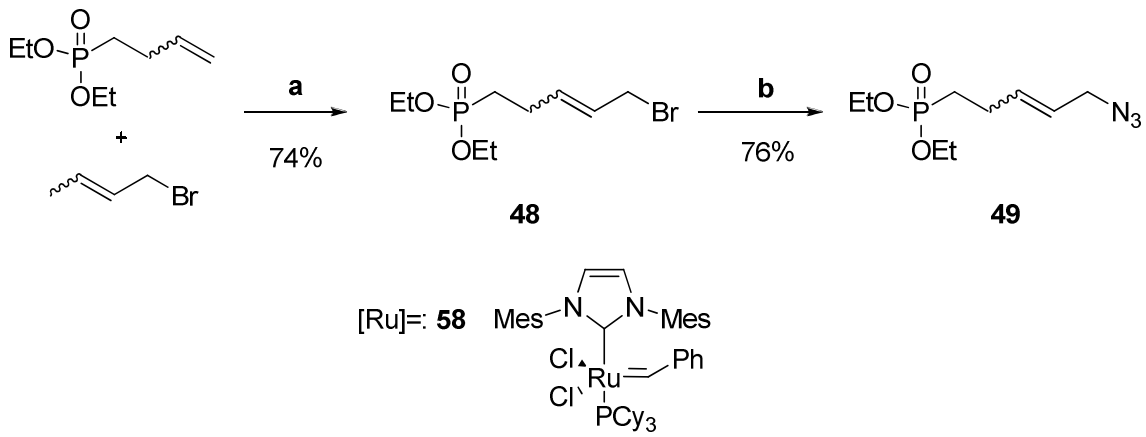
Entry	**(±)-47,** R=	Catalyst	Solvent	Conditions	Conversion (%)[b]
1	**(a)** -Ph	[CuBr(IMes)]	^{t}BuOH/H_2O 1/1	70°C, 24 h	0
2		-	^{t}BuOH/H_2O 1/1	70°C, 24 h	0
3		[Cu^0/$CuSO_4$]	^{t}BuOH/H_2O 1/1	70°C, 24 h	0
4	**(b)** -CH_2OH	[CuCl(IPr)]	^{t}BuOH/H_2O 1/1	70°C, 24 h	0
5		[CuCl(IPr)]	MeCN	70°C, 24 h	0
6		[CuCl(IPr)]	^{t}BuOH/H_2O 1/1	MW, 70°C, 1 h	0
7		[CuCl(IPr)]	^{t}BuOH/H_2O 1/1	MW, 125°C, 1 h	0
8	**(c)** -C(O)OMe	-	^{t}BuOH/H_2O 1/1	MW, 125°C, 1 h	88[c]
9		[CuBr(SIMes)]	^{t}BuOH/H_2O 1/1	MW, 125°C, 1 h	87

[a] Reaction conditions: azide **(±)-6** (0.1 mmol), alkyne (1.05 equiv), Cu^0 (80 mol%)/$CuSO_4$ (20 mol%) or [CuX(NHC)] (5 mol%), solvent (1 mL). MW = Microwave irradiation. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product. [c] 100% with alkyne (1.1 equiv).



AZT

Eventually, two last azido-nucleosidic analogues were tested for the [3+2] cycloaddition with 2-butyne-1,4-diol (Table 16). 3'-Azido-3'-deoxythymidine (AZT), known as potent HIV inhibitor,[145] is commercially available but it could also be synthesized by a simple and efficient reported procedure.[146] The synthesis of the azido-phosphonate **49** is depicted in Scheme 28. The olefin cross-metathesis reaction of crotyl bromide with diethyl-3-butenyl phosphonate afforded the desired diethyl 5-bromopent-3-enylphosphonate **48** in 74% yields as a mixture of *E*- and *Z*-isomers. The cross-metathesis and the catalyst **58** will not be presented herein but will be considered in details in the second chapter. The stereoisomers could not be separated by silica gel column chromatography. ^{1}H NMR analysis allowed for the determination of a *ratio* major/minor 85:15. Although the *E* isomer might probably be the major, the attribution *E*/*Z* was not possible. The azido-phosphonate **49** was obtained by substitution of the bromide by azide.[147]



Scheme 28. Reagents and conditions: (a) [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, 3 h. (b) NaN_3, CH_3CN, reflux, 2 days.

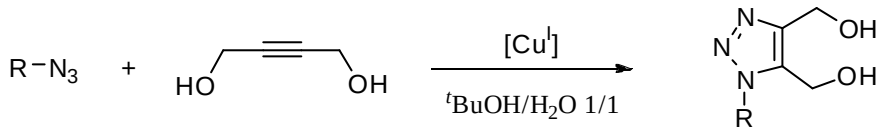
Neat condition being also impossible with these substrates, 1,3-dipolar cycloaddition reactions were performed in a 1/1 mixture ^{t}BuOH/water. [CuCl(IPr)] and [CuBr(SIMes)] were both inefficient (entries 1,3). Once again, the azido substrates might not be sufficiently activated to perform the cycloaddition reaction

[145] (a) Mitsuya, H.; Weinhold, K.J.; Furman, P.A.; St. Clair, M.H.; Nusinoff Lehrman, S.; Gallo, R.C.; Bolognesi, D.; Barry, D.W.; Broder, S. *P. Natl. Acad. Sci.USA* **1985**, *82*, 7096-7100. (b) Fischl, M.A.; Richman, D.D.; Grieco, M.H.; Gottlieb, M.S.; Volberding, P.A.; Laskin, O.L.; Leedom, J.M.; Groopman, J.E.; Mildvan, D.; Schooley, R.T.; et al *N. Engl. J. Med.* **1987**, *317*, 185-191.

[146] Czernecki, S.; Valery, J.M. *Synthesis* **1991**, 239-240.

[147] Laureyn, I.; Stevens, C.V.; Soroka, M.; Malysa, P. *Arkivoc* **2003**, *4*, 102-115.

Table 16. [3+2] Cycloaddition of azido-nucleoside analogues and 2-butyne-1,4-diol.[a]



Entry	Substrat	Catalyst (5 mol%)	Conditions	Conversion (%)[b]
1	**AZT**	-	70°C, 24 h	0
2		[CuBr(SIMes)]	70°C, 24 h	0
3	**49**	[CuCl(IPr)]	MW, 125°C, 5 h	0

[a] Reaction conditions: azide (0.1 mmol), 2-butyne-1,4-diol (1.05 equiv), [CuX(NHC)] (5 mol%), ^{t}BuOH/H_2O 1:1 (1 mL). MW = Microwave irradiation. [b] Conversions are average of two runs and were determined by ^{1}H NMR of the crude product.

5.4. Conclusion

In summary, the catalytic activity of the NHC-copper(I) complexes in the 1,3-dipolar cycloaddition of azide and internal alkynes were found to be non-existent or very low in some examples. Under thermal heating, both activated and non-activated disubstituted alkynes reacted with the benzyl azide to form the corresponding trisubstituted triazoles. However, the cycloaddition did not proceed with less active azide such as azido-nucleoside analogues unless a strong electron-deficient alkyne was used. Influence on the regioselectivity of the reaction was not observed when unsymmetrical alkynes were used. Conversion rates and selectivities were mainly governed by the substituents of the alkynes and the reaction conditions.

6. CONCLUSIONS AND PERSPECTIVES

In conclusion, we have conduced a thorough study of the synthesis of triazolo-carbanucleosides *via* copper(I)-catalyzed Huisgen cycloaddition with terminal and internal alkynes. We have demonstrated the beneficial effect of copper(I)-based catalysts and microwave irradiation in the preparation of 1,4-disubstituted-1,2,3-triazolo-carbanucleosides.[148] Shorter reaction times and higher conversions were hence obtained when compared to thermal heating. The best results were observed with the inexpensive $Cu^0/CuSO_4$ mixture. The presence of a NHC ligand on the copper center appears to enhance the catalytic

[148] Broggi, J.; Díez-González, S.; Petersen, J.L.; Berteina-Raboin, S., Nolan, S.P.; Agrofoglio, L.A. *Synthesis* **2008**, 141-148.

activity when compared to $[Cu(CH_3CN)_4]PF_6$. However, the cationic complex has the additional advantage of being efficient in both aqueous and organic media. As part of our smallpox drug discovery program, the optimized conditions were then applied to the versatile, simple and efficient synthesis of racemic and D-configured 1,4-disubstituted-triazolo-carbanucleosides.[149] Unfortunately, the novel racemic or enantiomerically pure carbanucleoside compounds did not show any cytotoxicity or significant antiviral activity on infected vaccinia virus cells. They were neither substrate for the human thymidine kinase nor for the human uracil cytosine kinase. Comparing the evaluated compounds to known anti-pox nucleosides, the structure-activity relationship study suggest that 1,4-disubstituted-1,2,3-triazoles are not adequate bases for smallpox inhibition. Extension of the study to the preparation of 1,4,5-trisubstituted-triazoles has shown that there is a negligible copper(I)-catalysts effect on the reaction between azides and symmetrical or unsymmetrical internal alkynes. Regioselectivity were not affected either.

In the domain of nucleoside chemistry, these original azido compounds could be important candidates and versatile precursors not only for cycloaddition with diverse dipolarophiles but also for various transformations involving azides[109] such as the Staudinger reduction for the preparation of iminophosphorane and primary amines, or the Curtius rearrangement for *iso*cyanates, or the Schmidt rearrangement for imines, etc.... The method optimized for the 1,3-dipolar cycloaddition of these azidocarbanucleosides with terminal alkynes could be applied to other azido-nucleoside analogues and thus could be an efficient tool for the synthesis of 1,2,3-triazolo-nucleosides. The preparation of 1,4,5-trisubstituted-triazolo-carbanucleosides is still an important challenge as the synthetic methods in this domain are still limited. Ruthenium-catalyzed 1,3-dipolar cycloaddition, that have shown some promising insights, should be an interesting way to access 1,4,5-trisubstituted-1,2,3-triazolo nucleosidic analogues.

From a biological point of view, the failure of our 1,4-disubstituted-triazolo-carbanucleosides as smallpox inhibitors prompted us to examine a different class of nucleosides that have also shown interesting activities in the search for anti-pox therapies : Acyclic nucleoside phosphonate analogues.

[149] (a) Broggi, J.; Joubert, N.; Díez-González, S.; Berteina-Raboin, S.; Zevaco, T.; Nolan, S.P.; Agrofoglio, L.A. *Tetrahedron* **2009**, *65*, 1162-1170. (b) Broggi, J.; Kumamoto, H.; Berteina-Raboin, S.; Nolan, S.P.; Agrofoglio, L.A. *Eur. J. Org. Chem.* **2009**, 1880-1888.

7. Résumé du chapitre I:

La cycloaddition alcyne–azidure, un outil efficace pour la synthèse de 1,2,3-triazolo-carbanucléosides

Ces dernières décennies, l'émergence des maladies virales comme première cause mondiale de mortalité a multiplié le développement de nouveaux agents thérapeutiques parmi lesquels les nucléosides sont largement représentés. Divers carbanucléosides comprenant une partie 1,2,3-triazole, présentés comme analogues de la ribavirine, ont été synthétisés et ont montré des activités anti-virales intéressantes contre le VIH-1,[52] le virus varicella-zoster,[53] ou le virus de la vaccine.[54] L'enjeu pharmaceutique de concevoir de nouveaux agents anti-viraux plus efficaces et moins toxiques nous a encouragé à optimiser et étendre la synthèse de cette classe de 1,2,3-triazolo-carbanucléosides *via* la cycloaddition 1,3-dipolaire de Huisgen catalysée par du Cu^{I}.

La cycloaddition 1,3-dipolaire développée par Rolf Huisgen[55] est une manière efficace, reproductible et rapide de générer une large variété d'hétérocycles à 5 chaînons. La plus étudiée étant la réaction entre un azidure et une alcyne terminale qui permet la formation de 1,2,3-triazoles, connus pour leurs propriétés antivirales et antibiotiques.[56] La découverte en 2002 des catalyseurs au cuivre de degré d'oxydation (I)[58,59] a permit une réaction rapide et régiosélective qui produit exclusivement le composé disubstitué en position 1,4 contrairement au mélange de régioisomères 1,4- et 1,5- observé par chauffage classique (Schéma 1).[55,57] Cette cycloaddition 1,3-dipolaire d'alcyne-azidure catalysée par le cuivre (I) est actuellement l'approche la plus générale et efficace pour la préparation de dérivés 1,2,3 triazoles 1,4-disubstitués. L'espèce catalytique Cu^{I} active[72] peut être directement formée par addition d'un ligand sur un sel de cuivre(I),[59,73] ou préparée *in situ* par réduction d'un sel de Cu^{II},[57,58] par oxydation du métal Cu^{0},[66] ou par comproportionation de Cu^{II}/Cu^{0}.[57,58,74] Parmi les catalyseurs de cuivre(I) bien définis, les complexes portant un ligand stabilisateur de type carbène *N*-hétérocyclique (CNH) ont prouvé être des espèces hautement stables ayant des activités catalytiques significatives dans diverses réactions.[88] En plus de leur efficacité dans la réaction entre un alcyne terminal et un azidure, ils ont permis notamment les premiers exemples de cycloaddition par catalyse au cuivre(I) avec des alcynes internes.[93]

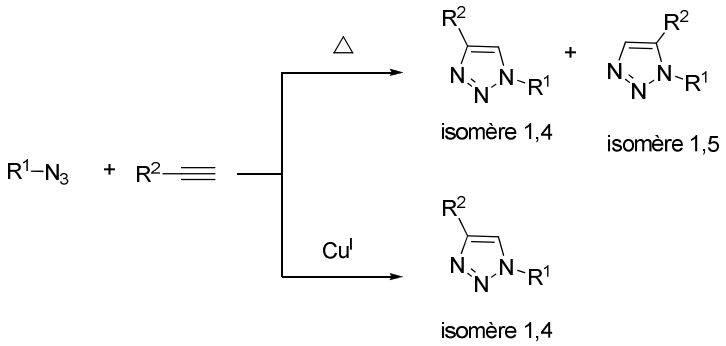


Schéma 1. Cycloaddition de Huisgen par voie thermique ou par catalyse au cuivre.

Pour développer ce nouvel outil simple et optimum adapté à la préparation de (±)-1,2,3-triazolo-carbanucléosides 1,4-disubstitués, nous avons étudié l'activité de trois systèmes au cuivre dans la cycloaddition 1,3-dipolaire de Huisgen. Les complexes de Cu^I $[Cu(CH_3CN)_4PF_6]$ et [CuBr(IMes)], et le mélange $Cu^0/CuSO_4$ ont été choisi pour cette étude. Leur influence a été analysée en fonction du substituent de l'alcyne, du solvant et de la méthode de chauffage. L'intermédiaire azidure **(±)-6** a été obtenu *via* une synthèse malonique[96] puis par ouverture nucléophilique de l'époxyde contraint **8** (Schéma 2).

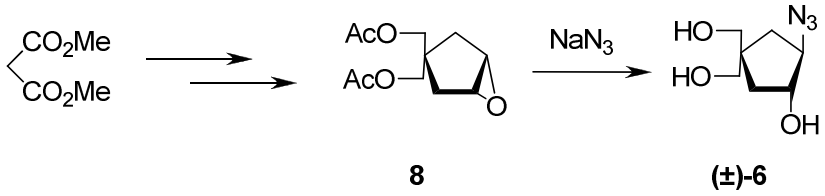
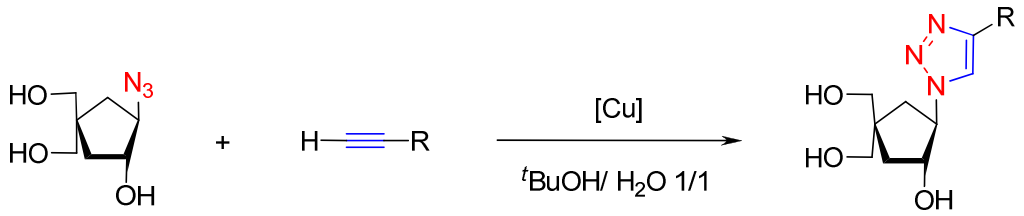


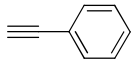
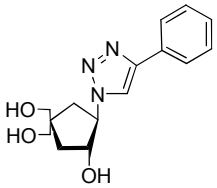
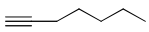
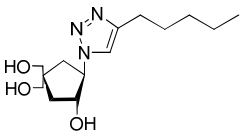
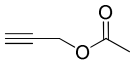
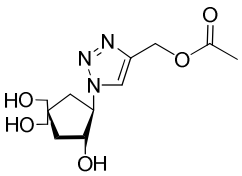
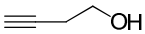
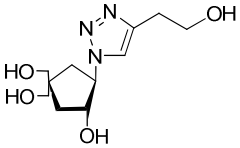
Schéma 2. Synthèse de l'azidocarbanucléoside **(±)-6**.

A partir de l'azidure **(±)-6** et différentes alcynes terminales substituées par des groupements aryles, alkyles ou fonctionnalisées, divers 1,2,3-triazolo-carbanucléosides substitués en position 1,4 ont été préparés avec succès (**(±)-9-12**). Les trois systèmes catalytiques ont été utilisés sous chauffage classique (75°C) ou micro-onde (125°C) (Tableau 1). L'irradiation micro-onde a eu un effet favorable évident en terme de temps et de rendement de réaction quelque soit le catalyseur (exemple entrée 2). Similairement à la littérature,[55,102] les alcynes déficientes en électron (entrées 3,4) ont été plus réactives que celles riches en électron (entrées 1,2). Comparé au complexe de cuivre $[Cu(CH_3CN)_4PF_6]$, les temps de réaction ont été réduits lorsque le complexe [CuBr(IMes)] était utilisé suggérant un effet stabilisateur bénéfique du ligand CNH lors de la cycloaddition (entrées 2,3,4). Quelque soit la méthode de chauffage et l'alcyne, les meilleurs résultats ont été obtenus avec $Cu^0/CuSO_4$ comme catalyseur précurseur. Ce système a l'avantage d'être peu coûteux et facilement éliminé par extraction du mélange réactionnel final. Cependant, il est limité à des substrats compatibles avec un milieu aqueux.

Tableau 1. Cycloaddition de Huisgen entre l'azidure **(±)-6** et différentes alcynes.[a,b]



(±)-6 **(±)-9-12**

Entrée	Alcyne	Triazole		Cu^0 (80 mol%) $CuSO_4$ (20 mol%)	$[Cu(CH_3CN)_4PF_6]$ (5 mol%)	[CuBr(IMes)] (5 mol%)
1		 **(±)-9**	Δ	**40 min**	**13 h**	**5 jours**
			conv (%)	100	100	95
			rdt (%)	98	99	91
			MO	**2 min**	**15 min**	**9 h**
			conv (%)	100	100	100
			rdt (%)	98	98	94
2		 **(±)-10**	Δ	**5 jours**	**5 jours**	**5 jours**
			conv (%)	80	0	51
			rdt (%)	75	0	40
			MO	**1 h**	**10 h**	**2 h**
			conv (%)	100	79	100
			rdt (%)	98	60	93
3		 **(±)-11**	Δ	**< 1 min**	**5 jours**	**2 h**
			conv (%)	100	73	100
			rdt (%)	96	17	70
			MO	**< 1 min**	**2 min**	**5 min**
			conv (%)	100	100	100
			rdt (%)	95	92	93
4		 **(±)-12**	Δ	**2 min**	**5 jours**	**1 h**
			conv (%)	100	75	100
			rdt (%)	95	71	96
			MO	**2 min**	**2 h**	**15 min**
			conv (%)	100	100	100
			rdt (%)	95	92	96

[a] Conditions réactionnelles: azidure **(±)-6** (0.27 mmol), alcyne (1.05 équiv.), $^tBuOH/H_2O$ 1:1 (2 mL); Micro-onde (MO): T = 125°C, Chauffage thermal (Δ): T = 75°C. [b] Les conversions sont une moyenne d'au moins deux essais et ont été déterminées par RMN ^1H du produit brut.

Alternativement, les réactions de cycloaddition ont pu être menées dans des solvants organiques en présence d'une quantité sub-stoechiométrique de $[Cu(CH_3CN)_4PF_6]$ ou [CuBr(IMes)]. Les premiers essais ont montré que le complexe CNH était moins efficace dans l'eau ou dans un mélange CH_2Cl_2/MeOH que dans ^{t}BuOH/H_2O. Par contre $[Cu(CH_3CN)_4PF_6]$ a pu être utilisé avec succès dans les deux types de milieu : CH_2Cl_2/MeOH et ^{t}BuOH/H_2O. Les rendements étaient similaires dans les deux solvants. Cependant, il a été observé que la réactivité des alcynes change en fonction du solvant. Les conditions de réaction optimisées ont été efficacement appliquées à la synthèse de trois autres composés triazolo-carbocyclique **(±)-13-15** de cette série racémique (Schéma 3). La deacylation du triazole **(±)-11** dans une solution d'ammoniaque a fourni l'hydroxymethyle correspondant **(±)-16** (Schéma 4).

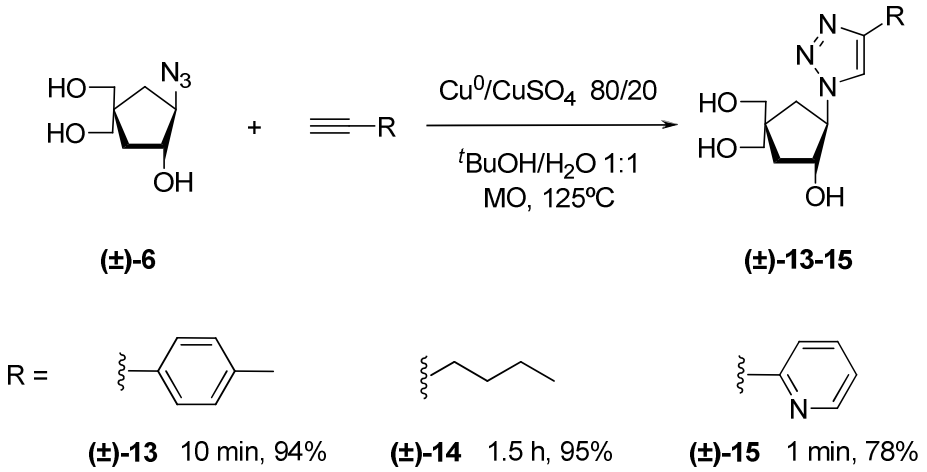


Schéma 3. Cycloaddition 1,3-dipolaire catalysée par $Cu^0/CuSO_4$ et assistée par micro-onde.

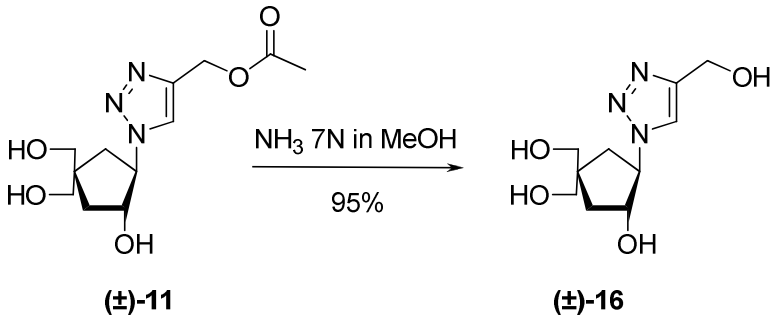


Schéma 4. Synthèse du dérivé hydroxymethyl **(±)-16**.

Dans le but d'exemplifier la méthode, cette procédure simple et efficace, optimisée par l'effet bénéfique d'un catalyseur de cuivre(I) et du chauffage micro-onde a été ensuite appliquée à la synthèse de triazolo-carbanucléosides en série énantiosélective.

Récemment, des énantiomères de configuration D de nucléosides carbocycliques ont montré de meilleures activités anti-virales que leurs analogues de configuration L.[106] La synthèse énantiospécifique de carbanucléosides est donc d'un grand intérêt pour l'exploration

de cette classe de composés.[108] Cependant, il existe actuellement peu de méthode pratique pour une large préparation stéréospécifique d'intermédiaires optiquement actifs. Nous avons donc réenvisagé une synthèse plus efficace et rapide de l'azido-carbanucléoside **31**[109] *via* une métathèse de fermeture de cycle et des réactions de Wittig et de Mitsunobu stéréocontrolées (Schéma 5). Cet intermédiaire azidure **31** optiquement actif a ensuite été engagé dans une réaction de cycloaddition 1,3 dipolaire avec plusieurs alcynes terminaux selon les conditions optimales précédemment établies (Schéma 6). Après déprotection, les D-1,2,3-triazolo-carbanucléosides 1,4-disubstitués (**38-43**) ont été obtenus avec des rendements modérés à excellent et énantiopures.

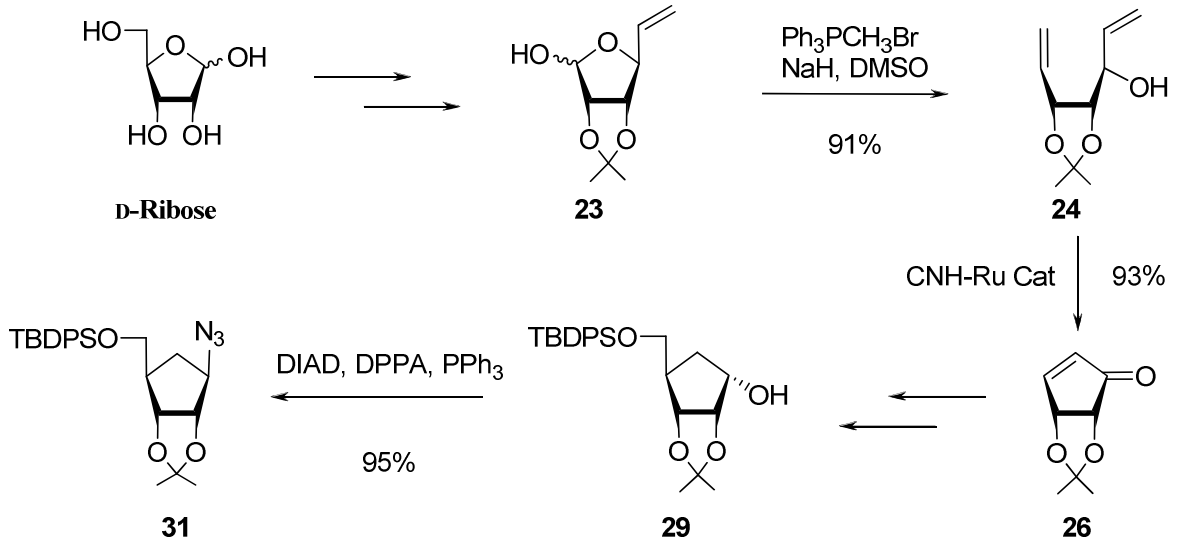


Schéma 5. Synthèse de l'intermédiaire azidure optiquement actif **31**.

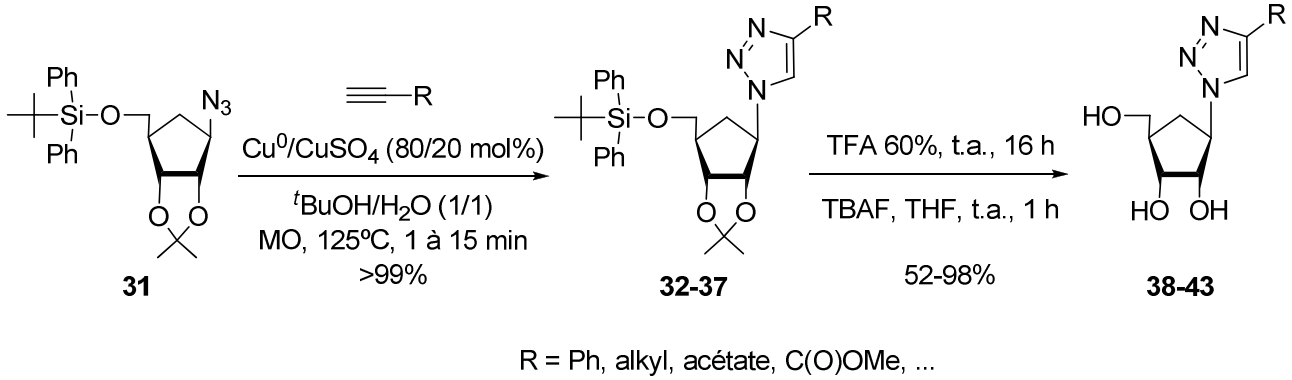


Schéma 6. Synthèse des D-triazolo-carbanucléosides 1,4-disubstitués **38-43**.

Finalement, l'efficacité et la généralité de la méthode optimisée pour la préparation de triazolo-carbanucléosides 1,4-disubstitués nous ont encouragés à tester la réactivité de complexes de cuivre(I) dans la synthèse de 1,2,3-triazoles 1,4,5-trisubstitués *via* la cycloaddition de Huisgen. Seulement deux exemples de cycloaddition catalysée au cuivre entre un azidure et un alcyne interne ont été reportés dans la litérature.[93,141] Afin d'évaluer le

domaine d'application et les limitations de cette réaction, nous avons donc entrepris d'évaluer l'activité catalytique de complexes Cu^{I}-CNH dans la cycloaddition entre l'azidure de benzyle et diverses alcynes internes symétriques ou asymétriques (Schéma 7).

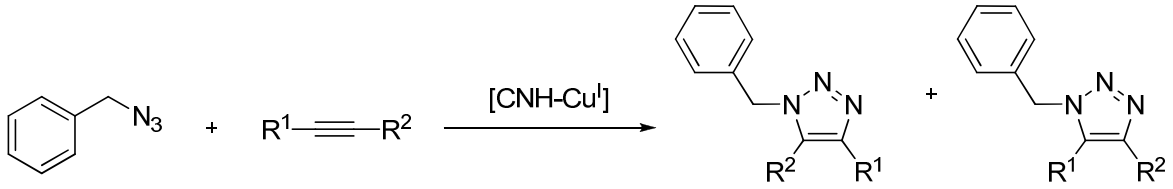


Schéma 7. Cycloaddition 1,3-dipolaire entre l'azidure de benzyle et des alcynes internes.

Plusieurs complexes de cuivre(I) contenant un ligand CNH ainsi que différentes conditions réactionnelles ou additifs ont été étudiés. Malheureusement, ces complexes de CNH-cuivre(I) n'ont eu aucune influence ni sur le déroulement ni sur la régioselectivité de la réaction de cycloaddition. Les taux de conversion étaient similaires avec ou sans catalyseur. Des substrats azidure de type nucléosidique, moins réactifs que l'azidure de benzyle, ont également été testés. Seulement dans un cas d'alcynes disubstitués (fortement déficient en électron), un triazole trisubstitué a pu être isolé; toutefois, il s'est avéré que le cuivre ne catalysait pas cette réaction.

En conclusion, nous avons développé un outil simple et efficace pour la synthèse de 1,2,3-triazolo-carbanucléosides 1,4-disubstitués *via* une cycloaddition 1,3-dipolaire de Huisgen catalysée par du cuivre(I) et assistée par irradiations micro-ondes.[148] Cette méthode a été appliquée à la préparation d'une série racémique et d'une série enantiopure de nouveaux analogues carbanucléosidiques.[149] Tous ces composés ont été testés contre des cellules infectées par les virus de la vaccine et du cowpox afin de déterminer leurs activités anti-virales et leurs toxicités cellulaires. Malheureusement, aucun des composés synthétisés ne s'est avéré inhibiteurs *in vitro* de ces virus. Les complexes de CNH-cuivre(I) n'ont révélé aucune activité catalytique sur le déroulement de la réaction de cycloaddition d'alcynes internes. Les taux de conversion et la régiosélectivité étaient principalement influencés par les substituents de l'alcyne et les conditions de la réaction.

Chapter I:

Alkyne - azide cycloaddition, an efficient tool for 1,2,3-triazolo-carbanucleoside synthesis

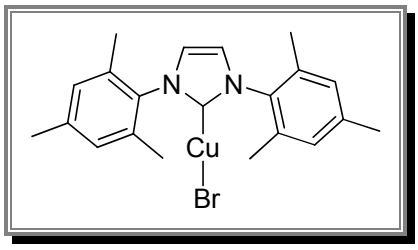
Experimental section

General methods

Commercially available chemicals were used as received. Microwave reactions were carried out in a Biotage AB Initiator EXP EU with a maximum power of 300W. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}). Compounds were visualized by UV irradiation and/or spraying with ethanol solution 2.5% in phosphomolybdic acid, followed by charring at 150°C. Column chromatography was performed on silica gel 60 M (0.040–0.063 mm). ^{1}H NMR spectra were recorded on 250 MHz, 300 MHz or 400 MHz spectrometers, and ^{13}C NMR on 62.9 MHz, 100 MHz or 125 MHz spectrometers at room temperature, using deuterated solvents as internal standard. Chemical shifts are given in ppm and multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), q_i (quintuplet) and m (multiplet). Assignments of NMR spectra follow standard nucleosides nomenclature: triazole bases are numbered from *N*-1 to *C*-5 and carbocycles are numbered from *C*-1' to *C*-7' with *C*-5' and *C*-7' for the two 4'-hydroxymethyl chains in the racemic series and from *C*-1' to *C*-6' with *C*-5' for the 4-hydroxymethyl chain in the optically active series. Similar conventions apply for the corresponding hydrogen atoms. HRMS analyses were performed by the Mass Spectrometry Facility of the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain).

2. STUDY OF DIFFERENT COPPER(I) CATALYSTS FOR THE 1,3-DIPOLAR CYCLOADDITION OF (±)-1,4-DISUBSTITUTED-1,2,3-TRIAZOLO CARBANUCLEOSIDES

[CuBr(IMes)]



Procedure:

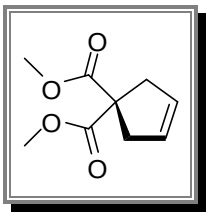
Inside a glovebox, copper(I) bromide (0.520 g, 3.63 mmol, 1.4 equiv), IMes·HCl (0.848 g, 2.52 mmol) and sodium *tert*-butoxide (0.243 g, 2.52 mmol, 1 equiv) were loaded in a vial and stirred in dry THF (18 mL) overnight at room temperature outside the glovebox. After filtration of the reaction mixture over a plug of celite (THF), the filtrate was mixed with pentane to form a precipitate. A second filtration afforded the title complex as an off-white complex (0.70 g, 62%).

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.01 (s, 4H, H^{Ar} + NC*H*=), 2.36 (s, 6H, CH_3), 2.12 (s, 12H, CH_3).

^{13}C NMR: (125 MHz, $CDCl_3$): δ 180.0 (C, N*C*N), 139.4 (C, C^{Ar}), 135.0 (C, C^{Ar}), 134.5 (CH, C^{Ar}), 129.4 (CH, C^{Ar}), 122.2 (CH, N*C*H=), 21.1 (CH_3), 17.7 (CH_3).

Elemental analysis: calcd for $C_{21}H_{24}BrCuN_2$ (447.88): C, 56.32, H, 5.40, N, 6.25. Found: C, 56.61, H, 5.66, N, 6.20.

Dimethyl-cyclopent-3-ene-1,1-dicarboxylate (1)



Procedure:

To a stirred solution of dimethyl malonate (11.4 mL, 0.1 mol) in DMF (150 mL) at 0°C, lithium hydride (2.00 g, 0.25 mol, 2.5 equiv) was added. The reaction mixture was stirred at 0ºC for 4 h. Then, *cis*-1,4-dichloro-2-butene (12.6 mL, 0.12 mol, 1.2 equiv) was added and the mixture was allowed to warm up to room temperature. After 3 days, the resulting solution was cooled at 0ºC, diluted with petroleum ether/Et_2O 8:2 (100 mL) and poured into cold water (50 mL). The aqueous layer was extracted with petroleum ether/Et_2O 8:2 (4 x 50 mL), the combined organic layers were washed with an aqueous solution saturated in $NaHCO_3$ (3 x 50 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was triturated with pentane and dried to give compound **1** as a white crystalline solid (18.20 g, 99%).

^{1}H NMR: (250 MHz, $CDCl_3$) δ 5.57 (s, 2H, HC=), 3.70 (s, 6H, CH_3O), 2.98 (s, 4H, CH_2).

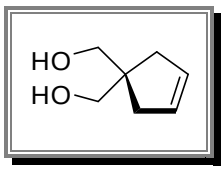
^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 172.7 (C=O), 127.8 (C=), 58.8 (C), 52.9 (OCH_3), 41.0 (CH_2).

HRMS (ESI): *m/z* calcd for $C_9H_{12}O_4Na$ (M^+ + Na) 207.0633, found 207.0633.

IR: (KBr) 1731 cm^{-1} (C=O), 1435 cm^{-1} (C=C).

CAS: 84646-68-4

Cyclopent-3-ene-1,1-diyldimethanol (2)



Procedure:

To a suspension of $LiAlH_4$ (2.04 g, 54 mmol, 3.4 equiv) in 50 mL of diethyl ether stirred at 0°C under argon atmosphere, a solution of **1** (2.90 g, 15.7 mmol) in 20 mL of diethyl ether was added dropwise. The mixture was stirred for 1 h at room temperature. Then, at 0°C, water (2 mL), an aqueous solution 3 N in NaOH (2 mL) and water (6 mL) were successively added dropwise and stirring was continued for 15 min more. The resulting mixture was then filtered over celite and rinsed several times with diethyl ether. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Compound **2** was obtained as a white solid (1.72 g, 85%).

^{1}H NMR: (250 MHz, $CDCl_3$) δ 5.61 (s, 2H, HC=), 3.68 (s, 2H, C*H*$_2$OH), 3.67 (s, 2H, C*H*$_2$OH), 2.81 (bs, 2H, OH), 2.22 (s, 4H, CH_2).

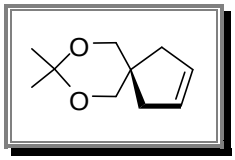
^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 128.6 (C=), 68.0 (CH_2OH), 47.6 (C), 38.5 (CH_2).

HRMS (ESI): *m/z* calcd for $C_7H_{12}O_2Na$ (M^+ + Na) 151.0735, found 151.0735.

IR: (KBr) 3301 cm^{-1} (OH).

CAS: 76910-02-6

8,8-Dimethyl-7,9-dioxa-spiro[4.5]dec-2-ene (3)



Procedure:

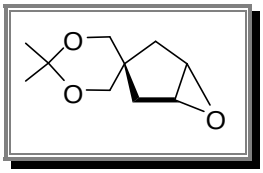
To a solution of **2** (1.72 g, 13 mmol) in DMF (10 mL), maintained at 0°C under argon atmosphere, 2-methoxypropene (2.6 mL, 27 mmol, 2 equiv) and a small amount of *p*-toluenesulfonic acid were added. After 16 h stirring at room temperature, a small amount of $NaHCO_3$, water (60 mL) and EtOAc (50 mL) were added to the reaction mixture. The aqueous layer was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was finally dried over $MgSO_4$, filtered, and concentrated under reduced pressure (Caution, product **3** is volatile). The product **3** was obtained as a yellow oil (2.03 g, 90%).

^{1}H NMR: (250 MHz, $CDCl_3$) δ 5.61 (s, 2H, HC=), 3.67 (s, 4H, CH_2O), 2.25 (s, 4H, CH_2), 1.43 (s, 6H, CH_3).

^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 128.8 (C=), 97.8 (*C*$(CH_3)_2$), 69.5 (CH_2O), 40.9 (C), 40.3 (CH_2), 24.0 (CH_3).

CAS: 391612-66-1

2-Methoxy-8,8-dimethyl-7,9-dioxa-spiro[4.5]decane (4)



Procedure:

To a solution of **3** (2.03 g, 12 mmol) in CH_2Cl_2 (40 mL) under argon atmosphere, 3-chloroperoxybenzoic acid 77% (4.06 g, 18 mmol, 1.5 equiv) was added at 0°C. The reaction mixture was stirred at room temperature for 4 days before pouring CH_2Cl_2 (50 mL). The resulting solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and the aqueous layer was then extracted with CH_2Cl_2 (4 x 50 mL). The combined organic

layers were washed with a saturated aqueous solution of $NaHCO_3$ (3 x 50 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (50 mL). Finally, the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain compound **4** as a yellow solid (2.22 g, 100%).

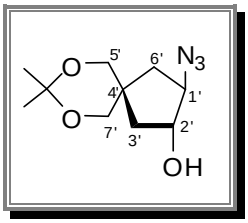
^{1}H NMR: (250 MHz, $CDCl_3$) δ 3.45 (s, 2H, CH_2O), 3.39 (s, 2H, CH_2O), 3.32 (s, 2H, CH), 1.92 (d, 2H, *J* = 14.8 Hz, C*H*H), 1.36 (d, 2H, *J* = 14.8 Hz, CH*H*), 1.22 (s, 6H, CH_3).

^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 96.8 ($C(CH_3)_2$), 70.0 (CH_2O), 69.0 (CH_2O), 57.0 (CH), 39.1 (C), 34.6 (CH_2), 23.3 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{10}H_{17}O_3$ (M^+ + H) 185.1178, found 185.1173.

CAS: 391612-66-1

(±)-3-Azido-8,8-dimethyl-7,9-dioxa-spiro[4.5]decan-2-ol (5)



Procedure:

To a solution of **4** (1.34 g, 7.3 mmol) in a mixture 8:2 of MeOH/H_2O (80 mL), sodium azide (0.95 g, 14 mmol, 2 equiv) was added. The reaction mixture was refluxed for 3 days and solvents were evaporated under reduced pressure. The oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:5 to 2:8) to yield **(±)-5** as a yellow oil (1.49 g, 90%).

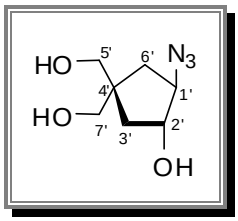
^{1}H NMR: (250 MHz, $CDCl_3$) δ 4.08 (q, 1H, *J* = 6.0 Hz, $H^{1'}$), 3.76 (q, 1H, *J* = 6.0 Hz, $H^{2'}$), 3.68-3.55 (m, 4H, $H^{5'}$ + $H^{7'}$), 2.10 (dd, 1H, *J* = 14.2, 6.0 Hz, $H^{3'}$), 1.94 (dd, 1H, *J* = 14.2, 6.0 Hz, $H^{6'}$), 1.60-1.49 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.40 (s, 6H, CH_3).

^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 98.0 ($C(CH_3)_2$), 76.4 (CH, $C^{1'}$), 70.1 (CH_2, $C^{5'}$), 70.0 (CH_2, $C^{7'}$), 67.5 (CH, $C^{2'}$), 39.2 (CH_2, $C^{6'}$), 38.7 (C, $C^{4'}$), 36.1 (CH_2, $C^{3'}$), 24.4 (CH_3), 23.3 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{10}H_{18}N_3O_3$ (M^+ + H) 228.1348, found 228.1351.

IR: (neat) 3418 cm^{-1} (OH), 2106 cm^{-1} (N_3).

(±)-2-Azido-4,4-bis-hydroxymethyl-cyclopentanol (6)



Procedure:

To a solution of **8** (0.65 g, 2.9 mmol) in a MeOH/H_2O 8:2 mixture (20 mL), sodium azide (0.37 g, 5.8 mmol, 2 equiv) were added. The reaction mixture was refluxed for 4 h. Then, solvents were evaporated under reduced pressure and the oily residue was purified by silica gel column chromatography (petroleum ether /EtOAc 5:5 to 2:8) to yield **(±)-6** as a colorless oil (0.50 g, 93%).

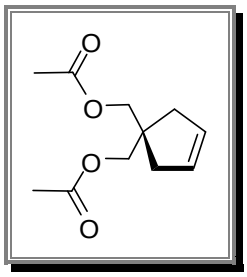
^{1}H NMR: (250 MHz, CD_3OD) δ 3.94 (q, 1H, *J* = 7.2 Hz, $H^{1'}$), 3.67 (q, 1H, *J* = 7.6 Hz, $H^{2'}$), 3.44 (s, 2H, $H^{5'}$), 3.40 (s, 2H, $H^{7'}$), 1.92 (dd, 1H, *J* = 13.7 and 7.4 Hz, $H^{3'}$), 1.87 (dd, 1H, *J* = 13.5 and 7.2 Hz, $H^{6'}$), 1.49-1.40 (m, 2H, $H^{6'}$+ $H^{3'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 77.2 (CH, $C^{1'}$), 68.9 (CH, $C^{2'}$), 68.0 (CH_2, $C^{5'}$), 67.9 (CH_2, $C^{7'}$), 46.1 (C, $C^{4'}$), 38.3 (CH_2, $C^{6'}$), 34.4 (CH_2, $C^{3'}$).

HRMS (ESI): *m/z* calcd for $C_7H_{13}N_3O_3Na$ (M^+ + Na) 210.0855, found 210.0854.

IR: (neat) 3340 cm^{-1} (OH), 2108 cm^{-1} (N_3).

Cyclopent-3-ene-1,1-diylbis(methylene) diacetate (7)



Procedure:

To a solution of **2** (0.5 g, 3.9 mmol) in pyridine (5 mL) under argon atmosphere, acetic anhydride (0.74 mL, 7.8 mmol, 2 equiv) was added at 0°C. The reaction was stirred for 3 h at room temperature, and then the solvent was coevaporated with toluene to obtain compound **7** as a yellow oil (0.75 g, 90%).

^{1}H NMR : (250 MHz, $CDCl_3$) δ 5.61 (s, 2H, HC=), 4.04 (s, 4H, CH_2O), 2.25 (s, 4H, CH_2), 2.06 (s, 6H, CH_3).

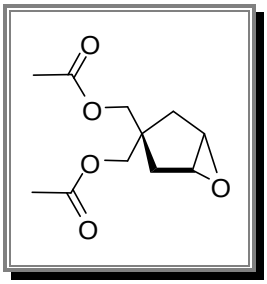
^{13}C NMR : (62.9 MHz, $CDCl_3$) δ 171.4 (C=O), 128.7 (C=), 67.3 (CH_2O), 44.9 (C), 39.2 (CH_2), 21.0 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}O_4Na$ (M^+ + Na) 235.0946, found 235.0939.

IR: (neat) 1724 cm^{-1} (C=O), 1240 cm^{-1} (CO).

CAS: 76910-03-7

6-Oxabicyclo[3.1.0]hexane-3,3-diylbis(methylene) diacetate (8)



Procedure:

To a solution of **7** (0.75 g, 3.5 mmol) in CH_2Cl_2 (8 mL), 3-chloroperoxybenzoic acid 77% (1.19 g, 5.3 mmol, 1.5 equiv) was added at 0°C under argon atmosphere. The mixture was stirred at room temperature. After 72 h of reaction, CH_2Cl_2 (20 mL) was poured and the resulting solution was washed with an aqueous saturated $Na_2S_2O_3$ solution (2 x 20 mL). The aqueous layer was then extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with an aqueous saturated $NaHCO_3$ solution (3 x 20 mL) and an aqueous saturated $Na_2S_2O_3$ solution (30 mL). Finally, the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:2 to 5:5) to give **8** as a colorless oil (0.65 g, 80%).

^{1}H NMR: (250 MHz, $CDCl_3$) δ 3.95 (s, 2H, CH_2O), 3.89 (s, 2H, CH_2O), 3.49 (s, 2H, CH), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.96 (d, 2H, J = 14.8 Hz, CH_aH_b), 1.64 (d, 2H, J = 14.8 Hz, CH_aH_b).

^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 171.1 (C=O), 170.9 (C=O), 68.5 (CH_2O), 67.8 (CH_2O), 58.1 (CH), 43.9 (C), 33.7 (CH_2), 20.9 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}O_5Na$ (M^+ + Na) 251.0895, found 251.0900.

IR: (neat) 1738 cm^{-1} (C=O), 1232 cm^{-1} (COC).

CAS: 76910-04-8

(±)-9-12: General procedures for the 1,3-dipolar cycloaddition under microwave irradiation

Using $Cu^0/CuSO_4$. A solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, copper powder (13.5 mg, 80 mol%), a water solution 1 M of copper sulfate (54 μL, 20 mol%) and the alkyne (1.05 equiv) were added in turn. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125°C. Upon completion of the reaction, the vial was cooled to 50°C by air jet cooling before being opened.

Using $[Cu(CH_3CN)_4]PF_6$. A solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH or CH_2Cl_2/MeOH 95:5 (2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, tetrakis(acetonitrile)copper hexafluorophosphate (5 mg, 5 mol%) and the alkyne (1.05 equiv) were added in turn. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125°C. Upon completion of the reaction, the vial was cooled to 50°C by air jet cooling before being opened.

Using [CuBr(IMes)]. A solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, [CuBr(IMes)] (6 mg, 5 mol%) and the alkyne (1.05 equiv) were added in turn. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125°C. Upon completion of the reaction, the vial was cooled to 50°C by air jet cooling before being opened.

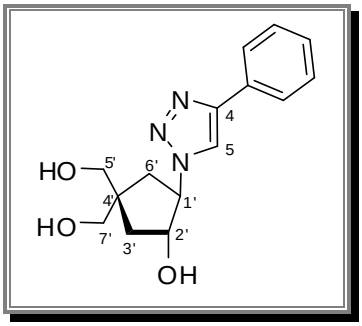
(±)-9-12: General procedures for the 1,3-dipolar cycloaddition under thermal heating

Using $Cu^0/CuSO_4$. Using a carousel reaction station, a solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) was prepared in a test tube. Copper powder (13.5 mg, 80 mol%), a water solution 1 M of copper sulfate (54 µL, 20 mol%) and the alkyne (1.05 equiv) were added in turn. The reaction mixture was then heated at 75°C.

Using $[Cu(CH_3CN)_4]PF_6$. In a carousel reaction station, a solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) was prepared in a reaction tube. Tetrakis(acetonitrile)copper hexafluorophosphate (5 mg, 5 mol%) and the alkyne (1.05 equiv) were added in turn. The mixture was then heated by at 75°C.

Using [CuBr(IMes)]. In a carousel reaction station, a solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) was prepared in a reaction tube. [CuBr(IMes)] (6 mg, 5 mol%) and the alkyne (1.05 equiv) were added in turn. The reaction mixture was then heated at 75°C.

(±)-4,4-Bis(hydroxymethyl)-2-(4-phenyl-*1H*-1,2,3-triazol-1-yl)cyclopentanol (9)



Procedure:

The title compound was prepared from 31 µL of phenylacetylene (0.28 mmol, 1.05 equiv). The reaction mixture was filtered over a plug of celite (MeOH) and the filtrate was concentrated under reduced pressure. The oily

residue was then dissolved in 20 mL of EtOAc and washed twice with a saturated $NaHCO_3$ aqueous solution (5 mL) and once with brine (5 mL). The aqueous phases were extracted twice with EtOAc (20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield compound **(±)-9** as a white resin.

Reaction times and yields according to the catalyst and the reaction conditions:

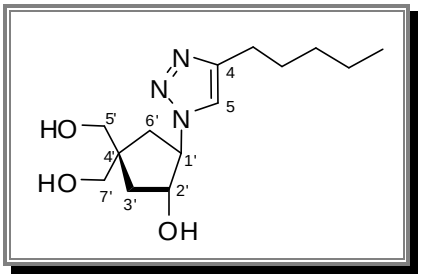
	$Cu^0/CuSO_4$	$[Cu(CH_3CN)_4]PF_6$		[CuBr(IMes)]
		^{t}BuOH/H_2O	CH_2Cl_2/MeOH	
Δ	**40 min**	**13 h**	-	**5 days**
yield (%)	98	99		91
MW	**2 min**	**15 min**	**5 min**	**9 h**
yield (%)	98	98	99	94

^{1}H NMR: (250 MHz, CD_3OD) δ 8.38 (s, 1H, H^5), 7.81 (d, 2H, *J* = 7.2 Hz, H^{Ar}), 7.42 (t, 2H, *J* = 7.5 Hz, H^{Ar}), 7.33 (t, 1H, *J* = 7.5 Hz, H^{Ar}), 4.82-4.71 (m, 1H, $H^{1'}$), 4.53 (q, 1H, *J* = 9.0 Hz, $H^{2'}$), 3.54 (s, 2H, $H^{5'}$), 3.53 (s, 2H, $H^{7'}$), 2.27 (dd, 1H, *J* = 13.5 and 8.3 Hz, $H^{6'}$), 2.15-2.10 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.66 (dd, 1H, *J* = 13.4 and 9.5 Hz, $H^{3'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 148.6 (C, C^4), 131.8 (C, C^{Ar}), 130.0 (CH, $2C^{Ar}$), 129.3 (CH, C^{Ar}), 126.6 (CH, $2C^{Ar}$), 121.4 (CH, C^5), 77.0 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.9 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.3 (CH_2, $C^{3'}$), 35.8 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z*: calcd for $C_{15}H_{19}N_3O_3Na$ (M^+ + Na) 312.1324, found 312.1320.

(±)-4,4-Bis(hydroxymethyl)-2-(4-pentyl-*1H*-1,2,3-triazol-1-yl)cyclopentanol (10)



Procedure:

From 37 µL of 1-heptyne (0.28 mmol, 1.05 equiv) and following the procedure described for the preparation of **(±)-9**, **(±)-10** was obtained as a colorless oil.

Reaction times and yields according to the catalyst and the reaction conditions:

	$Cu^0/CuSO_4$	$[Cu(CH_3CN)_4]PF_6$		[CuBr(IMes)]
		^{t}BuOH/H_2O	CH_2Cl_2/MeOH	
Δ	**5 days**	**5 days**	-	**5 days**

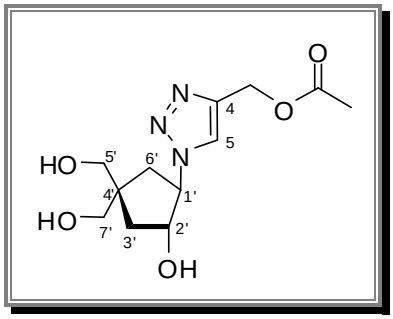
yield (%)	75	0		40
MW	**1 h**	**10 h**	**2 h**	**2 h**
yield (%)	98	60	93	93

^{1}H NMR: (250 MHz, CD_3OD) δ 7.80 (s, 1H, H^5), 4.72-4.61 (m, 1H, $H^{1'}$), 4.45 (q, 1H, *J* = 8.9 Hz, $H^{2'}$), 3.51 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.68 (t, 2H, *J* = 7.7 Hz, =C–C*H*$_2$), 2.21 (dd, 1H, *J* = 13.5 and 8.2 Hz, $H^{6'}$), 2.10-2.01 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.74-1.64 (m, 2H, =C–CH_2C*H*$_2$), 1.61 (dd, 1H, *J* = 13.4 and 9.5 Hz, $H^{3'}$) 1.39-1.32 (m, 4H, C*H*$_2$C*H*$_2$$CH_3$), 0.92 (t, 3H, *J* = 7.0 Hz, CH_3).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 150.0 (C, C^4), 122.3 (CH, C^5), 76.9 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.3 (CH_2, $C^{3'}$), 35.8 (CH_2, $C^{6'}$), 32.5 (*C*$H_2$$CH_2$$CH_3$), 30.3 (=C–$CH_2$*C*$H_2$), 26.3 (=C–*C*$H_2$), 23.4 (*C*$H_2$$CH_3$), 14.3 ($CH_3$).

HRMS (ESI): *m/z*: calcd for $C_{14}H_{25}N_3O_3Na$ (M^+ + Na) 306.1794, found 306.1793.

(±)-Acetic acid 1-(2-hydroxy-4,4-bis(hydroxyl-methyl)cyclopentyl)-*1H*-1,2,3-triazol-4-ylmethyl ester (11)



Procedure:

The title compound was prepared from 28 μL of propargyl acetate (0.28 mmol, 1.05 equiv). The reaction mixture was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography (EtOAc/MeOH 1:0 to 95:5). Compound **(±)-11** was isolated as a colorless oil.

Reaction times and yields according to the catalyst and the reaction conditions:

	$Cu^0/CuSO_4$	$[Cu(CH_3CN)_4]PF_6$		[CuBr(IMes)]
		^{t}BuOH/H_2O	CH_2Cl_2/MeOH	
Δ	**< 1 min**	**5 days**	-	**2 h**
yield (%)	96	17		70
MW	**< 1 min**	**2 min**	**15 min**	**5 min**
yield (%)	95	92	93	93

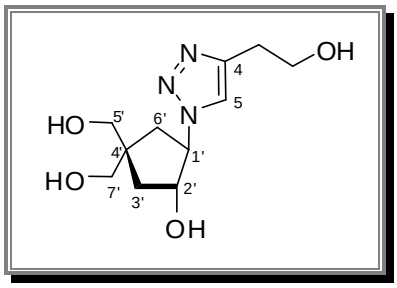
^{1}H NMR: (250 MHz, CD_3OD) δ 8.08 (s, 1H, H^5), 5.18 (s, 2H, CH_2), 4.76-4.65 (m, 1H, $H^{1'}$), 4.45 (q, 1H, *J* = 9.0 Hz, $H^{2'}$), 3.52 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.22 (dd, 1H, *J* = 13.5 and 8.2 Hz, $H^{6'}$), 2.10-2.04 (m, 2H, $H^{3'}$ + $H^{6'}$), 2.05 (s, 3H, CH_3), 1.62 (dd, 1H, *J* = 13.4 and 9.5 Hz, $H^{3'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 172.4 (C, C(O)), 143.8 (C, C^4), 125.0 (CH, C^5), 76.9 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.84 (CH_2, $C^{5'}$), 67.78 (CH_2, $C^{7'}$), 58.4 (CH_2), 45.5 (C, $C^{4'}$), 38.3 (CH_2, $C^{3'}$), 35.7 (CH_2, $C^{6'}$), 20.7 (CH_3).

HRMS (ESI): *m/z*: calcd for $C_{12}H_{19}N_3O_5Na$ (M^+ + Na) 308.1222, found 308.1229.

IR: (neat) 3357 cm^{-1} (OH), 1727 cm^{-1} (C=O), 1242-1039 cm^{-1} (C-O).

(±)-4,4-Bis(hydroxymethyl)-2-[4-(2-hydroxyethyl)-*1H*-1,2,3-triazol-1-yl]cyclopentanol (12)



Procedure:

The title compound was prepared from 21 µL of 3-butyn-1-ol (0.28 mmol, 1.05 equiv). The reaction mixture was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography (EtOAc/MeOH 1:0 to 95:5). Compound **(±)-12** was isolated as a colorless oil.

Reaction times and yields according to the catalyst and the reaction conditions:

	$Cu^0/CuSO_4$	$[Cu(CH_3CN)_4]PF_6$		[CuBr(IMes)]
		^{t}BuOH/H_2O	CH_2Cl_2/MeOH	
Δ	**2 min**	**5 days**	-	**1 h**
yield (%)	95	71		96
MW	**2 min**	**2 h**	**6 h**	**15 min**
yield (%)	95	92	91	96

^{1}H NMR: (250 MHz, CD_3OD) δ 7.86 (s, 1H, H^5), 4.69-4.65 (m, 1H, $H^{1'}$), 4.44 (q, 1H, *J* = 8.9 Hz, $H^{2'}$), 3.81 (t, 2H, *J* = 6.5 Hz, CH_2OH), 3.51 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.91 (t, 2H, *J* = 6.6 Hz, =C-CH_2), 2.21 (dd, 1H, *J* = 13.5 and 8.3 Hz, $H^{6'}$), 2.10-2.03 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.61 (dd, 1H, *J* = 13.4 and 9.6 Hz, $H^{3'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 145.9 (C, C^4), 123.2 (CH, C^5), 77.0 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 62.1 (CH_2OH), 45.5 (C, $C^{4'}$), 38.2 (CH_2, $C^{3'}$), 35.7 (CH_2, $C^{6'}$), 29.9 (=C-CH_2).

HRMS (ESI): *m/z*: calcd for $C_{11}H_{19}N_3O_4Na$ (M^+ + Na) 280.1273, found 280.1269.

IR: (neat) 3301 cm^{-1} (OH), 1111-1039 cm^{-1} (C-O).

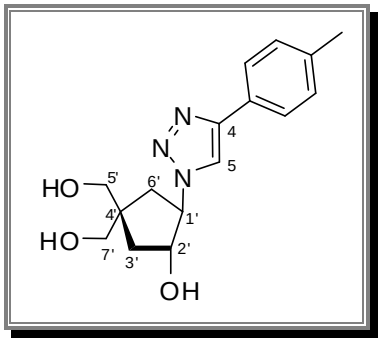
3. (±)-1,4-DISUBSTITUTED -1,2,3-TRIAZOLO-4'-HYDROXYMETHYL CARBANUCLEOSIDES AS POTENTIAL SMALLPOX INHIBITORS

(±)-13-15: General procedures for the 1,3-dipolar cycloaddition under microwave irradiation

Method A. A solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, copper powder (13.5 mg, 80 mol%), a water solution 1 M of copper sulfate (54 μL, 20 mol%) and the alkyne (1.05 equiv) were added in turn. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125°C. Upon completion of the reaction, the vial was cooled to 50°C by air jet cooling before being opened.

Method B. A solution of azide **(±)-6** (50 mg, 0.27 mmol) in CH_2Cl_2/MeOH 95:5 (2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, tetrakis(acetonitrile)copper hexafluorophosphate (10 mg, 10 mol%) and the alkyne (1.5 equiv) were added. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125°C. Upon completion of the reaction, the vial was cooled to 50°C by air jet cooling before being opened.

(±)-4,4-Bis(hydroxymethyl)-2-(4-p-tolyl-*1H*-1,2,3-triazol-1-yl)cyclopentanol (13)



Procedure:

Method A: The title compound was prepared from 4-ethynyltoluene (36 μL) after 10 min of microwave irradiation.

Method B: The title compound was prepared from 4-ethynyltoluene (50 μL) after 10 min of microwave irradiation.

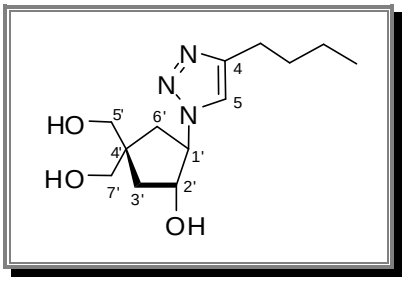
The reaction mixture was filtered over a plug of celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2 x 5 mL) and brine (5 mL). The aqueous phases were extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield compound **(±)-13** as a white solid (**A:** 76 mg, 94%; **B:** 80 mg, 99%).

^{1}H NMR: (250 MHz, CD_3OD) δ 8.33 (s, 1H, H^5), 7.69 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 7.24 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 4.85-4.72 (m, 1H, $H^{1'}$), 4.52 (q, 1H, *J* = 9.0 Hz, $H^{2'}$), 3.54 (s, 2H, $H^{5'}$), 3.53 (s, 2H, $H^{7'}$), 2.36 (s, 3H, CH_3), 2.26 (dd, 1H, *J* = 13.5, 8.1 Hz, $H^{6'}$), 2.14-2.08 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.65 (dd, 1H, *J* = 13.5 and 9.0 Hz, $H^{3'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 156.5 (C, C^4), 139.4 (C, C^{Ar}), 130.6 (CH, C^{Ar}), 129.0 (C, C^{Ar}), 126.6 (CH, C^{Ar}), 121.1 (CH, C^5), 77.0 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.9 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 45.6 (C, $C^{4'}$), 38.3 (CH_2, $C^{3'}$), 35.8 (CH_2, $C^{6'}$), 21.3 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_3O_3Na$ (M^+ + Na) 326.1481, found 326.1490.

(±)-4,4-Bis(hydroxymethyl)-2-(4-butyl-*1H*-1,2,3-triazol-1-yl)cyclopentanol (14)



Procedure:

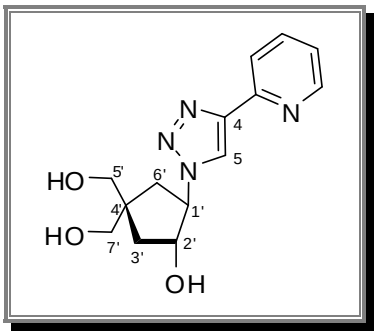
Method A: The title compound was prepared from 1-hexyne (32 µL) after 1.5 h of microwave irradiation.
Method B: The title compound was prepared from 1-hexyne (45 µL) after 1.25 h of microwave irradiation.
The reaction mixture was filtered over a plug of celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2 x 5 mL) and brine (5 mL). The aqueous phases were extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield compound **(±)-14** as a colorless oil (**A:** 68 mg, 95%; **B:** 70 mg, 98%).

^{1}H NMR: (250 MHz, CD_3OD) δ 7.77 (s, 1H, H^5), 4.82-4.57 (m, 1H, $H^{1'}$), 4.41 (q, 1H, *J* = 8.0 Hz, $H^{2'}$), 3.48 (s, 2H, $H^{5'}$), 3.46 (s, 2H, $H^{7'}$), 2.65 (t, 2H, *J* = 7.5 Hz, =C–CH_2), 2.17 (dd, 1H, *J* = 13.5 and 8.5 Hz, $H^{6'}$), 2.06-1.96 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.67-1.53 (m, 3H, $H^{3'}$ + =C–CH_2CH_2), 1.43-1.25 (m, 2H, C$H_2$$CH_3$), 0.91 (t, 3H, *J* = 7.5 Hz, CH_3).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 150.0 (C, C^4), 122.3 (CH, C^5), 76.9 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.3 (CH_2, $C^{3'}$), 35.8 (CH_2, $C^{6'}$), 32.7 (=C–$CH_2$$CH_2$), 26.0 (=C–$CH_2$), 23.3 ($CH_2$$CH_3$), 14.1 ($CH_3$).

HRMS (ESI): *m/z* calcd for $C_{13}H_{24}N_3O_3$ (M^+ + H) 270.1818, found 270.1824.

(±)-4,4-Bis(hydroxymethyl)-2-(4-pyridin-2-yl-*1H*-1,2,3-triazol-1-yl)cyclopentanol (15)



Procedure:

Method A: The title compound was prepared from 2-ethynylpyridine (28 µL) after 1 min of microwave irradiation.

Method B: The title compound was prepared from 2-ethynylpyridine (40 µL) in CH_2Cl_2/MeOH 1:1 (2 mL) after 10 min of microwave irradiation.

The reaction mixture was concentrated under reduced pressure and the residue was purified by a silica gel column chromatography (EtOAc/MeOH 1:0 to 95:5). Compound **(±)-15** was obtained as a colorless oil (**A:** 61 mg, 78%; **B:** 47 mg, 60%).

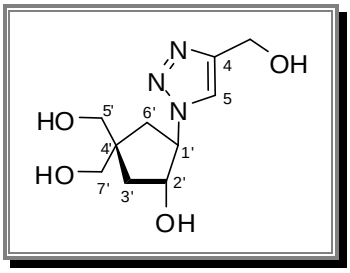
^{1}H NMR: (250 MHz, DMSO) δ 8.66 (s, 1H, H^5), 8.59 (d, 1H, *J* = 3.8 Hz, H^{Ar}), 8.03 (d, 1H, *J* = 7.8 Hz, H^{Ar}), 7.90 (t, 1H, *J* = 7.8 Hz, H^{Ar}), 7.34 (t, 1H, *J* = 5.8 Hz, H^{Ar}), 4.73-4.61 (m, 1H, $H^{1'}$), 4.33 (q, 1H, *J* = 9.0 Hz, $H^{2'}$), 3.32 (s, 2H, $H^{5'}$), 3.31 (s, 2H, $H^{7'}$), 2.09 (dd, 1H, *J* = 13.2 and 8.2 Hz, $H^{6'}$), 1.97-1.85 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.48 (dd, 1H, *J* = 12.9 and 9.0 Hz, $H^{3'}$).

^{13}C NMR: (62.9 MHz, DMSO) δ 150.1 (C, C^{Ar}), 149.5 (CH, C^{Ar}), 147.0 (C, C^4), 137.3 (CH, C^{Ar}), 122.9 (CH, C^{Ar}), 122.0 (CH, C^5), 119.4 (CH, C^{Ar}), 75.1 (CH, $C^{2'}$), 66.8 (CH, $C^{1'}$), 66.1 (CH_2, $C^{5'}$), 65.9 (CH_2, $C^{7'}$), 44.0 (C, $C^{4'}$), 37.3 (CH_2, $C^{3'}$), 34.5 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_4O_3$ (M^+ + H) 291.1457, found 291.1465.

IR: (neat) 3250 cm^{-1} (OH), 1666-1572 cm^{-1} (C=C, C=N), 1117-1039 cm^{-1} (C-O).

(±)-4,4-Bis(hydroxymethyl)-2-(4-hydroxymethyl-*1H*-1,2,3-triazol-1-yl)cyclopentanol (16)



Procedure:

The deacetylation of compound **(±)-11** (73 mg, 0.25 mmol) was carried out at 4ºC overnight without stirring in a methanol solution 7 N of ammonia (2 mL). Compound **(±)-16** was obtained after solvent evaporation as a colorless oil (59 mg, 95%).

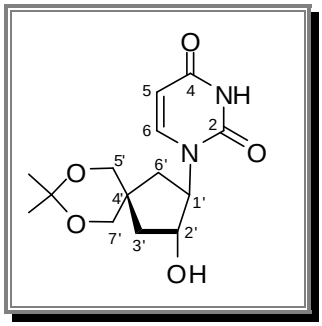
^{1}H NMR: (250 MHz, CD_3OD) δ 7.98 (s, 1H, H^5), 4.75-4.59 (m, 1H, $H^{1'}$), 4.68 (s, 2H, CH_2OH), 4.46 (q, 1H, *J* = 9.0 Hz, $H^{2'}$), 3.52 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.22 (dd, 1H, *J* = 13.5 and 8.2 Hz, $H^{6'}$), 2.12-2.00 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.62 (dd, 1H, *J* = 13.5 and 9.0 Hz, $H^{3'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 148.7 (C, C^4), 123.3 (CH, C^5), 76.9 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 56.5 (CH_2OH), 45.5 (C, $C^{4'}$), 38.3 (CH_2, $C^{3'}$), 35.7 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{10}H_{17}N_3O_4Na$ (M^+ + Na) 266.1117, found 266.1119.

IR: (neat) 3263 cm^{-1} (OH), 1121-1038 cm^{-1} (C-O).

(±)-1-(-3-Hydroxy-8,8-dimethyl-7,9-dioxaspiro[4.5]decan-2-yl)pyrimidine-2,4(*1H,3H*)-dione (17a)



Procedure:

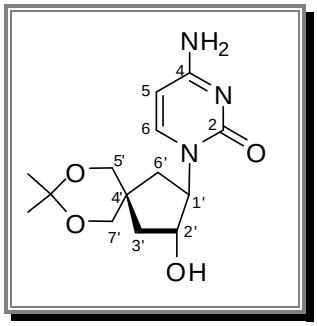
Epoxide **4** (0.22 g, 1.22 mmol, 1.05 equiv), uracil (0.13 g, 1.16 mmol) and a small amount of K_2CO_3 were dissolved in dry DMF (4 mL). The reaction mixture was heated at 136ºC for 20 h. After concentration, the resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:5 to 0:1) to yield **(±)-17a** as a white solid (0.1 g, 32%).

^{1}H NMR: (250 MHz, CD_3OD) δ 7.67 (d, 1H, *J* = 8.0 Hz, H^6), 5.69 (d, 1H, *J* = 8.0 Hz, H^5), 4.55-4.36 (m, 2H, $H^{1'}$ + $H^{2'}$), 3.70 (s, 4H, $H^{5'}$ + $H^{7'}$), 2.16-2.01 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.69 (dd, 1H, *J* = 13.5 and 10.8 Hz, $H^{6'}$), 1.45-1.37 (m, 1H, $H^{3'}$), 1.39 (s, 3H, CH_3), 1.37 (s, 3H, CH_3).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 166.3 (C, C^4), 153.0 (C, C^2), 144.8 (CH, C^6), 102.5 (CH, C^5), 99.1 (C), 73.0 (CH, $C^{2'}$), 70.5 (CH_2, $C^{5'}$ + $C^{7'}$), 65.0 (CH, $C^{1'}$), 39.2 (CH_2, $C^{3'}$), 37.4 (C, $C^{4'}$), 35.0 (CH_2, $C^{6'}$), 24.7 (CH_3), 23.5 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{14}H_{20}N_2O_5Na$ (M^+ + Na) 319.1270, found 319.1284.

(±)-4-Amino-1-(-3-hydroxy-8,8-dimethyl-7,9-dioxaspiro[4.5]decan-2-yl)pyrimidin-2(*1H*)-one (17b)



Procedure:

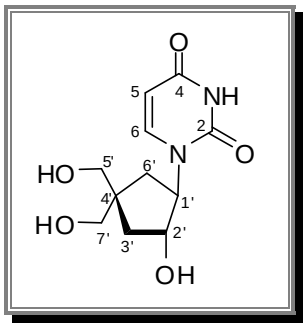
Epoxide **4** (0.23 g, 1.23 mmol, 1.05 equiv), cytosine (0.13 g, 1.17 mmol) and a small amount of K_2CO_3 were dissolved in dry DMF (4 mL). The reaction mixture was heated at 136ºC for 20 h. After concentration, the resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 5:1) to yield **(±)-17b** as a white solid (0.2 g, 57%).

^{1}H NMR: (250 MHz, CD_3OD) δ 7.64 (d, 1H, *J* = 7.5 Hz, H^6), 5.88 (d, 1H, *J* = 7.5 Hz, H^5), 4.54-4.41 (m, 2H, $H^{1'}$ + $H^{2'}$), 3.71 (s, 2H, $H^{5'}$), 3.70 (s, 2H, $H^{7'}$), 2.16-2.06 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.71-1.61 (m, 1H, $H^{6'}$), 1.47-1.37 (m, 1H, $H^{3'}$), 1.39 (s, 3H, CH_3), 1.37 (s, 3H, CH_3).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 167.3 (C, C^4), 159.3 (C, C^2), 145.1 (CH, C^6), 99.1 (CH, C^5), 96.0 (C), 73.2 (CH, $C^{2'}$), 70.6 (CH_2, $C^{5'}$ + $C^{7'}$), 66.3 (CH, $C^{1'}$), 39.8 (CH_2, $C^{3'}$), 37.6 (C, $C^{4'}$), 35.5 (CH_2, $C^{6'}$), 24.3 (CH_3), 23.9 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{14}H_{22}N_3O_4$ (M^+ + H) 296.1610, found 296.1607.

(±)-1-(-2-Hydroxy-4,4-bis(hydroxymethyl)-cyclopentyl)pyrimidine-2,4(*1H,3H*)-dione (18a)



Procedure:

Compound **(±)-17a** (0.1 g, 0.34 mmol) was dissolved in a 60% TFA aqueous solution (4 mL). After 24 h stirring at room temperature and evaporation of the solvent, **(±)-18a** was obtained as a white solid (85 mg, 98%).

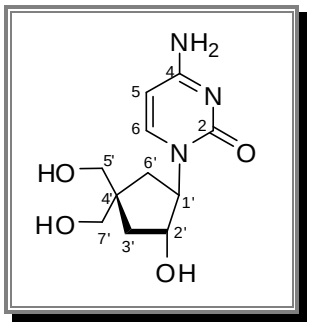
^{1}H NMR: (250 MHz, CD_3OD) δ 7.68 (d, 1H, *J* = 8.0 Hz, H^6), 5.71 (d, 1H, *J* = 8.0 Hz, H^5), 4.67-4.55 (m, 1H, $H^{1'}$), 4.44-4.34 (m, 1H, $H^{2'}$), 3.47 (s, 4H, $H^{5'}$ + $H^{7'}$), 2.04-1.92 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.70-1.46 (m, 2H, $H^{3'}$ + $H^{6'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 166.3 (C, C^4), 153.2 (C, C^2), 144.2 (CH, C^6), 102.6 (CH, C^5) 74.0 (CH, $C^{2'}$), 68.1 (CH_2, $C^{5'}$), 67.9 (CH_2, $C^{7'}$), 64.3 (CH, $C^{1'}$), 44.9 (C, $C^{4'}$), 37.9 (CH_2, $C^{3'}$), 33.3 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}N_2O_5Na$ (M^+ + Na) 279.0957, found 279.0969.

IR: (neat) 3308 cm^{-1} (OH), 1691 cm^{-1} (C=O), 1267 cm^{-1} (C-N), 1075-1014 cm^{-1} (C-O).

(±)-4-Amino-1-(-2-hydroxy-4,4-bis(hydroxymethyl)cyclopentyl)pyrimidin-2(*1H*)-one (18b)



Procedure:

Compound **(±)-17b** (0.1 g, 0.34 mmol) was dissolved in a 60% TFA aqueous solution (4 mL). After 24 h stirring at room temperature and evaporation of the solvent, the resulting yellow precipitate was washed with EtOAc (5 mL) and then with diethyl ether. **(±)-18b** was obtained as a white solid (54 mg, 62%).

^{1}H NMR: (250 MHz, CD_3OD) δ 7.88 (d, 1H, *J* = 7.5 Hz, H^6), 6.04 (d, 1H, *J* = 7.5 Hz, H^5), 4.65 (q, 1H, *J* = 9.4 Hz, $H^{1'}$), 4.42 (q, 1H, *J* = 9.4 Hz, $H^{2'}$), 3.47 (s, 4H, $H^{5'}$ + $H^{7'}$), 2.06-1.97 (m, 2H, $H^{3'}$ + $H^{6'}$), 1.71-1.48 (m, 2H, $H^{3'}$ + $H^{6'}$).

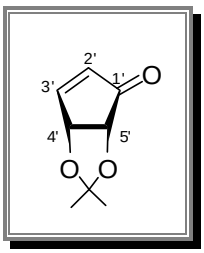
^{13}C NMR: (62.9 MHz, CD_3OD) δ 161.1 (C, C^4), 149.6 (C, C^2), 148.2 (CH, C^6), 94.9 (CH, C^5), 74.1 (CH, $C^{2'}$), 68.0 (CH_2, $C^{5'}$), 67.8 (CH_2, $C^{7'}$), 65.8 (CH, $C^{1'}$), 45.0 (C, $C^{4'}$), 37.7 (CH_2, $C^{3'}$), 33.3 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}N_3O_4$ (M^+ + H) 256.1297, found 256.1285.

IR: (neat) 3666 cm^{-1} (NH_2), 3107 cm^{-1} (OH), 1672 cm^{-1} (C=O, C=N), 1640 cm^{-1} (C=C), 1261 cm^{-1} (C-N), 1065-1014 cm^{-1} (C-O).

4. SYNTHESIS OF OPTICALLY ACTIVE D-1,4-DISUBSTITUTED-TRIAZOLO-CARBANUCLEOSIDES *VIA* A KEY D-AZIDO INTERMEDIATE

(4*R*,5*R*)-(-)-4,5-*O*-*Iso*propylidene-2-cyclopentenone (26)



Procedure:

D-ribose was converted to the diene **24** in six steps according to known Chu's procedure.[113]
A solution of diene **24** (7.0 g, 38 mmol) in anhydrous CH_2Cl_2 (200 mL) was added to [Ru]= catalyst **58** (0.48 g, 1.5 mol%) under N_2 atmosphere. After 1 h stirring at 24 °C, pyridinium chlorochromate (12.3 g, 57 mmol, 1.5 equiv) was added to the resulting dark brown mixture. The reaction mixture was stirred at room temperature for 12 h and filtered over a silica gel pad (EtOAc). The filtrate was concentrated *in vacuo*, and the resulting residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc 9:1), to give the instable compound **26** (4.63 g, 79%) as a white crystal.

$[\alpha]_D^{27}$ = -74.5 (*c* = 0.35, $CHCl_3$).

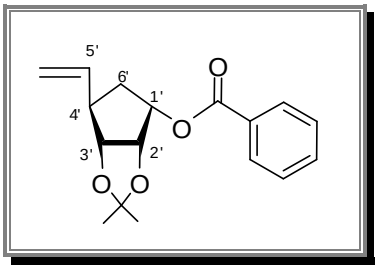
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.60 (dd, 1H, *J* = 5.9 and 2.3 Hz, $H^{3'}$), 6.21 (d, 1H, *J* = 5.9 Hz, $H^{2'}$), 5.26 (dd, 1H, *J* = 5.5 and 2.3 Hz, $H^{4'}$), 4.46 (d, 1H, *J* = 5.5 Hz, $H^{5'}$), 1.42 (s, 6H, CH3).

^{13}C NMR : (100 MHz, $CDCl_3$) δ 202.9 (C, CO), 159.5 (CH, $C^{3'}$), 134.2 (CH, $C^{2'}$), 115.5 (C), 78.6 (CH, $C^{4'}$), 76.5 (CH, $C^{5'}$), 27.4 (CH_3), 26.1 (CH_3).

MS (ESI): (M^+ + Na) 177.0 *m/z*.

CAS: 115509-13-2

[(1*S*,2*S*,3*R*,4*R*)-2,3-(*O*-*Iso*propylidenedioxy)-4-vinyl]cyclopentyl benzoate (28)



Procedure:

26 was converted to **27** according to Schneller's procedure.[115]

A THF (40 mL) solution of **27** (4.46 g, 24.5 mmol) was dropwise added to a suspension of $LiAlH_4$ (1.67 g, 44.1 mmol, 1.8 equiv) in THF (100 mL) at 0 °C under Ar. After 5 min stirring, the reaction mixture was allowed to warm up to room temperature and stirred further 3 h. H_2O (1 mL), 15% NaOH aqueous solution (1 mL) and H_2O (1 mL) were added in turn at 0 °C. The solution was filtrated over a short celite pad and the filtrate was concentrated under reduced pressure. To a CH_3CN (40 mL) solution of the resulting residue, 4-dimethylaminopyridine (6.01 g, 49.0 mmol, 2 equiv), *N*,*N*-di*iso*propylethylamine (8.54 mL, 49.0 mmol, 2 equiv) and benzoyl chloride (5.6 mL, 49.0 mmol, 2 equiv) were added at 0 °C under Ar. After 2 h stirring at room temperature, the reaction mixture was diluted with EtOAc and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1). **28** (5.54 g, 79% for 2 steps) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -66.6 (*c* = 0.1, $CHCl_3$).

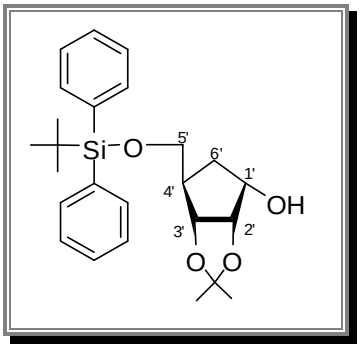
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.09 (d, 2H, *J* = 8.5 Hz, H^{Ar}), 7.57 (t, 1H, *J* = 7.4 Hz, H^{Ar}), 7.45 (t, 2H, *J* = 7.8 Hz, H^{Ar}), 5.83 (ddd, 1H, *J* = 17.1, 10.5 and 6.6 Hz, $H^{5'}$), 5.20-5.12 (m, 3H, H_2C= + $H^{1'}$), 4.80 (t, 1H, *J* = 5.6 Hz, $H^{2'}$), 4.54 (d, 1H, *J* = 5.6 Hz, $H^{3'}$), 2.88 (bs, 1H, $H^{4'}$), 2.36-2.29 (m, 1H, $H^{6'}$), 2.09-2.03 (m, 1H, $H^{6'}$), 1.43 (s, 3H, CH_3), 1.32 (s, 3H, CH_3).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.3 (C, CO), 137.8 (CH, $C^{5'}$), 133.1 (CH, C^{Ar}), 130.3 (C, C^{Ar}), 129.9 (CH, $2C^{Ar}$), 128.4 (CH, $2C^{Ar}$), 115.8 (CH_2, H_2C=), 111.9 (C), 84.4 (CH, $C^{3'}$), 78.3 (CH, $C^{2'}$), 73.8 (CH, $C^{1'}$), 44.2 (CH, $C^{4'}$), 32.5 (CH_2, $C^{6'}$), 26.3 (CH_3), 24.7 (CH_3).

HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_4Na$ (M^+ + Na) 311.1259, found 311.1259.

IR: (neat) 1710 cm^{-1} (C=O), 1637 cm^{-1} (C=C), 1491, 1453, 1372 cm^{-1} (C=C aromatic), 1268-1047 cm^{-1} (C-O).

[(1*S*,2*S*,3*R*,4*R*)-2,3-(*O*-*Iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl] cyclopentanol (29)



Procedure:

To a solution of **28** (4.51 g, 15.6 mmol) and $NaIO_4$ (6.69 g, 31.3 mmol, 2 equiv) in MeOH/acetone/H_2O (1:1:1, 240 mL), a solution of OsO_4 (2.5 wt% in ^{t}BuOH) (1 mL) was added at room temperature. After 1.5 h stirring, the

reaction mixture was filtrated over a celite pad and concentrated. The resulting residue was diluted with CH_2Cl_2 and then washed with brine. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The crude **A** aldehyde was obtained as an oil and directly used in next step without further purification. To a MeOH (100 mL) solution of crude **A**, $NaBH_4$ (1.18 g, 31.3 mmol, 2 equiv) was added at –78 ^oC. After 40 min stirring at room temperature, AcOH (2 mL) and acetone (100 mL) were added and the resulting reaction mixture was concentrated. The reaction mixture was diluted with CH_2Cl_2 and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. This crude alcohol **B** was used in next step without further purification. To the CH_3CN (50 mL) solution of crude alcohol **B**, 4-dimethylaminopyridine (2.11 g, 17.2 mmol, 1.1 equiv), imidazole (1.38 g, 20.3 mmol, 1.3 equiv) and *tert*-butylchlorodiphenylsilane (5.26 mL, 20.3 mmol, 1.3 equiv) were added at room temperature under N_2. After 1 h stirring, the reaction mixture was diluted with EtOAc and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtrated and concentrated to give the crude **C**. Freshly prepared 0.5M NaOMe solution in MeOH (100 mL) was added to crude **C** at 0 $^{\circ}C$ and stirred for 16 h at room temperature. AcOH (8.6 mL) was added and the reaction mixture was concentrated. The resulting residue was diluted with CH_2Cl_2 and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The oily residue was purified by silica gel column chromatography (petroleum ether/ EtOAc 3:1). **29** (5.01 g, 76% for 4 steps) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -47.7 (*c* = 0.1, $CHCl_3$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 4H, H^{Ar}), 7.45-7.36 (m, 6H, H^{Ar}), 4.50 (d, 1H, *J* = 5.8 Hz, $H^{3'}$), 4.44 (t, 1H, *J* = 5.8 Hz, $H^{2'}$), 4.25-4.18 (m, 1H, $H^{1'}$), 3.58 (dd, 1H, *J* = 10.3 and 5.6 Hz, $H^{5'}$), 3.51 (dd, 1H, *J* = 10.3 and 5.6 Hz, $H^{5'}$), 2.41 (d, 1H, *J* = 8.3 Hz, OH), 2.24-2.23 (m, 1H, $H^{4'}$), 1.93-1.82 (m, 2H, $H^{6'}$), 1.50 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.04 (s, 9H, ^{t}Bu).

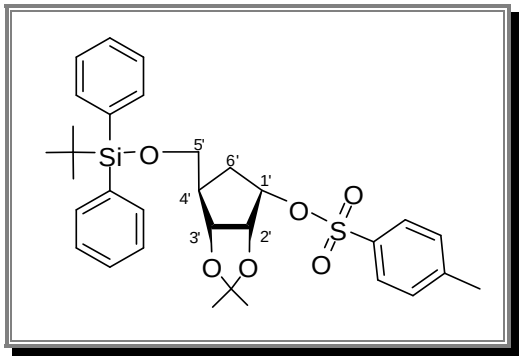
^{13}C NMR: (100 MHz, $CDCl_3$) δ 135.8 (CH, $2C^{Ar}$), 135.7 (CH, $2C^{Ar}$), 133.3 (C, $2C^{Ar}$), 129.9 (CH, $2C^{Ar}$), 127.9 (CH, $4C^{Ar}$), 111.3 (C), 82.9 (CH, $C^{3'}$), 79.7 (CH, $C^{2'}$), 71.9 (CH, $C^{1'}$), 65.3 (CH_2, $C^{5'}$), 44.1 (CH, $C^{4'}$), 35.5 (CH_2, $C^{6'}$), 27.0 (^{t}Bu), 26.3 (CH_3), 24.4 (CH_3), 19.3 (C-Si).

HRMS (ESI): *m/z* calcd for $C_{25}H_{34}O_4NaSi$ (M^+ + Na) 449.2124, found 449.2121.

IR: (neat) 3520 cm^{-1} (OH), 1471, 1427, 1381 cm^{-1} (C=C aromatic), 1209-1040 cm^{-1} (C-O).

CAS: 112543-76-7

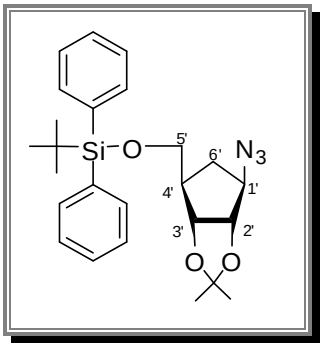
[(1*S*,2*R*,3*R*,4*R*)-1-(Methylbenzenesulfonate)-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (30)



Procedure:

To a CH_3CN (15 mL) solution of **29** (0.5 g, 1.17 mmol), 4-dimethylaminopyridine (0.2 g, 1.76 mmol, 1.5 equiv) and *N*,*N*-di*iso*propylethylamine (0.3 mL, 1.76 mmol, 1.5 equiv) at 0ºC, *p*-toluenesulfonyl chloride (0.34 g, 1.76 mmol, 1.5 equiv) was added. After 10 min stirring, the reaction mixture was allowed to warm up at room temperature. After 24 h stirring, the reaction mixture was diluted with CH_2Cl_2 and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The oily residue was purified by silica gel column chromatography (petroleum ether/ EtOAc 6:1). **30** (0.59 g, 87%) was obtained as a colorless oil.

[(1*R*,2*S*,3*R*,4*R*)-1-Azido-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (31)



Procedure from 30:

A DMF (4 mL) solution of **30** (0.22 g, 0.38 mmol), sodium azide (0.12 g, 1.9 mmol, 5 equiv) and 18-crown-6 ether (0.12 g, 0.46 mmol, 1.2 equiv) was heated for 3 h at 140ºC. The reaction mixture was diluted with EtOAc and then washed with brine. The aqueous phases were extracted with EtOAc and the combined organic layers were dried over $MgSO_4$. The oily residue was purified by silica gel column chromatography (petroleum ether/ EtOAc 9:1). **31** (0.12 g, 69%) was obtained as a yellow oil.

Procedure from 29:

To a THF (80 mL) solution of **29** (2.0 g, 4.72 mmol) and PPh_3 (3.82 g, 14.16 mmol, 3 equiv), a mixture of di*iso*propyl azodicarboxylate (2.8 mL, 14.16 mmol, 3 equiv) and diphenylphosphoryl azide (3.07 mL, 14.16 mmol, 3 equiv) in THF (20 mL) was dropwise added at 0 °C under Ar. After 7 h stirring at room temperature, EtOH (30 mL) was added and stirred for 30 min. After evaporation of all the volatiles, the oily residue was purified by silica gel column chromatoguraphy (petroleum ether/ EtOAc 100:1 to 50:1). **31** (2.03 g, 95%) was obtained as a yellow oil.

$[\alpha]_D^{26}$ = -19.0 (*c* = 0.1, $CHCl_3$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H, H^{Ar}), 7.46-7.37 (m, 6H, H^{Ar}), 4.46 (dd, 1H, *J* = 6.2 and 2.5 Hz, $H^{3'}$), 4.31 (dd, 1H, *J* = 6.2 and 3.5 Hz, $H^{2'}$), 3.92 (td, 1H, *J* = 6.0 and 2.8 Hz, $H^{1'}$), 3.69 (dd, 1H, *J* = 10.3 and 7.0 Hz, $H^{5'}$), 3.63 (dd, 1H, *J* = 10.3 and 7.0 Hz, $H^{5'}$), 2.37 (q_id, 1H, *J* = 7.0 and 2.5 Hz, $H^{4'}$), 2.22 (dt, 1H, *J* = 13.8 and 7.0 Hz, $H^{6'}$), 1.75 (dt, 1H, *J* = 13.8 and 5.7 Hz, $H^{6'}$), 1.46 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.07 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 135.8 (CH, $2C^{Ar}$), 135.7 (CH, $2C^{Ar}$), 133.6 (C, $2C^{Ar}$), 129.9 (CH, $2C^{Ar}$), 127.9 (CH, $4C^{Ar}$), 111.7 (C), 85.1 (CH, $C^{2'}$), 82.1 (CH, $C^{3'}$), 67.0 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 47.0 (CH, $C^{4'}$), 31.7 (CH_2, $C^{6'}$), 27.0 (^{t}Bu + CH_3), 24.6 (CH_3), 19.4 (C-Si).

^{29}Si NMR: (79.5 MHz, $CDCl_3$) – 104.4 (bs, Si).

HRMS (ESI): *m/z* calcd for $C_{25}H_{33}N_3O_3NaSi$ (M^+ + Na) 474.2189, found 474.2207.

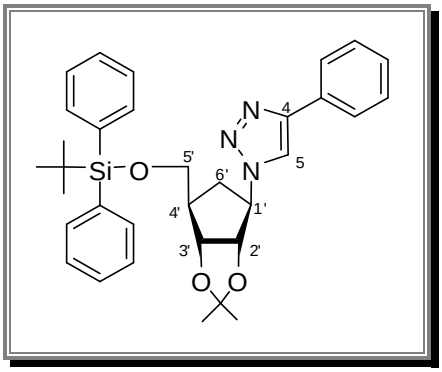
IR: (neat) 2102 cm^{-1} (N_3), 1472, 1427, 1382 cm^{-1} (C=C aromatic), 1160-1043 cm^{-1} (C-O).

CAS: 112543-78-9

(-)-32-37: General procedure for the 1,3-dipolar cycloaddition under microwave irradiation

A solution of azide **31** (50 mg, 0.1 mmol) in a 1/1 mixture of water and *t*BuOH (1 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, copper powder (5.6 mg, 80 mol%), a water solution 1 M of copper sulfate (22 μL, 20 mol%) and the alkyne (1.05 equiv) were added in turn. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125°C. Upon completion of the reaction, the vial was cooled to 50°C by air jet cooling before being opened. The reaction mixture was then filtered over a plug of celite (EtOAc) and the filtrate was concentrated under reduced pressure. The oily residue was then dissolved in 20 mL of EtOAc and washed twice with a saturated $NaHCO_3$ solution (5 mL) and once with brine (5 mL). The aqueous phases were extracted twice with EtOAc (20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure

[(1*R*,2*S*,3*R*,4*R*)-1-(4-Phenyl-*1H*-1,2,3-triazol-1-yl)-2,3-(*O-iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (32)



Procedure:

The title compound was prepared from phenylacetylene (13 µL) after 5 min of microwave irradiation. Compound **32** (61 mg, >99%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -25.7 (*c* = 0.4, $CHCl_3$).

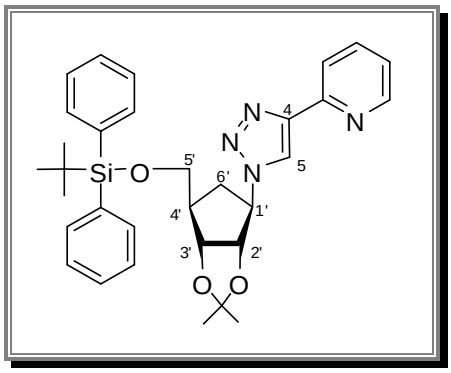
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.85 (dd, 2H, *J* = 8.5 and 1.4 Hz, H^{Ar}), 7.84 (s, 1H, H^5), 7.65 (dd, 4H, *J* = 7.8 and 1.4 Hz, H^{Ar-Si}), 7.46-7.31 (m, 9H, $6H^{Ar-Si}$ + $3H^{Ar}$), 4.86-4.77 (m, 2H, $H^{2'}$ + $H^{1'}$), 4.61 (dd, 1H, *J* = 6.9 and 4.0 Hz, $H^{3'}$), 3.82-3.75 (m, 2H, $H^{5'}$), 2.64-2.42 (m, 3H, $H^{4'}$ + $H^{6'}$), 1.57 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.08 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 147.9 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 130.8 (C, C^{Ar}), 129.9 (CH, $2C^{Ar-Si}$), 128.9 (CH, $2C^{Ar}$), 128.3 (CH, C^{Ar}), 127.9 (CH, $4C^{Ar-Si}$), 125.9 (CH, $2C^{Ar}$), 119.4 (CH, C^5), 113.6 (C), 85.1 (CH, $C^{2'}$), 81.2 (CH, $C^{3'}$), 66.5 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 45.9 (CH, $C^{4'}$), 33.7 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (^{t}Bu), 25.1 (CH_3), 19.5 (C-Si).

^{29}Si NMR: (79.5 MHz, $CDCl_3$) – 103.9 (bs, Si).

HRMS (ESI): *m/z* calcd for $C_{33}H_{39}N_3O_3NaSi$ (M^+ + Na) 576.2658, found 576.2642.

[(1*R*,2*S*,3*R*,4*R*)-1-(4-Pyridin-2-yl-*1H*-1,2,3-triazol-1-yl)-2,3-(*O-iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (33)



Procedure:

The title compound was prepared from 2-ethynyl pyridine (12 μL) after 1 min of microwave irradiation. Compound **33** (61 mg, >99%) was obtained as a light brown foam.

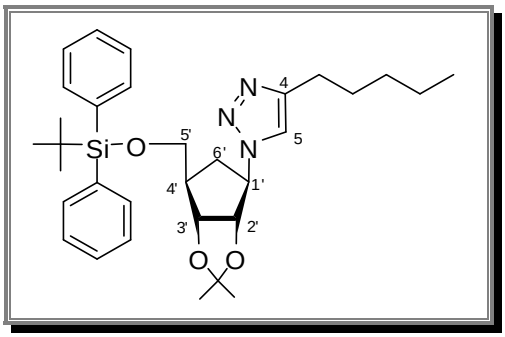
$[\alpha]_D^{27}$ = -25.7 (*c* = 0.16, $CHCl_3$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H, N-CH), 8.24 (s, 1H, H^5), 8.18 (d, 1H, *J* = 7.6 Hz, =C-CH=), 7.78 (t, 1H, *J* = 7.6 Hz, =C-CH=C*H*), 7.64 (dd, 4H, *J* = 6.4 and 1.2 Hz, H^{Ar-Si}), 7.44-7.36 (m, 6H, H^{Ar-Si}), 7.23 (bs, 1H, N-CH=C*H*), 4.87-4.81 (m, 2H, $H^{2'}$ + $H^{1'}$), 4.59 (dd, 1H, *J* = 6.4 and 4.0 Hz, $H^{3'}$), 3.81-3.74 (m, 2H, $H^{5'}$), 2.66-2.59 (m, 1H, $H^{6'}$), 2.49-2.40 (m, 2H, $H^{4'}$ + $H^{6'}$), 1.55 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.07 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 150.5 (C, =C), 149.5 (CH, N-CH), 148.5 (C, C^4), 137.0 (CH, =C-CH=*C*H), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 129.9 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 123.0 (CH, N-CH=*C*H), 121.8 (CH, C^5), 120.4 (CH, =C-*C*H=), 113.7 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 66.6 (CH, $C^{1'}$), 64.2 (CH_2, $C^{5'}$), 45.8 (CH, $C^{4'}$), 33.9 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (^{t}Bu), 25.1 (CH_3), 19.4 (C-Si).

HRMS (ESI): *m/z* calcd for $C_{32}H_{38}N_4O_3NaSi$ (M^+ + Na) 577.2635, found 577.2629.

[(1*R*,2*S*,3*R*,4*R*)-1-(4-Pentyl-*1H*-1,2,3-triazol-1-yl)-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (34)



Procedure:

The title compound was prepared from 1-heptyne (15 μL) after 15 min of microwave irradiation. Compound **34** (60 mg, >99%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -22.5 (*c* = 0.4, $CHCl_3$).

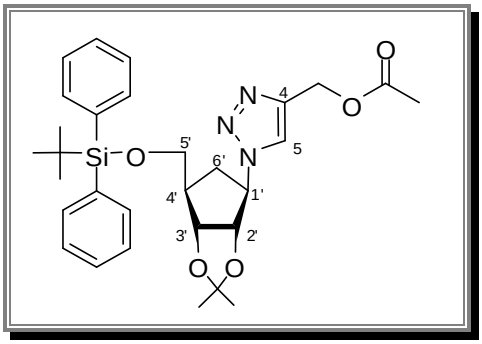
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.64 (dd, 4H, *J* = 7.8 and 1.4 Hz, H^{Ar-Si}), 7.45-7.35 (m, 6H, H^{Ar-Si}), 7.33 (s, 1H, H^5), 4.80-4.77 (m, 1H, $H^{2'}$), 4.74-4.70 (m, 1H, $H^{1'}$), 4.56 (dd, 1H, *J* = 6.8 and 4.0 Hz, $H^{3'}$), 3.79-3.74 (m, 2H, $H^{5'}$), 2.70 (t, 2H, *J* = 7.6 Hz, =C-CH_2), 2.56-2.52 (m, 1H, $H^{6'}$), 2.51-2.37 (m, 2H, $H^{4'}$ + $H^{6'}$), 1.68-1.64 (m, 2H, =C-CH_2-CH_2), 1.54 (s, 3H, CH_3), 1.37-1.33 (m, 4H, (CH_2)$_2$-CH_3), 1.29 (s, 3H, CH_3), 1.06 (s, 9H, ^{t}Bu), 0.89 (t, 3H, *J* = 7.2 Hz, $(CH_2)_2$-CH_3).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.6 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 129.9 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 120.2 (CH, C^5), 113.5 (C), 85.1 (CH, $C^{2'}$), 81.2 (CH, $C^{3'}$), 66.2 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 45.8

(CH, $C^{4'}$), 33.9 (CH_2, $C^{6'}$), 31.6 (CH_2, CH_2-CH_2-CH_3), 29.3 (CH_2, =C-CH_2-CH_2), 27.6 (CH_3), 27.0 (^{t}Bu), 25.8 (CH_2, =C-CH_2), 25.1 (CH_3), 22.5 (CH_2, CH_2-CH_3), 19.4 (C-Si), 14.1 (CH_2, CH_2-CH_3).

HRMS (ESI): *m/z* calcd for $C_{32}H_{45}N_3O_3NaSi$ (M^+ + Na) 570.3128, found 570.3125.

[(1*R*,2*S*,3*R*,4*R*)-1-(4-Methyl-acetyl-*1H*-1,2,3-triazol-1-yl)-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (35)



Procedure:

The title compound was prepared from propargyl acetate (12 µL) after 1 min of microwave irradiation. Compound **35** (60 mg, >99%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -20.7 (*c* = 0.4, $CHCl_3$).

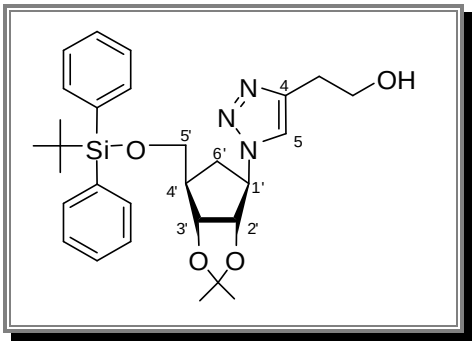
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.67-7.63 (m, 5H, H^5 + $H^{Ar\text{-}Si}$), 7.45-7.36 (m, 6H, $H^{Ar\text{-}Si}$), 5.21 (s, 2H, =C-CH_2), 4.8-4.70 (m, 2H, $H^{2'}$ + $H^{1'}$), 4.57 (dd, 1H, *J* = 6.8 and 4.4 Hz, $H^{3'}$), 3.80-3.73 (m, 2H, $H^{5'}$), 2.57-2.52 (m, 1H, $H^{6'}$), 2.48-2.35 (m, 2H, $H^{4'}$ + $H^{6'}$), 2.08 (s, 3H, CO-CH_3), 1.54 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.07 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.0 (CO), 142.9 (C, C^4), 135.7 (CH, $4C^{Ar\text{-}Si}$), 133.4 (C, $2C^{Ar\text{-}Si}$), 129.9 (CH, $2C^{Ar\text{-}Si}$), 127.9 (CH, $4C^{Ar\text{-}Si}$), 123.5 (CH, C^5), 113.7 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 66.6 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 57.7 (CH_2, =C-CH_2), 45.7 (CH, $C^{4'}$), 33.9 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (^{t}Bu), 25.1 (CH_3), 21.0 (CH_3, CO-CH_3), 19.4 (C-Si).

HRMS (ESI): *m/z* calcd for $C_{30}H_{39}N_3O_5NaSi$ (M^+ + Na) 572.2557, found 572.2554.

IR: (neat) 1741 cm^{-1} (C=O), 1471, 1427, 1381 cm^{-1} (C=C aromatic), 1229 cm^{-1} (C-O), 1111-1030 cm^{-1} (C-O).

[(1*R*,2*S*,3*R*,4*R*)-1-(4-(2-Hydroxyethyl)-*1H*-1,2,3-triazol-1-yl)-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (36)



Procedure:

The title compound was prepared from 3-butyn-1-ol (9 µL) after 1 min of microwave irradiation. Compound **36** (57 mg, >99%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -13.3 (*c* = 0.17, $CHCl_3$).

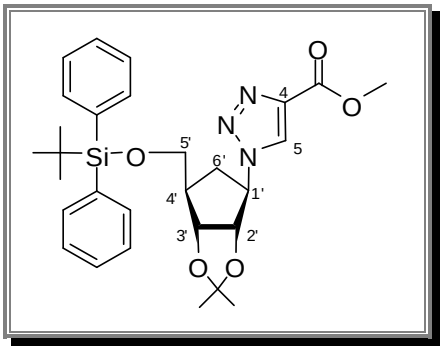
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 (dd, 4H, *J* = 8.0 and 1.2 Hz, $H^{Ar\text{-}Si}$), 7.46 (s, 1H, H^5), 7.44-7.36 (m, 6H, $H^{Ar\text{-}Si}$), 4.80-4.69 (m, 2H, $H^{2'}$ + $H^{1'}$), 4.57 (dd, 1H, *J* = 6.8 and 4.0 Hz, $H^{3'}$), 3.95 (t, 2H, *J* = 5.4 Hz, CH_2-OH), 3.80-3.73 (m, 2H, $H^{5'}$), 2.95 (t, 2H, *J* = 5.4 Hz, =C-CH_2), 2.63 (s, 1H, OH), 2.57-2.52 (m, 1H, $H^{6'}$), 2.48-2.35 (m, 2H, $H^{4'}$ + $H^{6'}$), 1.54 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.07 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 145.7 (C, C^4), 135.7 (CH, $4C^{Ar\text{-}Si}$), 133.4 (C, $2C^{Ar\text{-}Si}$), 129.9 (CH, $2C^{Ar\text{-}Si}$), 127.9 (CH, $4C^{Ar\text{-}Si}$), 121.3 (CH, C^5), 113.6 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 66.4 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 61.8 (CH_2, CH_2-OH), 45.8 (CH, $C^{4'}$), 33.8 (CH_2, $C^{6'}$), 28.8 (CH_2, =C-CH_2), 27.6 (CH_3), 27.0 (^{t}Bu), 25.1 (CH_3), 19.4 (C-Si).

HRMS (ESI): *m/z* calcd for $C_{29}H_{39}N_3O_4NaSi$ (M^+ + Na) 544.2608, found 544.2614.

IR: (neat) 3390 cm^{-1} (OH), 1471, 1427, 1380 cm^{-1} (C=C aromatic), 1210-1064 cm^{-1} (C-O).

[(1*R*,2*S*,3*R*,4*R*)-1-(4-Methyl carboxylate-*1H*-1,2,3-triazol-1-yl)-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (37)



Procedure:

The title compound was prepared from methyl propiolate (10 μL) after 1 min of microwave irradiation. Compound **37** (59 mg, >99%) was obtained as an orange oil.

$[\alpha]_D^{27}$ = -20.8 (*c* = 0.15, $CHCl_3$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.16 (s, 1H, H^5), 7.63 (dd, 4H, *J* = 6.4 and 1.2 Hz, H^{Ar-Si}), 7.45-7.36 (m, 6H, H^{Ar-Si}), 4.80-4.73 (m, 2H, $H^{2'}$ + $H^{1'}$), 4.57 (dd, 1H, *J* = 6.2 and 4.2 Hz, $H^{3'}$), 3.95 (s, 3H, OCH_3), 3.77-3.76 (m, 2H, $H^{5'}$), 2.62-2.54 (m, 1H, $H^{6'}$), 2.49-2.37 (m, 2H, $H^{4'}$ + $H^{6'}$), 1.54 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.07 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 161.3 (C, CO), 140.0 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.4 (C, $2C^{Ar-Si}$), 130.0 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 127.3 (CH, C^5), 113.8 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 67.0 (CH, $C^{1'}$), 64.1 (CH_2, $C^{5'}$), 52.3 (OCH_3), 45.6 (CH, $C^{4'}$), 33.7 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (^{t}Bu), 25.1 (CH_3), 19.5 (C-Si).

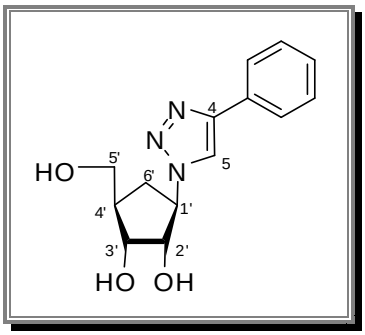
HRMS (ESI): *m/z* calcd for $C_{29}H_{37}N_3O_5NaSi$ (M^+ + Na) 558.2400, found 558.2394.

IR: (neat) 1727 cm^{-1} (C=O), 1471, 1427, 1382 cm^{-1} (C=C aromatic), 1239 cm^{-1} (C-O), 1066-1042 cm^{-1} (C-O).

General procedure for the synthesis of (-)-38-43

The protected triazole (0.1 mmol) was stirred overnight in an aqueous solution of trifluoroacetic acid (60% v/v) (2 mL) at room temperature. After evaporation of all the volatiles, the obtained oil was dissolved in THF (2 mL) and tetrabutyl ammonium fluoride trihydrate (33 mg, 0.1 mmol, 1.05 equiv) was added. The reaction mixture was stirred for 1 h at room temperature. After evaporation of all the volatiles, the resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 98:2).

(1*R*,2*S*,3*R*,4*R*)-1-(4-Phenyl-*1H*-1,2,3-triazol-1-yl)-2,3-dihydroxy-4-(hydroxymethyl) cyclopentane (38)



Procedure:

The title compound was prepared from **32** (55 mg, 0.1 mmol) and was obtained as a white solid **38** (24 mg, 86%).

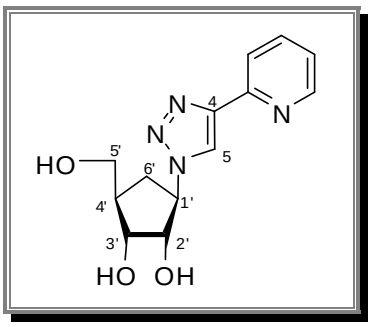
$[\alpha]_D^{27}$ = -65.0 (*c* = 0.2, CH_3OH).

^{1}H NMR: (400 MHz, CD_3OD) δ 8.39 (s, 1H, H^5), 7.81 (d, 2H, *J* = 7.5 Hz, H^{Ar}), 7.43 (t, 2H, *J* = 7.5 Hz, H^{Ar}), 7.34 (t, 1H, *J* = 7.5 Hz, H^{Ar}), 4.95-4.90 (m, 1H, $H^{1'}$), 4.29 (dd, 1H, *J* = 8.0 and 5.0 Hz, $H^{2'}$), 4.03 (dd, 1H, *J* = 5.0 and 3.5 Hz, $H^{3'}$), 3.67 (d, 2H, *J* = 6.0 Hz, $H^{5'}$), 2.52 (dt, 1H, *J* = 13.5 and 8.5 Hz, $H^{6'}$), 2.29-2.23 (m, 1H, $H^{4'}$), 1.99-1.93 (m, 1H, $H^{6'}$).

^{13}C NMR: (100 MHz, CD_3OD) δ 148.6 (C, C^4), 131.7 (C, C^{Ar}), 130.0 (CH, $2C^{Ar}$), 129.3 (CH, C^{Ar}), 126.6 (CH, $2C^{Ar}$), 121.7 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.7 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 46.8 (CH, $C^{4'}$), 31.0 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{14}H_{17}N_3O_3Na$ (M^+ + Na) 298.1168, found 298.1181.

(1*R*,2*S*,3*R*,4*R*)-1-(4-Pyridin-2-yl-*1H*-1,2,3-triazol-1-yl)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentane (39)



Procedure:

The title compound was prepared from **33** (59 mg, 0.1 mmol). After purification by column chromatography, the obtained precipitate was washed with CH_2Cl_2 to eliminate the color. Compound **39** (29 mg, 98%) was isolated as a white solid.

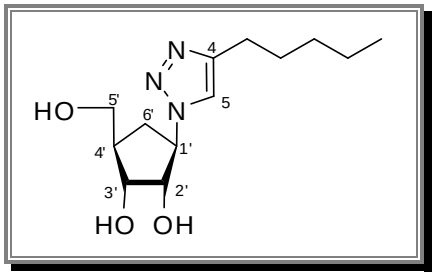
$[\alpha]_D^{27}$ = -33.6 (*c* = 0.3, CH_3OH).

^{1}H NMR: (400 MHz, DMSO-d^6) δ 8.65 (s, 1H, H^5), 8.59 (d, 1H, *J* = 4.4 Hz, N-CH), 8.02 (d, 1H, *J* = 7.6 Hz, =C-CH=), 7.89 (td, 1H, *J* = 7.6 and 1.6 Hz, =C-CH=C*H*), 7.34 (ddd, 1H, *J* = 7.6, 4.4 and 0.8 Hz, N-CH=C*H*), 5.09 (d, 1H, *J* = 6.8 Hz, $C^{2'}$-OH), 4.87-4.82 (m, 1H, $H^{1'}$), 4.78-4.76 (m, 2H, $C^{3'}$-OH + $C^{5'}$-OH), 4.16-4.10 (m, 1H, $H^{2'}$), 3.84-3.81 (m, 1H, $H^{3'}$), 3.47-3.42 (m, 2H, $H^{5'}$), 2.35 (dt, 1H, *J* = 13.2 and 8.6 Hz, $H^{6'}$), 2.10-2.03 (m, 1H, $H^{4'}$), 1.81-1.73 (m, 1H, $H^{6'}$).

^{13}C NMR: (100 MHz, DMSO-d^6) δ 150.2 (C, =C), 149.8 (CH, N-CH), 147.3 (C, C^4), 137.6 (CH, =C-CH=*C*H), 123.3 (CH, N-CH=*C*H), 122.7 (CH, C^5), 119.8 (CH, =C-*C*H=), 76.9 (CH, $C^{2'}$), 72.2 (CH, $C^{3'}$), 65.0 (CH, $C^{1'}$), 63.0 (CH_2, $C^{5'}$), 45.5 (CH, $C^{4'}$), 30.0 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{13}H_{16}N_4O_3Na$ (M^+ + Na) 299.1120, found 299.1120.

(1*R*,2*S*,3*R*,4*R*)-1-(4-Pentyl-*1H*-1,2,3-triazol-1-yl)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentane (40)



Procedure:

The title compound was prepared from **34** (58 mg, 0.1 mmol). The residue was purified by silica gel column chromatoguraphy (EtOAc). Compound **40** (25 mg, 88%) was obtained as a white solid.

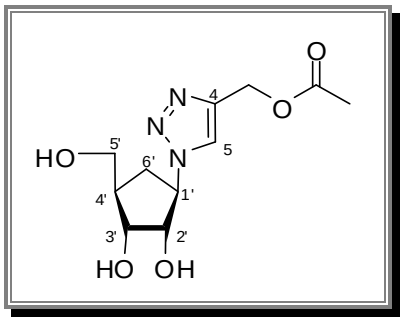
$[\alpha]_D^{27}$ = -13.2 (*c* = 0.2, CH_3OH).

^{1}H NMR: (250 MHz, CD_3OD) δ 7.81 (s, 1H, H^5), 4.94-4.77 (m, 1H, $H^{1'}$), 4.21 (dd, 1H, *J* = 8.0 and 5.0 Hz, $H^{2'}$), 3.99 (dd, 1H, *J* = 5.3 and 3.5 Hz, $H^{3'}$), 3.65 (d, 2H, *J* = 6.0 Hz, $H^{5'}$), 2.69 (t, 2H, *J* = 7.5 Hz, =C-CH_2), 2.46 (dt, 1H, *J* = 13.5 and 8.5 Hz, $H^{6'}$), 2.26-2.19 (m, 1H, $H^{4'}$), 1.91-1.84 (m, 1H, $H^{6'}$), 1.70-1.62 (m, 2H, =C-CH_2-CH_2), 1.38-1.32 (m, 4H, (CH_2)$_2$-CH_3), 0.91 (t, 3H, *J* = 6.6 Hz, (CH_2)$_2$-CH_3).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 149.0 (C, C^4), 122.5 (CH, C^5), 78.0 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.4 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 46.7 (CH, $C^{4'}$), 32.5 (CH_2, *C*H_2-CH_2-CH_3), 31.0 (CH_2, $C^{6'}$), 30.3 (CH_2, =C-CH_2-*C*H_2), 26.3 (CH_2, =C-*C*H_2), 23.4 (CH_2, *C*H_2-CH_3), 14.3 (CH_2, CH_2-*C*H_3).

HRMS (ESI): *m/z* calcd for $C_{13}H_{23}N_3O_3Na$ (M^+ + Na) 292.1637, found 292.1626.

(1*R*,2*S*,3*R*,4*R*)-1-(4-Methyl-acetyl-*1H*-1,2,3-triazol-1-yl)-2,3-dihydroxy-4-(hydroxymethyl) cyclopentane (41)



Procedure:

The title compound was prepared from **35** (58 mg, 0.1 mmol). The residue was purified by silica gel column chromatoguraphy (EtOAc). Compound **41** (22 mg, 76%) was obtained as a colorless oil.

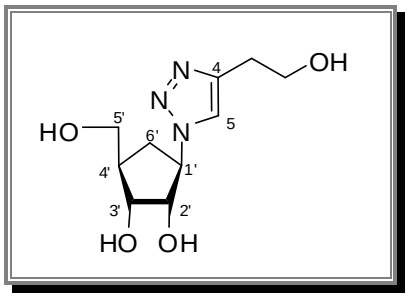
^{1}H NMR: (250 MHz, CD_3OD) δ 8.09 (s, 1H, H^5), 5.18 (s, 2H, =C-CH_2), 4.92-4.81 (m, 1H, $H^{1'}$), 4.22 (dd, 1H, *J* = 8.3 and 5.3 Hz, $H^{2'}$), 3.99 (dd, 1H, *J* = 5.3 and 3.5 Hz, $H^{3'}$), 3.64 (d, 2H, *J* = 5.6 Hz, $H^{5'}$), 2.47 (dt, 1H, *J* = 13.2 and 8.5 Hz, $H^{6'}$), 2.29-2.16 (m, 1H, $H^{4'}$), 2.06 (s, 3H, CO-CH_3), 1.97-1.83 (m, 1H, $H^{6'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 172.3 (CO), 143.8 (C, C^4), 125.3 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.6 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 58.2 (CH_2, =C-*C*H_2), 46.8 (CH, $C^{4'}$), 31.0 (CH_2, $C^{6'}$), 20.6 (CH_3, CO-*C*H_3).

HRMS (ESI): *m/z* calcd for $C_{11}H_{17}N_3O_5Na$ (M^+ + Na) 294.1066, found 294.1073.

IR: (neat) 3360 cm^{-1} (OH), 1731 cm^{-1} (C=O), 1229 cm^{-1} (C-O), 1160-1042 cm^{-1} (C-O).

(1*R*,2*S*,3*R*,4*R*)-1-(4-(2-Hydroxyethyl)-*1H*-1,2,3-triazol-1-yl)-2,3-dihydroxy-4-(hydroxymethyl) cyclopentane (42)



Procedure:

The title compound was prepared from **36** (57 mg, 0.1 mmol). After purification by column chromatography, the obtained precipitate was washed with CH_2Cl_2 to eliminate the color. Compound **42** (21 mg, 80%) was obtained as a white solid.

$[\alpha]_D^{27}$ = -26.6 (*c* = 0.15, CH_3OH).

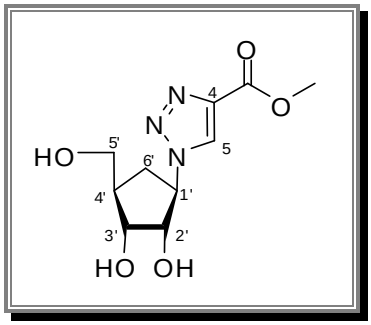
^{1}H NMR: (400 MHz, CD_3OD) δ 7.87 (s, 1H, H^5), 4.87-4.80 (m, 1H, $H^{1'}$), 4.21 (dd, 1H, *J* = 8.4 and 5.3 Hz, $H^{2'}$), 3.99 (dd, 1H, *J* = 5.3 and 3.6 Hz, $H^{3'}$), 3.82 (bs, 2H, C*H*$_2$-OH), 3.65 (d, 2H, *J* = 6.0 Hz, $H^{5'}$), 2.91 (t, 2H, *J* = 6.6 Hz, =C-C*H*$_2$), 2.46 (dt, 1H, *J* = 13.2 and 8.5 Hz, $H^{6'}$), 2.27-2.19 (m, 1H, $H^{4'}$), 1.93-1.85 (m, 1H, $H^{6'}$).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.3 (C, C^4), 123.4 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.9 (CH, $C^{3'}$), 66.5 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 62.1 (CH_2, CH_2-OH), 46.7 (CH, $C^{4'}$), 31.0 (CH_2, $C^{6'}$), 29.9 (CH_2, =C-*C*H_2).

HRMS (ESI): *m/z* calcd for $C_{10}H_{17}N_3O_4Na$ (M^+ + Na) 266.1117, found 266.1111.

IR: (neat) 3294 cm^{-1} (OH), 1201-1050 cm^{-1} (C-O).

(1*R*,2*S*,3*R*,4*R*)-1-(4-Methyl-carboxylate -*1H*-1,2,3-triazol-1-yl)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentane (43)



Procedure:

The title compound was prepared from **37** (59 mg, 0.1 mmol). After purification by column chromatography, the obtained precipitate was washed with CH_2Cl_2 to eliminate the color. Compound **43** (15 mg, 52%) was obtained as a white solid.

$[\alpha]_D^{27}$ = -28.0 (*c* = 0.2, CH_3OH).

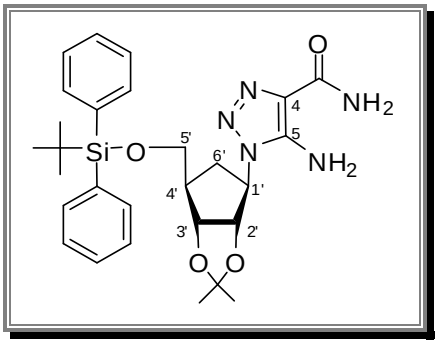
^{1}H NMR: (250 MHz, CD_3OD) δ 8.62 (s, 1H, H^5), 4.97-4.78 (m, 1H, $H^{1'}$), 4.25 (dd, 1H, *J* = 8.5 and 5.3 Hz, $H^{2'}$), 4.00 (dd, 1H, *J* = 5.3 and 3.2 Hz, $H^{3'}$), 3.92 (s, 3H, OCH_3), 3.65 (d, 2H, *J* = 6.0 Hz, $H^{5'}$), 2.57-2.45 (m, 1H, $H^{6'}$), 2.30-2.19 (m, 1H, $H^{4'}$), 1.99-1.87 (m, 1H, $H^{6'}$).

^{13}C NMR: (62.9 MHz, CD_3OD) δ 162.4 (C, CO), 140.3 (C, C^4), 129.2 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.9 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 52.5 (OCH_3), 46.8 (CH, $C^{4'}$), 30.8 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{10}H_{15}N_3O_5Na$ (M^+ + Na) 280.0909, found 280.0913.

IR: (neat) 3363 cm^{-1} (OH), 1731 cm^{-1} (C=O), 1226 cm^{-1} (C-O), 1142-1055 cm^{-1} (C-O).

[(1*R*,2*S*,3*R*,4*R*)-1-(4-Amido-5-amino-*1H*-1,2,3-triazol-1-yl)-2,3-(*O*-*iso*propylidenedioxy)-4-(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (44)



Procedure:

In a dry flask, sodium metal (11 mg, 0.48 mmol, 2 equiv) was dissolved in dry EtOH (1 mL) under N_2. To a solution of **31** (100 mg, 0.22 mmol) in dry EtOH (10 mL) under N_2, the prepared sodium ethoxide solution was

added dropwise. After the addition of 2-cyanoacetamide (21 mg, 0.25 mmol, 1.1 equiv), the reaction mixture was refluxed for 48 h. The residue was purified by silica gel column chromatoguraphy (petroleum ether/EtOAc 1:3). Compound **44** (6 mg, 5%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = -32.4 (*c* = 0.1, $CHCl_3$).

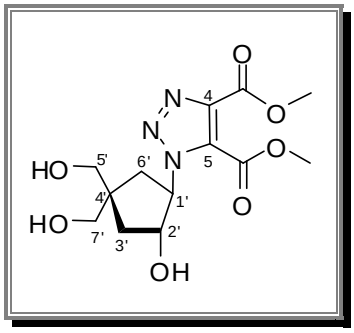
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.66 (dd, 4H, *J* = 7.6 and 1.6 Hz, H^{Ar-Si}), 7.46-7.37 (m, 6H, H^{Ar-Si}), 6.68 (bs, 1H, CON*H*H), 5.64 (s, 2H, NH_2), 5.30 (bs, 1H, CONH*H*), 4.57 (dd, 1H, *J* = 7.2 and 4.4 Hz, $H^{3'}$), 4.52-4.49 (m, 1H, $H^{2'}$), 4.33 (dt, 1H, *J* = 12.4 and 6.4 Hz, $H^{1'}$), 3.84-3.76 (m, 2H, $H^{5'}$), 2.76 (dd, 1H, *J* = 25.2 and 12.4 Hz, $H^{6'}$), 2.61-2.54 (m, 1H, $H^{6'}$), 2.52-2.46 (m, 1H, $H^{4'}$), 1.59 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.07 (s, 9H, ^{t}Bu).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.7 (CO), 145.5 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 130.0 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 122.9 (C, C^5), 114.2 (C), 85.1 (CH, $C^{2'}$), 81.5 (CH, $C^{3'}$), 64.3 (CH_2, $C^{5'}$), 63.7 (CH, $C^{1'}$), 45.3 (CH, $C^{4'}$), 31.2 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (^{t}Bu), 25.1 (CH_3), 19.5 (C-Si).

HRMS (ESI): *m/z* calcd for $C_{28}H_{37}N_5O_4NaSi$ (M^+ + Na) 558.2513, found 558.254.

IR: (neat) 3325 cm^{-1} (NH), 1654 cm^{-1} (C=O), 1458, 1421, 1380 cm^{-1} (C=C aromatic), 1254 cm^{-1} (C-N), 1210-1003 cm^{-1} (C-O).

(±)-Dimethyl-1-(2-hydroxy-4,4-bis(hydroxymethyl)cyclopentyl)-*1H*-1,2,3-triazole-4,5-dicarboxylate (47c)



Procedure:

To a solution of azide **(±)-6** (50 mg, 0.27 mmol) in a 1/1 mixture of water and *t*BuOH (2 mL) in a glass vial equipped with a magnetic stirring bar, dimethyl acetylenedicarboxylate (36 µL, 0.30 mmol, 1.1 equiv) was added. The vial was sealed with an aluminum/Teflon crimp top and then irradiated at 125°C for 1 h. After cooling to 50°C by air jet, the resulting mixture was purified by silica gel column chromatography (EtOAc/MeOH 98:2). Compound **(±)-47c** was obtained as a colorless oil (79 mg, 89%).

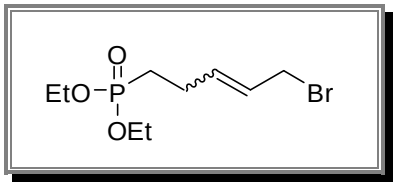
^{1}H NMR: (400 MHz, CD_3OD) δ 4.98 (q, 1H, *J* = 8.8 Hz, $H^{1'}$), 4.59 (q, 1H, *J* = 8.8 Hz, $H^{2'}$), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.52-3.50 (m, 4H, $H^{5'}$ + $H^{7'}$), 2.23 (m, 2H, $H^{6'}$), 2.07 (dd, 1H, *J* = 13.3 and 8.8 Hz, $H^{3'}$), 1.61 (dd, 1H, *J* = 13.3 and 8.8 Hz, $H^{3'}$).

^{13}C NMR: (100 MHz, CD_3OD) δ 161.8 (C=O), 160.5 (C=O), 140.0 (C, C^4), 133.2 (C, C^5), 76.8 (CH, $C^{2'}$), 68.4 (CH, $C^{1'}$), 67.7 (CH_2, $C^{5'}$+ $C^{7'}$), 54.0 (OCH_3), 53.0 (OCH_3), 45.7 (C, $C^{4'}$), 37.9 (CH_2, $C^{3'}$), 35.3 (CH_2, $C^{6'}$).

HRMS (ESI): *m/z* calcd for $C_{13}H_{19}N_3O_7Na$ (M^+ + Na) 352.1121, found 352.1127.

IR: (neat) 3357 cm^{-1} (OH), 1731 cm^{-1} (C=O), 1226 cm^{-1} (C-O), 1143-1028 cm^{-1} (C-O).

Diethyl 5-bromopent-3-enylphosphonate (48)



Procedure:

To a CH_2Cl_2 (10 mL) solution of crotyl bromide (0.2 mL, 1.94 mmol) and diethyl-3-butenyl phosphonate (0.74 mL, 3.9 mmol, 2 equiv), [Ru]=catalyst **58** (82 mg, 5 mol%) was added and the resulting solution was refluxed for 3 h. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 1:2). Compound **48** was obtained as a yellow oil (0.41 g, 74%, major/minor *ratio* = 85:15).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.84-5.59 (m, 2H, HC=CH), 4-12-4.02 (m, 4H, O-C*H*$_2$), 3.99 (d, 0.3H, *J* = 8.4 Hz, CH_2-Br minor), 3.93 (d, 1.7H, *J* = 6.8 Hz, CH_2-Br major), 2.49-2.45 (m, 2H, C*H*$_2$-HC=), 1.86-1.78 (m, 2H, P-CH_2), 1.33 (t, 6H, *J* = 7.0 Hz, CH_3).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 134.6 (d, CH, *J* = 16.7 Hz, P-$(CH_2)_2$-H*C*=), 127.3 (CH, =*C*H-CH_2-Br), 61.7 (d, CH_2, *J* = 6.4 Hz, O-*C*H_2), 32.8 (CH_2, CH_2-Br), 25.2 (d, CH_2, *J* = 4.5 Hz, *C*H_2-HC=), 25.1 (d, CH_2, *J* = 140.4 Hz, P-CH_2), 16.6 (d, CH_3, *J* = 6.0 Hz, CH_3).

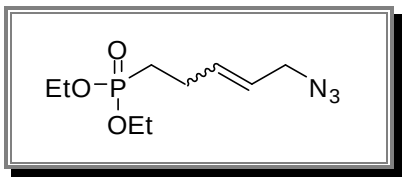
^{31}P NMR: (162 MHz, $CDCl_3$) δ 31.47 (P minor), 30.75 (P major).

HRMS (APCI): *m/z* calcd for $C_9H_{19}O_3BrP$ (M^+ + H) 285.0255, found 285.0251.

IR: (neat) 1240 cm^{-1} (P=O), 1204 cm^{-1} (CH_2-Br), 1020 cm^{-1} (P-O-C).

CAS: 214619-70-2

Diethyl 5-azidopent-3-enylphosphonate (49)



Procedure:

To a dry CH_3CN (20 mL) solution of **48** (0.39 g, 1.36 mmol), sodium azide (0.35 g, 5.44 mmol, 4 equiv) was added and the solution was refluxed for 2 days. After filtration over $MgSO_4$ and evaporation of all the volatiles,

the residue was purified by chromatography on silica gel (petroleum ether/EtOAc 1:2). Compound **49** was obtained as a yellow oil (0.26 g, 76%, major/minor *ratio* = 85:15).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.83-5.68 (m, 1H, *H*C=CH), 5.62-5.54 (m, 1H, HC=C*H*), 4-16-4.04 (m, 4H, O-CH_2), 3.84 (d, 0.3H, *J* = 7.6 Hz, CH_2-N_3 minor), 3.73 (d, 1.7H, *J* = 6.0 Hz, CH_2-N_3 major), 2.44-2.34 (m, 2H, CH_2-HC=), 1.88-1.73 (m, 2H, P-CH_2), 1.34 (t, 6H, *J* = 7.0 Hz, CH_3).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 135.0 (d, CH, *J* = 17.1 Hz, P-$(CH_2)_2$-H*C*=), 124.0 (CH, =*C*H-CH_2-N_3), 61.6 (d, CH_2, *J* = 6.6 Hz, O-*C*H_2), 52.6 (CH_2, CH_2-N_3), 25.3 (d, CH_2, *J* = 140.2 Hz, P-CH_2), 25.2 (d, CH_2, *J* = 4.6 Hz, *C*H_2-HC=), 16.4 (d, CH_3, *J* = 5.8 Hz, CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.83.

HRMS (ESI): *m/z* calcd for $C_9H_{18}N_3O_3NaP$ (M^+ + Na) 270.0983, found 270.0989.

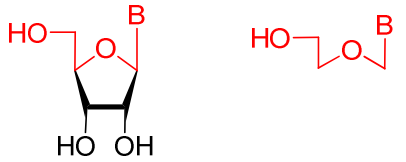
IR: (neat) 2100 cm^{-1} (N_3), 1240 cm^{-1} (P=O), 1028 cm^{-1} (P-O-C).

Chapter II:

Acyclic nucleoside phosphonates *via* cross-metathesis

1. INTRODUCTION

Since the discovery of the first successful antiviral drug in 1974, interests have been refocused on compounds where the heterocycle and sugar components of the nucleoside have departed significantly from the natural form. In this context, acyclic nucleosides have emerged as an important class of anti-viral agents.[150] They differ from nucleoside analogues in that they contain only a partial nucleoside structure: the sugar ring is replaced by an open-chain structure (Figure 19).



Nucleosides **Acyclic Nucleosides**

Figure 19. Structures of nucleosides and acyclic nucleosides compared.

1.1. Generality on Acyclic Nucleosides

Acyclovir is an acyclic guanosine analogue and a very potent inhibitor of viral DNA polymerase commonly-used for instance in the treatment of herpes virus infections (Figure 20).[151] Similarly to the mechanism of action presented for nucleosides (Cf. Introduction, Figure 4), acyclovir has to be converted into acyclo-guanosine triphosphate (acyclo-GTP) to inhibit the virus replication. Viral thymidine kinase, more effective than the cellular one, allows for selective first phosphorylation to the acyclo-guanosine monophosphate (acyclo-

[150] (a) Johansson, N.G. *Adv. Antivir. Drug Design* **1993**, 187-177. (b) De Clercq, E. *Nucleos. Nucleot.* **1994**, *13*, 1271-1295. (c) Freeman, S.; Gardiner, J.M. *Mol. Biotechnol.* **1996**, *5*, 125-137. (d) Shuter, J. *Cancer Invest.* **1999**, *17*, 145-152. (e) Tan, X.; Chu, C.K.; Boudinot, F.D. *Adv. Drug Deliver. Rev.* **1999**, *39*, 117-151. (f) Snoeck, R.; Andrei, G.; De Clercq, E. *Expert Opin. Invest. Drugs* **2000**, *9*, 1743-1751. (g) Firestine, S.M. *Expert Opin. Ther. Pat.* **2004**, *14*, 1139-1151. (h) Danta, M.; Dusheiko, G. *Int. J. Clin. Pract.* **2004**, *58*, 877-886. (i) Genova-Kalou, P.; Dundarova, D. *Probl. Infect. Parasit. Dis.* **2007**, *35*, 14-16.

[151] (a) Elion, G.B.; Furman, P.A.; Fyfe, J.A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H.J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716-5720. (b) Schaeffer, J.H.; Beauchamp, L.; De Miranda, P.; Elion, G.; Bauer, D.J.; Collins, P. *Nature* **1978**, *272*, 583-585. (c) Furman, P.A.; St. Clair, M.H.; Fyfe, J.A.; Rideout, J.L.; Keller, P.M.; Elio, G.B. *J. Virol.* **1979**, *32*, 72-77.

GMP). This monophosphate form is further phosphorylated into the active triphosphate form, by cellular kinases. Thanks to its greater affinity for viral than cellular polymerase, acyclo-GTP is selectively incorporated into viral DNA, resulting in chain termination. In view of its extreme selectivity and low cytotoxicity, acyclovir was seen as the start of a new era in antiviral therapy.

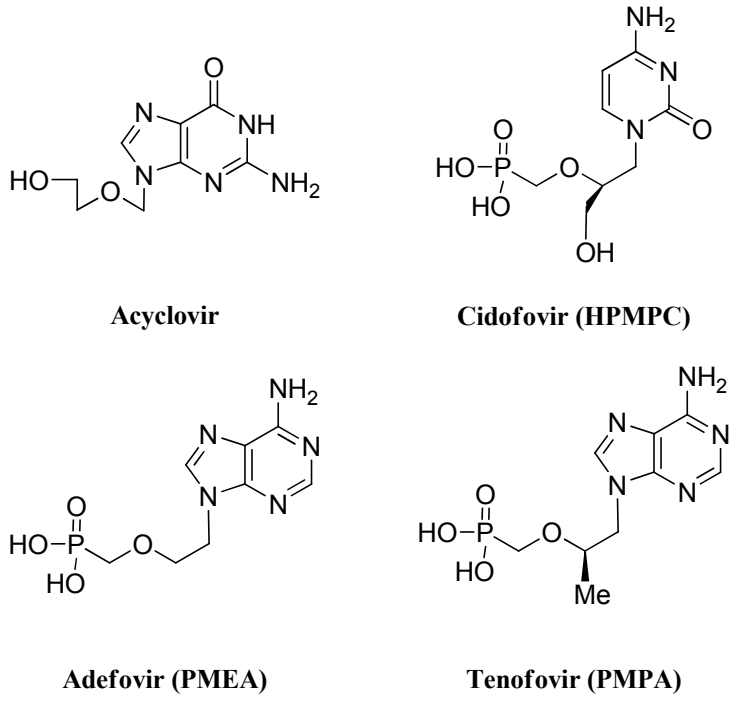


Figure 20. Acyclic nucleoside analogues with broad variety of anti-viral activities.

All the same, the real breakthrough was brought in 1986 with the concept of acyclic nucleoside phosphonate (ANP) analogues developed by Erik De Clercq and Antonin Holý research groups.[152] Since then, they have exhibited a remarkable broad-spectrum activity against HIV, HBV, papilloma-, herpes-, adeno-, pox- and cytomegalo- virus.[153] Tenofovir (PMPA), adefovir (PMEA) and cidofovir (HPMPC) belong to this pharmacopoeia (Figure 20). ANPs contain phosphonate-substituted aliphatic chain which makes them thus independent of the first limiting phosphorylation step by viral enzymes,[154] in contrast to acyclovir. Moreover, P-C bond of phosphonate group is more resistant to cellular *phosphatases* than P-O bond of regular nucleotide's phosphate group. In their mechanism of

[152] (a) De Clercq, E.; Holý, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C. *Nature* **1986**, *323*, 464-467. (b) De Clercq, E.; Sakuma, T.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosenberg, I.; Holý, A. *Antiviral Res*. **1987**, *8*, 261-272. (c) De Clercq, E.; Holý, A.; Rosenberg, I. *Antimicrob. Agents Chemother.* **1989**, *33*, 185-191.

[153] (a) Holý, A. *Curr. Pharm. Design* **2003**, *9*, 2567-2592. (b) De Clercq, E. *Clin. Microbiol. Rev.* **2003**, *16*, 569-596. (c) De Clercq, E. *Expert Rev. Anti-infect. Ther.* **2003**, *1*, 21-43. (d) De Clercq, E.; Holý, A. *Nat. Rev. Drug Discov.* **2005**, *4*, 928-940. (e) Holý, A. *Antivir. Res.* **2006**, *71*, 248-253. (f) De Clercq, E. *Biochem. Pharmacol.* **2007**, *73*, 911-922. (g) De Clercq, E. *Antivir. Res.* **2007**, *75*, 1-13. (h) Hostetler, K.Y. *Adv. Antivir. Drug Design* **2007**, *5*, 167-184.

[154] De Clercq, E. *Nature Rev. Microbiol.* **2004**, *2*, 704-720.

action, ANPs follow a similar strategy based on DNA chain termination (Figure 21).[154] Once they have penetrated into the cell, they need two subsequent phosphorylations to be converted to a diphosphate form (triphosphate analog), which can be incorporated into the viral DNA and act as an obligatory DNA chain terminator. However, ANPs frequently failed to exhibit biological activity *in vitro* due to their poor cell penetration. In fact, their double negative charge at physiological pH reduces penetration through cell membrane resulting in a low oral bioavailability. It is a serious obstacle for certain applications and would disqualify the drug, *e.g*. for oral application. Thus to circumvent this problem, ANPs can be converted to phosphonodiester forms which are designed to penetrate into the cell by virtue of their reduced polarity. Once in the cell, decomposition of the acyclonucleotide prodrug by successive enzymatic and chemical degradations liberates the antiviral nucleoside phosphonate. *In vivo* studies indicated that the prodrugs were highly orally bioavailable and more active than their parent compounds.[155]

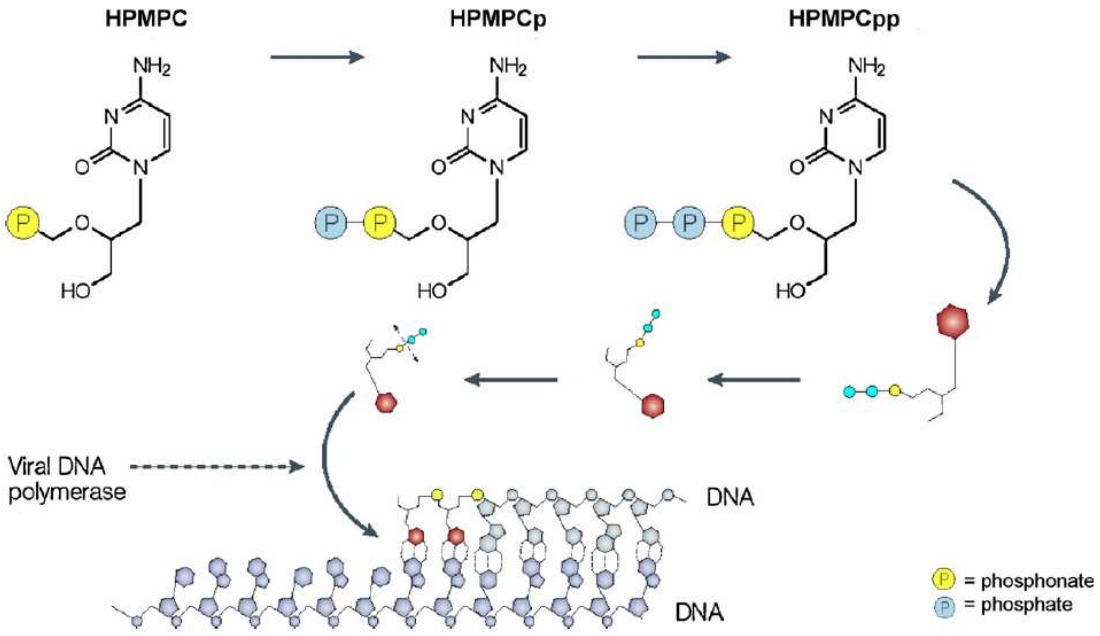
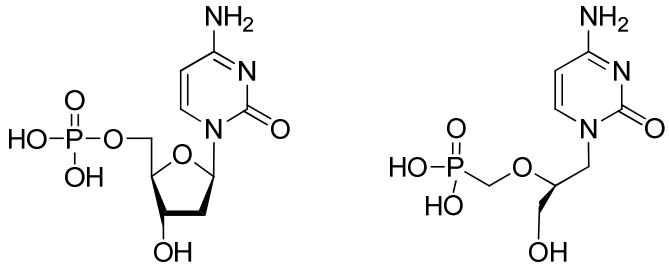


Figure 21. Mechanism of action of cidofovir.[154]

[155] Ciesla, S.L.; Trahan, J.; Wan, W.B.; Beadle, J.R.; Aldern, K.A.; Painter, G.R.; Hostetler, K.Y. *Antivir. Res.* **2003**, *59*, 163-171. (b) Keith, K.A.; Wan, W.B.; Ciesla, S.L.; Beadle, J.R.; Hostetler, K.Y.; Kern, E.R. *Antimicrob. Agents Chemother.* **2004**, *48*, 1869-1871. Lebeau, I.; Andrei, G.; Dal Pozzo, F.; Beadle, J.R.; Hostetler, K.Y.; De Clercq, E.; van den Oord, J.; Snoeck, R. *Antimicrob. Agents Chemother.* **2006**, *50*, 2525-2529.

For instance, cidofovir ((*S*)-HPMPC, Vistide®)[152b,156,157] is a mimic of deoxy-cytidine-5'-monophosphate (Figure 22) and is licensed as an injectable antiviral medication for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients. It suppresses CMV replication by potent and selective inhibition of viral DNA synthesis. Furthermore, the great potential of cidofovir in the treatment of poxvirus infections contributes significantly to its popularity as, at present, there are any therapeutic alternatives.[158] However, HPMPC has to be administrated intravenously because of poor oral absorption[159] and it exhibits nephrotoxicity after prolonged treatments.[160] These disadvantages limit the administrable dose and the efficiency of the medicament. Moreover, strains of the vaccinia virus resistant to HPMPC have been reported.[161]



Deoxy-cytidine-5'-monophosphate **Cidofovir (HPMPC)**

Figure 22. Cidovofir, mimic of the deoxy-cytidine-5’-monophosphate.

Because of therapeutic potential and to circumvent toxicity problems, novel acyclic nucleoside phosphonate analogues have been investigated. In this perspective, several approaches for the synthesis and modification of ANPs either on the nucleoside base or on the side chain have been developed. Structure-antiviral activity relationship (SAR) studies have demonstrated that the margins of structural alteration on the side chain are very narrow and

[156] (a) Holý, A. *Nucleos. Nucleot.* **1987**, *6*, 147-155. (b) Bronson, J.J.; Ghazzouli, I.; Hitchcock, M.J.; Webb, R.R.; Martin, J.C. *J. Med. Chem.* **1989**, *32*, 1457-1463. (c) Holý, A.; Votruba, I.; Merta, A.; Cerny, J.; Vesely, J.; Vlach, J.; Sediva, K.; Rosenberg, I.; Otmar, M.; Hrebabecky, H. *Antiviral Res.* **1990**, *13*, 295-311.

[157] For reviews on clinical applications, see: (a) Snoeck, R.; Sakuma, T.; De Clercq, E.; Rosenberg, I.; Holý, A. *Antimicrob. Agents Chemother.* **1988**, *32*, 1839-1844. (b) Naesens, L.; Snoeck, R.; Andrei, G.; Balzarini, J.; Neyts, J.; De Clercq, E. *Antivir. Chem. Chemother.* **1997**, *8*, 1-23. (c) De Clercq, E. *Collect. Czech. Chem. Commun.* **1998**, *63*, 480-506. (c) Safrin, S.; Cherrington, J.; Jaffe, H.S. *Adv. Exp. Med. Biol.* **1999**, 458, 111-120. (d) De Clercq, E.; Andrei, G.; Balzarini, J.; Hatse, S.; Liekens, S.; Naesens, L.; Neyts, J.; Snoeck, R. *Nucleos. Nucleot.* **1999**, *18*, 759-771. (e) Snoeck, R.; Noel, J.C.; Muller, C.; De Clercq, E.; Bossens, M. *J. Med. Virol.* **2000**, *60*, 205-209.

[158] (a) De Clercq, E. *Antiviral Res.* **2002**, *55*, 1-13. (b) De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, *14*, 289-300. (c) Magee, W.C.; Aldern, K.A.; Hostetler, K.Y.; Evans, D.H. *Antimicrob. Agents Chemother.* **2008**, *52*, 586-597.

[159] (a) Beadle, J.R.; Hartline, C.; Aldern, K.A.; Rodriguez, N.; Harden, E.; Kern, E.R.; Hostetler, K.Y. *Antimicrob. Agents Chemother*, **2002**, *46*, 2381-2386. (b) Kern, E.R.; Hartline, C.; Harden, E.; Keith, K.; Rodriguez, N.; Beadle, J.R.; Hostetler, K.Y. *Antimicrob. Agents Chemother.* **2002**, *46*, 991-995.

[160] (a) Jacobson, M. *N. Engl. J. Med.* **1997**, *337*, 105-114. (b) Cundy, K.C. *Clin. Pharmacokinet.* **1999**, *36*, 127-143.

[161] (a) Andrei, G.; Gammon, D.B.; Fiten, P.; De Clercq, E.; Opdenakker, G.; Snoeck, R.; Evans, D.H. *J. Virol.* **2006**, *80*, 9391-9401. (b) Becker, M.N.; Obraztsova, M.; Kern, E.R.; Quenelle, D.C.; Keith, K.A.; Prichard, M.N.; Luo, M.; Moyer, R.W. *Virol J* **2008**, *5*, 58-65.

that the specificity of antiviral action is mainly determined by its structure.[162] Two families of purine and pyrimidine ANPs with promising activities have emerged: 2'-(phosphonomethoxy)alkyl and unsaturated phosphonoalkenyl derivatives.

1.2. Synthesis of Acyclic (Phosphonomethoxy)alkyl Nucleosides

It has already been well established that 2'-(phosphonomethoxy)alkyl (PMA) derivatives of purine and pyrimidine bases possess significant antiviral and cytostatic activity.[163] According to their activity spectrum,[153] they can be classified in two categories (Figure 23): (i) the "HPMP" (3'-hydroxy-2'-(phosphonomethoxy)propyl) derivatives, comprising among others the adenine derivative HPMPA,[164] its guanine counterpart HPMPG,[165] and the cytosine derivative HPMPC (Cidofovir),[157] which are active against a broad variety of DNA viruses, and (ii) the "PME" (2'-(phosphonomethoxy)ethyl) and "PMP" (2'-(phosphonomethoxy)propyl) derivatives, represented by, respectively, PMEA (adefovir)[152,166] and PMPA (tenofovir),[167] which are primarily active against hepadna- and retroviruses like HIV. Substitution of the 2'-(phosphonomethoxy)ethyl chain of PME congeners at the position *C*-2' by a hydroxymethyl group led to ANPs of the HPMP type and a methyl group affords PMP derivatives. Interestingly, any other variation of the length or substitution at the position *C*-2' of the side chain resulted in total loss of antiviral activity.[168]

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[162] Holý, A.; Günter, J.; Dvořáková, H.; Masojídková, M.; Andrei, G.; Snoeck, R.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1999**, *42*, 2064-2086.

[163] Reviews: (a) Holý, A. in *"Advances in Antiviral Drug Design"*; De Clercq, E., Ed.; JAI Press: Greenwich, United States, **1994**, 179-232. (b) Holý, A. in *"Recent Advances in Nucleosides: Chemistry and Chemotherapy"*; Chu, C.K., Ed.; Elsevier Science B.V., **2002**, 167-238.

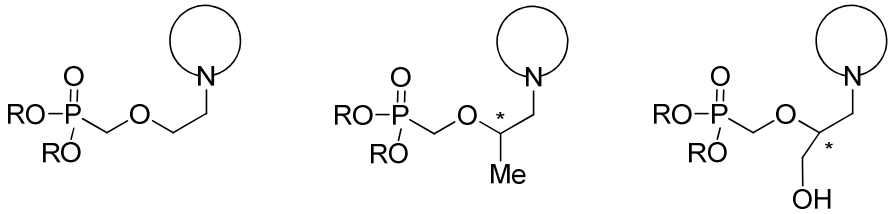
[164] (a) Baba, M.; Konno, K.; Shigeta, S.; De Clercq, E. *Eur. J. Clin. Microbiol. Infect. Dis.* **1987**, *6*, 158-160. (b) Maudgal, P.C.; De Clercq, E.; Huyghe, P. *Invest. Ophthalmol. Vis. Sci.* **1987**, *28*, 243-248. (c) Mul, Y.M.; van Miltenburg, R.T.; De Clercq, E.; Van der Vliet, P.C. *Nucl. Acids Res.* **1989**, *17*, 8917-8929.

[165] (a) Terry, B.J.; Mazina, K.E.; Tuomari, A.V.; Haffey, M.L.; Hagen, M.; Feldman, A.; Slusarchyk, W.A.; Young, M.G.; Zahler, R.; Field, A.K. *Antiviral Res.* **1988**, *10*, 235-251. (b) Yu, K.L.; Bronson, J.J.; Yang, H.; Patick, A.; Alam, M.; Brankovan, V.; Datema, R.; Hitchcock, M.J.; Martin, J.C. *J. Med. Chem.* **1992**, *35*, 2958-2969. (c) Smee, D.F.; Barnett, B.B.; Sidwell, R.W.; Reist, E.J.; Holý, A. *Antiviral Res.* **1995**, *26*, 1-9.

[166] (a) Pauwels, R.; Balzarini, J.; Schols, D.; Baba, M.; Desmyter, P.; Rosenberg, I.; Holý, A.; De Clercq, E. A*ntimicrob. Agents Chemother.* **1988**, *32*, 1025-1030. (b) Balzarini, J.; Naesens, L.; Herdewijn, P.; Rosenberg, I.; Holý, A.; Pauwels, R.; Baba, M.; Johns, D.G.; De Clercq, E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 332-336.

[167] (a) Balzarini, J.; Holý, A.; Jindřich, J.; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. *Antimicrob. Agents Chemother.* **1993,** *37*, 332-338. (b) Holý, A., Masojídková, M. *Collect. Czech. Chem. Commun.* **1995,** *60*, 1196-1212. (c) Holý,, A.; Dvořáková, H.; Masojídková, M. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1390-1409. (d) Balzarini, J.; Aquaro, S.; Perno, C. F.; Witvrouw, M.; Holý, A.; De Clercq, E. *Biochem. Biophys. Res. Commun.* **1996**, *219*, 337-341.

[168] (a) Kim, C.U.; Luh, B.Y.; Misco, P.F.; Bronson, J.J.; Hitchcock, M.J.; Ghazzouli, I.; Martin, J.C. *J. Med. Chem.* **1990**, *33*, 1207-1213. (b) Dvořáková, H.; Holý, A.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1994**, *59*, 2069-2094. (c) Liboska, R.; Masojídková, M.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1996**, *61*, 313-332. (d) Alexander, P.; Krishnamurthy, V.V.; Prisbe, E. J. *J. Med. Chem.* **1996**, *39*, 1321-1330. (e) Kim, A.; Hong, J.H.; Oh, C.H. *Nucleos. Nucleot. Nucl.* **2006**, *25*, 1399-1406.



"PME" **"PMP"** **"HPMP"**

Figure 23. 2'-(Phosphonomethoxy)alkyl (PMA) derivatives of purine and pyrimidine bases.

a) Preparation of the 2'-(Phosphonomethoxy)alkyl side chain (PME, PMP, HPMP):

There are two approaches for the preparation of 2'-(phosphonomethoxy)alkyl derivatives of purine and pyrimidine bases (Scheme 29): (a) condensation of the appropriate *N*-(2-hydroxyalkyl) heterocyclic base with dialkyl phosphonate methyl tosylate in the presence of sodium or lithium hydride or (b) alkylation of the heterocyclic base with an appropriate organophosphorus synthon bearing the features of the side chain.

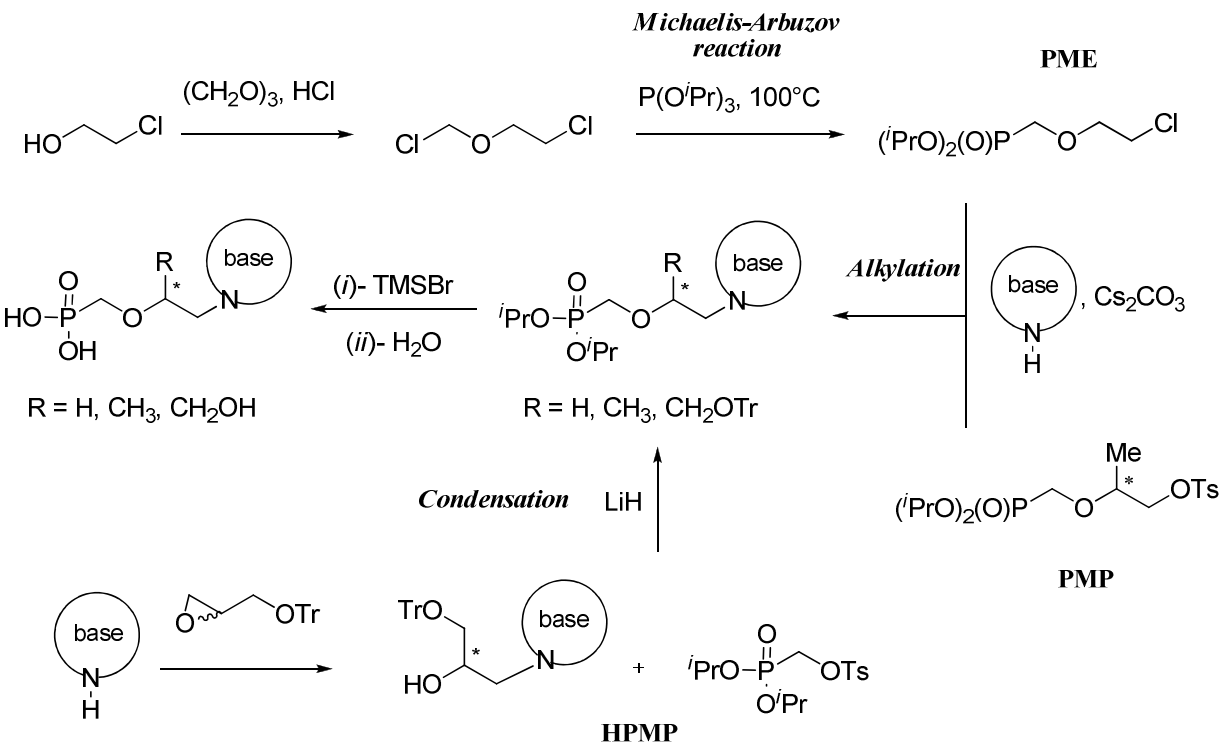
This latter method has been mostly applied to the synthesis of PME and PMP nucleotide analogues. Di*iso*propyl 2-(chloroethoxy)methylphosphonate, obtained *via* Michaelis-Arbuzov reaction[169] with trialkyl phosphate (Scheme 29), was used as phosphonate synthon for PME series.[162,170] While PMP derivatives were afforded by alkylation with the propyl tosylate analogue.[167c] After alkylation, the diester purine or pyrimidine phosphonate intermediates were converted to the free phosphonic acids by transsilylation with bromotrimethylsilane (TMSBr) followed by alkaline hydrolysis of the intermediary bis(trimethylsilyl)ester.

Preparation of HPMP derivatives has been usually realized following the strategy (a) (Scheme 29).[171] Treatment of purine or pyrimidine bases with (*R*)- or (*S*)-tritylglycidol gave 2-hydroxy-3-(trityloxy)propyl intermediates which were directly reacted with di*iso*propyl [(tosyloxy)methyl]phosphonate. The resulting trityl-containing diester was treated with TMSBr to deprotect simultaneously both trityl and phosphonate ester groups.

[169] (a) Arbuzov, B.A. *Pure Appl. Chem.* **1964**, *9*, 307-335. (b) Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

[170] Holý, A.; Rosenberg, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **1989**, *54*, 2190-2210.

[171] (a) Holý, A. *Collect. Czech. Chem. Commun.* **1993**, *58*, 649-674. (b) Holý, A.; Votruba, I.; Tloušťová, E.; Masojídková, M. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1545-1592. (c) Valiaeva, N.; Beadle, J.R.; Aldern, K.A.; Trahan, J.; Hostetler, K.Y. *Antiviral Res.* **2006**, *72*, 10-19.



Scheme 29. Synthesis of 2'-(phosphonomethoxy)alkyl of purine and pyrimidine bases.

b) Modification of the heterocycle:

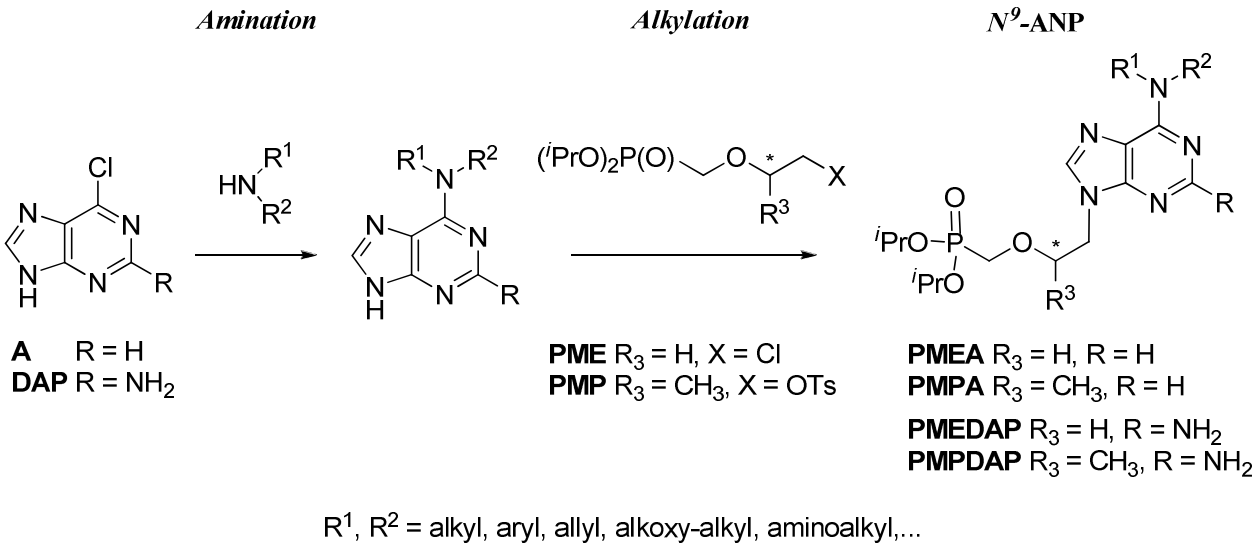
Additional acyclic nucleotide analogues of the PMA-type were prepared by direct transformations on the heterocyclic base investigating systematically the relation structure-activity for PMP, PME or HPMP series.[163a] Halogenation, transformation of halogeno derivatives *via* cross-coupling reaction, hydrolysis and/or deamination reactions were performed either on the appropriate *N*-PMA intermediates or on the free phosphonic derivatives.[162,172] SAR studies revealed that the pharmacophore of 9-substituted purine acyclic nucleoside phosphonates is characterized by the presence of amino groups at the position *C*-2 and/or *C*-6 of the pyrimidine part of the purine system. The role of the amino group may consist just in its basicity or in the formation of hydrogen bonds with some (enzyme) counterparts. It comprises N^9-PME or N^9-PMP derivatives bearing adenine (A),[167d] guanine (G),[165b] or 2,6-diaminopurine (DAP)[167a,d] base and their 8-aza and 3-deazapurine congeners.[173] While N^6-substitution in adenine and 2,6-diaminopurine derivatives still preserves the (antiviral and/or cytostatic) activity in the N^9-PME and N^9-(*R*)or(*S*)-PMP

[172] (a) Hocek, M.; Masojídková, M.; Holý, A. *Collect. Czech. Chem. Commun.* **1997**, *62*, 136-146. (b) Hockova, D.; Masojídková, M.; Holý, A. *Collect. Czech. Chem. Commun.* **2005**, *70*, 247-258.

[173] (a) Dvořáková, H.; Holý, A. *Collect. Czech. Chem. Commun.* **1993**, *58*, 1419-1429. (b) Franchetti, P.; Sheikha, G. A.; Cappellacci, L.; Messina, L.; Grifantini, M.; Loi, A. G.; Demontis, A.; Spiga, M. G.; La Colla, P. *Nucleos. Nucleot.* **1994**, *13*, 1707-1719. (c) Franchetti, P.; Abusheikha, G.; Cappellacci, L.; Grifantini, M.; Demontis, A.; Piras, G.; Loi, A. G.; La Colla, P. *J. Med. Chem.* **1995**, *38*, 4007-4013. (d) Holý, A.; Dvořáková, H.; Jindřich, J.; Masojídková, M.; Buděšínský , M.; Balzarini, J.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996,** *39*, 4073-4088.

series,[171b,174] other alterations of amino groups generally result in complete loss of activity.[172,175]

As depicted in Scheme 30, the preparation of N^9-ANPs substituted at the 6-amino function of A or DAP consisted in transformation of 6-chloropurine or 2-amino-6-chloropurine by action of excess primary or secondary amines followed by alkylation of the resulting N^6-substituted base with proper phosphonate synthons.[174c] N^6-substituted ANPs could also be synthesised *via* first alkylation of the chloropurine prior to the amination (Scheme 31). N^7-isomers of PMA adenine and 2,6-diaminopurine were obtained as by-product under the conditions of this second route.



Scheme 30. Synthesis of N^6-substituted adenine and 2,6-diaminopurine N^9-PMA derivatives.

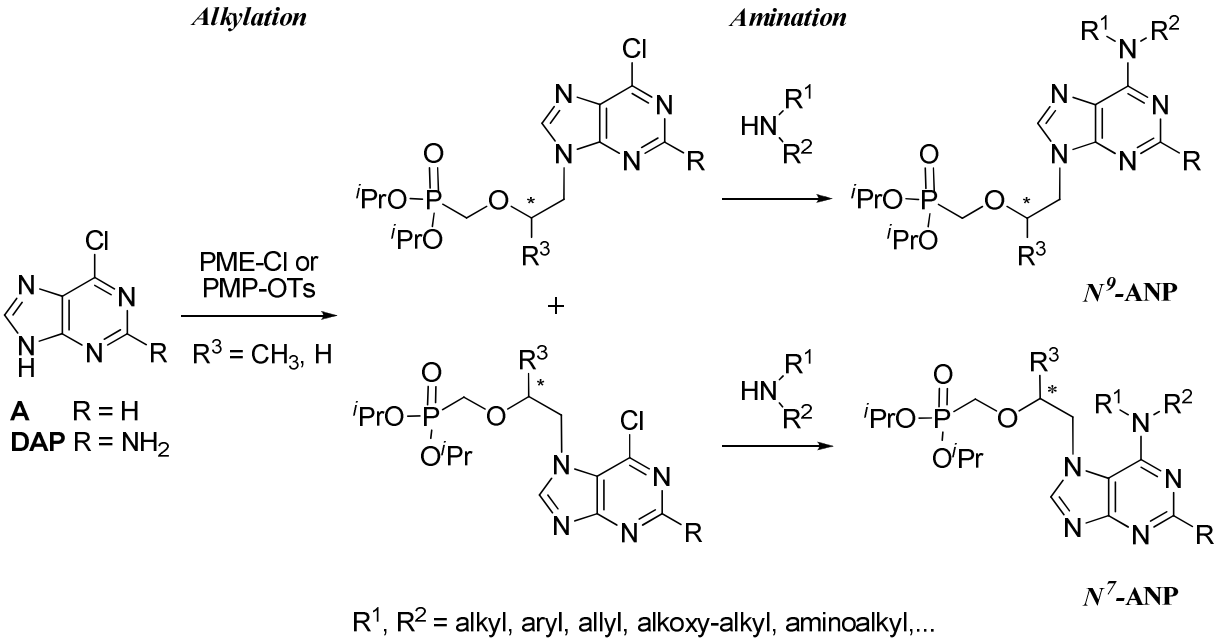
All other purine (hypoxanthine, xanthine)[175a] as well as all pyrimidine (thymine, uracil)[152b,162] PMA-derivatives lacking the amino function were inactive against DNA viruses. Except for the cytosine derivative, pyrimidine ANPs have been less explored than purine analogues, their inhibitory ability being limited to thymidine phosphorylase.[176] Alterations of cytosine, thymine or uracil bases and their 6-aza and 3-deazapyrimidine congeners consisted mainly in halogenation or cross-coupling reactions to introduce halogen, alkyl or aryl

[174] (a) Holý, A.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq E. *Antiviral Res.* 1995, *26*, A231. (b) Holý, A.; Zídek, Z.; Votruba, I. *Collect. Czech. Chem. Commun.* **1996**, *61*, S182-S187.

[175] (a) Hocek, M.; Masojídková, M.; Holý, A. *Collect. Czech. Chem. Commun.* **1995**, *60*, 875-882. (b) Hocek, M.; Masojídková, M.; Holý, A.; Andrei, G.; Snoeck, R.; Balzarini, J.; De Clercq, E. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1525-1537.

[176] Esteban-Gamboa, A.; Balzarini, J.; Esnouf, R.; De Clercq, E.; Camarasa, M.-J.; Pérez-Pérez, M.-J. *J. Med. Chem.* **2000**, *43*, 971-983.

substituents at the *C*-5 position.[162,177] Alkylation of pyrimidine bases with phosphonoalkyl groups could be directed either at the *N*-1, *N*-3, *C*-6 or *O*-4 positions.



Scheme 31. Synthesis of N^6-substituted adenine and 2,6-diaminopurine N^9-PMA and N^7-PMA derivatives.

More recently, a new class of ANP analogues has been designed where the base moiety is a pyrimidine such as 2,4-diaminopyrimidine (DAPy) linked to the aliphatic phosphonate side chain *via* an ether linkage through an oxygen atom at the *C*-6 position (instead of the *N*-1 position) of the pyrimidine ring. Interestingly, molecular modelling have demonstrated that these novel 6-[2'-(phosphonomethoxy)ethoxy] (PMEO) DAPy series mimic an incomplete purine ring (Figure 24).[178] Compounds that contain a substituent at the *C*-5 position of the pyrimidine base may even better mimic the purine skeleton.

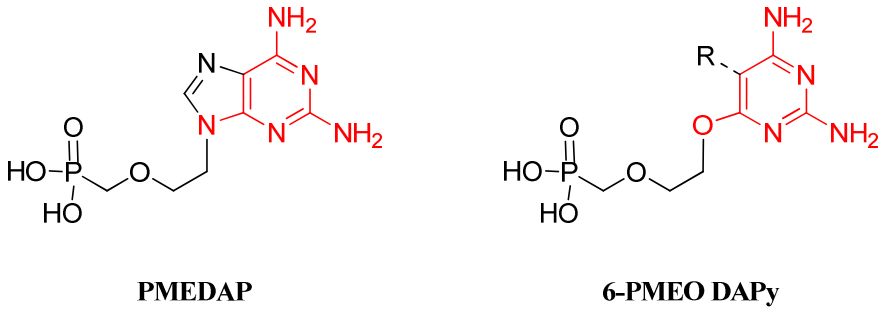
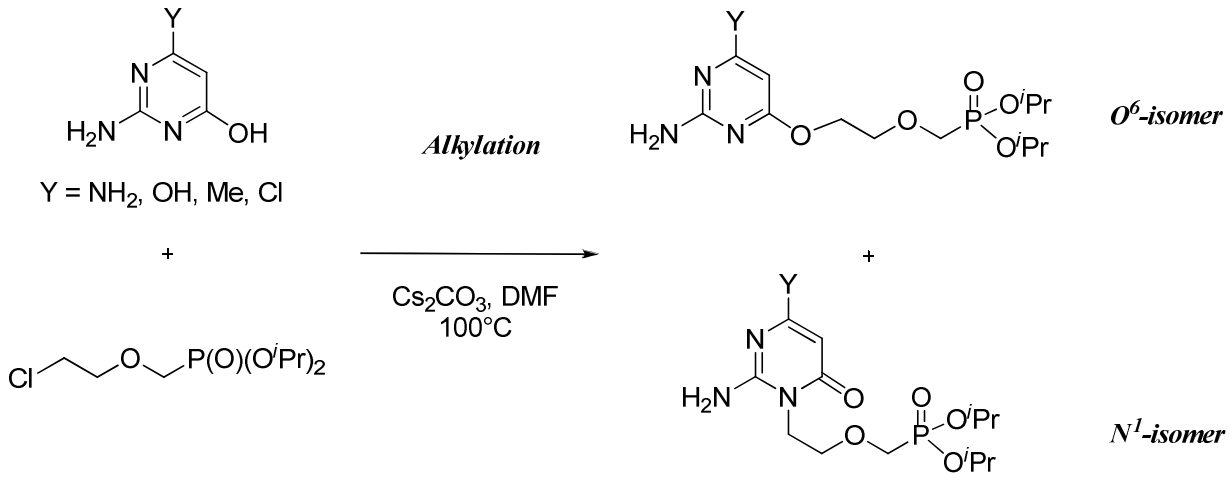


Figure 24. Structural similarities between PMEDAP and 6-PMEO DAPy derivatives.

[177] (a) Pomeisl, K.; Pohl, R.; Holý, A.; Votruba, I. *Collect. Czech. Chem. Commun.* **2005**, 70, 1465-1481. (b) Pomeisl, K.; Pohl, R.; Holý, A.; Votruba, I. *Collect. Czech. Chem. Commun.* **2006**, 71, 595-624. (c) Pomeisl, K.; Votruba, I.; Holý, A.; Pohl, R. *Nucleos. Nucleot. Nucl.* **2007**, *26*, 1025-1028. (d) Pomeisl, K.; Holý, A.; Votruba, I.; Pohl, R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1364-1367. (e) Pomeisl, K.; Holý, A.; Votruba, I. *Nucleic Acids Symposium Series No.* **2008**, *52*, 657-658.

[178] Ying, C.; Holý, A.; Hocková, D.; Havlas, Z.; De Clercq, E.; Neyts, J. *Antimicrob. Agents Chemother.* **2005**, *49*, 1177-1180.

Alkylation of 2-amino-4-substituted-6-hydroxypyrimidines by the di*iso*propyl 2-(chloroethoxy)methylphosphonate afforded a mixture of O^6-alkyl and N^1-alkyl regioisomers (Scheme 32).[179] It should be noted that the reaction of 2,4-diamino-6-hydroxypyrimidine with [(*R*)- or (*S*)-2-(di*iso*propylphosphoryl)methoxy]propyl tosylate gave the enantiomeric 2,4-diamino-O^6-PMP-pyrimidines without formation of the N^1-isomers. The isomeric diesters gave, on treatment with bromotrimethylsilane followed by hydrolysis, the free phosphonic acids.



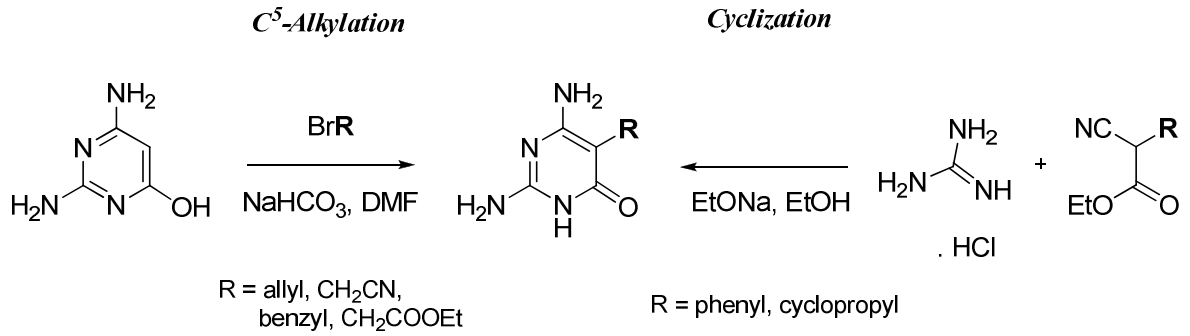
Scheme 32. Synthesis of 2-amino-4-substituted O^6-PMEO-pyrimidines and N^1-PME-pyrimidin-6-ones.

The similar alkylation strategy applied to DAPy bases bearing various substituents at the *C*-5 position led to the preparation of 5-substituted 2,4-diamino-6-[2'-(phosphonomethoxy) ethoxy]pyrimidines and their N^1-regioisomers.[180,181] Two synthetic methods were used to prepare the starting 5-substituted-2,4-diaminopyrimidine bases (Scheme 33): (a) direct regioselective C^5-alkylation of pyrimidine base with strong electrophiles or (b) formation of pyrimidine ring by cyclization of ethyl cyanoacetates with guanidine.

[179] Holý, A.; Votruba, I.; Masojídková, A.G.; Snoeck, R.; Neasens, L.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2002**, *45*, 1918-1929.

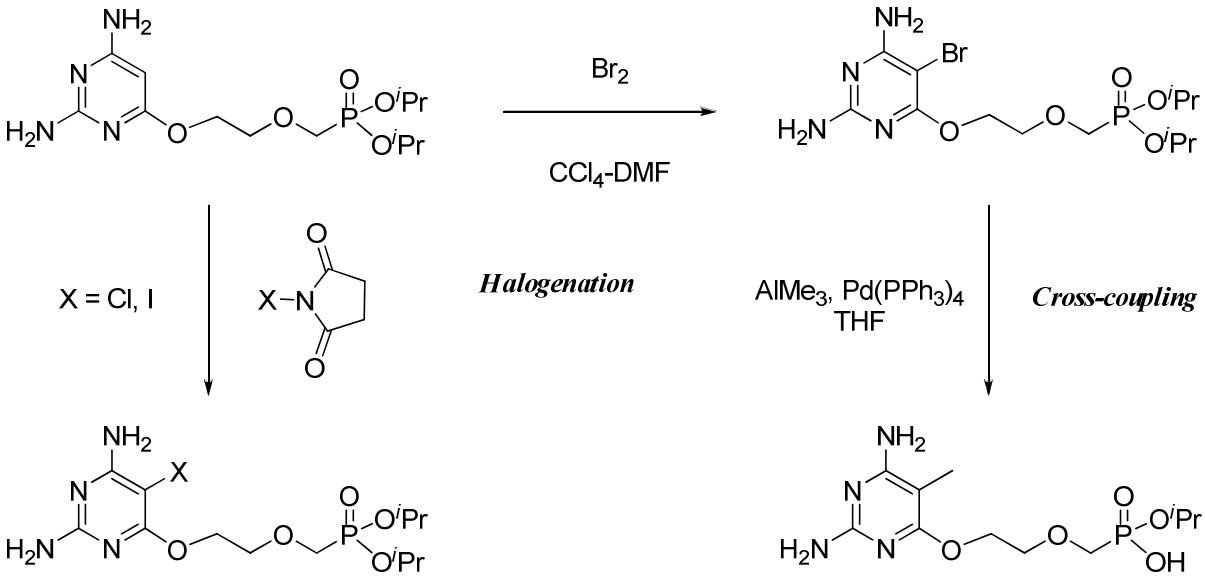
[180] Hocková, D.; Holý, A.; Holý, M.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2003**, *46*, 5064-5073.

[181] Hocková, D.; Holý, A.; Holý, M.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem.* **2004**, *12*, 3197-3202.



Scheme 33. Direct C^5-alkylation of 2,4-diamino-6-hydroxypyrimidine base or formation of pyrimidine ring by cyclization.

5-Halogeno derivatives (Br, Cl, I) were also prepared *via* halogenation reactions (Scheme 34) on the preformed diester protected molecule of the O^6-2,4-diamino-isomer. Interestingly, deprotection of the 5-iodo derivative under TMSBr conditions gave the 5-unsubstituted 2,4-pyrimidine derivative as the main product. As an alternative approach to introduce an alkyl on the *C*-5 position, the cross-coupling of 5-bromo ANP with organometallic reagents was also considered. Using trimethylaluminum, the 5-methyl derivative was obtained in moderate yield as a mixture of mono- and diester (Scheme 34). Attempts to extend this method to the synthesis of the 5-ethyl analogue using triethylaluminum under the same conditions failed.



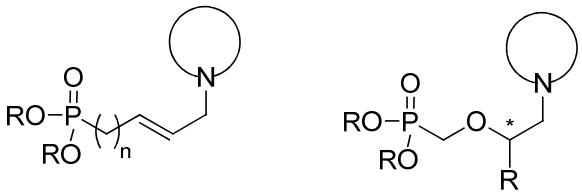
Scheme 34. Modulation on acyclic 2,4-diaminopyrimidine phosphonates.

While none of the N^1-[2'-(phosphonomethoxy)ethyl]pyrimidin-6-one isomers have antiviral activity, among 6-PMEO pyrimidine series, compounds derived from 2,4-diaminopyrimidine, notably 5-Me, 5-Br and 5-Cl, and 2-amino-4-hydroxypyrimidine

significantly inhibited replication of retroviruses and herpes viruses in cell culture.[182] SAR studies suggested that 6-PMEO or 6-PMPO pyrimidines must bear an (unsubstituted) amino group concomitantly on both *C*-2 and *C*-4, or an amino on *C*-2 and an OH group on *C*-4, to display antiviral activity.[179]

1.3. Synthesis of Unsaturated Phosphonoalkenyl Nucleosides

Acyclic unsaturated phosphonoalkenyl nucleoside derivatives contain a double bond, mainly on the position $C^{2'}$-$C^{3'}$ of the side chain (Figure 25). Since the ethenyl unit has an appreciable electron-withdrawing effect,[183] alkenylphosphonic acid should conserve the electronegativity usually brought by the oxygen atom in phosphonomethoxy analogues.[184] This structural feature of the unsaturated carbohydrate mimic has previously influenced the ability of cyclic nucleoside analogues to participate in antiviral mechanisms.[185] For example, the double bond present in the sugar moiety of stavudine™ or abacavir™, two potent inhibitors of HIV replication, appears to play a crucial role in binding to the HIV reverse transcriptase (Figure 26).[186]



"Phosphonalkenyl" **"PMA"**

Figure 25. Acyclic unsaturated phosphonoalkenyl and phosphonomethoxy derivatives.

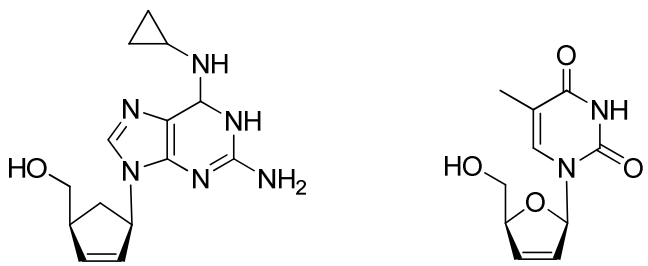
[182] (a) Balzarini, J.; Pannecouque, C.; De Clercq, E.; Aquaro, S.; Perno, C.-F.; Egberink, H.; Holý, A. *Antimicrob. Agents Chemother.* **2002**, *46*, 2185-2193. (b) De Clercq, E.; Andrei, G.; Balzarini, J.; Leyssen, P.; Naesens, L.; Neyts, J.; Pannecouque, C.; Snoeck, R.; Ying, C.; Hocková, D.; Holý, A. *Nucleos. Nucleot. Nucl.* **2005**, *24*, 331-341. (c) Balzarini, J.; Schols, D.; Van Laethem, K.; De Clercq, E.; Hocková, D.; Masojídková, A.G.; Holý, A. *J. Antimicrob. Chemother.* **2007**, *59*, 80-86.

[183] Hansch, C.; Leo, A.J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, United States, **1979**.

[184] Kim, C.U.; Luh, B.Y.; Misco, P.F.; Bronson, J.J.; Hitchcock, M.J.M.; Ghazzouli, I.; Martin, J.C. *J. Med. Chem.* **1990**, *33*, 1207-1213.

[185] (a) Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemother.* **1987**, *31*, 907-910. (b) Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E.; Desmyter, J.; Vandeputte, M. *Biochem. Biophys. Res. Commun.* **1987**, *142*, 128-134. (c) Lin, T.S.; Schinazi, R.F.; Prusoff, W.H. *Biochem. Pharmacol.* **1987**, *36*, 2713-2718. (d) Kim, C.U.; Luh, B.Y.; Martin. J.C. *J. Org. Chem.* **1991**, *56*, 2642-2647. (e) De Clercq E. *AIDS* **1992**, *8*, 119-134. (f) Tisdale, M.; Alnadaf, T.; Cousens, D. *Antimicrob. Agents Chemother.* **1997**, *41*, 1094-1098. (g) Hervey, P.S.; Perry, C.M. *Drugs* **2000**, *60*, 447-479.

[186] Choo, H.; Chong, Y.; Chu. C.K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1993-1996.



Abacavir **Stavudine**

Figure 26. Structure of Abacavir™ and Stavudine™.

a) General preparation of unsaturated phosphonates:

Unsaturated phosphonates were primarily formed under the Michaelis-Arbuzov reaction,[169] or phosphonylation of unsaturated aldehydes (Pudovic reaction),[187] or metal catalyzed cross-coupling of hydrogen phosphonates to allenes or alkynes[188] (Scheme 35).

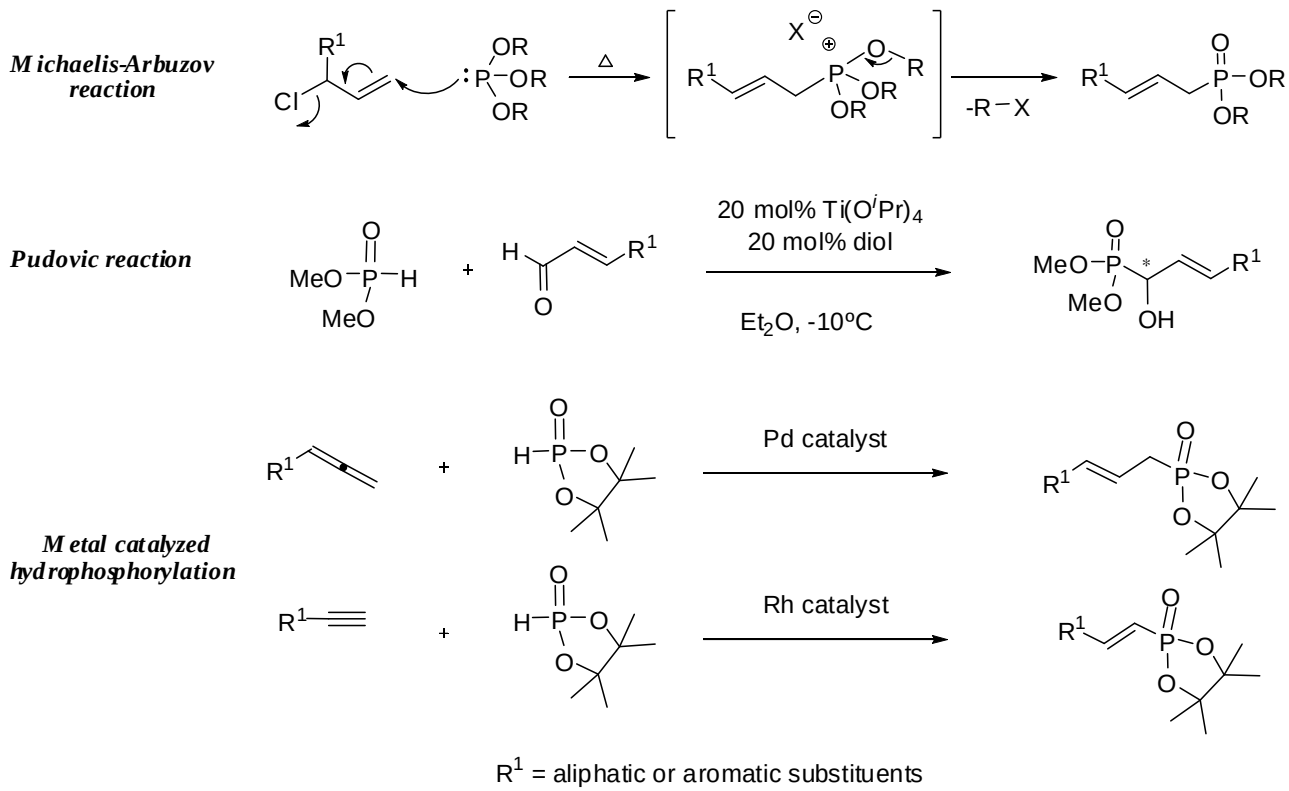
The Michaelis-Arbuzov reaction, the most versatile method for the formation of carbon-phosphorus bonds, has been widely used between α-allyl halides and trialkyl phosphites for the synthesis of dialkyl allylphosphonates.[169] Nevertheless, this method often suffers from elimination and/or loss of olefin stereochemical integrity, due to high reaction temperatures and provide low regioselectivity in the case of highly substituted phosphonate products.

Under the conditions of the Pudovic reaction, addition of dimethyl phosphite to cinnamaldehydes, catalyzed by titanium alkoxide based catalytic systems, afforded allylic α-hydroxyphosphonates.[187d-e]

Finally, the palladium-catalyzed regio- and stereoselective hydrophosphorylation of allenes, having either an aliphatic or an aromatic substituent, offered a convenient and clean route to *trans* allylphosphonates.[188b] The high reactivity of the five-membered cyclic hydrogen phosphonate could also contribute to the hydrophosphorylation of terminal alkynes, which affords high yields of the corresponding (*E*)-ethenylphosphonates with excellent regio- and stereoselectivities.[188c] Functional groups such as chloro, cyano, hydroxy, thienyl, and silyl all tolerated the reaction conditions.

[187] (a) Rath, N.P; Spilling, C.D. *Tetrahedron Lett.* **1994**, *35*, 227-230. (b) Arai, S.; Bougauchi, M.; Sasai, H.; Shibisaki, M. *J. Org. Chem.* **1996**, *61*, 2926-2927. (c) Wiemer, D.F. *Tetrahedron* **1997**, *53*, 16609-16644. (d) Groaning, M.D.; Rowe, J.; Spilling, C.D. *Tetrahedron Lett.* **1998**, *39*, 5485-5488. (e) Rowe, B.J.; Spilling, C.D. *Tetrahedron: Asymmetry* **2001**, *12*, 1701-1708.

[188] (a) Hirao, T.; Masunaga, T.; Oshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, *21*, 3595-3598. (b) Zhao, C.-Q.; Han, L. B.; Tanaka, M. *Organometallics* **2000**, *19*, 4196-4198. (c) Zhao, C.-Q.; Han, L.B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1929-1932.



Scheme 35. Different synthetic routes for the preparation of unsaturated phosphonates.

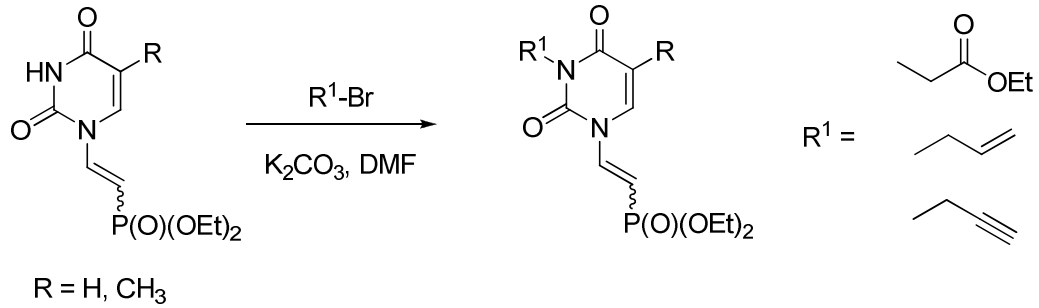
b) Synthesis of phosphonoethenyl nucleosides (PEth):

Imbach and coll. prepared series of (*Z*)- and (*E*)-diethyl-2'-(purin-9-yl/pyrimidin-1-yl)ethylen-1'-ylphosphonate using a Michael type addition for the coupling of nucleoside bases and diethylethynyl phosphonate (Scheme 36).[189] The N^1-alkylation of pyrimidine or purine bases was performed with 0.5 equivalent of potassium carbonate as base, and gave both *Z* and *E* isomers in a good overall yield. All isomers were isolated after purification by silica gel column chromatography. The isomer *ratio* (*Z*/*E*) depended upon the nature of the base as the *E* isomer becomes major for pyrimidine analogues (*Z/E* = 20:80), while *Z/E* = 80:20 for purine analogues.

Scheme 36. Synthesis of (*Z*)- and (*E*)-diethyl-2'-(purin-9-yl/pyrimidin-1-yl)ethylen-1'-ylphosphonates.

[189] Lazrek, H.B.; Rochdi, A.; Khaider, H.; Barascut, J.L.; Imbach, J.L.; Panncouque, C.; Witrouw, M.; De Clercq E. *Tetrahedron* **1998**, *54*, 3807-3816.

In order to introduce structural modification, the uracil and thymine analogues could further be alkylated at the position *N*-3 with an ethoxycarbonylmethyl, allyl or propargyl group (Scheme 37).[190] However, none of the $C^{1'}$-$C^{2'}$ unsaturated ethenylphosphonic acid nucleoside analogues showed marked *in vitro* inhibitory effect on the replication of a number of DNA and RNA virus.



Scheme 37. Alkylation on the position *N*-3 of thymine and uracil.

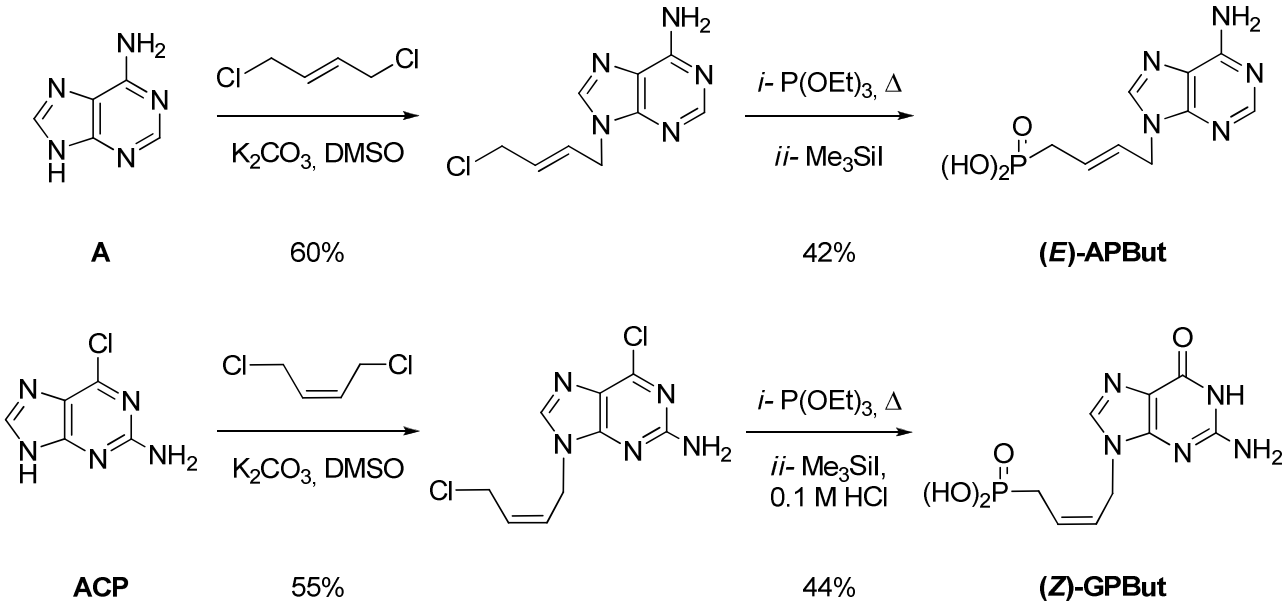
c) Synthesis of phosphonobutenyl nucleosides (PBut):

To the best of our knowledge, the first example of unsaturated alkenylphosphonic acid bearing a nucleoside base were reported in 1992 by Megati et al.[191] Following a linear approach, N^9-alkylation of adenine or 2-amino-6-chloropurine (ACP), a guanine precursor, with *cis*- or *trans*-1,4-dichloro-2-butene afforded the corresponding 9-(4-chloro-2-buten-1-y1)adenine and 2-amino-6-chloropurine (Scheme 38).[192] Subsequent Michaelis-Arbuzov reaction of the (*Z*)- or (*E*)-chloroalkene intermediates refluxing in triethyl phosphite led to the expected 2'-butenylphosphonates.[191] Dealkylation of the latter products, coupled in the case of ACP with acid hydrolysis, led to (*E*)-adenine and (*Z*)-guanine 2'-butenylphosphonic acids with moderate overall yields.

[190] Rochdi, A.; Taourirte, M.; Lazrek, H.B.; Barascut, J.L.; Imbach, J.L. *Molecules* **2000**, *5*, 1139-1145.

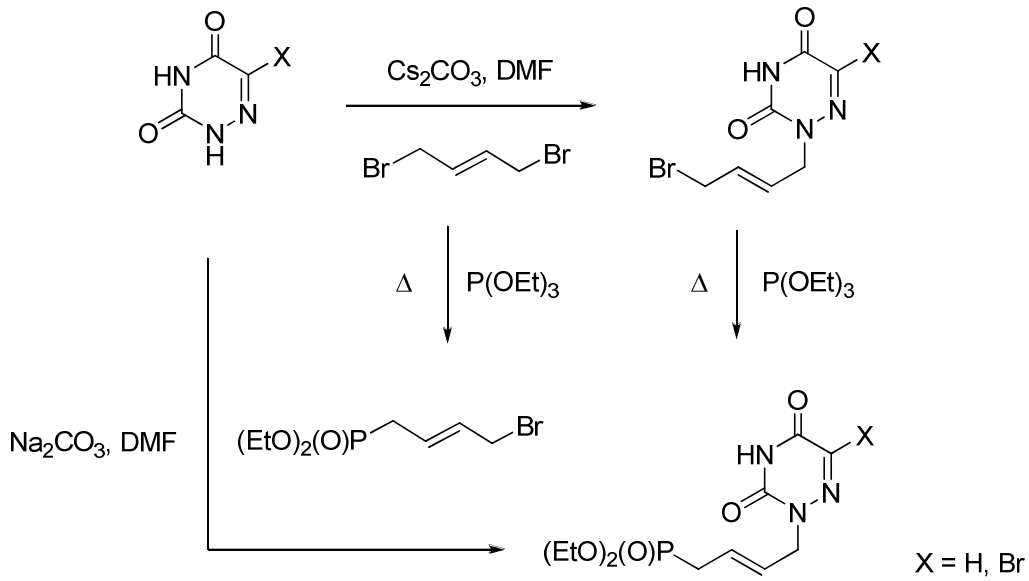
[191] Megati, S.; Phadtare, S.; Zemlicka, J. *J. Org. Chem.* **1992**, *57*, 2320-2327.

[192] (a) Phadtare, S.; Zemlicka, J. *J. Med. Chem.* **1987**, *30*, 437-440. (b) Phadtare, S.; Kessel, D.; Corbett, T.H.; Renis, H.E.; Court, B.A.; Zemlicka, J. *J. Med. Chem.* **1991**, *34*, 421-429.



Scheme 38. First reported synthesis of (*Z*)- and (*E*)-2'-phosphonobutenyl nucleosides.

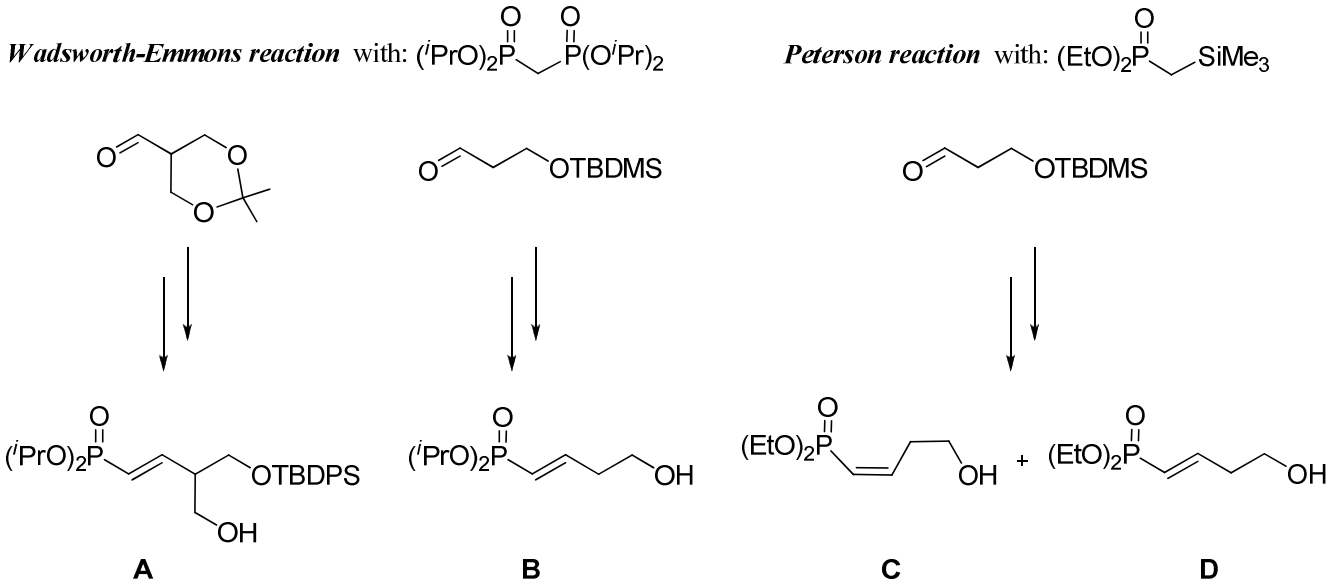
Similar strategy was applied to the synthesis of (*E*)-PBut 6-azauracil and 5-bromo-6-azauracil *via* (*E*)-bromo-alkenyl acyclonucleoside intermediates (Scheme 39).[193] A second convergent synthetic route consisted of realizing the phosphonylation of the (*E*)-1,4-dibromobutene prior the N^1-alkylation of the nucleobases. Amazingly, depyrimidination occurred when deprotection of ANPs were carried out with trimethylsilylbromide.



Scheme 39. Synthesis of (*E*)-PBut 6-azauracil and 5-bromo-6-azauracil.

[193] Kabbaj, Y.; Lazrek, H.B.; Barascut, J.L.; Imbach, J.L. *Nucleos. Nucleot. Nucl.* **2005**, *24*, 161-172.

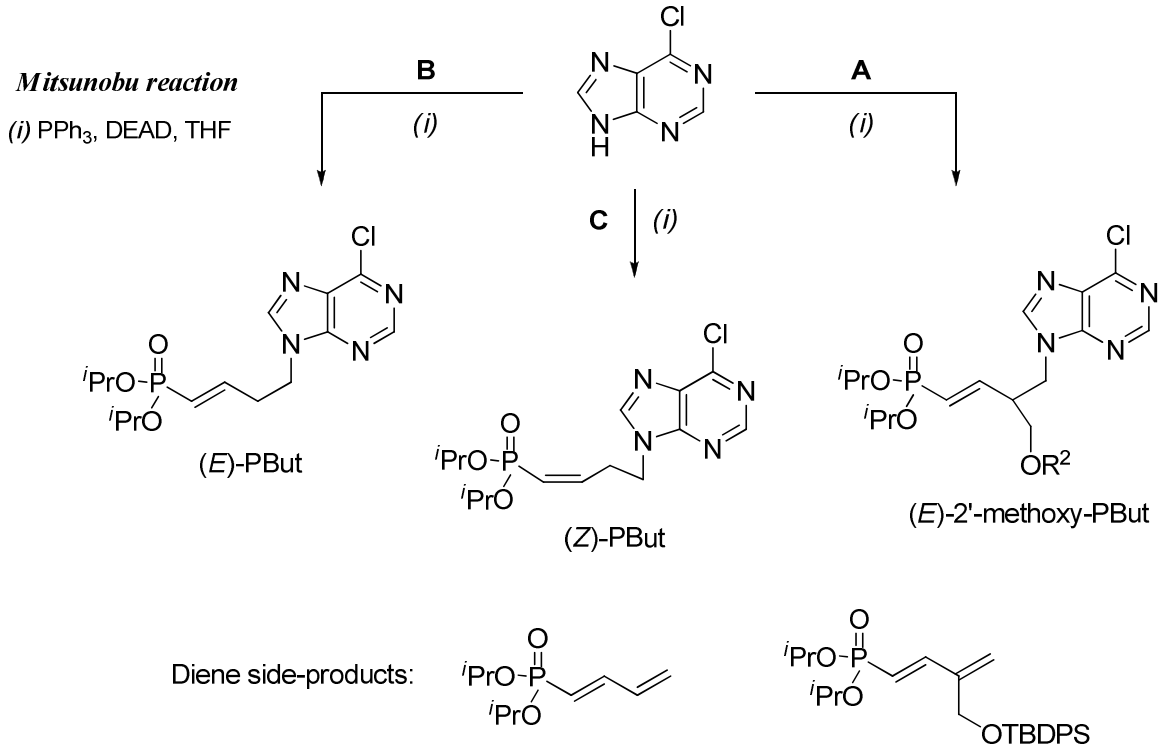
In 1993, some examples of acyclo PBut nucleoside analogues bearing the double bond on the position $C^{3'}$-$C^{4'}$ of the side chain have also been obtained using a convergent approach.[194] The alkenylphosphonate moiety of the acyclic substituents was introduced by Wadsworth-Emmons or Peterson olefination of aldehydes to afford after deprotection the desired alcohols (Scheme 40). The Wadsworth-Emmons reaction gave exclusively (*E*)-but-1-enylphosphonate isomers (**A** and **B**), while Peterson reaction provided the chromatographically separable (*Z*)- and (*E*)-alkenes (**C** and **D**) in the *ratio* of 5:2.



Scheme 40. Preparation of the (4-hydroxybut-l-enyl)phosphonate moieties.

Coupling of the 6-chloropurine with the required (4-hydroxybut-l-enyl)phosphonates under Mitsunobu conditions afforded exclusive alkylation at the *N*-9 position of the purine albeit in poor yields (Scheme 41). Moreover, substantial quantities of phosphonobutyl-dienes were observed as elimination by-products in all Mitsunobu reactions. Further adequate treatments of the PBut 6-chloropurines gave the adenine derivatives. The same strategy was used for the synthesis of PBut guanine and 2,6-diaminopurine derivatives from the coupling of 2-amino-6-chloropurine with the different alcohols and subsequent transformations. At the concentrations tested, most of the synthesized compounds showed no significant activity against HIV, CMV or HSV except in some cases albeit with reduced potency relative to phosphonomethoxy analogues.

[194] Harnden, M.R.; Parkin, A.; Parratt, M.J.; Perkins, R.M. *J. Med. Chem.* **1993**, *36*, 1343-1355.



Scheme 41. Synthesis of 6-Chloro-9-[4'-(diethoxyphosphoryl)but-3'-enyl]purines.

d) Synthesis of phosphonopentenyl nucleosides (PPen):

The phosphonopentenyl side chain (PPen) of acyclic nucleotides were designed to resemble the corresponding portion of 2',3'-didehydro-2',3'-dideoxynucleosides such as stavudine™ (Figure 27) and to improve binding of the diphosphate to the target viral polymerases.[195] It was also hypothesized that the $C^{2'}$-$C^{3'}$ unsaturated PPen structure might be more flexible than related cyclic analogues, which should increase binding within the polymerase complex and facilitate approach of the α-phosphorous to the 3'-OH of the replicating viral DNA.

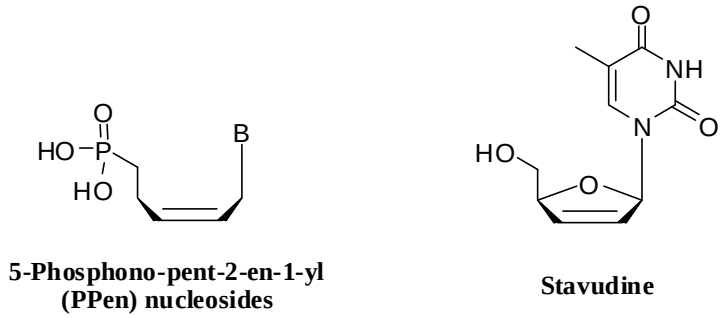
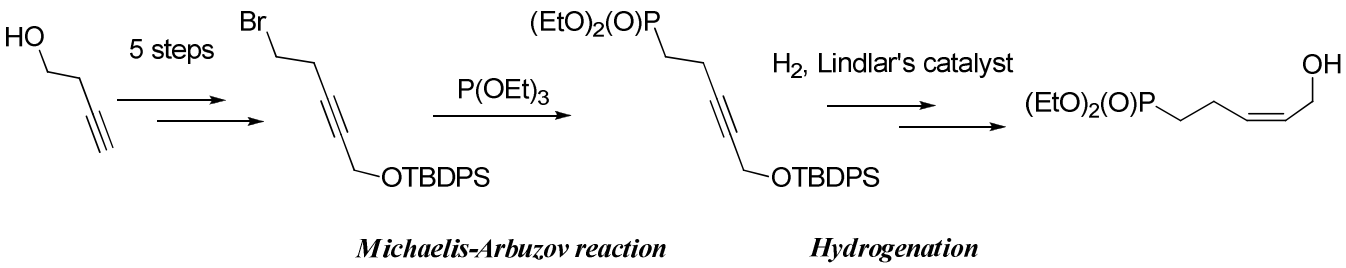


Figure 27. Structure of PPen nucleosides compared with Stavudine™.

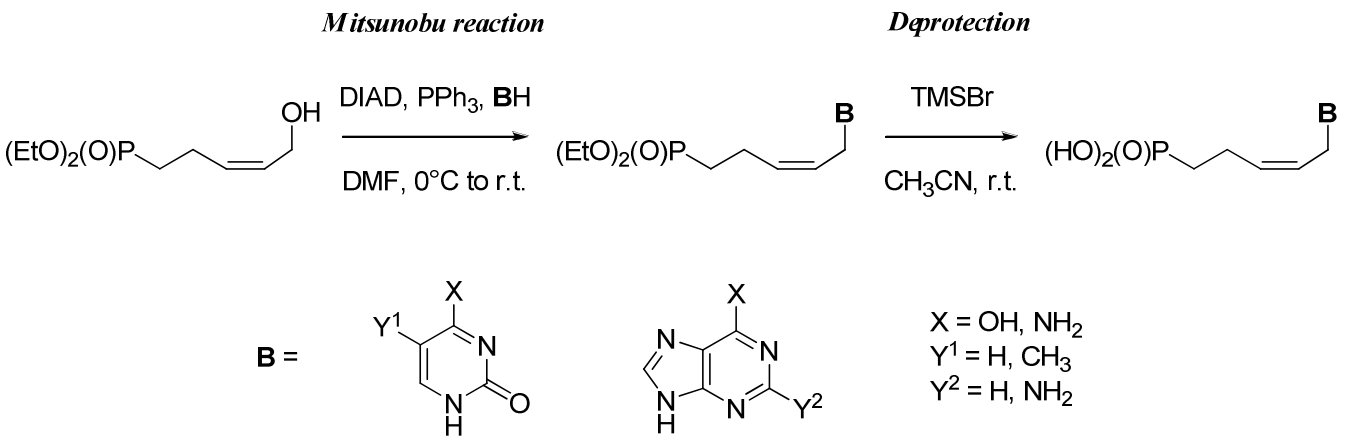
In due time of our work, Hostetler and coll. synthesized the first *Z*-series of (*Z*)-5'-phosphono-pent-2'-en-1'-yl (PPen) analogues of the bases (B) adenine, thymine, guanine,

[195] Choo, H.; Beadle, J.R.; Chong, Y.; Trahan, J.; Hostetler, K.Y. *Bioorg. Med. Chem.* **2007**, *15*, 1771-1779.

cytosine, and uracil and their hexadecyloxypropyl esters.[195] Their synthetic strategy consisted in introducing the *cis*-double bond through partial hydrogenation of a triple bond to give a hydroxyphosphonopentenyl intermediate (Scheme 42) which could be coupled to various nucleobases (Scheme 43). Thus after hydroxymethylation of 3-butyn-1-ol and subsequent bromination in 40% overall yield, the resulting silyl-protected 5-bromopent-2-yn-1-ol underwent Michaelis-Arbuzov reaction in $P(OEt)_3$ to afford the diethyl phosphonate analogue in 98% yield (Scheme 42). Partial hydrogenation over Lindlar's catalyst gave the key hydroxyphosphonate intermediate with a *cis*-double bond. Mitsunobu reaction of this compound with various nucleobases provided the (*Z*)-PPen nucleosides (Scheme 43) in moderate to good yields, followed by dealkylation using TMSBr to give the corresponding phosphonic acids.



Scheme 42. Synthesis of the key intermediate (*Z*)-diethyl 5-hydroxypent-3-enylphosphonate.



Scheme 43. Synthesis of 5'-phosphono-pent-2'-en-1'-yl nucleosides.

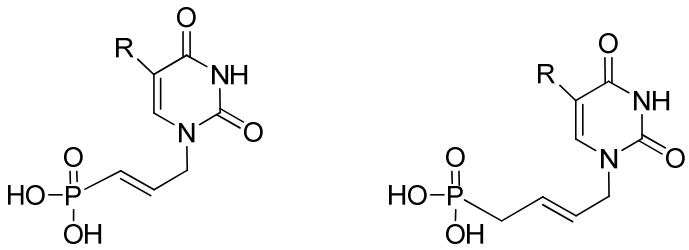
The antiviral activity of the synthesized PPen nucleosides and their hexadecyloxypropyl (HDP) derivatives were evaluated against several DNA virus (HIV, VV, HBV, HSV,…).[195,196] The unmodified PPen nucleosides (A, U, C, T, G) were inactive, probably due to the double negative charge associated with the phosphonate group that impaired transport of drug

[196] Choo, H.; Beadle, J.R.; Kern, E.R.; Prichard, M.N.; Keith, K.A.; Hartline, C.B.; Trahan, J.; Aldern, K.A.; Korba, B.E.; Hostetler, K.Y. *Antimicrob. Agents Chemother.* **2007**, *51*, 611-615.

through the cell membrane. However, when esterified with the HDP group, substantial activity was noted in most cases suggesting that the active HDP-PPen nucleosides enter cells and are metabolized to the corresponding PPen nucleoside diphosphates. HDP-PPen-G was the most broadly active PPen nucleoside. Interestingly, HDP-PPen-U did not inhibit any of the viruses against which it was tested.

1.4 Strategy Developed in our Group for the Synthesis of Unsaturated ANPs

In order to develop a more efficient procedure for synthesizing unsaturated ANPs and as part of an on-going program on orthopox virus, Agrofoglio and coworkers have recently studied the synthesis of several *hitherto* unknown acyclic nucleoside phosphonates with 2'-propenyl or 2'-butenyl side chains (Figure 28).[197] The key synthetic steps leading to these compounds involved palladium-mediated C^5-alkylation of the uracil moiety and ruthenium-catalyzed olefin cross-metathesis reaction for the assembly of the unsaturated side chain using vinyl or allyl phosphonate partners.



2-propenyl ANP **2-butenyl ANP**

Figure 28. Unsaturated acyclic C^5-modified uracil phosphonates.

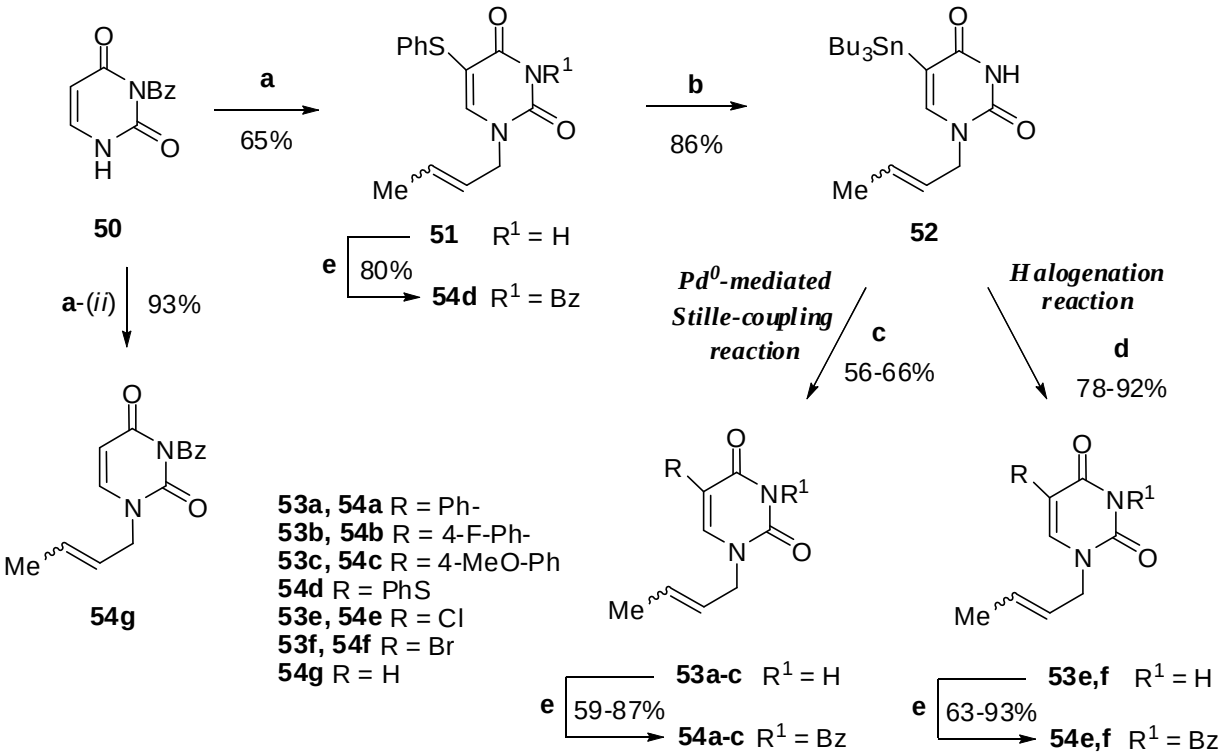
<u>a) Palladium(0)-mediated C^5-alkylation of the uracil ring:</u>

For the introduction of various functionalities on the *C*-5 position of the uracil ring, we selected the 5-phenylthiouracil derivative (**51**) as synthetic common intermediate for the construction of either C^5-halogeno- (**53e**,**f**) or C^5-aryl-substitued uracil analogues (**53a-c**) (Scheme 44). Thus, the 5-phenylthio derivative (**51**) was prepared from N^3-benzoyl uracil by (*i*) introduction of phenylthio group at the *C*-5 position, (*ii*) crotylation of the *N*-1 position, and (*iii*) debenzoylation of *N*-3 position in 65% over three steps. By treating **51** with tributyltin radical, a sulfur-extrusive stannylation[198] occurred and the desired tin derivative **52**

[197] Kumamoto, H.; Topalis, D.; Broggi, J.; Pradère, U.; Roy, V.; Berteina-Raboin, S.; Nolan, S.P.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J.-M.; Agrofoglio, L.A. *Tetrahedron* **2008**, *64*, 3517-3526.

[198] Tanaka, H.; Hayakawa, H.; Obi, K.; Miyasaka, T. *Tetrahedron* **1986**, *42*, 4187-4195.

was obtained in high yields. On the one hand, the Pd^0-mediated Stille-coupling reaction[199] involving **52** allowed for the isolation of the desired C^5-aryl substituted derivatives (**53a-c**) with yields ranging from 56 to 66%. On the other hand, compound **52** was easily converted into the 5-chloro (**53e**), 5-bromo (**53f**) derivatives by simple treatment with NCS or NBS, respectively. A final benzoylation afforded the desired protected analogues **54a-f**. Compound **54g** was obtained by simple N^1-crotylation of the N^3-benzoyl uracil **50**.



Scheme 44. Reagent and conditions: (a) (*i*) PhSH, NCS, pyridine, CH_3CN, reflux, Ar, 16 h; (*ii*) Crotyl bromide, K_2CO_3, DMF, r.t., Ar, 40 min; (*iii*) NH_3, MeOH, 0°C, 16 h; (b) Bu_3SnH, AIBN, Et_3N, toluene, reflux, Ar, 2 h; (c) RI, $PdCl_2(PPh_3)_2$ (10 mol%), CuI, DMF, r.t., Ar, 15 h; (d) NXS, THF, Ar; (e) BzCl, DMAP, *i*-Pr_2NEt, CH_3CN, r.t., Ar, 1 h.

b) NHC-Ru^{II} catalyzed olefin cross-metathesis:

Over the past decades, the olefin metathesis reaction[200] has emerged as an indispensable and versatile tool for advanced organic synthesis,[201] mainly due to the introduction of various

[199] Palladium-assisted reactions for the construction of nucleosides will be discussed more in details in the third chapter, see references herein cited.

[200] For reviews on metathesis, see: (a) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140-3172; *Angew. Chem., Int. Ed.* **2000**, *39*, 3013-3043. (b) Trnka, T.M.; Grubbs, R.H. *Acc. Chem. Res.* **2001**, *34*, 18-29. (c) *Handbook of Metathesis*, Grubbs, R.H., Ed.; Wiley-VCH: Weinheim, Germany, **2003**. (d) Astruc, D. *New J. Chem.* **2005**, *29*, 42-56. e) Deshmukh, P.H.; Blechert, S. *Dalton Trans.* **2007**, 2479-2491.

[201] For reviews on synthetic applications, see: (a) Deiters, A.; Martin, S.F. *Chem. Rev.* **2004**, *104*, 2199-2238. (b) McReynolds, M.D.; Dougherty, J.M.; Hanson, P.R. *Chem. Rev.* **2004**, *104*, 2239-2258. (c) Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chem.* **2005**, *117*, 4564-4601; *Angew. Chem., Int. Ed.* **2005**, *44*, 4490-4527. (d) Van de Weghe, P.; Bisseret, P.; Blanchard, N.; Eustache, J. *J. Organomet. Chem.* **2006**, *691*, 5078-5108. (e) Donohoe, T.J.; Orr, A.J.; Bingham, M. *Angew. Chem.* **2006**, *118*, 2730-2736; *Angew. Chem., Int. Ed.* **2006**, *45*, 2664-2670. (f) Gradillas, A.; Pérez-

ruthenium catalysts such as those developed by Grubbs (**55**-**57**),[202] Hoveyda (**59**)[203] or Nolan (**58**)[204] (Figure 29). Among the several metal-based complexes enabling olefin metathesis transformations, ruthenium–benzylidene (**56**-**58**) precatalysts[202c,205] are the most widely used in light of their stability and their tolerance towards functionalised substrates. However, other pre-catalysts yielding the same active species, such as boomerang-type (**59**) pre-catalysts[203,206] and indenylidene (**60**) complexes,[207] have also proven to be efficient facilitators of olefin metathesis.

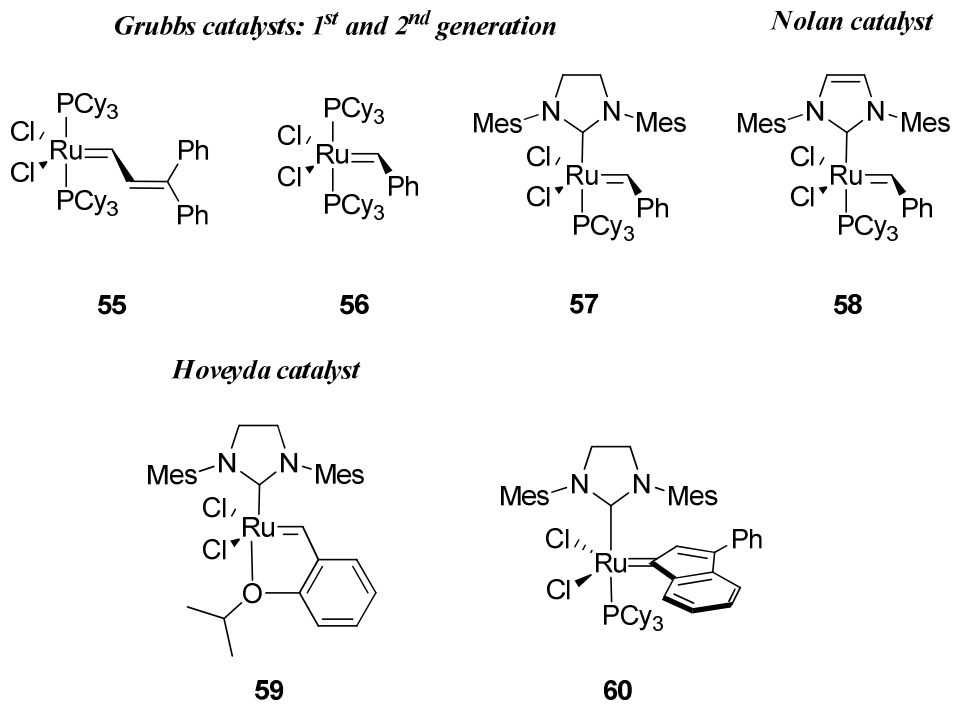


Figure 29. Representative Ru-based metathesis pre-catalysts.

Castells, J. *Angew. Chem.* **2006**, *118*, 6232-6247; *Angew. Chem., Int. Ed.* **2006**, *45*, 6086-6101. (g) Hoveyda, A.H.; Zhugralin, A.R. *Nature* **2007**, *450*, 243-251. (h) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767-2784.

[202] (a) Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975. (b) Fu, G.C.; Nguyen, S.T.; Grubbs, R.H. *J. Am. Chem. Soc.* **1993**, *115*, 9856-9857. (c) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem.* **1995**, *107*, 2179-2181; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039-2041. (d) Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* **1999**, *1*, 953-956. (e) Scholl, M.; Trnka, T.M.; Morgan, J.P.; Grubbs, R.H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.

[203] (a) Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus, P.J.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799. (b) Garber, S.B.; Kingsbury, J.S.; Gray, B.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

[204] Huang, J.; Stevens, E.D.; Nolan, S.P.; Petersen, J.L. *J. Am. Chem. Soc.* **1999**, *121*, 2674-2678.

[205] (a) Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110. (b) Roberts, A.N.; Cochran, A.C.; Rankin, D.A.; Lowe, A.B.; Schanz, H.-J. *Organometallics* **2007**, *25*, 6515-6518.

[206] (a) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794-796. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403-2405. (c) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed*. **2002**, *41*, 4038-4040. (d) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk,V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318-9325. (e) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arlt, D.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13652-13653. (f) Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan; S.P.; Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225-4228.

[207] Boeda, F.; Clavier, H.; Nolan, S.P. *Chem. Commun.* **2008**, 2726-2740.

This plethora of active catalysts has permitted the democratisation of metathesis reactions as a carbon-carbon double bond-forming tool. Numerous types of metathesis reaction have thus been developed, spanning from ring-closing metathesis (RCM)[208] and cross metathesis (CM)[209] to ring-opening metathesis polymerization (ROMP), acyclic diene metathesis polymerization (ADMET),[210] enyne metathesis,[211] ring-rearrangement metathesis (RRM),[212] or also tandem processes[213] (Figure 30). Naturally, the nucleoside chemistry has as well largely benefited from outlooks of this powerful reaction as recently reviewed by our group.[214] A number of nucleosidic structures, such as carba-, acyclo-, (2',3'-didehydro-2',3'-dideoxy)- or polycyclic nucleosides, have been constructed using olefin metathesis.

For this purpose, the benzylidene(IMes)dichloro(tricyclohexylphosphine) ruthenium(II) [Ru=CHPhCl$_2$(IMes)(PCy$_3$)] (**58**) has been already successfully used by us in the preparation of unsaturated carbocyclic intermediates *via* RCM,[215] as well in the synthesis of acyclonucleosides *via* CM.[216]

[208] (a) Conrad J.C.; Fogg, D.E. *Curr. Org. Chem.* **2006**, *10*, 185-202. (b) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740-5750. (c) Chattopadhyay, S.K.; Karmakar, S.; Biswas, T.; Majumdar, K.C. Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919-3952.

[209] Connon, S.J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900-1923.

[210] (a) Slugovc, C. *Macromol. Rapid Commun.* **2004**, *25*, 1283-1297. (b) Bielawski, C.W.; Grubbs, R.H. *Prog. Polym. Sci.* **2007**, *32*, 1-29.

[211] (a) Diver, S.T.; Giessert, A.J. *Chem. Rev.* **2004**, *104*, 1317-1382. (b) Diver, S.T. *J. Mol. Catal. A-Chem.* **2006**, *254*, 29-42. (c) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55-66. (d) Diver, S.T. *Coord. Chem. Rev.* **2007**, *251*, 671-701. (e) Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121-135.

[212] Holub, N.; Blechert, S. *Chem. Asian J.* **2007**, *2*, 1064-1082.

[213] Dragutan, V.; Dragutan, I. *J. Organomet. Chem.* **2006**, *691*, 5129-5147.

[214] (a) Jeong, L.S.; Lee, J.A. *Antivir. Chem. Chemother.* **2004**, *15*, 235-250. (b) Amblard, F.; Nolan, S.P.; Agrofoglio, L.A. *Tetrahedron* **2005**, *61*, 7067-7080. (c) Agrofoglio, L.A.; Nolan, S.P. *Curr. Top. Med. Chem.* **2005**, *5*, 1541-1558.

[215] (a) Gillaizeau, I.; Charamon, S.; Agrofoglio, L.A. *Tetrahedron Lett.* **2001**, *42*, 8817-8819. (b) Agrofoglio, L.A.; Amblard, F.; Nolan, S.P.; Charamon, S.; Gillaizeau, I.; Zevaco, T.A.; Guenot, P. *Tetrahedron* **2004**, *60*, 8397-8404. See also: Chapter I, 4.1.a) Synthesis of the D-2-cyclopentenone **26**.

[216] (a) Amblard, F.; Nolan, S.P.; Gillaizeau, I.; Agrofoglio, L.A. *Tetrahedron Lett.* **2003**, *44*, 9177-9180. (b) Amblard, F.; Nolan, S.P.; Schinazi, R.F.; Agrofoglio, L.A. *Tetrahedron* **2005**, *61*, 537-544.

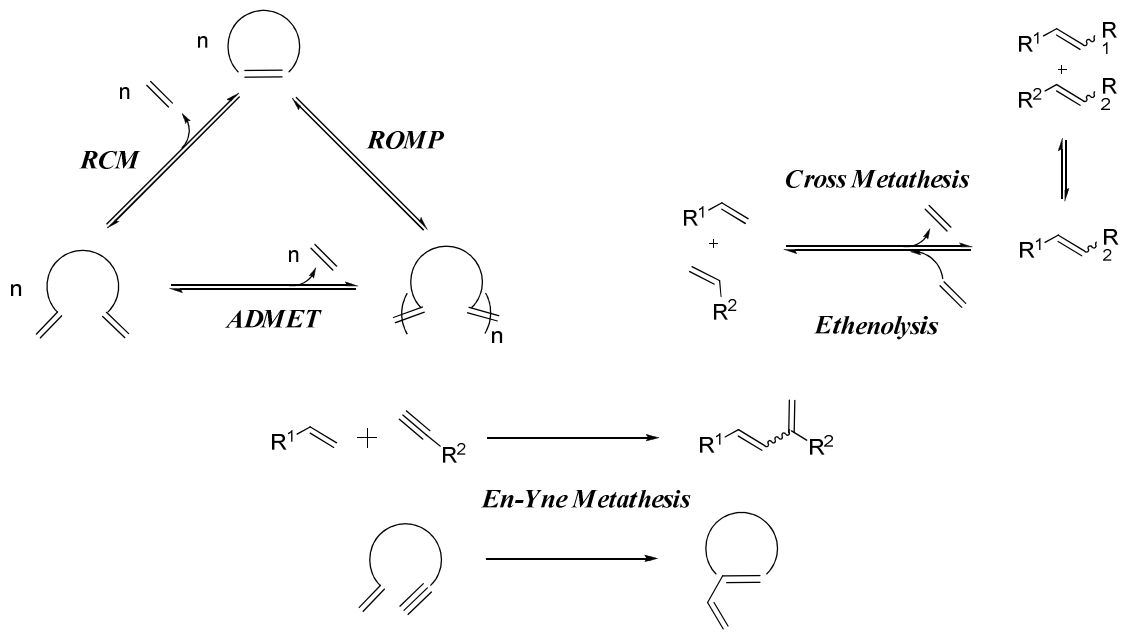
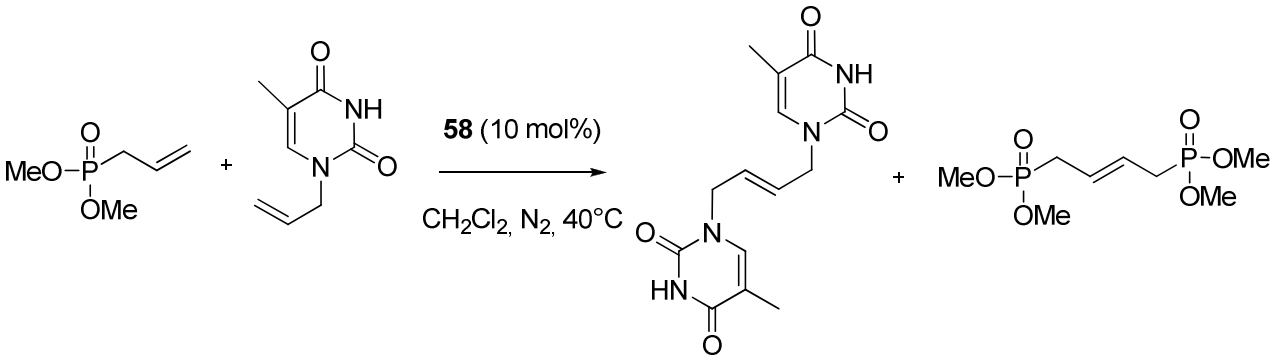


Figure 30. A variety of olefin metathesis reactions.

For the second key step of our unsaturated ANPs synthesis, we proposed a new way to obtain quickly unsaturated acyclophosphonate nucleosides using cross-metathesis in the presence of **58**. Preliminary investigations on the CM of N^1-allylthymine and allylphosphonic acid dimethyl ester had led to the exclusive formation of homodimers (Scheme 45).[216b] This result was in agreement with the general empirical model reported by Grubbs et al. for olefin reactivity in CM.[217] In fact, categorizing the olefins according to their abilities to undergo homodimerization *via* self-metathesis and by the stability of those homodimers, these two terminal olefins appeared to be of type I meaning that they were able to undergo a rapid homodimerization.



Scheme 45. Formation of homodimers *via* self cross-metathesis.

Based on this model, we turned our attention to the CM of the more reactive and less homodimerizable N^1-crotyl uracil derivatives (**54a-g**) with vinylic or allylic phosphonate partners (Scheme 46). In the presence of 4 equivalents of phosphonate reagent, the expected

[217] Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

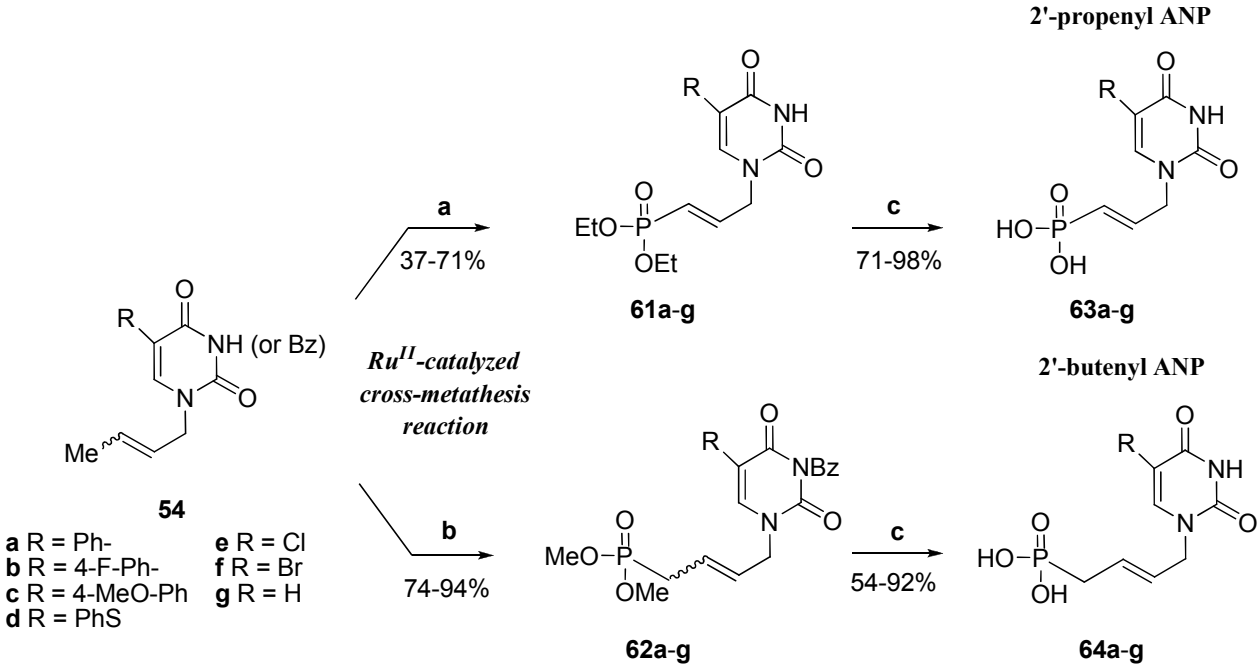
cross-coupling heterodimers were obtained in majority compared to the homodimers. 3'-Phosphono-prop-2'-en-1'-yl uracil (U-PPro) derivatives (**61a-g**) were isolated in moderate to good yield as only the *E*-isomer. 4'-Phosphono-but-2'-en-1'-yl uracil (U-PBut) derivatives (**62a-g**) were obtained as a mixture of major and thermodynamically stable *E*-isomer with the minor *Z*-isomer present in small amount (average *E*/*Z ratio* 8:2). Both isomers could be separated by liquid chromatography on silica gel.

It has to be noted that C^5-substituted uracil derivatives could be engaged without the protection at the *N*-3 position in CM reaction when diethyl vinyl phosphonate was employed, while the N^3-benzoyl protection was necessary to obtain the desired 2'-butenyl phosphonates (**62a-g**) in good yields. These results indicated that the allyl diethylphosphonate would be more active metathesis partner than the vinyl analogue. Compounds **61a-g** and **62a-g** were deprotected by treatment with TMSBr to afford the desired PPro and PBut uracil phosphonic acids.

Of note, the iodine was also selected as substituent and 5-I-U-PPro and 5-I-U-PBut were synthesised following the same procedure. However, like already observed for 5-I-DAP-PMEOs of Balzarini and coll.,[180] problems of deiodination were encountered under the phosphonate deprotection conditions affording the 5-unsubstituted uracil derivatives. In the quest of a milder manner, only one of the two methyl of the 5-iodo uracil 2'-butenyl phosphonate could be removed using a partial deprotection method giving selectively the mono ester.[218] Unfortunately, this compound was not an appropriate candidate according to the biological study requirement. Recently, we have also synthesised several N^4-alkylated cytosine butenyl ANPs using microwave heating methodology and the same olefin cross-metathesis procedure.[219]

[218] (a) Turhanen, P.A.; Ahlgren, M.J.; Järvinen, T.; Vepsäläinen, J.J. *Synthesis* **2000**, 633-637. (b) Turhanen, P.A.; Vepsäläinen, J.J. *Synthesis* **2005**, 3063-3066.

[219] Roy, V.; Mieczkowski, A.; Topalis, D.; Berteina-Raboin, S.; Deville-Bonne, D.; Nolan, S.P.; Agrofoglio, L.A. *Synthesis* **2008**, *13*, 2127-2133.



Scheme 46. Reagent and conditions: (a) Diethyl vinyl phosphonate (4 equiv), [Ru]=catalyst **58** (5 mol%), CH_2Cl_2, reflux, Ar, 22 h; (b) Dimethyl allyl phosphonate (4.0 equiv), [Ru]=catalyst **58** (5 mol%), CH_2Cl_2, reflux, Ar, 16 h; (c) TMSBr (4.0 equiv), CH_2Cl_2, r.t., 60 h.

c) Biologic activities:

The anti-viral activity of synthesized compounds was tested on Vero cells infected by vaccinia virus (Lister strain) or by cowpox virus (Brighton strain). As expected for unprotected phosphonic acids, no significant activities were observed. In parallel, the binding affinity of those new acyclic phosphonate analogues with hUMP-CMP kinase (human uridine-cytosine monophosphate kinase, hUCK), hTMP or vvTMP kinase (human or vaccinia virus thymidine monophosphate kinases) was examined in order to determine their ability to be recognized by the enzymes as substrates and thus to be phosphorylated into active forms.[220] The synthesized compounds, whatever the acyclic side chain length or the nature of the C^5-substitution, were not substrates of the hUCK enzyme. However, most of them, like the 5-Cl-U-PPro (**63e**), were competitive inhibitors meaning that these phosphonates were able to bind the active sites of the enzyme, hence blocking access to natural substrates and phosphorylation process. Among all the tested ANPs with hTMPK, the series of (*E*)-U-PBut analogues with a halogen on the *C*-5 position (**64e,f**) appeared to have the best binding affinity with the enzyme. The bromo (**64f**) and chloro (**64e**) phosphonates derivatives were

[220] (a) Topalis, D.; Kumamoto, H.; Amaya Velasco, M.-F.; Dugue, L.; Haouz, A.; Alexandre, J.A.C.; Gallois-Montbrun, S.; Alzari, P.M.; Pochet, S.; Agrofoglio, L.A.; Deville-Bonne, D. *FEBS J.* **2007**, *274*, 3704-3714. (b) Topalis, D.; Kumamoto, H.; Alexandre, J.A.C.; Dugué, L.; Pochet, S.; Berteina-Raboin, S.; Agrofoglio, L.A.; Deville-Bonne, D. *Nucleos. Nucleot. Nucl.* **2007**, *26*, 1369-1373.

very good substrates of the hTMPK[221] and were more readily phosphorylated than the AZT monophosphate, a well known substrate of hTMPK. Although the binding affinity was feebler, they were also phosphorylated by the vvTMPK. None of the C^5-aryl substituted U-PBut or U-PPro compounds was metabolized by the hTMPK or vvTMPK. It was suggest that this lack of phosphorylation in the propenyl series might result from an unproductive positioning of the ligand in the acceptor site. The shorter size and flexibility of the acyclic part did not allow for a good fixation of the U-PPro in the enzyme cavity, prohibiting notably direct phosphate transfer from the donor (ATP) to the acceptor phosphonate nucleotide. On the other hand, the comparison of 5-Br-U-PBut (**64f**) and deoxythymidine monophosphate (dTMP, natural substrate of hTMPK) in three-dimensional model of the hTMPK/substrate complex clearly showed a good superposition of the uracil bases (Figure 31). The acyclic part of the phosphonate also followed the $C^{1'}$-*O*-$C^{4'}$ segment of the dTMP with a similar positioning for the double bond and the oxygen. However, PBut's side chain being slightly shorter, phosphates moieties were not well superposed. The increase of the distance between the phosphate of 5-Br-U-PBut (**64f**) and the ATP site could explain the lower reactivity of the ANP compared to the natural substrate. The presence of the 3'-hydroxyl which interact with the enzyme cavity might also be responsible for the high affinity of dTMP.

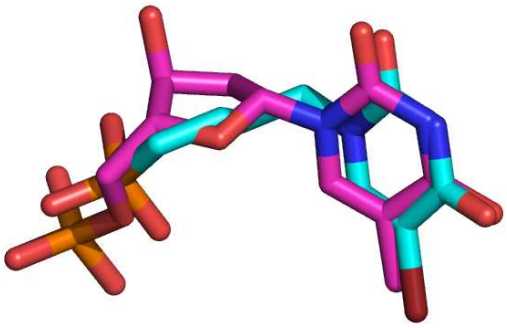
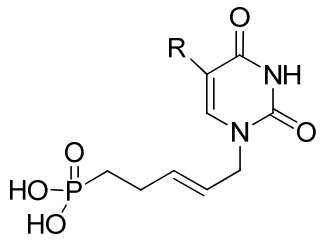


Figure 31. Comparison of dTMP (magenta) and (*E*)-5-Br-U-PBut (**64f**) (cyan) after docking in the active site of the hTMPK.

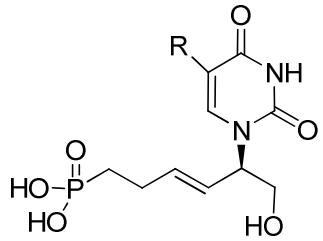
As enhanced antiviral activity is correlated to a high intracellular concentration of the diphosphate active form, we decided to search for new pyrimidine acyclic nucleotide analogues possessing improved binding and substrate properties towards hUCK, hTMPK and vvTMPK. The size of the acyclic side chain has proved to be an important parameter in the process of substrate recognition. The longer carbon side chain of 4'-phosphono-but-2'-en-1'-yl uracil derivatives induced better catalytic efficiency than the propenyl analogues. However, the butenyl phosphonates were still shorter than the corresponding phosphate moiety in

[221] (*E*)-5-Br-U-PBut (**64f**): Km = (90 ± 10) µM and kcat/Km = (9000 ± 500) $M^{-1}s^{-1}$; (*E*)-5-Cl-U-PBut (**64e**) Km = (130 ± 30) µM and kcat/Km = (4100 ± 100) $M^{-1}s^{-1}$; AZT-MP: Km = 12 µM and kcat/Km = 1000 $M^{-1}s^{-1}$.

dTMP, natural substrates of hTMPK. Accordingly, we speculated than an acyclic uracil phosphonate containing an unsaturated five carbons side chain could enhance the enzyme-catalyzed phosphorylation of the C^5-modified uracil phosphonic acids. We remember that the series of HDP-PPen nucleosides proposed by Hostetler and co. had anti-pox effects, implying that the free phosphonic acids were likely metabolized by UMP-CMPK and TMPK. Their ten step synthesis had been limited to the introduction of unmodified natural nucleoside base and only afforded the (*Z*)-isomer. We thus decided to extend the synthetic method previously developed for nucleoside propenyl and butenyl phosphonates to pentenyl derivatives (Figure 32). In a second part, we will present an original strategy to target optically active acyclic nucleoside phosphonates bearing a hydroxymethyl group on the side chain (Figure 32). Indeed, cidofovir is efficiently phosphorylated by UCK, more active than TMP kinases, underlining the importance of a polar group on the *C*-1' position of the acyclic part.



C^5-substituted uracil PPen



C^5-substituted uracil 1'-hydroxymethyl-PPen

Figure 32. Uracil pentenyl phosphonate targets.

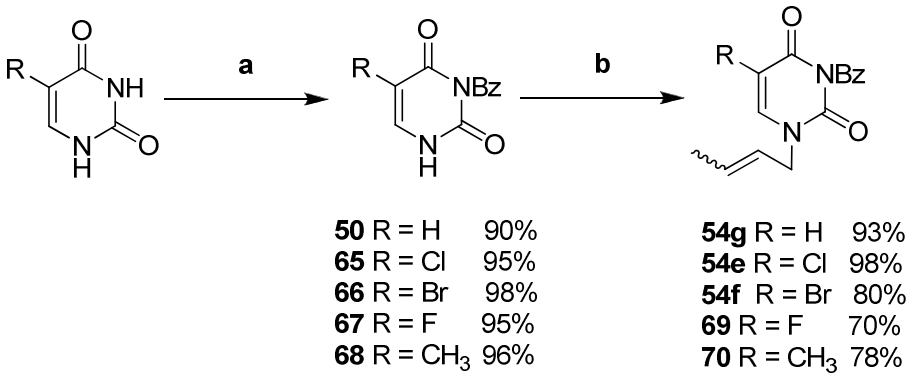
2. C^5-SUBSTITUTED URACIL PENT-2'-ENYL PHOSPHONATES

According to the previous structure-activity relationship conclusions, uracil phosphonates modified on the *C*-5 position by a halogen were better substrates for TMP kinases while bigger substituents like aryls had a negative effect. Therefore, we decided to limit our new series of nucleosidic pentenyl phosphonates (PPen) to uracil bases where R = H, F, Cl, Br, and CH_3. These C^5-substituents were chosen as function of their electronegativity and steric hindrances in order to evaluate their influence on the enzyme affinity.

a) Synthesis of the crotyl intermediates:

Instead of introducing the substitution in a later step, N^1-crotylation reactions were efficiently realized on the corresponding C^5-substituted N^3-benzoyl base (**50**, **65-68**) as uracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, and thymine were commercially available (Scheme 47). Interestingly, the N^1-alkylation of N^3-benzoyl bromouracil (**66**) did not performed at room temperature and the reaction had to be heated up to 70°C to give the

crotylated product **54f** in 80% yield. Of note, heating under reflux condition furnished the debenzoylated 5-Br-U crotyl product.

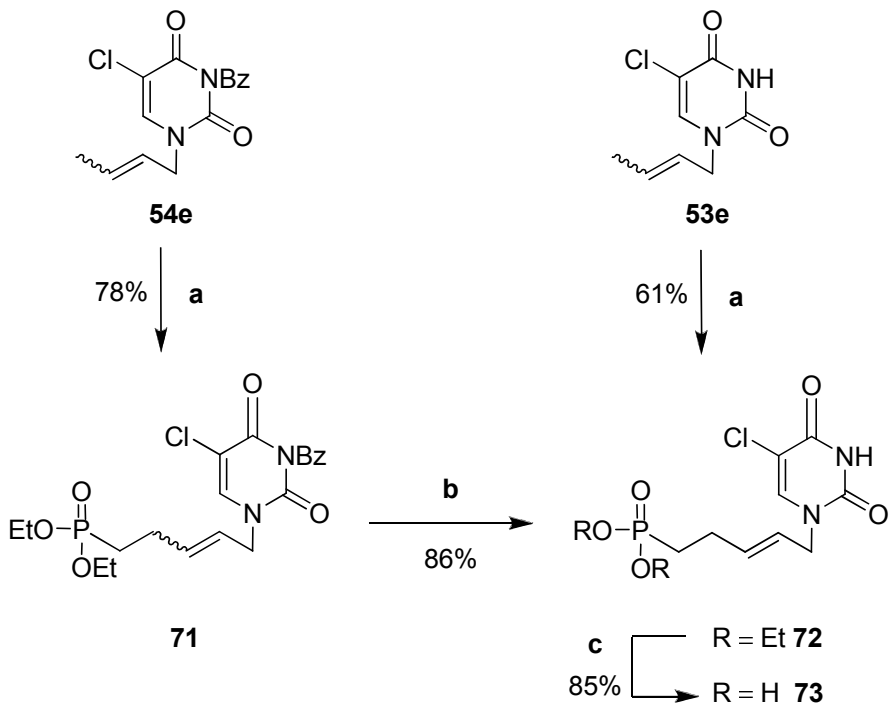


Scheme 47. Reagent and conditions: (a) Benzoyl chloride, pyridine/CH_3CN 2:5, r.t., 24 h; (b) Crotyl bromide, K_2CO_3, DMF, r.t. (70°C for **54f**), Ar, 1 h.

b) PPen uracil *via* cross metathesis:

The conditions of the cross-metathesis reaction using 5 mol% of catalyst **58** were first examined with the C^5-chloro uracil crotyl intermediate and the diethyl 3-butenylphosphonate as partner. According to Grubbs' general empirical model, this olefins combination should favour the formation of the heterodimer.[217] The previously synthesised 5-Cl-U crotyl (**53e**) and its N^3-benzoyl analogue (**54e**) were independently engaged in CM reactions affording the respective 5-Cl-U-PPen in 61% (**72**) and 78% (**71**) yields (Scheme 48). Like for the PBut series, the protection of the nitrogen was required to improve the yield of metathesis reaction. It has already been reported that a major drawback associated with the use of amine-containing systems in olefin metathesis concerns their ability to coordinate to metal-alkylidene complexes and to interfere unproductively with catalytic activity.[201i] In both cases, metathesis products were obtained as a mixture of the two olefin isomers with a *ratio* major/minor 9:1. Both isomers could be separated by liquid chromatography on silica gel. ^{1}H NMR analysis confirmed the stereochemistry of the main product: the coupling constant of the olefinic protons (15.2 Hz) was in agreement with the major formation of the thermodynamically stable *E*-isomer. Only the *E*-isomer was involved in the next step. The deprotection of the benzoyl group in ammonia solution afforded compound (*E*)-**72** in good yield and allowed for an extra purification step on column chromatography to eliminate the persistent colored trace of ruthenium catalyst. The last step consisted in the conversion of the diester uracil phosphonate (**72**) into the phosphonic acid (**73**) *via* classical transsilylation with TMSBr followed by alkaline hydrolysis. However, an unexpected problem occurred during the first tentative of deprotection of the phosphonate intermediate leading to a complex mixture. Semi-HPLC preparative separation coupled with mass analysis revealed the presence

of three products: the expected compound **73** ((M-H)$^-$: *m/z* = 293.0) and two unidentified side products containing respectively one ((M-H + Br)$^-$: *m/z* = 372.9) or two bromide atoms ((M-H + 2Br)$^-$: *m/z* = 452.8) of more than **73**. Bromotrimethylsilane is a well known mild and selective reagent for cleavage of lactones, epoxides, acetals, phosphonate esters and certain ethers, but it can also function as brominating agent. It generates HBr in the contact of air and moisture and free Br_2 upon prolonged storage.[222] One might assume that traces of moisture have engendered the bromination of the double bond of our pentenyl side chain. Of note, the colorless reaction mixture turned orange after addition of the TMSBr. Therefore, special care was taken for the deprotection of the ANPs in the following attempts. Under strictly anhydrous conditions, (*E*)-5-chlorouracil pentenyl phosphonic acid (**73**) was obtained in good yield after shortened reaction with freshly opened TMSBr followed by extraction in ELGA® water.

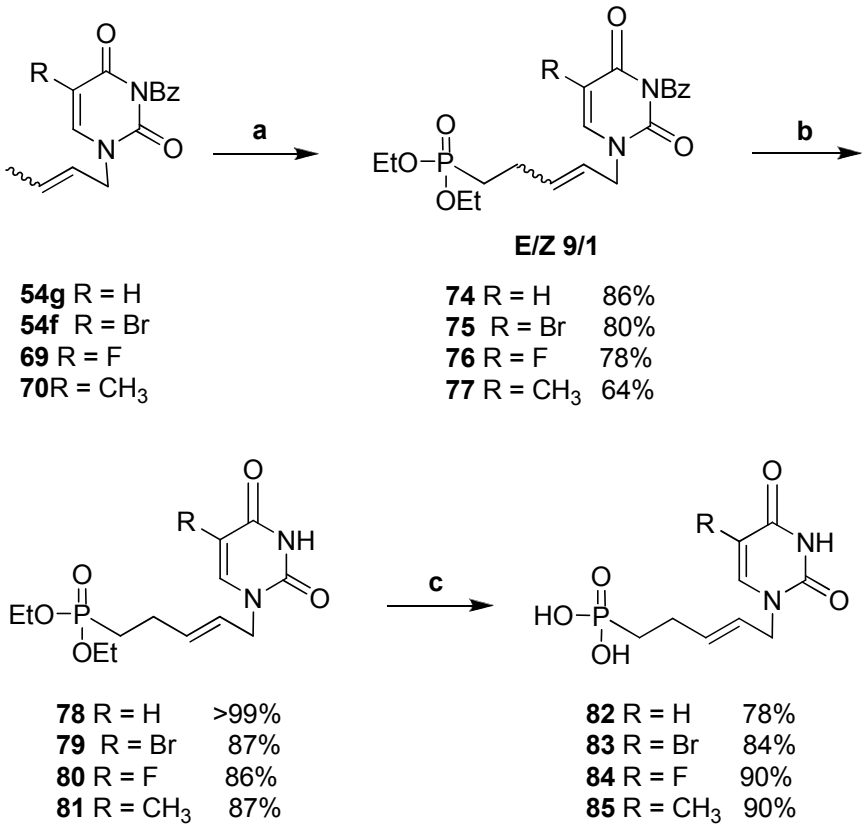


Scheme 48. Reagent and conditions: (a) Diethyl 3-butenylphosphonate (4 equiv), [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, Ar, 8 h; (b) NH_3 7 N in MeOH, 4°C, overnight; (c) TMSBr, CH_2Cl_2, r.t., Ar, 12 h.

During this optimization quest, we also noticed that reducing the excess of the expensive butenyl phosphonate reagent to two equivalents (compared to four equivalents for the previous vinyl and allyl phosphonates) had no negative effect on the yield of the CM. On the contrary, it had the advantage to reduce the formation of side products like the dimer of

[222] Martinelli, M.J. in *"Encyclopedia of Reagents for Organic Synthesis"*, Vol. 4; Paquette, L.A., Ed.; John Wiley & Sons, Inc.: New York, United States, **1995**, 784-786.

the phosphonate reagent. This latter has a polarity similar to uracil pentenyl phosphonates. The purification of the desired ANP compound was thus facilitated as it could be more easily separated from the dimer. The optimized strategy was applied to the cross-metathesis reaction between the uracil crotyl intermediates (**54g**, **54f**, **69**, **70**) and two equivalents of diethyl 3-butenylphosphonate (Scheme 49). The N^3-benzoyl C^5-modified uracil PPen (**74-77**) were synthesized in moderate to good yields as a separable mixture of *E*- and *Z*-isomers (*E*/*Z ratio* of 9:1). After subsequent deprotection steps from the *E*-isomers, the expected uracil pentenyl phosphonic acids (**82-85**) were obtained in good overall yields.



Scheme 49. Reagent and conditions: (a) Diethyl 3-butenylphosphonate (2 equiv), [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, Ar, 8 h; (b) NH_3 7 N in MeOH, 4°C, overnight; (c) TMSBr, CH_2Cl_2, r.t., Ar, 12 h.

c) Conclusion:

In this first part, we have successfully expanded our previous method to the synthesis of new acyclic nucleoside phosphonates in five steps. The cross-metathesis reaction has been re-optimized for these pentenyl derivatives. However, the major difference between these new unsaturated ANPs and cidofovir is the presence of a polar group on the acyclic part that could cause a decrease of the affinity for the enzyme. It is probable that the hydroxymethyl group of HPMPC have an important effect on the structure of the enzyme active site allowing a better

captivity of the nucleoside phosphonate. The second goal of this project was thus the enantioselective synthesis of acyclic nucleoside phosphonates bearing a hydroxymethyl group on the side chain.

3. ENANTIOSELECTIVE HYDROXYMETHYL PHOSPHONONUCLEOSIDES

Following the information given by the enzyme study, we first targeted an enantiomerically pure 5'-phosphono-pent-2'-en-1'-yl with a uracil as nucleobase and a hydroxymethyl as $C^{1'}$-substituent. More than a straight synthesis, the idea was also to develop a methodology for the preparation of various unsaturated ANP bearing a functional group on the *C*-1' position (Figure 33).

The adopted strategy consisted in:

1 - Preparing the optically active (*R*)-1,2-*iso*propylidene-2-butene intermediate by Wittig reaction starting from chiral L-gulono-1,4-lactone. Starting from D-mannitol could also afford its (*S*)-enantiomer.

2 - This butene diol would be involved as partner in a Ru-catalyzed cross-metathesis reaction with butenyl phosphonate to give the 1-hydroxymethyl-pentenyl phosphonate side chain. Using different phosphonate reagents, like the vinyl or allyl phosphonate, as partner in the CM would allow the formation of acyclic diol side chain with various lengths.

3 - Finally, the uracil could be introduced *via* Pd-catalyzed allylic amination[223] affording after subsequent deprotection the corresponding (*R*)-uracil 1'-hydroxymethyl-pentenyl phosphonic acid. One can imagine extending this allylation, the so-called Tsuji-Trost reaction,[224] to different natural as well as modified heterocyclic bases.

4 - At the phosphonate stage, it would be also possible to replace the hydroxyl group by different functional groups (N_3, NH_2, OAc,…).

[223] Johannsen, M.; Jørgensen, K.A. *Chem. Rev.* **1998,** *98*, 1689-1708.

[224] (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361-4401. (b) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395-422. (c) Trost, B.M. *Acc. Chem. Res.* **1996**, *29*, 355-364.

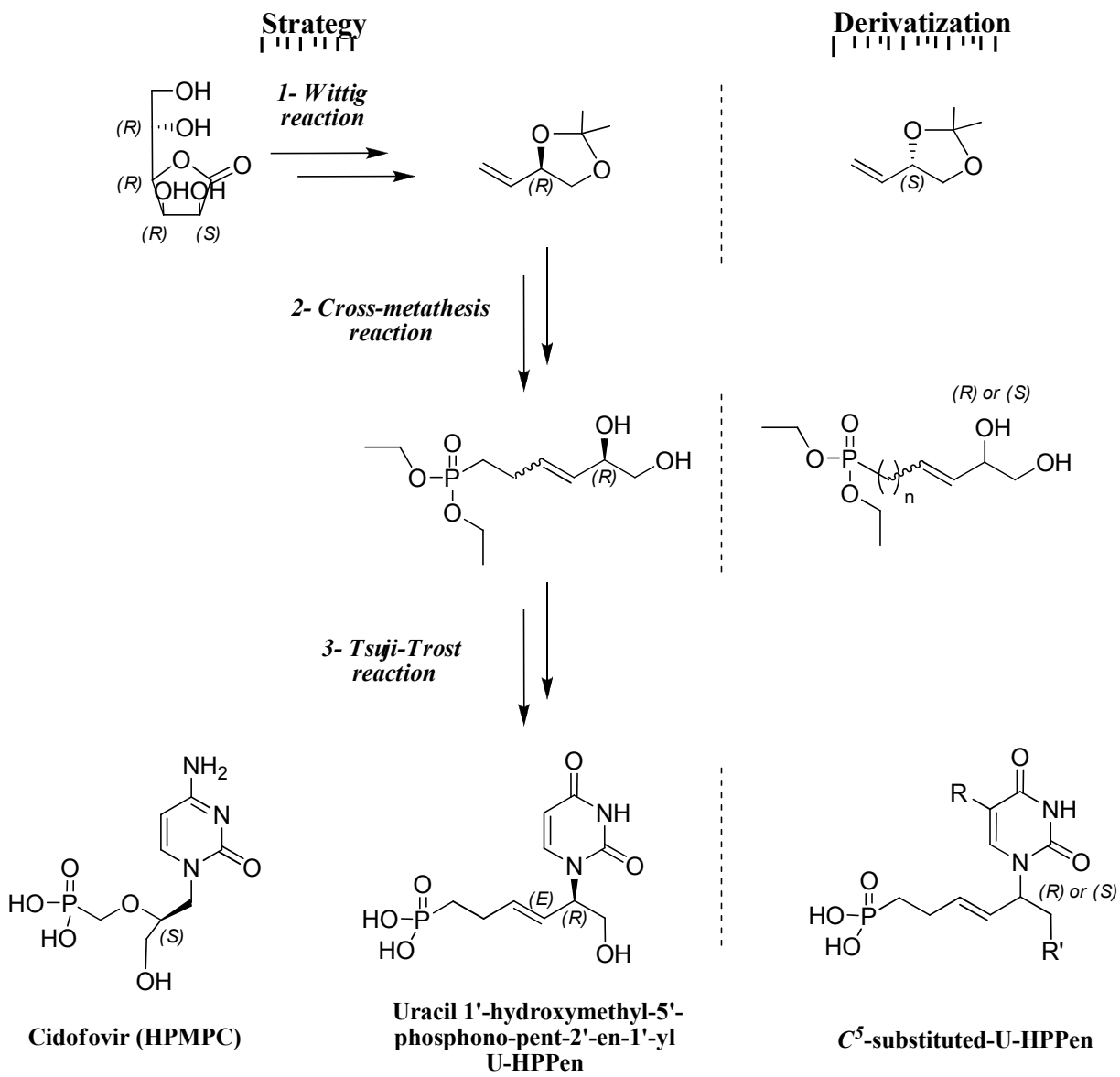


Figure 33. Strategy for the synthesis of uracil 1'-hydroxymethyl-pentenyl phosphonate derivatives.

a) Preparation of the optically active (*R*)-1,2-*iso*propylidene-2-butene:

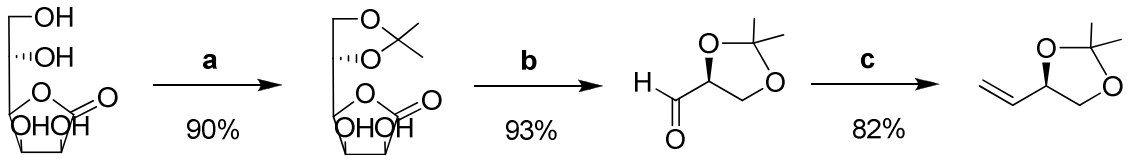
According to known procedure,[225] L-gulono-1,4-lactone was selectively protected with 2-methoxypropene to provide (*S*)-5,6-*O*-*iso*propylidene-L-gulono-1,4-lactone **86** followed by oxidative cleavage to yield optically pure L-(*S*)-glyceraldehyde acetonide **87** (Scheme 50). Optically pure glyceraldehyde acetonides are widely used in the synthesis of enantiomerically pure compounds.[226] D-(*R*)-glyceraldehyde acetonide can also be easily obtained from the inexpensive D-mannitol.[227] The procedure followed here uses readily available, non-toxic

[225] (a) Hubschwerlen, C. *Synthesis* **1986**, 962-964 (b) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1993**, *72*, 1-5.

[226] Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447-488.

[227] (a) Baer, E.; Fischer, H.O.L. *J. Biol. Chem.* **1939**, *128*, 463-473. (b) Schmid, R.; Bryant, J.D. *Org. Synth.* **1993**, *72*, 6-12; *Org. Synth., Coll. Vol. IX* **1998**, 450-456.

starting materials, and can be easily scaled up. However, the oxidation reaction and its work up revealed to be tedious.



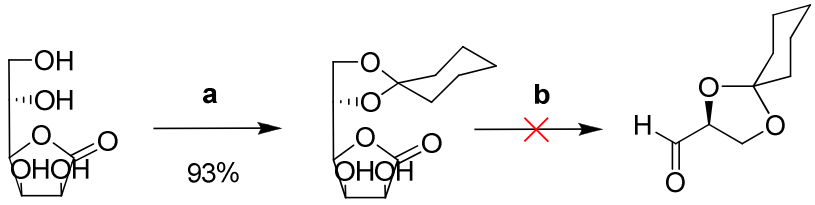
86 **87** **88**

Scheme 50. Reagent and conditions: (a) 2-Methoxypropene, PTSA, DMF, r.t., 16 h; (b) $NaIO_4$, H_2O, r.t., 1 h; (c) Methyltriphenylphosphonium bromide, *n*-BuLi, THF, Ar, -78ºC to r.t., 20 h.

During the course of this oxidative cleavage, the pH of the solution had to be carefully controlled with a pH-meter and the end point was set to pH 5.5 by adding dropwise an aqueous solution 3N of NaOH at a rate such that the temperature did not exceed 7°C. It had to be kept absolutely in a range of pH 4-6 to avoid a wealth of side reactions. Indeed, low pH values favor hydrolysis of the *iso*propylidene protective group while high pH values lead to epimerization of the formed aldehyde. Treatment of the crude also appeared to be quite complex. A published gas chromatography analysis reported that, at this point, 95% of the theoretical amount of the glyceraldehyde acetonide was contained in this aqueous phase.[225b] However, GC analysis of the aqueous layer still indicated the presence of about 30% of the total amount of aldehyde after six extractions with CH_2Cl_2. Alternatively, this crude in aqueous solution could be used for further chemical transformations[225a] if the reaction conditions allowed it but could not be stored for more than 6 h at 0°C. In fact, (*S*)-glyceraldehyde acetonide is an unstable liquid that starts to polymerize on standing even at low temperature. But it can be depolymerized by distillation before use. Hence, we realized repeated extractions with CH_2Cl_2 to recuperate the majority of the final glyceraldehyde acetonide **87**. We noticed that using ethyl acetate as extraction solvent increased the yield of the process. However, it was more complicated to carefully evaporate EtOAc without loosing the volatile aldehyde. The distillation was realized in a Kugelrohr apparatus cooling the bulbs with dry ice-acetone**.** The freshly prepared aldehyde **87** was immediately submitted to Wittig reaction to furnish the (*R*)-butene **88** in good yield following the procedure published for the (*S*)-enantiomer.[228] Given that the difficult synthesis of the glyceraldehyde **87**, we considered as an alternative the preparation of the less volatile and higher lipophile (*S*)-2,3-*O*-Cyclohexylidene-L-glyceraldehyde **90** from oxidation of 5,6-*O*-Cyclohexylidene-L-gulono-

[228] Guncheol, K.; Seon, Y.J. *Bull. Korean Chem. Soc.* **2001**, *22*, 1156-1158.

1,4-lactone **89** (Scheme 51).[229] However, polymerization of the aldehyde **90** was mainly observed even controlling the pH of the oxidation or after distillation of the crude.



89 **90**

Scheme 51. Reagent and conditions: (a) Cyclohexanone dimethyl ketal, CSA, DMF, r.t., 3 d; (b) $NaIO_4$, $NaHCO_3$, H_2O/THF, r.t., 8 h.

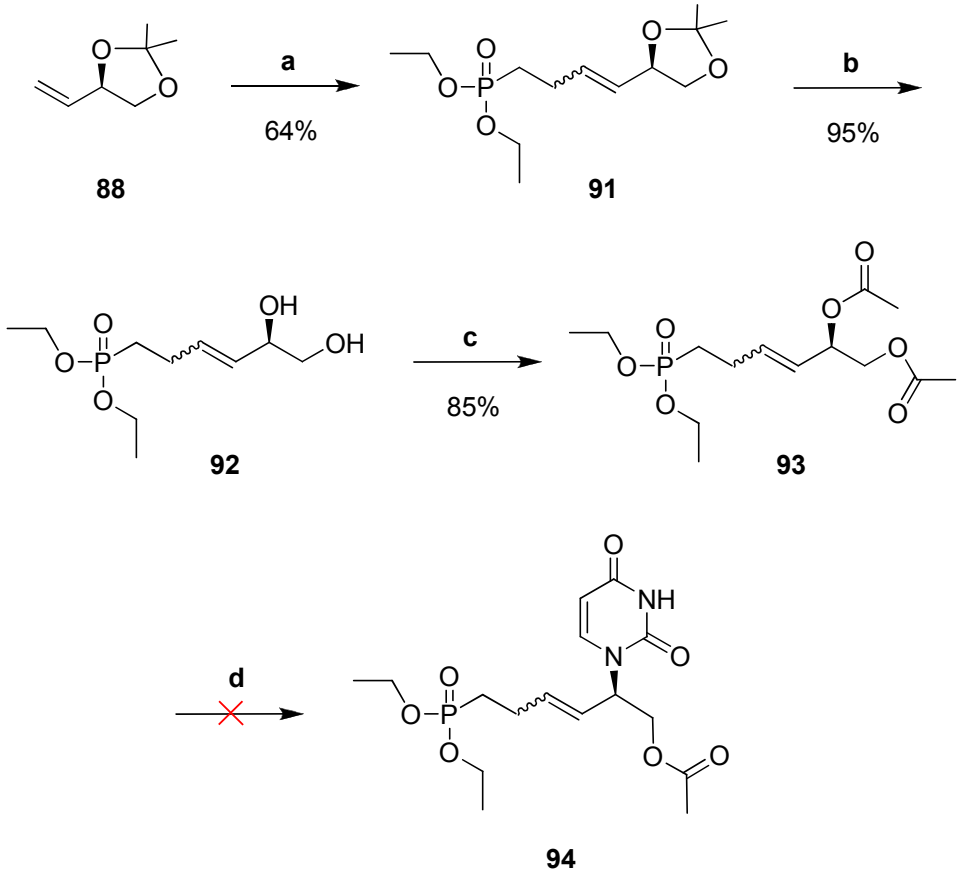
b) Synthesis of the chiral substituted side chain and introduction of the nucleobase:

The (*R*)-*3*,4-*O*-*iso*propylidene-butene **88** in hand, we engaged it as partner in cross-metathesis reaction with diethyl 3-butenyl phosphonate in order to obtain the optically active acyclic pentenyl side chain moiety (Scheme 52). **91** was obtained in moderate yield as an inseparable mixture of *E*/*Z* isomers (*E*/*Z ratio* 9:1). The stereochemistry of the major olefin was confirmed by ^{1}H NMR spectroscopy indicating a coupling constant of 15.2 Hz for the olefinic proton. In parallel, we tested the feasibility of the CM reaction with allyl and vinyl phosphonate reagents (Scheme 53). Starting for the racemic *3*,4-*O*-*iso*propylidene-butene **95**, more economically and synthetically practical for a test, we obtained the butenyl **96** and propenyl phosphonate **97** (only the *E* isomer) acyclic parts in 72% and 30% yield respectively.

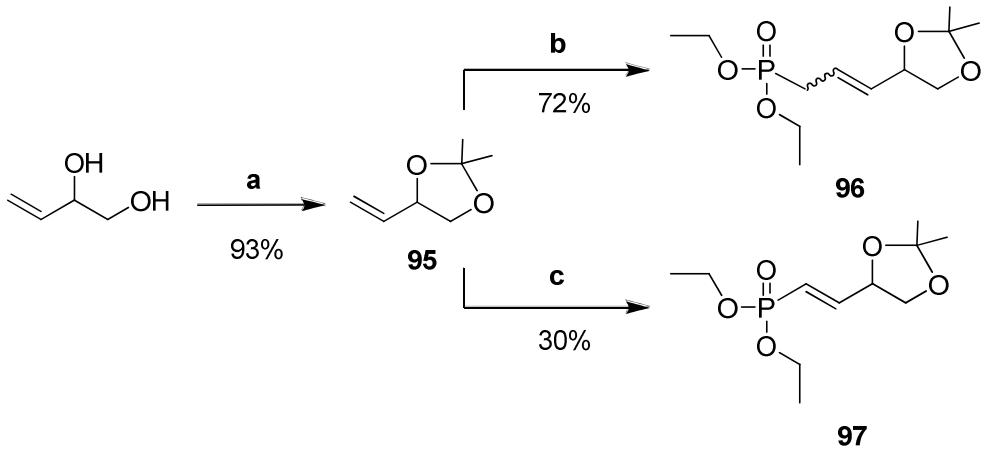
After removal of the *iso*propylidene group under acidic condition, the resulting diol **92** were converted into the corresponding allylic diacetate **93** (Scheme 52). The coupling of the uracil base was carried out using the Pd^0-catalyzed enantioselective Tsuji-Trost allylic amination to obtain the desired 1'-substituted pentenyl phosphonate **94** with a global retention of configuration.[230] Unfortunately, all attempts to introduce the heterocycle on **93** under various classical conditions[215b] failed.

[229] (a) Schmidt, C.R.; Bradley, D.A. *Synthesis* **1992**, 587-590. (b) López, S.; Fernández-Trillo, F.; Midón, P.; Castedo, L.; Saá, C. *J. Org. Chem.* **2005**, *70*, 6346-6352.

[230] Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, *102*, 4730-4743.

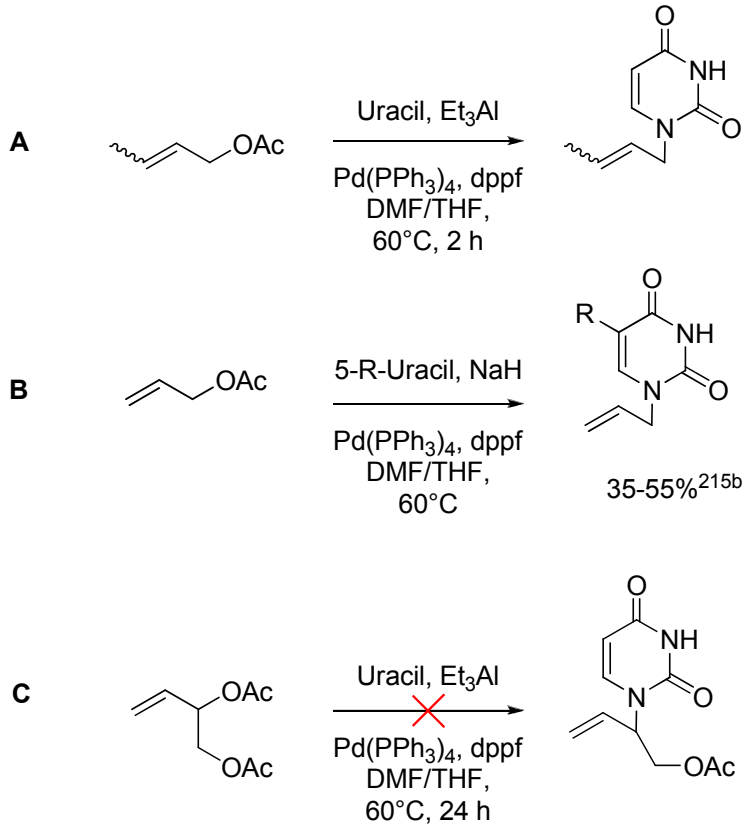


Scheme 52. Reagent and conditions: (a) Diethyl 3-butenylphosphonate, [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, Ar, 24 h; (b) TFA 60%, r.t., overnight; (c) Ac_2O, pyridine, Ar, 0°C to r.t., 16 h; (d) Uracil, NaH or Et_3Al, $Pd(PPh_3)_4$, dppf, DMF/THF, Ar, 60°C, 16 h.



Scheme 53. Reagent and conditions: (a) 2,2-Dimethoxypropane, PPTS, acetone, r.t., overnight; (b) Diethyl allyl phosphonate, [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, Ar, 24 h; (c) Diethyl vinyl phosphonate, [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, Ar, 24 h.

In presence of triethylaluminium as base,[231] the reaction only led to the recovering of starting material. Yet, tests on simple surrogates proved that the catalytic system was operational as it led to the N^1-crotyl uracil[197] when the Pd^0-catalyzed coupling of crotyl acetate with uracil was performed (Scheme 54, **A**). Similar preparation of *N*-allyl derivatives by coupling of commercially available allylic acetate with various pyrimidines has also been previously done in the laboratory (**B**).[216b] Interestingly, the allylic *N*-alkylation of uracil with the 3,4-diacetoxy-1-butene failed under the same conditions (**C**). This result suggests a steric hindrance from the second acetoxy group that could prevent the coordination of the Pd^0 complex or the attack of the nucleophile on the π-allyl complex. On the other hand, using NaH as base led to the total consumption of the starting material **93** according to TLC. However, none UV or ^{1}H NMR visible coupling product was detected. Acetate is a well known leaving group for the Tsuji-Trost reaction. The AcO^- group liberated through formation of the π-allyl complex is sufficiently nucleophile to enter in competition with the nucleobase and to attack this complex on different positions.[232] Hence, we might have obtained the rearrangement product from the re-addition of the acetate leaving group.

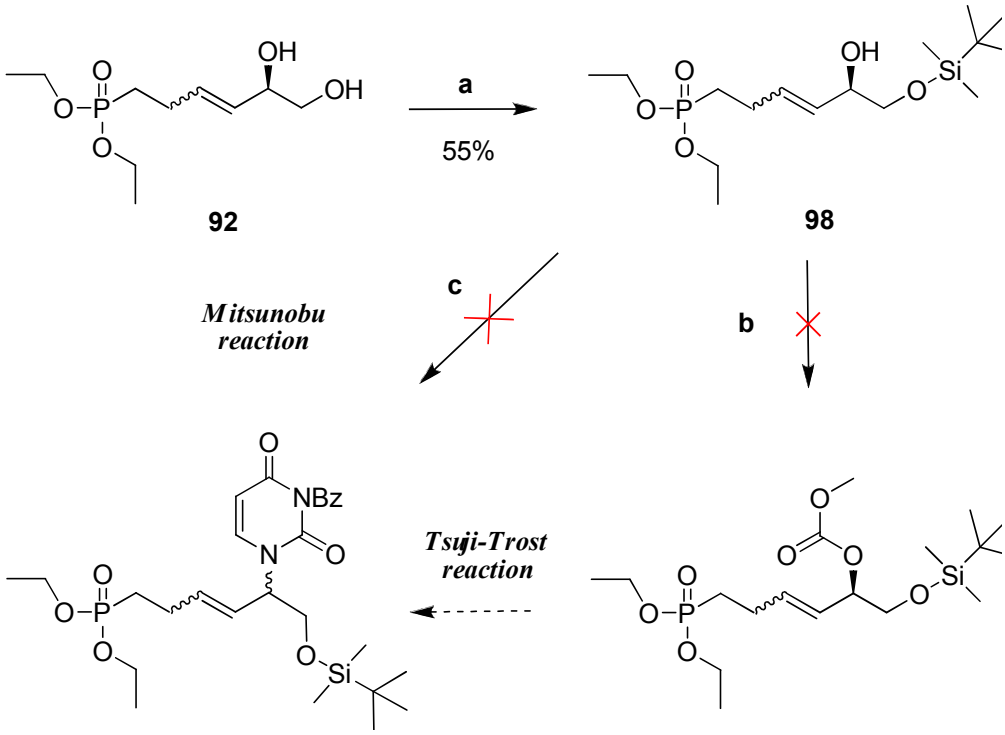


Scheme 54. Tests of the Pd^0 catalytic system for the Tsuji-Trost reaction on simple surrogates.

[231] Kapeller, H.; Marschner, C.; Weissenbacher, M.; Griengl, H. *Tetrahedron* **1998**, *54*, 1439-1456.

[232] Lindner, T.; Kazmaier, U. *Adv. Synth. Catal.* **2005**, *347*, 1687-1695.

In the case of a carbonate leaving group, the formation of the complex is irreversible as it is followed by liberation of MeO^-, poor nucleophile, along with CO_2 making only possible the addition of the heterocyclic base.[233] We thus decided to turn our attention to the more reactive allylic carbonate derivative **99** for the Tsuji-Trost reaction (Scheme 55). First, the primary hydroxyl was protected with a silyl group by slow addition of *tert*-butyldimethylsilyl chloride to afford only the mono-substituted analogue **98**. Following published procedure,[232] we tried to introduce the carbonate functionality on the allylic alcohol using methyl chloroformate in the presence of pyridine and DMAP. Surprisingly, the reaction condition did not achieve the introduction of the carbonate group, but instead led to the deprotection of the silyl group affording the diol **92**. Finally, we attempted to introduce the protected N^3-benzoyl uracil **50** directly on **92** *via* Mitsunobu reaction.[234] Only starting material was recovered.



Scheme 55. Reagent and conditions: (a) *tert*-Butyldimethylsilyl chloride, imidazole, CH_2Cl_2, 0°C to r.t., 4 h; (b) Methyl chloroformate, pyridine, DMAP, CH_2Cl_2, 0°C to r.t., 16 h. (c) N^3-Benzoyl uracil **50**, PPh_3, DIAD, THF, r.t. or 60°C, 24 h.

[233] (a) de Oliveira, R.N.; Mendonça Jr., F.J.B.; Sinou, D.; de Melo, S.J.; Srivastavab, R.M. *Synlett* **2006**, 3049-3052. (b) Evans, P.A.; Lai, K.W.; Zhang, H.-R.; Huffman, J.C. *Chem. Commun.* **2006**, 844-846.
[234] Liao, X.; Butora, G.; Olsen, D.B.; Carroll, S.S.; McMasters, D.R.; Leone, J.F.; Stahlhut, M.; Doss, G.A.; Yang, L.; MacCoss, M. *Tetrahedron Lett.* **2008**, *49*, 4149-4152.

4. CONCLUSIONS AND PERSPECTIVES

Based on the biologic results of our previous unsaturated acyclic uracil phosphonates, we speculated that the introduction of a longer carbon side chain and/or a polar group on the *C*-1' position of the acyclic part could enhance the binding affinity of unsaturated ANPs with the enzyme involved in the phosphorylation process. Therefore, we undertook to synthesize two new series of structurally modified acyclic uracil phosphonates responding *a priori* to the enzyme requirements. The key step of the synthetic routes consisted in a cross-metathesis reaction mediated by NHC-containing ruthenium complex.

In the first part, a readjusted synthetic procedure afforded new series C^5-substituted uracil pentenyl phosphonic acids with good overall yields. Starting from commercially available C^5-modified uracil bases, the general strategy were reduced to five steps. Unsaturated acyclic phosphonates were efficiently generated *via* olefin cross-metathesis with protected uracil crotyl intermediates. Unfortunately, despite five carbons acyclic moiety and although substrates of the hTMPK, the series of (*E*)-C^5-substituted-U-PPen appeared to be less phosphorylated by the enzyme than the butenyl analogues. The catalytic efficiencies of the 5-Br- and the 5-Cl-U-PPen were well below compared to the bromo and chloro butenyl derivatives. They also inhibited the hUMP-CMPK but with a relatively low affinity. They were not interesting substrates of the vvTMPK.

In a second part, we tried to synthesize a new series of enantiomerically pure uracil pentenyl phosphonates bearing a polar hydroxymethyl group on the *C*-1' position of the acyclic part. The acyclic five carbon side chain was prepared in six steps starting from L-gulono-1,4-lactone. The key step of its synthesis consisted in a cross-metathesis reaction between the optically active *iso*propylidene-butene and the diethyl 3-butenyl phosphonate. We have demonstrated that this strategy can be extended to the formation of propenyl and butenyl side chain using the appropriate phosphonate reagent. Unfortunately, we were not able to introduce the uracil base either under Tsuji-Trost or Mitsunobu conditions. At the time, this project is still underway in the laboratory.

From a biological point of view, phosphonic acid moities advantageously allow for avoiding the first limiting phosphorylation step by kinase. However, their polar character limits the penetration of the corresponding acyclic nucleoside through cell membranes, hence lowing down their biodisponibility. This drawback explains the lack of anti-vaccinia virus activity observed for our series of unsaturated ANPs, though some are good substrates of the

enzyme responsible for the phosphorylation into the active form. Therefore, syntheses and biological evaluations of unsaturated ANP prodrugs bearing protecting groups on the phosphonic acid moiety are greatly necessary to evaluate the real potency of these new ANPs.

5. Résumé du chapitre II:

Synthèse de nouveaux nucléosides phosphonates acycliques *via* métathèses croisées

Depuis la découverte en 1974 du premier médicament anti-viral, la recherche s'est attelée à la synthèse de composés nucléosidiques dont les parties hétérocyclique et sucre diffèrent significativement de la forme naturelle. Dans ce contexte, les nucléosides acycliques[150] et plus particulièrement les nucléosides phosphonates acycliques (NPA)[152] se sont imposés comme une classe importante d'anti-viraux. Ils ont déjà prouvé leur efficacité contre plusieurs virus tel le VIH, l'herpes, ou la variole.[153] Les NPA sont composés d'une chaîne carbonée ouverte au lieu de la traditionnelle partie sucre cyclique. Cette partie acyclique comporte généralement un atome d'oxygène comme dans la forme naturelle mais celui-ci peut aussi être remplacé par une liaison double.[195,196] De plus, les NPA sont terminés par un groupement phosphonate plus résistant aux enzymes qu'un groupement phosphate et qui permet d'éviter la première étape limitante de phosphorylation.[154]

Afin d'améliorer les performances anti-virales de ces composés, il est primordial d'effectuer la synthèse de nouveaux nucléosides phosphonates acycliques structurellement modifiés et d'étudier les conséquences de ces changements au niveau intracellulaire. Des analyses d'affinité avec l'enzyme hTMPK ont montré que la longueur de la chaîne acyclique avait une influence sur la reconnaissance de la molécule en tant que substrat de cette enzyme.[220] Des phosphonates acycliques portant une chaîne latérale insaturée de quatre carbones et une base uracile modifiée en position *C*-5 se sont avérés être de très bons substrats de la hTMPK.[220] Les ANP, comme le cidofovir,[152b,156,157] contenant un substituent polaire sur leur partie acyclique ont également de bonne efficacité catalytique.

La synthèse de ces analogues phosphonates est également un enjeu. Il existe peu de stratégie efficace décrite dans la littérature menant à de larges bibliothèques de composés. Le but de notre projet était donc de développer de nouvelles méthodologies pour la synthèse rapide et efficace de nucléosides phosphonates acycliques ayant une chaîne carbonée insaturée de cinq carbones substituée ou non par un groupement hydroxyle en position *C*-1'. La structure de ces molécules a été étudiée en fonction des possibles interactions avec le site

actif de l'enzyme. Les substituents en position *C*-5 de la base uracile (R = H, F, Cl, Br et CH_3) ont été choisis pour leurs différentes propriétés électroniques et stériques.

En première partie, reprenant le principe d'une méthode développée au laboratoire,[197] nous avons synthétisé une série de nouveaux uraciles phosphonates acycliques composés d'une chaîne latérale insaturée de cinq carbones. Les étapes clés de cette synthèse consistaient à introduire un groupement crotyle sur des bases uraciles modifiées afin d'utiliser les intermédiaires obtenus (**54g-f**, **69-70**) comme partenaires dans une réaction de métathèse croisée avec le but-3-ényl phosphonate de diéthyle (Schéma 8). A partir de bases substituées en *C*-5 commerciales, les intermédiaires uraciles benzoylés en *N*-3 (**50**, **65-68**) ont été aisément crotylés en *N*-1. La réaction de métathèse croisée en présence de 5 mol% de catalyseur au ruthénium a donné pour chaque uracile phosphonate acyclique insaturé (**71**, **74-77**) un mélange des deux isomères *E* et *Z* (*ratio* 9:1) séparable par chromatographie. Après deprotection, les acides phosphoniques correspondant (**73**, **82-85**) ont été obtenus avec un bon rendement global après cinq étapes de synthèse.

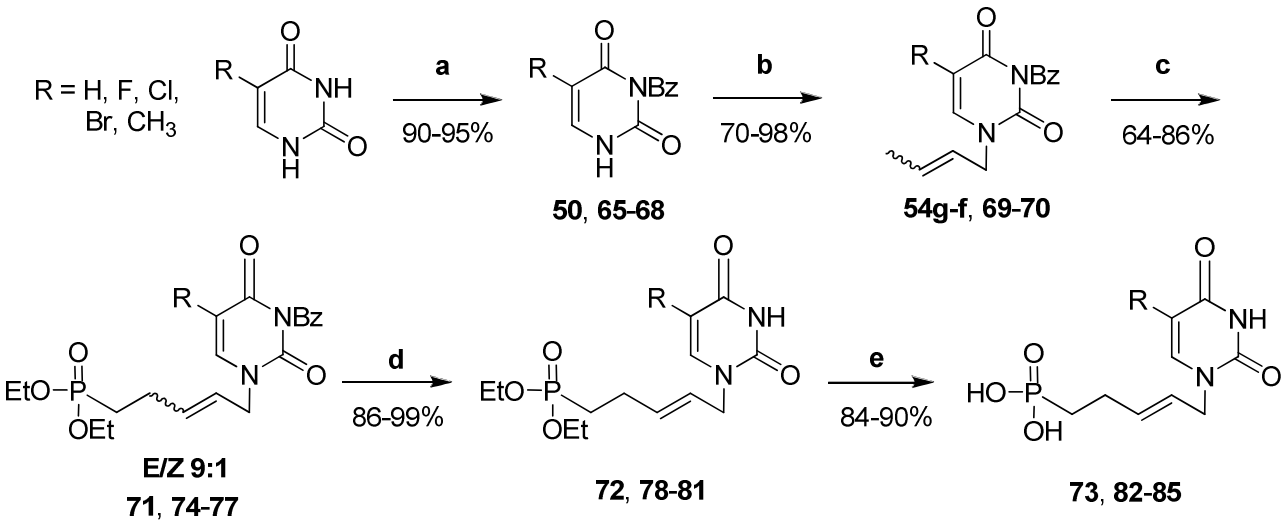


Schéma 8. Conditions réactionnelles: (a) Chlorure de benzoyle, pyridine/CH_3CN 2:5, t.a., 24 h; (b) Bromure de crotyle, K_2CO_3, DMF, t.a., Ar, 1 h; (c) But-3-ényl phosphonate de diéthyl (2 équiv.), [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, 8 h; (d) NH_3 7 N dans MeOH, 4°C, 16 h; (e) TMSBr, CH_2Cl_2, t.a., Ar, 12 h.

La différence majeure entre le cidofovir et les uraciles phosphonates insaturés préparés se situe au niveau de la substitution de la chaîne acyclique du cidofovir par un groupement hydroxyméthyle. La différence d'affinité avec l'enzyme mesurée entre les deux types de molécules pourrait être due à l'absence de ce groupement polaire. La seconde partie de ce projet consistait donc en la synthèse énantiosélective de composés phosphonates insaturés portant un substituent en position *C*-1' de la chaîne acyclique. La stratégie adoptée avait également pour but de développer une nouvelle méthodologie permettant un accès facile et

rapide à une large variété de nucléosides phosphonates acycliques substitués en *C*-1' par un groupement fonctionnel.

Nous avons ciblé la synthèse énantiopure de l'uracil 5'-phosphono-pent-2'-én-1'-yl (Schéma 9). Les étapes clés consistaient en la préparation d'un (*R*)-1,2-*iso*propylidéne butène optiquement actif partant d'une lactone chirale à travers une réaction de Wittig, suivi du couplage de cet alcène avec un phosphonate butényle par réaction de métathèse croisée et enfin finissant par l'introduction de la base uracile sur le phosphonate acyclique par réaction de Tsuji-Trost.[224]

Après protection sélective de la L-gulono-1,4-lactone avec un groupement *iso*propylidène, le L-(*S*)-glycéraldéhyde acétonide **87** énantiomériquement pure est obtenu à partir de **86** sous des conditions de clivage oxydant et d'isolement soigneusement contrôlées (Schéma 9).[225] L'aldéhyde **87** fraîchement préparé est immédiatement soumis à une réaction de Wittig afin de fournir le (*R*)-butène **88** avec un bon rendement de 82%.[228] Le (*R*)-*3*,4-*O*-*iso*propylidène-butène **88** est engagé comme partenaire dans une réaction de métathèse croisée catalysée au ruthénium aboutissant à la formation de la chaîne latérale pentényle acyclique **91**. Après clivage du groupement protecteur, les hydroxyles du diol allylique **92** sont convertis en acétates, bon groupement partant pour la réaction de Tsuji-Trost palladocatalysée.[223] Malheureusement, le couplage de la base uracile au diacétate allylique **93** sous différentes conditions d'amination allylique n'a pas donné le produit espéré **94**.

Une étude des conditions opératoires à partir de substrats plus simple a montré un possible gène stérique du second groupement acétate défavorable à l'approche du complexe au palladium(0) ou à l'attaque du nucléophile en position allylique. Les autres alternatives envisagées, tel l'utilisation d'un carbonate comme groupement partant ou l'introduction de la base uracile benzoylée en *N*-3 par réaction de Mitsunobu, ont également échoué.

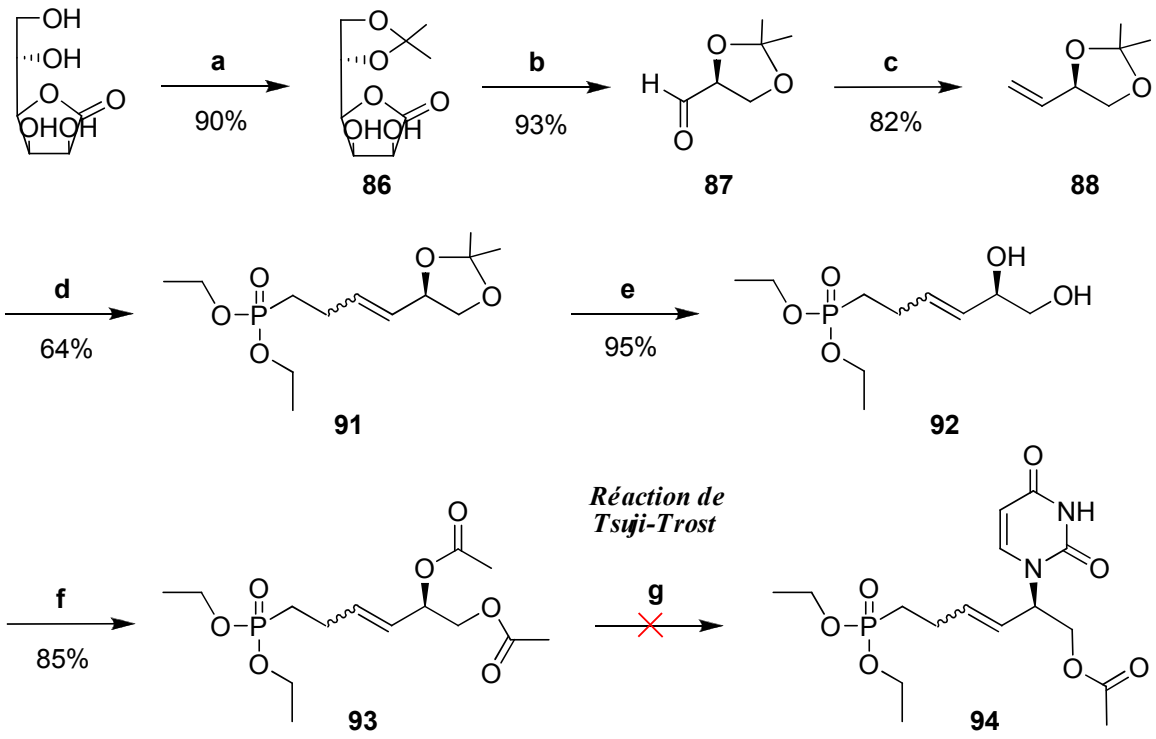


Schéma 9. Conditions réactionnelles: (a) 2-Methoxypropène, PTSA, DMF, t.a., 16 h; (b) $NaIO_4$, H_2O, t.a., 1 h; (c) Methyltriphenylphosphonium bromide, *n*-BuLi, THF, Ar, -78ºC à t.a., 20 h (d) 3-Buténylphosphonate de diéthyl, [Ru]= **58** (5 mol%), CH_2Cl_2, reflux, 24 h; (e) TFA 60%, t.a., 16 h; (f) Ac_2O, pyridine, Ar, 0°C à t.a., 16 h; (g) Uracile, NaH ou Et_3Al, $Pd(PPh_3)_4$, dppf, DMF/THF, Ar, 60°C, 16 h.

En conclusion, nous avons entrepris la synthèse de deux nouvelles séries d'uraciles phosphonates acycliques modifiés structurellement pour répondre aux critères de reconnaissance par l'enzyme. En première partie, une procédure optimisée a permis d'obtenir la série d'uraciles pentényles phosphonates substitués en position *C*-5 par des halogènes ou par un méthyle avec un bon rendement globale. Partant d'hétérocycles modifiés commerciaux, la synthèse a été réduite à cinq étapes, dont une étape clé de métathèse croisée. Malheureusement, les composés pentényles synthétisés se sont révélés moins bons substrats de la hTMPK et par conséquent moins bien phosphorylés que leurs analogues butényles précédemment reportés par notre groupe. Ils sont également inhibiteurs de l'hUMP-CMPK mais dans une moindre mesure. Dans un second temps, nous avons tenté de synthétiser de manière énantiosélective des pentényles phosphonates insaturés portant un substituent polaire sur leur chaîne acyclique. La chaîne latérale optiquement active de cinq carbones a été préparée en six étapes *via* métathèse croisée d'un alcène chiral issu de la L-gulono-1,4-lactone. Cependant, nous n'avons pas été capable d'introduire la base uracile en position allylique de cette chaîne acyclique que ce soit sous les conditions de la réaction de Tsuji-Trost ou de Mitsunobu.

Chapter II:

Acyclic nucleoside phosphonates *via* cross-metathesis

Experimental section

General methods

Commercially available chemicals were used as received. CH_2Cl_2 was distilled from CaH_2 prior use. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}). Compounds were visualized by UV irradiation and/or spraying with water solution of potassium permanganate $KMnO_4$, followed by charring at 150°C. Column chromatography was performed on silica gel 60 M (0.040–0.063 mm). ^{1}H NMR spectra were recorded on 250 MHz or 400 MHz spectrometers, ^{13}C NMR on 62.9 MHz or 100 MHz spectrometers, and ^{31}P on 162 MHz spectrometer at room temperature, using deuterated solvents as internal standard. Chemical shifts are given in ppm and multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), q_i (quintuplet) and m (multiplet). Assignments of NMR spectra follow standard nucleosides nomenclature: nucleoside bases are numbered from *N*-1 to *C*-6 and acyclic chains are numbered from *C*-1' to *C*-5'. Similar conventions apply for the corresponding hydrogen atoms. HRMS analyses were performed by the Mass Spectrometry Facility of the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain).

2. *C*^{5}-SUBSTITUTED URACIL PENT-2-ENYL PHOSPHONATES

50, 65-68: General procedure for *N*^{3}-benzoylation of uracil analogues (Procedure A)

To a solution of *C*^{5}-substituted uracil (1 g) in a 2/5 mixture of pyridine and acetonitrile (21 mL) was added benzoyl chloride (3 equiv). The reaction mixture was stirred 24 h at room temperature. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (petroleum ether/ EtOAc 5:5 to 0:1).

54g-f, 69-70: General procedure for crotylation of *N*^{3}-Benzoyl-uracil analogues (Procedure B)

To a DMF (12 mL) solution of *N*^{3}-benzoyl *C*^{5}-substituted-uracil (1 g) were added K_2CO_3 (1.05 equiv) and crotyl bromide (1.05 equiv) under argon atmosphere. After 1 h stirring at room temperature, the reaction mixture was diluted with EtOAc and then washed with an aqueous saturated NH_4Cl solution. The aqueous phases were extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:5).

71, 74-77: General procedure for cross-metathesis with diethyl 3-butenylphosphonate (Procedure C)

A mixture of protected *N*^{3}-benzoyl-*N*^{1}-crotyl-*C*^{5}-substituted uracil (0.5 g), diethyl 3-butenylphosphonate (2 equiv), and ruthenium catalyst **58** (5 mol%) added in turn in CH_2Cl_2 (30 mL) was refluxed for 8 h under argon atmosphere. After evaporation of all the volatiles, the residue was purified by chromatography on silica gel (EtOAc) to yield the desired compound.

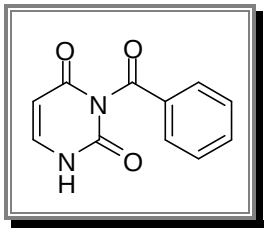
72, 78-81: General procedure for the deprotection of N^3-Benzoyl-uracil analogues (Procedure D)

The debenzoylation of C^5-substituted uracil pentenyl phosphonate (0.4 g) was carried out at 4ºC overnight in a methanol solution 7 N of ammonia (40 mL). After evaporation of all the volatiles, the residue was purified by chromatography on silica gel (EtOAc/MeOH 95:5) to yield the desired compound.

73, 82-85: General procedure for the deprotection of phosphonate diesters (Procedure E)

To a dry CH_2Cl_2 (10 mL) solution of C^5-substituted uracil phosphonate diester (0.1 g), TMSBr (6 equiv) was added at room temperature under argon atmosphere. After 12 h stirring, MeOH (5 mL) was added to the reaction mixture which was then concentrated under reduced pressure with heating (ca. 60 °C). Coevaporations were repeated five times with MeOH (5 mL). The residue was dissolved in deionized H_2O (ELGA® Water, 10 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 5 mL) and lyophilised to yield the expected phosphonic acid compound.

N^3-Benzoyl-uracil (50)



Procedure:

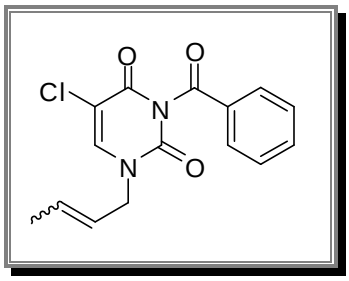
The title compound was prepared from uracil (1 g, 8.9 mmol) and benzoyl chloride (3 mL, 26.7 mmol, 3 equiv) following procedure **A**.

Compound **50** (1.74 g, 90%) was obtained as a white solid.

^{1}H NMR: (400 MHz, acetone-d6) δ 10.3 (bs, 1H, NH), 8.01 (m, 2H, H^{Ar}), 7.75 (tt, 1H, J = 7.6 and 1.1 Hz, H^{Ar}), 7.66 (d, 1H, J = 7.8 Hz, H^6), 7.59 (t, 2H, J = 7.6 Hz, H^{Ar}), 5.73 (d, 1H, J = 7.8 Hz, H^5).

CAS: 2775-87-3.

N^{3}-Benzoyl-5-chloro- *N*^{1}-crotyluracil (54e)



Procedure:

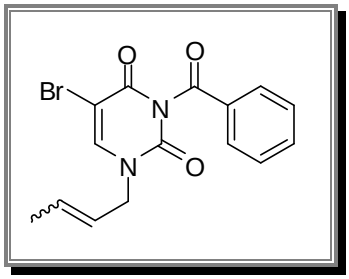
The title compound was prepared from **65** (1 g, 4.0 mmol), K_2CO_3 (0.58 g, 4.19 mmol, 1.05 equiv) and crotyl bromide (0.43 mL, 4.19 mmol, 1.05 equiv) following procedure **B**.

Compound **54e** (1.19 g, 98%, major/minor *ratio* = 80:20) was obtained as a white resin.

^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.91 (d, 2H, *J*= 7.5 Hz, H^{Ar}), 7.65 (t, 1H, *J*= 7.5 Hz, H^{Ar}), 7.51 (s, 1H, H^{6}), 7.51-7.46 (m, 2H, H^{Ar}), 5.96-5.77 (m, 1H, $H^{3'}$), 5.56-5.41 (m, 1H, $H^{2'}$), 4.38 (d, 0.4H, *J* = 7.0 Hz, $H^{1'}$ minor), 4.28 (d, 1.6H, *J* = 7.0 Hz, $H^{1'}$ major), 1.75 (d, 3H, *J*= 6.5 Hz, $H^{4'}$).

CAS: 1023339-53-8.

N^{3}-Benzoyl-5-bromo- *N*^{1}-crotyluracil (54f)



Procedure:

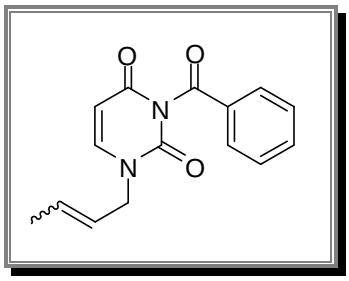
The title compound was prepared from **66** (1 g, 3.39 mmol), K_2CO_3 (0.49 g, 3.56 mmol, 1.05 equiv) and crotyl bromide (0.37 mL, 3.56 mmol, 1.05 equiv) after 1 h stirring at 70ºC following procedure **B**.

Compound **54f** (0.95 g, 80%, major/minor *ratio* = 75:25) was obtained as a colorless oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.91 (d, 2H, *J*= 7.5 Hz, H^{Ar}), 7.66 (t, 1H, *J*= 7.5 Hz, H^{Ar}), 7.61 (s, 0.7H, H^{6} major), 7.60 (s, 0.3H, H^{6} minor), 7.50 (t, 2H, *J*= 7.5 Hz, H^{Ar}), 5.96-5.82 (m, 1H, $H^{3'}$), 5.56-5.46 (m, 1H, $H^{2'}$), 4.44 (d, 0.5H, *J* = 7.0 Hz, $H^{1'}$ minor), 4.31 (d, 1.5H, *J* = 7.0 Hz, $H^{1'}$ major), 1.77 (d, 3H, *J*= 6.5 Hz, $H^{4'}$).

CAS: 1023339-58-3.

N^3-Benzoyl-N^1-crotyluracil (54g)



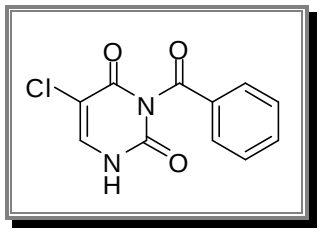
Procedure:

The title compound was prepared from **50** (1 g, 4.6 mmol), K_2CO_3 (0.67 g, 4.86 mmol, 1.05 equiv) and crotyl bromide (0.5 mL, 4.86 mmol, 1.05 equiv) following procedure **B**.
Compound **54g** (1.16 g, 93%, major/minor *ratio* = 80:20) was obtained as a colorless oil.

^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.96 (d, 2H, *J*= 8.5 Hz, H^{Ar}), 7.69-7.64 (m, 1H, H^{Ar}), 7.49-7.55 (m, 2H, H^{Ar}), 7.34 (d, 1H, *J* = 8.0 Hz, H^6), 5.85-5.75 (m, 1H, $H^{3'}$), 5.73 (d, 1H, *J* = 8.0 Hz, H^5), 5.57-5.45 (m, 1H, $H^{2'}$), 4.38 (d, 0.4H, *J* = 7.0 Hz, $H^{1'}$ minor), 4.26 (d, 1.6H, *J* = 7.0 Hz, $H^{1'}$ major), 1.72 (d, 3H, *J*= 6.3 Hz, $H^{4'}$).

CAS: 1023339-21-0.

N^3-Benzoyl-5-chloro-uracil (65)



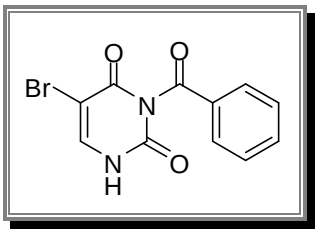
Procedure:

The title compound was prepared from 5-chlorouracil (1 g, 6.8 mmol) and benzoyl chloride (2.36 mL, 20 mmol, 3 equiv) following procedure **A**.
Compound **65** (1.63 g, 95%) was obtained as a white solid.

^{1}H NMR: (400 MHz, CD_3OD) δ 7.99 (m, 2H, H^{Ar}), 7.86 (s, 1H, H^6), 7.74 (t, 1H, *J* = 7.6 Hz, H^{Ar}), 7.57 (t, 2H, *J* = 7.6 Hz, H^{Ar}).

CAS: 214687-03-3.

N^{3}-Benzoyl-5-bromo-uracil (66)



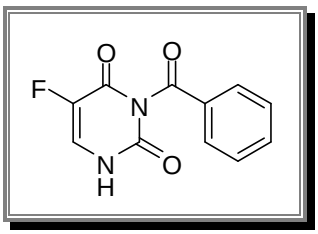
Procedure:

The title compound was prepared from 5-bromouracil (1 g, 5.2 mmol) and benzoyl chloride (1.80 mL, 15.7 mmol, 3 equiv) following procedure **A**.
Compound **66** (1.51 g, 98%) was obtained as a white solid.

^{1}H NMR: (250 MHz, acetone-d6) δ 8.02 (m, 2H, H^{Ar}), 8.01 (s, 1H, H^{6}), 7.72 (t, 1H, *J* = 7.5 Hz, H^{Ar}), 7.56 (t, 2H, *J* = 7.5 Hz, H^{Ar}).

CAS: 206762-91-6.

N^{3}-Benzoyl-5-fluoro-uracil (67)

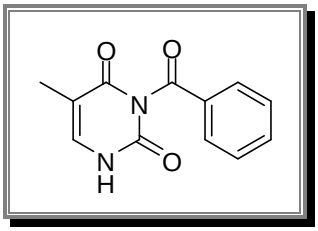


Procedure:

The title compound was prepared from 5-fluorouracil (1 g, 7.7 mmol) and benzoyl chloride (2.66 mL, 23 mmol, 3 equiv) following procedure **A**.
Compound **67** (1.71 g, 95%) was obtained as a white solid.

CAS: 61251-77-2.

N^{3}-Benzoyl-thymine (68)

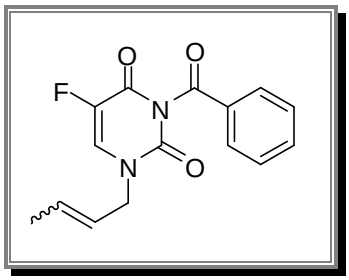


Procedure:

The title compound was prepared from thymine (1 g, 7.9 mmol) and benzoyl chloride (2.74 mL, 23.8 mmol, 3 equiv) following procedure **A**.
Compound **68** (1.74 g, 96%) was obtained as a white solid.

CAS: 4330-20-5.

N^3-Benzoyl-5-fluoro- *N*^{1}-crotyluracil (69)



Procedure:

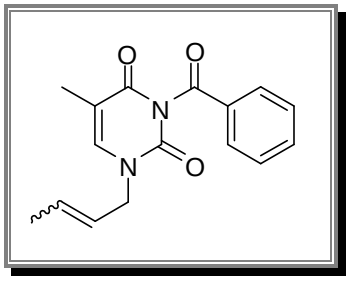
The title compound was prepared from **67** (1 g, 4.27 mmol), K_2CO_3 (0.62 g, 4.48 mmol, 1.05 equiv) and crotyl bromide (0.46 mL, 4.48 mmol, 1.05 equiv) following procedure **B**.

Compound **69** (0.86 g, 70%, major/minor *ratio* = 80:20) was obtained as a colorless oil.

^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.92 (d, 2H, *J*= 8.0 Hz, H^{Ar}), 7.64 (t, 1H, *J*= 8.0 Hz, H^{Ar}), 7.51 (t, 2H, *J*= 8.0 Hz, H^{Ar}), 7.35 (d, 1H, H^6), 5.96-5.74 (m, 1H, $H^{3'}$), 5.59-5.42 (m, 1H, $H^{2'}$), 4.40 (d, 0.4H, *J* = 6.5 Hz, $H^{1'}$ minor), 4.29 (d, 1.6H, *J* = 6.5 Hz, $H^{1'}$ major), 1.78 (d, 3H, *J*= 6.5 Hz, $H^{4'}$).

HRMS (ESI): *m/z* calcd for $C_{15}H_{13}FN_2O_3Na$ (M^+ + Na) 311.0796, found 311.0792.

N^3-Benzoyl- *N*^{1}-crotylthymine (70)



Procedure:

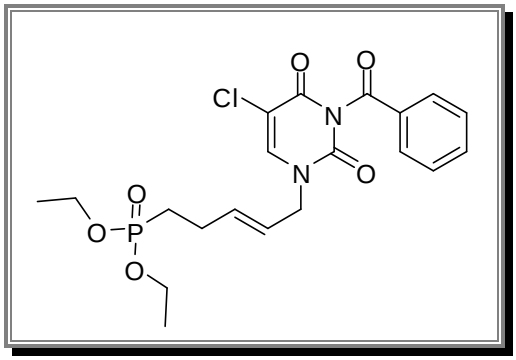
The title compound was prepared from **68** (1 g, 4.34 mmol), K_2CO_3 (0.63 g, 4.56 mmol, 1.05 equiv) and crotyl bromide (0.47 mL, 4.56 mmol, 1.05 equiv) following procedure **B**.

Compound **70** (0.96 g, 78%, major/minor *ratio* = 80:20) was obtained as a colorless oil.

^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.90 (m, 2H, H^{Ar}), 7.63 (m, 1H, H^{Ar}), 7.49 (m, 2H, H^{Ar}), 7.08 (s, 1H, H^6), 5.84-5.65 (m, 1H, $H^{3'}$), 5.76-5.61 (m, 1H, $H^{2'}$), 4.39 (d, 0.4H, *J* = 6.5 Hz, $H^{1'}$ minor), 4.27 (d, 1.6H, *J* = 6.5 Hz, $H^{1'}$ major), 1.95 (s, 3H, CH_3), 1.75 (d, 3H, *J*= 6.5 Hz, $H^{4'}$).

CAS: 882659-57-6.

(*E*)-*N*^{3}-Benzoyl-5-chloro-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)uracil (71)



Procedure:

The title compound was prepared from **54e** (0.5 g, 1.64 mmol), diethyl 3-butenylphosphonate (1.26 mL, 6.57 mmol, 4 equiv) and ruthenium catalyst **58** (70 mg, 5 mol%) following procedure **C**.

Final compound (0.58 g, 78%) was obtained as a mixture of the two olefin isomers (*E*/*Z ratio* = 9:1). *E*-isomer (**71**) was isolated as a colorless oil by column chromatography and characterized.

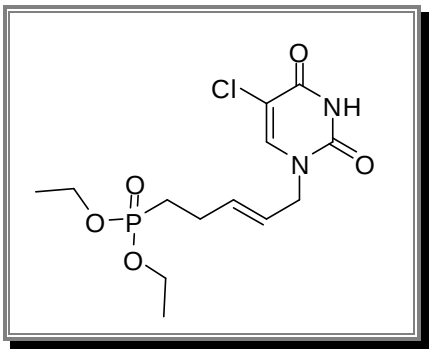
^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.89 (d, 2H, *J*= 7.5 Hz, H^{Ar}), 7.65 (t, 1H, *J*= 7.5 Hz, H^{Ar}), 7.57 (s, 1H, H^6), 7.53-7.45 (m, 2H, H^{Ar}), 5.86 (dt, 1H, *J* = 6.5 and 15.0 Hz, $H^{3'}$), 5.55 (dt, 1H, *J* = 6.5 and 15.0 Hz, $H^{2'}$), 4.31 (d, 2H, *J* = 6.5 Hz, $H^{1'}$), 4.14-4.02 (m, 4H, OCH_2), 2.46-2.32 (m, 2H, $H^{4'}$), 1.88-1.75 (m, 2H, $H^{5'}$), 1.30 (t, 6H, *J*= 7.0 Hz, OCH_2-CH_3).

^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 167.7 (CO), 158.4 (CO, C^4), 148.9 (CO, C^2), 140.5 (CH, C^6), 137.0 (d, CH, *J*= 15.3 Hz, $C^{3'}$), 135.5 (CH, C^{Ar}), 131.0 (C, C^{Ar}), 130.6 (CH, $2C^{Ar}$), 129.3 (CH, $2C^{Ar}$), 123.2 (CH, $C^{2'}$), 108.8 (C, C^5), 61.8 (d, CH_2, *J*= 6.5 Hz, OCH_2), 50.1 (CH_2, $C^{1'}$), 25.4 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 25.0 (d, CH_2, *J*= 141.7 Hz, $C^{5'}$), 16.6 (d, CH_3, *J*= 5.9 Hz, OCH_2-CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 33.53.

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}ClN_2O_6NaP$ (M^+ + Na) 477.0958, found 477.0937.

(*E*)-5-Chloro-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)uracil (72)



Procedure:

The title compound was prepared from **71** (0.4 g, 0.88 mmol) following procedure **D**.
Compound **72** (0.27 g, 86%) was obtained as a colorless oil.

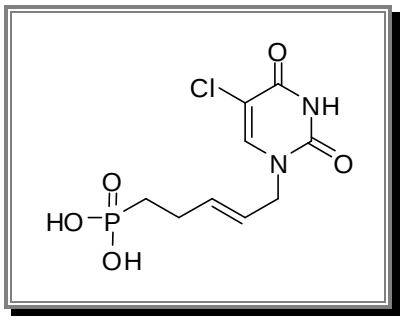
^{1}H NMR: (250 MHz, $CDCl_3$) δ 9.98 (bs, 1H, NH), 7.44 (s, 1H, H^{6}), 5.89-5.76 (m, 1H, $H^{3'}$), 5.58-5.47 (m, 1H, $H^{2'}$), 4.29 (d, 2H, *J* = 6.5 Hz, $H^{1'}$), 4.16-4.01 (m, 4H, OCH_2), 2.45-2.31 (m, 2H, $H^{4'}$), 1.89-1.76 (m, 2H, $H^{5'}$), 1.30 (t, 6H, *J*= 7.0 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 159.6 (CO, C^{4}), 150.2 (CO, C^{2}), 140.6 (CH, C^{6}), 136.1 (d, CH, *J*= 15.4 Hz, $C^{3'}$), 123.7 (CH, $C^{2'}$), 108.9 (C, C^{5}), 61.8 (d, CH_2, *J*= 6.5 Hz, OCH_2), 49.74 (CH_2, $C^{1'}$), 25.3 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 25.0 (d, CH_2, *J*= 141.7 Hz, $C^{5'}$), 16.5 (d, CH_3, *J*= 5.9 Hz, OCH_2-*C*H$_3$).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.68.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}ClN_2O_5NaP$ (M^+ + Na) 373.0696, found 373.0690.

(*E*)-5-Chloro-*N*^{1}-(5'-dihydroxyphosphinyl-2'-pentenyl)uracil (73)



Procedure:

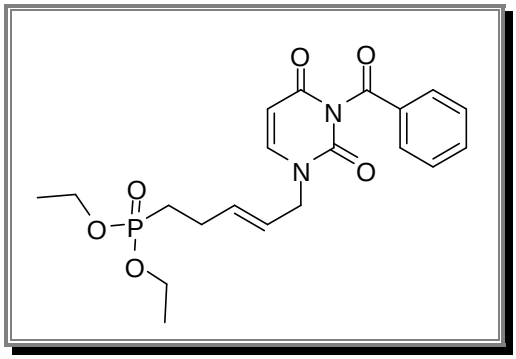
The title compound was prepared from **72** (0.1 g, 0.29 mmol) and TMSBr (0.23 mL, 1.71 mmol, 6 equiv) following procedure **E**.
Compound **73** (71 mg, 85%) was obtained as a white solid.

^{1}H NMR: (250 MHz, CD_3OD) δ 7.88 (s, 1H, H^6), 5.86 (dt, 1H, *J* =6.4 and 15.2 Hz, $H^{3'}$), 5.62 (dt, 1H, *J* =6.0 and 15.2 Hz, $H^{2'}$), 4.32 (d, 2H, *J* = 6.0 Hz, $H^{1'}$), 2.62-2.32 (m, 2H, $H^{4'}$), 1.88-1.75 (m, 2H, $H^{5'}$).

^{13}C NMR: (100.6 MHz, CD_3OD) δ 161.3 (CO, C^4), 151.2 (CO, C^2), 143.0 (CH, C^6), 135.7 (d, CH, *J*= 16.3 Hz, $C^{3'}$), 124.6 (CH, $C^{2'}$), 108.3 (C, C^5), 50.1 (CH_2, $C^{1'}$), 27.4 (d, CH_2, *J*= 144.0 Hz, $C^{5'}$), 25.0 (d, CH_2, *J*= 4.2 Hz, $C^{4'}$).

^{31}P NMR: (162 MHz, CD_3OD) δ 29.32.

(*E*)-*N*^{3}-Benzoyl-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)uracil (74)



Procedure:

The title compound was prepared from **54g** (0.5 g, 1.85 mmol), diethyl 3-butenylphosphonate (0.7 mL, 3.7 mmol, 2 equiv) and ruthenium catalyst **58** (78 mg, 5 mol%) following procedure **C**.

Final compound (0.67 g, 86%) was obtained as a mixture of the two olefin isomers (*E*/*Z ratio* = 9:1). *E*-isomer (**74**) was isolated as a colorless oil by column chromatography and characterized.

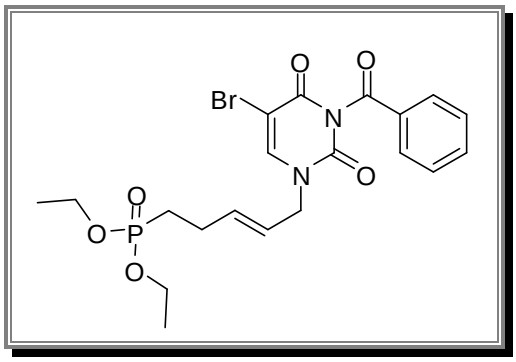
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.91 (d, 2H, *J*= 7.5 Hz, H^{Ar}), 7.64 (t, 1H, *J*= 7.5 Hz, H^{Ar}), 7.48 (t, 2H, *J*= 7.5 Hz, H^{Ar}), 7.30 (d, 1H, *J*= 8.0 Hz, H^6), 5.88-5.76 (m, 1H, $H^{3'}$), 5.80 (d, 1H, *J*= 8.0 Hz, H^5), 5.57 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{2'}$), 4.31 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 4.15-4.02 (m, 4H, OCH_2), 2.44-2.35 (m, 2H, $H^{4'}$), 1.86-1.77 (m, 2H, $H^{5'}$), 1.31 (t, 6H, *J*= 6.8 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 168.9 (CO), 162.5 (CO, C^4), 149.8 (CO, C^2), 143.6 (CH, C^6), 136.1 (d, CH, *J*= 15.5 Hz, $C^{3'}$), 135.2 (CH, C^{Ar}), 131.6 (C, C^{Ar}), 130.5 (CH, 2C^{Ar}), 129.3 (CH, 2C^{Ar}), 123.8 (CH, $C^{2'}$), 102.4 (C, C^5), 61.8 (d, CH_2, *J*= 6.5 Hz, OCH_2), 49.8 (CH_2, $C^{1'}$), 25.4 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 25.1 (d, CH_2, *J*= 141.6 Hz, $C^{5'}$), 16.6 (d, CH_3, *J*= 5.9 Hz, OCH_2-*C*H$_3$).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.65.

HRMS (ESI): *m/z* calcd for $C_{20}H_{25}N_2O_6NaP$ (M^+ + Na) 443.1348, found 443.1352.

(*E*)-*N*^{3}-Benzoyl-5-bromo-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)uracil (75)



Procedure:

The title compound was prepared from **54f** (0.5 g, 1.43 mmol), diethyl 3-butenylphosphonate (0.55 mL, 2.86 mmol, 2 equiv) and ruthenium catalyst **58** (61 mg, 5 mol%) following procedure **C**.

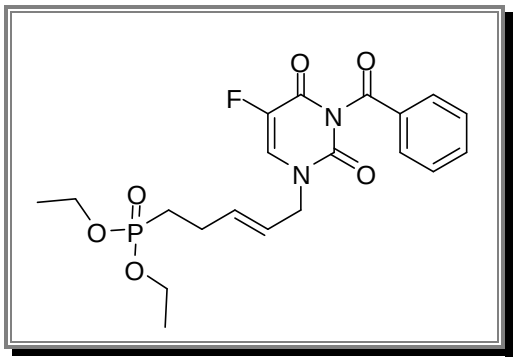
Final compound (0.57 g, 80%) was obtained as a mixture of the two olefin isomers (*E*/*Z ratio* = 9:1). *E*-isomer (**75**) was isolated as a colorless oil by column chromatography and characterized.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, *J*= 7.2 Hz, H^{Ar}), 7.67 (s, 1H, H^{6}), 7.63 (t, 1H, *J*= 7.2 Hz, H^{Ar}), 7.46 (t, 2H, *J*= 7.5 Hz, H^{Ar}), 5.85 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{3'}$), 5.53 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{2'}$), 4.29 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 4.13-4.00 (m, 4H, OCH_2), 2.41-2.32 (m, 2H, $H^{4'}$), 1.84-1.76 (m, 2H, $H^{5'}$), 1.29 (t, 6H, *J*= 7.0 Hz, OCH_2-CH_3).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 167.7 (CO), 158.3 (CO, C^{4}), 149.1 (CO, C^{2}), 143.1 (CH, C^{6}), 136.8 (d, CH, *J*= 15.4 Hz, $C^{3'}$), 135.4 (CH, C^{Ar}), 131.0 (C, C^{Ar}), 130.5 (CH, $2C^{Ar}$), 129.3 (CH, $2C^{Ar}$), 123.2 (CH, $C^{2'}$), 96.2 (C, C^{5}), 61.7 (d, CH_2, *J*= 6.5 Hz, OCH_2), 50.1 (CH_2, $C^{1'}$), 25.3 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 24.9 (d, CH_2, *J*= 141.6 Hz, $C^{5'}$), 16.5 (d, CH_3, *J*= 5.9 Hz, OCH_2-CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.49.

(*E*)-*N*^{3}-Benzoyl-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)-5-fluoro-uracil (76)



Procedure:

The title compound was prepared from **69** (0.5 g, 1.73 mmol), diethyl 3-butenylphosphonate (0.66 mL, 3.47 mmol, 2 equiv) and ruthenium catalyst **58** (73 mg, 5 mol%) following procedure **C**.

Final compound (0.59 g, 78%) was obtained as a mixture of the two olefin isomers (*E*/*Z ratio* = 9:1). *E*-isomer (**76**) was isolated as a white solid by column chromatography and characterized.

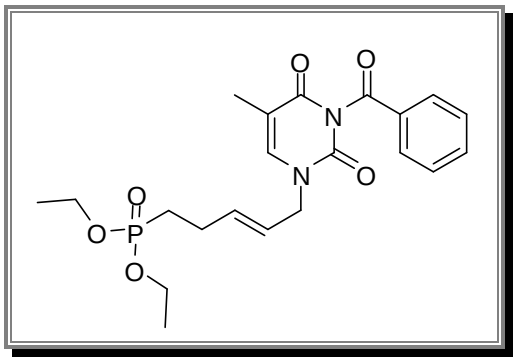
^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J*= 7.2 Hz, H^{Ar}), 7.70 (t, 1H, *J*= 7.6 Hz, H^{Ar}), 7.54 (t, 2H, *J*= 7.6 Hz, H^{Ar}), 7.48 (d, 1H, *J* = 5.6 Hz, H^{6}), 5.82 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{3'}$), 5.52 (dt, 1H, *J* = 5.2 and 16.8 Hz, $H^{2'}$), 4.34 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 4.20-4.08 (m, 4H, OCH_2), 2.55-2.38 (m, 2H, $H^{4'}$), 1.92-1.82 (m, 2H, $H^{5'}$), 1.27 (t, 6H, *J*= 7.2 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 167.2 (CO), 156.1 (d, CO, *J* = 27.1 Hz, C^{4}), 148.2 (CO, C^{2}), 140.0 (d, C, *J* = 240.0 Hz, C^{5}), 137.0 (d, CH, *J*= 14.8 Hz, $C^{3'}$), 134.4 (CH, C^{Ar}), 130.1 (C, C^{Ar}), 129.6 (CH, $2C^{Ar}$), 128.3 (CH, $2C^{Ar}$), 127.5 (d, CH, *J* = 32.6 Hz, C^{6}), 122.2 (CH, $C^{2'}$), 61.6 (d, CH_2, *J*= 6.5 Hz, OCH_2), 49.8 (CH_2, $C^{1'}$), 25.3 (d, CH_2, *J*= 5.0 Hz, $C^{4'}$), 24.9 (d, CH_2, *J*= 141.8 Hz, $C^{5'}$), 16.4 (d, CH_3, *J*= 6.0 Hz, OCH_2-*C*H$_3$).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.43.

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}FN_2O_6NaP$ (M^+ + Na) 461.1254, found 461.1243.

(*E*)-*N*^{3}-Benzoyl-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)thymine (77)



Procedure:

The title compound was prepared from **70** (0.5 g, 1.76 mmol), diethyl 3-butenylphosphonate (0.67 mL, 3.52 mmol, 2 equiv) and ruthenium catalyst **58** (74 mg, 5 mol%) following procedure **C**.

Final compound (0.49 g, 64%) was obtained as a mixture of the two olefin isomers (*E*/*Z ratio* = 9:1). *E*-isomer (**77**) was isolated as a white solid by column chromatography and characterized.

^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.90 (d, 2H, *J*= 7.6 Hz, H^{Ar}), 7.63 (t, 1H, *J*= 7.6 Hz, H^{Ar}), 7.48 (t, 2H, *J*= 7.6 Hz, H^{Ar}), 7.12 (s, 1H, H^{6}), 5.73 (dt, 1H, *J* = 6.8 and 15.2 Hz, $H^{3'}$), 5.52 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{2'}$), 4.30 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 4.17-4.03 (m, 4H, OCH_2), 2.78-2.34 (m, 2H, $H^{4'}$), 1.95 (s, 3H, CH_3), 1.89-1.78 (m, 2H, $H^{5'}$), 1.32 (t, 6H, *J*= 7.2 Hz, OCH_2-C*H*$_3$).

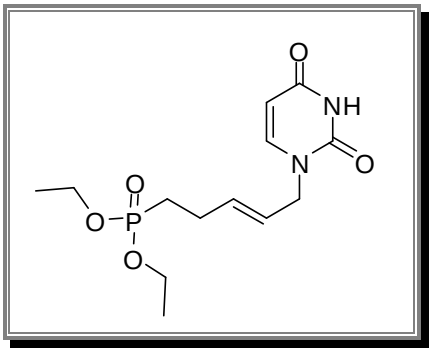
^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 169.1 (CO), 163.1 (CO, C^{4}), 149.8 (CO, C^{2}), 139.4 (CH, C^{6}), 135.7 (d, CH, *J*= 15.6 Hz, $C^{3'}$), 135.0 (CH, C^{Ar}), 131.7 (C, C^{Ar}), 130.5 (CH, $2C^{Ar}$), 129.2 (CH, $2C^{Ar}$), 124.0 (CH, $C^{2'}$), 111.0

(C, C^5), 61.7 (d, CH_2, *J*= 6.4 Hz, OCH_2), 49.5 (CH_2, $C^{1'}$), 25.3 (d, CH_2, *J*= 4.5 Hz, $C^{4'}$), 25.1 (d, CH_2, *J*= 141.6 Hz, $C^{5'}$), 16.5 (d, CH_3, *J*= 5.9 Hz, OCH_2-CH_3), 12.4 (CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.63.

HRMS (ESI): *m/z* calcd for $C_{21}H_{27}N_2O_6NaP$ (M^+ + Na) 457.1504, found 457.1501.

(*E*)-*N*^{1}-(5'-Diethoxyphosphinyl-2'-pentenyl)uracil (78)



Procedure:

The title compound was prepared from **74** (0.4 g, 0.95 mmol) following procedure **D**.
Compound **78** (0.3 g, >99%) was obtained as a colorless oil.

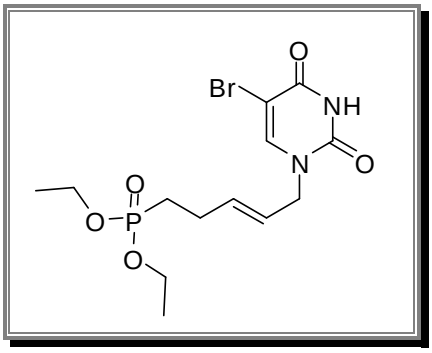
^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.61 (bs, 1H, NH), 7.18 (d, 1H, *J*= 8.0 Hz, H^6), 5.77 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{3'}$), 5.68 (d, 1H, *J*= 8.0 Hz, H^5), 5.53 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{2'}$), 4.28 (d, 2H, *J* = 6.0 Hz, $H^{1'}$), 4.12-4.02 (m, 4H, OCH_2), 2.40-2.31 (m, 2H, $H^{4'}$), 1.84-1.76 (m, 2H, $H^{5'}$), 1.29 (t, 6H, *J*= 7.0 Hz, OCH_2-CH_3).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 163.9 (CO, C^4), 151.0 (CO, C^2), 143.8 (CH, C^6), 135.2 (d, CH, *J*= 15.8 Hz, $C^{3'}$), 124.1 (CH, $C^{2'}$), 102.5 (C, C^5), 61.7 (d, CH_2, *J*= 6.5 Hz, OCH_2), 49.4 (CH_2, $C^{1'}$), 25.3 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 25.0 (d, CH_2, *J*= 141.6 Hz, $C^{5'}$), 16.5 (d, CH_3, *J*= 5.9 Hz, OCH_2-CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.74.

HRMS (ESI): *m/z* calcd for $C_{13}H_{21}N_2O_5NaP$ (M^+ + Na) 339.1086, found 339.1070.

(*E*)-5-Bromo-*N*^{1}-(5'-diethoxyphosphinyl-2'-pentenyl)uracil (79)



Procedure:

The title compound was prepared from **75** (0.4 g, 0.8 mmol) following procedure **D**.
Compound **79** (0.28 g, 87%) was obtained as a colorless oil.

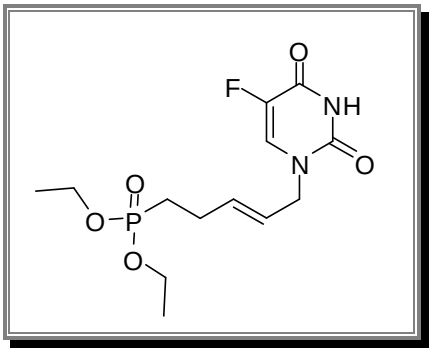
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.69 (bs, 1H, NH), 7.54 (s, 1H, H^6), 5.85 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{3'}$), 5.55 (dt, 1H, *J* = 6.4 and 15.2 Hz, $H^{2'}$), 4.31 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 4.12-4.04 (m, 4H, OCH_2), 2.45-2.37 (m, 2H, $H^{4'}$), 1.88-1.80 (m, 2H, $H^{5'}$), 1.32 (t, 6H, *J*= 7.0 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 159.2 (CO, C^4), 150.0 (CO, C^2), 143.2 (CH, C^6), 136.4 (d, CH, *J*= 15.5 Hz, $C^{3'}$), 123.6 (CH, $C^{2'}$), 96.7 (C, C^5), 61.8 (d, CH_2, *J*= 6.5 Hz, OCH_2), 49.9 (CH_2, $C^{1'}$), 25.4 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 25.0 (d, CH_2, *J*= 141.8 Hz, $C^{5'}$), 16.6 (d, CH_3, *J*= 5.9 Hz, OCH_2-*C*H_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.49.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}BrN_2O_5NaP$ (M^+ + Na) 417.0191, found 417.0181.

(*E*)-*N*^{1}-(5'-Diethoxyphosphinyl-2'-pentenyl)-5-fluoro-uracil (80)



Procedure:

The title compound was prepared from **76** (0.4 g, 0.91 mmol) following procedure **D**.
Compound **80** (0.26 g, 86%) was obtained as a colorless oil.

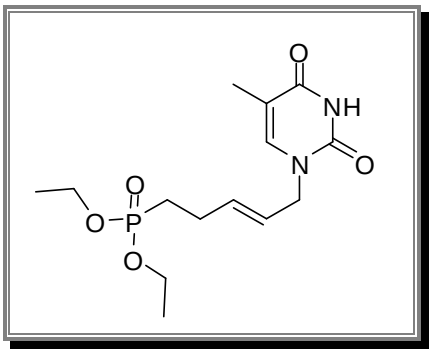
^{1}H NMR: (250 MHz, $CDCl_3$) δ 10.33 (bs, 1H, NH), 7.32 (d, 1H, *J* = 5.6 Hz, H^6), 5.82 (dt, 1H, *J* = 6.6 and 15.2 Hz, $H^{3'}$), 5.52 (dt, 1H, *J* = 6.8 and 15.2 Hz, $H^{2'}$), 4.27 (d, 2H, *J* = 6.8 Hz, $H^{1'}$), 4.17-4.03 (m, 4H, OCH_2), 2.62-2.31 (m, 2H, $H^{4'}$), 1.90-1.78 (m, 2H, $H^{5'}$), 1.30 (t, 6H, *J*= 7.2 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 157.0 (d, CO, *J*= 26.0 Hz, C^4), 149.2 (CO, C^2), 140.1 (d, C, *J*= 237.2 Hz, C^5), 136.4 (d, CH, *J*= 15.05 Hz, $C^{3'}$), 127.3 (d, CH, *J*= 32.6 Hz, C^6), 123.2 (CH, $C^{2'}$), 61.3 (d, CH_2, *J*= 6.5 Hz, OCH_2), 49.0 (CH_2, $C^{1'}$), 24.8 (d, CH_2, *J*= 4.6 Hz, $C^{4'}$), 24.5 (d, CH_2, *J*= 141.6 Hz, $C^{5'}$), 16.0 (d, CH_3, *J*= 5.9 Hz, OCH_2-*C*H_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.83.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}FN_2O_5NaP$ (M^+ + Na) 357.0992, found 357.1009.

(*E*)-*N*^{1}-(5'-Diethoxyphosphinyl-2'-pentenyl)-thymine (81)



Procedure:

The title compound was prepared from **77** (0.4 g, 0.92 mmol) following procedure **D**.
Compound **81** (0.26 g, 87%) was obtained as a colorless oil.

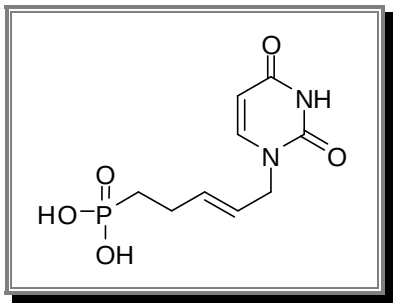
^{1}H NMR: (250 MHz, $CDCl_3$) δ 9.90 (bs, 1H, NH), 7.00 (s, 1H, H^{6}), 5.72 (dt, 1H, *J* = 6.3 and 15.5 Hz, $H^{3'}$), 5.51 (dt, 1H, *J* = 6.3 and 15.5 Hz, $H^{2'}$), 4.25 (d, 2H, *J* = 6.3 Hz, $H^{1'}$), 4.19-4.00 (m, 4H, OCH_2), 2.63-2.31 (m, 2H, $H^{4'}$), 1.94-1.72 (m, 2H, $H^{5'}$), 1.88 (s, 3H, CH_3), 1.29 (t, 6H, *J*= 7.0 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 163.1 (CO, C^{4}), 149.6 (CO, C^{2}), 138.2 (CH, C^{6}), 133.2 (d, CH, *J*= 14.1 Hz, $C^{3'}$), 122.9 (CH, $C^{2'}$), 109.4 (C, C^{5}), 60.1 (d, CH_2, *J*= 6.5 Hz, OCH_2), 47.5 (CH_2, $C^{1'}$), 23.7 (d, CH_2, *J*= 4.5 Hz, $C^{4'}$), 23.5 (d, CH_2, *J*= 141.4 Hz, $C^{5'}$), 15.0 (d, CH_3, *J*= 5.9 Hz, OCH_2-*C*H_3), 10.8 (CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.81.

HRMS (ESI): *m/z* calcd for $C_{14}H_{23}N_2O_5NaP$ (M^+ + Na) 353.1242, found 353.1231.

(*E*)-*N*^{1}-(5'-Dihydroxyphosphinyl-2'-pentenyl)uracil (82)



Procedure:

The title compound was prepared from **78** (0.1 g, 0.32 mmol) and TMSBr (0.25 mL, 1.90 mmol, 6 equiv) following procedure **E**.
Compound **82** (64 mg, 78%) was obtained as a white solid.

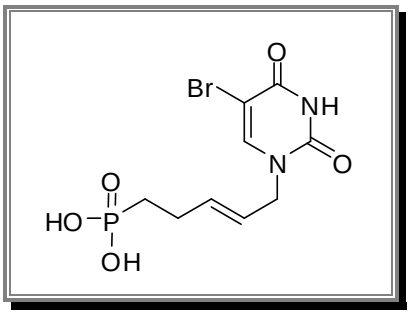
^{1}H NMR: (250 MHz, CD_3OD) δ 7.53 (d, 1H, *J* = 8.0 Hz, H^6), 5.80 (dt, 1H, *J* =6.4 and 15.6 Hz, $H^{3'}$), 5.63 (d, 1H, *J* = 8.0 Hz, H^5), 5.61 (dt, 1H, *J* =6.0 and 15.6 Hz, $H^{2'}$), 4.29 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 2.58-2.30 (m, 2H, $H^{4'}$), 1.89-1.75 (m, 2H, $H^{5'}$).

^{13}C NMR: (100.6 MHz, CD_3OD) δ 166.7 (CO, C^4), 142.6 (CO, C^2), 146.9 (CH, C^6), 135.7 (d, CH, *J*= 16.4 Hz, $C^{3'}$), 125.6 (CH, $C^{2'}$), 102.3 (C, C^5), 50.4 (CH_2, $C^{1'}$), 28.0 (d, CH_2, *J*= 144.0 Hz, $C^{5'}$), 26.5 (d, CH_2, *J*= 4.3 Hz, $C^{4'}$).

^{31}P NMR: (162 MHz, CD_3OD) δ 30.17.

HRMS (ESI): *m/z* calcd for $C_9H_{12}N_2O_5P$ (M^- - H) 259.0484, found 259.0496.

(*E*)-5-Bromo-*N*^{1}-(5'-dihydroxyphosphinyl-2'-pentenyl)uracil (83)



Procedure:

The title compound was prepared from **79** (0.1 g, 0.25 mmol) and TMSBr (0.2 mL, 1.52 mmol, 6 equiv) following procedure **E**.
Compound **83** (72 mg, 84%) was obtained as a white solid.

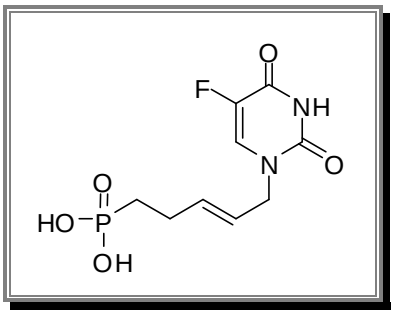
^{1}H NMR: (250 MHz, CD_3OD) δ 7.97 (s, 1H, H^6), 5.86 (dt, 1H, *J* =6.6 and 15.2 Hz, $H^{3'}$), 5.63 (dt, 1H, *J* =6.4 and 15.2 Hz, $H^{2'}$), 4.29 (d, 2H, *J* = 6.0 Hz, $H^{1'}$), 2.62-2.32 (m, 2H, $H^{4'}$), 1.89-1.78 (m, 2H, $H^{5'}$).

^{13}C NMR: (100.6 MHz, CD_3OD) δ 161.9 (CO, C^4), 151.9 (CO, C^2), 146.1 (CH, C^6), 136.2 (d, CH, *J*= 16.5 Hz, $C^{3'}$), 125.1 (CH, $C^{2'}$), 96.5 (C, C^5), 50.6 (CH_2, $C^{1'}$), 28.0 (d, CH_2, *J*= 144.0 Hz, $C^{5'}$), 26.5 (d, CH_2, *J*= 4.2 Hz, $C^{4'}$).

^{31}P NMR: (162 MHz, CD_3OD) δ 29.31

HRMS (ESI): *m/z* calcd for $C_9H_{11}BrN_2O_5P$ (M^- - H) 336.9589, found 336.9577.

(*E*)-*N*^{1}-(5'-Dihydroxyphosphinyl-2'-pentenyl)-5-fluoro-uracil (84)



Procedure:

The title compound was prepared from **80** (0.1 g, 0.30 mmol) and TMSBr (0.24 mL, 1.79 mmol, 6 equiv) following procedure **E**.
Compound **84** (75 mg, 90%) was obtained as a white solid.

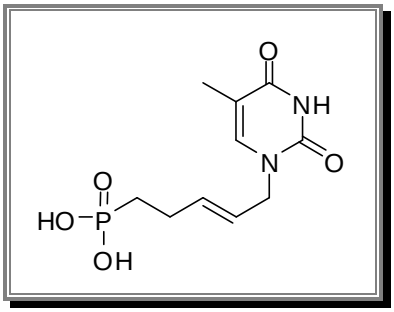
^{1}H NMR: (250 MHz, CD_3OD) δ 7.78 (d, 1H, *J* = 6.4 Hz, H^6), 5.86 (dt, 1H, *J* =6.8 and 15.2 Hz, $H^{3'}$), 5.61 (dt, 1H, *J* =6.4 and 15.2 Hz, $H^{2'}$), 4.30 (d, 2H, *J* = 6.4 Hz, $H^{1'}$), 2.62-2.31 (m, 2H, $H^{4'}$), 1.91-1.78 (m, 2H, $H^{5'}$).

^{13}C NMR: (100.6 MHz, CD_3OD) δ 160.0 (d, CO, *J* = 25.7 Hz, C^4), 151.5 (CO, C^2), 141.9 (d, C, *J* = 232.5 Hz, C^5), 136.4 (d, CH, *J*= 16.3 Hz, $C^{3'}$), 130.8 (d, CH, *J* = 33,2 Hz, C^6), 125.4 (CH, $C^{2'}$), 50.7 (CH_2, $C^{1'}$), 28.2 (d, CH_2, *J*= 144.0 Hz, $C^{5'}$), 26.8 (d, CH_2, *J*= 4.2 Hz, $C^{4'}$).

^{31}P NMR: (162 MHz, CD_3OD) δ 29.65.

HRMS (ESI): *m/z* calcd for $C_9H_{11}FN_2O_5P$ (M^- - H) 277.0390, found 277.0383.

(*E*)-*N*^{1}-(5'-Dihydroxyphosphinyl-2'-pentenyl)-thymine (85)



Procedure:

The title compound was prepared from **81** (0.1 g, 0.30 mmol) and TMSBr (0.24 mL, 1.81 mmol, 6 equiv) following procedure **E**.
Compound **85** (75 mg, 90%) was obtained as a white solid.

^{1}H NMR: (250 MHz, CD_3OD) δ 7.41 (s, 1H, H^6), 5.80 (dt, 1H, *J* =6.3 and 15.4 Hz, $H^{3'}$), 5.61 (dt, 1H, *J* =6.0 and 15.4 Hz, $H^{2'}$), 4.29 (d, 2H, *J* = 6.0 Hz, $H^{1'}$), 2.63-2.30 (m, 2H, $H^{4'}$), 1.90-1.80 (m, 2H, $H^{5'}$), 1.88 (s, 3H, CH_3).

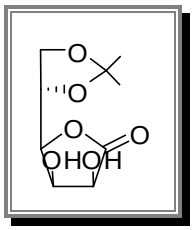
^{13}C NMR: (100.6 MHz, CD_3OD) δ 166.6 (CO, C^4), 152.6 (CO, C^2), 142.5 (CH, C^6), 135.1 (d, CH, *J*= 16.5 Hz, $C^{3'}$), 125.6 (CH, $C^{2'}$), 111.1 (C, C^5), 50.0 (CH_2, $C^{1'}$), 27.6 (d, CH_2, *J*= 144.0 Hz, $C^{5'}$), 26.2 (d, CH_2, *J*= 4.3 Hz, $C^{4'}$), 12.0 (CH_3).

^{31}P NMR: (162 MHz, CD_3OD) δ 29.41.

HRMS (ESI): *m/z* calcd for $C_{10}H_{14}N_2O_5P$ (M^- - H) 273.0640, found 273.0633.

3. ENANTIOSELECTIVE 1'-HYDROXYMETHYL PHOSPHONONUCLEOSIDES

(*S*)-5,6-*O*-*Iso*propylidene-L-gulono-1,4-lactone (86)



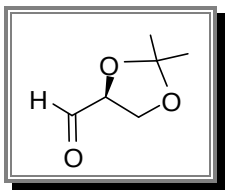
Procedure:

To a solution of L-gulono-1,4-lactone (10 g, 56 mmol) in DMF (50 mL) were added a small amount of *p*-toluenesulfonic acid and 2-methoxypropene (10.75 mL, 112 mmol, 2 equiv) at 0°C. The solution was stirred at room temperature for 24 h and then treated with sodium carbonate (5 g). The resulting suspension was vigorously stirred for additional 2 h, filtered and the filtrate was concentrated under reduced pressure. Crystallization was induced by addition of toluene (9 mL) to the yellow syrupy residue. The precipitate was filtered and washed with hexane/EtOH 9/1 (4 mL) to give compound **86** (11g, 90%) as a white solid.

^{1}H NMR: (250 MHz, CD_3OD) δ 4.41 (d, 1H, *J* = 4.5 Hz, H^2), 4.46-4.32 (m, 3H, H^3 + H^4 + H^5), 4.20 (dd, 1H, *J* = 8.7 and 6.2 Hz, H^6), 3.83 (dd, 1H, *J* = 8.7 and 6.2 Hz, H^6), 1.41 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

CAS: 94697-68-4.

(*S*)-*2,3-O-Iso*propylidene-L-glyceraldehyde (87)



Procedure:

To a suspension of sodium periodate (16.86 g, 78.8 mmol, 2 equiv) in water (50 mL) cooled to 0°C was added dropwise an aqueous solution 3 N of NaOH (~ 30 mL) at a rate such that the temperature does not exceed 7°C. The final pH of the suspension was adjusted to 5.5. The cooling bath was removed and compound **86** (8.6 g, 39.4 mmol) was added in one portion. The temperature of the mixture was kept below 30°C and the pH was

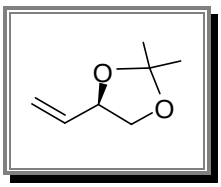
maintained at 5.5 during the course of the reaction by addition of aqueous solution 15% of sodium carbonate. The suspension was further stirred at room temperature for 1 h, saturated with sodium chloride and filtered. The white solid was washed thoroughly with brine (2 x 10 mL) and the pH of the combined aqueous layers was adjusted to 6.7 with aqueous solution 15% of sodium carbonate before extraction with CH_2Cl_2 (6 x 30 mL) and EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and slowly concentrated to about 10 mL under monitored reduced pressure (T° bath = 30°C, Pressure = 300 mbar). The remaining solution was further concentrated by bulb-to-bulb distillation under reduced pressure (200 mbar) at 35°C. After gradual increase of the temperature bath to 80°C, the title compound was distilled (50°C) and collected in a bulb cooled with dry ice-acetone bath. Compound **87** (4.77 g, 93%) was obtained as a colorless liquid (Caution, **87** is an unstable liquid that starts to polymerize on standing even at low temperature. It can be depolymerized by distillation before use).

$[\alpha]_D^{27}$ = - 48.8 (*c* = 1.25, C_6H_6).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.69 (d, 1H, *J* = 1.6 Hz, H^1), 4.36 (ddd, 1H, *J* = 7.2, 4.8 and 1.6 Hz, H^2), 4.14 (dd, 1H, *J* = 8.8 and 7.2 Hz, H^3), 4.08 (dd, 1H, *J* = 8.8 and 4.8 Hz, H^3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3).

CAS: 22323-80-4.

(*R*)-*3,4-O-Iso*propylidene-butene (88)



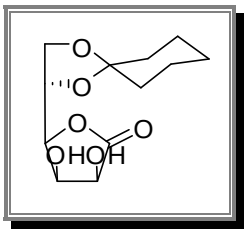
Procedure:

n-Butyl lithium (24.6 mL, 46.8 mmol, 1.3 equiv) was added slowly to a solution of methyltriphenylphosphonium bromide (15.43 g, 43.2 mmol, 1.2 equiv) in THF (90 mL) at -78°C under inert atmosphere. The solution was warmed up to room temperature, and aldehyde **87** (4.68 g, 36 mmol) in THF (10 mL) was added. After 20 h stirring at room temperature, the reaction mixture was diluted with EtOAc (150 mL). The organic layer was washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and slowly concentrated to about 10 mL under reduced pressure (T° bath = 25°C). The remaining solution was separated by vacuum distillation to afford compound **88** (3.78 g, 82%) as a colorless liquid (Caution, compound **88** is very volatile).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.80 (ddd, 1H, *J* = 7.0, 10.0 and 17.2 Hz, H^2), 5.32 (dd, 1H, *J* = 1.0 and 17.2 Hz, H^1), 5.18 (dd, 1H, *J* = 1.0 and 10.4 Hz, H^1), 4.47 (m, 1H, H^3), 4.08 (dd, 1H, *J* = 6.0 and 8.0 Hz, H^4), 3.57 (t, 1H, *J* = 8.0 Hz, H^4), 1.41 (s, 3H, CH_3), 1.37 (s, 3H, CH_3).

CAS: 127001-96-1.

(*S*)-5,6-*O*-Cyclohexylidene-L-gulono-1,4-lactone (89)



Procedure:

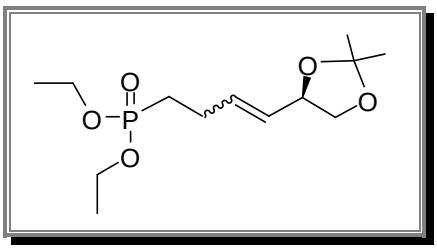
To a suspension of L-gulono-1,4-lactone (1 g, 5.6 mmol) and (+)-camphor-10-sulfonic acid (26 mg, 0.11 mmol, 0.02 equiv) in dry DMF (5 mL) was added cyclohexanone dimethyl ketal (1.87 mL, 12.3 mmol, 2.2 equiv) and the mixture was allowed to react for 3 days. Et_3N (0.3 mL) was then added and the resulting solution was concentrated in vacuum (60 °C). Dilution in toluene (4 mL) and cooling at 4°C afforded a solid that was filtered, dissolved in MeOH and recrystallized at -20°C, to give the title compound **89** as a white solid (1.35 g, 93%).

$[\alpha]_D^{27}$ = 24.0 (*c* = 0.11, CH_3OH).

^{1}H NMR: (400 MHz, DMSO-d^6) δ 5.87 (d, 1H, *J* = 7.4 Hz, OH), 5.43 (d, 1H, *J* = 4.2 Hz, OH), 4.41 (dd, 1H, *J* = 7.4 and 4.5 Hz, H^2), 4.28-4.24 (m, 2H, H^3 + H^4), 4.22-4.13 (m, 1H, H^5), 4.06 (dd, 1H, *J* = 8.7 and 6.2 Hz, H^6), 3.75 (dd, 1H, *J* = 8.7 and 6.2 Hz, H^6), 1.59-1.45 (m, 8H, CH_2), 1.40-1.29 (m, 2H, CH_2).

CAS: 102335-37-5.

(*R*)-Diethyl-*5,6-O-Iso*propylidene-hex-3-enylphosphonate (91)



Procedure:

To a CH_2Cl_2 (80 mL) solution of compound **88** (3.25 g, 25.3 mmol) and diethyl 3-butenylphosphonate (9.69 mL, 50.6 mmol, 2 equiv), [Ru]=catalyst **58** (1 g, 5 mol%) was added and the resulting solution was refluxed for 24 h. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 5:5). Compound **91** was obtained as a light brown oil (4.74 g, 64%, *E*/*Z ratio* = 9:1).

$[\alpha]_D^{27}$ = - 114.9 (*c* = 0.13, $CHCl_3$).

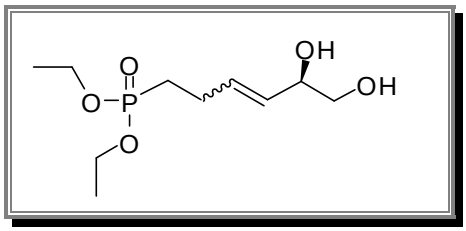
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.79 (dt, 1H, *J* = 6.4 and 15.2 Hz, H^4), 5.50-5.44 (m, 1H, H^3), 4.47-4.41 (m, 1H, H^2), 4.11-4.02 (m, 5H, H^1 + OCH_2), 3.53 (t, 1H, *J* = 8.0 Hz, H^1), 2.37-2.28 (m, 2H, H^5), 1.83-1.74 (m, 2H, H^6), 1.39 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.29 (t, 6H, *J*= 7.0 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 133.9 (d, CH, *J*= 17.5 Hz, C^4), 128.4 (CH, C^3), 109.3 (C), 77.0 (CH, C^2), 69.5 (CH_2, C^1), 61.6 (d, CH_2, *J*= 6.5 Hz, OCH_2), 26.8 (CH_3), 26.0 (CH_3), 25.3 (d, CH_2, *J*= 4.3 Hz, C^5), 25.2 (d, CH_2, *J*= 140.9 Hz, C^6), 16.5 (d, CH_3, *J*= 5.9 Hz, OCH_2-*C*H_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 30.98.

HRMS (ESI): *m/z* calcd for $C_{13}H_{25}O_5NaP$ (M^+ + Na) 315.1337, found 315.1339.

(*R*)-Diethyl-5,6-dihydroxy-hex-3-enylphosphonate (92)



Procedure:

Compound **91** (4.5 g, 15.4 mmol) was stirred overnight in an aqueous solution of trifluoroacetic acid (60% v/v) (20 mL) at room temperature. After evaporation of all the volatiles, the resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 9:1). Compound **92** (3.69 g, 95%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = - 49.1 (*c* = 0.65, $CHCl_3$).

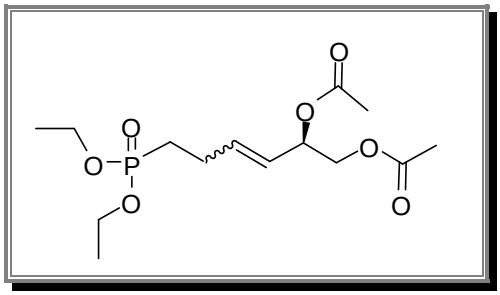
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.83-5.49 (m, 2H, H^4 + H^3), 4.28-4.19 (m, 1H, H^2), 4.17-4.03 (m, 4H, OCH_2), 3.69-3.62 (m, 1H, H^1), 3.55-3.50 (m, 1H, H^1), 2.80 (bs, 2H, OH), 2.43-2.33 (m, 2H, H^5), 1.85 (dt, 2H, *J*= 7.7 and 17.8 Hz, H^6), 1.32 (t, 6H, *J*= 7.2 Hz, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 131.3 (d, CH, *J*= 12.5 Hz, C^4), 130.6 (CH, C^3), 72.6 (CH, C^2), 66.3 (CH_2, C^1), 61.8 (d, CH_2, *J*= 6.5 Hz, OCH_2), 25.4 (d, CH_2, *J*= 5.8 Hz, C^5), 25.3 (d, CH_2, *J*= 141.9 Hz, C^6), 16.5 (d, CH_3, *J*= 5.4 Hz, OCH_2-*C*H_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 34.30.

HRMS (ESI): *m/z* calcd for $C_{10}H_{21}O_5NaP$ (M^+ + Na) 275.1024, found 275.1032.

(*R*)-Diethyl-5,6-diacetoxy-hex-3-enylphosphonate (93)



Procedure:

To a solution of **92** (0.5 g, 2.0 mmol) in pyridine (15 mL) under argon atmosphere, acetic anhydride (0.75 mL, 8.0 mmol, 4 equiv) was added at 0°C. After 16 h stirring at room temperature, the solvent was coevaporated with toluene. The oily residue was diluted with CH_2Cl_2 (10 mL) and then washed with water (2 x 5 mL). The organic layer was dried over $MgSO_4$ and filtered. After evaporation of all the volatiles, the resulting residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 5:5). Compound **93** (0.57 g, 85 %) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = - 13.3 (*c* = 0.22, $CHCl_3$).

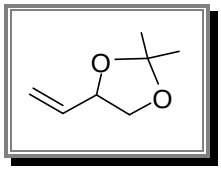
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.88-5.58 (m, 2H, H^4 + H^3), 5.50-5.45 (m, 1H, H^2), 4.26-4.20 (m, 1H, H^1), 4.14-4.04 (m, 5H, H^1 + OCH_2), 2.40-2.31 (m, 2H, H^5), 2.07 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.85-1.76 (m, 2H, H^6), 1.34-1.30 (m, 6H, OCH_2-C*H*$_3$).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 170.8 (CO), 170.2 (CO), 134.7 (d, CH, *J*= 16.9 Hz, C^4), 125.0 (CH, C^3), 71.8 (CH, C^2), 65.1 (CH_2, C^1), 61.7 (d, CH_2, *J*= 6.5 Hz, OCH_2), 25.4 (d, CH_2, *J*= 4.5 Hz, C^5), 25.1 (d, CH_2, *J*= 141.2 Hz, C^6), 21.2 (CH_3), 20.9 (CH_3), 16.5 (d, CH_3, *J*= 6.2 Hz, OCH_2-*C*H_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 33.90.

HRMS (ESI): *m/z* calcd for $C_{14}H_{25}O_7NaP$ (M^+ + Na) 359.1236, found 359.1224.

*3,4-O-Iso*propylidene-butene (95)



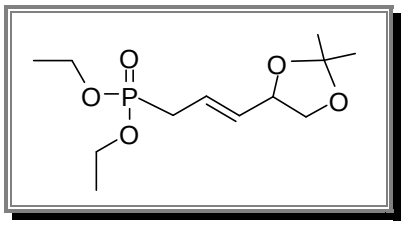
Procedure:

To a solution of 3,4-dihydroxy-1-butene (1 mL, 11.9 mmol) in acetone (10 mL) was added 2,2-dimethoxypropane (2.9 mL, 23.7 mmol, 2 equiv) and a small amount of pyridine *p*-toluenesulfonate. After overnight stirring at room temperature, a small amount of $NaHCO_3$ was added and the reaction mixture was slowly concentrated under reduced pressure. The resulting solution was diluted with CH_2Cl_2 (10 mL) and then washed with water (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and slowly concentrated under reduced pressure. Compound **95** (1.42 g, 93%) was obtained as a colorless liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.80 (ddd, 1H, *J* = 7.0, 10.0 and 17.2 Hz, H^2), 5.32 (dd, 1H, *J* = 1.0 and 17.2 Hz, H^1), 5.18 (dd, 1H, *J* = 1.0 and 10.4 Hz, H^1), 4.47 (m, 1H, H^3), 4.08 (dd, 1H, *J* = 6.0 and 8.0 Hz, H^4), 3.57 (t, 1H, *J* = 8.0 Hz, H^4), 1.41 (s, 3H, CH_3), 1.37 (s, 3H, CH_3).

CAS: 83968-02-9.

(*R*)-Diethyl-*4,5-O-Iso*propylidene-pent-2-enylphosphonate (96)



Procedure:

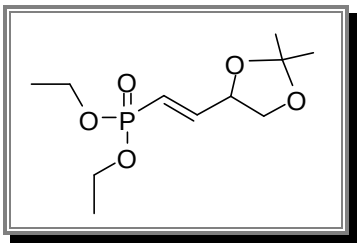
To a CH_2Cl_2 (10 mL) solution of compound **95** (0.1 g, 0.78 mmol) and diethyl allyl phosphonate (0.54 mL, 3.1 mmol, 4 equiv), [Ru]=catalyst **58** (33 mg, 5 mol%) was added and the resulting solution was refluxed for 24 h. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 5:5). Compound **96** was obtained as a light brown oil (0.16 g, 72%, only isomer *E*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.79-5.70 (m, 1H, H^4), 5.64-5.57 (m, 1H, H^3), 4.51-4.45 (m, 1H, H^2), 4.12-4.04 (m, 5H, H^1 + OCH_2), 3.56 (t, 1H, *J* = 7.8 Hz, H^1), 2.58 (dd, 2H, *J* = 7.2 and 21.8 Hz, H^5), 1.39 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.29 (t, 6H, *J*= 7.0 Hz, OCH_2-CH_3).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 133.1 (d, CH, *J*= 14.3 Hz, C^3), 123.6 (d, CH, *J*= 11.0 Hz, C^4), 109.4 (C), 76.6 (d, CH, *J*= 2.1 Hz, C^2), 69.3 (d, CH_2, *J*= 3.7 Hz, C^1), 62.0 (d, CH_2, *J*= 6.6 Hz, OCH_2), 30.4 (d, CH_2, *J*= 140.0 Hz, C^5), 26.8 (CH_3), 25.9 (CH_3), 16.5 (d, CH_3, *J*= 5.3 Hz, OCH_2-CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 26.49.

(*R*)-Diethyl-*3,4-O-Iso*propylidene-but-1-enylphosphonate (97)



Procedure:

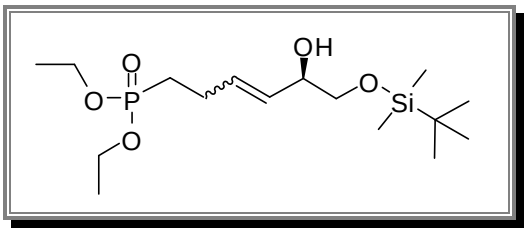
To a CH_2Cl_2 (10 mL) solution of compound **95** (0.12 g, 0.98 mmol) and diethyl vinyl phosphonate (0.61 mL, 3.9 mmol, 4 equiv), [Ru]=catalyst **58** (41.7 mg, 5 mol%) was added and the resulting solution was refluxed for 24 h. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 5:5). Compound **97** was obtained as a light brown oil (77 mg, 30%, only isomer *E*).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.72 (ddd, 1H, *J* = 5.0, 17.0 and 22.0 Hz, H^3), 6.00 (ddd, 1H, *J* = 1.4, 17.0 and 19.8 Hz, H^4), 4.66-4.60 (m, 1H, H^2), 4.17 (dd, 1H, *J* = 6.7 and 8.2 Hz, H^1), 4.11-4.04 (m, 4H, OCH_2), 3.66 (dd, 1H, *J* = 7.1 and 8.2 Hz, H^1), 1.42 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.31 (t, 6H, *J*= 7.0 Hz, OCH_2-CH_3).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 149.3 (d, CH, *J*= 5.6 Hz, C^3), 118.4 (d, CH, *J*= 188.0 Hz, C^4), 110.4 (C), 75.9 (d, CH, *J*= 22.6 Hz, C^2), 68.8 (d, CH_2, *J*= 2.0 Hz, C^1), 62.0 (dd, CH_2, *J*= 4.0 and 5.5 Hz, OCH_2), 26.5 (CH_3), 25.8 (CH_3), 16.5 (d, CH_3, *J*= 6.4 Hz, OCH_2-*C*H_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 17.59.

(*R*)-Diethyl-5-hydroxy-6-*tert*-butyldimethylsilanoxy-hex-3-enylphosphonate (98)



Procedure:

To a CH_2Cl_2 (2 mL) solution of compound **92** (0.1 g, 0.4 mmol) and imidazole (30.3 mg, 0.45 mmol, 1.1 equiv) at 0°C was added dropwise over 30 min a CH_2Cl_2 (2 mL) solution of *tert*-butyldimethylsilyl chloride (64.1 mg, 0.42 mmol, 1.05 equiv). The reaction mixture was stirred at room temperature for 4 h and then washed with water (2 x 2 mL). The organic layer was dried over $MgSO_4$ and filtered. After evaporation of all the volatiles, the resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 95:5). Compound **98** (81.7 mg, 55%) was obtained as a colorless oil.

$[\alpha]_D^{27}$ = - 6.2 (*c* = 0.33, $CHCl_3$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.83-5.44 (m, 2H, H^4 + H^3), 4.16-4.04 (m, 5H, H^1 + OCH_2), 3.65-3.60 (m, 1H, H^2), 3.50-3.40 (m, 1H, H^1), 2.40-2.30 (m, 2H, H^5), 1.86-1.77 (m, 2H, H^6), 1.32 (t, 6H, *J*= 7.5 Hz, OCH_2-C*H*$_3$), 0.90 (s, 9H, ^{t}Bu), 0.08 (s, 6H, CH_3).

^{13}C NMR: (100.6 MHz, $CDCl_3$) δ 131.9 (d, CH, *J*= 17.9 Hz, C^4), 121.9 (CH, C^3), 72.6 (CH, C^2), 67.3 (CH_2, C^1), 61.7 (d, CH_2, *J*= 6.5 Hz, OCH_2), 26.0 (CH_3, ^{t}Bu), 25.4 (d, CH_2, *J*= 4.8 Hz, C^5), 25.3 (d, CH_2, *J*= 140.8 Hz, C^6), 18.4 (C), 16.5 (d, CH_3, *J*= 5.6 Hz, OCH_2-*C*H_3), -5.23 (2CH_3).

^{31}P NMR: (162 MHz, $CDCl_3$) δ 34.34.

^{32}Si NMR: (79.5 MHz, $CDCl_3$) δ -113.17.

HRMS (ESI): *m/z* calcd for $C_{16}H_{35}O_5NaSiP$ (M^+ + Na) 389.1889, found 389.1892.

Chapter III:
NHC-containing complexes in palladium-catalyzed reactions, new insights for nucleoside synthetic strategy

1. INTRODUCTION

The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis. Among them, late transition metal-catalyzed reactions are certainly the most important tool to access variety of appealing pharmacomodulations.[235] In the first and second chapter of this manuscript, we have already presented the synthesis of two very different series of nucleoside analogues using ruthenium-mediated metathesis or cycloaddition reaction in the presence of copper complexes. However, it would an inaccuracy not to mention the probably most resourceful methodology in the nucleoside chemistry: palladium-catalyzed reactions.

1.1 Palladium-assisted Approaches in Nucleoside Chemistry

In a continuously increasing field, Pd-catalyzed addition, substitution and cross-coupling reactions have proven to be an efficient route to nucleosides and have thus focus much attention.[236,237] Sonogashira,[238] Stille,[239] Suzuki-Miyaura,[240] Neghishi,[241] Heck[242] and

[235] (a) Sato, T.; Ito, R.; Hayakawa, Y.; Noyori, R. *Tetrahedron Lett.* **1978**, *21*, 1829-1832. (b) Bergstrom, D.E. *Nucleos. Nucleot.* **1982**, *1*, 1-34. (c) Daves, Jr. G.D. *Carbohydrates* **1992**, 49-65. (d) Martinez, L.E.; Nugent, W.A.; Jacobsen, E.N. *J. Org. Chem.* **1996**, *61*, 7963-7966. (e) Velcicky, J.; Lanver, A.; Lex, J.; Prokop, A.; Wieder, T.; Schmalz, H-.G. *Chem-Eur. J.* **2004**, *10*, 5087-5110. (f) Stambasky, J.; Kocovsky, P.; Hocek, M. *Collection Symposium Series* **2005**, *7*, 277-278. (g) Novak, P.; Pohl, R.; Kotora, M.; Hocek, M. *Org. Lett.* **2006**, *8*, 2051-2054. (h) Izawa, K. *Shokubai* **2007**, *49*, 189-194. (i) Kocovsky, P.; Malkov, A.V. *Pure Appl. Chem.* **2008**, *80*, 953-966.

[236] Agrofoglio, L.A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003,** *103*, 1875-1916.

[237] (a) Sinou, D.; Moineau, C. *Recent Research Developments in Organic Chemistry* **1999**, *3*, 1-7. (b) Lakshman, M.K. *J. Organomet. Chem.* **2002**, *653*, 234-251. (c) Trost, B.M. *J. Org. Chem.* **2004**, *69*, 5813-5837. (d) Hocek, M. *Nucleic Acids Symposium Series* **2005**, 29-30.

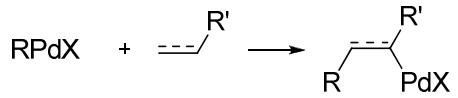
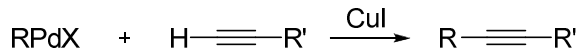
[238] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627-630. (c) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917-923. (d) Sonogashira, K. in *"Comprehensive Organic Synthesis"*, Vol. 3; Trost, B.M., Fleming, I., Eds.; Pergamon Press: New York, United States, **1991**, 521-549.

[239] (a) Stille, J.K. *Pure Appl. Chem.* **1985**, *57*, 1771-1780; (b) *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524; (c) *Angew. Chem.* **1986**, *98*, 504-519; (d) Mitchell, T.N. *Synthesis* **1992**, 803-815.

[240] (a) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866-867. (b) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519 (c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178-184; (d) *Pure Appl. Chem.* **1984**, *66*, 213-222; (e) *Pure*

Tsuji-Trost[243] cross-coupling reactions are the principal types of organopalladated assisted transformations encountered for C-C bond formations (Table 17).

Table 17. Principal Palladium-catalyzed cross-coupling reactions.

Reaction	Transformation	Reaction's name
	Insertion	Heck
RPdX + R'M ⟶ R-R'	Transmetallation	M = Sn Stille M = B Suzuki M = Zn Neghishi
	Transmetallation Cu -> Pd	Sonogashira
	π-allyl complexes	Tsuji-Trost

Main modifications consist in functionalization of heterocyclic bases or sugar moieties by introduction of substituents on different positions (Figure 34).[236] Examples of base-sugar coupling reactions have also been performed *via* Tsuji-Trost[244] or Heck reactions.[245]

Although applications of Pd-assisted reactions for modulation on pyrimidine and purine nucleosides have been widely developed and optimized, they have largely been confined to C-C bond-forming reaction. The emergence of *hitherto* less explored techniques mediated by the organopalladated-chemistry has strongly focused the attention of researchers and pharmaceutical industries. One of the most relevant illustrations is the recent development of C-N cross coupling reactions applied to the synthesis of *N*-functionalized nucleosides.

Appl. Chem. **1985**, *57*, 1749-1758; (f) *Pure Appl. Chem.* **1991**, *63*, 419-422; (g) *J. Organomet. Chem.* **1999**, *576*, 147-168. (h) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933. (i) Chemler, S.R.; Trauner, D.; Danishefsky, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544-4568.

[241] (a) Stevenson, T.M.; Bhanu Prasad, A.S.; Rao Citineni J.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8375-8378. (b) Negishi, E.-I. *J. Organomet. Chem.* **2002**, *653*, 34-40.

[242] (a) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581-584. (c) Julia, M.; Duteil, M. *Bull. Soc. Chim. Fr.* **1973**, 2791-2794. (d) Heck, R.F. *Palladium reagents in organic synthesis*; Academic Press Inc.: Orlando, United States, **1985**.

[243] (a) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395-422. (b) Trost, B.M. *Acc. Chem. Res.* **1996**, *29*, 355-364.

[244] Trost, B.M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621-622.

[245] Zhang, H.-C.; Daves, G.D. *J. Org. Chem.* **1993**, *58*, 2557-2560.

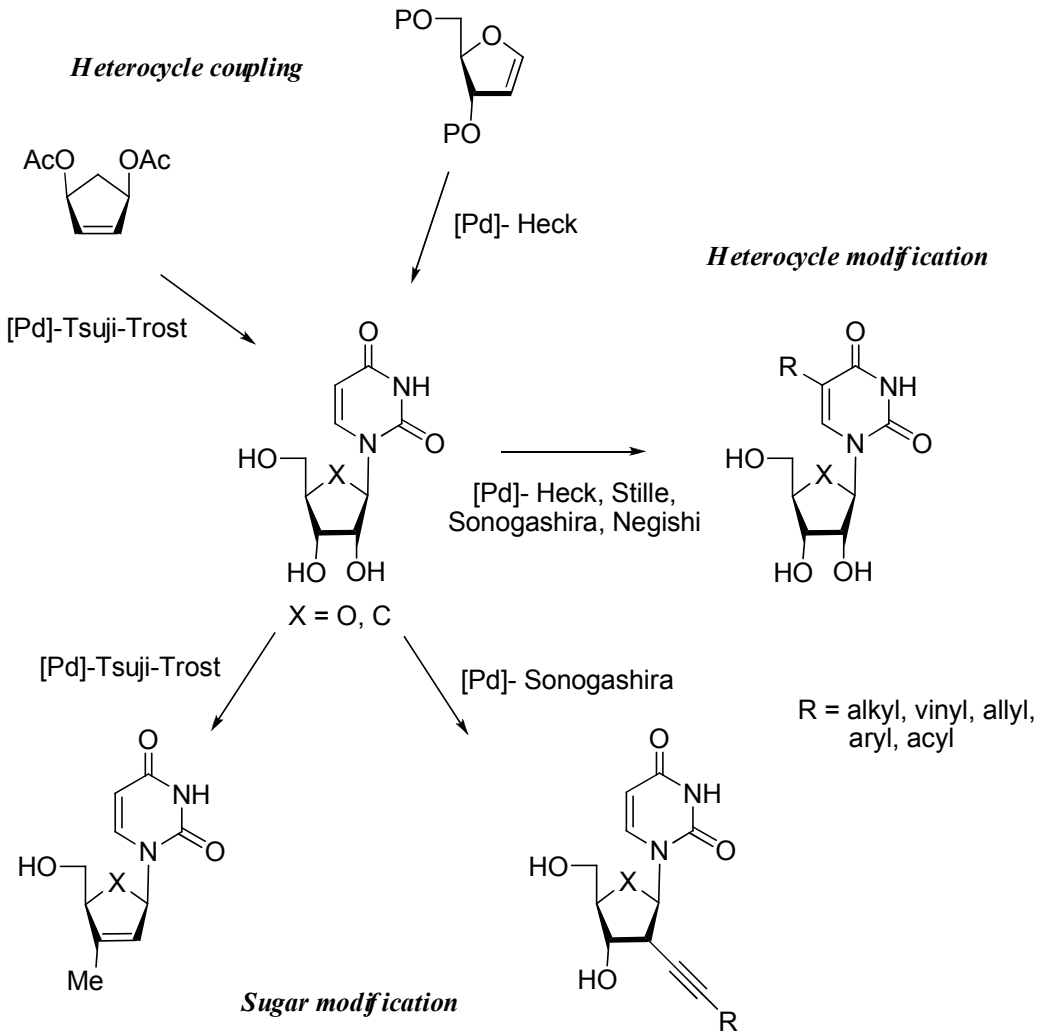


Figure 34. Main palladium-assisted modifications on nucleosides.

a) C-N cross coupling reactions on nucleosides:

Carbon-nitrogen, carbon-oxygen and carbon-sulfur bonds represent common features in natural products, pharmaceuticals, agrochemicals and industrial polymers.[246] Hence, formation of carbon–heteroatom bonds by transition–metal-catalyzed cross-coupling methodologies has been extensively studied during the past few years.[247] The Pd-catalyzed cross-coupling of aryl halides with amines derivatives have recently emerged as a versatile technique to generate C-N bonds.[248,249] Following this strategy, several nucleosides have been

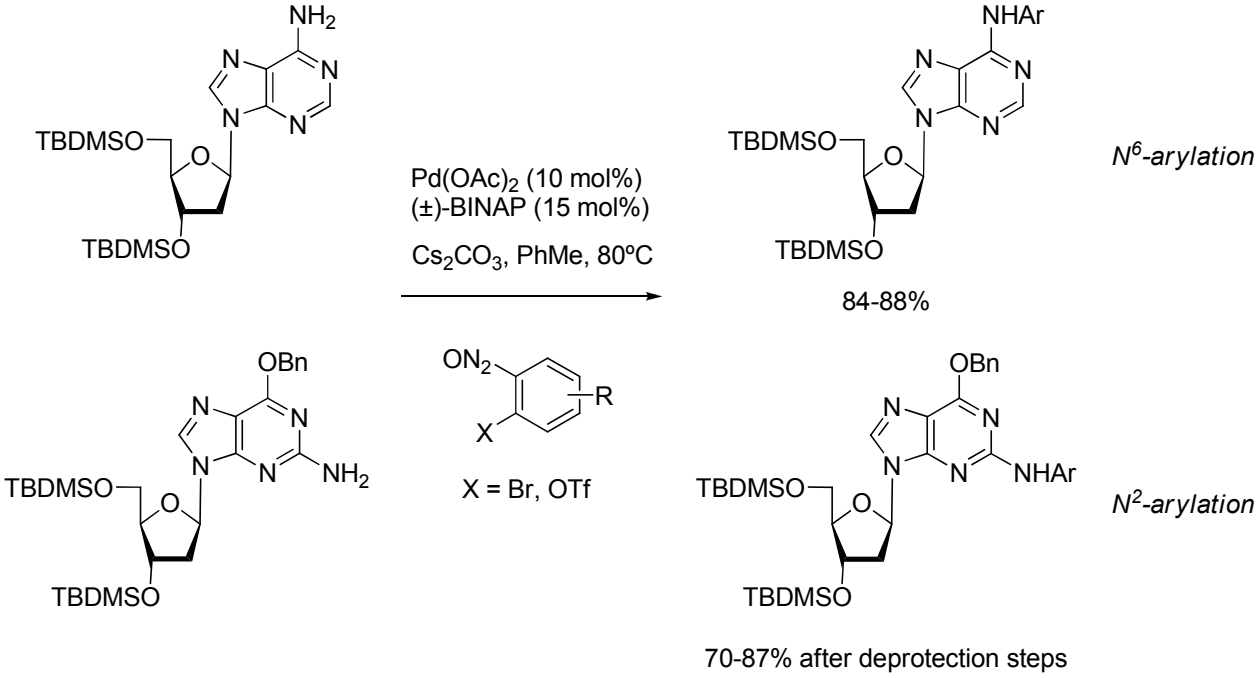
[246] (a) Negwer, M. in *"Organic-Chemical Drugs and Their Synonyms: (An International Survey)"*, 7th ed.; Akademie Verlag: Berlin, Germany, **1994**. (b) CRC *Handbook of Pesticides*; Milne, G.W.A., Ed.; CRC Press: Boca Raton, United States, **1994**. (c) Singer, R.A.; Sadighi, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 213-214. (d) Theil, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 2345-2347. (e) Cristau, P.; Vors, J-.P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859-7870.

[247] de Meijere, A.; Diederich, F., Eds. *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, **2004**.

[248] (a) Hartwig, J. F. *Angew Chem. Int. Ed.* **1998**, *37*, 2046-2067. (b) Yang, B.H.; Buchwald, S.L. *J. Organomet. Chem.* **1999**, *576*, 125-146.

[249] (a) Littke, A.F.; Fu, G.C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176-4211. (b) Muci, A.R.; Buchwald, S.L. *Top. Curr. Chem.* **2002**, *219*, 131-209.

efficiently *N*-functionalized on diverse positions of purine bases.[236] Much of the development in this area has stemmed from excellent studies on purine 2'-deoxynucleosides by the research groups of Lakshman.[250] Since purine nucleobases contain exocyclic amino groups, the adenine and guanine derivatives themselves can serve as amine components in Pd-catalyzed C-N cross-coupling at the *N*-6 or *N*-2 position respectively (Scheme 56).[251]



Scheme 56. Pd-catalyzed synthesis of N^6-nitroaryl- and N^2-nitroaryl-2'-deoxynucleosides from amine precursors.[251]

Alternatively, easily obtained *C*-6 haloadenine,[252,253] *C*-8[254] or *C*-2[253,255] haloguanine adducts can be subjected to Pd-catalyzed amination giving rise to N^8-, N^6- and N^2-aryl 2'deoxynucleosides (Scheme 57). Despite simpler access to amine purine donors, the second strategy involving halogenated nucleoside and aryl amines is generally more effective. Apart from this, 2'-deoxynucleoside-2'-deoxynucleoside dimers were also formed by similar cross-coupling strategy between the halo and the amino adducts.[256] Thus, Pd-catalyzed C-N bond formation raises the possibility of a novel approach to prepare various *N*-functionalized purine

[250] (a) Lakshman, M.K. *J. Organomet. Chem.* **2002**, *653*, 234-251. (b) Lakshman, M.K. *Curr. Org. Synth.* **2005**, *2*, 83-112.

[251] De Riccardis, F.; Bonala, R.R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, *121*, 10453-10460.

[252] Lakshman, M.K.; Keeler, J.C.; Hilmer, J.H.; Martin, J.Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090-6091.

[253] Lakshman, M.K.; Hilmer, J.H.; Martin, J.Q.; Keeler, J.C.; Dinh, Y.Q.V.; Ngassa, F.N.; Russon, L.M. *J. Am. Chem. Soc.* **2001**, *123*, 7779-7787.

[254] (a) Wang, Z.; Rizzo, C. *Org. Lett.* **2001**, *3*, 565-568. (b) Meier, C.; Gräsl, S. *Synlett* **2002**, 5, 802-804.

[255] (a) Bonala, R.R.; Shishkina, I.G.; Johnson, F. *Tetrahedron Lett.* **2000**, *41*, 7281-7284. (b) Harwood, E.A.; Hopkins, P.B.; Sigurdsson, S.T. *J. Org. Chem.* **2000**, *65*, 2959-2964.

[256] (a) Harwood, E.A.; Sigurdsson, S.T.; Edfeldt, N.B.F.; Reid, B.R.; Hopkins, P.B. *J. Am. Chem. Soc.* **1999**, *121*, 5081-5082. (b) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293-295.

ribo and 2'-deoxyribo nucleoside analogs with interesting biologic activities.[250] Indeed, many such modified nucleosides are important for a wide range of therapeutic applications, yielding facile access to: modulators of adenosine A1 and A2 receptors, cytokinines that stimulate plant cell growth and division, inhibitors of bacterial and mammalian DNA polymerases as well as cancer cell growth.[257] Several mutagens and carcinogens are metabolically activated to electrophiles that subsequently alkylate adenine and guanine bases in DNA. The resulting alteration of the intracellular DNA can ultimately be reflected in mutations and even oncogenesis. Therefore, *N*-modified nucleosides bearing these carcinogens and mutagens at the *C*-6, *C*-2, and *C*-8 positions, like poly- and monocyclic aromatic amines,[258] are important for structural, biochemical, and biological studies.[254,259]

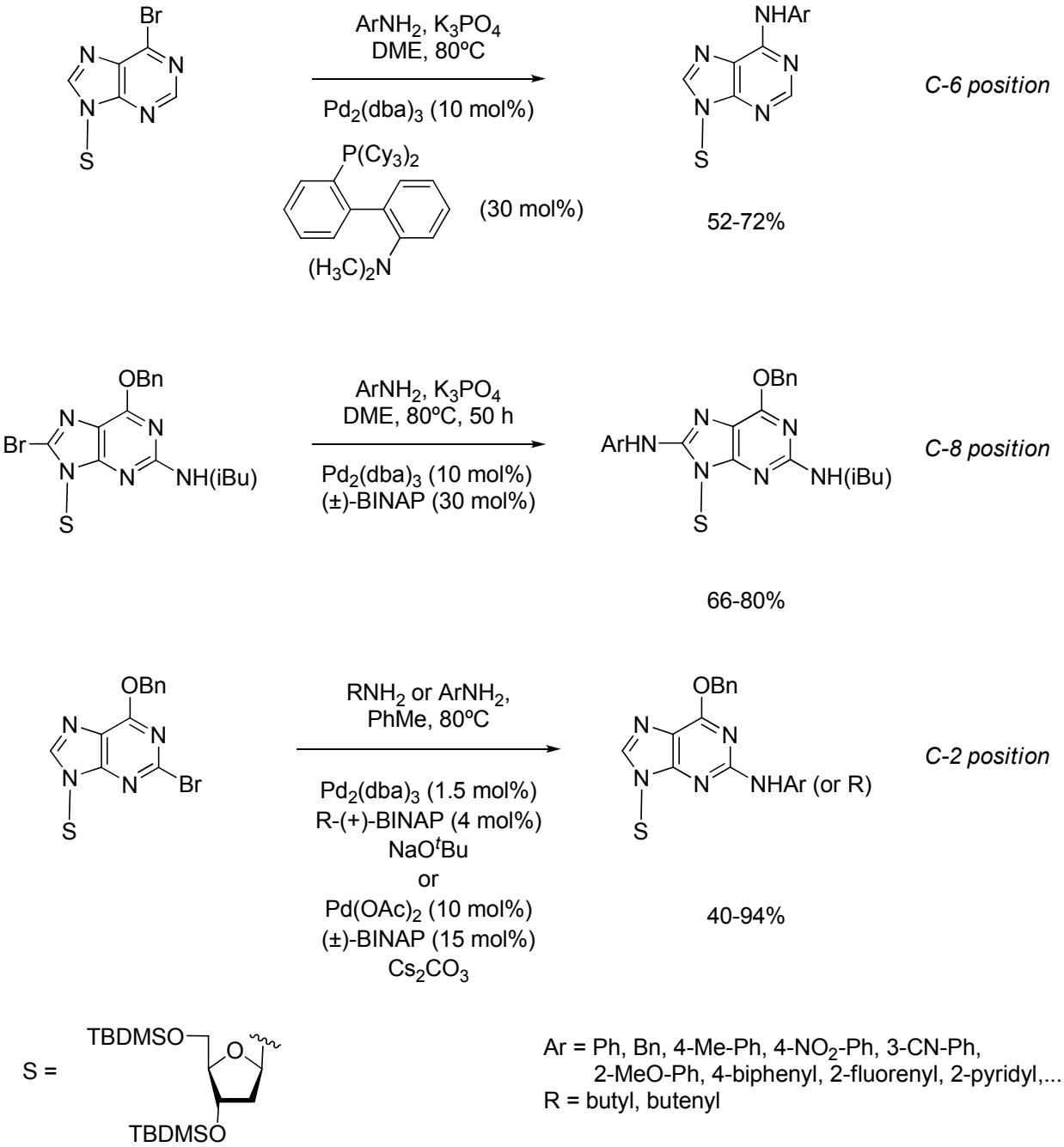
Nonetheless, weaknesses in the synthetic strategy were numerous. Only activated aryl bromides or triflates produced moderate to good yields. Other positions of the purine base had to be protected to remove the unfavorable acidic protons that may have obstructed arylamination. This protection/deprotection strategy leads to easy separation, but inevitably adds two steps to synthetic procedures, reduces the overall yields, and sometimes requires expensive chemicals for protection. Despite some recent improvements in the versatility of the aryl substituent,[259,260] many drawbacks are still encountered. Excepted one example of chloro nucleoside,[260a] substrates are limited still to aryl bromides or triflates. Amination conditions require high temperatures, long reaction times and large quantities of the Pd salt and the *in situ*-introduced ligand.

[257] (a) Miller, C.O. *Ann. Rev. Plant Physiol.* **1961**, *12*, 395-408. (b) Schnebli, H.P.; Hill, D.L.; Bennett, Jr. L.L. *J. Biol. Chem.* **1967**, *242*, 1997-2004. (c) Montgomery, J.A.; Hewson, K. *J. Med. Chem.* **1968**, *11*, 48-52. (d) Henderson, T.R.; Frihart, C.R.; Leonard, N.J.; Schmitz, R.Y.; Skoog, F. *Phytochemistry* **1975**, *14*, 1687-1690. (e) Daly, J.W. *J. Med. Chem.* **1982**, *25*, 197-207. (f) Wright, G.E.; Dudycz, L.W. *J. Med. Chem.* **1984**, *27*, 175-181. (g) Jacobson, K.A.; van Galen, P.J.M.; Williams, M. *J. Med. Chem.* **1992**, *35*, 407-422. (h) Bråthe, A.; Gundersen, L.-L.; Rise, F.; Eriksen, A.B.; Vollsnes, A.V.; Wang, L.N. *Tetrahedron* **1999**, *55*, 211-228.

[258] (a) Neumann, H.G. *J. Cancer Res. Clin. Oncol.* **1986**, *112*, 100-106. (b) Beland, F.A.; Kadlubar, F.F. *Environ. Health Perspect*. **1985**, *62*, 19-30.

[259] (a) Kool, E.T.; Morales, J.C.; Guckian, K.M. *Angew. Chem., Int. Ed.* **2000**, *39*, 990-1009. (b) Wood, R.D.; Mitchell, M.; Sgouros, J.; Lindahl, T. *Science* **2001**, *291*, 1284-1289. (c) Schoffers, E.; Olsen, P.D.; Means, J.C. *Org. Lett.* **2001**, *3*, 4221- 4223. (d) Gillet, L.C. J.; Shärer, O.D. *Org. Lett.* **2002**, *4*, 4205-4208. (e) Johnson, F.; Bonala, R.; Tawde, D.; Torres, M.C.; Iden, C.R. *Chem. Res. Toxicol.* **2002**, *15*, 1489-1494. (f) Lakshman, M.K.; Gunda, P. *Org. Lett.* **2003**, *5*, 39-42. (g) Lakshman, M.K.; Ngassa, F.N.; Bae, S.; Buchanan, D.G.; Hahn, H.-G.; Mah, H. *J. Org. Chem.* **2003**, *68*, 6020-6030. (h) Chakraborti, D.; Colis, L.; Schneider, R.; Basu, A.K. *Org. Lett.* **2003**, *5*, 2861-2864. (e) Stover, J.S.; Rizzo, C.J. *Org. Lett.* **2004**, *6*, 4985-4988. (f) Elmquist, C.E.; Stover, J.S.; Wang, Z.; Rizzo, C.J. *J. Am. Chem. Soc.* **2004**, *126*, 11189-11201.

[260] (a) Lakshman, M.K.; Gunda, P. *Org. Lett.* **2003**, *5*, 39-42. (b) Ngassa, F.N.; DeKorver, K.A.; Melistas, T.S.; Yeh, E.A.-H.; Lakshman, M.K. *Org. Lett.* **2006**, *8*, 4613-4616. (c) Takamura-Enya, T.; Enomoto, S.; Wakabayashi, K. *J. Org. Chem.* **2006**, *71*, 5599-5606.



Scheme 57. C-N cross-coupling at the *C*-6, *C*-8 and *C*-2 positions of halopurine precursors.

Beyond the various applications for complex molecules assembly by C-X bonds formation, Pd-catalyzed reactions are a method of choice for the functionalization of therapeutic molecules on different positions. The large number of possible combinations renders even more difficult the manipulation of multifunctional compounds. Even before rapidity and efficiency, selectivity has thus become an inescapable parameter required in the list of competences of a catalyst. Hydrogenation is one example of reaction that is particularly dependent of this constraint and that would thus beneficiate from the development of new catalysts.

b) Palladium-catalyzed hydrogenation of nucleosides:

The reduction of carbon-carbon multiple bonds by transition metal-catalyzed hydrogenation is one of the most important reaction in organic chemistry.[261] Numerous important applications are found in the petrochemical, pharmaceutical and food industries. Basically, this exothermic process consists in the addition of hydrogen to an unsaturated C=C double (or C≡C triple) bonds using hydrogen gas and a catalyst to produce thermodynamically more stable and saturated (or reduced) organic compounds. Palladium and platinum are the most commonly used metal catalysts for reduction of nonpolarized C-C double bonds, but hydrogenation can also be performed with nickel, rhodium, or ruthenium. The choice of catalyst depends on the compound to be reduced. The nucleoside applications are well representative of this principle. Rhodium on activated alumina has been employed for the reduction of furan ring to tetrahydrofuran derivatives,[262] and ruthenium catalysts for the monoreduction of cyclic imides to lactams[263] or in tandem reactions with RCM for the hydrogenation of alkene.[264] Nonetheless, the most represented reductive method is undoubtedly the heterogeneous palladium-catalyzed hydrogenation because of its chemoselectivity for C=C double bonds and benzylic C–X bonds over C=O groups. Examples extend from the hydrogenation of oxa-, aza- or cyclopentene rings[265] to the total reduction of triple bond.[266]

Hydrogenolysis[267] of benzyl (Bn) or carboxybenzyl (Cbz) ethers and amines catalysed by palladium on charcoal (Pd/C) or Pearlman's catalyst ($Pd(OH)_2$)[268] is probably the most commonly used procedure for the cleavage of these protecting groups by gaseous H_2 (Scheme 58).[269] In principle, this process is orthogonal to conditions used for the removal of many other protecting groups.

[261](a) Ellis, C. *Hydrogenation of Organic Substances* 3rd ed.; Van Nostrand Company: New York, United States, **1930**. (b) de Vries, J.G.; Elsevier, C.J. *Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, Germany **2007**.

[262] Feiertag, P.; Albert, M.; Nettekoven, U.; Spindler, F. *Org. Lett.* **2006**, *8*, 4133-4135.

[263] Aoun, R. ; Renaud, J.-L.; Dixneuf, P.H.; Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2021-2023.

[264] Børsting, P.; Nielsen, K.E.; Nielsen, P. *Org. Biomol. Chem.* **2005**, *3*, 2183-2190.

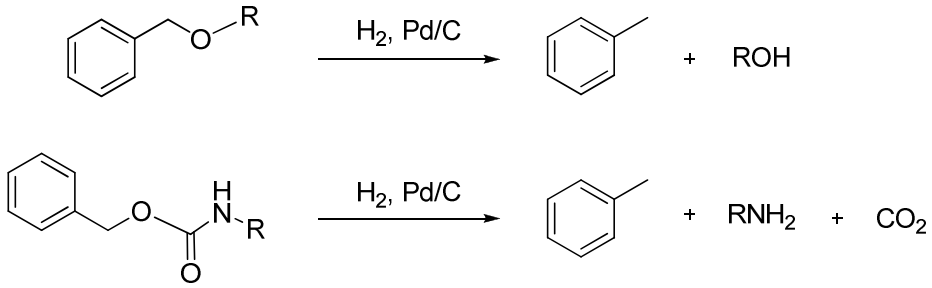
[265] (a) Park, K.H.; Rapoport, H. *J. Org. Chem.* **1994**, 59, 394-399. (b) Costenaro, E.R.; Fontoura, L.A.M; Oliveira, D.F.; Correia, C.R.D. *Tetrahedron Lett.* **2001**, *42*, 1599-1602. (c) Bambuch, V.; Pohl, R.; Hocek, M. *Eur. J. Org. Chem.* **2008**, 2783-2788.

[266] (a) Sági, G.; Őtvös, L.; Ikeda, S.; Andrei, G.; Snoeck, R.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 1307-1311. (b) Saito, Y.; Matsumoto, K.; Bag, S.S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron* **2008**, *64*, 3578-3588.

[267] Connor, R.; Adkins, H. *J. Am. Chem. Soc.* **1932**, *54*, 4678-4690.

[268] Pearlman, W.M. *Tetrahedron Lett.* **1967**, *17*, 1663-1664.

[269] Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis* 3rd Ed.; John Wiley & Sons: New York, United States, **1999**.



Scheme 58. Benzyl ether and carboxybenzyl amine deprotection *via* catalytic hydrogenation.

In the field of nucleoside chemistry, the benzyl moiety is primarily used as a monophosphate protecting group,[270] receiving limited attention as a hydroxyl or amine protecting group. This may be because of difficulties, longer reaction times and side reactions that arise during hydrogenolysis of benzyl-protected nucleosides.[271,272] For instance, cleavage of *N*-benzyl moieties, like *N*-benzyl sulfonamides or carboxamides, can be quite problematic as the protecting group is resistant to hydrogenolysis.[272,273] High pressure hydrogenolysis protocol did not solve the problem as it could not prevent the concomitant deprotection of other protecting groups or the reduction of alkenes present in the molecule.[272c] Finally, one of the major drawback encountered under hydrogenolysis conditions is the undesirable reduction of the pyrimidine C^5-C^6 double bond, considering that the separation of the nucleobase from its reduced dihydro side-product is nontrivial.[271,272c-d,274]

To circumvent that problem, transfer hydrogenolysis, using cyclohexadiene as the hydrogen source and 10 mol% palladium on charcoal as catalyst, has been reported by Rapoport[275] as a method to avoid reduction of the pyrimidine C^5-C^6 alkene. Transfer hydrogenolysis of uridine protected by Cbz, more labile than benzyl ether counterparts, gave under this conditions no appreciable reduction of the nucleobase (Scheme 59).[272d]

[270] Freel Meyers, C.L.; Borch, R.F. *Org. Lett.* **2001**, *3*, 3765-3768.

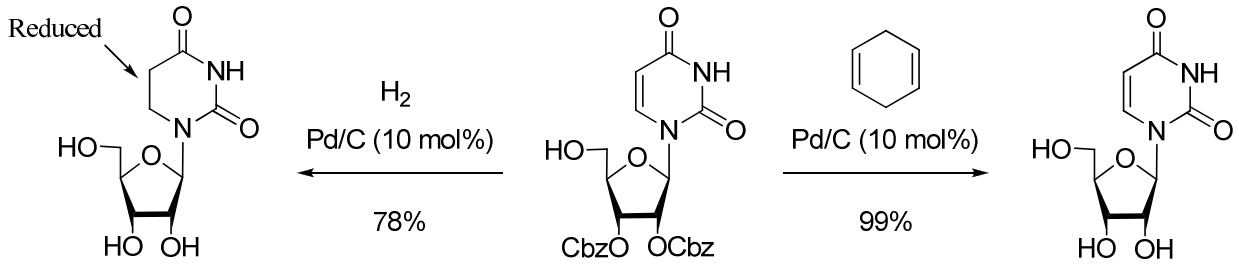
[271] Le Corre, L.; Gravier-Pelletier, C.; Le Merrer, Y. *Eur. J. Org. Chem.* **2007**, 5386-5394.

[272] (a) Poss, M.A.; Reid, J.A. *Tetrahedron Lett.* **1992**, *33*, 7291-7292. (b) Johnson, D.C., II; Widlanski, T.S. *Synthesis* **2002**, *6*, 809-815. (c) Johnson, D.C., II; Widlanski, T.S. *Tetrahedron Lett.* **2004**, *45*, 8483-8487. (d) Johnson, D.C., II; Widlanski, T.S. *Org. Lett.* **2004**, *6*, 4643-4646.

[273] (a) Luzzio, F.A.; Menes, M.E. *J. Org. Chem.* **1994**, *59*, 7167-7272. (b) Bar, N.C.; Patra, R.; Achari, B.; Mandal, S.B. *Tetrahedron* **1997**, *53*, 4727-4738.

[274] (a) Christensen, L.F.; Broom, A.D. *J. Org. Chem.* **1972**, *37*, 3398-3401. (b) Reitz, G.; Pfleiderer, W. *Chem. Ber.* **1975**, *108*, 2878-2894. (c) Pedersen, D.S.; Koch, T. *Synthesis* **2004**, 578-582.

[275] Watkins, B.E.; Kiely, J.S.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 5702-5708.



Scheme 59. Cbz-Deprotection of uridine *via* hydrogenolysis or transfer hydrogenolysis.

On the other hand, the complete catalytic hydrogenation of the C^5-C^6 double bond of pyrimidine nucleotides may reveal necessary, particularly in binding affinity and biologic study cases.[276,277] It has been usually carried out under mild conditions with pressurized hydrogen and palladium on carbon or rhodium on activated alumina as catalyst, affording dihydrouridyl derivatives quantitatively.[277]

5,6-Dihydro-5-fluorouracil (5-DHFU) is an interesting example for which a practical chemical synthesis is not available. 5-DHFU is a metabolite of the chemotherapy drug 5-fluorouracil (5-FU)[278] of importance for biological studies. 5-DHFU has been prepared in 50% yield by enzymatic reduction[279] of 5-FU and in very low yield (6.5%) by hydrogenation.[280] Classical hydrogenation of the C=C bond using 10 mol% Pd/C as catalyst in methanol under an atmosphere of hydrogen gives an inseparable 85:15 mixture of 5-DHFU and 5,6-dihydrouracil (DHU), the latter being formed by hydrogenolysis of the C-F bond (Scheme 60).[281] Hydrogenolysis of vinylic and aliphatic C-F bonds is a common problem under these conditions.[282] Various hydrogenation conditions, like the use of the homogeneous Wilkinson's catalyst[283] [$RhCl(PPh_3)_3$]or triethylamine to poison the catalyst, were ineffective on the course of the reaction.[281]

[276] Luvino, D.; Smietana, M.; Vasseur, J.-J. *Tetrahedron Lett.* **2006**, *47*, 9253-9256.

[277] (a) Cohn, W.E.; Doherty, D.G. *J. Am. Chem. Soc.* **1956**, *78*, 2863-2866. (b) Itaya, T.; Matsumoto, H. *Tetrahedron Lett.* **1978**, *42*, 4047-4050. (c) Blount, K.F.; Tor, Y. *Chem. Bio. Chem.* **2006**, *7*, 1612-1621.

[278] Bocci, G.; Danesi, R.; Allegrini, G.; Innocenti, F.; Di Paolo, A.; Falcone, A.; Conte, P.F.; Del Tacca, M. *Eur. J. Clin. Pharmacol.* **2002**, *58*, 593-595.

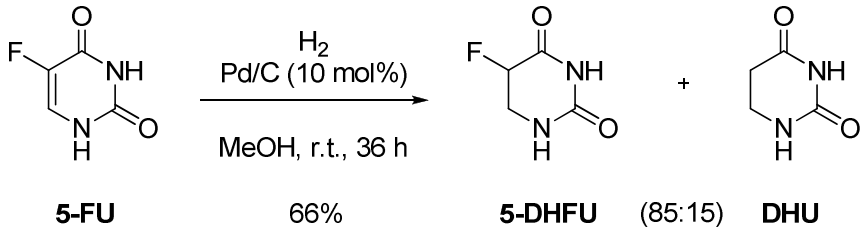
[279] Porter, D.J.T.; Harrington, J.A.; Almond, M.R.; Lowen, G.T.; Spector, T. *Biochem. Pharmacol.* **1994**, *48*, 775-779.

[280] Duschinsky, R.; Pleven, E.; Heidelberger, C. *J. Am. Chem. Soc.* **1957**, *79*, 4559-4560.

[281] LaFrate, A.L.; Katzenellenbogen, J.A. *J. Org. Chem.* **2007**, *72*, 8573-8576.

[282] (a) Allmendinger, T.; Dandois, C.; Walliser, B. *Tetrahedron Lett.* **1991**, *32*, 2735-2736. (b) Engman, M.; Diesen, J.S.; Paptchikhine, A.; Andersson, P.G. *J. Am. Chem. Soc.* **2007**, *129*, 4536-4537.

[283] Osborn, J.A.; Jardine, F.H.; Young, J.F.; Wilkinson, G. *J. Chem. Soc. (A)* **1966**, 1711-1732.



Scheme 60. Heterogeneous Pd-catalyzed hydrogenation of 5-fluorouracil.

Organopalladated assisted cross-coupling reactions and transformations have proven their high value in the nucleoside domain and the chemistry in general. Multiple innovations in term of organic synthesis would not have been possible without the available panel of palladium catalysts. Yet, some problems still remain and the development of more efficient and versatile tools is consequently a constant need. **In this purpose, we have focused our attention to a recent class of homogeneous and well-defined palladium catalysts: NHC NHC-Palladium complexes.**

1.2 NHC-Palladium Complexes

In the area of palladium-mediated cross-coupling reactions, palladium compounds are usually employed in either the Pd^0 or Pd^{II} oxidation state (Figure 35).[247,284] The ligandless Pd^0-active specie is obtained *in situ* after liberation of coordination site or/and reduction of the Pd^0 or Pd^{II} precatalyst. Pd^{II} complexes are usually more air- and moisture-stable and thus represent more practical precursors of the active species. Palladium complexes can also be *in situ* prepared by mixture of commercially available palladium salts and strongly binding phosphine[285] or carbene ligands.[286] Nevertheless, well-defined Pd-complexes have shown to exhibit better catalytic performances than their *in situ*-generated analogues.[287] More particularly, NHC-containing Pd-catalysts[286] have proven to be an excellent alternative to catalytic systems involving tertiary phosphines.[288] The σ-donating character of NHC ligands allows for the synthesis of well-defined, air- and moisture-stable NHC-palladium(II).

[284] Braga, A.A.C.; Ujaque, G.; Maseras, F. *Computational Modeling for Homogeneous and Enzymatic Catalysis* **2008**, 109-130.

[285] (a) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, *4*, 431-440. (b) Mauger, C.C.; Mignani, G.A. *Aldrichimica Acta* **2006**, *39*, 17-24.

[286] (a) Kantchev, E.A.B., O'Brien, C.J.; Organ, M.G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768-2813. (b) Díez-González, S.; Nolan, S.P. *Top. Organomet. Chem.* **2007**, *21*, 47-82.

[287] (a) Lebel, H.; Janes, M.K.; Charette, A.B.; Nolan, S.P. *J. Am. Chem. Soc.* **2004**, *126*, 5046-5047. (b) Frisch, A.C.; Zapf, A.; Briel, O.; Kayser, B.; Shaikh, N.; Beller, M. *J. Mol. Catal. A-Chem.* **2004**, *214*, 231-239.

[288] (a) Kuwano, R.; Utsunomiya, M.; Hartwig, J.F. *J. Org. Chem.* **2002**, *67*, 6479-6486. (b) Hooper, M.W.; Hartwig, J.F. *Organometallics* **2003**, *22*, 3394-3403. (c) Hooper, M. W.; Utsunomiya, M.; Hartwig, J.F. *J. Org. Chem.* **2003**, *68*, 2861-2873. (d) Huang, X.; Anderson, K.W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2003**, *125*, 6653-6655. (e) Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* **2003**, *125*, 13978-13980.

Moreover, NHC ligands provide stabilization of the low-coordinated catalytically active Pd^0 species involved in the catalytic cycle (Figure 35), thus minimizing oxidative degradation and side reactions observed with tertiary phosphines.[289]

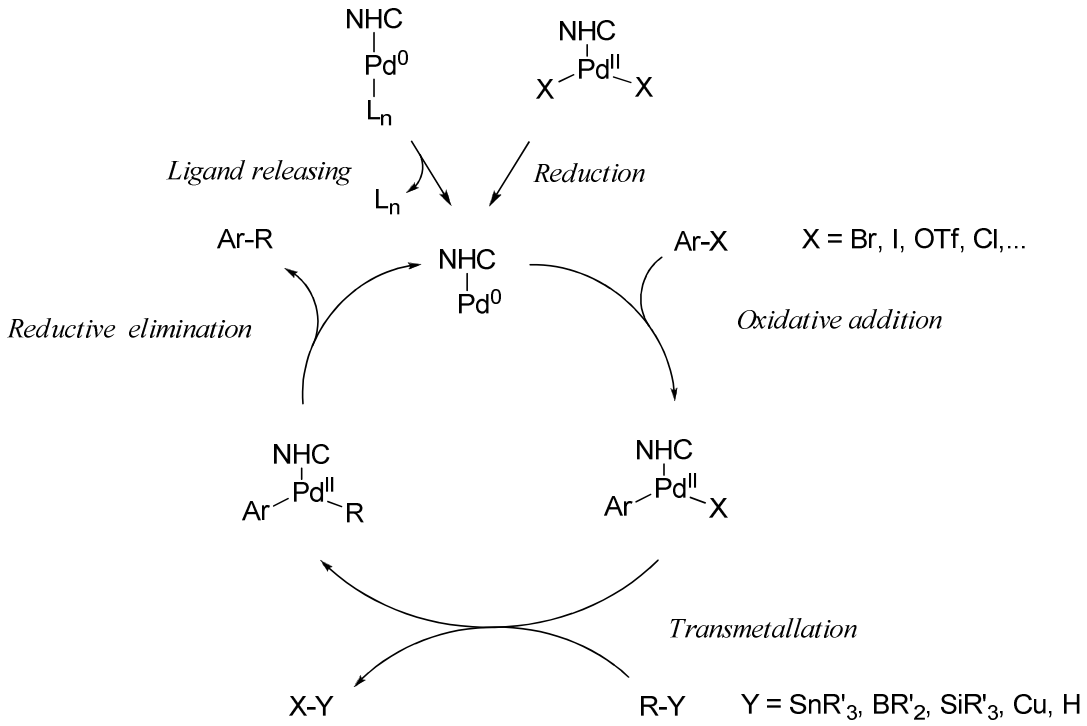


Figure 35. Catalytic cycle of NHC-Pd complex in cross coupling reactions.

Since the first phosphine-free monocarbenepalladium(0) complexes proposed by Beller,[290] a number of well-defined structures such as dimer,[291] allyl,[292] cinnamyl,[293] pyridine (PEPPSI),[294] or acac (acetylacetonate)[295] have been investigated and these complexes exhibit

[289] (a) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734-4735. (b) Reetz, M.T.; Lohmer, G.; Schwickardi, *R. Angew. Chem., Int. Ed.* **1998**, *37*, 481-485. (c) Littke, A.F.; Fu, G.C. *J. Org. Chem.* **1999**, *64*, 10-11. (d) Hartwig, J.F.; Kawatsura, M.; Hauck, S.I.; Shaughnessy, K.H.; Alcazar-Roman, L.M. *J. Org. Chem.* **1999**, *64*, 5575-5580. (e) Wolfe, J.P.; Singer, R.A.; Yang, B.H.; Buchwald, S.L. *J. Am. Chem.Soc.* **1999**, *121*, 9473-9474. (f) Beletskaya, I.P.; Cheprakov, A.V. *Chem. Rev.* **2000**, *100*, 3009-3066.

[290] (a) Jackstell, R.; Gómez Andreu, M.; Frisch, A.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Röttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem.* **2002**, *114*, 1028-1031; *Angew. Chem. Int. Ed.* **2002**, *41*, 986-989. (b) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031-3033. (c) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem.-A Eur. J.* **2002**, *8*, 3901-3906.

[291] (a) Jensen, D.R.; Sigman, M.S. *Org. Lett.* **2003**, *5*, 63-65. (b) Ma, Y.; Song. C.; Jiang. W.; Xue, G.; Cannon, J.F.; Wang, X.; Andrus, M.B. *Org. Lett.* **2003**, *5*, 4635-4638.

[292] (a) Viciu, M.S.; Germaneau, R.F.; Nolan, S.P. *Org. Lett.* **2002**, *4*, 4053-4056. (b) Viciu, M.S.; Germaneau, R.F.; Navarro-Fernandez, O.; Stevens, E.D.; Nolan, S.P. *Organometallics* **2002**, *21*, 5470-5472. (c) Viciu, M.S.; Navarro, O.; Germaneau, R.F.; Kelly, R.A., III; Sommer, W.; Marion, N.; Stevens, E.D.; Cavallo, L.; Nolan, S.P. *Organometallics* **2004**, *23*, 1629-1635.

[293] (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E.D.; Scott, N.M.; Nolan S.P. *J. Am. Chem. Soc.* **2006**, *128*, 4101-4111. (b) Navarro, O.; Marion, N.; Mei, J.; Nolan, S.P. *Chem. Eur. J.* **2006**, *12*, 5142-5148.

[294] Organ, M.G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E.A.B.; O'Brien, C.J.; Sayah, M.; Valente, C. *Chem. Eur. J.* **2008**, *14*, 2443-2452.

excellent catalytic activity in the Suzuki-Miyaura, Heck, Buchwald-Hartwig, or Stille cross-coupling reactions (Figure 36).

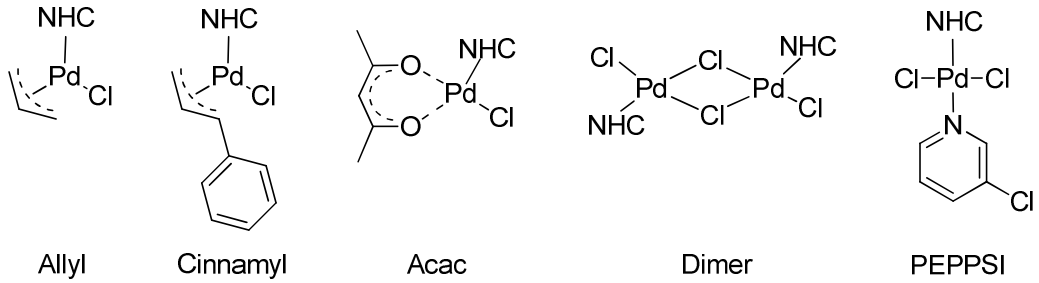


Figure 36. Structures of NHC-Pd^{II} precatalysts efficient in cross-coupling reactions.

In summary, the drawbacks encountered in Pd-mediated transformations of nucleosides, as well as in various organic compound syntheses, clearly leave space for improvements. Versatile and selective scope, economically advantageous quantity of palladium, mild conditions, high yields and purities are some of the parameters that could be enhanced. Well-defined NHC-containing Pd complexes represent good candidates to reach these objectives since they have already shown great potential in the field of cross-coupling reactions.

In this perspective, we decided to conduct the assessment of new NHC-Pd complexes as tools in the catalysis of C-C, C-N and C-O bond formations. To explore and optimize their catalytic capacities, the study was carried out on simple surrogates before further possible applications to nucleosides. Hence, we first present the synthesis of two new well-defined, air- and moisture-stable NHC-bearing palladium(II) precatalysts. Their catalytic activities were evaluated in different cross-coupling reactions. In a second part, the potential of new well-defined and moisture-stable homogeneous NHC-Pd^{0} complexes will be examined in the transfer hydrogenation of alkenes using acid formic as reducing agent.

[295] (a) Navarro, O.; Marion, N.; Scott, N.M.; Gonzalez, J.; Amoroso, D.; Bell, A.; Nolan, S.P *Tetrahedron* **2005**, *61*, 9716-9722. (b) Marion, N.; de Frémont, P.; Puijk, I.M.; Ecarnot, E.C.; Amoroso, D.; Bell, A.; Nolan, S.P. *Adv. Synth. Catal.* **2007**, *349*, 2380-2384.

2. NHC-CONTAINING *N-C*-PALLADACYCLE COMPLEXES IN CROSS-COUPLING REACTIONS

2.1 Generality on NHC-containing Palladacycles

In recent years, complexes juxtaposing the highly σ-donating properties and sterically demanding properties of NHCs with the stability imparted by palladacycle scaffolds[296] have also been investigated.[297] Under cross-coupling conditions, palladacycles are shown to decompose with the liberation of the catalytically active ligandless palladium(0).[297] In 2003, Nolan's group published the first *N*,*N*-dimethyl biphenylamine (DMBPA) complexes combining nitrogen-carbon-palladacycle framework with unsaturated NHCs (Figure 37, **101** and **102**).[298,299] These appeared to be efficient precatalysts in the Buchwald-Hartwig reaction, α-ketone arylation, Suzuki-Miyaura coupling, and dehalogenation reaction.[299,300,301]

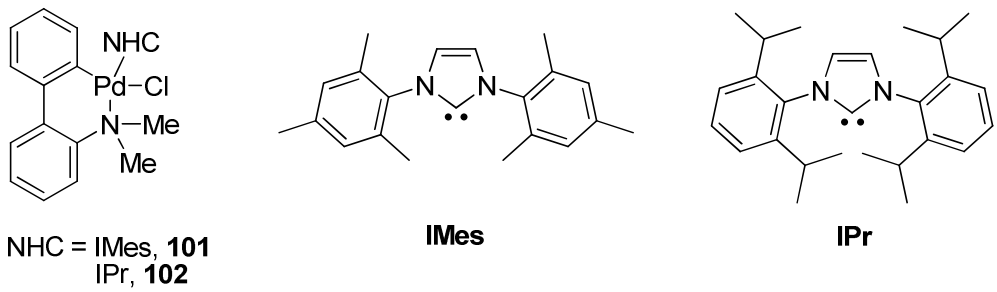


Figure 37. DMBPA *N-C*-palladacycle complexes bearing unsaturated NHC ligands.

Independently, Iyer reported applications in Mizoroki-Heck cross-coupling[302] of the previously described saturated NHC-containing dimethylbenzylamine (DMBA) palladacycle **103** (Figure 38).[303] These researchers obtained moderate to good yields at very low catalyst loading (0.0016 mol% Pd). However, reactions were carried out with aryl bromides or

[296] (a) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917-1927. (b) Bedford, R.B. *Chem. Commun.* **2003**, 1787-1796.

[297] (a) Beletskaya, I.P.; Cheprakov, A.V. *J. Organomet. Chem.* **2004**, *689*, 4055-4082. (b) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553-1582. (c) Dupont, J.; Consorti, C.S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527-2571.

[298] (a) Scott, N.M.; Nolan, S.P. in *"N-heterocyclic Carbenes in Synthesis"*, Nolan, S.P., Ed.; Wiley-VCH: Weinheim, Germany, **2006**, 55-70. (b) Nielsen, D.J.; Cavell, K.J. in *"N-heterocyclic Carbenes in Synthesis"*, Nolan, S.P., Ed.; Wiley-VCH: Weinheim, Germany, **2006**, 73-100.

[299] Viciu, M.S.; Kelly, R.A., III; Stevens, E.D.; Naud, F.; Studer, M. Nolan, S.P. *Org. Lett.* **2003**, *5*, 1479-1482.

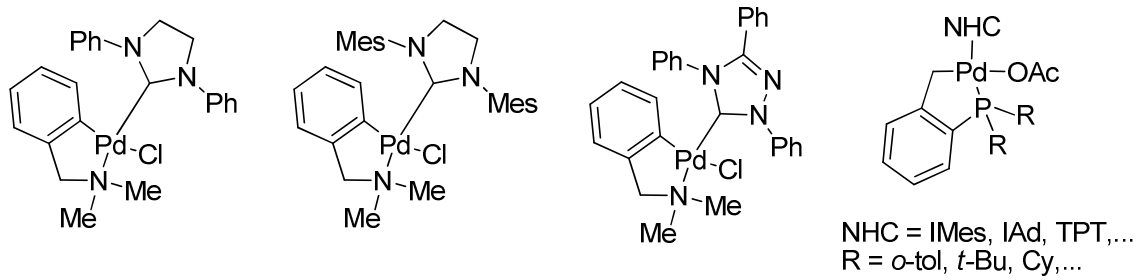
[300] Navarro, O.; Kelly, R.A., III; Nolan, S.P. *J. Am. Chem. Soc.* **2003**, *125*, 16194-16195.

[301] Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R.A., III; Nolan, S.P. *J. Org. Chem.* **2006**, *71*, 685-692.

[302] Iyer, S.; Jayanthi, A. *Synlett* **2003**, 1125-1128.

[303] Hiraki, K.; Onishi, M.; Sewaki, K.; Sugino, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2548-2550.

activated aryl chlorides at very high temperature (140ºC).[302,304] In 2005, Herrmann published an other *N*-palladacycle coupled with a triazolin-5-ylidene (TPT) **105** and the first series of NHC-substituted phospha-palladacycles **106**, showing also high thermal stability.[305] At elevated temperature, Heck reactions were performed with phospha-palladacycles **106** which proved efficient for the olefination of deactivated aryl bromides. The *N*-palladacycle **105** was the only one capable of coupling an aryl chloride quantitatively. In contrast to **106**, palladium black was formed in the presence of **105**.



103 **104** **105** **106**

Figure 38. DMBA and phospha-palladacycle complexes bearing NHC ligands.

The constant need for more efficient catalysts prompted us to develop new NHC-containing *N*-*C*-palladacycle complexes. Due to their convenient synthesis and the stability of the free NHC, unsaturated imidazol-2-ylidenes are widely used as ancillary ligands. In spite of similar steric and electronic properties,[306] unsaturated and saturated NHCs are often found to exhibit significantly different activity in catalysis. Olefin metathesis[307] is one such example but palladium-catalyzed cross-coupling reactions also demonstrate the differences between saturated and unsaturated NHC supporting ligands.[292,293] In order to examine whether such differences could be observe in the related palladacyclic scaffolds examined in 2003, we undertook to synthesize and fully characterize two new saturated NHC-containing Pd(cycle) complexes: [PdCl(Cycle)(SIMes)] (**107**) and [PdCl(Cycle)(SIPr)] (**108**) (Figure 39). Their catalytic activity was evaluated in different cross-coupling reactions.

[304] Iyer, S.; Kulkarni G.M.; Ramesh, C. *Tetrahedron* **2004**, *60*, 2163-2172.

[305] (a) Frey, G.D.; Schütz, J.; Herdtweck, E.; Herrmann, W.A. *Organometallics* **2005**, *24*, 4416-4426. (b) Frey, G.D.; Herrmann, W.A. *J. Organomet. Chem.* **2005**, *690*, 5876-5880.

[306] (a) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485-2495. (b) Kelly, R. A., III; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202-210.

[307] (a) Ritter, T.; Hejl, A.; Wenzel, A.G.; Funk, T.W.; Grubbs, R.H. *Organometallics* **2006**, *25*, 5740-5745. (b) Clavier, H.; Nolan, S.P. *Chem. Eur. J.* **2007**, *13*, 8029-8036.

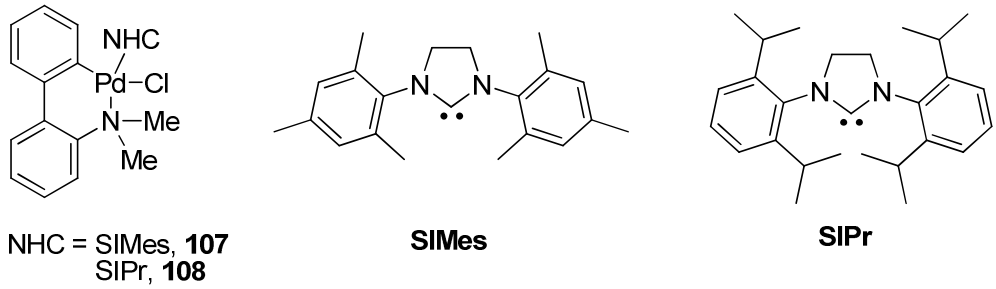
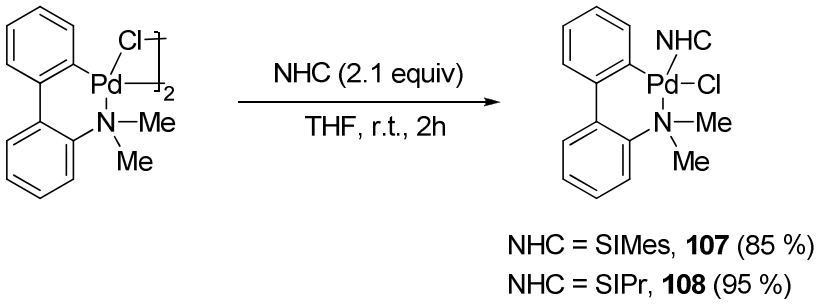


Figure 39. DMBPA *N-C*-palladacycle complexes bearing saturated NHC ligands.

2.2 Synthesis and Structure Determination of the Saturated NHC-containing N-C-Palladacycle Complexes

The reactions leading to [PdCl(Cycle)(SIMes)] (**107**) and [PdCl(Cycle)(SIPr)] (**108**) complexes involved the coordination of the NHC to the palladium center by μ-chloride displacement and simple cleavage of the dimer $[PdCl(Cycle)]_2$ by two equivalents of NHC ligands, such as SIMes and SIPr, giving rise to the expected 16-electron species [PdCl(Cycle)(NHC)] (Scheme 61) in good to excellent isolated yields. Of note, these complexes were found perfectly air- and moisture-stable and thus could be handle in air. The ^{1}H NMR spectra of **107** and **108** showed a characteristic resonance at 4 ppm for the imidazolidine protons. The ^{13}C NMR spectra displayed characteristic low-field resonances for the carbenic carbon at around 198-201 ppm, while the carbenic carbon resonance for the unsaturated complexes **101** and **102** was found at higher field (173-175 ppm).[299] Elemental analyses and high-resolution mass spectroscopy also confirmed the compositions of **107** and **108**.



Scheme 61. Synthesis of palladium complexes **107** and **108**.

To unambiguously establish the structure of complexes **107** and **108**, suitable crystals for single-crystal diffraction studies were obtained by slow diffusion of *n*-octane in DCM saturated solutions of **107** and **108**. Ball-and-stick representations with selected bond distances and angles are presented in Figure 40 (**107**) and Figure 41 (**108**). Complexes **107** and **108** show the expected distorted square-planar geometry around the metal center with

bond angles between 85° and 94°. Both **107** and **108** having the NHC ligand and amino group disposed *trans* to each other. In order to satisfy the square-planar geometry of the complexes, the biphenyl ligand is twisted. Of note, the *N*-aryl substituents of the saturated NHC are much more tilted to each other compared to the unsaturated NHC IMes and IPr (complexes **101** and **102**)[299] probably due to the skewed geometry of the NHC backbone. In general, the Pd–C(NHC) distances in **107** and **108** suggest single-bond character, and are in good accord with their almost exclusive σ-donor character. The Pd-C(NHC) bond lengths in **107** (1.9684(11) Å) and **108** (1.9788(9) Å) are significantly smaller to analogous distances in related palladacycle carbene complexes (2.038 Å in **101**, 1.992 Å in **102** and 1.991(1) Å in *N*,*N*'-dimethylbenzylamine **104** bearing SIMes).[299,308] Other bond distances were found comparable to those reported for similar complexes.

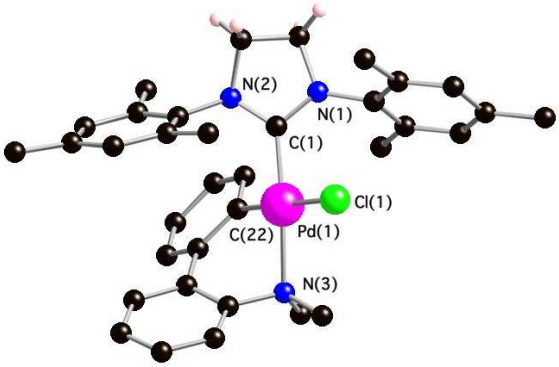


Figure 40. Ball-and-stick representation of [PdCl(Cycle)(SIMes)] (**107**). Most hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–C(1) 1.9684(11), Pd(1)–C(22) 2.0053(11), Pd(1)–N(3) 2.1957(10), Pd(1)–Cl(1) 2.3911(3); C(1)–Pd(1)–N(3) 175.27(4), C(1)–Pd(1)–C(22) 88.96(4), C(22)–Pd(1)–Cl(1) 178.82(3).

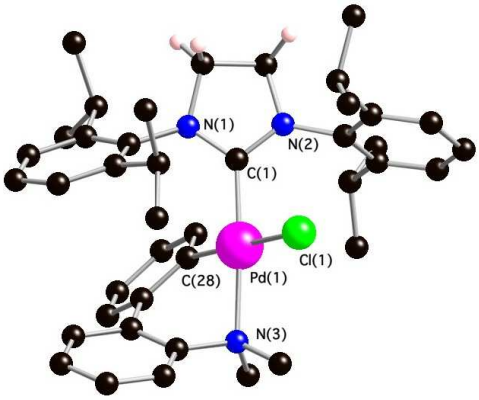


Figure 41. Ball-and-stick representation of [PdCl(Cycle)(SIPr)] (**108**). Most hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–C(1) 1.9788(9), Pd(1)–C(28) 2.0007(10), Pd(1)–N(3) 2.2033(9), Pd(1)–Cl(1) 2.3966(3); C(1)–Pd(1)–N(3) 175.58(4), C(1)–Pd(1)–C(28) 90.34(4), C(28)–Pd(1)–Cl(1) 177.22(3).

[308] Gökçe, A. G.; Günay, M. E.; Aygün, M.; Çetinkaya, B.; Büyükgüngör, O. *J. Coord. Chem.* **2007**, *60*, 805-813.

Table 18. Crystallographic data for compounds [PdCl(Cycle)(NHC)]

	[PdCl(Cycle)(SIMes)] **107**	[PdCl(Cycle)(SIPr)] **108**
chemical formula	$C_{36}H_{42}Cl_2N_3Pd$	$C_{42}H_{54}Cl_3N_3Pd$
fw	694.03	813.63
space group	Pbca	P2(1)/n
cryst syst	orthorhombic	monoclinic
a, Å	13.6779(6)	10.3012(5)
b, Å	14.7453(6)	20.3145(10)
c, Å	32.7016(12)	19.4043(8)
α, deg	90	90
β, deg	90	98.103(2)
γ, deg	90	90
Z	8	4
D_{calc}, g cm^{-3}	1.398	1.344
μ (Mo), mm^{-1}	0.754	0.693
$F(000)$	2872	1696
θ range, deg	3.03 to 39.28	2.88 to 39.81
no. of reflns collected	57986	48649
no. of unique reflns/R_{int}	19144/0.0306	22808/0.0262
no. of params/restraints	387/0	480/4
final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0326$, $wR_2 = 0.0768$	$R_1 = 0.0326$, $wR_2 = 0.0833$
R indices (all indices)	$R_1 = 0.0466$, $wR_2 = 0.0836$	$R_1 = 0.0439$, $wR_2 = 0.0896$
goodness-of-fit on F^2	1.025	1.022
peak/hole, e Å^{-3}	0.873 and -0.995	1.717 and -0.791

Under the continual search for enhanced carbon–heteroatom bonds forming systems, the catalytic activity of our new well-defined, air- and moisture-stable palladium(II) complexes was evaluated in the Buchwald-Hartwig *N*-arylation of amines and *O*-arylation of phenols.

2.3 Reactivity in the Buchwald-Hartwig Aryl Amination

Among cross-coupling reactions, the *N*-aryl amination has emerged as a practical and popular method for the formation of carbon-nitrogen bonds.[248a,309] The classical copper-mediated Ullmann and more recently developed palladium(0)-catalyzed Buchwald-Hartwig coupling of amines with aryl halides are commonly used methods. However, the Ullmann type reaction generally suffers from important limitations such as elevated reaction temperatures (≥ 140°C), high catalyst loading and poor substrate generality.[310] These

[309] Wolfe, J.P.; Wagaw, S.; Marcoux, J.F.; Buchwald, S.L. *Acc. Chem. Res.* **1998**, *31*, 805-818.

[310] (a) Antilla, J.C.; Baskin, J.M.; Barder, T.E.; Buchwald, S.L. *J. Org. Chem.* **2004**, *69*, 5578-5587. (b) Altman, R.A.; Anderson, K.W.; Buchwald, S.L. *J. Org. Chem.* **2008**, *73*, 5167-5169 and references therein.

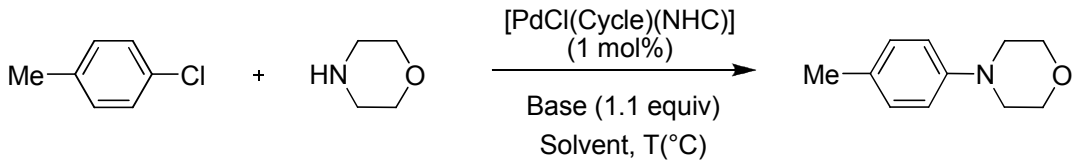
drawbacks encourage the development of Pd-based catalyst systems for the preparation of aryl amines. Therefore, having two new saturated NHC-containing *N-C*-palladacycle complexes on hand, we initiated a study focusing on their catalytic activity in the aryl amination using 4-chlorotoluene and morpholine as standard substrates (Table 19).

a) Optimisation of the Buchwald-Hartwig reaction conditions:

First, we explored the reactivity of saturated **107** and **108** versus the unsaturated [PdCl(Cycle)(IPr)] (**102**), using the conditions previously described.[299] In several precedent cases, Nolan's group[292c,293] and others[311] reported that SIPr-containing complexes perform better than IPr analogues in the Buchwald-Hartwig amination. Surprisingly in this case, **102** (IPr) and **108** (SIPr) did not show any differences in term of reactivity (entries 1 and 2). On the other hand, pre-catalyst **107** bearing the smaller NHC SIMes displayed a low activity at 50ºC (entry 3), confirming that as a general trend less bulky NHCs complexes bearing mesityl as imidazole substituents are less catalytically efficient.[298,299] The reactions conducted with **102** were previously performed at 70ºC, in 3 mL of dioxane and with NaO^{t}Bu as base.[299] We re-examined these conditions for **108**. As expected, reaction proceeded faster at 70ºC (entry 5). However under milder conditions, at 50ºC, amination still occurred in reasonable reaction times (entry 1). At room temperature, unfortunately reaction time was increased to three days to reach a 89% conversion (entry 4), even under re-optimized conditions the arylation proceeded poorly (entry 15). 1,2-Dimethoxyethane (DME) appeared to be a better solvent than dioxane for this *N*-arylation (entry 6). In *iso*propanol, only dehalogenation was observed (entry 9).[298,301] The reaction proceeded well with strong bases such as KO^{t}Bu or NaO^{t}Bu whereas others were completely ineffective (NaOH and NaOMe, respectively entries 11 and 12). The result presented in entry 10 underlines the importance of the counter anion of the base for the activation of the catalyst. Complete conversion was reached in only 5 min with KO^{t}Bu at 50ºC while 1 h was necessary with NaO^{t}Bu. Finally, better catalytic performances were obtained with increasing reaction mixture concentration (entry 13). Thus, reaction conditions were improved compared to those reported for palladacycle-catalyzed Buchwald-Hartwig cross-coupling[299] although they were found similar to the ones found for [PdCl(R-allyl)(NHC)][297] or Pd-PEPPSI catalysts.[294] Once again, reactivity of **108** versus **102** was compared with the new conditions (entries 13 and 14). **108** was slightly more efficient than **102**, but this difference is small.

[311] Stauffer, S.R.; Lee, S.; Stambuli, J.P.; Hauck, S.I.; Hartwig, J.F. *Org.Lett.* **2000**, *2*, 1423-1426.

Table 19. Optimization of the aryl amination of 4-chlorotoluene by morpholine catalyzed by [PdCl(Cycle)(NHC)].[a]



Entry	Catalyst	Base	Solvent	T(ºC)	Time	GC Conversion (%)[b]
1	**102**	NaO^{t}Bu	0.3M Dioxane	50	2 h	94
2	**108**	NaO^{t}Bu	0.3M Dioxane	50	2 h	93
3	**107**	NaO^{t}Bu	0.3M Dioxane	50	48 h	21
4	**108**	NaO^{t}Bu	0.3M Dioxane	r.t.	72 h	89
5	**108**	NaO^{t}Bu	0.3M Dioxane	70	40 min	91
6	**108**	NaO^{t}Bu	0.3M DME	50	1 h	92
7	**108**	NaO^{t}Bu	0.3M THF	50	2 h	93
8	**108**	NaO^{t}Bu	0.3M Toluene	50	2 h	40
9	**108**	NaO^{t}Bu	0.3M ^{i}PrOH	50	30 min	0[c]
10	**108**	KO^{t}Bu	0.3M DME	50	5 min	96
11	**108**	NaOH	0.3M DME	50	2 h	0[d]
12	**108**	NaOMe	0.3M DME	50	2 h	0[d]
13	**108**	KO^{t}Bu	1M DME	50	2 min	96
14	**102**	KO^{t}Bu	1M DME	50	5 min	95
15	**108**	KO^{t}Bu	1M DME	r.t.	1 h	25
16	**108**	KO^{t}Bu	1M DME	50, MW[e]	5 min	90
17	-	KO^{t}Bu	1M DME	50	24 h	0[d]

[a] Reaction conditions : 4-chlorotoluene (1 mmol), morpholine (1.1 mmol), [PdCl(Cycle)(NHC)] (1 mol%), base (1.1 mmol). [b] Conversions are average of at least two runs. [c] 95% of toluene as dehalogenation product. [d] Starting material recovered. [e] MW = Microwave.

b) Pre-catalyst [PdCl(Cycle)(SIPr)] in the *N*-arylation of various amines:

The arylation of the morpholine was extended to a range of unactivated and other aryl chlorides (Table 20). With typical aryl-amination substrates, all reactions proceeded with good GC conversions and reaction times ranged from 2 min to 3 h (entries 1-5). The system was tolerant of a variety of functional groups. The secondary cyclic amine was easily coupled with various aryl chlorides: activated (entry 3), neutral (entries 1 and 2), unactivated (entry 5) as well as heteroaromatic chlorides (entry 4). Sterically hindered aryl chlorides such as mono

or di *ortho*-substituted chlorobenzene exhibited reactions slightly slower than those for non-hindered analogues (entries 2 and 5). In most cases, final compounds were isolated in excellent yields. Pyridine and *o*-methoxy derivatives were found volatile (entries 4, 5).

Then, we explored more unusual (less commonly employed) aryl chlorides as partners for the Buchwald-Hartwig reaction (entries 6-9). 1-chloro-4-nitrobenzene and 3-chlorothiophene were completely unreactive under our optimized reaction conditions (entries 6 and 7). Morpholinylbenzene compounds bearing an electron-withdrawing group such as carboxylic or amide group are useful building blocks in the synthesis of new drugs and therefore of commercial value.[312] The morpholinobenzoic acids were previously prepared either *via* Pd-catalysed amination from ethyl bromobenzoate or by direct nucleophilic aromatic substitution of fluorobenzonitrile with subsequent hydrolysis of the resulting intermediates.[312a,313] 4-Morpholinobenzamide was obtained by substitution of the 4-fluorobenzamide[313] or by Pd-mediated coupling of the polymer bound aryl bromide.[314] Although two equivalents of base were required, complex **108** appeared to catalyze, under mild conditions, the amination of 4-chlorobenzamide and 3-chlorobenzoic acid with good yields and without side reaction (entries 8 and 9). No reaction occurred in both cases with only one equivalent of KO^{t}Bu, presumably a faster deprotonation of the carboxylic function occurs over the generation of the active species and productive cross-coupling reaction.

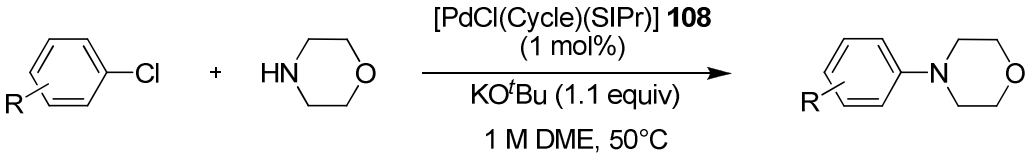
Extending the scope to *N*-methylaniline as secondary amine partner instead of the highly active morpholine also gave high yields using both activated and unactivated chlorides (Table 21). Nevertheless, compared to morpholine, the more hindered aniline reacted slightly slower (entries 1 and 5).

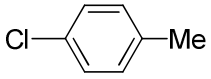
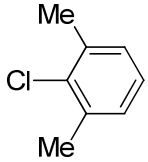
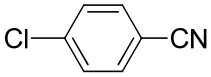
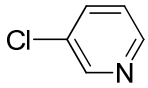
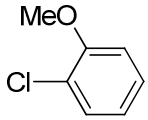
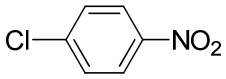
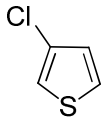
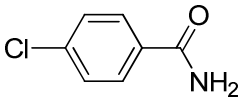
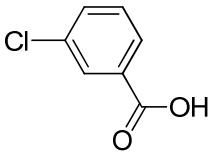
[312] (a) Brown, D.S.; Belfield, A.J.; Brown, G.R.; Campbell, D.; Foubister, A.; Masters, D.J.; Pike, K.G.; Snelson, W.L.; Wells, S.L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5383-5387. (b) Oberboersch, S.; Schunk, S.; Reich, M.; Hees, S.; Jostock, R.; Engels, M.; Kless, A.; Christoph, T.; Schiene, K.; Germann, T.; Bijsterveld, E. PCT Int. Appl. WO2008040492, **2008**.

[313] Tian, W. PCT Int. Appl. WO0187865, **2001**.

[314] Willoughby, C.A.; Chapman, K.T. *Tetrahedron Lett.* **1996**, *37*, 7181-7184.

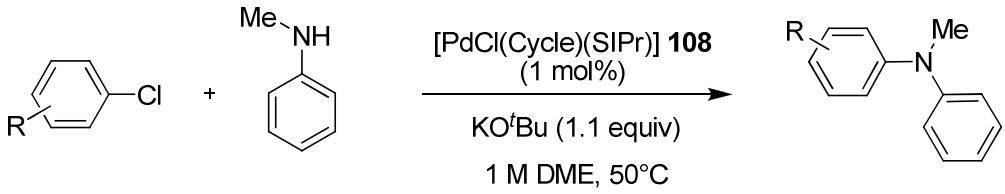
Table 20. Cross coupling of morpholine with various aryl chlorides mediated by **108**.[a]

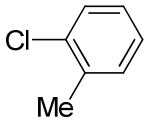
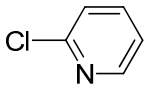
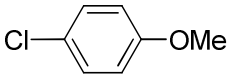
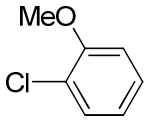


Entry	Ar-Cl	Time	GC Conversion (%)[b]	Yield (%)[c]
1		2 min	96	91
2		3 h	83	74
3		1 h	96	90
4		2 h	95	95
5		2 h	88	68
6		24 h	0	-
7		24 h	0	-
8		24 h	62[d]	61
9		24 h	>99[d]	>99

[a] Reaction conditions : aryl chloride (1 mmol), morpholine (1.1 mmol), [PdCl(Cycle)(SIPr)] **108** (1 mol%), KO^{t}Bu (1.1 mmol), DME (1 mL), T = 50ºC. [b] Conversions are average of at least two runs. [c] Isolated Yields. [d] KO^{t}Bu (2.2 mmol), DME (2 mL) and conversions were mesured by ^{1}H NMR.

Table 21. Cross coupling of aniline and various aryl halides catalyzed by **108**.[a]

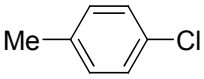
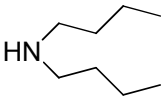
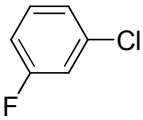
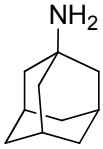
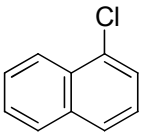
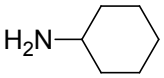
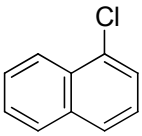
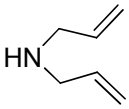
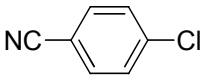
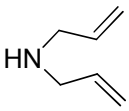
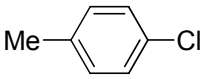
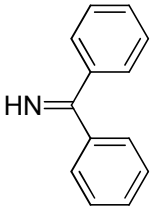


Entry	Ar-Cl	Time	GC Conversion (%)[b]	Yield (%)[c]
1		20 min	98	97
2		3 h	96	93
3		30 min	97	94
4		2 h	82	81
5		9 h	96	94

[a] Reaction conditions : aryl chloride (1 mmol), N-methylaniline (1.1 mmol), [PdCl(Cycle)(SIPr)] **108** (1 mol%), KO^{t}Bu (1.1 mmol), DME (1 mL), T = 50ºC. [b] Conversions are average of at least two runs. [c] Isolated Yields.

A range of amines was also tested as partners for the coupling reaction (Table 22). The less reactive and sterically hindered dibutylamine reacted smoothly with 2-chlorotoluene in high yields (entry 1). Primary amines appeared to be compatible with our catalytic system. The 1-chloro-3-fluorobenzene was rapidly coupled to the bulky 1-adamantylamine in quantitative yield (entry 2) without any formation of the diarylated product. As well, the primary amine, cyclohexylamine, produced straightforwardly the biologically interesting naphthylamine (entry 3). The diallylamine, absent from previous *N*-arylation study, was unreactive under these conditions either with neutral or activated aryl chlorides (entries 4, 5). Unfortunately, benzophenone imine could not be coupled with 4-chlorotoluene in DME (entries 6) and attempts performed in toluene also failed.

Table 22. Cross coupling of various amines and aryl halides mediated by **108**.[a]

Entry	Ar-Cl	HNRR'	Time	GC Conversion (%)[b]	Yield (%)[c]
1			4 h	98	99
2			30 min	97	99
3			4 h	98	99
4			24 h	0	-
5			24 h	0[d]	-
6			24 h	0	-

[a] Reaction conditions : aryl chloride (1 mmol), amine (1.1 mmol), [PdCl(Cycle)(SIPr)] **108** (1 mol%), KO^{t}Bu (1.1 mmol), DME (1 mL), T = 50ºC. [b] Conversions are average of at least two runs. [c] Isolated Yields. [d] Decomposition of the 4-Chlorobenzonitrile observed.

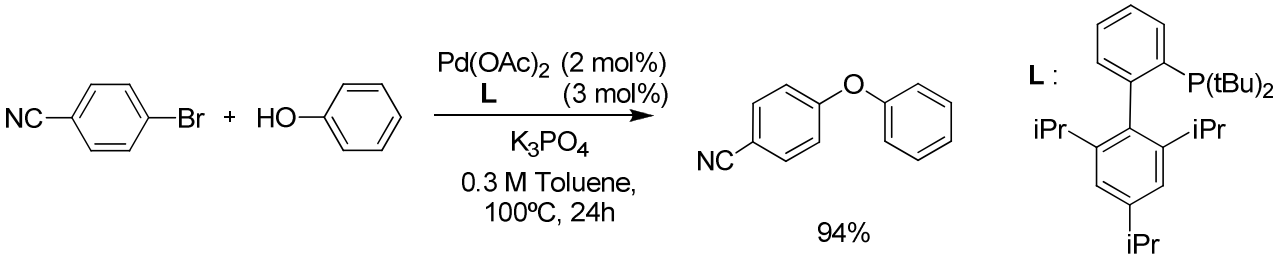
The more challenging and delicate Pd-catalyzed *O*-arylation reactions of phenol derivatives have been less explored than the *N*-arylation of amines. The efficiency and versatility of the SIPr-containing *N*-*C*-palladacycle **108** in the aryl amination prompted us to evaluate its catalytic activity in the formation of carbon-oxygen bonds.

2.4 Reactivity in the Buchwald-Hartwig O-Arylation of Phenols

Synthesis of diaryl ethers has been mostly achieved *via* copper-mediated Ullmann coupling reaction of aryl halides and phenols.[315] However, harsh conditions such as high temperature, the requirement of stoichiometric quantities of copper catalysts, the poor variety

[315] (a) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853-854. (b) Sawyer, J.S. *Tetrahedron* **2000**, *56*, 5045-5065.

of substrates and the moderate yields have greatly limited the potential of this reaction.[316] Efforts in this field over the past years have led to the development of palladium catalysts systems which enable diaryl and aryl alkyl ether formation under milder conditions.[317] Buchwald's[318] and Hartwig's[319] pioneering works accounted for the restricted palladium-catalyzed coupling of electron-deficient aryl bromides and tertiary alcohols or electron-rich phenols. Despite a large amount of palladium and bulky phosphine ligands, low yields were generally obtained. Latter, newly developed electron-rich bulky biaryl dialkyl phosphine ligands greatly improved the scope and generality of Pd-catalyzed diaryl ether formation (Scheme 62). This system allowed for the cross-coupling of electron-deficient, -neutral, and -rich aryl halides with a variety of activated and unactivated phenols.[317a,320] Reaction tolerated common functional groups and heteroaryl halides, final biaryl ethers were obtained in good yields. During the redaction of this manuscript, *in situ* generated palladium complexes with NHC ligands (1,3-dialkylimidazolium bromide derivatives) have been reported for the first time in the coupling of aryl halides with a variety of phenols (Scheme 63).[321] They were able to complete in good yields the etherification of electron-deficient or sterically hindered phenols with various aryl chlorides. In order to complete the scope and improve the reaction conditions, our well-defined palladium(II) complexe [PdCl(Cycle)(SIPr)] **108** was evaluated in the *O*-arylation of phenol with arylbromides and arylchlorides.



Scheme 62. Example of Pd-catalyzed C-O bond formation with Buchwald's ligand.[320]

[316] (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433-1456. (b) Chen, Y-.J.; Chen, H-.H. *Org. Lett.* **2006**, *8*, 5609-5612.

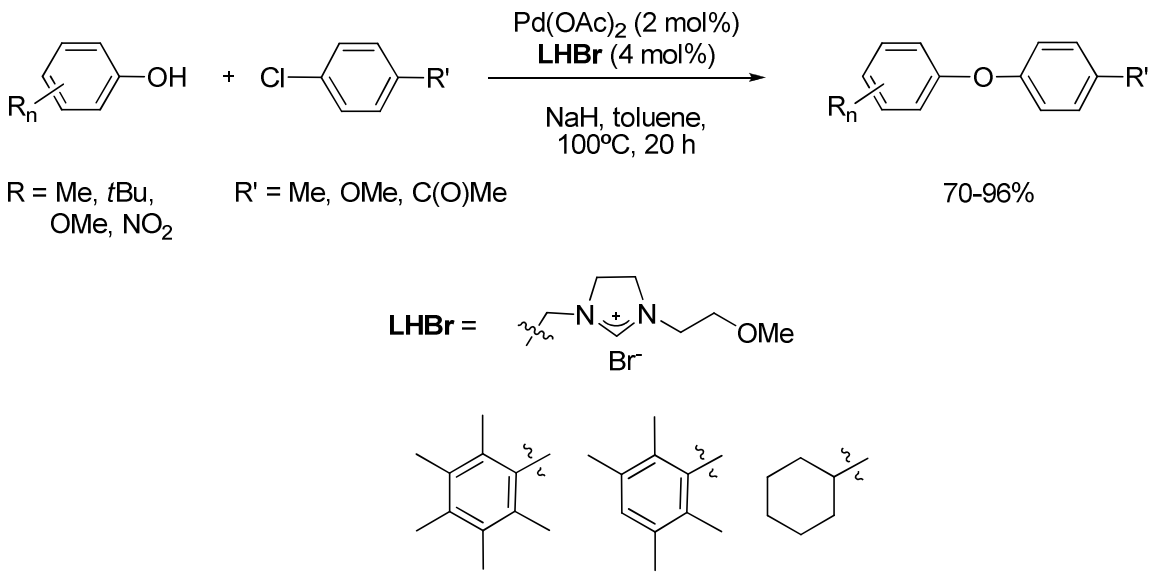
[317] (a) Aranyos, A.; Old, D.W.; Kiyomori, A.; Wolfe, J.P.; Sadighi, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1999**, *121*, 4369-4378. (b) Mann, G.; Incarvito, C.; Rheigold, A.L.; Hartwig, J.F. *J. Am. Chem. Soc.* **1999**, *121*, 3224-3225. (c) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J.F. *J. Am. Chem. Soc.* **2000**, *122*, 10718-10719. (d) Torraca, K.E.; Huang, X.; Parrish, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, *123*, 10770-10771. (e) Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237-3240.

[318] Palucki, M.; Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, *119*, 3395-3396.

[319] (a) Mann, G.; Hartwig, J.F. *J. Am. Chem. Soc.* **1996**, *118*, 13109-13110. (b) Mann, G.; Hartwig, J.F. *Tetrahedron Lett.* **1997**, *38*, 8005-8008.

[320] Burgos, C.H.; Barder, T.E.; Huang, X.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321-4326.

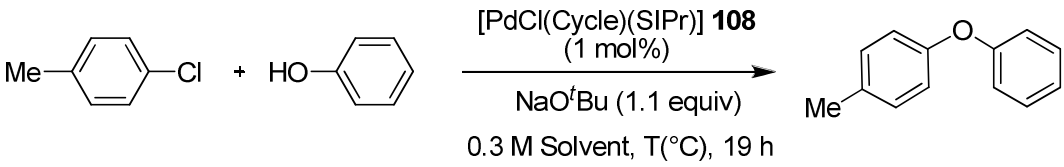
[321] Akkoç, M.; Gürbüz, N.; Çetinkaya, E.; Özdemir, I. *Synlett*, **2008**, 1781-1784.



Scheme 63. *In situ* generated NHC-Pd complexes in the coupling of aryl halides with a variety of phenols.[321]

We initiated the study using 4-chlorotoluene, previously well coupled with amines, and phenol as standard substrates (Table 23). At room temperature, the cross-coupling reaction did not proceed and only starting materials were recovered (entry 1). Unfortunately, at higher temperature including microwave heating (entries 2 and 3) and in a different solvent (entry 4), the phenol was not coupled to the chloride neither. After 19 h, palladium black was observed in the reaction solution.

Table 23. Tentative of *O*-arylation of the phenol with 4-chlorotoluene.[a]



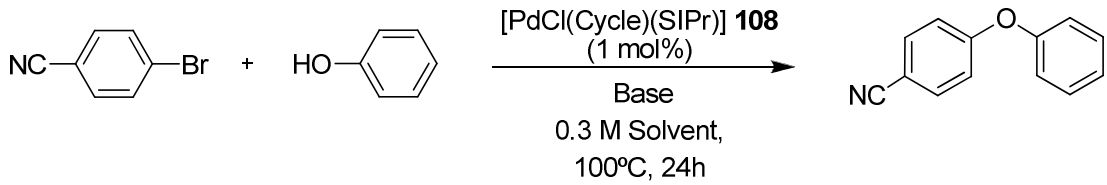
Entry	Solvent	T(°C)	GC Conversion
1	Toluene	25	-
2	Toluene	100	-
3	Toluene	100, MW[b]	-
4	Dioxane	100	-

[a] Reaction conditions : 4-chlorotoluene (0.5 mmol), phenol (0.6 mmol), [PdCl(Cycle)(SIPr)] **108** (1 mol%), NaO^{t}Bu (0.55 mmol), solvent (1.7 mL), 19 h. [b] 2 h of microwave irradiation

We then investigated the coupling of more activated aryl bromide bearing an electron-withdrawing functional group. However, the 4-bromobenzonitrile could not be coupled with

the phenol (Table 24). Once again, only starting materials were recovered. Under the same conditions used by Buchwald and co-workers (Scheme 62), the reaction did not proceed (entry 4). As the activation of the catalyst **108** required a strong base, 0.01 equivalent of sodium *tert*-butoxide was added to the phosphate base (entries 3 and 4). At that stage, we assumed the lack of activity of [PdCl(Cycle)(SIPr)] (**108**) for the *O*-arylation reactions and our efforts were not further pursued.

Table 24. Tentative of *O*-arylation of the phenol with 4-bromobenzontrile.[a]



Entry	Base (equiv)	Solvent	GC Conversion
1	NaO^{t}Bu (1.1)	Dioxane	-
2	NaO^{t}Bu (1.1)	Toluene	-
3	K_3PO_4 (2) / NaO^{t}Bu (0.01)	Dioxane	-
4	K_3PO_4 (2) / NaO^{t}Bu (0.01)	Toluene	-

[a] Reaction conditions : 4-bromobenzonitrile (0.5 mmol), phenol (0.6 mmol), [PdCl(Cycle)(SIPr)] **108** (1 mol%), base, solvent (1.7 mL), 100ºC, 24 h.

Economically and industrially, the reactions conditions obtained with [PdCl(palladacycle)(NHC)] systems are very appealing. However, the synthesis of the palladacycle biphenyl ligand requires harsh conditions and/or is low yielding, a significant hurdle. In view of a more convenient method, palladium(II) complexes **107** and **108** were used for the preparation of the palladacycle biphenyl ligand through a Suzuki-Miyaura cross coupling.

2.5 Application to the Synthesis of the N,N-Dimethylbiphenyl-2-amine Ligand via Suzuki-Miyaura Cross-coupling

In the literature, the synthesis of the *N*,*N*-dimethylbiphenyl-2-amine was first described in 1939 by Evans and Williams.[322] Beyond using the highly toxic methyl sulphate as methylating agent, they claimed to obtain the product in very good yield (94%) starting from the 2-aminodiphenyl. However, Popkin and co-workers reported in 1944 that the previously published yield was a mixture of the dimethyl and monomethyl compounds in a 66:34

[322] Evans, D.P.; Williams, R. *J. Chem. Soc.* **1939**, 1199-1202.

ratio.[323] By conducting the methylation with methanol under high temperature and pressure, the product *ratio* was improved to 87:13 with a reduced yield of 85%. Other procedures also gave mixtures and the product was usually isolated in poor yields.[324] Finally to date, the only appealing procedure to this ligand was reported in 2003 using formaldehyde and sulphuric acid at -10ºC to methylate in good yield the 2-aminodiphenyl.[325] Here, we have synthezised *N*,*N*-dimethylbiphenyl-2-amine by employing a Suzuki-Miyaura cross coupling using one of our novel NHC-palladacycle complexes. In addition to representing an original catalytic application, this specific example represents an unusual strategy: *using a catalyst as a synthetic tool for the synthesis of a biaryl compound that is an organic moiety of this same catalyst.*

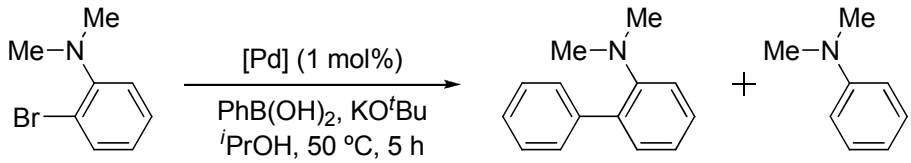
We first tested the feasibility of the coupling reaction with several catalysts synthesized in our laboratory (Table 25). Excluding the Pd-acac complex[295] that did not exhibit any activity in the desired cross coupling reaction (entry 8), all catalysts tested allowed for good conversions to the desired product in 5 h. The main problem observed was the formation of byproduct **111**, resulting from the dehalogenation of the starting material, in significant amount (≥ 50%). The cycle-, allyl-,[292] and cinnamyl[293] NHC-Pd series, known for their high reactivity, showed the most interesting results with a *ratio* close to 1:1. Compared to the unsaturated congeners, the reduction/cross-coupling *ratio* was decreased when saturated NHCs were used ([PdCl(Cycle)(NHC)] or [PdCl(allyl)(NHC)], (entries 1, 3-5). In order to improve these results, reaction conditions were re-examined using [PdCl(Cycle)(SIMes)] (**107**) (Table 26).

[323] Popkin, A.H.; Perretta, G.M.; Selig, R. *J. Am. Chem. Soc.* **1944**, *66*, 833-834.

[324] (a) Chen, Q.; Li, Z. *J. Fluorine Chem.* **1994**, *66*, 59-62. (b) Creencia, E.C.; Horaguchi, T. *J. Heterocyclic Chem.* **2006**, *43*, 1441-1446.

[325] Azzena, U.; Cattari, M.; Melloni, G.; Pisano, L. *Synthesis* **2003**, 2811-2814.

Table 25. Catalyst screening for the synthesis of the *N*,*N*-dimethylbiphenyl-2-amine ligand.[a]



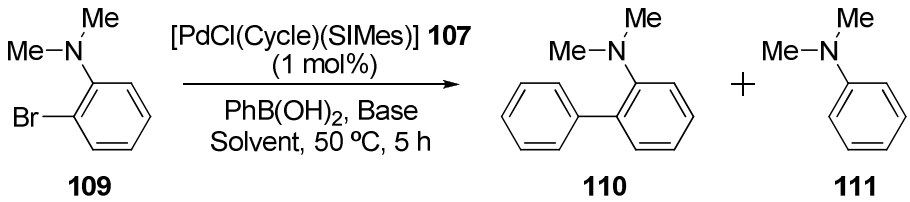
109 **110** **111**

Entry	[Pd]	Conv. (%)[b]	Ratio **110**/**111**[b]
1	[PdCl(Cycle)(IPr)] **102**	92	1:1.5
2	[PdCl(Cycle)(SIMes)] **107**	92	1:1.0
3	[PdCl(Cycle)(SIPr)] **108**	91	1:1.1
4	[PdCl(allyl)(IPr)]	83	1:7.3
5	[PdCl(allyl)(SIPr)]	79	1:1.1
6	[PdCl(cin)(SIPr)]	96	1:1.05
7	$[PdCl_2(SIPr)]_2$	95	1:1.8
8	[PdCl(acac)(IPr)]	< 2	-
9	$[Pd(OAc)_2(H_2O)(SIPr)]$	80	1:2.6

[a] Reaction conditions: 2-bromo-*N*,*N*'-dimethylaniline **109** (1 mmol), phenylboronic acid (1.1 mmol), [Pd] (1 mol%), KO^{t}Bu (1.2 mmol), tech. grade ^{i}PrOH (2 mL), T = 50 ºC, time = 5 h. [b] Determined by ^{1}H NMR spectroscopy, average of two runs.

Different non- or protic, non- or coordinating solvents were tested and surprisingly the reaction could only be carried out in *iso*propanol (entry 1). The optimization of the base showed that carbonate bases were inefficient (entries 11 and 12). A smaller counter anion caused a conversion decrease in parallel with an increase in dehalogenation (entry 8). Finally, despite only moderate conversion after 5 h, an important change in the *ratio* in favor for **110** occurred using KOH and KOMe (entries 9 and 10). The optimized conditions were used for the synthesis of **110** in large scale (Scheme 64). The reaction time was optimized to 16 h and 88% of **110** was isolated and the formation of **111** was greatly reduced.

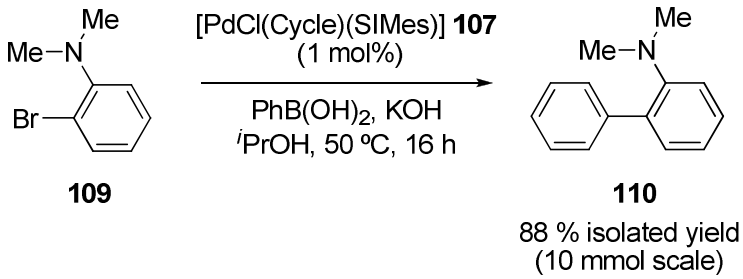
Table 26. Solvent and base screening for the synthesis of the *N*,*N*-dimethylbiphenyl-2-amine ligand.[a]



109 **110** **111**

Entry	Solvent	Base	Conv. (%)[b]	Ratio **110**/**111**[b]
1	^{i}PrOH	KO^{t}Bu	92	1:1.0
2	EtOH	KO^{t}Bu	< 2	-
3	MeOH	KO^{t}Bu	< 2	-
4	DME	KO^{t}Bu	< 2	-
5	dioxane	KO^{t}Bu	< 2	-
6	THF	KO^{t}Bu	< 2	-
7	Toluene	KO^{t}Bu	< 2	-
8	^{i}PrOH	NaO^{t}Bu	52	1:1.4
9	^{i}PrOH	KOMe	15	1:0.3
10	^{i}PrOH	KOH	66	1:0.2
11	^{i}PrOH	K_2CO_3	< 2	-
12	^{i}PrOH	Cs_2CO_3	< 2	-

[a] Reaction conditions: 2-bromo-*N*,*N*'-dimethylaniline **109** (1 mmol), phenylboronic acid (1.1 mmol), [PdCl(Cycle)(SIMes)] **7** (1 mol%), base (1.2 mmol), solvent (2 mL), T = 50 ºC, time = 5 h. [b] Determined by ^{1}H NMR spectroscopy, average of two runs.

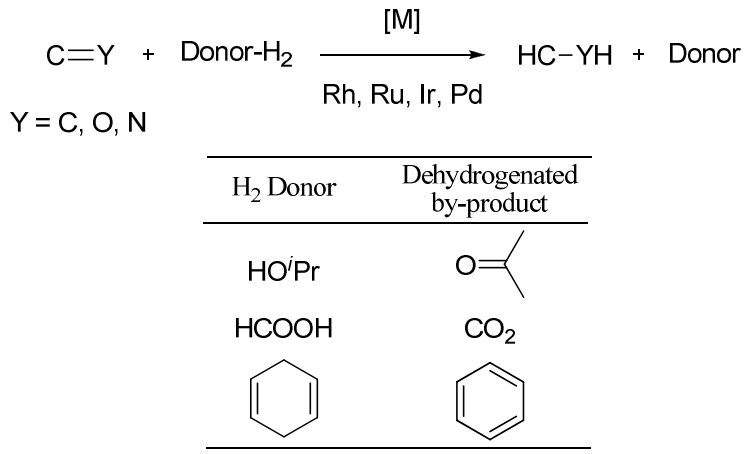


Scheme 64. Large scale synthesis of *N*,*N*-dimethylbiphenyl-2-amine ligand **110**.

3. NHC–PHOSPHANE Pd^0 COMPLEXES IN TRANSFER HYDROGENATION WITH FORMIC ACID AS REDUCING AGENT

3.1 General Features of Pd^0-catalyzed Transfer Hydrogenation

Among the various available processes for the transition metal-catalyzed hydrogenation of unsaturated compounds,[261] catalytic transfer hydrogenation has emerged as a viable alternative to the commonly used reduction method involving hazardous molecular hydrogen or metal hydrides.[326] The process entails hydrogen abstraction from the reagent (hydrogen donor) by means of the catalyst (heterogeneous or homogeneous), followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor) (Scheme 65). The list of H-acceptors includes alkenes, ketones, α,β-unsaturated carbonyl compounds, α,β-unsaturated acids and esters, imines and nitro compounds. Most of the reagents employed are organic molecules: unsaturated hydrocarbons such as cyclohexene or cyclohexadiene, primary or secondary alcohols like methanol, benzyl alcohol, or propan-2-o1, and formic acid and its salts have been successfully used to this end. The use of hydrogen donors has some advantages over the use of molecular hydrogen since it avoids operational risks and the necessity of pressure vessels. Additionally, rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor.



Scheme 65. General transfer hydrogenation reactions promoted by homogeneous transition metal catalysts.

[326] For reviews on transfer hydrogenation reactions, see: (a) Brieger, G.; Nestrick, T. *Chem. Rev.* **1974**, *74*, 567-580. (b) Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* **1985**, *85*, 129-170. (c) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051-1069. (d) de Graauw, C.F.; Peters, J.A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007-1017. (e) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102. (f) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226-236. (g) Samec, J.S.M.; Bäckvall, J.-E.; Andersson, P.G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237-248.

In this context, selective, mild and effective reducing promoters in transfer hydrogenation (TH), such as palladium-supported, ruthenium, iridium and rhodium catalysts, have been of considerable interest and well described.[327] Nevertheless, most of the very active catalysts for transfer hydrogenation have failed for the challenging non-polarized C=C bond case giving low yields or over-reduction[328] products.[329] Up to date only few homogeneous catalytic palladium-based systems have been reported for selective reduction of alkenes under transfer hydrogen conditions.[327a,330]

In this project, we were interested in the transfer hydrogenation of olefins with formic acid as the hydrogen source.[331] Formic acid, containing 4.4 wt% of hydrogen, is a potential hydrogen-storage material for application in energy feedstock and fuel-cell technology.[332] It has the advantage over other sources of hydrogen that only gaseous products are formed (H_2/CO_2) during its decomposition, hence preventing the accumulation of by-products. Few examples with Pd/C as catalyst have been reported in the literature.[333] However, several drawbacks were described. Notably, Pd/C was employed in high loading and large excess of formic acid was required (~ 12 equiv). In order to lower the quantity of HCOOH (~ 3 equiv), a base such triethylamine or potassium formate could be added to generate the formate ion.

[327] (a) Cortese, N.A.; Heck, R.F. *J. Org. Chem.* **1978**, *43*, 3985-3987. (b) Beaupere, D.; Bauer, P.; Nadjo, L.; Uzan, R. *J. Organomet. Chem.* **1982**, *238*, C12-C14. (c) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C. *Synlett* **1993**, 478-480. (d) Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron-Asymmetry* **1995**, *6*, 705-718. (e) Khai, B.T.; Arcelli, A. *Tetrahedron Lett.* **1996**, *37*, 6599-6602. (f) Tsutomu, A.; Seiji, O.; Yoshihito, W.; Shunichi, F. *J. Am. Chem. Soc.* **2003**, *125*, 4149-4154. (g) Selvam, P.; Sonavane, S.U.; Mohapatra, S.K.; Jayaram, R.V. *Tetrahedron Lett.* **2004**, *45*, 3071-3075. (h) Miecznikowski, J.R.; Crabtree, R.H. *Polyhedron* **2004**, *23*, 2857-2872.

[328] Over-reduction reactions imply that other functions present in the substrate, such as carbonyls, are also reduced during the transfer hydrogenation of the alkene.

[329] (a) Casey, C.P.; Singer, S.W.; Powell, D.R.; Hayashi, R.K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090-1100. (b) Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915-928. (c) Black, P.J.; Cami-Kobeci, G.; Edwards, M.G.; Slatford, P.A.; Whittlesey, M.K.; Williams, J.M.J. *Org. Biomol. Chem.* **2006**, *4*, 116-125. (d) Sharma, A.; Kumar, V.; Sinha, A.K. *Adv. Synth. Catal.* **2006**, *348*, 354-360. (e) Campaña, A.G.; Estévez, R.E.; Fuentes, N.; Robles, R.; Cuerva, J.M.; Buñuel, E.; Cárdenas, D.; Oltra, J.E. *Org. Lett.* **2007**, *9*, 2195-2198.

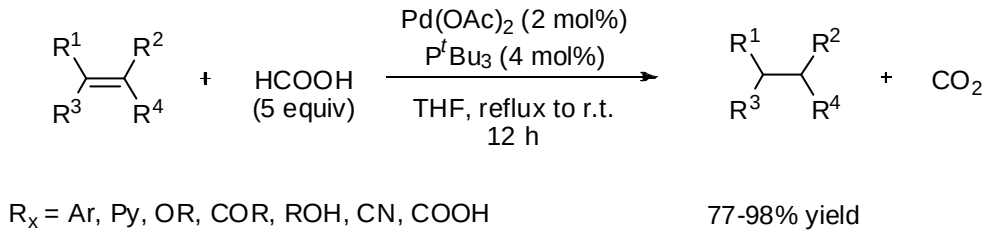
[330] (a) Visintin, M.; Spogliarich, R.; Kaspar, J.; Graziani, M. *J. Mol. Catal.* **1984**, *24*, 277-280. (b) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. *Synlett* **1991**, 27-28. (c) Basu, B.; Bhuiyan, Md. M.H.; Das, P.; Hossain, I. *Tetrahedron Lett.* **2003**, *44*, 8931-8934. (d) Baán, Z.; Finta, Z.; Keglevich, G.; Hermecz, I. *Tetrahedron Lett.* **2005**, 46, 6203-6204.

[331] For representative examples of metal-catalyzed transfer hydrogenation with formic acid, see: (a) Vol'pin, M.E.; Kukolev, V.P.; Chernyshev, V.O.; Kolomnikov, I.S. *Tetrahedron Lett.* **1971**, *12*, 4435-4438. (b) Nanjo, K.; Suzuki, K.; Sekiya, M. *Chem. Lett.* **1976**, 1169-1172. (c) Blum, J.; Pribar, I.; Alper, H. *J. Mol. Catal.* **1986**, *37*, 359-367. (d) Khai, B.T.; Arcelli, A. *J. Organomet. Chem.* **1986**, *309*, C63-C66. (e) Ram, S.; Ehrenkaufer, R.E. *Synthesis* **1988**, 91-94. (f) Khai, B.T.; Arcelli, A. *J. Org. Chem.* **1989**, *54*, 949-953. (g) Basu, B.; Das, S.; Das, P.; Nanda, A.K. *Tetrahedron Lett.* **2005**, *46*, 8591-8593.

[332] (a) Zaidman. B.; Wiener, H.; Sasson, Y. *Int. J. Hydrogen Energy* **1986**, *11*, 341-347. (b) Hyde, J.R.; Poliakoff, M. *Chem. Commun.* **2004**, 1482-1483. (c) Ogo, S.; Nishida, H.; Hayashi, H.; Murata, Y.; Fukuzumi, S. *Organometallics* **2005**, *24*, 4816-4823. (d) Garcia-Verdugo, E.; Liu, Z.; Ramirez, E.; Garcia-Serna, J.; Fraga- Dubreuil, J.; Hyde, J.R.; Hamley, P.A.; Poliakoff, M. *Green Chem.* **2006**, *8*, 359-364. (e) Fellay, C.; Dyson, P.J.; Laurenczy, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 3966-3968.

[333] (a) Boudjouk, P.; Han, B.H. *J. Catal.* **1983**, *79*, 489-492. (b) Alper, H.; Vasapollo, G. *Tetrahedron Lett.* **1992**, *33*, 7477-7480. (c) Ranu, B.C.; Sarkar, A. *Tetrahedron Lett.* **1994**, *35*, 8649-8650. (d) Berthold, H.; Schotten, T.; Honig, H. *Synthesis* **2002**, *11*, 1607-1610. (e) Prasad, K.; Jiang, X.; Slade, J.S.; Clemens, J.; Repič, O.; Blacklock, T.J. *Adv. Synth. Cat.* **2005**, *347*, 1769-1773.

Recently, Brunel has reported the scope of a selective homogeneous Pd-PR_3-catalyzed reduction of alkenes under transfer hydrogen conditions.[334] Pd^0-PR_3 complexes, formed *in situ* from $Pd(OAc)_2$ and tertiary phosphine ligands, were proposed as the active catalysts. Aromatic, strained and functionalized substrates were reduced in moderate to good yields with a good tolerance for ketone, ether, phenol, alcohol or nitrile groups. Reduction was mainly observed in the case of conjugated double bonds (with prior isomerization for some substrates). However, this methodology has limitations, for instance sterically hindered substrates could not be efficiently hydrogenated.



Scheme 66. Pd-PR_3-catalysed transfer hydrogenation with formic acid.

As mentioned above, compared to *in situ* systems, well-defined complexes lead to better catalytic performances.[287] NHC-containing Pd-catalysts[286] have also proven to be an excellent alternative to catalytic systems involving tertiary phosphines.[288] It therefore seemed of great interest to evaluate the catalytic activity of well-defined Pd^0 systems bearing NHC and PR_3 ligands.

3.2 Synthesis of Mixed NHC-Phosphane Palladium(0) Complexes

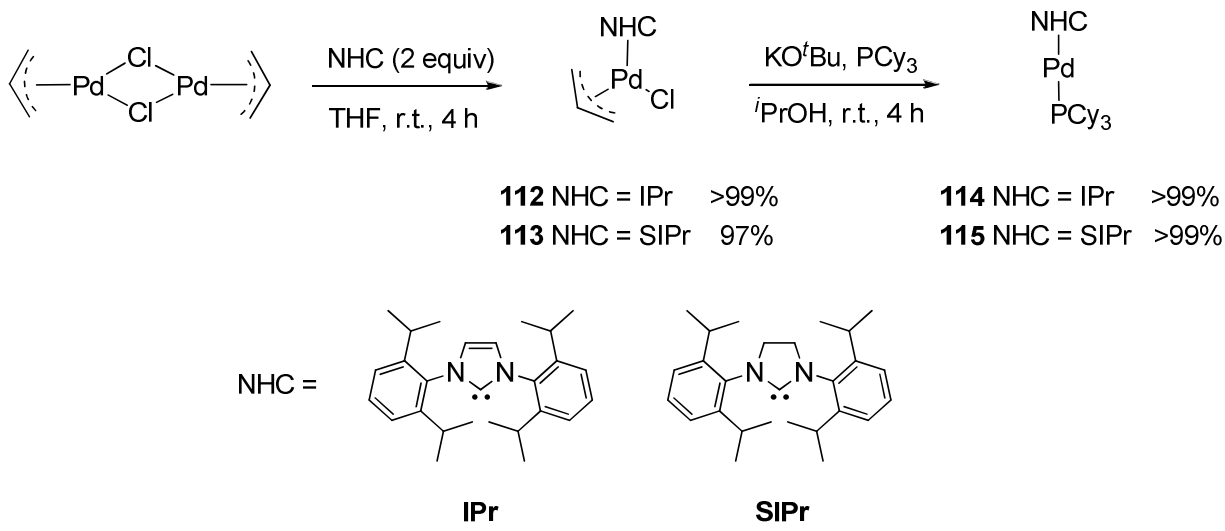
Attention has focused on the development of NHC-containing Pd^{II} systems that have proven particularly useful for cross coupling reactions.[286] On the other hand, fewer reports on well-defined NHC-Pd^0 catalysts have appeared as they are more difficult to isolate and quite air-sensitive.[335] The interesting feature of well-defined Pd^0 complexes compare to Pd^{II} species is that no reduction of the Pd center prior to catalysis is required.[336] However, catalytic studies showed that $[Pd^0(NHC)_2]$ complexes generally displayed moderate activity in cross-coupling

[334] (a) Brunel, J.M. *Tetrahedron* **2007**, *63*, 3899-3906. (b) Brunel, J.M. *Synlett* **2007**, *2*, 330-332.

[335] (a) McGuinness, D.S.; Cavell, K.J.; Skelton, B.W.; White, A.H. *Organometallics* **1999**, *18*, 1596-1605. (b) Titcomb, L.R.; Caddick, S.; Cloke, F.G.N.; Wilson, D.J.; McKerrecher, D. *Chem. Commun.* **2001**, 1388-1389. (c) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem. Eur. J.* **2002**, *8*, 3901-3906. (d) Jackstell, R.; Gómez Andreu, M.; Frisch, A.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Röttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem.* **2002**, *114*, 1028-1031; *Angew. Chem., Int. Ed.* **2002**, *41*, 986-989. (e) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031-3033. (f) Altenhoff, G.; Goddard, R.; Lehmann, C.W.; Glorius, F. *Angew. Chem.* **2003**, *115*, 3818-3821; *Angew. Chem., Int. Ed.* **2003**, *42*, 3690-3693. (g) Sprengers, J.W.; Wassenaar, J.; Clement, N.D.; Cavell, K.J.; Elsevier, C.J. *Angew. Chem.* **2005**, *117*, 2062-2065; *Angew. Chem., Int. Ed.* **2005**, *44*, 2026-2029. (h) Clement, N.D.; Cavell, K.J.; Ooi, L.-L. *Organometallics* **2006**, *25*, 4155-4165.

[336] *In situ* reduction of Pd^{II} precursors is a procedure that may generate inactive palladium species, especially palladium black.

reactions.[335b,337] As mono-NHC Pd^0 moieties are believed to be the active catalytic species in cross-coupling reactions,[338] Nolan and co-workers presumed that replacing one NHC by a less σ-donating ligand could lead to improved catalytic activity.[339] Tertiary phosphanes (PR_3) were selected as candidates as they are able to stabilize the highly unsaturated Pd^0 complex and they can also be released from the metal center, to allow initiation of the catalytic cycle. Various mixed NHC-phosphane Pd^0 complexes [Pd(NHC)(PR_3)] were synthesized following a procedure that tolerates the tuning of the nature of both the NHC and the phosphane.[339] [Pd(IPr)(PCy_3)] (**114**) and [Pd(SIPr)(PCy_3)] (**115**) were chosen for this catalytic transfer hydrogenation study and prepared according to this method (Scheme 67). In parallel with this project, hydrogenation of alkenes mediated by these well-defined [Pd(NHC)(PR_3)] systems has also been carried out with hydrogen gas.[340] [Pd(IPr)(PCy_3)] (**114**) and particularly [Pd(SIPr)(PCy_3)] (**115**) exhibited the best activities in these cases.



Scheme 67. Synthesis of palladium complexes **114** and **115**.

The palladium sources [PdCl(allyl)(IPr)] (**112**) and [PdCl(allyl)(SIPr)] (**113**) were obtained following a large-scale one-pot synthese involving the coordination of the NHC to the palladium center and simple cleavage of the dimer $[PdCl(allyl)]_2$ by two equivalents of free NHC ligands, such as IPr and SIPr.[341] The reactions gave rise to the expected 16-electron

[337] (a) Böhm, V.P.W.; Gstöttmayr, CW.K.; Weskamp, T.; Herrmann, W.A. *J. Organomet. Chem.* **2000**, *595*, 186-190. (b) Caddick, S.; Cloke, F.G.N.; Clentsmith, G.K.B.; Hitchcock, P.B.; McKerrecher, D.; Titcomb, L.R.; Williams, L.R.V. *J. Organomet. Chem.* **2001**, *617-618*, 635-639. (c) Arentsen, K.; Caddick, S.; Cloke, F.G.N. *Tetrahedron* **2005**, *61*, 9710-9715.

[338] Christmann, U.; Vilar, R. *Angew. Chem.* **2005**, *117*, 370-378; *Angew. Chem., Int. Ed.* **2005**, *44*, 366-374.

[339] Fantasia, S.; Nolan, S.P. *Chem. Eur. J.* **2008**, *14*, 6987-6993.

[340] Jurčík, V.; Nolan, S.P.; Cazin, C.S.J. *Chem. Eur. J.*, **2009**, *15*, 2509-2511.

[341] Navarro, O.; Nolan, S.P. *Synthesis* **2006**, 366-367.

species [PdCl(allyl)(NHC)] in excellent isolated yields. Reaction of [PdCl(allyl)(NHC)] and tricyclohexylphosphane (PCy_3), in the presence of a base afforded the mixed dicoordinate species [Pd(IPr)(PCy_3)] **114** and [Pd(SIPr)(PCy_3)] **115** in excellent yields. Of note, while complexes **112** and **113** are perfectly air- and moisture-stable and thus can be handle in air, exposure of [Pd(NHC)(PCy_3)] **114** and **115** to air does not lead to decomposition, but to the oxo-complex [Pd(NHC)(PCy_3)(O_2)], which is stable both in the solid state and in solution. Therefore, manipulations of [Pd(NHC)(PCy_3)] and reactions were performed under inert atmosphere.

3.3 Reactivity of NHC-Phosphane Pd^0 Systems in Transfer Hydrogenation Reactions

The catalytic activities of the two mixed NHC-phosphane Pd^0 complexes were evaluated in the reduction of olefinic carbon-carbon double bond by transfer hydrogenation (TH). *Trans*-stilbene was used as standard substrate for the optimization and formic acid (HCOOH) as the "controlled" source of hydrogen.

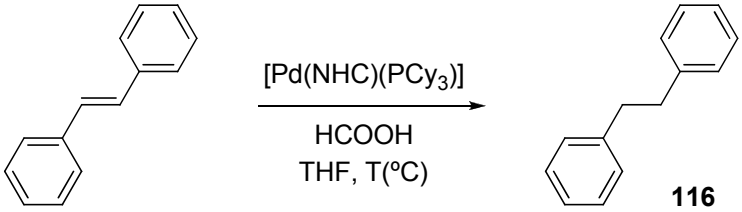
a) Optimization of transfer hydrogenation conditions:

First, we explored the reactivity of [Pd(IPr)(PCy3)] **114** for the reduction of the conjugated double bond of *trans*-stilbene in the presence of an excess of formic acid (5 equivalents) (Table 27, entry 1). 90% conversion to 1,2-diphenylethane **116** was reached after 16 h at 60°C and complete conversion after 24 h. The optimum catalyst loading was found to be 0.2 mol% (Table 27, entries 1-4). To test the hydrogen delivery capabilities of the hydrogen donor, the amount of formic acid was decreased to 1.05 equivalents. Complete conversion was obtained under these conditions, in agreement with the total delivery of theoretical optimum amount of hydrogen (Table 27, entry 5). Moreover, this decrease of the HCOOH quantity drastically shortened the reaction time. Total TH of *trans*-stilbene was accomplished using 0.5 mol% of **114** in less than 3 h. It is possible that an excess of HCOOH saturates the catalyst and thus inhibits the TH reaction. Under the same conditions, the activity of [Pd(SIPr)(PCy3)] **115** was slightly higher than the one of **114** (Table 27, entries 5 and 7). Kinetic experiments showed that the complex **115** has a turnover frequency (TOF)[342] higher than the one of **114** (55% after 30 min *versus* 27%, respectively). Nevertheless, reaction conversions with both catalysts were found equivalent after 1 h. This behavior is coherent with previous observations reporting that SIPr-containing complexes performed

[342] The turnover number (TON) is the number of moles of substrate that a mole of catalyst can convert before becoming inactivated. The term turnover frequency (TOF) is used to refer to the turnover per unit time.

better than IPr analogues in Pd-mediated reactions,[292c,293,311] especially in hydrogenation reactions catalyzed by two-coordinate Pd^0 species.[340] It suggest also that, despite a faster initiation step, the decay of SIPr-containing complex **115** occurred as well earlier in solution. At room temperature, the reaction proceeded poorly even after 24 h (Table 27, entry 9).

Table 27. Optimization of *trans*-stilbene transfer hydrogenation with formic acid as reducing agent and catalyzed by [Pd(NHC)(PCy_3)] complexes.[a]



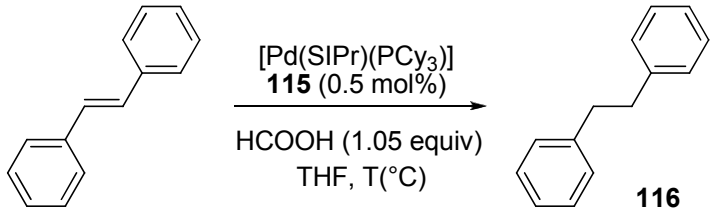
Entry	Catalyst	Pd (mol%)	HCOOH (equiv)	T(ºC)	Time	Conv. (%)[b]
1	**114** (IPr)	1	5	60	16 h 24 h	90 100
2	**114** (IPr)	0.5	5	60	3 h 16 h 24 h	75 96 100
3	**114** (IPr)	0.2	5	60	16 h 24h	88 100
4	**114** (IPr)	0.1	5	60	24 h 48 h	84 89
5	**114** (IPr)	0.5	1.05	60	30 min 1 h 2 h 3 h	27 92 96 100
6	**114** (IPr)	0.2	1.05	60	14 h 24h	32 100
7	**115** (SIPr)	0.5	1.05	60	30 min 1 h 2 h	55 91 100
8	**115** (SIPr)	0.5	1.05	reflux (15 min) then r.t.	15 min 2 h 6 h	10 25 93
9	**115** (SIPr)	0.5	1.05	r.t.	2 h 24 h	<1 12
10[c]	**115** (SIPr)	0.5	1.05	60	30 min 1 h	1 15
11	-	1 Pd/C	1.05	60	1 h	7
12	-	-	1.05	60	24 h	<1

[a] Reaction conditions: *trans*-stilbene (0.5 mmol), THF (2 mL). [b] Determined by ^{1}H NMR spectroscopy, average of at least two runs. [c] ^{i}PrOH (2 mL)

However, when the reaction was stirred for 15 min to reflux then cooled, complete conversion into **116** was reached after 6 h at room temperature (Table 27, entry 8). This result underlined the need of a thermal activation of the catalyst prior to catalysis in order to generate the active species. While alcohol solvents had a beneficial effect on hydrogenation with H_2 gas and catalyzed by **115**,[340] in our case poor reduction of *trans*-stilbene was observed in *i*PrOH (Table 27, entry 10). When the TH reaction was carried out in the absence of palladium source, no reduction occurred and only 7% conversion was obtained with 1 mol% of palladium on charcoal (Table 27, entries 11 and 12).

During this optimization, we also noticed that the concentration had an effect on the conversion rate of the TH reaction (Table 28).[343]

Table 28. Influence of the concentration on the Pd^0-catalyzed reduction of *trans*-stilbene under TH conditions.[a]



Entry	THF (mL)	T(°C)	Time	Conv. (%)[b]
1	1	reflux (15 min) then r.t.	2 h	10
2	2	reflux (15 min) then r.t.	2 h	25
3	3	reflux (15 min) then r.t.	2 h	36
4	5	reflux (15 min) then r.t.	2 h	27
5	10	reflux (15 min) then r.t.	2 h	5
6	3	60	30 min	30
7	2	60	30 min	55
8	2	60	30 min	28[c]
9	2	60	30 min	20[d]

[a] Reaction conditions: *trans*-stilbene (0.5 mmol), HCOOH (0.53 mmol), [Pd(SIPr)(PCy_3)] **115** (0.5 mol%). [b] Determined by ^{1}H NMR spectroscopy, average of at least two runs. [c] Reaction carried out in closed schlenk flask (25 mL). [d] Reaction carried out releasing the pressure *via* connection to a bubbler.

[343] Of note, the presented transfer hydrogenations had been realized in a closed vial of 4 mL volume capacity for entries 1-3 and 6-7, or of 20 mL volume capacity for entries 4-5.

After the 15 min of reflux and 2 h at room temperature, 36% of **116** were achieved from a diluted reaction mixture (0.17 M) (Table 28, entry 3) whereas a lower yield was obtained at higher concentration (25% and 10% obtained at 0.25 M and 0.5 M, respectively) (Table 28, entries 1 and 2). Higher dilution slowed the reaction rate (Table 28, entries 4 and 5).

On the other hand, the inverse trend was observed at 60°C. After 30 min, a better conversion was reached when the reaction was carried out at a higher concentration of 0.25 M than at 0.17 M (Table 28, entries 6 and 7). We hypothesized that these reactivity variations as a function of the volume of solvent could be related to an effect of the pressure in the reaction vessel. Indeed, CO_2 gas is liberated from formic acid during the progression of the TH and this releasing of CO_2 might increase at elevated temperature. However, if the solvent occupies a large part of the vial space, it would hinder the gas releasing and thus inhibit the reaction. Hence, in a closed system mainly occupied by solvent, the lack of space for gas could hamper the formation of CO_2 from the formic acid and consequently the addition of H_2. While a high concentration (0.25 M) would assure sufficient space for the released gas, improving the reduction rate. Nonetheless, it does not explain why at room temperature, a diluted reaction mixture favoured the transfer hydrogenation. Further experiments were necessary to understand these contradictions.

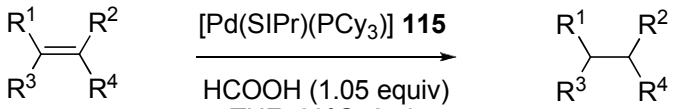
We chose to carry out the TH in a larger vessel and in an open system (Table 28, entries 8 and 9). Surprisingly, the reaction was slowed when the pressure in the vial was diminished or eliminated. This time, the results were in disagreement with the first hypothesis but were consistent with the ones found at room temperature (Table 28, entries 1-5). They traduce the need for a certain pressure applied on the reaction mixture. If H_2 is also released during the course of the TH, this would explain the equilibrium of pressure required between the pressurized addition of H_2 and the liberation of CO_2, and thus the influence of the volume of solvent on this equilibrium shift. These preliminary outcomes raised numerous questions about the evolution of the NHC/PR_3-Pd^0-catalyzed transfer hydrogenation reaction using formic acid as hydrogen source. A mechanistic study is currently underway in our laboratory to determine how the formic acid is added onto the catalyst and how the hydrogen is delivered onto the double bond.

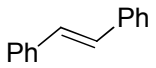
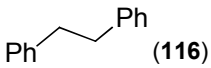
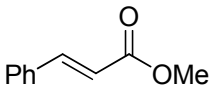
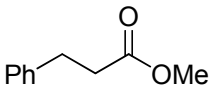
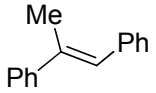
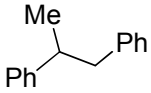
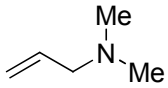
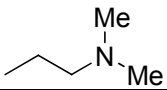
<u>b) Scope of the transfer hydrogenation with formic acid:</u>

The optimized reaction conditions were then applied to the transfer hydrogenation of various substrates containing a C=C double bond. After 2 h stirring at 60ºC, 1,2-diphenylethane **116** was obtained in good isolated yield when using 0.5 mol% of

[Pd(SIPr)(PCy_3)] **115** and 1.05 equivalent of HCOOH in THF (Table 29, entry 1). However, the same TH conditions applied to other substrates appeared to be inefficient. After 24 h stirring at 60ºC, no reaction or poor conversions were obtained (Table 29, entries 2-4). Using two equivalent of HCOOH lowered even more the percentage of conversion, as expected with respect to the results obtained during optimization of conditions. Increasing the catalyst loading had a beneficial effect on the conversion (Table 29, entries 2-3). In order to have a method applicable to a large panel of substrates, the catalyst loading was increased to 2 mol%.

Table 29. [Pd(SIPr)(PCy_3)]-catalyzed reduction of alkenes under optimized TH conditions.[a]

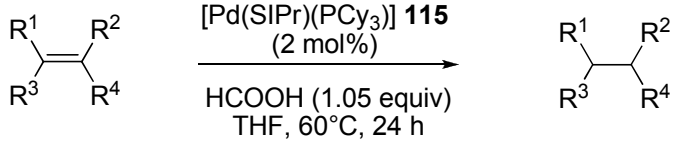


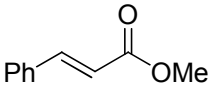
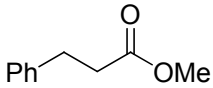
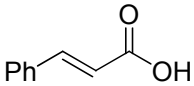
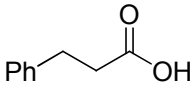
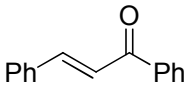
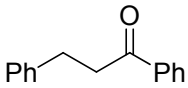
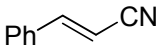
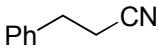
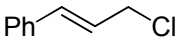
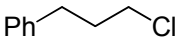
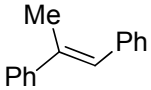
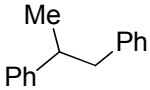
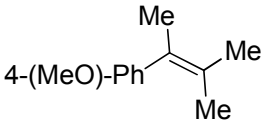
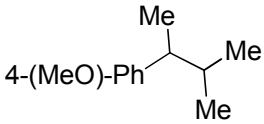
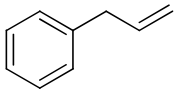
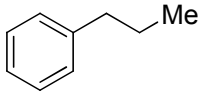
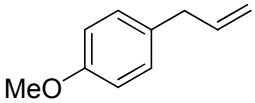
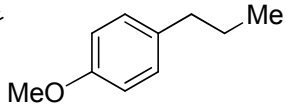
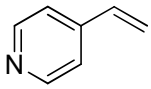
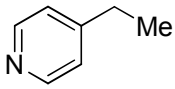
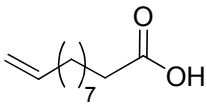
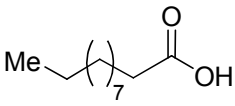
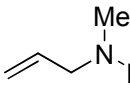
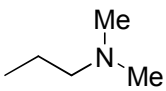
Entry	Substrate	Product	Pd (mol%)	Conv. (%)[b]
1		 (**116**)	0.5	100 (93)[d]
2			0.5 1	36 78
3			0.5 1	15 21
4			0.5	0

[a] Reaction conditions: substrate (0.5 mmol), HCOOH (0.53 mmol) THF (2 mL), 60ºC, 24 h. [b] Determined by GC, average of at least two runs. Isolated yield given in parentheses. [d] 2 h.

The reduction of a variety of substrates such as cyclic and acyclic olefins, α,β-unsaturated aldehydes, α,β-unsaturated ketones and other α,β-unsaturated carbonyl compounds was hence investigated. The presence of functional groups such as acids, esters, ketones or nitriles did not affect the hydrogenation and excellent isolated yields were obtained in all cases (Table 30, entries 1-4). No reduction of the functional groups was observed. Surprisingly, cinnamyl chloride could not be reduced (Table 30, entry 5). Entries 6 and 7 clearly show that the transfer hydrogenation of internal tri- or tetra-substituted double bonds was problematic as conversions obtained were low. The reduction of terminal alkenes proceeded to complete conversion (Table 30, entries 8, 9 and 11), except for *N*,*N*-dimethylallylamine and 4-vinylpyridine which were converted in 44 and 80%, respectively (Table 30, entries 10 and 12). The nitrogen atom might poison the palladium center of the catalyst.

Table 30. [Pd(SIPr)(PCy_3)]-catalyzed reduction of various alkenes under transfer hydrogen conditions using formic acid as reducing agent.[a]



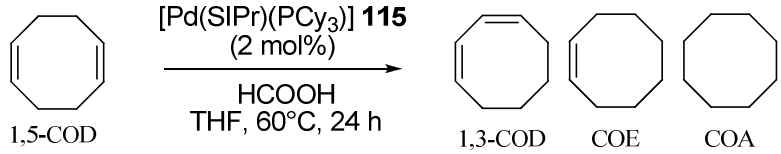
Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]
1			99	94
2			100[d]	98
3			97	97
4			94	94
5			0	-
6			33	36[d]
7			10	10[d]
8			100	>99[e]
9			94	94
10			80	75
11			100	96
12			-	44[d]

[a] Reaction conditions: substrate (0.5 mmol), HCOOH (0.53 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h (reaction time not optimized). [b] Determined by GC, average of at least two runs. [c] Isolated yield unless otherwise stated. [d] ^{1}H NMR conversion. [e] Yield determined by ^{1}H NMR using hexamethylbenzene as internal standard.

It has to be noted that in the case of allylanisole and allylbenzene (Table 30, entries 8 and 9), isomerization was observed prior to the reduction.[344] The isomerisation of double bonds with transition-metal catalysts is well established in organic chemistry[345] and has already been observed both in homogeneous and heterogeneous hydrogenation catalysis.[346] In the reaction of allyl benzene the use an excess of formic acid, led to propenyl benzene as the major product with a *ratio* Propenyl benzene/Propyl benzene 80:19 after 24 h stirring at 60ºC.

The reduction of cyclooctadiene (COD) and cyclooctene (COE) was first evaluated under the standard conditions. However, it rapidly showed itself to be an unusual study case. Indeed, in these particular examples, the formic acid quantity appeared to have an unexpected influence on the outcomes of the hydrogenation reaction. First attempts with 1,5-cyclooctadiene in the presence of one equivalent of formic acid revealed a mixture of products, including the starting material (1,5-COD), 1,3-COD due to isomerisation and the hydrogenated product (COE) (Table 31, entry 1). Similar proportions were obtained by increasing the catalyst loading.

Table 31. Transfer hydrogenation of the 1,5-cyclooctadiene.



Entry	HCOOH (equiv)	Products - GC Conv. (%)			
		1,5-COD	1,3-COD	COE	COA
1	1	20	24	56	0
2	2	5	7	88	0
3	5	0.5	0.8	96	2.7

Compared with olefins, harsh conditions are usually required for the hydrogenation of dienes and particularly cyclic dienes.[347] 1,5-COD is known to bind late transition-metal leading to stable organometallic complexes including Pd species and this "*anchor-type*" interaction of both 1,5-COD double bonds with a metallic center could hinder hydrogen

[344] Formation of prop-1-enylbenzene and 1-methoxy-4-(prop-1-enyl)benzene were respectively observed by ^{1}H NMR in the early stages of the reaction (< 1 h) and subsequently reduced without consequence.

[345] Herrmann, W.A.; Prinz, M. in "*Applied homogeneous catalysis with organometallic compounds*" Vol 3, 2nd Ed, Cornils, B., Herrmann, W.A., Eds.; Wiley-VCH: Weinheim, Germany, **2002**, 1119-1130.

[346] (a) Smith, G.V.; Roth, J.A.; Desai, D.S.; Kosco, J.L. *J. Catal.* **1973**, *30*, 79-85. (b) Smith, G.V.; Wang, Y.; Song, R.; Jackson, M. *Catal. Today* **1998**, *44*, 119-127.

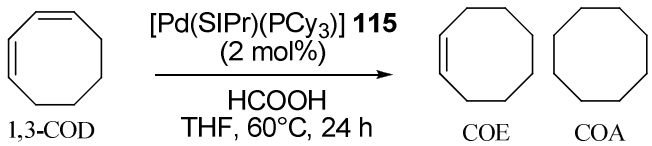
[347] (a) Raoult, Y.; Choukroun, R.; Basso-Bert, M.; Gervais, D. *J. Mol. Catal.* **1992**, *72*, 47-58. (b) Tavares, A.; Wolke, S.I.; Gomes da Rosa, R. *J. Catal.* **2008**, *254*, 374-382.

coordination.[348] Hence, an excess of formic acid (to displace the equilibrium) did not slow the catalyst activity but unlike allowed for a complete and selective conversion into COE (Table 31, entry 3).

The puzzling point of this last experiment was the selective hydrogenation of only one double bond and the nearly inexistent formation of the completely hydrogenated product (cyclooctane, COA) under this excess of hydrogen. In a homogenous hydrogenation mixture, there is a competition between the 1,3-COD and the COE for the catalytic active site. However, the hydrogenation of 1,3-COD, involving the highly stable η^3-allyl intermediate formed by M-H addition, is thermodynamically favoured.[349] Studies on the kinetics of this reaction have shown that the hydrogenation of COE is totally suppressed in the presence of 1,3-COD.[350] Consequently, the dienes in the reaction media are almost completely hydrogenated before the concentration of the monoene increases to the point that it gains access to the metal center.

Hence, transfer hydrogenation of 1,3-COD afforded selectively 96% of COE when the amount of HCOOH was limited to one "theoretical" equivalent of H_2 (Table 32, entry 1). While formation of COA was a majority when an excess of HCOOH was employed and 1,3-COD was totally consumed (Table 32, entry 3).

Table 32. Transfer hydrogenation of the 1,3-cyclooctadiene.



Entry	HCOOH (equiv)	Products - GC Conv. (%)		
		1,3-COD	COE	COA
1	1	0	96	4
2	2	0	74	26
3	5	0	39	60

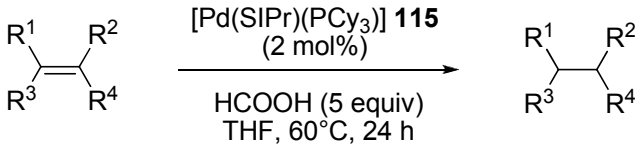
[348] Mouraa, F.C.C.; dos Santosa, E.N.; Lagoa, R.M.; Vargasb, M.D.; Araujoa, M.H. *J. Mol. Catal. A-Chem.* **2005**, *226*, 243-251.

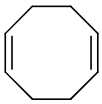
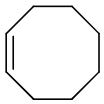
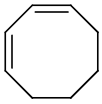
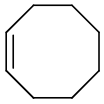
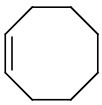
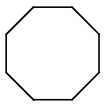
[349] (a) Parshall, G.W. *J. Am. Chem. Soc.* **1972**, *94*, 8716-8719. (b) Schmidt, A.; Haidar, R.; Schomäcker, R. *Cat. Today* **2005**, *104*, 305-312. (c) Wuchter, N.; Schäfer, P.; Schüler, C.; Gaube, J.; Miehe, G.; Fuess, H. *Chem. Eng. Technol.* **2006**, *29*, 1487-1495.

[350] (b) Arnold, H.; Döbert, F.; Gaube, J. in *"Handbook of Heterogeneous Catalysis"* Ertl, G., Knözinger, H., Weitkamp, J., Eds.; VCH: Weinheim, Germany, **1997**. (c) Haas, T.; Gaube, J. *Chem. Eng. Technol.* **1989**, *12*, 45-53.

The isolated yields of COE starting either from 1,5- or 1,3-COD and using the appropriate amount of HCOOH are summarized in Table 33 (entries 1 and 2). Finally, like observed in the case of 1,5-COD, the formic acid quantity had an influence on the progress of the transfer hydrogenation of COE. Only partial reduction to cyclooctane was observed, with a *ratio* COE/COA 60:40, when using one equivalent of HCOOH. An excess was required to afford quantitative conversion of COE into COA (Table 33, entry 3).

Table 33. Optimum transfer hydrogenation of cyclooctenyl derivatives.[a]

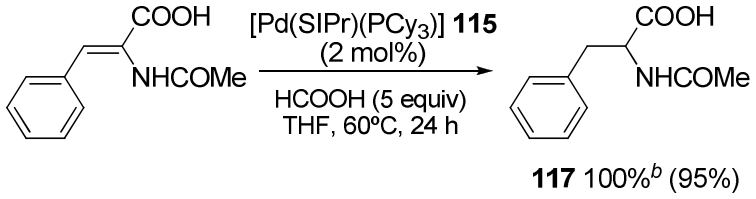


Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]
1			96	82
2			96[d]	53
3			100	83[e]

[a] Reaction conditions : substrate (0.5 mmol), HCOOH (2.5 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h (reaction time not optimized). [b] Determined by GC, average of at least two runs.[c] Isolated yield unless otherwise stated. [d] HCOOH (1.05 equiv). [e] Yield determined by ^{1}H NMR using hexamethyl-benzene as internal standard.

α-Acetamidocinnamic acid is a tri-substituted alkene difficult to reduce.[334] Using our system, transfer hydrogenation of this challenging olefin required 5 equivalents of formic acid to reach quantitative conversion to the desired saturated **117** (Scheme 68). Decreasing the amount of HCOOH led to lower catalytic activity. According to the literature the acidic proton of formic acid (HCOO-*H*) is supposed to be the one added on the palladium center as hydride specie.[334,351] One can imagine that we have competition between the addition of the acidic proton from HCOOH and the one from the acid group of the substrate both present in equivalent quantities. The *ratio* between the two *H*-coordinated Pd intermediates could thus be shifted towards dehydrogenation of HCOOH and liberation of H_2 when formic acid is used in excess, enabling for complete conversion of α-acetamidocinnamic acid.

[351] Yu, J.; Spencer, J.B. *Chem. Eur. J.* **1999**, *5*, 2237-2240.

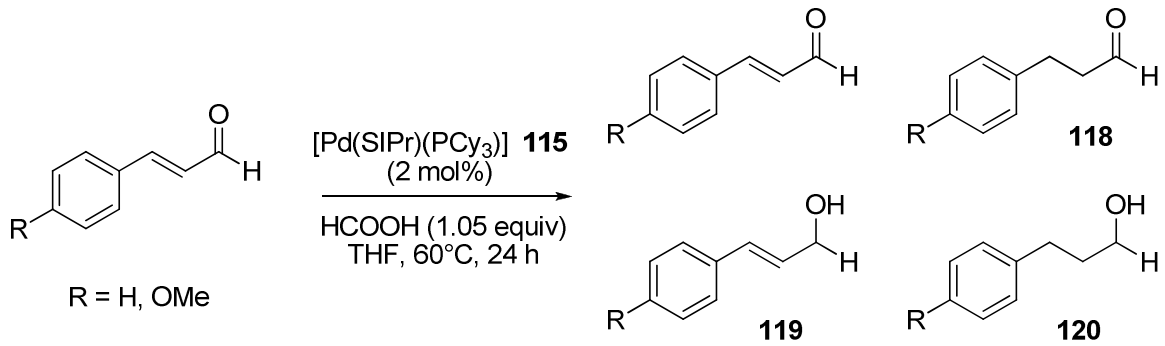


Scheme 68. Transfer hydrogenation of α-acetamidocinnamic acid.
[b] Determined by ^{1}H NMR spectroscopy, average of at least two runs, isolated yield given in parentheses.

So far, although full conversions could not always be reached, NHC/PR_3-Pd^0-catalyzed transfer hydrogenation reactions gave exclusively the saturated derivatives of the reactive olefin substrates. Unfortunately, this selectivity was not systematically observed and some limitations of our mixed NHC/PCy_3-Pd^0 system were encountered during the scope of this work.

c) Limitations of the mixed NHC/PCy_3-Pd^0 system:

The first important limitation of this system concerns aldehydes. The reduction of both tested cinnamaldehydes gave a mixture of products, including mainly 3-phenylpropenol **119** and the over-reduced 3-phenylpropanol **120** (Scheme 69). In order to decrease the catalytic activity and increase the selectivity, an excess of HCOOH was used, unfortunately without success. Hydrogenation of the aldehyde seemed to be prior to the alkene.



Scheme 69. Reaction conditions: substrate (0.5 mmol), HCOOH (0.53 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h.

Transfer hydrogenation of 1,4-cyclohexadiene, using two equivalents of formic acid to reduce both double bonds, led to the formation of mostly the desired cyclohexane and benzene (Table 34, entry 1). When an excess of HCOOH was employed, the tendency was inversed and benzene became the major product. It is interesting to underline here the ability

of our dicoordinated Pd^0 complex to dehydrogenate 1,4-cyclohexadiene and thus to use it as potential hydrogen source.[352]

Under the optimized conditions, the transfer hydrogenation of 2-cyclohexen-1-one gave good yields of cyclohexanone (84%) and reduction of the ketone or isomerization product of the starting compound was not observed (Table 34, entry 2). However, the formation of phenol from Pd-mediated dehydrogenation of starting material was detected. The literature reports similar formation of phenol as more stable aromatic side product during the Pd-catalyzed reduction of 2-cyclohexen-1-one.[353] Nevertheless, to the best of our knowledge, only one publication from 1944 reported cyclohexenone as hydrogen source in Pd/C-catalysed transfer hydrogenation reaction.[354] 2-Cyclohexenone in its enolic form is a dihydrobenzene derivative, and its preparation by vapor-phase dehydration of 2-hydroxycyclohexanone gives considerable phenol.

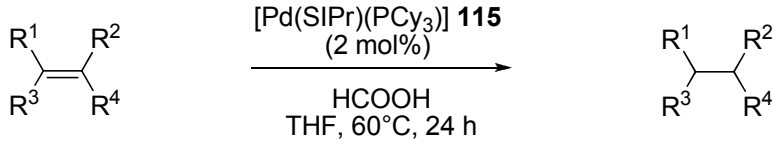
We also evaluated the activity of our catalytic system in the TH of an imine. Transfer hydrogenation is more difficult for imines than for aldehydes and ketones, and few examples are known.[329e] Two equivalents of formic acid were required to generate the saturated amine in good yields (Table 34, entry 3). With an excess of HCOOH, the proportion of final compound was diminished and dibenzyl was detected as a side product.

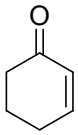
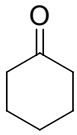
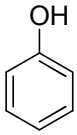
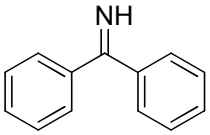
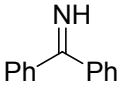
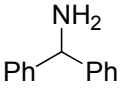
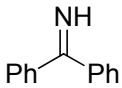
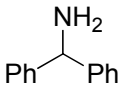
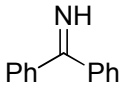
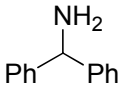
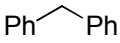
[352] For examples of 1,4-cyclohexadiene as hydrogen source in heterogeneous TH, see: (a) Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194-4196. (b) Shima, H.; Yamaguchi, T. *J. Catal.* **1984**, *90*, 160-164. (c) Bajwa, J.S. *Tetrahedron Lett.* **1992**, *33*, 2299-2302. (d) Tietze, L.F.; Noebel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971-8977. (e) Quinn, J.F.; Razzano, D.A.; Golden, K.C.; Gregg, B.T. *Tetrahedron Lett.* **2008**, *49*, 6137-6140.

[353] (a) Bhaduri, S.; Mukesh, D.; Sharma, K. *J. Chem. Soc., Chem. Com.* **1990**, *21*, 1506-1508. (b) Dell'Anna, M.M.; Gagliardi, M.; Mastrorilli, P.; Suranna, G.P.; Nobile, C.F. *J. Mol. Catal. A-Chem.* **2000**, *158*, 515-520.

[354] Orchin, M. *J. Am. Chem. Soc.* **1944**, *66*, 535-538.

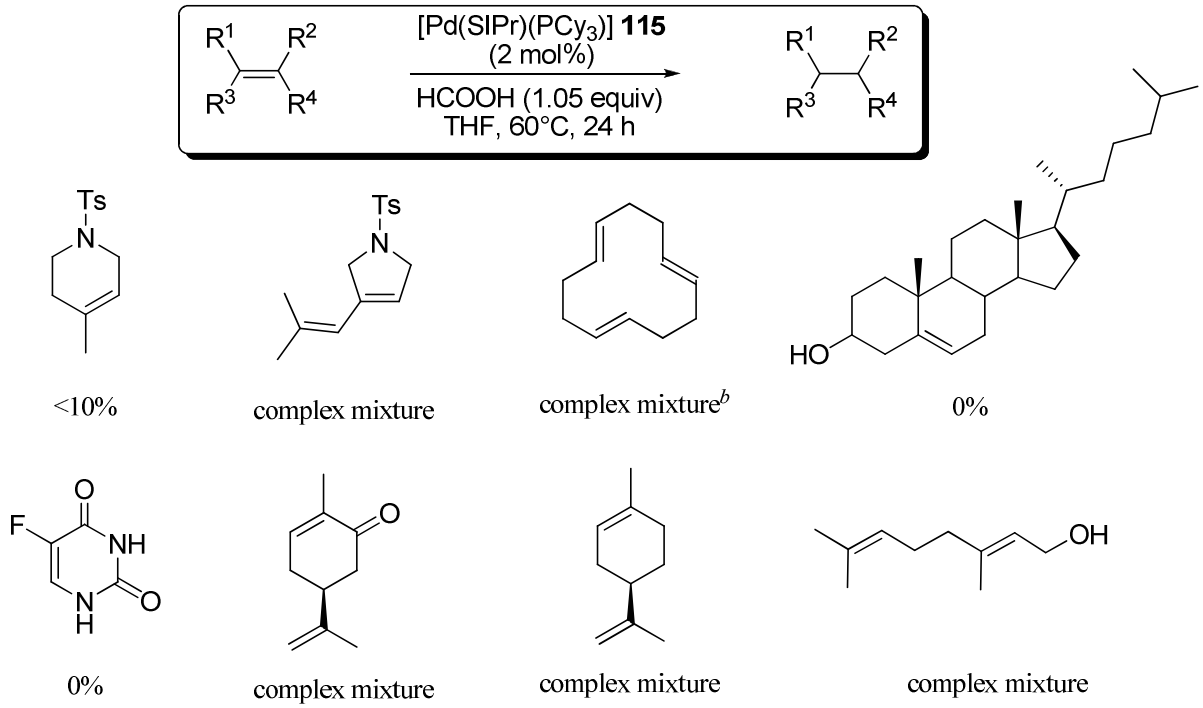
Table 34. Unselective TH associated with the formation side products.[a]



Entry	Substrate	HCOOH (equiv)	Products - ^{1}H NMR Conversions		
1		2.1	67%	10%	23%
		5.0	25%	13%	62%
2		1.05	 84%	 16%	
3		1.05	 92%	 8%	
		2.1	 32%	 68%	
		5.0	 56%	 35%	 9%

[a] Reaction conditions : substrate (0.5 mmol), [Pd(SIPr)(PCy$_3$)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h.

To illustrate the versatility of the present catalyst system, we examined the TH reaction of various challenging unsaturated compounds (Scheme 70), unfortunately without success. Even the previously presented case of 5-fluorouracil failed. Neither hydrogenation of the pyrimidine double bond or reduction of the C-F bond was observed when using 2 mol% of catalyst in THF or in DMF.



Scheme 70. Reaction conditions: substrate (0.5 mmol), HCOOH (0.53 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h. [b] HCOOH (5 equiv).

d) NHC/PR_3-Pd^0-catalyzed transfer semi-hydrogenation with formic acid:

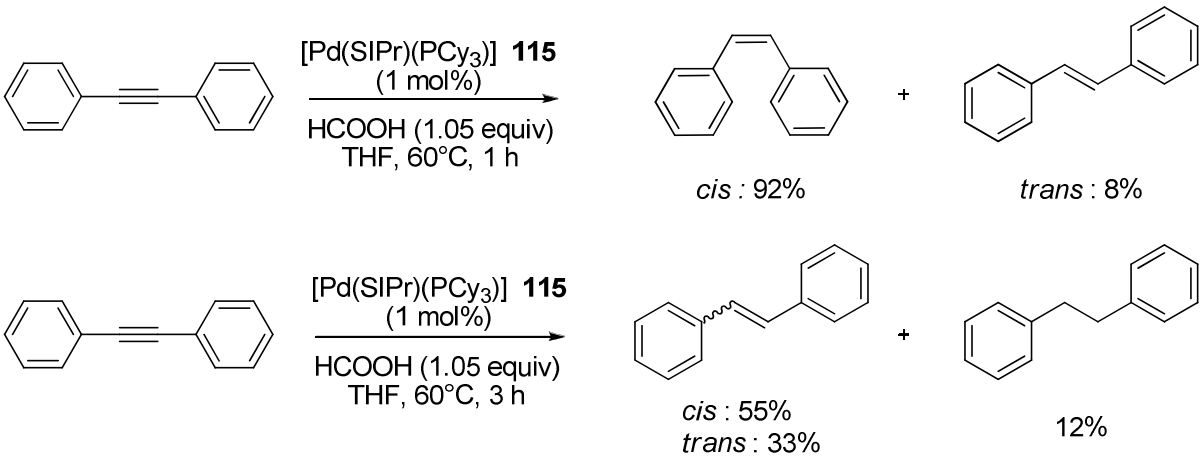
Although several homogeneous catalytic systems are known for the transfer hydrogenation of alkenes, only few have been reported for the transfer semi-hydrogenation of alkynes to alkenes.[355] The main drawback is usually the further hydrogenation of the product alkene to the corresponding alkane. The semi-reduction of alkynes is traditionally performed with Lindlar's catalyst and dihydrogen. This system reduces alkynes to *Z*-alkenes but requires an elaborate experimental setup and strict monitoring of the hydrogen uptake to prevent over-reduction to the alkane. Other drawbacks of this system are partial isomerization of the *Z*-alkene to the *E*-alkene, double-bond shift, and problems of reproducibility.[356] Thus, the development of a general method in combination with an efficient catalyst for this important transformation remains a challenge. Recently, Elsevier and co-workers have reported the first stereo- and chemo-selective semi-reduction of aromatic as well as aliphatic internal alkynes under hydrogen-transfer conditions using a five-fold excess of formic acid/triethylamine as

[355] (a) Boudjouk, P.; Han, B.-H. *J. Catal.* **1983**, *79*, 489-492. (b) Tani, K.; Ono, N.; Okamoto, S.; Sato, F. *J. Chem. Soc. Chem. Commun.* **1993**, 386-387. (c) van Laren, M.W.E.; Elsevier, C.J. *Angew. Chem.* **1999**, *111*, 3926-3929. *Angew. Chem. Int. Ed.* **1999**, *38*, 3715-3717. (d) Sato, F. in *"Handbook of Organopalladium Chemistry for Organic Synthesis"* Negishi, E-.I., Ed.; John Wiley & Sons, Inc.: Hoboken, United States, **2002**, 2759-2765. (e) Kluwer, A.M.; Koblenz, T.S.; Jonischkeit, T.; Woelk, K.; Elsevier, C.J. *J. Am. Chem. Soc.* **2005**, *127*, 15470-15480. (f) Alonso, F.; Osante, I.; Yus, M. *Tetrahedron* **2007**, *63*, 93-102.

[356] (a) Lindlar, H.; *Helv. Chim. Acta* **1952**, *35*, 446-450. (b) Molnár, A.; Sárkány, A.; Varga, M. *J. Mol. Catal. A-Chem.* **2001**, *173*, 185-221.

hydrogen donor.[357] The catalyst for this reaction was proposed to be zero-valent Pd complex generated *in situ* from a Pd^0 precursor and a NHC ligand.

Thus, the activity of the well-defined [Pd(SIPr)(PCy_3)] **115** was also examined in the transfer semi-hydrogenation of diphenylacetylene using only one equivalent of formic acid. We were pleased to observe that, after only 1 h stirring at 60°C, *cis*-stilbene was obtained as the major product (92%) (Scheme 71). Of note, proportions of *trans*-stilbene and diphenylethane slightly increased after prolonged time (3 h). In our case, addition of triethylamine (1.05 equiv) gave a mixture of the three reduced forms after 1 h and with similar *ratio* observed after prolonged times without NEt_3.



Scheme 71. Transfer semi-hydrogenation of diphenylacetylene using formic acid.

<u>e) NHC/PR_3-Pd^0-catalyzed transfer hydrogenation using different sources of hydrogen:</u>

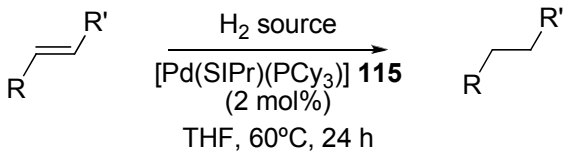
As aforementioned, cyclic alkenes derivatives that are capable of aromatization, such as cyclohexene and 1,3-cyclohexadiene, can donate hydrogen to monosubstituted and disubstituted alkenes using late-transition metal catalysts. During this work, we noticed the abilities of our mixed NHC/PCy_3-Pd^0 system to dehydrogenate some unsaturated substrates leading to the formation of more stable aromatic derivatives. Therefore, we decided to evaluate their activity in TH reactions using these unsaturated compounds as hydrogen source instead of formic acid.

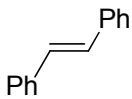
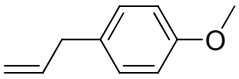
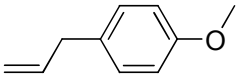
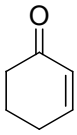
Using 1,4-cyclohexadiene as hydrogen donor,[352] we were able to partially convert *trans*-stilbene and 4-allylanisole into their respective saturated derivatives (Table 35, entries 1-4). Two equivalents of 1,4-cyclohexadiene were necessary to reach 33% of **116** but only one equivalent to afford 31% of 1-methoxy-4-propylbenzene. Surprisingly, while an excess of hydrogen source was favorable for the reduction of *trans*-stilbene, it was disfavorable in the

[357] Hauwert, P.; Maestri, G.; Sprengers, J.W.; Catellani, M.; Elsevier, C.J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3223-3226.

case of 4-allylanisole. Of note, formation of cyclohexane or cyclohexene was hardly observed excluding a competition between the reduction of the substrate and the hydrogen source. The formation of 1-methoxy-4-(prop-1-enyl)benzene, the isomerized derivative of 4-allylanisole, was observed in both cases (*ratio* propylbenzene/prop-1-enylbenzene 60:40) (Table 35, entries 3 and 4). On the other hand, 1-methoxy-4-propylbenzene was obtained as the major product (49%) when two equivalents of cyclohexanone were used (Table 35, entry 6). Only 9% of the isomerized product was detected and 42% of starting material was recovered. Although full conversions could not be reached under these conditions, we have shown that our mixed SIPr/PCy_3-Pd^0 system was able to dehydrogenate 1,4-cyclohexadiene or cyclohexanone and to transfer the extracted hydrogen for the reduction of unsaturated substrates. To the best of our knowledge, we report here the first transfer hydrogenation reactions using such hydrogen donors with homogeneous palladium-catalysts. Only palladium on charcoal or metal oxide catalysts have been used in previously published examples.[352,354] A more thorough study is envisaged in the laboratory in order to define the optimal conditions and the potential of these TH reactions.

Table 35. NHC/NCy_3-Pd^0-catalyzed transfer hydrogenation with different sources of hydrogen.[a]



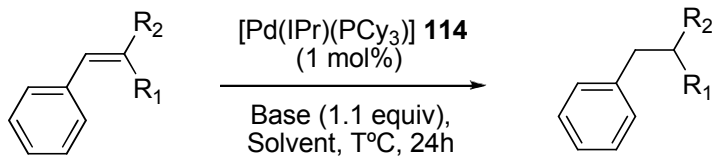
Entry	Substrate	H_2 source (equiv)	Conv. (%)[b]
1		(1)	8
2		(2)	33
3		(1)	31
4		(2)	13
5		 (1)	0
6		(2)	49

[a] Reaction conditions: substrate (0.5 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h. [b] Determined by ^1H NMR.

Primary or secondary alcohols as solvent and hydrogen donor are frequently used in combination with a base and late-transition metal complexes for the hydrogenation of C=X

double bonds such as ketones, aldehydes, imines or alkenes.[326] Recently, ruthenium, rhodium and iridium complexes containing NHC ligands have proven to be efficient catalysts in the transfer hydrogenation of ketones in the presence of 2-propanol.[358] 2-Propanol is easy to use, inexpensive, and environmentally friendly. The generated acetone can also be easily removed to shift any unfavorable equilibrium.[326e] Iridium(I) triazole-based NHC complexes have also showed good activity for transfer hydrogenation on C=O, C=N, and C=C double bonds in 2-propanol with K_2CO_3.[359] Therefore, we were interested in the evaluation of [Pd(SIPr)(PCy_3)] **115** in the transfer hydrogenation of alkenes in alcohols. Unfortunately, our NHC/PCy_3-Pd^0 system did not allow for the reduction of *trans*-stilbene or α-acetamidocinnamic acid when alcohols were used as the hydrogen source. *Iso*propanol and cyclopentanol were unsuccessfully used as hydrogen donors in the presence of different bases at various temperatures.

Table 36. Transfer hydrogenation on C=C double bonds in alcohols.[a]



Entry	Substrate	Base	Solvent	TºC	Conv. (%)[b]
1	R_1= H, R_2= Ph	KO^{t}Bu	^{i}PrOH	60 80	<1 <1
2	R_1= H, R_2= Ph	K_2CO_3	^{i}PrOH	80	<1
3	R_1= H, R_2= Ph	K_2CO_3	cyclopentanol	100	<1
4	R_1= NHCOMe, R_2= COOH	KO^{t}Bu	^{i}PrOH	80	<1
5	R_1= NHCOMe, R_2= COOH	K_2CO_3	^{i}PrOH	80	<1

[a] Reaction conditions: substrate (0.5 mmol), base (0.55 mmol), [Pd(IPr)(PCy_3)] **114** (1 mol%), solvent (2 mL), 24 h. [b] Determined by ^{1}H NMR spectroscopy, average of at least two runs.

[358] (a) Fekete, M.; Joo, F. *Collect. Czech. Chem. Commun.* **2007**, *72*, 1037-1045. (b) Pontes da Costa, A.; Viciano, M.; Sanaú, M.; Merino, S.; Tejeda, J.; Peris, E.; Royo, B. *Organometallics* **2008,** *27*, 1305-1309. (c) Kownacki, I.; Kubicki, M.; Szubert, K.; Marciniec, B. *J. Organomet. Chem.* **2008**, *693*, 321-328. (d) Türkmen, H.; Pape, T.; Hahn, F.E.; Çetinkaya; B. *Organometallics* **2008,** *27*, 571-575. (e) Yang, L.; Krüger, A.; Neels, A.; Albrecht, M. *Organometallics* **2008,** *27*, 3161-3171.

[359] Gnanamgari, D.; Moores, A.; Rajaseelan, E.; Crabtree, R.H. *Organometallics* **2007**, *26*, 1226-1230.

4. CONCLUSIONS AND PERSPECTIVES

Palladium-mediated chemistry is certainly a constantly growing field and applications are numerous in many domains. The development of new efficient and selective palladium catalysts has become, over the past few years, a primordial objective. In this context, well-defined NHC-containing Pd complexes have emerged as indispensable tools in the catalysis of C-C, C-N and C-O bond formations. Nevertheless, certain classes of reactions have been less explored and weaknesses are still encountered in catalytic systems. The great potential of newly developed NHC-based Pd^{II} and Pd^{0} complexes prompted us to evaluate their catalytic activities in two distinct types of reaction: the Buchwald-Hartwig arylation of amines and the transfer hydrogenation of unsaturated compounds.

In the first instance, two saturated NHC-containing *N*,*N*-dimethyl biphenylamine (DMBPA) palladacycle complexes were synthesized and fully characterized. The reactivity of these well-defined, air- and moisture-stable palladium(II) precatalysts was evaluated in the Buchwald-Hartwig amination for a range of unactivated and diverse aryl chlorides.[360] Both aryl and alkyl primary and secondary amines were well tolerated by the [PdCl(Cycle)(SIPr)] complex. Moreover, the catalytic system was found compatible with reactive functions such as carboxylic acid and amide. [PdCl(Cycle)(NHC)] complexes bearing saturated and unsaturated NHCs, did not show any striking differences in term of reactivity. The reactivity of [PdCl(Cycle)(SIPr)] was also tested in the *O*-arylation of phenol with arylbromides and arylchlorides. Unfortunately, no coupling was observed in the tests carried out. In addition, the Suzuki-Miyaura cross coupling using the [PdCl(Cycle)(SIMes)] was applied to the synthesis of the biphenyl ligand employed to synthesize the catalyst.

In the second instance, we assessed of new mixed NHC-phosphane Pd^{0} complexes [Pd(NHC)(PR_3)] in the transfer hydrogenation of C=C double bonds. The reduction of a variety of cyclic and acyclic olefins substrates bearing diverse functional groups was investigated and excellent isolated yields were obtained when using NHC-containing Pd^{0} catalyst and an optimum amount of formic acid. Transfer hydrogenation of internal or terminal alkenes proceeded with moderate to complete conversions. Unexpectedly, an excess of formic acid was crucial to reach complete conversion for some examples. While in other cases, control of the amount of hydrogen allowed for the selective hydrogenation of only one of the two double bonds present in the substrate. However, an important limitation of our

[360] Broggi, J.; Clavier, H.; Nolan, S.P. *Organometallics* **2008**, *27*, 5525-5531.

mixed NHC/PCy_3-Pd^0 system was encountered for the transfer hydrogenation of challenging or aldehyde-containing unsaturated compounds. On the other hand, stereo- and chemoselective transfer semi-hydrogenation of an alkyne to the corresponding *cis*-alkene using only one equivalent of formic acid appeared to be achievable with such well-defined zero-valent Pd complex bearing a NHC ligand. Finally, our mixed NHC/PCy_3-Pd^0 system also proved capable of dehydrogenating cyclic alkenes derivatives that are capable of aromatization and to transfer the extracted hydrogen for the reduction of unsaturated substrates. To the best of our knowledge, we report here the first transfer hydrogenation reactions using such hydrogen donors with homogeneous palladium-catalysts.

These different results raised interesting questions about the mechanism of NHC/PR_3-Pd^0-catalyzed transfer hydrogenation reactions using formic acid as hydrogen source. NMR studies are currently undertaken in our laboratory to determine how the formic acid is added on the catalyst and how the hydrogen is delivered on the double bond.

In general, we hope the accessible synthetic routes presented will facilitate the development of further applications of these NHC-based palladium complexes. For nucleoside syntheses, these well-defined pre-catalysts are likely to be valuable alternative to *in situ* generated phosphine-Pd complexes. In the case of *N*-arylation reactions, in addition to being more stable and practical, they might permit milder reaction conditions and the use of unactivated chloride substrates. Moreover, results have underlined the compatibility of these systems with various functions often encountered in nucleoside chemistry. Potential applications are thus numerous in the field of pharmacomodulations.

5. Résumé du chapitre III:

Complexes contenant un CNH pour des réactions palladocatalysées, des nouveaux outils pour la conception de nucléosides

Les réactions de couplage croisé et les transformations assistées par des complexes organopalladiés se sont particulièrement développées depuis de nombreuses années. Ces réactions régio- et stéréospécifiques permettent de nombreuses modulations et une adaptation à un grand nombre de substrats, ce qui en fait actuellement un outil de choix en chimie des nucléosides (Figure 1).[236-243] Les complexes de palladium sont ainsi utilisés lors de couplages avec différents dérivés organométalliques comme dans les réactions de Stille, de Corriu-Kumada, de Hiyama et de Suzuki-Miyaura. Il existe également des couplages avec des alcynes (réaction de Sonogashira) ou des alcènes (réaction de Heck), et enfin des réactions d'allylations catalysées au Pd^0 (réaction de Tsuji-Trost). Bien que les applications visant à la modification de bases purine ou pyrimidine sont nombreuses et optimisées, elles se sont essentiellement limitées à la formation de liaisons C-C. Parmi toutes les possibilités qu'offrent ces réactions pallado-catalysées, nous nous sommes donc plus particulièrement intéressés à deux types de réactions moins étudiées : la *N*-arylation d'amines de Buchwald-Hartwig et l'hydrogénation par transfert de substrats insaturés. Pour ce faire, deux types de catalyseurs de palladium contenant un ligand CNH nous sont apparus comme de bons candidats pour la synthèse de nouvelles liaisons C-N et C-C.

En effet, ces multiples innovations en synthèse organique n'auraient pas été possibles sans le panel de catalyseurs de palladium à la disposition du chimiste. Pourtant des problèmes persistent et le développement de nouveaux outils plus efficace et versatile est de ce fait constamment sollicité. Au même titre que l'efficacité et la rapidité, la sélectivité est devenue un paramètre incontournable dans la liste de compétences d'un catalyseur. Dans cette perspective, nous nous sommes intéressés à cette récente classe de catalyseurs homogènes et bien définis: les complexes de palladium-CNH.[286] Ces derniers ont montré de meilleurs activités catalytiques que leurs analogues générés *in situ*.[287] De plus, les catalyseurs palladiés contenant un ligand CNH ont prouvé être d'excellente alternative aux systèmes catalytiques impliquant des phosphines tertiaires.[288] De part leur caractère σ-donneur, les ligands CNH permettent la synthèse de catalyseur au palladium bien définis et stable à l'eau et l'air.

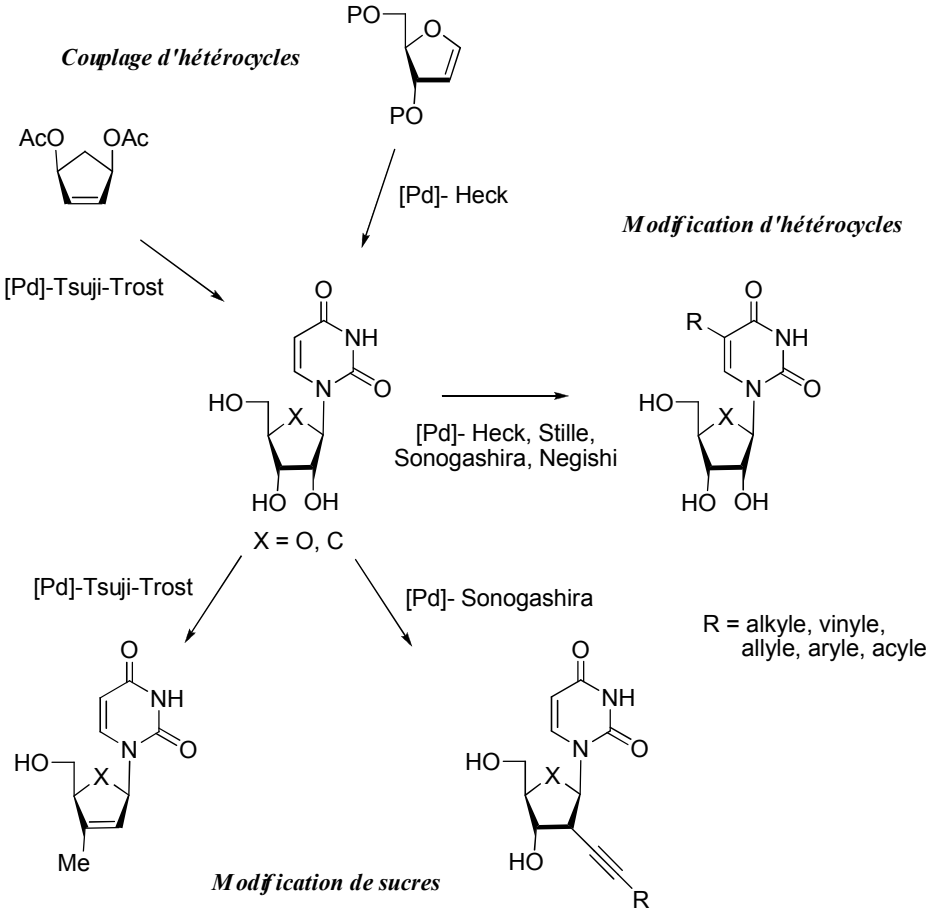


Figure 1. Principales réactions de modifications nucléosidiques assistées par un catalyseur de palladium.

Dans une première partie, nous avons donc préparé deux nouveaux précatalyseurs CNH-palladium(II) bien définis, stable à l'eau et à l'air (Schéma 10). Les complexes combinant les propriétés σ-donneuses et stériques des CNH avec la stabilité reconnue des structures palladacycles[296] ont déjà prouvé leur efficacité dans des réactions de Buchwald-Hartwig, d'arylation de α-cétones, de couplage de Suzuki-Miyaura ou de déhalogénation.[297,299,300,301] La réaction menant aux complexes [PdCl(Cycle)(SIMes)] (**107**) et [PdCl(Cycle)(SIPr)] (**108**) consistait en une coordination du CNH au centre palladium et un clivage du dimère $[PdCl(Cycle)]_2$ par deux équivalents de ligand CNH, tel SIMes ou SIPr. Les espèces attendus [PdCl(Cycle)(NHC)] à 16 électrons ont été obtenus avec des rendements bons à excellents.

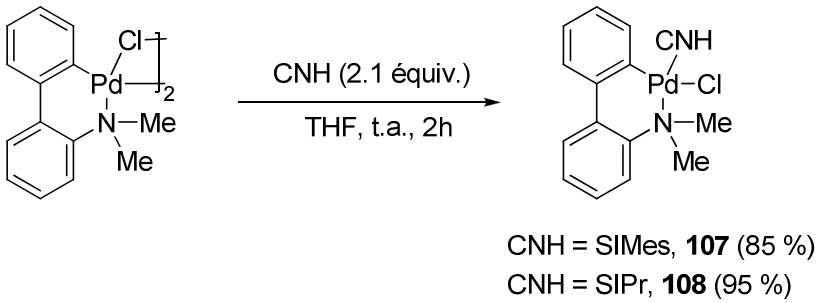


Schéma 10. Synthèse des complexes au palladium **107** et **108**.

Les activités catalytiques de ces nouveaux complexes saturés CNH-palladacycle ont été évaluées dans la réaction de *N*-arylation d'amines de Buchwald-Hartwig. L'optimisation des conditions réactionnelles a montré que le système catalytique [PdCl(Cycle)(SIPr)] (**108**) procédait efficacement en présence d'une base forte telle KO^{t}Bu et dans le DME à 50°C. Ces paramètres se sont avérés plus avantageux que ceux précédemment déterminés pour les couplages de Buchwald-Hartwig catalysés par des palladacycles.[299] Ces conditions réactionnelles optimisées ont ensuite été appliquées avec succès à la synthèse d'un large panel d'amines *N*-arylées (Schéma 11). La majorité des réactions d'amination ont été réalisées avec de bonnes conversions CG et dans des temps réactionnels courts donnant lieu à de très bons rendements. Des chlorures d'aryles activés, neutres ou non-activés, ainsi que des chlorures hétéroaromatiques, ont pu être facilement couplés aux différents substrats aminés qu'ils soient encombrés stériquement ou non. De plus notre système catalytique s'est avéré tolérant à de nombreux groupements fonctionnels. En présence de deux équivalents de base, le complexe **108** a catalysé l'amination de composés de type morpholinobenzène portant des groupements électro-attracteurs tel un acide carboxylique ou une amide, des éléments important dans la synthèse de nouveaux médicaments.[312] L'efficacité et la versatilité du complexe de palladium(II) [PdCl(Cycle)(SIPr)] **108** pour la réaction de Buchwald-Hartwig nous a également mené à tester son activité catalytique dans la réaction de *O*-arylation de phénols moins explorée et plus délicate que la *N*-arylation d'amines. Malheureusement, quelque soit les conditions réactionnelles et le type d'aryles utilisés, notre système CNH-palladacycle n'a pas été capable de catalyser la formation de liaison carbone-oxygène.

Economiquement et industriellement parlant, les conditions réactionnelles obtenues avec ces systèmes [(CNH)Pd(palladacycle)Cl] sont très attractives. Cependant la synthèse du ligand palladacycle biphényle requiert des conditions difficiles et/ou donne de faible rendement, un obstacle important pour une large application. En vue d'une méthode plus commode, nous avons entrepris d'utiliser nos nouveaux complexes de palladium(II) **107** et **108** dans la préparation du ligand *N*,*N*-diméthylbiphényl-2-amine *via* couplage croisé de Suzuki-Miyaura (Schéma 12). En plus d'être une application catalytique originale, cet exemple représente une stratégie peu commune : *l'utilisation d'un catalyseur en tant qu'outil dans la synthèse d'un composé biaryle qui est une partie organique de ce même catalyseur*. Parmi les différents catalyseurs au palladium testés dans cette réaction de couplage, les séries (CNH)Pd-cycle, -allyle,[292] et -cinnamyle[293] ont montré les résultats les plus intéressants, et plus particulièrement les dérivés saturés. Lors de cette réaction de Suzuki-Miyaura, le problème de formation d'un sous produit, issu de la déhalogénation du produit de départ **109**,

a pu être contourné en utilisant le complexe [PdCl(Cycle)(SIMes)] (**107**) dans l'*iso*propanol en présence d'hydroxyde de potassium. Le ligand **110** a été synthétisé en grande quantité avec un rendement de 88% après 16 h à 50°C.

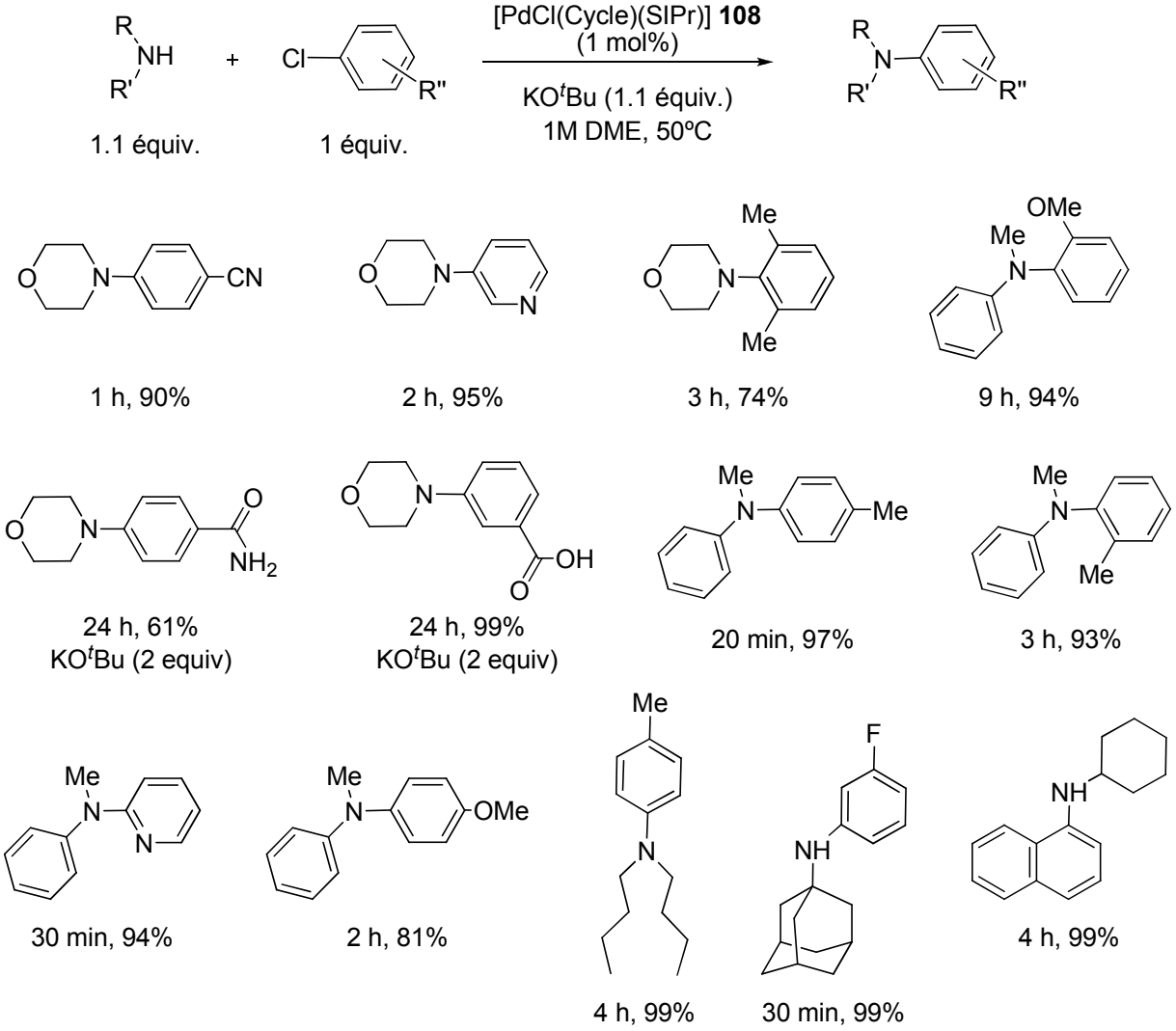


Schéma 11. Réaction de *N*-arylation de Buchwald-Hartwig sur différentes amines.

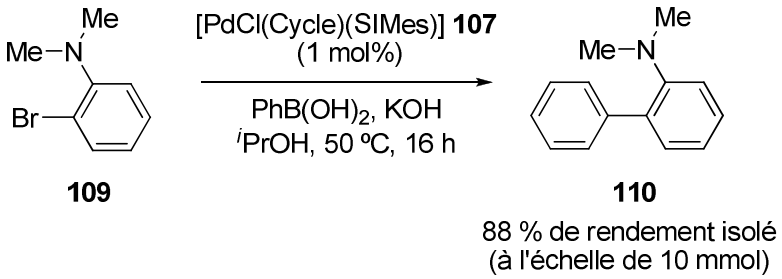


Schéma 12. Synthèse en grande quantité du ligand *N*,*N*-diméthylbiphényl-2-amine **110**.

Dans une seconde partie, le potentiel de nouveaux complexes de palladium(0) homogènes et dicoordinés par un ligand CNH et une phosphine a été examiné pour des

réactions d'hydrogénation d'alcènes par transfert. L'acide formique a été utilisé comme source d'hydrogène dans cette étude. Les catalyseurs bien-définis au Pd^0 permettent d'éviter l'étape de reduction *in situ* d'un précuseur de Pd^{II}, souvent source de décomposition de l'espèce active en palladium noir.[335] L'équipe du Pr Nolan a récemment préparé un nouveaux type de complexes [(CNH)Pd(PR_3)] combinant les propriétés σ-donneuses des ligands CNH avec les propriétés stabilisatrices des phosphines tertiaires (PR_3).[339] Parmi les divers complexes au Pd^0 mixtes, [Pd(IPr)(PCy_3)] (**114**) et [Pd(SIPr)(PCy_3)] (**115**) ont été choisis dans le cadre de ce projet et préparés avec de très bons rendements selon la méthode reportée (Schéma 13).[339]

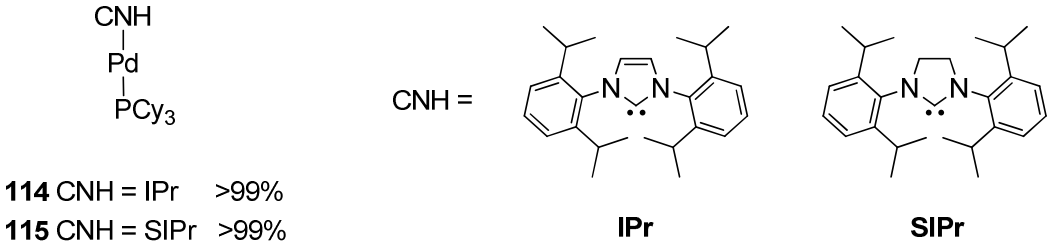


Schéma 13. Complexes de palladium(0) **114** et **115**.

L'activité catalytique de ces deux complexes au Pd^0 mixant CNH et phosphine a été évaluée dans la réaction de réduction de liaisons carbone-carbone de différentes oléfines par hydrogénation par transfert. Les conditions réactionnelles optimales déterminées à partir de la réduction du *trans*-stilbène ont montré qu'il était plus approprié de conduire cette réaction catalysée par [Pd(SIPr)(PCy_3)] **115** dans le THF à 60°C en présence d'un seul équivalent d'acide formique. Ces dernières appliquées à l'hydrogénation par transfert de divers substrats contenant une double liaison C=C ont permis la synthèse des composés saturés correspondant avec des conversions allant de faible à totale (Schéma 14). D'excellents rendements ont été obtenus lors de la réduction d'oléfines cycliques ou acycliques portant un groupement fonctionnel tel un acide, un ester, une cétones ou un nitrile. Curieusement, le dérivé chloré n'a pu être hydrogéné. Tandis que la réducion des alcènes terminaux ou internes a procédé efficacement, l'hydrogénation des doubles liaisons tri- ou tetra-substituées a été problèmatique et seulement de faibles conversions ont été mesurées. Le contrôle de la quantité théorique d'hydrogène a permis l'hydrogénation sélective de seulement une des deux liaisons du 1,3-cyclooctadiéne. Une importante limitation de notre système catalytique mixte CNH/PCy_3-Pd^0 a été observée lors de la tentative de réduction de composés insaturés plus challenging ou contenant un aldéhyde. Selon le cas, aucune réaction ou un mélange complexe ont été obtenus.

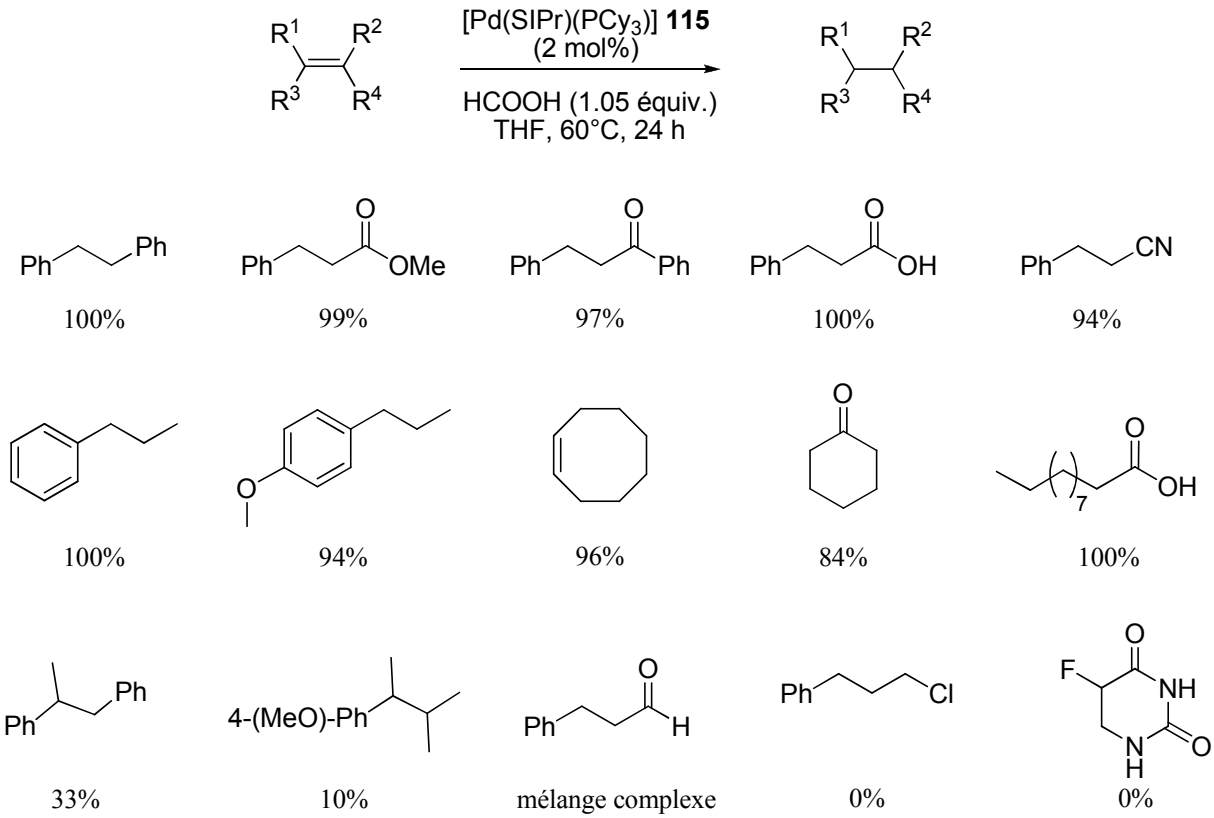
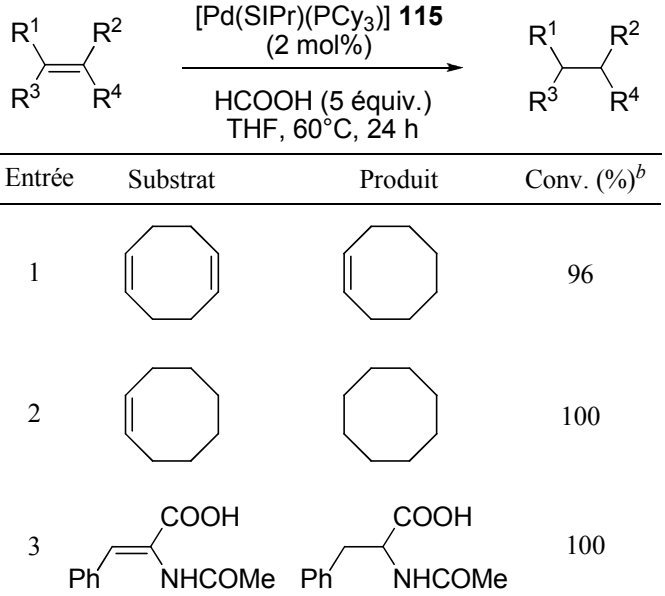


Schéma 14. Hydrogénation par transfert de diverses oléfines. (Les conversions obtenues par chromatographie gaz sont indiquées entre parenthèse).

De manière inattendue, un excès d'acide formique s'est avéré nécessaire dans certains cas pour obtenir une conversion complète (Tableau 2). L'acide α-acétamidocinnamique (tri-substitué), le 1,5-cyclooctadiéne et le cyclooctène n'ont pu être hydrogéné quantitativement que lorsque cinq équivalents de HCOOH étaient employés.

Bien que plusieurs systèmes catalytiques homogènes sont connus pour l'hydrogénation par transfert d'alcène, seulement quelques exemples ont été reportés pour la semi-hydrogénation par transfert d'alcynes en alcènes.[355] Nous avons donc également testé l'activité de [Pd(SIPr)(PCy_3)] **115** pour la semi-hydrogénation du diphéylacétylène (Schéma 15). Après seulement 1 h d'agitation à 60°C et en présence de seulement un équivalent d'acide formique, le *cis*-stilbène a été obtenu comme le produit majoritaire (92%). Les formations du *trans*-stilbène et du diphényléthane sont observées si le temps de la réaction est prolongé.

Tableau 2. Cas particulier d'hydrogénation par transfert nécessitant cinq équivalents d'acide formique.[a]



Entrée	Substrat	Produit	Conv. (%)[b]
1			96
2			100
3			100

[a] Conditions réactionnelles : substrat (0.5 mmol), HCOOH (2.5 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h. [b] Determiné par CG, moyenne d'au moins deux essais.

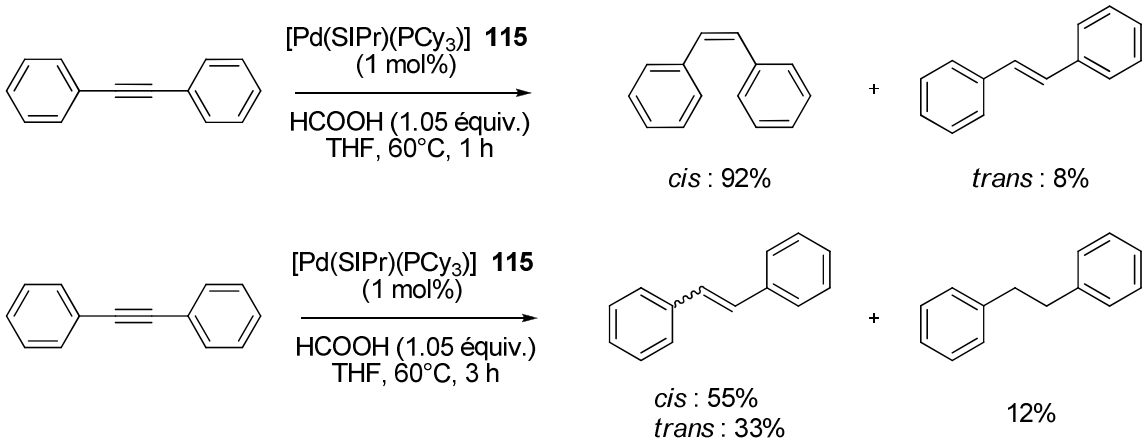
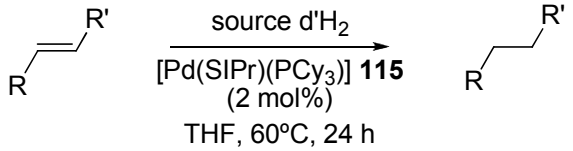


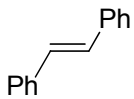
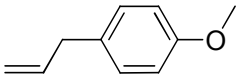
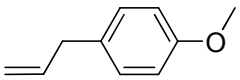
Schéma 15. Semi-hydrogénation par transfert du diphénylacétylène.

Au cours de cette etude, nous avons également remarqué que notre système dicoordiné CNH/PCy_3-Pd^0 était capable de déhydrogéné des alcènes cycliques en leurs dérivés aromatiques et de transférer l'hydrogène extrait pour la réduction de substrats insaturés. Nous avons donc évalué l'activité de **115** dans l'hydrogénation d'oléfines avec le 1,4-cyclohexadiène ou la 2-cyclohexèn-1-one comme source d'hydrogène (Tableau 3). Dans chaque cas, le *trans*-stilbène et le 4-allylanisole ont été partiellement convertis en leurs dérivés saturés respectifs. A notre connaissance, nous reportons ici les premières réactions d'hydrogénation par transfert employant de tels donneurs d'hydrogène et catalysées par un

catalyseur au palladium homogène. Finalement, des alcools primaires ont également été utilisés à la fois comme solvants et donneurs d'hydrogène en combinaison avec une base et notre complexe au palladium(0) pour l'hydrogénation de double liaisons C=C. Malheuresement, le système catalytique CNH/PCy_3-Pd^0 n'a pas permit la réduction d'alcènes dans un alcool.

Tableau 3. Hydrogénation par transfert avec différentes sources d'hydrogène.



Entrée	Substrat	source d'H_2 (équiv.)	Conv. (%)[b]
1		(1)	8
2		(2)	33
3		(1)	31
4		(2)	13
5		(1)	0
6		(2)	49

[a] Conditions réactionnelles: substrat (0.5 mmol), [Pd(SIPr)(PCy_3)] **115** (2 mol%), THF (2 mL), 60ºC, 24 h. [b] Determiné par ^{1}H RMN.

Ces dernières années, le développement de nouveaux catalyseurs au palladium plus efficaces et sélectifs est devenu un objectif primordial pour la formation de liaisons C-C, C-N ou C-O. Dans ce contexte, nous avons préparés de nouveaux complexes bien-définis contenant un ligand carbène *N*-hétérocyclique et nous avons testé leurs aptitudes dans deux types de réactions catalysées au palladium : la *N*-arylation d'amines de Buchwald-Hartwig et l'hydrogénation par transfert de composés insaturés. Les complexes palladacycles saturés, stable à l'air et à l'humidité, ont fourni une excellente activité catalytique dans le couplage de diverses amines et chlorures d'aryles. De plus, la réaction de couplage croisé de Suzuki-Miyaura a été appliquée à la préparation du ligand biphényle utilisé dans la synthèse du catalyseur. Malgrès quelques limitations, les complexes au palladium(0) mixtes CNH-posphine ont quant à eux montré d'intéressantes aptitudes dans la réduction d'alcènes terminaux ou fonctionalisés par hydrogénation par transfert.

Chapter III:

NHC-containing complexes in palladium-catalyzed reactions, new insights for nucleoside synthetic strategy

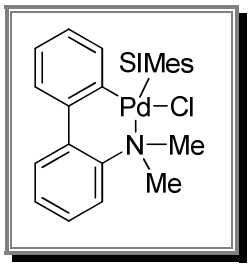
Experimental section

General methods

All reactions were performed under an inert atmosphere of argon or nitrogen using standard high-vacuum or Schlenk techniques or in an MBraun glovebox containing less than 1 ppm oxygen and water. Solvents were distilled from appropriate drying agents or were dispensed from a solvent purification system from Innovative Technology, other anhydrous solvents were purchased from Aldrich and degassed prior to use by purging with dry argon and were kept over molecular sieves. Flash column chromatography was performed on silica gel 60 (230-400 mesh). ^{1}H and ^{13}C, ^{19}F Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 Ultrashield NMR spectrometer. Gas Chromatography analyses were performed on an Agilent 6890 apparatus equipped with a flame ionization detector and a silicon column (30 m, 320 µm, film thickness: 0.25 µm). GC-MS spectra were recorded on GC MS Agilent 5973 equipped with a Electronic Ionization chamber (E.I). HRMS analyses were performed by the Mass Spectrometry Facility of the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain). Elemental analyses were performed at the Universidad Complutense de Madrid. The CIF files of crystal structures **107** and **108** have been deposited with the CCDC, No. CCDC-688389 and 688388, respectively Copies of the data can be obtained free of charge on applications to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336 033; http://www.ccdc.cam.ac.uk; e-mail: deposit@ccdc.cam.ac.uk.

2. NHC-CONTAINING *N-C*-PALLADACYCLE COMPLEXES IN CROSS-COUPLING REACTIONS

[PdCl(Cycle)(SIMes)] (107)



Procedure:

In a glovebox, a scintillation vial was charged with a stirring bar, 135 mg (0.2 mmol) of palladacycle dimer, 130 mg (0.42 mmol) of SIMes and 10 mL of dry THF. The reaction mixture was stirred for 2 h at room temperature. Outside of the glovebox, the reaction mixture was filtered over a plug of celite and solvent was evaporated *in vacuo*. The remaining solid was triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane. 220 mg (85% yield) of a white off solid were obtained.

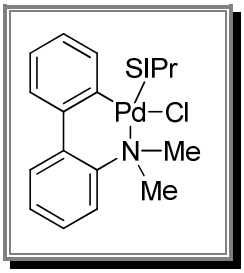
^{1}H NMR: (400 MHz, CD_2Cl_2) δ 7.25 (d, ^{3}J(H,H) = 6.8 Hz, 1H, H^{Ar}), 7.16 (dt, ^{3}J(H,H) = 7.7 Hz, ^{4}J(H,H) = 1.6 Hz, 1H, H^{Ar}), 7.11-7.07 (m, 2H, H^{Ar}), 7.04-6.99 (m, 1H, H^{Ar}), 6.97-6.90 (m, 5H, H^{Ar}), 6.48 (s, 2H, H^{Ar}), 4.02-3.97 (m, 1H, CH_2-CH_2), 3.94-3.83 (m, 1H, CH_2-CH_2), 3.74-3.69 (m, 2H, CH_2-CH_2), 2.90 (s, 3H, CH_3-N), 2.80 (s, 3H, CH_3-N), 2.53 (s, 3H, CH_3^{Mes}), 2.41 (s, 3H, CH_3^{Mes}), 2.36 (s, 3H, CH_3^{Mes}), 2.26 (s, 3H, CH_3^{Mes}), 2.17 (s, 3H, CH_3^{Mes}), 1.52 (s, 3H, CH_3^{Mes}).

^{13}C NMR: (100 MHz, CD_2Cl_2) δ 198.2 (C, N-*C*-N), 152.0 (C, C^{Ar}), 147.2 (C, C^{Ar}), 142.2 (C, C^{Ar}), 140.4 (C, C^{Ar}), 138.5 (C, C^{Ar}), 137.4 (C, C^{Ar}), 137.2 (CH, C^{Ar}), 137.1 (C, C^{Ar}), 136.6 (C, C^{Ar}), 136.4 (C, C^{Ar}), 136.0 (C, C^{Ar}), 135.4 (C, C^{Ar}), 135.3 (C, C^{Ar}), 129.6 (CH, C^{Ar}), 129.5 (CH, C^{Ar}), 129.3 (CH, C^{Ar}), 128.8 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 125.1 (CH, C^{Ar}), 124.1 (CH, C^{Ar}), 124.0 (CH, C^{Ar}), 115.9 (CH, C^{Ar}), 52.6 (CH_2, CH_2-CH_2), 51.1 (CH_3, CH_3-N), 50.4 (CH_2, CH_2-CH_2), 49.9 (CH_3, CH_3-N), 20.7 (CH_3, C^{Mes}), 20.5 (CH_3, C^{Mes}), 19.8 (CH_3, C^{Mes}), 17.5 (CH_3, C^{Mes}).

HRMS (ESI): *m/z* calcd for $C_{35}H_{40}N_3Pd$ (M^+ - Cl) 608.2257, found 608.2237.

Elemental analysis: calcd (%) for $C_{35}H_{40}N_3ClPd$ (644.59): C 65.22, H 6.25, N 6.52; found: C 65.09, H 6.46, N 6.47.

[PdCl(Cycle)(SIPr)] (108)



Procedure:

In a glovebox, a scintillation vial was charged with a stirring bar, 405 mg (0.6 mmol) of palladacycle dimer, 500 mg (1.26 mmol) of SIPr, and 20 mL of dry THF. The reaction mixture was stirred 2 h at room temperature. Outside of the glovebox, the reaction mixture was filtrated over a plug of celite and solvent was evaporated *in vacuo*. The remaining solid was triturated with pentane and the precipitate was collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane. 830 mg (95% yield) of a white off solid were obtained.

^{1}H NMR: (400 MHz, CD_2Cl_2) δ 7.44 (t, ^3J(H,H) = 7.5 Hz, 1H, H^{Ar}), 7.35 (d, ^3J(H,H) = 7.2 Hz, 1H, H^{Ar}), 7.28 (d, ^3J(H,H) = 7.4 Hz, 1H, H^{Ar}), 7.17-7.11 (m, 3H, H^{Ar}), 7.03-6.95 (m, 4H, H^{Ar}), 6.86-6.83 (m, 3H, H^{Ar}), 6.69 (d, ^3J(H,H) = 7.4 Hz, 1H, H^{Ar}), 4.19-4.10 (m, 2H, C*H*(CH_3)$_2$), 4.04-3.97 (m, 2H, CH_2-CH_2), 3.87-3.82 (m, 2H, CH_2-CH_2), 3.27 (septet, ^3J(H,H) = 6.6 Hz, 1H, C*H*(CH_3)$_2$), 2.86 (s, 3H, CH_3-N), 2.60 (septet, ^3J(H,H) = 6.4 Hz, 1H, C*H*(CH_3)$_2$), 2.06 (s, 3H, CH_3-N), 1.70 (d, ^3J(H,H) = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.58 (d, ^3J(H,H) = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.44 (d, ^3J(H,H) = 6.7 Hz, 3H, CH(CH_3)$_2$), 1.30 (d, ^3J(H,H) = 6.7 Hz, 3H, CH(CH_3)$_2$), 1.08 (d, ^3J(H,H) = 6.5 Hz, 3H, CH(CH_3)$_2$), 0.98 (d, ^3J(H,H) = 6.5 Hz, 3H, CH(CH_3)$_2$), 0.93 (d, ^3J(H,H) = 6.2 Hz, 3H, CH(CH_3)$_2$), 0.47 (d, ^3J(H,H) = 6.3 Hz, 3H, CH(CH_3)$_2$).

^{13}C NMR: (100 MHz, CD_2Cl_2) δ 200.6 (C, N-*C*-N), 152.7 (C, C^{Ar}), 148.2 (C, C^{Ar}), 147.8 (C, C^{Ar}), 147.2 (C, C^{Ar}), 145.7 (C, C^{Ar}), 145.6 (C, C^{Ar}), 142.9 (C, C^{Ar}), 141.6 (C, C^{Ar}), 138.0 (C, C^{Ar}), 136.8 (C, C^{Ar}), 135.9 (CH, C^{Ar}), 129.6 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 126.7 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 125.3 (CH, C^{Ar}), 124.7 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 124.4 (CH, C^{Ar}), 123.5 (CH, C^{Ar}), 122.8 (CH, C^{Ar}), 116.2 (CH, C^{Ar}), 55.5 (CH_2, CH_2-CH_2), 52.7 (CH_2, CH_2-CH_2), 50.6 (CH_3, CH_3-N), 50.3 (CH_3, CH_3-N), 29.0 (CH, *C*H(CH_3)$_2$), 28.7

(CH, *C*H(CH_3)$_2$), 28.3 (CH, *C*H(CH_3)$_2$), 28.2 (CH, *C*H(CH_3)$_2$), 27.2 (CH_3, CH(*C*H_3)$_2$), 26.9 (CH_3, CH(*C*H_3)$_2$), 26.0 (CH_3, CH(*C*H_3)$_2$), 25.5 (CH_3, CH(*C*H_3)$_2$) 24.7 (CH_3, CH(*C*H_3)$_2$), 24.1 (CH_3, CH(*C*H_3)$_2$), 23.3 (CH_3, CH(*C*H_3)$_2$), 22.9 (CH_3, CH(*C*H_3)$_2$).

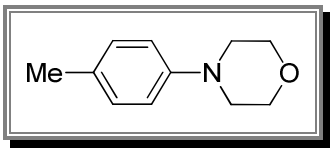
HRMS (ESI): *m/z* calcd for $C_{41}H_{52}N_3Pd$ (M^+ - Cl) 692.3196, found 692.3178.

Elemental analysis: calcd (%) for $C_{41}H_{52}N_3ClPd$ (728.74): C 67.57, H 7.19, N 5.77; found: C 67.74, H 6.91, N 5.60.

General Procedure for the Buchwald-Hartwig Cross-Coupling Reaction

In a glovebox, to a screw cap septum vial equipped with a magnetic stirring bar were added in turn [PdCl(Cycle)(SIPr)] **108** (1 mol%, 7.3 mg), potassium *tert*-butoxide (1.1 mmol, 120 mg), and anhydrous DME (1 mL). Outside the glovebox, the amine (1.1 mmol) and the aryl chloride (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was, before loading of the solvent, charged in the vial inside the glovebox. The reaction mixture was then stirred at 50ºC. When the reaction reached completion, or no further conversion was observed by gas chromatography, the volatiles were removed *in vacuo*.

4-p-tolylmorpholine (Table 20, entry 1)



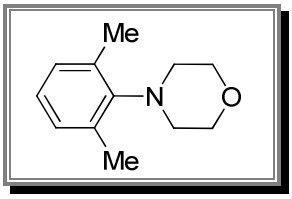
Procedure:

The general procedure followed by silica gel chromatography (DCM) afforded 320 mg (91%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.09 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 6.83 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 3.86 (t, 4H, *J* = 4.0 Hz, O-CH_2), 3.11 (t, 4H, *J* = 4.0 Hz, N-CH_2), 2.28 (s, 3H, CH_3).

CAS: 3077-16-5.

N-(2,6-Dimethylphenyl)morpholine (Table 20, entry 2)



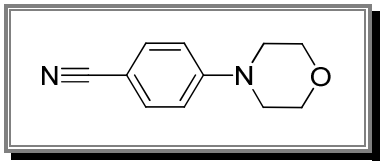
Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 8/2) afforded 140 mg (74%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.02-6.95 (m, 3H, H^{Ar}), 3.80 (t, 4H, *J* = 4.0 Hz, O-CH_2), 3.10 (t, 4H, *J* = 4.0 Hz, N-CH_2), 2.35 (s, 6H, CH_3).

CAS: 255835-91-7.

N-(4-Cyanophenyl)morpholine (Table 20, entry 3)



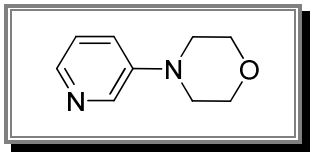
Procedure:

The general procedure followed by silica gel chromatography (DCM) afforded 170 mg (90%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.51 (dt, 2H, *J* = 8.0 and 4.0 Hz, H^{Ar}), 6.86 (dt, 2H, *J* = 8.0 and 4.0 Hz, H^{Ar}), 3.85 (t, 4H, *J* = 4.0 Hz, O-CH_2), 3.28 (t, 4H, *J* = 4.0 Hz, N-CH_2).

CAS: 10282-31-2.

N-(3-Pyridyl)morpholine (Table 20, entry 4)



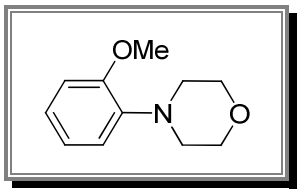
Procedure:

The general procedure followed by silica gel chromatography (EtOAc/MeOH 98:2) afforded 152 mg (95%) of the title compound as a clear volatile liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.31 (s, 1H, H^{Ar}), 8.14 (t, 1H, *J* = 3.0 Hz, H^{Ar}), 7.18 (t, 2H, *J* = 3.0 Hz, H^{Ar}), 3.88 (t, 4H, *J* = 4.8 Hz, O-CH_2), 3.19 (t, 4H, *J* = 4.8 Hz, N-CH_2).

CAS: 92670-29-6.

N-(2-Methoxyphenyl)morpholine (Table 20, entry 5)



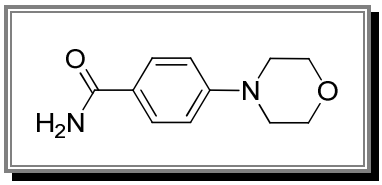
Procedure:

The general procedure followed by silica gel chromatography (DCM) afforded 130 mg (68%) of the title compound as a clear volatile liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.04-6.99 (m, 1H, H^{Ar}), 6.94 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 6.88 (d, 1H, *J* = 8.0 Hz, H^{Ar}), 3.90 (t, 4H, *J* = 4.0 Hz, O-CH_2), 3.87 (s, 3H, CH_3), 3.07 (t, 4H, *J* = 4.0 Hz, N-CH_2).

CAS: 27347-13-3.

4-Morpholinobenzamide (Table 20, entry 8)



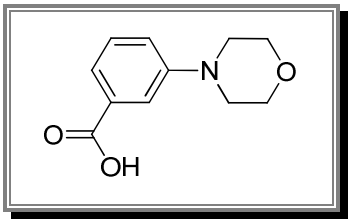
Procedure:

The general procedure was followed using potassium *tert*-butoxide (2.2 mmol, 240 mg) and anhydrous DME (2 mL). The reaction mixture was then dissolved in 30 mL of EtOAc and washed once with a 0.1N HCl solution (20 mL). After adjusting the pH to 5 with a 3N NaOH solution, the aqueous phase was extracted six times with EtOAc. Subsequent flash chromatography on silica gel (EtOAc/MeOH 9:1) afforded 128 mg (61%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, DMSO-d^6) δ 7.76 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 7.71 (bs, 1H, N*H*H), 7.02 (bs, 1H, NH*H*), 6.94 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 3.73 (t, 4H, *J* = 4.0 Hz, O-CH_2), 3.20 (t, 4H, *J* = 4.0 Hz, N-CH_2).

CAS: 183557-77-9.

3-Morpholinobenzoic acid (Table 20, entry 9)



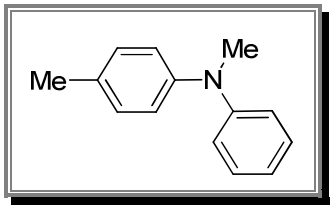
Procedure:

The general procedure was followed using potassium *tert*-butoxide (2.2 mmol, 240 mg) and anhydrous DME (2 mL). The reaction mixture was then dissolved in 30 mL of EtOAc and washed once with a 0.1N HCl solution (20 mL). After adjusting the pH to 5 with a 3N NaOH solution, the aqueous phase was extracted six times with EtOAc. Subsequent flash chromatography on silica gel (EtOAc/MeOH 9:1) afforded 207 mg (>99%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, CD_3OD) δ 7.59 (s, 1H, H^{Ar}), 7.51 (d, 1H, *J* = 8.0 Hz, H^{Ar}), 7.34 (t, 1H, *J* = 8.0 Hz, H^{Ar}), 7.20 (dd, 1H, *J* = 8.0 and 1.9 Hz, H^{Ar}), 3.84 (t, 4H, *J* = 4.0 Hz, O-CH_2), 3.18 (t, 4H, *J* = 4.0 Hz, N-CH_2).

CAS: 215309-00-5.

N-Methyl-*N*-*p*-tolylaniline (Table 21, entry 1)



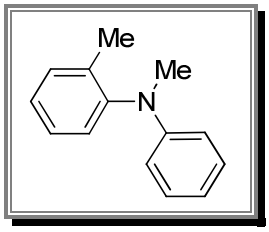
Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 98/2) afforded 192 mg (97%) of the title compound as a clear liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H, H^{Ar}), 7.12-7.10 (m, 2H, H^{Ar}), 7.00-6.98 (m, 2H, H^{Ar}), 6.92-6.90 (m, 2H, H^{Ar}), 6.86 (tt, 1H, *J* = 7.3 and 1.0 Hz, H^{Ar}), 3.28 (s, 3H, N-CH_3), 2.32 (s, 3H, CH_3).

CAS: 38158-65-5.

N-Methyl-*N*-(2-methylphenyl)aniline (Table 21, entry 2)



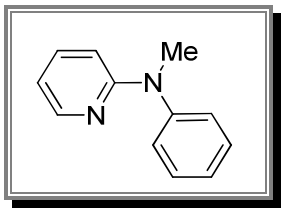
Procedure:

The general procedure followed by silica gel chromatography (Pentane) afforded 184 mg (93%) of the title compound as a clear liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.22-7.13 (m, 6H, H^{Ar}), 6.70 (t, 1H, *J* = 7.4 Hz, H^{Ar}), 6.52 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 3.22 (s, 3H, N-CH_3), 2.14 (s, 3H, CH_3).

CAS: 6590-44-9.

2-(*N*-Methylanilino)pyridine (Table 21, entry 3)



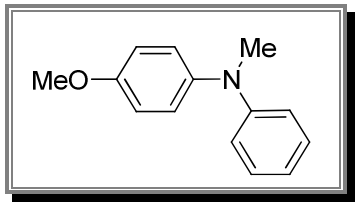
Procedure:

The general procedure followed by silica gel chromatography (DCM) afforded 170 mg (94%) of the title compound as a clear liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.22 (ddd, 1H, *J* = 5.0, 1.9 and 0.8 Hz, H^{Ar}), 7.41-7.37 (m, 2H, H^{Ar}), 7.32-7.19 (m, 4H, H^{Ar}), 6.60 (ddd, 1H, *J* = 7.0, 5.0 and 0.8 Hz, H^{Ar}), 6.52 (d, 1H, *J* = 8.5 Hz, H^{Ar}), 3.47 (s, 3H, N-CH_3).

CAS: 62093-17-8.

N-Methyl-*N*-phenyl-4-methoxyaniline (Table 21, entry 4)



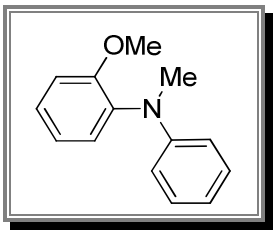
Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 5/5) afforded 170 mg (81%) of the title compound as a clear liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.21-7.17 (m, 2H, H^{Ar}), 7.10-7.07 (m, 2H, H^{Ar}), 6.91-6.88 (m, 2H, H^{Ar}), 6.80-6.76 (m, 3H, H^{Ar}), 3.81 (s, 3H, O-CH_3), 3.25 (s, 3H, N-CH_3).

CAS: 55251-46-2.

N-Methyl-*N*-phenyl-2-methoxyaniline (Table 21, entry 5)



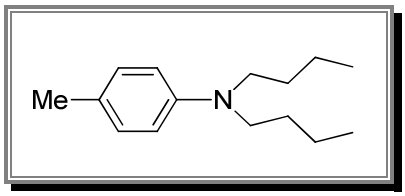
Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 5/5) afforded 200 mg (94%) of the title compound as a clear liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.23-7.14 (m, 4H, H^{Ar}), 7.00-6.95 (m, 2H, H^{Ar}), 6.71 (t, 1H, *J* = 8.0 Hz, H^{Ar}), 6.65 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 3.78 (s, 3H, O-CH_3), 3.22 (s, 3H, N-CH_3).

CAS: 263917-74-4.

Dibutyl(4-tolyl)amine (Table 22, entry 1)



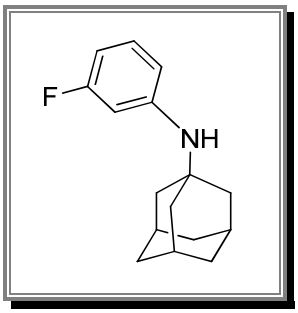
Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 8/2) afforded 218 mg (99%) of the title compound as a clear liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 6.57 (d, 2H, *J* = 8.0 Hz, H^{Ar}), 3.22 (t, 4H, *J* = 7.6 Hz, N-CH_2), 2.23 (s, 3H, CH_3), 1.58-1.50 (m, 4H, CH_2), 1.38-1.29 (m, 4H, C*H*$_2$-CH_3), 0.93 (t, 6H, *J* = 7.4 Hz, CH_2-C*H*$_3$).

CAS: 31144-33-9.

N-(3-fluorophenyl)-1-Adamantylamine (Table 22, entry 2)



Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 6/4) afforded 243 mg (99%) of the title compound as a white precipitate.

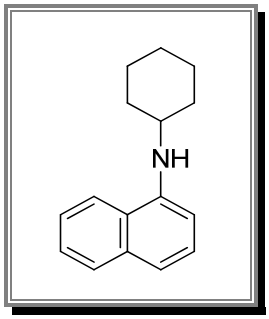
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.04 (q, 1H, *J* = 6.0 Hz), 6.50-6.46 (m, 2H), 6.43-6.38 (m, 1H), 3.49 (bs, 1H), 2.12 (bs, 3H), 1.90 (d, *J* = 2.8 Hz, 6H), 1.72-1.65 (m, 6H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.7 (d, C, C^3), 148.2 (d, C, C^1), 129.9 (d, CH, C^5), 113.5 (d, CH, C^6), 104.6 (d, CH, C^4), 104.2 (d, CH, C^2), 52.3 (C), 43.3 ($3CH_2$), 36.63 ($3CH_2$), 29.83 (3CH).

^{19}F NMR: (376 MHz, $CDCl_3$) δ -113.34 (s).

HRMS (ESI): *m/z* calcd for $C_{16}H_{21}FN$ (M^+ + H) 246.1658, found 246.1667.

N-Cyclohexyl-1-naphthylamine (Table 22, entry 3)



Procedure:

The general procedure followed by silica gel chromatography (Pentane/DCM 7/3) afforded 223 mg (99%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H, H^{Ar}), 7.45-7.38 (m, 2H, H^{Ar}), 7.32 (t, 1H, *J* = 8.0 Hz, H^{Ar}), 7.18 (d, 1H, *J* = 8.0 Hz, H^{Ar}), 6.63 (d, 1H, *J* = 8.0 Hz, H^{Ar}), 4.26 (bs, 1H, NH), 3.51-3.44 (m, 1H, N-CH), 2.18 (dd, 2H, *J* = 13.0 and 3.0 Hz, N-CH-C*H*H), 1.81 (dt, 2H, *J* = 13.0 and 4.0 Hz, N-CH-CH*H*), 1.72-1.67 (m, 1H, *p*-C*H*H), 1.50-1.24 (m, 5H, CH_2 + *p*-C*H*H).

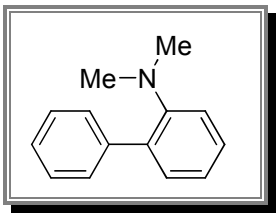
CAS: 26863-63-8.

General Procedure for the *O*-arylation reaction

With the 4-chlorotoluene: In a glovebox, to a screw cap septum vial equipped with a magnetic stirring bar were added in turn [PdCl(Cycle)(SIPr)] **108** (3.6 mg, 1 mol%), sodium *tert*-butoxide (53 mg, 0.55 mmol, 1.1 equiv), phenol (57 mg, 0.6 mmol, 1.2 equiv) and anhydrous solvent (1.7 mL, 0.3 M). Outside the glovebox, the 4-chlorotoluene (59 µl, 0.5 mmol) was injected through the septum. The reaction mixture was stirred for 19 h at the temperature stated in the Table 23 and a sample was then injected in gas chromatography.

With the 4-bromobenzonitrile: In a glovebox, to a screw cap septum vial equipped with a magnetic stirring bar were added in turn [PdCl(Cycle)(SIPr)] **108** (3.6 mg, 1 mol%), sodium *tert*-butoxide (53 mg, 0.55 mmol, 1.1 equiv) (or tri-Potassium phosphate (0.21 g, 1 mmol, 2 equiv) and sodium *tert*-butoxide (0.5 mg, $5x10^{-6}$ mol, 0.01 equiv)), phenol (57 mg, 0.6 mmol, 1.2 equiv), 4-bromobenzonitrile (91 mg, 0.5 mmol) and anhydrous solvent (1.7 mL, 0.3 M). The reaction mixture was stirred at 100ºC for 24 h and a sample was then injected in gas chromatography.

N,N-dimethylbiphenyl-2-amine (110)



Procedure:

A Schlenk tube was charged with a stirring bar, 65 mg (0.1 mmol) of [PdCl(Cycle)(SIMes)] **103**, 1.34 g (11 mmol) of phenylboronic acid, 672 mg (12 mmol) of grinded KOH, 1.3 mL (10 mmol) of 2-bromo-*N,N*-dimethylaniline and 20 mL of *i*PrOH. The reaction mixture was stirred for 16h at 50ºC and then filtrated over a plug a celite. Purification of crude mixture by silica gel chromatography (pentane/diethyl ether, 98/2) afforded the title product as a colorless oil (1.73 g, 88%).

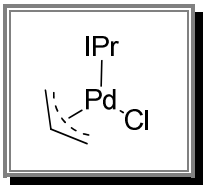
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.6 Hz, 2H, H^{Ar}), 7.46 (t, ^3J(H,H) = 7.6 Hz, 2H, H^{Ar}), 7.38-7.32 (m, 2H, H^{Ar}), 7.29 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.6 Hz, 1H, H^{Ar}), 7.12-7.08 (m, 2H, H^{Ar}), 2.62 (s, 6H, CH_3-N).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 151.3 (C, C^{Ar}), 142.0 (C, C^{Ar}), 134.2 (C, C^{Ar}), 131.7 (CH, CH^{Ar}), 128.7 (CH, CH^{Ar}), 128.3 (CH, CH^{Ar}), 128.1 (CH, CH^{Ar}), 126.5 (CH, CH^{Ar}), 121.5 (CH, CH^{Ar}), 117.6 (CH, CH^{Ar}), 43.4 (CH_3, CH_3-N).

HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N$ 198.1283 (M^+), found 198.1293.

3. NHC–PHOSPHANE Pd^0 COMPLEXES IN TRANSFER HYDROGENATION WITH FORMIC ACID AS REDUCING AGENT

[PdCl(allyl)(IPr)] (112)



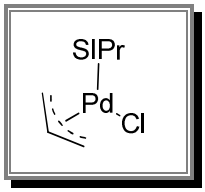
Procedure:

In a glovebox, a scintillation vial was charged with a stirring bar, IPr carbene (0.45 g, 1.15 mmol, 2.1 equiv) and dry THF (10 mL). Once dissolved, the palladium dimer $[PdCl(allyl)]_2$ (0.2 g, 0.55 mmol) was added and the mixture was stirred at room temperature overnight. Outside of the glovebox, the reaction mixture was filtered over celite. After evaporation of all the volatiles *in vacuo*, the remaining solid was triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane. Compound **112** was obtained as a white off solid (620 mg, >99%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.44 (t, 2H, *J* = 7.6 Hz, H^{Ar}), 7.30-7.27 (m, 4H, H^{Ar}), 7.17 (s, 2H, N-HC=), 4.82 (septuplet, 1H, *J* = 6.3 Hz, H^{allyl}), 3.91 (dd, 1H, *J* = 2.0 and 7.6 Hz, H^{allyl}), 3.14 (septuplet, 2H, *J* = 6.8 Hz, C*H*$(CH_3)_2$), 3.05 (d, 1H, *J* = 6.4 Hz, H^{allyl}), 2.87 (septuplet, 2H, *J* = 6.8 Hz, C*H*$(CH_3)_2$), 2.79 (d, 1H, *J* = 13.2 Hz, H^{allyl}), 1.57 (s, 1H, H^{allyl}), 1.40 (d, 6H, *J* = 6.8 Hz, CH_3), 1.35 (d, 6H, *J* = 6.8 Hz, CH_3), 1.19 (d, 6H, *J* = 6.8 Hz, CH_3), 1.10 (d, 6H, *J* = 6.8 Hz, CH_3).

CAS: 478980-03-9.

[PdCl(allyl)(SIPr)] (113)



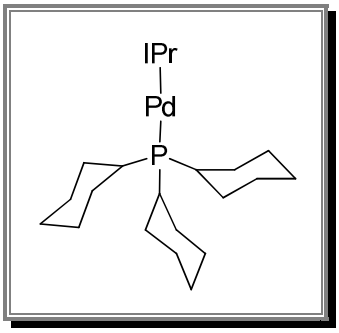
Procedure:

In a glovebox, a scintillation vial was charged with a stirring bar, SIPr carbene (1.12 g, 2.87 mmol, 2.1 equiv) and dry THF (20 mL). Once dissolved, the palladium dimer $[PdCl(allyl)]_2$ (0.5 g, 1.36 mmol) was added and the mixture was stirred at room temperature overnight. Outside of the glovebox, the reaction mixture was filtered over celite. After evaporation of all the volatiles *in vacuo*, the remaining solid was triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane. Compound **113** was obtained as a white off solid (1.53 g, 97%).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.35 (t, 2H, *J* = 7.6 Hz, H^{Ar}), 7.25-7.21 (m, 4H, H^{Ar}), 4.78 (septuplet, 1H, *J* = 6.3 Hz, H^{allyl}), 4.08-4.01 (m, 4H, C*H*$_2$-C*H*$_2$), 3.89 (dd, 1H, *J* = 1.6 and 7.6 Hz, H^{allyl}), 3.51 (septuplet, 2H, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 3.43 (septuplet, 2H, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 3.03 (d, 1H, *J* = 6.8 Hz, H^{allyl}), 2.74 (d, 1H, *J* = 13.6 Hz, H^{allyl}), 1.47 (d, 6H, *J* = 6.8 Hz, CH_3), 1.37 (d, 6H, *J* = 6.8 Hz, CH_3), 1.35 (m, 1H, H^{allyl}), 1.30 (d, 6H, *J* = 6.8 Hz, CH_3), 1.26 (d, 6H, *J* = 6.8 Hz, CH_3).

CAS: 478980-01-7.

[Pd(IPr)(PCy$_3$)] (114)



Procedure:

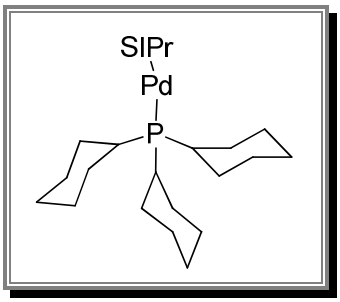
In a glovebox, [PdCl(allyl)(IPr)] **112** (0.1 g, 0.175 mmol) and KO^{t}Bu (24.3 mg, 0.199 mmol) were dissolved in ^{i}PrOH (15 mL). Tricyclohexylphosphane was then added (52.1 mg, 0.186 mmol). After 4 h stirring at room temperature, the yellow solution was filtered. Evaporation of the solvent affords **114** as a yellow solid (0.14 g, >99%).

^{1}H NMR: (400 MHz, C_6D_6) δ 7.27 (t, 2H, *J* = 8.0 Hz, H^{Ar}), 7.19 (d, 4H, *J* = 8.0 Hz, H^{Ar}), 6.48 (s, 2H, N-HC=), 3.01 (septuplet, 4H, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.83 (d broad, 6H, CH_2^{Cy}), 1.71 (d, 12H, *J* = 7.0 Hz, CH_3), 1.75-1.65 (m broad, 12H, CH_2^{Cy}), 1.49-1.41 (m, 3H, CH^{Cy}), 1.32-1.17 (m, 12H, CH_2^{Cy}), 1.23 (d, 12H, *J* = 7.0 Hz, CH_3).

^{31}P NMR: (162 MHz, C_6D_6) δ 49.42.

CAS: 1071609-75-0.

[Pd(SIPr)(PCy$_3$)] (115)



Procedure:

In a glovebox, [PdCl(allyl)(SIPr)] **113** (0.1 g, 0.174 mmol) and KO^{t}Bu (21.3 mg, 0.175 mmol) were dissolved in ^{i}PrOH (15 mL). Tricyclohexylphosphane was then added (48.9 mg, 0.175 mmol). After 5 h stirring at room temperature, the yellow solution was filtered. Evaporation of the solvent affords **115** as a yellow solid (0.13 g, >99%).

^{1}H NMR: (400 MHz, C_6D_6) δ 7.36 (dd, 2H, *J* = 7.0 and 8.0 Hz, H^{Ar}), 7.28 (d, 4H, *J* = 8.0 Hz, H^{Ar}), 3.48 (s, 4H, N-H_2C), 3.43 (septuplet, 4H, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 1.91 (d, 12H, *J* = 7.0 Hz, CH_3), 1.86-1.77 (m broad, 15H, CH_2^{Cy}), 1.56-1.48 (m, 3H, CH^{Cy}), 1.45 (d, 12H, *J* = 7.0 Hz, CH_3), 1.32-1.17 (m broad, 15H, CH_2^{Cy}).

^{31}P NMR: (162 MHz, C_6D_6) δ 48.11.

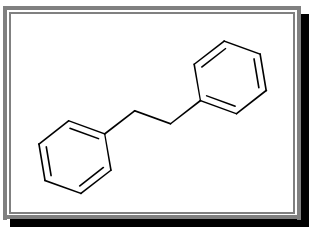
CAS: 1071609-81-8.

General Procedure for the transfer hydrogenation reaction

In a glovebox, [Pd(SIPr)(PCy$_3$)] **115** (7.6 mg, 2 mol%) were dissolved in anhydrous THF (2 mL) in a screw cap septum vial equipped with a magnetic stirring bar. Outside the glovebox, the unsaturated substrate (0.5 mmol) and formic acid (20 µL, 0.53 mmol, 1.05 equiv) were injected in turn through the septum. If the starting material was a solid, it was, before loading of the solvent, charged in the vial inside the glovebox. The reaction mixture

was then stirred at 60ºC for 24 h. Unless otherwise stated, the THF was carefully removed *in vacuo* and the brown residue was filtered over a pad of silica gel with CH_2Cl_2. The solvent was removed under controlled reduced pressure, giving the hydrogenated product.

1,2-Diphenylethane 116 (Table 29, entry 1)



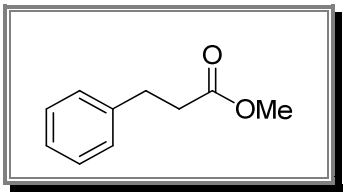
Procedure:

In the presence of 0.5 ml% of **115** (1.9 mg) and after 2 h stirring at 60°C, the general procedure afforded 85 mg (93%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 4H, H^{Ar}), 7.21-7.18 (m, 6H, H^{Ar}), 2.93 (s, 4H, CH_2).

CAS: 103-29-7.

Methyl 3-phenylpropanoate (Table 30, entry 1)



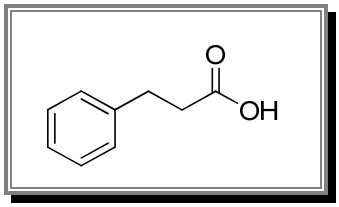
Procedure:

The general procedure afforded 77 mg (94%) of the title compound as a colorless liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.30-7.28 (m, 2H, H^{Ar}), 7.22-7.18 (m, 3H, H^{Ar}), 3.67 (s, 3H, OCH_3), 2.95 (t, 2H, J = 7.8 Hz, C(O)-CH_2), 2.63 (t, 2H, J = 7.8 Hz, CH_2).

CAS: 103-25-3.

3-Phenylpropanoic acid (Table 30, entry 2)



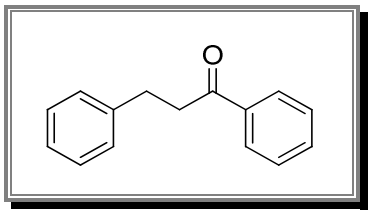
Procedure:

The general procedure afforded 74 mg (98%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.66 (bs, 1H, OH), 7.28 (t, 2H, *J* = 7.5 Hz, H^{Ar}), 7.21-7.18 (m, 3H, H^{Ar}), 2.95 (t, 2H, *J* = 7.8 Hz, C(O)-CH_2), 2.67 (t, 2H, *J* = 7.8 Hz, CH_2).

CAS: 501-52-0.

1,3-Diphenylpropan-1-one (Table 30, entry 3)



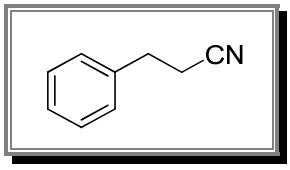
Procedure:

The general procedure afforded 102 mg (97%) of the title compound as a colorless oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 7.9 Hz, H^{Ar}), 7.55 (t, 1H, *J* = 7.4 Hz, H^{Ar}), 7.45 (t, 2H, *J* = 7.7 Hz, H^{Ar}), 7.31-7.18 (m, 5H, H^{Ar}), 3.30 (t, 2H, *J* = 7.7 Hz, C(O)-CH_2), 3.07 (t, 2H, *J* = 7.7 Hz, CH_2).

CAS: 1083-30-3.

3-Phenylpropanenitrile (Table 30, entry 4)



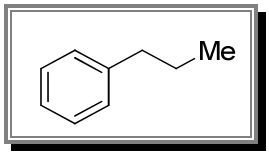
Procedure:

The general procedure afforded 62 mg (94%) of the title compound as a yellow oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H, H^{Ar}), 7.27-7.21 (m, 3H, H^{Ar}), 2.93 (t, 2H, *J* = 7.4 Hz, CH_2-CN), 2.59 (t, 2H, *J* = 7.4 Hz, CH_2).

CAS: 645-59-0.

1-Propylbenzene (Table 30, entry 8)



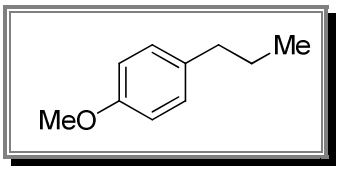
Procedure:

The general procedure afforded 30 mg (>99%) of the title compound. The yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H, H^{Ar}), 7.18-7.15 (m, 3H, H^{Ar}), 2.58 (t, 2H, J = 7.6 Hz, CH_2), 1.64 (sextuplet, 2H, J = 7.5 Hz, CH_2-CH_3), 0.94 (t, 3H, J = 7.4 Hz, CH_3).

CAS: 103-65-1.

1-Methoxy-4-propylbenzene (Table 30, entry 9)



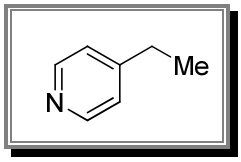
Procedure:

4-Allylanisole was distilled from CaH_2 prior use. The general procedure afforded 71 mg (94%) of the title compound as a colorless liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01-6.97 (m, 2H, H^{Ar}), 6.75-6.71 (m, 2H, H^{Ar}), 3.68 (s, 3H, OCH_3), 2.43 (t, 2H, J = 7.5 Hz, CH_2), 1.51 (sextuplet, 2H, J = 7.5 Hz, CH_2-CH_3), 0.84 (t, 3H, J = 7.3 Hz, CH_3).

CAS: 104-45-0.

4-Ethylpyridine (Table 30, entry 10)



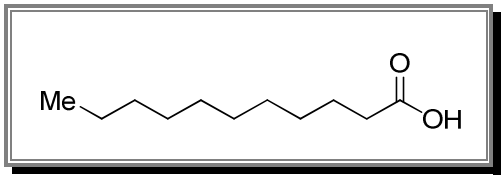
Procedure:

The general procedure afforded 40 mg (75%) of the title compound as a yellow oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.48 (d, 2H, J = 4.8 Hz, H^{Ar}), 7.12 (d, 2H, J = 4.8 Hz, H^{Ar}), 2.64 (q, 2H, J = 7.6 Hz, CH_2), 1.25 (t, 3H, J = 7.6 Hz, CH_3).

CAS: 536-75-4.

Undecanoic acid (Table 30, entry 11)



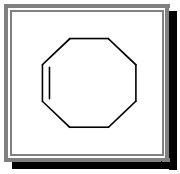
Procedure:

The general procedure afforded 90 mg (96%) of the title compound as a light yellow liquid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.48 (bs, 1H, OH), 2.36 (t, 2H, *J* = 7.4 Hz, C(O)-CH_2), 1.65 (qi, 2H, *J* = 7.4 Hz, C(O)-CH_2-C*H*$_2$), 1.28 (bs, 14H, CH_2), 0.89 (t, 3H, *J* = 6.7 Hz, CH_3).

CAS: 112-37-8.

Cis-cyclooctene (Table 33, entries 1 and 2)



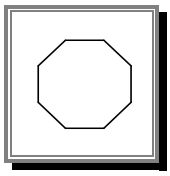
Procedure:

Starting from 1,5-cyclooctadiene and formic acid (100 µL, 2.5 mmol, 5 equiv), the general procedure afforded 45 mg (82%) of the title compound as a colorless liquid.
Starting from 1,3-cyclooctadiene, the general procedure afforded 29 mg (53%) of the title compound as a colorless liquid. (Caution, *cis*-cyclooctene is volatile)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.68-5.60 (m, 2H, =CH), 2.16 (bs, 4H, =CH-C*H*$_2$), 1.51 (s, 8H, CH_2).

CAS: 931-87-3.

Cyclooctane (Table 33, entry 3)



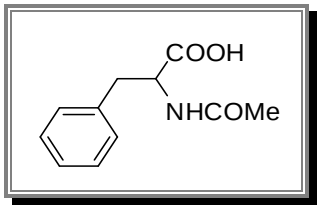
Procedure:

Starting from *cis*-cyclooctene and using 5 equiv of formic acid (100 µL, 2.5 mmol), the general procedure afforded 47 mg (83%) of the title compound. The yield was determined by ^{1}H NMR using hexamethylbenzene as internal standard. (Caution, cyclooctane is volatile)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 1.57 (s, 16H, CH_2).

CAS: 292-64-8.

2-Acetamido-3-phenylpropanoic acid (117)



Procedure:

Using 5 equiv of formic acid (100 µL, 2.5 mmol), the general procedure afforded 98 mg (95%) of the title compound as a white solid.

^{1}H NMR: (400 MHz, DMSO-d^6) δ 8.10 (d, 1H, *J* = 8.0 Hz, NH), 7.22-7.11 (m, 5H, H^{Ar}), 4.35 (td, 1H, *J* = 4.9 and 9.0 Hz, CH_2-C*H*), 2.98 (dd, 1H, *J* = 4.9 and 13.8 Hz, CH_2-CH), 2.77 (dd, 1H, *J* = 9.5 and 13.8 Hz, CH_2-CH), 1.71 (s, 3H, CH_3).

CAS: 7782-51-6.

Conclusion

In the last decades, nucleoside analogues have played a major role in the treatment of viral infectious diseases, such as AIDS, hepatitis, herpes, smallpox or influenza. Nevertheless, the apparition of new or mutated viruses highlights the need for more potent and resistant antiviral therapeutics. The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis. Among them, late-transition metal-catalyzed reactions are certainly the most important methods to access variety of appealing pharmacomodulations. However, applications are not exhaustive and each particular case implies the optimization of the catalytic system to circumvent the problems of efficiency, versatility or selectivity often encountered. Among all the available homogeneous catalysts, our attention has focused on a class of complexes that have remarquebly improved the organometallic field these last years, but that have been not so much represented in the nucleoside chemistry: The *N*-heterocyclic carbenes-containing complexes. The general guiding line of this Ph.D. work was to develop new useful tools for organometallic reactions that could be further applied to the synthesis of nucleosides.

In the first chapter, we have conduced a thorough study of the synthesis of triazolo-carbanucleosides *via* copper(I)-catalyzed Huisgen cycloaddition with terminal and internal alkynes. We have demonstrated the beneficial effect of copper(I)-based catalysts and microwave irradiation in the preparation of 1,4-disubstituted-1,2,3-triazolo-carbanucleosides. The presence of a NHC ligand on the copper center appears to enhance the catalytic activity when compared to $[Cu(CH_3CN)_4]PF_6$. However, the cationic complex has the additional advantage of being efficient in both aqueous and organic media. As part of our smallpox drug discovery program, the optimized conditions were then applied to the versatile, simple and efficient synthesis of racemic and D-configured 1,4-disubstituted-triazolo-carbanucleosides. Unfortunately, the novel compounds did not show any cytotoxicity or significant antiviral activity suggesting that 1,4-disubstituted-1,2,3-triazoles are not adequate bases for smallpox inhibition. Extension of the study to the preparation of 1,4,5-trisubstituted-triazoles has shown that there is a negligible copper(I)-catalysts effect on the reaction between azides and symmetrical or unsymmetrical internal alkynes.

In the second chapter, we were interested in the synthesis of a class of nucleosides that have also shown interesting activities in the search for anti-pox therapies: Acyclic nucleoside phosphonate analogues. We speculated that the introduction of a longer carbon side chain and/or a polar group on the *C*-1' position of the acyclic part could enhance the binding affinity of unsaturated ANPs with the enzyme involved in the phosphorylation process. The key step of the synthetic routes consisted in a cross-metathesis reaction mediated by NHC-containing ruthenium complex. In a first time, a readjusted synthetic procedure afforded new series C^5-substituted uracil pentenyl phosphonic acids with good overall yields. Unsaturated acyclic phosphonates were efficiently generated *via* olefin cross-metathesis with protected uracil crotyl intermediates. Unfortunately, the series of (*E*)-C^5-substituted acyclic uracil phosphonates appeared to be less phosphorylated by the enzyme than the previously published analogues. In a second part, we attempted to develop a new original strategy for the preparation of various unsaturated optically active acyclic nucleoside phosphonates bearing a functional group on the *C*-1' position of the side chain. The acyclic unsaturated side chain was prepared in six steps starting from L-gulono-1,4-lactone. The key step of its synthesis consisted in a cross-metathesis reaction between the optically active *iso*propylidene-butene and phosphonate reagents. Unfortunately, we were not able to introduce the uracil base either under Tsuji-Trost or Mitsunobu conditions.

The development of new powerful and selective palladium catalysts has become over the past few years a primordial objective. In this context, well-defined NHC-containing Pd complexes have emerged as indispensable tools in the catalysis of C-C, C-N and C-O bond formations. In this third chapter, the great potential of newly developed well-defined NHC-based Pd^{II} and Pd^0 complexes prompts us to evaluate their catalytic activities in two distinct types of reaction. Two air- and moisture-stable saturated NHC-containing palladacycle complexes were first synthesized and then successfully used in the Buchwald-Hartwig amination of a range of unactivated and diverse aryl chlorides. In addition, the Suzuki-Miyaura cross coupling using the [PdCl(Cycle)(SIMes)] was applied to the synthesis of the biphenyl ligand employed to synthesize the catalyst. In a second time, we have conducted the assessment of new mixed NHC-phosphane Pd^0 complexes in the transfer hydrogenation of C=C double bonds. Despite some limitations, the selective reduction of a variety of cyclic and acyclic olefins substrates bearing diverse functional groups was observed and excellent isolated yields were obtained by using an optimum amount of formic acid. On the other hand, stereo- and chemoselective transfer semihydrogenation of an alkyne to the corresponding *cis*-

alkene using only one equivalent of formic acid appeared to be achievable with such well-defined mixed NHC/PCy_3-Pd^0 system. Finally, this complex also proved to be able to dehydrogenate cyclic alkenes derivatives that are capable of aromatization and to transfer the extracted hydrogen for the reduction of unsaturated substrates. To the best of our knowledge, we report here the first transfer hydrogenation reactions using such hydrogen donors with homogeneous palladium-catalysts.

In conclusion, we have demonstrated that late-transition metal catalysts bearing an NHC ligand can be used as practical tools in challenging reactions. Ruthenium-, copper- or palladium-based catalysts were efficiently applied in the synthesis of various nucleoside analogues. Nevertheless, the aforementioned applications are just a sample of NHC-containing systems abilities in organometallic catalysis. We have underlined the compatibility of these metal complexes with various functions often encountered in organic chemistry. Potential applications are thereby numerous and varied in the field of catalytic transformations.

ANNEX

Publications

1 - Broggi, J.; Kumamoto, H.; Berteina-Raboin, S.; Nolan, S.P.; Agrofoglio, L.A. **Click Azide-Alkyne Cycloaddition for the Synthesis of D-(-)-1,4-disubstituted-triazolo-carbanucleosides.** *Eur. J. Org. Chem.* **2009,** 1880-1888**.**

2 - Broggi, J.; Joubert, N.; Díez-González, S.; Berteina-Raboin, S.; Zevaco, T.; Nolan, S.P.; Agrofoglio, L.A. **Synthesis of (±)-1,2,3-triazolo-3'-deoxy-4'-hydroxymethyl carbanucleosides *via* 'click' cycloaddition.** *Tetrahedron* **2009**, *65*, 1162-1170.

3 - Broggi, J.; Clavier, H.; Nolan, S.P. ***N*-Heterocyclic Carbenes (NHCs) Containing *N-C*-Palladacycle Complexes: Synthesis and Reactivity in Aryl Amination Reactions.** *Organometallics* **2008**, *27*, 5525-5531.

4 - Broggi, J.; Díez-González, S.; Petersen, J.L.; Berteina-Raboin, S.; Nolan, S.P.; Agrofoglio, L.A. **Study of copper(I) catalysts for the synthesis of carbanucleosides *via* azide-alkyne 1,3-dipolar cycloaddition.** *Synthesis* **2008**, 141-148.

5 - Kumamoto, H.; Topalis, D.; Broggi, J.; Pradère, U.; Roy, V.; Berteina-Raboin, S.; Nolan, S.P.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J.-M.; Agrofoglio, L.A. **Preparation of acyclo nucleoside phosphonate analogues based on cross-metathesis.** *Tetrahedron* **2008**, *64*, 3517-3526.

6 - Agrofoglio, L.A.; Amblard, F.; Broggi, J. and Garnier, E. "**Recent insigth into the synthesis of the 'non-classical' *O*- or *N*-heterocyclic bases of nucleosides**" in *Modern Approaches to the Synthesis of O- and N-Heterocycles*, Kaufman, T. S., Larghi, E. L., Eds.; Research SignPost, Trivandrum, India, **2007**.

7 - Broggi, J.; Joubert, N.; Aucagne, V.; Zevaco, T.; Berteina-Raboin, S.; Nolan, S.P.; Agrofoglio, L.A. **Study of Different Copper (I) Catalysts for the Click Chemistry Approach to Carbanucleosides.** Nucleosides, Nucleotides & Nucleic Acids, **2007**, *26*, 779-783.

8 - Broggi, J.; Joubert, N.; Aucagne, V.; Berteina-Raboin, S.; Diez-Gonzalez, S.; Nolan, S.; Topalis, D.; Deville-Bonne, D.; Balzarini, J.; Neyts, J.; Andrei, G.; Snoeck, R.; Agrofoglio, L.A. **Alkyne-Azide Click Chemistry Mediated Carbanucleosides Synthesis.** Nucleosides, Nucleotides & Nucleic Acids, **2007**, *26*, 1391-1394.

Study of Copper(I) Catalysts for the Synthesis of Carbanucleosides via Azide–Alkyne 1,3-Dipolar Cycloaddition

Julie Broggi,[a] Silvia Díez-González,[b] Jeffrey L. Petersen,[c] Sabine Berteina-Raboin,[a] Steven P. Nolan,*[b] Luigi A. Agrofoglio*[a]

[a] Institut de Chimie Organique et Analytique, UMR 6005, Université d'Orléans, 45067 Orléans, France
Fax +33(2)38417281; E-mail: luigi.agrofoglio@univ-orleans.fr

[b] Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16, 43007 Tarragona, Spain

[c] C. Eugene Bennet Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045, USA

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Abstract: The activity of three copper(I)-based catalytic systems in the preparation of various 1,2,3-triazolyl-carbanucleosides via the Huisgen azide–alkyne 1,3-dipolar cycloaddition is presented. The influence of the alkyne substituent, solvent, and heating mode were studied. The preparation of [1,2-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]bromocopper [(IMes)CuBr] is discussed.

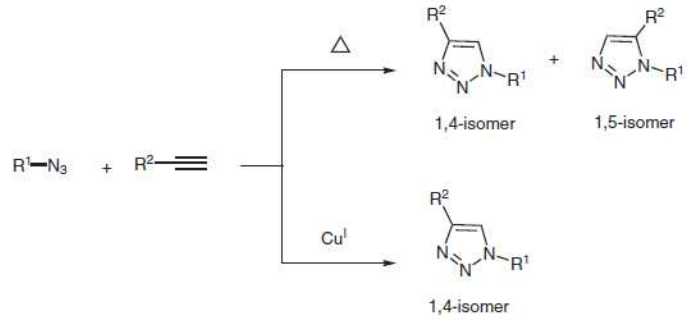
Key words: copper(I) catalysts, Huisgen 1,3-dipolar cycloaddition, carbanucleosides, N-heterocyclic carbenes

1,3-Dipolar cycloaddition reactions have attracted much interest over the last few decades, Rolf Huisgen being the father of concept.[1] Dipolar cycloadditions generate a large variety of five-membered heterocycles in a rapid, reproducible, and efficient manner. The reaction between an azide and a terminal alkyne is one of the most popular Huisgen cycloadditions. The resulting 1,2,3-triazoles have been intensively studied because of their antiviral and antimicrobial activities.[2] Under thermal conditions, this reaction usually affords a mixture of 1,4- and 1,5-disubstituted regioisomers[1,3] (Scheme 1). Since copper(I) has recently been found to be an efficient and regiospecific catalyst for this process,[4,5] this transformation now represents a general and mild approach for the preparation of 1,4-disubstituted 1,2,3-triazole derivatives.

In light of its impressive selectivity, efficiency, and scope, the copper(I)-catalyzed alkyne–azide 1,3-dipolar cycloaddition (CuAAC) fulfills the stringent criteria of 'click' chemistry.[6] Moreover, this process allows for the assembly of complex molecules and thus generates novel structures unknown hitherto as pharmacophores.[7] In the search for new therapeutic agents, nucleosides with a five-membered-ring nucleobase are known to be of high potential value.[2e,8] Accordingly, this 1,3-dipolar cycloaddition has been used to synthesize novel nucleosidic analogues.[9]

Active copper(I) catalytic species can be prepared in situ by reduction of copper(II) salts,[3,4] oxidation of copper(0) metal,[10] or copper(II)/copper(0) comproportionation.[3,11] Supported, reusable, and heterogeneous catalysts have also been studied.[12] Copper(I) salts have been less used[5,13,14] because of their thermodynamic instability and the formation of undesired alkyne–alkyne coupling products sometimes observed in their presence.[5,15] Nevertheless, nitrogen- or phosphorus-based ligands have been shown to protect the metal center from oxidation and disproportionation, while enhancing its catalytic activity.[16]

N-Heterocyclic carbene (NHC) containing copper(I) complexes[17] have been reported to catalyze efficiently a number of reactions[18] such as alkenation[19] or hydrosilylation[20] of carbonyl compounds and cyclopropanation reactions.[21] These highly stable species have also shown remarkable activity in the Huisgen cycloaddition, allowing, notably, for the unprecedented use of an internal alkyne in this copper-catalyzed transformation.[22]



Scheme 1 Thermal and copper-catalyzed Huisgen cycloaddition

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Biographical Sketches

Julie Broggi received her M.Sc. in organic chemistry from the Université de Nice Sophia-Antipolis, France, in 2005. She started her Ph.D. on nucleoside chemistry under the supervision of Professor L. A. Agrofoglio at the Université d'Orléans, France. She is currently a visiting student in the group of Professor Steven P. Nolan at the Institute of Chemical Research of Catalonia in Tarragona, Spain. Her research interests are focused on the applications of transition-metal complexes in the synthesis of nucleosides.

Dr. Silvia Díez-González received her M.Sc. in organic chemistry from the Universidad del País Vasco (Spain) and the Université Paris XI (France) where she then completed her Ph.D. on organosilicon chemistry. In 2004, she obtained a postdoctoral position in the research group of Professor Steven P. Nolan at the University of New Orleans. In 2006, she followed him to the ICIQ in Tarragona where she was offered a position as Group Coordinator. Her research interests are currently focused on the development and catalytic applications of copper complexes.

Jeffrey L. Petersen received his B.A. degree in chemistry from Carthage College in 1969 and completed his Ph.D. degree at the University of Wisconsin – Madison under the direction of L. F. Dahl in 1974. After brief postdoctoral studies at Argonne National Laboratories with J. M. Williams and at Northwestern University with B. M. Hoffman and T. J. Marks, he began his academic career in 1975 at West Virginia University. His research interests focus on the synthesis, reactivity, and structural characterization of electrophilic group 4 organometallic complexes. He has served on the editorial advisory boards of *Inorganic Chemistry*, *Organometallics*, and the *Journal of Coordination Chemistry*.

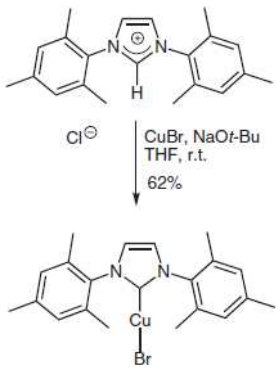
Sabine Berteina-Raboin received her Ph.D. degree in organic chemistry from the University of Paris XI in 1994 with Prof. A. Lubineau. After a year of research in the Analytical Research and Development Department of Bristol-Myers Squibb (Paris, France) and 2.5 years of postdoctoral work in the field of combinatorial chemistry in the group of Dr. A. De Mesmaeker, first in the Central Research Laboratories of Ciba, then in the Novartis Crop Protection division in Basel, Switzerland, she joined the Institute of Organic and Analytical Chemistry of the University of Orléans (France) in 1998 as Assistant Professor. Her research interests include heterocyclic chemistry and solid-phase synthesis of pharmacologically interesting molecules.

Prof. Steven P. Nolan received his B.Sc. in chemistry from the University of West Florida and his Ph.D. from the University of Miami where he worked under the supervision of Professor Carl D. Hoff. After a postdoctoral stay with Professor Tobin J. Marks at Northwestern University, he joined the Department of Chemistry of the University of New Orleans in 1990. He is now Group Leader and ICREA Fellow at the ICIQ in Tarragona (Spain). His research interests include organometallic chemistry and homogeneous catalysis.

Prof. Luigi A. Agrofoglio received his B.Sc. and his Ph.D. in chemistry from the University of Nice-Sophia Antipolis under the supervision of Professor Roger Condom. After a first postdoctoral stay with Professor Jean-Pierre Sommadossi at University of Alabama at Birmingham, and a second with Professor C. K. Chu at University of Georgia at Athens, he joined the Institute of Organic and Analytical Chemistry (UMR CNRS 6005) in 1995; he is now Group Leader. His research interests include organic chemistry and nucleic acid chemistry of pharmacologically interesting molecules, especially those targeting an antiviral and antitumor activity.

Thus, as part of our efforts in drug discovery, we herein report the activity of three different copper(I)-based catalytic systems in the synthesis of 1,2,3-triazolyl-carbanucleosides. Tetrakis(acetonitrile)copper hexafluorophosphate {$[Cu(MeCN)_4]PF_6$}, [1,2-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]bromocopper [(IMes)CuBr], and the mixture copper(0)/copper(II) sulfate [$Cu(0)/CuSO_4$] were chosen for this study.

(IMes)CuBr was prepared from the corresponding azolium and copper salts in the presence of a strong base (Scheme 2). The structure of this air- and moisture-stable complex was elucidated by single-crystal diffraction from suitable crystals grown from dichloromethane–hexane solutions. The resulting ball-and-stick representation is shown in Figure 1. This copper complex is isomorphous with its chloride analogue,[23] and both species crystallize in the same orthorhombic space group, *Fdd*2.[24] The observed Cu–C(1) bond length is comparable to known Cu–C bonds in NHC–copper complexes.[25]



Scheme 2 Synthesis of (IMes)CuBr

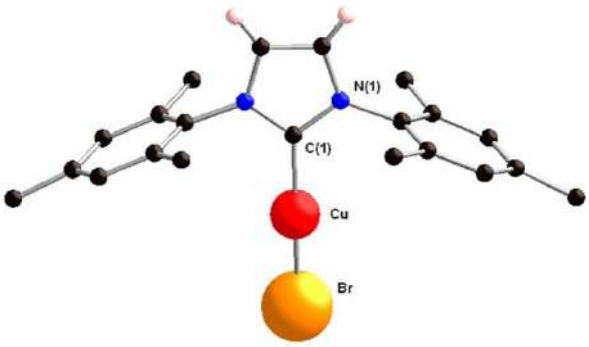
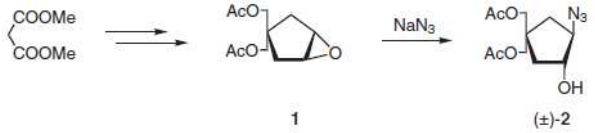


Figure 1 Ball-and-stick drawing for (IMes)CuBr. Selected bond lengths (Å): Cu–C(1) = 1.897(6), Cu–Br = 2.2101(7). Selected bond angles (°): C(1)–Cu–Br = 180.000(1), N(1)–C(1)–N(1) = 105.1(5).

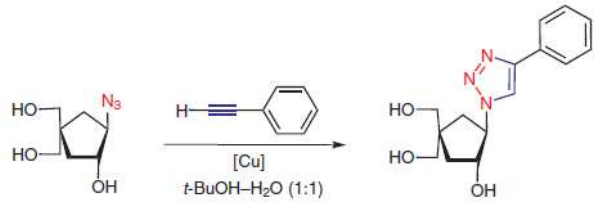
The starting azidocarbocycle **2** was obtained via a well-known malonic synthesis[26] followed by the ring-opening of epoxide **1** with sodium azide[27] (Scheme 3); deacylation also occurred under azidation conditions.



Scheme 3 Synthesis of the azidocarbocycle 2

We first investigated the optimal conditions for the cycloaddition of azide **2** and phenylacetylene with different catalysts (Table 1). Reactions were carried out in a mixture of *tert*-butyl alcohol–water (1:1) under thermal or microwave heating. Microwave heating is known as a powerful technique to promote a variety of chemical reactions.[28] Recently, some examples of microwave-assisted alkyne–azide cycloadditions have been reported to show

Table 1 Optimization Studies[a]



Catalyst	Concn (mol%)	Conditions	Time	Conversion[b] (%)
no catalyst	–	MW	10 h	43
$Cu(0)/CuSO_4$	80/20	r.t.	11 h	100
$Cu(0)/CuSO_4$	80/20	Δ	40 min	100
$Cu(0)/CuSO_4$	80/20	MW	2 min	100
$Cu(0)/CuSO_4$	80/20	Δ,P	2 min	79
$Cu(0)/CuSO_4$	80/20	Δ,P	20 min	100
$[Cu(MeCN)_4]PF_6$	2	MW	2 h	50
$[Cu(MeCN)_4]PF_6$	5	MW	15 min	100
$[Cu(MeCN)_4]PF_6$	10	MW	10 min	100
$[Cu(MeCN)_4]PF_6$	15	MW	5 min	100
$[Cu(MeCN)_4]PF_6$	20	MW	3 min	100
(IMes)CuBr	2	MW	10 h	100
(IMes)CuBr	5	MW	9 h	100
(IMes)CuBr	10	MW	7 h	100
(IMes)CuBr	15	MW	6.5 h	100
(IMes)CuBr	20	MW	6.5 h	100

[a] Reaction conditions: **2** (0.27 mmol), PhC≡CH (1.05 equiv), *t*-BuOH–H_2O (1:1, 2 mL); microwave (MW), 125 °C; thermal heating under pressure (Δ,P), 125 °C; thermal heating (Δ), 75 °C.
[b] Conversions are an average of two runs and were determined by ^1H NMR of the crude product.

a substantial decrease in reaction times.[29] These results can be rationalized by the proposed polar transition states of this cycloaddition, favorable for a microwave activation.[30] In our case, in the absence of copper, total conversion could not be reached after several hours of irradiation and, as expected, two regioisomeric cycloadducts were obtained.[31,32] In the presence of Cu(0)/$CuSO_4$, the regioselective conversion into triazolyl-carbanucleoside (±)-**3** was complete after only two minutes of microwave irradiation at 125 °C. A similar result was obtained when the reaction was carried out thermally under pressure at the same temperature during 20 minutes. The reaction took 40 minutes to proceed under thermal heating and 11 hours at room temperature. These results might indicate the existence of a specific microwave effect in this copper-catalyzed cycloaddition beyond the pressure and temperature effects.

For both copper(I) complexes, a study of the adequate catalyst loading was carried out. For $[Cu(MeCN)_4]PF_6$, 5 mol% loading was found optimal to assure a short reaction time. However, with (IMes)CuBr the observed reaction time was surprisingly longer (9 h with 5 mol%). However, this catalyst loading was maintained for the substrate screening in order to obtain comparable results.

From azide **2** and alkynes, various 1,2,3-triazolyl-carbanucleosides with a 4′-*C*-hydroxymethyl group (±)-**3–6** were successfully prepared; the three catalytic systems were used under thermal (75 °C) and microwave (125 °C) heating (Table 2).

$[Cu(MeCN)_4]PF_6$ and (IMes)CuBr were found to be slightly soluble in the hot mixture of solvents. Most cycloaddition reactions were completed after short reaction times with no observable formation of byproducts. In most examples, microwave irradiation had an evident beneficial effect in terms of reaction time and yield. For example, using classical heating, sluggish reactions with hept-1-yne were observed with any of the three catalytic systems (Table 2, entry 2). However, under microwave irradiation, complete conversion was achieved with Cu(0)/$CuSO_4$ or (IMes)CuBr after short reaction times (1 and 2 h, respectively). In the case of $[Cu(MeCN)_4]PF_6$, microwave irradiation only allowed for a conversion of 79%, however there was no reaction with conventional heating. As has been previously reported,[1,12d,33] electron-poor alkynes (Table 2, entries 3, 4) were more reactive than electron-rich ones (Table 2, entries 1, 2). Different isolation techniques were also required according to the substitution of the alkyne moiety. Whereas triazoles with electron-donating substituents at the 4-position, (±)-**3** and (±)-**4**, were isolated in high yield and with high purity after simple extraction into ethyl acetate, triazoles with electron-withdrawing groups, (±)-**5** and (±)-**6**, had to be purified on silica gel due to their high solubility in water.

In the case of triazole (±)-**5**, partial decomposition was observed after prolonged reaction times. For example, after refluxing for five days in the presence of $[Cu(MeCN)_4]PF_6$, only 17% of the expected triazole was isolated together with 56% of the corresponding 4-(hydroxymethyl)triazole (Table 2, entry 3). This acetate cleavage could be mediated by the copper(I) species present in the reaction mixture.[34] The use of microwave irradiation decreased the reaction time and allowed for a higher yield of compound (±)-**5**.

Overall, reaction times were reduced using the NHC complex versus the cationic $[Cu(MeCN)_4]PF_6$ (entries 2, 3, 4). These results suggest a beneficial effect of the NHC ligand in this cycloaddition reaction. The poor reactivity of phenylacetylene with (IMes)CuBr compared to other catalysts can not be explained at the present time and is currently being investigated.

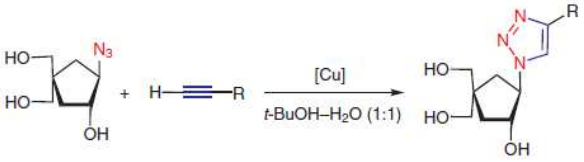
For all entries presented in Table 2, the best results were obtained with Cu(0)/$CuSO_4$ as catalyst precursor, regardless of the heating method. This system has the advantage of being inexpensive and easily removed from the reaction mixture by simple extraction. Combined with *tert*-butyl alcohol–water as solvent mixture and microwave irradiation, it seems to be the most suitable method for the synthesis of triazolyl-carbanucleosides. However, this catalytic system could be limited to substrates compatible with aqueous media.

Alternatively, these cycloaddition reactions could still be carried out in organic solvents in the presence of $[Cu(MeCN)_4]PF_6$ or (IMes)CuBr. Moreover, sub-stoichiometric quantities of copper could be used with these two catalysts. Dichloromethane was chosen as the organic solvent and 5% of methanol was added in order to dissolve the azide **2** and to enhance the microwave effect. First attempts with phenylacetylene showed that the NHC complex was less efficient in water or in a dichloromethane–methanol mixture than in *tert*-butyl alcohol–water (Table 3). Longer reaction times were required in order to reach good conversions. This tendency was confirmed with the prop-2-ynyl acetate; two hours for complete conversion in dichloromethane–methanol (Table 3) versus five minutes in *tert*-butyl alcohol–water (Table 2, entry 3).

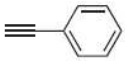
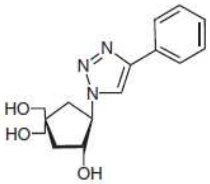
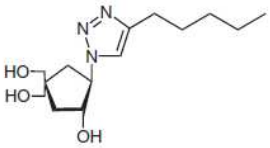
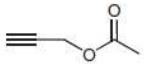
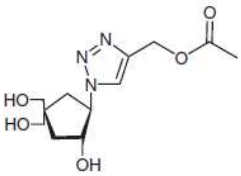
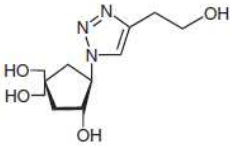
In our previous studies, NHC–copper complexes were found to be more efficient in water than in organic solvents.[22] However, all reagents and the catalyst were insoluble in water. In the present case, the solubility of **2** in water could explain the low conversion in this solvent (20%). The NHC complex was also difficult to separate from the formed triazoles.

Results obtained for the cycloaddition of **2** and different alkynes in the presence of $[Cu(MeCN)_4]PF_6$ under microwave irradiation in *tert*-butyl alcohol–water or dichloromethane–methanol mixtures are presented in Table 4. Even if similar results were obtained in both cases, it is important to note that the alkyne reactivity switched as a function of the solvent employed. Electron-poor alkynes were more reactive in aqueous media than in organic solvents (Table 4, entries 3, 4). However, shorter reaction times were required in organic media in the case of triaz-

Table 2 Alkynes Screening[a,b]



(±)-**2** (±)-**3–6**

Entry	Alkyne	Triazoles (±)-**3–6**		$Cu(0)/CuSO_4$ (80/20 mol%)	$[Cu(MeCN)_4]PF_6$ (5 mol%)	(IMes)CuBr (5 mol%)
1		 (±)-**3**	Δ	40 min	13 h	5 d
			conversion (%)	100	100	95
			yield (%)	98	99	91
			MW	2 min	15 min	9 h
			conversion (%)	100	100	100
			yield (%)	98	98	94
2		 (±)-**4**	Δ	5 d	5 d	5 d
			conversion (%)	80	0	51
			yield (%)	75	0	40
			MW	1 h	10 h	2 h
			conversion (%)	100	79	100
			yield (%)	98	60	93
3		 (±)-**5**	Δ	<1 min	5 d	2 h
			conversion (%)	100	73	100
			yield (%)	96	17	70
			MW	<1 min	2 min	5 min
			conversion (%)	100	100	100
			yield (%)	95	92	93
4		 (±)-**6**	Δ	2 min	5 d	1 h
			conversion (%)	100	75	100
			yield (%)	95	71	96
			MW	2 min	2 h	15 min
			conversion (%)	100	100	100
			yield (%)	95	92	96

[a] Reaction conditions: **2** (0.27 mmol), alkyne (1.05 equiv), *t*-BuOH–H_2O (1:1, 2 mL); microwave (MW), 125 °C; thermal heating (Δ),75 °C.
[b] Conversions are an average of two runs and were determined by ^1H NMR of the crude product.

Table 3 Solvent Effect for (IMes)CuBr[a]

Alkyne	Triazole	Solvent	Time	Conversion[b] (%)
PhC≡CH	(±)-**3**	*t*-BuOH–H_2O (1:1)	9 h	100
PhC≡CH	(±)-**3**	H_2O	10 h	20
PhC≡CH	(±)-**3**	CH_2Cl_2–MeOH (95:5)	10 h	57
HC≡CCH_2OAc	(±)-**5**	CH_2Cl_2–MeOH (95:5)	2 h	100

[a] Reaction conditions: **2** (0.27 mmol), alkyne (1.05 equiv), (IMes)CuBr (5 mol%), solvent (2 mL), MW, 125 °C.
[b] Conversions are an average of two runs and were determined by ^{1}H NMR of the crude product.

Table 4 Catalytic Activity of $[Cu(MeCN)_4]PF_6$ in Aqueous and Organic Media[a]

Entry	Triazole	*t*-BuOH–H_2O (1:1)		CH_2Cl_2–MeOH (95:5)	
		Time	Yield (%)	Time	Yield (%)
1	(±)-**3**	15 min	98	5 min	99
2	(±)-**4**	10 h	60[b]	2 h	93
3	(±)-**5**	2 min	92	15 min	93
4	(±)-**6**	2 h	92	6 h	91

[a] Reaction conditions: **2** (0.27 mmol), alkyne (1.05 equiv), solvent (2 mL), MW, 125 °C.
[b] Conversion = 79%.

oles with electron-donating substituents (Table 4, entries 1, 2).

The regioselectivity of the reaction under microwave irradiation was confirmed by using ^{1}H,^{13}C long range NMR experiments (HMBC). The selective formation of 1,4-disubstituted 1,2,3-triazoles was confirmed by the correlations highlighted in Figure 2. Notably, a long-range correlation between the H1′ of the sugar and the carbon bearing the 1*H*-triazole H5 was observed.

In conclusion, we have demonstrated the beneficial effect of microwave irradiation in the preparation of triazolylcarbanucleosides via 1,3-dipolar cycloaddition. Shorter reaction times and higher conversions are, hence, obtained when compared to thermal heating. The best results were obtained with the inexpensive Cu(0)/$CuSO_4$ mixture. The presence of a NHC ligand on the copper center appears to enhance the catalytic activity when compared to $[Cu(MeCN)_4]PF_6$. However, the cationic complex has the additional advantage of being efficient in both aqueous and organic media. The biological activity and toxicity of the synthesized triazoles against Vaccinia virus cells are under examination.

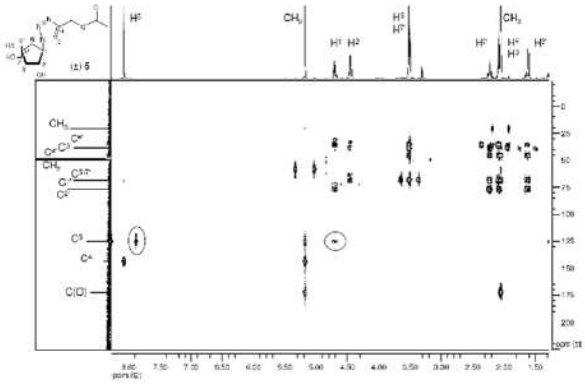


Figure 2 HMBC spectra for (±)-**5**

Commercially available chemicals were used as received. Microwave reactions were carried out in a Biotage AB Initiator EXP EU with a maximum power of 300 W. Reactions were monitored by TLC analysis using silica gel plates (Kieselgel 60 F_{254}). Compounds were visualized by UV irradiation and/or spraying with 2.5% phosphomolybdic acid in EtOH soln, followed by charring at 150 °C. Column chromatography was performed on silica gel 60 M (0.040–0.063 mm); petroleum ether = PE. ^{1}H NMR spectra were recorded on 250 MHz or 300 MHz spectrometers, and ^{13}C NMR on 62.9 MHz or 125 MHz spectrometers at r.t., using TMS as the internal standard. The attribution of NMR signals was made according to the numbering used for (±)-**5** in Figure 2. HRMS analyses were performed by the Mass Spectrometry Facility at the Institute of Chemical Research of Catalonia (ICIQ), Tarragona (Spain).

2-Azido-4,4-bis(hydroxymethyl)cyclopentanol [(±)-2]

To a soln of **1**[27] (2.20 g, 9.7 mmol) in MeOH–H_2O (8:2, 80 mL), NaN_3 (1.25 g, 19.4 mmol, 2 equiv) was added and the mixture was refluxed for 4 h. The solvents were evaporated under reduced pressure and the oily residue was purified by column chromatography (silica gel, PE–EtOAc, 5:5 to 2:8) to yield **2** (1.68 g, 93%) as a colorless oil.

^{1}H NMR (250 MHz, CD_3OD): δ = 3.94 (q, *J* = 7.2 Hz, 1 H, H1′), 3.67 (q, *J* = 7.6 Hz, 1 H, H2′), 3.44 (s, 2 H, H5′), 3.40 (s, 2 H, H7′), 1.92 (dd, *J* = 13.7, 7.4 Hz, 1 H, H3′), 1.87 (dd, *J* = 13.5, 7.2 Hz, 1 H, H6′), 1.49–1.40 (m, 2 H, H6′, H3′).

^{13}C NMR (62.9 MHz, CD_3OD): δ = 77.2 (CH, C1′), 68.9 (CH, C2′), 68.0 (CH_2, C5′), 67.9 (CH_2, C7′), 46.1 (C, C4′), 38.3 (CH_2, C6′), 34.4 (CH_2, C3′).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_7H_{13}N_3NaO_3$: 210.0855; found: 210.0854.

[1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]bromocopper [(IMes)CuBr]

Inside a glovebox, CuBr (0.520 g, 3.63 mmol), IMes·HCl (0.848 g, 2.52 mmol), and *t*-BuONa (0.243 g, 2.52 mmol) were loaded in a vial and stirred in anhyd THF (18 mL) overnight at r.t. outside the glovebox. After filtration of the mixture through a plug of Celite (THF), the filtrate was mixed with pentane to form a precipitate. A second filtration afforded the title complex (0.70 g, 62%) as an off-white complex.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (s, 6 H, H^{Ar}, NC*H*=), 2.36 (s, 6 H, CH_3), 2.12 (s, 12 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.0 (C, N*C*N), 139.4 (C, C^{Ar}), 135.0 (C, C^{Ar}), 134.5 (CH, C^{Ar}), 129.4 (CH, C^{Ar}), 122.2 (CH, N*C*H=), 21.1 (CH_3), 17.7 (CH_3).

Anal. Calcd for $C_{21}H_{24}BrCuN_2$ (447.88): C, 56.32; H, 5.40; N, 6.25. Found: C, 56.61; H, 5.66; N, 6.20.

1,3-Dipolar Cycloaddition under Microwave Irradiation; General Procedures

Using Cu(0)/CuSO$_4$: A soln of azide **2** (50 mg, 0.27 mmol) in *t*-BuOH–H$_2$O (1:1, 2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, Cu powder (13.5 mg, 80 mol%), 1 M CuSO$_4$ in H$_2$O (54 µL, 20 mol%) and finally the alkyne (1.05 equiv) were added. The vial was sealed with an aluminum/Teflon crimp top and the mixture was then irradiated at 125 °C. Upon completion of the reaction, the vial was cooled to 50 °C by air jet cooling before opening.

Using [Cu(MeCN)$_4$]PF$_6$: A soln of azide **2** (50 mg, 0.27 mmol) in *t*-BuOH–H$_2$O (1:1, 2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, [Cu(MeCN)$_4$]PF$_6$ (5 mg, 5 mol%) and the alkyne (1.05 equiv) were added. The vial was sealed with an aluminum/Teflon crimp top and the mixture was then irradiated at 125 °C. Upon completion of the reaction, the vial was cooled to 50 °C by air jet cooling before opening.

Using (IMes)CuBr: A soln of azide **2** (50 mg, 0.27 mmol) in *t*-BuOH–H$_2$O (1:1, 2 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, (IMes)CuBr (6 mg, 5 mol%) and the alkyne (1.05 equiv) were added. The vial was sealed with an aluminum/Teflon crimp top and the mixture was then irradiated at 125 °C. Upon completion of the reaction, the vial was cooled to 50 °C by air jet cooling before opening.

1,3-Dipolar Cycloaddition under Thermal Heating; General Procedures

Using Cu(0)/CuSO$_4$: Using a carousel reaction station, a soln of azide **2** (50 mg, 0.27 mmol) in *t*-BuOH–H$_2$O (1:1, 2 mL) was prepared in a test tube. Cu powder (13.5 mg, 80 mol%), 1 M CuSO$_4$ in H$_2$O (54 µL, 20 mol%) and finally the alkyne (1.05 equiv) were added. The mixture was then heated at 75 °C.

Using [Cu(MeCN)$_4$]PF$_6$: In a carousel reaction station, a soln of azide **2** (50 mg, 0.27 mmol) in *t*-BuOH–H$_2$O (1:1, 2 mL) was prepared in a reaction tube. [Cu(MeCN)$_4$]PF$_6$ (5 mg, 5 mol%) and the alkyne (1.05 equiv) were added. The mixture was then heated at 75 °C.

Using (IMes)CuBr: In a carousel reaction station, a soln of azide **2** (50 mg, 0.27 mmol) in *t*-BuOH–H$_2$O (1:1, 2 mL) was prepared in a reaction tube. (IMes)CuBr (6 mg, 5 mol%) and the alkyne (1.05 equiv) were added. The mixture was then heated at 75 °C.

4,4-Bis(hydroxymethyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclopentanol [(±)-3]

The title compound was prepared from phenylacetylene (31 mL, 0.28 mmol, 1.05 equiv). The mixture was filtered through a plug of Celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with sat. NaHCO$_3$ soln (2 × 5 mL) and brine (1 × 5 mL). The aqueous phases were extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield (±)-**3** as a white resin.

^{1}H NMR (250 MHz, CD$_3$OD): δ = 8.38 (s, 1 H, H5), 7.81 (d, *J* = 7.2 Hz, 2 H, HAr), 7.42 (t, *J* = 7.5 Hz, 2 H, H^{Ar}), 7.33 (t, *J* = 7.5 Hz, 1 H, H^{Ar}), 4.82–4.71 (m, 1 H, H1′), 4.53 (q, *J* = 9.0 Hz, 1 H, H2′), 3.54 (s, 2 H, H5′), 3.53 (s, 2 H, H7′), 2.27 (dd, *J* = 13.5, 8.3 Hz, 1 H, H6′), 2.15–2.10 (m, 2 H, H3′, H6′), 1.66 (dd, *J* = 13.4, 9.5 Hz, 1 H, H3′).

^{13}C NMR (62.9 MHz, CD$_3$OD): δ = 148.6 (C, C4), 131.8 (C, C^{Ar}), 130.0 (CH, 2 C^{Ar}), 129.3 (CH, C^{Ar}), 126.6 (CH, 2 C^{Ar}), 121.4 (CH, C5), 77.0 (CH, C2′), 68.8 (CH, C1′), 67.9 (CH$_2$, C5′), 67.8 (CH$_2$, C7′), 45.5 (C, C4′), 38.3 (CH$_2$, C3′), 35.8 (CH$_2$, C6′).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for C$_{15}$H$_{19}$N$_3$NaO$_3$: 312.1324; found: 312.1320.

4,4-Bis(hydroxymethyl)-2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)cyclopentanol [(±)-4]

From hept-1-yne (37 mL, 0.28 mmol, 1.05 equiv) and following the procedure described for the preparation of (±)-**3**, (±)-**4** was obtained as a transparent oil.

^{1}H NMR (250 MHz, CD$_3$OD): δ = 7.80 (s, 1 H, H5), 4.72–4.61 (m, 1 H, H1′), 4.45 (q, *J* = 8.9 Hz, 1 H, H2′), 3.51 (s, 2 H, H5′), 3.50 (s, 2 H, H7′), 2.68 (t, *J* = 7.7 Hz, 2 H, =CC*H*$_2$), 2.21 (dd, *J* = 13.5, 8.2 Hz, 1 H, H6′), 2.10–2.01 (m, 2 H, H3′, H6′), 1.74–1.64 (m, 2 H, =CCH$_2$C*H*$_2$), 1.61 (dd, *J* = 13.4, 9.5 Hz, 1 H, H3′) 1.39–1.32 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.92 (t, *J* = 7.0 Hz, 3 H, CH$_3$).

^{13}C NMR (62.9 MHz, CD$_3$OD): δ = 150.0 (C, C4), 122.3 (CH, C5), 76.9 (CH, C2′), 68.5 (CH, C1′), 67.9 (CH$_2$, C5′), 67.8 (CH$_2$, C7′), 45.5 (C, C4′), 38.3 (CH$_2$, C3′), 35.8 (CH$_2$, C6′), 32.5 (*C*H$_2$CH$_2$CH$_3$), 30.3 (=CCH$_2$*C*H$_2$), 26.3 (=C*C*H$_2$), 23.4 (*C*H$_2$CH$_3$), 14.3 (CH$_3$).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for C$_{14}$H$_{25}$N$_3$NaO$_3$: 306.1794; found: 306.1793.

1-[2-Hydroxy-4,4-bis(hydroxymethyl)cyclopentyl]-1*H*-1,2,3-triazol-4-ylmethyl Acetate [(±)-5]

The title compound was prepared from propargyl acetate (28 mL, 0.28 mmol, 1.05 equiv). The mixture was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc–MeOH, 1:0 to 95:5). Compound (±)-**5** was isolated as a clear oil.

^{1}H NMR (250 MHz, CD$_3$OD): δ = 8.08 (s, 1 H, H5), 5.18 (s, 2 H, CH$_2$), 4.76–4.65 (m, 1 H, H1′), 4.45 (q, *J* = 9.0 Hz, 1 H, H2′), 3.52 (s, 2 H, H5′), 3.50 (s, 2 H, H7′), 2.22 (dd, *J* = 13.5, 8.2 Hz, 1 H, H6′), 2.10–2.04 (m, 2 H, H3′, H6′), 2.05 (s, 3 H, CH$_3$), 1.62 (dd, *J* = 13.4, 9.5 Hz, 1 H, H3′).

^{13}C NMR (62.9 MHz, CD$_3$OD): δ = 172.4 [C, C(O)], 143.8 (C, C4), 125.0 (CH, C5), 76.9 (CH, C2′), 68.8 (CH, C1′), 67.84 (CH$_2$, C5′), 67.78 (CH$_2$, C7′), 58.4 (CH$_2$), 45.5 (C, C4′), 38.3 (CH$_2$, C3′), 35.7 (CH$_2$, C6′), 20.7 (CH$_3$).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for C$_{12}$H$_{19}$N$_3$NaO$_5$: 308.1222; found: 308.1229.

2-[4-(2-Hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]-4,4-bis(hydroxymethyl)cyclopentanol [(±)-6]

The title compound was prepared from but-3-yn-1-ol (21 mL, 0.28 mmol, 1.05 equiv). The mixture was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc–MeOH, 1:0 to 95:5). Compound (±)-**6** was isolated as a clear oil.

^{1}H NMR (250 MHz, CD$_3$OD): δ = 7.86 (s, 1 H, H5), 4.69–4.65 (m, 1 H, H1′), 4.44 (q, *J* = 8.9 Hz, 1 H, H2′), 3.81 (t, *J* = 6.5 Hz, 2 H, C*H*$_2$OH), 3.51 (s, 2 H, H5′), 3.50 (s, 2 H, H7′), 2.91 (t, *J* = 6.6 Hz, 2 H, =CC*H*$_2$), 2.21 (dd, *J* = 13.5, 8.3 Hz, 1 H, H6′), 2.10–2.03 (m, 2 H, H3′, H6′), 1.61 (dd, *J* = 13.4, 9.6 Hz, 1 H, H3′).

^{13}C NMR (62.9 MHz, CD$_3$OD): δ = 145.9 (C, C4), 123.2 (CH, C5), 77.0 (CH, C2′), 68.5 (CH, C1′), 67.9 (CH$_2$, C5′), 67.8 (CH$_2$, C7′), 62.1 (CH$_2$OH), 45.5 (C, C4′), 38.2 (CH$_2$, C3′), 35.7 (CH$_2$, C6′), 29.9 (=C*C*H$_2$).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for C$_{11}$H$_{19}$N$_3$NaO$_4$: 280.1273; found: 280.1269.

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References

(1) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1; Padwa, A., Ed.; Wiley: New York, **1984**.

(2) (a) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33. (b) Finley, K. T. *The Chemistry of Heterocyclic Compounds*, Vol. 39; Wiley: New York, **1980**, 349. (c) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225. For therapeutic activities see: (d) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1986**, *29*, 2262. (e) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (f) Chen, M. D.; Lu, S. J.; Yuag, G. P.; Yang, S. Y.; Du, X. L. *Heterocycl. Commun.* **2000**, *6*, 421. (g) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.

(3) Wang, Q.; Chittaboina, S.; Barnhill, H. N. *Lett. Org. Chem.* **2005**, *2*, 293.

(4) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

(5) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(6) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

(7) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

(8) (a) Alonso, R.; Camarasa, M. J.; Alonso, G.; de las Heras, F. G. *Eur. J. Med. Chem.* **1980**, *15*, 105. (b) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De Clercq, E.; Balzarini, J.; Camarasa, M. J. *Antiviral Chem. Chemother.* **1998**, *9*, 481. (c) Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R. F.; Agrofoglio, L. A. *Bioorg. Med. Chem.* **2003**, *11*, 3633.

(9) (a) San-Felix, A.; Alvarez, R.; Velazquez, S.; De Clercq, E.; Balzarini, J.; Camarasa, M. J. *Nucleosides Nucleotides* **1995**, *14*, 595. (b) Yamashita, M.; Mallikarjuna Reddy, P.; Kato, Y.; Krishna Reddy, V.; Suzuki, K.; Oshikawa, T. *Carbohydr. Res.* **2001**, *336*, 257. (c) Lazrek, H. B.; Taourirte, M.; Oulih, T.; Barascut, J. L.; Imbach, J. L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. *Nucleosides, Nucleotides Nucleic Acids* **2001**, *20*, 1949. (d) Joubert, N.; Schinazi, R. F.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 11744. (e) Guezguez, R.; Bougrin, K.; El Akri, K.; Benhida, R. *Tetrahedron Lett.* **2006**, *47*, 4807.

(10) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

(11) Quader, S.; Boyd, S. E.; Jenkins, I. D.; Houston, T. A. *J. Org. Chem.* **2007**, *72*, 1962.

(12) (a) Durán Pachón, L.; Van Maarseveen, J. H.; Rothenberg, R. *Adv. Synth. Catal.* **2005**, *347*, 811. (b) Aucagne, V.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186. (c) Lipshutz, B. H.; Taft, B. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 8235. (d) Chassaing, S.; Kumarraja, M.; Sani Souna Sido, A.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883.

(13) Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 4505.

(14) Feng, L.; Zhang, X.; Yu, Z.; Wang, J.; Gu, Z. *Chem. Mater.* **2002**, *14*, 4021.

(15) For the copper-catalyzed coupling of terminal alkynes (i.e., the Glaser reaction), see: (a) Glaser, C. *Ber. Dtsch. Chem Ges.* **1869**, *2*, 422. (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

(16) (a) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951. (b) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853. (c) Meng, J.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett.* **2005**, *46*, 4543. (d) Gerard, B.; Ryan, J.; Beeler, A. B.; Porco, J. A. Jr. *Tetrahedron* **2006**, *62*, 6405.

(17) For recent reviews on NHC ligands, see: (a) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, **2006**. (b) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: Berlin, **2007**.

(18) Díez-González, S.; Nolan, S. P. *Synlett* **2007**, 2158.

(19) Lebel, H.; Davi, D.; Díez-González, S.; Nolan, S. P. *J. Org. Chem.* **2007**, *72*, 144.

(20) (a) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157. (b) Díez-González, S.; Scott, N. M.; Nolan, S. P. *Organometallics* **2006**, *25*, 2355.

(21) Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10846.

(22) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558.

(23) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784.

(24) File CCDC 654537 contains the complete crystallographic data for (IMes)CuBr. These data can be obtained free of charge from The Cambridge Crystallographic Data center via www.ccdc.cam.ac.uk/data–request/cif.

(25) For representative examples, see: (a) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 1191. (b) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics* **2006**, *25*, 4097; see also ref. 20a and 23.

(26) Depres, J. P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928.

(27) Paulsen, H.; Maass, U. *Chem. Ber.* **1981**, *114*, 346.

(28) For reviews on microwave-assisted reactions see: (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (c) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, **2002**. (d) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

(29) (a) Louërat, F.; Bougrin, K.; Loupy, A.; Ochoa de Retana, A. M.; Pagalday, J.; Palacios, F. *Heterocycles* **1998**, *48*, 161. (b) Rijkers, D. T. S.; Van Esse, G. W.; Merkx, R.; Brouwer, A. J.; Jacobs, H. J. F.; Pieters, R. J.; Liskamp, R. M. J. *Chem. Commun.* **2005**, 4581. (c) Perissutti, E.; Frecentese, F.; Fiorino, F.; Severino, B.; Cirillo, D.; Santagada, V.; Caliendo, G. *J. Heterocycl. Chem.* **2007**, *44*, 815. See also: (d) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.

(30) For mechanistic studies on CuAAC, see: (a) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 2210. (b) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 2001; see also ref. 10.

(31) Ratio 1,4-triazole/1,5-triazole = 65:35.

(32) Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077.

(33) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2005**, 51.

(34) Trost, B. M.; Ball, Z. T.; Jöge, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 7922.

FULL PAPER

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Click Azide-Alkyne Cycloaddition for the Synthesis of D-(–)-1,4-Disubstituted Triazolo-Carbanucleosides

Julie Broggi,[a,b,c] Hiroki Kumamoto,[a] Sabine Berteina-Raboin,[a] Steven P. Nolan,[b,c] and Luigi A. Agrofoglio*[a]

Dedicated to Professor J. M. Robins on the occasion of his 70th birthday

Keywords: Nucleosides / Carbanucleosides / Antiviral agents / Olefin metathesis / Huisgen cycloaddition / Ribavirin / Poxvirus

A revisited and improved synthesis of an optically active azido-carbanucleoside is reported. This azido precursor is used in the successful and versatile synthesis of enantiomerically pure D-(–)-1,4-disubstituted 1,2,3-triazolo-carbanucleosides via copper(I)-catalyzed and microwave-assisted Huisgen 1,3-dipolar cycloaddition.
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Introduction

Natural D-nucleosides and their L-counterparts usually exhibit different antiviral activities and toxicities.[1] Regarding carbocyclic nucleosides,[2,3] enantiomers with a β-D-configuration exhibited significantly better antiviral effects than their L-analogues as they appear to be better candidate for enzyme targeting and enzyme activation (phosphorylation). In the search for less toxic and more potent inhibitors of the *S*-adenosylhomocysteine SAH *hydrolase*, an enzyme involved in methyl transfer reactions,[4] many D-carbocyclic analogues have emerged as effective inhibitors of vaccinia virus.[5,6] Therefore, the enantiospecific syntheses of carbanucleosides are crucial for further exploration of this class of compounds.[7] The synthetic approach deals principally with access to the enantiomerically pure highly oxygenated cyclopentane skeleton. However, the overall availability of optically active derivatives remains limited due to the lack of convenient methodologies for large-scale and stereospecific preparation of key intermediates. Thus, new synthetic intermediates for enantiomerically pure carbocyclic nucleosides are of significant interest.

We report here the revisited and improved large-scale synthesis of an optically active azido-carbanucleoside as a flexible building block for further synthetic elaboration[8] This azido-precursor was used in the successful and versatile synthesis of 1,4-disubstituted D-(–)-1,2,3-triazolo-carbanucleosides via copper(I)-catalyzed and microwave-assisted Huisgen 1,3-dipolar cycloaddition.[9] Previously, we and others had reported the synthesis of diverse carbanucleosides bearing a 1,2,3-triazole moiety, structurally related to ribavirin,[10,11] with interesting antiviral activities against HIV-1,[12] varicella-zoster virus,[13] or vaccinia virus.[14] In

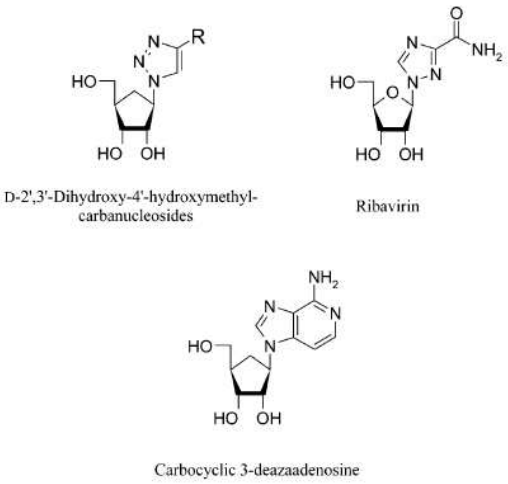

Figure 1. Structure–activity relationship.

[a] Institut de Chimie Organique et Analytique (ICOA) UMR-6005 CNRS, Université de Orléans, 45067 Orléans, France
Fax: +33-2-38417281
E-mail: luigi.agrofoglio@univ-orleans.fr
[b] Institute of Chemical Research of Catalonia (ICIQ), 16, Av. Països Catalans, 43007 Tarragona, Spain
[c] School of Chemistry, University of St Andrews, St Andrews, KY16 9ST, UK
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order to examine structure-activity relationships and include former results, we opted to study a 2′,3′-dihydroxy-4′-hydroxymethyl-substituted carbocyclic moiety structurally related to the anti-pox agent ribavirin and to carbocyclic 3-deazaadenosine (Figure 1).

Results and Discussion

To the best of our knowledge, the only synthesis of the D-azido-carbanucleoside **8** was reported in 1988 by Tadano et al.[15] and it was used as precursor for the synthesis of carbocyclic nucleoside antibiotics. The synthetic approach used consisted in targeting the optically active carbocyclic skeleton using carbohydrates as starting materials. However, the enantioselectivity across numerous steps could not be controlled and tedious purifications by repeated column chromatography were necessary to separate the different epimers. Herein, we present an enantiomerically controlled synthesis of **8** in 16 steps (Scheme 1). To access the key optically active azide intermediate **8**, we selected the D-2-cyclopentenone **3** known as a versatile synthon for various D-carbocyclic nucleosides.[16] The first practical procedures to obtain **3** were reported by Jeong et al.[17] starting from inexpensive D-isoascorbic acid and then by Chu et al.[19] from D-ribose. The first method was problematic in large-scale preparation due to the extreme sensitivity of many intermediates as well as difficulties in controlling the stereoselective oxidation and reduction steps. Hence in spite of some variations brought to the approach, we chose to follow the second procedure[19] for the larger-scale synthesis of **3** taking advantage of the existing stereogenic centers of D-ribose (Scheme 1).

In both Jeong's and Chu's procedures, the ring-closing metathesis (RCM)[18] reaction of the diene **1** was performed using Grubbs' catalyst.[20] In our case, the RCM reaction to afford the D-cyclopentenol **2** was carried out using 1.5 mol-% of the Ru catalyst **9** developed by Nolan et al.[21] (Figure 2). Diene **1** was completely converted to **2** within 1 h of reaction at 25 °C. However, since the ring-closed cyclopentenol **2** is highly volatile, the desired D-2-cyclopentenone **3** was directly obtained in 79% overall yield from **1** by oxidation of the secondary alcohol under PCC oxidation conditions without isolation of cyclopentenol **2**.

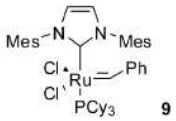
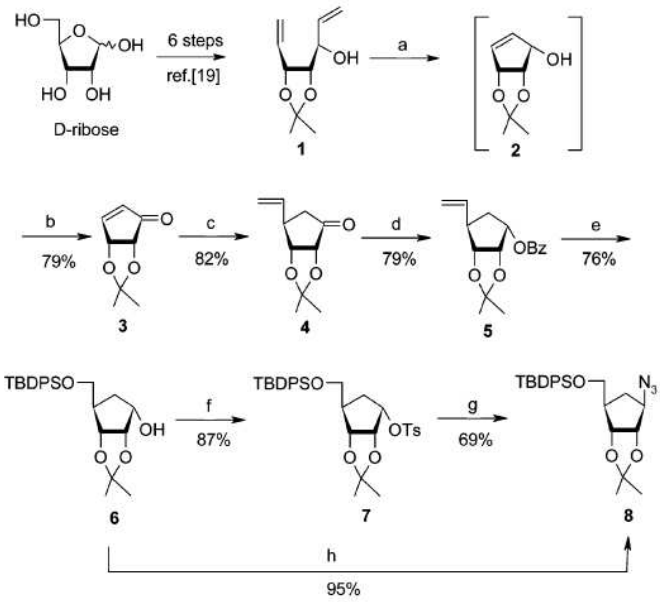


Figure 2. Ruthenium catalyst **9**.

Compound **3** was then easily converted to unstable *exo*-olefin **4** following Schneller's method (Scheme 1).[22] This synthetic approach consists in using a vinyl group as a mask for the hydroxymethyl group of carbocyclic nucleosides.



Scheme 1. Reagents and conditions: (a) [Ru] = **9** (1.5 mol-%), anhydrous CH_2Cl_2, 24 °C, 1 h; (b) pyridinium chlorochromate, CH_2Cl_2, room temp., 12 h; (c) vinylmagnesium bromide, CuBr·Me_2S, TMSCl, HMPA, THF, –78 °C, 3 h; (d) *(i)* $LiAlH_4$, THF, 0 °C to room temp., 2 h; *(ii)* BzCl, DMAP, *i*Pr_2NEt, CH_3CN, 0 °C to room temp., 2 h; (e) *(i)* OsO_4, $NaIO_4$, MeOH/acetone/H_2O, room temp., 30 min; *(ii)* $NaBH_4$, MeOH, –78 °C to room temp., 40 min; *(iii)* *tert*-butylchlorodiphenylsilane, imidazole, DMAP, CH_3CN, room temp., 1 h; *(iv)* NaOMe, MeOH, 0 °C to room temp., 15 h; (f) TsCl, *i*Pr_2NEt, DMAP, CH_3CN, 0 °C to room temp., 24 h; (g) NaN_3, 18-crown-6, DMF, 140 °C, 2 h; (h) DIAD, DPPA, PPh_3, THF, 0 °C to room temp., 7 h.

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The incorporation of a vinyl group onto a cyclopentyl ring by 1,4-enone addition is known to be a high-yielding reaction.[23]

Copper(I) bromide–dimethyl sulfide complex induces the formation of an organocuprate via transmetallation with vinylmagnesium bromide.[24] This less reactive organocuprate leads to a regioselective 1,4-addition of the vinyl group to α,β-unsaturated ketones. On the other hand, addition of TMSCl-HMPA promotes the conjugate addition by trapping the magnesium enolate intermediate with TMSCl.[25] The role of HMPA may be to cleave the dimer frequently engendered by cuprates.[26] Thus, 1,4-addition of vinylmagnesium bromide to **3** cleanly afforded ketone **4** in 82% yield. Freshly opened vinylmagnesium bromide (*not* chloride!) is essential to successfully carry out this reaction. After stereoselective reduction of ketone **4** and subsequent benzoylation, benzoate **5** was afforded in moderate yield. The silyl ether **6** was obtained in good yield from **5** by i) oxidative glycol cleavage of *exo*-olefin using osmium tetroxide/sodium periodate, ii) sodium borohydride reduction of the resulting aldehyde, iii) protection of primary alcohol, and iv) debenzoylation sequence. Finally, we first tried to introduce an azide function by simple tosylation and S_N2 azidation. However, the overall yield of the desired **8** was only 60% for two steps. On the other hand, the application of Mitsunobu azidation[27] appeared to be more convenient for the synthesis of **8**. Alcohol **6** was treated with diisopropyl azodicarboxylate (DIAD) and diphenyl phosphoryl azide (DPPA) in the presence of PPh_3. Azide **8** was obtained in 95% yield as the single stereoisomer. The enantioselective addition of azide function with inversion of configuration was confirmed by NOESY spectroscopy (Figure 3). Unlike the correlation observed between $H^{1'}$ and $H^{2'}$ in the α-cyclopentanol **6**, only correlations between $H^{1'}$ and the two $H^{6'}$ were detected in the β-oriented azido carbocycle **8**.

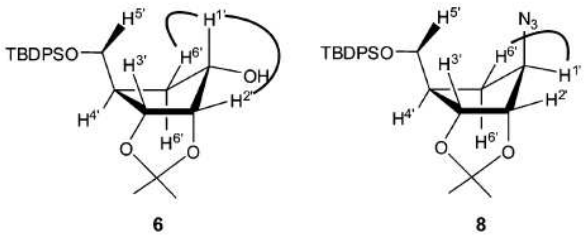
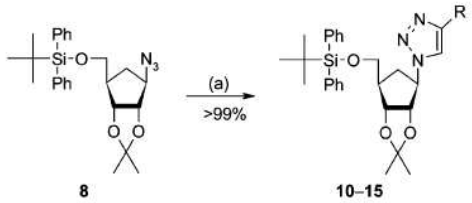


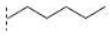
Figure 3. NOESY correlations of **6** and **8**.

Then, we performed the Huisgen 1,3-dipolar cycloaddition[9] between enantiomerically pure azidocarbocycle **8** and various terminal alkynes under the optimized reaction conditions previously reported for racemic series of 1,4-disubstituted (±)-1,2,3-triazolo-4′-hydroxymethyl-carbanucleosides.[28] A mixture copper Cu^0/copper sulfate $Cu^{II}SO_4$,[29] in situ comproportionated to form Cu^I, was used as a water soluble catalyst to obtain selectively the 1,4-disubstituted regioisomer.[30] This option is particularly attractive, as copper metal and copper sulfate are inexpensive. In a mixture water/*tert*-butyl alcohol under microwave irradiation,[31] $Cu^0/CuSO_4$-catalyzed reactions were performed with complete conversion of **8** into the desired 1,4-disubstituted triazoles **10**–**15** in extremely short reaction times (<15 min) and with no observable formation of by-products (Table 1). These results demonstrated that this previously developed method[28] was also applicable to different azido-carbanucleosidic substrates even if the latter contained protecting groups. According to the "click" chemistry prerogatives,[32] the reaction was stereoselective, versatile, and insensitive to oxygen and water. Even, the electron-deficient 1-heptyne reacted within a few minutes (Table 1, entry 3). Compounds **10**–**15** were isolated in high yield and purity by simple liquid-liquid extraction.

Table 1. Microwave assisted 1,3-dipolar cycloaddition of azido derivative **8**.



Reaction conditions: (a) azide **8** (0.1 mmol), alkyne (1.05 equiv.), Cu^0 (80 mol-%)/$CuSO_4$ (20 mol-%), *t*BuOH/H_2O (1:1) (1 mL), microwave (MW): T = 125 °C.

Entry	R	Triazole	Time [min]
1		**10**	5
2		**11**	1
3		**12**	15
4		**13**	1
5		**14**	1
6		**15**	1

The regioselectivity of the cycloaddition reaction under microwave irradiation was confirmed by using ^1H and ^{13}C long-range NMR experiments (HMBC). The selective formation of 1,4-disubstituted 1,2,3-triazoles was confirmed by a long-range correlation between the $H^{1'}$ of the sugar and the carbon bearing the 1*H*-triazole H^5 (Figure 4).

Finally, deprotection of the isopropylidene and the silyloxy groups afforded the final optically active compounds **16**–**21** in moderate to quantitative yields (Table 2). According to NOESY experiments, the β-configuration is conserved during the 1,3-dipolar cycloaddition. As for azide **8**, only correlations between $H^{1'}$ and the two $H^{6'}$ were detected in the β-oriented triazolo-carbanucleosides.

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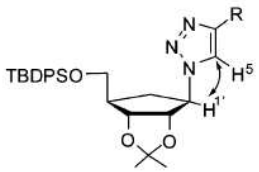
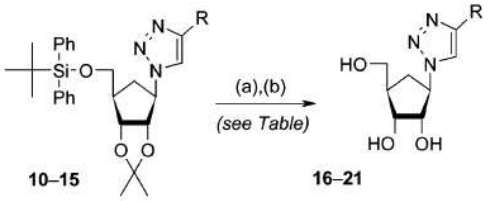
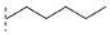


Figure 4. HMBC correlation for 1,4-disubstituted 1,2,3-triazoles **10–15**.

Table 2. Deprotection of 1,4-disubstituted 1,2,3-triazolo-carbanucleosides **10–15**.[a]



Reaction conditions: (a) triazole **10-15** (0.1 mmol), TFA 60% (2 mL), r.t., 16 h; (b) TBAF (1.05 equiv.), THF (2 mL), r.t., 1 h.

Entry	R	Triazole	Yield (%)
1		**16**	86
2		**17**	98
3		**18**	88
4		**19**	76
5		**20**	80
6		**21**	52

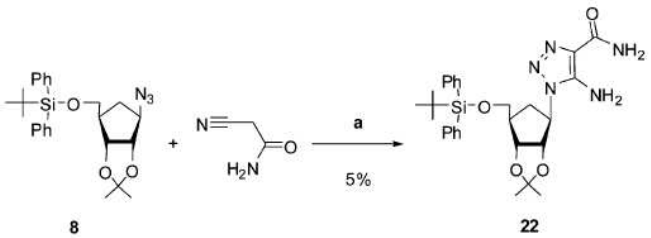
The synthesis of an optically pure 1,4,5-trisubstituted triazolo-carbanucleoside was also attempted. To achieve the synthesis of **22**, we applied our protocol previously optimized for 1,2,3-triazolo-3′-deoxy-carbanucleosides,[33] inspired by the reported 1,3-dipolar cycloaddition of azides and 2-cyanoacetamide.[34] In spite of reaction times of 48 h in refluxing ethanol, the starting material **8** was almost completely recovered (Scheme 2). Nevertheless, 5% of the expected compound **22** could be isolated and characterized.

Conclusions

In conclusion, we have explored the syntheses of D-configured 1,4-disubstituted 1,2,3-triazolo-carbanucleosides via optimized copper(I)-catalyzed microwave-assisted alkyne–azide Huisgen cycloaddition. The preparation of an enantiomerically pure cyclopentane azide derivative was achieved using an optically active enone intermediate, readily obtained by published procedure on a multi-gram scale. Final Mitsunobu azidation proved a superior method compared to traditional tosylation and S_N2 azidation sequence. The D-azide was then sucessfully reacted with different terminal alkynes to afford the corresponding 1,4-disubstituted D-(–)-1,2,3-triazolo-carbanucleosides, confirming the efficiency of the developed tool for different azido-carbanucleosidic substrates. Despite a carbocyclic 3-deazaadenosine-like carbocycle moiety, none of the synthesized compounds showed any cytotoxicity or significant antiviral activity on infected vaccinia virus cells. Comparing the evaluated compounds to known *anti*-pox nucleosides, the structure-activity relationship study suggests that 1,4-disubstituted 1,2,3-triazoles are not adequate bases for smallpox inhibition. In the domain of nucleoside chemistry, this original azido compound could be an important candidate and versatile precursor not only for cycloaddition with diverse dipolarophiles but also for various transformations involving azides.

Experimental Section

General: Commercially available chemicals were used as received. Microwave reactions were carried out in a Biotage Initiator with a maximum power of 300 W and temperatures were measured by IR sensor. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}). Compounds were visualized by UV irradiation and/or spraying with ethanol solution 2.5% in phosphomolybdic acid, followed by charring at 150 °C. Column chromatography was performed on Silica Gel 60 M (0.040–0.063 mm). ^{1}H NMR spectra were recorded on 250 MHz or 400 MHz spectrometers, and ^{13}C NMR on 62.9 MHz or 125 MHz spectrometers at room temperature, using deuterated solvents as the internal standard. Chemical shifts are given in ppm



Scheme 2. Reagents and conditions: (a) EtONa, EtOH, reflux, N_2, 48 h.

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and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), q_i (quintuplet) and m (multiplet). Assignments of NMR spectra follow standard nucleosides nomenclature: triazole bases are numbered from N-1 to C-5 and carbocycles are numbered from C-1′ to C-6′ with C-5′ for the 4-hydroxymethyl chain. Similar conventions apply for the corresponding hydrogen atoms.

(4*R*,5*R*)-(–)-4,5-Isopropylidenedioxy-2-cyclopenten-1-one (3): D-Ribose was converted into the diene **1** in six steps according to Chu's procedure.[19] A solution of diene **1** (7.0 g, 38 mmol) in anhydrous CH_2Cl_2 (200 mL) was added to [Ru] = catalyst **9** (0.48 g, 1.5 mol-%) under N_2 atmosphere. After 1 h of stirring at 24 °C, pyridinium chlorochromate (12.3 g, 57 mmol, 1.5 equiv.) was added to the resulting dark brown mixture. The reaction mixture was stirred at room temperature for 12 h and filtered through a silica gel pad (EtOAc). The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 9:1), to give the unstable compound **3** (4.63 g, 79%) as a white crystalline solid. $[\alpha]_D^{27}$ = –74.5 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 5.9 and 2.3 Hz, 1 H, H$^{3'}$), 6.21 (d, *J* = 5.9 Hz, 1 H, H$^{2'}$), 5.26 (dd, *J* = 5.5 and 2.3 Hz, 1 H, H$^{4'}$), 4.46 (d, *J* = 5.5 Hz, 1 H, H$^{5'}$), 1.42 (s, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9 (C, CO), 159.5 (CH, C$^{3'}$), 134.2 (CH, C$^{2'}$), 115.5 (C), 78.6 (CH, C$^{4'}$), 76.5 (CH, C$^{5'}$), 27.4 (CH_3), 26.1 (CH_3) ppm. MS (ESI): (M^+ + Na) *m*/*z* 177.0. CAS: 115509-13-2.

(1*S*,2*S*,3*R*,4*R*)-2,3-Isopropylidenedioxy-4-vinylcyclopentyl Benzoate (5): Compound **3** was converted into **4** according to Schneller's procedure.[22] A THF (40 mL) solution of **4** (4.46 g, 24.5 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.67 g, 44.1 mmol, 1.8 equiv.) in THF (100 mL) at 0 °C under Ar. After 5 min of stirring, the reaction mixture was warmed to room temperature and stirred a further 3 h. H_2O (1 mL), 15% NaOH aqueous solution (1 mL) and H_2O (1 mL) were added in turn at 0 °C. The solution was filtered through a short celite pad and the filtrate was concentrated under reduced pressure. To a MeCN (40 mL) solution of the resulting residue, 4-(dimethylamino)pyridine (6.01 g, 49.0 mmol, 2 equiv.), *N*,*N*-diisopropylethylamine (8.54 mL, 49.0 mmol, 2 equiv.) and benzoyl chloride (5.6 mL, 49.0 mmol, 2 equiv.) were added at 0 °C under Ar. After 2 h of stirring at room temperature, the reaction mixture was diluted with EtOAc and then washed with aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with EtOAc and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 5:1). **5** (5.54 g, 79% for 2 steps) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –66.6 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.5 Hz, 2 H, H^{Ar}), 7.57 (t, *J* = 7.4 Hz, 1 H, H^{Ar}), 7.45 (t, *J* = 7.8 Hz, 2 H, H^{Ar}), 5.83 (ddd, *J* = 17.1, 10.5 and 6.6 Hz, 1 H, H$^{5'}$), 5.20–5.12 (m, 3 H, H_2C = +H$^{1'}$), 4.80 (t, *J* = 5.6 Hz, 1 H, H$^{2'}$), 4.54 (d, *J* = 5.6 Hz, 1 H, H$^{3'}$), 2.88 (br. s, 1 H, H$^{4'}$), 2.36–2.29 (m, 1 H, H$^{6'}$), 2.09–2.03 (m, 1 H, H$^{6'}$), 1.43 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3 (C, CO), 137.8 (CH, C$^{5'}$), 133.1 (CH, C^{Ar}), 130.3 (C, C^{Ar}), 129.9 (CH, 2C^{Ar}), 128.4 (CH, 2C^{Ar}), 115.8 (CH_2, H_2C=), 111.9 (C), 84.4 (CH, C$^{3'}$), 78.3 (CH, C$^{2'}$), 73.8 (CH, C$^{1'}$), 44.2 (CH, C$^{4'}$), 32.5 (CH_2, C$^{6'}$), 26.3 (CH_3), 24.7 (CH_3) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{17}H_{20}NaO_4$ (M^+ + Na) 311.1259, found 311.1259. IR (neat): $\tilde{\nu}$ = 1710 (C=O), 1637 (C=C), 1491, 1453, 1372 (C=C aromatic), 1268–1047 (C–O) cm^{-1}.

(1*S*,2*S*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxycyclopentan-1-ol (6): To a solution of **5** (4.51 g, 15.6 mmol) and $NaIO_4$ (6.69 g, 31.3 mmol, 2 equiv.) in MeOH/acetone/H_2O (1:1:1, 240 mL), a solution of OsO_4 (2.5 wt.-% in *t*BuOH) (1 mL) was added at room temperature. After 1.5 h of stirring, the reaction mixture was filtered through a celite pad and concentrated. The resulting residue was diluted with CH_2Cl_2 and then washed with brine. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. The crude **A** aldehyde was obtained as an oil and directly used in the next step without further purification. To a MeOH (100 mL) solution of crude **A**, $NaBH_4$ (1.18 g, 31.3 mmol, 2 equiv.) was added at –78 °C. After 40 min of stirring at room temperature, AcOH (2 mL) and acetone (100 mL) were added and the resulting reaction mixture was concentrated. The reaction mixture was diluted with CH_2Cl_2 and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. This crude alcohol **B** was used in the next step without further purification. To the MeCN (50 mL) solution of crude alcohol **B**, 4-(dimethylamino)pyridine (2.11 g, 17.2 mmol, 1.1 equiv.), imidazole (1.38 g, 20.3 mmol, 1.3 equiv.) and *tert*-butylchlorodiphenylsilane (5.26 mL, 20.3 mmol, 1.3 equiv.) were added at room temperature under N_2. After 1 h of stirring, the reaction mixture was diluted with EtOAc and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with EtOAc and the combined organic layers were dried with $MgSO_4$, filtered and concentrated to give the crude **C**. Freshly prepared 0.5 M NaOMe solution in MeOH (100 mL) was added to crude **C** at 0 °C and stirred for 16 h at room temperature. AcOH (8.6 mL) was added and the reaction mixture was concentrated. The resulting residue was diluted with CH_2Cl_2 and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. The oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1). Compound **6** (5.01 g, 76% for 4 steps) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –47.7 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 4 H, H^{Ar}), 7.45–7.36 (m, 6 H, H^{Ar}), 4.50 (d, *J* = 5.8 Hz, 1 H, H$^{3'}$), 4.44 (t, *J* = 5.8 Hz, 1 H, H$^{2'}$), 4.25–4.18 (m, 1 H, H$^{1'}$), 3.58 (dd, *J* = 10.3 and 5.6 Hz, 1 H, H$^{5'}$), 3.51 (dd, *J* = 10.3 and 5.6 Hz, 1 H, H$^{5'}$), 2.41 (d, *J* = 8.3 Hz, 1 H, OH), 2.24–2.23 (m, 1 H, H$^{4'}$), 1.93–1.82 (m, 2 H, H$^{6'}$), 1.50 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.04 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8 (CH, 2C^{Ar}), 135.7 (CH, 2C^{Ar}), 133.3 (C, 2C^{Ar}), 129.9 (CH, 2C^{Ar}), 127.9 (CH, 4C^{Ar}), 111.3 (C), 82.9 (CH, C$^{3'}$), 79.7 (CH, C$^{2'}$), 71.9 (CH, C$^{1'}$), 65.3 (CH_2, C$^{5'}$), 44.1 (CH, C$^{4'}$), 35.5 (CH_2, C$^{6'}$), 27.0 (*t*Bu), 26.3 (CH_3), 24.4 (CH_3), 19.3 (C-Si) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{34}O_4NaSi$ (M^+ + Na) 449.2124, found 449.2121. IR (neat): $\tilde{\nu}$ = 3520 (OH), 1471, 1427, 1381 (C=C aromatic), 1209–1040 (C–O) cm^{-1}. CAS: 112543-76-7.

(1*S*,2*R*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxy-1-tosyloxycyclopentane (7): To a CH_3CN (15 mL) solution of **6** (0.5 g, 1.17 mmol), 4-dimethylaminopyridine (0.2 g, 1.76 mmol, 1.5 equiv.) and *N*,*N*-diisopropylethylamine (0.3 mL, 1.76 mmol, 1.5 equiv.) at 0 °C, *p*-toluenesulfonyl chloride (0.34 g, 1.76 mmol, 1.5 equiv.) was added. After 10 min of stirring, the reaction mixture was warmed to room temperature. After 24 h of stirring, the reaction mixture was diluted with CH_2Cl_2 and then washed with an aqueous saturated $NaHCO_3$ solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. The oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1). **7** (0.59 g, 87%) was obtained as a colourless oil. The compound was pure enough by TLC to be directly engaged into the next reaction.

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(1*R*,2*S*,3*R*,4*R*)-1-Azido-4-[(*tert*-butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxycyclopentane (8). Procedure from 7: A DMF (4 mL) solution of **7** (0.22 g, 0.38 mmol), sodium azide (0.12 g, 1.9 mmol, 5 equiv.) and 18-crown-6 ether (0.12 g, 0.46 mmol, 1.2 equiv.) was heated for 3 h at 140 °C. The reaction mixture was diluted with EtOAc and then washed with brine. The aqueous phases were extracted with EtOAc and the combined organic layers were dried with $MgSO_4$. The oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 9:1). **8** (0.12 g, 69%) was obtained as a yellow oil. **Procedure from 6:** To a THF (80 mL) solution of **6** (2.0 g, 4.72 mmol) and PPh_3 (3.82 g, 14.16 mmol, 3 equiv.), a mixture of diisopropyl azodicarboxylate (2.8 mL, 14.16 mmol, 3 equiv.) and diphenylphosphoryl azide (3.07 mL, 14.16 mmol, 3 equiv.) in THF (20 mL) was added dropwise at 0 °C under Ar. After 7 h of stirring at room temperature, EtOH (30 mL) was added and stirred for 30 min. After evaporation of all volatiles, the oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 100:1 to 50:1). **8** (2.03 g, 95%) was obtained as yellow oil. $[\alpha]_D^{26}$ = –19.0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H, H^{Ar}), 7.46–7.37 (m, 6 H, H^{Ar}), 4.46 (dd, *J* = 6.2 and 2.5 Hz, 1 H, $H^{3'}$), 4.31 (dd, *J* = 6.2 and 3.5 Hz, 1 H, $H^{2'}$), 3.92 (td, *J* = 6.0 and 2.8 Hz, 1 H, $H^{1'}$), 3.69 (dd, *J* = 10.3 and 7.0 Hz, 1 H, $H^{5'}$), 3.63 (dd, *J* = 10.3 and 7.0 Hz, 1 H, $H^{5'}$), 2.37 (q_id, *J* = 7.0 and 2.5 Hz, 1 H, $H^{4'}$), 2.22 (dt, *J* = 13.8 and 7.0 Hz, 1 H, $H^{6'}$), 1.75 (dt, *J* = 13.8 and 5.7 Hz, 1 H, $H^{6'}$), 1.46 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8 (CH, $2C^{Ar}$), 135.7 (CH, $2C^{Ar}$), 133.6 (C, $2C^{Ar}$), 129.9 (CH, $2C^{Ar}$), 127.9 (CH, $4C^{Ar}$), 111.7 (C), 85.1 (CH, $C^{2'}$), 82.1 (CH, $C^{3'}$), 67.0 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 47.0 (CH, $C^{4'}$), 31.7 (CH_2, $C^{6'}$), 27.0 (*t*Bu + CH_3), 24.6 (CH_3), 19.4 (C Si) ppm. ^{29}Si NMR (79.5 MHz, $CDCl_3$): δ = –104.4 (br. s, Si) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{33}N_3NaO_3Si$ (M^+ + Na) 474.2189, found 474.2207. IR (neat): $\tilde{\nu}$ = 2102 (N_3), 1472, 1427, 1382 (C=C aromatic), 1160–1043 (C–O) cm^{-1}. CAS: 112543-78-9.

General Procedures for the 1,3-Dipolar Cycloaddition Under Microwave Irradiation. Synthesis of (–)-10–15: A solution of azide **8** (50 mg, 0.1 mmol) in a 1:1 mixture of water and *t*BuOH (1 mL) was prepared in a glass vial equipped with a magnetic stirring bar. Then, copper powder (5.6 mg, 80 mol-%), a water solution 1 M of copper sulfate (22 µL, 20 mol-%) and the alkyne (1.05 equiv.) were added in turn. The vial was sealed with an aluminum/Teflon® crimp cap and the reaction mixture was then irradiated at 125 °C. Upon completion of the reaction, the vial was cooled to 50 °C by air jet cooling before being opened. The reaction mixture was then filtered through a plug of celite (EtOAc) and the filtrate was concentrated under reduced pressure. The oily residue was then dissolved in 20 mL of EtOAc and washed twice with a saturated $NaHCO_3$ solution (5 mL) and once with brine (5 mL). The aqueous phases were extracted twice with EtOAc (20 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure.

(1*R*,2*S*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxy-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclopentane (10): The title compound was prepared from phenylacetylene (13 µL) after 5 min of microwave irradiation. Compound **10** (61 mg, >99%) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –25.7 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 8.5 and 1.4 Hz, 2 H, H^{Ar}), 7.84 (s, 1 H, H^5), 7.65 (dd, *J* = 7.8 and 1.4 Hz, 4 H, H^{Ar-Si}), 7.46–7.31 (m, 9 H, $6H^{Ar-Si}$ + $3H^{Ar}$), 4.86–4.77 (m, 2 H, $H^{2'}$ + $H^{1'}$), 4.61 (dd, *J* = 6.9 and 4.0 Hz, 1 H, $H^{3'}$), 3.82–3.75 (m, 2 H, $H^{5'}$), 2.64–2.42 (m, 3 H, $H^{4'}$ + $H^{6'}$), 1.57 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.08 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 130.8 (C, C^{Ar}), 129.9 (CH, $2C^{Ar-Si}$), 128.9 (CH, $2C^{Ar}$), 128.3 (CH, C^{Ar}), 127.9 (CH, $4C^{Ar-Si}$), 125.9 (CH, $2C^{Ar}$), 119.4 (CH, C^5), 113.6 (C), 85.1 (CH, $C^{2'}$), 81.2 (CH, $C^{3'}$), 66.5 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 45.9 (CH, $C^{4'}$), 33.7 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (*t*Bu), 25.1 (CH_3), 19.5 (C Si) ppm. ^{29}Si NMR (79.5 MHz, $CDCl_3$): δ =-103.9 (br. s, Si) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{33}H_{39}N_3NaO_3Si$ (M^+ + Na) 576.2658, found 576.2642.

(1*R*,2*S*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxy-1-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]cyclopentane (11): The title compound was prepared from 2-ethynyl pyridine (12 µL) after 1 min of microwave irradiation. Compound **11** (61 mg, >99%) was obtained as a light brown foam. $[\alpha]_D^{27}$ = –25.7 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (br. s, 1 H, N-CH), 8.24 (s, 1 H, H^5), 8.18 (d, *J* = 7.6 Hz, 1 H, =C-CH=), 7.78 (t, *J* = 7.6 Hz, 1 H, =C-CH=C*H*), 7.64 (dd, *J* = 6.4 and 1.2 Hz, 4 H, H^{Ar-Si}), 7.44–7.36 (m, 6 H, H^{Ar-Si}), 7.23 (br. s, 1 H, N-CH=C*H*), 4.87–4.81 (m, 2 H, $H^{2'}$ + $H^{1'}$), 4.59 (dd, *J* = 6.4 and 4.0 Hz, 1 H, $H^{3'}$), 3.81–3.74 (m, 2 H, $H^{5'}$), 2.66–2.59 (m, 1 H, $H^{6'}$), 2.49–2.40 (m, 2 H, $H^{4'}$ + $H^{6'}$), 1.55 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5 (C, =C), 149.5 (CH, N-CH), 148.5 (C, C^4), 137.0 (CH, =C-CH=*C*H), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 129.9 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 123.0 (CH, N-CH=*C*H), 121.8 (CH, C^5), 120.4 (CH, =C-*C*H=), 113.7 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 66.6 (CH, $C^{1'}$), 64.2 (CH_2, $C^{5'}$), 45.8 (CH, $C^{4'}$), 33.9 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (*t*Bu), 25.1 (CH_3), 19.4 (C-Si) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{32}H_{38}N_4NaO_3Si$ (M^+ + Na) 577.2635, found 577.2629.

(1*R*,2*S*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxy-1-(4-pentyl-1*H*-1,2,3-triazol-1-yl)cyclopentane (12): The title compound was prepared from 1-heptyne (15 µL) after 15 min of microwave irradiation. Compound **12** (60 mg, >99%) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –22.5 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 7.8 and 1.4 Hz, 4 H, H^{Ar-Si}), 7.45–7.35 (m, 6 H, H^{Ar-Si}), 7.33 (s, 1 H, H^5), 4.80–4.77 (m, 1 H, $H^{2'}$), 4.74–4.70 (m, 1 H, $H^{1'}$), 4.56 (dd, *J* = 6.8 and 4.0 Hz, 1 H, $H^{3'}$), 3.79–3.74 (m, 2 H, $H^{5'}$), 2.70 (t, *J* = 7.6 Hz, 2 H, =C-CH_2), 2.56–2.52 (m, 1 H, $H^{6'}$), 2.51–2.37 (m, 2 H, $H^{4'}$ + $H^{6'}$), 1.68–1.64 (m, 2 H, =C-CH_2-CH_2), 1.54 (s, 3 H, CH_3), 1.37–1.33 [m, 4 H, $(CH_2)_2$-CH_3], 1.29 (s, 3 H, CH_3), 1.06 (s, 9 H, *t*Bu), 0.89 [t, *J* = 7.2 Hz, 3 H, $(CH_2)_2$-CH_3] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 129.9 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 120.2 (CH, C^5), 113.5 (C), 85.1 (CH, $C^{2'}$), 81.2 (CH, $C^{3'}$), 66.2 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 45.8 (CH, $C^{4'}$), 33.9 (CH_2, $C^{6'}$), 31.6 (CH_2, *C*H_2-CH_2-CH_3), 29.3 (CH_2, =C-CH_2-*C*H_2), 27.6 (CH_3), 27.0 (*t*Bu), 25.8 (CH_2, =C-*C*H_2), 25.1 (CH_3), 22.5 (CH_2, *C*H_2-CH_3), 19.4 (C-Si), 14.1 (CH_2, CH_2-*C*H_3) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{32}H_{45}N_3NaO_3Si$ (M^+ + Na) 570.3128, found 570.3125.

(1*R*,2*S*,3*R*,4*R*)-1-[4-(Acetoxymethyl)-1*H*-1,2,3-triazol-1-yl]-4-[(*tert*-butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxycyclopentane (13): The title compound was prepared from propargyl acetate (12 µL) after 1 min of microwave irradiation. Compound **13** (60 mg, >99%) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –20.7 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 5 H, H^5 + H^{Ar-Si}), 7.45–7.36 (m, 6 H, H^{Ar-Si}), 5.21 (s, 2 H, =C-CH_2), 4.8–4.70 (m, 2 H, $H^{2'}$ + $H^{1'}$), 4.57 (dd, *J* = 6.8 and 4.4 Hz, 1 H, $H^{3'}$), 3.80–3.73 (m, 2 H, $H^{5'}$), 2.57–2.52 (m, 1 H, $H^{6'}$), 2.48–2.35 (m, 2 H, $H^{4'}$ + $H^{6'}$), 2.08 (s, 3 H, CO-CH_3), 1.54 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (CO), 142.9 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.4

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(C, $2C^{Ar-Si}$), 129.9 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 123.5 (CH, C^5), 113.7 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 66.6 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 57.7 (CH_2, =C-CH_2), 45.7 (CH, $C^{4'}$), 33.9 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (*t*Bu), 25.1 (CH_3), 21.0 (CH_3, CO-CH_3), 19.4 (C-Si) ppm. HRMS (ESI) *m/z* calcd. for $C_{30}H_{39}N_3NaO_5Si$ (M^+ + Na) 572.2557, found 572.2554. IR (neat): $\tilde{\nu}$ = 1741 (C=O), 1471, 1427, 1381 (C=C aromatic), 1229 (C–O), 1111–1030 (C–O) cm^{-1}.

(1*R*,2*S*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-1-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]-2,3-isopropylidenedioxycyclopentane (14): The title compound was prepared from 3-butyn-1-ol (9 µL) after 1 min of microwave irradiation. Compound **14** (57 mg, >99%) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –13.3 (*c* = 0.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 8.0 and 1.2 Hz, 4 H, H^{Ar-Si}), 7.46 (s, 1 H, H^5), 7.44–7.36 (m, 6 H, H^{Ar-Si}), 4.80–4.69 (m, 2 H, $H^{2'}$ + $H^{1'}$), 4.57 (dd, *J* = 6.8 and 4.0 Hz, 1 H, $H^{3'}$), 3.95 (t, *J* = 5.4 Hz, 2 H, CH_2-OH), 3.80–3.73 (m, 2 H, $H^{5'}$), 2.95 (t, *J* = 5.4 Hz, 2 H, =C-CH_2), 2.63 (s, 1 H, OH), 2.57–2.52 (m, 1 H, $H^{6'}$), 2.48–2.35 (m, 2 H, $H^{4'}$ + $H^{6'}$), 1.54 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.4 (C, $2C^{Ar-Si}$), 129.9 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 121.3 (CH, C^5), 113.6 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 66.4 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 61.8 (CH_2, CH_2-OH), 45.8 (CH, $C^{4'}$), 33.8 (CH_2, $C^{6'}$), 28.8 (CH_2, =C-CH_2), 27.6 (CH_3), 27.0 (*t*Bu), 25.1 (CH_3), 19.4 (C-Si) ppm. HRMS (ESI) *m/z* calcd. for $C_{29}H_{39}N_3NaO_4Si$ (M^+ + Na) 544.2608, found 544.2614. IR (neat): $\tilde{\nu}$ = 3390 (OH), 1471, 1427, 1380 (C=C aromatic), 1210–1064 (C–O) cm^{-1}.

(1*R*,2*S*,3*R*,4*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3-isopropylidenedioxy-1-(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)cyclopentane (15): The title compound was prepared from methyl propiolate (10 µL) after 1 min of microwave irradiation. Compound **15** (59 mg, >99%) was obtained as an orange oil. $[\alpha]_D^{27}$ = –20.8 (*c* = 0.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, H^5), 7.63 (dd, *J* = 6.4 and 1.2 Hz, 4 H, H^{Ar-Si}), 7.45–7.36 (m, 6 H, H^{Ar-Si}), 4.80–4.73 (m, 2 H, $H^{2'}$ + $H^{1'}$), 4.57 (dd, *J* = 6.2 and 4.2 Hz, 1 H, $H^{3'}$), 3.95 (s, 3 H, OCH_3), 3.77–3.76 (m, 2 H, $H^{5'}$), 2.62–2.54 (m, 1 H, $H^{6'}$), 2.49–2.37 (m, 2 H, $H^{4'}$ + $H^{6'}$), 1.54 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3 (C, CO), 140.0 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.4 (C, $2C^{Ar-Si}$), 130.0 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 127.3 (CH, C^5), 113.8 (C), 85.0 (CH, $C^{2'}$), 81.1 (CH, $C^{3'}$), 67.0 (CH, $C^{1'}$), 64.1 (CH_2, $C^{5'}$), 52.3 (OCH_3), 45.6 (CH, $C^{4'}$), 33.7 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (*t*Bu), 25.1 (CH_3), 19.5 (C-Si) ppm. HRMS (ESI) *m/z* calcd. for $C_{29}H_{37}N_3NaO_5Si$ (M^+ + Na) 558.2400, found 558.2394. IR (neat): $\tilde{\nu}$ = 1727 (C=O), 1471, 1427, 1382 (C=C aromatic), 1239 (C–O), 1066–1042 (C–O) cm^{-1}.

General Procedure for Deprotection. Synthesis of (–)-16–21: The protected triazole (0.1 mmol) was stirred overnight in an aqueous solution of trifluoroacetic acid (60% v/v) (2 mL) at room temperature. After evaporation of all volatiles, the resulting oil was dissolved in THF (2 mL) and tetrabutyl ammonium fluoride trihydrate (33 mg, 0.1 mmol, 1.05 equiv.) was added. The reaction mixture was stirred for 1 h at room temperature. After evaporation of all volatiles, the residue was purified by silica gel column chromatography (EtOAc/MeOH, 98:2).

(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclopentane (16): The title compound was prepared from **10** (55 mg, 0.1 mmol) and was obtained as a white solid **16** (24 mg, 86%). $[\alpha]_D^{27}$ = –65.0 (*c* = 0.2, CH_3OH). ^1H NMR (500 MHz, CD_3OD): δ = 8.39 (s, 1 H, H^5), 7.81 (d, *J* = 7.5 Hz, 2 H, H^{Ar}), 7.43 (t, *J* = 7.5 Hz, 2 H, H^{Ar}), 7.34 (t, *J* = 7.5 Hz, 1 H, H^{Ar}), 4.95–4.90 (m, 1 H, $H^{1'}$), 4.29 (dd, *J* = 8.0 and 5.0 Hz, 1 H, $H^{2'}$), 4.03 (dd, *J* = 5.0 and 3.5 Hz, 1 H, $H^{3'}$), 3.67 (d, *J* = 6.0 Hz, 2 H, $H^{5'}$), 2.52 (dt, *J* = 13.5 and 8.5 Hz, 1 H, $H^{6'}$), 2.29–2.23 (m, 1 H, $H^{4'}$), 1.99–1.93 (m, 1 H, $H^{6'}$) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 148.6 (C, C^4), 131.7 (C, C^{Ar}), 130.0 (CH, $2C^{Ar}$), 129.3 (CH, C^{Ar}), 126.6 (CH, $2C^{Ar}$), 121.7 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.7 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 46.8 (CH, $C^{4'}$), 31.0 (CH_2, $C^{6'}$) ppm. HRMS (ESI) *m/z* calcd. for $C_{14}H_{17}N_3NaO_3$ (M^+ + Na) 298.1168, found 298.1181.

(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-1-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]cyclopentane (17): The title compound was prepared from **11** (59 mg, 0.1 mmol). After purification by column chromatography, the obtained precipitate was washed with CH_2Cl_2 to eliminate the colour. Compound **17** (29 mg, 98%) was isolated as a white solid. $[\alpha]_D^{27}$ = –33.6 (*c* = 0.3, CH_3OH). ^1H NMR (400 MHz, [D_6]DMSO): δ = 8.65 (s, 1 H, H^5), 8.59 (d, *J* = 4.4 Hz, 1 H, N-CH), 8.02 (d, *J* = 7.6 Hz, 1 H, =C-CH=), 7.89 (td, *J* = 7.6 and 1.6 Hz, 1 H, =C-CH=C*H*), 7.34 (ddd, *J* = 7.6, 4.4 and 0.8 Hz, 1 H, N-CH=C*H*), 5.09 (d, *J* = 6.8 Hz, 1 H, $C^{2'}$-OH), 4.87–4.82 (m, 1 H, $H^{1'}$), 4.78–4.76 (m, 2 H, $C^{3'}$-OH + $C^{5'}$-OH), 4.16–4.10 (m, 1 H, $H^{2'}$), 3.84–3.81 (m, 1 H, $H^{3'}$), 3.47–3.42 (m, 2 H, $H^{5'}$), 2.35 (dt, *J* = 13.2 and 8.6 Hz, 1 H, $H^{6'}$), 2.10–2.03 (m, 1 H, $H^{4'}$), 1.81–1.73 (m, 1 H, $H^{6'}$) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ= 150.2 (C, =C), 149.8 (CH, N-CH), 147.3 (C, C^4), 137.6 (CH, =C-CH=*C*H), 123.3 (CH, N-CH=*C*H), 122.7 (CH, C^5), 119.8 (CH, =C-*C*H=), 76.9 (CH, $C^{2'}$), 72.2 (CH, $C^{3'}$), 65.0 (CH, $C^{1'}$), 63.0 (CH_2, $C^{5'}$), 45.5 (CH, $C^{4'}$), 30.0 (CH_2, $C^{6'}$) ppm. HRMS (ESI) *m/z* calcd. for $C_{13}H_{16}N_4NaO_3$ (M^+ + Na) 299.1120, found 299.1120.

(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-1-(4-pentyl-1*H*-1,2,3-triazol-1-yl)cyclopentane (18): The title compound was prepared from **12** (58 mg, 0.1 mmol). The residue was purified by silica gel column chromatography (EtOAc). Compound **18** (25 mg, 88%) was obtained as a white solid. $[\alpha]_D^{27}$ = –13.2 (*c* = 0.2, CH_3OH). ^1H NMR (250 MHz, CD_3OD): δ = 7.81 (s, 1 H, H^5), 4.94–4.77 (m, 1 H, $H^{1'}$), 4.21 (dd, *J* = 8.0 and 5.0 Hz, 1 H, $H^{2'}$), 3.99 (dd, *J* = 5.3 and 3.5 Hz, 1 H, $H^{3'}$), 3.65 (d, *J* = 6.0 Hz, 2 H, $H^{5'}$), 2.69 (t, *J* = 7.5 Hz, 2 H, =C-CH_2), 2.46 (dt, *J* = 13.5 and 8.5 Hz, 1 H, $H^{6'}$), 2.26–2.19 (m, 1 H, $H^{4'}$), 1.91–1.84 (m, 1 H, $H^{6'}$), 1.70–1.62 (m, 2 H, =C-CH_2-CH_2), 1.38–1.32 [m, 4 H, $(CH_2)_2$-CH_3], 0.91 [t, *J* = 6.6 Hz, 3 H, $(CH_2)_2$-CH_3] ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 149.0 (C, C^4), 122.5 (CH, C^5), 78.0 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.4 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 46.7 (CH, $C^{4'}$), 32.5 (CH_2, *C*H$_2$-CH_2-CH_3), 31.0 (CH_2, $C^{6'}$), 30.3 (CH_2, =C-CH_2-*C*H$_2$), 26.3 (CH_2, =C-*C*H$_2$), 23.4 (CH_2, *C*H$_2$-CH_3), 14.3 (CH_2, CH_2-*C*H$_3$) ppm. HRMS (ESI) *m/z* calcd. for $C_{13}H_{23}N_3NaO_3$ (M^+ + Na) 292.1637, found 292.1626.

(1*R*,2*S*,3*R*,4*R*)-1-[4-(Acetoxymethyl)-1*H*-1,2,3-triazol-1-yl]-2,3-dihydroxy-4-(hydroxymethyl)cyclopentane (19): The title compound was prepared from **13** (58 mg, 0.1 mmol). The residue was purified by silica gel column chromatography (EtOAc). Compound **19** (22 mg, 76%) was obtained as a colorless oil. ^1H NMR (250 MHz, CD_3OD): δ = 8.09 (s, 1 H, H^5), 5.18 (s, 2 H, =C-CH_2), 4.92–4.81 (m, 1 H, $H^{1'}$), 4.22 (dd, *J* = 8.3 and 5.3 Hz, 1 H, $H^{2'}$), 3.99 (dd, *J* = 5.3 and 3.5 Hz, 1 H, $H^{3'}$), 3.64 (d, *J* = 5.6 Hz, 2 H, $H^{5'}$), 2.47 (dt, *J* = 13.2 and 8.5 Hz, 1 H, $H^{6'}$), 2.29–2.16 (m, 1 H, $H^{4'}$), 2.06 (s, 3 H, CO-CH_3), 1.97–1.83 (m, 1 H, $H^{6'}$) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 172.3 (CO), 143.8 (C, C^4), 125.3 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.6 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 58.2 (CH_2, =C-CH_2), 46.8 (CH, $C^{4'}$), 31.0 (CH_2, $C^{6'}$), 20.6 (CH_3, CO-CH_3) ppm. HRMS (ESI) *m/z* calcd. for $C_{11}H_{17}N_3NaO_5$ (M^+ + Na) 294.1066, found 294.1073. IR (neat): $\tilde{\nu}$ = 3360 (OH), 1731 (C=O), 1229 (C–O), 1160–1042 (C–O) cm^{-1}.

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(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-1-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]-4-(hydroxymethyl)]cyclopentane (20): The title compound was prepared from **14** (57 mg, 0.1 mmol). After purification by column chromatography, the obtained precipitate was washed with CH_2Cl_2 to eliminate the colour. Compound **20** (21 mg, 80%) was obtained as a white solid. $[\alpha]_D^{27}$ = –26.6 (*c* = 0.15, CH_3OH). ^1H NMR (400 MHz, CD_3OD): δ = 7.87 (s, 1 H, H^5), 4.87–4.80 (m, 1 H, $H^{1'}$), 4.21 (dd, *J* = 8.4 and 5.3 Hz, 1 H, $H^{2'}$), 3.99 (dd, *J* = 5.3 and 3.6 Hz, 1 H, $H^{3'}$), 3.82 (br. s, 2 H, CH_2-OH), 3.65 (d, *J* = 6.0 Hz, 2 H, $H^{5'}$), 2.91 (t, *J* = 6.6 Hz, 2 H, =C-CH_2), 2.46 (dt, *J* = 13.2 and 8.5 Hz, 1 H, $H^{6'}$), 2.27–2.19 (m, 1 H, $H^{4'}$), 1.93–1.85 (m, 1 H, $H^{6'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (C, C^4), 123.4 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.9 (CH, $C^{3'}$), 66.5 (CH, $C^{1'}$), 64.4 (CH_2, $C^{5'}$), 62.1 (CH_2, CH_2-OH), 46.7 (CH, $C^{4'}$), 31.0 (CH_2, $C^{6'}$), 29.9 (CH_2, =C-CH_2) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{10}H_{17}N_3NaO_4$ (M^+ + Na) 266.1117, found 266.1111. IR (neat): $\tilde{\nu}$ = 3294 (OH), 1201–1050 (C–O) cm^{-1}.

(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-1-[4-(methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]cyclopentane (21): The title compound was prepared from **15** (59 mg, 0.1 mmol). After purification by column chromatography, the obtained precipitate was washed with CH_2Cl_2 to eliminate the colour. Compound **21** (15 mg, 52%) was obtained as a white solid. $[\alpha]_D^{27}$ = –28.0 (*c* = 0.2, CH_3OH). ^1H NMR (250 MHz, CD_3OD): δ = 8.62 (s, 1 H, H^5), 4.97–4.78 (m, 1 H, $H^{1'}$), 4.25 (dd, *J* = 8.5 and 5.3 Hz, 1 H, $H^{2'}$), 4.00 (dd, *J* = 5.3 and 3.2 Hz, 1 H, $H^{3'}$), 3.92 (s, 3 H, OCH_3), 3.65 (d, *J* = 6.0 Hz, 2 H, $H^{5'}$), 2.57–2.45 (m, 1 H, $H^{6'}$), 2.30–2.19 (m, 1 H, $H^{4'}$), 1.99–1.87 (m, 1 H, $H^{6'}$) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 162.4 (C, CO), 140.3 (C, C^4), 129.2 (CH, C^5), 78.2 (CH, $C^{2'}$), 73.8 (CH, $C^{3'}$), 66.9 (CH, $C^{1'}$), 64.3 (CH_2, $C^{5'}$), 52.5 (OCH_3), 46.8 (CH, $C^{4'}$), 30.8 (CH_2, $C^{6'}$) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{10}H_{15}N_3NaO_5$ (M^+ + Na) 280.0909, found 280.0913. IR (neat): $\tilde{\nu}$ = 3363 (OH), 1731 (C=O), 1226 (C–O), 1142–1055 (C–O) cm^{-1}.

(1*R*,2*S*,3*R*,4*R*)-1-(5-Amino-4-carbamoyl-1*H*-1,2,3-triazol-1-yl)-2,3-isopropylidenedioxy-4-[(*tert*-butyldiphenylsilyloxy)methyl]cyclopentane (22): In a dry flask, sodium metal (11 mg, 0.48 mmol, 2 equiv.) was dissolved in dry EtOH (1 mL) under N_2. To a solution of **8** (100 mg, 0.22 mmol) in dry EtOH (10 mL) under N_2, the prepared sodium ethoxide solution was added dropwise. After the addition of 2-cyanoacetamide (21 mg, 0.25 mmol, 1.1 equiv.), the reaction mixture was refluxed for 48 h. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1:3). Compound **22** (6 mg, 5%) was obtained as a colourless oil. $[\alpha]_D^{27}$ = –32.4 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 7.6 and 1.6 Hz, 4 H, H^{Ar-Si}), 7.46–7.37 (m, 6 H, H^{Ar-Si}), 6.68 (br. s, 1 H, CON*H*H), 5.64 (s, 2 H, NH_2), 5.30 (br. s, 1 H, CONH*H*), 4.57 (dd, *J* = 7.2 and 4.4 Hz, 1 H, $H^{3'}$), 4.52–4.49 (m, 1 H, $H^{2'}$), 4.33 (dt, *J* = 12.4 and 6.4 Hz, 1 H, $H^{1'}$), 3.84–3.76 (m, 2 H, $H^{5'}$), 2.76 (dd, *J* = 25.2 and 12.4 Hz, 1 H, $H^{6'}$), 2.61–2.54 (m, 1 H, $H^{6'}$), 2.52–2.46 (m, 1 H, $H^{4'}$), 1.59 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7 (CO), 145.5 (C, C^4), 135.7 (CH, $4C^{Ar-Si}$), 133.5 (C, $2C^{Ar-Si}$), 130.0 (CH, $2C^{Ar-Si}$), 127.9 (CH, $4C^{Ar-Si}$), 122.9 (C, C^5), 114.2 (C), 85.1 (CH, $C^{2'}$), 81.5 (CH, $C^{3'}$), 64.3 (CH_2, $C^{5'}$), 63.7 (CH, $C^{1'}$), 45.3 (CH, $C^{4'}$), 31.2 (CH_2, $C^{6'}$), 27.6 (CH_3), 27.0 (*t*Bu), 25.1 (CH_3), 19.5 (C-Si) ppm. HRMS (ESI) *m*/*z* calcd. for $C_{28}H_{37}N_5O_4NaSi$ (M^+ + Na) 558.2513, found 558.254. IR (neat): $\tilde{\nu}$ = 3325 (NH), 1654 (C=O), 1458, 1421, 1380 (C=C aromatic), 1254 (C–N), 1210–1003 (C–O) cm^{-1}.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds.

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[1] a) J. Zemlicka, *Pharmacol. Therapeut.* **2000**, *85*, 251–266; b) G. Y. Song, V. Paul, H. Choo, J. Morrey, R. W. Sidwell, R. F. Schinazi, C. K. Chu, *J. Med. Chem.* **2001**, *44*, 3985–3993; c) G. Gumina, S. Olgen, C. K. Chu, *Antivir. Nucleos.* **2003**, 77–189; d) L. A. Agrofoglio, *Curr. Org. Chem.* **2006**, *10*, 333–362.

[2] For the synthesis of carbocyclic nucleosides: a) V. E. Marquez, M. I. Lim, *Med. Res. Rev.* **1986**, *6*, 1–40; b) D. M. Huryn, M. Okabe, *Chem. Rev.* **1992**, *92*, 1745–1768; c) L. A. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl, R. Guedj, *Tetrahedron* **1994**, *50*, 10611–10684; d) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229–9272; e) L. A. Agrofoglio, S. R. Challand, In; *Acyclic, Carbocyclic and L-Nucleosides*; Kluwer Academic Publishers: Dordrecht, **1998**; f) E. Ichikawa, K. Kato, *Curr. Med. Chem.* **2001**, *8*, 385–423; g) O. R. Ludek, C. Meier, *Synthesis* **2006**, *13*, 2101–2109.

[3] For the antiviral activities of carbocyclic nucleosides: a) J. Balzarini, E. De Clercq, *Pharmacochemistry Library* **1990**, *14*, 175–194; b) V. E. Marquez, *Adv. Antivir. Drug Des.* **1996**, *2*, 89–146; c) S. W. Schneller, *Curr. Top. Med. Chem.* **2002**, *2*, 1087–1092; d) J. Neyts, E. De Clercq, *Antivir. Res.* **2003**, *57*, 25–33; e) R. O. Baker, M. Bray, J. W. Huggins, *Antivir. Res.* **2003**, *57*, 13–23; f) E. De Clercq, J. Neyts, *Rev. Med. Virol.* **2004**, *14*, 289–300.

[4] a) M. S. Wolfe, R. T. Borchardt, *J. Med. Chem.* **1991**, *34*, 1521–1530; b) S. L. Mosley, B. A. Bakke, J. M. Sadler, N. K. Sunkara, K. M. Dorgan, Z. S. Zhou, K. L. Seley-Radtke, *Bioorg. Med. Chem.* **2006**, *14*, 7967–7971.

[5] a) C. K. Chu, Y. H. Jin, R. O. Baker, J. Huggins, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 9–12; b) C. Simons, Q. Wu, T. T. Htar, *Curr. Top. Med. Chem.* **2005**, *5*, 1191–1203; c) B. Arumugham, H.-J. Kim, M. N. Prichard, E. R. Kern, C. K. Chu, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 285–287.

[6] a) E. De Clercq, *Antimicrob. Agents Chemother.* **1985**, *28*, 84–89; b) S. R. Narayanan, B. T. Keller, D. R. Borcherding, S. A. Scholtz, R. T. Borchardt, *J. Med. Chem.* **1988**, *31*, 500–503.

[7] a) B. M. Trost, R. Madsen, S. D. Guile, A. E. H. Elia, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1569–1572; b) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229–9272; c) J. B. Rodriguez, M. J. Comin, *Mini-Rev. Med. Chem.* **2003**, *3*, 95–114.

[8] For a comprehensive review about the versatility of organoazides in modern synthetic chemistry, see: S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240. For a review on the synthesis of azido-nucleosides, see: T. Pathak, *Chem. Rev.* **2002**, *102*, 1623–1668.

[9] a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; b) R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, vol. 1; A. Padwa (Eds.), Wiley, New York, **1984**.

[10] R. G. Gish, *J. Antimicrob. Chemother.* **2006**, *57*, 8–13.

[11] a) J. T. Witkowski, R. K. Robins, G. P. Khare, R. W. Sidwell, *J. Med. Chem.* **1973**, *16*, 935–937; b) W. Markland, T. J. McQuaid, J. Jain, A. D. Kwong, *Antimicrob. Agents Chemother.* **2000**, *44*, 859–866; c) J. Z. Wu, C.-C. Lin, Z. J. Hong, *J. Antimicrob. Chemother.* **2003**, *52*, 543–546.

[12] Y. Saito, V. Escuret, D. Durantel, F. Zoulim, R. F. Schinazi, L. A. Agrofoglio, *Bioorg. Med. Chem.* **2003**, *11*, 3633–3639.

[13] I. Pérez-Castro, O. Caamaño, F. Fernández, M. D. García, C. López, E. De Clercq, *Org. Biomol. Chem.* **2007**, *5*, 3805–3813.

[14] H. Cho, D. L. Bernard, R. W. Sidwell, E. R. Kern, C. K. Chu, *J. Med. Chem.* **2006**, *49*, 1140–1148.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[15] a) K. Tadano, H. Maeda, M. Hoshino, Y. Iimura, *Chem. Lett.* **1986**, 1081–1084; K. Tadano, H. Maeda, M. Hoshino, Y. Iimura, *J. Org. Chem.* **1987**, *52*, 1946–1956; b) K. Tadano, M. Hoshino, S. Ogawa, T. Suami, *J. Org. Chem.* **1988**, *53*, 1427–1432.
[16] a) H. J. Bestmann, D. Roth, *Synlett* **1990**, 751–753; b) D. R. Borcherding, S. A. Scholtz, R. T. Borchardt, *J. Org. Chem.* **1987**, *52*, 5457–5461.
[17] a) W. J. Choi, J. G. Park, S. J. Yoo, H. O. Kim, H. R. Moon, M. W. Chun, Y. H. Jung, L. S. Jeong, *J. Org. Chem.* **2001**, *66*, 6490–6494; b) H. R. Moon, W. J. Choi, H. O. Kim, L. S. Jeong, *Tetrahedron: Asymmetry* **2002**, *13*, 1189–1193.
[18] For recent reviews on RCM: a) J. C. Conrad, D. E. Fogg, *Curr. Org. Chem.* **2006**, *10*, 185–202; b) A. Michaut, J. Rodriguez, *Angew. Chem. Int. Ed.* **2006**, *45*, 5740–5750; c) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahaman, B. Roy, *Tetrahedron* **2007**, *63*, 3919–3952.
[19] a) Y. H. Jin, P. Liu, J. Wang, R. Baker, J. Huggins, C. K. Chu, *J. Org. Chem.* **2003**, *68*, 9012–9018; b) Y. H. Jin, C. K. Chu, *Tetrahedron Lett.* **2002**, *43*, 4141–4143.
[20] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041; b) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
[21] a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678; b) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
[22] M. Yang, W. Ye, S. W. Schneller, *J. Org. Chem.* **2004**, *69*, 3993–3996.
[23] C. R. Johnson, Y. F. Chen, *J. Org. Chem.* **1991**, *56*, 3344–3351.
[24] a) H. Gilman, R. G. Jones, L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630–1634; b) J. F. Normant, *Synthesis* **1972**, 63–80.
[25] a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6015–6018; E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019–6022; b) A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.* **1986**, *27*, 1047–1050; c) E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4029–4032.
[26] a) M. T. Reett, F. Wang, K. Harms, *J. Chem. Soc., Chem. Commun.* **1991**, 1309–1311; b) M. Kanai, Y. Nakagawa, K. Tomioka, *Tetrahedron* **1999**, *55*, 3831–3842.
[27] a) O. Mitsunobu, Y. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382; b) O. Mitsunobu, *Synthesis* **1981**, 1–28; c) Y. Yoshimura, K. Kitano, K. Yamada, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki, A. Matsuda, *J. Org. Chem.* **1997**, *62*, 3140–3152.
[28] J. Broggi, S. Díez-González, J. L. Petersen, S. Berteina-Raboin, S. P. Nolan, L. A. Agrofoglio, *Synthesis* **2008**, 141–148.
[29] a) A. Deiters, T. A. Cropp, M. Mukerji, J. W. Chin, J. C. Anderson, P. G. Schultz, *J. Am. Chem. Soc.* **2003**, *125*, 11782–11783; b) L. V. Lee, M. L. Mitchell, S.-J. Huang, V. V. Fokin, K. B. Sharpless, C.-H. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588–9589; c) P. Appukkuttan, W. Dehaen, V. V. Fokin, E. A. Van der Eycken, *Org. Lett.* **2004**, *6*, 4223–4225; d) W.-H. Zhan, H. N. Barnhill, K. Sivakumar, H. Tian, Q. Wang, *Tetrahedron Lett.* **2005**, *46*, 1691–1695; e) S. Quader, S. E. Boyd, I. D. Jenkins, T. A. Houston, *J. Org. Chem.* **2007**, *72*, 1962–1979.
[30] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.
[31] a) U. Pradere, V. Roy, T. R. McBrayer, R. F. Schinazi, L. A. Agrofoglio, *Tetrahedron* **2008**, *64*, 9044–9051; b) J. Broggi, N. Joubert, V. Aucagne, S. Berteina-Raboin, S. Díez-González, S. P. Nolan, D. Topalis, D. Deville-Bonne, J. Balzarini, J. Neyts, G. Andrei, R. Snoeck, L. A. Agrofoglio, *Nucleosides Nucleic Acids* **2007**, *26*, 1391–1394; c) K. El Akri, K. Bougrin, J. Balzarini, A. Faraj, R. Benhida, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6656–6659; d) R. Guezguez, K. Bougrin, K. El Akri, R. Benhida, *Tetrahedron Lett.* **2006**, *47*, 4807–4811 (and ref. 29); e) P. Appukkuttan, W. Dehaen, V. V. Fokin, E. Van der Eycken, *Org. Lett.* **2004**, *6*, 4223–4225.
[32] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
[33] N. Joubert, R. F. Schinazi, L. A. Agrofoglio, *Tetrahedron* **2005**, *61*, 11744–11750.
[34] a) D. F. Ewing, G. Goethals, G. Mackenzie, P. Martin, G. Ronco, L. Vanbaelinghem, P. Villa, *J. Carbohydr. Chem.* **1999**, *18*, 441–450; D. F. Ewing, G. Goethals, G. Mackenzie, P. Martin, G. Ronco, L. Vanbaelinghem, P. Villa, *Carbohydr. Res.* **1999**, 190–196.

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N-Heterocyclic Carbenes (NHCs) Containing *N*-*C*-Palladacycle Complexes: Synthesis and Reactivity in Aryl Amination Reactions

Julie Broggi, Hervé Clavier, and Steven P. Nolan*

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

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Starting from the corresponding dimer, new saturated NHC-containing *N*,*N*-dimethyl biphenylamine (DMBPA) palladacycle complexes have been synthesized and fully characterized. Catalytic activity of these well-defined, air- and moisture-stable palladium(II) complexes was evaluated in the Buchwald−Hartwig amination involving a range of unactivated aryl chlorides. From a practical perspective, the reaction conditions required when using [(NHC)Pd(palladacycle)Cl] systems are very appealing. The organic biphenyl ligand used in the synthesis of the palladacycles has been synthesized using a Suzuki−Miyaura cross-coupling employing the novel palladacycle-NHC complexes.

Introduction

N-heterocyclic carbene (NHC)-containing transition metal complexes[1] have been reported to efficiently catalyze a number of reactions such as ruthenium-mediated metathesis,[2] cycloaddition, and hydrosylilation using copper complexes,[3] gold-catalyzed transformations,[4] palladium-mediated cross-coupling reactions,[5] among others. The NHCs have gained great popularity as they are, in most cases, better σ-donors than phosphines, and possess in general higher thermal stability, and the use of NHC as supporting ligand usually leads to better complex stability.[6] Especially in the area of palladium-mediated cross-coupling reactions, NHC-containing Pd-catalysts[5] have proven to be an excellent alternative to catalytic systems involving tertiary phosphines.[7] The σ-donating character of NHC ligands allows for the synthesis of well-defined, air- and moisture-stable NHC-bearing palladium(II). Moreover, NHC ligands provide stabilization of the low-coordinated catalytically active Pd(0) species involved in the catalytic cycle, thus minimizing oxidative degradation and side reactions observed with tertiary phosphines.[8] A number of structures of NHC-Pd complexes such as dimer,[9] allyl,[10] cinnamyl,[11] pyridine (PEPPSI),[12] or acac (acetylacetonate)[13] have been investigated, and these complexes exhibit excellent catalytic activity.

Complexes juxtaposing the highly σ-donating properties and sterically demanding properties of NHCs with the stability imparted by palladacycle scaffolds[14] have also been investigated.[15] In 2003, our group published the first *N*,*N*-dimethyl biphenylamine (DMBPA) complexes combining nitrogen−carbon−palladacycle framework with unsaturated NHCs (Figure 1, **1** and **2**).[16,17] These appeared to be efficient precatalysts in the Buchwald−Hartwig reaction, α-ketone arylation, Suzuki−

* Corresponding author. E-mail: snolan@iciq.es.

(1) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (b) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (c) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer-Verlag: Berlin, Germany, 2007. (d) Clavier, H.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect B: Org. Chem.* **2007**, *103*, 193–222. (e) Boeda, F.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect B: Org. Chem.* **2008**, *104*, 184–210.

(2) (a) *Handbook of Metathesis*; Grubbs, R. H.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1−3. (b) Despagnet-Ayoub, E.; Ritter, T. *Top. Organomet. Chem.* **2007**, *21*, 193–218. (c) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726–764.

(3) Díez-González, S.; Nolan, S. P. *Synlett* **2007**, 2158–2167.

(4) (a) Lin, I. J. B.; Vasam, C. S. *Can. J. Chem.* **2005**, *83*, 812–825. (b) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* [Online early access]. DOI: 10.1039/b711132k, **2008**.

(5) (a) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768–2813. (b) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776–1782.

(6) (a) Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874–883. (b) Scott, N. M.; Clavier, H.; Mahjoor, P.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2008**, *27*, 3181–3186.

(7) (a) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479–6486. (b) Hooper, M. W.; Hartwig, J. F. *Organometallics* **2003**, *22*, 3394–3403. (c) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861–2873. (d) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655. (e) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980.

(8) (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11. (b) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481–485. (c) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734–4735. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (f) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580. (g) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474.

(9) (a) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63–65. (b) Ma, Y.; Song, C.; Jiang, W.; Xue, G.; Cannon, J. F.; Wang, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 4635–4638.

(10) (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056. (b) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470–5472. (c) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629–1635.

(11) (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111. (b) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.−Eur. J.* **2006**, *12*, 5142–5148.

(12) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. *Chem. Eur. J.* **2008**, *14*, 2443–2452.

(13) (a) Navarro, O.; Marion, N.; Scott, N. M.; Gonzalez, J.; Amoroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron* **2005**, *61*, 9716–9722. (b) Marion, N.; de Frémont, P.; Puijk, I. M.; Ecarnot, E. C.; Amoroso, D.; Bell, A.; Nolan, S. P. *Adv. Synth. Catal.* **2007**, *349*, 2380–2384.

(14) (a) Bedford, R. B. *Chem. Commun.* **2003**, 1787–1796. (b) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917–1927.

(15) (a) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055–4082. (b) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582. (c) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.

(16) (a) Scott, N. M.; Nolan, S. P. In *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2006; p 55−70. (b) Nielsen, D. J.; Cavell, K. J. In *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2006; p 73−100.

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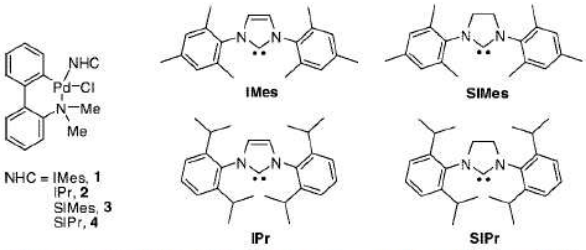


Figure 1. DMBPA *N-C*-palladacycle complexes bearing NHC ligands.

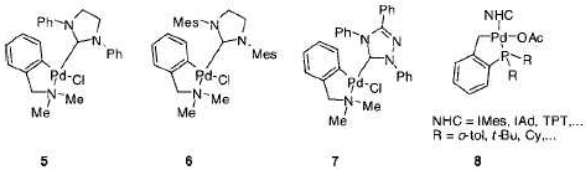


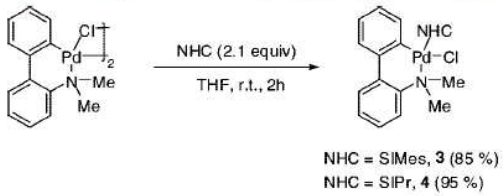
Figure 2. DMBA and phospha-palladacycle complexes bearing NHC ligands.

Miyaura coupling, and dehalogenation reaction.[17−19] Independently, Iyer reported applications in Mizoroki−Heck cross-coupling[20] of the previously described saturated NHC-containing dimethylbenzylamine (DMBA) palladacycle **5** (Figure 2).[21] These researchers obtained moderate to good yields at very low catalyst loading (0.0016 mol% Pd). However, reactions were carried out with aryl bromides or activated aryl chlorides at very high temperature (140 °C).[20,22] In 2005, Herrmann published another *N*-palladacycle coupled with a triazolin-5-ylidene (TPT) **7** and the first series of NHC-substituted phospha-palladacycles **8**, also showing high thermal stability.[23] At elevated temperature, Heck reactions were performed with phospha-palladacycles **8**, which proved efficient for the olefination of deactivated aryl bromides. The *N*-palladacycle **7** was the only one capable of quantitatively coupling an aryl chloride. In contrast to **8**, palladium black was formed in the presence of **7**.

The constant need for more efficient catalysts prompted us to develop new NHC-containing *N-C*-palladacycle complexes. Because of their convenient synthesis and the stability of the free NHC, unsaturated imidazol-2-ylidenes are widely used as ancillary ligands. In spite of similar steric and electronic properties,[24] unsaturated and saturated NHCs are often found to exhibit significantly different activity in catalysis. Olefin metathesis[25] is one such example, but palladium-catalyzed cross-coupling reactions also demonstrate the differences between

(17) Viciu, M. S.; Kelly, R.A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479–1482.
(18) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195.
(19) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685–692.
(20) Iyer, S.; Jayanthi, A. *Synlett* **2003**, 1125–1128.
(21) Hiraki, K.; Onishi, M.; Sewaki, K.; Sugino, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2548–2550.
(22) Iyer, S.; Kulkarni, G. M.; Ramesh, C. *Tetrahedron* **2004**, *60*, 2163–2172.
(23) (a) Frey, G. D.; Schütz, J.; Herdtweck, E.; Herrmann, W. A. *Organometallics* **2005**, *24*, 4416–4426. (b) Frey, G. D.; Herrmann, W. A. *J. Organomet. Chem.* **2005**, *690*, 5876–5880.
(24) (a) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485–2495. (b) Kelly, R. A., III; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202–210.
(25) (a) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745. (b) Clavier, H.; Nolan, S. P. *Chem.−Eur. J.* **2007**, *13*, 8029–8036.

Scheme 1. Synthesis of Palladium Complexes 3 and 4



saturated and unsaturated NHC supporting ligands.[10,11] In order to examine whether such differences could be observed in the related palladacyclic scaffolds examined in 2003, we report here the synthesis and full characterization of new saturated NHC-containing Pd(cycle) complexes. The catalytic activity of these new well-defined, air- and moisture-stable palladium(II) complexes was evaluated in the Buchwald−Hartwig amination and used for the synthesis of the palladacycle biphenyl ligand through a Suzuki−Miyaura cross-coupling.

Results and Discussion

Synthesis and Structure Determination of [(SIMes)Pd(Cycle)Cl] (3) and [(SIPr)Pd(Cycle)Cl] (4). The reactions leading to the titled complexes involved the coordination of the NHC to the palladium center by simple cleavage of the dimer $[Pd(Cycle)Cl]_2$ by two equivalents of NHC ligands, such as SIMes and SIPr, giving rise to the expected 16-electron species [(NHC)Pd(Cycle)Cl] (Scheme 1) in good to excellent isolated yields. Of note, these complexes were found perfectly air- and moisture-stable and thus could be handle in air. The ^{1}H NMR spectra of **3** and **4** showed a characteristic resonance at 4 ppm for the imidazolidine protons. The ^{13}C NMR spectra displayed characteristic low-field resonances for the carbenic carbon at around 198−201 ppm, while the carbenic carbon resonance for the unsaturated complexes **1** and **2** was found at a higher field (173−175 ppm).[17] Elemental analyses and high-resolution mass spectroscopy also confirmed the compositions of **3** and **4**.

To unambiguously establish the structure of complexes **3** and **4**, suitable crystals for single-crystal diffraction studies were obtained by slow diffusion of *n*-octane in DCM saturated solutions of **3** and **4**. Ball-and-stick representations with selected bond distances and angles are presented in Figures 3 (**3**) and 4 (**4**). Complexes **3** and **4** show the expected distorted square-planar geometry around the metal center with bond angles

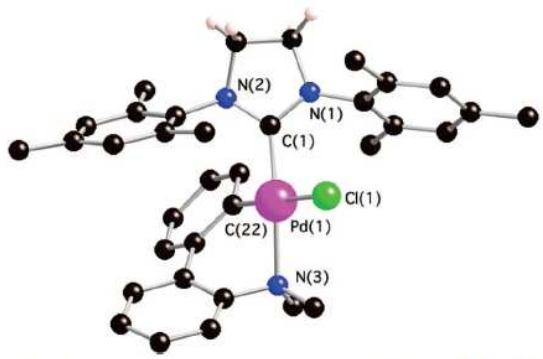


Figure 3. Ball-and-stick representation of [(SIMes)Pd(Cycle)Cl] (**3**). Most hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) 1.9684(11), Pd(1)−C(22) 2.0053(11), Pd(1)−N(3) 2.1957(10), Pd(1)−Cl(1) 2.3911(3); C(1)−Pd(1)−N(3) 175.27(4), C(1)−Pd(1)−C(22) 88.96(4), and C(22)−Pd(1)−Cl(1) 178.82(3).

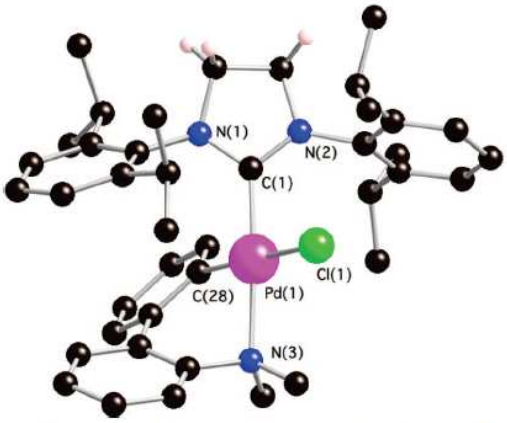


Figure 4. Ball-and-stick representation of [(SIPr)Pd(Cycle)Cl] (**4**). Most hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) 1.9788(9), Pd(1)−C(28) 2.0007(10), Pd(1)−N(3) 2.2033(9), Pd(1)−Cl(1) 2.3966(3); C(1)−Pd(1)−N(3) 175.58(4), C(1)−Pd(1)−C(28) 90.34(4), and C(28)−Pd(1)−Cl(1) 177.22(3).

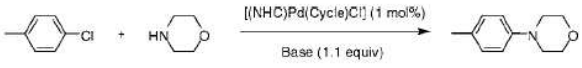
Table 1. Crystallographic Data for Compounds [(NHC)Pd(Cycle)Cl]

	[(SIMes)Pd(Cycle)Cl] (3)	[(SIPr)Pd(Cycle)Cl] (4)
chemical formula	$C_{36}H_{42}Cl_2N_3Pd$	$C_{42}H_{54}Cl_3N_3Pd$
fw	694.03	813.63
space group	*Pbca*	*P*2 (1)/*n*
cryst syst	orthorhombic	monoclinic
a, Å	13.6779(6)	10.3012(5)
b, Å	14.7453(6)	20.3145(10)
c, Å	32.7016(12)	19.4043(8)
α, deg	90	90
β, deg	90	98.103(2)
γ, deg	90	90
Z	8	4
D_{calc}, g cm^{-3}	1.398	1.344
μ (Mo), mm^{-1}	0.754	0.693
F(000)	2872	1696
θ range, deg	3.03 to 39.28	2.88 to 39.81
no. of reflns collected	57986	48649
no. of unique reflns/R_{int}	19144/0.0306	22808/00.0262
no. of params/restraints	387/0	480 /4
final *R* indices [*I* >2 *σ* (*I*)]	R_1 = 00.0326, wR_2 = 00.0768	R_1 = 0.0326, wR_2 = 0.0833
R indices (all indices)	R_1 = 00.0466, wR_2 = 00.0836	R_1 = 0.0439, wR_2 = 0.0896
goodness-of-fit on F^2	1.025	1.022
peak/hole, e Å^{-3}	0.873 and −00.995	1.717 and − 0.791

between 85° and 94°. Both **3** and **4** having the NHC ligand and amino group disposed trans to each other. In order to satisfy the square-planar geometry of the complexes, the biphenyl ligand is twisted. Of note, the *N*-aryl substituents of the saturated NHC are much more tilted to each other than the unsaturated NHC IMes and IPr (complexes **1** and **2**),[17] probably due to the skewed geometry of the NHC backbone. In general, the Pd−C(NHC) distances in **3** and **4** suggest single-bond character and are in good accord with their almost exclusive *σ*-donor character. The Pd−C(NHC) bond lengths in **3** (1.9684(11) Å) and **4** (1.9788(9) Å) are significantly smaller to analogous distances in related palladacycle carbene complexes (2.038 Å in **1**, 1.992 Å in **2**, and 1.991(1) Å in *N,N'*-dimethylbenzylamine **6** bearing SIMes).[17,26] Other bond distances were found comparable to those reported for similar complexes (Table 1).

Optimization of the Buchwald−Hartwig Reaction Conditions. Among cross-coupling reactions, the *N*-aryl amination has emerged as a practical and popular method for the formation

Table 2. Optimization of the Aryl Amination of 4-Chlorotoluene by Morpholine Catalyzed by [(NHC)Pd(Cycle)Cl] Complexes[a]



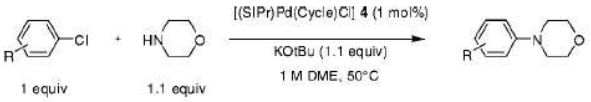
entry	catalyst	base	solvent	*T* (°C)	time	conversion GC[b]
1	**2**	NaO^{t}Bu	0.3 M dioxane	50	2 h	94%
2	**4**	NaO^{t}Bu	0.3 M dioxane	50	2 h	93%
3	**3**	NaO^{t}Bu	0.3 M dioxane	50	48 h	21%
4	**4**	NaO^{t}Bu	0.3 M dioxane	r.t.	72 h	89%
5	**4**	NaO^{t}Bu	0.3 M dioxane	70	40 min	91%
6	**4**	NaO^{t}Bu	0.3 M DME	50	1 h	92%
7	**4**	NaO^{t}Bu	0.3 M THF	50	2 h	93%
8	**4**	NaO^{t}Bu	0.3 M toluene	50	2 h	40%
9	**4**	NaO^{t}Bu	0.3M^{i}PrOH	50	30 min	0%[c]
10	**4**	KO^{t}Bu	0.3 M DME	50	5 min	96%
11	**4**	NaOH	0.3 M DME	50	2 h	0%[d]
12	**4**	NaOMe	0.3 M DME	50	2 h	0%[d]
13	**4**	KO^{t}Bu	1 M DME	50	2 min	96%
14	**2**	KO^{t}Bu	1 M DME	50	5 min	95%
15	**4**	KO^{t}Bu	1 M DME	r.t.	1 h	25%
16	**4**	KO^{t}Bu	1 M DME	50, MW[e]	5 min	90%
17	-	KO^{t}Bu	1 M DME	50	24 h	0%[d]

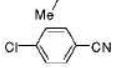
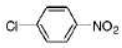
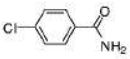
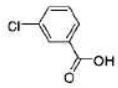
[a] Reaction conditions: 4-chlorotoluene (1 mmol), morpholine (1.1 mmol), [(NHC)Pd(Cycle)Cl] (1 mol%), base (1 0.1 mmol). [b] Conversions are the average of at least two runs. [c] 95% of toluene as dehalogenation product. [d] Starting material recovered. [e] MW = microwave.

of carbon−nitrogen bonds.[27] The classical copper-mediated Ullmann and the more recently developed palladium(0)-catalyzed Buchwald−Hartwig aryl coupling are commonly used methods. However, the Ullmann type reaction generally suffers from important limitations such as elevated reaction temperatures (≥140 °C), high catalyst loading, and poor substrate generality.[28] These drawbacks encourage the development of Pd-based catalyst systems for the preparation of aryl amines. Therefore, having two new saturated NHC-containing *N-C*-palladacycle complexes on hand, we initiated a study focusing on their catalytic activity in aryl amination using 4-chlorotoluene and morpholine as standard substrates (Table 2). First, we explored the reactivity of saturated **3** and **4** versus the unsaturated [(IPr)Pd(Cycle)Cl] (**2**), using the conditions previously described.[17] In several precedent cases, we[10c,11] and others[29] reported that SIPr-containing complexes perform better than IPr analogues in the Buchwald−Hartwig amination. Surprisingly, in this case, **2** (IPr) and **4** (SIPr) did not show any differences in terms of reactivity (entries 1 and 2). However, precatalyst **3** bearing the smaller NHC SIMes displayed a low activity at 50 °C (entry 3), confirming that as a general trend less bulky NHCs complexes bearing mesityl as imidazole substituents are less catalytically efficient.[16,17] The reactions conducted with **2** were previously performed at 70 °C, in 3 mL of dioxane and with NaO^{t}Bu as base.[17] We re-examined these conditions for **4**. As expected, the reaction proceeded faster at 70 °C (entry 5). However, under milder conditions, at 50 °C, amination still occurred in reasonable reaction times (entry 1). At room

(26) Gökçe, A. G.; Günay, M. E.; Aygün, M.; Çetinkaya, B.; Büyükgüngör, O. *J. Coord. Chem.* **2007**, *60*, 805–813.
(27) (a) Yang, B. H.; Buchwald, S. L. J. *Organomet. Chem.* **1999**, *576*, 125–146. (b) de Meijere, A.; Diederich, F., Eds. *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.
(28) (a) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587. (b) Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5167–5169, and references therein.
(29) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423–1426.

Table 3. Cross Coupling of Morpholine with Various Aryl Chlorides Mediated by 4[a]



entry	Ar-Cl	time	conversion GC[b]	yield[c]
1		2 min	96%	91%
2		3 h	83%	74%
3		1 h	96%	90 %
4		2 h	95%	95%
5		2 h	88%	68%
6		24 h	0%	-
7		24 h	0%	-
8		24 h	62%[d]	61%
9		24 h	>99%[d]	>99%

[a] Reaction conditions: aryl chloride (1 mmol), morpholine (1.1 mmol), [(SIPr)Pd(Cycle)Cl] **4** (1 mol %), KO^{t}Bu (1.1 mmol), DME (1 mL), T = 50 °C. [b] Conversions are the average of at least two runs. [c] Isolated yields. [d] KO^{t}Bu (2.2 mmol), DME (2 mL), and conversions were measured by ^{1}H NMR.

temperature, unfortunately the reaction time was increased to three days to reach an 89% conversion (entry 4), and even under reoptimized conditions, the arylation proceeded poorly (entry 15). 1,2-Dimethoxyethane (DME) appeared to be a better solvent than dioxane for this N-arylation (entry 6). In isopropanol, only dehalogenation was observed (entry 9).[16,19] The reaction proceeded well with strong bases such as KO^{t}Bu or NaO^{t}Bu, whereas others were completely ineffective (NaOH and NaOMe, respectively, entries 11 and 12). The result presented in entry 10 emphasizes the importance of the counteranion of the base for the activation of the catalyst. Complete conversion was reached in only 5 min with KO^{t}Bu at 50 °C, while 1 h was necessary with NaO^{t}Bu. Finally, better catalytic performances were obtained with increasing reaction mixture concentration (entry 13). Thus, reaction conditions were improved compared to those reported for palladacycle-catalyzed Buchwald−Hartwig cross-coupling,[17] although they were found to be similar to the ones found for [(NHC)Pd(R-allyl)Cl][10] or Pd-PEPPSI catalysts.[12] Once again, the reactivity of **4** versus **2** was compared with the new conditions (entries 13 and 14). Compound **4** was slightly more efficient than **2**, but this difference is small.

Precatalyst 4 in the Buchwald−Hartwig Reaction. The arylation of the morpholine was extended to a range of unactivated and other aryl chlorides (Table 3). With typical arylamination substrates, all reactions proceeded with good GC conversions and reaction times ranged from 2 min to 3 h (entries 1−5). The system was tolerant of a variety of functional groups. The secondary cyclic amine was easily coupled with various aryl chlorides: activated (entry 3), neutral (entries 1 and 2), unactivated (entry 5) as well as heteroaromatic chlorides (entry 4). Sterically hindered aryl chlorides such as mono or di ortho-substituted chlorobenzene exhibited reactions slightly slower than those for nonhindered analogues (entries 2 and 5). In most cases, final compounds were isolated in excellent yields. Pyridine and *o*-methoxy derivatives were found to be volatile (entries 4, 5). Then, we explored more unusual (less commonly employed) aryl chlorides as partners for the Buchwald−Hartwig reaction (entries 6−9). 1-Chloro-4-nitrobenzene and 3-chlorothiophene were completely unreactive under our optimized reaction conditions (entries 6 and 7). Morpholinylbenzene compounds bearing an electron-withdrawing group such as carboxylic or amide group are useful building blocks in the synthesis of new drugs and are therefore of commercial value.[30] The morpholinobenzoic acids were previously prepared either via Pd-catalyzed amination from ethyl bromobenzoate or by direct nucleophilic aromatic substitution of fluorobenzonitrile with subsequent hydrolysis of the resulting intermediates.[30a,31] 4-Morpholinobenzamide was obtained by substitution of the 4-fluorobenzamide[31] or by Pd-mediated coupling of the polymer bound aryl bromide.[32] Although two equivalents of base were required, complex **4** appeared to catalyze, under mild conditions, the amination of 4-chlorobenzamide and 3-chlorobenzoic acid with good yields and without a side reaction (entries 8 and 9). No reaction occurred in both cases with only one equivalent of KO^{t}Bu; presumably, a faster deprotonation of the carboxylic function occurs over the generation of the active species and the productive cross-coupling reaction. Extending the scope to *N*-methylaniline as partner instead of the highly active morpholine also gave high yields using both activated and unactivated chlorides (Table 4). Nevertheless, compared to morpholine, the aniline reacted slightly slower (entries 1 and 5).

A range of amines was also tested as partners for the coupling reaction (Table 5). The less reactive and sterically hindered dibutylamine reacted smoothly with 2-chlorotoluene in high yields (entry 1). Primary amines appeared to be compatible with our catalytic system. The 1-chloro-3-fluorobenzene was rapidly coupled to the bulky 1-adamantylamine in quantitative yield (entry 2) without any formation of the diarylated product. Also, the primary amine, cyclohexylamine, straightforwardly produced the biologically interesting naphthylamine (entry 3). The diallylamine, absent from the previous *N*-arylation study, was unreactive under these conditions either with neutral or activated aryl chlorides (entries 4 and 5). Unfortunately, benzophenone imine could not be coupled with 4-chlorotoluene in DME (entry 6), and attempts performed in toluene also failed.

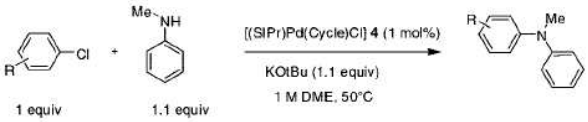
Application to the Synthesis of the *N,N*-Dimethylbiphenyl-2-amine Ligand. Economically and industrially, the reaction conditions obtained with [(NHC)Pd(palladacycle)Cl] systems are very appealing. However, the synthesis of the palladacycle biphenyl ligand requires harsh conditions and/or is low yielding, which is a significant hurdle. In the literature, the synthesis of the *N,N*-dimethylbiphenyl-2-amine was first described in 1939

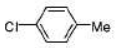
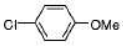
(30) (a) Brown, D. S.; Belfield, A. J.; Brown, G. R.; Campbell, D.; Foubister, A.; Masters, D. J.; Pike, K. G.; Snelson, W. L.; Wells, S. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5383–5387.

(31) (b) Oberboersch, S.; Schunk, S.; Reich, M.; Hees, S.; Jostock, R.; Engels, M.; Kless, A.; Christoph, T.; Schiene, K.; Germann, T.; Bijsterveld, E. PCT Int. Appl. WO2008040492, 2008. (c) Tian, W. PCT Int. Appl. WO0187865, 2001.

(32) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181–7184.

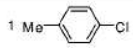
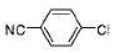
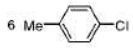
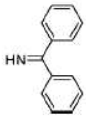
Table 4. Cross Coupling of Aniline and Various Aryl Halides Catalyzed by 4[a]



entry	Ar-Cl	time	conversion GC[b]	yield[c]
1		20 min	98%	97%
2		3 h	96%	93%
3		30 min	97%	94%
4		2 h	82%	81%
5		9 h	96%	94%

[a] Reaction conditions: aryl chloride (1 mmol), *N*-methylaniline (1.1 mmol), [(SIPr)Pd(Cycle)Cl] **4** (1 mol%), KOtBu (1.1 mmol), DME (1 mL), and $T = 50$ °C. [b] Conversions are the average of at least two runs. [c] Isolated yields.

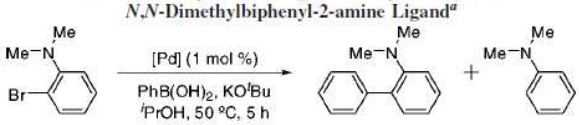
Table 5. Cross Coupling of Various Amines and Aryl Halides Mediated by 4[a]

entry	Ar-Cl	HNRR'	time	conversion GC[b]	yield[c]
1			4 h	98%	99%
2			30 min	97%	99%
3			4 h	98%	99%
4			24 h	0%	-
5			24 h	0%[d]	-
6			24 h	0%	-

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [(SIPr)Pd(Cycle)Cl] **4** (1 mol%), KO^{t}Bu (1.1 mmol), DME (1 mL), and $T = 50$ °C. [b] Conversions are the average of at least two runs. [c] Isolated yields. [d] Decomposition of the 4-chlorobenzonitrile observed.

by Evans and Williams.[33] Beyond using the highly toxic methyl sulfate as methylating agent, they claimed to obtain the product in very good yield (94%) starting from the 2-aminodiphenyl. However, Popkin and co-workers reported in 1944 that the previously published yield was a mixture of the dimethyl and monomethyl compounds in a 66:34 ratio.[34] By conducting the methylation with methanol under high temperature and pressure, the product ratio was improved to 87:13 with a reduced yield of 85%. Other procedures also gave mixtures, and the product was usually isolated in poor yields.[35] Finally to date, the only appealing procedure to this ligand was reported in 2003 using formaldehyde and sulfuric acid at −10 °C to methylate 2-aminodiphenyl in good yield.[36] Here, we have synthezised *N,N*-dimethylbiphenyl-2-amine by employing Suzuki−Miyaura cross-coupling using one of our novel palladacycle-NHC complexes. In addition to representing an original catalytic application, this specific example represents an unusual strategy: *using a catalyst as a synthetic tool for the synthesis of a biaryl compound that is an organic moiety of this same catalyst.*

Table 6. Catalyst Screening for the Synthesis of the *N,N*-Dimethylbiphenyl-2-amine Ligand[a]



entry	[Pd]	% conv[b]	ratio 10/11[b]
1	[(IPr)Pd(Cycle)Cl] **2**	92	1/1.5
2	[(SIMes)Pd(Cycle)Cl] **3**	92	1/1.0
3	[(SIPr)Pd(Cycle)Cl] **4**	91	1/1.1
4	[(IPr)Pd(ally)Cl]	83	1/7.3
5	[(SIPr)Pd(allyl)Cl]	79	1/1.1
6	[(SIPr)Pd(cin)Cl]	96	1/1.05
7	$[(SIPr)PdCl_2]_2$	95	1/1.8
8	[(IPr)Pd(acac)Cl]	>2	
9	$[(SIPr)Pd(OAc)_2(H_2O)]$	80	1/2.6

[a] Reaction conditions: 2-bromo-*N,N'*-dimethylaniline **9** (1 mmol), phenylboronic acid (1.1 mmol), [Pd] (1 mol %), KO^{t}Bu (1 0.2 mmol), tech. grade ^{i}PrOH (2 mL), $T = 50$ °C, and time = 5 h. [b] Determined by ^{1}H NMR spectroscopy; average of two runs.

We first tested the feasibility of the coupling reaction with several catalysts synthesized in our laboratory (Table 6). Excluding the Pd-acac complex[13] that did not exhibit any activity in the desired cross-coupling reaction (entry 8), all catalysts tested allowed for good conversions to the desired product in 5 h. The main problem observed was the formation of byproduct **11**, resulting from the dehalogenation of the starting material, in significant amount (≥50%). The cycle-, allyl-,[10] and cinnamyl-(NHC)Pd[11] series, known for their high reactivity, showed the most interesting results with a ratio close to 1/1. Compared to the unsaturated congeners, the reduction/cross-coupling ratio was decreased when saturated NHCs were used ([(NHC)Pd(Cycle)Cl] or [(NHC)Pd(allyl)Cl], (entries 1 and 3−5). In order to improve these results, reaction conditions were re-examined using [(SIMes)Pd(Cycle)Cl] (**3**) (Table 7).

Different non- or protic, non- or coordinating solvents were tested, and surprisingly, the reaction could only be carried out in isopropanol (entry 1). The optimization of the base showed that carbonate bases were inefficient (entries 11 and 12). A smaller counteranion caused a conversion decrease in parallel with an increase in dehalogenation (entry 8). Finally, despite only moderate conversion after 5 h, an important change in the ratio in favor of **10** occurred using KOH and KOMe (entries 9 and 10). The optimized conditions were used for the synthesis

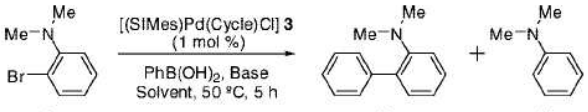
(33) Evans, D. P.; Williams, R. *J. Chem. Soc.* **1939**, 1199–1202.

(34) Popkin, A. H.; Perretta, G. M.; Selig, R. *J. Am. Chem. Soc.* **1944**, *66*, 833–834.

(35) (a) Chen, Q.; Li, Z. *J. Fluorine Chem.* **1994**, *66*, 59–62. (b) Creencia, E. C.; Horaguchi, T. *J. Heterocyclic Chem.* **2006**, *43*, 1441–1446.

(36) Azzena, U.; Cattari, M.; Melloni, G.; Pisano, L. *Synthesis* **2003**, 2811–2814.

Table 7. Solvent Ant Base Screening for the Synthesis of the *N,N*-Dimethylbiphenyl-2-amine Ligand[a]

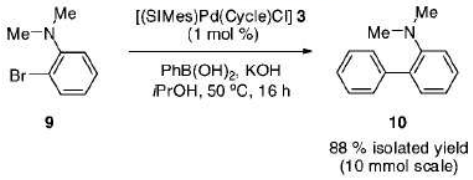


9 **10** **11**

entry	solvent	base	% conv[b]	ratio 10/11[b]
1	^{i}PrOH	KO^{t}Bu	92	1/1.0
2	EtOH	KO^{t}Bu	>2	
3	MeOH	KO^{t}Bu	>2	
4	DME	KO^{t}Bu	>2	
5	dioxane	KO^{t}Bu	>2	
6	THF	KO^{t}Bu	>2	
7	Toluene	KO^{t}Bu	>2	
8	^{i}PrOH	NaO^{t}Bu	52	1/1.4
9	^{i}PrOH	KOMe	15	1/0.3
10	^{i}PrOH	KOH	66	1/0.2
11	^{i}PrOH	K_2CO_3	>2	
12	^{i}PrOH	Cs_2CO_3	>2	

[a] Reaction conditions: 2-bromo-*N,N'*-dimethylaniline **9** (1 mmol), phenylboronic acid (1.1 mmol), [(SIMes)Pd (Cycle)Cl] **3** (1 mol %), base (1.2 mmol), solvent (2 mL), T = 50 °C, and time = 5 h. [b] Determined by^1 H NMR spectroscopy; average of two runs.

Scheme 2. Large Scale Synthesis of *N,N*-Dimethylbiphenyl-2-amine Ligand 10



of **10** in large scale (Scheme 2). The reaction time was optimized to 16 h, and 88% of **10** was isolated, and the formation of **11** was greatly reduced.

In conclusion, two well-defined, air- and moisture-stable saturated NHC-containing *N-C*-palladacycle complexes were synthesized and fully characterized. Their reactivity was evaluated in the Buchwald−Hartwig amination of a range of unactivated and diverse aryl chlorides.[37] Both aryl and alkyl primary and secondary amines were well tolerated by the [(SIPr)Pd(Cycle)Cl] complex. Moreover, the catalytic system was found to be compatible with reactive functions such as carboxylic acid and amide. [(NHC)Pd(Cycle)Cl] complexes bearing saturated and unsaturated NHCs did not show any differences in terms of reactivity. In addition, the Suzuki−Miyaura cross-coupling using [(SIMes)Pd(Cycle)Cl] was applied to the synthesis of the biphenyl ligand employed to synthesize the catalyst. We hope this more accessible synthetic route will facilitate the development of further applications of these dimethylbiphenylamine palladacycle complexes.

Experimental Section

General Considerations. All reactions were performed under an inert atmosphere of argon or nitrogen using standard high-vacuum or Schlenk techniques or in an MBraun glovebox containing less than 1 ppm oxygen and water. Solvents were distilled from appropriate drying agents or were dispensed from a solvent purification system from Innovative Technology; other anhydrous solvents were purchased from Aldrich and degassed prior to use by purging with dry argon and were kept over molecular sieves. Flash column chromatography was performed on silica gel 60 (230−400 mesh). ^{1}H and ^{13}C, ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 Ultrashield NMR spectrometer. High resolution mass spectroscopy (HRMS) analyses were performed at the ICIQ. Elemental analyses were performed at Universidad Complutense de Madrid.

Synthesis of [(SIMes)Pd(cycle)Cl] (3). In a glovebox, a scintillation vial was charged with a stirring bar, 135 mg (0.2 mmol) of palladacycle dimer, 130 mg (0.42 mmol) of SIMes, and 10 mL of dry THF. The reaction mixture was stirred for 2 h at room temperature. Outside of the glovebox, the reaction mixture was filtered over a plug of celite, and solvent was evaporated *in vacuo*. The remaining solid was triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane; 220 mg (85% yield) of an off white solid was obtained.^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.25 (d, ^{3}J(H,H) = 6.8 Hz, 1H, H^{Ar}), 7.16 (dt, ^{3}J(H,H) = 7.7 Hz, ^{4}J(H,H) = 1.6 Hz, 1H, H^{Ar}), 7.11−7.07 (m, 2H, H^{Ar}), 7.04−6.99 (m, 1H, H^{Ar}), 6.97−6.90 (m, 5H, H^{Ar}), 6.48 (s, 2H, H^{Ar}), 4.02−3.97 (m, 1H, CH_2-CH_2), 3.94−3.83 (m, 1H, CH_2-CH_2), 3.74−3.69 (m, 2H, CH_2-CH_2), 2.90 (s, 3H, CH_3-N), 2.80 (s, 3H, CH_3-N), 2.53 (s, 3H, CH_3^{Mes}), 2.41 (s, 3H, CH_3^{Mes}), 2.36 (s, 3H, CH_3^{Mes}), 2.26 (s, 3H, CH_3^{Mes}), 2.17 (s, 3H, CH_3^{Mes}), 1.52 (s, 3H, CH_3^{Mes}). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 198.2 (C, N-*C*-N), 152.0 (C, C^{Ar}), 147.2 (C, C^{Ar}), 142.2 (C, C^{Ar}), 140.4 (C, C^{Ar}), 138.5 (C, C^{Ar}), 137.4 (C, C^{Ar}), 137.2 (CH, C^{Ar}), 137.1 (C, C^{Ar}), 136.6 (C, C^{Ar}), 136.4 (C, C^{Ar}), 136.0 (C, C^{Ar}), 135.4 (C, C^{Ar}), 135.3 (C, C^{Ar}), 129.6 (CH, C^{Ar}), 129.5 (CH, C^{Ar}), 129.3 (CH, C^{Ar}), 128.8 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 125.1 (CH, C^{Ar}), 124.1 (CH, C^{Ar}), 124.0 (CH, C^{Ar}), 115.9 (CH, C^{Ar}), 52.6 (CH_2, CH_2−CH_2), 51.1 (CH_3, CH_3−N), 50.4 (CH_2, CH_2−CH_2), 49.9 (CH_3, CH_3−N), 20.7 (CH_3, C^{Mes}), 20.5 (CH_3, C^{Mes}), 19.8 (CH_3, C^{Mes}), 17.5 (CH_3, C^{Mes}). HRMS (ESI): *m/z* calcd for $C_{35}H_{40}N_3Pd$: 608.2257 [M^+ − Cl]; found 608.2237. Anal. Calcd for $C_{35}H_{40}N_3ClPd$ (MW 644.59): C, 65.22; H, 6.25; N, 6.52. Found: C, 65.09; H, 6.46; N, 6.47.

Synthesis of [(SIPr)Pd(Cycle)Cl] (4). In a glovebox, a scintillation vial was charged with a stirring bar, 405 mg (0.6 mmol) of palladacycle dimer, 500 mg (1.26 mmol) of SIPr, and 20 mL of dry THF. The reaction mixture was stirred 2 h at room temperature. Outside of the glovebox, the reaction mixture was filtrated over a plug of celite, and solvent was evaporated *in vacuo*. The remaining solid was triturated with pentane, and the precipitate was collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane; 830 mg (95% yield) of an off white solid was obtained. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.44 (t, ^{3}J(H,H) = 7.5 Hz, 1H, H^{Ar}), 7.35 (d, ^{3}J(H,H) = 7.2 Hz, 1H, H^{Ar}), 7.28 (d, ^{3}J(H,H) = 7.4 Hz, 1H, H^{Ar}), 7.17−7.11 (m, 3H, H^{Ar}), 7.03−6.95 (m, 4H, H^{Ar}), 6.86−6.83 (m, 3H, H^{Ar}), 6.69 (d, ^{3}J(H,H) = 7.4 Hz, 1H, H^{Ar}), 4.19−4.10 (m, 2H, $CH(CH_3)_2$), 4.04−3.97 (m, 2H, CH_2-CH_2), 3.87−3.82 (m, 2H, CH_2-CH_2), 3.27 (septet, ^{3}J(H,H) = 6.6 Hz, 1H, $CH(CH_3)_2$), 2.86 (s, 3H, CH_3-N), 2.60 (septet, ^{3}J(H,H) = 6.4 Hz, 1H, $CH(CH_3)_2$), 2.06 (s, 3H, CH_3-N), 1.70 (d, ^{3}J(H,H) = 6.6 Hz, 3H, $CH(CH_3)_2$), 1.58 (d, ^{3}J(H,H) = 6.6 Hz, 3H, $CH(CH_3)_2$), 1.44 (d, ^{3}J(H,H) = 6.7 Hz, 3H, $CH(CH_3)_2$), 1.30 (d, ^{3}J(H,H) = 6.7 Hz, 3H, $CH(CH_3)_2$), 1.08 (d, ^{3}J(H,H) = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.98 (d, ^{3}J(H,H) = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.93 (d, ^{3}J(H,H) = 6.2 Hz, 3H, $CH(CH_3)_2$), 0.47 (d, ^{3}J(H,H) = 6.3 Hz, 3H, $CH(CH_3)_2$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 200.6 (C, N-*C*-N), 152.7 (C, C^{Ar}), 148.2 (C, C^{Ar}), 147.8 (C, C^{Ar}), 147.2 (C, C^{Ar}), 145.7 (C, C^{Ar}), 145.6 (C, C^{Ar}), 142.9 (C, C^{Ar}), 141.6 (C, C^{Ar}), 138.0 (C, C^{Ar}), 136.8 (C, C^{Ar}), 135.9 (CH, C^{Ar}), 129.6 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 126.7 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 125.3 (CH, C^{Ar}), 124.7 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 124.4 (CH, C^{Ar}), 123.5 (CH, C^{Ar}), 122.8 (CH, C^{Ar}), 116.2 (CH, C^{Ar}), 55.5 (CH_2, CH_2−CH_2), 52.7 (CH_2, CH_2−CH_2), 50.6 (CH_3,

(37) The reactivity of [(SIPr)Pd(Cycle)Cl] (**4**) was also tested in the *O*-arylation of phenol with arylbromides and arylchlorides. Unfortunately, no coupling was observed in the few tests carried out.

CH_3−N), 50.3 (CH_3, CH_3−N), 29.0 (CH, $CH(CH_3)_2$), 28.7 (CH, $CH(CH_3)_2$), 28.3 (CH, $CH(CH_3)_2$), 28.2 (CH, $CH(CH_3)_2$), 27.2 (CH_3, $CH(CH_3)_2$), 26.9 (CH_3, $CH(CH_3)_2$), 26.0 (CH_3, $CH(CH_3)_2$), 25.5 (CH_3, $CH(CH_3)_2$) 24.7 (CH_3, $CH(CH_3)_2$), 24.1 (CH_3, $CH(CH_3)_2$), 23.3 (CH_3, $CH(CH_3)_2$), 22.9 (CH_3, $CH(CH_3)_2$). HRMS (ESI): *m/z* calcd for $C_{41}H_{52}N_3Pd$: 692.3196 [M^+ − Cl]; found 692.3178. Anal. Calcd for $C_{41}H_{52}N_3ClPd$ (MW 728.74): C, 67.57; H, 7.19; N, 5.77. Found: C, 67.74; H, 6.91; N, 5.60.

General Procedure for the Buchwald−Hartwig Cross-Coupling Reaction. In a glovebox, to a screw cap septum vial equipped with a magnetic stir bar were added in turn [(SIPr)Pd(Cycle)Cl] (1 mol %, 7.3 mg), potassium *tert*-butoxide (1.1 mmol, 120 mg), and anhydrous DME (1 mL). Outside the glovebox, the amine (1.1 mmol) and the aryl chloride (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was, before loading of the solvent, charged in the vial inside the glovebox. The reaction mixture was then stirred at 50 °C. When the reaction reached completion or no further conversion was observed by gas chromatography, the volatiles were removed *in vacuo*.

4-*p*-Tolylmorpholine (Table 3, Entry 1) CAS [3077-16-5]. The general procedure followed by silica gel chromatography (DCM) afforded 320 mg (91%) of the title compound as a white solid.

***N*-(2,6-Dimethylphenyl)morpholine (Table 3, Entry 2) CAS [255835-91-7].** The general procedure followed by silica gel chromatography (pentane/DCM 8/2) afforded 140 mg (74%) of the title compound as a white solid.

***N*-(4-Cyanophenyl)morpholine (Table 3, Entry 3) CAS [10282-31-2].** The general procedure followed by silica gel chromatography (DCM) afforded 170 mg (90%) of the title compound as a white solid.

***N*-(3-Pyridyl)morpholine (Table 3, Entry 4) CAS [92670-29-6].** The general procedure followed by silica gel chromatography (EtOAc/MeOH 98/2) afforded 152 mg (95%) of the title compound as a clear volatile liquid.

***N*-(2-Methoxyphenyl)morpholine (Table 3, Entry 5) CAS [27347-13-3].** The general procedure followed by silica gel chromatography (DCM) afforded 130 mg (68%) of the title compound as a clear volatile liquid.

4-Morpholinobenzamide (Table 3, Entry 8) CAS [183557-77-9]. The general procedure was followed using potassium *tert*-butoxide (2.2 mmol, 240 mg) and anhydrous DME (2 mL). The reaction mixture was then dissolved in 30 mL of EtOAc and washed once with a 0.1 N HCl solution (20 mL). After adjusting the pH to 5 with a 3 N NaOH solution, the aqueous phase was extracted six times with EtOAc. Subsequent flash chromatography on silica gel (EtOAc/MeOH 9/1) afforded 128 mg (61%) of the title compound as a white solid.

3-Morpholinobenzoic acid (Table 3, Entry 9) CAS [215309-00-5]. The general procedure was followed using potassium *tert*-butoxide (2.2 mmol, 240 mg) and anhydrous DME (2 mL). The reaction mixture was then dissolved in 30 mL of EtOAc and washed once with a 0.1 N HCl solution (20 mL). After adjusting the pH to 5 with a 3 N NaOH solution, the aqueous phase was extracted six times with EtOAc. Subsequent flash chromatography on silica gel (EtOAc/MeOH 9/1) afforded 207 mg (>99%) of the title compound as a white solid.

***N*-Methyl-*N*-*p*-tolylaniline (Table 4, Entry 1) CAS [38158-65-5].** The general procedure followed by silica gel chromatography (pentane/DCM 98/2) afforded 192 mg (97%) of the title compound as a clear liquid.

***N*-Methyl-*N*-(2-methylphenyl)aniline (Table 4, Entry 2) CAS [6590-44-9].** The general procedure followed by silica gel chromatography (pentane) afforded 184 mg (93%) of the title compound as a clear liquid.

2-(*N*-Methylanilino)pyridine (Table 4, Entry 3) CAS [62093-17-8]. The general procedure followed by silica gel chromatography (DCM) afforded 170 mg (94%) of the title compound as a clear liquid.

***N*-Methyl-*N*-phenyl-4-methoxyaniline (Table 4, Entry 4) CAS [55251-46-2].** The general procedure followed by silica gel chromatography (pentane/DCM 5/5) afforded 170 mg (81%) of the title compound as a clear liquid.

***N*-Methyl-*N*-phenyl-2-methoxyaniline (Table 4, Entry 5) CAS [263917-74-4].** The general procedure followed by silica gel chromatography (pentane/DCM 5/5) afforded 200 mg (94%) of the title compound as a clear liquid.

Dibutyl(4-tolyl)amine (Table 5, Entry 1) CAS [31144-33-9]. The general procedure followed by silica gel chromatography (pentane/DCM 8/2) afforded 218 mg (99%) of the title compound as a clear liquid.

***N*-(3-Fluorophenyl)-1-adamantylamine (Table 5, Entry 2).** The general procedure followed by silica gel chromatography (pentane/DCM 6/4) afforded 243 mg (99%) of the title compound as a white precipitate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (q, 1H, J = 6.0 Hz), 6.50−6.46 (m, 2H), 6.43−6.38 (m, 1H), 3.49 (bs, 1H), 2.12 (bs, 3H), 1.90 (d, J = 2.8 Hz, 6H), 1.72−1.65 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, C, C^3), 148.2 (d, C, C^1), 129.9 (d, CH, C^5), 113.5 (d, CH, C^6), 104.6 (d, CH, C^4), 104.2 (d, CH, C^2), 52.3 (C), 43.3 ($3CH_2$), 36.63 ($3CH_2$), 29.83 (3CH). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.34 (s). HRMS (ESI): *m/z* calcd for $C_{16}H_{21}FN$ (M^+ + H) 246.1658, found 246.1667.

***N*-Cyclohexyl-1-naphthylamine (Table 5, Entry 3) CAS [26863-63-8].** The general procedure followed by silica gel chromatography (pentane/DCM 7/3) afforded 223 mg (99%) of the title compound as a white solid.

***N*,*N*-Dimethylbiphenyl-2-amine (10).** A Schlenk tube was charged with a stirring bar, 65 mg (0.1 mmol) of [(SIMes)Pd(Cycle)Cl] **3**, 1.34 g (11 mmol) of phenylboronic acid, 672 mg (12 mmol) of ground KOH, 1.3 mL (10 mmol) of 2-bromo-*N*,*N*-dimethylaniline, and 20 mL of *i*PrOH. The reaction mixture was stirred for 16 h at 50 °C and then filtrated over a plug a celite. Purification of crude mixture by silica gel chromatography (pentane/diethyl ether, 98/2) afforded the title product as a colorless oil (1.73 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, ^{3}J(H,H) = 8.0 Hz, ^{4}J(H,H) = 1.6 Hz, 2H, H^{Ar}), 7.46 (t, ^{3}J(H,H) = 7.6 Hz, 2H, H^{Ar}), 7.38−7.32 (m, 2H, H^{Ar}), 7.29 (dd, ^{3}J(H,H) = 7.6 Hz, ^{4}J(H,H) = 1.6 Hz, 1H, H^{Ar}), 7.12−7.08 (m, 2H, H^{Ar}), 2.62 (s, 6H, CH_3-N). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3 (C, C^{Ar}), 142.0 (C, C^{Ar}), 134.2 (C, C^{Ar}), 131.7 (CH, CH^{Ar}), 128.7 (CH, CH^{Ar}), 128.3 (CH, CH^{Ar}), 128.1 (CH, CH^{Ar}), 126.5 (CH, CH^{Ar}), 121.5 (CH, CH^{Ar}), 117.6 (CH, CH^{Ar}), 43.4 (CH_3, CH_3−N). HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N$: 198.1283 [M^+]; found 198.1293.

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Supporting Information Available: CIF files of crystal structures **3** and **4** have been deposited with the CCDC, No. CCDC-688389 and 688388, respectively. Copies of the data can be obtained free of charge on applications to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336 033; http://www.ccdc.cam.ac.uk; e-mail: deposit@ccdc.cam.ac.uk. This material is available free of charge via the Internet at http://pubs.acs.org.

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Scientific Communications

Oral Communication

1 - SyCOCAL IV – Mézière en Brenne, France - May 21-24, 2006
« Développement et Applications de la Chimie "Click " »
Broggi, J. ; Berteina-Raboin, S. ; Agrofoglio, LA.

Poster Communications

1 - 2nd EuChems Chemistry Congress - Torino, Italy - 16-20 September 2008
"Palladacycle complexes containing saturated *N*-heterocyclic carbene (NHC): Synthesis and reactivity in C-N cross coupling reactions"
Broggi, J.; Clavier, H.; Nolan S.P.

2 - SyCOCALPC V – La Rochelle, France – 13-16 May 2007
"Phosphononucléosides acycliques par métathèse croisée et couplage au Pd(0) "
Broggi, J.; Kumamoto, H.; Pradere, U.; Roy, V. ; Berteina-Raboin, S. ; Topalis, D. ; Deville- Bonne, D. ; Agrofoglio, L.A.

3 - XVII International Roundtable – Bern, Switzerland – September 3-7, 2006
"Alkyne –Azide Click Chemistry Mediated Carbanucleosides Synthesis"
Broggi, J. ; Joubert, N.; Aucagne, V.; Berteina-Raboin, S. ; Nolan, SP.; Topalis, D.; Deville-
Bonne, D.; Balzarini, J. ; Neyts, J.; Andrei, G.; Snoeck, R.; Agrofoglio, LA.

4 - XVII International Roundtable – Bern, Switzerland – September 3-7, 2006
"Study of Different Copper(I) Catalysts for the Click Chemistry Approach to Carbanucleosides"
Broggi, J. ; Joubert, N.; Aucagne, V.; Berteina-Raboin, S. ; Nolan, SP.; Agrofoglio, LA.

5 - SyCOCAL IV – Mézière en Brenne, France – May 21-24, 2006
"Développement et Applications de la Chimie "Click " ".
Broggi, J. ; Berteina-Raboin, S. ; Agrofoglio, LA.

6 - 18ème Journée Régionale de la Chimie, SFC – Toulon, France – April 07, 2005
"Conjugués Peptide-AZT et Peptide-MP-AZT : un nouveau concept de Prodrogues"
Liotard, JF.; Broggi, J.; Di Giorgio, A.; Patino, N.; Boggetto, N.; Reboud, M.; Aubertin AM.; Condom, R.

Julie BROGGI

Contribution des Catalyseurs Contenant un Carbène *N*-Hétérocyclique pour la Chimie des Nucléosides

Résumé

Ces dernières années, les analogues nucléosidiques ont eu un rôle majeur dans le traitement de maladies virales infectieuses tels le SIDA, les hépatites, l'herpès, la variole ou la grippe. Cependant, l'apparition de nouveaux virus ou de mutations virales ont renforcé la nécessité de développer des antiviraux plus efficaces et plus résistants. L'intensive recherche de dérivés nucléosidiques cliniquement actifs a permis l'émergence d'une multitude de nouvelles approches pour leurs synthèses. Parmi ce panel, les réactions catalysées par des métaux de transition tardifs font certainement partie des méthodes les plus importantes pour accéder à une large gamme de pharmacomodulations.

Lors de ce projet de recherche, nous nous sommes intéressés à la conception, la synthèse et la découverte de nouveaux dérivés nucléosidiques en tant qu'antiviraux contre le virus de la variole. Pour ce faire, nous avons ciblé des 1,2,3-triazolo-carbanucléosides en série racémique ou énantiosélective ainsi que des nucléosides phosphonates acycliques. Dans un effort de développement et/ou d'amélioration de leurs méthodes de synthèse, nous avons également étudié la contribution de complexes au ruthénium et au cuivre contenant un carbène *N*-hétérocyclique (CNH) dans des réactions de métathèse croisée et de cycloaddition 1,3-dipolaire de Huisgen. Enfin, en vue d'obtenir des outils efficaces utilisables en synthèse nucléosidique, nous avons développés des nouveaux complexes au palladium portant un ligand CNH et testé leurs réactivités dans des réactions de *N*-arylation de Buchwald-Hartwig et d'hydrogénation d'oléfines.

Nucléoside carbocyclique, nucléoside phosphonate acyclique, carbène *N*-hétérocyclique, catalyse organométallique.

Contribution of *N*-Heterocyclic Carbene-Containing Catalysts in the Nucleoside Chemistry

Abstract

In the last decades, nucleoside analogues have played a major role in the treatment of viral infectious diseases, such as AIDS, hepatitis, herpes, smallpox or influenza. Nevertheless, the apparition of new or mutated viruses highlights the need of more potent and resistant antiviral therapeutics. The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis. Among them, late-transition metal-catalyzed reactions are certainly the most important methods to access variety of appealing pharmacomodulations.

In this research project, we were interested in the conception, the synthesis and the discovery of new nucleoside derivatives as antiviral agents against smallpox viruses. Hence, we have targeted racemic or enantiomerically pure 1,2,3-triazolo-carbanucleosides as well as acyclic nucleoside phosphonates. In our effort into the development or/and the improvement of their synthetic methodologies, we have also studied the contribution of ruthenium and copper complexes bearing *N*-heterocyclic carbene (NHC) ligands in cross-metathesis and Huisgen 1,3-dipolar cycloaddition reactions. Finally, in order to obtain efficient tools useful in nucleoside synthesis, we have developed new NHC-containing palladium complexes and examined their reactivity in Buchwald-Hartwig *N*-arylation and olefins hydrogenation reactions.

Carbocyclic nucleoside, acyclic nucleoside phosphonate, *N*-heterocyclic carbene, organometallic catalysis.

ICOA, Institut de Chimie Organique et Analytique
UMR 6005 - UFR Sciences - BP 6759 - rue de Chartres
45067 Orléans cedex 2