UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT
ROVIRA I VIRGILI

Hydroacylation and C-N Coupling Reactions. Mechanistic Studies and Application in the Nucleoside Synthesis

Patricia Marcé Villa

Dissertation presented to receive the degree of Doctor of the Universitat Rovira i Virgili, European Mention

UNIVERSITAT ROVIRA I VIRGILI
Departament de Química Analítica i Química Orgànica
Tarragona, Abril 2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT
ROVIRA I VIRGILI

DEPARTAMENT DE QUIMICA ANALITICA
I QUIMICA ORGANICA

C/ Marcel.lí Domingo s/n
Campus Sescelades
43007 Tarragona
Tel. 34 977 55 97 69
Fax 34 977 55 84 46
e-mail: secqaqo@urv.net

Sergio Castillón Miranda, Catedràtic del Departament de Química Analítica i Química Orgànica de la Universitat Rovira i Virgili,

CERTIFICA:

Que el present treball titulat: “Hydroacylation and C-N Coupling Reactions. Mechanistic Studies and Application in the Nucleoside Synthesis”, que presenta Patricia Marcé per a optar al grau de Doctor, ha estat realitzat sota la meva immediata direcció als laboratoris de Química Orgànica del departament de Química Analítica i Química Orgànica de la Universitat Rovira i Virgili.

Tarragona, Abril de 2008

Prof. Sergio Castillón Miranda

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Me gustaría agradecer a todas las personas que han hecho posible la realización de este trabajo. Empezando por mi director de tesis Prof. Sergio Castillón, muchas gracias por haberme dado la oportunidad de realizar la tesis en tu grupo y por tu apoyo en los momentos difíciles (que no han sido pocos), y por tener las puertas de tu despacho abiertas siempre que lo he necesitado. Tus consejos y tu perseverancia han hecho que este camino haya sido un poco más fácil. Además me llevo muy gratos recuerdos de todas las cenas que tanto tú como Carmen habéis organizado siempre con tanto cariño.

Mis más sinceros agradecimientos al resto de doctores del Área de Química Orgánica, especialmente a la Dra. Yolanda Díaz y a la Dra. Maribel Matheu por todo el apoyo prestado y por estar siempre dispuestas a ayudar.

También me gustaría agraceder al Dr. Carles Bo por haberme permitido trabajar en su grupo durante un tiempo y por todo su apoyo recibido y ayuda a la hora de hacer los cálculos teóricos que se presentan en este trabajo. Gracias por tu paciencia y por enseñar a una química orgánica a hacer algunos calculines. Gracias Marta por trabajar conmigo día a día la temporada que estuve en el ICIQ y a todos los compañeros por su cálida bienvenida.

I would like to express my gratitude to Prof. Piet W. N. M. van Leeuwen from The University of Amsterdam for hosting me in his group and giving me the opportunity to work in such a beautiful place. I would also like to thank all the members of his research group for their kindly welcome, and especially Miguel, Fabrizio, Pierre, Ivo, Sanders and Franco for their friendship.

Gracias a los compañeros de laboratorio con los que he pasado la mayoría del tiempo, con los que he trabajado codo a codo y me han aguantado mis malos momentos, me han sabido dar consejos y me han ayudado tanto durante estos cuatro años. A los que cuando llegué ya estaban en el laboratorio y con los que he compartido la mayoría de momentos, Miguel, Omar, y David. Tampoco puedo olvidarme de los compañeros del laboratorio vecino: Antonio con el que he compartido largas charlas sobre química y a Andrea. A los nuevos que se incorporan Javi e Irene y a los que ya no són tan nuevos Isidro y Pep.

También me gustaría dar las gracias a los compañeros del área de química inorgánica, Jesús, Aitor, Vanesa y Bianca que aunque no hemos trabajado en el mismo laboratorio también he compartido con ellos muy buenos momentos y algún que otro congreso. Molt especialment volia agraïr a Clara, amiga i companya no només aquest quatre anys de doctorat sino també als quatre anys de carrera que vam compartir, amb qui he viscut molt bons moments i moltes nits sense dormir (i no només quan sortiem el dijous sinó que també alguna nit d'estudi intens les vespres dels exàmens). Gràcies per estar sempre que t'he necessitat. A Cyril con el

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

que he pasado muchas horas de RMN y con el que sin su ayuda el último capítulo de mi tesis no habría sido posible.

No quiero olvidarme de mis amigas Rosa, Cristina y Vero con las que he compartido muchos cafés y confidencias. Muchas gracias por escucharme y aguantarme en los malos momentos, sin vuestra compañía nada hubiése sido lo mismo.

Voldria dedicar un especial agraïment a David, que no només ha sigut el meu company de laboratori. Gràcies per ajudarme amb la química fora i dins del laboratori, per saber-me escoltar i per estar a prop meu tant en els bons com en els mals moments. Gràcies per entendre'm més que ningú i per fer-me riure sempre que he estat baixa de moral. Sense tu aquests últims dos anys no hauríen sigut el mateix.

A mis padres y a mi abuelita que han vivido tan de cerca toda mi trayectoria, gracias por vuestro apoyo y por vuestra paciencia, gracias por estar siempre tan próximos y siempre estar dispuestos a echarme una mano en todo lo referente a mi vida. Gracias por ser como sois.

Gracias avi por haber tenido tanta fe en mí, y por creer que siempre sería capaz de hacer todo lo que me propusiera, siempre me diste muchos ánimos. Me hubiera gustado que estuvieses aquí para compartir estos momentos contigo. Siempre te llevaré en mi corazón.

Muchas gracias a todos.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

AcOH	Acetic acid
Ad	Adenine
ADF	Amsterdam Density Functional
Ar	Aromatic
B	Nucleic Base
BHT	2,6-di-t-butyl-4-methylphenoxide
Bn	Benzyl
COD	1,5-Cyclooctadiene
COSY	Correlated spectroscopy
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DFT	Discrete Fourier Transformation
DIBAL-H	Diisobutylaluminium hydride
DKR	Dynamic Kinetic Resolution
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMTCl	4,4'-Dimethoxytrityl chloride
dppe	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
ee	Enantiomeric excess
ees	Enantiomeric excesses
en	Ethylenediamine
equiv	Equivalent

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Et_2O	Diethy ether
EtOAc	Ethyl Acetate
GC	Gas Chromathography
HMBC	Heteronuclear multiple-bond correlation
HMPA	Hexamethylphosphoric triamide
HSQC	Heteronuclear single-quantum correlation
***i*-PrOH**	*iso*-Propanol
KR	Kinetic Resolution
LiHMDS	Lithium hexamethyldisilazide
MeOH	Methanol
MeONa	Sodium methoxide
MHz	Megaherzt
MS	Molecular sieve
N-435	Novozyme 435
NaOAc	Sodium acetate
NaO^tBu	Sodium *tert*-butoxide
NBD	Norbornadiene
NBS	N-Bromosuccinimide
***n*-BuLi**	*n*-Butyllithium
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMBCl	*p*-Methoxybenzyl chloride
PSC	Pseudomonas Cepacea
Py	Pyridine
RCM	Ring-Closing Metathesis
rt	Room temperature
TBAF	Tetrabutylammonium fluoride

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

TBDPSCl	*tert*-Butyldiphenylsilyl chloride
***t*-BuLi**	*tert*-Butyllithium
TC	Thiophene 2-carboxylate
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Triflate (Trifluoromethanesulfonic)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thy	Thymine
TIPSOTf	Triisopropylsilyl triflate
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMNO	Trimethylamine-N-oxide
TMS	Tetramethylsilane
TMSCN	Trimethylsilyl cyanide
TS	Transition state
TsCl	*p*-Toluenesulfonyl chloride
ZORA	Zero Order Approximation

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

ISBN:978-84-691-8840-8/DL: T-1262-2008

TABLE OF CONTENTS

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

1. Introduction

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Nucleosides are fundamental building blocks in biological systems and are sequentially phosphorylated by kinases into their mono-, di- and triphosphates. The resulting nucleotides are processed into nucleic acids by polymerases.[1,2] The search for nucleoside analogs that function as non-toxic, selective inhibitors of kinases and polymerases for the control of viral diseases and cancer has been the subject of intense research.[3] Nucleoside analogs that are good substrates for cellular kinases, but are resistant to other host enzymes such as phosphorylases, which cleave the glycosidic bond of natural nucleosides, are essential for the development of useful therapeutic agents.

The finding that dideoxynucleosides, such as ddC (2',3'-dideoxycytidine, **1**), ddI (2',3'-dideoxyinosine, **2**), and AZT (3'-azido-3'deoxythymidine, **3**) were potentially effective therapeutic agents for the treatment of acquired immunodeficiency syndrome (AIDS) has triggered new developments in the chemistry of these compounds and their analogs. AZT (**3**), ddI (**2**), ddC (**1**), and d4T (**4**), among others, are drugs currently used for the treatment of AIDS (Figure 1).

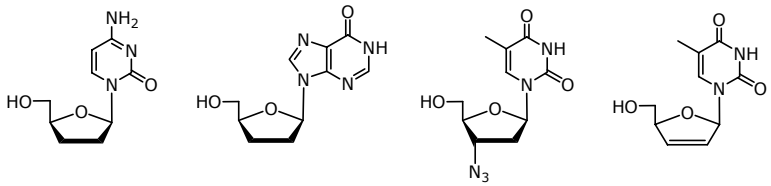


Figure 1. Examples of dideoxynucleosides.

However, those nucleosides that have shown activity in infected patients, have also demonstrated toxicities and other side effects.[4] In light of the need for more stable and effective antiviral agents, the synthesis of a new class of nucleosides called

[1] (a) Mizuno, Y. *The Organic Chemistry of Nucleic Acids*, Kadansha LTD: Tokyo (and Elsevier Science Amsterdam), 1986. (b) Ueda, T. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed., Plenum Press: New York, 1988, Vol.1, Chapter 1.

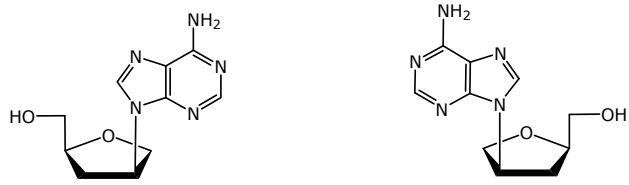
[2] (a) Srivasta, P. C.; Robins, R. K.; Meyer, R. B., Jr. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed., Plenum Press: New York, 1988, Vol.1, Chapter 2. (b) Revenkar, G. R.; Robins, K. R. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed., Plenum Press: New York, 1988, Vol.2, Chapter 4.

[3] (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofolio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (c) Huryn, D.; Okabe, M. *Chem. Rev*. **1992**, *92*, 1745. (d) Marquez, V.; Lim, M. *Med. Res. Rev*. **1986**, *6*, 1. (e) Roberts, S.; Biggadike, K.; Borthwick, A.; Kirk, B. *Topics in Medicinal Chemistry*, Ed.; P. R., Royal Society of Chemistry, **1988**, 172.

[4] Nair, V.; Sells, T. B. *Biochim. Biophys. Acta* **1992**, *1119*, 201.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

isonucleosides, which have the nitrogen base at the 2' or 3' position (Figure 2), has been developed.[5] In these compounds the *cis* configuration of the 5'-CH_2OH and the purinic or pyrimidinic base is maintained. The stability in acidic media of these compounds has been widely demonstrated.



(*S*,*S*)-*iso*-ddA **(*R*,*R*)-*iso*-ddA**

Figure 2. Examples of isonucleosides.

Another important discovery in this field was that the replacement of the oxygen in the sugar position of the nucleoside with a methylene (CH_2) unit resulted in carbocyclic nucleoside analogs that are highly resistant to phosphorylases.[6]

While the carbocyclic analogs of adenosine were first described by Shealy in 1966, it was the discovery that the natural carbocyclic nucleosides aristeromycin (**5**) and neplanocin (**6**) display antibiotic and antitumor activity that sparked the search for other carbocyclic nucleoside analogs with biological activity. Subsequently, other synthetic carbocyclic nucleosides with important therapeutic properties were discovered. In particular, carbovir (**7**), the structurally related abacavir (**8**), and BCA (**9**) have been shown to have antiviral activity directed against human immunodeficiency virus (HIV) (Figure 3). Phase III clinical trials indicate that abacavir succinate reduces viral load in HIV infected patients by >99% after 12 weeks of dosing, and moreover, no toxic side effects were observed in the patients treated with the drug.[7]

[5] (a) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S. *J. Med. Chem*. **1992**, *35*, 2347. (b) Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarcyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem*. **1993**, *36*, 1221. (c) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother*. **1995**, 1017.
[6] Bricaud, H.; Herdewijn, P.; DeClerq, E. *Biochem. Pharmacol*. **1983**, 3583.
[7] Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

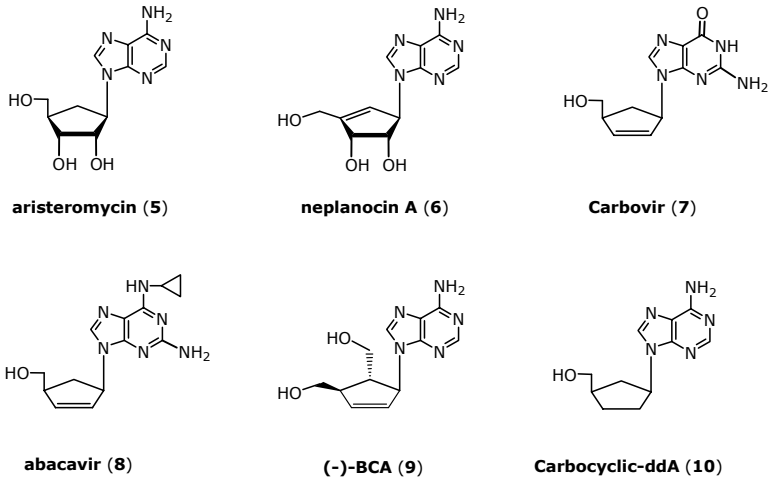


Figure 3. Examples of carbocyclic nucleosides.

While the exact mechanism of these antivirals is not completely understood, they are pro-drugs which are sequentially phosphorylated by cellular kinases to the corresponding triphosphates. The triphosphate is incorporated into replicating viral DNA chain by HIV reverse transcriptase, and chain termination results since there is no 3' hydroxyl group for further elongation of the chain. In addition, the 5' triphosphate or the oligonucleotide may act as a competitive inhibitor of the reverse transcriptase.[7]

Although promising new antiviral agents have been discovered, the search for potent inhibitors of a variety of infective agents continues. The intense search for clinically useful carbocyclic nucleosides and dideoxynucleosides has resulted in a wealth of new approaches for their synthesis, and more importantly, their enantioselective synthesis.

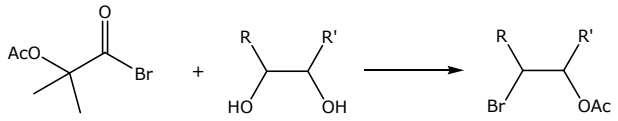
The synthesis of dideoxynucleosides and analogs from nucleosides has been studied extensively. The ribonucleoside-based synthesis is quite attractive since ribonucleosides are commercially available and not as expensive as their 2'-deoxy counterparts. The ribonucleoside with a modified base can also be readily prepared in an efficient manner. Moreover, if available, 2'-deoxyribonucleosides provide a quick entry to the synthesis of dideoxynucleosides and 3'-substituted analogs.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

1.1. Synthesis of Dideoxynucleosides

- From 2',3'-unsaturated precursors

The Mattocks reaction,[8] the abnormal reaction of 1,2-diols with α-acetoxyisobutyryl bromide (**11**) to furnish the bromoacetate **13**, was reexamined by Moffatt and co-workers[9] and successfully applied to nucleoside chemistry.[9,10]



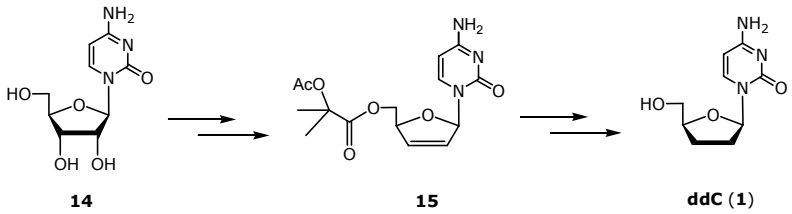
11 **12** **13**

Scheme 1. Mattocks reaction.

The reductive elimination of the resulting bromoacetate **13** furnished 2',3'-unsaturated 2',3'-dideoxynucleosides, such as **15**, by using a chromous ion complex,[11] electrochemical reduction,[12] zinc/acetic acid,[13] and zinc/copper pair.[14] The zinc/copper protocol appeared to be the most versatile, and this procedure has been employed for the synthesis of carbocyclic-ddA (**10**),[14] ddC (**1**),[15] ddG,[16] and ddI (**2**).[16] The unsaturated nucleosides, such as **15**, were converted to dideoxynucleosides by catalytic hydrogenation on Pd-carbon[14,15,17] or on Raney Ni (Scheme 2).[16] A direct conversion of the bromoacetate into the dideoxynucleoside by catalytic hydrogenation was not satisfactory due to the concomitant formation of the corresponding monodeoxynucleoside.[10a] Later, the selectivity of this direct reduction was improved by utilizing aqueous acetonitrile as solvent and a NaOAc-Na_2CO_3 mixture as the base in the hydrogenation.[18]

---

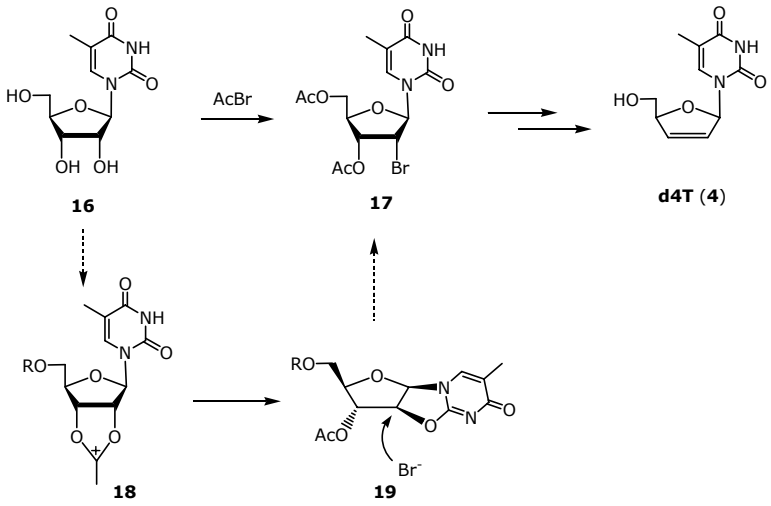
[8] Mattocks, A. R. *J. Chem. Soc*. **1964**, 1918.
[9] Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc*. **1973**, *95*, 4016.
[10] (a) Rusell, A. F.; Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc*. **1973**, *95*, 4025. (b) Russell, A. F.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 3179.
[11] Jain, T. C.;Jenkins, I. D.;Russell, A. F.; Verhevden, J. P. H.; Moffatt, I. J. G. *J. Org. Chem.* **1974**, *39*, 30.
[12] (a) Mengel, R.; Seifert, J.-M. *Tetrahedron Lett*. **1977**, 4203. (b) Adachi, T.; Iwasaki, T.; Inoue, I.; Miyoshi, M. *J. Org. Chem.* **1979**, *44,* 1404.
[13] Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem.* Scand. **1982**, *B36,* 251.
[14] Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett*. **1984**, *25*, 367.
[15] (a) Belica, P. S.; Hung, T. N.; Manchand, P. S.; Partridge, J. J.; Tam, S. US 4900828, 1990. (b) Manchand, P. S.; Belica, P. S.; Holman, M. J.; Huang, T.-N.; Maehr, H.; Tam, S. Y.-K.; Yang, R. T. *J. Org. Chem.* **1992**, *57*, 3473.
[16] Yoshioka, H.; Kojima, E.; Ishida, S.; Yoshioka, H.; Murakami, K. Jpn. Kokai Tokkyo Koho JP 02-91096, 1990.
[17] Mansuri, M. M.; Starrett, J. E., Jr.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780.
[18] Shiragami, H.; Hie, Y.; Iwagami, T. Jpn. Kokai Tokkyo Koho JP 02-117689, 1990.



14 **15**

Scheme 2. Synthesis of dideoxynucleosides by Mattocks reaction.

A variant of the Mattocks reaction using acetyl bromide[19] has been successfully applied to the synthesis of d4T (**4**).[17] The Mattocks reaction of uridine analogs (such as **16**) is not only regiospecific but also stereospecific to give 2-deoxy-2-bromo-3-*O*-acetyl-β-D-ribonucleosides (such as **17**) due to the anchimeric assistance of the oxygen at the 2-position in the pyrimidine (Scheme 3).



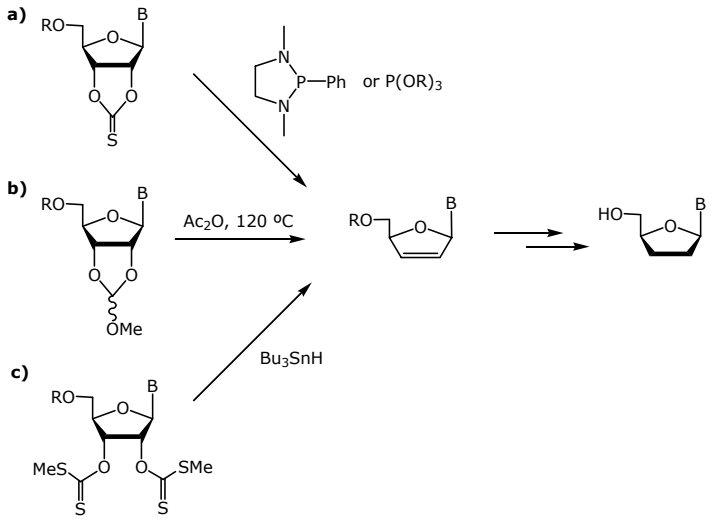
16 **17** **18** **19**

Scheme 3. Synthesis of d4T (**4**).

In the case of other nucleosides, such as **14**, or purine nucleosides, the formation of the bromoacetate was usually not regiospecific, and a mixture of *trans* bromoacetates was obtained. The corresponding bromoacetate could be prepared by the treatment of adenosine with tetraacetoxysilane and phosphorus tribromide in the presence of boron trifluoride etherate.[20]

[19] Marumoto, R.; Honjo, M. *Chem. Pharm. Bull*. **1974**, *22*, 128.
[20] Kondo, K.; Adachi, T.; Inoue, I. *J. Org. Chem.* **1977**, *42*, 3967.

The introduction of 2',3' unsaturation could also be achieved by the Corey-Winter reaction,[21] by fragmentation of cyclic orthoformates (Eastwood olefination)[22], and by radical reaction (Barton deoxygenation)[23] (Scheme 4).



Scheme 4. a) Corey-Winter reaction; b) Eastwood olefination; c) Barton deoxygenation.

The base-promoted elimination of mesylates **21** and **22**, oxetane **23**, and anhydronucleoside **24** were studied in 1960s (Scheme 5).[24] The syntheses of 2',3'-didehydro-2',3'-dideoxyguanosine (d4G)[25] and d4T (**4**)[26] were successfully carried

[21] (a) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677. (b) Ruyle, W. V.; Shen, T. Y.; Patchett, A. A. *J. Org. Chem.* **1965**, *30*, 4353. (c) Dudycz, L. W. *Nucleosides Nucleotides* **1989**, *8*, 35. (d) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett*. **1982**, *23*, 1979. (e) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem*. **1989**, *54*, 2217. (f) Rosowsky, A.; Solan, V. C.; Sodroski, J. G.; Ruprecht, R. M. *J. Med. Chem.* **1989**, *32*, 1135.

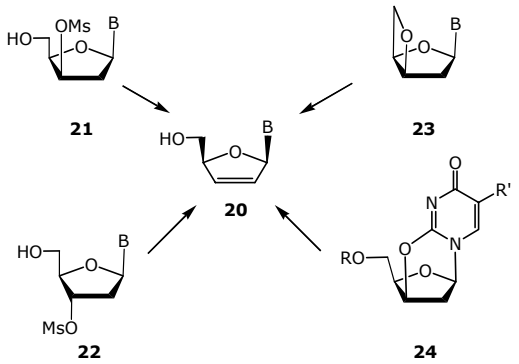
[22] (a) Crank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1392. (b) Josan, J. S.; Eastwood, F. W. *Aust. J. Chem.* **1968**, *21*, 2013. (c) Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* **1986**, 879. (c) Shiragami, H.; Irie, Y.; Shirae, H.; Yokozeki, K.; Yasuda, N. *J. Org. Chem*. **1988**, *53*, 5170.

[23] (a) Prisbe, E. J.; Martin, J. C. *Synth. Commun.* **1985**, *15*, 401. (b) Kim, C.-H.; Marquez, V. E.; Broder, S.; Mitsuya, H.; Driscoll, J. S. *J. Med. Chem.* **1987**, *30*, 862. (c) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem*. **1987**, *30*, 1270. (d) Sekine, M.; Nakanishi, T. *J. Org. Chem.* **1990**, *55*, 924. (e) Webb, R. R., II; Wos, J. A.; Martin, J. C. *Nucleosides Nucleotides* **1988**, *7*, 147. (f) David, S.; De Sennyey, G. *Carbohydr. Res*. **1980**, *82*, 45. (g) Lin, T.-S.; Yang, J.-H.; Liu, M.-C.; Zhu, J.-L. *Tetrahedron Lett*. **1990**, *31*, 3829. (h) Serafinowski, P. *Synthesis* **1990**, 411. (i) Barton, D. H. R.; Jang, D. O.*;* Jaszberenyi, J. Cs. *Tetrahedron Lett*. **1991**, *32*, 2569.

[24] (a) Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205. (b) McCarthy, J. R., Jr.; Robins, M. J.; Townsend, L. B.; Robins, R. K. *J. Am. Chem. Soc*. **1966**, *88*, 1549. (c) Horwitz, J. P.; Chua, J.; Noel, M. *Tetrahedron Lett*. **1966**, 1343. (d) Horwitz, J. P.; Chua, J.; Noel, M.; Donatti, J. T. *J. Org. Chem.* **1967**, *32*, 817.

[25] Herdewijn, P.; Balzarini, J.; Baba, M.; Pauwels, R.; Van Aerschot, A.; Janssen, G.; De Clercq, E. *J. Med. Chem.* **1988**, *31*, 2040.

out using this procedure. The photosensitized electron-transfer reaction was recently used in the synthesis of purine 3'-azido-2',3'-dideoxynucleosides.[27] Other methods involving the deiodination of 3'-iodonucleosides,[28] desulfurization of 3'-mercaptonucleosides[29] or iodine-catalysed elimination of vicinal iodo-mesylates[30] have been reported. The synthesis of 2',3'-dideoxypurine nucleosides by a bacterial transglycosylation has also been described.

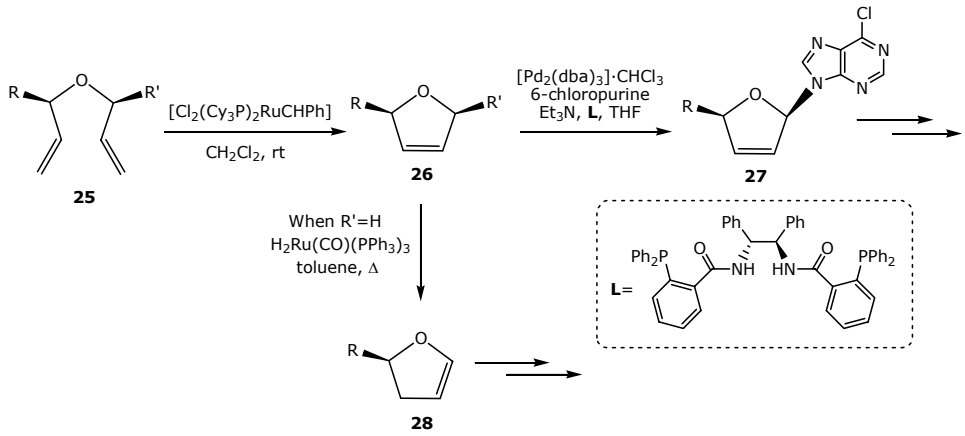


Scheme 5. Examples of synthesis of d4T analogues by an elimination reaction.

The formation of a 3,4-dihydrofuran **26** has been recently achieved by ring-closing metathesis from alkene **25**.[31] Once **26** is obtained, the coupling with the nucleic base take place easily by using a palladium complex[32] affording **27**; then additional transformations lead to the desired nucleoside. Moreover, the isomerization of the double bond could transform compound **26** into 2,3-dihydrofuran **28**, which could also be applied in the synthesis of 2',3'-dideoxynucleosides, as will be explained later (Scheme 6).

[26] Mansuri, M. M.; Starrett, J. E., Jr.; Ghazzouli, I.; Hitchcock, M. J. M.; Sterzycki, R. Z.; Brankovan, V.; Lin, T.-S.; August, E. M.; Prusoff, W. H.; Sommadossi, J.-P.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 461.
[27] (a) Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M.; Matauura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3115. (b) Almond, M. R.; Collins, J. L.; Reitter, B. E.; Rideout, J. L.; Freeman, G. A.; St. Clair, M. H. *Tetrahedron Lett*. **1991**, *32*, 5745.
[28] (a) Pfitzner, K. E.; Moffatt, J. G. *J. Org. Chem.* **1964**, *29*, 1508. (b) Chu, C. K.; Schinazi, R. F.; Ahn, M. K.; Ullae, G. V.; Gu, Z. P. *J. Med. Chem*. **1989**, *32*, 612.
[29] Robins, M. J.; Robins, R. K. *J. Am. Chem. Soc*. **1964**, *86*, 3585.
[30] Robins, M. J.; Jones, R. A.; Mengel, R. J. *J. Am. Chem. Soc*. **1976**, *98*, 8213.
[31] Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem. Eur. J*. **2003**, *9*, 4442.
[32] Trost, B. M.; Shi, Z. *J. Am. Chem. Soc*. **1996**, *118*, 3037.

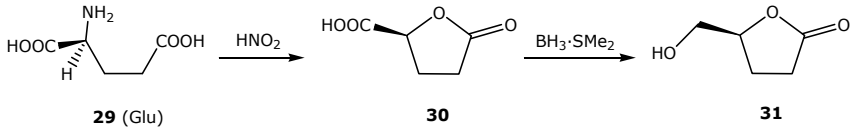
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 6. Synthesis of dideoxynucleosides by ring-closing metathesis.

- From lactones

The butyrolactone **31**, a logical precursor of 2,3-dideoxynucleosides, has been previously prepared from L-glutamic acid,[33] from D-manitol[34] and from D-ribonolactone.[35] The low cost of L-glutamic acid and the few steps required for the synthesis of the carbocyclic nucleoside precursor, make the route from this material the preferred one. The nitrous acid deamination of L-glutamic acid (**29**), which proceeds with full retention of configuration due to the participation of the neighbouring α-carboxylate group,[36] followed by selective reduction of the carboxylic acid **30** with borane-dimethyl sulphide, readily affords the lactone **31** (Scheme 7).[33b]

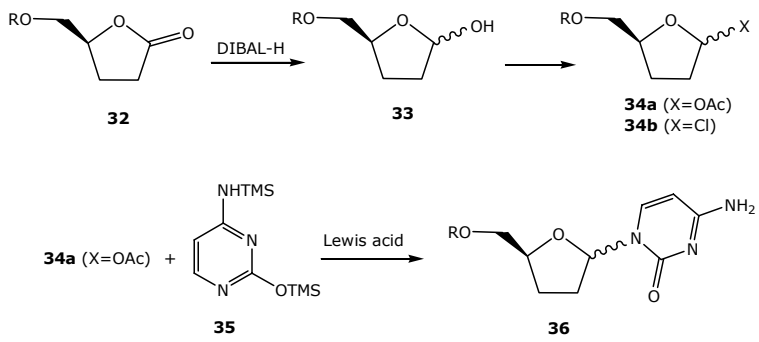


Scheme 7. Synthesis of the lactone **31** from L-glutamic acid (**29**).

[33] (a) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. (b) Ravid, U.; Silveratein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.
[34] Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 951.
[35] (a) Lundt, I.; Pedersen, C. *Synthesis* **1986**, 1052. (b) Camps, P.; Font, C. J.; Orutuño, R. M.; Ponsati, O. *Tetrahedron* **1982***, 38, 2395.* (c) Katsuki, J.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 4963.
[36] Cervinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2927.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

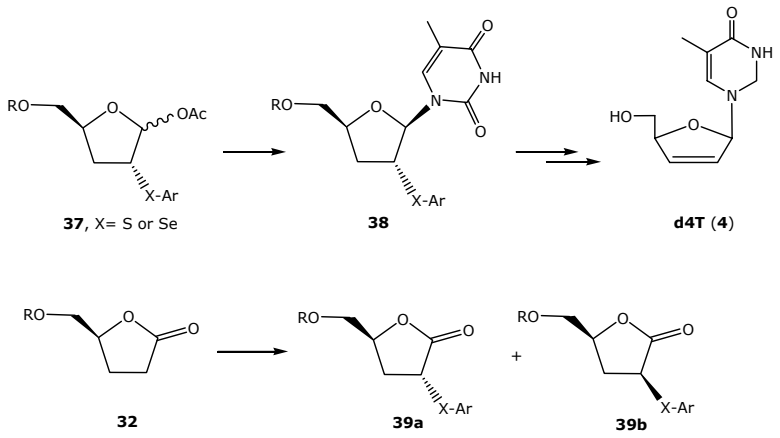
The protected lactone **32** was reduced with DIBAL-H to the corresponding lactol **33**, which was then converted to the required sugar moiety, acetate **34a** (X = OAc)[37] or chloride **34b** (X = Cl).[38] The acetate **34a** has been coupled with silylated pyrimidines (such as **35**)[37a-37c] and purine[37c,37d] bases in the presence of Lewis acids such as ethylaluminum dichloride,[37a] trimethylsilyl bromide,[37c] and trimethylsilyl triflate.[37b,37d] The chloride has also been treated with the anions of purine bases.[38] The resulting anomeric mixture of nucleosides **36** (usually *ca*. 1:1) can be separated chromatographically (Scheme 8).[39]



Scheme 8. Synthesis of **36** from the protected lactone **32**.

The possibility of using a 2,3-dideoxyribose with a substituent at the 2-position, which would not only direct the condensation toward the formation of the β-anomer but also be disposable, was explored. Phenylselenenyl[40] and arylsulfenyl[41] groups have served for this purpose, and high β-selectivities have been achieved in the synthesis of d4T (**4**). However, the requisite precursor **39a** has to be separated from its epimer **39b** chromatographically (Scheme 9).

[37] (a) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem*. **1988**, *53*, 4780. (b) Agyei-Aye, K.; Baker, D. C. *Carbohydr. Res*. **1988**, *183*, 261. (c) Farina, V.; Benigni, D. A. *Tetrahedron Lett.* **1988**, *29*, 1239. (d) Chu, C. K.; Ullas, G. V.; Jeong, L. S.; Ahn, S. K.; Doboszewki, B.; Lin, Z. X.; Beach, J. W.; Schinazi, R. F. *J. Med. Chem*. **1990**, *33*, 1553.
[38] Seela, F.; Bourgeois, W.; Muth, H.-P.; Rosemeyer, H. *Heterocycles* **1989**, *29*, 2193.
[39] (a) Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993. (b) Wengel, J.; Lau, J.; Pedersen, E. B.; Nielsen, C. M. *J. Org. Chem*. **1991**, *56*, 3591. (c) Mikhailopulo, I. A.; Poopeiko, N. E.; Pricota, T. I.; Sivets, G. G.; Kvasyuk, E. I.; Barzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 2195.
[40] Chu, C. K.; Babu, J. R.; Beach, J. W.; Ahn, S. K.; Huaug, H.; Jeong, L. S.; Lee, S. J. *J. Org. Chem.* **1990**, *66*, 1418.
[41] Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1990**, *31*, 1815.

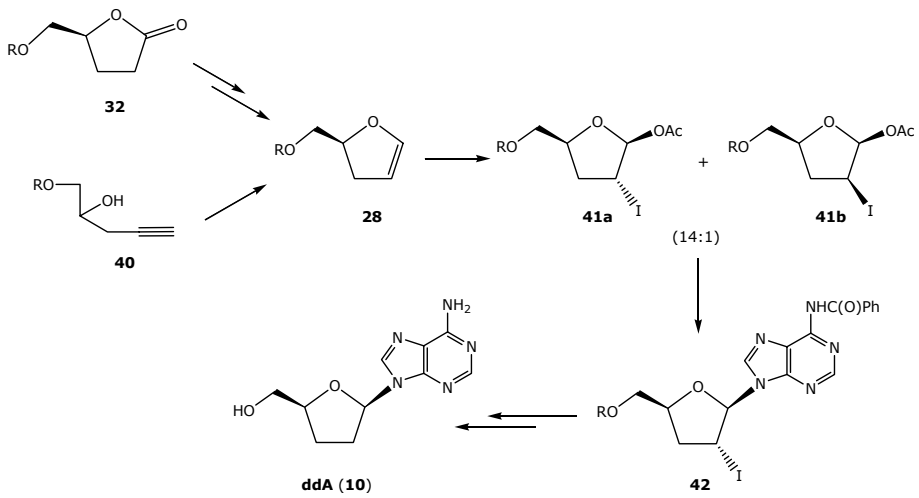


Scheme 9. Use of control substituents at position 2 to obtain d4T (**4**).

- From 2,3-dihydrofuran derivatives

Another method commonly used in the synthesis of 2',3´-dideoxinucleosides proceeds via the formation of the corresponding dihydrofuran **28**, which can be obtained from the lactone **32**[42] by elimination of a selenoxide[43,44] or by the cycloisomerization reaction of propargylic alcohol (**40**).[45] Once the dihydrofuran is achieved, the addition of acetic acid and NIS produces the acetoxy intermediate **41a** and its stereoisomer **41b** in a ratio of 14:1. The regiospecificity and the high stereoselectivity in this reaction are a consequence of the sterically favoured α-face approach of NIS. The resulting α-halonium anion is then attacked from the β-face by the acetoxy anion to give **41a** as a major product. Then the mixture is coupled with the silylated N6-benzoyladenine to give the adenosine analogue **42**. The addition of adenine to **41a** appears to proceed with retention of configuration at the C-2 position due to the neighbouring group participation of the C-3 iodine. Hydrogenolysis of iodine **42** and cleavage of the protecting group gave the desired ddA (**10**) (Scheme 10). The d4T (**4**) could be also achieved by a similar procedure.[42,45]

[42] Kim, C. U.; Misco, P. F. *Tetrahedron Lett*. **1992**, *33*, 5733.
[43] Bravo, F.; Kassou, M.; Díaz, Y.; Castillón, S. *Carbohydr. Res*. **2001**, *336*, 83.
[44] Díaz, Y.; El-Laghdach, A., Matheu, M. I.; Castillón, S. *J. Org. Chem*. **1997**, *62*, 1501.
[45] McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118,* 6648.



Scheme 10. Synthesis of dideoxynucleosides via a dihyfrofuran precursor.

A similar procedure, but carrying out the glycosylation reaction in *one-pot* from **28** and using PhSeCl as an activator, was also reported by our group.[44]

1.2. Synthesis of Carbocyclic Nucleosides

- Methods for coupling the heterocyclic base with the carbocyclic ring

There are two fundamental approaches for the construction of carbocyclic nucleosides: 1) Attachment of a nucleic acid base to an appropriately functionalized carbocyclic ring by a substitution reaction and 2) linear construction of the heterocycle from an amine present in the carbocycle.

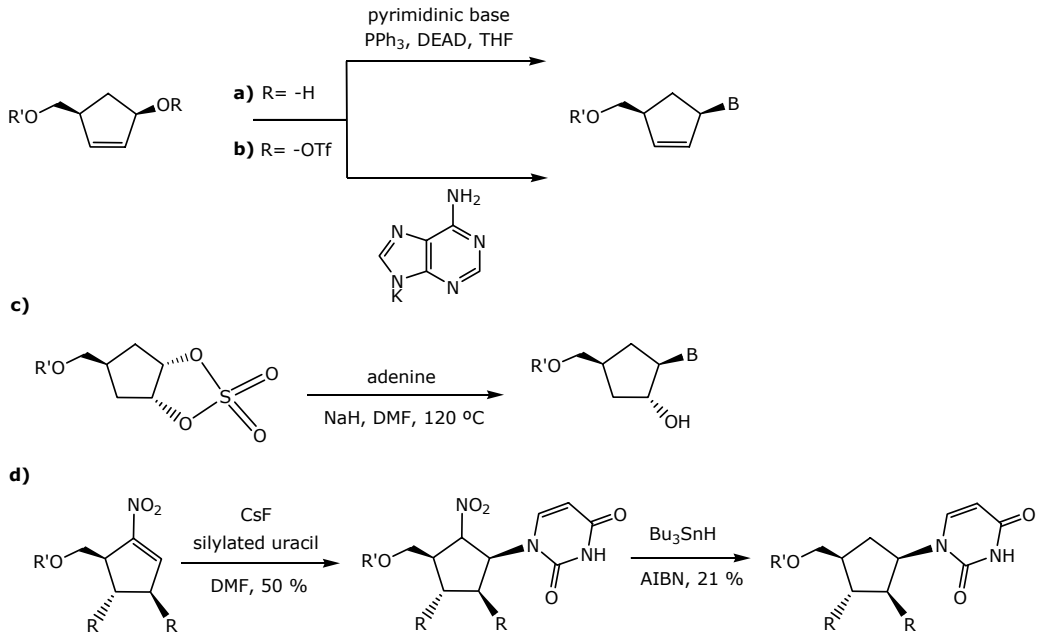
1) Direct coupling of a nucleic base with the carbocylic pseudo-sugar

Direct substitution can be accomplished by several methods: a) palladium-catalysed displacement of an allylic ester or carbonate, which was pioneered by Trost;[46] b) Mitsunobu coupling with a cycloalkanol;[47] c) nucleophilic displacement of a halide ion or activated hydroxyl such as a mesylate, tosylate, or triflate; d) ring-opening of an epoxide or cyclic sulfate; and e) Michael addition to an olefin activated by a carbonyl or other electron withdrawing group[48] (Scheme 11). Direct coupling of a heterocyclic base provides a more convergent approach to carbocyclic nucleosides, but introduces

[46] (a) Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110,* 621. (b) Crimming, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192.
[47] (a) Mitsunobu, O.; *Synthesis* **1981**, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (c) Wachuneister, J.; Classon, B.; Samuelsson, B.; Kvarnstrom, D. *Tetrahedron* **1995***, 51,* 2029.
[48] Yoshikawa, M.; Yokokawa, Y.; Inuoe, Y.; Yamaguchi, S.; Murakami, N.; Kitigawa, I. *Tetrahedron* **1994**, *50,* 9961.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

the problem of regioselectivity with respect to attack by the base. With purines, attachment at the N9, N7 and N3 nitrogens is possible and is often observed as is the case in natural nucleoside synthesis. Adenine is often attached directly, although protection of the 6-amino group is sometimes beneficial. Guanine has a low solubility in organic solvents and is typically introduced by attachment of 2-amino-6-chloropurine followed by hydrolytic displacement of the 6-chloride.[49]

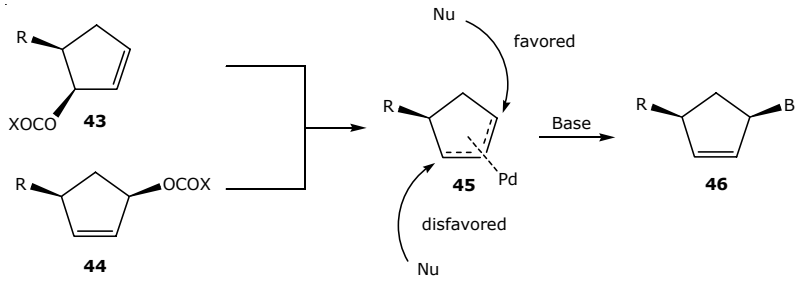


Scheme 11. Direct coupling of the base with the carbocylic pseudo-sugar.

Palladium-catalysed substitutions of allylic leaving groups have found wide application in carbocyclic nucleoside synthesis. An allylic ester, carbonate or epoxide is treated with a palladium (0) catalyst to generate an intermediate allyl palladium complex **45** that reacts with an anion of a purine or pyrimidine (Scheme 12). Three points are worth noting: 1) either of two regioisomeric allyl esters **43** or **44** can in principle provide access to the same palladium complex; 2) the palladium complex undergoes nucleophilic attack at the less hindered carbon; 3) since palladium first displaces the allylic ester and then a nucleophile displaces palladium, the substitution reaction occurs with retention of configuration, although allylic rearrangement can

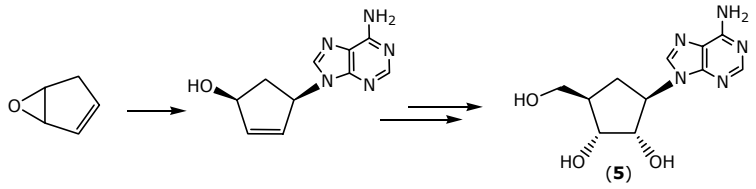
[49] Clausen, F. P.; Juhl-Christensen, J. *Organic Prep. and Proc. Int.* **1993**, *25,* 373.

occur.[50] The use of an epoxide or carbonate as the leaving group precludes the need for an external base to deprotonate the heterocyclic base. Since carboxylates are less basic, a stoichiometric amount of base must be added to deprotonate the heterocyclic base when esters are utilized as the leaving group.



Scheme 12. Palladium-catalysed substitutions.

The first example of direct substitution of a heterocyclic base on a carbocycle through a palladium-catalysed substitution was reported by Trost in a racemic synthesis of aristeromycin (**5**) (Scheme 13).[46a]



Scheme 13. Synthesis of aristeromycin (**5**) by Trost.

2) Construction of the heterocyclic base from an aminocycloalkane

The heterocyclic base of carbocyclic nucleosides can also be introduced through a linear strategy in which an amino group is used to construct the heterocycle.[51] The amino group becomes the N9 of a purine moiety or the N1 of a pyrimidine.

[50] Trost, B. M.; Verhoeven, T. R. "Comprehensive Organometallic Chemistry", Wilkinson, G., ed. Pergamon Press, Oxford, 1982, vol.8, p.799.

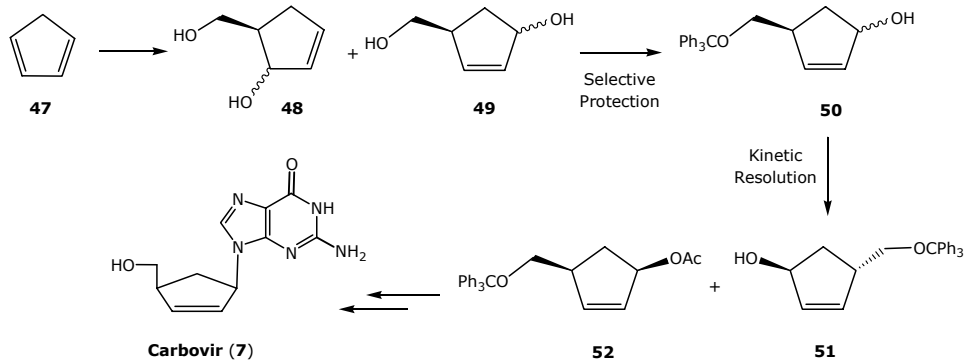
[51] (a) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, I. L.; Tsuruo, T. *J. Med. Chem.* **1992**, *35,* 1882. (b) Evans, C. T.; Roberts, S. M.; Shoberu, K. A.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 589. (c) Wyatt, P. G.; Anslow, A. S.; Coombs, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G. *Nucleosides and Nucleotides* **1995***, 14,* 2039.

- Procedures of formation of cyclopentane ring

1) From cyclopentadiene

a) By Prins reaction

Roberts began a synthesis of (-)-carbovir by exploiting the known Prins reaction[52] of cyclopentadiene (**47**) with aqueous formaldehyde to produce a mixture of *cis* and *trans* **48** and **49** (Scheme 14). The racemic trityl ether **50** was obtained by selective protection of the primary alcohol and chromatographic separation of the mixture. The racemic alcohol was resolved enzymatically to produce acetate **52** in 95% ee.[53] palladium-catalysed coupling of acetate **52** with 2-amino-6-chloropurine provided carbovir (**7**) after removal of the trityl ether and displacement of the chloride.



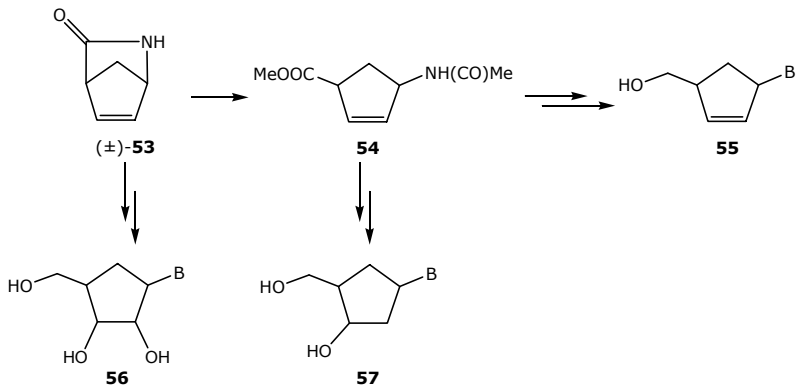
Scheme 14. Kinetic resolution in the synthesis of carbocyclic nucleosides.

Other techniques used in order to resolve the mixture of **48** and **49** have been described, such as derivatization reactions for subsequent separation of the mixture by chromatography[54] or crystallization.

[52] Bajorek, J. J.; Battaglia, R.; Pratt, G.; Suthedand, J. K. Y. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1243.
[53] Evans, C. T.; Roberts, S. M.; Shoberu, I. C. A.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 589.
[54] (a) Popescu, A.; Hecnfeldt, A.-B.; Gronowitz, S.; Johansson, N. G. *Nucleosides and Nucleotides* **1995**, *14*, 1233. (b) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Palmer, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 313.

b) By reaction with TsCN

The bicyclic lactam **53**, which is readily prepared from the cycloaddition product of cyclopentadiene and tosylcyanide by aqueous hydrolysis, has been a key building block in many syntheses of carbocyclic nucleosides (Scheme 15).[55] Usually when this strategy was employed, the nucleosides were obtained as racemic mixtures that could be separated by chromatography, crystallization or kinetic resolution in the appropriate intermediate step; thus, racemic syntheses of the analogs **55**[51b] and **56**[56] have been reported using different pathways from lactam **53**. In contrast, the analogs of **57**[57,58] could be obtained stereoselectively.

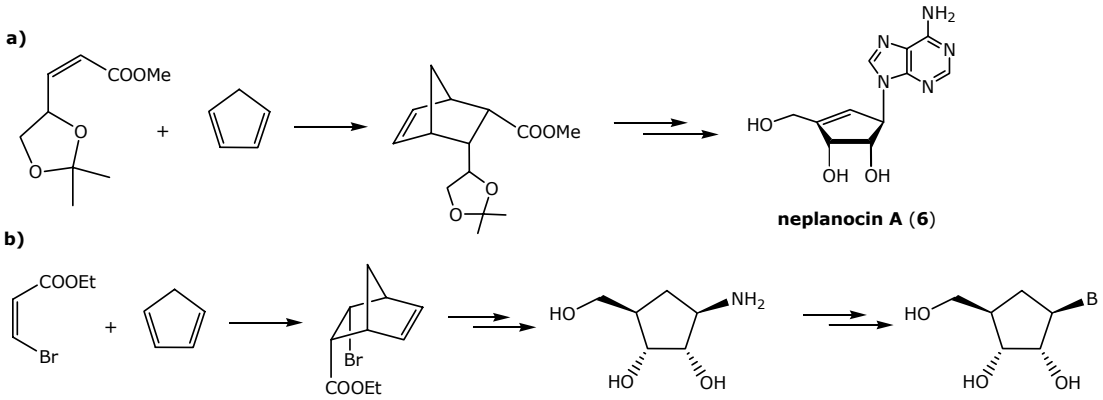


Scheme 15. Synthesis of carbocyclic nucleosides from lactam **53**.

c) By Diels-Alder reaction

The asymmetric Diels-Alder reaction has also been applied in the synthesis of carbocyclic nucleosides. The most representative examples using cyclopentadiene as the diene are shown in Scheme 16 (path a[59] and b[60]).

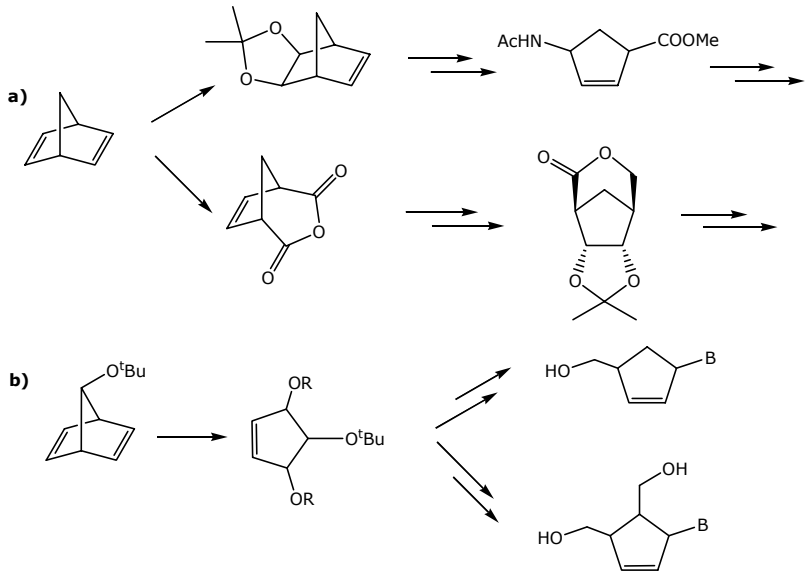
[55] Daluge, S. M. "*Therapeutic Nucleosides*" US 5034394, 1991.
[56] (a) Csuk, R.; Dorr, P. *Tetrahedron: Asymmetry* **1994**, *5*, 269. (b) Csuk, R.; Dorr, P. *Tetrahedron* **1995**, *51,* 5789.
[57] (a) Bray, B. L.; Dolan, S. C.; Halter, B.; Lackey, J. W.; Schilling, M. B.; Tapolczay, D. J. *Tetrahedron Lett.* **1995**, *36*, 4483. (b) Wyatt, P. G.; Anslow, A. S.; Coombs, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G. *Nucleosides and Nucleotides* **1995**, *14,* 2039.
[58] Katagiri, N.; Matsuhashi, Y.; Kokufuda, I.-L.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38,* 1961.
[59] (a) Díaz, M.; Ibarzo, J.; Jiménez, J. M., Ortuño, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 129. (b) Casas, R.; Chen, Z.; Díaz, M.; Hanafi, N.; Ibarzo, J., Jiménez, J. M.; Ortuño, R. M. *Anales de Química* **1995**, *1*, 568. (c) Arita, M.; Adachi, K.; Ito, Y.; Sawa, H.; Ohno, M. *J. Am. Chem. Soc*. **1983**, *103*, 4049.
[60] Boyer, S. J.; Leahy, J. W. *J. Org. Chem*. **1997**, *62*, 3976.



Scheme 16. Diels-Alder reaction in the synthesis of carbocyclic nucleosides.

2) From bicyclic [2.2.1] heptenes

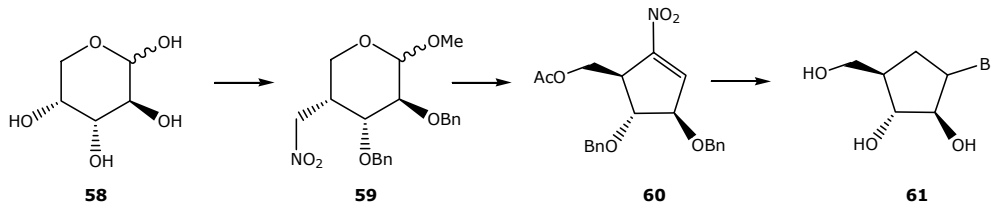
Several approaches to the carbocyclic subunit from bicyclic [2.2.1] heptenes have been reported. The ready availability of starting materials in large quantities makes this an attractive approach. However, the need to cleave the bicyclic system and the requirement that one carbon be excised from the cleavage product increases the overall number of steps in this strategy. Some representative examples are given in Scheme 17.[7]



Scheme 17. Synthesis of carbocyclic nucleosides from bicyclic [2.2.1] heptenes.

3) From carbohydrates and amino acids ("Chiral Pool")

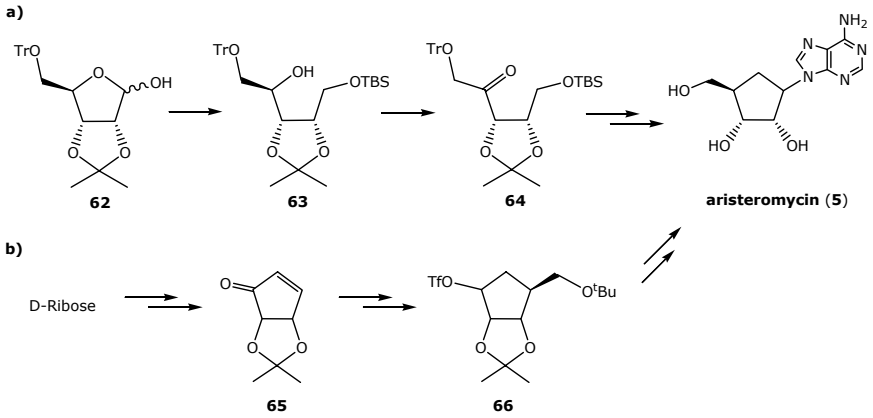
Several recent syntheses of carbocyclic nucleosides have been accomplished by starting from natural carbohydrates and amino acids, the "chiral pool". The Yoshikawa synthesis of some 2'-β-carbocyclic nucleosides began with the transformation of D-arabinose (**58**) to **59**. A ring contraction was then executed by hydrolysis of the acetal, which effected an aldol addition of the nitronate on the resulting aldehyde to obtain **60** (Scheme 18).[61]



Scheme 18. Synthesis of carbocyclic nucleosides from D-arabinose.

D-Ribose was also used as the starting material in the syntheses of carbocyclic nucleosides. For instance, the Ohira[62] synthesis of (-)-aristeromycin and the Chu[63] synthesis of some L-carbocyclic nucleoside analogs. The Ohira synthesis begins by conversion of the acetonide **62**, which is derived from D-ribose, to the alcohol **63** by reduction of the aldehyde and protection of the primary alcohol. Oxidation of the secondary alcohol produced the ketone **64**. Next, a C-H insertion reaction[64] was employed to close the carbocyclic ring (Scheme 19, path a). Chu's methodology involved the synthesis of the enone **65**, which was converted into triflate **66**. Direct displacement of the triflate afforded the corresponding nucleoside analog (Scheme 19, path b).

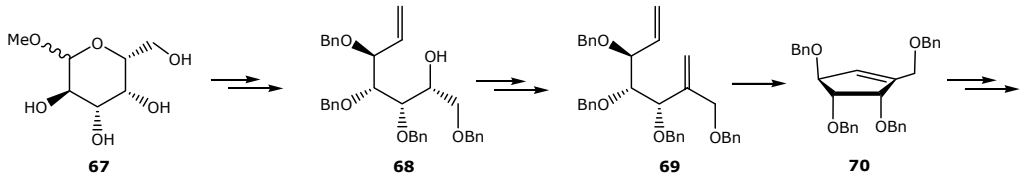
[61] Yoshikawa, M.; Yokokawa, Y.; Inuoe, Y.; Yamaguchi, S.; Murakami, N. *Tetrahedron* **1994**, *50*, 9961.
[62] Ohira, S.; Sawamoto, T.; Yamata, M. *Tetrahedron Lett.* **1995**, *36*, 1537.
[63] Wang, P.; Agrofoglio, L. A.; Newton, M.G.; Chu, C. K. *Tetrahedron Lett.* **1997**, *38,* 4207.
[64] Ohira, S.; Okay, K.; Moritani, T. *J. Chem. Soc., Chem. Commun*. **1992**, 721.



Scheme 19. a) Ohira synthesis and b) Chu synthesis of carbocyclic nucleosides from D-ribose.

The cyclopentenyl precursor can also be obtained from optically pure methyl-tetra-*O*-benzyl-D-galactopyranoside through a ring-closing metathesis step. This strategy holds the advantage of establishing three asymmetric centers on the cyclopentenyl moiety.[65]

The appropriate functionalized precursor **70** was made on a preparative scale from the chiral methyl-α-D-galactopyranoside **67**, through the (+)-diene **69** as a key chiral intermediate. The ring-closing metathesis,[66] first key step of this reaction, was accomplished by exposure of diene **69** to 10 mol% of a second generation ruthenium catalyst to yield the chiral cyclopentenyl analogue **70** (Scheme 20).[67,68]



Scheme 20. Synthesis of carbocyclic nucleosides by RCM.

[65] Agrofolio, L. A.; Amblard, F.; Nolan, S. P.; Charamon, S.; Gillaizeau, I.; Zevacco, T. A., Guenot, P. *Tetrahedron* **2004**, *60*, 8397.

[66] For overviews on metathesis, see: (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 58. (b) Schuster, M.; Blechert, S. Angew. *Chem. Int. Ed. Engl*. **1997**, *36*, 2037. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

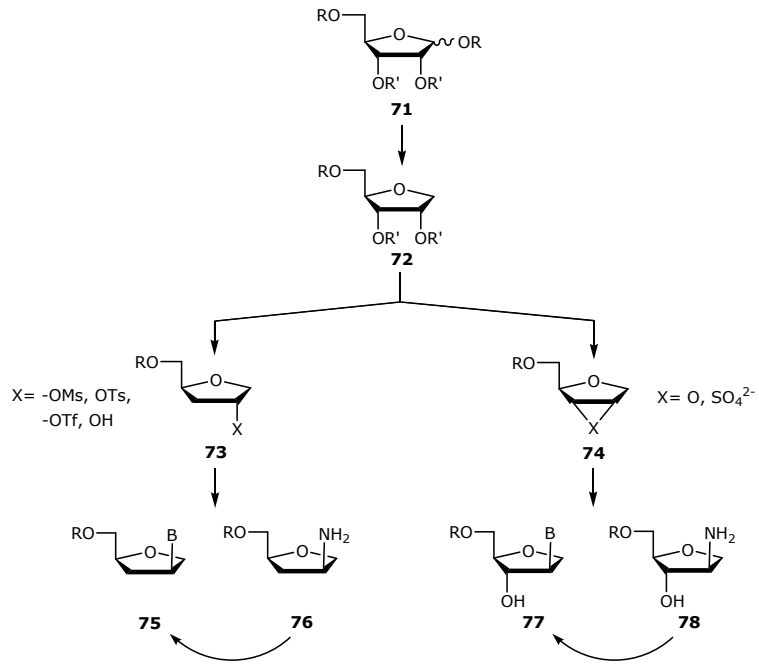
[67] Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev*. **2003**, *103*, 1875 and references cited herein.

[68] Related approaches to nucleosides or carbasugar via a RCM reported: (a) Gillaizeau, I.; Lagoja, I. M.; Nolan, S. P.; Aucagne, V.; Rozenski, J.; Herdewijn, P.; Agrofoglio, L. A. *Eur. J. Org. Chem*. **2003**, *4*, 666. (b) Amblard, F.; Nolan, S. P.; Gillaizeau, I.; Agrofoglio, L. A. *Tetrahedron Lett*. **2003**, *44*, 9177. (c) 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. (d) Lee, K.; Cass, C.; Jacobsen, K. A. *Org. Lett*. **2001**, *3*, 597. (e) Ko, O. H.; Hong, J. H. *Tetrahedron Lett*. **2002**, *43*, 6399. (f) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189. (g) Montembault, M.; Bourgougnon, N.; Lebreton, J. *Tetrahedron Lett*. **2002**, *43*, 8091. (h) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett*. **2000**, *41*, 7801.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

1.3. Synthesis of Isonucleosides

The most common methods for the formation of isonucleosides are shown in Scheme 21. The key step involves the precursor **72** which can be obtained from D-furanosides. Thus, the most successful procedure described is the treatment of the corresponding methyl furanoside with $Et_3SiH/BF_3{\cdot}OEt_2$. This mixture of reagents provides the deoxygenation of position 1, achieving the 1,4-anhydroalditol derivative **72**. The next step consists of the coupling of the nucleic base with **73** or **74**. When **73** (X= -OMs, -OTs, -OTf) is used as a precursor, the reaction is usually carried out by using K_2CO_3, 18-crown-6 and DMF in the presence of the nucleic base, leading to **75**.[69] When X=OH the reaction commonly applied to obtain **75** is the Mitsunobu reaction.[47] Isonucleosides can also be obtained by ring-opening of epoxide **74** using the nucleic base as nucleophile.[70] When this methodology was used, mixtures of 2'- and 3'-isonucleosides were obtained. To improve these results, the corresponding sulphates **74** were used, with excellent results.[71]



Scheme 21. Overview of isonucleoside synthesis.

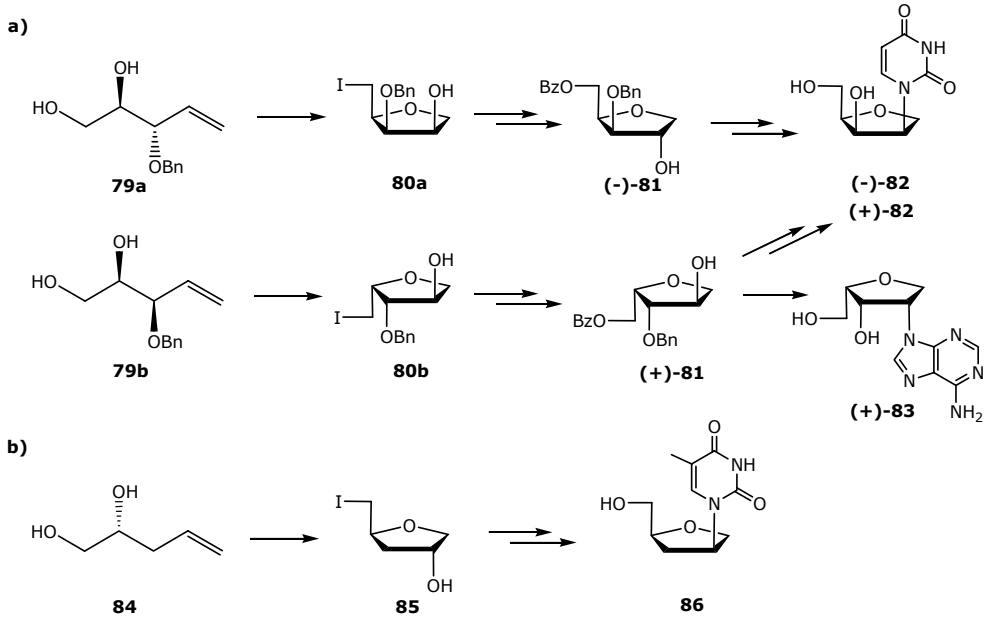
[69] (a) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Todaro, L. J.; Weigele, M. *Tetrahedron Lett*. **1989**, *30*, 6259. (b) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc*. **1992**, *114*, 7951. (c) Navarre, N.; Preston, P. N.; Tsytovich, A. V., Wightman, R. H. *J. Chem. Research* **1996**, 444. (d) Zintek, L. B.; Jahnke, T. S.; Nair, V. *Nucleosides & Nucleotides* **1996**, *15*, 69. (e) Nuesca, Z. M.; Nair, V. *Tetrahedron Lett*. **1994**, *35*, 2485.

[70] (a) Montgomery, J. A.; Clayton, S. D.; Thomas, H. J. *J. Org. Chem*. **1975**, *40*, 1923. (b) Montgomery, J. A.; Thomas, H. J. *J. Org. Chem*. **1978**, *43*, 541. (c) Yang, Z. J.; Yu, W.; Min, J. M.; Ma, L. T.; Zhang, L. H. *Tetrahedron: Asymmetry* **1997**, *8*, 2739. (d) Tian, X.-B.; Min, J.-M.; Zhang, L.-H. *Tetrahedron: Asymmetry* **2000**, *11*, 1877. (e) Jung, M. E.; Toyota, A. *Tetrahedron Lett*. **2000**, *41*, 3577.

[71] Bera, S.; Nair, V. *Tetrahedron Lett*. **2001**, *42*, 5813.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Our group also reported the synthesis of isonucleosides using precursors **79a** and **79b**, which gave the tetrahydrofurans **(-)-80** and **(+)-80** by iodine-induced cyclization of the appropriate protected pentene-triols **79a** and **79b**, respectively. Then following the appropriate steps, the corresponding isonucleosides were obtained properly (Scheme 22, path a).[72] The isonucleosides **86** are formed from the pentenediol **84** by an iodine-induced cyclization followed by substitution of iodine (Scheme 22, path b) by *p*-nitrobenzoate and introduction of the uracil by Mitsunobu reaction.[73]

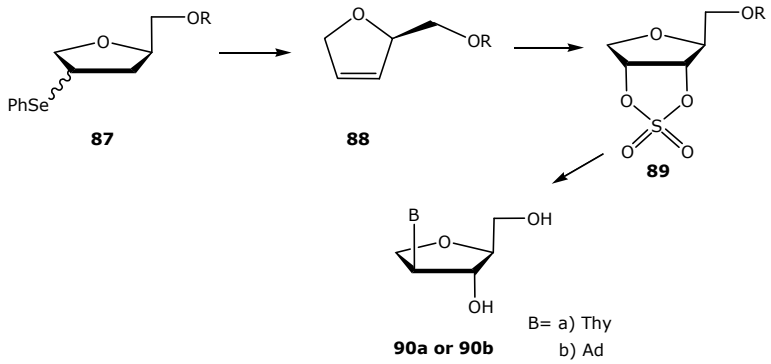


Scheme 22. Synthesis of isonucleosides and isodideoxynucleosides by iodoetherification.

The enantiopure dihydrofuran **88** was synthesised by regioselective elimination of the selenoxide obtained from selenenyl derivative **87**,[74] which in turn was obtained in a straightforward manner from glycidol. Dihydroxylation of **88** and subsequent reaction with thionyl chloride and $RuCl_3$ led to sulphate **89**. The reaction of **89** with adenine or thymine in the presence of a base and subsequent cleavage of the protecting group afforded isonucleosides **90** (Scheme 23).[75]

[72] Bravo, F.; Díaz, Y.; Castillón, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1635.
[73] Díaz, Y. Bravo, F.; Castillón, S. *J. Org. Chem*. **1999**, *64*, 6508.
[74] Bravo, F.; Viso, A.; Castillón, S. *J. Org. Chem*. **2003**, *68*, 1172.
[75] Aragonés, S.; Bravo, F.; Díaz, Y.; Matheu, M. I., Castillón, S. *Tetrahedron Lett*. **2003**, *44*, 3771.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 23. Synthesis of L-isonucleosides.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

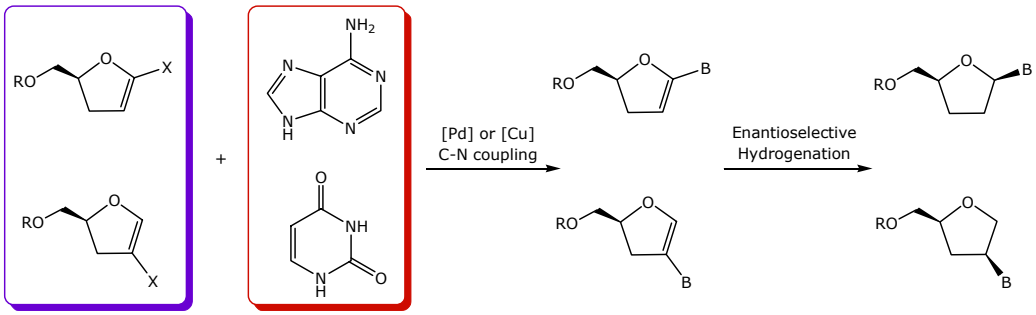
2. Objectives

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

OBJECTIVES

1. As was mentioned in the introduction, there are many methodologies designed to obtain iso-, 2',3'-dideoxynucleosides and carbocyclic nucleosides, but most of them generate α/β mixtures.

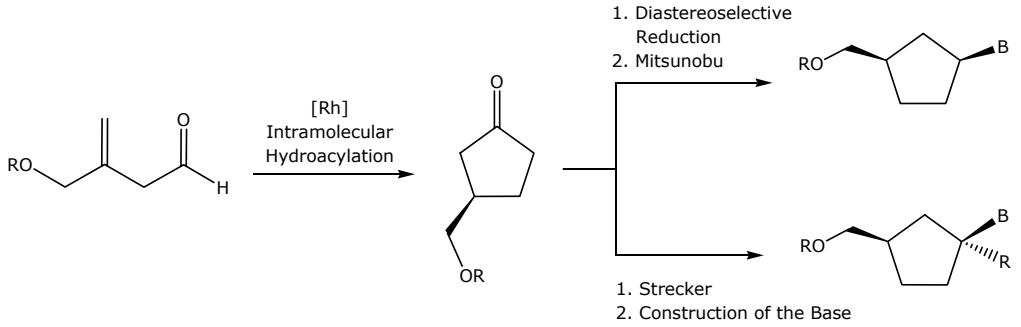
   In order to synthesised 2',3'-dideoxynucleosides and isonucleosides in a highly diastereoselective way, we will explore a new procedure based on the coupling of a vinyl halide with a puric or pyrimidinic base. The enantioselective hydrogenation of the double bond, which is expected to be completely diastereoselective, will give the desired nucleoside in a straightforward manner (Scheme 24).



Scheme 24. Synthesis of iso- and 2',3'-dideoxynucleosides by C-N coupling and enantioselective hydrogenation as key steps.

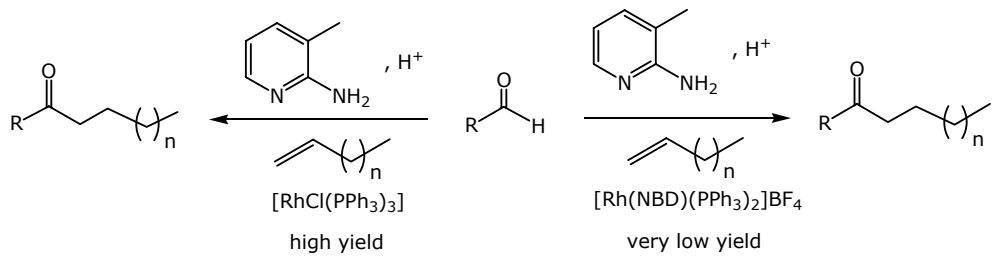
2. A second objective is to develop a new methodology to obtain carbocyclic nucleosides using an intramolecular enantioselective hydroacylation reaction as a key step. The chiral cyclopentanone resulting from the hydroacylation reaction is an appropriate intermediate for the synthesis of carbocyclic nucleosides and branched-carbocyclic nucleosides, as is shown in Scheme 25.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 25. New synthesis of carbocyclic nucleosides.

3. In previous studies carried out in our laboratory, the chelation-assisted intermolecular hydroacylation reaction was studied, and we observed a different behaviour for neutral and cationic rhodium catalysts. In this context, a third objective of this thesis is to carry out a mechanistic study looking for an explanation for these results. This study will be carried out using NMR studies and DFT calculations (Scheme 26).



Scheme 26. Intermolecular hydroacylation reaction using neutral and cationic rhodium catalysts.

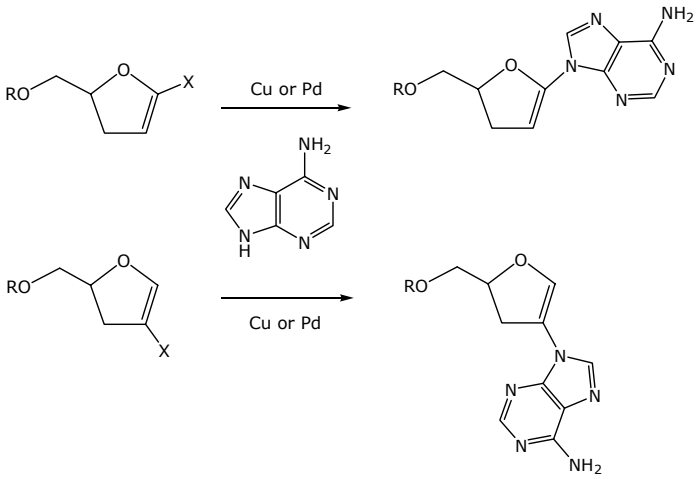
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

3. Approach to the Synthesis of Dideoxy- and Isonucleosides by C-N Coupling Reactions

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

3.1. ANTECEDENTS

As described in the general objectives, we decided to explore a new method for the stereoselective synthesis of 2',3'-dideoxynucleosides and isonucleosides based on new access to the corresponding vinyl halides that will be involved in the C-N coupling with nucleic bases.



Scheme 27. Approach to the synthesis of 2',3'-dideoxynucleosides and isonucleosides by C-N coupling using palladium or copper catalysts.

In recent years the palladium- and copper-catalysed cross-coupling reaction of aryl halides with amines, amides and heterocyclic compounds has been widely studied. Some representative examples of this reaction related to our goal will be presented.

In our study the nitrogen bases should be purinic and pyrimidinic but in the literature there are not examples of this kind of coupling, so this process could be extrapolated from the coupling of vinyl halides and amides or heterocycles such as imidazole. There are not many examples of the latter kind of coupling either; therefore the coupling between the N-heterocycles and aryl halides instead of vinyl halides will be discussed.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

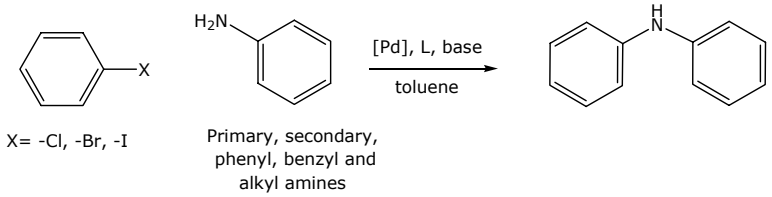
3.1.1. C-N COUPLINGS USING PALLADIUM CATALYSTS

The N-arylation of amines catalysed by palladium complexes has been widely studied, and there are numerous examples described in the literature. In contrast, the coupling of vinyl or aryl halides with amides or heterocyclic compounds has been scarcely studied.

- Coupling of Amides with:

Aryl halides, tosylates and triflates.

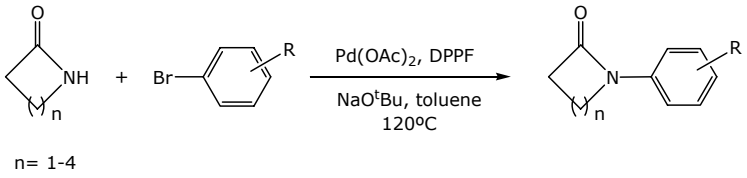
Palladium-catalysed C-N bond-forming reactions between aryl halides and amides have been less studied than the corresponding couplings with amines.[76] These amination reactions were typically carried out between 80 and 100ºC in toluene. The catalysts used initially were $[PdCl_2\{P(O\text{-}C_6H_4Me)_3\}_2]$, $[Pd\{P(O\text{-}C_6H_4Me)_3\}_2]$ or a combination of $Pd_2(dba)_3$ and $P(O\text{-}C_6H_4Me)_3$. Such processes have excellent functional group tolerance and wide substrate scope. Later, several kinds of monophosphines and diphosphines, different conditions and many varieties of substrates have been used in this coupling,[77,78] and it has become a well-established reaction (Scheme 28).



Scheme 28. Heterocoupling between aryl halides and amines.

Concerning the coupling of aryl halides with amides, Shakespeare[79] demonstrated that intermolecular reactions between lactams and aryl bromides could be effected with a Pd/DPPF catalytic system (Scheme 29).

[76] (a) Hartwig, J. F. *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 2046. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem*. **1999**, *64*, 5575. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem*. **1999**, *576*, 125. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **2000**, *65*, 1144. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem*. **2000**, *65*, 1158 and references therein.
[77] Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc*. **1996**, *118*, 7217.
[78] Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **1996**, *61*, 1133.
[79] Shakespeare, W. C. *Tetrahedron Lett*. **1999**, *40*, 2035.



Scheme 29. C-N coupling between lactams and aryl bromides.

Skerjl described the arylation of *tert*-butylcarbazate with a DPPF/$Pd(OAc)_2$ catalyst,[80] and Arterburn extended this method to the reaction of halopyridines.[81] In a related process, Hartwig reported that aryl bromides and chlorides can be effectively coupled with *tert*-butyl carbamate by using P(*t*-Bu)$_3$ as a ligand and sodium phenoxide as a base.[76b] The couplings of vinylogous amides[82] and ureas[83] have also been reported. Buchwald *et al*. reported a reasonably general Pd-based catalyst for the intermolecular coupling of aryl halides and amides.[84]

To establish the viability of the amide coupling process, Buchwald undertook an intensive screening of a variety of ligands and reaction variables. He found that a Pd catalyst using Xantphos (**91**, Figure 4),[85] a ligand developed by van Leeuwen,[86] with Cs_2CO_3 as the base and THF or 1,4-dioxane as the solvent provided the most generally successful catalyst for the coupling of amides[87] with activated (electron deficient) as well as electronically neutral aryl halides.

Subsequently Buchwald found a new class of biaryl monophosphines that were highly active in several cross-coupling reactions (**92**-**99**).[88] Their continuing studies in this area have led to the discovery of a structural derivative of these ligands that gives rise to a catalytic system with both a greater activity and stability than those previously used. The study of this system has led them to try reactions and substrate combinations that have been recalcitrant in the application of previous catalysts.

[80] Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543.
[81] Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351.
[82] Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109.
[83] Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381.
[84] Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.
[85] (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 10251. (b) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem*. **1999**, *64*, 6019
[86] (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081. (b) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett*. **1999**, *40*, 3789. For a kinetic study of Xantphos/Pd-catalysed amine arylation reactions, see: (c) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475.
[87] Yin, J.; Buchwald, S. L. *J. Amer. Chem. Soc*. **2002**, *124*, 6043.
[88] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

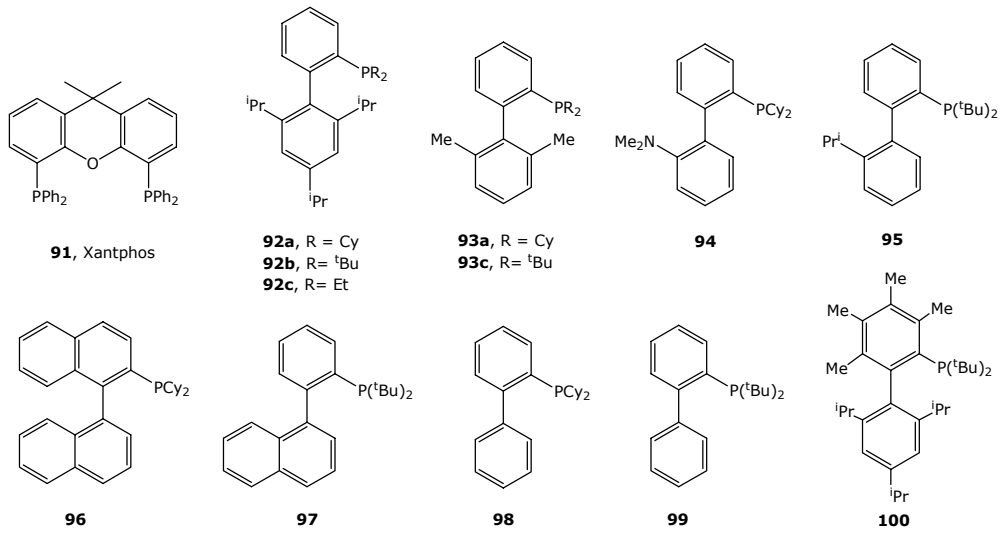


Figure 4. Most common ligands used in C-N couplings.

Buchwald *et al*. had previously noted a significant influence of the size of the dialkylphosphino group on the rate and efficacy of reactions using these ligands. They found an interesting and unexpected interplay between the nature of the phosphino group and that of the 2 and 6 substituents on the bottom ring. For example, ligand **92c**, with the smallest PR_2 group is ineffective, whereas **92b**, with the largest PR_2 group, is only moderately active. The best compromise is seen in **92a**. Likewise, **92a** is far superior to **93a**, as the *ortho* methyl groups either do not provide enough steric bulk or are more prone to cyclometalation.[89,90]

Encouraged by their findings, they sought to ascertain if previously unattainable processes could be accomplished using **92a**. For example, they had been able, for the first time, to couple amides and carbamates with tosylates,[87,91] and the coupling of pyrrolidinone, primary amides, *N*-methyl formamide, and *N*-Boc amide proceeded with good to excellent yield. It was necessary in these cases to add a catalytic quantity of phenyl boronic acid to ensure complete conversion of the Pd(II) pre-catalyst to Pd(0). The best results were obtained using K_2CO_3 as the base in *t*-BuOH,[92] other solvents (toluene, dioxane) provided much slower reaction rates.

[89] (a) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789. (b) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.
[90] Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Kaplars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
[91] Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.
[92] For a Pd-catalysed oxidation reaction accelerated by *t*-BuOH as a co-solvent, see: Bagdanoff, J. T.; Ferreira, E. M.; Stolz, B. M. *Org. Lett.* **2003**, *5*, 835.

Recently, Messaoudi reported the coupling of 3-bromoquinoline-2(1H)-one with 4-methoxybenzamide and better results were found when Xantphos and **92a** were employed as a ligands (Table 1).[93]

Vinyl halides and tosylates

For many palladium-catalysed reactions, enol triflates can also function as reactive coupling partners;[94] however, this has only recently been extended to the amination of a simple enol triflate to afford an enamine.[95] The related amidation of an enol triflate would constitute a straightforward synthesis of enamides, which are valuable substrates for asymmetric hydrogenation reactions and hence for the synthesis of optically pure amines.

The reaction conditions are very similar to those used for the C-N couplings with aryl amides, but in this case there are only a few examples reported in the literature. Ligands such as BINAP and DPPF have been applied in the coupling with this kind of substrate, but the most used ligand is Xantphos, since it provided excellent results even when the BINAP and DPPF catalysts gave poor yields.[96] In Table 1, some examples of the coupling of vinyl and aryl halides are shown.

Table 1. C-N coupling with amides and vinyl and aryl halides.

Lit.	Amide	Substrate	Ligand	Base	Reaction conditions	Yield (%)
84	Lactames, benzamides	aryl triflates and halides	**91**	Cs_2CO_3	dioxane, 100ºC[a]	89-96
87	Benzamides, lactames, carbamates	aryl halides	**91**	Cs_2CO_3	dioxane, 100ºC[a]	66-98
96	Butyrolactam		**91**	Cs_2CO_3	dioxane, 50ºC[b]	97
90	Carbamates, benzamides	aryl tosylates	**92a**	K_2CO_3	$PhB(OH)_2$, *t*-BuOH, 110ºC[a]	85-95
93	Benzamides, carbamates, lactames	2-bromoquinoline	**91**,**92a**	Cs_2CO_3	dioxane, 100ºC[a]	70-95
97	Amides	bromocoumarins	**91**	Cs_2CO_3	dioxane, 100ºC[a]	60-87

a) $Pd(OAc)_2$ was used, b) $Pd_2(dba)_3$ was used.

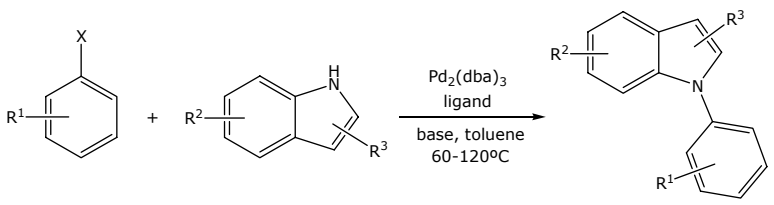
[93] Messaoudi, S.; Audisio, D.; Brion, J.-D.; Alami, M. *Tetrahedron* **2007**, *63*, 10202.
[94] (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508. (b) Scott, W. J.; McMurray, J. E. *Acc. Chem. Res*. **1988**, *21*, 47.
[95] (a) Willis, M. C.; Brace, G. N. *Tetrahedron Lett*. **2002**, *43*, 9085. (b) Hicks, F. A.; Brookhardt, M. *Org. Lett*. **2000**, *2*, 219.
[96] Wallace, D. J.; Klauber, D. J.; Chen, C.; Volante. R. P. *Org. Lett*. **2003**, *5*, 4749.
[97] Audisio, D.; Messaoudi, S.; Peyrat, J.-F., Brion, J.-D.; Alami, M. *Tetrahedron Lett*. **2007**, *48*, 6928

- Coupling of Heterocycles with Aryl and Vinyl halides

The palladium-catalysed amination of aryl halides and sulfonates has been the focus of intense research in recent years, particularly from the Buchwald and Hartwig laboratories. Hartwig was the first to describe this methodology for the arylation of indoles using Pd/DPPF and Pd/BINAP catalytic systems.[98] Using these catalysts, Hartwig and co-workers were able to efficiently combine indole with aryl bromides that had electron-withdrawing substituents in the *para* position. Electronically neutral aryl bromides required the use of long reaction times and high temperatures and proceeded in moderate yield.

Recently, Hartwig reported several examples of the use of the Tosoh system (Pd/P(*t*-Bu)$_3$) for the *N*-arylation of indoles. This protocol shortens the reaction time for the reactions of electronically neutral aryl bromides and decreases the temperature for the process to 100ºC.[76b] While one example of the reaction of 3-substituted indole with a simple *ortho*-substituted aryl bromide (*o*-bromotoluene) was described, reactions of similar substrates with "simple indoles" were reported to give mixtures of three products via *N*-arylation, C-arylation, and a combination of the two.

Then Buchwald reported the coupling of substituted indoles that are unsubstituted in the 3-position with *ortho*-substituted aryl halide and triflate substrates, and utilized a variety of 2-, 7-, and polysubstituted indoles by using Pd/(**92a**-**94**) and Pd/**100** (Figure 4) catalytic systems to provide high yields of the desired product (Scheme 30).[99,100]



Scheme 30. Coupling of azoles with aryl halides and triflates.

Table **2** shows some examples of the C-N coupling of heterocycles with vinyl and aryl halides.

[98] Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827.
[99] Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett*. **2000**, *2*, 1403.
[100] Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew, Chem. Int. Ed*. **2006**, *45*, 6523.

Table 2. Representative examples of C-N coupling of heterocycles.[a]

Lit.	Heterocycle	Substrate	Ligand	Base	Conditions	Yield (%)
101	Pyrrole	vinyl bromides	P(*t*-Bu)$_3$	LiO^{t}Bu	toluene-DME 82ºC	60-99
76b	Pyrroles and indoles	aryl bromides	P(*t*-Bu)$_3$	Cs_2CO_3	toluene 100ºC	72-88
99	Indole	aryl bromides	**96**	NaO^{t}Bu	toluene 120ºC	75-90
99	Indole	aryl triflates	**94**,**96**	K_3PO_4	toluene 80-100ºC	87-90
100	Indazoles, pyrazoles	aryl bromides and het-X	**92b**	NaO^{t}Bu	toluene 60-105ºC	62-99
100	Benzimidazole, imidazole	aryl bromides and het-X	**100**	K_3PO_4	toluene 100ºC	70-94

a) $Pd_2(dba)_3$ was used as a precursor catalysts.

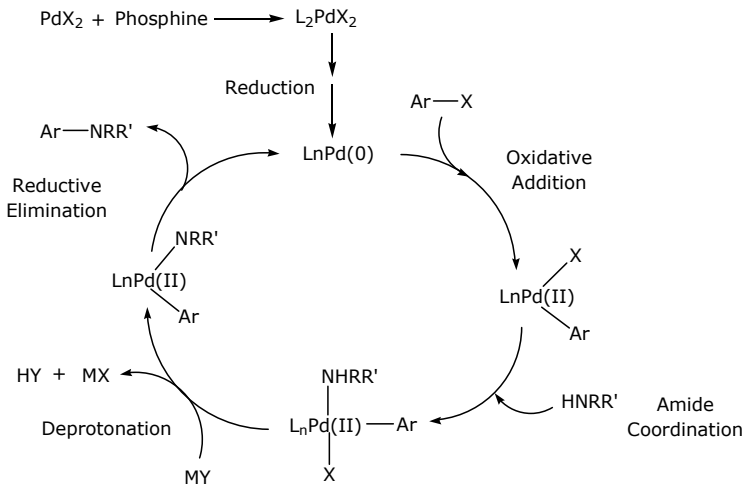
- Mechanistic Considerations

The catalytic cycle proposed for this reaction is the same as that for the coupling between aryl halides and amines and is described in Scheme 31.

Firstly the catalyst precursor, usually a Pd(II) species, is reduced under the reaction conditions, and at the same time this species is coordinated by the phosphine ligand to lead to the Pd(0) complex, which is the real catalyst. Once the catalyst is formed, the oxidative addition of the aryl halide takes place, and then the amide coordination is performed.

Once the amide coordination to the palladium complex has proceeded, the base deprotonates the amide, and subsequently the catalyst is regenerated by a reductive elimination process to give the final product.

[101] Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett*. **2002**, *4*, 623.



Scheme 31. Proposed mechanism for the C-N coupling of amides and aryl halides.

3.1.2. C-N COUPLING USING COPPER CATALYSTS

At the beginning of the last century, Fritz Ullmann and Irma Goldberg started their pioneering work on copper-mediated and copper-catalysed coupling reactions.[102] In comparison to the corresponding palladium-catalysed coupling reactions, the copper-catalysed versions seem to be less sensitive to the choice of metal source. In many cases, precursors as different as copper powder and air sensitive copper(I) salts proved to be suitable for the conversion of components in high yields. On the other hand, the selection of a ligand, the choice of the solvent and the base likewise plays an important role as for palladium catalysis. A selection of ligand additives in the copper catalysis toolbox is outlined in Scheme 32.

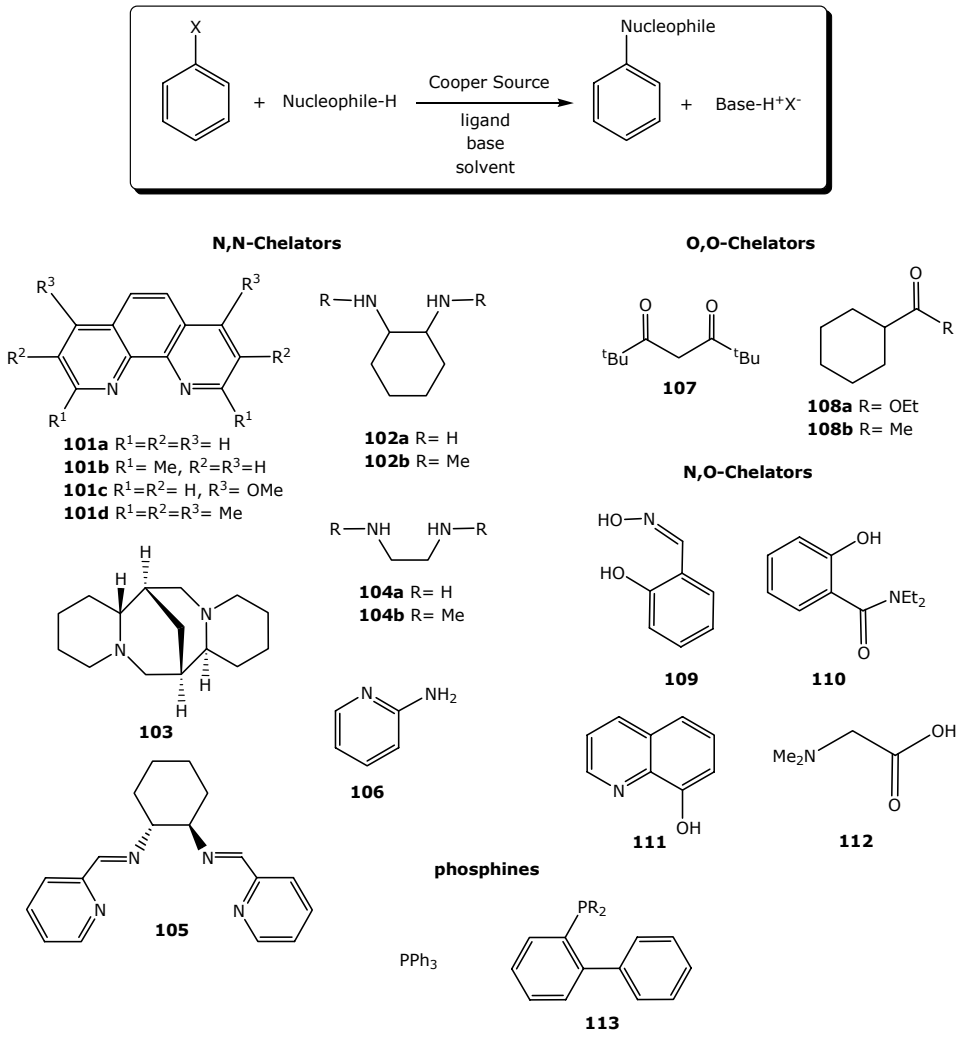
Neutral bidentate ligands appear to be in the majority of the reactions protocols. The variety of donor combinations included N,N-, O,O- and N,O chelators as well as phosphines. The wide choice of bidentate ligands implies great opportunities for selecting the base in order to fine-tune reaction conditions.

Even if the focus is on mild reactions conditions, the required temperatures range from 80-120ºC, which excludes low boiling point solvents. Toluene is commonly

[102] (a) Ullman, F. *Ber. Dtsh. Chem. Ges*. **1904**, *37*, 83. (b) Goldberg, I. *Ber. Dtsh. Chem. Ges*. **1906**, *39*, 1691.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

used, but is unsuitable in certain cases and can be replaced by dioxane or polar solvents such as NMP or DMF.



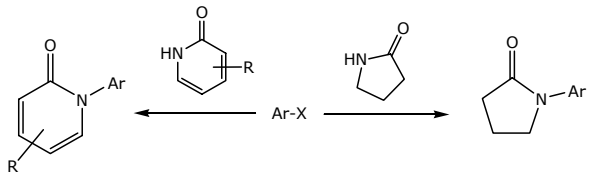
Scheme 32. Ligand toolbox for copper catalysed cross couplings.

- Coupling of Amides with:

Aryl halides

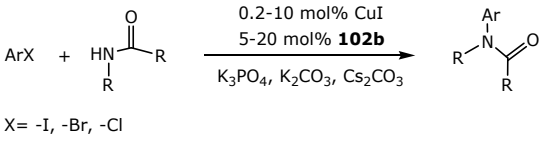
The amidation of aromatic halides has been the subject of intense studies in the past 10 years. This field was opened by Goldberg by the condensation of benzamide with bromobenzene with a trace of copper in refluxing nitrobenzene.[103]

Some 90 years later, Ukita reported the reaction of several bromo- and iodoaromatics with different aromatic amides in DMF as solvent at 120ºC using potassium carbonate as a base (Scheme 33).[104]



Scheme 33. Amidation of heterocycles by Ukita.

Later, the Cu/**102b**[105]catalytic system (Scheme 32) was employed, allowing the coupling of a wide range of amides with bromo- and iodoaromatics and even chloroarenes, including open-chain alkylamides, under mild conditions and in good yields (Scheme 34).[106]



Scheme 34. Coupling of aryl halides and amides.

Several examples of these reactions indicate that copper-catalysed reactions can be advantageous over palladium-catalysed protocols due to their wider functional group tolerance and the smaller chance of heavy metal contamination in the final product. A brief study of several readily available copper compounds as alternative catalyst

[103] Golberg, I. *Chem. Ber*. **1906**, *39*, 1691.
[104] Sugahara, M.; Ukita, T. *Chem. Pharm. Bull*. **1997**, *45*, 719.
[105] Kaplars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2001**, *123*, 7727.
[106] Kaplars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421.

precursors was also carried out. Copper metal, Cu_2O, CuI, and CuCl (among others) produced acceptable results in the arylation of *N*-methylformamide.[107]

The choice of the base plays a more important role than the nature of the copper pre-catalyst. Amidation of aryl iodides proceeds best with K_3PO_4 as the base; the reaction is much slower if K_2CO_3 is used instead. In contrast, many amidation reactions of aryl bromides, which typically react more slowly than aryl iodides, fail in the presence of K_3PO_4. In those cases, complete conversion of the aryl bromide can nevertheless be achieved if K_3PO_4 is replaced by a weaker base such as K_2CO_3.

Buchwald observed that the rate of deprotonation of the amide has to match the rate of the amidation reaction. If an excess of the deprotonated amide is formed, it impedes the desired aryl amidation reaction, presumably via formation of an unreactive cuprate complex.[106,108] An overview of the procedures is presented in Table 3.[109]

Table 3. Optimized reactions conditions for copper-catalysed coupling of Ar-X and Amides.[a]

Lit	X	Ar	Amide	Base	Ligand[b]	Reaction conditions	Yields[c]
110	I	Thiophenes, subst. aryls	lactames, arylamides	K_3PO_4, Cs_2CO_3	**104a**	polar aprotic and unpolar solvents, reflux 24 h	41-95% (22)
106 105	Br Cl I	Subst. aryl, thiophenes	lactames, carbamates, arylamides, amides, formamides	K_3PO_4, Cs_2CO_3, K_2CO_3	**102b** **104b**	dioxane, toluene	51-97% (75+52)
111	I	Subst. aryl	hydrazines	Cs_2CO_3	**101a** or none	tunable N-selectivity, DMF 80ºC	43-97% (9)
104	I Br	Subst. aryl, thiophenes, pyridines, quinolines	phtalazinones pyrrolidones isoquinolones benzotriazinones hydroxypyridines quinolines	K_2CO_3	none	DMF, DMSO, NMP, 150ºC, 6 h	14-91% (35)

a) In all cases the copper source was CuI. b) Ligands are shown in Scheme 32. c) In parentheses: number of examples reported.

[107] Weston, P. E.; Adkins, H. *J. Am. Chem. Soc.* **1928**, *50*, 859.
[108] Bacon, R. G. R.; Karim, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 272.
[109] Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.
[110] Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427.
[111] Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

Vinyl halides

In the literature there are not many examples of coupling between vinyl halides and amides in order to obtain enamides. The yields are very variable depending on the substrate, the copper source and the reaction conditions employed. Table 4 shows some examples of this kind of coupling.

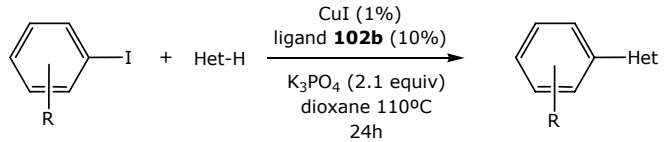
Table 4. Copper catalysed N-vinylation of lactames.

Lit.	X	Vinyl	Ligand	Precursor	Solvent	Base	Yield (%)
112	I	Alkylics	**102b**	CuTC, CuI	dioxane 90ºC	K_3PO_4	56-46
113	I	Cyclohexenes	**112**	CuI	dioxane 60ºC	Cs_2CO_3	85
114	I	Phenyl, esther	**101d**	$Cu(CH_3CN)_4PF_6$	DMA 92ºC	Rb_2CO_3	60-90
115	Br	Alkylics	**104b**	CuI	toluene 76-90ºC	K_2CO_3	100

- Coupling of Heterocycles with:

Aryl halides

Buchwald reported the successful mono-arylation of imidazoles with aryl bromides and iodides using copper triflate and phenanthroline (**101a**) or dibenzylidene acetone as ligands.[116] An extension of this methodology has been achieved by the use of cyclohexane diamine (**102a**) as a ligand to synthesize various arylated heterocycles.[105] Arylated imidazoles, indoles, carbazoles, pyrazoles, and phtalazines were accessible by this copper catalysed process (Scheme 35).



Scheme 35. Synthesis of arylated heterocycles.

An overview of other procedures is given in

Table **5**.

[112] Coleman, R. S.; Liu, P.-H. *Org. Lett*. **2004**, *6*, 577.
[113] Pan, X.; Cai, Q.; Ma, D. *Org. Lett*. **2004**, *6*, 1808.
[114] Han, C.; Shen, R.; Su, S.; Porco, J. A. *Org. Lett*. **2004**, *6*, 27.
[115] Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 3667.
[116] Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett*. **1999**, *40*, 2657.

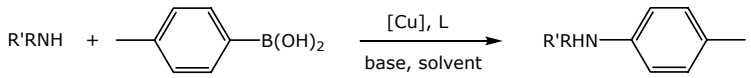
Table 5. Optimized reactions conditions for copper-catalysed arylation of N-heterocycles.[a]

Lit	X	Heterocycle	Base	Ligand[b]	Reaction conditions	Yields[c]
105	Br Cl I	Pyrazoles, indazoles, 7-azaindoles, phthalazinones, indoles, pyrroles, carbazoles, benzimidazoles, imidazoles	K_3PO_4, Cs_2CO_3, K_2CO_3	**102a**	dioxane 100ºC, 24 h	62-99% (52)
110	I	Pyrroles, indoles	K_3PO_4, Cs_2CO_3	**104a**	dioxane 100ºC	87-96% (2)
117	I Br	Subst. indoles	K_3PO_4	**102b** **104b**	toluene 100ºC	57-96% (60)

a) In all cases the copper source was CuI and the substrate was Ar-X. b) ligands are shown in Scheme 32. c) In parentheses: number of examples reported.

Aryl boronic acids

Chan *et al.* and Lam and co-workers simultaneously published original papers which had a significant impact on establishing the substrate scope and pre-optimal reaction conditions in the cross-coupling of aryl boronic acids and nitrogen nucleophiles (Scheme 36).[118,119]



Scheme 36. General reaction between aryl boronic acids and nitrogen nucleophiles.

An impressive range of nucleophiles was successfully tested, and suitable substrates for the reaction, which included amines, anilines, amides, imides, ureas, carbamates, sulfonamides, and aromatic heterocycles (imidazoles, pyrazoles, triazoles, tetrazoles, benzimidazoles, and indazoles) were reported.[118] However, no true substrate trend emerged in these reactions.

Much of the early base screening was carried out on the reaction with *p*-tolylboronic acid as aryl donor. For this substrate, it would appear that Et_3N was the best choice. In all the reactions investigated with N-nucleophiles, the use of Et_3N as a base resulted in yields superior to those obtained with pyridine. However, for the preparation of compounds including imidazoles, benzimidazoles, pyrazoles and other

[117] Antilla, J. C.; Kaplars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 11684.
[118] Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933.
[119] Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941.

azoles from the range of heteroarenes examined as nucleophiles, it appears that pyridine was the base of choice, as no examples were recorded with the supposedly equally efficient Et_3N. 1,2,3-triazoles, tetrazoles, 1,2,4-triazoles and indazoles gave low yields in the coupling reactions (from 6 to 26% yield).

An empirical order has been established for the solvent in terms of reaction yield:

CH_2Cl_2 » 1,4-dioxane=NMP=THF=DMF » EtOAc=toluene=DMSO »» MeOH.

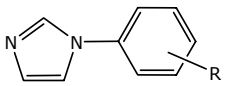
Cundy and Forsyth presented several additional examples and confirmed the capricious nature of the reaction: no substrate trend was observed in terms of the basicity of the amine and the sigma-donating effect of the aryl boronic acids.[120] In fact, on the basis of these findings and those of Chan and Lam, it could be concluded that the general reaction conditions had to be adapted for each substrate type in the N-arylation reaction.

In perhaps the most important development since the copper-mediated N-arylation of boronic acids, Collman and Zhong reported the catalytic version of this reaction.[121] Imidazole was used as a standard N-nucleophile with phenylboronic acid as the aryl donor. It was also shown that Cu(II) alternatives in the form of [Cu(OH)ClTMEDA] (formed in situ by the reaction of oxygen and the commercially available dimer $[\{Cu(OH)TMEDA\}_2]Cl_2$) were potent catalysts. Table 6 shows the electronic and structural diversity in the boronic acids selected for this study. In all cases, reaction conditions were found that led good to excellent yields (52–98%).

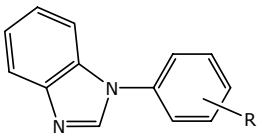
Environmentally friendly reaction procedures are fashionable, especially when performed in water.[122] Collman *et al*. studied exactly the above reaction with the same substrates and catalyst species, and reported the first examples of N-arylation of imidazoles in water.[123] The yields for the same products are shown in red in Table 6.

[120] Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett*. **1998**, *39*, 7979.
[121] Collman, J. P.; Zhong, M. *Org. Lett*. **2000**, *2*, 1233.
[122] *Organic Synthesis in Water*, Ed.: P. A. Grieco, Blackie Academic & Professional, London, 1998.
[123] Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem*. **2001**, *66*, 1528.

Table 6. N-arylation of imidazoles in organic solvent and in aqueous media.



114 R= *p*-Me
115 R= *p*-F
116 R= *p*-OMe
117 R= *o*-Me
118 R= *o*-OMe

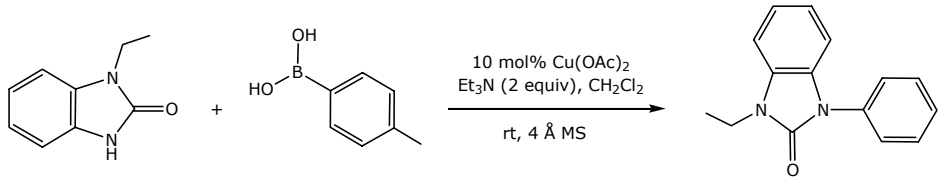


119 R= H
120 R= *p*-Me
121 R= *p*-OMe

product	Yield	product	Yield
114	71% 63%	**118**	5% 52%[a]
115	58% 26%	**119**	46%
116	63% 51%	**120**	98% 19%[b] 44%
117	74 % 55%	**121**	69% 28%

Conditions: Boronic acid (2 equiv), $[\{Cu(OH)TMEDA\}_2]Cl_2$ (10 mol%), O_2, CH_2Cl_2, rt overnight. Yields in red for reactions in water. a) 3 equiv of 2-methoxyphenylboronic acid were used. b) 4 Å MS were added and the reaction mixture was stirred under ambient conditions.

Lam *et al*. also reported an important alternative to this catalytic cross-coupling of aryl boronic acids and amines in the presence of $Cu(OAc)_2$ (10 mol%) and a co-oxidant additive (other than oxygen).[124] The best systems explored involved $Cu(OAc)_2$ and a combination of pyridine N-oxide (PNO) (1.1 equiv) and air, TEMPO (1.1 equiv) and air, or just oxygen (Scheme 37).



Co-oxidant: **PNO** > **TEMPO** > **NMO** > **nitroxide** > **oxaziridine** > **$NaBO_3 \cdot H_2O$** > **$K_3Fe(CN)_6$** > ***m*-CPBA**
69% 64% 62% 55% 48% 31% 11% 6%

Scheme 37. Cross-coupling reaction using a co-oxidant additive.

The range of substrates that work well in this transformation includes benzimidazolones, isatins, phthalimides, piperidines, indazoles, anilines, pyridones, sulfonamides, saccharin, and benzimidazoles (Figure 5).

[124] Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett*. **2001**, *42*, 3415.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2007

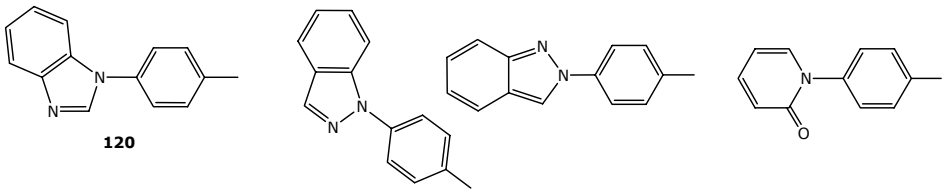


Figure 5. Most relevant examples of N-arylation of heterocycles.

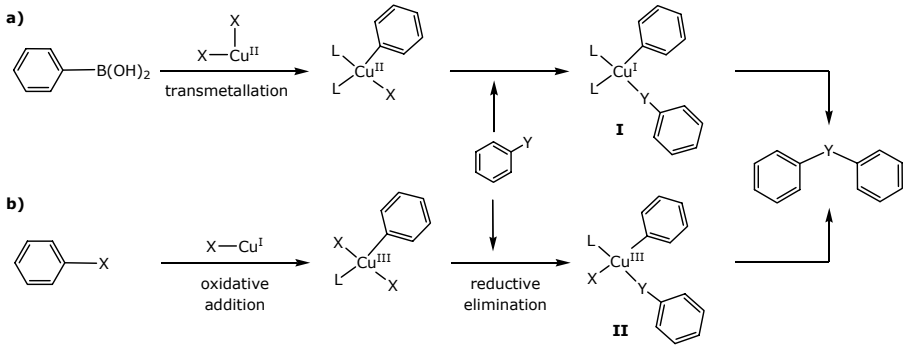
- Mechanistic Considerations

The mechanism of the Ullmann arylation of alcohols has not been well-established.[125] As most studies devoted to the use of this reaction are synthetically oriented, only proposals for the mechanistic rationale have been discussed, some of which are relatively speculative in nature. As can be seen from the many examples presented above, copper sources are diverse, but, in general, the most universal starting copper source is a Cu(I) or Cu(II) species. It seems most likely that Cu(II) is not the catalytic species in the reaction. Furthermore, it has been ascertained that radical mechanisms can be ruled out, as the reactions are not inhibited when radical scavenger additives (such as 1,1-diphenylethylene) are included.

An unresolved issue is whether the oxidation state of the intermediate is Cu(I) or Cu(III) or indeed an equilibrium (or disproportionation) controlled by the reduction potential of the Cu couple. It was later shown that the presence of an oxidizing atmosphere (air, oxygen, or co-oxidant) improves the arylation reaction, lending some substantial support to the idea that perhaps species **I** can be oxidized to **II** prior to the reductive elimination (Scheme 38). In this plausible mechanism, the following processes and species could be involved:

1) Transmetalation of boronic acid and copper catalyst.
2) N-nucleophile coordinates to Cu(II): reduction potential of the Cu(III)/Cu(II) couple decreases.
3) Oxygen oxidizes Cu(II) to Cu(III) (putative); ready for reductive elimination.
4) Product eliminated and Cu(I) species ready to regenerate catalytic species.

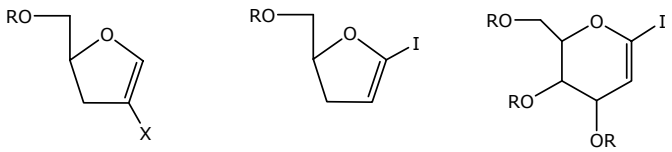
[125] Paine, A. *J. Am. Chem. Soc*. **1987**, *109*, 1496.



Scheme 38. Plausible mechanism for the copper-catalysed arylation with: a) boronic acid; b) halides X= Cl, Br, I. Y= NH.

3.2. RESULTS AND DISCUSSION

As was mentioned above, the objective of this chapter is to develop a new procedure for the synthesis of 2',3'-dideoxynucleosides and isonucleosides based on a C-N coupling reaction between 4-halo-2,3-dihydrofurans **122**, 5-iodo-2,3-dihydrofurans **123** and 1-iodo-D-glucal* **124** (Figure 6). Few examples describing the synthesis of these kinds of vinyl halides can be found in the literature. For this reason, we thought that it was worthwhile to explore new synthetic procedures first.



122 **123** **124**

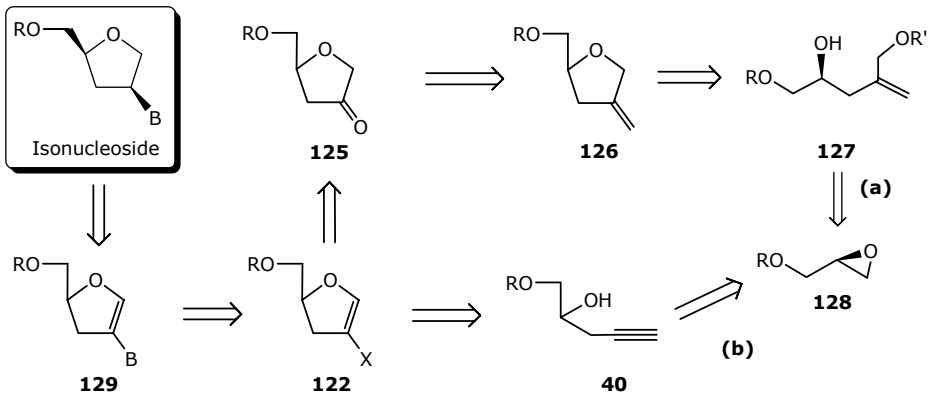
Figure 6. Vinyl halides proposed as dideoxynucleoside and isonucleoside precursors.

3.2.1. Approach to the Synthesis of 4-halo-2,3-dihydrofuran Derivatives

Initially we tackle the synthesis of isonucleosides, and for this purpose the synthesis of 4-halo-dihydrofuran **122** was required. We considered two different routes for synthesising this compound: a) compound **122** could be obtained from ketone **125**, which could arise from the ozonolysis of methylentetrahydrofuran **126** and the latter

* Compounds **122** and **123** are numbered as tetrahydrofuran derivatives and **124** is numbered following the nomenclature of carbohydrates.

could be obtained by ring-opening of epoxide **128** using an alkenyl cuprate and further cyclization; b) via 5-*endo*-dig cyclization of **40**, which in turn would be obtained by ring-opening of epoxide **128** with lithium acetylide. (Scheme 39, paths a and b).



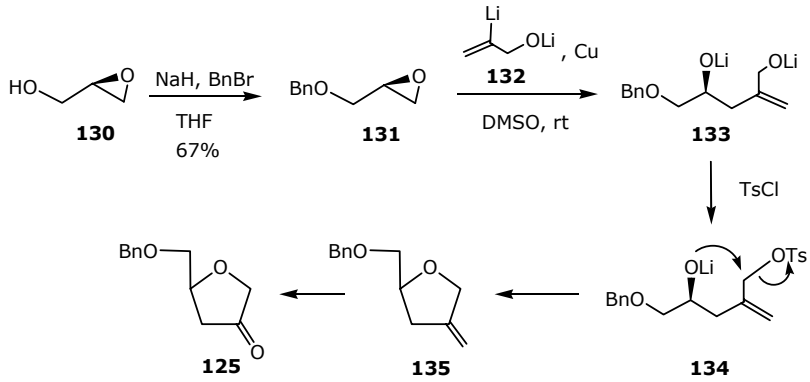
Scheme 39. Retrosynthetic analysis for isonucleoside synthesis.

- Nucleophilic Substitution

The choice of the protecting group of *R*-glycidol (**130**, Scheme 40) merited careful consideration. Our previous studies had suggested that the benzyl ether was the most appropriate protecting group because of its high stability under the strongly basic conditions required in the following steps. Thus, the *R*-glycidol (**130**) was reacted with benzyl bromide to give compound **131** in 67% yield.[126]

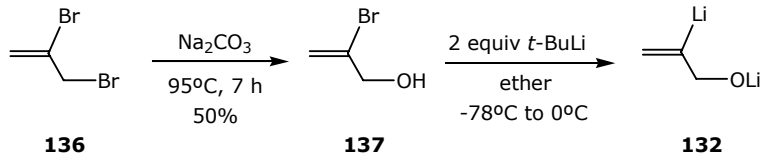
Then, the ring-opening of the epoxide **131** with the alkenyl lithium **132** would give **133**. It can be envisaged that selective reaction of a primary alcohol in **133** with TsCl would afford **134**, from which the methylentetrahydrofuran **135** could be achieved by means of an intramolecular nucleophilic substitution reaction (Scheme 40). The ozonolysis of **135** would lead to the corresponding ketone.

[126] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley & Sons 1999, p. 76-77.



Scheme 40. Proposed pathway for synthesising **135**.

The required alkenyl lithium compound **132** was synthesised as shown in Scheme 41. The starting material for this synthesis was 2,3-dibromoprop-1-ene (**136**) which was treated with 10% sodium carbonate solution at 95ºC giving the alcohol **137** in 50% yield.[127] Subsequently 2-bromoprop-2-en-1-ol (**137**) was transformed into **132** by reaction with *tert*-butyllithium at low temperature.[128]

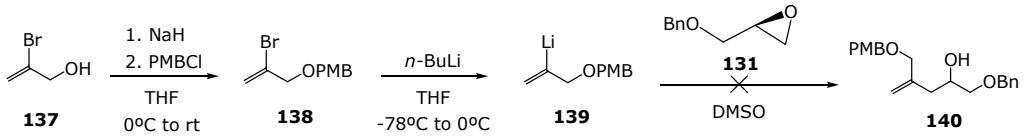


Scheme 41. Synthesis of **132**.

Then benzylglycidol **131** was reacted with **132** in DMSO at rt. Initial attempts to isolate the diol derived from **133** were unsuccessful, because of its high solubility in the aqueous media after the work-up with an ammonium chloride solution. Even when a continuous extraction was carried out, no reaction product could be recovered.

In light of these results, we considered protecting **137** as a *p*-methoxybenzyl ether (PMB), since it can be cleaved selectively in the presence of the benzyl group (Scheme 42).

[127] Hatch, L. F.; Alexander, H. E.; Randolph, J. D. *J. Org. Chem*. **1950**, *15*, 654.
[128] Corey, E. J.; Widiger, G. N. *J. Org. Chem*. **1975**, *40*, 2975.

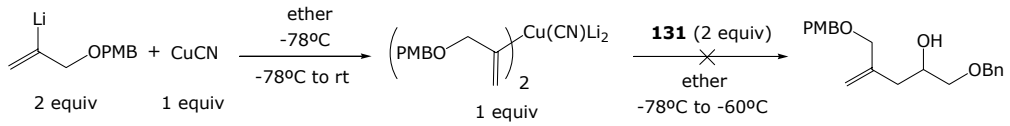


137 138 139 140

Scheme 42. Proposed pathway for synthesising **140**.

Thus, **137** was treated with *p*-methoxybenzyl chloride, affording **138** in 60% yield.[126] Then, **138** was treated with *n*-BuLi and subsequently with the epoxide **131**, but a complex mixture of products was obtained, and no product could be isolated. Moreover, the analysis of the crude reaction by ^{1}H and ^{13}C NMR did not show the characteristic signals of the *p*-methoxybenzyl group in the final product structure, confirming that the product **140** was not obtained.

The organocopper reagents are highly desirable reagents for organic synthesis. They often react stereoselectively and do not possess the extreme basicity of Grignard reagents. Consequently, they can be used to synthesize organic compounds that are highly functionalized.[129] For this reason we tried the ring-opening of the epoxide **131** using the higher order organocopper **141** (Scheme 43).



139 141 140

Scheme 43. Using of organocopper reagents for synthesising **140**.

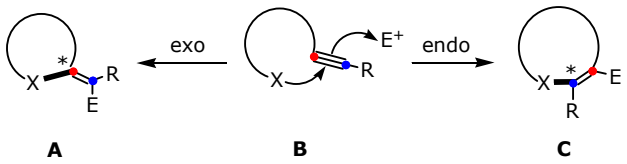
However, when epoxide **131** was reacted with the cyanocuprate **141**, formed *in situ*, ^{1}H and ^{13}C NMR spectra of the residue did not show the presence of *p*-methoxybenzyl in the final products. Consequently, this pathway was discarded and we focused on the study of the 5-*endo*-dig cyclization pathway.

[129] Taylor, R. J. K. *Organocopper Reagents; A Practical Approach*, Oxford University Press, 1994, p. 108.

- 5-*endo*-dig Cyclization

The cyclization reactions of acyclic compounds involving double bonds or tetrahedral carbons have been widely studied, but only few examples are reported when the substrate contains a triple bond.

The ring-forming reactions are important and common processes in organic chemistry. Baldwin elucidated a set of simple empirical rules that he had found useful in predicting the relative facility of different ring closures (3- to 7-membered rings). The predicted pathways are those in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for reaction. The disfavoured cases are subject to severe distortions of bond angles and distances. Thus, Baldwin described a ring-forming process with the prefix *exo*, when the breaking bond is exocyclic (**A**) to the smallest so formed ring and *endo* (**C**) when the breaking bond is endocyclic (Scheme 44).[130]



Scheme 44. *Endo* and *exo* cyclization.

Further, a numerical prefix was used to describe the ring size, corresponding to the number of atoms constituting the skeleton of the cycle, and finally the suffixes Tet, Trig and Dig to indicate the geometry of the carbon atom undergoing the ring closure reaction (asterisk, Scheme 44). The suffixes refer to tetrahedral, trigonal and digonal carbon atoms respectively.

As a consequence of the larger atomic radii and bond distances in atoms of the second periodic row, the geometric constraints on disfavoured ring closures may be bypassed for those atoms. Therefore, a condition for applying these rules is that **X** (Scheme 44) must be a first row element. The physical bases of the rules lie in the stereochemical requirements of the transition state for the various tetrahedral, trigonal and digonal ring closure processes. Baldwin's rules are summarized in the Table 7. It is important to note that structural modifications can dramatically affect the cyclization mode.

[130] Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734.

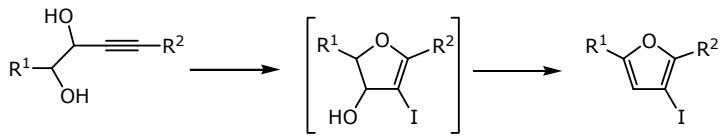
Table 7. Baldwin's rules describing the favoured and disfavoured cyclizations.

Cycle	EXO			ENDO		
	Tet	Trig	Dig	Tet	Trig	Dig
3	✓	✓	×	✓	×	✓
4	✓	✓	×	✓	×	✓
5	✓	✓	✓	×	×	✓
6	✓	✓	✓	×	✓	✓
7	✓	✓	✓	×	✓	✓

✓= favoured cyclization; ×= disfavoured cyclization

The addition of heteroatomic nucleophiles to triple bonds is an important reaction that often requires high activation energy.[131] The intramolecular additions take place faster, and they are widely studied in indole and iodofuran formation. Usually these reactions are catalysed by a base. In most of the reactions found in the literature, after the cyclization, an aromatization of the new structure occurred. Thus the reaction equilibrium is shifted in the direction of the final products.

Knight has studied the formation of iodofurans **144** by iodine-induced cyclization (Scheme 45).[132] The key step for this reaction is an iodine-induced 5-*endo*-dig cyclization of the acetylenic diols **142**, which spontaneously lose water to give **144**.



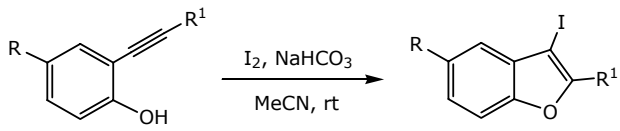
142 **143** **144**

Scheme 45. Synthesis of β-iodofurans **144**.

The key cyclizations were developed in dichloromethane using 3 equiv each of I_2 and $NaHCO_3$ mixed at 0ºC, followed by stirring without further cooling for 3h. This kind of reaction is usually also carried out in acetonitrile as a solvent, which leads to excellent results. In this case, though, the reaction in dichloromethane afforded better yields.

[131] Rodríguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed*. **2000**, *39*, 2488.
[132] El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett*. **2001**, *42*, 5945.

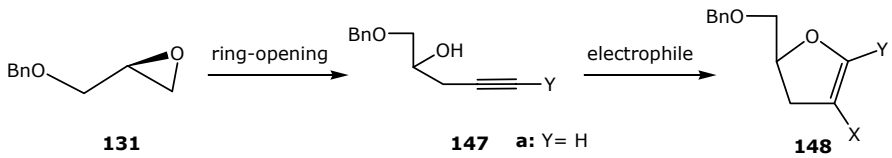
In this context, the iodocyclization of *o*-alkynylphenols (**145**) in acetonitrile using 3 equiv of I_2 and $NaHCO_3$ in mild conditions provided a new expeditious synthesis of 2-substituted-3-iodobenzofurans (**146**, Scheme 46).[133]



145 **146**

Scheme 46. Iodocyclization of **145**.

In light of the reported 5-*endo*-dig cyclizations described above, we considered obtaining the 4-halo-2,3-dihydrofuran (**148**) by this methodology (Scheme 47).



131 **147** **a:** Y= H **b:** Y= Ph **c:** Y= $SiMe_3$ **148**

Scheme 47. 5-*endo*-dig cyclizations from **147** in order to achieve **148**.

In order to obtain **147**, the ring-opening of **131** with different acetylenes and different reactions conditions was studied (Table 8).

Table 8. Ring-opening of (*R*)-benzylglycidol (**131**) using different acetylenes.

entry	Acetilene	Reaction conditions	Product	Yield (%)
1	LiC≡CH(en)	DMSO, rt	**147a**	60
2	HC≡C—Ph	*n*-BuLi, $BF_3{\cdot}OEt_2$, Et_2O, -78ºC	**147b**	50
3	HC≡C—$SiMe_3$	*n*-BuLi, $BF_3{\cdot}OEt_2$, Et_2O, -78ºC	**147c**	60

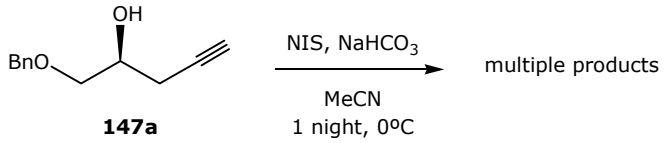
[133] Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

The ring-opening of the epoxide **131** with a lithium acetylide ethylenediamine complex proceeded in dimethylsulfoxide at rt (Table 8, entry 1). The formation of **147a** was confirmed by ^{1}H and ^{13}C NMR. In ^{1}H NMR the epoxide signals were shifted to low field due to disappearance of the ring strain. Moreover, new signals at 2.58 and 2.02 ppm corresponding to the hydroxyl group and acetylenic proton, respectively, were apparent. When the ^{13}C spectrum was recorded, the carbons belonging to the epoxide were also unshielded. New signals arising from the triple bond at 80.4 and 70.8 ppm were detected.

The ring-opening of the epoxide with phenylacetylene (entry 2) was carried out in diethyl ether by adding *n*-butyllithium and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) at -78ºC to afford **147b** in 50% yield. In ^{1}H NMR, the signals showed roughly the same shift those in **147a**. New signals at 7.15-7.30 ppm as a multiplet integrating to 10 protons showed the presence of two phenyl groups. In ^{13}C NMR, the carbons belonging to the triple bond at δ 85.7 and 82.9 were observed.

Finally **147c** was obtained in 60% yield in the same conditions explained above (entry 3). Its structure was also determined by spectroscopic techniques. In ^{1}H NMR the signal of the new hydroxyl group at δ 2.41 and a singlet at δ 0.2 integrating to 9 protons confirmed the ring-opening of the epoxide and the presence of the trimethylsilyl group, respectively.

Once the acetylenes were obtained, the study of the corresponding iodo-induced cyclization was carried out. The first attempt at cyclization was performed with the acetylene **147a** employing *N*-iodosuccinimide (NIS) as iodo-electrophile source and $NaHCO_3$ as a base (Scheme 48), but the formation of multiple products occurred and the purification could not be carried out properly.

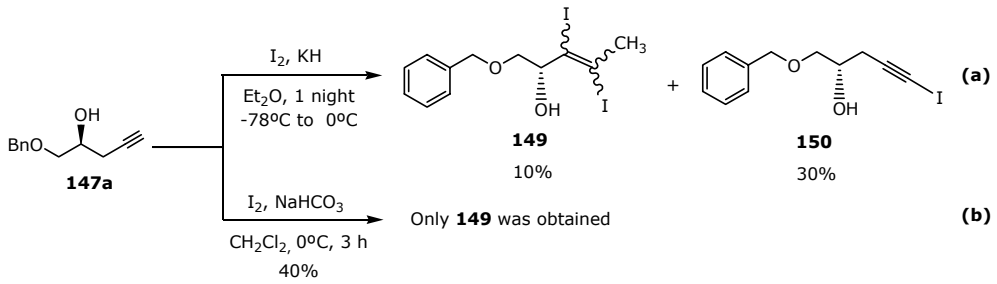


147a

Scheme 48. Reaction of **147a** using NIS and $NaHCO_3$ in MeCN.

In light of this result, I_2 was employed as an electrophile source and a stronger base such as potassium hydride was used (Scheme 49, path a), with the expectation that the deprotonation of the hydroxyl group would increase its nucleophilicity, favouring its reaction with the triple bond. Two products were obtained, but no cyclization product was isolated. The ^{1}H NMR of one of them showed the following signals: a) at 7-8 ppm, the aromatic protons; b) at 3.56 and 3.50 ppm, two double doublets

corresponding to the CH_2 moiety neighbour to the C-OH group; c) a multiplet at 4.42 ppm, which was assigned to the proton bound to the C-OH, which exhibited a big shift relative to the starting material; d) at 2.68 ppm, a singlet integrating three protons, corresponding to a methyl group, which due to its chemical shift should be bound to a double bond and e) no protons linked to a triple or double bound were apparent; moreover, the signals corresponding to the methylene protons neighbouring the acetylene group in the starting material were not detected either. From this spectroscopic data, it was proposed that a triple bond isomerization had occurred, which could be explained not only by the new methyl group signal but also by the unshielded signal corresponding to the proton attached to the C-OH moiety.



Scheme 49. Reaction of **147a**. a) using I_2 and KH; b) using I_2 and $NaHCO_3$.

In ^{13}C NMR spectrum the disappearance of the sp carbons was observed. The spectrum also showed signals of the aromatic carbons, three signals corresponding to carbons bonded to oxygen ($2xCH_2$ and 1xCH), a methyl signal and two new signals at 105.6 and 95.3 ppm belonging to quaternary carbons. These signals cannot correspond to common double bond carbons, and comparing with similar compounds described in the literature,[134] it was suggested that these could correspond to double bond carbons bonded to iodine. Taking into account these data, and that no double bond protons were observed in ^1H NMR, the structure **149** was assigned to this product. The stereochemistry of the double bond could not be determined.

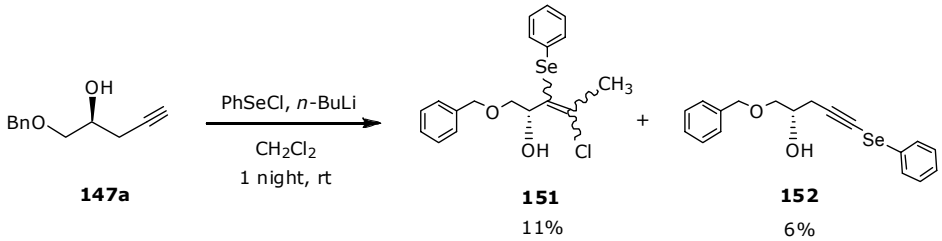
With respect to the second product formed, the ^1H NMR analysis showed the same signals as the starting material but shifted to higher fields. In addition, the acetylene proton was not observed.

When the ^{13}C NMR was recorded, the acetylenic carbon neighbouring the methylene group was observed at 114.5 ppm, while the corresponding carbon in the starting material appeared at 80.4 ppm. The formation of **150** as the other secondary product was proposed due to the high basicity of the reaction conditions employed. The products **149** and **150** were obtained in low yields, 10 and 30% respectively.

[134] Terent'ev, A. O.; Borisov, D.A.; Krylov, I. B., Nikishin, G. I. *Synthetic Communications* **2007**, *37*, 3151.

In view of these results, the reaction was conducted under the conditions described by Knight: a weaker base, $NaHCO_3$, and CH_2Cl_2 as a solvent were used. The product obtained was **149** in 40% yield (Scheme 49, path b), and no cyclization product could be isolated.

In order to study the influence of the electrophile, phenylselenenyl chloride was employed. The reaction was carried out in CH_2Cl_2 at 0ºC, and *n*-BuLi was employed as a base, in order to increase oxygen nucleophilicity. The NMR analysis of the products obtained showed roughly the same signals as the compounds **149** and **150**. The proposed structures for the new compounds were **151** and **152** and are shown in Scheme 50.



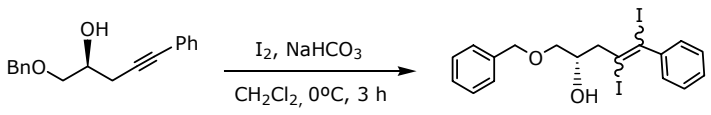
147a **151** 11% **152** 6%

Scheme 50. Reaction of **147a** using PhSeCl.

Another strategy used to increase nucleophilicity of the oxygen was the formation of the alkoxy stannyl derivative, but the resulting mixture gave multiple products and no product could be isolated and therefore characterized.

In order to improve the results obtained, the electronic properties of the acetylene group were changed, using electron-donating groups such as the phenyl group (**147b**) or electron-withdrawing groups such as the trimethylsilyl (**147c**) in the terminal acetylene position. It is important to note that Knight *et al*. employed non-terminal acetylenes to perform the 5-*endo*-dig cyclizations.[132]

When the reaction of the phenylacetilene **147b** using I_2 and $NaHCO_3$ in CH_2Cl_2 was carried out, compound **153** was obtained in 40% yield (Scheme 51).[135]



147b **153**

Scheme 51. Reaction of **147b** using I_2 and $NaHCO_3$.

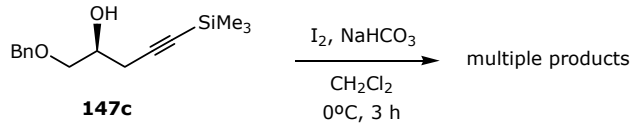
[135] Knight, D. W. *Progress in Heterocyclic Chemistry* **2002**, *14*, 19.

The formation of **153** was determined by ^{1}H and ^{13}C NMR. The ^{1}H NMR analysis showed: a) at 7.2-7.4 ppm, the signals arising from the phenyl group integrating 10 protons, which indicated the presence of two aromatic rings in the molecule; b) two double doublets at 3.68 and 3.58 ppm, corresponding to the CH_2 groups neighbouring oxygen; c) a multiplet at 4.39 ppm, which showed a coupling constant with the signals at 3.68 and 3.58 ppm and is characteristic of a proton attached to a C-OH; d) at 3.05 ppm, a double doublet integrating two protons, which arises from the CH_2 moiety attached to the double bond. All of these signals were detected at lower field than in the starting material.

When the ^{13}C NMR was recorded, the signals of the quaternary carbons corresponding to the acetylene were unshielded (from 85.9 and 82.7 to 99.8 and 89.7 respectively); thus the structure **153** was proposed, which indicates that iodine addition to the double bond occurred and that the isomerization did not proceed. As in the other cases, the stereochemistry of the double bond could not be determined.

In all the cases, the proton and carbon assignments were carried out by two-dimensional spectroscopic techniques such as gCOSY and gHSQC.

When the trimethylsilylacetylene **147c** was reacted in similar conditions, a mixture of multiple products was obtained, and the purification could not be carried out properly.

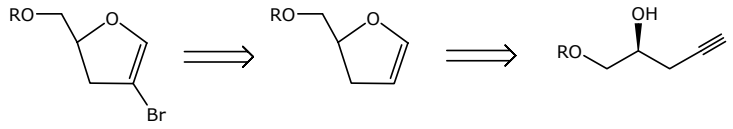


147c

Scheme 52. Reaction of **147c** using I_2 and $NaHCO_3$.

- Addition-Elimination

In light of these results, we explored other procedures in order to obtain the halodihydrofuran. Compound **122** could arise from dihydrofuran **28** by means of bromine addition to the double bond and subsequent elimination using a base. Dihydrofuran **28** could be obtained as well by a cycloisomerization using acetylenic alcohol **40** (Scheme 53).

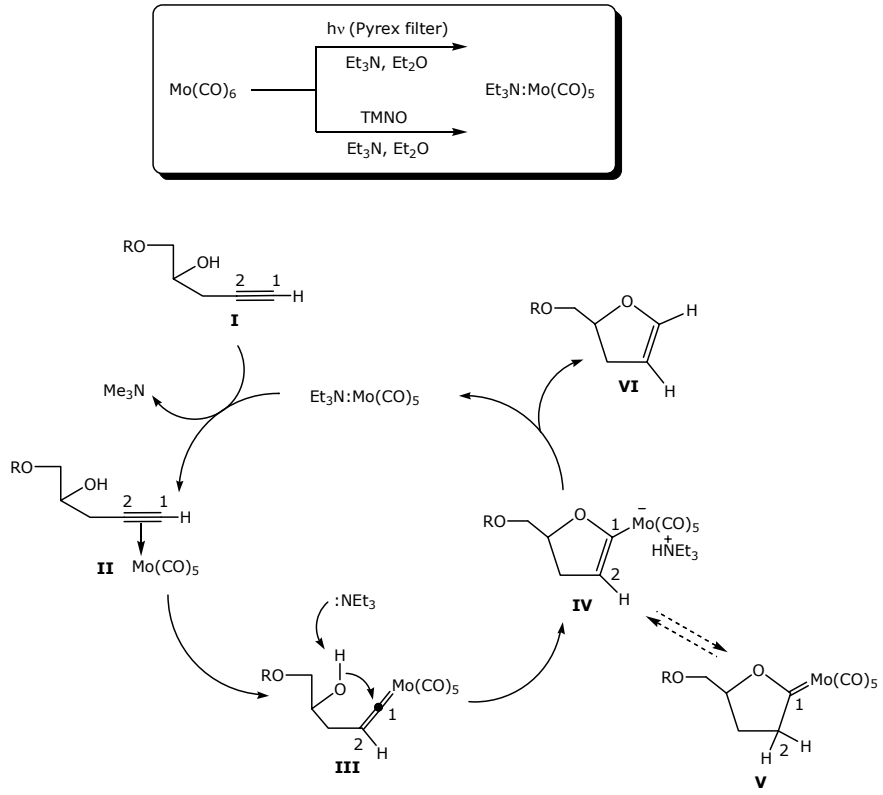


122 **28** **40**

Scheme 53. Alternative pathway to obtain the 4-bromodihydrofuran **122**.

McDonald *et al*. reported the formation of 2,3-dihydrofurans by cycloisomerization reaction in the presence of stoichiometric amounts of a trialkylamine-pentacarbonyl molybdenum complex by a cycloisomerization reaction. The molybdenum complex can be obtained by photolysis[136] or by reaction of the precursors with TMNO (trimethylamine-N-oxide)[137] (Scheme 54).

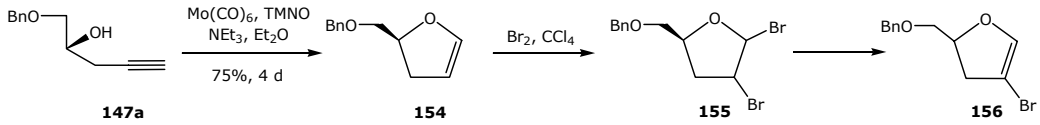
The cycloisomerization reaction proceeds by initial rearrangement of an η^2-metal-alkyne complex **II** to a vinylidene complex **III**.[138] Base-induced cyclization of the nucleophilic alcohol might then afford the cyclic anionic intermediate **IV** (Scheme 54). Although protonation of **IV** at C-2 would provide the neutral carbene **V**, protonation at C-1 affords the dihydrofuran **VI** and regenerates $Et_3N{:}Mo(CO)_5$ as a potential catalyst.



Scheme 54. Proposed mechanism for cycloisomerization of **I**.

[136] McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc*. **1994**, *116*, 9363.
[137] McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Townw, T. B.; Treiber, K. D. *J. Org. Chem*. **1993**, *58*, 6952.
[138] (a) Bruce, M. I.; Swincer, A. G. Adv. *Organomet. Chem*. **1983**, *22*, 59. (b) Bruce, M. I. *Chem. Rev*. **1991**, *91*, 197.

Thus, dihydrofuran **154** was obtained in 75% yield by treating **147a** with $Mo(CO)_6$-TMNO in the presence of triethylamine. Then, the bromination[139] and elimination of **154** to obtain **156** was conducted in two steps without isolation of the intermediate **155** (Scheme 55). Although **155** was not isolated, the ^{13}C NMR of the reaction crude showed characteristic signals at δ 95.4 (C-5), 69.7 (C-2), 53.6 (C-4) and 32.7 (C-3).



147a **154** **155** **156**

Scheme 55. Synthesis of **156**.

The elimination step in order to obtain the 4-bromodihydrofuran **156** was carried out in several conditions, but all the attempts did not give the desired final product. The reaction conditions employed in the elimination reaction are shown in Table 9. In all cases complex mixtures of products were obtained. Three kinds of bases were employed. Firstly, a tertiary amine such as Et_3N, which is used in many cases to perform this reaction, was added to the reaction mixture, but a complex mixture was obtained.[140] In light of the unsuccessful results, a stronger base such as DBU[139] was employed, but no pure products were isolated. Finally a base with more steric hindrance was applied, but a mixture of multiple products was achieved as well.

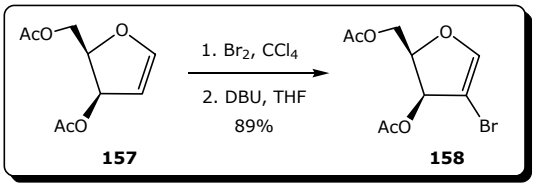
Table 9. Reaction conditions employed in the elimination reaction.

Base	Conditions	Product
Et_3N	CH_2Cl_2, 0ºC	multiple products
DBU	THF, 0ºC	multiple products
2,6-di-*t*-Bu-pyridine	CH_2Cl_2, 0ºC	multiple products

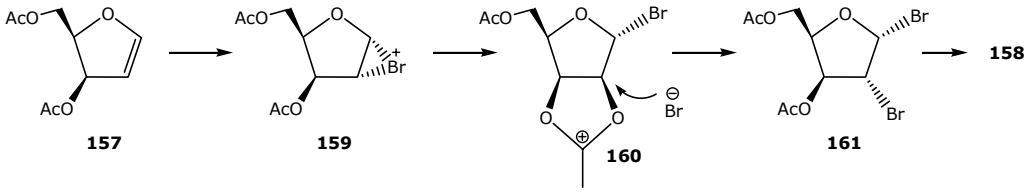
It was supposed that in those reaction conditions, the bromination gave the *trans* product, and the elimination reaction take place when the bromine and the proton implied in the elimination reaction are in a *trans* disposition. Thus in our substrate the elimination does not take place.

[139] Obayashi, M.; Schlosser, M. *Chem. Lett*. **1985**, 1715.
[140] Fogh, A.; Lundt, I.; Pedersen, C.; Rasmussen, P. *Acta Chem. Scand. B* **1977**, *31*, 768.

In contrast, in the literature the synthesis of **158** from **157** in excellent yields by using this methodology was reported (Scheme 56).[139] We speculate that the reaction might take place through the *cis*-dibromotetrahydrofuran. The stereoselectivity of the addition can be controlled by the neighbouring acetate in such way that when the bromonium intermediate **159** is formed, presumably on the opposite face from the acetate, it is opened by the acetate to form the stabilized intermediate **160**. The final attack of the incoming bromide will lead to the *cis* addition product **161**. From **161** the elimination reaction can take place easily. This mechanism could explain other similar results found in the literature.[141]



157 **158**



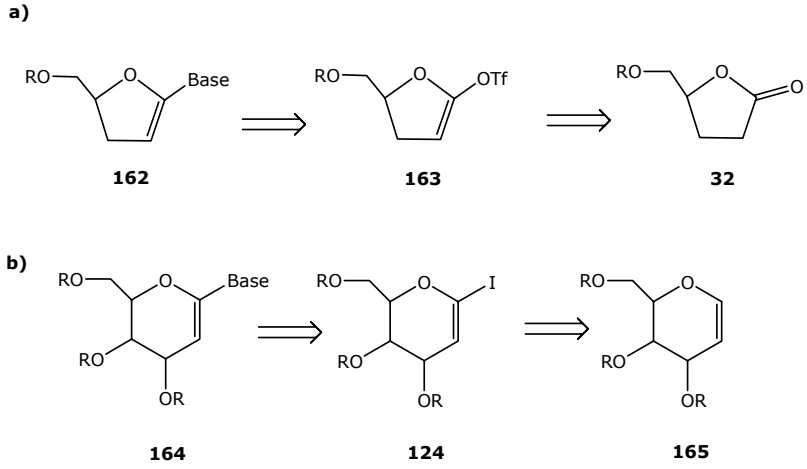
157 **159** **160** **161**

Scheme 56. Synthesis of **158** by bromine addition and subsequent elimination.

[141] Teichman, M.; Descotes, G.; Lafont, D. *Synthesis* **1993**, 889.

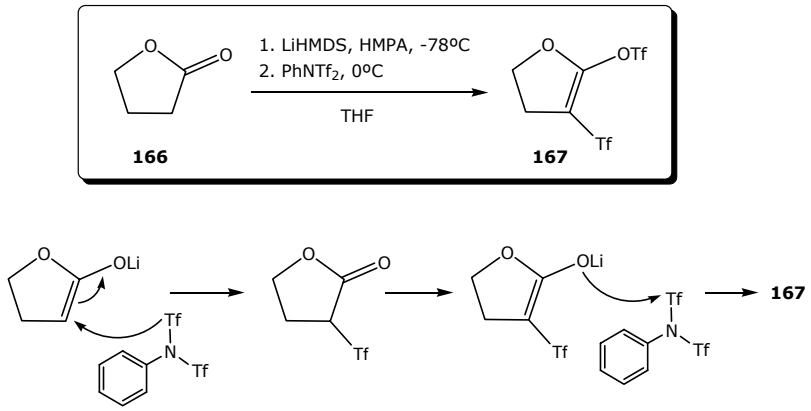
3.2.2. Synthesis of Enol Triflates and 1-Iodo-D-Glucal Derivatives

The synthesis of 4-halo-2,3-dihydrofurans was given up, and we tackled the synthesis of 2'- and 2',3'-dideoxynucleosides, still aiming to use a C-N coupling as a key step. For this, the synthesis of **163** from the commercially available lactone **32** and the synthesis of **124** from 3,4,6-tris-*O*-(triisopropylsilyl)-D-glucal was envisaged (Scheme 57).



Scheme 57. Retrosynthetic analysis for compounds **162** and **164**.

Initially, in order to obtain the enol triflate, the reaction was tested in the γ-butyrolactone. A solution of γ-butyrolactone in THF was added to a solution of lithium hexamethyldisilazide (LiHMDS) and hexamethylphosphoric triamide (HMPA) at -78ºC, and then a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhNTf_2$) in THF was added. Surprisingly, when the reaction was finished, the isolated product was the 5-trifluoromethanesulfonyloxy-4-trifluoromethanesulfonyl-2,3-dihydrofuran (**167**) in 45% yield, along with the starting material **166**.

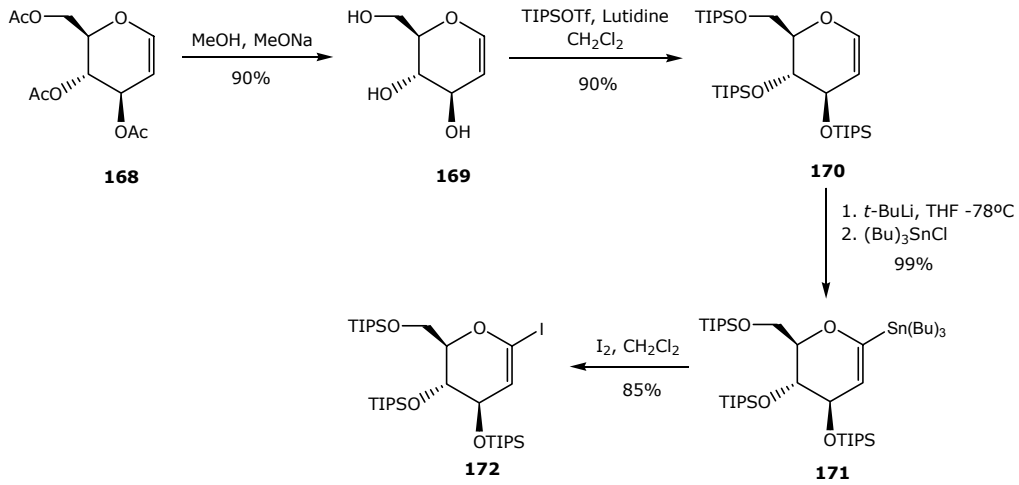


Scheme 58. Synthesis of **167**.

Usual conditions using lithium diisopropylamide in THF led to almost the same results as above, and no trace amount of the desired enol triflate was detected. The product obtained can be formed from the initial formation of the triflyl lactone followed by the *O*-triflation of the enol. These results agree with those reported in the literature, where it has been reported that ε-caprolactone and δ-valerolactone give the expected enol triflate, while γ-butyrolactone affords product **167**.[142]

Due to the difficulty of obtaining the enol triflate, we moved to the synthesis of the corresponding iodo derivatives, but before working with highly reactive dihydrofurans, we decided to check the reaction in the corresponding pyran derivatives. For this reason we planned to synthesise 1-iodo-3,4,6-tris-*O*-(triisopropylsilyl)-D-glucal **172**. The direct synthesis of **172** by treatment of **170** with *t*-BuLi and subsequent addition of iodine has been described to give poor yields.[143] However, the results were improved when starting from the stannylene derivative **171**.[144,145]

[142] Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett*. **1989**, 1313.
[143] Boyd, E.; Hallett, M. R.; Jones, R. V. H.; Painter, J. E.; Patel, P.; Quayle, P.; Waring, A. J. *Tetrahedron Lett*. **2006**, *47*, 8337.
[144] Friesen, R. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1969.
[145] Somsák, L. *Chem. Rev*. **2001**, *101*, 81.



Scheme 59. Synthesis of **172** via stannylene derivative **171**.

Thus, the tri-*O*-acetyl-D-glucal was hydrolyzed by treatment with MeONa in MeOH to afford D-glucal (**169**) in 90% yield. Then, this compound was reacted with triisopropylsilyl triflate (TIPSOTf) to furnish **170** in 90% yield. Previous assays using TIPSCl required long reaction times and afforded lower yields (Table 10).

Table 10. Reaction condition tested in the protection of D-glucal.

entry	Reaction conditions	Yield (%)	Lit
1	TIPSCl, imidazole, DMF, 48 h, 90ºC	70%	146
2	TIPSOTf, lutidine, CH_2Cl_2, 5 h, rt	90%	147

The stannylene derivative **171** was obtained in quantitative yield by treatment of **170** with *t*-BuLi at -78ºC and subsequent addition of tributyltin chloride.[148] Then the reaction of **171** with iodine in CH_2Cl_2 gave the 1-iodo-D-glucal in 85% yield.[149] The spectroscopic data of **169**, **170**, **171** and **172** were consistent with those reported.

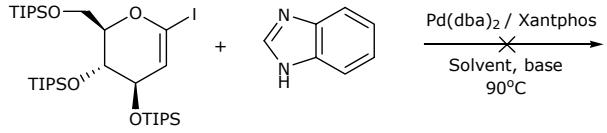
[146] Leullouche, J.-P.; Koeller, S. *J. Org. Chem.* **2001**, *66*, 693.
[147] Abe, H.; Terauchi, M.; Matsuda, A.; Shuto, S. *J. Org. Chem*. **2003**, *68*, 7439.
[148] Friesen, R. W.; Sturino, C. F.; Daljeet, A. K.; Kolaczewska, A. *J. Org. Chem*. **1991**, *56*, 1944.
[149] Friesen, R. W.; Loo, R. W. *J. Org. Chem*. **1991**, *56*, 4821.

3.2.3. Study of C-N Coupling Reactions from 1-Iodo-D-glucal

The study of the coupling reaction started with compound **172** and benzimidazole (**173**) as the base model. Taking into account the optimal procedures reported in the literature and presented in the introduction of this chapter, $Pd(dba)_2$ was used as the catalyst precursor, Xantphos as the ligand and Cs_2CO_3 as the base.[87,79]

Different attempts were carried out with different solvents and the ratio palladium/ligand was also changed (Table 11). In all cases the starting material was recovered, and no conversion to the final product was observed.

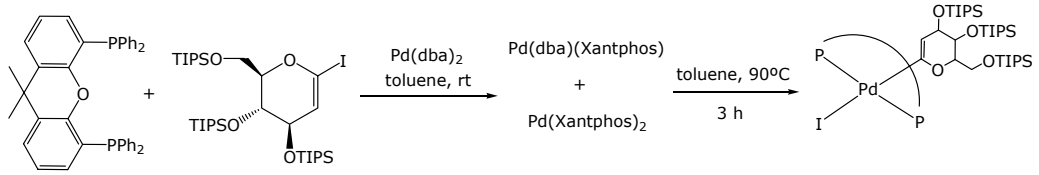
Table 11. First approach to the C-N coupling of **172** with benzimidazole.



172 **173**

entry	172 (mmol)	173 (mmol)	Pd/L	Base (mmol)	Solvent
1	1	1.2	0.01/0.015	1.4 Cs_2CO_3	1 M dioxane
2	1	1.2	0.01/0.015	1.4 Cs_2CO_3	1 M dioxane
3	1	1.1	0.01/0.03	1.4 Cs_2CO_3	0.25 M toluene
4	1	1.1	0.01/0.03	1.4 NaO^tBu	0.25 M toluene

Looking for information about the evolution of this reaction, an NMR study of the oxidative addition step was carried out. Thus, an NMR tube was charged with toluene-d_8 and equimolar amounts of **172**, Xantphos and $Pd(dba)_2$ (Scheme 60).



91 **172** **174**

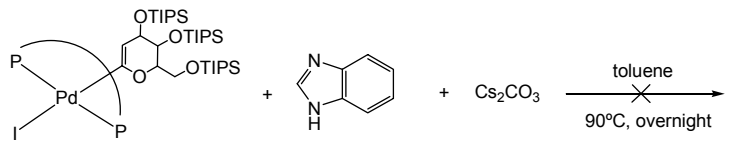
Scheme 60. Oxidative addition of 1-iodo-D-glucal to $Pd(dba)_2$/Xantphos complexes.

Before warming the sample ^{1}H and $^{31}P\{^{1}H\}$ NMR were recorded. In the $^{31}P\{^{1}H\}$ spectrum two new signals were apparent, indicating the formation of two new compounds corresponding to Pd(Xantphos)(dba) and Pd(Xantphos)$_2$ species, which are described in the literature.[150] The former complex showed two double doublets at 10.2 and 8.1 ppm with a coupling constant of J_{PP}= 11 Hz. Pd(Xantphos)$_2$ presented two broad singlets at 3.14 ppm and 0.25 ppm.

Once the initial palladium complexes were detected, the sample was warmed for 3 h at 90ºC. In $^{31}P\{^{1}H\}$ NMR, a disappearance of the signals belonging to Pd(Xantphos)$_2$ and Pd(Xantphos)(dba) species was observed, and a new signal at 10 ppm was apparent, which could have arisen from the oxidative addition product. These kinds of products are described to have similar δ values.[151] Moreover, the signals corresponding to the vinylic proton of the glucal moiety were detected at lower field than the 1-iodo-glucal.

Then, the isolation of the oxidative addition product was tried following the same procedure explained above by precipitating the complex by the addition of ether. However, the desired product could not be isolated. The isolated precipitate not only did not show the corresponding vinyl proton, but also the protecting group signals were not apparent.

The NMR experiment was repeated in order to study the C-N coupling. Thus, once complex **174** was detected, benzimidazole and cesium carbonate were added. After heating the sample overnight no new product was detected by NMR (Scheme 61).



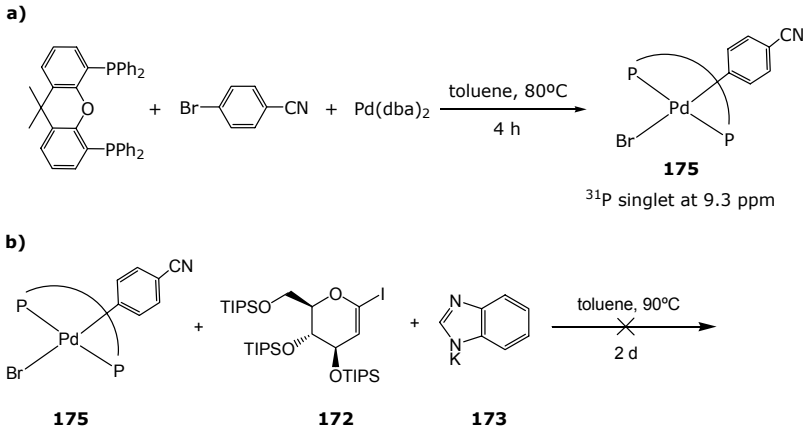
174 **173**

Scheme 61. Coupling of the palladium complex **174** with benzimidazole (**173**).

In light of these results [(Xantphos)Pd(*p*-C_6H_4CN)(Br)] (**175**) was synthesised, since it has been described to be a more effective catalyst in the C-N coupling reactions (Scheme 62, path a).[151,86e,87] Moreover, in order to increase the nucleophilicity of the nitrogen base the potassium benzimidazolate was formed (Scheme 62, path b).[98] But

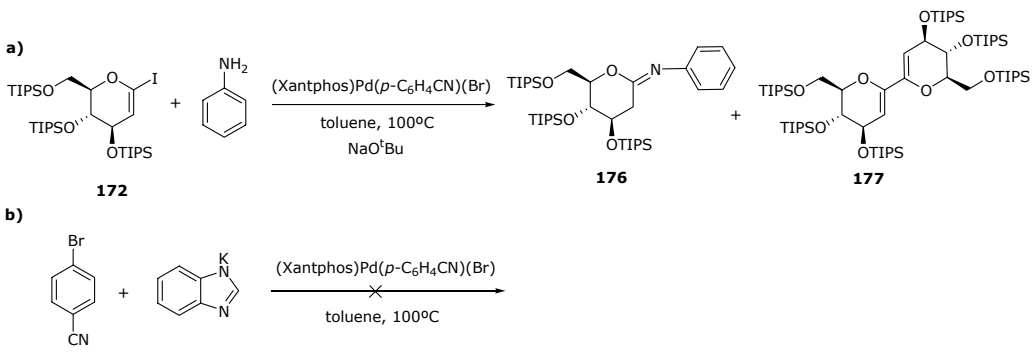
[150] Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82.
[151] Fujita, K.; Yamashita, M.; Puschman, F.; Martinez, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044.

after heating the mixture for two days at 90ºC, no reaction product could be detected by NMR analysis, and the starting material was recovered.



Scheme 62. Synthesis of **175** and test of coupling using potassium benzimidazolate.

At this point, it was supposed that these unsuccessful results could be due to the kind of nitrogen base. These compounds do not give favoured couplings because of their weak basicity.[100] In order to study the nature of the base, two different couplings were explored. One involved the coupling of 1-iodoglucal (**172**) with aniline, since this compound is easily coupled not only with aryl halide but also with vinyl halides.[115,90] The other coupling was carried out between *p*-bromobenzonitrile and potassium benzimidazolate. It has been reported in the literature that *p*-bromobenzonitrile gives oxidative addition to the palladium complexes easily.



Scheme 63. a) C-N coupling between the 1-iodo-D-glucal (**172**) and aniline; b) C-N coupling between *p*-bromobenzonitrile and potassium benzimidazolate.

When the C-N coupling between aniline and 1-iodoglucal (**172**) was carried out, the the NMR analysis of the reaction mixture exhibited (Scheme 63, path a): the signal corresponding to the vinylic proton of the starting material at 5.38 ppm disappeared, and the new signal was shifted to low field (5.79 ppm). Moreover, in the ^{13}C NMR the signals corresponding to the vinyl moiety were shifted from 145.7 and 98.5 ppm, while in the starting material these signals were detected at 157.2 and 105.2 ppm, respectively. These signals were assigned to the homocoupling product (**177**),[153c] which has been described in the literature as the principal side product in the synthesis of C-aryl glycals.[152] Then the ^{13}C spectrum exhibited a new signal at 163.2 ppm that was assigned as the product of the C-N coupling (**176**), since this shift is characteristic of an iminic carbon. Moreover, the ^{1}H spectrum exhibited a new signal at 1.40 ppm which was assigned to the CH_2 moiety neighbouring imine group. When the coupling between the *p*-bromobenzonitrile and potassium benzimidazolate was carried out, no new product was detected.

The literature describes many C-C coupling reactions in which 1-iodoglucals are involved, for instance in the preparation of C-aryl glycals[148,149,153] and in carbonylation reactions in the presence of amines.[154] Moreover, we detected the oxidative addition product by NMR. It can be concluded that the problem is not the oxidative addition but the other catalytic steps.

Many C-N couplings between aryl halides and heterocycles described in the literature have been carried out employing copper as a catalyst. As has been discussed above, the most common ligands employed with this catalytic system are the N,N-ligands such as the diamines.[155] Thus, because of the unsuccessful results obtained with palladium catalysts, the catalytic system was changed to copper. The copper source of choice was CuI, due to its air-stability and because it is the one of the best catalysts described in the literature for the coupling of this kind of substrate.[106]

The required temperatures for this reaction range from 80-120ºC, which excludes low boiling point solvents. Toluene is commonly used, but is unsuitable in certain cases and can be replaced by dioxane or polar solvents as NMP or DMF. The choice of the solvent depends on the solubility of the substrates; thus due to the variety of the solvents employed a screening of different solvents was carried out. The solvents used for this reaction were toluene, DMF and dioxane.

---

[152] (a) Lehman, U.; Awasthi, S.; Minehan, T. *Org. Lett*. **2003**, *5*, 2405. (b) Dubois, E.; Beau, J.-M. *Carbohydr. Res*. **1992**, *228*, 103.

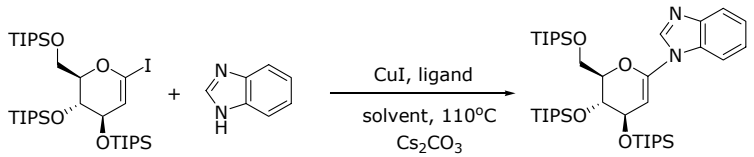
[153] (a) Dubois, E.; Beau, J.-M. *J. Chem. Soc., Chem. Commun*. **1990**, 1191. (b) Jeanneret, V.; Meerpoel, L.; Vogel, P. *Tetrahedron Lett*. **1997**, *38*, 543. (c) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem*. **1994**, *72*, 1262.

[154] Deagostino, A.; Larini, P.; Occhiato, E. G.; Pizzuto, L.; Prandi, C.; Venturello, P. *J. Org. Chem*. **2008**, *73*, 1941.

[155] Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem*. **2004**, *69*, 5578.

Table 12 shows the results of the different conditions used. The ligands tested were N,N'-dimethylethyl-1,2-diamine (**104b**) and phenantroline (**101b**). In all cases the ratio Cu:L employed was 1:2 and the molar ratio of sugar:benzimidazole:Cs_2CO_3 was 1:1.5:2. The conversions obtained were nil or very low. Only in the conditions in entries 4, 6 and 8, a small amount of a new product was detected. By ^1H NMR a new doublet signal at 5 ppm formed (the signal arising from the starting material was apparent at 5.38 ppm), which was attributed to the new product (**178**).

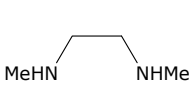
Table 12. C-N coupling using copper catalysts.



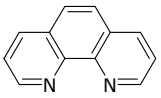
172 **173** **178**

entry	CuI	Ligand	Solvent	Conversion
1	20%	**104b**	DMF	0%
2	20%	**101a**	DMF	0%
3	50%	**104b**	DMF	0%
4	20%	**104b**	dioxane	2%
5	20%	**101a**	dioxane	0%
6	50%	**104b**	dioxane	2%
7	20%	**104b**	toluene	0%
8	20%	**101a**	toluene	4%

a) Conditions: In all the cases 1 mmol **172** was employed. The Cu:L ratio was 1:2 mmol; and 1.5 mmol of **173** and 2 mmol of Cs_2CO_3 were added.



104b



101a

The coupling between 1-iodo-glucal **172** and benzimidazole has remained reluctant using palladium and copper catalysts, but in spite of that, when using cooper very small conversions were detected. The problem seems related to the low reactivity of benzimidazole, since C-N coupling was obtained when other nitrogenated compounds such as aniline was used.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

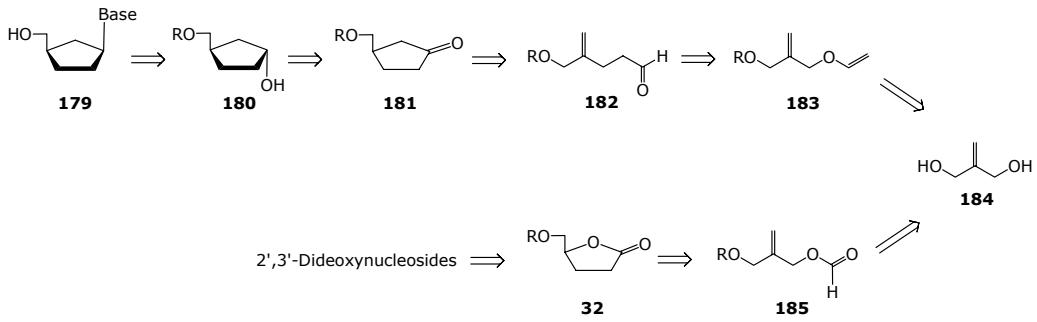
4. Intramolecular Enantioselective Hydroacylation and Diastereoselective Reduction in the Synthesis of Carbocyclic Nucleosides

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

4.1. RETROSYNTHETIC ANALYSIS

As was mentioned in the introduction, one of our goals is the synthesis of carbocyclic nucleosides **179**. This family of compounds has a cyclopentane backbone, which is considered to arise from an intramolecular hydroacylation reaction of compounds **185** and **182**. Scheme 64 depicts the retrosynthetic analysis for synthesising these types of nucleosides, wherein the key step is an intramolecular hydroacylation involving an unsaturated aldehyde. The hydroacylation reaction of formate **185** could produce lactone **32,** which could facilitate a new procedure for synthesising these kinds of lactones. Moreover, these reactions could be enantioselective by using an appropriate chiral phosphine (Scheme 64).



Scheme 64. Retrosynthetic analysis for carbocyclic nucleoside **179** and lactone **32**.

Compounds **182** and **185**, which are required to carry out the intramolecular hydroacylation reaction, could both be easily obtained from 2-methylene-1,3-propanediol (**184**). Once cyclopentanone **181** is obtained by the diastereoselective reduction of the carbonyl group, followed by a Mitsunobu reaction to incorporate the nucleic base and cleave the protecting group, carbocyclic nucleoside **179** is produced in a straightforward manner. The synthesis of 2',3'-dideoxynucleosides from lactone **32** has been already demonstrated.[156]

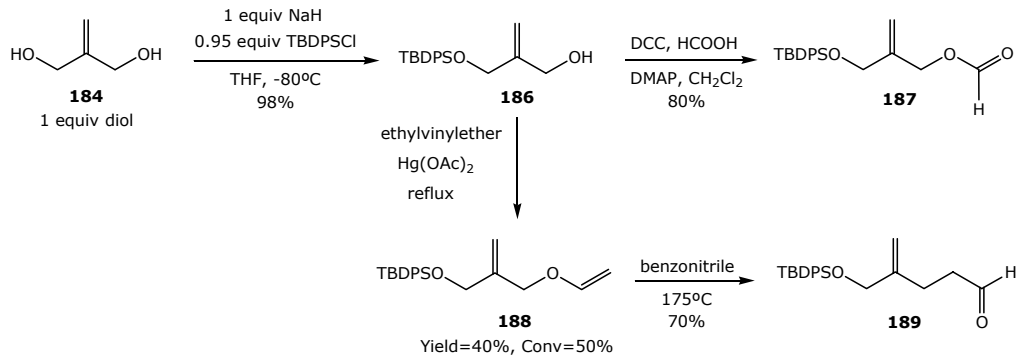
[156] (a) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem*. **1988**, *53*, 4780. (b) Agyei-Aye, K.; Baker, D. C. *Carbohydr. Res*. **1988**, *183*, 261. (c) Farina, V.; Benigni, D. A. *Tetrahedron Lett*. **1988**, *29*, 1239. (d) Chu, C. K.; Ullas, G. V.; Jeong, L. S.; Ahn, S. K.; Doboszewki, B.; Lin, Z. X.; Beach, J. W.; Schinazi, R. F. *J. Med. Chem*. **1990**, *33*, 1553. (e) Seela, F.; Bourgeois, W.; Muth, H.-P.; Rosemeyer, H. *Heterocycles* **1989**, *29*, 2193. (f) Huryn, D. M.; Masami O. *Chem. Rev.* **1992**, *92,* 1745. (g) Kim, C. U.; Misco, P. F. *Tetrahedron Lett*. **1992**, *33*, 5733.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

4.2. SYNTHESIS OF THE STARTING MATERIAL FOR THE HYDROACYLATION REACTION

The synthesis was started by selectively monoprotectioning the hydroxyl groups in compound **184**. To accomplish this, compound **184** was treated with NaH in THF and then with TBDPSCl to produce monoprotected alcohol **186** in 98% yield (Scheme 65).[157] This compound was used to synthesise **187** and **188**. Allyl formate **187** was obtained in 80% yield by reacting **186** with formic acid, DCC, and catalytic amounts of DMAP in CH_2Cl_2 as a solvent.[158] Afterwards, **188** was furnished from a transetherification reaction between **186** and ethyl vinyl ether using $Hg(OAc)_2$ as a catalyst.[159,160]

The Claisen rearrangement of allyl vinyl ethers and allyl aryl ethers is an important synthetic reaction for carbon-carbon bond formation, and has been widely used in organic chemistry to obtain these kinds of aldehydes.[161] Hence, heating compound **188** at 170ºC in benzonitrile produced a [3+3] sigmatropic rearrangement, leading to **189** at a yield of 70%.



Scheme 65. Synthesis of the starting materials.

The formation of these compounds was readily confirmed by ^1H and ^{13}C NMR. The ^1H NMR spectrum of compound **187** exhibited a typical signal corresponding to the formate proton at 8 ppm. Moreover, the methylene group attached to the formate group was unshielded with respect to **186** (from 4.2 to 4.7 ppm). In the ^{13}C NMR spectrum, a signal at 160.8 ppm correspornding to the carbonyl group was detected.

[157] Craig, D.; Henry, G. D. *Eur. J. Org. Chem*. **2006**, 3558.
[158] Vatèle J.-M. *Tetrahedron Lett.* **2005**, *46*, 2299.
[159] Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc*. **2000**, *122*, 12610.
[160] Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc*. **1957**, *79*, 2828.
[161] Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

The structure of vinyl ether **188** was determined by the same spectroscopic techniques. In the ^{1}H NMR spectrum, new signals were observed at 6.5 ppm, corresponding to a double doublet with an integral ratio of 1H, and two new peaks at δ 4.3 and 4.08, corresponding to double doublets with an integral ratio of 1H, each belonging to the new vinyl motif.

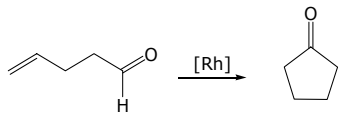
The ^{1}H NMR spectrum of **189** exhibited a quenching of the latter signals, as well as a production of new signals at 9.7, 2.56, and 2.36 ppm, corresponding to the aldehyde proton and the two CH_2 groups bound to the carbonyl and vinyl groups, respectively. In the ^{13}C NMR spectrum, the signal corresponding to the carbonyl group was apparent at 202 ppm, while two signals corresponding to the newly formed CH_2 groups were observed at δ 42 and 25. The correlation between the ^{1}H and ^{13}C for all compounds was conducted by gHSQC.

Thus, using this reaction pathway, the starting materials for the study of intramolecular hydroacylation were obtained in a straightforward manner.

4.3. INTRAMOLECULAR HYDROACYLATION

- Antecedents

Intramolecular hydroacylation is an attractive catalytic process that converts a pentenal to a cyclic ketone (Scheme 66). This process involves the scission of the acyl-hydrogen bond to produce a hydro-acyl intermediate, followed by the addition of the hydride and the acyl group to the double bond. Using rhodium-based catalysts, 5-membered ring products are almost always produced.

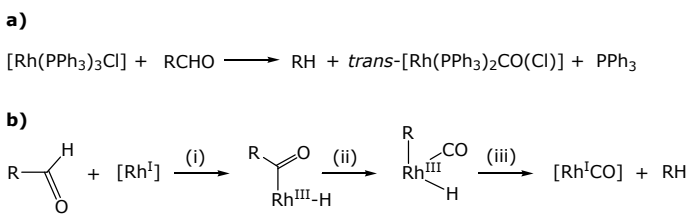


Scheme 66. The intramolecular hydroacylation of pentenals.

Hydroacylation is based on the observation of Tsuji[162] that aldehydes were decarbonylated by Wilkinson's catalysts (Scheme 67a). The mechanism of decarbonylation is believed to involve the steps shown in Scheme 67b.

[162] Tsuji, J.; Ohno, K. *Tetrahedron Lett*. **1965**, 3669.

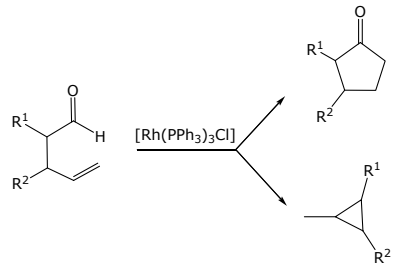
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 67. The mechanism of decarbonylation of aldehydes in the hydroacylation reaction.

The susceptibility of aldehydes to undergo oxidative addition (Scheme 67b, step ii) was later demonstrated by Suggs,[163] who isolated and characterised the hydro-acyl product resulting from the addition of 8-quinolinoaldehyde to Wilkinson's complex. The subsequent steps of acyl decarbonylation (step ii) and hydride insertion into the rhodium-carbon bond (step iii) are well known.[164]

The presence of the hydro-acyl intermediate in the decarbonylation mechanism suggested the possibility of intramolecular hydroacylation of 4-pentenals. This was first observed by Sakai[165] using Wilkinson's catalysts; however, the reaction was stoichiometric, producing a 30% yield of the cyclopentanone and a 30% yield of the cyclopropane (Scheme 68).



Scheme 68. Cyclopentanone and cyclopropane formation in the decarbonylation process.

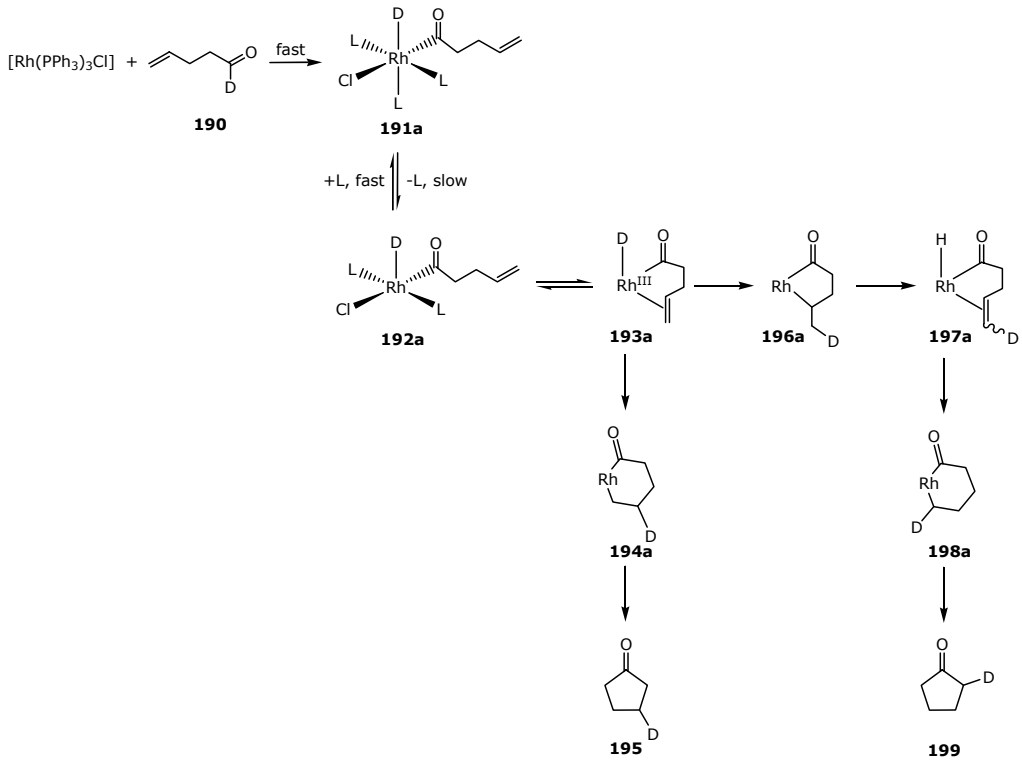
Miller[166] later demonstrated that the cyclization was, in fact, marginally catalytic, and that the turnover could be extended under an ethylene pressure. Following Miller's work, Larock[167] demonstrated a variety of substituted 4-pentenals that could be

[163] (a) Suggs, J. W. *J. Am. Chem. Soc*. **1978**, *100*, 640. (b) Suggs, J. W. *J. Am. Chem. Soc*. **1979**, 101, 489.
[164] Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936.
[165] Sakai, K.; Ido, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett*. **1972**, 1287.
[166] (a) Lachow, C. F.; Miller. R. G. *J. Am. Chem. Soc*. **1976**, *98*, 1281. (b) Campbell, R. E.; Miller, R. G. *J. Organomet. Chem*. **1980**, *186*, C27.
[167] Larock, R. C.pñlhgv; Oertle, K.; Potter, G. *J. Am. Chem. Soc*. **1982**, 1357.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

transformed by Wilkinson-type catalysts. Scheme 69 depicts the mechanism of the reaction, as determined by using a deuterium-labelled aldehyde. The nomenclature, **a** and **b**, used in these complexes refer to the similar intermediates involved in the neutral and cationic systems, respectively.

The first step involves the oxidative addition of the aldehyde C-H bond to rhodium (I) to produce **191a**, which is a process involved in the decarbonylation of aldehydes, and is demonstrated by the characterization of hydro-acyl species **193a** in two different systems, one of which involves 4-pentenal. The addition of a hydride to the double bond (**193a**→**194a**), followed by a reducing elimination step (**194a**→**195**), produces cyclopentanone. In addition to this direct pathway, the detection of **199** implies the formation of five-membered metallacycle **196a,** which, after β–elimination, produces **197a,** which collapses to **199** via **198a**.[168,169]

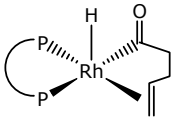


Scheme 69. The proposed mechanism of the hydroacylation of 4-pentenal using $[Rh(PPh_3)_3Cl]$.

Several interesting turnover rates and numbers have been obtained by increasing the rates of the hydroacylation steps over the rates of the competing steps that lead to side products.[164] To achieve this goal, cationic rhodium (I) complexes bearing one

[168] Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946.
[169] Milstein, D. *J. Chem. Soc., Chem. Commun*. **1982**, 1357.

chelating phosphine ligand have been used. It has been argued that the characteristics that favour this latter system over the neutral complexes derived from the Wilkinson's catalysts are the following. First, provided that the solvent molecules are weakly bound in the $[Rh(diphosphine)(solv)_2]^+$ catalysts, the six-coordinate rhodium (III) species that is formed after the oxidative addition of the acyl-hydrogen bond (**200**) will have two coordination positions available, thus permitting the coordination of the olefin, as illustrated in Figure 7. The presence of coordinated unsaturation in both the Rh(I) and Rh(III) was expected to accelerate catalysis since slow ligand dissociation does not impede the catalytic step, as shown earlier (Scheme 69, **191a**→**192a**).[169] Second, because of the positive charge and the presence of *cis*-disposed phosphines, carbonyl complexes of the $[Rh(diphosphine)(CO)_n]^+$ type were expected to be much less stable than the neutral, *trans*-disposed diphosphine complexes that are derived from Wilkinson's-type catalysts.



200

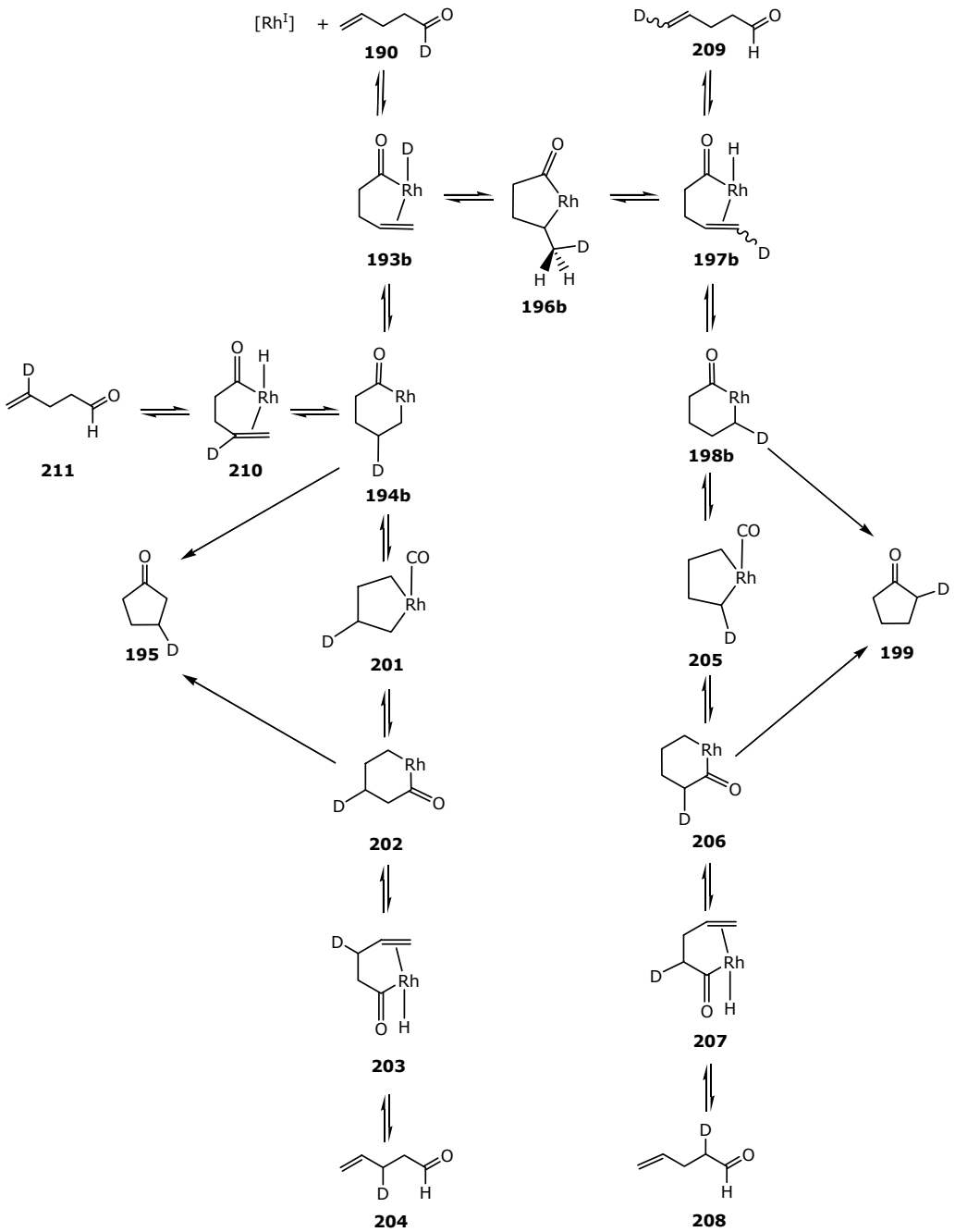
Figure 7. The oxidative addition product when cationic systems are used.

The mechanism shown in Scheme 69 was used as a starting point for the mechanistic study of $[Rh(diphosphine)(solv)_2]^+$ catalysts.[168] Numerous equilibrated catalyst-substrate adducts were observed. Most of these species are catalytically inactive, but could affect both the turnover rate and number. The higher the substrate to catalyst ratio, the slower the turnover rate, but the higher the turnover number. This substrate inhibition of rate appears to be related to the catalyst being tied up as catalytically unproductive adducts. The increase in turnover number seems to be related to the suppression of decarbonylation by substrate interaction. Unfortunately, no catalytic intermediates were identified, and a new mechanistic proposal was inferred from deuterium-labelling studies, which demonstrated that the cyclopentanone products contained deuterium in both the α and β positions, and remarkably, that deuterium appears and disappears at every carbon of 4-pentenal during the course of the catalysis. The implication of deuterium scrambling, which is believed to be directly related to the hydroacylation mechanism, is summarised in Scheme 70.

The mechanism for delivering the deuterium in the 5-position of **209** has been discussed (Scheme 69), but the stereochemistry (E and Z) of the deuterium at the double bond of **209** is known from ^2H NMR. Since the two hydrogen atoms of the monodeuterated methyl group of **196b** are diastereotopic, it might be expected that the chiraphos catalysts abstract these protons (by β-elimination) at different rates;

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

however, no diastereoselection was observed, and the E and Z isomers of **209** were produced in equal proportions.



Scheme 70. A detailed outline of the proposed mechanism for the hydroacylation of 4-pentenal using $[Rh(L\text{-}L)(solv)]^+$ (L-L= dppe and chiraphos) catalysts. The positive charge has been omitted, and all coordinatively unsaturated species shown in the diagram may contain either bound solvent or substrate molecules.

The mechanism that explains the appearance of the label at the 4-position in **211** involves the *β*-elimination of the six-membered metallacycle in **194b**. The generation of deuterium at the 3-position of **204** was assumed to occur via steps **194b** to **204**, which is a process that requires the carbonyl deinsertion of **194b** to produce the five-member metallacycle **201**. This species in **201** can reinsert CO to the original end of the ring to give back **194b,** or into the other end of the ring to give **202,** and thereby relocate the deuterium. After *β*–elimination, **202** produces **203,** which reductively eliminates to produce 4-pentenal **204**, which is labelled at the 3-position.

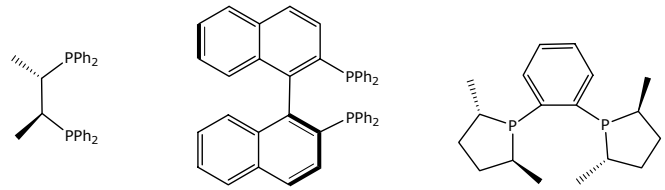
The generation of the 2-position-labelled 4-pentenal **208** involves a similar pathway. First, the deuterium is shifted to the 5-position via **196b**, whereafter, **197b** collapses to **208** via steps **198b** to **208,** which are completely analogous to those steps leading to **204**.

As previously discussed, catalytic intramolecular hydroacylation is promoted by complexes of the $[Rh(diphosphine)(solv)_2]^+$ type, wherein "solv" is a weakly coordinating solvent molecule. The first asymmetric transformation was reported by James,[170] who used bis-chiral diphosphine rhodium(I) complexes for the kinetic resolution of racemic mixtures of chiral 4-pentenals. Good enantioselectivity was observed, despite the elevated temperatures used. Sakai[171] later reported good to excellent enantioselectivities using $[Rh(chiral\ diphosphine)(solv)_2]^+$ catalysts for the conversion of 4-subtituted-4-pentenals to chiral 3-cyclopentanones. Bosnich[172] later examined the ligands (*S*,*S*)-chiraphos (**212**)[173] and (*S*)-BINAP (**213**)[174] (Figure 8). Thus, the incorporation of the chiral diphosphine into the catalyst facilitates the acquisition of optically pure products.

A number of chiral analogs of $[Rh(chiral\ diphosphine)(solv)_2]^+$ were studied by Bosnich to determine if high enantioselectivities could be obtained with 4-substituted-4-pentenals. Catalysts derived from the chiral phosphines (*S*,*S*)-chiraphos (**212**), (*S*)-BINAP (**213**), and (*S*,*S*)-Me-Duphos (**214**)[175] (Figure 8) provided interesting results.

[170] (a) James, B. R.; Young, C. G. *J. Chem. Soc., Chem. Commun*. **1983**, 1215. (b) James, B. R.; Young, C. G. *J. Organomet. Chem*. **1985**, *285*, 321.
[171] (a) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett*. **1989**, *30*, 6349. (b) Taura, Y.; Tanaka, M.; Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron* **1991**, *47*, 4879. (c) Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett*. **1992**, *33*, 6331.
[172] Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc*. **1994**, *116*, 1821.
[173] Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.
[174] Miyashita, A.; Yasuda, A.; Takya, H.; Toriuma, K.; Ito, T.; Sauchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
[175] Burk, M. J.; Cross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



212 **213** **214**

Figure 8. Phosphines used by Bosnich in asymmetric intramolecular hydroacylation.

For the catalysts formed by **212** and **213**, the major source of chiral induction is expected to derive from the chiral array of phenyl groups, where the chiral orientation therein is determined by the chirality of the chelate ring.[173,176] Both the (*S*,*S*)-chiraphos and (*S*)-BINAP have the same phenyl group chirality (Figure 9), but with different precise orientations.

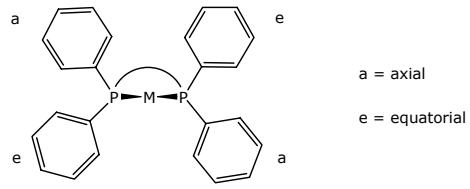


Figure 9. Twist sense for the phenyl groups of (*S*,*S*)-chiraphos and (*S*)-BINAP catalysts.

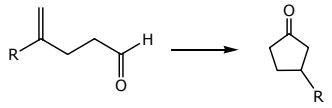
The chiral induction of **214** derives primarily from the methyl groups of the phosphacyclopentane substituents because the chelate ring is planar. Since **212** and **213** are structurally similar, the sense of induction for hydroacylation substrates is expected to be the same.[177]

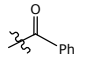
Table 13[172,178] lists several ee values that were observed with catalysts derived from phosphines **212**-**214** at 25 ºC. Catalyst loadings were between 2 and 4 mol%. The solvents used were CH_2Cl_2 and acetone. The chemical yields were > 95%.

[176] Bosnich, B.; Roberts, N. R. *Catalytic Aspects of Phosphine Complexes*; Alyea, E. C., Meek, D. W., Eds.; Advances in Chemistry Series, No. 196; American Chemical Society: Washington, DC, 1982; p 337.
[177] Bosnich, B. *Acc. Chem. Res*. **1998**, *31*, 667.
[178] Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Chem. Commun.* **1997**, 589.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Table 13. The asymmetric catalytic intramolecular hydroacylation of 4-substituted-4-pentenals using [Rh(chiral diphosphine)$(solv)_2]^+$ at 25ºC.[178]



		Chiral diphosphine		
		(*S*)-Binap	**(*S*,*S*)-Chiraphos**	**(*S*,*S*)-Me-Duphos**
entry	**R**	**ee % (config)**	**ee % (config)**	**ee % (config)**
1	*t*-Bu	>99 (*S*)	29 (*R*)	44 (*S*)
2		>99 (*S*)	41 (*R*)	--
3	Me_3Si	>99 (*S*)	8 (*R*)	64 (*S*)
4	$PhMe_2Si$	>99 (*S*)	15 (*R*)	61 (*S*)
5		87 (*S*)	13 (*R*)	--
6		94 (*S*)	64 (R)	--
7		>99 (*S*)	35 (*R*)	--
8		>99 (*S*)	11 (*R*)	--
9	Me	78 (*S*)	42 (*S*)	94 (*S*)
10	Et	60 (*S*)	45 (*S*)	95 (*S*)
11	*n*-Bu	--	--	94 (*S*)
12	Bn	--	--	94 (S)
13	*i*-Pr	60 (*S*)	45 (*S*)	96 (*S*)
14	C_5H_9	81 (*S*)	41 (*S*)	96 (*S*)
15	C_6H_{11}	69 (*S*)	50 (*S*)	94 (*S*)
16	Ph	70 (*S*)	78 (*S*)	46 (*S*)

The results are interesting for several reasons. First, substrates that bear tertiary and ester groups and use the (*S*)-BINAP catalyst produce products that are essentially enantiomerically pure. Second, substrates with acyl substituents using the same catalyst produce high ee values. Third, substrates bearing *n*-alkyl or isoalkyl groups using the (*S*,*S*)-Me-Duphos catalyst produce products with consistently high ee values. Fourth, despite the fact that (*S*,*S*)-chiraphos and (*S*)-BINAP catalysts have the same twist sense for phenyl groups (Figure 9), an opposite

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

absolute configuration of the products are produced in many cases, and for most cases, the chiraphos catalyst produces low ee values.

Overall, the results in Table 13 suggest that the (*S*)-BINAP and (*S*,*S*)-Me-Duphos catalysts provide high ee values for certain classes of substrates, and that seemingly small changes in the catalyst structure can have a large effect on the enantioselection.

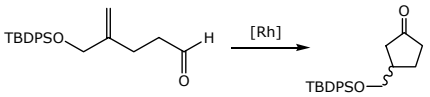
- Synthesis of 3-Silyloxymethylcyclopentanones

As per these results, the intramolecular hydroacylation of 4-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enal (**189**) was first studied using Wilkinson's catalysts (Table 14, entries 1 and 2) in CH_2Cl_2. In both cases, the chemical yield was modest, and only when the catalyst loading was increased to 50 mol%, was cyclopentanone **215** obtained with a moderate 65% yield. Hence, the study was continued using cationic catalysts with acetone as the solvent, which, accordingly, produced superior results. When dppe (**216**) (Figure 10) was employed as the ligand, no conversion was observed at low catalyst loading. Thus, the reaction did not proceed when 5 mol% of catalyst was used, even when the temperature of the reaction was increased (entries 4 and 5). Therefore, a larger catalyst loading was used (10 mol%) at room temperature, but no new product was observed during the reaction; hence the reaction was performed at reflux. Under these conditions, cyclopentanone **215** was obtained in 70% yield. Regardless of a higher catalyst loading or a higher reaction temperature, the chemical yield was not modified. DPPF (**217**)[179] (Figure 8a), which is a successful ligand in many transition metal catalysed processes, was tested under similar conditions as dppe, but the expected cyclopentanone was not obtained (entry 10).

[179] (a) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 1185. (b) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 303.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Table 14. The intramolecular hydroacylation study for **189**.[a]



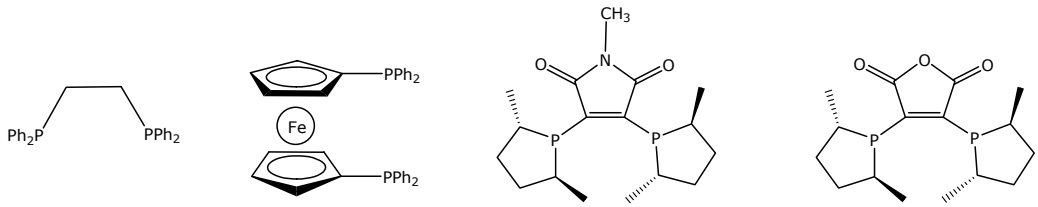
189 **215**

entry	[Rh]	mol% [Rh]	T	Time	Yield	ee % (config)[c]
1[b]	$RhCl(PPh_3)_3$	5	reflux	12 h	42%	--
2[b]		50	rt	3 h	65%	--
4	$[Rh(NBD)dppe]BF_4$	5	rt	12 h	--	--
5		5	reflux	12 h	--	
6		10	rt	12 h	--	
7		10	reflux	5 h	70%	
8		30	rt	5 h	70%	
9		50	rt	1 h	65%	
10	$[Rh(NBD)DPPF]BF_4$	30	reflux	--	--	--
11	$[Rh(NBD)(S,S)$-Me-Duphos$]BF_4$	5	reflux	12 h	85%	>98 (*S*)[d]
12	$[Rh(NBD)(R,R)$-Me-Duphos$]BF_4$	5	reflux	12 h	85%	>98 (*R*)[d]
13	$[Rh(COD)($**218**$)]BF_4$	5	reflux	12 h	--	--
14		10	reflux	12 h	--	--
15	$[Rh(COD)($**219**$)]BF_4$	5	reflux	12 h	--	--
16		10	reflux	12 h	--	--

Conditions: a) The reaction was conducted in acetone. b) CH_2Cl_2 was used as a solvent. c) ee determined by ^{13}C NMR. d) The other enantiomer was not observed.

Afterwards, asymmetric intramolecular hydroacylation was conducted using three kinds of phosphines: (*S*,*S*)-Me-Duphos (**214**), the structurally related catASimunMN(R) (**218**) [180,181], and catASimunM(R) (**219**)[180,182] (Figure 10).

[180] Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem*. **2003**, *68*, 1263.
[181] Holz, J.; Zayas, O.; Jiao, H.; Baumann, W.; Spannenberg, A.; Monsees, A.; Riermeier, T. H.; Almena, J.; Kadyrov R.; Börner, A. *Chem. Eur. J.* **2006**, *12*, 5001.
[182] Almena, J.; Monsees, A.; Kadyrov, R.; Riermeier, T. H.; Gotov, B.; Holz, J.; Börner, A. *Adv. Synth. Catal*. **2004**, *346*, 1263.



216 **217** **218** **219**

Figure 10. Phosphines used in the intramolecular hydroacylation study.

As was previously explained, the Me-Duphos catalyst is likely to provide high enantioselectivities for any 4-substituted pentenal bearing a primary or secondary carbon atom substituent (Table 13). In 4-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enal (**189**), the carbon directly attached to the vinyl is a secondary carbon, and therein, it has been suggested that this phosphine has the most potential for conducting the reaction.

Holz *et al.* provided evidence that the asymmetric hydrogenation of (*E*)- and (*Z*)-methyl 3-acetamidobutenoate, employing Rh(I) as a pre-catalyst with Me-Duphos as a chiral ligand, proceeds very fast and with a high enantioselectivity. Discussions of the homogeneous catalyst in the literature indicate that the fine-tuning of a catalyst may also be achieved by varying the bite angle of the diphosphine ligand.[183] A report by Orpen and Pringle *et al*. demonstrated that replacing the phenylene backbone in a Duphos-Rh catalyst by 1,2-cyclopentane significantly changed the enantioselectivity in the hydrogenation of unsaturated α-amino acid precursors.[184] In this context, we considered interesting to investigate the Me-Duphos, as well as the catASium diphosphines, which have the same phospholane ring as Me-Duphos, but at a different bite-angle.

Thus, the reaction of **189** in the presence of the catalytic system [Rh(NBD)-(*S*,*S*)-Me-Duphos]BF_4 afforded cyclopentanone **215*S*** in good yield and with excellent enantioselectivities. In contrast, when the (*R*,*R*)-Me-Duphos was used, the reaction afforded the opposite enantiomer. In both cases, the yield and the enantioselectivities were the same, and the reaction was strictly reproducible (Table 14, entries 11 and 12).

[183] Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans*. **1999**, 1519.
[184] Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Orpen, A. G.; Pringle, P. G. *Chem. Commun*. **2000**, 1663.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Unexpectedly, no reaction product was obtained when phosphines **218** and **219** were used (entries 13-16), even when the catalyst loading and the temperature were increased. This result may be due to the fact that these two phosphines have and smaller bite-angle and a shorter Rh-P distance.[180,185] It is reasonable to assume that a decrease in the bite-angle and a shortening of the Rh-P bond corresponds to a decrease in the distance between the catalytic centre and the ligand backbone. This should, therefore, affect the strength of the repulsive interactions between the catalyst and the prochiral substrate. Thus, the coordination of the substrate to the metallic centre using these kinds of phosphines could be more difficult due to the steric hindrance generated by the substrate.

The enantioselectivities of the cyclopentanone products were determined by the ^{13}C NMR of hydrazone **221** formed with optically active hydrazine **220** (Figure 11).[186] Roughly equal portions of the syn- and anti-isomers of **221** were formed. The ^{13}C NMR signals for the imine carbons of diastereomers **221** were well-separated singlets, with a pair for each geometric isomer.

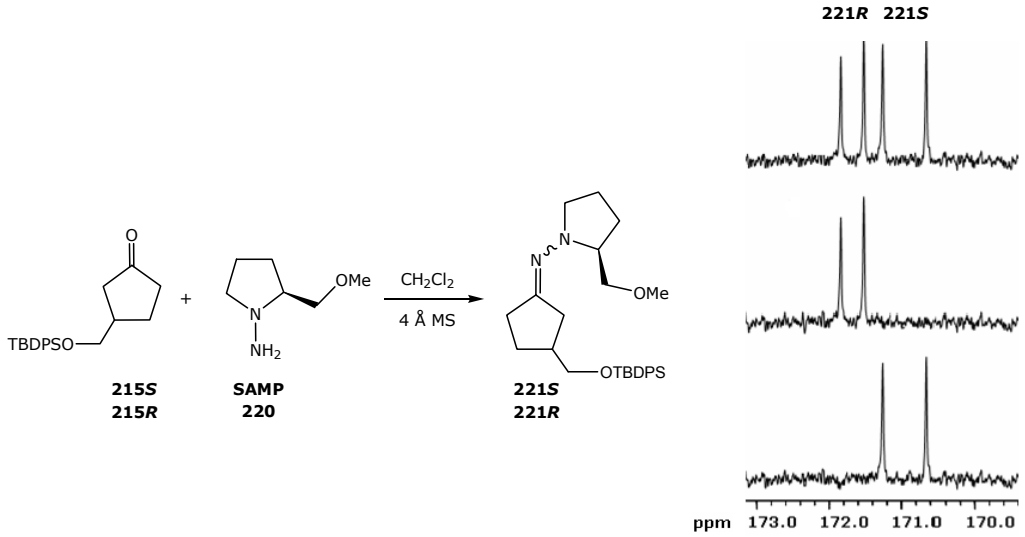


Figure 11. Determination of enantiomeric excesses by ^{13}C NMR via hydrazine synthesis. a) corresponding to the ^{13}C NMR of the racemic mixture (**221*S*** and **221*R***); b) ^{13}C NMR of the *S*-enantiomer (**221*S***); c) ^{13}C NMR of the *R*-enantiomer (**221*R***).

[185] Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc*. **1993**, *115*, 10125.
[186] Enders, D.; Eichenauer, H. *Tetrahedron Lett*. **1977**, 191.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Using a sufficient acquisition time and an appropriate pulse delay (5s), the enantiomeric excesses (ees) were determined to within an error of 5%. The assignments of the major and minor isomer signal positions were confirmed by the signals observed for the racemic samples of **221**, which were prepared from the achiral catalyst [Rh(NBD)dppe]BF_4. The assignments were based on the chemical shifts of the ^{13}C NMR imine carbon signals of **221**, and were made on the basis of similar imine carbon signals found in the literature.[172] Thus, it was found that the hydrazone **221** of the (*S*)-cyclopentanone enantiomer with an established absolute configuration always produced a ^{13}C NMR imine carbon signal upfield from the hydrazone of the *R* enantiomer.

When the ^{13}C NMR of the racemic product was recorded, signals were observed at δ 171.8, and 171.5, corresponding to the *R* enantiomer, and at 171.3 and 170.7 ppm, to the *S* enantiomer. Once the *R* enantiomer was produced from (*R*,*R*)-Me-Duphos, and the hydrazone formation proceeded, only signals at 171.8 and 171.5 were detected. Subsequently, in order to determine the absolute configuration, the optical rotation of the 3*R*-cyclopentanone was measured, resulting in $[\alpha]^{25}_D$(**215*R***)= 36.68 (c 0.2, CH_2Cl_2). The same procedure for the 3*S*-cyclopentanone was conducted, and therein, two ^{13}C NMR signals at 171.3 and 170.7 ppm were observed, corresponding to hydrazone, and the optical rotation of the 3*S*-cyclopentanona was $[\alpha]^{25}_D$ (**215*S***)= -37.96 (c 0.3, CH_2Cl_2). The differences between the two α_D values were most likely due to the experimental error.

Once the intramolecular hydroacylation of 4-((*tert*-butyldiphenyl silyloxy)methyl) pent-4-enal (**189**) was studied, the hydroacylation of formate **187** was performed in order to produce lactone **222**. [Rh(NBD)dppe]BF_4 and a reaction time of 12 h was used in all experimental runs (Table 15).

Table 15. Intramolecular hydroacylation of allyl formate (**187**).

187 **222** **223**

entry	Solvent	mol% [Rh]	T (ºC)	Yield	
				222	223
1	CH_3CN	1	81	--	--
2	PhCN	1	175	--	40%
3	acetone	10	56	--	--
4[a]	PhCN	--	175	--	--

a) no catalyst was added.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

In all of the tested conditions, no new product was detected; hence, formate **187** did not exhibit oxidative addition in the investigated conditions. To the best of our knowledge, there are no examples reported in the literature using this kind of substrate. In contrast, when benzonitrile was used as a solvent, a side product was observed (Table 15, entry 2). The structure of the formed product was determined by ^{1}H and ^{13}C NMR. Thus, when the ^{1}H NMR spectrum was recorded, the signal at 8.05 ppm, corresponding to the formate proton, disappeared and the $-CH_2-$ bound to the formate group at 4.25 ppm was also not detected. On the other hand, a new signal at δ 1.71 was observed, which was shown to correspond to $-CH_3$ by gHSQC. Moreover, the signals corresponding to the $-CH_2-$ groups attached to the silyloxy group and to the vinyl moiety were shifted to 5.18, 4.9, and 4.13 ppm, while in the starting material, these signals were detected at 5.4, 5.2, and 4.7 ppm, respectively. Furthermore, the protecting group was still present in the newly formed product. New ^{13}C NMR signals were detected at 144.4, 109.3, 67.5, and 19.3 ppm, corresponding to the quaternary carbon, the $-CH_2-$ vinylic carbon, the $-CH_2-$ moiety attached to the protecting group, and to the $-CH_3$ moiety, respectively. The phase of the peaks in the gHSQC indicated if the observed signals corresponded to $-CH_2-$ or $-CH_3$ carbons. It was concluded that all of these signals indicate the formation of compound **223** (Table 15), which can be formed through a retro-ene reaction.

In order to determine the influence of the catalyst on the retro-ene reaction, the transformation was performed in the same conditions, but without the presence of the catalyst (entry 4, Table 15). Subsequently, the formation of product **223** did not proceed.

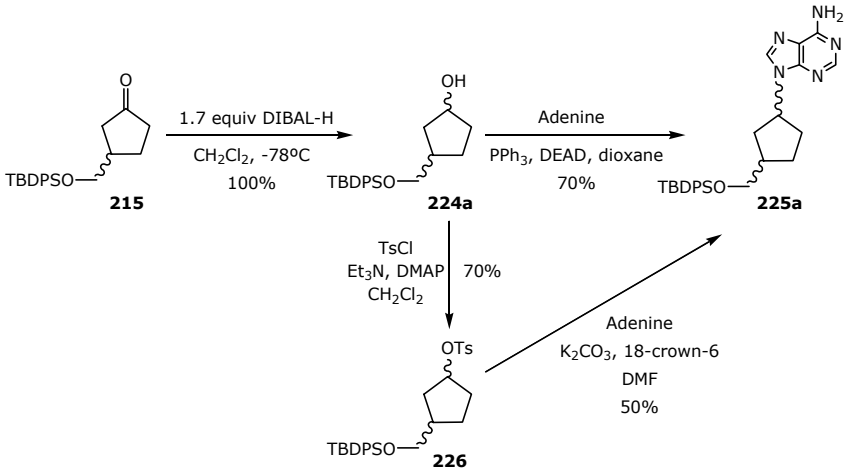
The retro-ene reaction of allyl acetals is a thermal sigmatropic rearrangement that is commonly used to produce olefins and esters.[187] The pyrolysis of N,N-dimethylglycinate[188] and trimethylsilyl 2-oxobicyclo[3.1.1]nonane-1-carboxylate[189] take place by the same mechanism. Moreover, examples from literature show this process is enhanced when a metal source is added to the reaction mixture.[190] Our results agree well with previously reported data.

[187] (a) Mutterer, F.; Morgen, J. M.; Biedermann, J. M.; Fleury, J. P.; Weiss, F. *Tetrahedron* **1970**, *26*, 477. (b) Giner, J.-L.; Arigoni, D. *Chem. Commun*. **2002**, 1388.
[188] Ibrahim, M. R.; Al-Awadi, N. A.; Ibrahim, Y. A.; Patel, M.; Al-Awadi, S. *Tetrahedron Lett*. **2007**, *63*, 4768.
[189] Bloch, R.; Boivin, F.; Bortolussi, M. *J. Chem. Soc., Chem. Commun*. **1976**, 371.
[190] Sotelo, E.; Coelho, A.; Raviña, E. *Tetrahedron Lett*. **2003**, *44*, 4459.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

4.4. SYNTHESIS OF CARBOCYCLIC (D/L)-ddA ANALOG

Once the formation of 3-((*tert*-butyldiphenylsilyloxy)methyl)cyclopentanone (**215**) was optimized, the next reactions were tested using the racemic substrate. The desired nucleoside **225a** can be obtained from cyclopentanol **224a** through a Mitsunobu reaction[47a] or by a S_N2 process from **226** (Scheme 71). In both reactions, a configuration inversion occurs.



Scheme 71. Synthesis of carbocyclic-ddA.

Therefore, **215** was reduced at a low temperature in a quantitative yield, using DIBAL-H and CH_2Cl_2 as the solvent, to produce a diastereomeric mixture of **224a**.[191] Once **224a** was obtained, the reaction of the cyclopentanol with *p*-toluenesulfonyl chloride produced **226**, which was then treated with adenine in DMF using K_2CO_3 and 18-crown-6.[192] The yield of the latter reaction was moderate, and for this reason, a Mitsunobu reaction was conducted from **224a**. Initially, the Mitsunobu reaction was tested using DMF as a solvent,[193] but failed to afford **225a** products. When the solvent was changed to dioxane,[194] nucleoside **225a** was obtained as a mixture of diastereoisomers in good yield. In contrast to the other reaction pathway, only one reaction is required to afford this nucleoside.

[191] Brady, T. B.; Kim, S. H.; Wen, K.; Kim, C.; Theodorakis, E. A. *Chem. Eur. J.* **2005**, *11*, 7175.
[192] Bravo, F. PhD. Thesis, Universitat Rovira i Virgili **2000**.
[193] (a) Díaz, Y.; Bravo, F.; Castillón, S. *J. Org. Chem*. **1999**, *64*, 6508. (b) Ludek, O. R.; Meier, C. *Synlett* **2006**, 324. (c) Rodríguez, J. B.; Comin, M. J. *Mini Reviews in Medicinal Chemistry* **2003**, *3*, 95.
[194] (a) Wang, J.; Busson, R.; Blaton, N.; Rozenski, J.; Herdewijn, P. *J. Org. Chem*. **1998**, *63*, 3051. (b) Véliz, E.; Beal, P. A. *Tetrahedron Lett*. **2006**, *47*, 3153.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

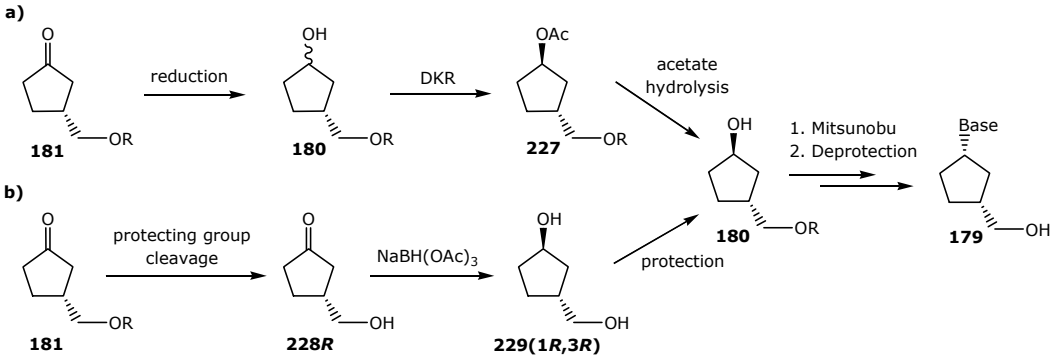
4.5. ENANTIOSELECTIVE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES BY STEREOSELECTIVE REDUCTION OF CYCLOPENTANONES

At this point, the stereoselective reduction of **215** is essential to the production of nucleoside **179** with the appropriate stereochemical purity. Both L and D isomers have been described in the literature, and have been demonstrated to be biologically active against HIV.[195] In principle, both stereoisomers can be obtained by the methodology developed in this work.

The most important factor for stereoselective reduction is that the substrate contains a stereocontrol group in the α-position; however, this is not the case in our substrate, making stereocontrol significantly more difficult.

We considered two alternatives to obtain the alcohol derivative with the required configuration, that is, by a direct reduction of the ketone using triacetoxyborohydride, or by the dynamic kinetic resolution (DKR) of a diastereomeric mixture of alcohols.[196,197]

Scheme 72 depicts the synthesis of the carbocyclic nucleosides by the aforementioned methodologies.



Scheme 72. Synthesis of carbocyclic nucleosides. a) using DKR; b) using $NaBH(OAc)_3$.

In order to carry out the DKR, the reduction of ketone **180** is necessary. After the DKR process, the resultant alcohol is acetate **227**, which is hydrolyzed to obtain alcohol **180**. Next, the Mitsunobu reaction is carried out. The stereoselective reduction of the ketone **181** could be carried out taking advantage of the reducing

[195] (a) Gudmundsson, K. S.; Daluge, S. M.; Condreay, L. D.; Johnson, L. C. *Nucleosides, Nucleotides & Nucleic acids* **2002**, *21*, 891. (b) Mansuri, M. M.; Farina, V.; Starrett, J. E.; Benigni, D. A.; Brankovandr, V.; Martin, J. C. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 65. (c) Pélicano, H.; Pierra, C.; Eriksson, S.; Gosselin, G.; Imbach, J.-L.; Maury, G. *J. Med. Chem*. **1997**, *40*, 3969.
[196] Pàmies, O.; Bäckvall, J. E. *Chem. Rev*. **2003**, *103*, 3247.
[197] Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem*. **1991**, *56*, 2656.

agent coordination ($NaBH(OAc)_3$) to the hydroxyl group. In this sense, **181** must be deprotected to furnish **228**. Once **229** is obtained, it must be protected again before performing the Mitsunobu reaction.

- Dynamic Kinetic Resolution (DKR)

Antecedents

In the past few decades, there has been a dramatic increase in the demand for enantiopure compounds for use as fine-chemicals and in material science applications. In response to this, enantioselective catalysis has developed into an important and expansive area in organic chemistry.[198]

In biocatalysis, lipases have become one of the most versatile classes of biocatalysts in organic synthesis. This is because lipases can accept a wide range of organic substrates, and work well in organic solvents. Lipases can be used as catalysts in either hydrolysis reactions and ester syntheses (acylation reactions). In both types of reactions, lipases usually react with a high enantioselectivity.[196]

The major application of enzymes in enantioselective organic chemistry is the kinetic resolution (KR) of racemates.[199] The drawback of KR is that a maximum of 50% of the starting material produces the target product. Three relatively easy approaches can be employed to overcome this problem, that is, using *meso* substrates (the "meso trick"),[200] combining KR with stereoinversion,[199] and by applying a dynamic kinetic resolution (DKR)[201,202] in which the non-reacting enantiomer is racemised *in situ* during the KR.

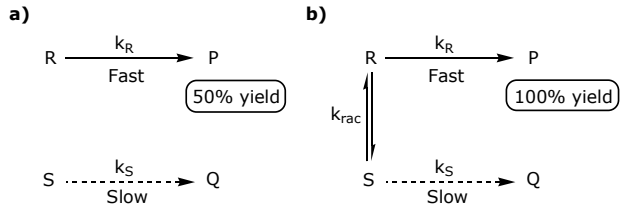
Alternatively, the enzymatic reduction of prochiral unsaturated substrates can also produce the product at a desirable 100% yield and 100% enantiomeric excess.[203]

In the past few years, Bäckvall has developed a new concept, in which a racemate is deracemised by combining an enzyme and a metal catalyst in *one-pot*, wherein enzymatic KR is combined with an *in situ* metal-based racemisation process.

There are three basic requirements for an efficient DKR. First, an efficient kinetic resolution has to be identified (i.e. $k_R >> k_S$). Second, an efficient racemisation method has to be chosen (i.e. $k_{rac} > 10k_S$). Third, the kinetic resolution and the racemisation procedures should be compatible with one another (Scheme 73).[204]

[198] (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, Springer-Verlag: Berlin, 1999. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.
[199] Stecher, H.; Faber, K. *Synthesis* **1997**, 1.
[200] Faber, K. Biotransformations in Organic Chemistry, Springer-Verlag: Berlin, 2000.
[201] Kim, M. J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol*. **2002**, *13*, 578.
[202] Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J. E. *Chem. Soc. Rev*. **2001**, *30*, 321.
[203] Stampfer, W.; Kosjek, B.; Christian, M.; Kroutil, W.; Faber, K. *Angew. Chem. Int. Ed. Engl*. **2002**, *41*, 1014.
[204] Pàmies, O.; Bäckvall, J. E. *Curr. Opin. Biotechnol*. **2003**, *14*, 407.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 73. Kinetic resolution versus dynamic kinetic resolution. a) Kinetic resolution; b) dynamic kinetic resolution. R and S represent the two enantiomers of the starting material; P and Q represent the two enantiomers of the product.

Chiral recognition by lipases can be explained by a model that describes the enantioselectivity mechanism in an enzymatic reaction. One example is the empirical rule of Kazlauskas *et al*.[197] This rule predicts, as exemplified for lipase *Pseudomonas cepacia*, enantiopreference towards a certain substrate, but cannot predict the degree of enantioselectivity.

For lipases, this model proposes an active site consisting of two pockets of different size, that is, a large and small size (Figure 12). The stereoselectivity for substrates bearing a small and a large substituent (e.g., a secondary alcohol, as shown in Figure 12) is explained by assuming that, when the secondary alcohol is subjected to resolution by lipase, the fast-reacting enantiomer binds to the active site in the manner depicted by Figure 12a; however, when the other enantiomer reacts with the lipase, it is forced to accommodate its large substituent into the smallest pocket (Figure 12b).

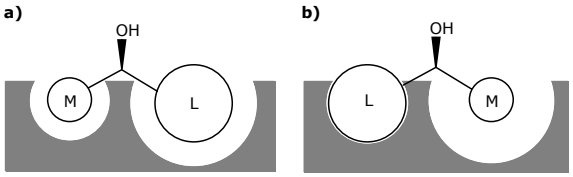
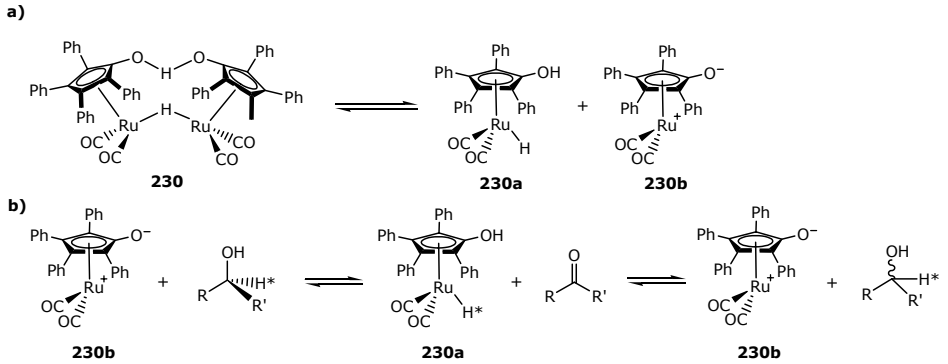


Figure 12. (a) The fast-reacting and (b) slow-reacting enantiomer in the active site model for lipases derived from Kazlauskas' rule.

As previously mentioned, DKR requires a metal catalyst for the racemisation process. Ru complexes have been commonly used as catalysts in this reaction. Scheme 74 depicts the racemization mechanism for Ru catalyst **230**. This catalyst has been selected as an example since, thus far, it is one of the few catalysts that has shown

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

a broad substrate scope when combined with an enzymatic kinetic resolution. An important feature of this complex is that no external base is needed as a cocatalyst, since one of the oxygens on the ligand acts as a basic centre. Thus, the reaction of the basic oxygen with an alcohol results in a proton abstraction, followed by the formation of ruthenium intermediate **230a**[205] and a ketone. The produced ketone is reduced by ruthenium intermediate **230a** to form the racemic alcohol and ruthenium species **230b**.



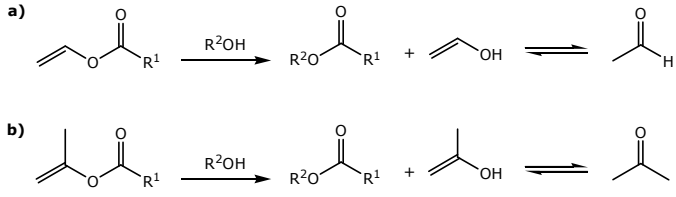
Scheme 74. The proposed mechanism for the racemisation of alcohols using ruthenium catalysts.

Results and discussion

In the first set of experiments, the efficiencies of different commercial lipases were investigated. For this purpose, diastereomeric cyclopentanols were selected. The enzymes *Candida Antarctica* lipase B (Novozyme 435, N-435) and *Pseudomonas cepacia* lipase (PSC) were screened in the KR of **224a** under different reaction conditions, using vinyl acetate, isopropenyl acetate, and *p*-chlorophenyl acetate as acyl donors. The use of vinyl acetate or isopropenyl acetate, which are well-known acyl donors, results in the formation of acetaldehyde and acetone, respectively, after the acyl transfer process (Scheme 75),[206] which has been demonstrated to interfere with the Ru catalyst **230** usually employed in the DKR.[207]

[205] Pàmies, O.; Bäckvall, J. E. *Chem. Eur. J.* **2001**, *7*, 5052.
[206] Ghanem, A.; Aboul-Enein, H. J. *Chirality* **2005**, *17*, 1.
[207] Persson, B. A.; Larsson, A. L. E.; LeRay, M.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.

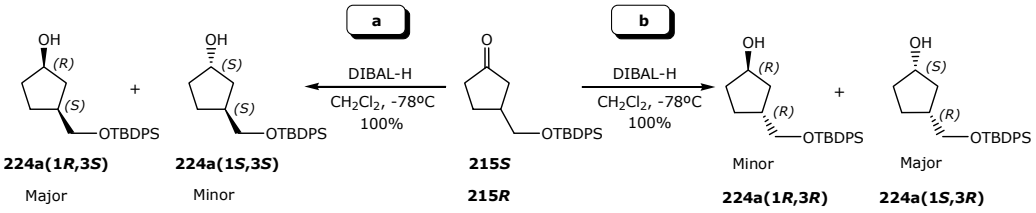
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 75. Lipase-catalysed irreversible transesterification: a) vinyl acetate; b) isopropenyl acetate.

In order to perform a first approximation to KR, these acyl donors were selected since are commercially available and appropriate to investigate the behaviour of 3-substituted cyclopentanols towards the enzymes. The results are summarised in Table 16.

The syntheses of the diastereomeric mixtures of 3*R* and 3*S*-substituted cyclopentanols were performed by reducing the 3*R*- and 3*S*-substituted cyclopentanone with DIBAL-H (Scheme 76). The reaction was conducted in CH_2Cl_2 at -78ºC, while 1.7 equiv of DIBAL-H was added to produce the corresponding cyclopentanol in quantitative yield.



Scheme 76. Reduction of a) 3*S*-cyclopentanone and b) 3*R*-cyclopentanone with DIBAL-H.

The ^{1}H NMR spectrum depicted the formation of two diastereomers at different ratios. A signal at δ 4.27 ppm, corresponding to the major product, and a signal at δ 4.36 ppm, corresponding to the minor product, were detected at a ratio of 2.5:1. It was hypothesised that the major product was obtained by the addition of the hydride in the opposite face of the *tert*-butyldiphenylsilyl group due to the steric hindrance generated by this protecting group. Therein, in order to determine the chemical shifts of the acetate products, an acetylation reaction was performed.[126] The subsequent ^{1}H NMR spectrum exhibited two new signals at 5.16 and 5.13 ppm,

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

corresponding to protons bound to the carbons linked to the acetoxy groups of the major and minor isomers, respectively.

Once the KR products were characterized, the study of the KR of cyclopentanol **224** was carried out. The KR results for these kinds of substrates are summarised in Table 16. The diastereomeric excess (de) and the diastereomeric ratio (dE) of the corresponding products obtained were determined by ^{1}H NMR.

Diastereoselectivity, or otherwise known as the diastereomeric ratio, is the parameter used to describe the stereoselectivity of a lipase-catalysed reaction. The dE-value is defined as the ratio of the specificity constants of two enantiomers, and can be expressed in terms of de_s and de_p, as shown in Equation 1.

A non-selective reaction has a dE-value of 1, while a dE-value above 20 is the minimum for an acceptable resolution.

$$dE = \frac{\ln\left[\frac{1 - de_s}{1 + (de_s / de_p)}\right]}{\ln\left[\frac{1 + de_s}{1 + (de_s / de_p)}\right]}$$

de_s = de of the starting material no-transformed

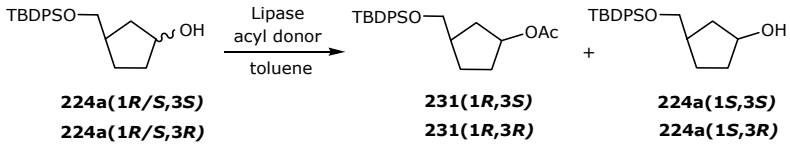
de_p = de of the final product

Equation 1. dE-value.

The KR was performed by first using (1*R/S*,3*S*)-cyclopentanol **224a(1*R/S*,3*S*)** in toluene, vinyl acetate as an acyl donor, PSC and N-435 at room temperature. Unfortunately, after 4 days, low or no conversion were observed. As per these results, the temperature was increased to 60ºC and isopropenyl acetate was used as the acyl donor, since it is known the latter is more suitable for the KR of secondary alcohols.[206] In this scenario, the conversion rate improved, and the enzyme N-435 exhibited the highest activity; however, the diastereomeric ratio was very low (entry 3). The diastereomeric ratio was superior using PSC (dE=466, entry 4), but the reaction failed to complete. Thus, in order to obtain a reasonable rate of **224a(1*R/S*,3*S*)** acylation, the amount of enzyme needed to be increased (entry 5). In addition, a basic requirement to achieve an efficient DKR is that the KR conditions have to be compatible with the *in situ* racemisation process. Therefore, 4-chlorophenylacetate was selected as a primary acyl donor, and the temperature was increased to 70ºC. Thus, the corresponding diastereomer was converted into the acetate product completely, but the calculated diastereoselectivity was lower (dE=100, entry 5). Subsequently, The behaviour of **224a(1*R/S*,3*R*)** was studied under these same conditions (entry 6), and produced the same results as those observed for **224a(1*R/S*,3*S*)**.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Table 16. Kinetic resolution of **224a**.[a]

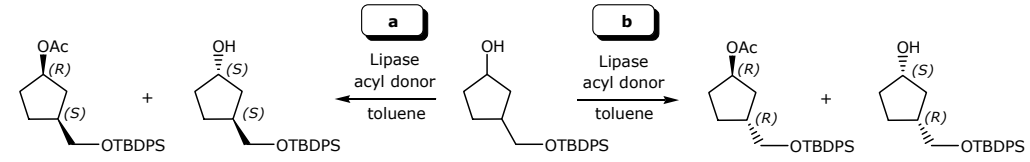


224a(1*R*/*S*,3*S*) **231(1*R*,3*S*)** **224a(1*S*,3*S*)**
224a(1*R*/*S*,3*R*) **231(1*R*,3*R*)** **224a(1*S*,3*R*)**

entry	Substrate	Enzyme	T (ºC)	Time	Acyl donor	% Conv[b]	% de of 231[b]	dE[c]
1	(1*R*/*S*,3*S*)	N-435	rt	4 d	vinyl acetate	13	> 99[d] (1*R*,3*S*)	297
2	(1*R*/*S*,3*S*)	PSC	rt	4 d	vinyl acetate	nr	--	--
3	(1*R*/*S*,3*S*)	N-435	60	12 h	isopropenyl acetate	90	60 (1*R*,3*S*)	20
4	(1*R*/*S*,3*S*)	PSC	60	24 h	isopropenyl acetate	68	>99[d] (1*R*,3*S*)	466
5[e]	(1*R*/*S*,3*S*)	PSC	70	24 h	*p*-ClPhOAc	75	87 (1*R*,3*S*)	100
6[e]	(1*R*/*S*,3*R*)	PSC	70	48 h	*p*-ClPhOAc	30	87 (1*R*,3*R*)	100

a) Reactions were performed on a 0.03 mmol scale, with a 2.5:1 diastereomeric mixture of **224a**, 1.5 mg of enzyme, and 0.09 mmol of acyl donor in 0.5 ml of toluene. b) Determined by ^{1}H NMR. c) Diastereomeric ratio. d) The other diastereomer was not observed. e) 15 mg of enzyme was added.

It is important to note that when the KR of **224a(1*R*/*S*,3*R*)** was performed, the reacting diastereomers were observed to be different than was in the case of the KR of **224a(1*R*/*S*,3*S*)**. In the former case, the enzyme converted the minor isomer into acetate product **231**, while in the latter case, the major isomer was converted to the acetate product. These results agree well with Kazlauska's rule (Figure 12) and the initial hypothesis that the hydride transfer from the DIBAL-H was executed from the opposite side of the protecting group (Scheme 76). Thus, when **224a(1*R*/*S*,3*S*)** is resolved by the enzyme, the *trans* isomer is acetylated. In contrast, when the **224a(1*R*/*S*,3*R*)** is resolved by the enzyme, the *cis* isomer is acetylated (Scheme 77).



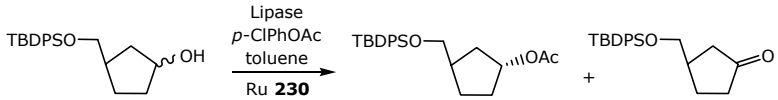
231(1*R*,3*S*) **224a(1*S*,3*S*)** **224a(1*R*/*S*,3*S*)** **231(1*R*,3*R*)** **224a(1*S*,3*R*)**
224a(1*R*/*S*,3*R*)

Scheme 77. Kinetic resolution of cyclopentanol a) **224a(1*R*/*S*,3*S*)** and b) **224a(1*R*/*S*,3*R*)**.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

On the basis of our preliminary KR results, the KR of cyclopentanol **224a**, using PSC and *p*-ClPhOAc as an acyl donor, was combined with a ruthenium catalyst via hydrogen transfer and the so-called Shvo´s catalyst in toluene.[208] The results are summarised in Table 17.

Table 17. Dynamic kinetic resolution of **224a**.[a]



224a(1*R*/*S*,3*R*) **224a(1*R*/*S*,3*S*)** **231(1*R*,3*S*)** **231(1*R*,3*R*)** **215*S*** **215*R***

entry	Substrate	Enzyme	Time (h)	% Conv[b]	% 215	% de of 231[b]	dE[c]
1[d]	(1*R*/*S*,3*R*)	N-435	24	87	52	52 (1*R*,3*R*)	6
2[d]	(1*R*/*S*,3*R*)	PSC	24	51	51	--	--
3[e]	(1*R*/*S*,3*S*)	PSC	48	77	54	80 (1*R*,3*S*)	11
4[f]	(1*R*/*S*,3*S*)	PSC	48	53	25	>99[h] (1*R*,3*S*)	230
5[f]	(1*R*/*S*,3*S*)	PSC	72	73	11	>99 [h] (1*R*,3*S*)	230
6[f,g]	(1*R*/*S*,3*R*)	PSC	72	93	--	>99 [h](1*R*,3*R*)	1057
7[f,g]	(1*R*/*S*,3*S*)	PSC	72	93	--	>99 [h] (1*R*,3*S*)	1057

a) Reactions were performed on a 0.03 mmol scale with 15 mg of enzyme, 0.09 mmol of *p*-ClPhOAc, and 4 mol% of Ru in 0.5 ml of toluene at 70ºC. b) Determined by ^{1}H NMR. c) Diastereomeric ratio. d) 1.5 mg of enzyme was added. e) 0.015 mmol of alcohol was added. f) H_2 gas was used. g) 6 mol% of Ru was added. h) The other diastereomer was not observed.

The first experimental run was performed using enzyme N-435, and exhibited a very high activity and low diastereomeric ratio (entry 1). When PSC was used, no acetylated product was observed (entry 2). In both cases, large amounts of the corresponding ketone **215*R*** formed during the hydrogen transfer process was observed (entries 1 and 2). Herein, several methods were investigated to increase efficiency by reducing the amount of formed ketone. Thus, two hydrogen sources were tested to push the reaction equilibrium back towards cyclopentanol **224a**. The addition of 0.015 mmol of 2,4-dimethyl-3-pentanol did not appreciably improve the reaction, that is, after 48 h, 77% of the reactants were converted to products, the diastereomeric ratio increased (dE=11, entry 3), and the ketone concentration was still high (54%). In order to improve these results, H_2 gas (1 bar) was added. H_2 effectively inhibited ketone formation, and the subsequently obtained diastereoselectivities were excellent (>99%, entries 4 and 5). After 48 h, 25% of

[208] Menasche, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885.

ketone **215*S*** was still detected (entry 4), and after 72 h, the ketone concentration was reduced to 11% (entry 5). As per these results, and in order to quench ketone formation, the catalyst loading was increased to 6 mol%. Under these conditions, the analysis of the reaction residue exhibited no ketone product, and the obtained conversion rate and diastereomeric ratio were excellent (dE=1057, entries 6 and 7).

Compound **231(1*R*,3*S*)**, a key intermediate for synthesising carbocyclic nucleosides, was obtained in excellent stereoselectivities by DKR from the diastereomeric mixture **224a**. Depending on which diastereomer is used as the starting material, a *cis* or *trans* product can be obtained. When **224a(1*R/S*,3*S*)** was used, the *trans* isomer was produced, while the KR of **224a(1*R/S*,3*R*)** produced the *cis* isomer with an excellent conversion rate and with excellent diastereoselectivities. The hydrolysis of the acetate will afford cyclopentanol in a straightforward manner.

- Diastereoselective Reduction

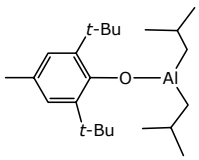
This kind of alcohol could be also achieved by a direct diastereoselective reduction of ketone **215** (Scheme 72). As was previously explained, the reduction of cyclopentanone using DIBAL-H produced two diastereomers at different ratios due to the steric hindrance generated by the *tert*-butyldiphenyloxy group (Scheme 76). Thus, it may be possible to increase the *trans* product formation by employing a bulkier reductive reagent, such as diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide (BHT) (**232**). Moreover, this reduction could be also performed by a coordinating reducing reagent, such as $NaBH(OAc)_3$, which needs the unprotected hydroxyl group.

Diisobutylaluminum 2,6-Di-t-butyl-4-methylphenoxide (BHT)

Until now, aluminium alkoxide **232** (Figure 13) has been used as a reducing reagent in prostaglandin synthesis.[209,210] The generality of this reagent has been examined by Iguchi *et al*. using a simple hydroxy-ketone and cyclic ketones with alkyl chains on the ring. The results obtained in this study revealed that, unlike the behaviour exhibited by the reduction of prostaglandin derivatives, aluminium reagent **232** showed no remarkable stereoselectivity in the case of the reduction of simple unhindered hydroxy-ketones.[210]

[209] (a) Iguchi, S.; Nakai, H.; Hayashi, M. *J. Org. Chem*. **1979**, *44*, 1363. (b) Binns, M. R.; Richard, K. H.; Lambert, D. E.; Schober, P. A. *Tetrahedron Lett*. **1985**, *26*, 3385. (c) Otera, J.; Niibo, Y.; Nozaki, H. *Tetrahedron Lett*. **1992**, *33*, 3655.
[210] Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 3033.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

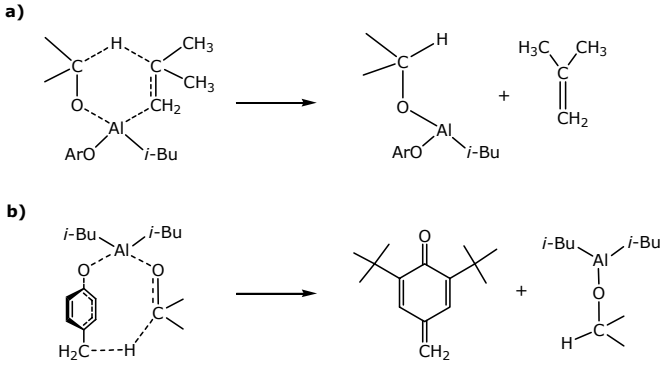


232

Figure 13. Diisobutylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide (**232**).

A plausible mechanism for the reduction of ketones using **232** involves an initial coordination of the trivalent aluminium reagent with the carbonyl group, followed by an intramolecular hydride transfer from the β-carbon of the isobutyl group, as shown in Scheme 78a.

Another possible mechanism for the reduction ketones using **232** uses the hydride source of this reagent, as derived from the methyl group of phenoxide (Scheme 78b). This mechanism was ruled out by the experimental results obtained by Iguchi *et al*.[210] This study demonstrated that at least one β-hydrogen of the alkyl group of dialkylaluminium phenoxides is indispensable for reduction. Based on the above consideration, it was concluded that the mechanism depicted in Scheme 78a was the most plausible.



Scheme 78. Plausible mechanisms for the reduction of ketones using **232**.

When the starting material for the KR was synthesised, that is, when the cyclopentanones were reduced using DIBAL-H, the two resultant diastereoisomers were obtained in different ratios, one being the *cis* product (minor), and the other, the *trans* product (major). At that time, the bulkier aluminium reagent was used to improve the discrimination between the two diastereoisomers, as per data from the literature; however, when the reaction was performed, no discrimination was

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

observed. The corresponding cyclopentanol was obtained in a 1:1 ratio. Hence, in this case, the obtained result was not as good as when DIBAL-H was used. This could be due to the absence of a large group in the α-position and also to the fact that the reaction was executed at higher temperatures than when DIBAL-H was used.

NaBH(OAc)$_3$

The reduction of aldehydes and ketones using NaBH(OAc)$_3$ is one of the most useful methods for synthesising primary and secondary alcohols.

It has been demonstrated that the intramolecular reduction of ketones using this reagent is sluggish.[211] Gribble exploited this using triacetoxyborohydrides from the sodium borohydride/acetic acid system, wherein the efficacy of these reagents was substantially increased in the presence of alcohols.[212] Thus, as suggested by Saksena, a hypothetical alkoxydiacetoxyborohydride intermediate might reduce proximal ketones, not simply because it can do so intramolecularly, but because it is actually a more potent reducing agent than the triacetoxyborohydride parent is (Figure 14).[213]

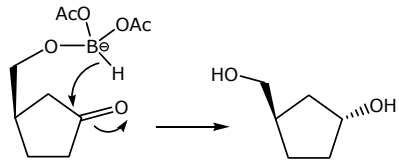


Figure 14. The mechanism of ketone reduction using NaBH(OAc)$_3$.

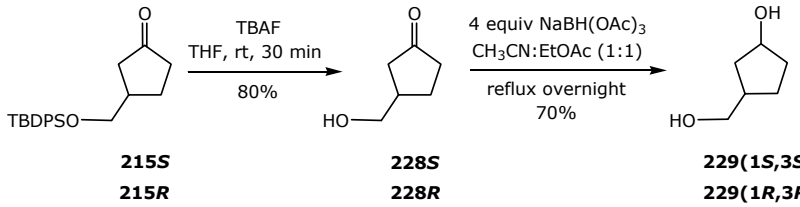
In order to reduce ketones using NaBH(OAc)$_3$, the *tert*-butyldiphenylsilyl group was deprotected from **215** by adding 1.5 equiv of TBAF in THF to afford **228** (Scheme 79) in 80% yield.

[211] (a) Gribble, G. W.; Nutaitis, C. F. *Tetrahedron Lett*. **1983**, *24*, 4287. (b) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett*. **1984**, *25*, 5449. (c) Tolstikov, G. A.; Odinokov, V. N.; Galeeva, R. I.; Bakeeva, R. S.; Akhunova, V. R. *Tetrahedron Lett*. **1979**, 4851.

[212] (a) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun*. **1975**, 535. (b) Hirao, A.; Itsuno, S.; Owa, M.; Nagami, S.; Mochizuki, H.; Zoorov, H.; Niakahama, S.; Yamazaki, N. J. *Chem. Soc., Perkin Trans. 1* **1981**, 900. (c) Nasipuri, D.; Sakar, A.; Konar, S. K.; Ghosh, A. *Indian J. Chem*. **1982**, *218*, 212.

[213] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 79. The enantioselective reduction of **228** using $NaBH(OAc)_3$.

Compound **228** was diastereoselectively reduced using this reagent in different solvents. The most commonly used solvents in this reaction are acetonitrile,[214] acetic acid,[211b,213,215] ethyl acetate,[211a,216] or mixtures of these solvents. Table 18 summarises the results obtained from this reduction using different reaction conditions.

Table 18. The reduction of **228** using $NaBH(OAc)_3$.[a]

entry	Starting material	Solvent	Yield	$[\alpha]^{25}_D$ (c 0.6, methanol)
1	**228*S***	acetic acid	40%	
2	**228*S***	ethyl acetate	20%	
3	**228*S***	ethyl acetate:acetonitrile (1:1)	70%	3.83
4	**228*R***	ethyl acetate:acetonitrile (1:1)	70%	-3.92

a) 4 equiv of $NaBH(OAc)_3$ was used.

When the reaction was conducted in acetic acid and ethyl acetate using 4 equiv of acetoxyborohydride, low conversions were observed (40 and 20%, respectively). Thus, a mixture of 1:1, ethyl acetate:acetonitrile was used. In this case, compound **229** was obtained in 70% yield. The formation of **229** was confirmed by ^1H and ^{13}C NMR. The former exhibited a new multiplet at 4.3 ppm, corresponding to CH bound to the new hydroxyl group. When the ^{13}C NMR was measured, the carbon peak corresponding to the carbonyl group was not detected, while a new signal at 74 ppm, which was shown by gHSQC to correlate with the proton at 4.3 ppm, was observed.

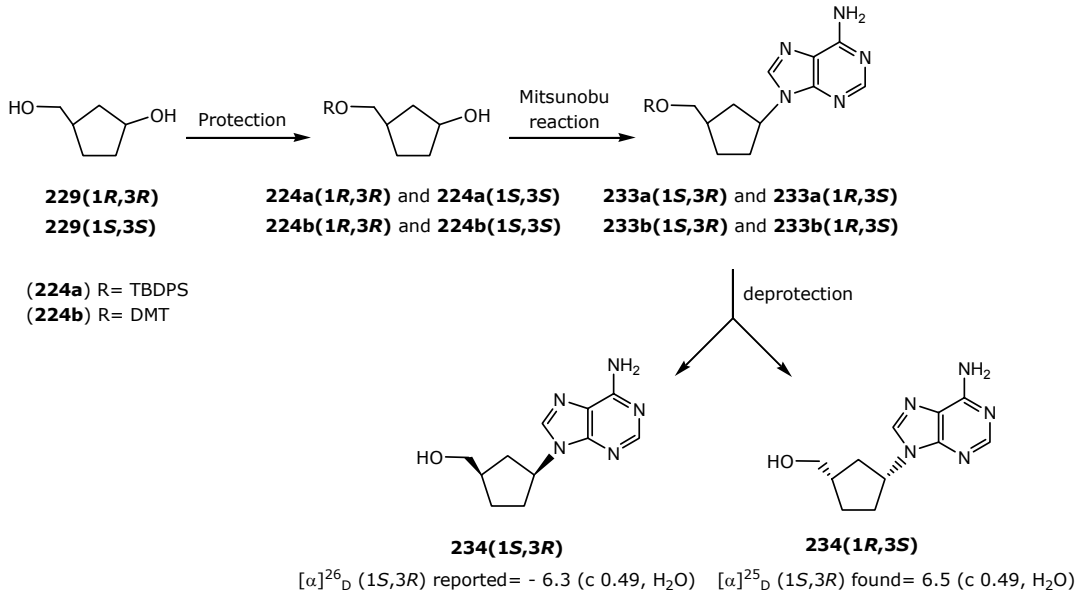
[214] Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem*. **1996**, *61*, 3849.
[215] (a) Saksena, A. K.; Mangiaracina P. *Tetrahedron Lett*. **1983**, *24*, 273. (b) Robins, M. J.; Sarker, S.; Samano, V.; Wnuk, S. F. *Tetrahedron* **1997**, *53*, 441. (c) Liu, Y.-T.; Wong, J. K.; Tao, M.; Osterman, R.; Sannigrahi, M.; Girijavallabhan, V. M.; Saksena, A. *Tetrahedron Lett*. **2004**, *45*, 6097.
[216] Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Starting materials **215*S*** and **215*R*** both provided the same results when these reaction conditions were applied, but afforded opposite enantiomers. This agrees well with the calculated optical rotation ($[\alpha]^{25}_D$(1*S*,3*S*)= 3.83 (c 0.6, methanol), $[\alpha]^{25}_D$(1*R*,3*R*)= -3.92 (c 0.6, methanol)), and these results were corroborated when the $[\alpha]_D^{25}$ of the final product (**234**) was measured and compared with the reported value.

Subsequently, the primary hydroxyl was protected with TBDPSCl in CH_2Cl_2 using Et_3N and DMAP affording **224a(1*R*,3*R*)**, in 65% yield. Additionally, the reaction of **224a(1*R*,3*R*)** with adenine under Mitsunobu conditions furnished **233a(1*S*,3*R*)** with good yields (70%, Scheme 71). A problem was encountered with the corresponding cleavage of this protecting group with TBAF, since after several purifications, the tetrabutylammonium fluoride could not be removed from **234(1*S*,3*R*)**. Several purifications were attempted, even using DOWEX 50WX8-400 resin, which has been reported to remove this salt.[217]

Thus, the protecting group used in this pathway was changed to DMT, which can be deprotected under acidic conditions, thereby facilitating the removal of secondary products.



Scheme 80. Reaction pathway for synthesising **234(1*R*,3*S*)**.

[217] (a) Parlow, J. J.; Vazquez, M. L.; Flynn, D. L. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2391. (b) Kaburagi, Y.; Kishi, Y. *Org. Lett*. **2007**, *9*, 723.

The reaction of **229(1*S*,3*S*)** with DMTCl using pyridine and DMAP furnished **224b(1*S*,3*S*)** in 60% yield. The reaction of **224b(1*S*,3*S*)** with adenine under Mitsunobu conditions afforded **233b(1*R*,3*S*)** in good yields. The deprotection of the DMT group in THF using TFA furnished **234(1*R*,3*S*)** in 75% yield. Following the same methodology, **234(1*S*,3*R*)** can also be obtained.

The presence of the nitrogen base in the final product after the Mitsunobu reaction was confirmed by ^{1}H and ^{13}C NMR. The ^{1}H NMR spectrum exhibited peaks corresponding to the adenine moiety at 8.3 and 7.9 ppm, as well as two protons corresponding to NH_2 at 6 ppm. Moreover, the CH proton bound directly to the nucleic base was shifted to 4.9 ppm, while in the starting material, this signal was detected at 4.4 ppm. The ^{13}C NMR spectrum exhibited signals at 155.6, 150.2, 138.7, and 120.1 ppm, corresponding to adenine. The carbon bound directly to the nitrogen base appeared at 55.6 ppm, which was unshielded with respect to the starting material (74 ppm).

It is important to note that the optical rotation for **234(1*S*,3*R*)** could not be measured because **234(1*S*,3*R*)** was not isolated properly due to the presence of the ammonium salt. In the pathway beginning with the dimethoxytrityl derivative, the optical rotation of **234(1*R*,3*S*)** was comparable to values reported in literature (Scheme 80) confirming the stereochemistry of the final product.

In conclusion, a new method for synthesising **234(1*R*,3*S*)** and **234(1*S*,3*R*)** nucleosides has been realised using an enantioselective intramolecular hydroacylation reaction and subsequent diastereoselective reduction of the ketone obtained in the former reaction. A subsequent Mitsunobu reaction and posterior deprotection of the corresponding protecting group affords the nucleoside with the desired configuration.

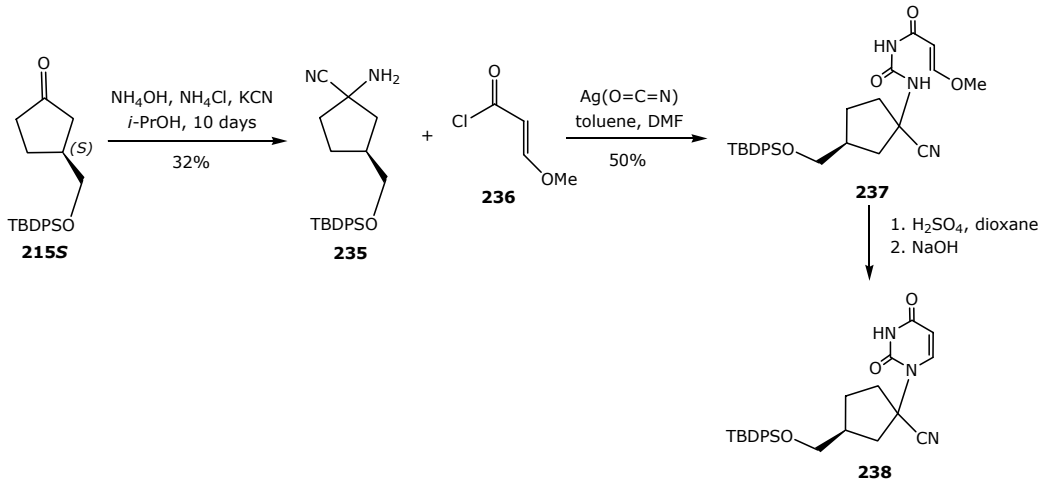
4.6. SYNTHESIS OF BRANCHED CARBOCYCLIC NUCLEOSIDES. STRECKER REACTION

Branched nucleosides are nucleosides that incorporate an alkylic chain in the structure. A particular group of these nucleosides are psico-nucleosides, which have a quaternary carbon that results from an alkylic chain and the nucleic base being linked to same carbon. As has been previously demonstrated, cyclopentanone derivatives prepared by intramolecular hydroacylation are appropriate intermediates for synthesising carbocyclic nucleosides. We also considered that these cyclopentanones offered the potential to create a quaternary centre, and herein, the Strecker reaction was most appropriate. This reaction incorporates amino and cyano groups into the carbonylic carbon, generating a quaternary centre. This reaction has been widely applied to the synthesis of α-aminonitriles to afford the corresponding α-

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

amino acids. The most common substrates used in this reaction are aldehydes, while there are only a few reports in literature that use cyclic pentanones as substrates.[218]

The synthesis of branched-carbocyclic nucleosides requires the construction of the base from the amino group. Therein, cyclopentanone **215*S*** was treated with NH_4OH and KCN in *i*-PrOH for 10 days to obtain α-aminonitrile **235** in 32% yield. The product was achieved as a mixture of *cis* and *trans* isomers. The formation of **235** was confirmed by ^1H and ^{13}C NMR. The ^1H spectrum exhibited the presence of the amine group at 4.92 ppm, while the ^{13}C NMR spectrum exhibited a new quaternary carbon and the CN signals at 54.3 ppm and 125 ppm, respectively. The ^1H spectrum did not show a spliting of the signals, which is characteristic of a diastereomeric mixture, while in contrast, all of the ^{13}C NMR signals were duplicated (Scheme 81).



Scheme 81. The Strecker reaction and construction of the nitrogen base.

The next step involved the construction of the nucleic base, and therein, compound **235** was treated with (*E*)-3-methoxyacryloyl chloride (**236**), which was previously synthesised using a reported method,[219] and silver cyanate, in a mixture of toluene and DMF, affording **237** in 50% yield. The presence of the newly added moiety was confirmed by ^1H and ^{13}C NMR. The ^1H NMR spectrum showed the quenching of signals corresponding to the amine protons and the presence of new signals at 10.31, 7.72, 5.42, and 3.75 ppm, corresponding to the carbamide protons, the new alkenyl and the OCH_3 group, respectively. The ^{13}C NMR spectrum depicted signals at 168.7 and 155.1 ppm, corresponding to carbonyl groups; 164.3 and 97.1 ppm, corresponding to the double bond carbons; 121.0 and 120.8 ppm, belonging to the nitrile group; and 57.9 ppm, arising from the OCH_3 group.

[218] Gröger, H. *Chem. Rev*. **2003**, *103*, 2795.
[219] Zhang, D.; Miller, M. J. *J. Org. Chem*. **1998**, *63*, 755.

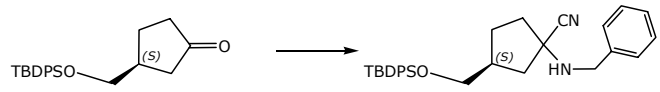
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Compound **237** was treated with sulphuric acid, and subsequently neutralized with sodium hydroxide, in order to acchieve **238**. A complex mixture of products was obtained from this process, and therein, the analysis of the reaction crude did not exhibit any signals corresponding to the nitrogen base.

In order to improve on the obtained results of the Strecker reaction, several methods to improve the yield were explored.

One of these alternative methods involves the synthesis of the imine precursor by reacting **215*S*** with benzylamine in toluene in the presence of 4 Å MS and *p*-toluenesulfonic acid as catalyst.[220] The reaction crude was analyzed by ^{1}H NMR and ^{13}C NMR, and the formation of the imine was confirmed by the presence of the proton signals from the benzylamine, and by the signal at 178.4 ppm, corresponding to the imine carbon. Once the formation of the imine was confirmed, the reaction crude was treated with TMSCN and $ZnCl_2$ in toluene;[220] however the ^{1}H and ^{13}C NMR spectra revealed only traces of the final product, **239** (Table 19, entry 1).

Table 19. Strecker reaction.



215*S* **239**

entry	Conditions	Conversion (%)	Lit
1	1. benzylamine, TsOH, toluene, 4 Å MS, reflux, 24 h 2. TMSCN, $ZnCl_2$, toluene	traces	220
2	benzylamine, TMSCN, I_2, CH_3CN, rt→ reflux, 48h	--	221
3	benzylamine, NaCN, AcOH, DMSO	--	222
4[a]	benzylamine, MK-10, CH_2Cl_2, TMSCN	traces	223
5[a]	benzylamine, KSF, CH_2Cl_2, TMSCN	traces	223
6[a]	1. benzylamine, MK-10, CH_2Cl_2 2. TMSCN	traces	223
7[a]	1. benzylamine, KSF, CH_2Cl_2 2. TMSCN	traces	223

a) All experimental runs were carried out at 300 W in the same amount of solvent. In these conditions, the sample was heated at 70ºC.

[220] Meyer, U.; Breitling, E.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2004**, *15*, 2029.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

The Strecker reaction was then conducted in *one-pot* using TMSCN and benzylamine, with iodine and acetonitrile as the solvent.[221] After 24 h, no new products were detected by TLC. The sample was then heated overnight, and still failed to produce new product (Table 19, entry 2).

The solvent, cyanide, and acid source were changed to DMSO, NaCN and acetic acid, however no new product was observed (Table 19, entry 3).[222]

As per these results, the Strecker reaction was conducted using montmorillonite, which can activate the carbonyl group and remove the water generated in the imine formation process. This methodology has been widely studied and has been successfully applied to several kinds of substrates. Additionally, if the sample is irradiated by microwaves, the reaction can be accelerated.[223] The montmorillonite activation process requires heating in an oven at 160ºC for 5 h.

The first experimental run was conducted using benzylamine, MK-10, and TMSCN in CH_2Cl_2. The reaction mixture was irradiated for 30 min, and no new product was observed. The sample was then irradiated for 1 h, and traces amounts of product were detected when the crude of the reaction was analyzed by NMR (Table 19, entry 4).

The montmorillonite MK-10 was changed to KSF, and similarly as before, the sample was irradiated for 30 min, 1 h, and 2 h reaction times, resulting in only traces of the desired product (Table 19, entry 5).

The reaction strategy was changed, that is, the imine was produced first. The subsequent reaction mixture, consisting of **215*S***, benzylamine, and MK-10 in CH_2Cl_2, was irradiated for 1 h. The reaction mixture was permitted to reach room temperature, TMSCN was added, and the mixture was again irradiated for 1 h; however no changes in the conversion rate were observed. The reaction times were increased for both the imine formation and the subsequent Strecker reaction, and again, failed to improve the conversion rate (Table 19, entry 6). This procedure was repeated using KSF, but the results did not change appreciably (Table 19, entry 7).

The use of NaCN and NH_4OH facilitated the production of aminonitrile with a low yield, while the other attempted procedures were completely unsuccessful. Consequently, alternative approaches are needed to further optimize this reaction.

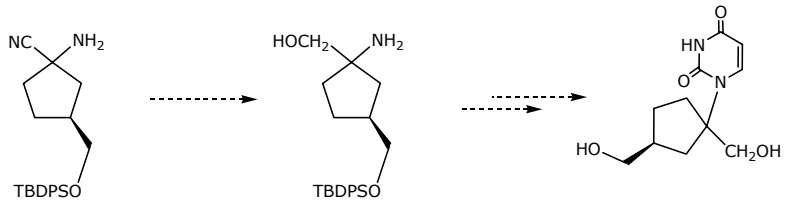
---

[221] Royer, L.; Surya, K. D.; Gibas, R. A. *Tetrahedron Lett*. **2005**, *46*, 4595.

[222] (a) Truong, M.; Lecornué, F.; Fadel, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1063. (b) Hazelard, D.; Fadel, A.; Girard, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1457. (c) Fadel, A.; Khesrani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 305.

[223] (a) Yadav, J. S.; Reddy, S.; Eeshwaraiah, B.; Srinivas, M. *Tetrahedron* **2004**, *60*, 1767. (b) Varma, R. S.; Dahiva, R. *Synlett* **1997**, 1245. (c) Varma, R. S.; Dahiba, R.; Kumar, S. *Tetrahedron Lett*. **1997**, *38*, 2039. (d) Vass, A.; Dudás, J.; Varma, R. S. *Tetrahedron Lett*. **1999**, *40*, 4951.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



235 **240** **241**

Scheme 82. An alternative to the synthesis of branched carbocyclic nucleosides.

The reduction of the aminonitrile to an aldehyde and then to alcohol must yield the hydroxymethylamino-derivative **240**. From this compound, it should be possible to integrate the nucleic base into the amino group, permitting the complete synthesis of branched-carbocyclic nucleosides (Scheme 82).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

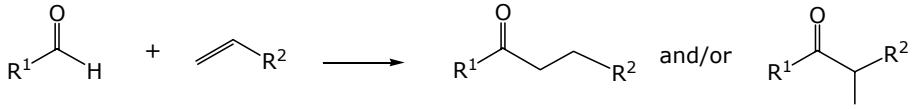
5. Neutral and Cationic Systems in Rh Catalysed Intermolecular Hydroiminoacylation. NMR and DFT studies

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

5.1. ANTECEDENTS

Hydroacylation is an atom-economic, transition metal-catalysed process that yields a ketone from an aldehyde and an alkene in one step, via C-H bond activation of the aldehyde followed by insertion of the olefin (Scheme 83). The synthetic scope of this reaction is limited by the tendency of the metal-acyl intermediates to undergo decarbonylation, affording reduced substrates. This problem can be easily circumvented in the intramolecular version, since the coordination of the alkene to give a chelate facilitates the reaction. After the pioneering work by Sakai[165] on intramolecular hydroacylation, mechanistic studies[166b,168,169,224] were carried out on reactions used for the synthesis of cylopentanones[164,225] and carbocycles of different sizes.[226] An enantioselective intramolecular hydroacylation process was also successfully used for the synthesis of cyclopentanones.[170a,171,172,178,227]



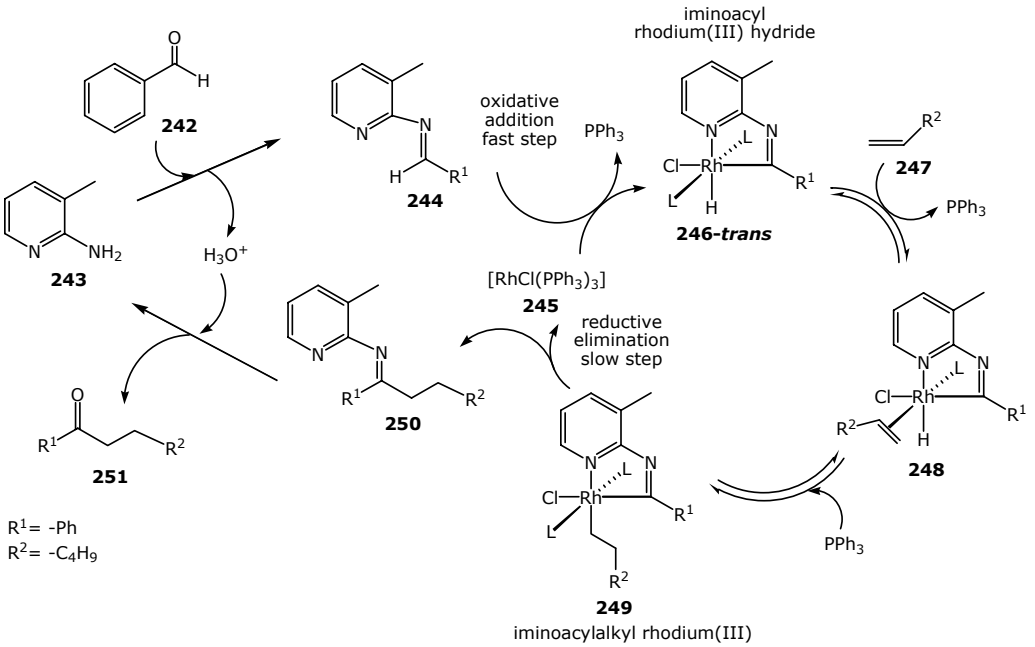
Scheme 83. Intermolecular hydroacylation reaction.

The development of the intermolecular process is, however, much more challenging, probably due to the complexity of avoiding the decarbonylation process. Initially, this process was achieved by completing the reaction under high pressures (or concentrations) of alkene and/or carbon monoxide.[228] Most of the work on intermolecular hydroacylation, however, has focused on modifying chelation procedures to stabilize the metal-acyl intermediate.[163a,229] Chelation assisted by oxygen,[179,230] sulfur,[231] or nitrogen atoms[163a,232] in the aldehyde substrate has been

[224] (a) Campbell, R. E.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824. (b) Milsten, D. *Acc. Chem. Res.* **1984**, *17*, 221.
[225] (a) Sakai, Y.; Ishiguro, K.; Funakoshi, K.; Ueno, K.; Suemune, H. *Tetrahedron Lett.* **1984**, *25*, 961. (b) Funakoshi, K.; Togo, N.; Taura, Y.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1776.
[226] (a) Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* **1991**, *32*, 3473. (b) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1218. (c) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610.
[227] (a) Tanaka, K.; Fu, G. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (b) Tanaka, K.; Fu, G. *J. Am. Chem. Soc.* **2002**, *123*, 10296. (c) Kundu, K.; McCullagh, J. V.; Morehead, A. T. Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042.
[228] Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451.
[229] For a recent review see: Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869.
[230] Miura, M.; Nomura, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 578.
[231] (a) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; McNally, S. J.; Currie, G. S. *J. Org. Chem.* **2006**, *71*, 5291. (b) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7618. (c) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; Currie, G. S. *Org. Lett.* **2005**, *7*, 2249. (d) Willis, M. C.; McNally, S. J.; Beswick, C. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 340.
[232] Wojcicki, A. *Adv. Organomet. Chem.* **1973**, *11*, 87.

reported. Double chelation methods, in which both the aldehyde and the alkene coordinate the rhodium center in a bidentate manner, and alkene-chelation involving an amide group have also been successfully used.[233] The use of anhydrides as acylating reagents[234] or [RhCp*][235] catalysts does not require chelation assistance.

Suggs showed that 2-amino-picoline-derived aldimines react with alkenes in the presence of $[RhCl(PPh_3)_3]$ to give ketimines.[163b] Jung developed a *one-pot* intermolecular hydroacylation procedure that forms, *in situ*, the 2-amino-picoline aldimine derivative, which reacts with an alkene in the presence of Wilkinson's catalyst to yield a ketimine. Later, the ketimine is hydrolyzed within the reaction media to provide the ketone (Scheme 84).[236] This procedure avoids having to use a coordinating atom that is permanently bound to the substrate. This method was also successfully applied in the hydroacylation of alkynes.[237]



Scheme 84. Proposed mechanism for the 2-picoline-assisted intermolecular hydroacylation of alkenes.

[233] (a) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Ogata-Imai, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144. (b) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365. (c) Tanaka, K.; Tanaka, M.; Suemune, H. *Tetrahedron Lett.* **2005**, *46*, 6053.

[234] Hong, T.-K.; Barchuck, A.; Krische, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6885.

[235] Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082.

[236] (a) Park, Y.-J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (b) Jun, C.-H.; Moon, C. W.; Lee, D. Y. *Chem. Eur. J.* **2002**, *8*, 2423. (c) Jun, C.-H.; Lee, D. Y.; Lee, H.; Hong, J.-B. *Angew. Chem. Int. Ed. Engl*. **2000**, *39*, 3070. (d) Jun, C.-H.; Hong, J.-B. *Org. Lett.* **1999**, *1*, 2161.

[237] (a) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B. I. *Angew. Chem. Int. Ed.* **2002**, *41*, 2146. (b) Lee, D. Y.; Hong, B. S.; Cho, E. G.; Lee, H.; Jung, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 6372. (c) Jun, C.-H.; Lee, H. *Pure Appl. Chem*. **2004**, *76*, 577.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

The mechanism of the intramolecular hydroacylation reaction has already been studied using both neutral[224,238] (Wilkinson´s catalyst) and cationic precursors.[224e] The rate-limiting step of this reaction is the reductive elimination of the product. Recently, a detailed computational study provided additional insights into this mechanism.[239] In contrast, the mechanism of intermolecular hydroacylation has been much less studied, but it is thought to be similar to that of the intramolecular version.[6-13] The benzaldehyde was shown to undergo fast oxidative addition to $[RhCl(PMe_3)_3]$, and the resulting hydride intermediate was isolated and characterized.[240] When the reaction was studied using deuterated benzaldehyde and ethene pressure, deuterium in the organic product was found to be present in the methyl and methylene groups in a ratio of 3:2, indicating that the alkene insertion was a reversible process.[228] In another study, reductive elimination was proposed to be the rate-determining step, and the other steps of the catalytic cycle were described as reversible processes.[177,224e,241]

Oxidative addition intermediates were also isolated when aldehydes that are able to form stable chelates were used.[163b] In particular, compound **246-*trans*** (Scheme 84) was isolated and characterized by NMR spectroscopy and X-ray diffraction.[242]

The mechanism of the *one-pot* 2-picoline-assisted intermolecular hydroacylation procedure has not yet been investigated. The catalytic cycle proposed for this reaction involves the following classical steps: the oxidative addition of the aldimine, followed by the coordination and insertion of the alkene into the Rh-H bond of the catalyst and concluded by the reductive elimination of the product and the regeneration of the starting Rh species.[243]

Preliminary studies carried out in our laboratory revealed a strong difference between the catalytic activity of neutral and cationic catalysts in the *one-pot* 2-picoline-assisted intermolecular hydroacylation. Here, we report a comparative mechanistic study of the intermolecular hydroiminoacylation of alkenes with the aldimine **244** and neutral and cationic rhodium complexes using *in situ* NMR techniques and computational DFT-based methods.

[238] Lau, K. Y.; Becker, Y.; Huang, F.; Baenziger, N.; Stille, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 566.
[239] Hyatt, I. E. D.; Anderson, H. K.; Morehead, A. T.; Sargent, A. L. *Organometallics* **2008**, *17*, 135.
[240] Milstein, D. *Organometallics* **1982**, *1* , 1549.
[241] Barnhart, R. W.; Bosnich, B. *Organometallics* **1995**, *14*, 4343.
[242] Albinati, A.; Arz, C.; Pregosin, P. S. *J. Organomet. Chem.* **1987**, *335*, 379.
[243] (a) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (b) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200. (c) Jun, C.-H.; Hoh, C.-W.; Na, S.-J. *Angew. Chem. Int. Ed.* **1998**, *37*, 145. (d) Jun, C.-H. *Chem. Soc. Rev*. **2004**, *33*, 610.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

5.2. RESULTS AND DISCUSSION

5.2.1. Catalysis

In the course of a study of the *one-pot* 2-picoline-assisted intramolecular hydroacylation of alkenes[244] and alkynes,[245] we previously explored the use of Montmorillonite K-10 (MK-10) as a reusable acid catalyst able to catalyze the imine formation and ketimine hydrolysis (see first and last steps in Scheme 83). However, MK-10 can also be used as a solid support for immobilizing and recovering the catalyst.[246]

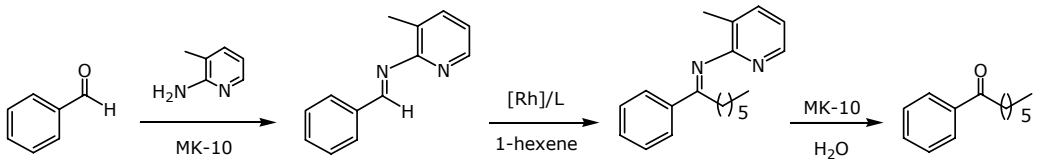
We therefore studied a series of cationic precursors of the formula $[Rh(cod)(L)_2]BF_4$, where L corresponds to phosphine and phosphite ligands, in the presence of 2-amino-3-picoline and MK-10 (Table 20). The hydroacylation reaction described should be considered as a sequence of three successive reactions: the formation of aldimine **244**, the Rh-catalysed hydroiminoacylation leading to ketimine **250**, and the hydrolysis of **250** yielding **251**. The rhodium catalyst is thus only involved in the hydroiminoacylation reaction, while MK-10 catalyzes the two other processes.

Comparing the results shown in entries 1-6, it is apparent that the neutral system $[RhCl(PPh_3)_3]$ (entry 1) provides a much higher conversion than any of the cationic catalytic systems (entries 2-6). Low conversions were obtained when monophosphines with different electronic properties (entries 2-5) were used. When a monophosphite ligand (entry 6) was used, no conversion was observed, probably because the phosphite was hydrolyzed under the reaction conditions. However, when a source of chloride was added to the reaction mixture (entry 7), a conversion comparable to that obtained with the neutral system was achieved (75%).

[244] Yáñez, X.; Claver, C.; Castillón, S.; Fernández, E. *Tetrahedron Lett.* **2003**, *44*, 1631.
[245] Yáñez, X.; Castillón, S. *J. Organomet. Chem.* **2007**, *692*, 1628.
[246] Claver, C.; Fernández, E.; Margalef-Català, R.; Medina, P.; Salagre P.; Sueiras, J. P. *J. Catal.* **2001**, *201*, 70.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Table 20. Rh-catalysed hydroacylation reaction of benzaldehyde with hexene in the presence of $RhClL_3$ and $[Rh(cod)L_2]BF_4$ using of MK-10 as an acid catalyst.[a]



242 **244** **250** **251**

entry	Ligand	Conversion (%)[b]
1[c]	PPh_3	80
2	PPh_3	7
3	$(p\text{-Me-Ph})_3P$	14
4	$(p\text{-F-Ph})_3P$	7
5	Ph_2EtP	9
6	$(MeO)_3P$	0
7[d]	$(p\text{-Me-Ph})_3P$	75
8[d]	dppb	11
9[d]	dppf	7

a) Conditions: Benzaldehyde (2.5 mmol), hexene (12.5 mmol), 2-amino-3-picoline (0.8 mol), $[Rh(cod)L_2]BF_4$ (0.05 mol), free ligand added (0.05 mol), MK-10 (80 mg), toluene (2ml), 110ºC, 2h. b) Conversion expressed as the ratio of **250**+**251** to **242**+**244**. c) $[RhCl(PPh_3)_3]$ as precursor. d) Addition of $BnMe_3NCl$ (0.5 mol).

In light of these results and in order to further investigate the role of neutral or cationic catalysts during the reaction, we decided to focus our study exclusively on the Rh-catalysed hydroiminoacylation reaction in the transformation of **244** into **250**.

Since our previous results indicated that the halogen plays an important role in the reaction, we studied the influence of the type of halide on the hydroiminoacylation reaction (Table 21). Using $PhMe_3N^+X^-$ (X= F, Cl, Br, I) as additives, the highest conversion was obtained with X= Cl (78%) (entry 2, Table 21). Lower conversions were obtained with X= Br (58%) (entry 3) and X= I (46%) (entry 4).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Table 21. Influence of the halide on the intermolecular hydroiminoacylation of 1-hexene with aldimine **244** to give **250** using the catalytic system [Rh(COD)P(*p*-$MeC_6H_4)_2$]BF_4.[a]

entry	Additive	Conversion (%)[b]
1	$PhMe_3NF$	20
2	$PhMe_3NCl$	78
3	$PhMe_3NBr$	58
4	$PhMe_3NI$	46

a) Conditions: aldimine (1.25 mmol), 1-hexene (3.13 mmol), {Rh(COD)[P(*p*-$MeC_6H_4)_3$]$_2$}[BF_4] (0.05 mmol, 4 mol%), 6 mol% of additivive, acetonitrile, 130 ºC, 1 h. b) Conversions determined by Gas Chromatography.

In light of these results, a mechanistic study using *in situ* NMR and DFT calculations was undertaken in order to gain insight into the difference between the neutral and the cationic rhodium systems catalyzing the 2-picoline-assisted intramolecular hydroacylation of alkenes.

5.2.2. Study of the Oxidative Addition Step

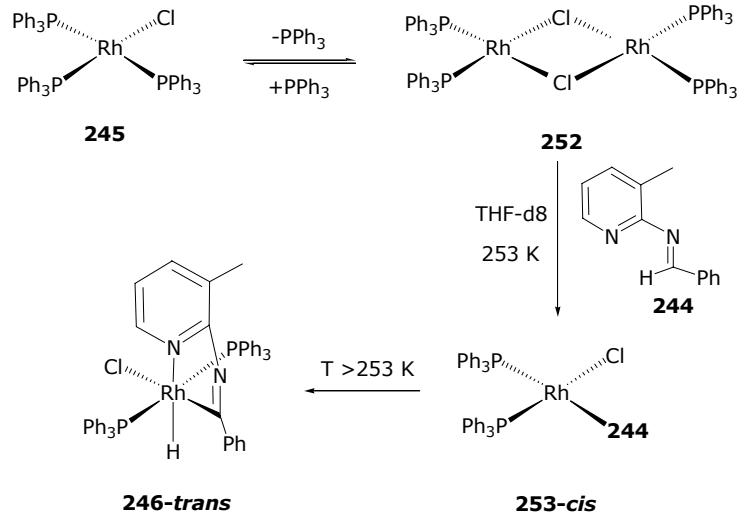
- Neutral system

As mentioned above, the complex RhClH{benzylidene-(3-methyl-pyridine-2-yl)-amine}($PPh_3)_2$ (**246-*trans***) that results from the oxidative addition of **244** to Rh$Cl(PPh_3)_3$ was previously isolated and characterized.[242]

Initially, this process was investigated by NMR spectroscopy. A d_8-THF solution of Rh$Cl(PPh_3)_3$ was charged into a 5 mm NMR tube fitted with a Young's tap. In the corresponding $^{31}P\{^1H\}$ spectrum, signals arising from this complex, the rhodium dimer [Rh(μ-Cl)$(PPh_3)_2]_2$ (**252**), and free PPh_3 were readily detected (Scheme 3). 1 equiv of aldimine **244** was then added at room temperature under inert atmosphere, and a new $^{31}P\{^1H\}$ spectrum was acquired. At this point, a new doublet signal at δ 33.1 (J_{RhP}= 116.6 Hz) was detected as the main species (90%) in solution, and the signal arising from PPh_3 increased in intensity. Small resonances corresponding to Rh$Cl(PPh_3)_3$ were also observed. In the ^1H spectrum, a hydride signal was observed at δ -11.14 and readily assigned to the oxidative addition product **246-*trans***. It was therefore concluded that at this temperature, the oxidative addition reaction occurs very rapidly. When the reaction was repeated at low temperature, no new signals were detected between 193 K and 243 K by ^1H and ^{31}P NMR spectroscopy. However, when the temperature of the sample was increased to 253 K, the signal corresponding to [Rh(μ-Cl)$(PPh_3)_2]_2$ was found to be lower in intensity, and two new mutually coupled signals were detected in the $^{31}P\{^1H\}$ spectrum at δ 54 and δ 50 as doublet of doublets (J_{RhP}= 196 and 170 Hz, J_{PP}= 47 Hz). This result indicated that a new Rh species containing two inequivalent phosphine ligands was formed. In the

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

corresponding ^{1}H spectrum, new low field signals were detected at δ 9.1 (s) and δ 9.0 (dd, J_{HH}= 1.8 and 5 Hz). When a gCOSY spectrum was acquired, the signal at δ 9.0 was correlated to two proton resonances in the aromatic region at δ 7.2 and δ 6.85, and these were assigned to the pyridyl unit of a new aldimine ligand. The high chemical shift of the resonance at δ 9.0 indicated that the pyridyl unit was coordinated to a Rh centre through the N atom. The signal at δ 9.1 was assigned to the N=CHPh group based on its similarity with the signal corresponding to free aldimine. The new compound formed was therefore identified as *cis*-$RhCl(PPh_3)_2$(**244**) (**253-*cis***, Scheme 85). Very similar NMR features were reported for the analogue complex $RhCl(PPh_3)_2$(pyridine).[242,247]



Scheme 85. Reactivity of $RhCl(PPh_3)_3$ in the presence of aldimine **244** in THF.

At this stage, the temperature of the sample was increased to 258 K. In the $^{31}P\{^{1}H\}$ spectrum, the signal corresponding to $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ was not detected, and the resonances for **253-*cis*** increased in intensity. Signals corresponding to the oxidative addition product **246-*trans*** were also detected. At this temperature, these resonances slowly increase in intensity. These observations indicated that the dimer species $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ reacts with **244** to form the intermediate species **253-*cis*** that yields the hydride complex **246-*trans*** at temperatures higher than 253 K (Scheme 85).

[247] (a) Heaton, B. T.; Iggo, J. A., Jacob, C.; Nadarajah, J.; Fontaine, M. A.; Messere, R.; Noels, A. F. *J. Chem. Soc. Dalton Trans*. **1994**, 2875. (b) Retondo, E.; Battaglia, G.; Arena, C. G.; Faraone, F. *J. Organomet. Chem*. **1991**, *419*, 399.

The detection and NMR characterization of species *cis*-RhCl(PPh_3)$_2$(**244**) (**253-*cis***) clearly showed that the oxidative addition step was initiated by the coordination of the aldimine **244** through the nitrogen atom of the pyridyl unit.

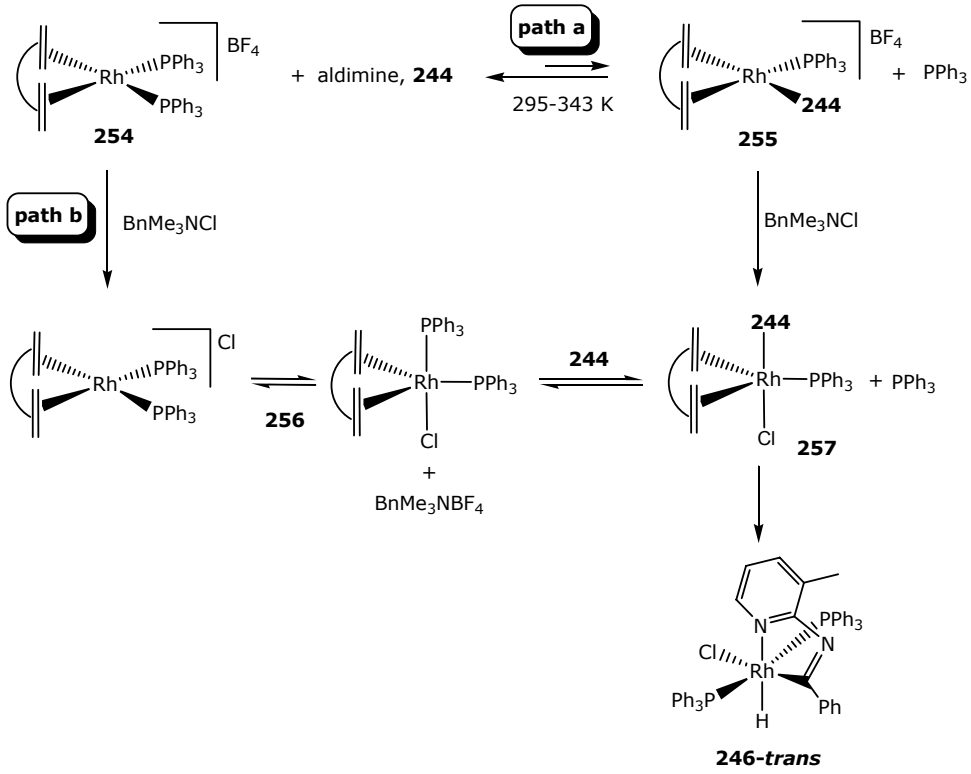
- Cationic system

*Reaction of [Rh(NBD)(PPh_3)$_2$]BF_4 (**254**) in the presence of aldimine **244***

The reactivity of the cationic precursor [Rh(NBD)(PPh_3)$_2$]BF_4 (**254**) in the presence of aldimine **244** was first investigated. A d_8-THF solution containing the complex **254** was charged into an NMR tube, and ^{1}H and ^{31}P{^{1}H} NMR spectra were recorded at room temperature. The expected signals for **254** were readily detected in the ^{31}P spectrum at δ 31.6 (d, J_{RhP}= 156 Hz). In the ^{1}H spectrum, the signals corresponding to the NBD ligand were detected at δ 2.51, δ 4.12, and δ 4.64 as singlet resonances (Table 3). Two equiv of aldimine **244** were then added under inert atmosphere, and a ^{1}H spectrum was immediately recorded at room temperature. The signals corresponding to **244** were readily detected as sharp signals. The resonances corresponding to the NBD ligand of **254**, however, were this time observed as broad signals.

In the corresponding ^{31}P{^{1}H} spectrum, the signal at δ 31.6 was observed as a very broad resonance, and no Rh-P coupling constant could be measured. Although no new product was detected under these conditions, the broadening of the signals of **254** was indicative of a fluxional behavior induced by the presence of **244**. When the temperature of the sample was lowered to 193 K, the ^{1}H and ^{31}P signals corresponding to **254** were detected as sharp signals, indicating that, at this temperature, the fluxional process was reduced. When the temperature of the sample was increased to 295 K, the signals were again observed to broaden. After several hours at room temperature, no new signals were detected and the sample was heated to 333 K. At this temperature, the ^{1}H signals for the NBD ligand of **254** were again detected as broad signals. In the ^{31}P{^{1}H} spectrum, two very broad signals were detected at δ –1.5 and δ 30.2. These resonances were assigned to free PPh_3 and **254** respectively, and it was concluded that a fast equilibrium between **254** and **255** was taking place (Scheme 4). Although the resonance of PPh_3 is usually observed at *ca*. δ -5, while **254** is observed at δ 31.6, a fast equilibrium between these species could explain such a shift. No new signals corresponding to the coordinated aldimine could be detected under these conditions. The involvement of **244** in this process was evident, however, as no such a fluxional behavior was observed in the absence of **244**. The detection of free PPh_3 suggests that substitution of a PPh_3 by **244** had occurred, as described in Scheme 86, path a.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 86. Intermediates in the reaction of cationic complex **254** with aldimine **244** in the absence (path a) and in the presence (path b) of $BnMe_3NCl$.

When the temperature of the sample was increased to 343 K, no new signals were detected by ^1H spectroscopy, and the resonances corresponding to **254** were found to be slightly sharper at this temperature. In the corresponding $^{31}P\{^1H\}$ spectrum, the signals for **254** and free PPh_3 were again detected. At 343 K the former signal was found to be sharper than at 313 K, whereas the resonance for PPh_3 was broader. The absence of hydride signal indicated that no stable oxidative addition product was formed under these conditions.

Reaction of $[Rh(NBD)(PPh_3)_2]BF_4$ (**254**) *in the presence of aldimine* **244** *and $BnMe_3NCl$*

The sample was therefore cooled to room temperature, and 3 equiv of $BnMe_3NCl$ were added under inert atmosphere. When a ^1H spectrum was recorded, signals corresponding to the NBD ligand of **254** were not observed, and three new signals at δ 4.10, δ 3.69, and δ 3.11 were detected and assigned to an NBD ligand of a new species formed under these conditions. In the aromatic region, due to the overlapping of signals arising from PPh_3 ligands, the aldimine **244**, and $BnMe_3NCl$, no clear changes could be observed. In the corresponding $^{31}P\{^1H\}$ spectrum, the signal for **254** was not detected, although a new broad resonance at δ 16.7 was observed as the only signal. It was therefore concluded that a new Rh complex containing at least one chelating NBD and one PPh_3 ligand was formed. Although we detected no signals indicating the presence of coordinated aldimine **244**, a fluxional process such as phosphine exchange could explain the detection of a broad ^{31}P resonance.

When the sample was cooled to 193 K, the ^{31}P signal corresponding to this species was detected at δ 26.9 as a broad peak; however, when the sample was warmed to 343 K, a hydride signal was detected at δ −11.14 as a quartet ($J_{RhH}=J_{PH}$= 13 Hz) and readily assigned to **246-*trans***. In the corresponding $^{31}P\{^1H\}$ spectrum, the doublet signal corresponding to **246-*trans*** was detected at δ 33.1 (J_{RhP}= 116 Hz). The detection of **246-*trans*** indicated that the oxidative addition process had occurred under these conditions.

When the reaction was monitored by ^{31}P NMR spectroscopy, the signal previously detected at δ 16.7 decreased in intensity, while the signal arising from **246-*trans*** increased in intensity. No other signals were detected during the reaction. After several hours at 343 K, total conversion to **246-*trans*** was achieved, indicating that a selective process was taking place. The species corresponding to the ^{31}P signal δ 16.7, formed prior to the formation of the oxidative addition product **246-*trans*** was therefore considered to be an intermediate in the oxidative addition process (Scheme 86, path a).

In order to identify this species, a new experiment was conducted. An NMR tube was first charged with a d_8-THF solution of **254**. ^1H and $^{31}P\{^1H\}$ spectra were recorded at room temperature, and the expected signals for **254** were readily detected. Three equiv of $BnMe_3NCl$ were then added to the solution, and new spectra were recorded. Signals for this reagent were readily detected at δ 3.14 (Me) and δ 4.63 (CH_2Ph) in the corresponding ^1H spectrum. The signals corresponding to the NBD ligand of **254** that were previously detected at δ 4.64, δ 4.12, and δ 2.51 were not observed, however, and three new signals at δ 4.32, δ 3.87, and δ 2.52 were detected. Correlations between these resonances in the corresponding gCOSY spectrum were observed, indicating the presence of a new NBD-containing species. Surprisingly, in

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

the corresponding $^{31}P\{^{1}H\}$ spectrum, no signals could be detected. When the temperature of the sample was decreased to 233K, a new signal was observed by ^{31}P NMR at δ 20.8 as a broad resonance. No other signal was detected at this temperature. At 193K, only one signal was detected at δ 29.9 as a very broad resonance. It was concluded from this experiment that **254** reacts in the presence of $BnMe_3NCl$ to yield a product **256** containing NBD and PPh_3 ligands and exhibiting a highly fluxional behavior under these conditions (Scheme 86, path b). The NMR features observed for **256** match the species described in Scheme 86, path b. Such a fluxional behavior was previously reported for Rh cationic systems containing a weakly coordinated halide ligand.[248]

Table 22. Selected NMR data for the complexes **246-*trans***, **254**, **257 and 256**.

Complex	T (K)	^{1}H NMR		^{31}P NMR		
		ligand	δ in ppm[a]	ligand	δ in ppm	J_{RhP}
246-*trans*	rt	hydride	-11.14 (d of t)	PPh_3	33.1 (d)	116.6
254	rt	NBD	2.51 (s, 2H) 4.12 (s, 2H) 4.64 (s, 4H)	PPh_3	31.6 (d)	156
257	rt			PPh_3	16.7 (bs)[b]	
256	rt	NBD	2.52 (s, 2H)	PPh_3	not observed	--
	233		3.87 (s, 2H)		20.8 (bs)	--
	193		4.32 (s, 4H)		29.9 (bs)	--

a) The ^{1}H NMR spectrum were recorded at rt. b) This signal has been proposed to arise from the average of **257** and free PPh_3, which are in equilibrium.

After the addition of 2 equiv of aldimine **244** to the solution at room temperature, only the signal at δ 16.7 was detected in the corresponding $^{31}P\{^{1}H\}$ NMR spectrum. In light of the high fluxionality of the complexes formed and the large shifts observed in ^{31}P NMR, we concluded that the signal detected at δ 16.7 arose from an average of the signals corresponding to the coordinated PPh_3 ligand from **257** and the free ligand. Indeed, the reported chemical shifts for complexes containing PPh_3, alkenes, chloride, and a nitrogen donor usually lie above 30 ppm, and although such signals were not detected, shifts towards this region were always observed when the temperature was lowered and the ligand exchange rate was thereby reduced.[224b]

[248] (a) Delis, J. G. P.; Aubel, P. G.; Vrieze, K.; van Leeuwen, P. W. N. M. *Organometallics* **1997**, *16*, 2948. (b) Groen, J. H.; van Leeuwen, P. W. N. M.; Vrieze, K. *J. Chem. Soc., Dalton Trans*. **1998**, 113. (c) Romeo, R.; Fenech, L.; Scolaro, L. M.; Albinati, A.; Macchioni, A.; Zuccaccia, C. *Inorg. Chem*. **2001**, *40*, 3293. (d) Albinati, A.; Kunz, R. W.; Amman, C. J.; Pregosin, P. S. *Organometallics* **1991**, *19*, 1800. (e) Gogoll, A.; Ornebro, J.; Grennberg, H.; Backwall, J. E. *J. Am. Chem. Soc*. **1994**, *116*, 3631.

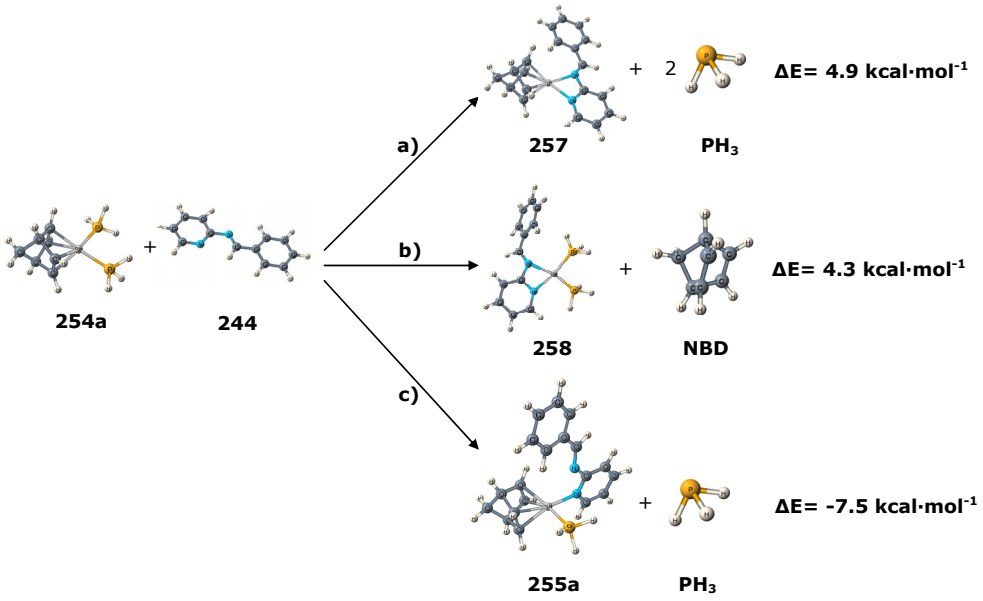
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Upon warming to 313 K, signals corresponding to the hydride complex **246-*trans*** were again detected, indicating that both pathways a and b lead to the same reaction product, as described in Scheme 86.

The results described in this section demonstrate that the oxidative addition of **244** does not yield stable products in the absence of a chloride source; however, in the presence of $BnMe_3NCl$, the hydride species **246-*trans*** formed by oxidative addition of **244** is readily detected as the only organometallic product. This reaction was shown to occur via the formation of the Rh phosphine complex **257**, for which the proposed structure is described in Scheme 86. Another reaction intermediate, namely **256**, formed by reaction of **254** and $BnMe_3NCl$, was also detected by ^{1}H and ^{31}P NMR spectroscopy. It should be noted that, when the reaction of **254** in the presence of the aldimine **244** and $BnMe_3NCl$ was looked at, the species **256** was not detected. This observation indicated **256** is not formed under these conditions or this species reacts very rapidly in the presence of **244**.

5.2.3. DFT Calculations

The thermodynamics of the reaction between the cationic complex $[Rh(NBD)(PPh_3)_2]BF_4$ (**254**) and the aldimine **244** (Scheme 86), previously studied by NMR, were studied with DFT methods (see Experimental section) to gain insight into the identity of the reaction product. PPh_3 was modeled by PH_3 to reduce the computational cost.



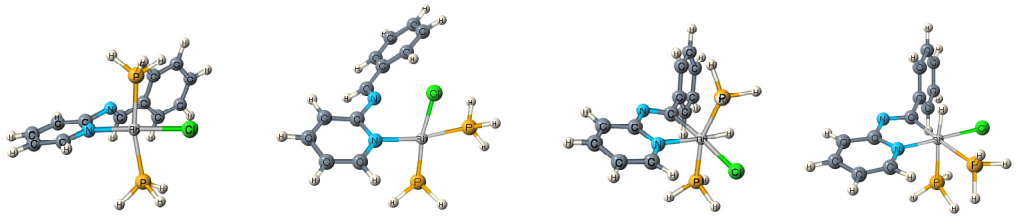
Scheme 87. Reaction pathways in the reaction of $[RhNBD(PH_3)_2]^+$ (**254a**) with aldimine **244**.

In the substitution reaction involving the cationic fragment $[Rh(NBD)(PH_3)_2]^+$ (**254a**) in the presence of aldimine **244,** three reaction pathways are possible (Scheme 87): dissociation of the two phosphines and coordination of the aldimine **244** in a chelate manner (path a), dissociation of NBD yielding $[Rh(PH_3)_2(\kappa^2\text{-}N,N\text{-}\mathbf{244})]^+$ (path b), or substitution of only one phosphine ligand to yield a fragment bearing one PH_3 ligand, NBD, and the aldimine **244** coordinated through the pyridine unit (path c).

In path a, two phosphines are displaced and the cationic species $[Rh(NBD)(\kappa^2\text{-}N,N\text{-}\mathbf{244})]^+$ (**257**) is formed with ΔE= 4.9 kcal·mol^{-1}. In path b, NBD is displaced to yield $[Rh(aldimine)(PH_3)_2]^+$ (**258a**) with ΔE= 4.3 kcal·mol^{-1}, and in path c, the dissociation of one phosphine ligand occurs, providing the species $[Rh(aldimine)(NBD)(PH_3)]^+$ (**255a**) with ΔE= -7.5 kcal·mol^{-1}. Based on these results, paths a and b were shown to be endothermic and, thus, energetically disfavoured; however, the dissociation of only one phosphine ligand and the coordination of the aldimine **244** through the pyridyl unit was shown to be an exothermic process. This result is in agreement with the detection of free PPh_3 in solution by NMR spectroscopy and supports the identity proposed for species **255** as the reaction product (Scheme 86).

The oxidative addition step of the intermolecular hydroacylation was then examined in both neutral and cationic systems. Intermediates and the corresponding transition states were determined for the neutral precursor $[Rh(aldimine)(PH_3)_2Cl]$ (**253a**). Although **255** (Scheme 86) is the only intermediate detected by NMR from the cationic complex **254**, it is reasonable to consider that this species must lose NBD and aldimine or phosphine must coordinate to rhodium before the oxidative addition takes place. Accordingly, we considered two possible structures: complex $[Rh(aldimine)(PH_3)_2]^+$ (**258a**), where aldimine is coordinated in a chelate manner; and complex $[Rh(aldimine)(py)(PH_3)_2]^+$ (**261a**), where aldimine is coordinated only through the pyridinic nitrogen. For the neutral complex **253a**, both the *cis* and the *trans* isomers were investigated. Consequently, for **246a** the relative stability of both the *cis* and the *trans* isomers was also considered (Figure 15). The species **253a** corresponds to the Rh precursor, while **246a** corresponds to the oxidative addition product.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



253a-*trans*
0 kcal·mol^{-1}

253a-*cis*
-3.7 kcal·mol^{-1}

246a-*trans*
-5.4 kcal·mol^{-1}

246a-*cis*
5.9 kcal·mol^{-1}

Figure 15. Molecular structures and energies for isomers *cis* and *trans* of the species **253a** and **246a**.

These results indicated that **253a-*cis***, in which the two phosphine ligands are located in a *cis* fashion, corresponds to the most stable isomer. This result is in agreement with the detection of **253-*cis*** in the NMR experiments. When the PH_3 ligands were in the *cis* position, however, the oxidative addition process was endothermic (9.6 kcal·mol^{-1}), while the process (**253a-*trans*→246a-*trans***) was shown to be exothermic (-5.4 kcal·mol^{-1}). This result is also in full agreement with the NMR experiments described earlier (see Annex for a comparison of the X-ray of **246-*trans*** iodide complex described by Albinati *et al*.[242] as well as DFT geometrical parameters, Figure S1).

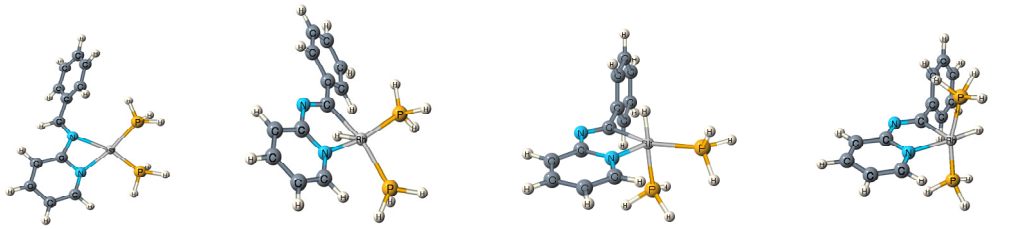
The oxidative addition process for species **253a-*trans*** to **246a-*trans*** was therefore studied. During the transition state search (**259**, Figure 16), a new intermediate was characterized that shows an agostic interaction between the rhodium centre and the C-H bond involved in the oxidative addition process. Note that in this structure the angle between the two phosphine ligands became rather narrow (101.5º) and that the C-H bond was elongated (1.102 Å in free aldimine **244**, 1.412 Å in **259**). This structure was computed to be above the reactant by 10.5 kcal·mol^{-1}. The corresponding transition state (**TS$_{253a\text{-}246a\text{-}trans}$**) was fully characterized and is shown in Figure 16. Here, we noted a close resemblance to the agostic intermediate, especially in regard to the P-Rh-P angle of 117.6º and the C-H bond length (1.759 Å). The energy difference between the transition state and the agostic intermediate is small, only 6.1 kcal·mol^{-1}, indicating the reactant-like nature of this TS. Starting from this TS structure, the geometry relaxed towards the agostic intermediate and the oxidative addition product, thus confirming that **TS$_{253a\text{-}246a\text{-}trans}$** is the transition state for this pathway (Figure 16).

259
10.5 kcal·mol^{-1}

$TS_{253a\text{-}246a\text{-}trans}$
16.6 kcal·mol^{-1}

Figure 16. Molecular structures and relative energies, referred to as **253a-*trans***, for the species involved in the reaction coordinate of the neutral complex.

For the cationic system, the rhodium precursor **258a**, the possible isomers of the oxidative addition products were optimized (**21a-*cis*** and **21a-*trans***), as well as the corresponding transition state. Our results show that the most favored pathway, although endothermic, corresponds to the case where the phosphine ligands of the product are in a *trans* fashion (Figure 17). The relative energy of the transition state **$TS_{258\text{-}21a\text{-}trans}$** was computed to be 21.5 kcal·mol^{-1} above the corresponding reactant **258**.



258
0 kcal·mol^{-1}

$TS_{258\text{-}260a\text{-}trans}$
21.4 kcal·mol^{-1}

260a-*cis*
28.2 kcal·mol^{-1}

260a-*trans*
11.5 kcal·mol^{-1}

Figure 17. Molecular structures and relative energies for **258**, *cis* and *trans* isomers for **260a,** and the corresponding transition state.

Furthermore, as the aldimine **244** is in excess under catalytic conditions with respect to the Rh catalyst, the coordination of a second aldimine molecule to the rhodium centre could not be discarded during the catalytic process. For this purpose, a pyridine molecule was used to model the aldimine in order to reduce the computational cost. As in the previous cases, reactant **261a**, transition state **$TS_{261a\text{-}262a,}$** and the corresponding product **262a** were characterized. In this case, the

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

energy barrier required to reach the TS was calculated to be 18.5 kcal·mol^{-1} (Figure 18).

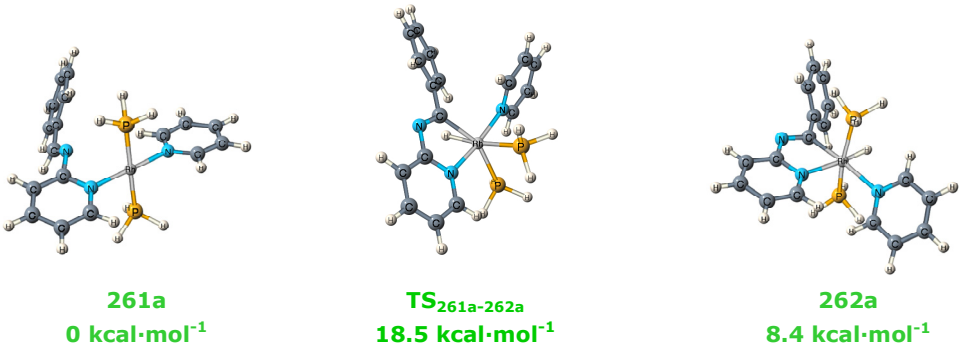


Figure 18. Calculated species involved in the reaction coordinate of cationic complex with pyridine.

In Figure 19, the reaction energy profile is shown for the neutral complex (black line), the cationic (red line), and the cationic with pyridine (green line) complexes. In the neutral pathway, the reaction is initiated by an agostic interaction (**259**) between the rhodium, carbon, and hydrogen involved in the oxidative addition process. The transition state was found to have an energy of 16.6 kcal·mol^{-1} relative to the starting material. The evolution of this TS affords the complex **246a-*trans***, which is the product of the oxidative addition process. The reaction is exothermic, and thus the formation of this product is favored. For the cationic complex **258a** (red line), the energy barrier is higher than for the neutral system (black line), and the reaction is therefore expected to be slower. Furthermore, for this cationic system, the oxidative addition was found to be endothermic, and the formation of the product is therefore disfavored. Moreover, in the cationic-pyridine system **261a**, the energy barrier is lower than in the cationic system but higher than in the neutral system. In both cationic complexes, the reaction is endothermic.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

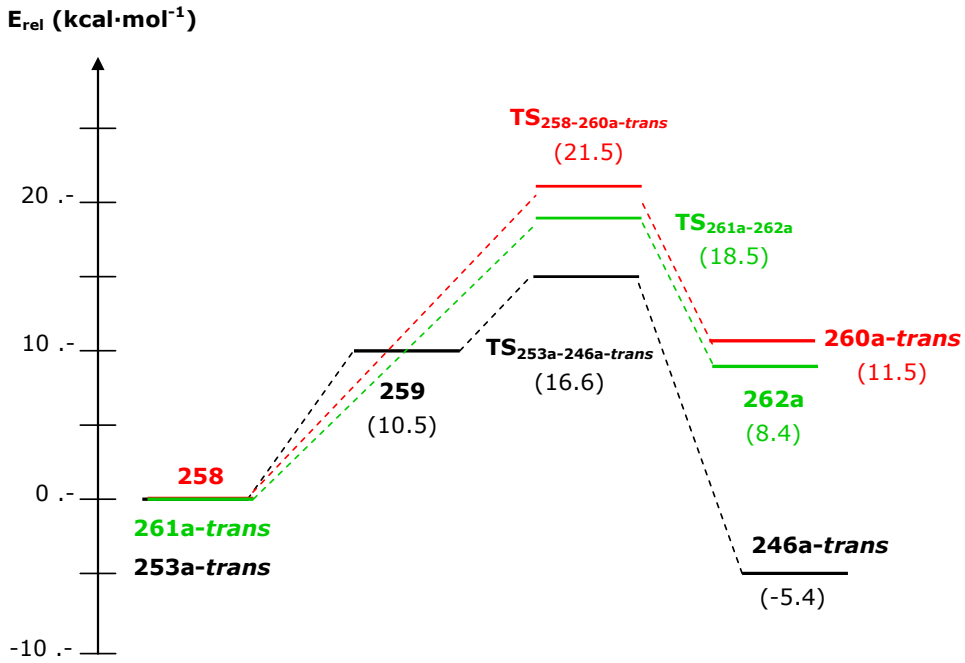


Figure 19. Calculated pathway for the oxidative addition process. Relative energies are given in kcal·mol^{-1} (in parentheses).

It is interesting to note that the transition state geometries are very similar in all three cases; the distances and angles did not present significant differences. The angle between the two phosphorous atoms and the metallic centre (P-Rh-P) and the carbon-hydrogen (C-H) distance involved in the oxidative addition process were the two parameters that changed the most. Regarding the P-Rh-P angle, the most stable transition state **TS$_{253a\text{-}246a\text{-}trans}$** was found to have the widest angle (117.6º); this angle was 90.8º and 95.9º for **TS$_{258\text{-}21a\text{-}trans}$** and **TS$_{261a\text{-}262a}$**, respectively. Moreover **TS$_{253a\text{-}246a\text{-}trans}$** showed the longest C-H bond (1.76 Å), while the **TS$_{258\text{-}21a\text{-}trans}$** and the **TS$_{261a\text{-}262a}$** showed a C-H distance equal to 1.58 Å and 1.51 Å, respectively. This analysis shows that the transition state structure for the neutral complex has the lowest energy and that its structure is closer to the oxidative addition product.

Furthermore, the experimental results show that the use of *cis*-chelating diphosphines reduces catalytic activity (Table 20, entries 8 and 9). Our calculations show that during the oxidative addition, noticeable changes in the angle P-Rh-P are required; such changes simply cannot take place when bidentate phosphines with restricted flexibility are used. For instance, in the neutral system **253a-*trans***, the P-

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Rh-P angle was 168.6º; in the transition to the agostic intermediate **259,** this angle decreased to 101.5º. When the TS was achieved, the angle increased to 117.6º. Finally, in the oxidative addition product **246a-*trans***, this value increased again to 163.2º. Such variations required the use of monodentate phosphines.

This observation could be explained by the coordination of one phosphine with the Rh center under these conditions, which would lower the electronic density of the metal, a key-factor in such an oxidative addition process. Furthermore, the energy barrier is higher in the cationic pathways than in the neutral pathway, and the reaction is therefore slower. Moreover, the oxidative addition product is less stable than the reactants; and its formation is thus disfavoured.

5.2.4. Study of the Alkene Insertion and Reductive Elimination Steps

- Reactivity of 246-*trans* in the presence of styrene

In order to investigate the insertion of styrene into the hydride of **246-*trans***, this compound was prepared according to reported procedures.[242] A 5 mm NMR tube was charged with a solution of **246-*trans*** in d_8-toluene, and 5 equiv of styrene were added under N_2 atmosphere. When ^1H and $^{31}P\{^1H\}$ spectra were recorded at 295 K, only signals corresponding to the reagents were apparent. The temperature was gradually increased to 100ºC, and spectra were recorded at intervals of 10ºC. No changes were observed in the $^{31}P\{^1H\}$ NMR spectra between 295 and 363 K. At 363 K, two new ^{31}P signals were detected at δ 45.5 (d, J_{RhP}= 163 Hz) and δ 52.9 (d, J_{RhP}= 198 Hz). The latter resonance was readily assigned to the previously reported dimeric species $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ (**252**)[249] (Figure 20a). It was concluded that the signal resonating at δ 45.5 and exhibiting a Rh-P coupling corresponded to a newly formed Rh species that contained at least one PPh_3 ligand. After a few minutes at this temperature, the signal corresponding to $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ was not observed, and a new resonance was detected at δ -4.7 (broad singlet), which was readily assigned to free PPh_3. The signal at δ 45.5 and that of free PPh_3 increased in intensity, while the resonance corresponding to the starting complex **246-*trans*** decreased (Figure 20b).

[249] Naaktgeboren, A. J.; Nolte, R. J.; Drenth, W. *J. Am. Chem. Soc.* **1980**, *102*, 3350.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

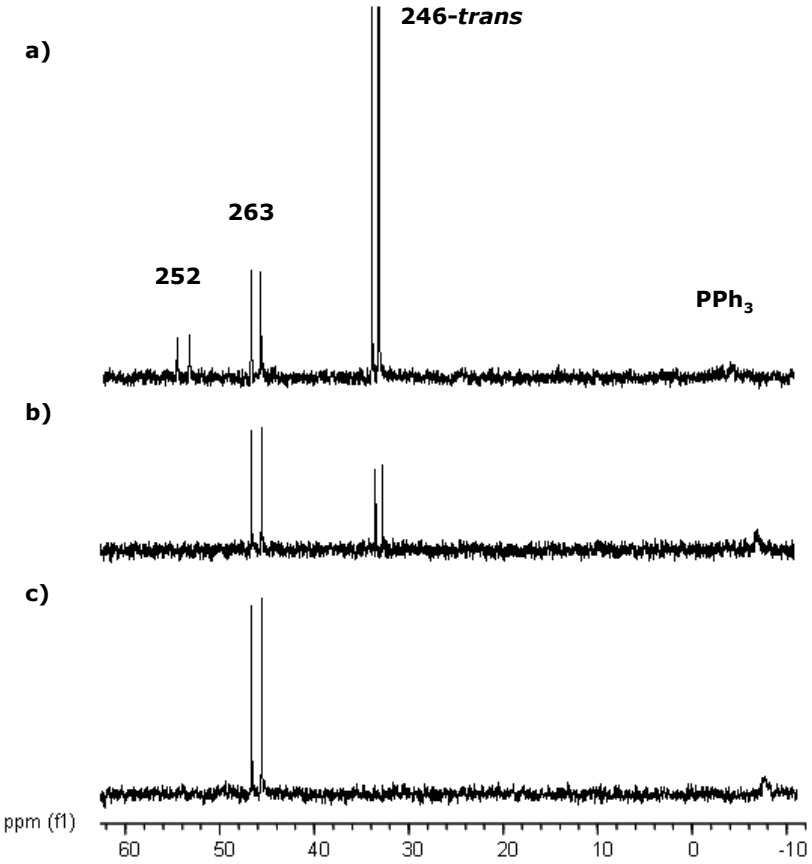


Figure 20. Sequence of $^{31}P\{^{1}H\}$ spectra of a d_8-toluene solution containing **246-*trans*** and styrene: a) at 363 K; b) at 363 K after a few minutes; c) at rt after reaction.

The identity of the new species formed was investigated using ^{1}H, ^{13}C, gCOSY, ^{1}H-^{13}C gHSQC, and ^{1}H-^{13}C gHMBC techniques. The most relevant data are the following: two protons signals at δ 2.75 (dd, J_{HH}= 7 and 14 Hz, 1H) and δ 3.20 (dd, J_{HH}= 8 and 14 Hz, 1H) were found to correlate with a ^{13}C signal at δ 38.1 exhibiting a singlet multiplicity, indicating the presence of a CH_2 unit; one ^{1}H resonance at δ 3.13 (q, J_{HH}= 8 Hz, 1H) was correlated with a doublet ^{13}C signal at δ 52.4 (J_{RhC}= 15.5 Hz), and phase discrimination indicated the presence of a CH unit; gHMBC analysis showed that the latter unit was neighboring the previously mentioned CH_2 unit and another group containing a quaternary carbon atom that resonated at δ 86.1 as a doublet (J_{RhC}= 15.5 Hz).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

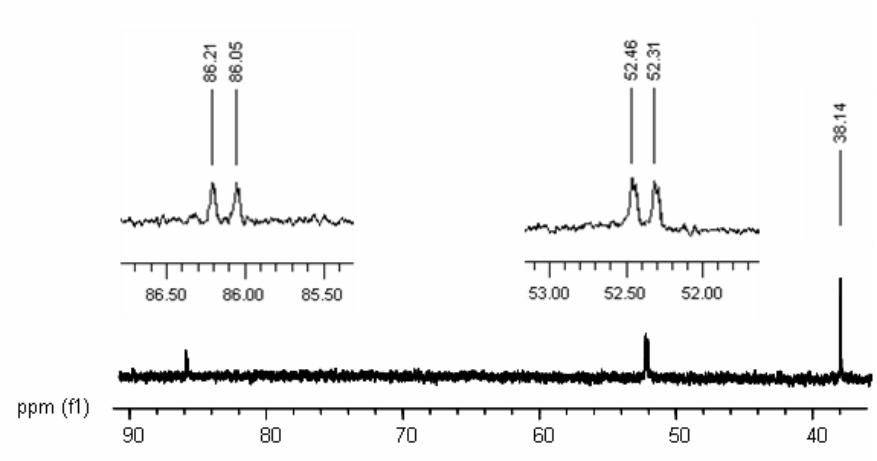


Figure 21. Selected region of the $^{13}C\{^{1}H\}$ spectrum of **263** at rt.

The higher chemical shift for the latter resonance (86.1 ppm) indicated the presence of a neighboring heteroatom. Furthermore, the detection of the signals at δ 52.4 and δ 86.1 as Rh-coupled resonances indicated that the corresponding carbon atoms were bound to the Rh center. It was therefore concluded that a $-CH_2-CH=C(R')N-$ unit was contained in the new product and was bound to the Rh center through the C=C double bond in a η^2-fashion. The absence of P-C coupling suggested that the vinylic moiety is situated in *cis* position in relation to the phosphine ligand(s). After analysis of the NMR spectra, the product was identified as $RhCl(PPh_3)$(**264a**) (**263**, Figure 22). To the best of our knowledge, this intermediate has not yet been reported.

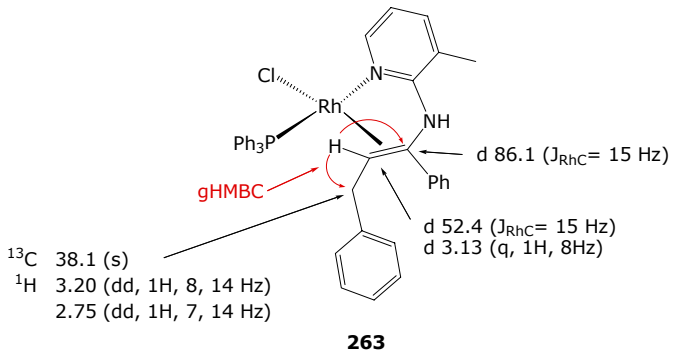
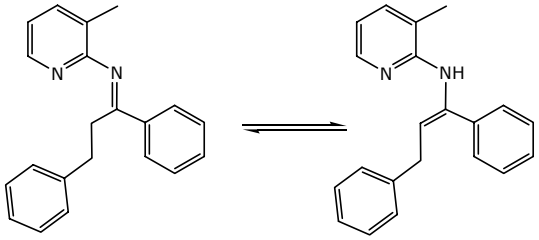


Figure 22. Relevant NMR data for complex **263**.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

The detection of this species reveals a tautomerism process between the organic substrates **264** and **264a** (Scheme 88).



264 **264a**

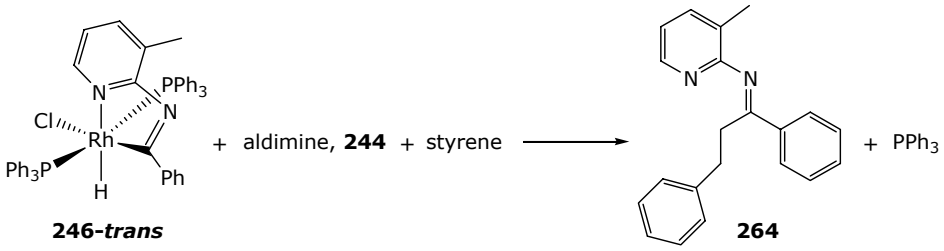
Scheme 88. Tautomerism of **264**.

When the temperature of the sample was increased to 373 K, the intensity of ^{31}P signals corresponding to the starting complex **246-*trans*** and to the dimeric species $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ (**252**) rapidly decreased, while those of **263** and free PPh_3 increased. After two hours at this temperature, the only Rh species detected in solution was **263**. When the temperature of the sample was decreased to 295 K and the sample was taken out of the NMR spectrometer, red crystals were observed at the bottom of the NMR tube. X-ray analysis of these crystals confirmed the identity of the complex $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$. Under these conditions complex **263** is the final product.

- Reaction of 246-*trans* in the presence of styrene and aldimine 244

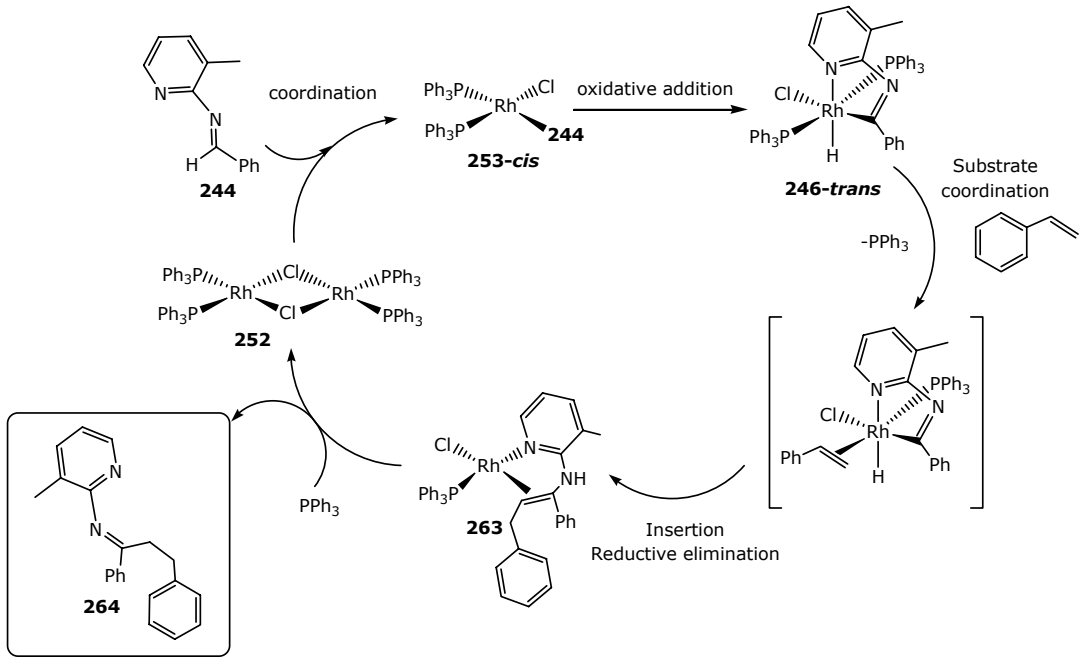
In order to investigate the effect of the presence of excess substrate, the reaction was repeated in the presence of 5 equiv of aldimine **244**. The temperature was gradually increased to 373 K, and the reaction was monitored by ^{1}H and ^{31}P NMR spectroscopy. As previously observed, the presence of free PPh_3 ligand in solution was observed at 353 K. Even at higher temperatures, however, no new ^{31}P signals were detected. At 363 and 373 K, the signal corresponding to the starting complex **246-*trans*** decreased in intensity, while that corresponding to free PPh_3 proportionally increased. Even after a few hours at 373 K, however, the signal corresponding to **246-*trans*** was still visible. In the ^{1}H spectrum, the only new signals detected were assigned to the organic product **264** formed by the catalytic reaction (Scheme 89). These results indicate that in the presence of aldimine in solution, the decoordination of the product from the Rh centre is a fast process.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008



Scheme 89. Reaction of **246-*trans*** styrene in the presence of aldimine **244**.

Based on these results, the catalytic cycle described in Scheme 90 is proposed.

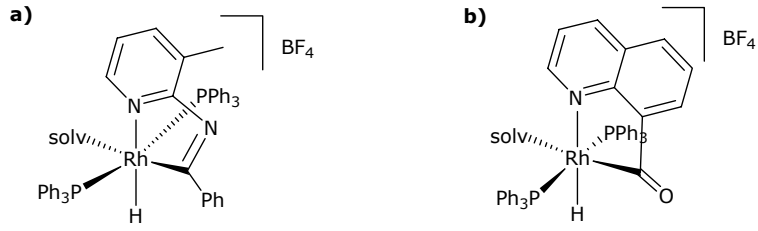


Scheme 90. Proposed catalytic cycle for the hydroiminoacylation of styrene catalysed by neutral Rh systems.

5.2.4. Formation of Cationic Rhodium Hydride Complex from 246-*trans* and Study of the Reactivity with Styrene

- Formation of cationic rhodium hydride complexes

In order to form cationic rhodium hydride complexes *in situ* and probe their reactivity toward the reagents involved in the hydroiminoacylation reaction, an NMR tube charged with the complex RhClH{benzylidene-(3-methyl-pyridine-2-yl)-amine}(PPh_3)$_2$ (**246-*trans***) was dissolved in CD_2Cl_2 and cooled to 194 K; then 1 equiv of $AgBF_4$ was added. The tube was quickly transferred into the NMR spectrometer that had been pre-cooled to 193 K, and ^1H and $^{31}P\{^1H\}$ spectra were recorded; only signals corresponding to the starting complex **246-*trans*** were observed (Figure 24a). The tube was then briefly taken out of the spectrometer, shaken at room temperature for a short time, and re-inserted into the NMR probe. In the ^1H spectrum recorded at 193 K, a hydride signal was then detected at δ -10.9 (dt, J_{RhH}= 16 Hz, J_{PH}=9 Hz). In the corresponding $^{31}P\{^1H\}$ spectrum, a new signal was detected at δ 36.8 (d, J_{RhP}= 114 Hz). The tube was warmed in the same manner a few times, and the reaction was monitored by NMR spectroscopy. The new signals increased in intensity, while the signals for **246-*trans*** decreased in the same proportion (Figure 24b). The new hydride product was found to exhibit similar spectral features to those of **246-*trans***, indicating small structural differences with **246-*trans***. The multiplicity of the hydride signal indicated that this species contained 2 equiv PPh_3 ligands. When temperature of the sample was slowly increased to room temperature, the broadening of the NMR signals for the new complex was observed, and at 293 K, the presence of bulk rhodium metal in the sample was evident, indicating the decomposition of the complex. The new complex was identified as **260-*trans*** (Figure 23a) with one solvent molecule coordinated to the rhodium centre. The instability of this species upon warming is in contrast to the report of Suggs, which described an analogue Rh hydride complex **265** containing a chelating acyl-quinonoline moiety as an indefinitely stable species at room temperature (Figure 23b).[163a]



260-*trans* **265**

Figure 23. Rhodium hydride complexes obtained by reacting the oxidative addition products with $AgBF_4$: a) characterized in this study; b) reported by Suggs.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

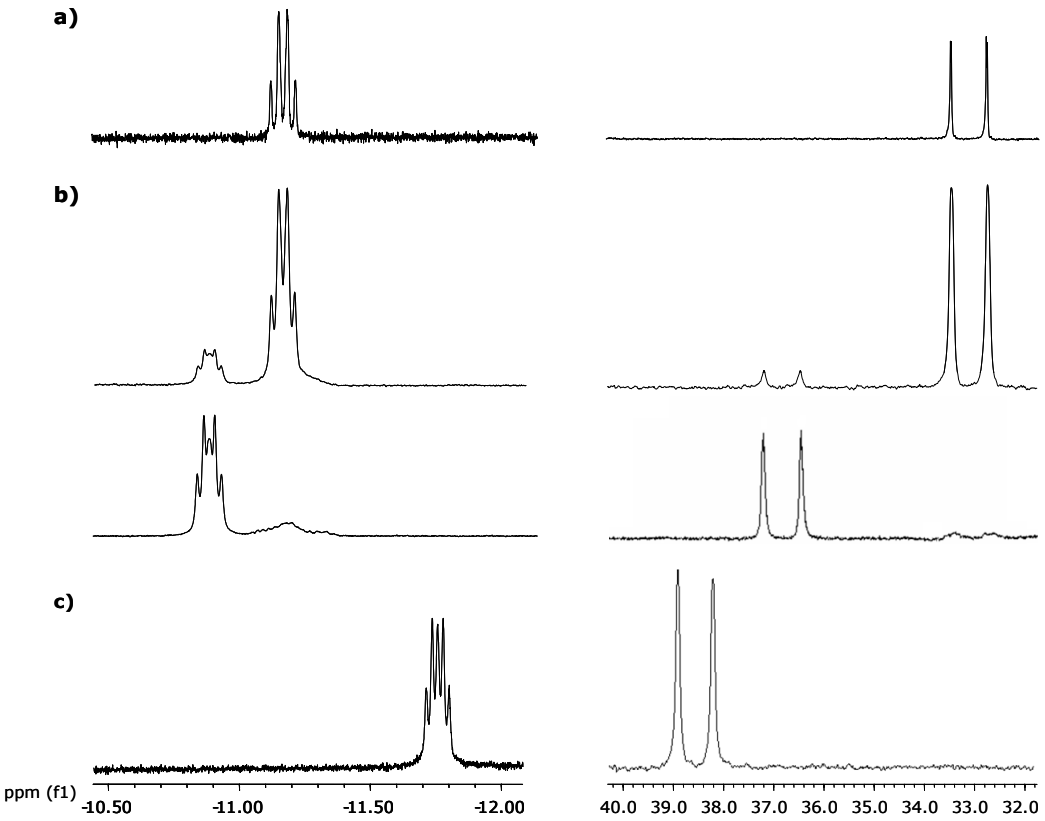
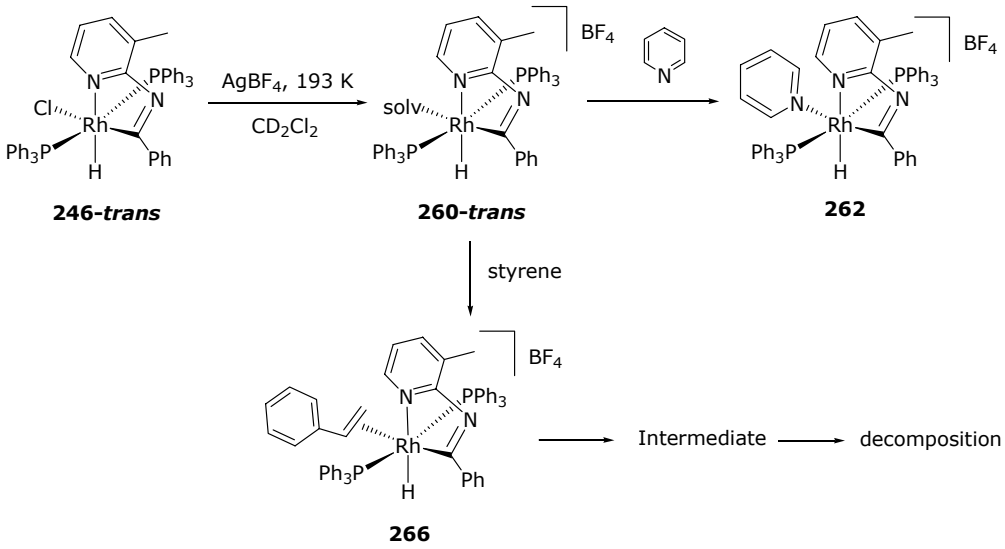


Figure 24. a) ^{1}H and $^{31}P\{^{1}H\}$ of **246-*trans*** in CD_2Cl_2. b) ^{1}H and $^{31}P\{^{1}H\}$ of **260-*trans*** formation in CD_2Cl_2. c) ^{1}H and $^{31}P\{^{1}H\}$ of cationic complex with pyridine **262** in CD_2Cl_2.

In order to probe the presence of a solvent molecule in this complex, the reaction was repeated, and 5 equiv of pyridine were added to the solution at low temperature. When new ^{1}H and $^{31}P\{^{1}H\}$ spectra were recorded, new signals corresponding to a new rhodium hydride complex were detected. In the $^{31}P\{^{1}H\}$ spectrum, a new doublet signal was detected at δ 38.5 (J_{RhP}= 114 Hz). In the ^{1}H spectrum, a new hydride signal was evident as a doublet of triplet at δ -11.8 (J_{RhH}= 16 Hz, J_{PH}= 9 Hz) (Figure 24c). A set of new aromatic peaks was also detected. When the temperature was slowly increased, some of the aromatic resonances were observed to coalesce; we attributed this effect to the rotation of a pyridine ligand. At room temperature, the signals corresponding to the new species were found to slightly broaden, but the complex was found to be stable for a few hours under these

conditions. This new species was fully characterized by NMR spectroscopy and identified as **262** (Scheme 91).



Scheme 91. Formation of cationic hydride rhodium complexes **260-*trans***, **262** and **266**.

- Reaction of [RhH{benzylidene-(3-methyl-pyridine-2-yl)-amine}(PPh_3)$_2$(solv)][BF_4] (**260-*trans***) *in the presence of styrene*

In order to investigate the reactivity of **260-*trans*** in the presence of styrene, an NMR tube was charged with **246-*trans*** in CD_2Cl_2 and reacted with $AgBF_4$ *in situ*. The formation of **260-*trans*** was monitored by ^{31}P NMR spectroscopy. 3 equiv of styrene were then added at 193 K, and the tube was transferred into the pre-cooled spectrometer at 193 K. The temperature of the sample was then gradually increased, and the reaction was monitored by ^{1}H and ^{31}P NMR. No new products were detected up to 233 K. At 243 K, a broad ^{31}P signal was detected at δ 36.75 (d, J_{RhP}= 110 Hz). In the corresponding ^{1}H spectrum, a new broad hydride signal was detected at δ -10.24. These signals were assigned to the alkene complex RhH{benzylidene-(3-methyl-pyridine-2-yl)-amine}(PPh_3)$_2$(η^2-styrene)][BF_4] (**266**). Upon warming the sample, a new hydride was detected at δ -10.66. Two new doublet signals were also detected in the $^{31}P\{^{1}H\}$ spectrum at δ 18.6 (d, J_{RhP}= 75 Hz) and δ 14.1 (d, J_{RhP}= 75 Hz). At 295 K, the hydride signal resonating at δ -10.24 rapidly decreased, while the intensity of the signal at δ -10.66 increased. After a few minutes, the signals corresponding to **266** could not be detected. Upon increasing the temperature, the ^{31}P signals resonating at δ 18.6 and δ 14.1 were found to broaden and finally to coalesce at δ 16.5 at 295 K (Scheme 91). At this temperature, however, all the

signals were found to broaden rapidly, and rhodium metal was observed in the NMR tube, indicating that the species present in solution were decomposing. The identity of the hydride species could not be determined; however, the presence of a hydride ligand indicated that the insertion of styrene into the Rh-H bond of **266** had not occurred. After a few hours at 295 K, the hydride signal was not observed, although the ^{31}P signal resonating at δ 16.5 was still detected, indicating that this signal was not correlated with the previously mentioned hydride species. No evidence for the formation of a new Rh species or the organic catalytic product was obtained when a $^{13}C\{^{1}H\}$ spectrum was acquired at this temperature. It was therefore concluded that the insertion of styrene into the Rh-H bond of the cationic system is a slow process, in contrast to the neutral system, for which this step is rapid and yields the intermediate **263**.

In conclusion, both cationic and neutral rhodium catalyst precursors were studied in the hydroiminoacylation of alkenes. Catalytic runs were performed using cationic systems and revealed to be poorly active under the reaction conditions used in this study. This observation was in contrast to the reported results for neutral rhodium systems under similar conditions, prompting us to investigate the mechanism of both reaction systems by NMR spectroscopy and DFT methods.

The oxidative addition step was studied using both NMR and DFT techniques. Using the neutral complex, this step is a thermodynamically favored process, as demonstrated by the isolation of the stable complex **246-*trans***. Furthermore, DFT calculations showed the existence of an agostic intermediate on the route to the CH activation product. In the cationic system, the oxidative addition reaction was shown by DFT calculations to be an endothermic process. This result was in agreement with the results obtained by NMR, in which an oxidative addition product was only detected in the presence of a chloride source. The precursor of oxidative addition formed after the addition of chloride has been identified as **257**.

Furthermore, the transition states involved in both systems were identified using DFT calculations, which demonstrated that the presence of chloride not only stabilizes the oxidative addition product but also lowers the energy barrier of the overall process.

The alkene insertion step was also studied using both systems with styrene as substrate. When the reaction was investigated in the absence of excess aldimine **244**, the complex **263** was detected as the main reaction intermediate in solution and fully characterized by multinuclear NMR spectroscopy. This result indicates that, in the absence of aldimine, the decoordination of the product is a slow process. This novel species was not detected, however, in the presence of **244**, and the detection of **246-*trans*** during the overall NMR experiment suggested that **246-*trans*** was the resting state of the catalytic process under these conditions. In the cationic system, the rhodium hydride styrene intermediate **266**, which corresponds to the alkene

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

coordination product from **260-*trans***, was detected and characterized by NMR spectroscopy. No evidence for alkene insertion was achieved, however, indicating that this reaction is a slow process. In contrast to the experiment performed with the neutral system, a large amount of metallic rhodium was formed during the reaction.

Using the neutral system, the stable complex $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ (**252**) was formed after reductive elimination of the organic product. This species was reported to be a precursor for the oxidative addition step, from which the catalytic cycle can be again initiated; however, in the cationic system, no stable rhodium species were detected, and the system quickly evolved towards decomposition.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

6. Conclusions

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

CONCLUSIONS

A new methodology in the synthesis of carbocyclic nucleosides has been performed using as a key step the enantioselective intramolecular hydroacylation reaction. The mentioned reaction leaded to the cyclopentanone **215** in good yields and excellent enantioselectivities. When (*S*,*S*)-Me-Duphos was used the 3*S*-cyclopentanone **215** was obtained, in contrast whether the (*R*,*R*)-Me-Duphos was employed the reaction proceed giving the opposite enantiomer. In both cases, the yield and the enantioselectivities were the same and the reaction was strictly reproducible.

The diastereoselective transformation of an important substrate in the carbocyclic nucleoside synthesis has been carried out by dynamic kinetic resolution of the cyclopentanol **224a**. Depending on the diastereomer used as starting material the *cis* or *trans* product was obtained. When **224a(1*R/S*,3*S*)** was employed the *trans* isomer was achieved. In contrast, the DKR of **224a(1*R/S*,3*R*)** lead to the *cis* isomer in an excellent conversions and diastereoselectivities. Then the hydrolysis of the acetate will afford the cyclopentanol in a straightforward way.

Moreover the diastereomeric reduction of the hydroxycyclopentanones **228*S*** and **228*R*** was performed using $NaBH(OAc)_3$ in good yields obtaining the enantiomers **229(1*S*,3*S*)** and **229(1*R*,3*R*)** depend on the starting material in excellent diastereoselectivities. Subsequently Mitsunobu reaction and posterior cleavage of the protecting group lead to the nucleoside in the desired configuration.

Both cationic and neutral rhodium catalyst precursors were studied in the hydroiminoacylation of alkenes. The oxidative addition step was studied using both NMR and DFT techniques. Using the neutral complex, this step is a thermodynamically favoured process, as demonstrated by the isolation of the stable complex **246-*trans***. Furthermore, DFT calculations showed the existence of an agostic intermediate on the route to the C-H activation product. In the cationic system, the oxidative addition reaction was shown by DFT calculations to be an endothermic process, hence unfavourable. This was in agreement with the NMR experiments, in which an oxidative addition product was only detected in the presence of a chloride source. The precursor of oxidative addition formed after the addition of chloride has been identified as **257**.

Furthermore, the transition states involved in both systems were identified using DFT calculations, which proved that the presence of chloride not only stabilize the oxidative addition product but also lower the energy barrier of the overall process.

Using the neutral system, the stable complex $[Rh(\mu\text{-}Cl)(PPh_3)_2]_2$ (**252**) was formed after reductive elimination of the organic product. This species was reported as a precursor for the oxidative addition step, from which the catalytic cycle can start

again. However in the cationic system, the system did not yield any stable rhodium species and quickly evolved towards decomposition.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

7. Experimental Section

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

EXPERIMENTAL SECTION

General Remarks

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4®). The other solvents were purified using standard procedures.[250] ^1H and ^{13}C NMR spectra were recorded on a Varian® Gemini 300 (300 MHz and 75 MHz respectively) or in a Varian® Mercury 400 (400 MHz and 100 MHz respectively) spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm) or H_3PO_4 (^{31}P) as external standard, unless otherwise specified. 2D correlation spectra (TOCSY, gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. Elemental analysis (C, H, N, S) was performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Científics (SRCiT-URV). Analytical thin layer chromatography (TLC) was performed on Merck® silica gel 60 F_{254} glass or aluminium plates. Compounds were visualized by UV (254 nm) irradiation or dipping the plate in a suitable developing solution.[251] Flash column chromatography was carried out using forced flow or by gravity of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1, 2, or 4 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Medium-pressure liquid chromatography (MPLC) was performed using SDS® silica gel 60 A CC (6-35μm).

All the staring materials, reagents, MK-10 and phosphines used were purchased from Fluka or Aldrich and used without further purification except the aldehydes, which were distilled prior to use. The catalytic reactions were monitored by GC on a Hewlett-Packard 5890A. Conversion was measured in an HP-5 column (25 m x 0.2 mm ∅). The oven temperature was set to 80ºC for 0.5 min and then increased 10ºC/min to 280ºC.

All complexes were synthesised using standard Schlenck techniques under nitrogen atmosphere. The precursor catalysts were purchased from Strem Chemicals and $AgBF_4$ from Sigma-Aldrich; both were used without further purification. The complexes $[Rh(COD)(MN(R))]BF_4$ and $[Rh(COD)(M(R))]BF_4$ were provided by

[250] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1989**.
[251] Reactivos Merck "Reactivos de coloración para cromatografía en capa fina y papel" E. Merck. Darsmtadt (RF Alemana) **1980**.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

Degussa. Compound **246-*trans*** was prepared according to literature methods.[242] All the deuterated solvents of grade 99.8%D packed in sealed ampoules were purchased from Euriso-top.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

General Procedures:

General procedure for C-N coupling catalysed by palladium

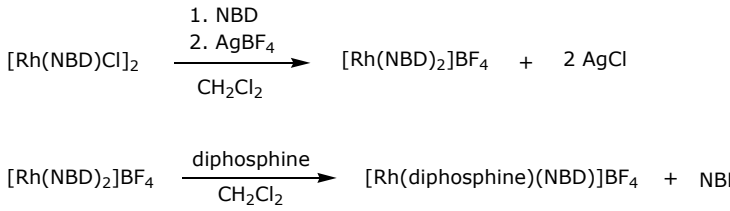
Method A: An oven-dried Schlenk tube with a magnetic stir bar under argon atmosphere was charged with Xantphos, $Pd(dba)_2$ or (Xantphos)Pd(*p*-C_6H_4CN)(Br) and Cs_2CO_3 or NaO^tBu (1.4 mmol) and dioxane (1 M) or toluene (0.25 M). After 1 min a solution of 1-iodo-3,4,6-tris-*O*-(triisopropylsilyl)-D-glucal (1 mmol) and the benzimidazole in the appropriate solvent was added (2 M) under argon. The tube was evacuate, back-filled with argon and capped with a rubber septum. The flask was immersed in a preheated bath at 90ºC and stirred for 24 h. Then was allowed to cool to rt, diluted in hexane and filtered through celite. The filter cake was being further washed with hexane. The filtrate was concentrated in vacuo to yield a residue which was analyzed by NMR.

Method B: An oven-dried Schlenk tube with a magnetic stir bar under argon atmosphere was charged with (Xantphos)Pd(*p*-C_6H_4CN)(Br) in toluene then a solution of **172** in toluene was added (2 M) under argon. A solution of a preformed potassium benzimidazolate in toluene (2M) (a solution of benzimidazole was treated with 1 equiv of KH in THF. Then the solvent was removed to add the toluene). The tube was evacuate, back-filled with argon and capped with a rubber septum. The flask was immersed in a preheated bath at 90ºC and stirred for 24 h. Then was allowed to cool to rt, diluted in hexane and filtered through celite. The filter cake was being further washed with hexane. The filtrate was concentrated in vacuo to yield a residue which was analyzed by NMR.

General procedure for C-N coupling catalysed by copper. After standard cycles of evacuation and back-fill with dry and pure argon, and oven-dried Schlenk tube was equipped with a magnetic stir bar was charged with CuI, ligand (in all cases the Cu:L ratio was 1:2), the benzimidazole (1.5 mmol) and Cs_2CO_3 (2 mmol) and the solvent was added (2 M respect to the copper precursor). A solution of 1-iodo-3,4,6-tris-*O*-(triisopropylsilyl)-D-glucal (1 mmol, 2.5 M in the solvent employed) was added at rt. The tube was evacuate, back-filled with argon and capped with a rubber septum. The mixture was heated in a bath at 110ºC (preheated to the required temperature) for the required time period. The reaction was carried out for 24 h. The reaction mixture was allowed to cool to rt, diluted in CH_2Cl_2 and filtered through celite. The filter cake was being further washed with CH_2Cl_2. The filtrate was concentrated in vacuo to yield a residue which was analyzed by NMR.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

General procedure for synthesising [Rh(NBD)(diphosphine)]BF_4 complexes[159]



[Rh(dppe)(NBD)]BF_4: [Rh(dppe)(NBD)]BF_4 was prepared according to the procedure of Bosnich *et al*.[164] To a solution of [Rh(NBD)Cl]$_2$ (1.54 g, 3.34 mmol, 1 equiv) in deoxygenated CH_2Cl_2 (50 ml) was added norbornadiene (0.914 g, 9.92 mmol, 3 equiv) freshly distilled from activated alumina. Then silver tetrafluoroborate (2.57 g, 10.0 mmol, 3.0 equiv) was added to the above solution in one portion. The deep red solution, with a white precipitate, was stirred at room temperature overnight. The reaction was filtered through Celite under argon, THF (10 ml) was added, and the volume was reduced to 5 ml. Upon standing, red-orange crystals formed which were collected by filtration and dried under vacuum to afford [Rh(NBD)$_2$]BF_4 (1.66 g, 60%).

To a solution of [Rh(NBD)$_2$]BF_4 (1.54 g, 3.52 mmol, 1 equiv) in deoxygenated CH_2Cl_2 (0.25 M) the corresponding diphosphine (1.4 g, 3.50 mmol, 0.995 equiv) was added over the course of one minute. The resulting ruby-red solution was stirred at room temperature for 10 min and then filtered through Celite under Argon. The volume of the filtrate was reduced to 5 ml and ether (0.7 M) was added dropwise. The resulting solution was stored at -10ºC overnight. The crystals formed were filtered, washed (10:1 ether:CH_2Cl_2), and dried under vacuum to afford [Rh(diphosphine)(NBD)]BF_4.

The spectroscopic data for the complexes [Rh(dppe)(NBD)]BF_4,[252] [Rh(Me-Duphos)(NBD)]BF_4,[252] [Rh(DPPF)(NBD)]BF_4[253] obtained by this methodology were consistent with those reported.

General procedure for intramolecular hydroacylation using Wilkinson's catalyst. The solvent (CH_2Cl_2) was dried and degassed immediately prior to use by bubbling argon for at least 10 min. A solution of 4-pentenal (0.1 g, 0.28 mmol) in CH_2Cl_2 (1 ml) was added dropwise to the stirred solution 0.08 M of $RhCl(PPh_3)_3$ in CH_2Cl_2 (1.77 ml). The reaction was monitored by TLC (hexane:EtOAc 5:1). When the reaction was completed the solution was concentrated in vacuo. The resulting residue was dissolved in ether and the precipitated formed was filtered off. After

[252] Drexler, H.-J.; Baumann, W.; Spannenberg, A.; Fischer, C.; Heller, D. *J. Organomet. Chem*. **2001**, *621*, 89.
[253] Brown, J. M.; Chalonder, P. A.; Kent, A. G.; Murrer, B. A.; Nicholson P. N.; Parker, D.; Sidebottom, P. J. *J. Organomet. Chem*. **1981**, *216*, 263.

removal of the solvent, the residue was purified by column chromatography on silica gel to afford the cyclopentanone (hexane:EtOAc 20:1 to 5:1).

General procedure for intramolecular hydroacylation using cationic catalysts. The solvent (acetone) was dried and degassed immediately prior to use by bubbling argon for at least 10 min. A solution of 0.04 M of rhodium catalyst was prepared, then hydrogen was bubbled through the [Rh(diphosphine)(NBD)]BF_4 solution for 5 min. Afterwards the solution was stirred for 15 min before the argon was bubbled through for 5 min to purge the hydrogen gas. A solution of 4-pentenal (0.1 g, 0.28 mmol) in 2 ml of acetone was added dropwise to the stirred solution of [Rh(diphosphine)(solvent)$_2$]BF_4 under Ar atmosphere. The reaction was monitored by TLC (hexane:EtOAc 5:1). When the reaction was completed the solution was concentrated in vacuo. The remaining residue was dissolved in ether and the unsolved Rh-complex was filtered off. After removal of the solvent, the residue was purified by column chromatography on silica gel to afford the cyclopentanone as a white solid (from hexane:EtOAc 20:1 to 5:1).

General procedure for the intermolecular hydroacylation of alkenes using cationic systems and chlorine source.[244] A mixture of benzaldehyde (2.5 mmol), 2-amino-picoline (0.8 mmol), 1-hexene (12.5 mmol), MK-10 (80 mg), [Rh(cod)L_2] and PR_3 (0.05 mmol) or alternatively $RhCl(PPh_3)_3$ (0.05 mmol) and $BnMe_3NCl$ (0.05 mol) in of toluene (2 ml) was heated to 110ºC for 2h. The resulting mixture was filtered and analyzed by GC.

General procedure for determination of enantiomeric excess in cyclopentanones. The crude cyclopentanones were converted to the diastereomeric hydrazone derivatives by reaction with (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (**220**) following the method of Enders.[186] The hydrazone may be syn or anti with respect to the 3-substituent, which paired to two possible enantiomers at the 3-position gives four possible diastereomers. The syn and anti isomers were formed in approximately equal amounts. The ees were calculated from the integrations of the diastereomeric imine carbon signals in the ^{13}C spectra. All four signals were used to calculate the ee, summing the appropriate sets. The signal noise-to-ratio in the imine region was greater than 100:1. With sufficient acquisition time and appropriate pulse delay (5s), enantiomeric excesses (ees) were determined to within 5%. The assignments were made on the basis of similar imines carbon signals found in the literature. The signals for known *S* enantiomer always appeared upfield from those of the *R* enantiomer.[172]

General procedure for DIBAL-H reduction. A solution of cyclopentanone **215** (100 mg, 0.28 mmol) in CH_2Cl_2 (2.4 ml) was cooled to -78ºC. To this solution 0.5 ml DIBAL-H (1 M in CH_2Cl_2, 0.5 1mmol) was added. The reaction was monitored by TLC (hexane:EtOAc 5:1) until the starting material was consumed. After 2 h at -78ºC, the reaction was quenched by adding MeOH and the mixture was allowed to reach rt.

Then water was added and the mixture was stirred for 30 min. The resulting solution was acidified with dilute sulphuric acid until pH 3. The mixture was extracted three times with additional CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$ and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc 5:1) to afford 99 mg of **224** (99% yield) of a diastereomeric mixture (*cis*:*trans* 2.5:1) as a yellowish syrup.

General procedure for Reduction using BHT. A solution of 3*S*-cyclopentanone **215** (10 mg, 0.028 mmol) in of toluene (1.4 ml) was cooled to -78ºC, then a solution of BHT[210] (0.28 mmol) in toluene was added slowly. Further stirring at -78ºC for 2 h no reaction was observed, then the temperature was increased to -40ºC until formation of cyclopentanol was observed by TLC (hexane:EtOAc 5:1). When the reaction was finished, the mixture was poured onto cold 1M hydrochloric acid, and extracted with EtOAc. The combined extracts were washed with aqueous sodium hydrogencarbonate solution, followed by brine, dried over magnesium sulphate, and concentrate in vaccuo. The residue was purified by flash chromatography (hexane:EtOAc, 5:1) to afford 7 mg of **224** (70% yield) as a yellowish syrup. The ratio of 1*S*:1*R* diastereoisomers was 1:1 and it was determined by ^{1}H-NMR.

General procedure for Kinetic Resolution. A solution of diastereomeric cyclopentanol **224** (10 mg, 0.03 mmol) and acyl donor (0.09 mmol) in dry toluene (0.5 ml) were degassed with argon for 5 min and the enzyme (N-435 or PSC) was then added. The mixture was stirred under argon atmosphere at 70ºC. The enzyme was filtered off and washed with toluene, the combined solvent was evaporated, and the residue was analyzed by ^{1}H NMR.

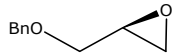
General procedure for Dynamic Kinetic Resolution using H_2. To a solution of diastereoisomeric cyclopentanol **224** (10 mg, 0.03 mmol) and acyl donor (0.09 mmol) in 0.5 ml dry toluene under argon were added ruthenium catalyst **230** (2.6 mg, 6 mol%) and enzyme (15 mg). The resulting mixture was bubbled with H_2 for 5 min, and the reaction mixture was stirred at 70ºC for 72 h under hydrogen atmosphere. The enzyme was then filtered off and washed with toluene. The combined toluene phases were evaporated and residue was analyzed by ^{1}H NMR.

General procedure for preparation of NMR samples. Typically, a 5 mm NMR tube fitted with a Young's valve was charged with *ca*. 15 mg of rhodium complex and dissolved in the appropriate deuterated solvent. Addition of the reagent(s) was completed under inert atmosphere at low temperature, when required. The sample was then transfer into the NMR spectrometer, which was previously set to the appropriate temperature.

Computational Methods

All DFT calculations were performed using the Amsterdam Density Functional (ADF2004.01) program developed by Baerends *et al*.[254,255,256] We used the local VWN[257] exchange-correlation potential with nonlocal Becke's exchange correction[258] and Perdew's correlation correction[259] (BP86). Relativistic corrections were introduced by scalar-relativistic Zero Order Regular Approximation (ZORA).[260,261,262] A triple-ζ plus polarisation basis set was used on all atoms. For non-hydrogen atoms a relativistic frozen-core potential was used, including 4d for rhodium, 2p for phosphorus and chlorine, 3p for iodine, and 1s for carbon and nitrogen. The Slater basis sets were extracted from the ADF library.

(2*S*)-1-*O*-Benzylglycidol (131)[263]



A mixture of THF (30 ml) and NaH (3.1 g, 77.5 mmol, 60% in mineral oil) was cooled to 0ºC. Then, (*R*)-glycidol (3 ml, 45.2 mmol) was added dropwise. After stirring the reaction for 1 h at 0ºC benzyl bromide (9.7 ml, 81.6 mmol) was added and the reaction was allowed to reach rt. The reaction was monitored by TLC (hexane:EtOAc 5:1); after stirring overnight isopropyl alcohol and water were added. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc 6:1) affording **131** (4.6 g, 67%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.35-7.29 (m, 5H, Ar); 4.60 (d, 2H, J= 11.6 Hz, CH_2Ph); 3.76 (dd, 1H, $J_{1b\text{-}1a}$= 11.2 Hz, $J_{1b,2}$= 2.8 Hz, H-1b); 3.42 (dd, 1H, $J_{1a\text{-}1b}$= 11.2 Hz, $J_{1a\text{-}2}$= 6 Hz, H-3a); 3.18 (m, 1H, H-2); 2.78 (pseudo-t, 1H, $J_{3a\text{-}3b}\approx J_{3a\text{-}2}$= 5.2 Hz, H-3a); 2.6 (dd, 1H, $J_{3b\text{-}3a}$= 5.2 Hz, $J_{3b\text{-}2}$= 2.8 Hz, H-3b).

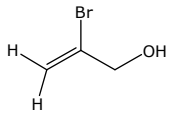
^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 140.0 (C, Ar); 128.5 (CH meta); 127.9 (CH, orto, para); 73.4 (CH_2Ph); 70.9 (C-1); 51.0 (C-2); 44.4 (C-3).

---

[254] Baerends, E. J.; Ellis, D. E.; Ros, P. *Chem. Phys.* **1973**, *2*, 41.
[255] te Velde, G.; Bickelhaupt, F. M.; van Gisbergen, S.; Guerra, C. F.; Baerends, E.; Snijders, J.; Ziegler, T. *J. Comput. Chem.* **2001**, *22,* 931.
[256] Guerra, C. F.; Snijders, J.; te Velde, G.; Baerends, E. *Theor. Chem. Acc.* **1998**, *99*, 391.
[257] Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
[258] Becke, A. *Phys. Rev. A* **1988**, *38*, 3098.
[259] (a) Perdew, J. P. *Phys Rev. B* **1986**, *34,* 7406. (b) Perdew, J. P. *Phys Rev. B* **1986**, *33,* 8822.
[260] van Lenthe, E.; Baerends, E.; Snijders, J. *J. Chem. Phys.* **1993**, *99,* 4597.
[261] van Lenthe, E.; Baerends, E.; Snijders, J. *J. Chem. Phys.* **1994**, *101,* 9783.
[262] van Lenthe, E.; Ehlers, A.; Baerends, E.; Snijders, J. *J. Chem. Phys.* **1999**, *110,* 8943.
[263] Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem*. **1990**, *55*, 4897.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

2-Bromo-2-propen-1-ol (137)[127]

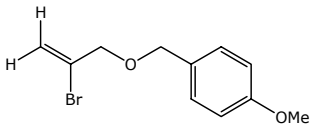


This bromo alcohol was prepared from 2,3-dibromo-1-propene by hydrolysis, using a 10% excess of 10% sodium carbonate solution at 95ºC for seven hours. The 2-bromo-2-propen-1-ol was separated from the reaction mixture by decantation, dried with magnesium sulfate, and distilled under vacuum. Compound **137** was isolated in 50% yield as a colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.94 (s, 1H, H-3b); 5.60 (s, 1H, H-3a); 4.24 (d, 2H, $J_{1\text{-}OH}$= 6.8 Hz, H-1); 2.00 (d, 1H, $J_{OH\text{-}1}$= 6.8 Hz, OH).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 132.6 (C-2); 116.5 (C-3); 67.8 (C-1).

1-*O*-(*p*-Methoxybenzyloxy)-2-bromo-2-propene (138)[264]



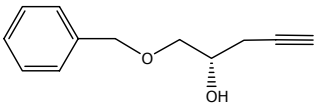
To a solution of NaH (0.25 g, 6.25 mmol, 60% in mineral oil) and dry THF (1.7 ml) cooled at 0ºC, 2-bromo-2-propen-1-ol (**137**) (0.5 g, 3.65 mmol) was added dropwise. The mixture was stirred at 0ºC for 1 h and the *p*-methoxybenzyl chloride (0.9 ml, 6.63 mmol) was added. After stirring overnight isopropyl alcohol and water were added. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc 9:1) affording **138** (0.56 g, 60%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.26 (d, 2H, J= 8.4 Hz, *p*-MeOPh); 6.87 (d, 2H, J= 8.4 Hz, *p*-MeOPh); 5.92 (d, 1H, $J_{3b\text{-}3a}$= 1.6 Hz, H-3b); 5.61 (dd, 1H, $J_{3a\text{-}3b}$= 1.6 Hz, $J_{3a\text{-}1}$= 0.8 Hz, H-3a); 4.46 (s, 2H, CH_2-*p*-MeOPh); 4.08 (t, 2H, $J_{1\text{-}3a}$= 0.8 Hz, H-1); 3.77 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.5, 133.8, 129.7 (*p*-MeOPh); 129.6 (*p*-MeOPh, C-2); 117.8 (C-3); 113.9 (*p*-MeOPh); 73.7 (C-1); 71.8 (CH_2-*p*-MeOPh); 55.3 (OCH_3).

[264] (a) Couladouros, E. A.; Vidali, V. P. *Chem. Eur. J.* **2004**, *10*, 3822. (b) Hoshi, H.; Ohnuma, T.; Aburaki, S.; Konishi, M.; Oki. O. *Tetrahedron Lett.* **1993**, *34*, 1047.

(2*S*)-1-(Benzyloxy)-pent-4-in-2-ol (147a)[265]

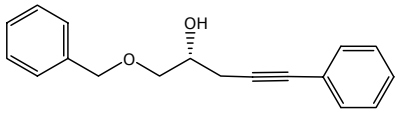


To a solution of lithium acetylide ethylenediamine complex (1.12 g, 12.16 mmol) in 11 ml of DMSO anhydrous was added dropwise a solution containing (*R*)-benzylglycidol (1 g, 6.09 mmol) and of DMSO (15 ml). The reaction was monitored by TLC (hexane:EtOAc 3:1) until the reaction was completed. After 3 h a saturated solution of ammonium chloride was added. The resultant mixture was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by radial chromatography (hexane:EtOAc 5:1) affording 0.7 g of **147a** as a brown syrup in 60% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38-7.30 (m, 4H, Ar); 4.59 (d, 2H, CH_2Ph); 3.97 (m, 1H, H-2); 3.61 (dd, 1H, J_{1a-1b}= 9.6 Hz, J_{1a-2}= 4 Hz, H-1a); 3.52 (dd, 1H, J_{1b-1a}= 9.6 Hz, J_{1b-2}= 6.4 Hz, H-1b); 2.58 (d, 1H, J_{OH-2}= 4.4 Hz, OH); 2.44 (dd, 2H, J_{3a-3b}= 6Hz, J_{3-5}= 2.8 Hz, H-3); 2.02 (t, 1H, J_{5-3a}=J_{5-3b}= 2.8 Hz, H-5)

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.9, 128.6, 128.0 (Ar); 80.4 (C-4); 73.6 (CH_2Ph); 72.9 (C-1); 70.8 (C-5), 68.9 (C-2); 23.6 (C-3).

(2*S*)-1-(Benzyloxy)-5-phenylpent-4-in-2-ol (147b)[266]



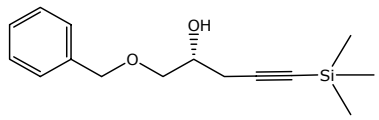
A solution of phenylacetylene (0.1 ml 0.91 mmol) in dry diethyl ether (1 ml) was cooled at -78ºC. Then 0.57 ml of *n*-butyllithium solution (1.6 M in THF, 0.91 mmol) was added dropwise. After 20 min boron trifluoride diethyl etherate (0.12 ml, 0.95 mmol) was added. Finally a solution of (*R*)-benzylglycidol (100 mg, 0.61 mmol) in diethyl ether (1 ml) was added dropwise into the preformed mixture. The reaction was monitored by TLC (hexane:EtOAc 3:1). After 5 h a saturated solution of ammonium chloride was added. The resulting mixture was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by radial chromatography (hexane:EtOAc 5:1) affording 0.16 g of **147b** as a yellow syrup in 50% yield.

[265] (a) Ishikawa, Y.; Nishiyama, S. *Heterocycles* **2004**, *63*, 539. (b) Sneddon, H. F.; van den Heuvel, A.; Hirsch, A. K. H.; Booth, R. A.; Shaw, D. M.; Gaunt, M. J.; Ley, S. V. *J. Org. Chem*. **2006**, *71*, 2715.
[266] Ool, T.; Kagoshima, N.; Ichikawa, H.; Maruoka, K. *J. Am. Chem. Soc*. **1999**, *121*, 3328.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.15-7.30 (m, 10H, Ar); 4.50 (s, 2H, CH_2Ph); 3.96 (m, 1H, H-2); 3.59 (dd, 1H, J_{1a-1b}= 9.6 Hz, J_{1a-2}= 3.6 Hz, H-1a); 3.48 (dd, 1H, J_{1b-1a}= 9.6 Hz, J_{1b-2}= 6.4 Hz, H-1b); 2.59 (dd, 2H, J_{3a-3b}= 6Hz, J_{3-2}= 2.8 Hz, H-3); 2.55 (d, 1H, J_{OH-2}= 4.8 Hz, OH)

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.0, 131.8, 128.6, 128.4, 128.1, 127.9, 123.5 (Ar); 85.7 (C-4); 82.9 (C-5); 73.6 (CH_2Ph); 73.1 (C-1); 69.2 (C-2); 24.7 (C-3).

(2*S*)-1-(Benzyloxy)-5-(trimethylsilyl)pent-4-in-2-ol (147c)[266]



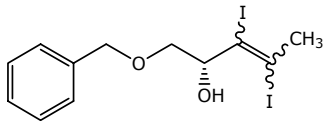
A solution of trimethylsilylacetylene (0.13 ml, 0.91 mmol) in dry diethyl ether (1 ml) was cooled at -78ºC. Then 0.57 ml of *n*-butyllithium solution (1.6 M in THF, 0.91 mmol) was added dropwise. After 20 minutes boron trifluoride diethyl etherate (0.12 ml, 0.95 mmol) was added. Finally a solution of (*R*)-benzylglycidol (100 mg, 0.61 mmol) in diethyl ether (1 ml) was added dropwise into the preformed mixture. The reaction was monitored by TLC (hexane:EtOAc 3:1). After 3 h a saturated solution of ammonium chloride was added. The resulting mixture was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by radial chromatography (hexane:EtOAc 5:1) affording 0.16 g of **147c** as a yellow syrup in 56% yield.

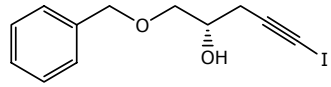
^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.14-7.23 (m, 4H, Ar); 4.43 (d, 2H, CH_2Ph); 3.81 (m, 1H, H-2); 3.46 (dd, 1H, J_{1a-1b}= 9.6 Hz, J_{1a-2}= 3.6 Hz, H-1a); 3.35 (dd, 1H, J_{1b-1a}= 9.6 Hz, J_{1b-2}= 6.4 Hz, H-1b); 2.41 (sa, 1H, OH); 2.35 (dd, 2H, J_{3a-3b}= 6.6 Hz, J_{3-2}= 4.8 Hz, H-3), 0.2 (s, 9H, $3CH_3$).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.0, 128.6, 128.0, 127.9 (Ar); 102.7 (C-5); 87.4 (C-4); 73.6 (CH_2Ph); 72.9 (C-1); 69.0 (C-2); 25.2 (C-3); 0.2 (CH_3).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

(2*R*)-1-(Benzyloxy)-3,4-diiodopent-3-en-2-ol (149) and (2*S*)-1-(benzyloxy)-5-iodopent-4-in-2-ol (150)





Procedure I: In a dry round bottom flask a solution of KH (91.3 mg, 0.68 mmol) in diethyl ether (13 ml) was prepared and cooled at 0ºC. Then a solution of (2*S*)-1-(benzyloxy)pent-4-in-2-ol (**147a**) (100 mg, 0.53 mmol) in Et_2O (6.2 ml) was added dropwise. Then the mixture was allowed to reach rt and subsequently was cooled to -78ºC and a solution of I_2 (0.4 g, 1.57 mmol) in Et_2O (4 ml) was added. The mixture was stirred overnight but by TLC (hexane:EtOAc 2:1) the formation of a new product was not observed. Thus the mixture was allowed to reach rt. The work-up of the reaction was performed before the complete disappearance of the starting material. Thus, a saturated solution of sodium thiosulfate was added and the resulting mixture was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by radial chromatography (hexane:EtOAc 4:1) affording 22.2 mg (10% yield) of **149** as a colourless liquid and 42.4 mg (30% yield) of **150** as a yellowish liquid.

Procedure II: A solution of **147a** (50 mg, 0.38 mmol) and $NaHCO_3$ (94.6 mg, 1.13 mmol) in methylene chloride (1.6 ml) was cooled to 0ºC and I_2 (0.2 g, 0.77 mmol) was added. The reaction mixture was stirred overnight and a saturated solution of sodium thiosulfate was then added. The mixture was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by medium pressure chromatography (hexane:EtOAc 2:1) affording 41.3 mg of **149** as a colourless liquid in 40% yield.

(2*R*)-1-(Benzyloxy)-3,4-diiodopent-3-en-2-ol (149)

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36-7.37 (m, 5H, Ar); 4.61 (d, 2H, J= 6 Hz, CH_2Ph); 4.42 (m, 1H, H-2); 3.56 (dd, 1H, $J_{1a\text{-}1b}$= 9.6 Hz, $J_{1a\text{-}2}$= 4 Hz, H-1a); 3.50 (dd, 1H, $J_{1b\text{-}1a}$= 9.6 Hz, $J_{1b\text{-}2}$= 8.4 Hz, H-1b); 2.68 (s, 3H, H-5); 2.62 (d, 1H, $J_{OH\text{-}2}$= 4.4 Hz, OH).

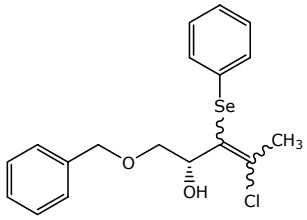
^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.8, 128.7, 128.1, 128.0 (Ar); 105.6 (C-3); 95.3 (C-4); 79.4 (C-2); 73.6 (CH_2Ph); 72.8 (C-1); 40.4 (C-5).

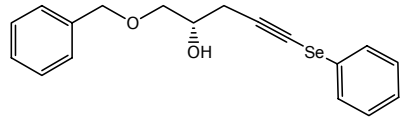
(2*S*)-1-(Benzyloxy)-5-iodopent-4-in-2-ol (150)

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36 (m, 4H, Ar); 4.60 (s, 2H, CH_2Ph); 4.24 (m, 1H, H-2); 3.59 (dd, 1H, J_{1a-1b}= 9.6 Hz, J_{1a-2}= 3.2 Hz, H-1a); 3.48 (dd, 1H, J_{1b-1a}= 9.6 Hz, J_{1b-2}= 5.6 Hz, H-1b); 2.98 (dd, 1H, J_{3a-3b}= 14.8 Hz, J_{3a-2}= 7.6 Hz, H-3a); 2.77 (dd, 1H, J_{3b-3a}= 14.8 Hz, J_{3b-2}= 5.6 Hz, H-3b); 2.36 (d, 1H, J_{OH-2}= 5.2 Hz, OH).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.0 (C-7); 128.8, 128.2, 128.1 (C-Ar); 114.5 (C-4); 73.8 (CH_2Ph); 72.9 (C-1); 70.4 (C-2); 53.7 (C-3).

(2*R*)-1-(Benzyloxy)-4-cloro-3-(phenylselenenyl)pent-3-en-2-ol (151) and (2*S*)-1-(benzyloxy)-5-(phenylselenenyl)pent-4-in-2-ol (152)





A solution of **147a** (100 mg, 0.53 mmol) in dry methylene chloride (7 ml) was cooled to 0ºC and 0.43 ml of n-butyllithium (1.6 M in THF, 0.69 mmol) and then 0.13 g of phenylselenyl chloride (0.68 mmol) were added, and the mixture was allowed to reach rt and was stirred overnight. The reaction was monitored by TLC (hexane:EtOAc 3:1) and the starting material was still visible. A saturated solution of $NaHCO_3$ was added to the mixture which was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by medium pressure chromatography (from hexane:EtOAc 40:1 to hexane:EtOAc 10:1) affording **151** (22.2 mg, 11% yield) as a yellow liquid and **152** (10.7 mg, 6% yield) as a yellow liquid.

(2*R*)-1-(Benzyloxy)-4-cloro-3-(phenylselenenyl)pent-3-en-2-ol (151)

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.19-7.37 (m, 10H, Ar); 5.17 (m, 1H, H-2); 4.52 (d, 2H, J= 3.6 Hz, CH_2Ph); 3.56 (m, 2H, H-1); 2.71 (d, 1H, J_{OH-2}= 7.2 Hz, OH); 2.38 (s, 3H, CH_3).

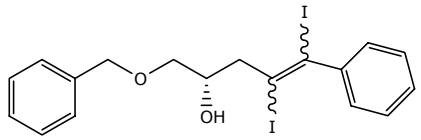
^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3, 138.0, 131.9, 130.0, 129.6, 128.6, 128.0, 127.9, 127.8, 126.8 (C-3, C-4, Ar); 73.5 (CH_2Ph); 73.0 (C-1); 71.0 (C-2); 27.5 (CH_3).

(2*S*)-1-(Benzyloxy)-5-(phenylselenenyl)pent-4-in-2-ol (152)

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.26-7.49 (m, 10H, Ar); 4.54 (s, 2H, CH_2Ph), 4.18 (m, 1H, H-2); 3.54 (dd, 1H, J_{1a-1b}= 9.6 Hz, J_{1a-2}= 3.6 Hz, H-1a); 3.42 (dd, 1H, J_{1b-1a}= 9.6 Hz, J_{1b-2}= 6.8 Hz, H-1b); 2.76 (dd, 1H, J_{3a-3b}= 14 Hz, J_{3a-2}= 7.6 Hz, H-3a); 2.58 (dd, 1H, J_{3b-3a}= 14 Hz, J_{3b-2}= 6 Hz, H-3b); 2.39 (d, 1H, J_{OH-2}= 4 Hz, OH).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1, 133.5, 130.8, 129.7, 128.8, 128.7, 128.2, 121.4 (Ar); 73.5 (CH_2Ph, C-1); 69.4 (C-2); 36.6 (C-3).

(2*S*)-1-(Benzyloxy)-4,5-diiodo-5-phenylpent-4-en-2-ol (153)

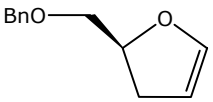


A solution of **147b** (100 mg, 0.26 mmol) and $NaHCO_3$ (67.5 mg, 0.80 mmol) in methylene chloride (2.2 ml) was cooled to 0ºC and I_2 (0.2 g, 1.13 mmol) was added. The reaction mixture was stirred overnight at rt and a saturated solution of sodium thiosulfate was added. The mixture was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by medium pressure chromatography (from hexane to hexane:EtOAc 2:1) affording 77.9 mg of **153** as a yellow syrup in 40% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.17-7.40 (m, 10H, Ar); 4.63 (s, 2H, CH_2Ph); 4.39 (m, 1H, H-2); 3.68 (dd, 1H, J_{1a-1b}= 9.6 Hz, J_{1a-2}= 3.6 Hz, H-1a); 3.58 (dd, 1H, J_{1b-1a}= 9.6 Hz, J_{1b-2}= 6.4 Hz, H-1b); 3.23 (dd, 1H, J_{3a-3b}= 14.4 Hz, J_{3a-2}= 7.6 Hz, H-3a); 3.05 (dd, 1H, J_{3b-3a}= 14.4 Hz, J_{3b-2}= 6 Hz, H-3b); 2.48 (d, 1H, J_{OH-2}= 4.8 Hz, OH).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.4, 138.0, 128.7, 128.6, 128.5, 128.4, 128.1, 121.0 (Ar); 99.8, 97.7 (C-4, C-5); 73.7 (C-6); 73.1 (C-1); 70.3 (C-2); 53.6 (C-3).

2*S*-(Benzyloxymethyl)-2,3-dihydrofuran (154)



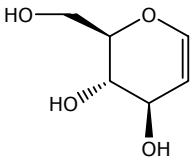
An oven-dried flask equipped with a stir bar and nitrogen inlet was charged with $Mo(CO)_6$ (1.42 g, 5.37 mmol), trimethylamine N-oxide (0.34 g, 4.56 mmol), anhydrous ether (108 ml), and triethylamine (18 ml, solvents distilled immediately prior to use). The suspension was stirred at 20ºC for 1 h. Alkynyl alcohol **147a** (2.05 g, 10.8 mmol, dissolved in 41 ml of ether) was added via syringe and stirred at 20ºC for 4 days. The solvent was removed in a vacuo and the residue was purified by silica gel chromatography (pentane:ether:trimethylamine= 100:0:1 to 100:5:0.5) to yield **154** as a colourless oil (1.74 g, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.33-7.23 (m, 5H, Ar); 6.27 (dd, 1H, J= 2Hz, J= 4.8 Hz, H-5); 4.84 (dd, 1H, J= 2.4 Hz, J= 5 Hz, H-4); 4.73 (m, 1H, H-2); 4.57 (dd, 2H, J= 9.2 Hz, J= 12.4 Hz, CH_2Ph); 3.56 (dd, 1H, J= 6.8 Hz, J= 10.4 Hz, OCH_2); 3.46 (dd, 1H, J= 4.4 Hz, J= 10.4 Hz, OCH_2); 2.63 (ddt, 1H, J= 2.4 Hz, J= 10.4 Hz, 15.2 Hz, H-3a); 2.33 (ddt, 1H, J= 2.4 Hz, 7.6 Hz, J= 15.2 Hz, H-3b).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 145.1 (C-5), 137.8, 128.4, 127.7, 127.8 (Ar); 99.0 (C-4); 79.8 (C-2); 73.4 (CH_2O); 72.3 (CH_2Ph); 31.6 (C-3).

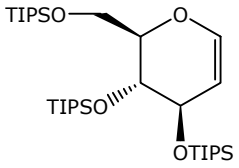
Anal. Calcd. for $C_{12}H_{14}O_2$: 75.76 C, 7.42 H. Found: 75.80 C, 7.40 H.

D-Glucal (169)



To a solution 3,4,6-tri-*O*-acetyl-D-glucal (3 g, 10 mmol) in methanol (30 ml) was added 0.6 g of NaOMe (11.11 mmol). After stirring at 20ºC for 3 h, DOWEX 50WX2-200 was added. The resultant mixture was stirred for 10 min and then filtrated. The solvent was evaporated in vacuo. The resulting crude was purified by flash chromatography in a short column with EtOAc as eluent to afford 1.53 g of **169** in 95% yield.

3,4,6-tris-*O*-Triisopropylsilyl-D-glucal (170)

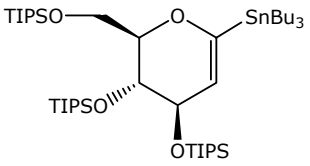


Procedure I: A solution of D-glucal (1.63 g, 11.15 mmol) in anhydrous DMF (50 ml) and imidazole (6 g, 88.13 mmol) was treated with TIPSCl (9.5 ml, 44.83 mmol) and the resulting mixture was heated at 70-95ºC for 24 h. Then, additional silyl chloride (2.4 ml, 11.33 mmol) was added and the solution was stirred for a further 24 h. The solution was diluted in water and extracted with ether. The organic layer was washed with water and saturated brine and dried ($MgSO_4$). Concentration and purification by column chromatography provided the product **170** as colourless oil (4.8 g, 70%).

Procedure II: To a solution of D-glucal (1 g, 6.84 mmol) and 2,6-lutidine (5.3 ml, 45.50 mmol) in CH_2Cl_2 (7 ml), 8.31 ml of TIPSOTf (30.80 mmol) were added dropwise at 0ºC. The mixture was stirred for 60 min at rt and then diluted with 14 ml of CH_2Cl_2. After stirring for 5 h the reaction was quenched with water, the aquous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the removal of the solvent afforded a crude product which was purified by column chromatography with pentane:CH_2Cl_2 (8:1) as eluent to give 3.8 g of **170** in 90% yield.

The spectroscopic data were consistent with those reported.[146]

1-(Tributylstannyl)-3,4,6- tris-*O*-(triisopropylsilyl)-D-glucal (171)

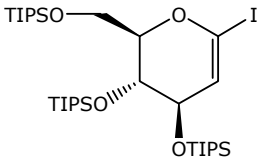


A solution of 3,4,6-tris-*O*-(triisopropylsilyl)-D-glucal (3.2 g, 5.2 mmol) in THF (65 ml) at -78ºC was treated with 1.6 M solution of *t*-BuLi in pentane (20 ml, 32 mmol) and the resulting solution was allowed to stir at 0ºC for 1 h. At this time the reaction was cooled at -78ºC, Bu_3SnCl (5 ml, 18.4 mmol) was added and the resulting mixture was warmed to rt for 15 min. The mixture was diluted in water and

extracted with Et_2O. The organic layer was washed with water, brine, and dried with $MgSO_4$. Concentration followed by purification by flash chromatography (pentane:CH_2Cl_2 8:1) provided 4.6 g of **171** as a colorless oil in 98% yield.

The spectroscopic data were consistent with those reported.[148]

1-Iodo-3,4,6-tris-*O*-(triisopropylsilyl)-D-glucal (172)



(NOTE: *Protect from light all the time*) A solution of **171** (5.39 g, 5.96 mmol) in 30 ml of CH_2Cl_2 anhydrous was prepared. Into a separated roundbottom flask was added iodine (3.03 g, 11.9 mmol) and 30 ml of CH_2Cl_2. The iodine solution was added dropwise via syringue over the solution of **171** until a pale purple color persisted. The reaction was immediately quenched by the addition of a $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under vacuum. The residue was purified by flash chromatography (pentane:CH_2Cl_2 8:1) provided **172** as a clear oil (3.97 g, 90% yield). Decomposition is evidenced by development of a dark brown colour.

The spectroscopic data were consistent with those reported.[149]

Preparation of (Xantphos)Pd(*p*-C_6H_4CN)(Br) (175)

$Pd(dba)_2$ (217 mg, 0.3774 mmol) and Xantphos (578.5 mg, 0.3774 mmol) were placed into a 100 ml flask. Toluene (15 ml) and 4-bromobenzonitrile (1.31 g, 7.2 mmol) were added, and the mixture was stirred at 80ºC for 4 h. After cooling to room temperature, the solution was filtered through Celite. The filtrate was evaporated in vacuum to a volume of 1 ml. Addition of ether (19 ml) gave a pale-yellow precipitate. The precipitate was filtered, washed with ether, and dried (227.6 mg, 70%).

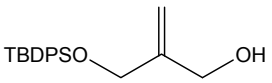
^{1}H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.64, 7.23, 6.75, 6.33 (m, 30H, Ar); 1.80 (br m, 6H, CH_3).

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ δ in ppm: 170.4, 155.6, 135.0, 131.0 (t, 23.1 Hz); 130.2, 128.6, 127.6, 124.7 (m, Ar); 121.6 (t, J= 22.1 Hz, Ar); 120.6 (CN); 104.0 (m, Ar); 36.4 ($C(CH_3)_2$); 28.7 (CH_3).

^{31}P NMR ($CDCl_3$, 121.5 MHz) δ in ppm: 9.37 (s).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

2-((*tert*-Butyldiphenylsilyloxy)methyl)prop-2-en-1-ol (186)[157]



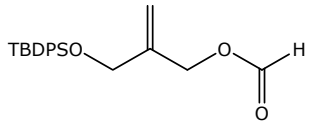
To NaH (2.28 g, 57.1 mmol, 60% dispersion in mineral oil) was added slowly by cannula a solution of 2-methylene-1,3-propanediol (**184**) (5.03 g, 57.1 mmol) in dry THF (44 ml) at 0ºC. After stirring for 70 min at room temperature under nitrogen, the solution was cooled to 0ºC and TBDPSCl (14.9 g, 14.1 ml, 54.2 mmol) was added over 2 min, turning the solution cloudy. The reaction mixture was stirred for 16 h at room temperature, the solvent was evaporated and the white residue was dissolved in a mixture of H_2O (50 ml) and Et_2O (50 ml). The aqueous layer was extracted with Et_2O (3 × 50 ml) and the combined organic layers were dried (Mg_2SO_4) and concentrated under reduced pressure to give a cloudy, colourless oil. The residue was purified by flash chromatography (hexane:EtOAc 5:1) to give **186** (15.7 g, 98%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.76-7.7 (m, 4H, Ar); 7.47-7.41 (m, 6H, Ar); 5.18 (s, 1H, H-3a); 5.13 (s, 1H, H-3b); 4.28 (s, 2H, H-4); 4.18 (s, 2H, H-1); 1.97 (bs, 1H, OH); 1.08 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 147.3 (C-2), 133.4, 135.7, 130.0, 127.9 (Ar); 111.3 (C-3); 65.7 (CH_2OSi); 64.6 (C-1); 27.0 (CH_3, *t*-Bu); 19.4 (C, *t*-Bu).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

2-((*tert*-Butyldiphenylsilyloxy)methyl)-propen-3-yl formate (187)



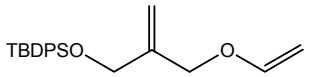
To a solution of **186** (0.2 g, 0.6 mmol) in CH_2Cl_2 (2.5 ml) at 0ºC was successively added DCC (0.16 g, 0.77 mmol), DMAP (0.011 g, 0.15 equiv) and formic acid (0.03 ml, 0.79 mmol). The mixture was allowed to reach rt. After stirring overnight at room temperature, the precipitate of urea was filtered off and the filtrate evaporated. The residue was purified by flash chromatography (hexane:EtOAc 10:1) affording the desired compound **187** (0.2 g, 90%) as an oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.04 (s, 1H, H-C(O)); 7.70-7.68 (m, 4H, Ar); 7.45-7.38 (m, 6H, Ar); 5.36 (d, 1H, J= 0.8 Hz, H-1a); 5.22 (s, 1H, J= 0.8 Hz, H-1b); 4.70 (s, 2H, H-3); 4.22 (s, 2H, CH_2OSi); 1.08 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 160.8 (C=O); 142.3 (C-3); 135.7, 133.4, 130.0, 127.9 (Ar); 114.0 (C-1); 64.5, 64.3 (C-3, CH_2OSi); 26.9 (CH_3, *t*-Bu); 19.4 (C, *t*-Bu).

Anal. Calcd. for $C_{21}H_{26}O_3Si$: 71.15 C; 7.39 H. Found: 71.18 C, 7.40 H.

2-*O*-((*tert*-Butyldiphenylsilyloxy)methyl)allyl vinyl ether (188)



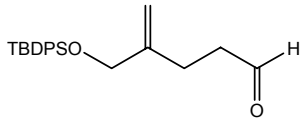
To a solution of **186** (4.6 g, 14.1 mmol) in ethyl vinyl ether (60 ml), mercuric acetate (0.9 g, 2.8 mmol) was added. After 2.5 h an additional amount of mercuric acetate (0.23 g, 0.7 mmol) was added, and then the solution was refluxed for 20 h. The reaction was cooled to 0°C and poured into a solution of Na_2CO_3 (10%, 100 ml) which was then extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting yellow oil was purified by flash chromatography (hexane:EtOAc 10:1) affording **188** (2 g, 40%) and unreacted starting material **186** (2.3 g, 50%) was also recovered.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.79-7.73 (m, 4H, Ar); 7.52-7.42 (m, 6H, Ar); 6.50 (dd, 1H, J= 14.1 Hz, J= 6.9 Hz, OCH=); 5.40 (m, 1H, H-1a); 5.26 (m, 1H, H-1b); 4.31 (m, 4H, H-17, H-3); 4.30 (dd, 1H, J_{1a-2} = 14.1 Hz, J= 2.1 Hz, $=CH_2$); 4.08 (dd, 1H, J= 6.9 Hz, J= 2.1 Hz, $=CH_2$); 1.15 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 151.6 (OCH=); 143.9 (C-2); 135.7, 133.6, 129.9, 127.9 (Ar); 112.6 (C-1); 87.4 (=CH_2); 69.1, 64.7 (CH_2OSi, C-3); 27.0 (CH_3, *t*-Bu); 19.5 (C, *t*-Bu).

Anal. Calcd. for $C_{22}H_{28}O_2Si$: 74.95 C, 8.01 H. Found: 75.0 C, 7.97 H.

4-((*tert*-Butyldiphenylsilyloxy)methyl)pent-4-enal (189)



A solution of **188** (2 g, 5.67 mmol) in benzonitrile (4 ml) was heated at 175ºC overnight. The reaction was monitored by TLC (hexane:EtOAc 8:1). When the reaction was finished the resulting oily residue was distillated under vacuum using a Buchi GKR-51 Kuglrohr oven to remove the benzonitrile. The purification of the crude oil by flash chromatography (hexane:EtOAc 8:1) afforded the 4-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enal (**189**) as a yellowwish syrup (0.14 g, 70%).

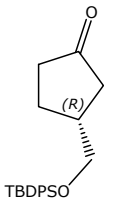
^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 9.74 (t, 1H, J= 1.6 Hz, H-1); 7.70-7.68 (m, 4H, Ar); 7.46-7.40 (m, 6H, Ar); 5.20 (m, 1H, CH_2OSi); 4.87 (m, 1H, CH_2OSi); 4.13 (app. s, 2H, H-6); 2.56 (td, 2H, J_{2-3}= 7.5 Hz, J_{2-1}= 1.6 Hz, H-2); 2.36 (t, 2H, J_{3-2}= 7.5 Hz, H-3); 1.08 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 202.2 (C-1); 146.5 (C-4); 135.7, 133.6, 129.9, 127.9 (Ar); 110.0 (CH_2OSi); 66.6 (C-6); 41.9 (C-2); 27.0 (CH_3, *t*-Bu); 25.1 (C-3); 19.5 (C, *t*-Bu).

FT-IR (neat) ν in cm^{-1}: 3071, 2930, 2856, 1725, 1427, 1108, 822, 740, 700, 613.

Anal. Calcd. for $C_{22}H_{28}O_2Si$: 74.95 C, 8.01 H. Found: 74.91 C, 8.07 H.

3*R*-((*tert*-Butyldiphenylsilyloxy)methyl)cyclopentanone (215R)



Following the general procedure for the intramolecular hydroacylation using cationic complexes **215R** was synthesised. The phosphine used to afford the **215*R*** enantiomer was the (*S*,*S*)-Me duphos. The final product was purified by flash chromatography (from hexane:EtOAc 20:1 to hexane:EtOAc 10:1) furnishing **215*R*** in 85% with enantioselectivities upper than 98%. The compound was isolated as white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.70-7.68 (m, 4H, Ar); 7.44-7.42 (m, 6H, Ar); 3.71 (d, 2H, J= 6 Hz, OCH_2); 2.48 (m, 1H, H-3); 2.33 (m, 2H, H-2, H-5); 2.20 (m, 1H, H-5); 2.11 (m, 2H, H-2, H-4); 1.82 (m, 1H, H-4); 1.1 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 219.8 (C-1); 137.7, 133.5, 129.9, 127.8 (Ar); 66.6 (OCH_2); 41.8 (C-2); 39.1 (C-3); 38.2 (C-5); 26.9 (CH_3, *t*-Bu); 25.8 (C-4) 19.4 (C, *t*-Bu).

FT-IR (neat) ν in cm^{-1}: 3070, 2957, 2929, 2857, 1738, 1471, 1426, 821, 699.

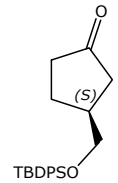
Anal. Calcd. for $C_{22}H_{28}O_2Si$: 74.95 C, 8.01 H. Found: 75.93 C, 8.04 H.

HRMS-ESI Calcd for $C_{22}H_{28}O_2SiNa$: 375.1757 (M+Na). Found: 375.1731.

$[\alpha]^{25}_D$ (215*R*)= 36.68 (c 0.2, CH_2Cl_2)

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

3*S*-((*tert*-Butyldiphenylsilyloxy)methyl)cyclopentanone (215S)

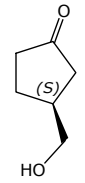


Following the general procedure for the intramolecular hydroacylation using cationic complexes **215*S*** was synthesised. The phosphine used to afford the **215*S*** enantiomer was the (*R*,*R*)-Me-Duphos The final product was purified by flash chromatography (from hexane:EtOAc 20:1 to hexane:EtOAc 10:1) furnished **215*S*** in 85% with enantioselectivities upper than 98%. The compound was isolated as white solid.

The spectroscopic data was the same of those mentioned for **215*R***.

$[\alpha]^{25}_D$ (215*S*)= -37.96 (c 0.3, CH_2Cl_2)

3*S*-(Hydroxymethyl)cyclopentanone (228*S*)[267]



A solution of **215*S*** (0.2 g, 0.57 mmol) in THF (16 ml) was treated with TBAF (1.13 ml, 1 M in THF, 1.13 mmol). The reaction was monitored by TLC (hexane:EtOAc 5:1) and after 30 minutes the starting material was completely disappeared. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc 1:5) to afford **228*S*** (51.8 mg, 80%) as a colourless syrup.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 3.61 (dd, 2H, J= 6 Hz, J= 2.4Hz, OCH_2); 2.74 (bs, 1H, OH); 2.44-2.23 (m, 3H, H-2a, H-3, H-5a); 2.2-2.1 (m, 2H, H-4a, H-5b); 1.97 (dd, 1H, J_{2a-2b}= 18 Hz, J_{2b-3} = 8.8 Hz, H-2b); 1.68 (m, 1H, H-4b).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 65.7 (OCH_2); 41.8 (C-2); 39.1 (C-3); 38.1 (C-5); 25.7 (C-4).

FT-IR (neat) ν in cm^{-1}: 3421, 2923, 1726, 1402, 1160, 1075, 1020.

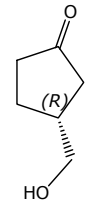
Anal. Calcd. for $C_6H_{10}O_2$: 63.14 C, 8.83 H. Found: 63.10 C, 8.87 H.

HRMS-ESI Calcd for $C_6H_{10}O_2Na$: 137.0579 (M+Na). Found: 137.0580.

$[\alpha]^{25}_D$ (228*S*)= -43.82 (c 0.84, acetone).

[267] Mase, M.; Watanabe, Y.; Toru, T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 2957.

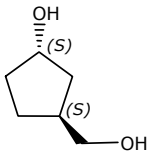
3*R*-(Hydroxymethyl)cyclopentanone (228*R*)



The experimental procedure and the ^{1}H, ^{13}C NMR, FT-IR and the elemental analisis are the same than the detailed above for 3*S*-(hydroxymethyl)cyclopentanone (**228*S***). The starting material employed for this reaction was **215*R***.

$[\alpha]^{25}_{D}$ (228*R*)= 43.91 (c 0.84, acetone).

(1*S*,3*S*)-3-(Hydroxymethyl)cyclopentanol (229(1*S*,3*S*))



A solution containing of **228*S*** (10 mg, 0.09mmol) and $NaBH(OAc)_3$ (74 mg, 0.35 mmol) in acetonitrile (0.75 ml) and ethyl acetate (0.75 ml) was refluxed overnight. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (EtOAc) to afford **229(1*S*,3*S*)** (7 mg, 70%).

^{1}H NMR (CD_3OD, 400 MHz) δ δ in ppm: 4.31 (m, 1H, H-1); 3.47 (d, 2H, J= 6.4 Hz, OCH_2); 3.83 (m, 1H, H-3); 1.92 (m, 2H, H-4a, H-5a); 1.78 (m, 1H, H-2a); 1.62 (m, 1H, H-5b); 1.50 (m, 1H, H-2b); 1.34 (m, 1H, H-4b).

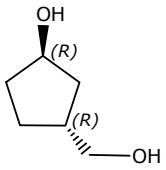
^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 74.0 (C-1); 67.2 (OCH_2); 40.5 (C-3); 39.2 (C-2); 35.2 (C-5); 27.4 (C-4).

Anal. Calcd. for $C_6H_{12}O_2$: 62.04 C, 10.41 H. Found: 61.98 C, 10.44 H.

HRMS-ESI Calcd for $C_6H_{12}O_2Na$: 139.0735 (M+Na). Found: 139.0738.

$[\alpha]^{25}_{D}$ (1*S*,3*S*)= 3.83 (c 0.6, methanol).

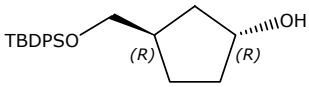
(1*R*,3*R*)-3-(Hydroxymethyl)cyclopentanol (229(1*R*,3*R*))



The experimental procedure was the same than the used for synthesising (1*S*,3*S*)-3-(hydroxymethyl) cyclopentanol **229(1*S*,3*S*)**. The spectroscopic data did not differ from the obtained for **229(1*S*,3*S*)**.

$[\alpha]^{25}_{D}$ (1*R*,3*R*)= -3.92 (c 0.6, methanol).

(1*R*,3*R*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)cyclopentanol (224a(1*R*,3*R*))



A solution containing of **229(1*R*,3*R*)** (10 mg, 0.086 mmol) in dichloromethane (0.2 ml), NEt_3 (36 μl, 0.26 mmol) freshly distilled and DMAP (1 mg, 0.1 equiv) was added. Then TBDPSCl (24 μl, 0.09 mmol) was added in small portions. After stirring overnight the solvent was removed under reduced pressure and the resulting mixture was purified by flash chromatography (hexane:EtOAc 5:1) to afford **224a(1*R*,3*R*)** (20 mg, 65%) as a colourless syrup.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.68-7.66 (m, 4H, Ar); 7.43-7.37 (m, 6H, Ar); 4.36 (m, 1H, H-1); 3.56 (d, 2H, J= 6 Hz, OCH_2); 2.45 (m, 1H, H-3); 1.91 (m, 2H, H-4a, H-5a); 1.74 (m, 1H, H-2a); 1.60 (m, 2H, H-5b, H-2b); 1.40 (m, 1H, H-4b); 1.1 (s, 9H, *t*-Bu).

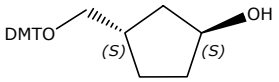
^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.8, 134.2, 129.7, 127.8 (Ar); 74.2 (C-1) 67.6 (OCH_2); 39.7 (C-3); 39.0 (C-2); 35.3 (C-5); 27.1 (CH_3, *t*-Bu); 26.6 (C-4); 19.5 (C, *t*-Bu).

Anal. Calcd. for $C_{22}H_{30}O_2Si$: 74.53 C, 8.53 H. Found: 74.56 C, 8.50 H.

HRMS-ESI Calcd for $C_{22}H_{30}O_2SiNa$: 377.1913 (M+Na). Found: 377.1913.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

(1*S*,3*S*)-3-((Dimethoxytrityloxy)methyl)cyclopentanol (224b(1*S*,3*S*))



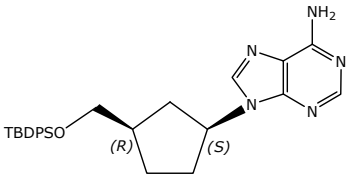
To a solution of **229(1*S*,3*S*)** (25 mg, 0.22 mmol) in pyridine (1.1 ml) DMAP (0.15 equiv) was added. Then 4,4'-dimethoxytrityl chloride (81 mg, 0.24 mmol) was added in small portions and the resulting mixture was stirred overnight. The reaction was monitored by TLC (hexane:EtOAc 5:2). Then MeOH was added and the reaction mixture was concentrated. Purification by silica gel column chromatography using Elution hexane:EtOAc 5:2 furnished pure **224b(1*S*,3*S*)** (64 mg, 70% yield) as a yellow syrup.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.44 (d, 2H, J= 8.2 Hz, Ph); 7.32 (d, 4H, J= 9Hz, *p*-MeOPh); 7.27 (d, 2H, J= 8.2 Hz, Ph); 7.20 (t, 1H, J= 7.2 Hz, Ph); 6.82 (d, 4H, J= 9Hz, *p*-MeOPh); 4.34 (m, 1H, H-1); 3.79 (s, 6H, -OCH_3); 2.96 (m, 2H, OCH_2); 2.52 (m, 1H, H-3); 2.05-1.28 (m, 6H, H-2, H-5, H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 158.4, 145.5, 136.8, 130.3, 127.9, 126.7, 113.2, 85.6 (Ar); 74.0 (C-1); 67.3 (OCH_2); 55.4 (-OCH_3); 39.8 (C-2); 37.9 (C-3); 35.2 (C-5); 27.4 (C-4).

Anal. Calcd. for $C_{27}H_{30}O_4$: 77.48 C, 7.22 H. Found: 77.50 C, 7.20 H.

9-[(1S,3R)-3-(((*tert*-Butyldiphenylsilyloxy)methyl))cyclopentyl]-9H-purin-6-amine (233a(1*S*,3*R*))[268]



To a solution containing of **224a(1*R*,3*R*)** (20 mg, 0.056 mmol) in dioxane (2 ml), adenine (15 mg, 0.11 mmol) and PPh_3 (30 mg, 0.11 mmol) were added and the mixture was stirred for 1 h until the complete solution of the reagents. Then DEAD (52 μl, 40% wt in toluene, 0.11 mmol) was added and the reaction was stirred for 3 h until the starting material was disappeared (TLC CH_2Cl_2:MeOH 20:1). The dioxane was removed under reduced pressure and the residue was purified by flash chromatography (from CH_2Cl_2:MeOH 40:1 to CH_2Cl_2:MeOH 20:1) to afford of **233a(1*S*,3*R*)** (18.6 mg, 70%) as a white syrup.

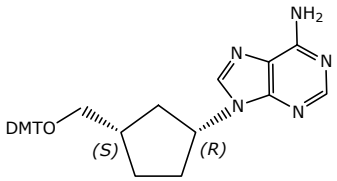
[268] Gudmundsson, K. S.; Daluge, S. M.; Condreay, L. D.; Johnson, L. C. *Nucleosides, Nucleotides & Nucleic Acids* **2002**, *21*, 891.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.34 (s, 1H, H-2); 7.85 (s, 1H, H-8); 7.67-7.65 (m, 4H, Ar); 7.43-7.37 (m, 6H, Ar); 5.81 (bs, 2H, NH_2); 4.89 (m, 1H, H-1'); 3.70 (m, 2H, OCH_2); 2.4-1.7 (m, 7H, H-2', H-3', H-4', H-5'); 1.07 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 155.5 (C-6); 152.7 (C-2); 138.7 (C-8); 135.8, 133.8, 129.9, 127.9 (Ar); 67.1 (OCH_2); 55.7 (C-1'); 40.2 (C-3'); 36.1 (C-2'); 32.3 (C-5'); 27.1 (CH_3, *t*-Bu); 26.6 (C-4'); 19.5 (C, *t*-Bu).

Anal. Calcd. for $C_{27}H_{33}N_5OSi$: 68.75 C, 7.05 H. Found: 68.80 C, 7.10 H.

9-[(1R,3S)-3-(((Dimethoxytrityloxy)methyl))cyclopentyl]-9H-purin-6-amine (233b(1*R*,3*S*))



Following the same procedure described for **233a(1*S*,3*R*)**, compound **233b(1*R*,3*S*)** was obtained in 75% yield as a colourless syrup.

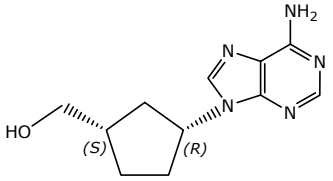
^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.34 (s, 1H, H-2); 7.43 (d, 2H, J= 8.0 Hz, Ph); 7.32 (d, 4H, J= 8.8Hz, *p*-MeOPh); 7.27 (d, 2H, J= 8.0 Hz, Ph); 7.21 (q, 1H, J= 7.26 Hz, Ph); 6.82 (d, 4H, J= 8.8 Hz, *p*-MeOPh); 5.81 (bs, 2H, NH_2); 4.90 (m, 1H, H-1'); 3.79 (s, 6H, -OCH_3); 3.13 (m, 2H, OCH_2); 2.53 (m, 1H, H-2'a); 2.42 (m, 1H, H-3'); 2.30 (m, 1H, H-5'a); 2.04-1.9 (m, 2H, H-5'b, H-4'b); 1.79-1.68 (m, 2H, H-4'b, H-2'b).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 158.6 (p-Ph); 155.6 (C-6); 150.2 (C-4); 145.3 (Ph); 138.7 (C-8); 136.5 (*p*-MeOPh); 130.2 (*p*-MeOPh); 128.3 (*m*-Ph); 128.0 (*o*-Ph); 126.9 (*p*-Ph); 120.1 (C-5); 113.2 (*p*-MeOPh); 85.9 (*p*-MeOPh); 66.9 (C-6'); 55.6 (C-1'); 55.4 (-OCH_3); 38.5 (C-3'); 37.0 (C-2'); 32.0 (C-5'); 27.3 (C-4').

Anal. Calcd. for $C_{32}H_{33}N_5O_3$: 71.75 C, 6.21 H, 13.07 N. Found: 71.83 C, 6.18 H, 13.10 N.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

([(1*R*,3*S*)-3-(6-Amino-9H-purin-9-yl)cyclopentyl]methanol and ([(1*S*,3*R*)-3-(6-amino-9H-purin-9-yl)cyclopentyl]methanol (234(1*R*,3*S*))[269]



From 233a(1*S*,3*R*): A solution of **233a(1*S*,3*R*)** (10 mg, 0.02 mmol) in THF (0.6 ml) was treated with TBAF (42 μl, 1 M in THF, 0.02 mmol). After 2 h the solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2:MeOH 20:1) to afford **234(1*S*,3*R*)**. The final product cannot be isolated as a pure compound. After several purifications the tetrabutylammonium salt could not be removed from the **234(1*S*,3*R*)**.

From 233b(1*R*,3*S*): To a solution of **233b(1*R*,3*S*)** (46 mg, 0.086 mmol) in THF (3 ml), TFA (5 μl) was added and the reaction mixture was stirred at room temperature for 1 day. A saturated solution of $NaHCO_3$ was then added and the solvent was removed under reduced pressure. Purification by silica gel column chromatography from CH_2Cl_2:MeOH 20:1 to CH_2Cl_2:MeOH 20:2 furnished pure **234(1*R*,3*S*)** (15 mg, 75% yield) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.34 (s, 1H, H-2); 7.89 (s, 1H, H-8); 5.93 (bs, 2H, NH_2); 4.88 (q, 1H, $J_{1'-2'}=J_{1'-5'}$= 8.4 Hz, H-1'); 3.72 (m, 2H, OCH_2); 2.49 (m, 1H, H-2a'); 2.38 (m, 1H, H-3'); 2.26 (m, 1H, H-5a'); 2.13 (m, 1H, H-5b'); 2.03-1.84 (m, 3H, H-2b',H-4).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 155.7 (C-6); 152.7 (C-2); 150.0 (C-4); 139.4 (C-8); 120.3 (C-5); 66.0 (OCH_2); 56.7 (C-1'); 40.1 (C-3'); 35.3 (C-2'); 32.8 (C-5'); 27.2 (C-4').

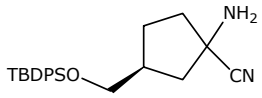
Anal. Calcd. for $C_{11}H_{15}N_5O$: 56.64 C, 6.48 H, 30.02 N. Found: 56.61 C, 6.52 H, 29.96 N

$[\alpha]^{25}_D$ (1*S*,3*R*) found= 6.5 (c 0.49, H_2O)

$[\alpha]^{26}_D$ (1*R*,3*S*) reported= -6.3 (c 0.49, H_2O)

[269] Saksena, A. K.; Girijavallabhan, V. M.; Ganguly, A. K. Process for Preparing Cyclopentyl Purine Derivatives. US 4999428, 1991.

(3*S*)-1-Amino-3-((*tert*-Butyldiphenylsilyloxy)methyl)cyclopentanecarbonitrile (235)

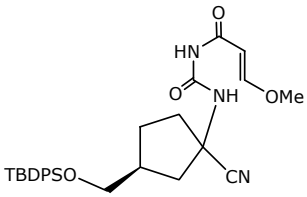


To a solution of **215*S*** (0.13 g, 0.37 mmol) in *i*-PrOH (0.4 ml), NH_4OH (1.9 ml, 0.38 mmol), NH_4Cl (0.05 g, 0.93 mmol) and KCN (0.06 g, 0.92 mmol) was added. The mixture was stirring for 10 days at rt. The organic solvent was evaporated under reduced pressure and the liquid residue was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The resulting mixture was purified by by flash chromatography (hexane:EtOAc 5:2) to afford a mixture of *cis* and *trans* **235** (48 mg, 32%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.67-7.66 (m, 4H, Ar); 7.46-7.37 (m, 6H, Ar); 4.92 (bs, 2H, NH_2); 3.61 (m, 2H, CH_2O); 2.57-1.63 (m, 7H, H-2, H-3, H-4, H-5); 1.07 (s, 9H, *t*-Bu).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.7, 133.7, 129.9, 127.9 (Ar); 125.2, 125.1 (CN); 67.2, 66.7 (CH_2O); 55.1, 54.3 (C-1); 43.7, 43.5 (C-3); 40.9, 40.7 (C-2); 40.3, 40.1 (C-5); 27.0 (CH_3, *t*-Bu); 26.7 (C-4); 19.5 (C, *t*-Bu).

(*E*)-N-((3*S*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)-1-cyanocyclopentyl carbamoyl)-3-methoxyacrylamide (237)

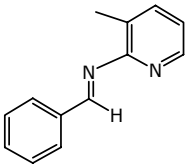


To a solution of **235** (36 mg, 0.095 mmol) in DMF (0.32 ml), a solution of (*E*)-3-methoxyacryloyl chloride[219] (35 mg, 0.29 mmol) and silver cyanate (66 mg, 0.44 mmol) in toluene (0.62 ml) was added. The resulting mixture was heated during 5 h. The crude was purified by radial chromatography (hexane:EtOAc 1:1) to afford **237** (24 mg, 50%) as a brown syrup.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 10.31 (bs, 1H, NH); 7.72 (d, 1H, J= 12 Hz, CH=); 7.64-7.62 (m, 4H, Ar); 7.44-7.39 (m, 6H, Ar); 5.45 (d, 1H, J= 12Hz, CH=); 3.74 (s, 3H, OCH_3); 3.59 (m, 2H, CH_2O); 2.68-1.65 (m, 7H, H-2, H-3, H-4, H-5); 1.05 (s, 9H, *t*-Bu).

^{3}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 168.7 (C=O); 164.3 (=CH); 155.1 (C=O); 135.7, 133.6, 129.9, 127.9 (Ar); 121.0, 120.8 (CN); 97.1 (=CH); 66.6, 66.3 (OCH2); 57.9 (OCH3); 42.2, 41.9 (C-3); 39.7, 39.6 (C-2); 39.1, 38.9 (C-5); 27.0 (CH_3, *t*-Bu); 26.4, 26.3 (C-5); 19.4 (C, *t*-Bu).

2-Benzylidene-3-methylpyridine (244)

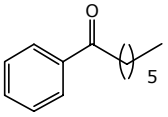


The synthesis of this compound was completed according to reported literature methods.[270] A solution of 2-amino-3-picoline (**243**, 4.83 g, 44.6 mmol) in THF (20 ml) was prepared and benzaldehyde (5 ml, 49.2 mmol) was added in the presence of molecular sieve (4 Å). The reaction mixture was refluxed for 12 h and then cooled to rt. The molecular sieve was removed by filtration. The solvent was evaporated in-vacuo and the resulting oily residue was distillated under vacuum using a Buchi GKR-51 Kugelrohr oven; affording **244** (7.88 g, 90%) as a yellow liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 9.1 (s, 1H, HC=N); 8.3 (dd, J= 1.6 Hz, J= 4.8 Hz, 1H, Py); 8.00 (dd, 2H, J= 2.4 Hz, J= 7.2 Hz, Ph); 7.54 (d, 1H, J= 7.6 Hz, Py); 7.48 (m, 3H, Ph); 7.07 (dd, 1H, J= 4.8 Hz, J= 7.2 Hz); 2.46 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 161.3 (-C=N); 159.2, 145.9, 136.6, 131.5, 129.6, 129.2, 128.9, 128.5, 127.4, 121.7, 17.5.

Heptanophenone (251)



This compound was obtained following the general procedure for the intramolecylar hydroacylation of alkenes using cationic systems.

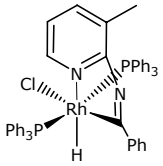
^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.95 (dd, 1H, J= 5.2, H-6 Py); 7.55-7.95 (m, 2H, Ph); 7.35 (dd, 1H, J= 5.2 Hz, H-4 Py); 6.90-7.10 (m, 3H, Ph); 6.66-6-76 (m, 1H, H-5 Py); 2.60 (t, 2H, J= 7.9 Hz, hexyl); 2.17 (s, 3H, CH_3 Py); 1.10-1.60 (m, 8H, hexyl); 0.80 (t, 3H, J= 6.8 Hz, CH_3 hexyl).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 171.3 (-C=N); 161.8 (C-2 Py); 148.3 (C-4 Py); 146.3 (C-6 Py); 138.7-120.3 (Ph); 119.4 (C-5 Py); 117.9 (C-3 Py); 31.4, 30.1, 29.8, 21.1 (C-hexyl); 18.8 (CH_3 Py); 13.8 (CH_3 hexyl); 2.3 (C-hexyl).

[270] Chul-Ho, J. *Bull. Korea. Chem. Soc*. **1990**, *11*, 187.

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

[RhHCl{(2-benzylidene)-3-methylpyridine}(PPh_3)$_2$] (246-*trans*)



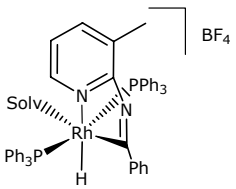
A solution of Wilkinson's catalyst $RhCl(PPh_3)_3$ (0.5 g, 0.54 mmol) and 2-benzylidene-3-methylpyridine **2** (0.1 g, 0.51 mmol) in *ca*. 35 ml THF was refluxed for 3 h. Half of the solvent was removed in-vacuo, and precipitation of the product was achieved by addition of cold n-hexane. After filtration, the product **246-*trans*** was isolated as a pale-yellow solid (0.35 g, 80%yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.39 (d, 1H, J= 5.6 Hz, Py); 7.65 (d, 2H, J=7.2 Hz, Ph); 7.43 (m, 12H, PPh_3); 7.28 (d, 1H, J= 7.6 Hz, Py); 7.13 (m, 18H, Ph); 6.87 (t, 1H, J= 7.2 Hz, PPh_3); 6.68 (dd, 2H, J= 7.2 Hz, J= 8.6 Hz, PPh_3); 6.52 (dd, J=5.6 Hz, J=7.6 Hz, Py); 2.5 (s, 3H, CH_3); -11.2 (overlapping d of t, 1H, J_{RhH}= 13 Hz, J_{PH}= 12 Hz).

^{13}C NMR (toluene-d8, 100.6 MHz) δ in ppm: 230.5 (dt, J_{RhC}= 32.6 Hz, J_{PC}= 7.5 Hz), 184.9-118.9 (Ar), 19.2 (CH_3).

^{31}P NMR ($CDCl_3$, 161.9 MHz) δ in ppm: 33.1 (d, J_{RhP}= 116.6 Hz).

[RhH{(2-benzylidene)-3-methylpyridine}(PPh_3)$_2$(solv)] at -40ºC (260-*trans*)

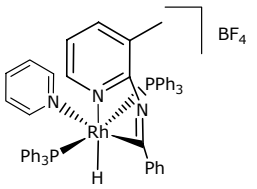


The procedure to obtain this compound has been explained in the results and discussion in the chapter 5.

^{1}H NMR (CD_2Cl_2, 400 MHz) δ in ppm: 8.23 (d, 1H, J= 4.4 Hz, Py); 7.61 (d, 2H, J=7.6 Hz, Ph); 7.33-7.20 (m, 31H, Ar); 7.1-6.78 (m, 4H, Py and Ph); 2.23 (s, 3H, CH_3); -10.86 (overlapping d of t, 1H, J_{RhH}= 16 Hz, J_{PH}= 9 Hz).

^{31}P NMR ($CDCl_3$, 161.9 MHz) δ in ppm: 36.8 (d, J_{RhP}= 118 Hz).

[RhH{(2-benzylidene)-3-methylpyridine}(PPh_3)$_2$(pyridine)] at rt (262)



The procedure to obtain this compound has been explained in the results and discussion in the chapter 5.

^{1}H NMR (CD_2Cl_2, 400 MHz) δ in ppm: 8.57 (bs, free py); 8.22 (d, 1H, J=5.2 Hz); 8.15 (bs, 1H, py); 7.81 (dd, 2H, J=8Hz, J=1.2Hz); 7.7-7.1 (m, 42H); 6.94 (t, 2H, J=8 Hz); 2.14 (s, -CH_3); -11.8 (overlapping d of t, 1H, J_{RhH}=16 Hz, J_{PH}=9 Hz).

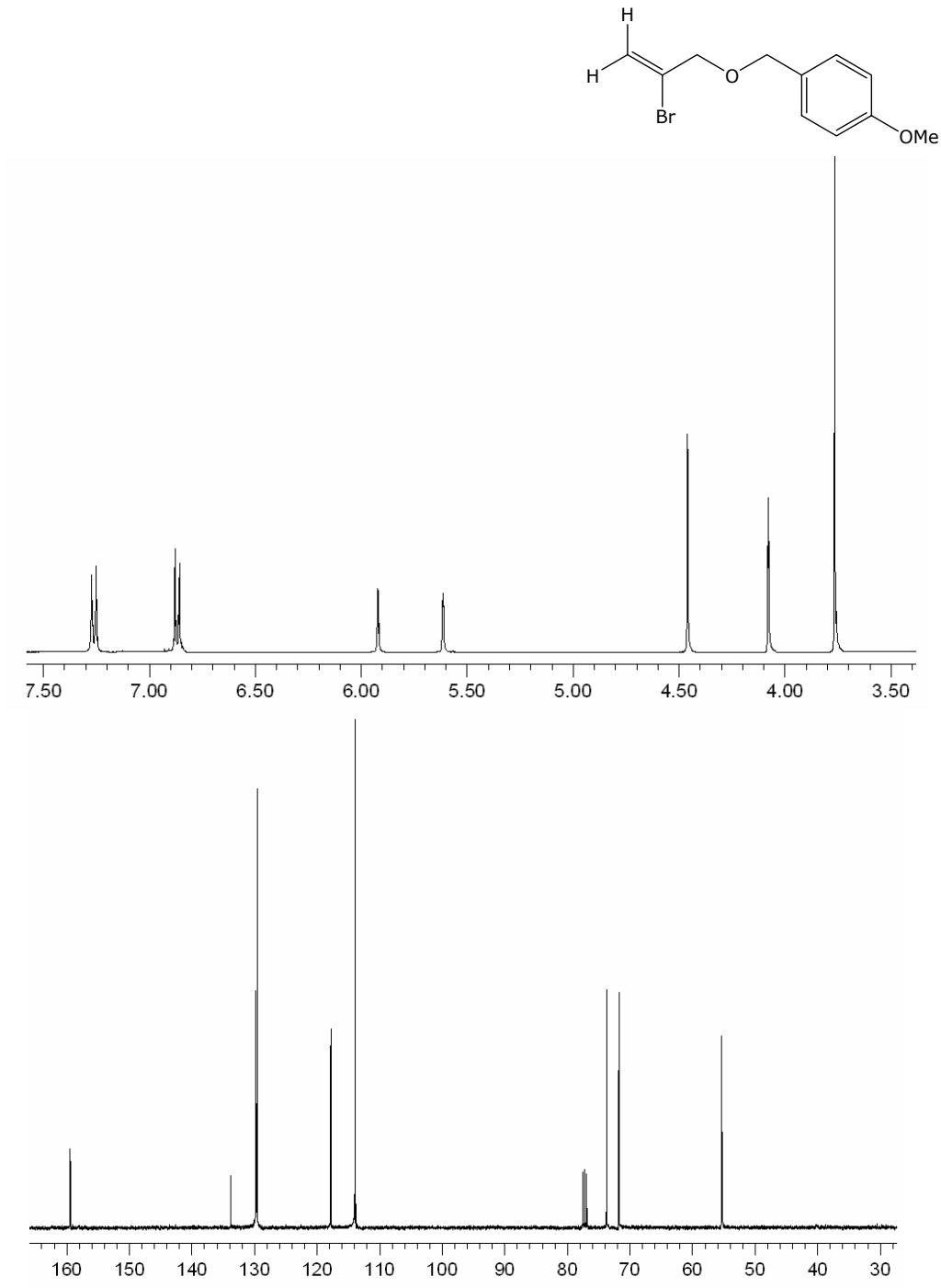
^{31}P NMR (CD_2Cl_2, 161.9 MHz) δ in ppm: 38.5 (d, J_{RhP}=114 Hz).

UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

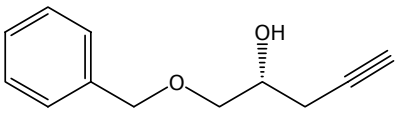
8. Annex

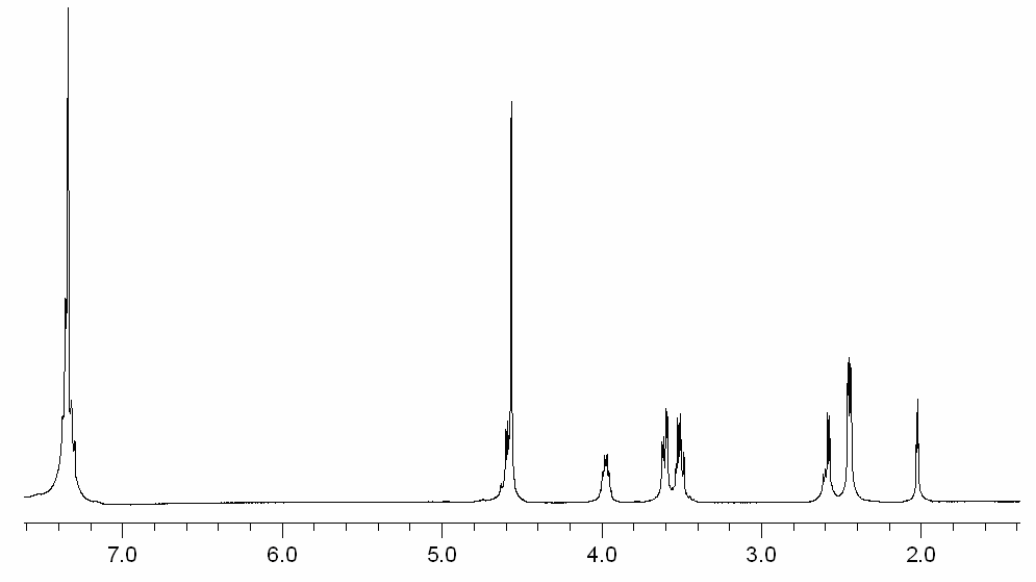
UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

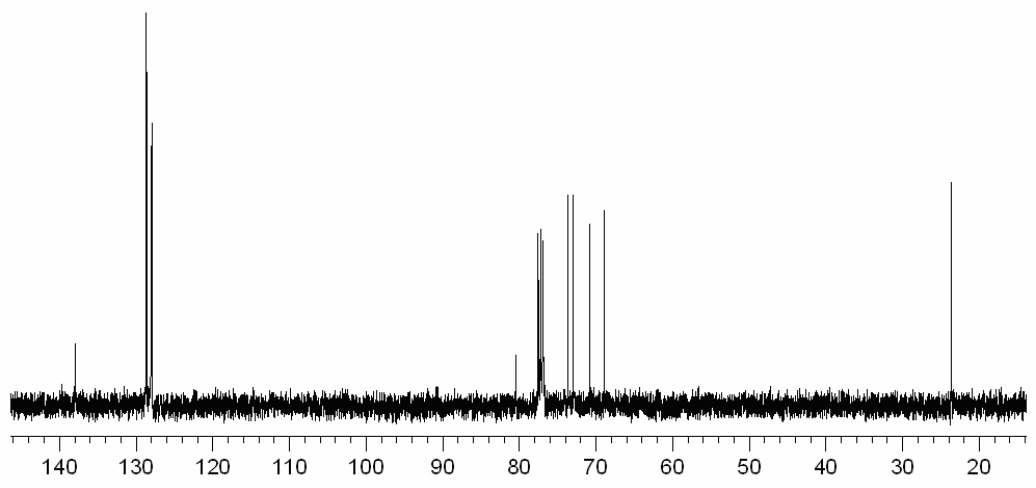
^{1}H and ^{13}C spectra of 1-*O*-(*p*-methoxybenzyloxy)-2-bromo-2-propene (138)



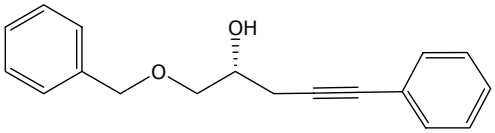
^{1}H and ^{13}C spectra of (2*S*)-1-(benzyloxy)pent-4-in-2-ol (147a)

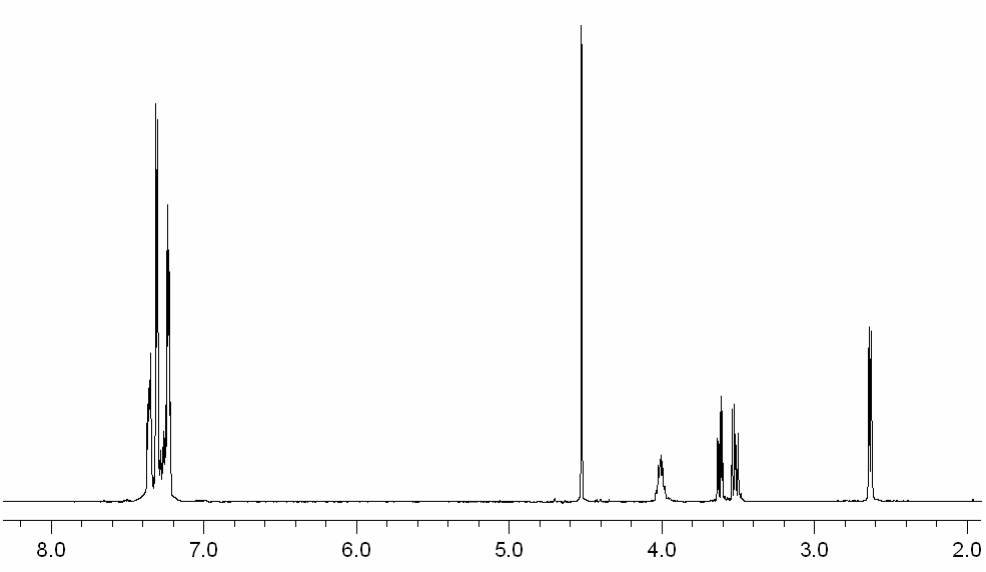


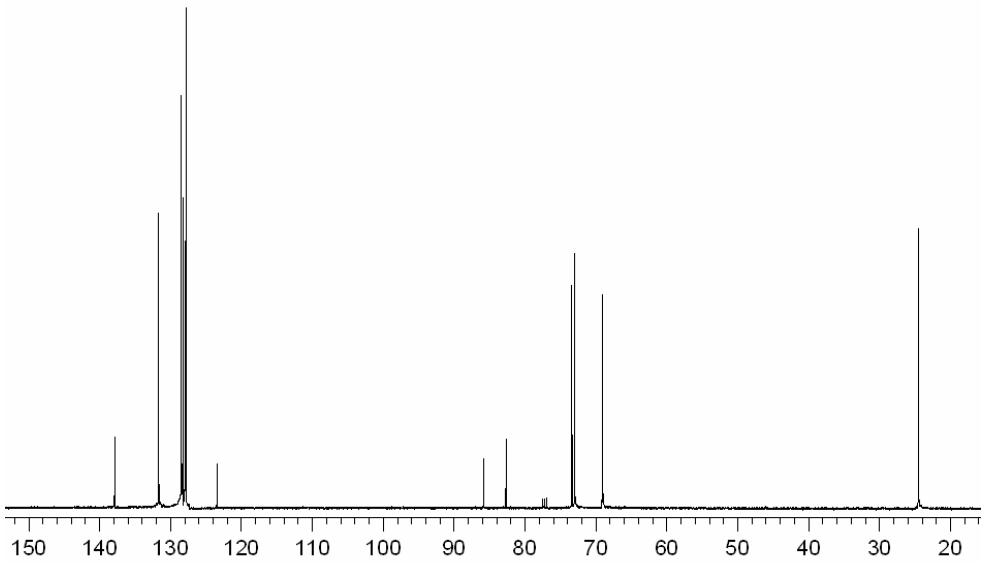




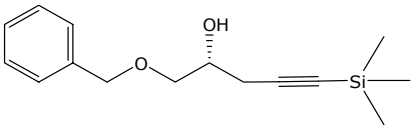
^{1}H and ^{13}C spectra of (2*S*)-1-(benzyloxy)-5-phenylpent-4-in-2-ol (147b)

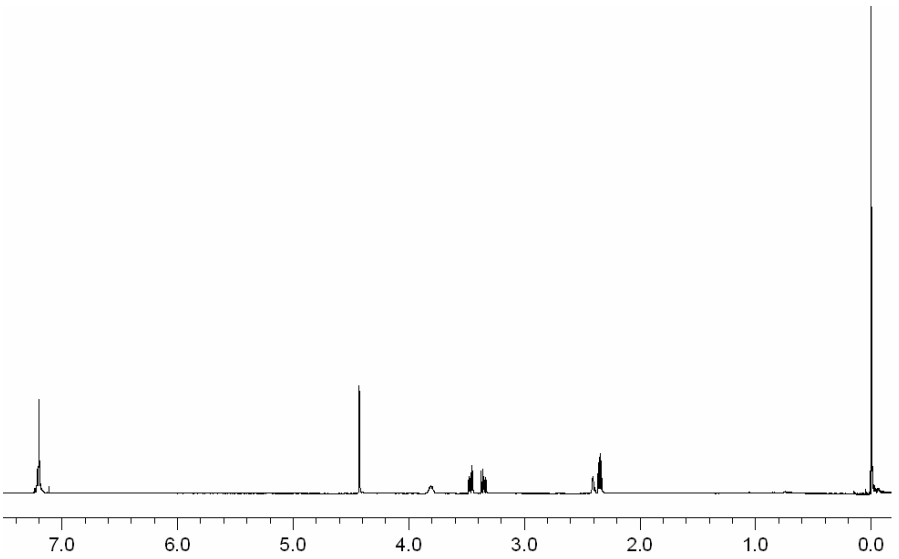


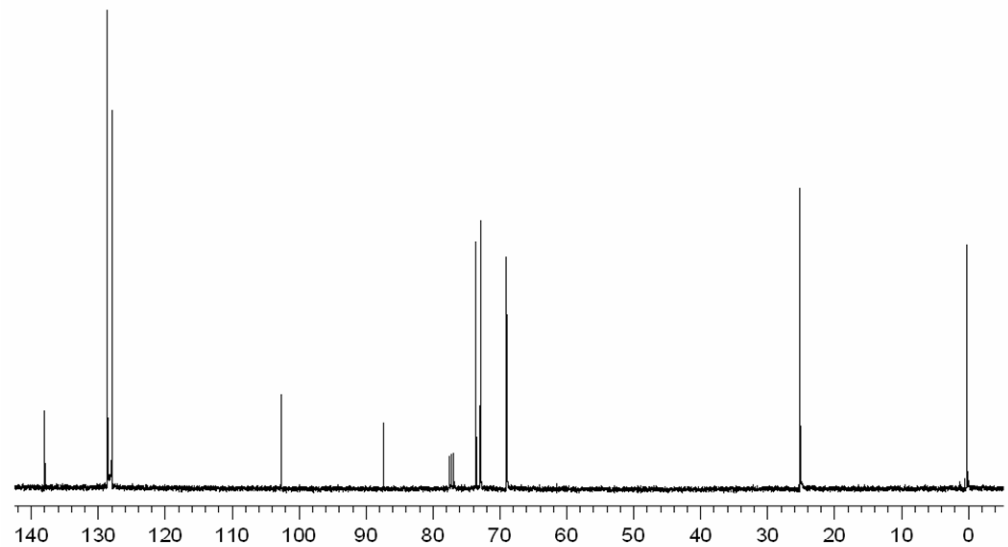




^{1}H and ^{13}C spectra of (2*S*)-1-(benzyloxy)-5-(trimethylsilyl)pent-4-in-2-ol (147c)

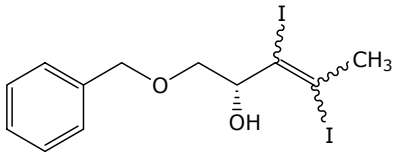


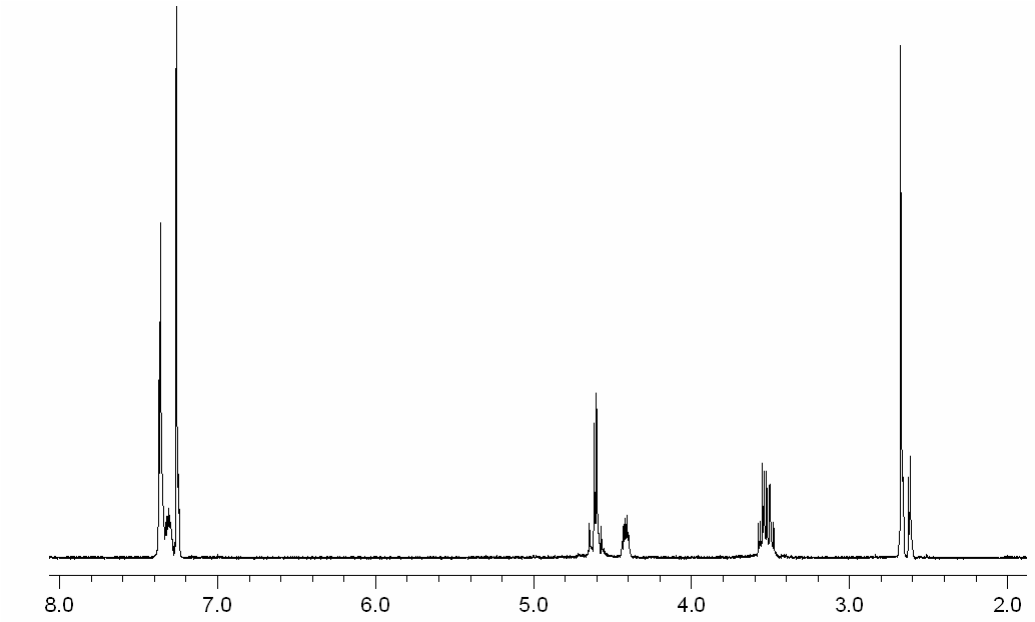


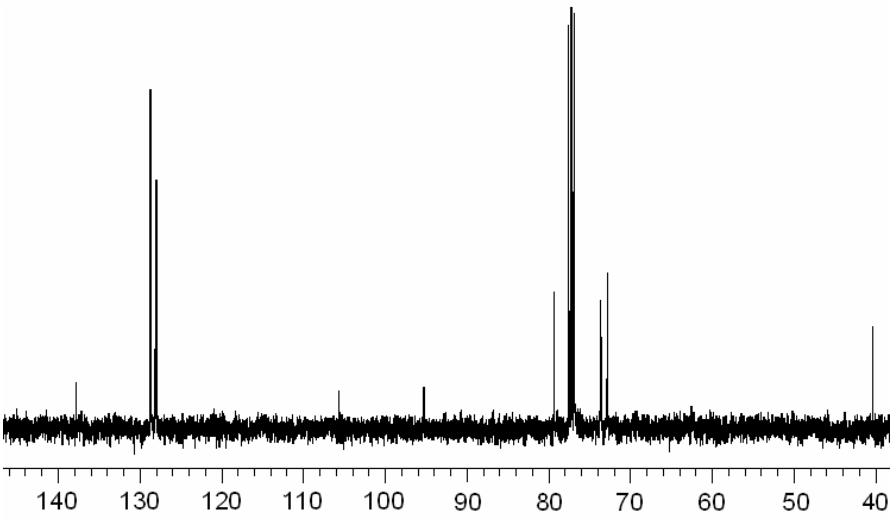


UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

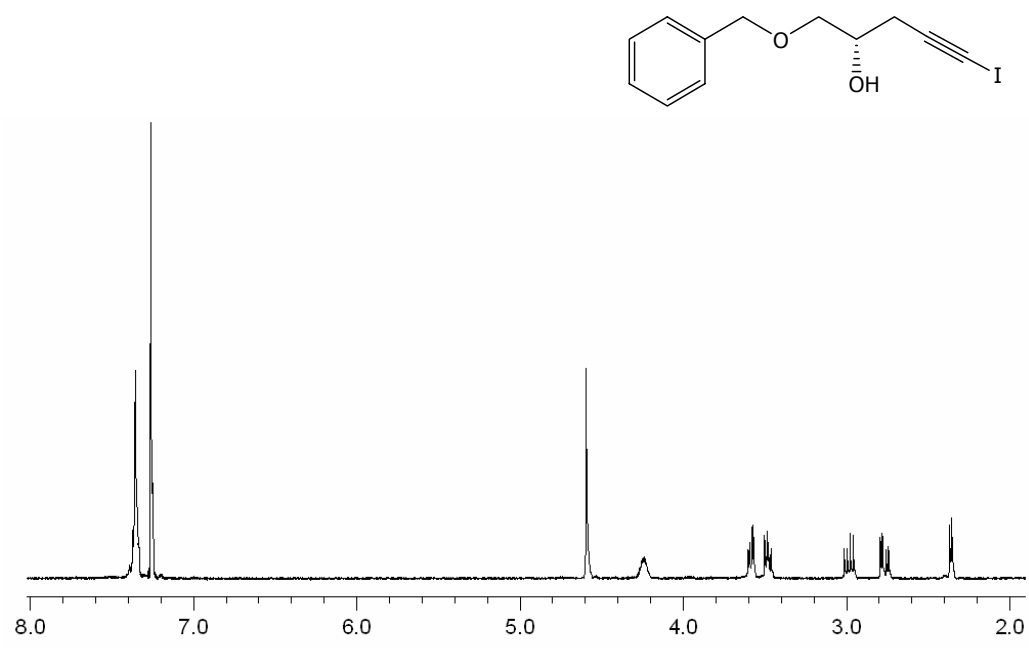
^{1}H and ^{13}C spectra of (2*R*)-1-(benzyloxy)-3,4-diiodopent-3-en-2-ol (149)

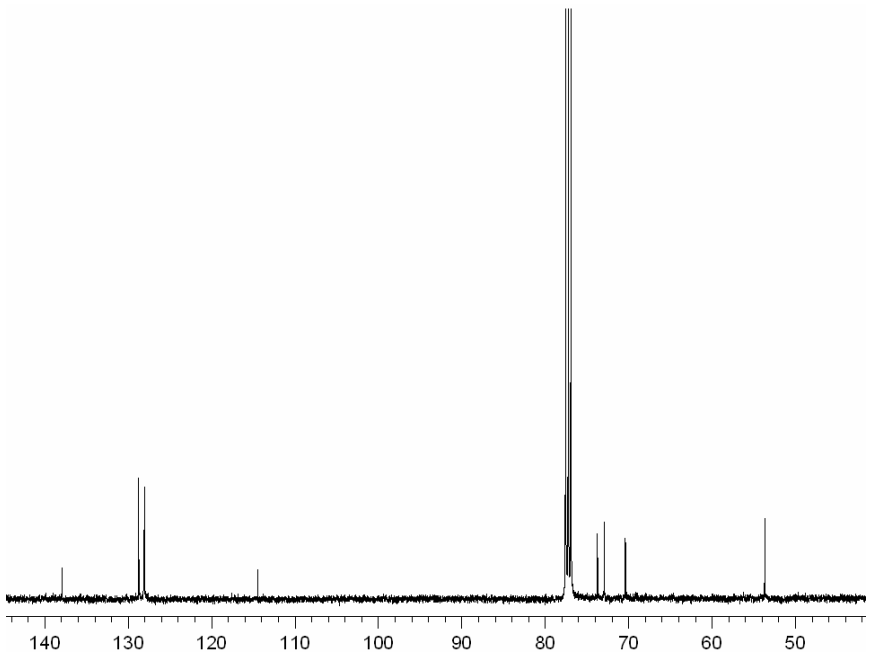






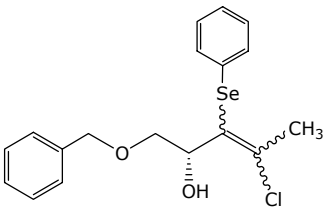
^{1}H and ^{13}C spectra of (2*S*)-1-(benzyloxy)-5-iodopent-4-in-2-ol (150)

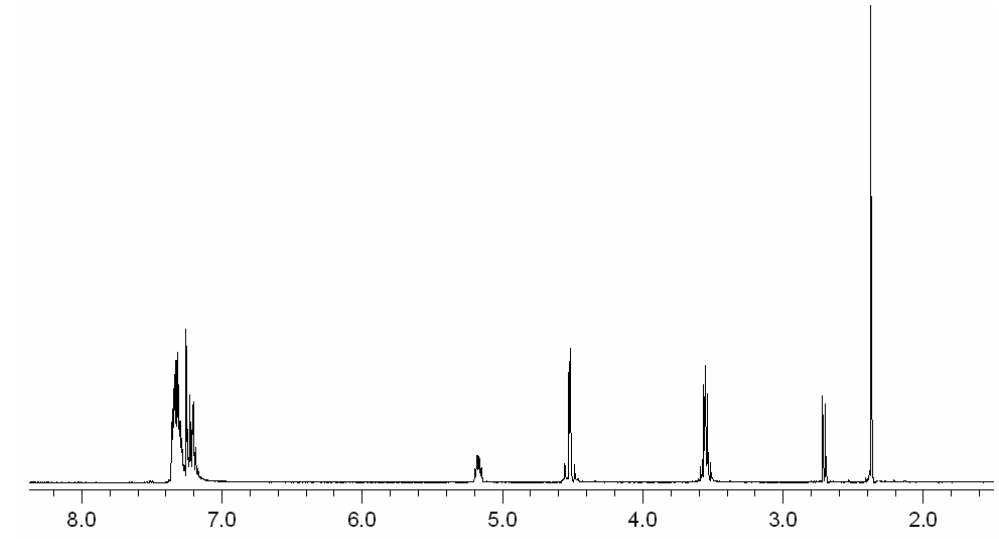


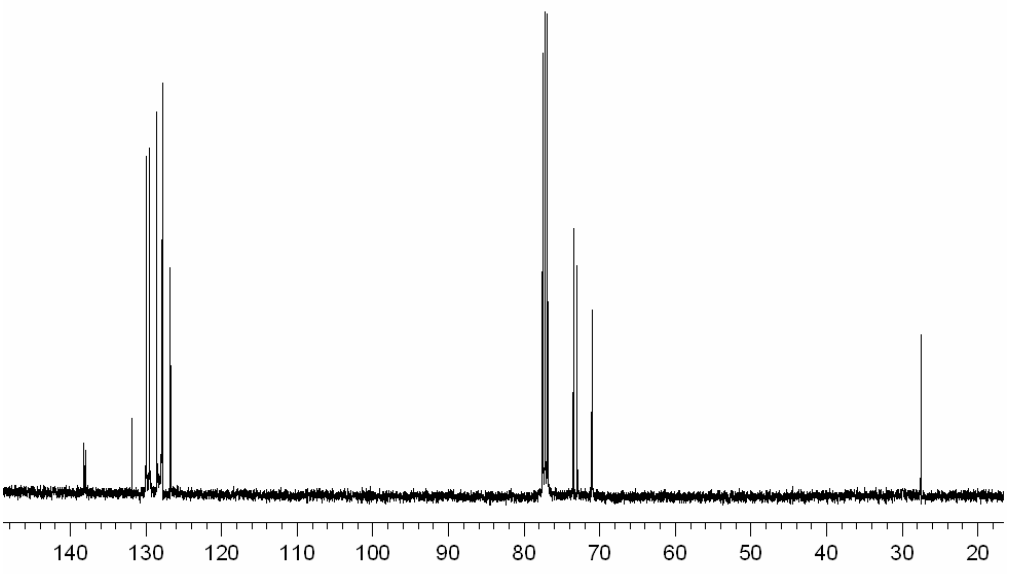


ISBN:978-84-691-8840-8/DL: T-1262-2008

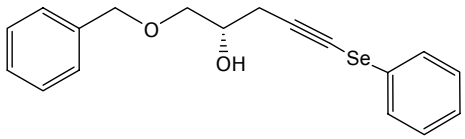
^{1}H and ^{13}C spectra of (2*R*)-1-(benzyloxy)-4-cloro-3-(phenylselenenyl)pent-3-en-2-ol (151)

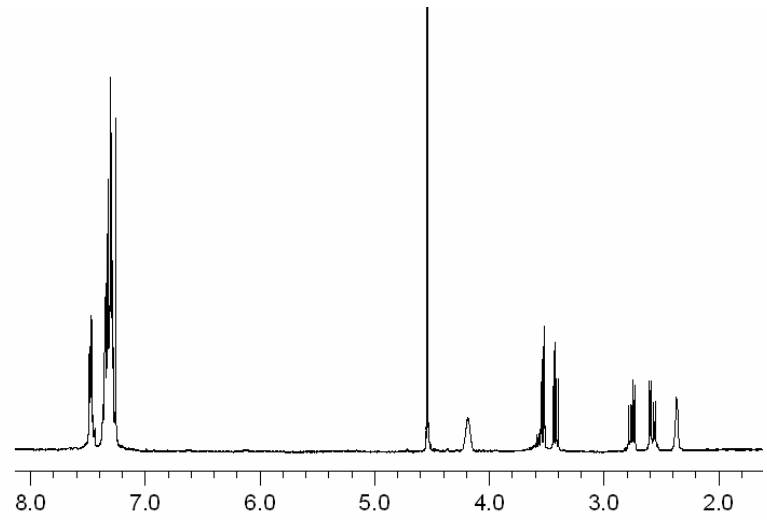


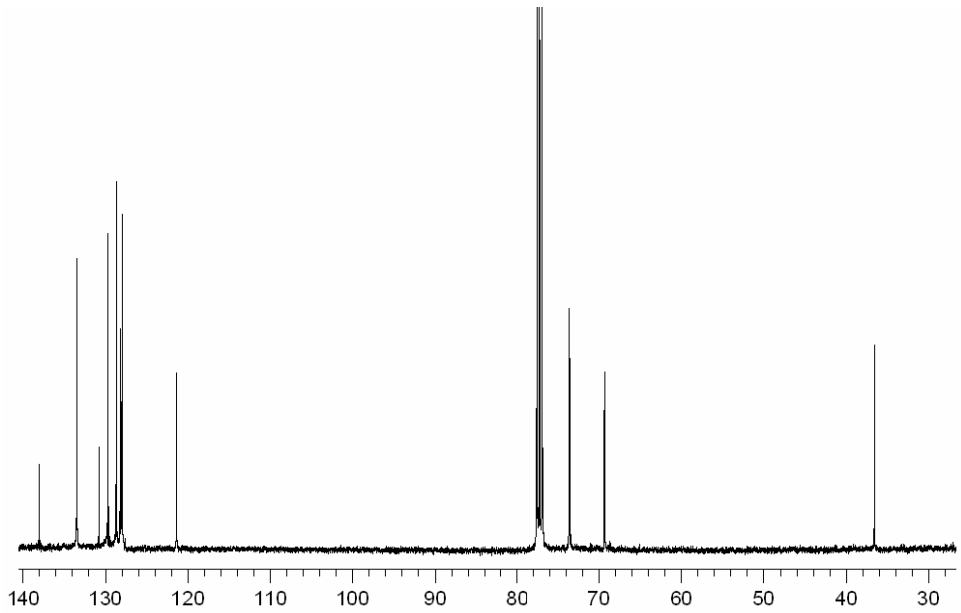




^{1}H and ^{13}C spectra of (2*S*)-1-(benzyloxy)-5-(phenylselenenyl)pent-4-in-2-ol (152)

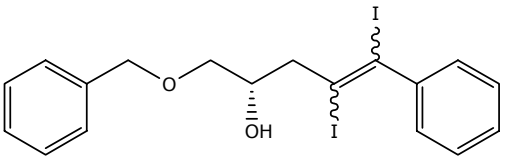


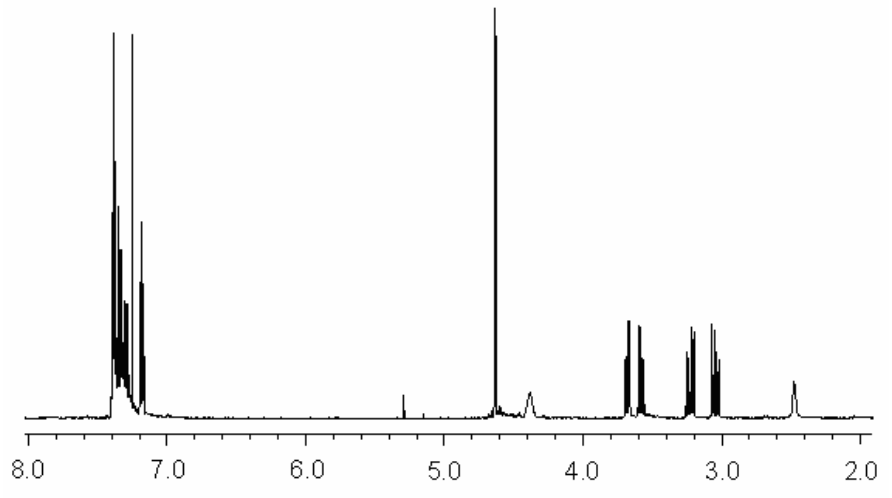


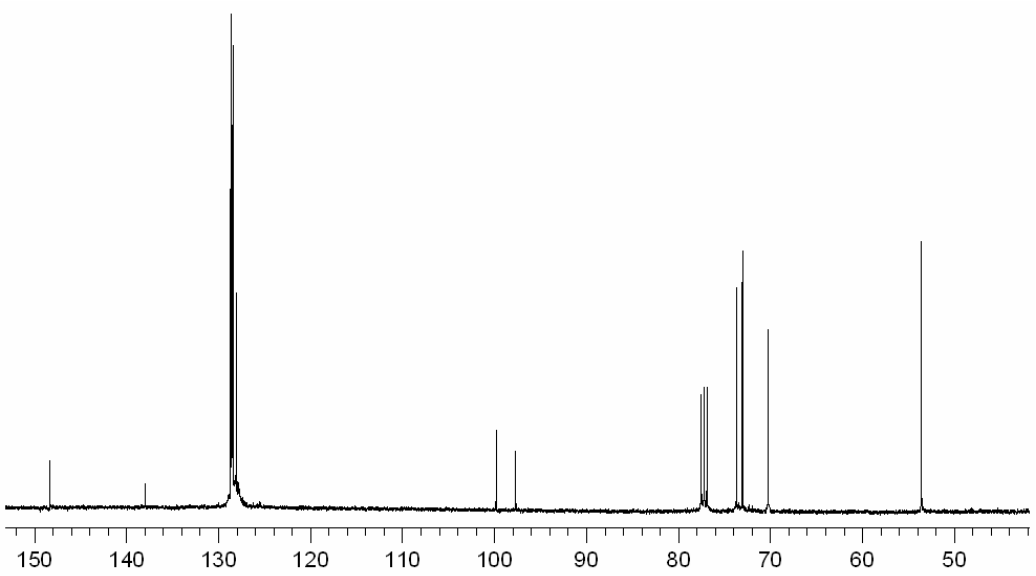


UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

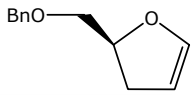
^{1}H and ^{13}C spectra of (2*S*)-1-(benzyloxy)-4,5-diiodo-5-phenylpent-4-en-2-ol (153)

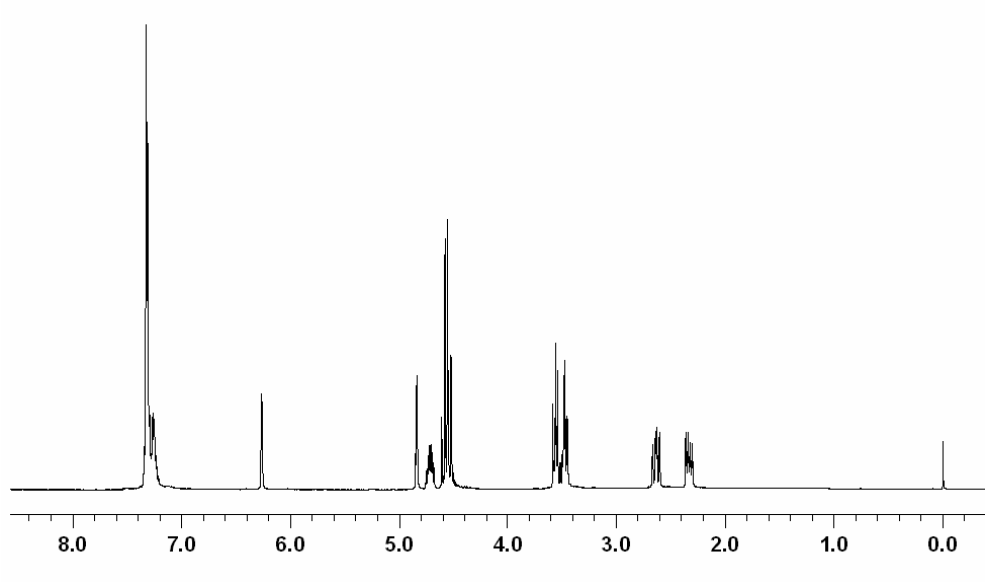


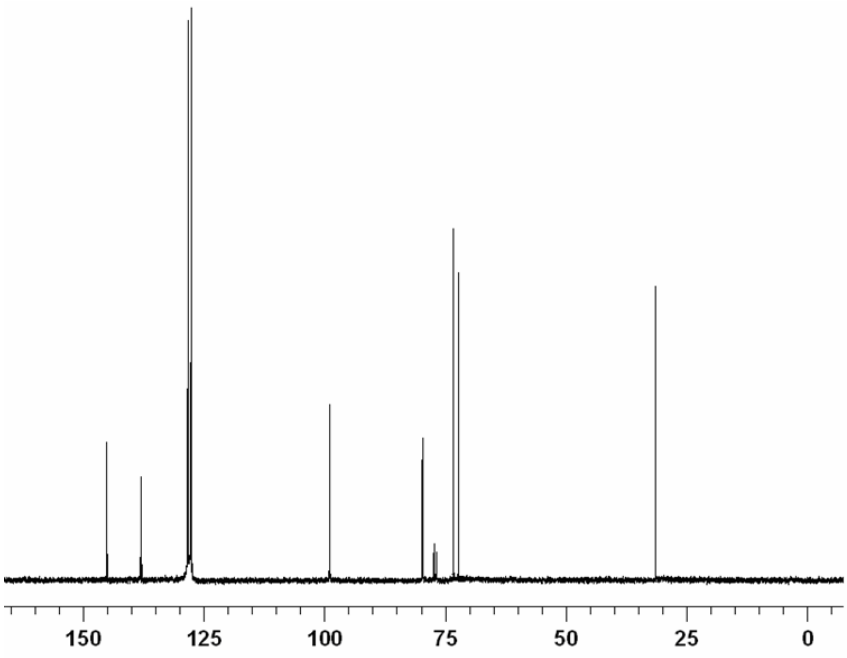




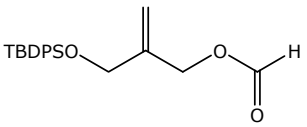
^{1}H and ^{13}C spectra of 2*S*-(benzyloxymethyl)-2,3-dihydrofuran (154)

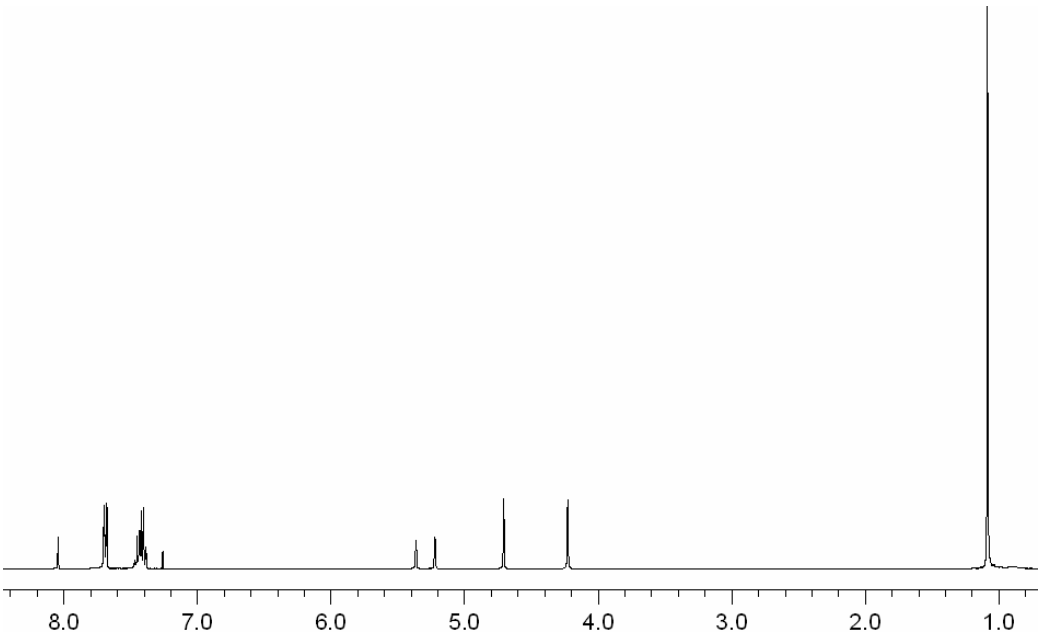


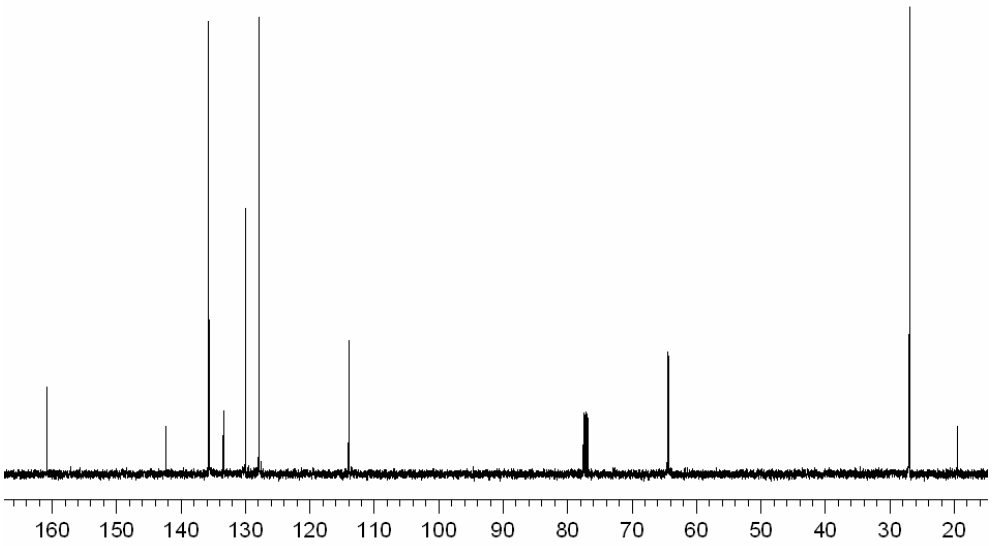




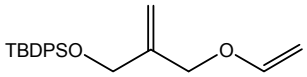
^{1}H and ^{13}C spectra of 2-((*tert*-butyldiphenylsilyloxy)methyl)-propen-3-yl formate (187)

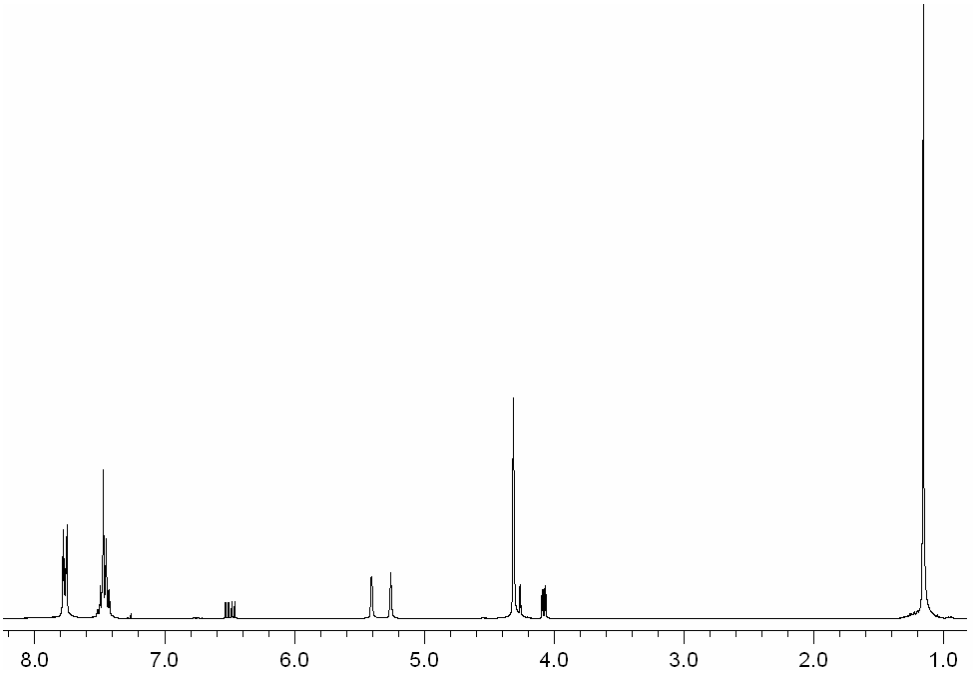


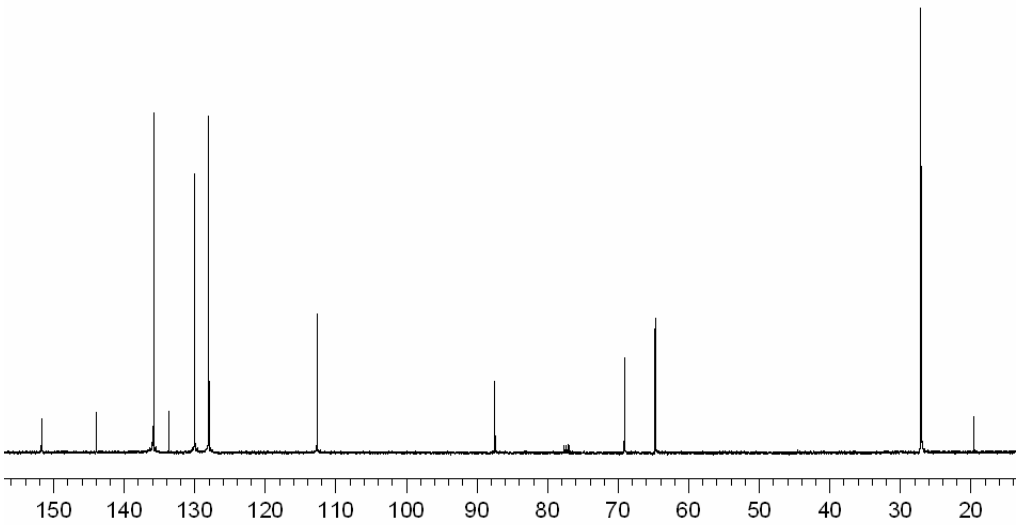




^{1}H and ^{13}C spectra of 2-*O*-((*tert*-butyldiphenylsilyloxy)methyl)allyl vinyl ether (188)

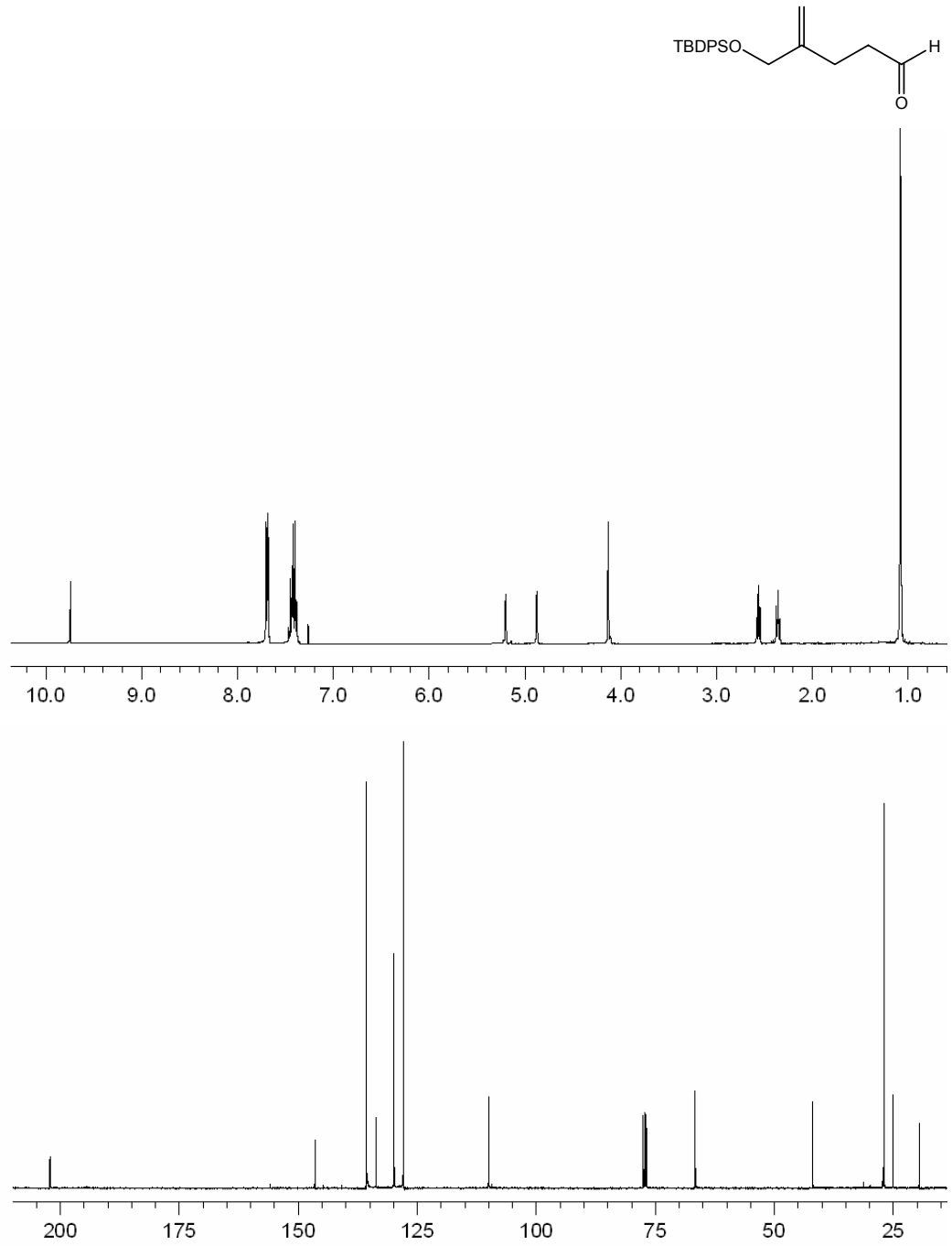




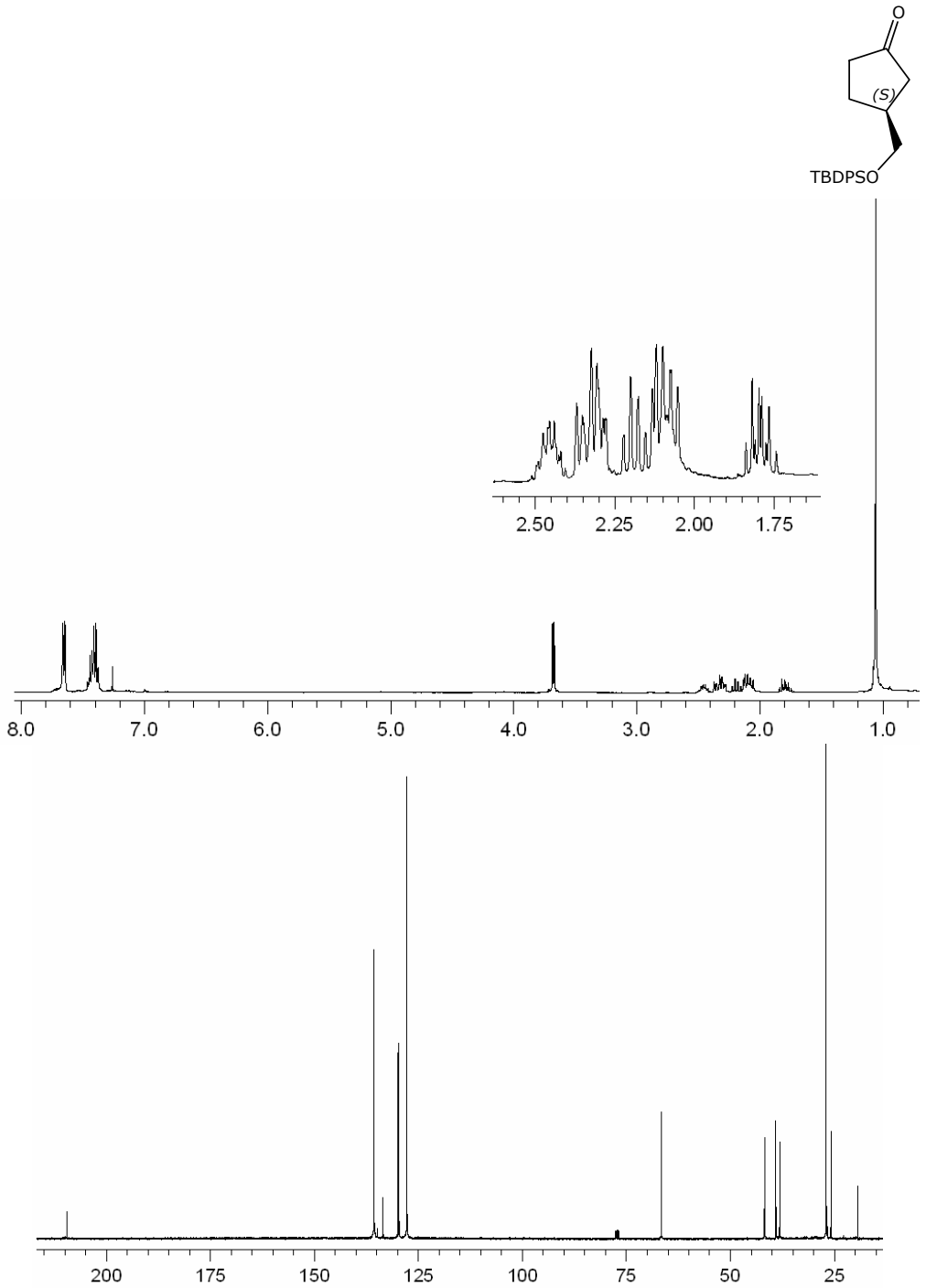


UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

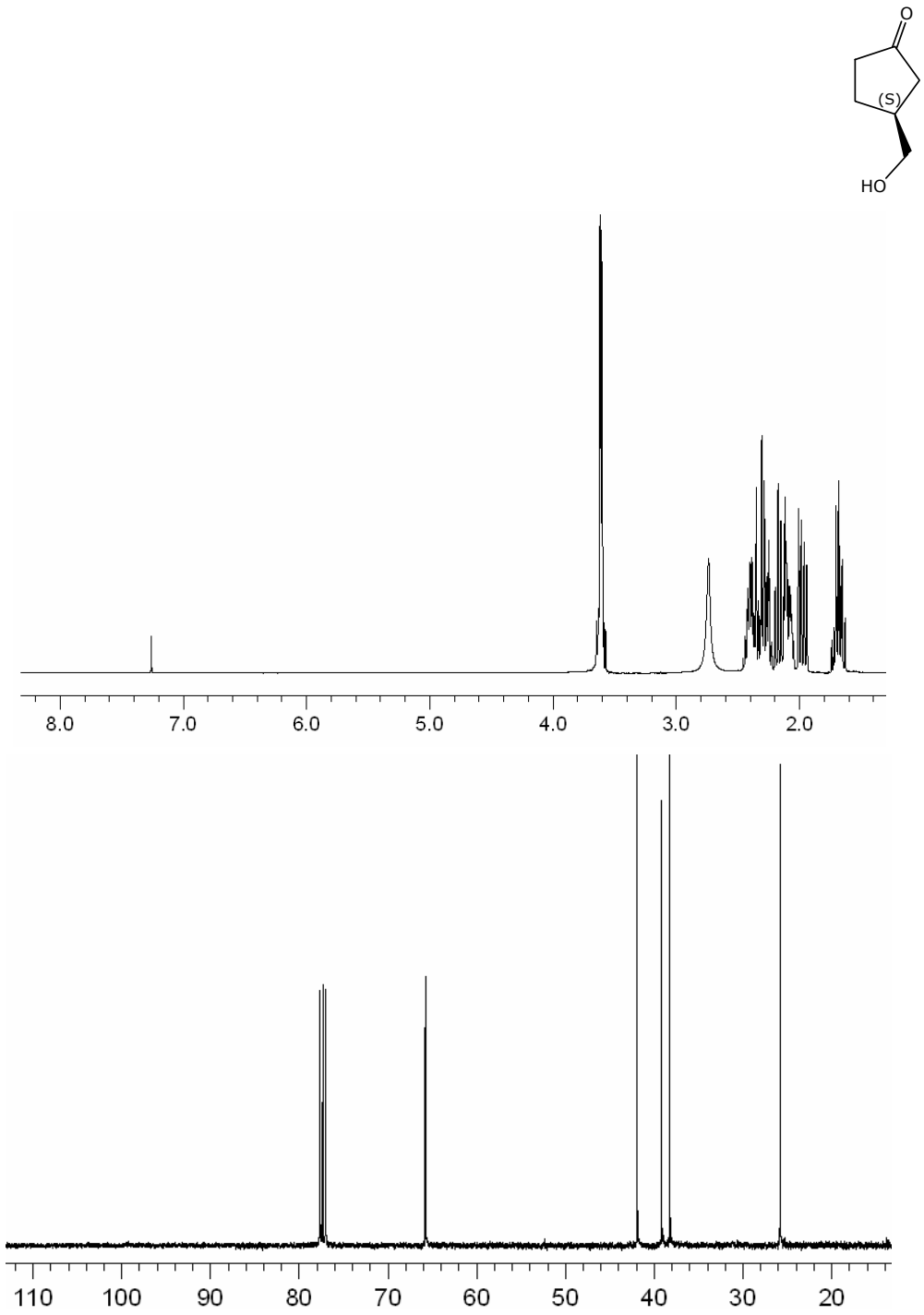
^{1}H and ^{13}C spectra of 4-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enal (189)



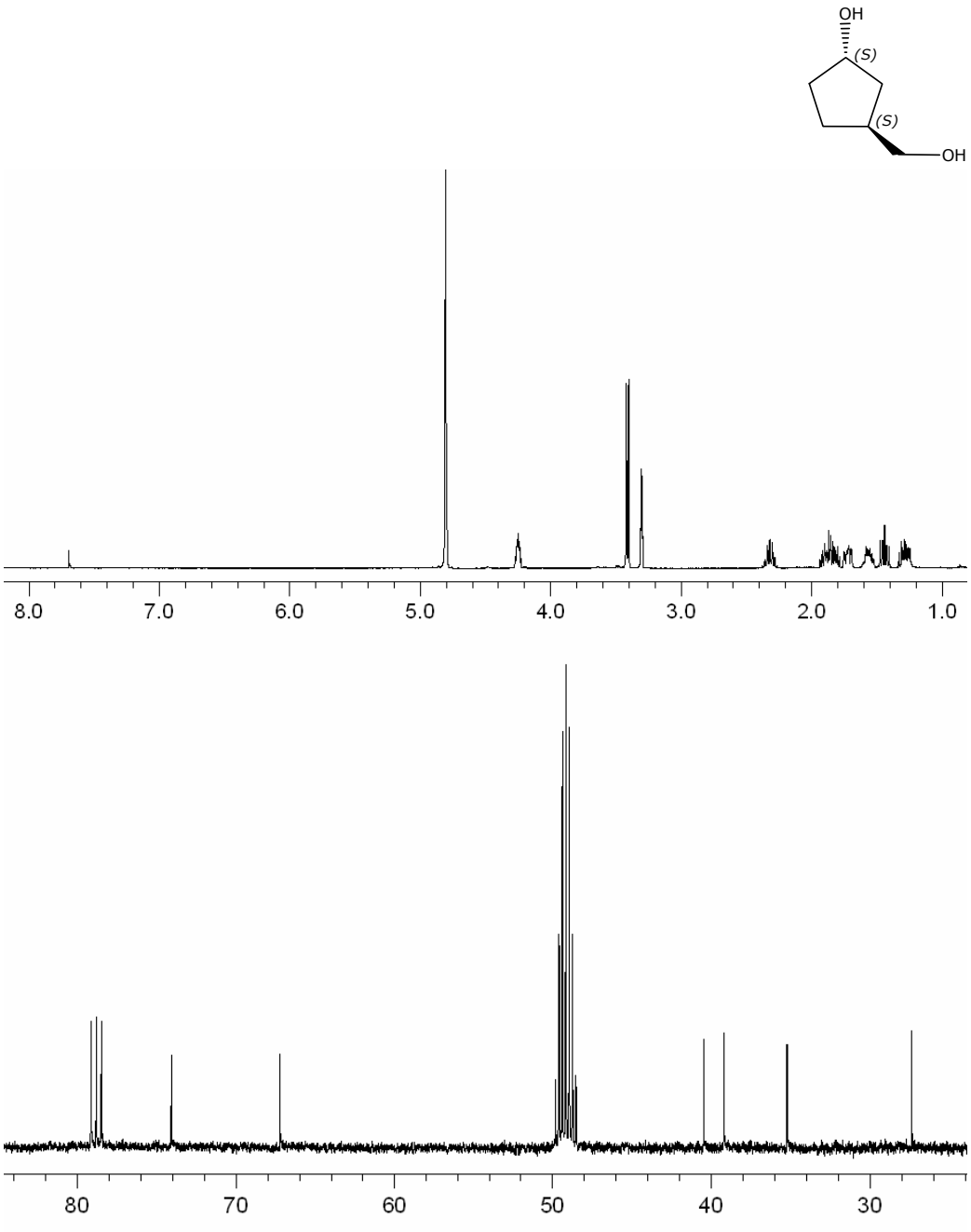
^{1}H and ^{13}C spectra of 3*R* and 3*S*-((*tert*-butyldiphenylsilyloxy)methyl) cyclopentanone (215*S*)



^{1}H and ^{13}C spectra of 3*S*-(hydroxymethyl)cyclopentanone (228*S*)

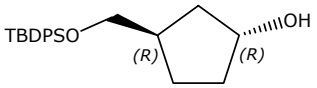


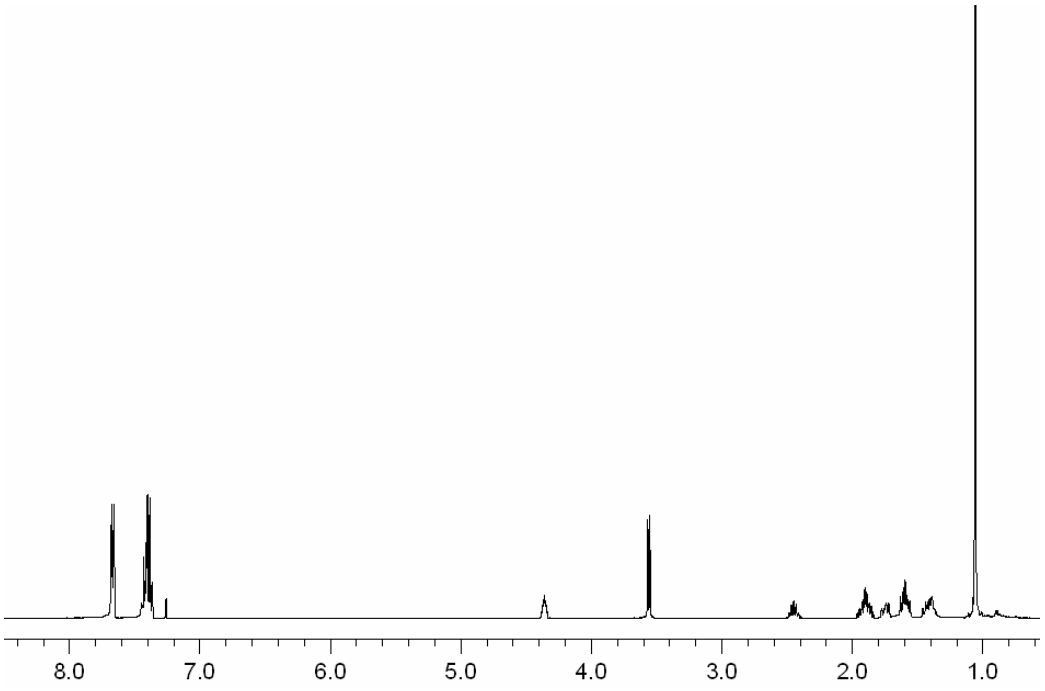
^{1}H and ^{13}C spectra of (1*S*,3*S*)-3-(hydroxymethyl)cyclopentanol (229(1*S*,3*S*))

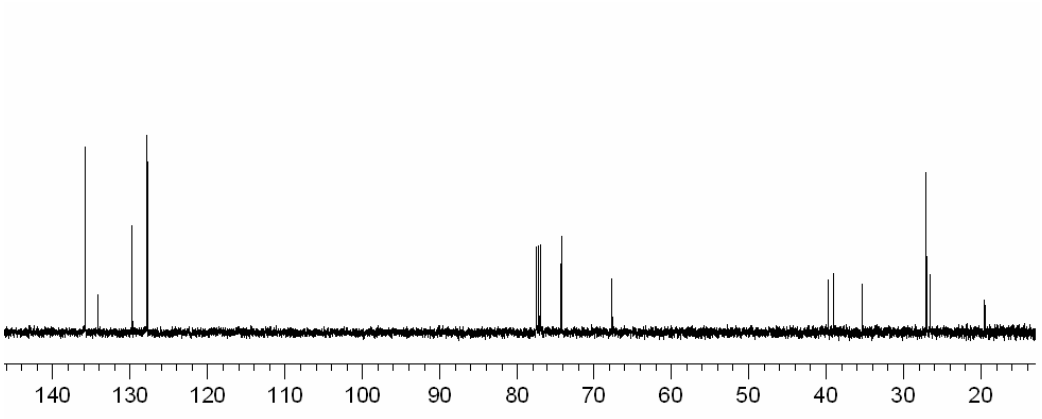


UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

^{1}H and ^{13}C spectra of (1*R*,3*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl) cyclopentanol (224a(1*R*,3*R*))

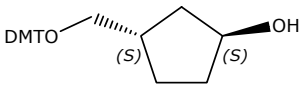


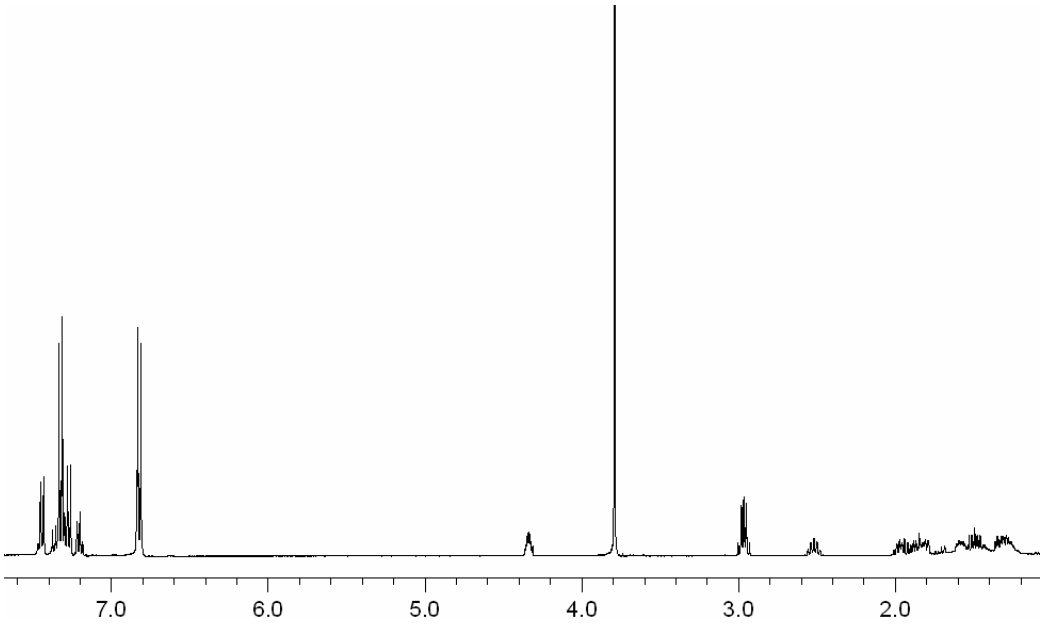


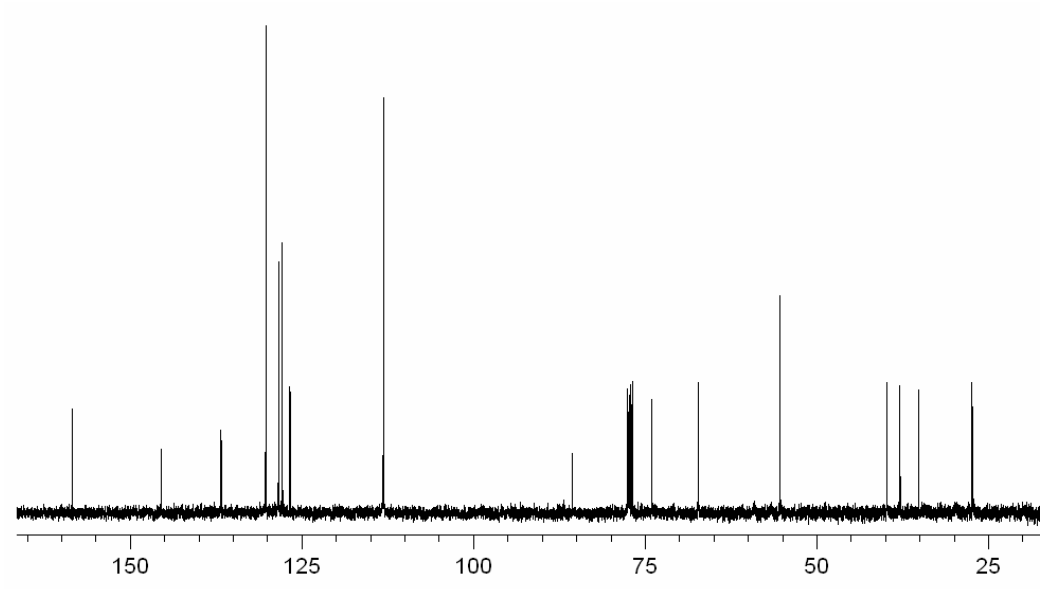


UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

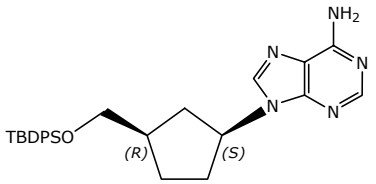
^{1}H and ^{13}C spectra of (1*S*,3*S*)-3-((dimethoxytrityloxy)methyl)cyclopentanol (224b(1*S*,3*S*))

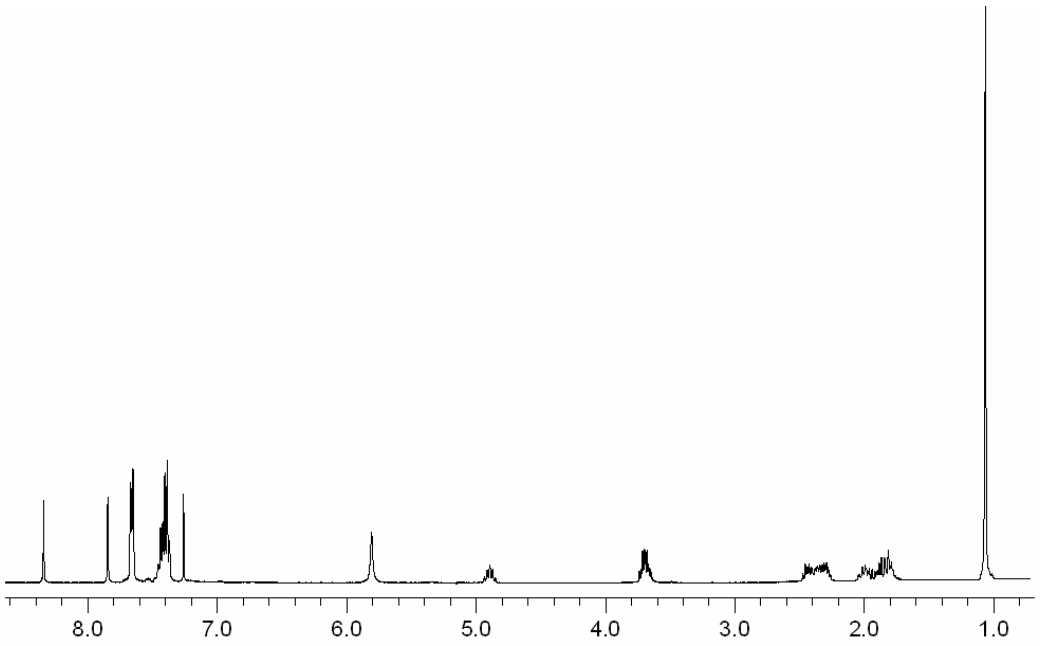


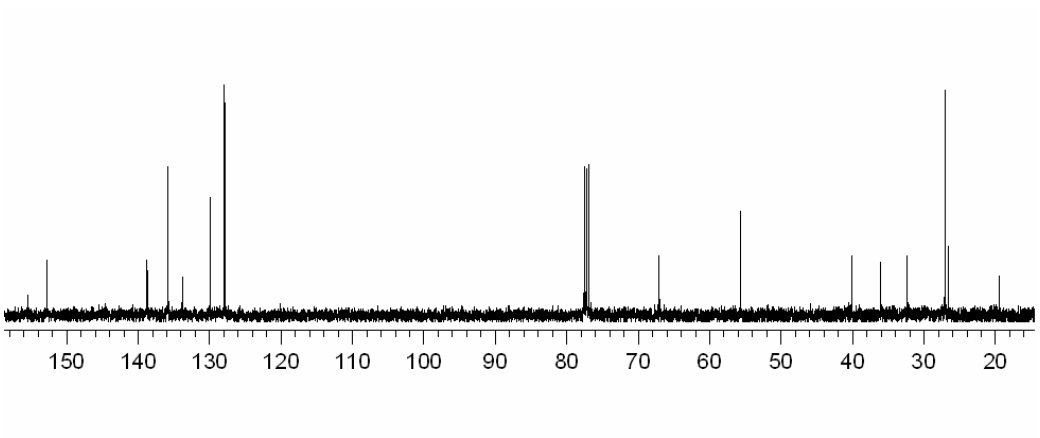




^{1}H and ^{13}C spectra of 9-[(1S,3R)-3-(((*tert*-butyldiphenylsilyloxy)methyl)) cyclopentyl]-9H-purin-6-amine (233a(1*S*,3*R*))

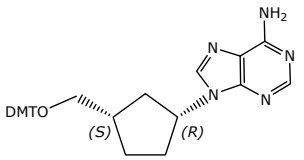


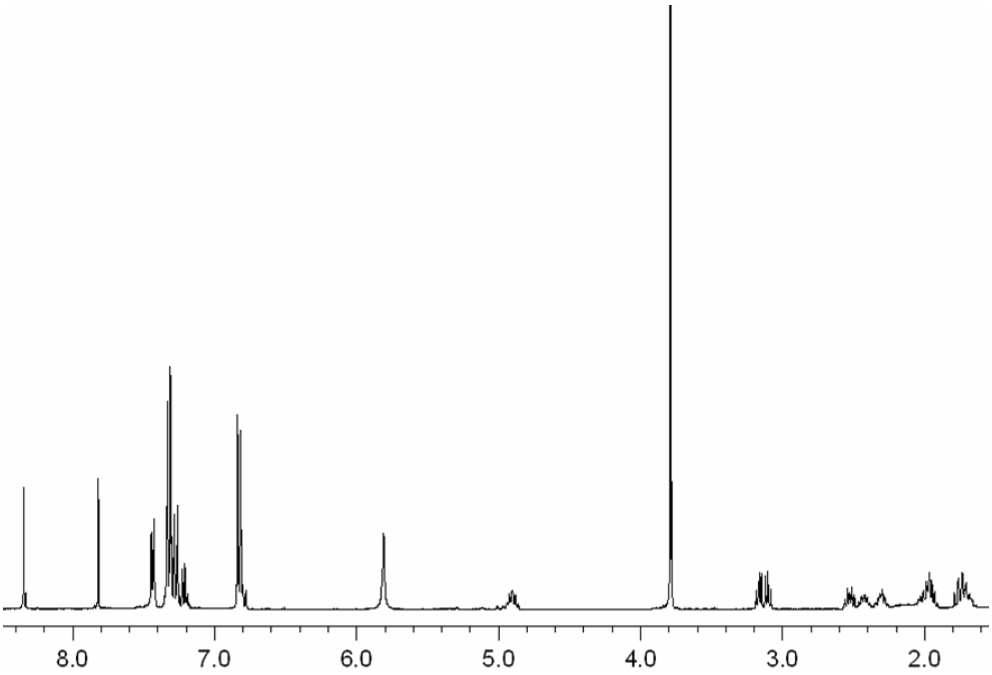


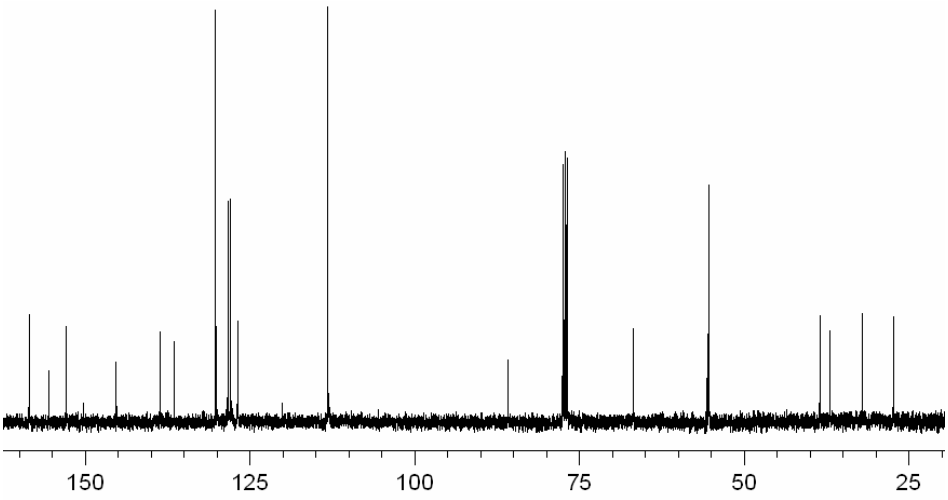


UNIVERSITAT ROVIRA I VIRGILI
HYDROACYLATION AND C-N COUPLING REACTIONS. MECHANISTIC STUDIES AND APPLICATION IN THE NUCLEOSIDE SYNTHESIS
Patricia Marcé Villa
ISBN:978-84-691-8840-8/DL: T-1262-2008

^{1}H and ^{13}C spectra of 9-[(1R,3S)-3-(((dimethoxytrityloxy)methyl)) cyclopentyl]-9H-purin-6-amine (233b(1*R*,3*S*))

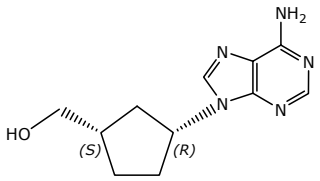


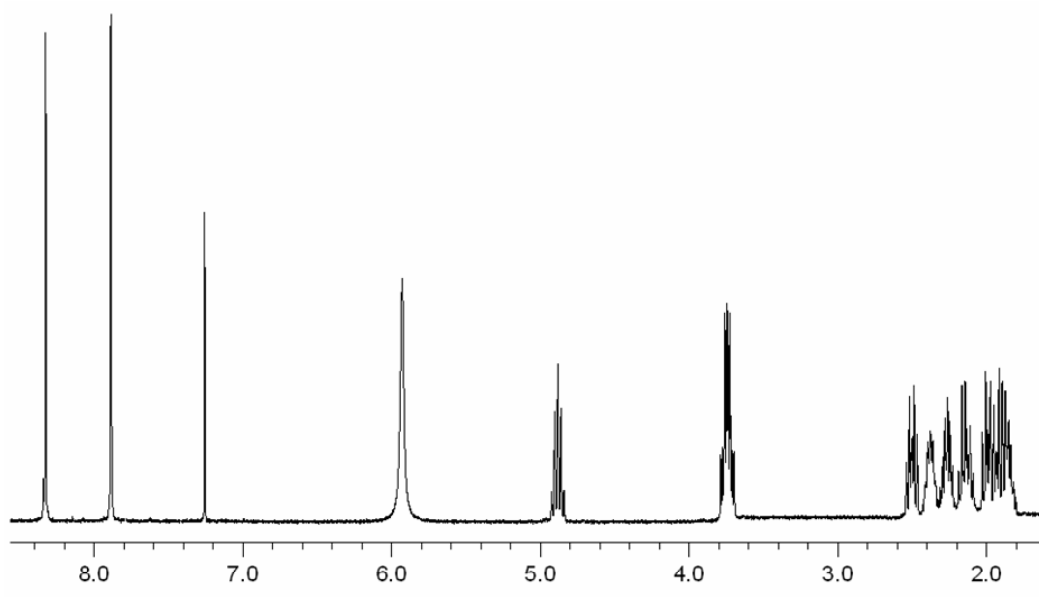


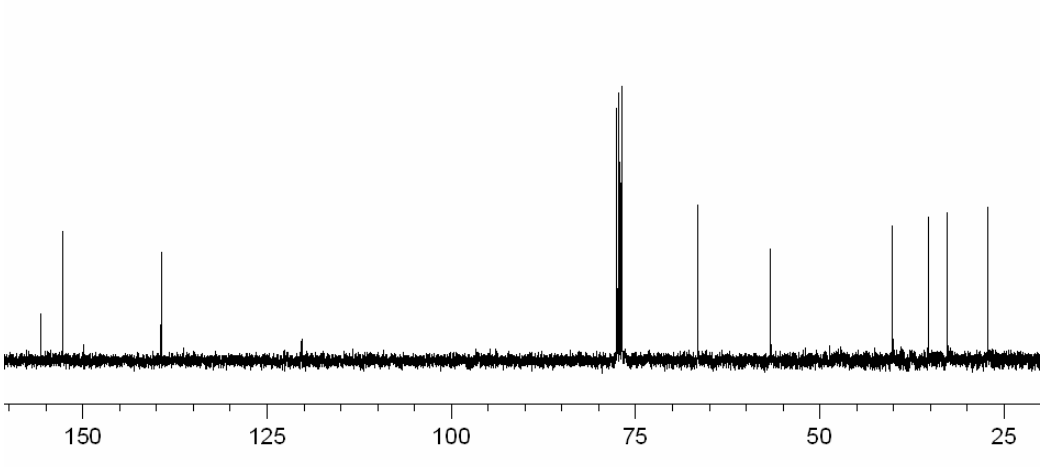


ISBN:978-84-691-8840-8/DL: T-1262-2008

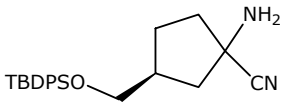
^{1}H and ^{13}C spectra of ([(1*R*,3*S*)-3-(6-amino-9H-purin-9-yl) cyclopentyl]methanol (234(1*R*,3*S*))

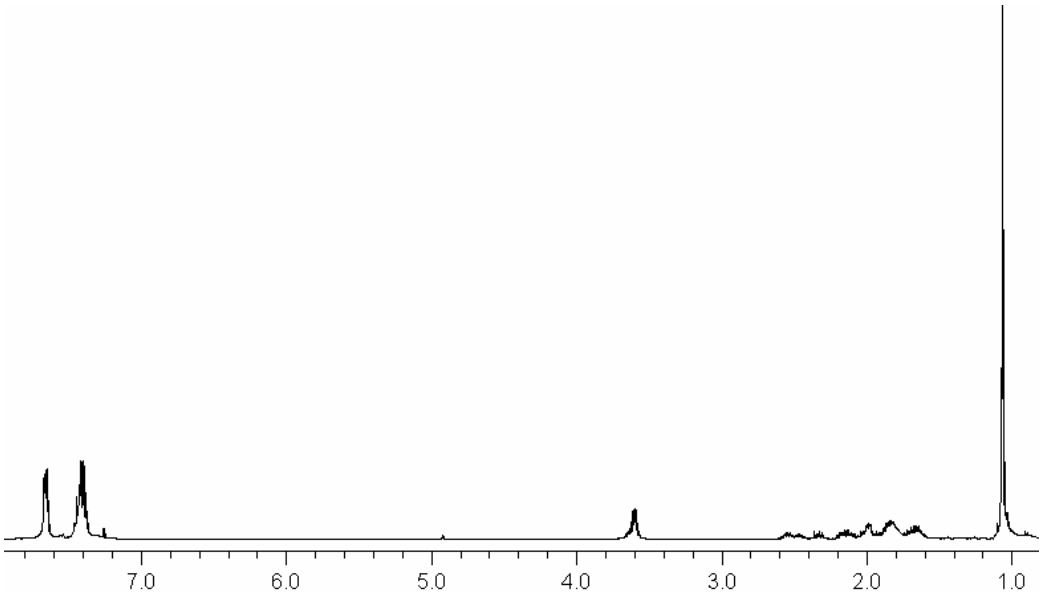


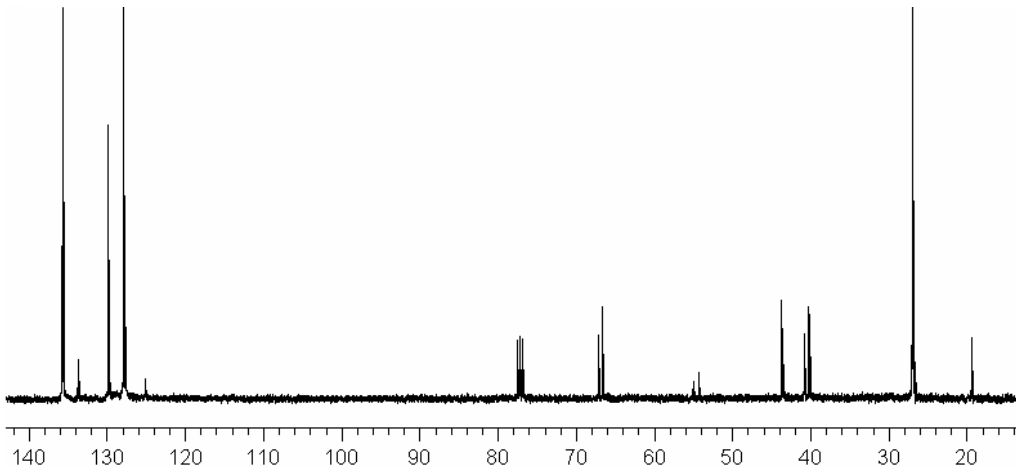




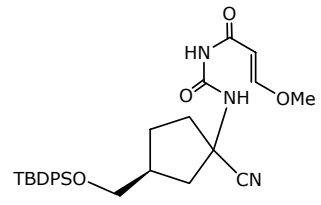
^{1}H and ^{13}C spectra of (3*S*)-1-Amino-3-((*tert*-butyldiphenylsilyloxy) methyl)cyclopentanecarbo-nitrile

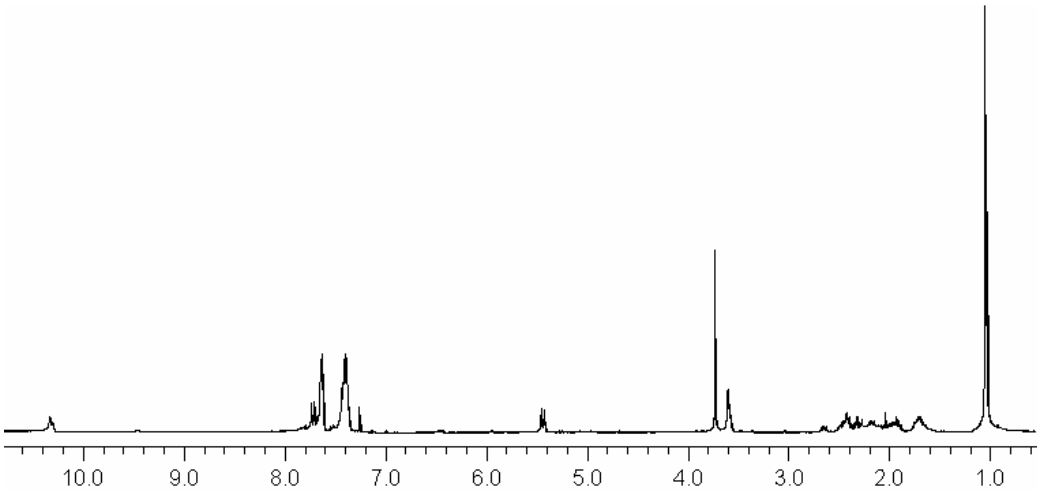


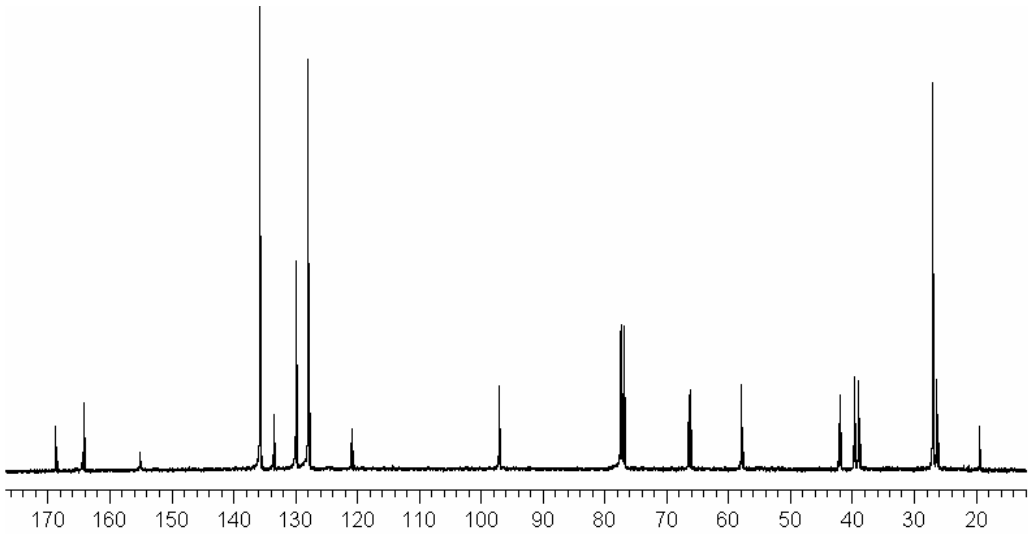


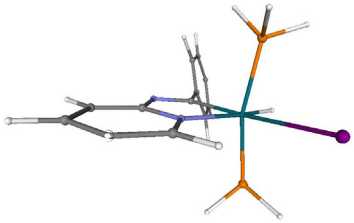


^{1}H and ^{13}C spectra of (*E*)-N-((3*S*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)-1-cyanocyclopentyl carbamoyl)-3-methoxyacrylamide









Distances	Angles
Rh-N= 2.15 (2.21)	P-Rh-P= 159.7 (164.9)
Rh-C= 1.98 (2.03)	N-Rh-C= 78.5 (76.5)
Rh-I= 2.771 (2.91)	P-Rh-I= 90.0 (89.3)
Rh-P= 2.33 (2.32)	P-Rh-I= 87.3 (82.1)
Rh-P= 2.33 (2.30)	I-Rh-C= 174.8 (171.6)
Rh-H= ---- (1.57)	I-Rh-N= 98.1 (96.1)

Figure S1. Molecular structure of **246-*trans*** iodine, and selected geometrical parameters for the X-ray structure (PPh_3 instead of PH_3) determined by Albinati *et al.*, and for the DFT structure (in parentheses) determined in this study.