Frédéric Liron

Chirality Transfer in Acyclic Allylic Systems and New Pd-Catalyzed Heck Reaction/ C-H Activation Cascades

München 2004

Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Chirality Transfer in Acyclic Allylic Systems and New Pd-Catalyzed Heck Reaction/ C-H Activation Cascades

von

Frédéric Liron

aus

Dijon, Frankreich

München
2004

Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs.3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Professor Dr. P. Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

München, am 03.06.2004

Frédéric Liron

Dissertation eingereicht am 15.06.2004

1. Gutachter: Prof. Dr. P. Knochel
2. Gutachter: Prof. Dr. W. Steglich

Mündliche Prüfung am 26.07.2004

This work was carried out from September 2000 to May 2004 under the guidance of Prof. Knochel at the Fakultät für Chemie und Pharmazie der Ludwig-Maximilians-Universität, Munich.

I would like to thank Prof. Knochel for giving me the opportunity to do my Ph. D. in his group and for his valuable help and the stimulating discussions throughout this work.

I am also very grateful to Prof. Steglich for agreeing to be my "Zweitgutachter", as well as Prof. Karaghiosoff, Langhals, Pfaendler and Heuschmann for the interest shown in this manuscript by accepting to be referees.

I would like to thank the Ludwig-Maximilians-Universität for financial support.

I am grateful to Dr. Ackermann, Helena Leuser and Delphine Renard for the careful correction of this manuscript.

I would like to thank Andrei Gavriouchine, Helena Leuser and Sylvie Perrone for fruitful collaborations in the fields of asymmetric rearrangements of phosphinites and asymmetric S_N2' subtitutions. I thank all past and present co-workers I have met in the AK Knochel for the nice working atmosphere.

Dr. Stephenson and Dr. Polborn I thank for measuring an INADEQUATE NMR experiment and an X-ray structure respectively, as well as the analytical team.

Parts of this Ph. D. have been published:

F. Liron, P. Knochel, "Asymmetric [2,3] Sigmatropic Rearrangement of Acyclic Allylic Phosphinites", *Chem. Commun.* **2004**, 304.

“ Zu viel, zu viel, [...]
laß´ mich zieh´n!“
R. Wagner , *Tannhäuser,* I,1.

TABLE OF CONTENTS

ABBREVIATIONS 9

GENERAL INTRODUCTION 11

1. Overview 12

1.1. Precedents in the use of self-immolative chirality 13

1.2. Preparation of chiral ligands 16

2. Objectives 18

PART I: CHIRALITY TRANSFER IN ACYCLIC ALLYLIC SYSTEMS 21

CHAPTER I: Asymmetric [2,3] Sigmatropic Rearrangement of Acyclic Allylic Phosphinites 22

1. Introduction 22

1.1. General considerations about [2,3] sigmatropic rearrangements 22

1.2. [2,3] sigmatropic rearrangements of allylic phosphinites 24

2. Optimization of asymmetric [2,3] sigmatropic rearrangements of acyclic allylic phosphinites and preparation of new chiral ligands 26

2.1. Optimization of the reaction on a racemic mixture 26

2.2. Enantioselective [2,3] sigmatropic rearrangement of acyclic allylic phosphinites 36

2.3. Preparation of a new P,N-ligand from (*R*)-**5g** 40

2.4. Influence of the R^1 substituent on the stereoselectivity 43

2.5. Studies on the rearrangement of (*Z*)- and (*E*)-**26** 43

2.6. Preparation of new chiral P,P-ligands from (*R*)-**36** 49

3. Evaluation of monophosphine **40** in asymmetric catalysis 56

4. Conclusion 56

CHAPTER II: Copper-mediated Asymmetric Allylic Substitution Reactions for the Preparation of Molecules bearing Enantiomerically-enriched Quaternary Centers 58

1. Introduction 58

2. Enantioselective preparation of quaternary centers using self-immolative chirality and S_N2' substitution reactions 61

2.1. Scope and limitations: regio-, stereo- and enantioselectivity of Copper-mediated allylic substitution reactions 61

2.2. Application to the synthesis of enantiomerically-enriched desymmetrized 1,3-diols, aldol compounds and tertiary alcohols 63
3. Conclusion 67
PART II: NEW Pd-CATALYZED HECK REACTION/C-H ACTIVATION CASCADES 69
1. Introduction 70
1.1. C(sp^3)-H activation 70
1.2. Heck reaction /C-H activation in tandem processes 75
2. Intramolecular Heck reaction /regioselective C-H activation cascades 77
2.1. Introduction 77
2.2. Optimization of the reaction conditions 79
2.2.1. Optimization of the preparation of **37** 79
2.2.2. Proposed mechanism of the intramolecular Heck reaction/ C-H activation cascade 80
2.3. Synthesis of carbocycles 81
2.4. Synthesis of heterocycles 83
2.4.1. Synthesis of heterocycle precursors 83
2.4.2. Synthesis of N-containing heterocycles 84
2.4.3. Synthesis of O-containing heterocycles 87
3. Conclusion 88
SUMMARY AND OUTLOOK 89
EXPERIMENTAL PART 97
1. General Considerations 98
2. Products 99
2.1. Asymmetric [2,3] sigmatropic rearrangements 99
2.1.1. Preparation of the starting allylic alcohols 99
2.1.2. Preparation of the allylic phosphine oxides 123
2.1.3. Further functionalization of allylic phosphine oxides 138
2.2. Asymmetric Cu-mediated allylic substitution reactions 141
2.2.1. Preparation of the substrates 141
2.2.2. Enantioselective Cu-mediated allylic substitution reactions 145
2.2.3. Derivatization of the alkenes 149
2.3. Intramolecular Heck reaction /C-H activation cascades 158
2.3.1. Preparation of the substrates 158

2.3.2. Preparation of carbocycles 164
2.3.3. Preparation of N-containing heterocycles 166
2.3.4. Preparation of complexes 169
2.3.5. Preparation of O-containing heterocycles 171
3. Crystallographic Data for Complex **68a** 173

ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
η	hapto (coordination chemistry)
Ac	acetyl
AIBN	azobis(isobutyronitrile)
atm.	atmosphere
Bn	benzyl
br.	broad
calcd.	calculated
CI	chemical ionization
Cy	cyclohexyl
dba	*trans*, *trans*-dibenzylideneacetone
d	doublet
dec.	decomposition
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
d.r.	diastereoisomeric ratio
ee	enantiomeric excess
equiv.	equivalent
EI	electronic ionisation
Et	ethyl
FAB	fast-atom bombardment
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i-Bu	isobutyl
INADEQUATE	Incredible Natural Abundance DoublE QUAntum Transfer Experiment
i-Pr	isopropyl

I.R.	infra-red
J	coupling constant (NMR)
LG	leaving group
M	molar
m	meta
m-CPBA	meta-chloroperbenzoic acid
m	multiplet
Me	methyl
min	minute
mol.	molar (percentage)
m.p.	melting point
MS	mass spectrometry
N.M.R.	nuclear magnetic resonance
Ph	phenyl
PMHS	polymethylhydrosiloxane
Pent	pentyl
Pr	*n*-propyl
q	quartet
rac	racemic
rt	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
Tf	triflate
THF	tetrahydrofurane
TMS	trimethylsilyl

GENERAL INTRODUCTION

1. Overview

The preparation of enantiomerically pure compounds is of fundamental importance for organic chemists.[1] There are more and more examples that stress the necessity to prepare enantiomerically pure products. In 1996, two thirds of the drugs in the development stage were chiral, 51% of which were developed as single enantiomers. Moreover, in the case of racemates, the pharmaceutical industry has to prove that the one or the other of the enantiomers has no deleterious effect on the patient´s health, showing the significance of enantiomerically pure compounds. Therefore, the market for enantiomerically pure drugs raised from $ 73 billion in 1996 to over $ 123 billion in 2000.[2] Consequently, the search for efficient syntheses of enantiomerically pure compounds is an active area of research in both academic and industrial laboratories.[3]

Strategies to prepare enantiomerically pure compounds can be devided into three main categories:

- Synthesis from the chiral pool,
- Resolution of racemates,
- Asymmetric synthesis.

The last approach includes the use of chiral auxiliaries,[4] enzymes,[5] catalysts and reagents.[6] Although the use of the first three approaches was intensively investigated, the use of chiral, non-racemic reagents has received only little attention over the last decades due to its lack of "atom-economy", a stoichiometric amount of the chiral agent being required.

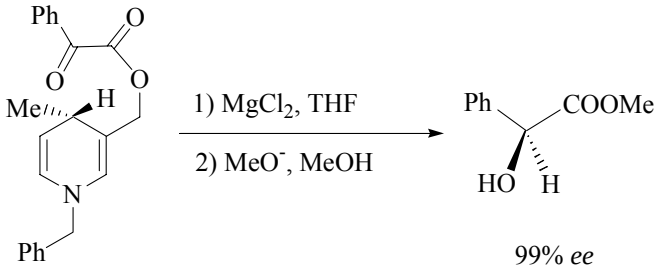
[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
[2] S. C. Stinson, *Chem. Eng. News* **2001**, *79*, 45.
[3] M. McCarthy, P. J. Guiry, *Tetrahedron* **2001**, *57*, 3809.
[4] R. A. Aitken, S. N. Kilenyi, *Asymmetric Synthesis*, Blackie, London, **1994**.
[5] C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, **1994**.
[6] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis, Springer*, Berlin, **1999**.

A chiral reagent can be used in two ways to install a new stereogenic center:

- The chiral reagent controls the formation of the newly created stereogenic center and the reaction yields a compound that contains two chiral centers in diastereo- and enantiomerically pure form,
- The chiral reagent allows the enantioselective formation of a stereogenic center and the initial source of chirality is lost during the process. This process is known as "self-immolative" chirality.[7]

1.1. Precedents in the use of self-immolative chirality

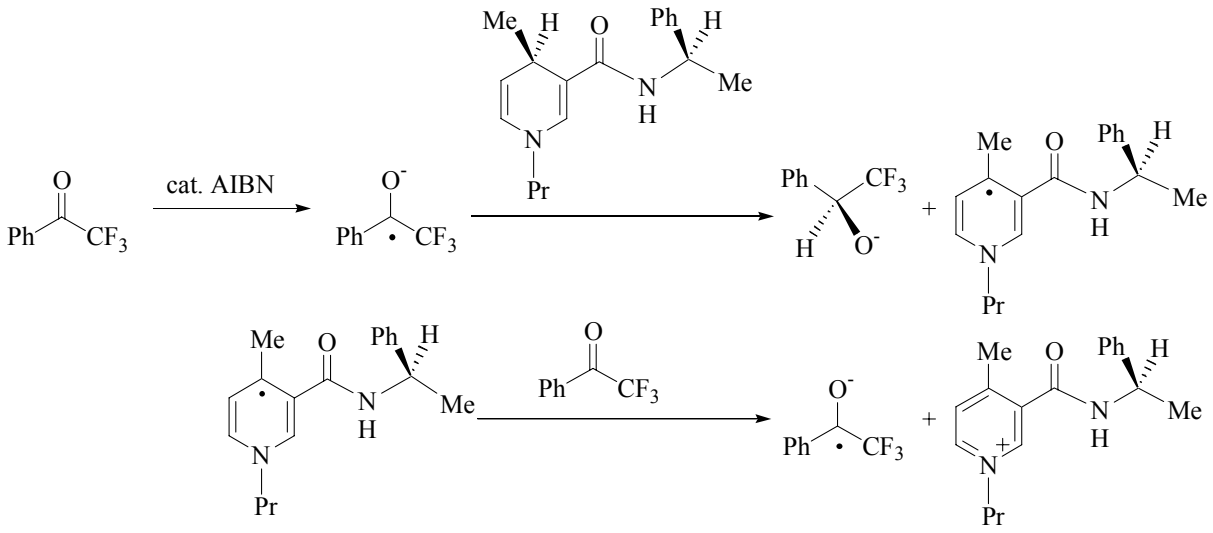
This concept was successfully used in an intramolecular manner for the asymmetric transfer of hydride (Scheme 1).[8] This process requires the presence of a magnesium salt. The alcohols were obtained in up to 99% *ee*.



Scheme 1. Self-immolative chirality in an intramolecular asymmetric hydride transfer reaction.

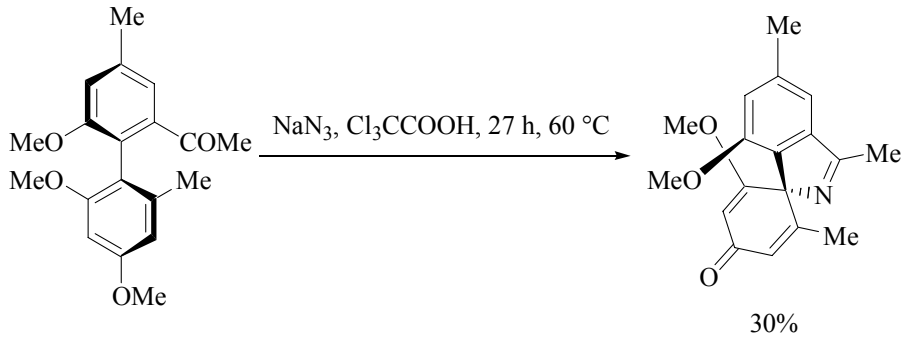
The same concept was used independently in an intermolecular manner by Tanner (Scheme 2).[9] Prochiral ketones were reduced by a chiral hydride donor in the presence of a catalytic amount of AIBN, yielding to a chiral alcohol with up to 68% *ee*.

[7] K. Mislow, *Introduction to Stereochemistry*, Benjamin, New York, **1966**, 131.
[8] A. I. Meyers, J. D. Brown, *J. Am. Chem. Soc.* **1987**, *109*, 3155.
[9] D. D. Tanner, A. Kharrat, *J. Am. Chem. Soc.* **1988**, *110*, 2968.



Scheme 2. Self-immolative chirality in an intermolecular asymmetric hydride transfer reaction.

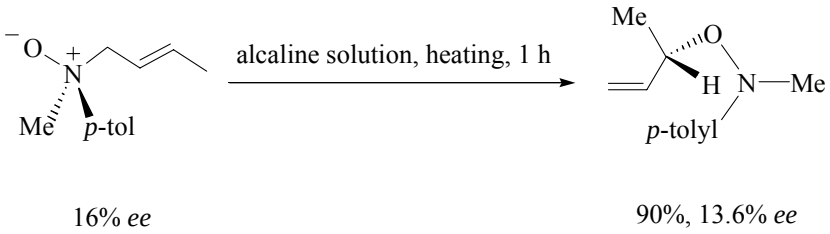
Sargent used the concept of self-immolative chirality to prepare a chiral spiro compound from an enantiomerically enriched biphenyl (Scheme 3).[10]



Scheme 3. Preparation of a chiral spiro compound from a chiral biphenyl.

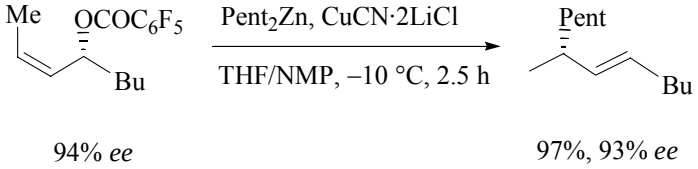
In 1976, Inouye reported an asymmetric [2,3] sigmatropic rearrangement of optically active allylic amine oxides to the corresponding alcohol (Scheme 4).[11] Here, the transfer of chirality was not complete due to free-radical side-reactions that led to racemization.

[10] R. W. Baker, R. V. Kyasnoor, M. V. Sargent, *Tetrahedron Lett.* **1999**, *40*, 3475.
[11] a) M. Moriwaki, Y. Yamamoto, J. Oda, Y. Inouye, *J. Org. Chem.* **1976**, *41*, 300; b) Y. Yamamoto, J. Oda, Y. Inouye, *J. Org. Chem.* **1976**, *41*, 303.



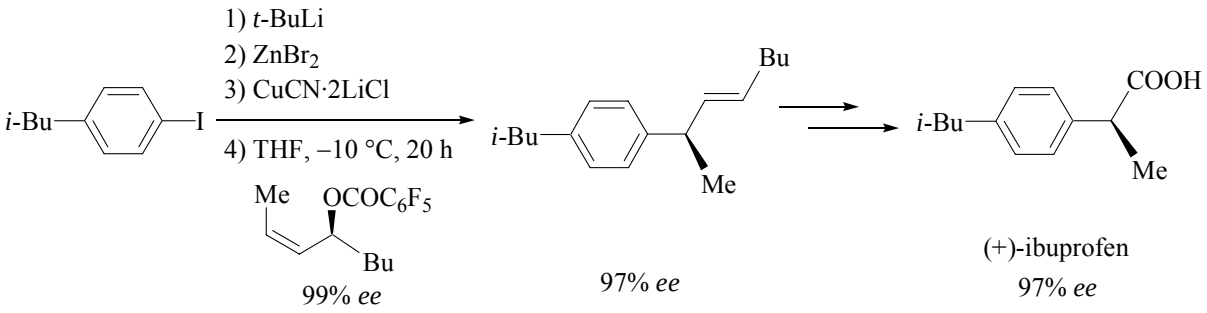
Scheme 4. Use of self-immolative chirality in asymmetric [2,3] sigmatropic rearrangements.

Recently, our group used this concept in asymmetric allylic substitution reactions.[12] Enantiomerically-enriched allylic alcohol derivatives underwent a smooth reaction with zinc cuprates to yield various new enantiomerically-enriched compounds in high yields and with a high chirality transfer (Scheme 5).



Scheme 5. Transfer of chirality in an asymmetric allylic substitution reaction.

The attractiveness of this method was examplified by the preparation of enantiomerically-enriched ibuprofen (Scheme 6).[12]

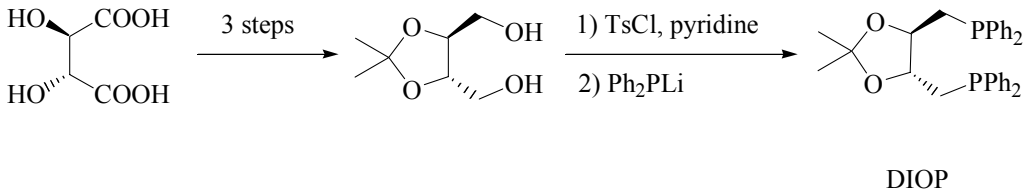


Scheme 6. Preparation of (+)-ibuprofen using self-immolative chirality.

[12] N. Harrington-Frost, H. Leuser, M. I. Calaza, F. F. Kneisel, P. Knochel, *Org. Lett.* **2003**, *5*, 2111.

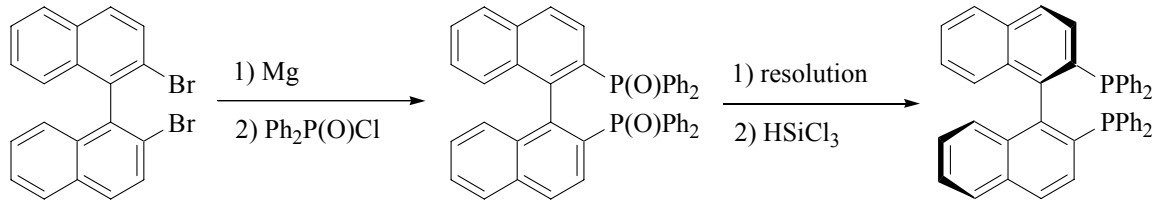
1.2. Preparation of chiral ligands

The importance of chiral ligands was acknowledged in 2001 when Knowles, Noyori and Sharpless were awarded the Nobel Prize for Chemistry for their work on asymmetric catalysis. Although very efficient catalysts have been developed, there is a need for new catalysts. Most of the popular ligands are either derived from the chiral pool (Kagan´s DIOP,[13] Scheme 7) or prepared by resolving a racemate (Noyori´s BINAP,[14] Scheme 8). Others bear a planar chirality (ferrocene-based ligands,[15] Scheme 9). Moreover, most of them bear a rigid backbone which reduces the number of possible conformations.



DIOP

Scheme 7. Preparation of DIOP.



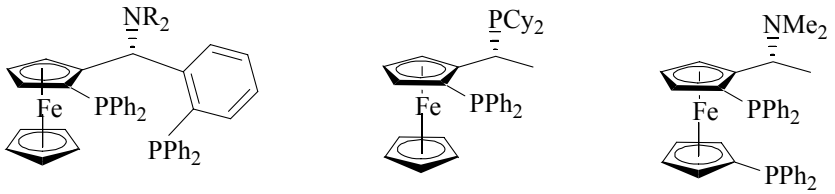
BINAP

Scheme 8. Preparation of BINAP.

[13] H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429.

[14] a) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932; b) H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, R. Noyori, *J. Org. Chem.* **1986**, *51*, 629; c) H. Takaya, S. Akutagawa, R. Noyori, *Org. Synth.* **1988**, *67*, 20.

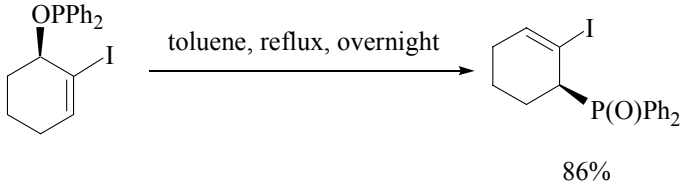
[15] For BPPFA, see: a) T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashina, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto, M. Kumada, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138; b) T. Hayashi, A. Yamazaki, *J. Organomet. Chem.* **1991**, *413*, 295; for TANIAPHOS, see: a) T. Ireland, G. Grossheimann, C. Wieser-Jeunesse, P. Knochel, *Angew. Chem.* **1999**, *111*, 3397; *Angew. Chem. Int Ed.* **1999**, *38*, 3212; b) T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. Eur. J.* **2002**, *8*, 843; for JOSIPHOS, see: A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062.



TANIAPHOS JOSIPHOS BPPFA

Scheme 9. Selected highly selective ferrocene-based ligands.

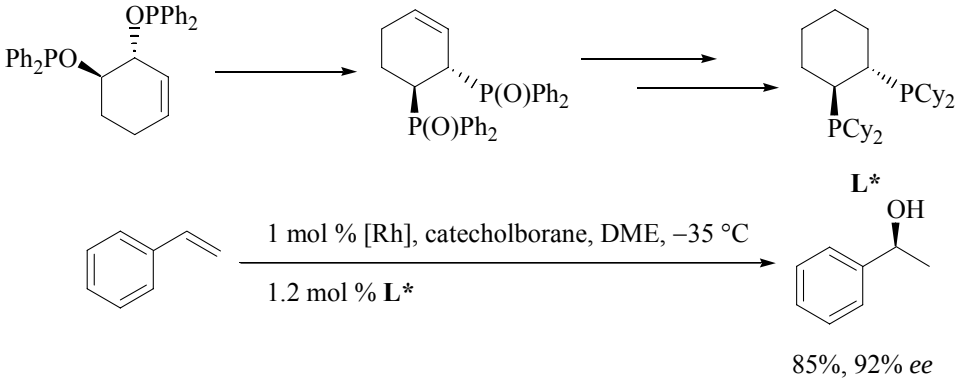
A novel method for the preparation of new chiral ligands was developed in our group and involves an asymmetric [2,3] sigmatropic rearrangement of allylic phosphinites (Scheme 10).[16]



86%

Scheme 10. Asymmetric [2,3] sigmatropic rearrangement of cyclic allylic phosphinites.

Starting from (1*R*,2*R*) 2-hydroxy-cyclohex-3-en-1-ol, this reaction led *via* a double [2,3] sigmatropic rearrangement to enantiomerically-enriched diphosphine oxides which were reduced to the corresponding diphosphines. These diphosphines proved to be efficient ligands in rhodium-catalyzed asymmetric hydroboration reactions (Scheme 11).[17]



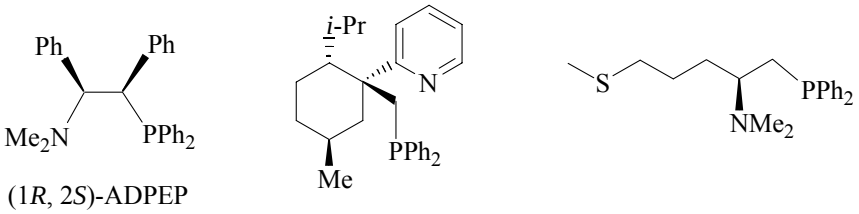
85%, 92% *ee*

Scheme 11. Preparation and application of ligands prepared *via* an asymmetric sigmatropic rearrangement.

[16] S. Demay, K. Harms, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 4981.
[17] S. Demay, F. Volant, P. Knochel, *Angew. Chem.* **2001**, *113*, 1272; *Angew. Chem. Int. Ed.* **2001**, *40*, 1235.

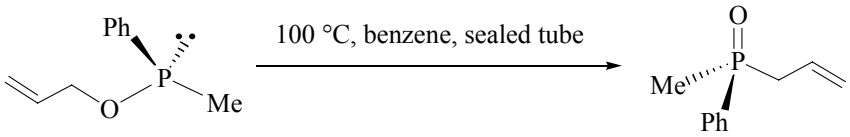
2. Objectives

As mentioned above, only few highly selective ligands have been prepared not bearing a rigid backbone. Selected examples of the most promising ligands designed so far are provided in Scheme 12.[18]



Scheme 12. Some new ligands lacking conformational rigidity.

As shown in Scheme 11, the asymmetric rearrangement of cyclic diphosphinites led to enantiomerically-enriched ligands. Mislow showed that this rearrangement occurs without racemization on phosphorus if an enantiomerically-enriched compound was used (Scheme 13).[19]



Scheme 13. Asymmetric [2,3] sigmatropic rearrangement using a chiral phosphorus atom.

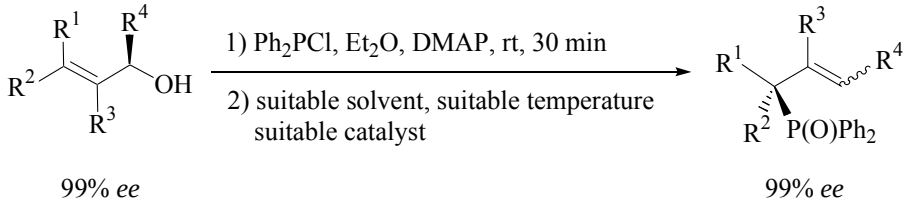
Following the concept of self-immolative chirality for the preparation of new ligands not bearing a rigid backbone, and in the preparation of chiral non-racemic quaternary centers *via* an asymmetric allylic substitution reaction, the aim of this work was the following:

- In the first part, the scope and limitations of the asymmetric [2,3] sigmatropic rearrangement, using the concept of self-immolative chirality was studied and the experimental conditions were optimized to prepare enantiomerically-enriched allylic phosphine oxides from enantiomerically-enriched allylic alcohols. Catalysts

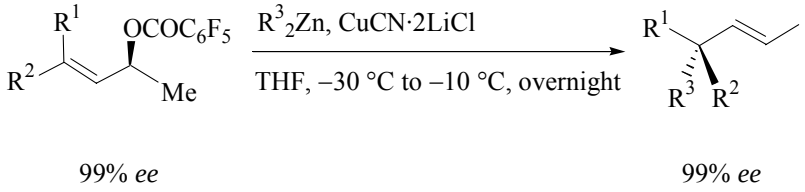
[18] a) G. Delapierre, G. Buono, *L´Act. Chim.* **February 2003**, 3; b) M. Hayashi, K. Takaoki, Y. Hashimoto, K. Saigo, *Enantiomer* **1997**, *2*, 293; c) C. G. Arena, F. Nicolo, D. Drommi, B. Giuseppe, F. Faraone, *Chem. Commun.* **1994**, 2251; d) B. K. Vriesema, R. M. Kellogg, *Tetrahedron Lett.* **1986**, *27*, 2049.
[19] A. W. Herriott, K. Mislow, *Tetrahedron Lett.* **1968**, 3013.

were also screened in order to perform the rearrangement at the lowest possible temperature. The enantioselectivity should be higher at lower temperature (Scheme 14). As shown in Scheme 4, asymmetric [2,3] sigmatropic rearrangements occur with good stereocontrol of the newly created stereogenic, if free-radical side-reactions can be avoided. Here, it will be of importance to obtain a complete transfer of chirality in order to get enantiomerically pure phosphines without the need for resolution of the enantiomers,

- The phosphine oxides obtained *via* the [2,3] sigmatropic rearrangement should then be reduced to enantiomerically-enriched phosphines. Complexes of these phosphines will be evaluated subsequently for their catalytic activity using standard reactions known in the literature,
- In the second part, the scope of the asymmetric allylic substitution reactions developed in our group based on the concept of the self-immolative chirality will be broadened. In view to prepare not only tertiary (Schemes 5 and 6), but also quaternary centers. A tertiary carbon enantiomerically enriched would in this case completely control the generation and the configuration of a quaternary one (Scheme 15). This would provide a simple access to quaternary carbon atoms, which are difficult to prepare using standard asymmetric reactions.



Scheme 14. Optimization of an asymmetric [2,3] sigmatropic rearrangement on an acyclic system.



Scheme 15. Enantiomerically-enriched quaternary centers prepared *via* an asymmetric allylic substitution.

PART I

CHIRALITY TRANSFER IN ACYCLIC ALLYLIC SYSTEMS

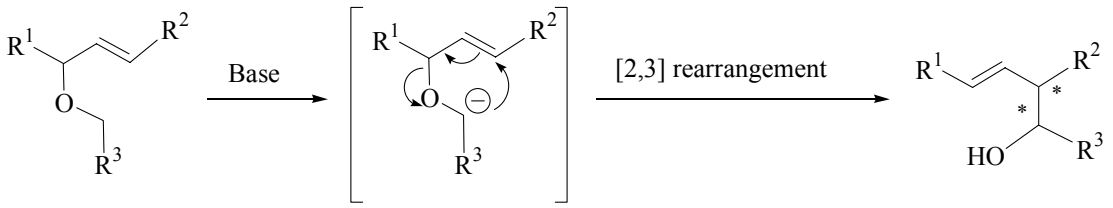
CHAPTER I

Asymmetric [2,3] Sigmatropic Rearrangement of Acyclic Allylic Phosphinites

1. Introduction

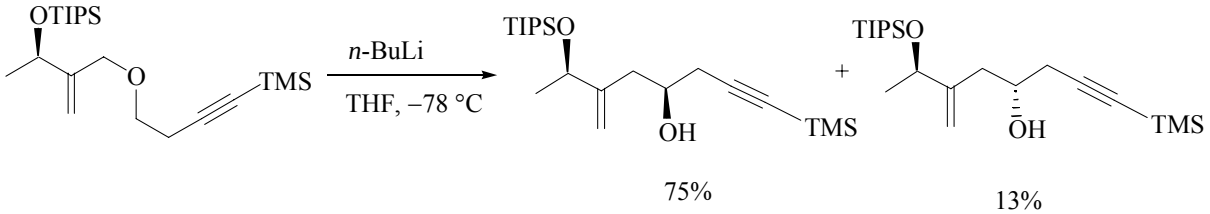
1.1 General considerations about [2,3] sigmatropic rearrangements

A well-known [2,3] sigmatropic rearrangement is the [2,3] Wittig rearrangement.[20] As can be seen from Scheme 16, it involves a carbanion in α position to an oxygen atom as the migrating terminus, yielding various types of homoallylic alcohols from allyl ethers.



Scheme 16. General equation for the [2,3] Wittig rearrangement.

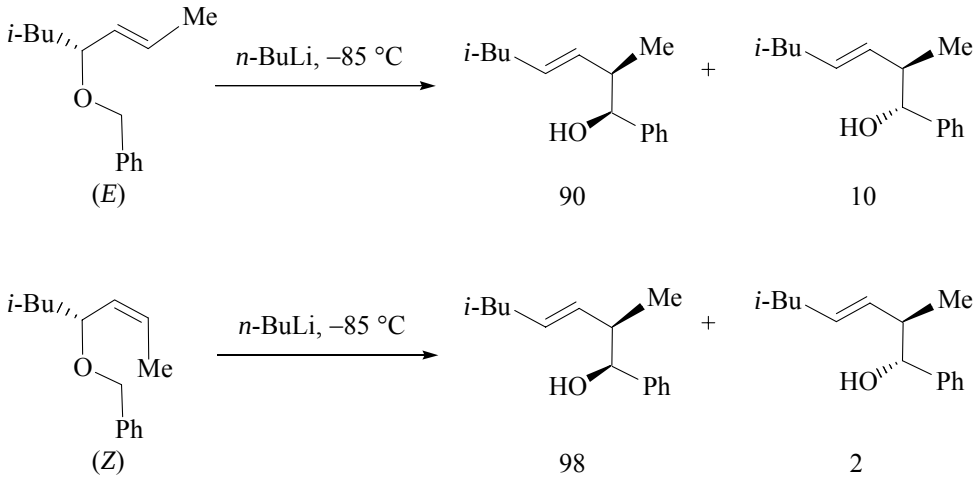
This rearrangement is typically performed at −78 °C. Therefore it has been intensively used in a diastereoselective manner. The created stereogenic center was controlled by the stereogenic center already present in the molecule as depicted in Scheme 17.[21]



Scheme 17. Diastereoselective [2,3] Wittig rearrangement.

[20] For reviews, see: a) T. Nakai, K. Tomooka, *Pure. Appl. Chem.* **1997**, *69*, 595; b) K. Mikami, T. Nakai, *Synthesis* **1991**, 594; c) T. Nakai, K. Mikami, *Chem. Rev.* **1986**, *86*, 885; d) R. W. Hoffmann, *Angew. Chem.* **1979**, *91*, 625.
[21] K. Tomooka, P.–H. Keong, T. Nakai, *Tetrahedron Lett.* **1995**, *36*, 2789.

The first example of chirality transfer was reported in 1971 by Baldwin and Patrick.[22] Since then, self-immolative chirality has been successfully used in an asymmetric [2,3] Wittig rearrangement at −85 °C (Scheme 18).[20] It is worth noting that the stereochemistry of the olefin was crucial. The (*E*) olefin led to a diastereomeric ratio of 90:10, while the (*Z*) olefin led to a ratio of 98:2.[23]

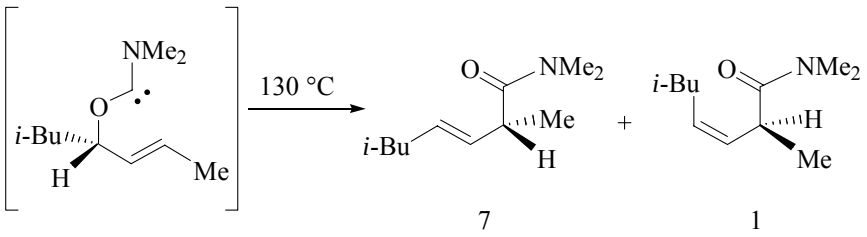


Scheme 18. Use of self-immolative chirality in a [2,3] Wittig rearrangement.

It appears from the literature that (*E*)/(*Z*) isomeric ethers give epimeric products. (*Z*) isomers react more selectively and are less influenced by structural changes. The final product is obtained as the (*E*) isomer.

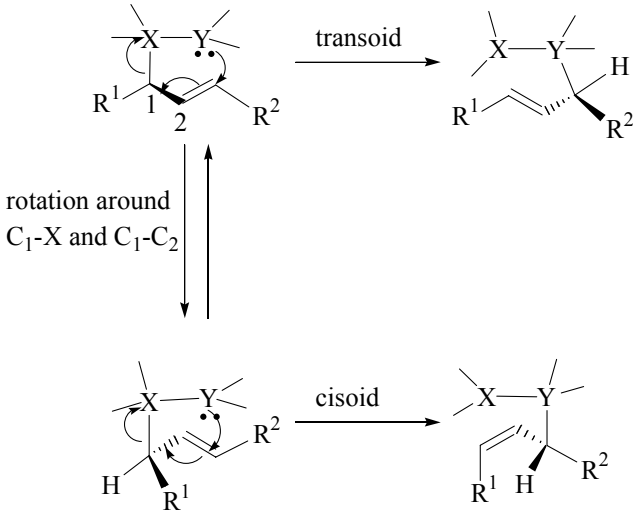
The Wittig rearrangement is known to be very selective, which might be partially due to the low temperature (typically −80 °C) at which the reaction is usually performed. Moreover, it involves a base, so that the rearrangement does not occur under neutral conditions. Neutral rearrangements are known as well, but, due to the flexible 5-membered ring intermediate,[20d] are often less stereoselective, as depicted in Scheme 19.[24]

[22] J. E. Baldwin, J. E. Patrick, *J. Am. Chem. Soc.* **1971**, *93*, 3556.
[23] N. Sayo, E. Kitahara, T. Nakai, *Chem. Lett.* **1985**, 259.
[24] a) G. Büchi, M. Cushman, H. Wüest, *J. Am. Chem. Soc.* **1974**, *96*, 5563; b) K. K. Chan, G. Saucy, *J. Org. Chem.* **1977**, *42*, 3828.



Scheme 19. Thermal [2,3] sigmatropic rearrangement with loss of stereo- and enantioselectivity.

This example shows that the energetic difference between the cisoid and the transoid intermediates[25] is that low to allow for both reaction products to be obtained with a comparable reaction rate (Scheme 20).



Scheme 20. Proposed intermediates in thermal [2,3] sigmatropic rearrangement.

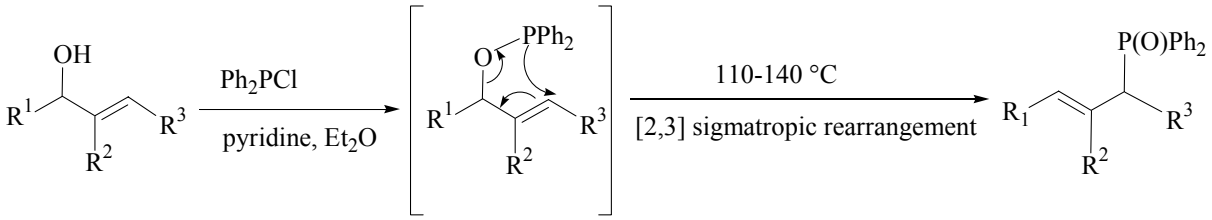
1.2. [2,3] sigmatropic rearrangements of allylic phosphinites

Although [2,3] sigmatropic rearrangements of propargylic phosphinites occur under very mild conditions[26] and, therefore, received much attention, the corresponding allylic phosphinites rearrange only upon heating and were neglected.

The first report was published in 1966. Allylic alcohols were treated with chlorodiphenylphosphine in the presence of a base and then heated between 110 and 140 °C

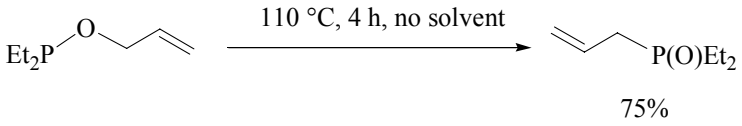
[25] P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4869.
[26] T. Pollok, H. Schmidbaur, *Tetrahedron Lett.* **1987**, *28*, 1085 and references therein.

for a few hours, yielding to the corresponding phosphine oxides, as depicted in Scheme 21.[27] This rearrangement was investigated only using racemic alcohols.



Scheme 21. The [2,3] sigmatropic rearrangement of allylic phosphinites to allylic phosphine oxides.

This rearrangement was extended to allyldiethylphosphinites by Pudovik (Scheme 22).[28]

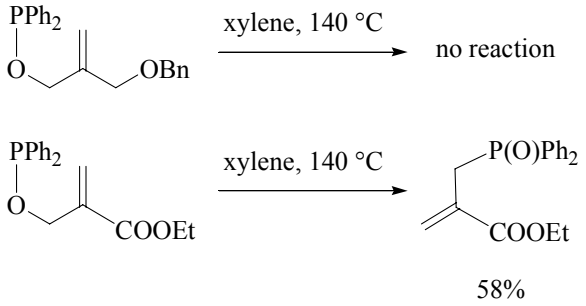


Scheme 22. [2,3] sigmatropic rearrangement of allyl diethylphosphinite.

Warren has studied the reactivity of the double bond in the phosphine oxide product. It underwent a cycloaddition with nitrile oxides, a Sharpless dihydroxylation, and Horner-Wittig elimination, but again these studies were performed with racemic mixtures.[29]

More interestingly, Harmata could perform the sigmatropic rearrangement of functionalized allyl diphenylphosphinites. This work demonstrated the importance of the substituents linked to the double bond (Scheme 23).[30]

[27] a) M. P. Savage, S. Tripett, *J. Chem. Soc. (C)* **1966**, 1842; b) M. P. Savage, S. Tripett, *J. Chem. Soc. (C)* **1967**, 1998.
[28] A. I. Pudovik, I. M. Aladzheva, L. V. Spirina, *Zh. Obshch. Khim.* **1967**, *37*, 700.
[29] a) S. K. Armstrong, E. W. Collington, J. G. Knight, A. Naylor, S. Warren, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1433; b) P. O´Brien, S. Warren, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2129; c) A. Nelson, S. Warren, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2645.
[30] M. Harmata, K. W. Carter, *Synth. Commun.* **1997**, *27*, 3027.



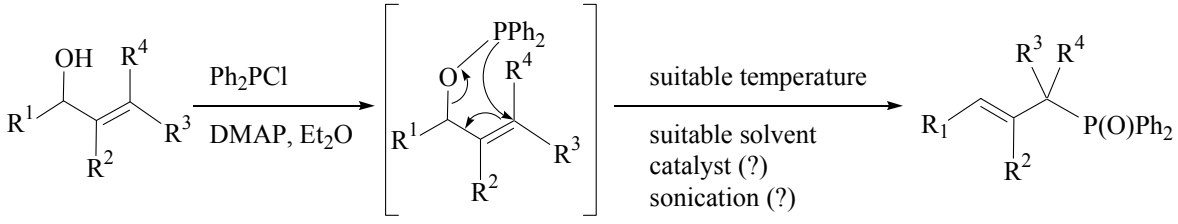
Scheme 23. [2,3] sigmatropic rearrangement of functionalized allyldiphenylphosphinites.

All studies on acyclic systems were performed on racemic mixtures so far. Mislow used P-chirogenic species to perform the rearrangement on open-chain systems. No detectable epimerization was observed (Scheme 13).[19] More recently, our group reported the first asymmetric [2,3] sigmatropic rearrangement bearing the stereogenic information on the carbon backbone, on cyclic systems (Schemes 10 and 11).[16,17]

2. Optimization of asymmetric [2,3] sigmatropic rearrangements of acyclic allylic phosphinites and preparation of new chiral ligands

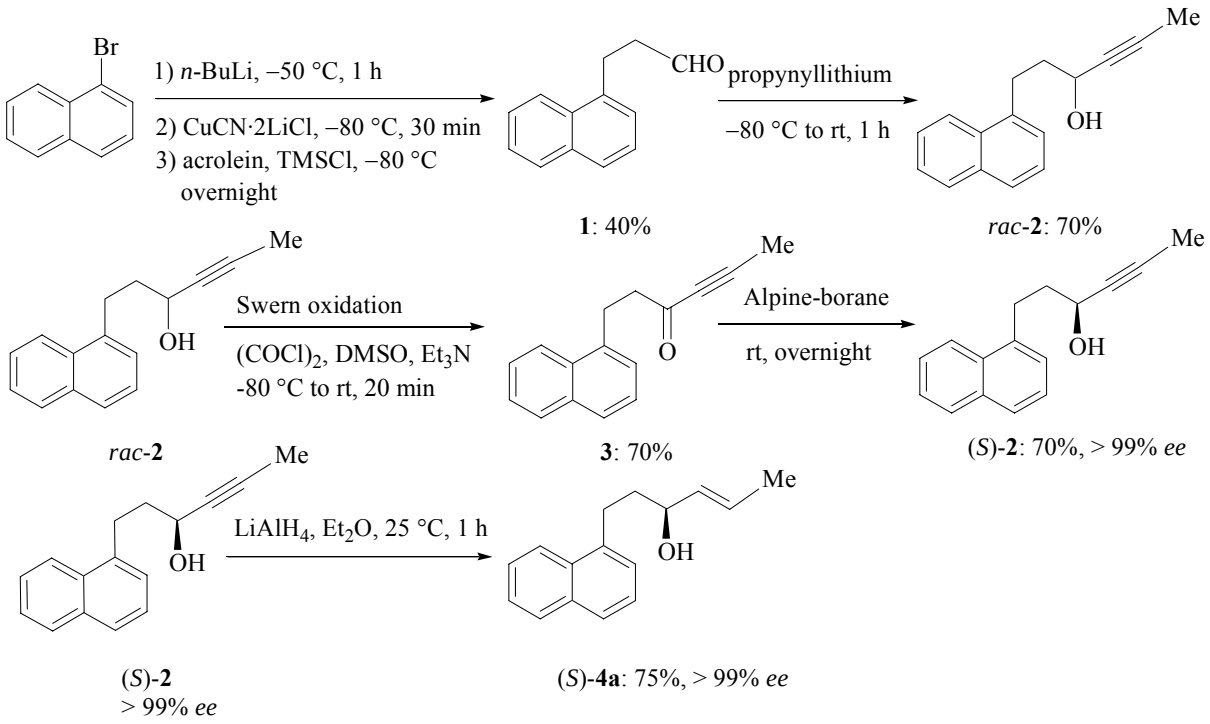
2.1. Optimization of the reaction on a racemic mixture

As previously shown (Schemes 21-23), the [2,3] sigmatropic rearrangements were carried out under rather harsh conditions and the reaction proved to be sensitive to functionalities. Therefore, it needed to be optimized: due to the free rotation in acyclic systems, one should perform the rearrangement under the mildest reaction conditions to ensure the most efficient transfer of chirality. Moreover, under the chosen reaction conditions, the procedure should tolerate some functional groups in view to prepare new ligands. We chose the following reaction as a model (Scheme 24).



Scheme 24. Optimization of a [2,3] sigmatropic rearrangement on a model reaction.

Alcohol **4a** could be easily obtained enantiomerically-enriched in five steps from commercially available 1-bromonaphthalene. First, 1-bromonaphthalene was treated with *n*-BuLi. The lithiated compound was transmetallated to give the copper species and underwent a smooth Michael addition. Aldehyde **1** was obtained in moderate yield. This aldehyde was reacted with propynyllithium (prepared according to the method of Suffert)[31] to give racemic alcohol **2**. This alcohol was oxidized to ketone **3** *via* a Swern oxidation[32] and reduced enantioselectively with Alpine-borane[33] to the enantiomerically-enriched (*S*)-**2**. This propargylic alcohol was reduced to the allylic alcohol **4a** by means of $LiAlH_4$ in good yield (Scheme 25).

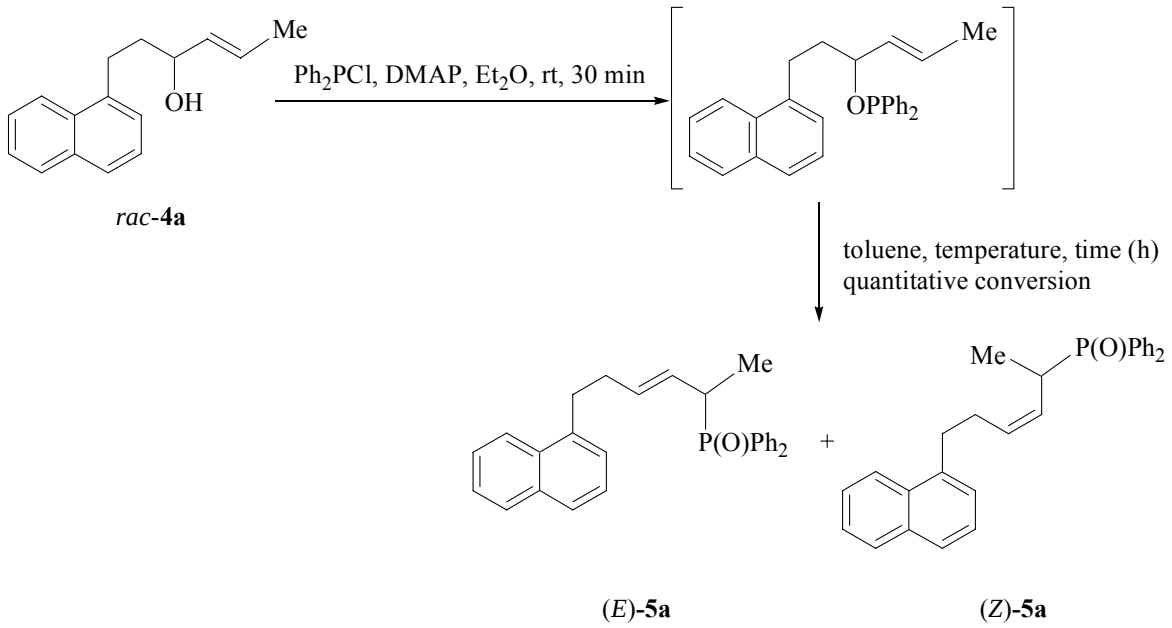


Scheme 25. Preparation of the starting material for the model reaction.

First, we optimized the temperature of the rearrangement. The racemic alcohol **4a** was treated with Ph_2PCl in Et_2O in the presence of DMAP. The resulting phosphinite was heated up to different temperatures in order to perform the reaction under the mildest conditions possible (Table 1).

[31] J. Suffert, D. Toussaint, *J. Org. Chem.* **1995**, *60*, 3550.
[32] A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480.
[33] H. C. Brown, G. G. Pai, *J. Org. Chem.* **1985**, *50*, 1384.

Table 1. Optimization of the reaction temperature for the [2,3] rearrangement.



rac-**4a**

(*E*)-**5a** (*Z*)-**5a**

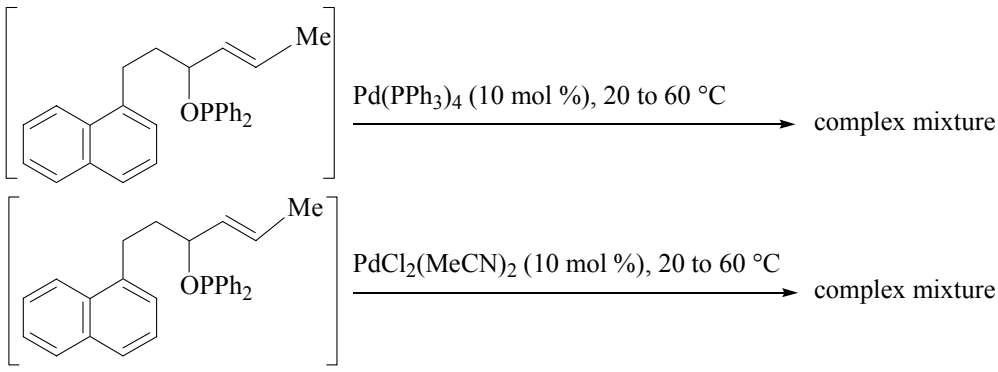
Entry	Temperature (°C)	Reaction Time (h)	Yield (%)[a]	(*E*)/(*Z*)[b]
1	110	1	75	97/3
2	80	4	75	98/2
3	70	10	60	98/2

a/ Isolated yield of analytically pure compound; b/ determined by ^{31}P N.M.R. spectroscopy of the crude mixture.

At 110 °C (Entry 1, Table 1), the rearrangement was complete within one hour, but the stereoselectivity was only 97/3. At lower reaction temperatures (Entries 2 and 3, Table 1), the rearrangement was complete after longer reaction times. The (*E*)/(*Z*) ratio was somewhat better, but still not complete. Unfortunately, the phosphinite did not rearrange at temperatures lower than 70 °C.

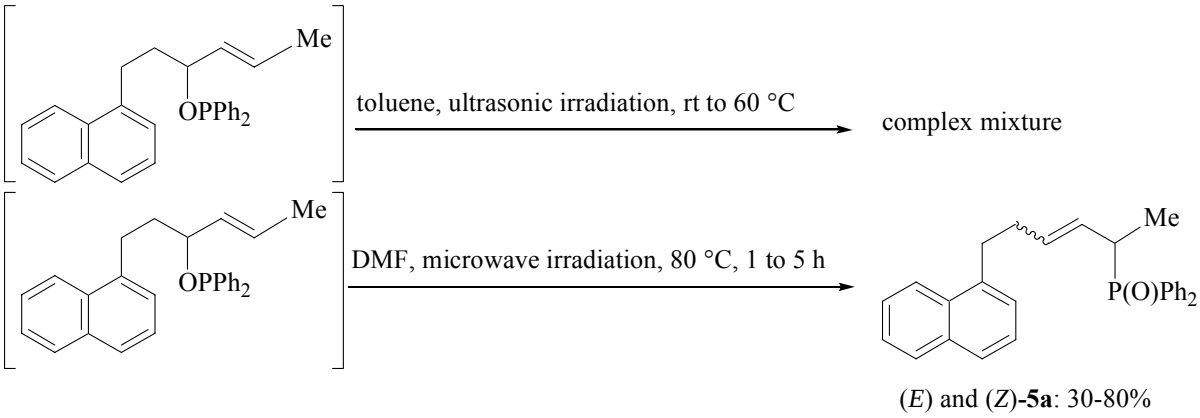
To carry out the rearrangement under milder conditions, we tried to catalyse the reaction by a palladium complex. By analogy with the well-known π–allyl chemistry of palladium,[34] we used as representative catalysts $Pd(PPh_3)_4$ and $PdCl_2(MeCN)_2$ (Scheme 26). No satisfactory result were obtained.

[34] J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, New York, **1995**.



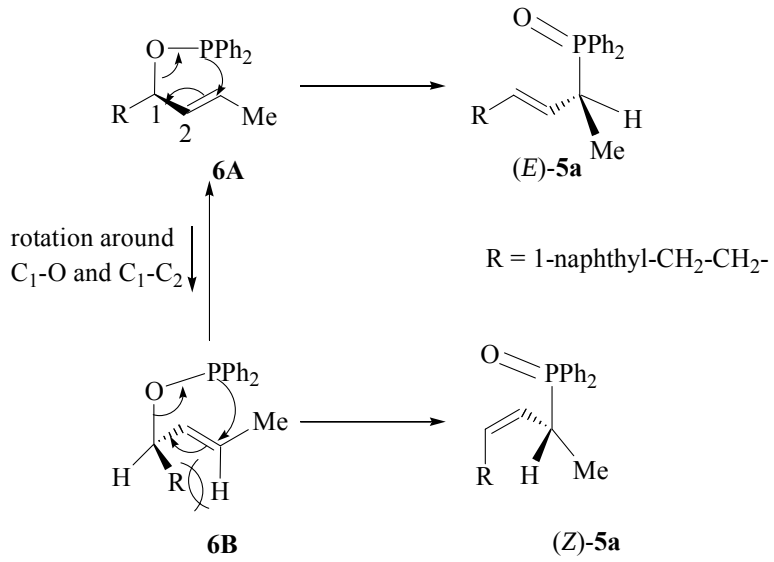
Scheme 26. Attempted Pd-catalyzed [2,3] sigmatropic rearrangement of an allylic phosphinite.

We tried to accelerate the rearrangement by physical methods. Ultrasonic or microwave irradiation did not lead to any improvement (Scheme 27).



Scheme 27. Physical activation of the rearrangement.

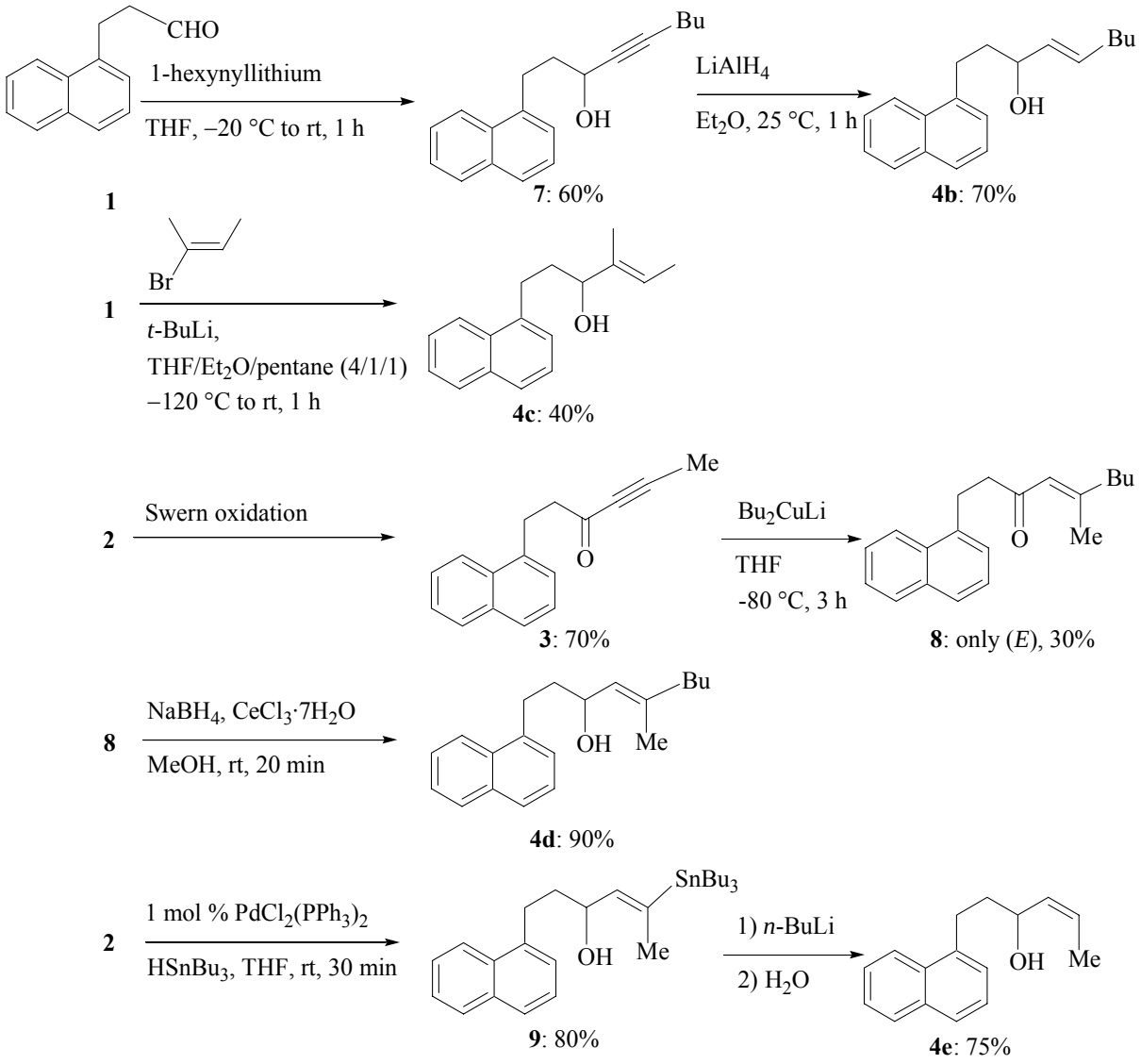
To account for the observed (*E*)/(*Z*) ratio, we have considered that two transition states were possible. Conformer **6A** would lead to the major product (*E*)-**5a**, whereas conformer **6B**, which is destabilized by allylic strain, would lead to the minor product (*Z*)-**5a** (Scheme 28). Moreover, the stereochemistry of the double bond would depend on the absolute configuration of the asymmetric center, the (*Z*) and (*E*) isomers giving rise to the one and the other enantiomer. To make a useful method to prepare enantiomerically-enriched ligands, it is necessary to obtain the product as one single isomer in pure form. From these transition states, it appeared that if we would replace the hydrogen atom *cis* to the R group by a methyl group, the allylic strain should be high enough to disfavor the pathway leading to the (*Z*) compound completely. Thereby, we should be able to improve the stereoselectivity.



Scheme 28. Proposed transition states for the [2,3] sigmatropic rearrangement.

The influence of other R^2, R^3 and R^4 groups (Scheme 24) was then studied. The corresponding alcohols **4b-e** were prepared as outlined in Scheme 29. Aldehyde **1** was reacted with 1-hexynyllithium to obtain alcohol **7** and subsequent reduction gave alcohol **4b** in satisfactory yield. Aldehyde **1** was also converted into alcohol **4c** according to Seebach[35] in moderate yield. Alcohol **2** was oxidized into the alkynyl ketone **3**. Subsequent carbocupration[36] and reduction[37] gave respectively ketone **8** and alcohol **4d** in moderate overall yield. Alcohol **2** was hydrostannylated[38] in good yield to give vinylstannane **9**. Vinylstannane **9** underwent a transmetallation to the lithio species, which was trapped with water to yield alcohol **4e**.

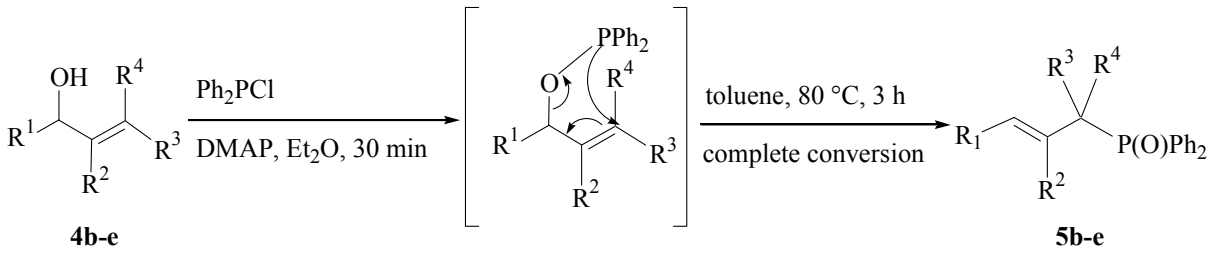
[35] H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, 4839.
[36] E. J. Corey, J. A. Katzellenberger, *J. Am. Chem. Soc.* **1969**, *91*, 1851.
[37] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454.
[38] H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857.



Scheme 29. Preparation of alcohols **4b-e**.

Alcohols **4b-e** were then subjected to the standard conditions previously elaborated (Table 1). The results are summarized in Table 2.

Table 2. Influence of the substituents on the stereoselectivity.



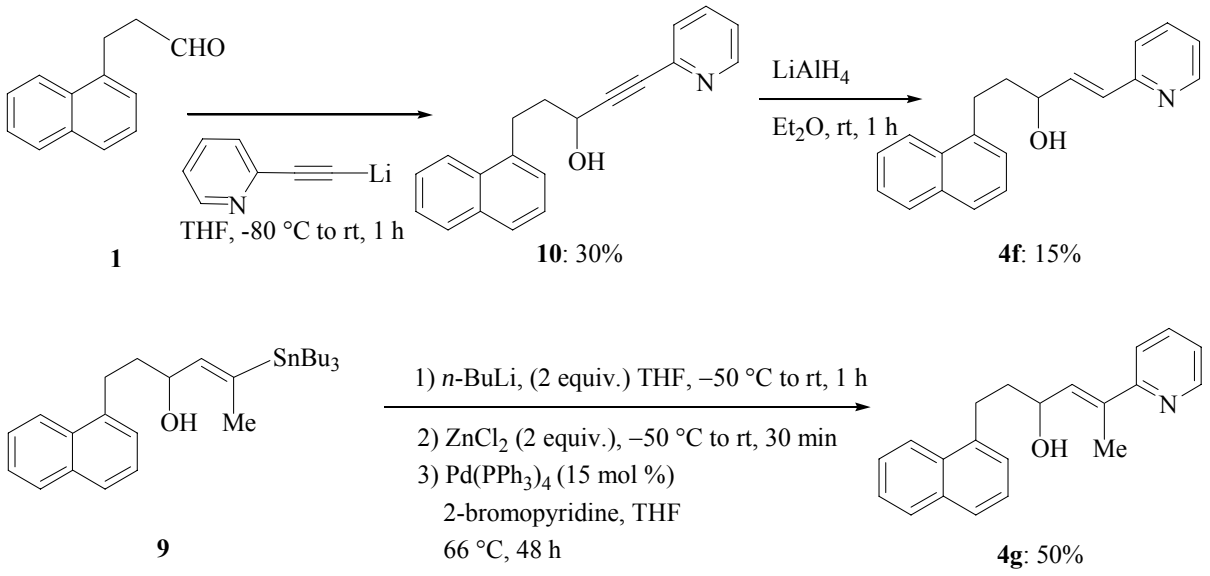
4b-e **5b-e**

Entry	Alcohol	Product	(*E*)/(*Z*)[a]	Yield (%)[b]
1	**4b**	**5b**	97/3	60
2	**4c**[c]	**5c**	95/5	50
3	**4d**	**5d**	>99/<1	50
4	**4e**	**5a**	>99/<1	50

a/ Determined by ^{31}P N.M.R. spectroscopy of the crude; b/ yield of analytically pure product; c/ 16 h at 80°C instead of 3 h.

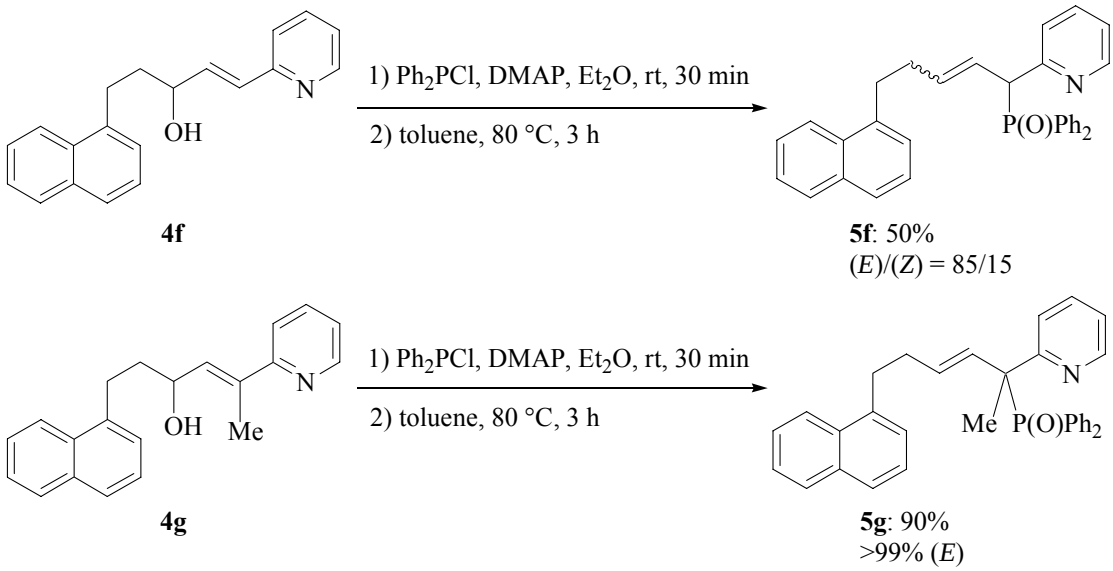
As can be seen from Table 2, the presence of a small substituent R^4 (R^4 = H, entries 1 and 2) led to lower (*E*)/(*Z*) ratios (95/5 to 97/3), whereas the presence of a methyl group gave rise to the sole (*E*) products (entries 3 and 4). The steric hindrance due to the methyl group on position R^2 disfavored the lower energy transition state and surprisingly led to a longer reaction time and a lower stereoselectivity (entry 2).

For ligand synthesis, the possibility of carrying out the rearrangement with a substrate bearing a heteroatom, for example a nitrogen-containing heterocycle, was of interest. First, we designed alcohols **4f-g** to study the tolerance of the rearrangement towards such substituents. The synthesis of these alcohols is shown in Scheme 30. 2-Ethynylpyridine was reacted with *n*-BuLi and treated subsequently with aldehyde **1** to give propargylic alcohol **10**. This alcohol was reduced to the corresponding allylic alcohol with $LiAlH_4$ in only low yield to afford alcohol **4f**. Alkenylstannane **9** was treated consecutively with *n*-BuLi and $ZnCl_2$ (2 equiv. each). The corresponding zinc reagent underwent a Negishi cross-coupling with 2-bromopyridine to afford alcohol **4g**.



Scheme 30. Preparation of alcohols **4f-g**.

Alcohols **4f-g** were subjected to the standard conditions (Table 1) and afforded the rearranged phosphine oxides as shown in Scheme 31.

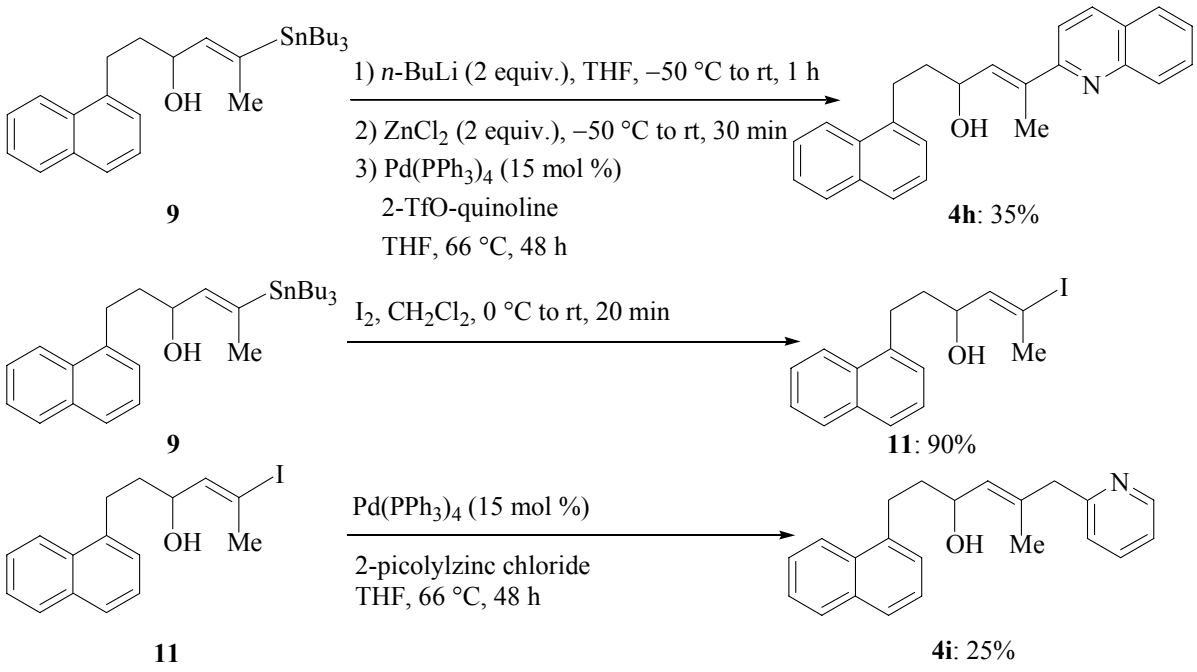


Scheme 31. Rearrangement of allylic alcohols bearing a nitrogen-containing heterocycle.

Scheme 31 shows that the rearrangement tolerated a pyridine ring. In the case of **4f**, the rearrangement led to a low (*E*)/(*Z*) ratio. This can be explained by two arguments: first, R^4 (substituent (*Z*) to the alcohol) was a hydrogen and such compounds gave in previous

experiments (*E*)/(*Z*) mixtures (Table 2); second, the acidic proton α to the phosphorus,[39] could be easily removed and the subsequent allylic anion can isomerize. In alcohol **4g**, R^4 was a methyl group. Such substrates showed in previous experiments high stereoselectivity and the position α to the phophorus did not bear any longer an acidic proton which could undergo isomerization.

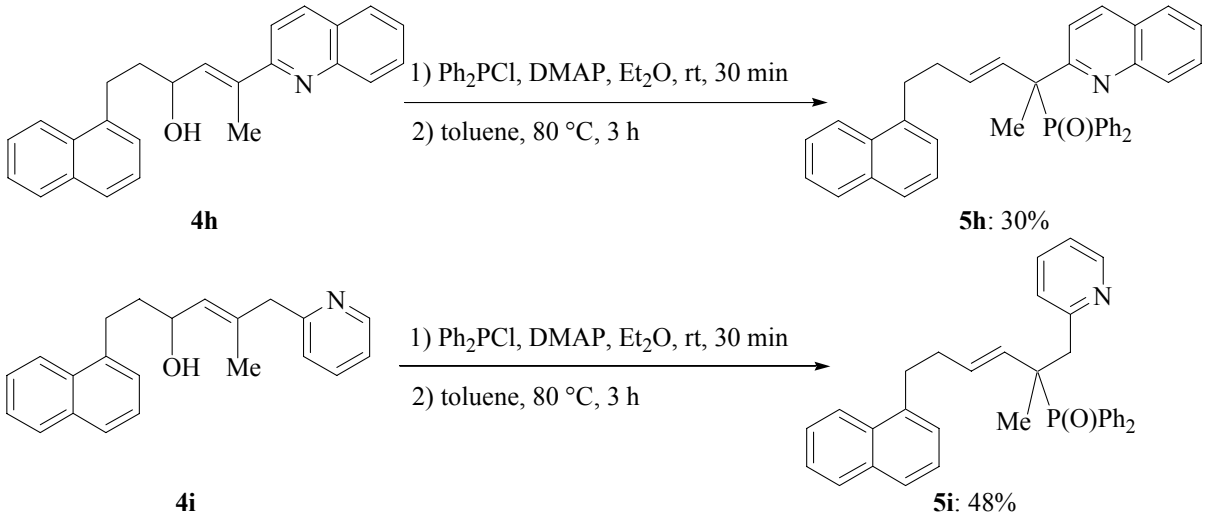
To prepare a variety of ligands precursors, we investigated the rearrangement with other substrates bearing nitrogen-containing heterocycles. The synthesis of these substrates is shown in Scheme 32. Alkenylstannane **9** was reacted successively with *n*-BuLi and $ZnCl_2$ (2 equiv. each). The corresponding zinc reagent underwent a Negishi cross-coupling with the triflate of 2-hydroxyquinoline to give alcohol **4h** in moderate yield. Alcohol **4i** was also obtained from stannane **9**, but the reaction partners in the Negishi cross-coupling were reversed: stannane **9** was converted to alkenyl iodide[40] **11** in high yield. This iodide underwent the cross-coupling reaction with 2-picolylzinc chloride[41] in moderate yield.



Scheme 32. Preparation of alcohols **4h-i**.

[39] C. Cardellicchio, G. Fracchiolla, F. Naso, P. Tortorella, W. Holody, K. M. Pietrusiewicz, *Tetrahedron Lett.* **1999**, *40*, 5773.
[40] F. Liron, M. Gervais, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron Lett.* **2003**, *44*, 2789.
[41] O. F. Beumel, Jr., W. N. Smith, B. Rybalka, *Synthesis* **1974**, 43.

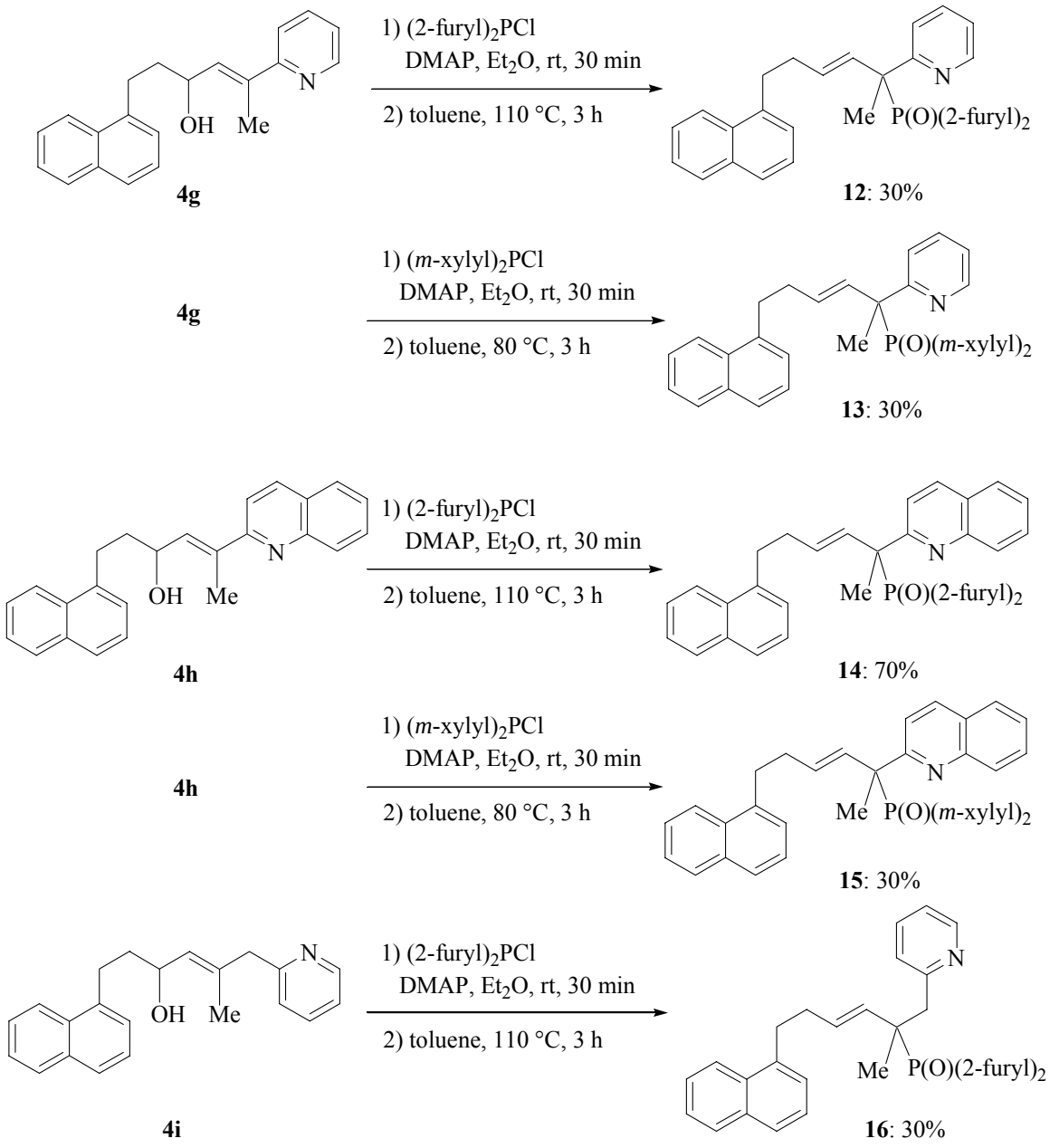
Alcohols **4h-i** were subjected to the standard conditions previously used (Table 1) and the corresponding phosphine oxides **5h-i** were obtained as the pure (*E*) isomers as judged by the ^{1}H and ^{31}P N.M.R. spectra of the crude mixture (Scheme 33).



Scheme 33. [2,3] sigmatropic rearrangement using **4h-i** as substrates.

Further, alcohols **4g-i** were treated with diverse chlorophosphines to broaden the scope of the methodology and to be able to fine tune the ligand reactivity. These reactions are depicted in Scheme 34.

In the same way as described above (Schemes 31 and 33), phosphine oxides **12-16** were obtained in moderate to good yields. Only the (*E*) isomers were detected. It is worth noting that the reactions carried out with (2-furyl)$_2$PCl required a higher reaction temperature (110 °C instead of 80 °C). This is consistent with the fact that the [2,3] sigmatropic rearrangement can be regarded as a nucleophilic attack of the phosphorus on the double bond. The phosphorus atom in chlorodifurylphosphine is less nucleophilic than in chlorodiphenylphosphine and the reaction requires harsher conditions to take place.

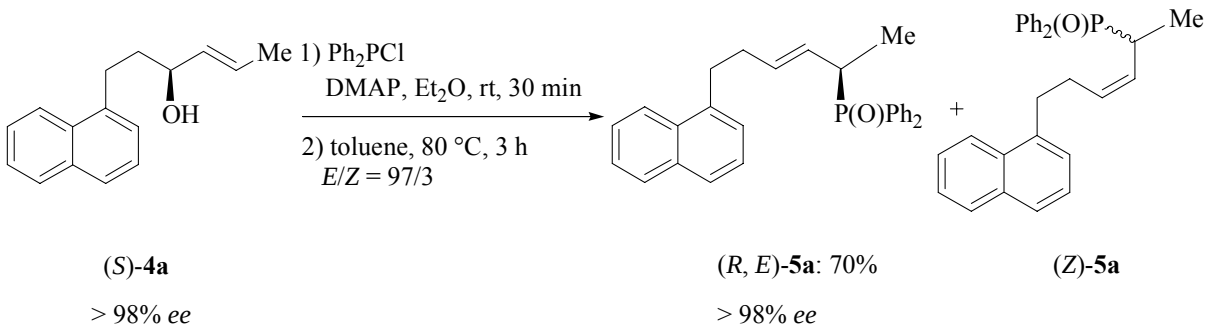


Scheme 34. Reactions of alcohols **4g-i** with various chlorophosphines.

2.2. Enantioselective [2,3] sigmatropic rearrangement of acyclic allylic phosphinites

So far, we optimized the reaction conditions to obtain selectively one stereoisomer under mild reaction conditions (Tables 1 and 2). This rearrangement was shown to be compatible with nitrogen-containing heterocycles, and various chlorophosphines were used. In order to prepare chiral non racemic ligands, their precursors (namely the corresponding phosphine oxides) must be prepared in enantiomerically-enriched form. First, we tried the

asymmetric rearrangement of alcohol (*S*)-**4a** (Scheme 25). This asymmetric rearrangement is presented in Scheme 35.



(*S*)-**4a**
> 98% *ee*

(*R*, *E*)-**5a**: 70%
> 98% *ee*

(*Z*)-**5a**

Scheme 35. Asymmetric [2,3] sigmatropic rearrangement with alcohol (*S*)-**4a**.

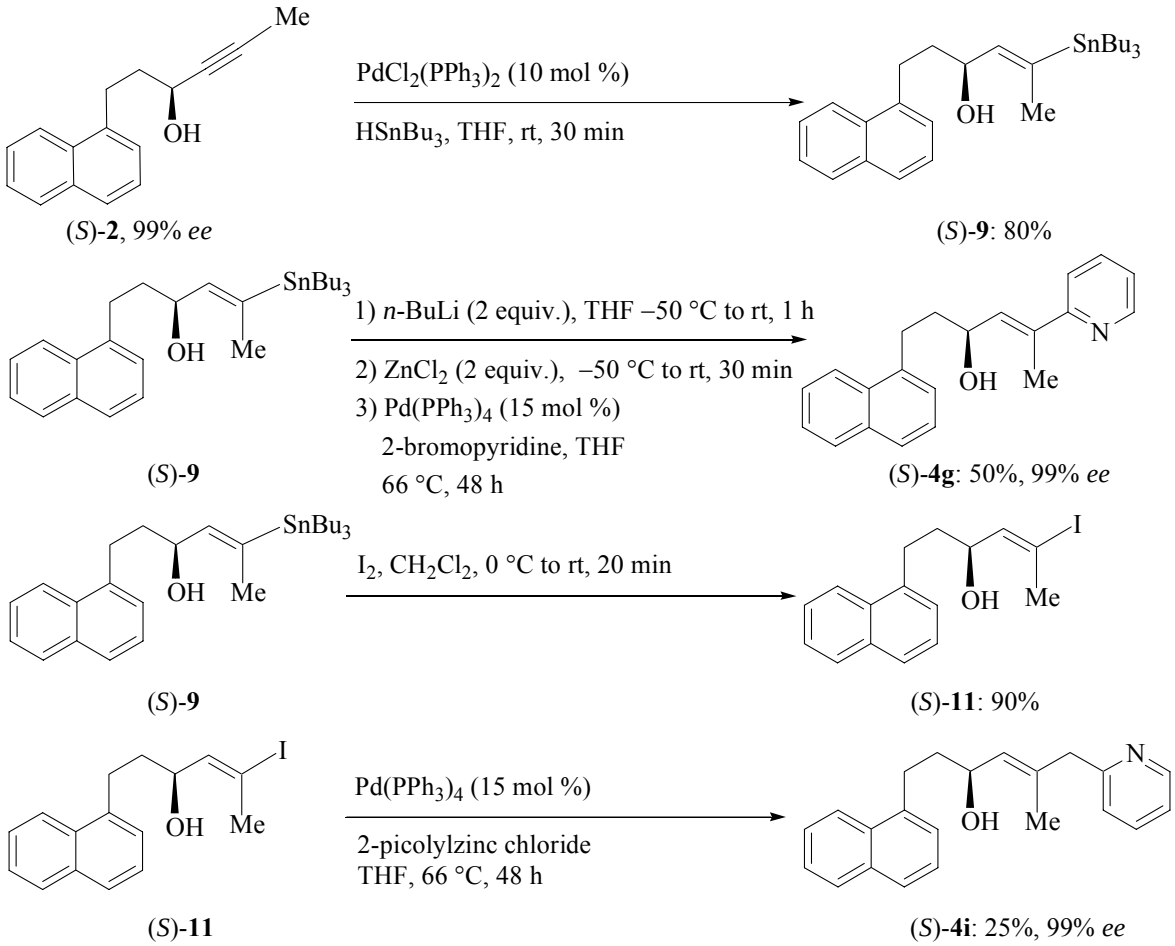
The enantiomerically-enriched (*R*, *E*) phosphine oxide **5a**[42] was obtained from the enantiomerically enriched alcohol **4a**. This shows that the favored transition state proposed for this rearrangement should be a rigid intermediate. This suggested a concerted synchronous mechanism. As our system could freely rotate, only such a mechanism could account for the complete transfer of chirality observed at 80 °C. This was confirmed by calculations.[43]

It was then investigated, whether this excellent transfer of chirality is as efficient when performed on the synthetically more interesting enantiomerically-enriched alcohols (*S*)-**4g** and (*S*)-**4i**. The (*S*) isomers of these alcohols were prepared from (*S*)-**2** (Scheme 25), following the procedures used to prepare the racemic mixtures (Schemes 30 and 32). As shown in Scheme 36, no loss of stereochemical information was observed during the reaction.[44]

[42] The enantiomeric excess of the phosphine oxide was determined as follows: the phosphine oxide was reacted with 1 equiv. of (*S*) mandelic acid for 4 days at rt in Et_2O. After evaporation of the solvents, the diastereomeric ratio of the complex was determined by measuring N.M.R. spectra (^1H and ^{31}P). By comparison between the spectra starting from the racemic alcohol and the ones from the enantiomerically pure alcohol, only one diastereomer could be observed, indicating our phosphine oxide was > 98% *ee*. This method was performed according to: J. Drabowicz, P. Łyżwa, J. Omelańczuk, K. M. Pietrusiewicz, M. Mikołajczyk, *Tetrahedron: Asymmetry* **1999**, *10*, 2757.

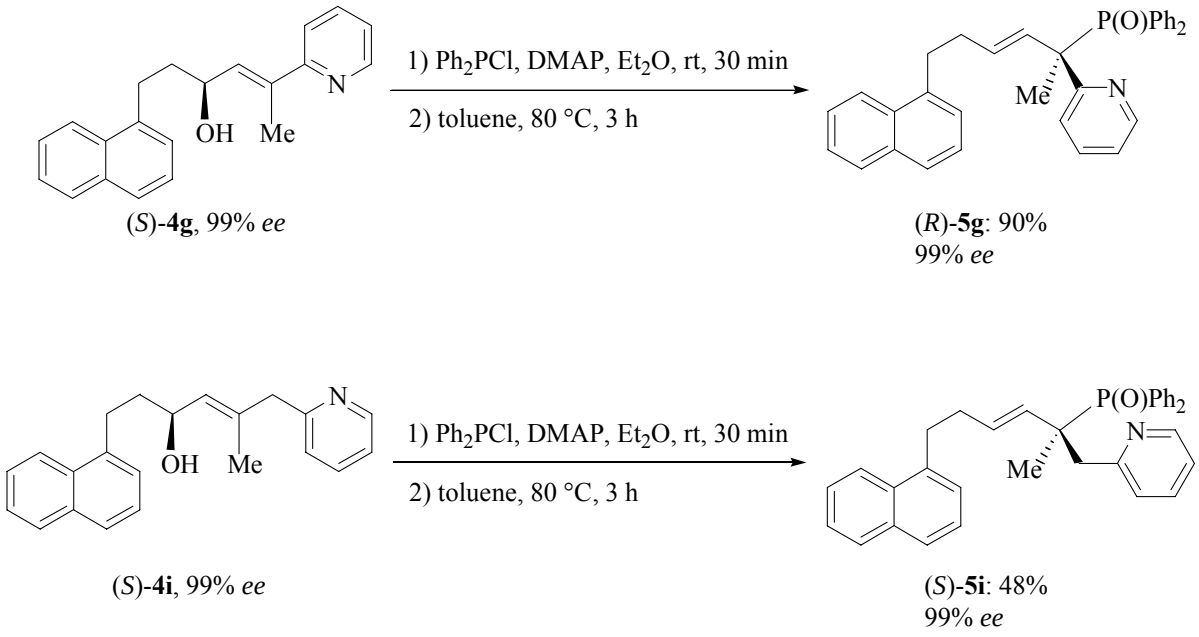
[43] K. Knapp, *Dissertation*, Munich, **2003**.

[44] Enantiomeric purity was determined by chiral HPLC. See experimental part for the resolution conditions.



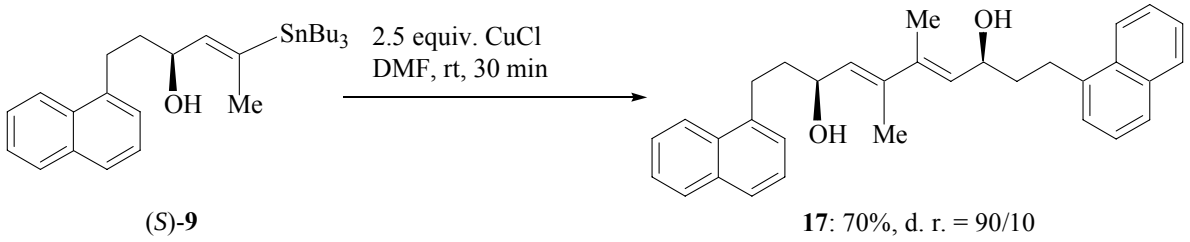
Scheme 36. Enantioselective synthesis of (*S*)-**4g** and (*S*)-**4i**.

With these enantiomerically pure allylic alcohols **4g** and **4i** in hand, the asymmetric [2,3] rearrangement of the corresponding phosphinites was investigated. As described in Scheme 37, these rearrangements proved to be highly stereoselective.



Scheme 37. Asymmetric [2,3] sigmatropic rearrangement starting from alcohols (*S*)-**4g** and (*S*)-**4i**.

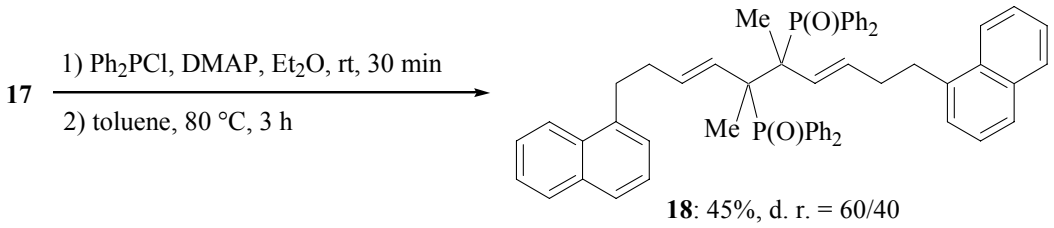
We were also interested in preparing C_2-symmetrical 1,2-diphosphines. As potential bidentate ligand precursor **17** was prepared from stannane (*S*)-**9** by a copper-mediated homocoupling reaction (Scheme 38).[45]



Scheme 38. Preparation of a C_2-symmetrical diol.

Altough we observed some epimerization during the homocoupling reaction, the measured diastereomeric ratio of 90/10[46] was sufficient to study the enantio- and diastereoselectivity of the rearrangement on this substrate. The rearrangement was carried out under the standard conditions outlined above (Table 1 and Scheme 39).

[45] E. Piers, E. J. McEachern, M. A. Romero, P. L. Gladstone, *Can. J. Chem.* **1997**, *75*, 694.
[46] Diastereomeric ratio was evaluated by measuring the integrals of the ^{1}H N.M.R. spectrum.

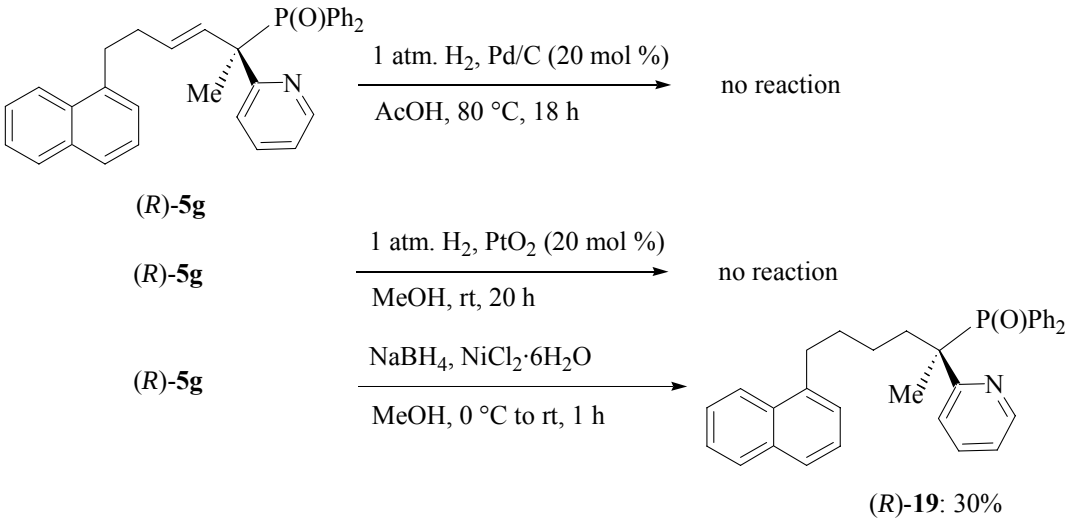


Scheme 39. Preparation of a C_2-symmetrical 1,2-diphosphine.

Unfortunately, we obtained the C_2-symmetrical 1,2-diphosphine oxide **18** with a diastereomeric ratio of only 60/40.[46] This shows that the rearrangement is highly sensitive to steric hindrance around the carbon with which the new phosphorus-carbon bond is formed. Another explanation for this rather disappointing result could be that both rearrangements did not take place simultaneously. In this case, the phosphine oxide formed first would influence the diastereoselectivity of the second rearrangement through a large steric hindrance during this second rearrangement.

2.3. Preparation of a new P,N-ligand from (*R*)-5g

Enantiomerically-enriched phosphine oxides bearing a nitrogen-containing heterocycle were obtained. It was of interest to further functionalize this compound to obtain a potential ligand for asymmetric catalysis. For this purpose, the double bond was reduced to a single bond and the phosphine oxide was finally reduced to the phosphine. The results for the reduction of the C-C double bond are summarized in Scheme 40.

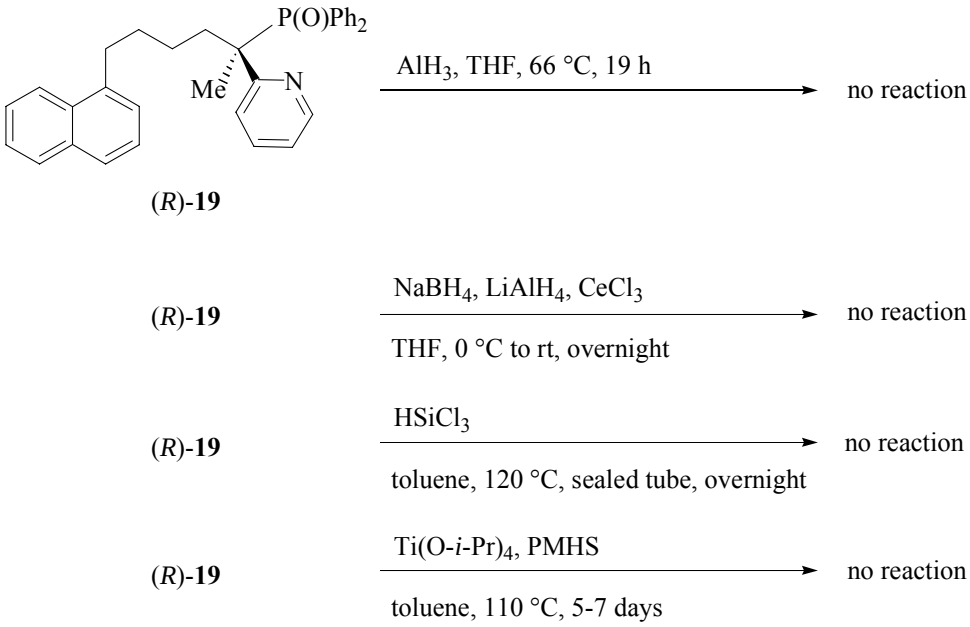


Scheme 40. Reduction of the double bond in phosphine oxide (*R*)-**5g**.

Reduction of the double bond using Pd on charcoal or PtO_2 did not occur, but nickel borohydride[47] effected the reduction under mild reaction conditions. Phosphine oxide **19** was obtained in moderate yield (Scheme 40).

Finally, the reduction of the phosphine oxide to the free phosphine was tried. The reduction was performed under a range of experimental conditions including aluminium hydride,[48] trichlorosilane[49] and cerium[50] or titanium[51]-mediated reductions. Unfortunately, none of these methods proved to be efficient, and the starting material was recovered unchanged (Scheme 41).

[47] a) T. Satoh, K. Nanba, S. Suzuki, *Chem. Pharm. Bull.* **1979**, *44*, 1661; b) W. R. Roush, M. Kageyama, R. Riva, B. B. Brown, J. S. Warmus, K. J. Moriarty, *J. Org. Chem.* **1991**, *56*, 1192; c) for a related reduction using $LiAlH_4$, see E. C. Ashby, J. J. Lin, *J. Org. Chem.* **1978**, *43*, 2567.
[48] A. Bootle-Wilbraham, S. Head, J. Longstaff, P. Wyatt, *Tetrahedron Lett.* **1999**, *40*, 5267.
[49] a) K. Naumann, G. Zon, K. Mislow, *J. Am. Chem. Soc.* **1969**, *91*, 7012; b) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946.
[50] a) T. Imamoto, T. Kusumoto, N. Suzuki, K. Sato, *J. Am. Chem. Soc.* **1985**, *107*, 5301; b) T. Imamoto, T. Takeyama, T. Kusumoto, *Chem. Lett.* **1985**, 1491.
[51] a) S. C. Berk, S. L. Buchwald, *J. Org. Chem.* **1992**, *57*, 3751; b) T. Coumbe, N. J. Lawrence, F. Muhammad, *Tetrahedron Lett.* **1994**, *35*, 625.



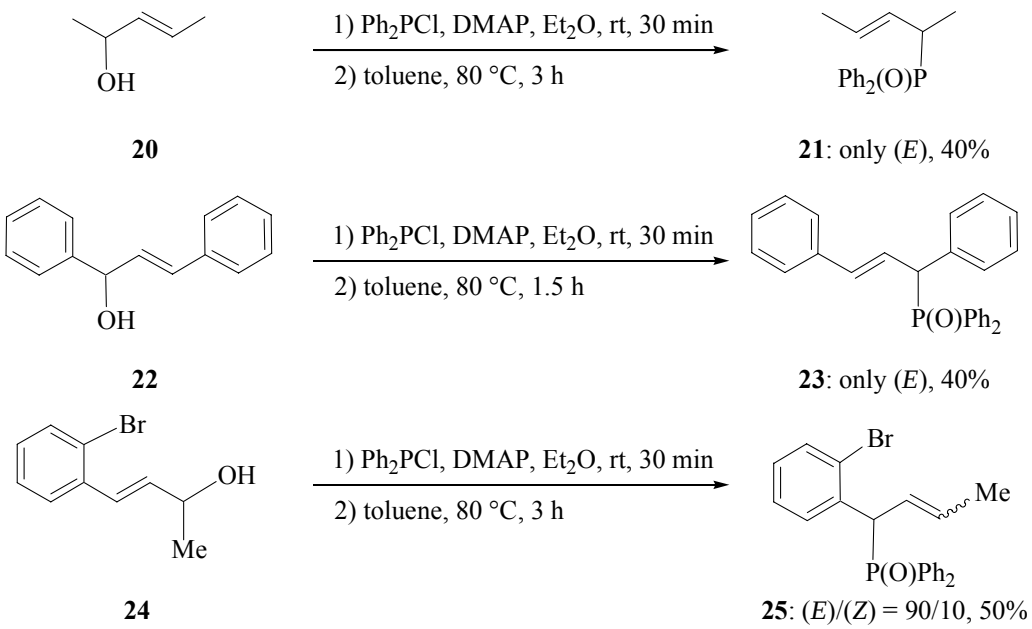
Scheme 41. Attempted reduction of (*R*)-**19**.

The failure of the reduction step from the phosphine oxide to the phosphine could be explained by three reasons:

- The quaternary center α to the phosphine oxide creates too much steric hindrance to allow the reducing agent to approach. Unfortunately, the quaternary carbon is needed to ensure an excellent stereo- and enantioselectivity during the asymmetric [2,3] sigmatropic rearrangement,
- The nitrogen atom in the pyridine ring may be coordinating to the reducing agent, thus making the reduction of the phosphine oxide to the phosphine impossible. This problem could be overcome by introducing the second coordinating center in a future synthesis of bidentate ligands after the reduction of the phosphine oxide,
- The naphthyl moiety might be so big that it generates significant steric hindrance. This steric effect together with the hindrance at the quaternary carbon makes the substrate so crowded that the reduction could not take place. A smaller substituent R^1 will be used to address this issue.

2.4. Influence of the R^1 substituent on the stereoselectivity

We studied the [2,3] sigmatropic rearrangement of the allylic phosphinites resulting from alcohols bearing as the R^1 substituent (Scheme 24) a methyl and a phenyl group. The results of these rearrangements are depicted in Scheme 42.



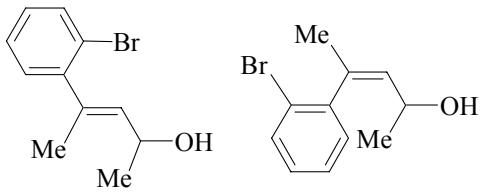
Scheme 42. Influence of the substituent R^1 on the stereoselectivity.

The phosphine oxide **21** (R^1 = Me) was obtained as the sole (*E*) isomer starting from alcohol **20**, showing that a large R^1 substituent was not crucial to obtain a stereoselective rearrangement. The phosphine oxide **23** (R^1 = Ph) was also obtained as the pure (*E*) isomer from **22**. The phosphine oxide **25** (R^1 = Me) was obtained as an (*E*)/(*Z*) mixture from alcohol **24**. This was consistent with previous results. When an aromatic ring was bonded to the same carbon atom as the phosphine oxide, mixtures were obtained (Scheme 31) unless this center was a quaternary carbon. Based on these considerations, we decided to introduce a methyl group on the benzylic position of **24**.

2.5. Studies on the rearrangement of (*Z*)- and (*E*)-26

According to Scheme 42, it should be possible to perform the [2,3] asymmetric sigmatropic rearrangement of an allylic phosphinite derived from an analog of **24**. As depicted in Scheme 43, both (*Z*) and (*E*) isomers of alcohol **26** appeared to be suitable

substrates for the rearrangement. The (*Z*) isomer was expected to be more easily prepared than the (*E*) one.[40,52]

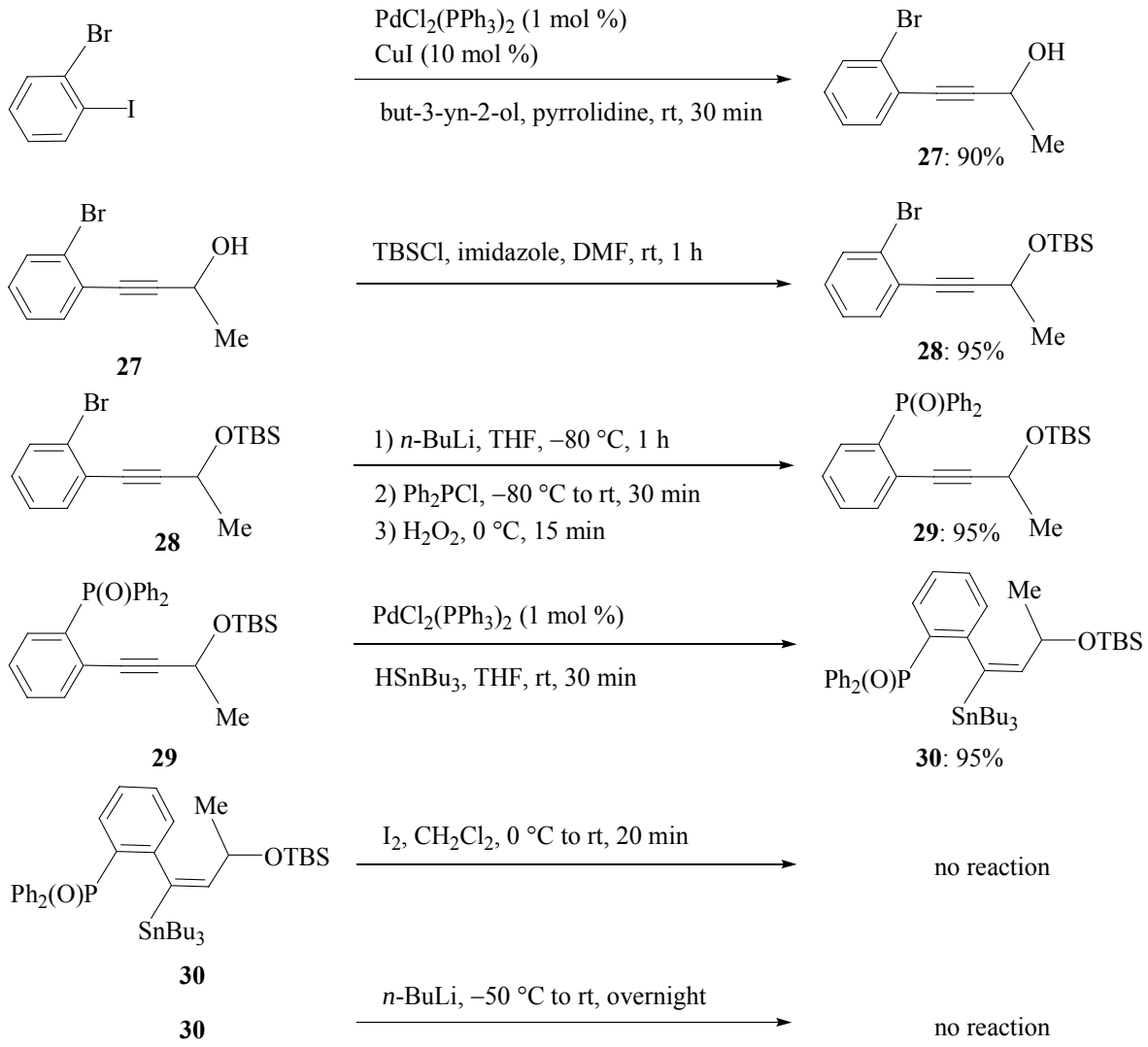


(*E*)-**26** (*Z*)-**26**

Scheme 43. (*E*) and (*Z*) isomers of alcohol **26**.

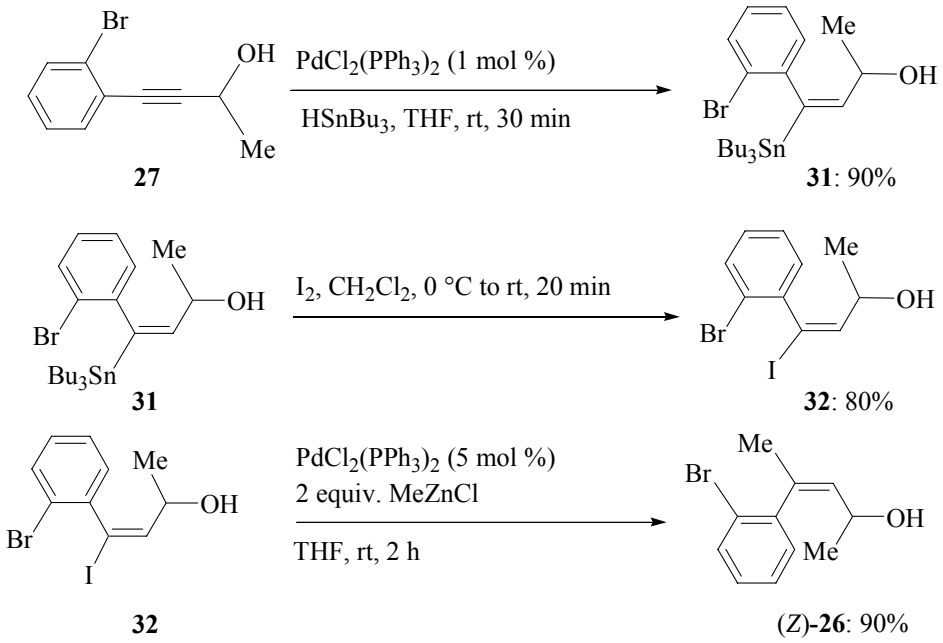
As difficulties to introduce a second coordinating atom by reaction with the bromine atom after the rearrangement were expected, we first tried to attach a phosphine oxide on the aromatic ring as shown in Scheme 44. 2-Bromo-iodobenzene underwent a Sonogashira-cross-coupling reaction to give alkyne **27** in high yield.[53] Alcohol **27** was protected as the silyl ether **28**. Ether **28** was treated with *n*-BuLi and the corresponding lithiated compound was quenched with PPh_2Cl, which gave after oxidation phosphine oxide **29**. Phosphine oxide **29** was hydrostannylated[38] and gave a single regioisomer[52] in high yield. The alkenylstannane **30** was subjected to reaction conditions for an iodolysis[40] and a Sn/Li exchange. Both reactions failed. Using the phosphine instead of its oxide **30** led to no improvement.

[52] F. Liron, P. Le Garrec, M. Alami, *Synlett* **1999**, 246.
[53] M. Alami, F. Ferri, G. Linstrumelle, *Tetrahedron Lett.* **1993**, *34*, 6403.



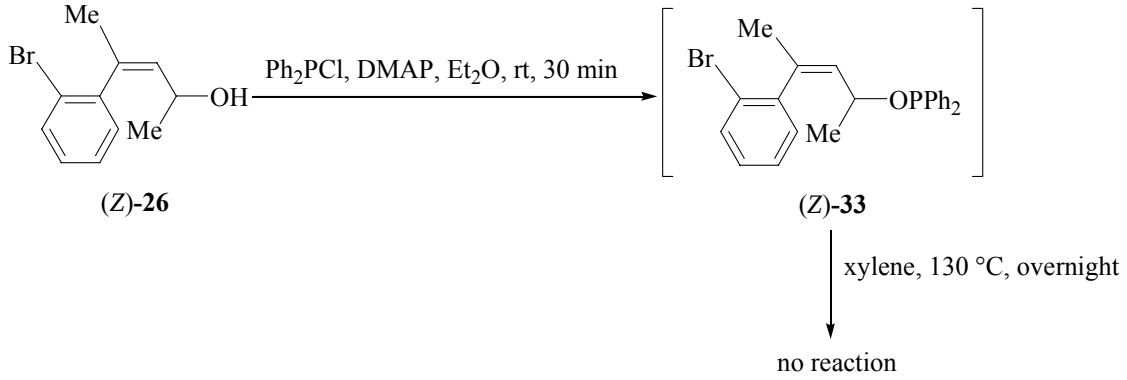
Scheme 44. Failed synthesis of a P-containing allylic alcohol.

Therefore, the phosphorus atom on the aromatic ring had to be installed at the end of the synthesis. A new route was then envisaged. Alcohol **27** was hydrostannylated[38] and gave stannane **31** as the only regioisomer.[52] Vinylstannane **31** underwent iodolysis[40] and the vinyl iodide **32** reacted with methylzinc chloride in a Negishi cross-coupling reaction[52] to give alcohol (*Z*)-**26** as described in Scheme 45.



Scheme 45. Synthesis of alcohol (*Z*)-**26**.

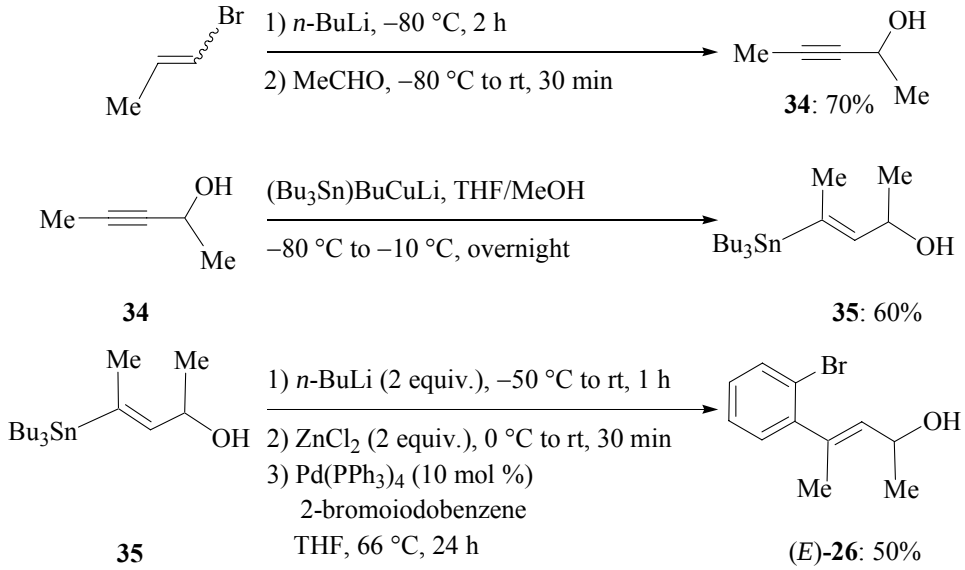
Alcohol (*Z*)-**26** was treated with Ph_2PCl in Et_2O in the presence of DMAP and the phosphinite (*Z*)-**33** was subjected to the reaction conditions elaborated above as depicted in Scheme 46.



Scheme 46. Attempted rearrangement using alcohol (*Z*)-**26**.

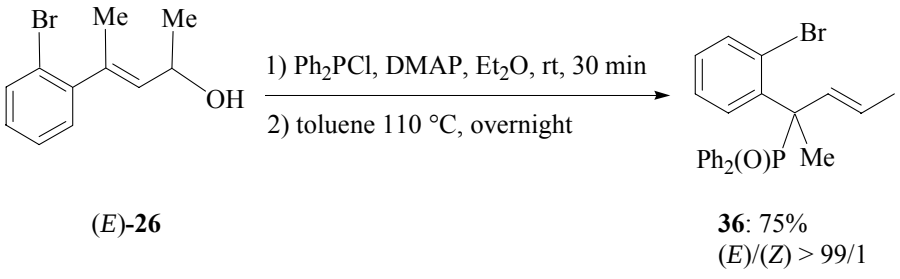
Phosphinite (*Z*)-**33** was obtained quantitatively as a mixture of two diastereomers, but heating to 130 °C overnight led to no rearrangement products. As postulated above, the steric hindrance on the γ carbon of the allylic system had a strong influence on the rearrangement and might have inhibited the reaction even under harsh reaction conditions.

Then, the synthesis of (*E*)-**26** was envisaged as follows (Scheme 47). Propynyllithium was prepared as described by Suffert[31] and reacted with acetaldehyde. Alcohol **34** was then obtained in a good yield and underwent a chemo-, regio- and stereoselective stannylcupration.[54] Alkenylstannane **35** was treated successively with *n*-BuLi and $ZnCl_2$ (2 equiv. each) and the corresponding zinc reagent underwent a Negishi cross-coupling reaction with 2-bromoiodobenzene, to obtain alcohol (*E*)-**26** in moderate yield.



Scheme 47. Preparation of (*E*)-**26**.

We then tried to perform the rearrangement on (*E*)-**26**. The alcohol was reacted with Ph_2PCl in Et_2O in the presence of DMAP and the resulting phosphinite was heated to 110 °C in toluene overnight (Scheme 48).

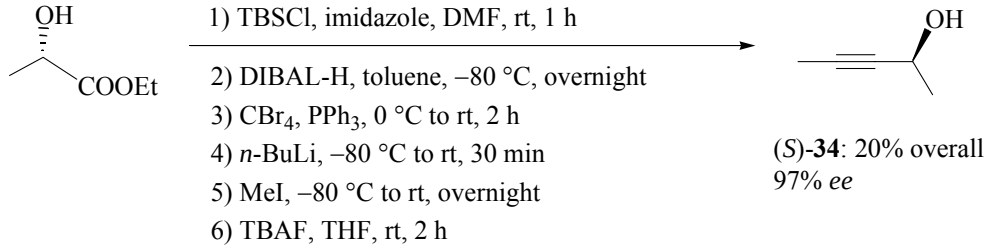


Scheme 48. [2,3] Sigmatropic rearrangement performed using alcohol (*E*)-**26**.

[54] J.-F. Betzer, F. Delaloge, B. Muller, A. Pancrazi, J. Prunet, *J. Org. Chem.* **1997**, *62*, 7768.

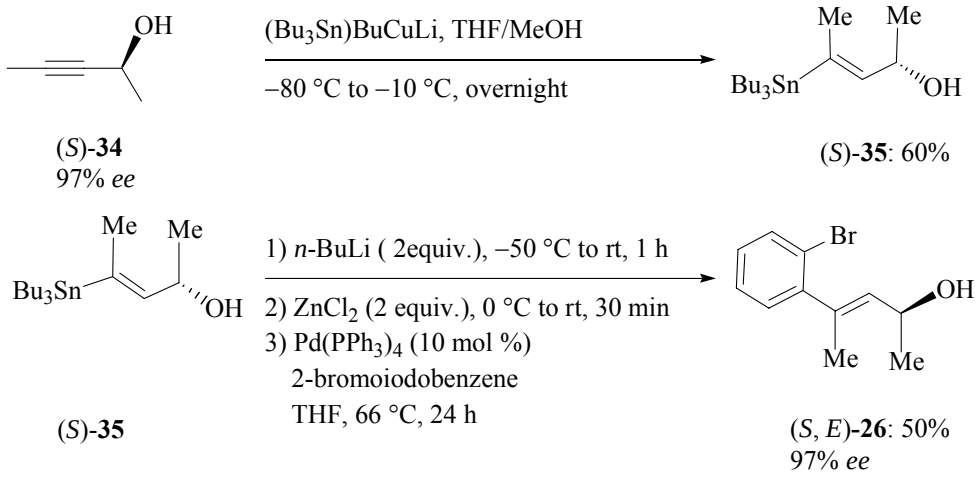
We obtained the expected phosphine oxide **36** as a single stereoisomer. It is worth noting that the reaction time was significantly longer and required heating to 110 °C overnight instead of heating to 80 °C for 3 h (Table 1 and Schemes 31 and 33). These harsh conditions had to be applied because the substrate was sterically hindered.

To prepare a chiral ligand, we had to perform the rearrangement on the enantiomerically pure alcohol (*E*)-**26**. We prepared the enantiomerically pure alcohol **34** as described by Marshall (Scheme 49).[55]



Scheme 49. Preparation of (*S*)-**34**.

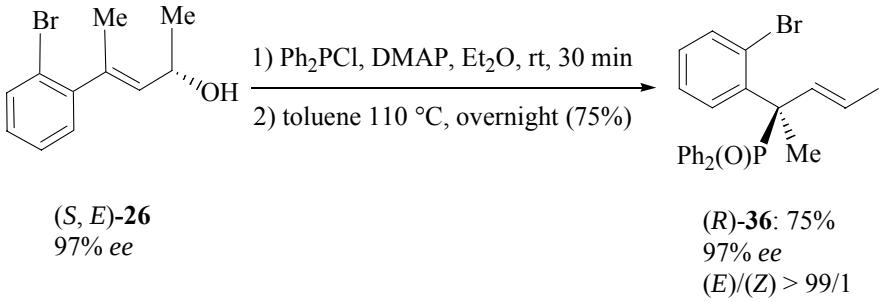
Starting from propargylic alcohol (*S*)-**34**, alcohol (*E*)-**26** was prepared according to Scheme 47. The enantiomerically pure alcohol was obtained and no epimerization was observed (Scheme 50).[44]



Scheme 50. Enantioselective synthesis of alcohol (*E*)-**26**.

[55] J. A. Marshall, S. Xie, *J. Org. Chem.* **1995**, *60*, 7230.

The asymmetric [2,3] sigmatropic rearrangement was then performed using enantiomerically-enriched (*E*)-**26**. As described in Scheme 51, the transfer of stereochemical information was complete.[42]



(*S*, *E*)-**26**
97% *ee*

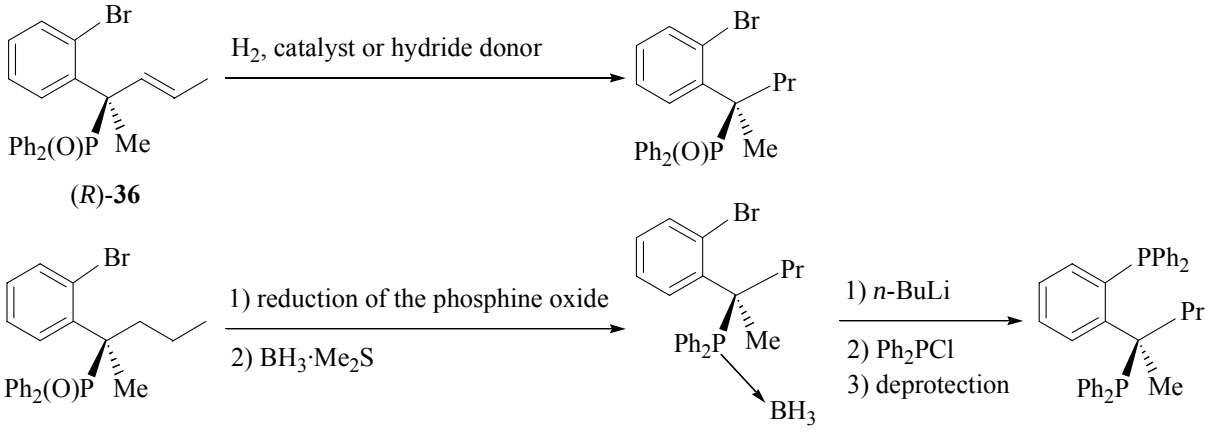
(*R*)-**36**: 75%
97% *ee*
(*E*)/(*Z*) > 99/1

Scheme 51. Preparation of the enantiomerically-enriched phosphine oxide **36**.

The [2,3] sigmatropic rearrangement could only be performed on (*E*)-**26**. As our goal is to prepare new bidentate ligands, we have now to introduce a phosphorus atom on the aromatic ring and reduce the phosphine oxide.

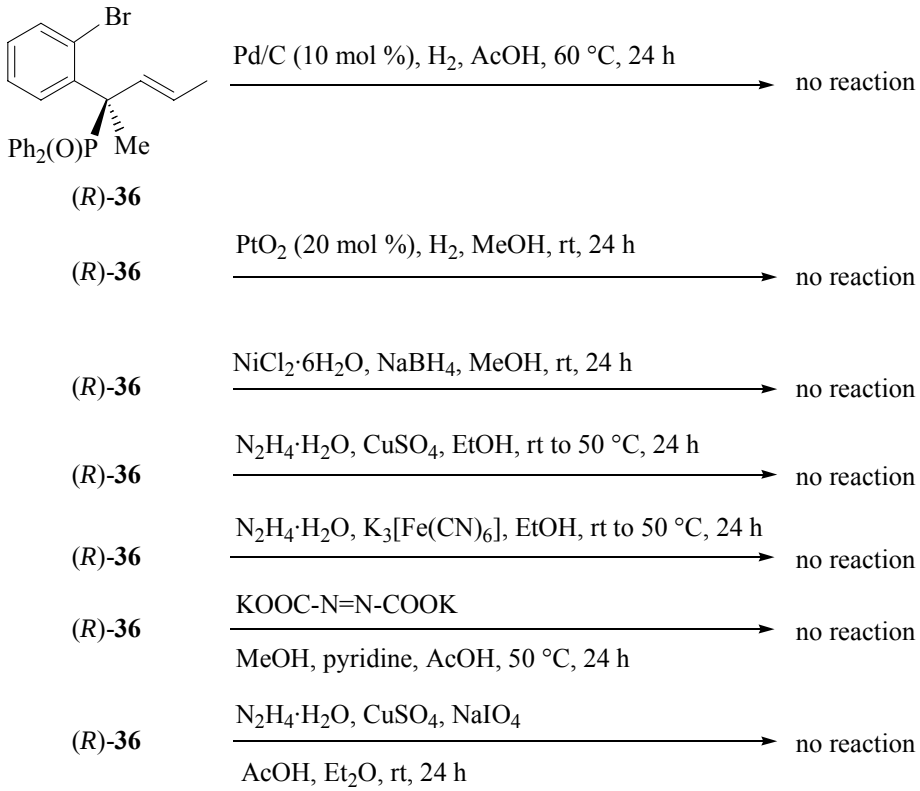
2.6. Preparation of new chiral P,P-ligands from 36

Phosphine oxide **36** was assumed to be a good precursor for new P,P-ligands. Through reduction of the C-C double bond and attachment of a second phosphorus center instead of the bromine atom, new chiral P,P-ligands should be obtained. As described in Scheme 52, we planned to reduce the C-C double bond first, reduce the phosphine oxide to the corresponding phosphine next and finally install the second phosphorus moiety.



Scheme 52. Planned synthesis of a new chiral P,P-ligand.

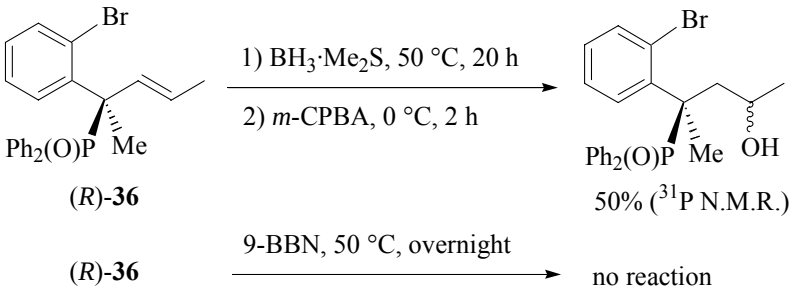
According to Scheme 52, we investigated the reduction of the C-C double bond first. Neither heterogeneous catalysis nor various methods using diimide[56] were efficient (Scheme 53).



Scheme 53. Attempted reduction of the C-C double bond of **36**.

As the reduction of the C-C double bond was unsuccessful, we tried to functionalize it. According to a procedure developed in the Knochel group, a sequence consisting of hydroboration-oxidation was looking promising.[57] The results are shown in Scheme 54.

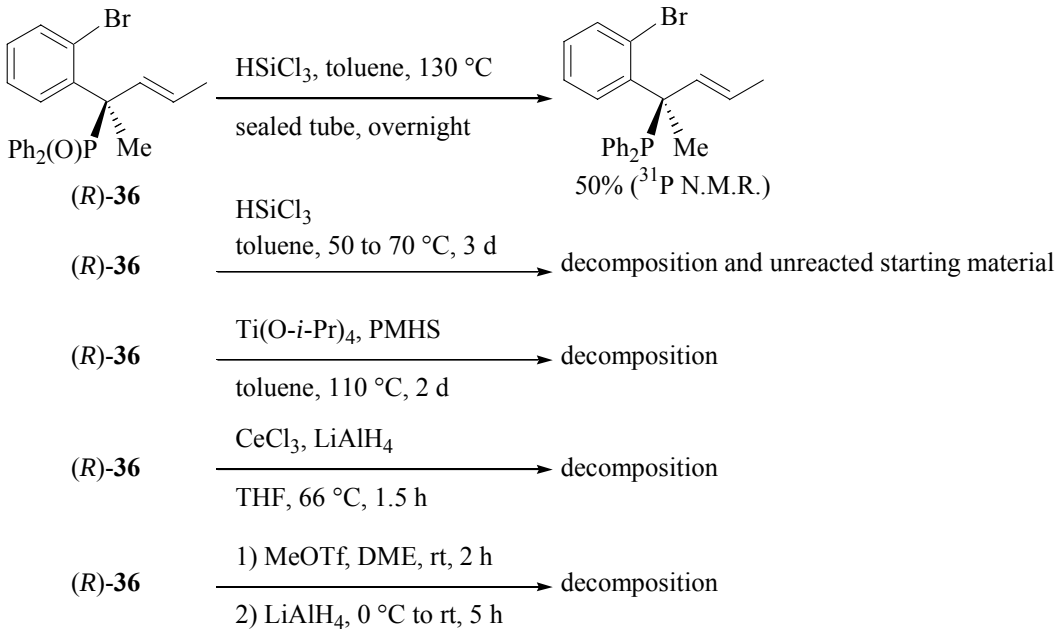
[56] D. J. Pasto, R. T. Taylor, *Org. React.* **1991**, *40*, 91.
[57] A. Gavriouchine, *Unpublished results*.



Scheme 54. Attempted hydroboration-oxidation of the C-C double bond.

When $BH_3 \cdot Me_2S$ was used as the hydroborating agent, a mixture of diastereoisomers was obtained in 50% yield together with 50% of decomposition products as judged by ^{31}P N.M.R. spectroscopy. As 9-BBN is a milder hydroborating agent, it was used instead but led to no hydroboration products.

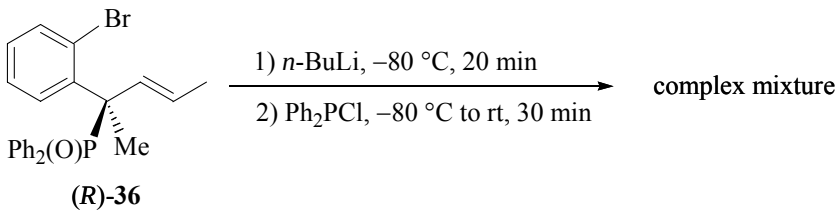
We then tried to reduce the phosphine oxide in the presence of the double bond (Scheme 55). A range of reducing conditions were investigated, but no satisfactory result were obtained. When using trichlorosilane as the reducing agent, 50% of decomposition products were obtained together with the expected product. Also the recently described method for sterically hindered phosphine oxides using MeOTf proved to be unsuccessful.[58]



Scheme 55. Attempted reduction of phosphine oxide **36** in the presence of the C-C double bond.

[58] T. Imamoto, S.-I. Kikuchi, T. Miura, Y. Wada, *Org. Lett.* **2001**, *3*, 87.

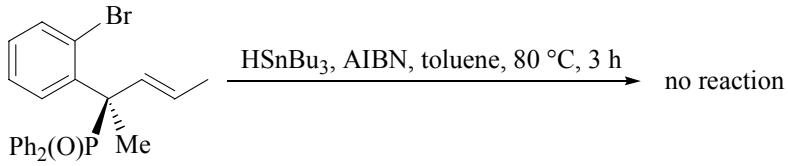
As our attempts to reduce the C-C double bond and to reduce the phosphine oxide failed, we envisaged then to introduce the second phosphorus moiety on **36** (Scheme 56). Therefore, *n*-BuLi was added to **36** and the lithio intermediate was trapped with Ph_2PCl. It led to a complex reaction mixture. This might be due to the incompatibility of the lithio compound with the phosphine oxide (Scheme 56).



(*R*)-**36**

Scheme 56. Attempted substitution of the bromine atom by a second phosphine moiety in the presence of the phosphine oxide.

We envisaged then a free-radical-mediated cyclization. This would lead to monophosphines.[59] Such ligands are powerful in the asymmetric Pd-catalyzed hydrosilylation of alkenes.[60] This radical-mediated cyclization was unsuccessful (Scheme 57).



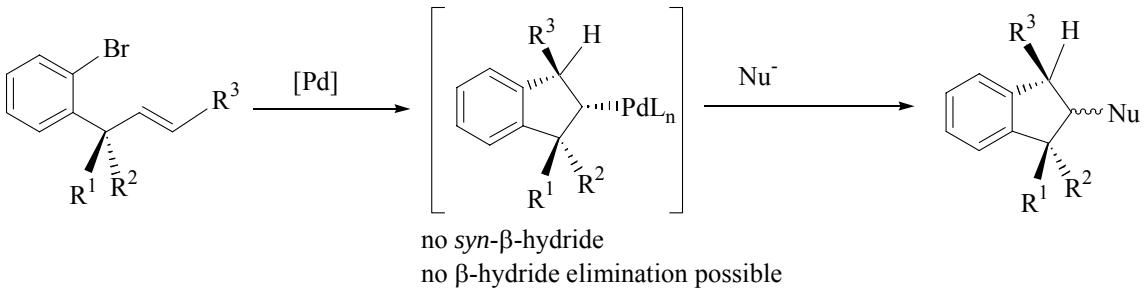
(*R*)-**36**

Scheme 57. Attempted radical-mediated cyclization of (*R*)-**36**.

We envisaged as alternative an intramolecular Heck reaction. For cyclizations following a 5-*endo-trig* pathway, the Pd intermediate would not bear a *syn*-β-hydride to undergo β–hydride elimination (Scheme 58).

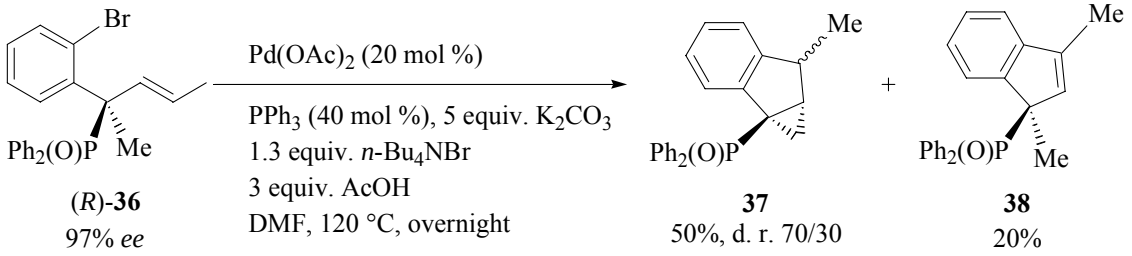
[59] For reviews about chiral monophosphines, see for example: a) F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315; b) T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354; c) T. Hayashi, *J. Organomet. Chem.* **1999**, *576*, 195.

[60] J. F. Jensen, B. Y. Svendsen, T. V. la Cour, H. L. Pedersen, M. Johannsen, *J. Am. Chem. Soc.* **2002**, *124*, 4558.



Scheme 58. Intramolecular Heck reaction leading to a stable Pd intermediate.

A nucleophile would then be necessary to trap the stable intermediate and regenerate the active catalyst.[61] An amine could be used as the nucleophile and allow for the introduction of second donor atom. We used acetic acid as an additive to study the feasability of the reaction. The results are depicted in Scheme 59.



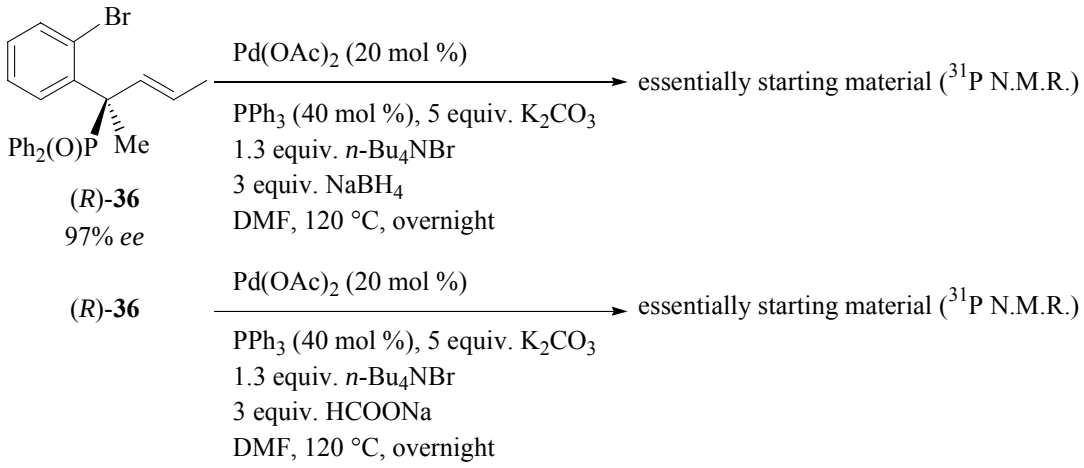
Scheme 59. Intramolecular Heck reaction/C-H activation cascade.

The cyclization proved to be partially diastereoselective, as we observed the formation of **38** due to a *syn*-β-hydride elimination. More interesting is the formation of **37**.[62] This compound was obtained *via* a regioselective C-H activation. Surprisingly, the rate of the C-H activation pathway was high enough to occur even in the presence of a *syn*-β-hydride, as **37** was obtained as a mixture of diastereoisomers. Disappointingly, the Pd intermediate could not be trapped by acetic acid. Other hydride donors were used. The influence of the nature of the

[61] See for example: a) R. C. Larock, N. H. Lee, *J. Org. Chem.* **1991**, *56*, 6253; b) R. Grigg, M. J. Dorrity, J. F. Malone, V. Sridharan, S. Sukirthalingam, *Tetrahedron Lett.* **1990**, *31*, 1343; c) R. Grigg, V. Logarathan, S. Sukirthalingam, V. Sridharan, *Tetrahedron Lett.* **1990**, *31*, 6573; d) R. Grigg, J. M. Sansano, V. Santhakumar, V. Sridharan, R. Thangavelanthum, M. Thornton-Pett, D. Wilson, *Tetrahedron* **1997**, *53*, 34; e) R. Grigg, J. M. Sansano, V. Santhakumar, V. Sridharan, *Tetrahedron Lett.* **1993**, *34*, 3163; e) A. Kojima, T. Takemoto, M. Sodeoka, M. Shibasaki, *Synthesis* **1998**, 581; f) M. Shibasaki, A. Kojima, S. Shimizu, *J. Heterocycl. Chem.* **1998**, *35*, 1057; g) A. Kojima, T. Takemoto, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1996**, *61*, 4876.

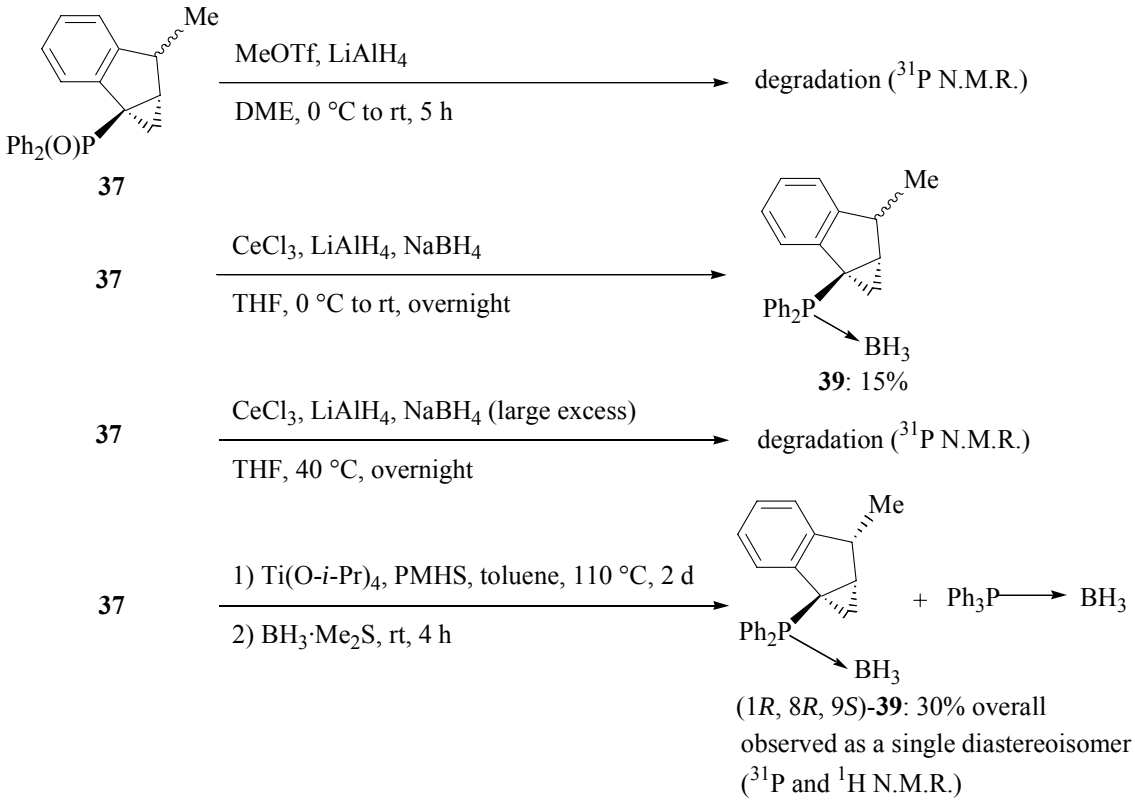
[62] Structure was assigned by INADEQUATE N.M.R. spectrum. Dr. D. S. Stephenson (Analytical Department of the Institute for Organic Chemistry, LMU Munich) is acknowledged for performing the INADEQUATE N.M.R. experiment.

hydride donor is illustrated in Scheme 60. Stronger hydride donors inhibited the reaction almost completely. This cascade will be presented in more detail in part two of this thesis.



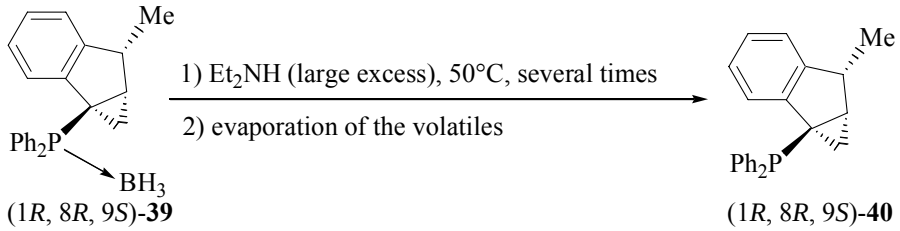
Scheme 60. Influence of the nature of the hydride donor.

Unfortunately, it was not possible to separate both diastereoisomers by column chromatography or crystallization. Phosphine oxide **37** was supposed to be less susceptible to degradation because no allylic system was present to stabilize the radical formed. We then studied the reduction of the phosphine oxide **38** to the phosphine and its *in situ* protection to the borane adduct **39** (Scheme 61).



Scheme 61. Reduction of phosphine oxide **37**.

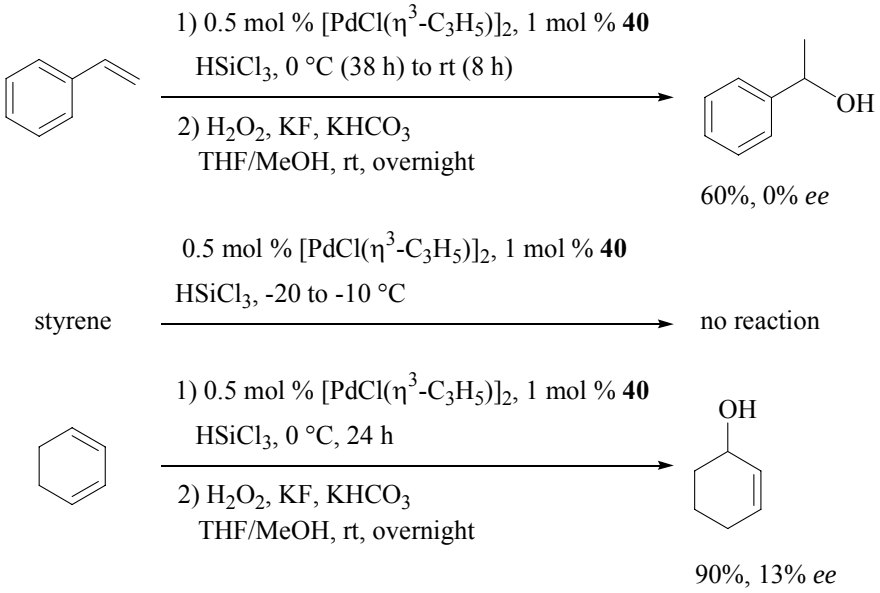
Using Lawrence´s method,[51b] we obtained the phosphine-borane **39** together with triphenylphosphine-borane. The mixture was recristallized from isohexane first and finally recrystallized from pentane. Surprisingly, phosphine-borane **39** was obtained as a single diastereoisomer, as judged by ^{31}P and ^{1}H N.M.R. spectroscopy. Phosphine-borane **39** was deprotected to yield the phosphine **40** and used *in situ* (Scheme 62).



Scheme 62. Final step in the synthesis of monophosphine **40**.

3. Evaluation of monophosphine 40 in asymmetric catalysis

As mentioned above, monophosphines are essentially powerful in the Pd-catalyzed hydrosilylation of alkenes.[59,60] We tested monophosphine **40** in this reaction on the test substrates cyclohexa-1,3-diene and styrene. The results are depicted in Scheme 63.



Scheme 63. Assessment of monophosphine **40** in the Pd-catalyzed hydrosilylation of alkenes.

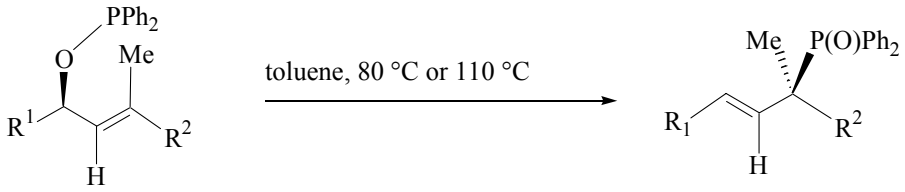
Although the reaction was completely regioselective, monophosphine **40** gave only racemic 2-phenylethanol from styrene. Lowering the temperature led to no reaction. Cyclohexadiene led to cyclohexenol in almost quantitative yield with only 13% *ee*.

4. Conclusion

We have shown that the [2,3] sigmatropic rearrangement could take place under much milder conditions than the ones described earlier. Heating a few hours to 80 or 110 °C allowed complete conversion of the phosphinite to the phosphine oxide.

We also investigated the influence of the substituents on the rearrangement. The size of the substituent on the α position of the allylic system proved to be less important (Scheme 42). Surprisingly, a substituent on the β position of the allylic system lowered the rate of the reaction considerably (Table 2). We showed that the size of the substituent on the γ position

of the allylic system is of crucial importance. A large substituent could lead to a loss of enantioselectivity (Scheme 39) or even inhibit the reaction (Scheme 27). To achieve good stereo- and enantioselectivity, the γ position of the allylic sytem should be disubstituted, thereby generating a chiral quaternary carbon. Scheme 64 summarizes these results.



> 99% *ee*

30-90%, > 99% *ee*

R^1 = small or large group

R^2 = aryl (*o*-substituted phenyl react slower), heteroaryl, alkyl (but tertiary alkyl are not suitable)

Scheme 64. Optimized conditions and substrate for performing an enantioselective [2,3] sigmatropic rearrangement of acyclic allylic phosphinites.

Interestingly, the rearrangement was compatible with the presence of nitrogen-containing heterocycles (pyridine, quinoline). The structures thus obtained were interesting ligand precursors, but the further functionalization of the phosphine oxides proved not to be trivial. We could however obtain one chiral diastereo- and enantiomerically-enriched monophosphine which was tested in the asymmetric Pd-catalyzed hydrosilylation of alkenes. Disappointing *ee´*s were obtained (Scheme 63).

CHAPTER II

Copper-mediated Asymmetric Allylic Substitution Reactions for the Preparation of Molecules bearing Enantiomerically-enriched Quaternary Centers

1. Introduction

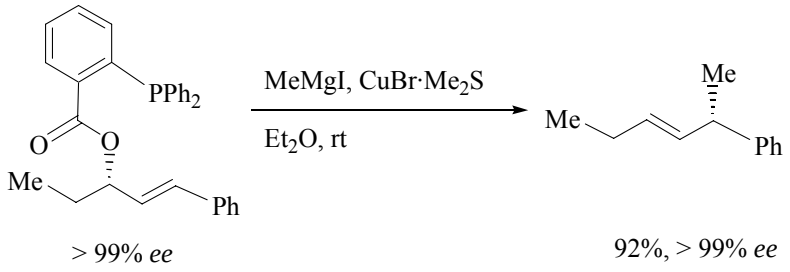
The preparation of enantiomerically-enriched quaternary carbon centers is an important field of research in organic synthesis.[63] Among the most efficient methods for the preparation of such centers in enantiomerically-enriched form, one can mention diastereoselective syntheses, where a chiral auxiliary controls the formation of the quaternary center formed. This auxiliary has to be removed after the reaction. This method lacks efficiency, because two additional steps are required to install and remove the chiral auxiliary.

To overcome this drawback, chiral ligands were used in Pd-catalyzed substitution on allylic systems. Among the most efficient examples were developed P,N-ligands like Pfaltz´s and Helmchen´s PHOX ligands.[64] Although very high *ee´*s were achieved, Pd-catalyzed allylic substitution reactions often lack regioselectivity, in case a non symmetrical allylic substrate is used. Moreover, the preparation of enantiomerically-enriched quaternary centers using this method was not reported so far and only stabilized nucleophiles were in general used efficiently in the preparation of tertiary centers. Cu-catalyzed allylic subtitution reactions do not suffer from these drawbacks.

The use of the concept of "self-immolative" chirality would lead directly to the desired product without installing and removing a chiral auxiliary. This has been used successfully for example by Breit.[65] In asymmetric S_N2' substitution reactions, Breit used a leaving group containing a phosphine. The cuprate could pre-coordinate to the phosphorus atom prior to

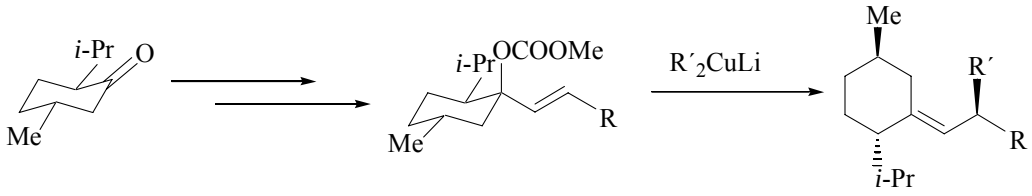
[63] I. Ojima, *Catalytic Asymmetric Synthesis*, VCH, New York, **1993**.
[64] See for example: G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336.
[65] a) B. Breit, P. Demel, *Adv. Synth. Catal.* **2001**, *343*, 429; b) B. Breit, P. Demel, *Modern Organocopper Chemistry*, VCH, Weilheim, **2002**, 188.

substitution. This led to excellent enantioselectivities in asymmetric *syn*-S_N2' substitution reactions. A representative example is shown in Scheme 65.[65a]



Scheme 65. Enantioselective *syn*-S_N2' substitution reaction.

Obviously, this method can only be used for *syn* substitution reactions. One example which matters with the use of "self-immolative" chirality for creating an enantionerically pure tertiary center was reported recently by Spino (Scheme 66).[66]

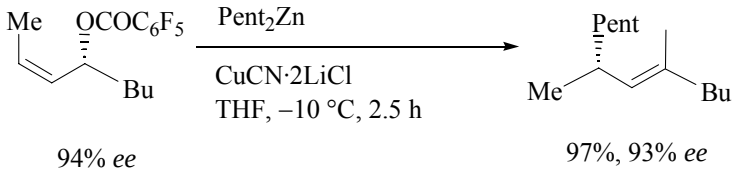


Scheme 66. Spino´s asymmetric substitution reaction based on self-immolative chirality.

Although this substitution was performed on the acyclic part of the molecule, this system was conformationally rigid due to the presence of the cyclohexyl moiety.

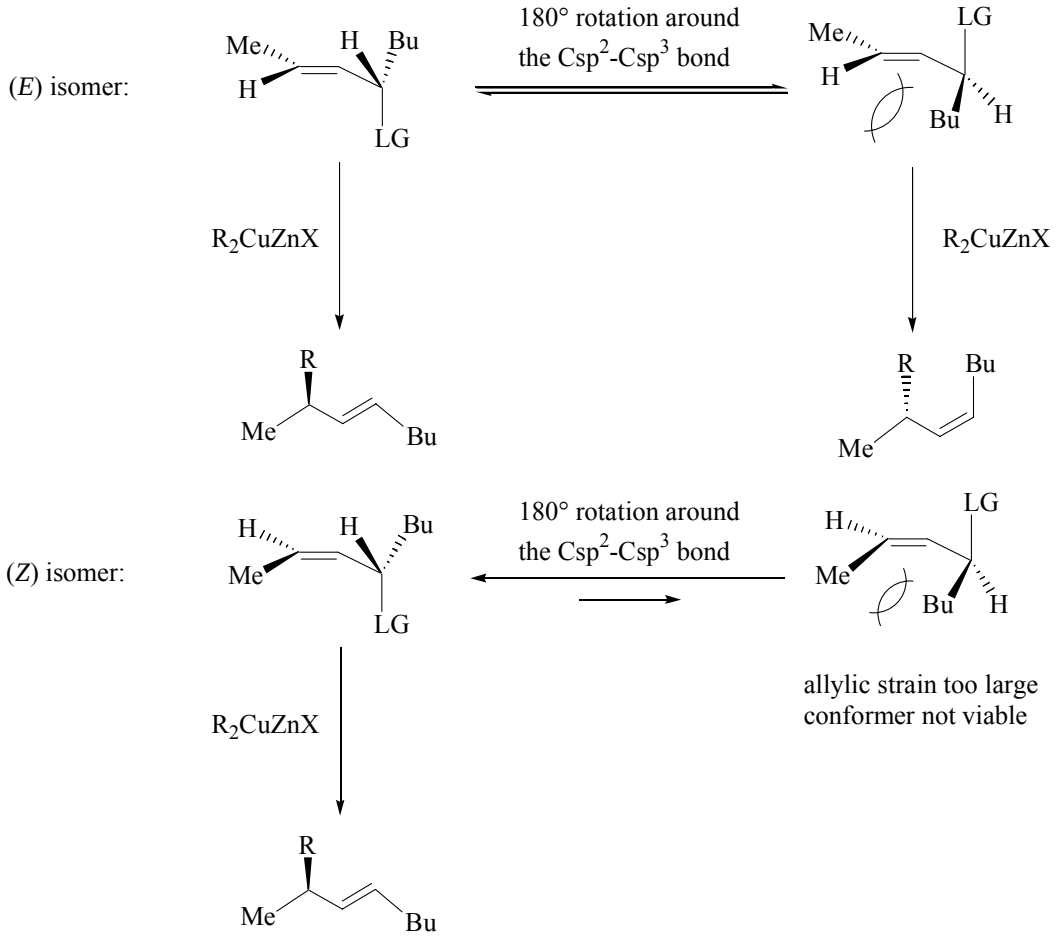
Copper-catalyzed S_N2' substitution reactions were performed in our group[12] using the principle of self-immolative chirality for the preparation of enantiomerically-enriched tertiary carbon centers on acyclic conformationally free substrates and without a directing group attached to the leaving group. An example is depicted in Scheme 67.

[66] a) C. Spino, C. Beaulieu, *J. Am. Chem. Soc.* **1998**, *120*, 11832; b) C. Spino, C. Beaulieu, J. Lafrenière, *J. Org. Chem.* **2000**, *65*, 7091.



Scheme 67. Preparation of an enantiomerically-enriched tertiary center using self-immolative chirality.

It was of crucial importance to use the (*Z*) isomer, as the (*E*) analog led to lower stereo- and enantioselectivities. This was due to the fact that the allylic strain in the (*E*) isomer was not high enough to ensure sufficient rigidity. As shown in Scheme 68, the allylic moiety in the (*E*) isomer could rotate and gave selectivities of 90:10 of inseparable isomers. The (*Z*) isomer did not allow such a rotation and selectivities were much better (Scheme 68).



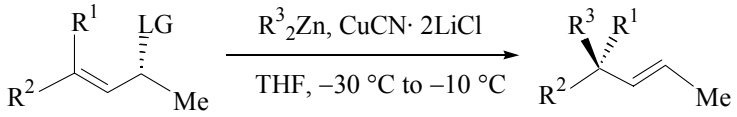
Scheme 68. Comparison of allylic strain in (*Z*) and (*E)* isomers.

As can be seen from Scheme 68, a lack of stereoselectivity is associated with a lack of enantioselectivity. The (*Z*) isomer did not undergo the rotation and gave the desired product with very high stereo- and enantioselectivity.

2. Enantioselective preparation of quaternary centers using chirality transfer and S_N2' substitution reactions

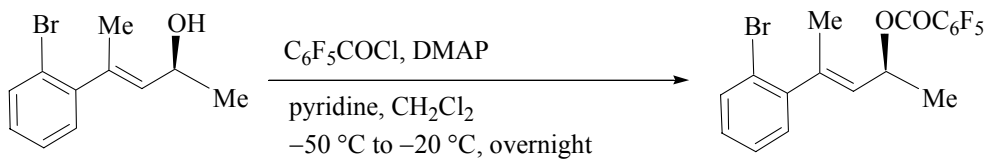
2.1. Scope and limitations: regio-, stereo- and enantioselectivity of Copper-mediated allylic substitution reactions

We planned to apply this procedure to the preparation of enantiomerically-enriched quaternary carbon centers. As a substituent will be *cis* to the carbon bearing the leaving group, the formation of the more sterically hindered rotamer should be disfavoured (as depicted in the right hand side of Scheme 68) and quaternary centers should be obtained with good stereo- and enantioselectivities (Scheme 69).



Scheme 69. Planned preparation of enantiomerically-enriched quaternary centers.

Enantiomerically-enriched alcohol (*E*)-**26** (Scheme 50) was assumed to be a suitable starting material and, as previously described,[12] the pentafluorobenzoate derivative was supposed to be an effective leaving group. Alcohol (*E*)-**26** was derivatized as follows (Scheme 70). The pentafluorobenzoate was obtained in nearly quantitative yield and without loss of enantiomeric purity.

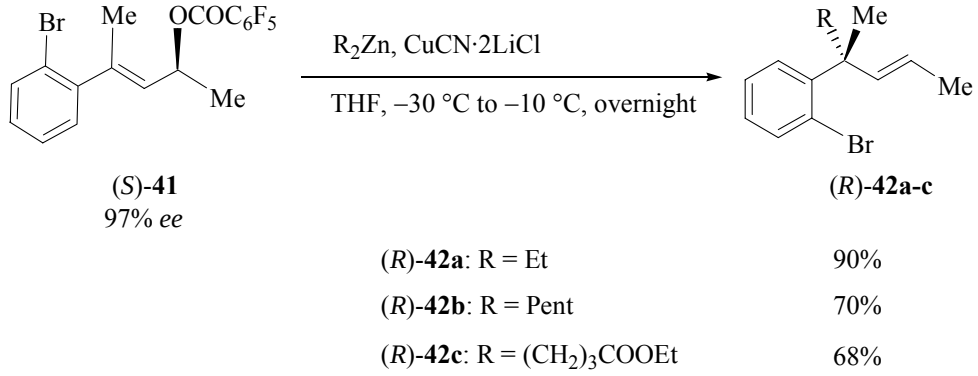


(*S*, *E*)-**26**
97% *ee*

(*S*)-**41**: 90%
97% *ee*

Scheme 70. Derivatization of alcohol (*S*, *E*)-**26** into (*S*)-**41**.

This enantiomerically-enriched alcohol derivative **41** underwent a copper-mediated allylic substitution reaction with various dialkylzinc reagents. The alkenes **42a-c** were obtained in good yield (Scheme 71).



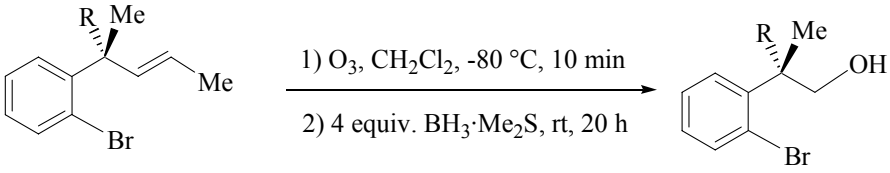
(*S*)-**41**
97% *ee*

(*R*)-**42a-c**

(*R*)-**42a**: R = Et	90%
(*R*)-**42b**: R = Pent	70%
(*R*)-**42c**: R = $(CH_2)_3COOEt$	68%

Scheme 71. Copper-mediated asymmetric allylic substitution reactions.

Enantiomeric excesses could not be determined with alkenes **42a-c**. They underwent a smooth ozonolysis and the intermediary ozonides were reductively cleaved to the corresponding alcohols **43a-c** using $BH_3 \cdot Me_2S$ as shown in Scheme 72.[67] Enantiomeric excesses could be determined for the alcohols by chiral HPLC.[44] Enantiomeric excesses for the alkenes **42a-c** were assumed to be as high as the ones determined for the alcohols.



(*R*)-**42a-c**

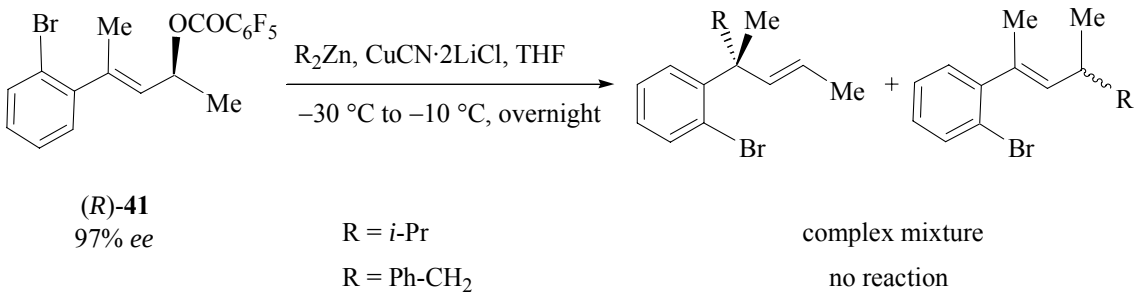
(*S*)-**43a-c**

(*S*)-**43a**: R = Et	60%, 92% *ee*
(*S*)-**43b**: R = Pent	70%, 96% *ee*
(*S*)-**43c**: R = $(CH_2)_3COOEt$	80%, 96% *ee*

Scheme 72. Ozonolysis of **42a-c** and reductive cleavage to the corresponding alcohols.

We then tried to extend this procedure to secondary alkyl and benzyl zinc cuprates. A secondary alkyl zinc cuprate led to a mixture of compounds and benzylzinc cuprate did not react (Scheme 73).

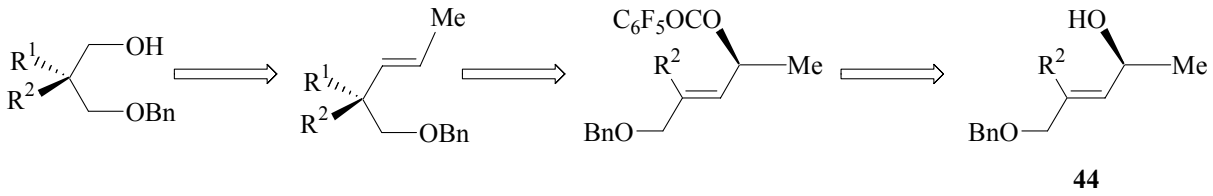
[67] L. A. Flippin, D. W. Gallagher, K. Jalali-Araghi, *J. Org. Chem.* **1989**, *54*, 1430.



Scheme 73. Attempted use of secondary alkyl and benzylzinc cuprates.

2.2. Application to the synthesis of enantiomerically-enriched desymmetrized 1,3-diols, aldol compounds and tertiary alcohols

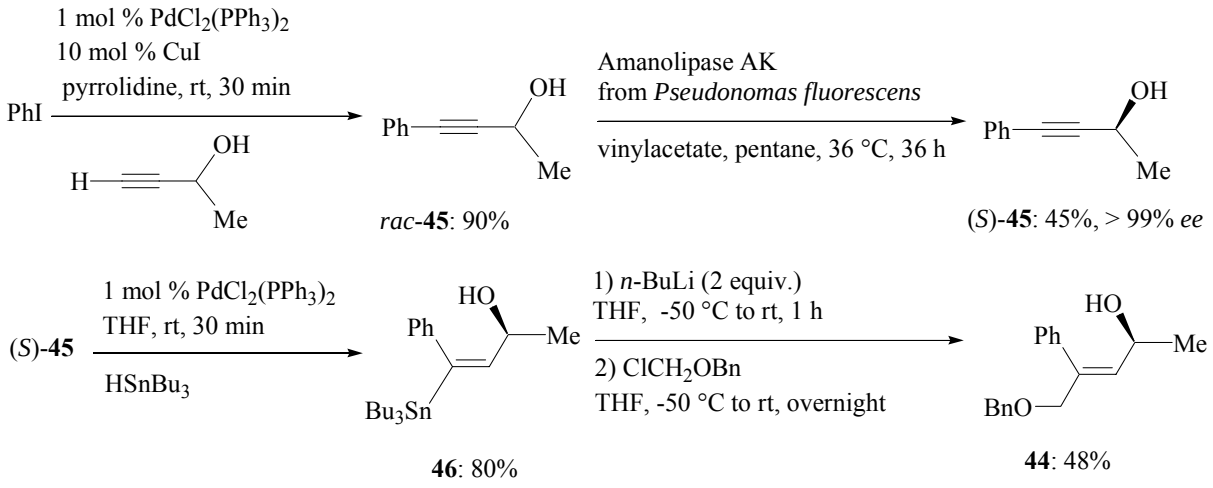
It then appeared to us that this asymmetric allylic substitution/ozonolysis sequence could be efficiently applied to desymmetrize 1,3-diols as depicted in Scheme 74.



Scheme 74. Retrosynthesis for the desymmetrization of 1,3-diols.

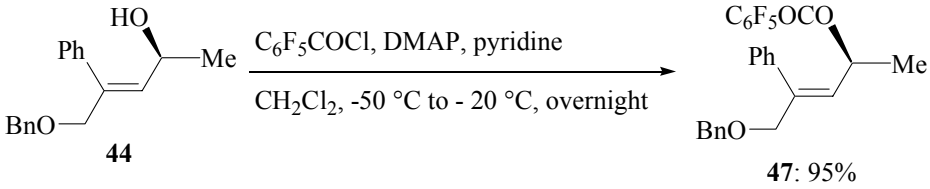
Enantiomerically-enriched alcohol **44** was prepared as follows (Scheme 75). Iodobenzene underwent a smooth Sonogashira cross-coupling reaction[53] with but-3-yn-2-ol to yield the expected arylalkyne **45** in high yield. The racemic alcohol was resolved *via* an enzyme-catalyzed enantioselective acylation.[68] Enantiomerically pure **45** was subjected to a Pd-catalyzed hydrostannylation[38] and yielded regioselectively the alkenylstannane **46**. **46** was reacted with *n*-BuLi (2 equiv.) and benzyl(chloromethyl)ether, yielding **44** in 48% yield.

[68] U. Kazmaier, F. L. Zumpe, *Eur. J. Org. Chem.* **2001**, 4067.



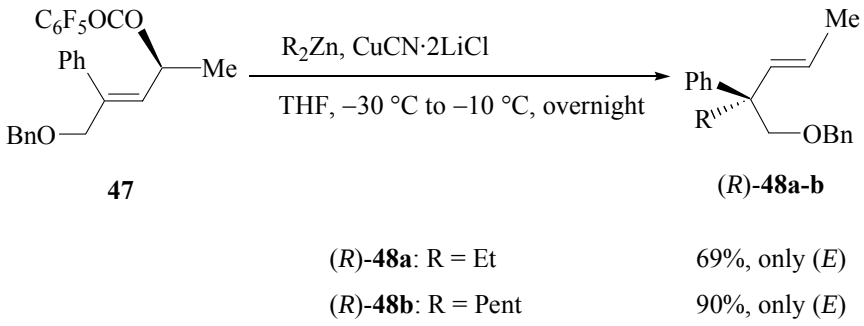
Scheme 75. Preparation of enantiomerically-enriched **44**.

44 was derivatized into its pentafluorobenzoate as previously described, yielding **47** in high yield (Scheme 76).



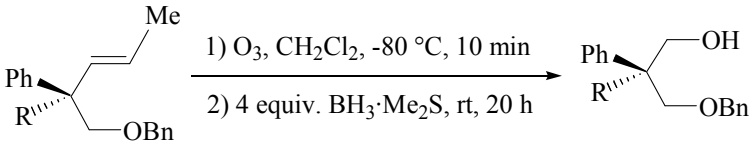
Scheme 76. Derivatization of enantiomerically-enriched alcohol **44**.

47 underwent a smooth copper-mediated asymmetric allylic substitution under the conditions described previously. The expected products **48a-b** were obtained as single regio- and stereoisomers (Scheme 77).



Scheme 77. Regio- and stereoselective copper-mediated allylic substitution reactions.

Alkenes **48a-b** were reacted with ozone and the corresponding ozonides were cleaved to alcohols by $BH_3 \cdot Me_2S$[67] as described in Scheme 78. The desymmetrized 1,3-diols **49a-b** were obtained in moderate yields and very high enantioselectivity.[44]



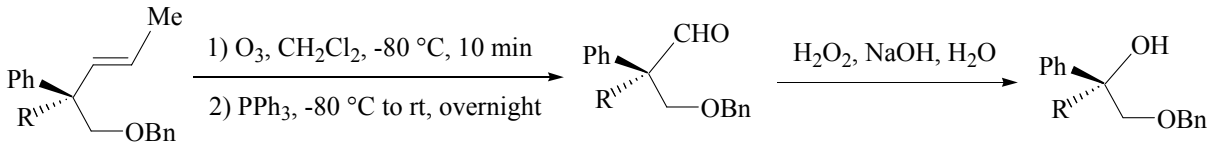
(*R*)-**48a-b** (*S*)-**49a-b**

(*S*)-**49a**: R = Et 66%, > 99% *ee*

(*S*)-**49b**: R = Pent 66%, > 99% *ee*

Scheme 78. Preparation of enantiomerically-enriched, desymmetrized 1,3-diols **49a-b**.

Alkenes **48a-b** were also assumed to be suitable substrates for the preparation of, on the one hand aldol compounds **50a-b** bearing an enantiomerically pure quaternary center, on the other hand enantiomerically-enriched tertiary alcohols **51a-b** as depicted in Scheme 79.

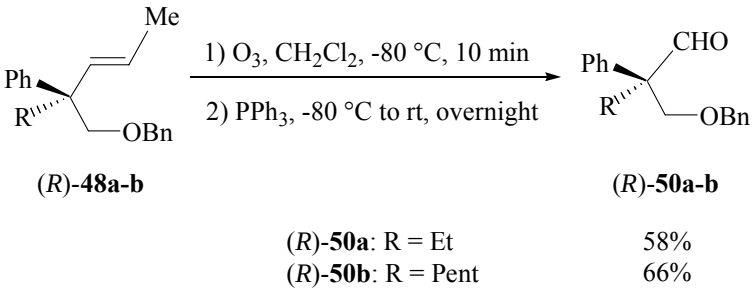


(*R*)-**48a-b** (*R*)-**50a-b** (*R*)-**51a-b**

Scheme 79. Planned stereoselective synthesis of enantiomerically-enriched aldol compounds **50a-b** and tertiary alcohols **51a-b**.

Alkenes **48a-b** were reacted with ozone and the ozonides were cleaved by PPh_3,[69] yielding the corresponding aldol compounds **50a-b** with very high enantioselectivity (Scheme 80).[70]

[69] O. Lorenz, C. R. Parks, *J. Org. Chem.* **1965**, *30*, 1976.
[70] F. F. Kneisel, *Dissertation*, LMU Munich, **2003**.

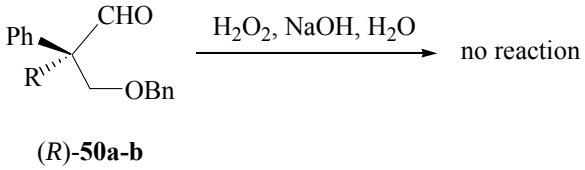


(*R*)-**48a-b** (*R*)-**50a-b**

(*R*)-**50a**: R = Et 58%
(*R*)-**50b**: R = Pent 66%

Scheme 80. Preparation of enantiomerically-enriched aldol compounds **50a-b** bearing an enantiomerically-enriched quaternary center.

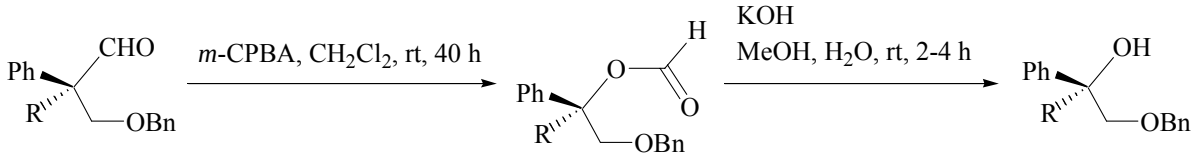
We expected these aldehydes **50a-b** to react with hydrogen peroxyde to yield in one step the expected tertiary alcohols.[71] Unfortunately, no reaction was observed (Scheme 81).



(*R*)-**50a-b**

Scheme 81. Planned synthesis of enantiomerically-enriched tertiary alcohols **51**.

We envisaged then a two-step procedure. Aldehydes **50a-b** underwent a smooth Bayer-Villiger oxidation.[72] The corresponding formates **52a-b** were obtained in satisfactory yield and cleaved to the enantiomerically-enriched tertiary alcohols **51a-b**, which were obtained in moderate yield and very high enantioselectivity (98% *ee*, Scheme 82).[44]



(*R*)-**50a-b** (*R*)-**52a-b** (*R*)-**51a-b**

(*R*)-**52a**: R = Et 73% (*R*)-**51a**: R = Et 70%, 99% *ee*
(*R*)-**52b**: R = Pent 68% (*R*)-**51b**: R = Pent 77%, 98% *ee*

Scheme 82. Preparation of enantiomerically-enriched tertiary alcohols **51a-b**.

[71] M. B. Hocking, *Can. J. Chem.* **1973**, *51*, 2384.
[72] I. M. Godfrey, M. V. Sargent, J. A. Elix, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.

3. Conclusion

The work was extended to (*Z*) analogues of alcohol **26** and to alkyl,alkyl-disubstituted substrates in our group by Kneisel[70] and Leuser and Perrone[73] respectively. In our case, this method proved to be limited to primary alkyl zinc cuprates. Secondary alkyl and benzyl zinc cuprates yielded either a mixture of products or no reaction.

For all substrates, a very good transfer of chirality was observed, then alcohols (*R*)-**43a-c** were obtained after three steps with *ee´*s in a range of 92-96%. This method offers possibilities to build up variously substitued quaternary carbon centers in high yield and with high enantioselectivity. It also allows the use of functionalized zinc reagents as demonstrated by the formation of (*R*)-**42c** bearing an ester function.

More interestingly, alkenes **48a-b** were found to be suitable substrates for the preparation of enantiomerically-enriched desymmetrized 1,3-diols **49a-b**. Olefins **48a-b** also underwent a smooth ozonolysis, yielding after reductive cleavage the corresponding aldol compounds **50a-b** bearing an enantiomerically-enriched quaternary center α to the carbonyl group. These aldehydes **50a-b** could be used in a two-step procedure to lead lo enantiomerically-enriched tertiary alcohols **51a-b**. This strategy could lead to a general method for preparing enantiomerically-enriched tertiary alcohols. These last compounds are especially interesting: as they bear a protected primary alcohol, further transformations can be envisaged, leading to enantiomerically-enriched functionalized tertiary alcohols.

[73] H. Leuser, S. Perrone, *Unpublished results*.

PART II

NEW Pd-CATALYZED HECK REACTION / C-H ACTIVATION CASCADES

1. Introduction

1.1. C(sp^3)-H activation

The C-H activation of C(sp^3)-H bonds is one of the current challenges in chemistry that is expected to have a major impact on both industrial and academic research. In the past, it was shown that C-H bond activations on alkanes can be performed by low- and high valent transition-metal complexes in stoichiometric and catalytic processes.

The high energy barrier of C-H bond cleavage is lowered when it is preceeded by cyclometalation, which is initiated by precoordination of the metal complex to a C-C bond or to a heteroatom in the molecule. This precoordination directs the metal center to the vicinity of the C-H bond to be broken.[74]

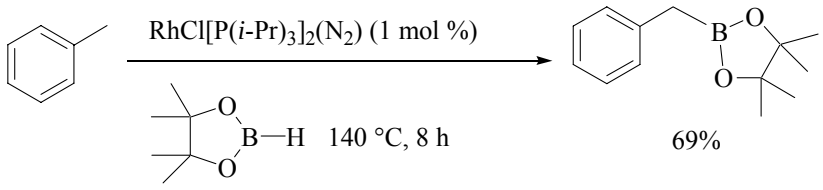
The first examples of C-H activation of C(sp^2) were described in direct mercuration at the end on the nineteenth century.[75] In the 1960s, C-H activation of C(sp^3)-H bonds was discovered. In the 1970s, platinum,[76] iridium,[77] cobalt,[78] ruthenium[79] and titanium[80] salts were used as oxidation catalysts of alkanes. Mechanistic studies have been carried out to understand this process.[81]

Although profitable practical applications are not developed yet, many examples of C-H activation at transition-metal centers under remarkably mild conditions occuring with high selectivities were reported.[82]

Among the most popular metals for performing C(sp^3)-H activations is rhodium. It was used recently for example in the direct preparation of benzylic boron species (Scheme 83).[83]

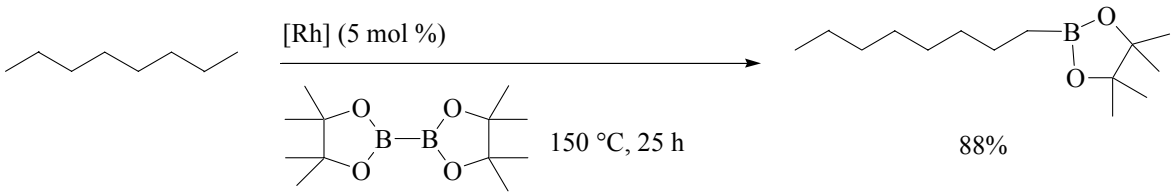
---

[74] See for example: C. Jia; T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633.
[75] A. E. Shilov, G. B. Shul´pin, *Chem. Rev.* **1997**, *97*, 2879.
[76] N. F. Gol´dshleger, V. V. Es´kova, A. E. Shilov, A. A. Shteinman, *Zh. Fiz. Khim.* **1972**, *46*, 1353.
[77] J. L. Garnett, M. A. Long, K. B. Peterson, *Aust. J. Chem.* **1974**, *27*, 1823.
[78] T. A. Cooper, W. A. Waters, *J. Chem. Soc. (B)* **1967**, 687.
[79] V. P. Tret´akov, L. N. Arzamaskova, Y. I. Ermakov, *Kinet. Katal.* **1974**, *15*, 538.
[80] E. A. Grigoryan, F. S. D´ychkovskiy, I. R. Mullagaliev, *Dokl. Akad. Nauk. SSSR* **1975**, *224*, 859.
[81] For a review, see: J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507.
[82] For a review, see: G. Dyker, *Angew. Chem.* **1999**, *111*, 1808; *Angew. Chem. Int. Ed.* **1999**, *38*, 1699.
[83] T. Ishayama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3.



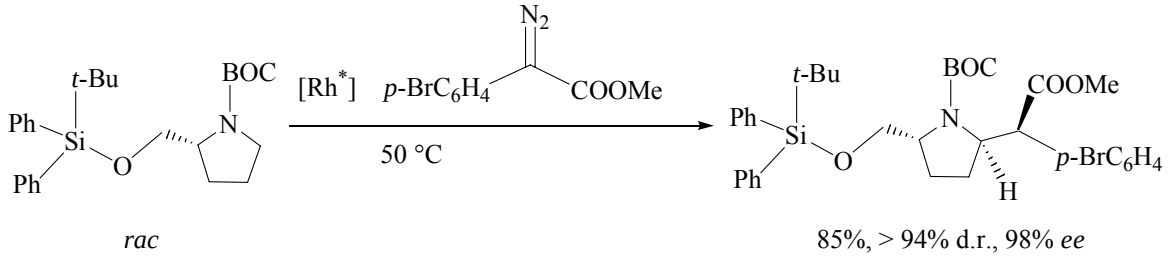
Scheme 83. Preparation of a benzylic boron reagent *via* a Rh-catalyzed C-H activation.

Terminal alkylboronic esters were also prepared in this way as shown in Scheme 84.[84]



Scheme 84. Preparation of terminal alkylboronic esters.

More interestingly, applications to the synthesis of functionalized compounds were found. The use of chiral rhodium complexes led to high diastereo- and enantioselectivities as depicted in Scheme 85.[85]

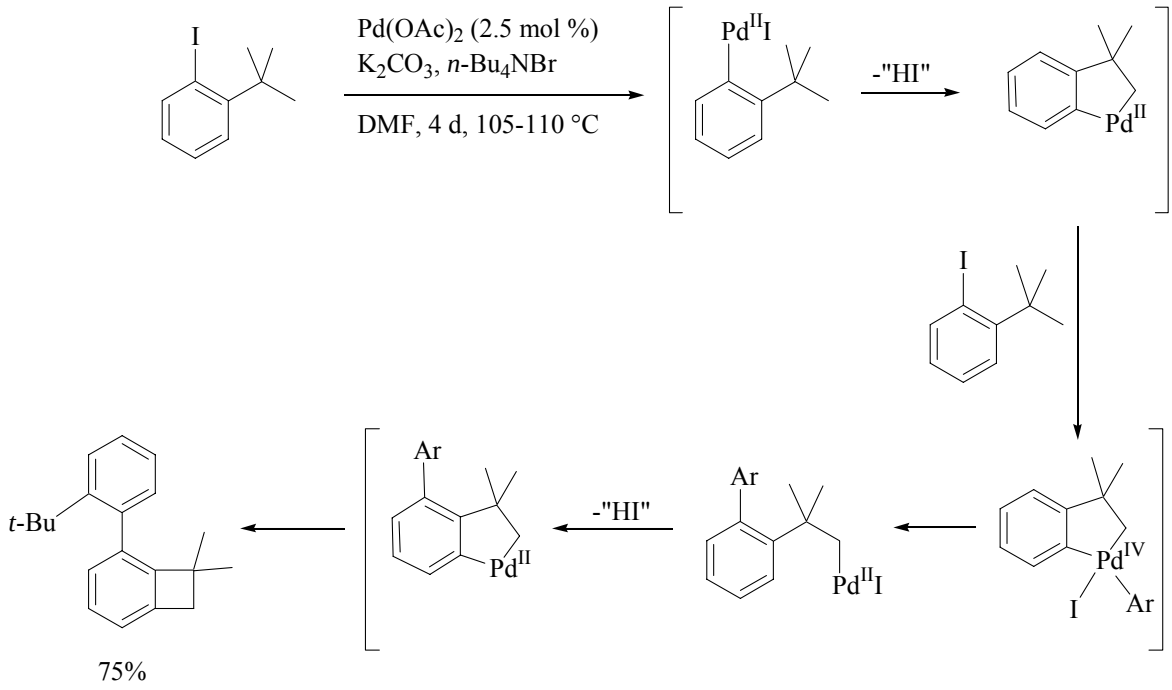


Scheme 85. Enantioselective intermolecular C-H activation in the preparation of functionalized compounds.

As rhodium is one of the most expensive transition-metals, cheaper palladium was recently investigated. Pd-catalyzed C-H activation found now broad applications.

[84] a) K. M. Waltz, J. F. Hartwig, *Science* **1997**, *277*, 211; b) H. Chen, S. Schlecht, T. C. Temple, J. F. Hartwig, *Science* **2000**, *287*, 1995; c) K. M. Waltz, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 11358; d) H. M. L. Davies, *J. Mol. Catal. A: Chemical* **2002**, *189*, 125.
[85] a) H. M. L. Davies, T. Hansen, D. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* **1999**, *121*, 6509.

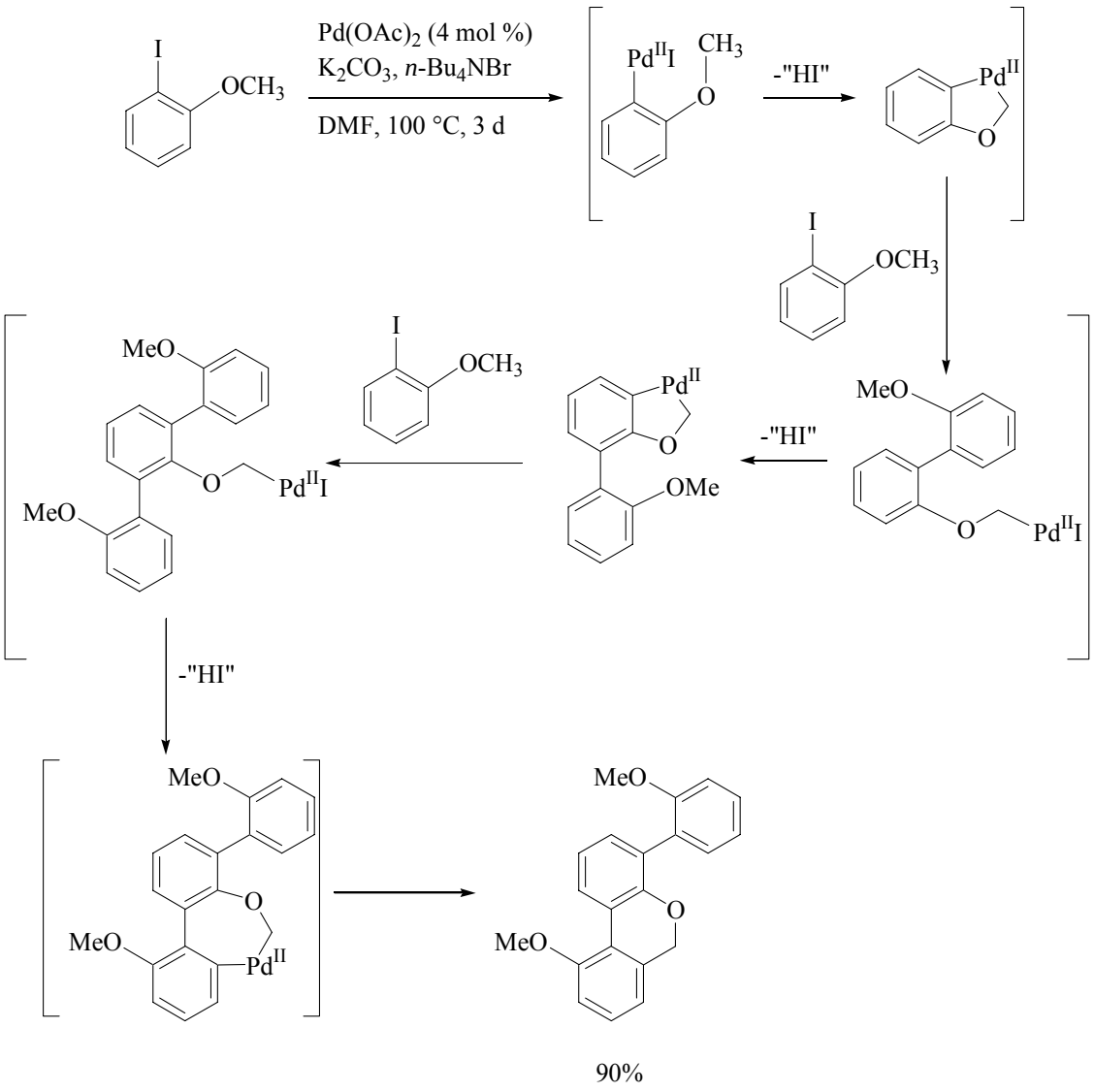
Dyker used a Pd-catalyzed C-H activation for the preparation of benzocyclobutane derivatives (Scheme 86).[86] The mechanism involved successive C-H activations and cross-coupling reactions. The products were obtained in good yields but after long reaction times.



Scheme 86. Preparation of benzocyclobutane derivatives (for clarity, ligands are omitted).

Dyker also used a Pd-catalyzed C-H activation in the preparation of heterocycles as depicted in Scheme 87.[87] These reactions followed a pathway similar to the one described in Scheme 86. Again, the products were obtained in good yields, but long reaction times were required.

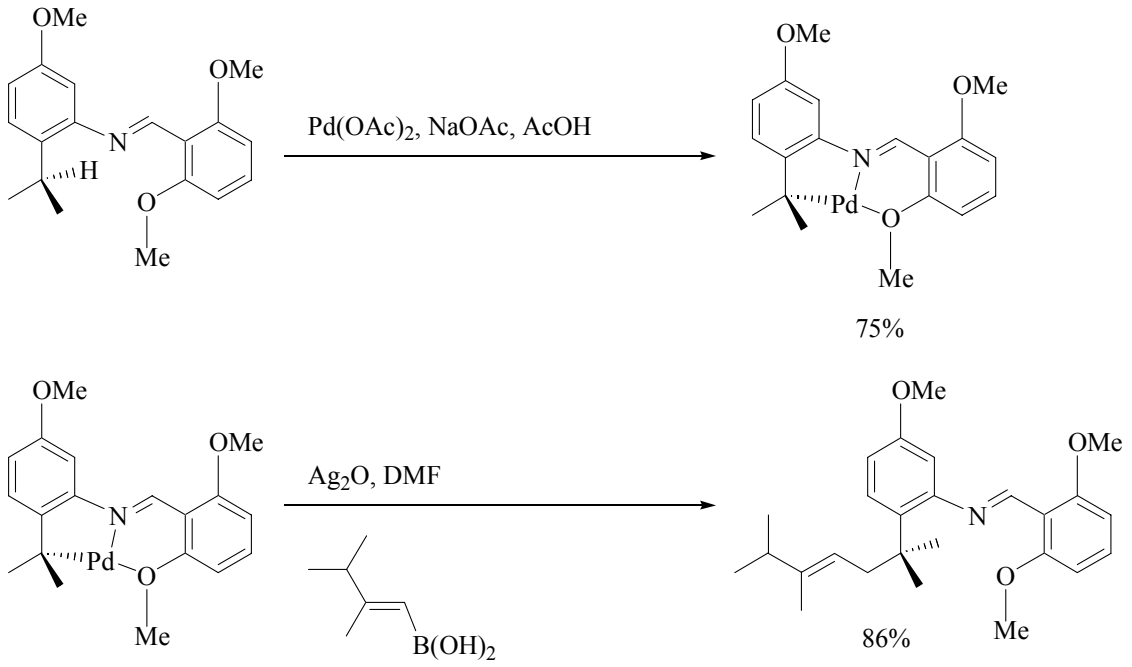
[86] G. Dyker, *Angew. Chem.* **1994**, *106*, 117; *Angew. Chem. Int. Ed.* **1994**, *33*, 103.
[87] a) G. Dyker, *Angew. Chem.* **1992**, *104*, 1079; *Angew. Chem. Int. Ed.* **1992**, *31*, 1023; b) G. Dyker, *J. Org. Chem.* **1993**, *58*, 6426; c) G. Dyker, *Chem. Ber.* **1994**, *127*, 739.



Scheme 87. Preparation of a heterocycle *via* a C-H activation (for clarity, ligands are omitted).

C-H activation has been recently reported as a key step in the synthesis of an advanced synthon for the preparation of Teleocidin B4.[88] This strategy required a stoichiometric amount of a palladium salt. A precoordination of the palladium atom to two heteroatoms led to a C-H activation and the intermediate formed was functionalized as shown in Scheme 88.

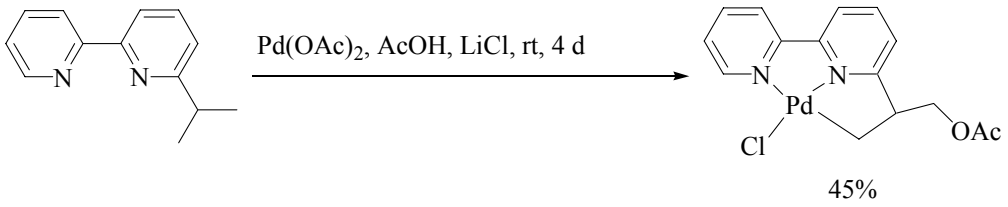
[88] B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856.



Scheme 88. Preparation of an advanced intermediate in a total synthesis using a Pd-catalyzed C-H activation.

In the reaction described above, only palladium salts were suitable for performing the C-H activation. This strategy was also used by the same group with thio ethers.[89] This illustrates that this reaction can be applied to other derivatives of this kind.

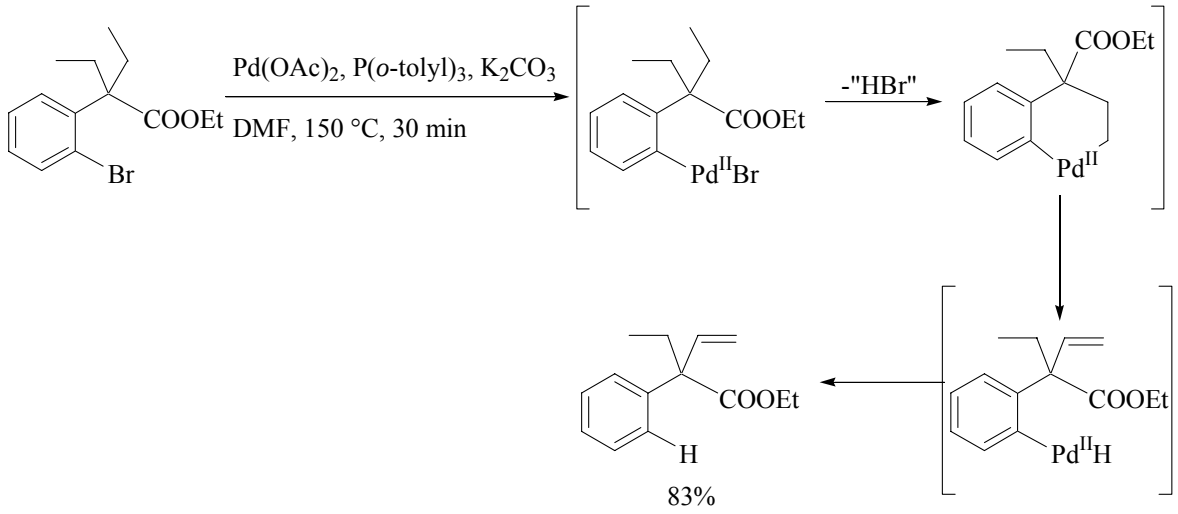
This concept of preformation of a complex with a bidentate ligand prior to C-H activation was also reported in the functionalization of substituted bipyridines as shown in Scheme 89.[90] This kind of complexes are intensively studied, because they proved to be efficient catalysts in a large number of reactions.[91]



Scheme 89. Functionalization of bipyridines via C-H activation.

[89] B. Sezen, R. Franz, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 13373.
[90] A. Zucca, M. A. Cinellu, M. V. Pinna, S. Stoccoro, G. Minghetti, M. Manassero, M. Sansoni, *Organometallics* **2000**, *19*, 4295.
[91] For recent reviews, see: a) J. T. Singleton, *Tetrahedron* **2003**, *59*, 1837; b)M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759.

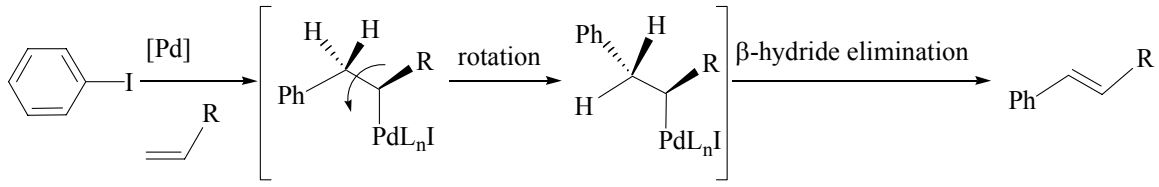
Recently, Baudoin reported a Pd-catalyzed debromination involving a C-H activation step as depicted in Scheme 90.[92]



Scheme 90. Pd-catalyzed debromination *via* a C-H activation reaction (for clarity, ligands are omitted).

1.2. Heck reaction/C-H activation in tandem processes

Normally, the palladium intermediate resulting from the carbopalladation step bears a *syn*-β-hydride which can undergo a β–hydride elimination as depicted in Scheme 91.

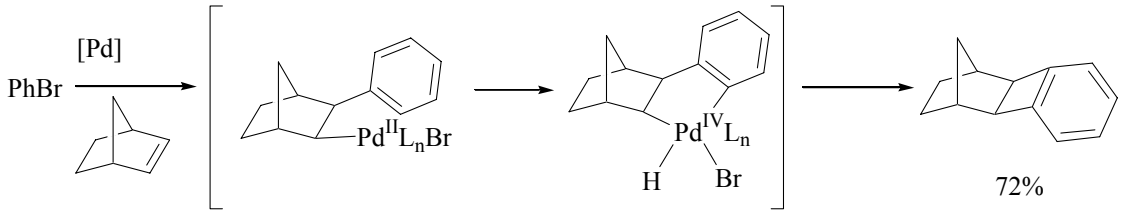


Scheme 91. General pathway in a Heck reaction.

However, this process is not possible when for example a cyclic alkene is used or when an intramolecular Heck reaction is carried out. In both cases, a *syn* carbopalladation takes place. The intermediate can not rotate as described in Scheme 91 and the stable palladium intermediate undergoes other processes to regenerate an active catalyst (Scheme 58). It is either trapped by a nucleophile[61,93] or it undergoes a C-H activation process. Typical

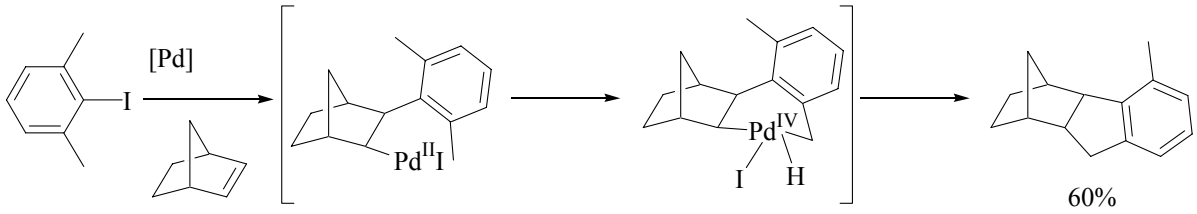
[92] O. Baudoin, A. Herrbach, F. Guéritte, *Angew. Chem.* **2003**, *115*, 5914; *Angew. Chem. Int. Ed.* **2003**, *42*, 5736.
[93] J. T. Link, *Org. React.* **2002**, *60*, 157.

examples of C-H activations have been reported using norbornene as alkene. The palladium intermediate often underwent a C-H activation on the aromatic ring (Scheme 92).[94]



Scheme 92. Heck reaction/C-H activation using norbornene as alkene.

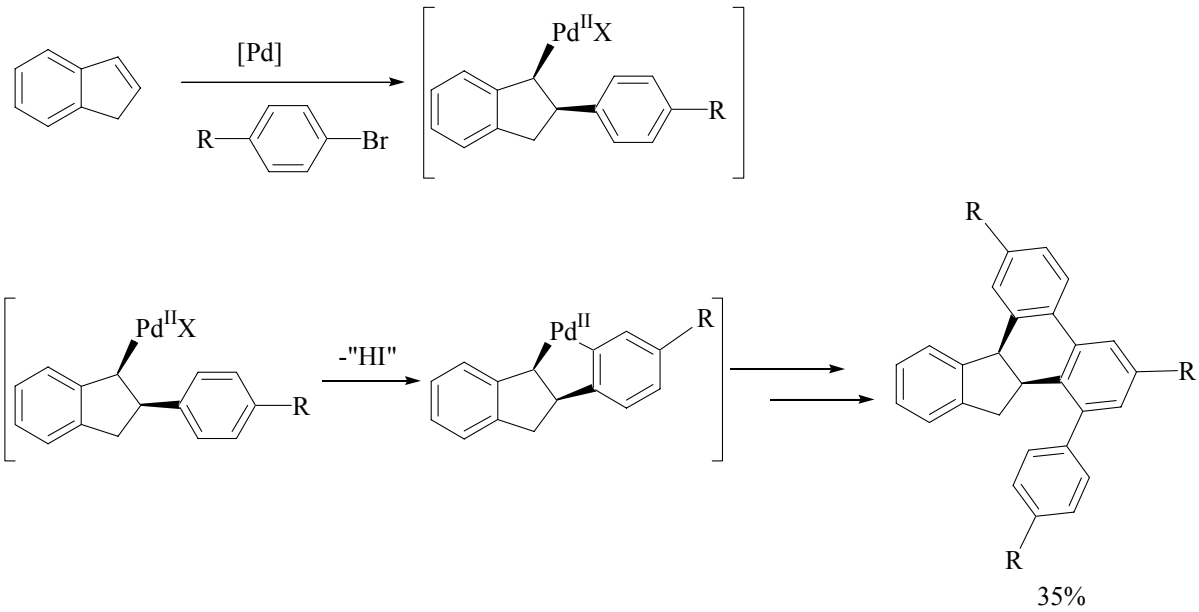
A variation of this reaction involved the C(sp^3)-H activation of a benzylic position (Scheme 93).[95]



Scheme 93. Heck reaction /C-H activation of a benzylic position (for clarity, ligands are omitted).

C(sp^2)-H activation was reported while performing a Heck reaction with indene. The adduct resulting from the *syn*-carbopalladation could not undergo a *syn*-β-hydride elimination could take place (Scheme 94).[96]

[94] See for example: a) S. Pache, M. Lautens, *Org. Lett.* **2003**, *5*, 4827; b) M. Catellani, M. C. Fagnola, *Angew. Chem.* **1994**, *106*, 2559; *Angew. Chem. Int. Ed.* **1994**, *33*, 2421; c) M. Catellani, *Synlett* **2003**, 298 and references therein.
[95] M. Catellani, E. Motti, S. Ghelli, *Chem. Commun.* **2000**, 2003.
[96] a) A. de. Meijere, S. Bräse, *J. Organomet. Chem.* **1999**, *576*, 88; b) O. Reiser, M. Weber, A. de Meijere, *Angew. Chem.* **1989**, *101*, 1071; *Angew. Chem. Int. Ed.* **1989**, *28*, 1037.



Scheme 94. Heck reaction/C-H activation using indene (for clarity, ligands are omitted).

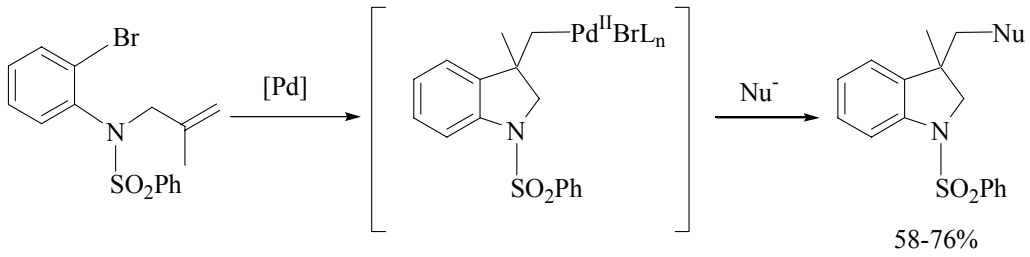
2. Intramolecular Heck reaction /regioselective C-H activation cascades

2.1. Introduction

Heck reaction /C-H activation cascades were investigated in the last years. These reactions only involved intermolecular cyclisation reactions on reactive alkenes like indenes and norbornenes. These processes were not reported using unactivated alkenes in an intramolecular manner.

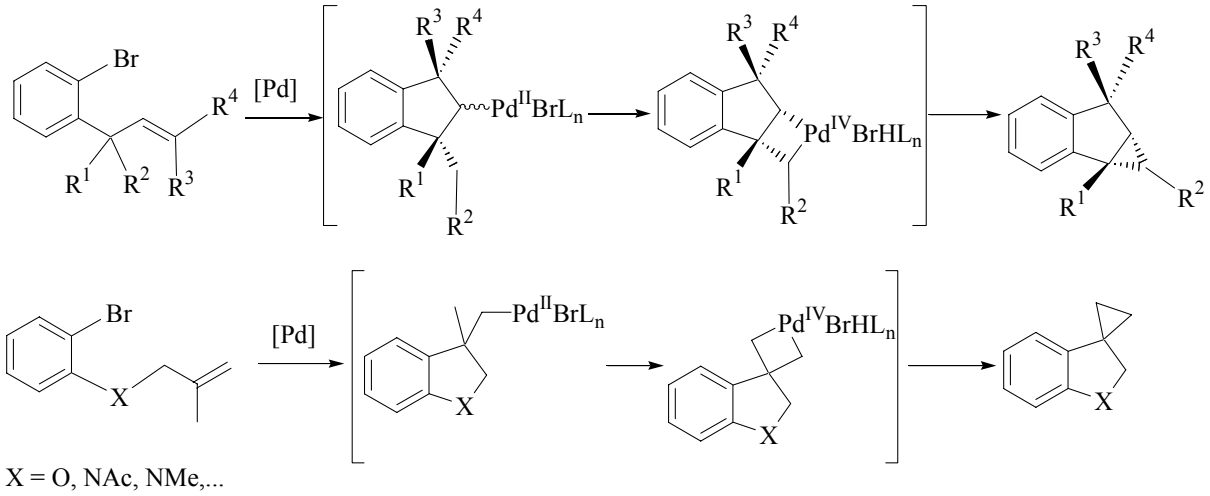
So far, the stable palladium adduct resulting from the carbopalladation was symmetrical. All available positions likely to undergo the C-H activation step were chemically equivalent.

Grigg and others[61] demonstrated that neopentylic palladium adducts resulting from intramolecular Heck reactions could be trapped with various nucleophiles (Scheme 95), but these systems were never studied in the absence of any nucleophile.



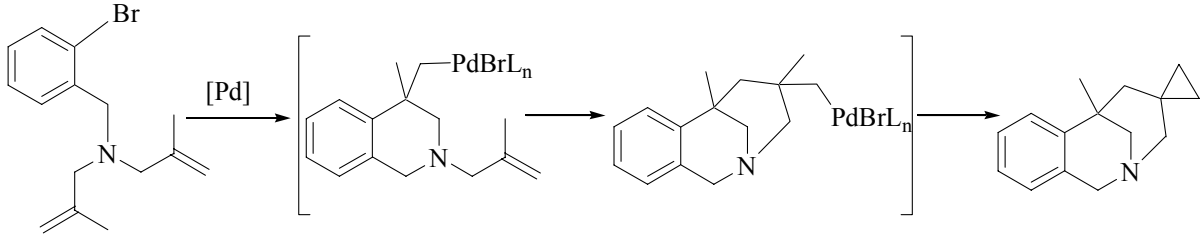
Scheme 95. Trapping stable palladium intermediates by a nucleophile.

If such systems were also able to undergo the C-H activation pathway, they could lead to interesting spiro or fused-ring compounds (Scheme 96).



Scheme 96. Expected C-H activation in products from intramolecular Heck reactions.

Ultimately, this could lead to the formation of the following interesting alkaloids (Scheme 97).



Scheme 97. Postulated synthesis of interesting alkaloids *via* a double Heck reaction/C-H activation cascade.

To make this reaction useful, it should occur under mild conditions, and both the carbopalladation **and** the C-H activation steps **must** be regioselective. To fulfill these requirements, we will first optimize the conditions to obtain phosphine oxide **37** in the most selective way.

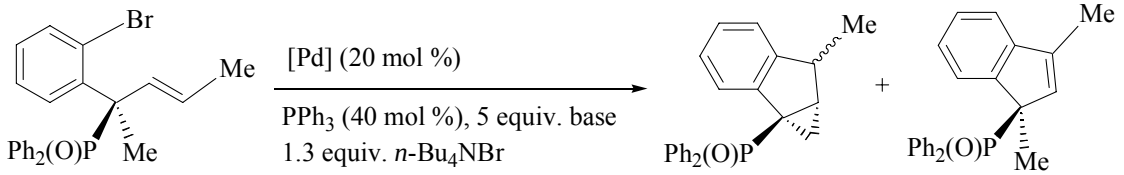
2.2. Optimization of the reaction conditions

2.2.1. Optimization of the synthesis of 37

As shown in Scheme 59 (see part I), phosphine oxide **36** was cyclized selectively to the tricyclic phosphine oxide **37**.

This reaction was optimized in view to get the best selectivity **37**/**38** and the best diastereomeric ratio between the two possible diastereomers of phosphine oxide **37**. The results of the investigation of various parameters are reported in Table 3.

Table 3. Optimization of the synthesis of phosphine oxide **37**.



(*R*)-**36**
97% *ee*

37

38

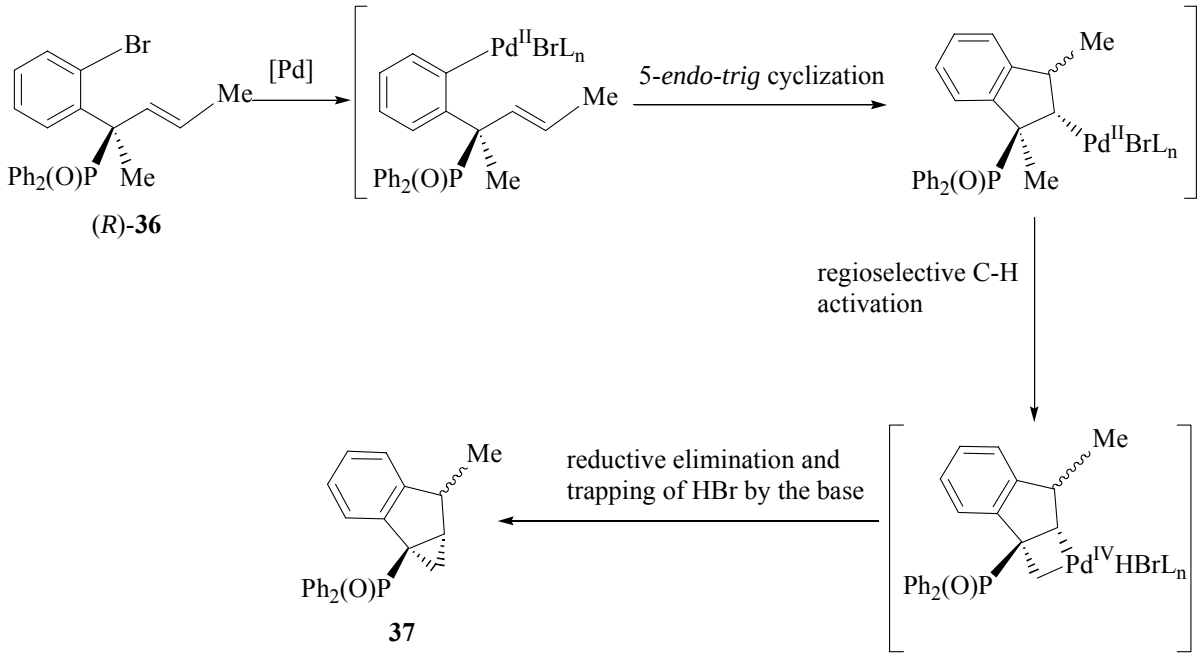
Entry	[Pd]	base	additive	T(°C)	36[a]	37[a]	38[a]
1	$Pd(OAc)_2$	K_2CO_3	AcOH	120	0	75 (d.r. = 80/20)	25
2	$Pd(OAc)_2$	K_2CO_3	AcOH	80	30	58 (d.r. = 60/40)	12
3	$Pd(OAc)_2$	K_2CO_3	AcOH	140	0	63 (d.r. = 65/35)	12
4	$Pd(OAc)_2$	K_2CO_3	$NaBH_4$	120	90	0	10
5	$Pd(OAc)_2$	K_2CO_3	HCOONa	120	60	20 (d.r. > 99/1)	10
6	$Pd(OAc)_2$	Ag_2CO_3	AcOH	80	94	6 (d.r. > 99/1))	0
7	$Pd(OAc)_2$	Ag_2CO_3	AcOH	100	60	20 (d.r. > 99/1)	15
8	$Pd(OAc)_2$	Ag_2CO_3	AcOH	120	0	90 (d.r. = 60/40)	10
9	$Pd(OAc)_2$	Ag_2CO_3	HCOONa	100	60	0	40
10	$Pd(PPh_3)_4$[b]	Et_3N	AcOH	80	100	0	0

a/ Ratios of products and diastereomeric ratios were determined by ^{31}P N.M.R. spectroscopy; b/ reaction carried out without additional PPh_3.

From Table 3, when $Pd(OAc)_2$ was used as a catalyst, the optimal temperature was 120 °C (entry 1). Higher or lower temperatures (entries 2 and 3) led to lower conversions or lower diastereoselectivites respectively. Switching the trapping reagent from AcOH to $NaBH_4$ inhibited the reaction and HCOONa led to lower conversion (entries 4 and 5). For HCOONa, a high diastereoselectivity was obtained, but the conversion was too low to be synthetically useful. When Ag_2CO_3 was used as a base, high diastereoselectivities were obtained, but with low conversions (entries 6 and 7). At 120 °C, a high conversion was obtained, but the diastereoselectivity was poor (entry 8). When using Ag_2CO_3, changing the trapping reagent led to low conversion (entry 9). The use of a Pd(0) species led to no conversion at 80 °C (entry 10). The conditions used first proved to be optimal in terms of **37**/**38** ratio and diastereoselectivity.

2.2.2. Proposed mechanism of the intramolecular Heck reaction/C-H activation cascade

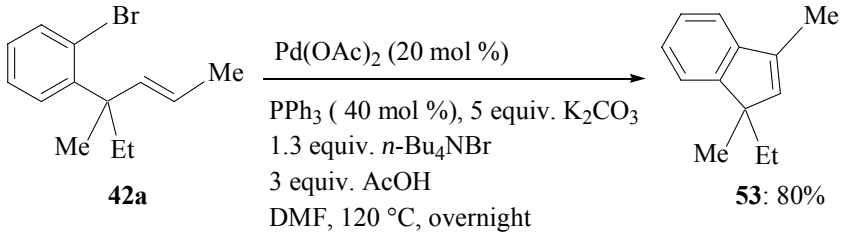
The reaction pathway involved a 5-*endo-trig*-cyclization followed by a regioselective C-H activation as described in Scheme 98.



Scheme 98. Proposed mechanism for the generation of phosphine oxide **37**.

2.3. Synthesis of carbocycles

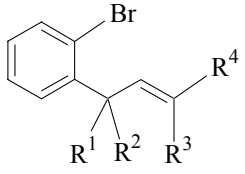
We turned our attention to the fact that it was possible to perform the C-H activation in the presence of a *syn*-β-hydride as demonstrated by the isolation of **37** as a mixture of diastereoisomers. **42a** was a good substrate to evaluate the influence of the steric hindrance (Thorpe-Ingold effect) on this pathway. The result is shown in Scheme 99. Only indene **53** coming from a β–hydride elimination was isolated. This shows the crucial importance of the Thorpe-Ingold effect in this reaction. When this effect was minimized, no C-H activation was observed. Interestingly, a single regioisomer was observed. The cyclization occured solely as a 5-*endo-trig* pathway and no 4-*exo-trig* cyclization product was observed.



Scheme 99. Influence of the steric hindrance on the C-H activation in the presence of a *syn*-β- hydride.

This result shows that, in case the steric hindrance is not large enough, a trisubstituted alkene is required for a potential C-H activation. The carbopalladation step will lead to an intermediate bearing no β–hydride to eliminate.

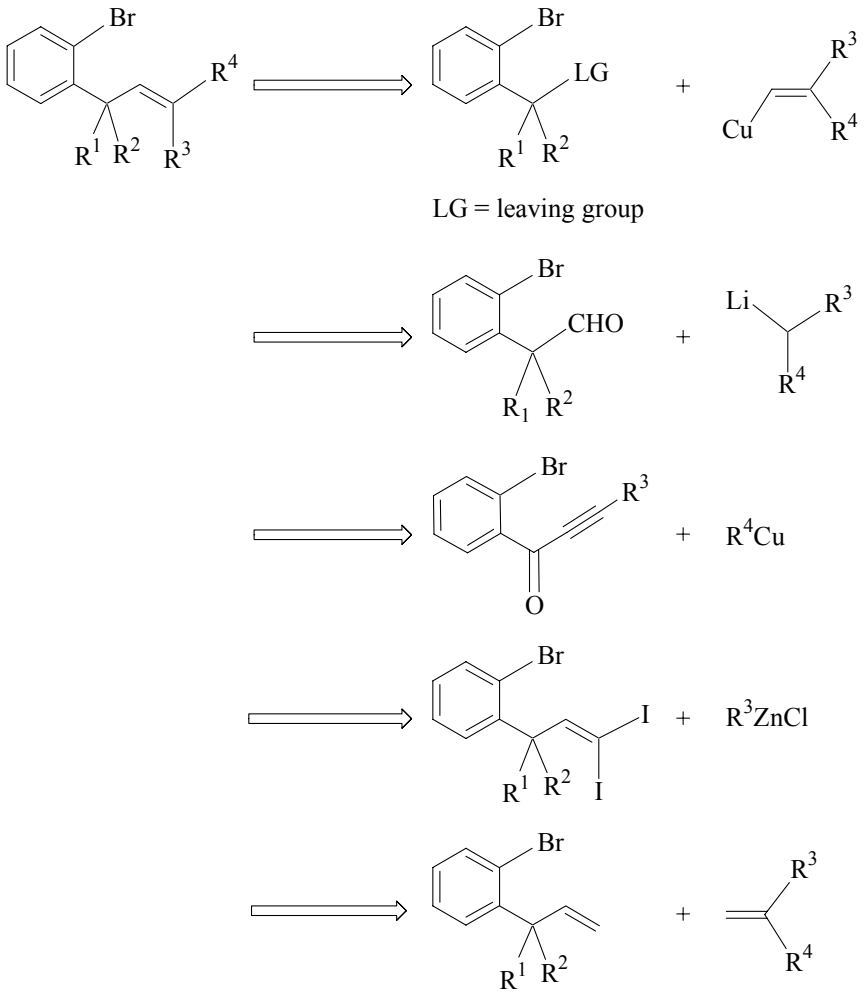
For this purpose, we prepared substrates of the following general structure (Scheme 100).



R^1 - R^4 = alkyl, benzyl

Scheme 100. General structure for carbocycle precursors.

We envisaged the following retrosynthetic analysis to prepare these compounds (Scheme 101). Unfortunately, none of them proved to be efficient enough to obtain the desired substrate in good yields.

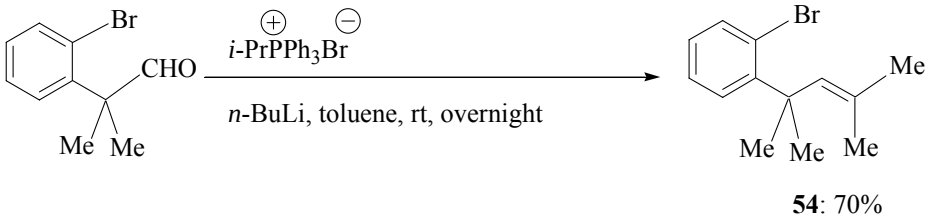


Scheme 101. Retrosynthetic pathways to prepare indene precursors.

Therefore, we synthesized these substrates *via* a Wittig reaction. This reaction has the major drawback that the preparation of a phosphonium salt on a secondary carbon atom is known to proceed sluggishly.

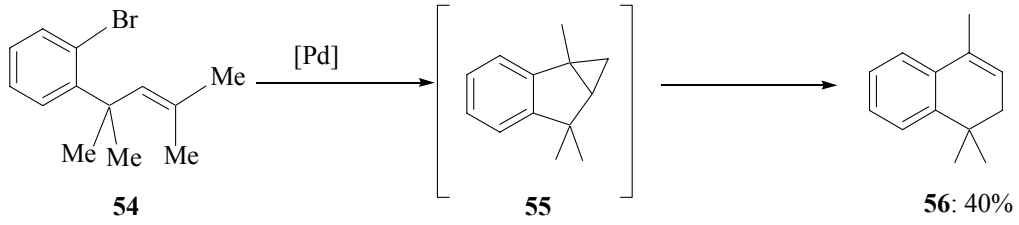
As shown in Scheme 102, we prepared as a model substrate alkene **54** from a known aldehyde.[97]

[97] C. Pascal, J. Dubois, D. Guénard, F. Guéritte, *J. Org. Chem.* **1998**, *63*, 6414.



Scheme 102. Preparation of alkene **54**.

Alkene **54** was subjected to the conditions described above. The result obtained is described in Scheme 103.



Scheme 103. Intramolecular Heck reaction/C-H activation cascade with **54** as a substrate.

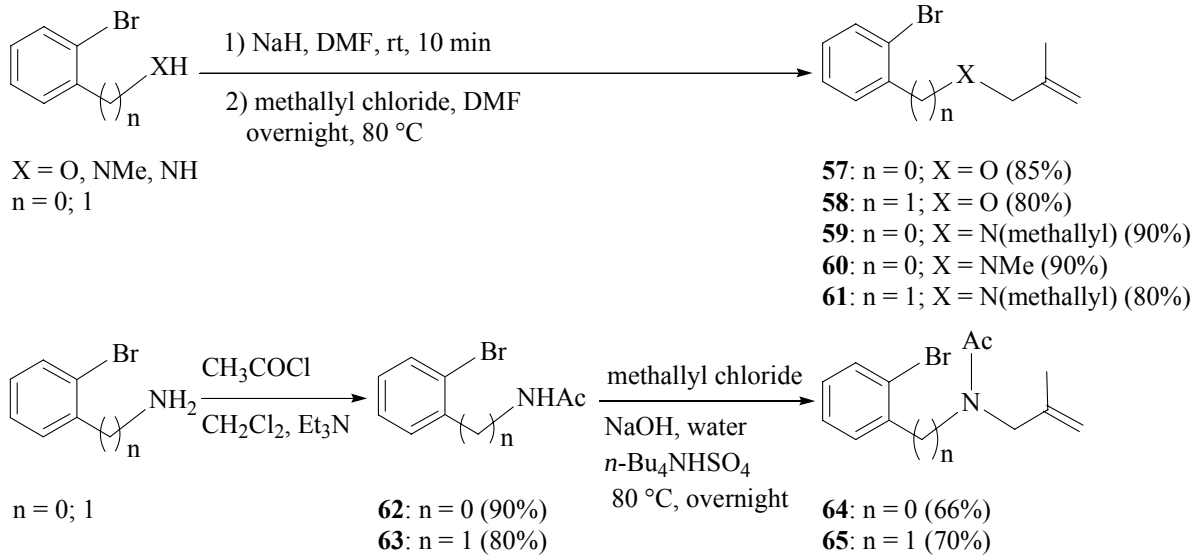
We expected the tricyclic compound **55**. Instead, we obtained as a single product the dihydronaphthalene **56**. This compound resulted from the opening of the bond between the 5- and 3-membered ring. Under the reaction conditions, the opened intermediate led to the alkene **56**.

2.4. Synthesis of heterocycles

2.4.1. Synthesis of heterocycle precursors

We prepared methallylated amines, amides and ethers as follows. Amines and ethers were treated with NaH and allylated with methallyl chloride in good to excellent yields. Amides were treated with methallyl chloride under phase-transfer conditions.[98] The preparation of substrates **57-65** is provided in Scheme 104.

[98] S. Krompiec, M. Pigulla, T. Bieg, W. Szczepankiewicz, N. Kuźnik, M. Krompiec, M. Kubick, *J. Mol. Catal. A : Chemical* **2002**, *189*, 169.



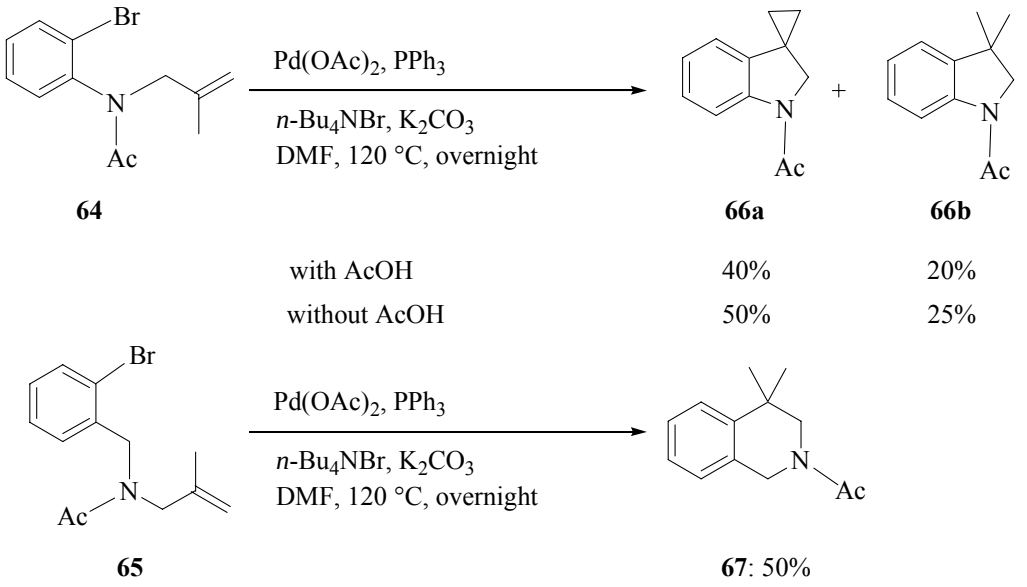
Scheme 104. Synthesis of heterocycle precursors.

2.4.2. Synthesis of N-containing heterocycles

We investigated first the reaction of amide **64**. Under the conditions described above, AcOH was one of the reactants. As depicted in Scheme 105, we observed a **66a**:**66b** ratio of 2:1. We repeated the reaction under the same conditions, but without AcOH. The same **66a**:**66b** ratio of 2:1 was observed in slightly better isolated yield. Therefore, AcOH had no role in the cyclization of **64** and **65**. The source of unexpected "hydrolyzed" products in Pd-catalyzed processes has been the subject of several studies but is presently obscure.[99]

When performing the same reaction with amide **65**, we could only observe the "hydrolyzed" product **67** and no derivative from any C-H activation could be detected. Such products are known as biologically interesting compounds in the treatment of psychiatric and cardiovascular diseases.

[99] G. K. Friestad, B. P. Branchaud, *Tetrahedron Lett.* **1995**, *36*, 7047.



Scheme 105. Influence of acetic acid in the conversion of **64** and **65**.

59 and **61** led surprisingly to the complexes **68a** and **69** in good yields as only 20 mol % of $Pd(OAc)_2$ was loaded (Scheme 106). Some "hydrolyzed" product **68b** was also observed in the case of **59**. In both cases, the remaining starting material was recovered unreacted. This led to the conclusion that the intermediate palladium species could be coordinated to the lone pair of the nitrogen. This complex was stable enough and did not undergo further reaction. An X-ray structure of **68a** showed that the palladium atom was coordinated to the nitrogen (Figure 1).[100]

[100] Dr. K. Polborn (Analytical Department of the Chemistry Department, LMU Munich) is acknowledged for measuring the X-ray structure of complex **68a**.

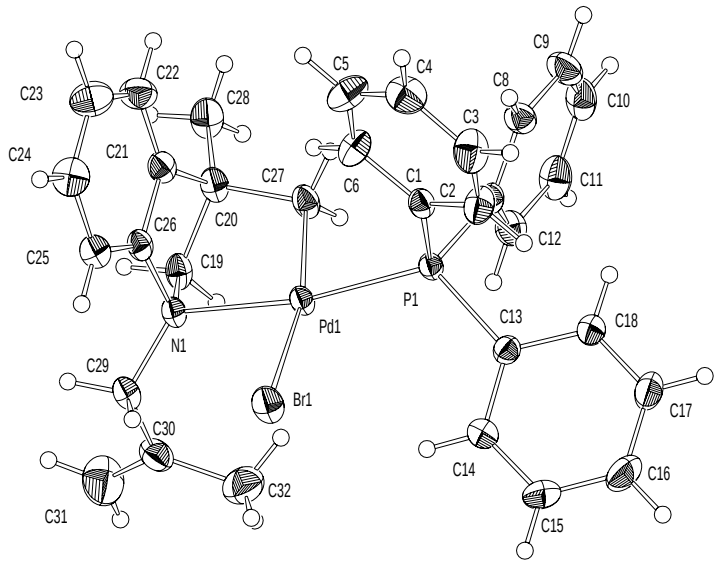
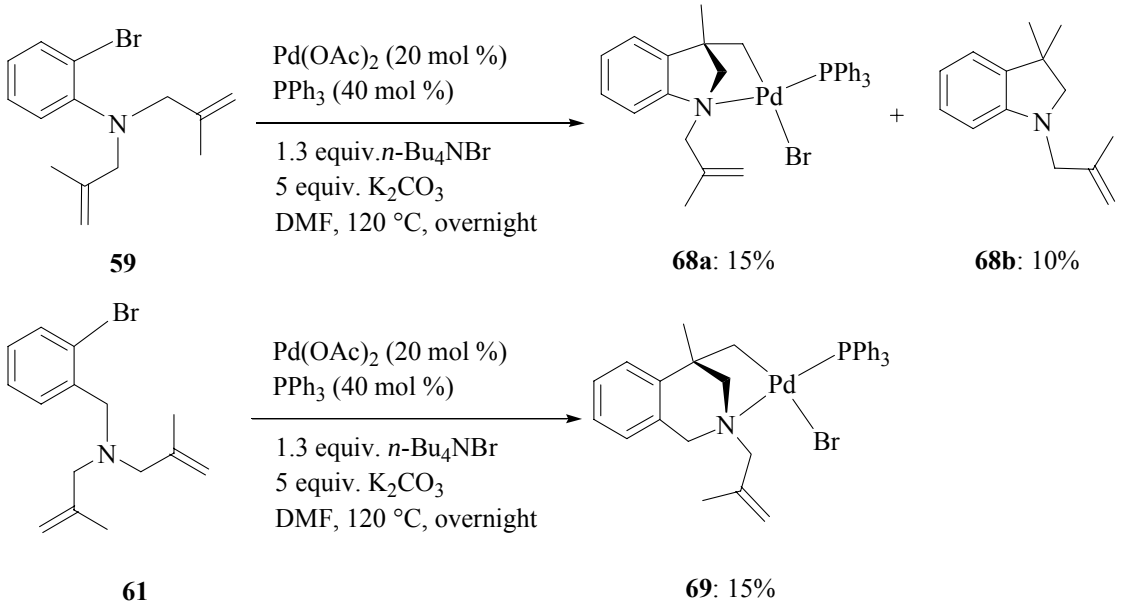


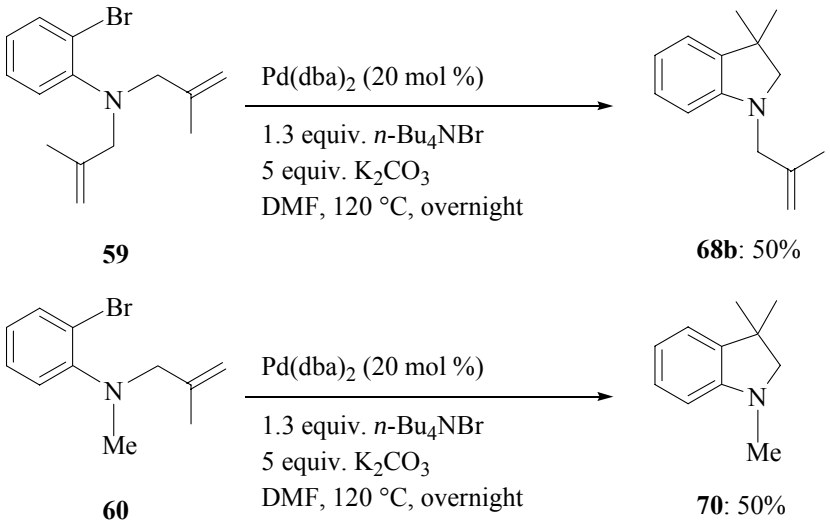
Figure 1. X-ray structure of complex **68a**.



Scheme 106. Reaction of amines **59** and **61** in the presence of PPh_3.

We postulated that the complex was stable due to the strong coordinating PPh_3. The use of more labile ligands such as dba could lead to a less stable complex, which could then undergo further reaction. We expected that the substrate could undergo a second Heck reaction with subsequent C-H activation.

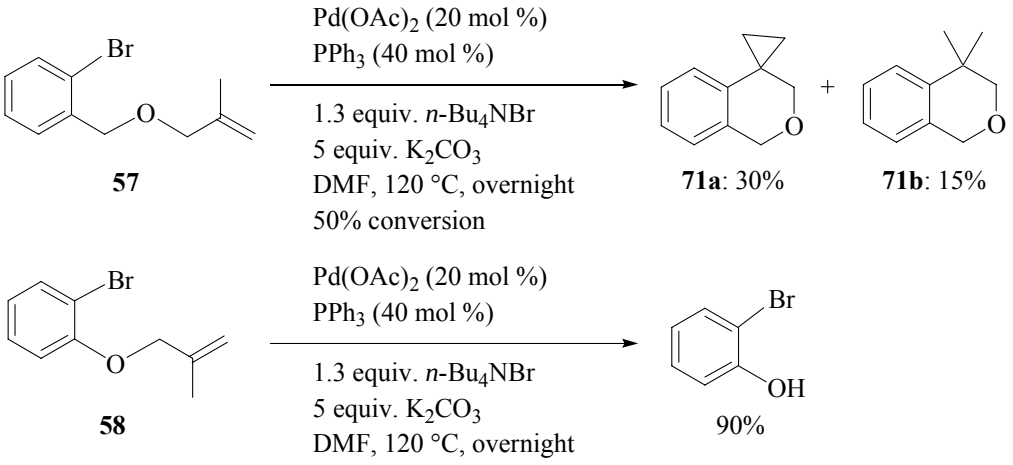
The results of the reactions of **59** and **60** using $Pd(dba)_2$ as a catalyst are depicted in Scheme 107. Only the "hydrolyzed" products **68b** and **70** were isolated.



Scheme 107. Reaction of **59** and **60** in the absence of a phosphine ligand.

2.4.3 Synthesis of O-containing heterocycles

We turned our attention to oxygen-containing heterocycles. As oxygen is a weaker donor compared to nitrogen, we used $Pd(OAc)_2$ as a catalyst. It has also the advantage of being less expensive than $Pd(dba)_2$. We have used ethers **57** and **58** as substrates. The results are depicted in Scheme 108.



Scheme 108. Heck reaction/C-H activation tandem reaction involving ethers **57** and **58**.

Ether **57** led to the both expected product **71a** and the "hydrolyzed" one **71b**. The overall yield of 45% was very good, as only 50% conversion was observed by reacting overnight. Ether **56** led surprisingly only to the deprotected phenol. This result involved the formation of a π–allyl complex. The phenolate ion is a better leaving group than the benzylalcoholate from **58** and amines from **59** and **61**, inducing the preferential formation and attack of a π–allyl complex.

3. Conclusion

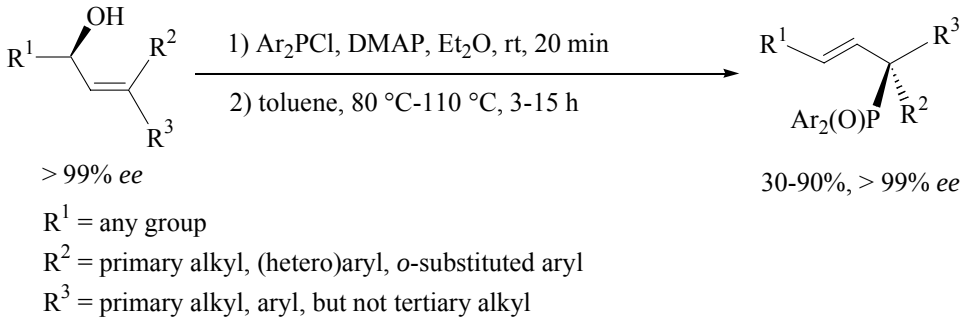
In this part, we have developed a new Pd-catalyzed tandem reaction involving an intramolecular Heck reaction followed by a regioselective C-H activation. In contrast to the work by Grigg and others[61] (Scheme 95), we did not trap the stable palladium intermediate with a nucleophile. As expected, the system underwent in most cases a regioselective C-H activation (Scheme 96). The resulting compounds were obtained as polycyclic substrates. Among them, we obtained in one step spiro, tricyclic compounds from various allylamines or ethers. The N-containing heterocycles are known as biologically active compounds. Although the yields were moderate, this method allows a straightforward preparation of such compounds (Schemes 105 and 108).

We have shown that the ligand bonded to the palladium was of crucial importance in the case of amines. By using a strongly coordinating ligand like PPh_3, we prepared new complexes **68a** and **69**. If a labile ligand like dba was used, the complexes were not stable and further reaction occurred and yielded the "hydrolyzed" products in case of amines **59** and **60** (Scheme 107).

SUMMARY AND OUTLOOK

In the first part, we have shown for two examples that the so-called "self-immolative" chirality can be used very efficiently in asymmetric synthesis.

Enantiomerically pure allylic alcohols were converted to the corresponding phosphinites, which upon heating rearranged cleanly to the enantiomerically pure allylic phosphine oxides. This reaction was optimized to ensure the best stereo- and enantiocontrol during the rearrangement. The optimized conditions are given in Scheme 109.

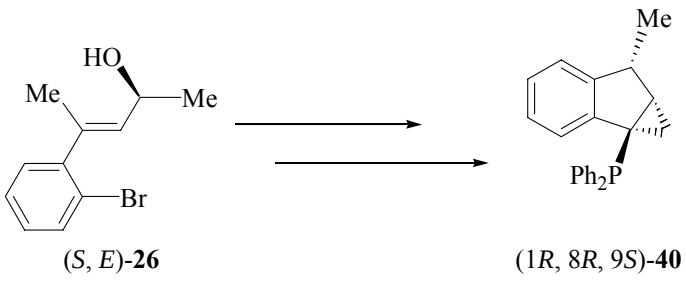


Scheme 109. Optimized conditions for the asymmetric [2,3] sigmatropic rearrangement of allylic phosphinites.

We have shown that, on the γ position of the allylic system, at least a methyl group must be attached *cis* to the alcohol. This makes the allylic strain large enough to avoid any disfavored transition states (Scheme 28).

We have also shown that the rearrangement was sensitive to steric hindrance on the γ position of the allylic system. Too many sterically demanding groups on this position led to no reaction or loss of enantioselectivity (Schemes 46 and 39 respectively).

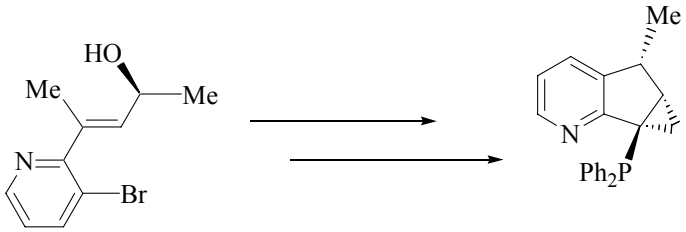
Further functionalization of the phosphine oxide proved not to be trivial. However, one monophosphine ligand was obtained and tested in the Pd-catalyzed asymmetric hydrosilylation of alkenes (Scheme 110).



(*S*, *E*)-**26** (1*R*, 8*R*, 9*S*)-**40**

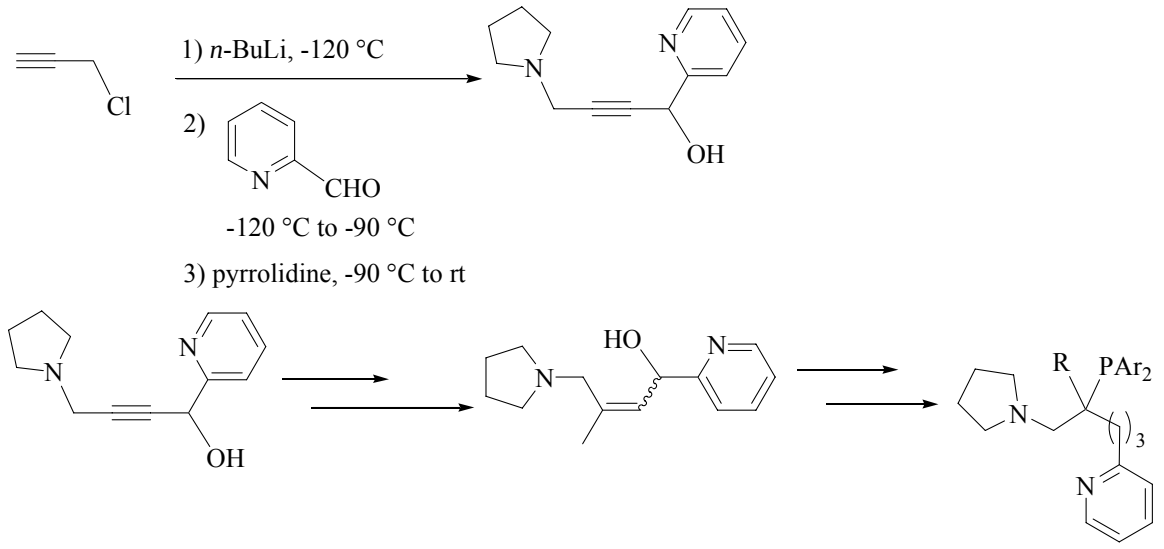
Scheme 110. Diastereo- and enantiomerically enriched monophophine **40**.

By replacing the benzene ring by a pyridine, it should be possible to obtain bidentate ligands by using the same procedure (Scheme 111). These ligands will be very rigid and should find some applications in the asymmetric catalysis.



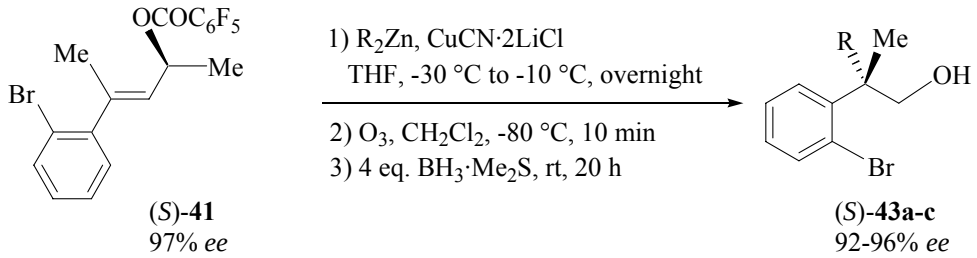
Scheme 111. A potential powerful analog of monophosphine **40**.

This asymmetric [2,3] sigmatropic rearrangement of acyclic allylic phosphinites should also find some applications in the preparation of tridentate ligands (Scheme 112). The efficiency of such ligands could be tested in Rh-catalyzed asymmetric transformations.



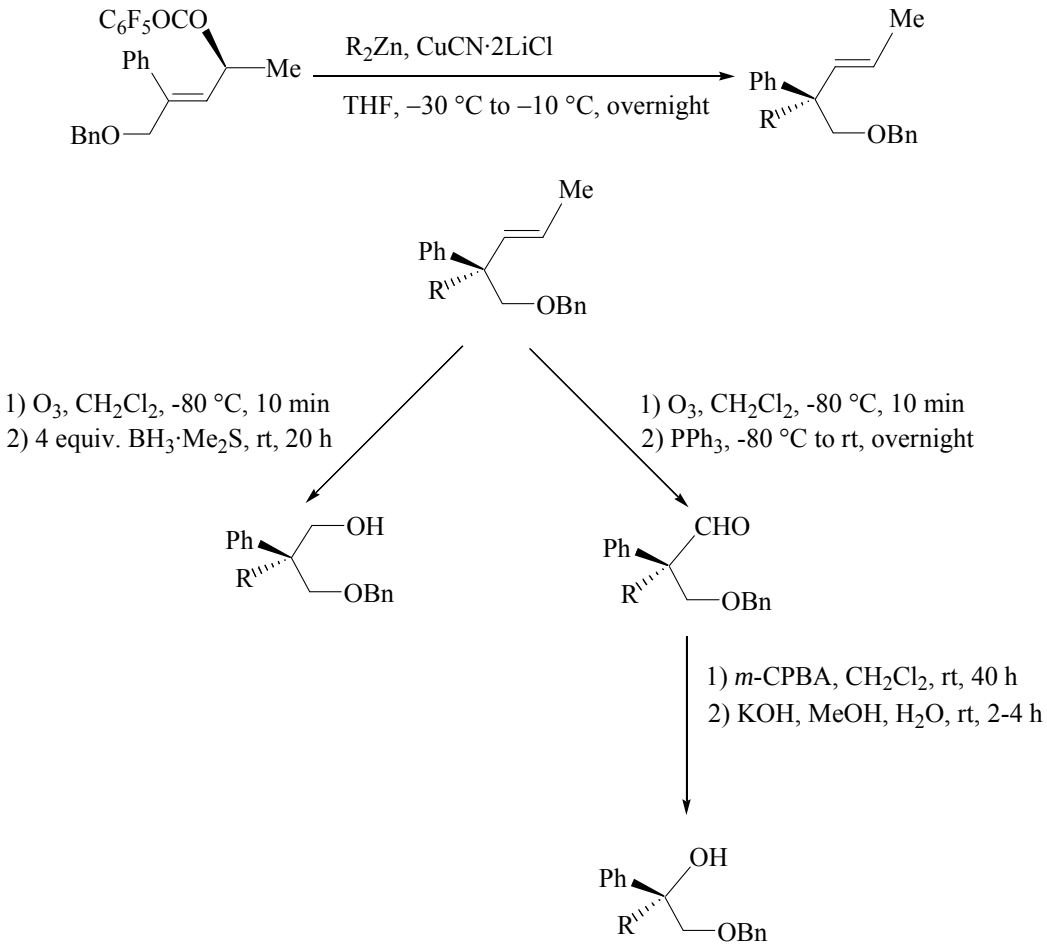
Scheme 112. Proposed route to new asymmetric tridentate ligands for asymmetric Rh-catalysis.

This concept of "self-immolative" chirality has also been used successfully in Cu-mediated asymmetric allylic substitution reactions on acyclic systems. This method allowed the preparation of highly enantiomerically-enriched quaternary centers (Scheme 71). Alkenes so obtained underwent ozonolysis. Subsequent reductive work-up led to alcohol bearing at the α position an enantiomerically-enriched quaternary center (Scheme 72). This is reported in Scheme 113.



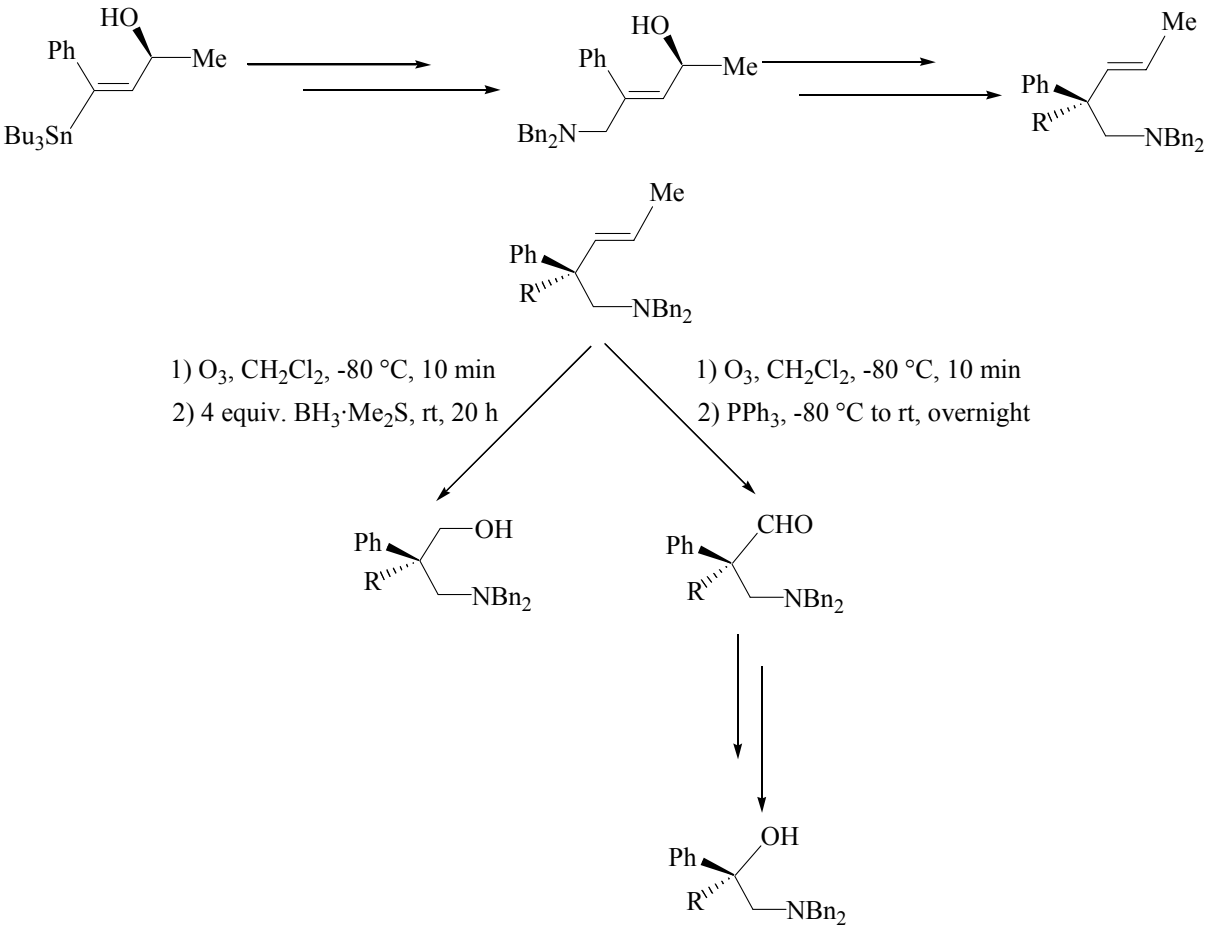
Scheme 113. Asymmetric allylic substitution reaction and ozonolysis leading to alcohols bearing an enantiomerically enriched quaternary center at the α position.

Alkenes **48a-b** proved to be highly versatile precursors. They could be at will be converted to desymmetrized 1,3-diols, aldol compounds bearing an enantiomerically-enriched quaternary center to the carbonyl group and further to enantiomerically-enriched tertiary alcohols as depicted in Scheme 114.



Scheme 114. Conversion of alkenes **48a-b** into various enantiomerically-enriched compounds.

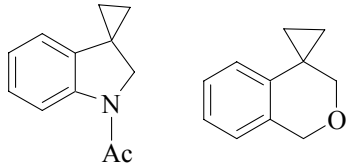
Of interest would be the synthesis of nitrogen-containing substrates. Such compounds could lead to enantiomerically-enriched 3-aminoalcohols and substituted ethanolamines. This last class of compounds is well-known as giving rise to numerous bioloically active compounds and the synthetic approach depicted in Scheme 115 would lead to a new, efficient and versatile enantioselective synthesis of such targets. As depicted in Scheme 115, it should be possible to prepare such substrates in the same way as that described for the oxygen-containing compounds.



Scheme 115. Envisaged pathways to enantiomerically-enriched 3-aminoalcohols and ethanolamine derivatives.

The preparation of the monophosphine **40** involved a Heck reaction/C-H activation tandem pathway. In the second part of this work, this tandem reaction was studied.

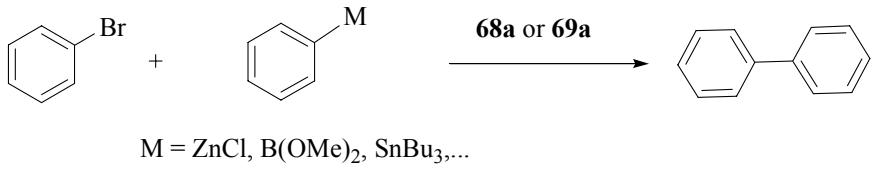
We have shown that this method could be useful to prepare tricyclic spiro compounds in one step from very simple substrates. This reaction has been used successfully in the preparation of indolines and benzo[*c*]pyranes (Scheme 116).



66a **71a**

Scheme 116. Synthesis of indoline and benzo[*c*]pyrane derivatives.

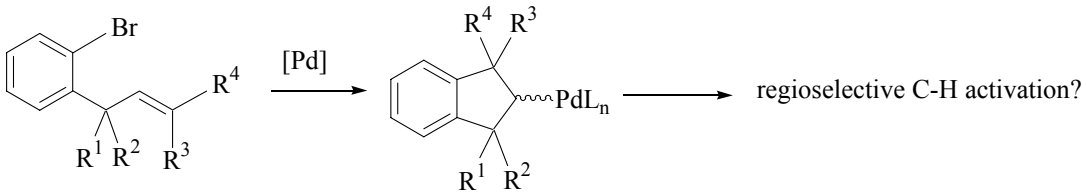
It was shown for amines that the choice of the ligand was of crucial importance. If a strongly coordinating ligand like PPh_3 was used, complexes were obtained (Scheme 106). It would be interesting to assess the efficiency of such complexes as catalysts, for example in cross-coupling reactions (Scheme 117).



M = ZnCl, $B(OMe)_2$, $SnBu_3$,...

Scheme 117. Assessing the usefullness of complexes **68a** and **69a**.

This reaction still has to be studied for the preparation of indenes and other hydrocarbon derivatives. The main problem here was the synthesis of the substrates as demonstrated in Scheme 101. The influence of all substituents being susceptible to undergo the C-H activation process should be studied as depicted in Scheme 118.



R^1-R^4 = Me, Et, *i*-Pr, *t*-Bu, Bn and combinations of these groups

Scheme 118. Testing the influence of substituents being able to undergo C-H activation.

EXPERIMENTAL PART

1. General Considerations

All reactions were carried out with magnetic stirring and under argon. Syringes were used to transfer reagents, and were purged with argon prior to use. Organolithium solutions were titrated using Paquette´s method.[101]

Solvents

Solvents were dried by distillation from drying agents as follows: dichloromethane and DMF (CaH_2), THF, ether and DME (Na/benzophenone), toluene (Na), methanol, ethanol and isopropanol (Mg), pyridine and triethylamine (KOH).

Reagents

Reagents of >98% purity were used directly. Ph_2PCl from ALDRICH was distilled prior to use. The following reagents were prepared according to described methods: Bu_3SnH,[102] TBDMSCl,[103] $Pd(dba)_2$,[104] $Pd(PPh_3)_4$,[104] $PdCl_2(PPh_3)_2$,[104] $PdCl_2$(dppp),[104] 2-(2-bromophenyl)-2-methylpropanal,[97] *N*-acetyl-2-bromoaniline,[105] (2*S*)-Pentyn-2-ol.[55]

Chromatography

Thin layer chromatography (TLC) was performed using aluminium coated with SiO_2 (Merck60, F-254). The spots were visualised by UV light and by treating the plate with different solutions:

- $KMnO_4$ (3g), K_2CO_3 (20g), KOH (0.3g) in water (300 mL)
- Phosphomolybdic acid (5g), $Ce(SO_4)_2$ (2g), conc. H_2SO_4 (12 mL) in water (230 mL).

Column chromatography was performed using 30 to 60 g of SiO_2 60 (0.04-0.063 mm) per gram of crude material.

---

[101] H. S. Lin, L. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[102] K. Hayashi, J. Iyoda, I. Shiihara, *J. Organomet. Chem.* **1967**, *10*, 81.
[103] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.
[104] E.-I. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, New York, **2002**.
[105] Y.-T. Park, M.-G. Song, M.-S. Kim, J.-H. Kwon, *Bull. Kor. Chem. Soc.* **2002**, *23*, 1208.

High Performance Liquid Chromatography (HPLC): Apparatus from Gynkotec firm with autosampler and a diode array UV-VIS detector. Chiral column: Chiracel OD-H (Diacel Chemical Industries) with *n*-heptane/*i*-propanol as a mobile phase. Racemic compounds were used for optimizing the operating conditions for the resolution of the enantiomer peaks.

Analysis

Analytical data collection was done as follows:

- Melting points were uncorrected and measured on a Dr. Tottoli (Büchi B-540) apparatus
- N.M.R. spectra were recorded on a Bruker ARX 200, AC 300, WH 400, 600 instruments. Chemical shifts were given relative to $CDCl_3$ (7.27 ppm for ^1H N.M.R., 77.0 ppm for ^{13}C N.M.R.). For ^{31}P N.M.R., 85% H_3PO_4 was used as an external standard. Tin-hydrogen coupling constants $J_{H\text{-}Sn}$ are given as the average of the ^{117}Sn and ^{119}Sn values
- Optical rotations were measured on a Perkin-Elmer 241 polarimeter
- IR spectra were recorded on a Nicolet 510 or a Perkin-elmer 281 spectrometer.

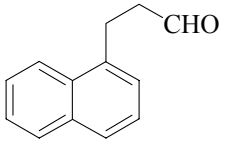
Mass spectra were recorded on a Varian CH 7A and high resolution mass spectra (HRMS) on a Varian MAT 711 spectrometers.

2. Products

2.1. Asymmetric [2,3] rearrangements

2.1.1 Preparation of the starting allylic alcohols

3-(Naphth-1-yl)-propanal **(1)**[106]



[106] G. E. Stokker, W. F. Hoffman, A. W. Alberts, E. J. Cragoe Jr., A. A. Deana, T. L. Gilfillan, J. W. Huff, F. C. Novello, J. D. Prugh, R. L. Smith, A. K. Willard, *J. Med. Chem.* **1985**, *28*, 347.

To a stirred solution of 1-bromonaphthalene (40 g, 200 mmol, 1 equiv.) in THF (400 mL) precooled to –80 °C was added *n*-BuLi (1.5 M in hexane, 140 mL, 200 mmol, 1 equiv.). The resulting yellow suspension was stirred for 1 h at –80 °C. 100 mL of a CuCN·2LiCl (1 M in THF) were slowly added. The yellow suspension was stirred for 15 min at –80 °C. TMSCl (52 mL, 480 mmol, 2.4 equiv.) and acrolein (14 mL, 200 mmol, 1 equiv.) were added simultaneously. The yellow solution was stirred overnight at –80 °C. It was quenched with 500 mL of water and extracted with 3 x 100 mL of Et_2O. The organic layer was washed with 50 mL portions of concentrated ammonia until the aqueous phase remained colourless. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 100/0 to 80/20), yielding 12 g (40%) of the aldehyde as a yellow oil which slowly crystallized.

m.p.: 30°C.

N.M.R.:

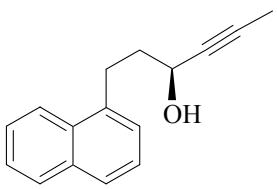
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 9.65 (s, 1H); 7.79 (m, 1H); 7.70-7.67 (m, 1H); 7.56 (m, 1H); 7.38-7.13 (m, 4H); 3.21 (t, J = 6Hz, 2H); 2.67 (m, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 201.9; 136.8; 134.4; 132.0; 129.4; 128.3; 127.6; 126.6; 126.4; 126.0; 123.7; 44.9; 25.5.

I.R. (KBr, cm^{-1}): 3050; 2825; 2725; 1725; 1600.

MS (EI, 70 eV): 184 (M^+, 100); 165 (14); 153 (21); 141 (100), 128 (30), 115 (24).

$C_{13}H_{12}O$ **HRMS**: Calcd. 184.0868 (M^+).
Found 184.0878 (M^+).

(3*S*)-1-(Naphth-1-yl)-hex-4-yn-3-ol **(2)**



Preparation of the racemic alcohol:

To a solution of bromopropene (12 g, 100 mmol, 1.5 equiv.) in THF (60 mL) precooled to –80 °C was added *n*-BuLi (1.5 M in hexanes, 100 mL, 220 mmol, 2.2 equiv.). The resulting milky solution was stirred at –80 °C for 2 h. The aldehyde **1** was then added and

the solution was warmed to rt. After 1 h, it was quenched with 200 mL of water and extracted with 3 x 30 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3), yielding 12 g (70%) of the *rac*-alcohol as a yellow oil which slowly cristallized.

Preparation of the enantiomerically pure alcohol:

To 36 g (150 mmol, 1.9 equiv.) of neat enantiomerically pure Alpine-borane were added 17 g (80 mmol, 1 equiv.) of neat ketone **3**. The brownish mixture was stirred at rt for 20 h. Acetaldehyde (8 mL) were added at 0 °C. The solution was stirred for 20 min. The volatiles were evaporated *in vacuo* at 70 °C for 1 h. The residue was cooled to 0 °C and 70 mL of Et_2O were added. 8 mL of ethanolamine were added. A precipitate was formed. It was stirred at rt for 15 min, then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 11 g (70%) of the product as a single enantiomer without recristallizing.

m.p.: 94-96 °C.

$[\alpha]_D^{20}$ (c = 0.8, Et_2O): +5.5

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.97 (m, 1H); 7.74-7.71 (m, 1H); 7.60-7.57 (m, 1H); 7.39-7.22 (m, 1H); 4.30 (m, 1H); 2.10 (br. s., 1H); 2.03-1.96 (m, 2H); 1.74 (d, *J* = 2 Hz, 3H).
^{13}C ($CDCl_3$, 75 MHz) δ(ppm): 138.1; 134.4; 132.3; 129.2; 128.1; 127.2; 126.5; 126.3; 126.0; 124.3; 81.9; 80.8; 62.7; 38.5; 29.0; 4.0.

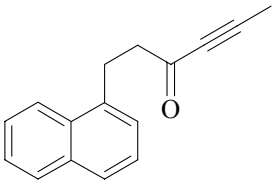
I.R. (KBr, cm^{-1}): 3300; 3220; 3045; 2225; 1595.

MS (EI, 70 eV): 224 (M^+, 40); 209 (10); 191 (20); 155 (17); 142 (100); 128 (12); 115 (14).

$C_{16}H_{16}O$	Calcd.:	C: 85.68%	H: 7.19%
	Found:	C: 85.77%	H: 7.16%

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 95/5, 0.6 mL/min): 32.1 min (*S*); 47.5 min (*R*).

1-(Naphth-1-yl)-hex-4-yn-3-one **(3)**



To a cooled (-80 °C) solution of oxalyl chloride (10 mL, 110 mmol, 1.1 equiv.) in CH_2Cl_2 (100 mL) was slowly added a solution of DMSO (30 mL, 220 mmol, 2.2 equiv.) in CH_2Cl_2 (100 mL), so that the temperature in the flask remained below –60 °C. 2 min after the end of the addition, the alcohol **2** (22 g, 100 mmol, 1 equiv.) in CH_2Cl_2 (100 mL) was added over 1 h. The resulting solution was stirred at –60 °C for 10 min, then 75 mL (500 mmol, 5 equiv.) of Et_3N were added. The solution was stirred for an additional 10 min at -60 °C, then warmed to rt and stirred for 30 minutes. It was quenched with 500 mL of water and extracted with 3 x 50 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (CH_2Cl_2). It yielded 16 g (70%) of the pure ketone as yellow needles.

m.p.: 52-54 °C.

N.M.R.:

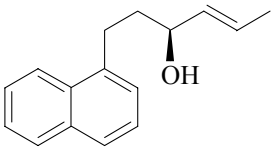
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.89 (m, 1H); 7.73 (m, 1H); 7.60 (m, 1H); 7.43-7.20 (m, 4H); 3.36-3.24 (m, 2H); 2.95-2.82 (m, 2H); 1.87 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 199.7; 136.8; 134.3; 132.3; 129.3; 127.5; 126.5; 126.4; 126.0 (2C); 123.8; 91.1; 80.6; 46.5; 27.4; 4.5.

I.R. (KBr, cm^{-1}): 3050; 2220; 1680; 1600.

MS (EI, 70 eV): 222 (M^+, 100); 207 (29); 179 (40), 155 (47); 141 (62); 115 (25).

$C_{16}H_{14}O$	Calcd.:	C: 86.45%	H: 6.35%
	Found:	C: 85.93%	H: 6.43%

(3*S*)-(*E*)-1-(Naphth-1-yl)-hex-4-en-3-ol **(4a)**



To $LiAlH_4$ (1.5 g, 40 mmol, 1 equiv.) in THF (50 mL) were added 9 g (40 mmol, 1 equiv.) of the alcohol **2** in THF (50 mL). When H_2 evolution has ceased, it was refluxed for 1 h. It was poured onto crushed ice and extracted with 3 x 50 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3), yielding 6.7 g (75%) of the alcohol as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.8, Et_2O): +5

N.M.R.:

^1H ($CDCl_3$, 300 MHz) δ(ppm): 7.94-7.91 (m, 1H); 7.71-7.69 (m, 1H); 7.55 (m, 1H); 7.36-7.20 (m, 4H); 5.52-5.42 (m, 2H); 3.99 (m, 1H); 3.06-2.95 (m, 2H); 1.86-1.78 (m, 3H); 1.57-1.55 (m, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.7; 134.6; 134.4; 132.4; 129.2; 127.5; 127.1; 126.4; 126.2; 126.0; 125.9; 124.4; 73.1; 38.6; 29.3; 18.2.

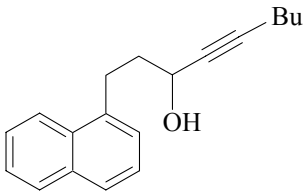
I.R. (film, cm^{-1}): 3350; 3045; 2940; 1600; 1510; 1400.

MS (EI, 70 eV): 226 (M^+, 71); 208 (13); 155 (21); 142 (100); 128 (13); 115 (16).

$C_{16}H_{18}O$	Calcd.:	C: 84.91%	H: 8.02%
	Found:	C: 84.40%	H: 8.10%

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 95/5, 0.6 mL/min): 25.9 min (*S*); 40.1 min (*R*).

1-(Naphth-1-yl)-non-4-yn-3-ol **(7)**



To a stirred, precooled (-20 °C) solution of 1.6 g (20 mmol, 1 equiv.) of hex-1-yne in THF (15 mL) was added *n*-BuLi (1.5 M in hexanes, 18 mL, 20 mmol, 1 equiv.). The yellow solution is stirred at –20 °C for 1 h, then the aldehyde **1** (3.6 g, 20 mmol, 1 equiv.) was added. The resulting orange solution was warmed up to rt and sirred for 1 h. It was quenched with 100 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3), yielding 2.6 g (60%) of the pure alcohol as a colourless oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.03-8.00 (m, 1H); 7.79-7.76 (m, 1H); 7.65-7.62 (m, 1H); 7.44-7.29 (m, 4H); 4.38 (t, *J* = 1.6 Hz, 1H); 3.21-3.15 (m, 2H); 2.21-2.15 (m, 2H); 2.06-2.02 (m, 2H); 1.7 (br. s., 1H); 1.46-1.35 (m, 4H); 0.85 (t, *J* = 7.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.1; 134.3; 132.3; 129.2; 127.2; 126.5; 125.9 (2C); 124.2; 86.5; 81.4; 62.8; 39.4; 31.2; 29.0; 18.8; 14.0.

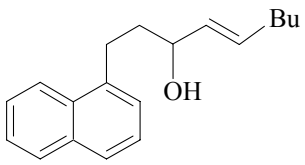
I.R. (film, cm^{-1}): 3370; 3050; 2215; 1670; 1600; 1465.

MS (EI, 70eV): 266 (M^+, 23); 209 (15); 191 (13); 153 (19); 142 (100).

$C_{19}H_{22}O$ **HRMS**: Calcd. 266.1671 (M^+).

Found 266.1660 (M^+).

(*E*)-1-(Naphth-1-yl)-non-4-en-3-ol **(4b)**



To a suspension of 75 mg (2 mmol, 4 equiv. of hydride) of $LiAlH_4$ in THF (3 mL) were added 530 mg (2 mmol, 1 equiv.) of alcohol **7** diluted in THF (2 mL). After the evolution of H_2 has ceased, it was refluxed for 2 h. It was poured onto crushed ice and extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 350 mg (70%) of the alcohol as a yellow oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.97-7.94 (m, 1H); 7.75-7.72 (m, 1H); 7.61-7.58 (m, 1H); 7.40-7.24 (m, 4H); 5.65-5.54 (m, 1H); 5.47-5.37 (m, 1H); 4.27-4.10 (m, 1H); 3.10-2.99 (m, 2H); 1.96-1.82 (m, 4H); 1.62 (br. s., 1H); 1.27-1.21 (m, 4H); 0.80 (t, *J* = 7.5 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 137.2; 132.9; 131.7; 131.5; 130.8; 127.7; 126.4; 125.6; 124.9; 124.7; 124.5; 122.8; 71.7; 37.2; 30.8; 30.3; 27.8; 21.2; 12.9.

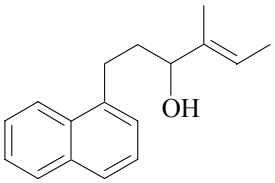
I.R. (film, cm^{-1}): 3350; 3050; 1600, 1400.

MS (EI, 70 eV): 268 (M^+, 14); 250 (10); 154 (20); 141 (100); 115 (11).

$C_{19}H_{24}O$ **HRMS**: Calcd. 268.1827 (M^+).

Found 268.1817 (M^+).

(*E*)- 4-Methyl-1-(naphth-1-yl)- hex-4-en-3-ol **(4c)**



To a precooled (-110 °C) solution of 1.2 g (9 mmol, 1 equiv.) of *trans*-2-bromopropene in a mixture of THF (28 mL), Et_2O (7 mL) and pentane (7 mL) was added *t*-BuLi (1.5 M in hexanes, 12 mL, 18 mmol, 2 equiv.). The yellow solution was stirred at –110 °C for 1 h, then warmed up to –90 °C. 1.7 g (9 mmol, 1 equiv.) of aldehyde **1** dissolved in THF (5 mL) were added. The solution was warmed up to rt and stirred for 2 h. It was quenched with 30 mL of water and extracted with 3 x 15 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 790 mg (40%) of the alcohol as a colourless oil.

N.M.R.:

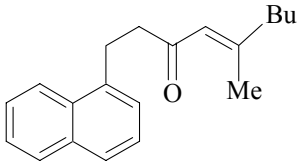
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.95-7.92 (m, 1H); 7.73-7.70 (m, 1H); 7.58-7.56 (m, 1H); 7.38-7.20 (m, 5H); 5.46-5.35 (m, 1H); 4.06-3.95 (m, 1H); 3.11-3.00 (m, 1H); 2.94-2.83 (m, 1H); 1.88-1.82 (m, 2H); 1.80 (br. s., 1H); 1.51-1.48 (m, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.8; 138.6; 134.4; 132.4; 129.3; 129.2; 127.0; 126.4; 126.3; 126.2; 124.4; 121.5; 78.0; 36.3; 29.7; 13.5; 11.6.

I.R. (film, cm^{-1}): 3400; 3050; 2245; 1600; 1510; 1395.

MS (EI, 70 eV): 240(M^+, 43); 154 (25); 141 (100); 128 (11); 115 (16); 85 (26).

$C_{17}H_{20}O$ **HRMS**: Calcd. 240.1514 (M^+).
Found 240.1502 (M^+).

(*E*)-5-Methyl-1-(naphth-1-yl)- non-4-en-3-one **(8)**



To a suspension of 260 mg (1.25 mmol, 0.5 equiv.) of CuI in Et_2O (2 mL) was added at –80 °C *n*-BuLi (1.1 M in hexane, 2.2 mL, 2.5 mmol, 1 equiv.). The black slurry was stirred for 30 min and 550 mg (2.5 mmol, 1 equiv.) of the ketone **3** dissolved in THF (1 mL) was added. The mixture was stirred for 1 h at –80 °C. 10 mL of water were added at –80 °C. It was extracted with 3 x 5 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 9/1), yielding 180 mg (30%) of the desired compound as a colourless oil.

N.M.R.:

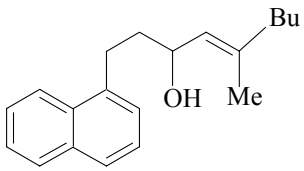
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.93 (m, 1H); 7.75 (m, 1H); 7.61 (m, 1H); 7.44-7.23 (m, 1H); 5.93 (d, *J* = 1.1 Hz, 1H); 3.29 (t, *J* = 7.9 Hz, 2H); 2.78 (m, 2H); 2.07 (d, *J* = 1 Hz, 3H); 2.00 (t, *J* = 7.5 Hz, 2H); 1.36-1.31 (m, 2H); 1.23-1.16 (m, 2H); 0.81 (t, *J* = 7.2 Hz, 3H).
^{13}C ($CDCl_3$, 75 MHz) δ(ppm): 200.4; 159.9; 137.9; 134.3; 132.1; 129.2; 127.2; 126.35; 126.3; 125.9; 125.6; 124.0; 123.3; 45.5; 41.4; 30.8; 27.6; 23.4; 22.8; 19.8; 14.3.

I.R. (film, cm^{-1}): 3050; 2955; 2930; 1685; 1620.

MS (EI, 70 eV): 280 (M^+, 48); 223 (24); 154 (33); 141 (87); 125 (100).

$C_{20}H_{24}O$ **HRMS**: Calcd. 280.1827 (M^+).
Found 280.1813 (M^+).

(*E*)-5-Methyl-1-(naphth-1-yl)- non-4-en-3-ol **(4d)**



In an opened flask were introduced 180 mg (0.6 mmol, 1 equiv.) of the ketone **8**, MeOH (2 mL) and 260 mg (0.7 mmol, 1.1 equiv.) of cerium (III) chloride heptahydrate. When all the salt has dissolved, 26 mg (0.7 mmol, 1.1 equiv.) of sodium borohydride were added. H_2 evolved and a strong exothermic effect occurred. It was stirred at rt for 15 min. It was quenched with 30 mL of water and extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 170 mg (90%) of the alcohol as a colourless oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.94 (m, 1H); 7.73-7.70 (m, 1H); 7.59-7.56 (m, 1H); 7.40-7.19 (m, 4H); 5.16 (m, 1H); 4.36 (m, 1H); 3.06-2.96 (m, 2H); 1.94-1.88 (m, 3H); 1.80-1.74 (m, 1H); 1.60 (br. s., 1H); 1.53 (d, *J* = 1.3 Hz, 3H); 1.32-1.16 (m, 4H); 0.80 (t, *J* = 7.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 139.8; 138.8; 134.4; 132.3; 129.2; 128.0; 127.0; 126.3; 126.2; 125.9; 124.3; 68.9; 39.7; 30.4; 29.4; 22.8; 17.1; 14.5.

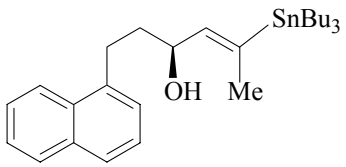
I.R. (film, cm^{-1}): 3350; 2950; 1660; 1510; 1460.

MS (EI, 70 eV): 282 (M^+, 10); 264 (12); 154 (21); 141 (100); 127 (20); 115 (17).

$C_{20}H_{26}O$ **HRMS**: Calcd. 282.1983 (M^+).

Found 282.1972 (M^+).

(3S)-(*E*)-1-(Naphth-1-yl)-5-tributylstannyl-hex-4-en-3-ol **(9)**



To a solution of 450 mg (2 mmol, 1 equiv.) of alcohol **2** and 21 mg (0.06 mmol, 0.03 equiv.) of $PdCl_2(PPh_3)_2$ in THF (2 mL) were added 0.9 mL (3 mmol, 1.5 equiv.) of $HSnBu_3$. The dark solutiom was stirred at rt for 30 min and the solvents were evaporated *in vacuo*. The crude was purified by flash chromatography (pentane/Et_2O, 85/15), yielding 800 mg (80%) of the desired product as the sole regioisomer as a colourless oil.

$[\alpha]_D^{20}$ (c = 3.8, Et_2O): -23

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.96 (m, 1H); 7.76-7.73 (m, 1H); 7.62-7.59 (m, 1H); 7.42-7.23 (m, 4H); 5.59-5.55 (m, $^3J_{H\text{-}Sn}$ = 75 Hz, 1H); 4.61-4.57 (m, 1H); 3.15-2.97 (m, 2H); 2.03-1.10 (m, 15H); 1.82 (m, 3H); 0.86-0.59 (m, 15H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 143.6; 142.6; 138.7; 134.4; 132.3; 129.2; 127.0; 126.3; 126.2; 126.0; 125.9; 124.2; 38.8; 29.6 ($J_{C\text{-}Sn}$ = 10 Hz); 29.3; 27.8 ($J_{C\text{-}Sn}$ = 17Hz); 20.2; 14.1; 9.6 ($J_{C\text{-}Sn}$ = 150 Hz).

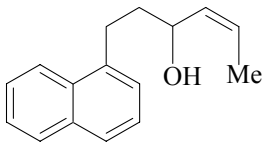
I.R. (film, cm^{-1}): 3320; 2950; 1460.

MS (EI, 70 eV): 515 (M^+, 0.12); 459 (100); 457 (75); 403 (12); 141 (72).

$C_{28}H_{44}OSn$ **HRMS**: Calcd. 459.1721 ($[M\text{-}Bu]^+$).

Found 459.1715 ($[M\text{-}Bu]^+$).

(*Z*)-1-(Naphth-1-yl)-hex-4-en-3-ol **(4e)**



To a precooled (-50 °C) solution of 680 mg (1.5 mmol, 1 equiv.) of **9** in THF (2 mL) was added *n*-BuLi (1.5 M in hexanes, 2 mL, 3 mmol, 2 equiv.). After the end of the addition, the deep red solution was warmed to rt and stirred for 1 h. It was quenched with 20 mL of water and extracted with 3 x 10 mL of CH_2Cl_2. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O/Et_3N, 6/4/0.01). It yielded 190 mg (75%) of the desired product as a colourless oil.

N.M.R.:

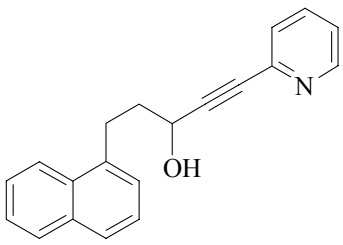
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.22-8.19 (m, 1H); 7.81-7.78 (m, 1H); 7.77-7.66 (m, 1H); 7.45-7.27 (m, 4H); 5.57-5.48 (m, 2H); 4.52 (m, 2H); 3.29-3.17 (m, 2H); 2.12-2.10 (m, 1H); 1.98-1.87 (m, 2H); 1.50 (dd, *J* = 5.4 Hz, *J* = 1.4 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 139.1; 135.0; 134.8; 132.9; 129.5; 127.4; 126.6; 126.4; 126.2; 126.1; 126.0; 124.6; 67.5; 39.3; 29.5; 13.7.

I.R. (film, cm^{-1}): 3370; 3040; 1600; 1510; 1400.

MS (EI, 70 eV): 226 (M^+, 16); 208 (10); 167 (28); 141 (100).

$C_{16}H_{18}O$ **HRMS**: Calcd. 226.1370 (M^+).
Found 226.1363 (M^+).

5-(Naphth-1-yl)-1-(2-pyridyl)-pent-1-yn-3-ol **(10)**



To a solution of 1.5 g (15 mmol, 1 equiv.) of 2-ethynylpyridine in THF (10 mL), was added at –20 °C *n*-BuLi (1.5 M in hexanes, 10 mL, 15 mmol, 1 equiv). The deep red solution

was stirred at this temperature for 1 h. 2.7 g (15 mmol, 1 equiv.) of aldehyde **1** dissolved in THF (10 mL) were added. The mixture was warmed to rt and stirred overnight. It was quenched with 50 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 1/1). It yielded 1.2 g (30%) of the alcohol as a red oil.

N.M.R.:

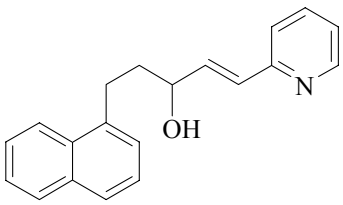
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.49-8.47 (m, 1H); 8.01 (m, 1H); 7.75 (m, 1H); 7.62-7.53 (m, 2H); 7.41-7.29 (m, 5H); 7.17-7.14 (m, 2H); 4.65 (t, *J* = 6.3 Hz, 1H); 3.26 (dt, *J* = 3 Hz; *J* = 9 Hz, 2H); 2.24-2.17 (m, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 150.2; 143.2; 137.8; 136.7; 134.3; 132.2; 129.2; 128.1; 127.6; 127.2; 126.3 (2C); 125.9; 124.4; 123.4; 91.1; 84.6; 62.4; 38.7; 28.9.

I.R. (film, cm^{-1}): 3250; 3060, 2870; 2230; 1590, 1430.

MS (EI, 70 eV): 287 (3); 269 (3); 184 (56); 165 (13); 153 (24); 141 (100); 128 (29); 115 (22); 103 (73).

$C_{20}H_{17}NO$ **HRMS**: Calcd. 287.1310 (M^+).
Found 287.1301 (M^+).

(*E*)-5-(Naphth-1-yl)-1-(2-pyridyl)-pent-1-en-3-ol **(4f)**



To a suspension of 100 mg (2.6 mmol, 4 equiv. of hydride) of $LiAlH_4$ in THF (2 mL) were added 750 mg (2.6 mmol, 1 equiv.) of alcohol **10**. After the evolution of H_2 has ceased, it was refluxed for 3 h. It was poured onto crushed ice and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_2O). It yielded 110 mg (15%) of the alcohol as a red oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.45-8.42 (m, 1H); 7.96 (m, 1H); 7.76-7.73 (m, 1H); 7.59 (m, 1H); 7.40-7.37 (m, 3H); 7.36-7.35 (m, 1H); 7.28-7.26 (m, 1H); 7.16-7.14 (m, 1H);

6.69-6.60 (m, 2H); 4.35 (m, 1H); 3.23-3.08 (m, 2H); 2.6 (br. s., 1H); 2.04-1.97 (m, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 155.7; 149.8; 138.4; 137.8; 137.0; 134.3; 132.3; 130.0; 129.2; 127.1; 126.4; 126.2; 126.0; 125.9; 124.3; 122.6; 122.1; 72.2; 38.4; 29.2.

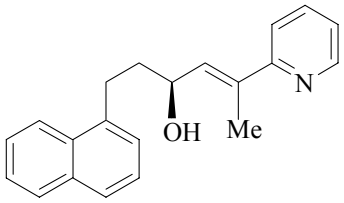
I.R. (film, cm^{-1}): 3350; 3060; 2240, 1600; 1430.

MS (EI, 70 eV): 289 (M^+, 11); 271 (20); 153 (20); 148 (70); 134 (30); 106 (100).

$C_{20}H_{19}NO$ **HRMS**: Calcd. 289.1466 (M^+).

Found 289.1459 (M^+).

(3*S*)-(*E*)-1-(Naphth-1-yl)-5-(2-pyridyl)-hex-4-en-3-ol **(4g)**



To a precooled (-50 °C) solution of 1.3 g (2 mmol, 1 equiv.) of the stannane **9** in THF (4 mL) was added *n*-BuLi (1.5 M in hexanes, 2.6 mL, 4 mmol, 2 equiv.). The first equiv. must be added very slowly to quench the free alcohol and avoid the exchange reaction and the second one somewhat faster. The resulting yellow to red solution was warmed to rt and stirred for 1 h. It was cooled to –50 °C and 4 mL of a 1 M solution of dry $ZnCl_2$ in THF were added. The colourless solution was warmed to rt and stirred for 20 min. It was then added to a solution of 640 mg (4 mmol, 2 equiv.) of 2-bromopyridine and 550 mg (0.1 mmol, 0.05 equiv.) of $Pd(PPh_3)_4$ in THF (2 mL). This mixture was refluxed for 24 h, quenched with 50 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pure Et_2O). It yielded 350 mg (50%) of the pure product as a red oil.

$[\alpha]_D^{20}$ (c = 3.0, CH_2Cl_2): +7.7

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.44-8.42 (m, 1H); 7.97-7.94 (m, 1H); 7.73-7.70 (m, 1H); 7.59-7.56 (m, 1H); 7.49-7.43 (m, 1H); 7.38-7.32 (m, 2H); 7.30-7.20 (m, 3H); 7.01-6.97 (m, 1H); 6.29 (d, *J* = 7.5 Hz, 1H); 4.59 (dt, *J* = 4.5 Hz; *J* = 9.9 Hz, 1H); 3.18-3.05 (m, 2H); 2.8 (br. s., 1H); 2.07-1.90 (m, 5H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 158.2 ; 147.7 ; 137.1 ; 135.4 ; 135.2 ; 132.8; 132.7; 130.8; 127.7; 125.6; 124.8; 124.7; 124.5; 124.4; 122.8; 120.9; 119.0; 67.2; 37.2; 27.7; 13.8

I.R. (film, cm^{-1}): 3320; 3050; 1590; 1430.

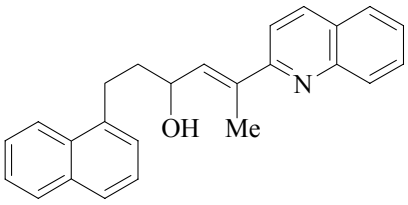
MS (EI, 70 eV): 303 (M^+, 7); 285 (11); 162 (28); 144 (45); 120 (100).

$C_{21}H_{21}NO$ **HRMS**: Calcd. 303.1637 (M^+).

Found 303.1630 (M^+).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 90/10, 0.4 mL/min): 75.6 min (*S*); 97.0 min (*R*).

(*E*)-1-(Naphth-1-yl)-2-(2-quinolyl)-hex-4-en-3-ol **(4h)**



To a precooled (-50 °C) solution of 1.5 g (3 mmol, 1 equiv.) of **9** in THF (5 mL) was added very slowly *n*-BuLi (1.5 M in hexanes, 4 mL, 6 mmol, 2 equiv.). After the end of the addition, the yellow solution was warmed to rt and stirred for 1 h. The yellow suspension was cooled to –50 °C and 6 mL (6 mmol, 2 equiv.) of a 1 M solution of dry $ZnCl_2$ in THF were added. The colourless solution was warmed to rt and stirred for 30 min. It was then transferred to a flask containing 58 mg (0.15 mmol, 0.05 equiv.) of $Pd(PPh_3)_4$ and 950 mg (3 mmol, 1 equiv.) of 2-trifluoromethanesulfonylquinoline in THF (2 mL). The solution was refluxed overnight. It was quenched with 20 mL of water and extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 1/1). It yielded 350 mg (35%) of the desired compound as a yellow solid.

m.p.: 99-101 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.99-7.95 (m, 1H); 7.89-7.86 (m, 1H); 7.73-7.69 (m, 1H); 7.59-7.54 (m, 4H); 7.42-7.29 (m, 3H); 7.26-7.21 (m, 2H); 6.33 (dd, *J* = 1.3 Hz, *J* = 8.4 Hz, 1H); 4.65 (m, 1H); 3.25-3.15 (m, 1H); 3.11-3.01 (m, 1H); 2.66 (br. s., 1H); 2.11 (d, *J* = 1.2 Hz, 3H); 2.10-1.90 (m, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 158.3; 146.5; 137.0; 136.3; 135.1; 134.2; 132.9; 130.8; 128.4; 127.7; 126.5; 126.3; 126.1; 125.5; 125.1; 124.8; 124.5; 124.4; 122.8; 117.4; 67.7; 37.1; 27.8; 13.8.

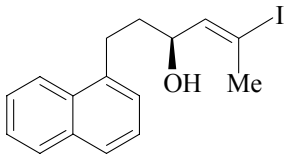
I.R. (KBr, cm^{-1}): 3350; 3060; 2250; 1600; 1500.

MS (EI, 70 eV): 353 (M^+, 3); 335 (16); 194 (100); 184 (34); 170 (20); 141 (19).

$C_{25}H_{23}NO$ **HRMS**: Calcd. 353.1739 (M^+).

Found 353.1759 (M^+).

(3*S*)-(*E*)-2-Iodo-1-(naphth-1-yl)-hex-4-en-3-ol **(11)**



This procedure was carried out in the dark and, all the glassware was protected from light by an aluminium foil. All the solvents were evaporated at room temperature to avoid isomerization and decomposition of the final alkenyl iodide.

To a solution of 7 g (14 mmol, 1 equiv.) of **9** in CH_2Cl_2 (20 mL) were added in one portion at 0 °C 3.7 g (15 mmol, 1.1 equiv.) of iodine. After the addition, the solution was warmed to rt and stirred for 20 min. It was quenched by 50 mL of a 1 M aqueous solution of KF. It was stirred for 30 min, filtered off over Celite and extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (CH_2Cl_2). It yielded 4.2 g (90%) of the pure vinyl iodide as a slightly yellow oil.

$[\alpha]_D^{20}$ (c = 2.8, CH_2Cl_2): +2.5

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.92-7.89 (m, 1H); 7.74-7.71 (m, 1H); 7.60-7.58 (m, 1H); 7.42-7.18 (m, 4H); 6.16-6.13 (m, 1H); 4.25 (q, *J* = 7.2 Hz, 1H); 3.10-2.91 (m, 2H); 2.27-2.24 (m, 3H); 1.95-1.70 (m, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 144.1; 138.0; 134.4; 132.2; 129.3; 127.3; 126.4 (2C); 126.0 (2C); 124.1; 98.6; 69.6; 38.1; 28.91; 28.88.

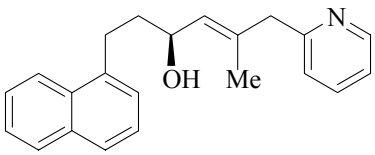
I.R. (film, cm^{-1}): 3550; 3340; 3040; 1640; 1510; 1400.

MS (EI, 70eV): 352 (M^+, 48); 225 (10); 207 (25); 155 (23); 141 (100).

$C_{16}H_{17}IO$ **HRMS**: Calcd. 352.0292 (M^+).

Found 352.0308 (M^+).

(3*S*)-(*E*)-2-Methyl-6-(naphth-1-yl)-1-(2-pyridyl)-hex-2-en-4-ol **(4i)**



To 10 mL of a 1 M solution of dry $ZnCl_2$ in THF were added at 0 °C 10 mL of a 1 M solution of 2-picolyllithium in THF. The resulting solution was stirred at rt for 20 minutes, then transferred to a flask containing 550 mg (0.1 mmol, 0.05 equiv.) of $Pd(PPh_3)_4$ and 710 mg (2 mmol, 1 equiv.) of **11** in THF (2 mL). The mixture was protected from light by an aluminium foil and stirred at rt overnight. It was quenched with 200 mL of water and extracted with 3 x 50 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_2O). It yielded 700 mg (25%) of the desired compound as a red oil.

$[\alpha]_D^{20}$ (c = 2.7, MeOH): -23.8

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.37 (br. s., 1H); 7.96-7.93 (m, 1H); 7.74-7.69 (m, 1H); 7.60-7.56 (m, 1H); 7.47-7.41 (m, 1H); 7.39-7.20 (m, 4H); 7.05-6.95 (m, 2H); 5.34 (dd, *J* = 1.2 Hz, *J* = 8.7 Hz, 1H); 4.42 (m, 1H); 3.41 (s, 2H); 3.07-3.01 (m, 3H); 2.00-1.92 (m, 1H); 1.87-1.77 (m, 1H); 1.53 (d, *J* = 1.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 158.7; 148.1; 137.3; 135.5; 135.1; 1332.8; 130.8; 130.0; 127.7; 125.5; 124.8; 124.7; 124.5; 124.4; 122.8; 122.2; 120.3; 67.1; 47.4; 37.5; 27.9; 16.2.

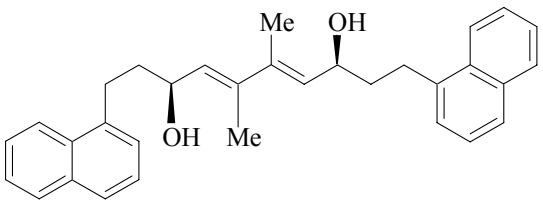
I.R. (film, cm^{-1}): 3340; 3060; 1590; 1430.

MS (EI, 70 eV): 317 (M^+, 10); 163 (11); 158 (21); 141 (17); 132 (100).

$C_{22}H_{23}NO$ **HRMS**: Calcd. 317.1713 (M^+).
Found 317.1719 (M^+).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 85/15, 0.8 mL/min): 37.5 min (*S*); 46.1 min (*R*).

(3*S*, 8*S*)-(*E*, *E*)-1,10-Bis (naphth-1-yl)-5,6-dimethyl-3-hydroxy-dec-4,6-dien-8-ol **(17)**



To a solution of 870 mg (1.6 mmol, 1 equiv.) of **9** in DMF (5 mL) were added 400 mg (4 mmol, 2.5 equiv.) of cuprous chloride. After a few seconds, the green solution turned brown. It was stirred overnight, then quenched with 30 mL of water and extracted with 3 x 15 mL of Et_2O. The combined organic layers were washed with 3 x 30 mL of water, dried over $MgSO_4$ and concentrated *in vacuo*. It was purified by flash chromatography (Et_2O) and yielded 200 mg (70%) of the pure diol as a colourless oil.

$[\alpha]_D^{20}$ (c = 3.6, CH_2Cl_2): -43

N.M.R.:

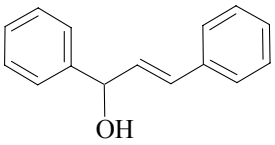
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.92-7.90 (m, 2H); 7.70-7.65 (m, 2H); 7.54 (m, 2H); 7.36-7.15 (m, 8H); 5.49 (dd, *J* = 1 Hz; *J* = 7.8 Hz, 2H); 4.43 (q, *J* = 7.8 Hz, 2H); 3.11-2.90 (m, 4H); 2.00-1.75 (m, 6H); 1.63 (d, *J* = 1 Hz, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.5; 138.3; 134.4; 132.3; 130.6; 129.2; 127.1; 126.35; 126.30; 126.0; 125.95; 124.2; 69.2; 39.0; 29.3; 15.1.

I.R. (film, cm^{-1}): 3370; 3040; 1600; 1510; 1400.

MS (EI, 70 eV): 450 (M^+, 0.06); 432 (1, M-H_2O); 414 (2, M-2H_2O); 312 (17); 269 (62); 184 (45); 141 (100).

$C_{32}H_{34}O_2$ **HRMS**: Calcd. 450.2558 (M^+).
Found 450.2587 (M^+).

(*E*)-1,3-Diphenyl-prop-2-en-1-ol **(22)**[107]



[107] H. Nomura, *Bull. Soc. Chim. Fr.* **1925**, *37*, 1245.

To a solution of 2 g (10 mmol, 1 equiv.) of (*E*)-benzylideneacetophenone and 3.8 g (10 mmol, 1 equiv.) of cerium (III) chloride heptahydrate in MeOH (15 mL) were added in one portion 400 mg (11 mmol, 1.1 equiv.) of sodium borohydride. It was stirred for 10 min. The solution was quenched with 100 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 6/4). It yielded 1.3 g (65%) of the alcohol as a colourless oil.

N.M.R.:

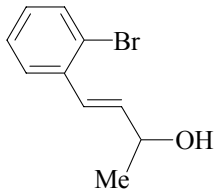
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.35-7.11 (m, 10H); 6.59 (dd, *J* = 1 Hz, *J* = 15.9 Hz, 1H); 6.29 (dd, *J* = 6.5 Hz, *J* = 15.8 Hz, 1H); 5.28 (d, *J* = 6.5 Hz, 1H); 2.07 (br. s., 1H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 143.2; 137.0; 1332.0; 131.0; 129.05-129.0 (m); 128.2; 127.0; 126.8; 75.5.

I.R. (film, cm^{-1}): 3350; 3060; 1490.

MS (EI, 70eV): 210 (M^+, 33); 192 (10); 105 (100).

$C_{15}H_{14}O$ **HRMS**: Calcd. 210.1045 (M^+).
Found 210.1028 (M^+).

(*E*)-1-(2-Bromophenyl)-but-1-en-3-ol **(24)**



To a solution of 440 mg (2 mmol, 1 equiv.) of *o*-bromobenzylidene acetone and 800 mg (2 mmol, 1 equiv.) of cerium (III) chloride heptahydrate in MeOH (5 mL) were added in one portion 80 mg (2 mmol, 1 equiv.) of sodium borohydride. H_2 and some heat evolved. It was stirred at rt for 30 min. It was quenched with 10 mL of 1 M HCl and extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane /Et_2O, 7/3). It yielded 370 mg (85%) of the alcohol as a colourless oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.56-7.51 (m, 2H); 7.31-7.24 (m, 1H); 7.14-7.08 (m, 1H); 6.93 (dd, *J* = 0.6 Hz, *J* = 15.6 Hz, 1H); 6.23 (dd, *J* = 6.3 Hz, *J* = 15.6 Hz); 4.55 (m, 1H); 1.86 (br. s., 1H); 1.41 (d, *J* = 6.3 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 137.0; 133.3; 129.2; 128.6; 127.9; 127.4; 124.1; 69.2; 23.7.

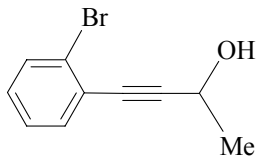
I.R. (film, cm^{-1}): 3350, 2970; 1470.

MS (EI, 70 eV): 211 ($[M\text{-}H_2O+H]^+$, 4); 185 (7), 183 (7); 147 (100).

$C_{10}H_{11}BrO$ **HRMS**: Calcd. 224.9875 ($[M\text{-}H]^+$, ^{79}Br).

Found 224.9895 ($[M\text{-}H]^+$, ^{79}Br).

1-(2-Bromophenyl)-but-1-yn-3-ol **(27)**[108]



To a solution of 2.8 g (10 mmol, 1 equiv.) of 2-bromoiodobenzene, 770 mg (11 mmol, 1.1 equiv.) of but-3-yn-2-ol and 350 mg (0.5 mmol, 0.05 equiv.) of $PdCl_2(PPh_3)_2$ in pyrrolidine (10 mL) were added 190 mg (1 mmol, 0.1 equiv.) of copper iodide. The solution was stirred at rt for 3 h. It was quenched with 70 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O,7/3). It yielded 2 g (90%) of the desired product as a yellow oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.59-7.56 (m, 1H); 7.49-7.44 (m, 1H); 7.28-7.13 (m, 2H); 4.82 (m, 1H); 2.56 (br. s., 1H); 1.59 (d, *J* = 6.6 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 133.8; 132.8; 129.9; 127.4; 125.9; 125.1; 96.1; 83.0; 59.2; 24.6.

I.R. (film, cm^{-1}): 3340; 2980; 1470.

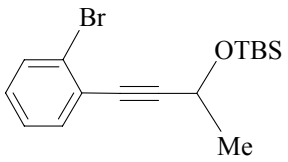
MS (EI, 70 eV): 226 (M^+, ^{81}Br, 8), 224 (8); 211 (24); 209 (29); 145 (100); 102 (66).

$C_{10}H_9BrO$ **HRMS**: Calcd. 223.9837 (M^+, ^{79}Br).

Found 223.9821 (M^+, ^{79}Br).

[108] T. Schubert, W. Hummel, M.-R. Kula, M. Müller, *Eur. J. Org. Chem.* **2001**, 4181.

3-(*tert*-Butyldimethylsilyloxy)-1-(2-bromophenyl)-but-1-yne **(28)**



To a solution of 675 mg (3 mmol, 1 equiv.) of **27** and 680 mg (10 mmol, 3.3 equiv.) of imidazole in DMF (3 mL) were added 540 mg (3.6 mmol, 1.2 equiv.) of *tert*-butyldimethylchlorosilane. The solution was stirred at rt overnight. It was quenched with 50 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 9/1). It yielded 1.2 g (95%) of the silylether as a colourless oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.40-7.37 (m, 1H); 7.28-7.24 (m, 1H); 7.08-7.03 (m, 1H); 6.99-6.93 (m, 1H); 4.62 (q, *J* = 6.5 Hz, 1H); 1.36 (d, *J* = 6.6 Hz, 3H); 0.76 (s, 9H); 0.01 (s, 3H); 0.00 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 133.8; 132.7; 129.6; 127.3; 125.6; 96.9; 82.2; 59.9; 25.7; 18.7; -4.1; -4.5.

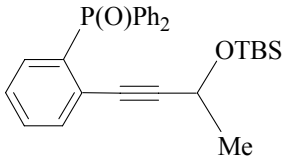
I.R. (film, cm^{-1}): 2955; 14709; 1250.

MS (EI, 70 eV): 339 ($[M-H]^+$, ^{81}Br, 1); 337 (M-H, ^{79}Br, 0.2); 283 (80); 281 (83); 239 (100); 237 (98); 209 (38); 207 (40).

$C_{16}H_{23}BrOSi$ **HRMS**: Calcd. 337.0623 ($[M-H]^+$, ^{79}Br).

Found 337.0609 ($[M-H]^+$, ^{79}Br).

3-(*tert*-Butyldimethylsilyloxy)-1-[2-(diphenylphosphinoyl)phenyl]-but-1-yne **(29)**



To a precooled (-50 °C) solution of 339 mg (1 mmol, 1 equiv.) of **28** in THF (2 mL) was added *n*-BuLi (1.5 M in hexanes, 0.63 mL, 1 mmol, 1 equiv.). The red soution was stirred for 1 h, then cooled to –80 °C. 240 mg (1.1 mmol, 1.1 equiv.) of neat Ph_2PCl were added dropwise. It was warmed to rt and stirred for 1 h. It was quenched with 10 mL of hydrogen

peroxyde and extracted with 3 x 5 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 420 mg (95%) of the desired product as a viscous, slightly yellow oil.

N.M.R.:

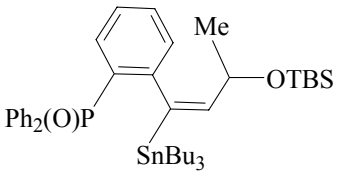
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.74-7.66 (m, 6H); 7.50-7.41 (m, 8H); 4.24 (q, *J* = 6.6 Hz, 1H); 1.00 (d, *J* = 6.6 Hz, 3H); 0.82 (s, 9H); 0.00 (s, 3H); -0.01 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 134.4; 134.3; 134.2; 133.5; 133.4; 133.1; 132.5; 132.45; 132.4; 132.3; 132.1-132.0 (m); 128.8; 128.7; 128.3; 128.1; 126.7 (d, *J* = 7 Hz); 100.1; 82.3 (d, *J* = 6 Hz); 59.6; 26.2; 24.7; 18.5; -4.2; -4.6. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 29.5.

I.R. (film, cm^{-1}): 3390; 3060; 2220; 1590; 1440; 1250.

MS (EI, 70 eV): 460 (M^+, 3); 403 (100); 359 (10).

$C_{28}H_{33}O_2PSi$ **HRMS**: Calcd. 460.1985 (M^+).
Found 460.1973 (M^+).

(*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-[2-(diphenylphosphinoyl)phenyl]-1-tributylstannyl-but-1-ene **(30)**



To a solution of 2.2 g (5 mmol, 1 equiv.) of **29** and 35 mg (0.05 mmol, 0.01 equiv.) of $PdCl_2(PPh_3)_2$ in THF (5 mL) were added dropwise 2 mL (6 mmol, 1.2 equiv.) of $HSnBu_3$. The dark solution was stirred at rt for 30 min. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 3.6 g (95%) of the desired product as a grey wax.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.70-7.48 (m, 12H); 7.24-7.15 (m, 1H); 7.08-7.01 (m, 1H); 5.57 (d, *J* = 8.7 Hz, $^3J_{H\text{-}Sn}$ = 40 Hz, 1H); 3.77-3.68 (m, 1H); 1.64-1.46 (m, 6H); 1.43-1.38 (m, 6H); 1.10-0.95 (m, 27H); 0.25 (s, 3H); 0.20 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 151.6 (d, *J* = 8 Hz); 147.3 (d, *J* = 4 Hz); 143.2; 135.2; 133.8; 133.6; 133.4; 132.5-131.9 (m); 129.4

(d, J = 10 Hz); 128.7 (d, J = 12 Hz); 128.3; 126.9; 124.4 (d, J = 13 Hz); 31.1; 29.5; 28.0; 17.9; 26.2; 14.1; 14.0; 12.8; 10.3; -3.2; -4.0. **^{31}P** ($CDCl_3$, 82 MHz): 29.5.

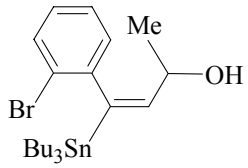
I.R. (KBr, cm^{-1}): 2960; 2850; 1460; 1200.

MS (EI, 70 eV): 736 ($[M\text{-}CH_3]^+$, 0.4); 695 (100); 405 (54); 303 (31).

$C_{40}H_{61}O_2PSiSn$ **HRMS**: Calcd. 751.3122 ($[M\text{-}H]^+$).

Found 751.3109 ($[M\text{-}H]^+$).

(*E*)-1-(2-Bromophenyl)-1-tributylstannyl-but-1-en-3-ol **(31)**



To a solution of 7.3 g (35 mmol, 1 equiv.) of **27** and 245 mg (0.35 mmol, 0.01 equiv.) of $PdCl_2(PPh_3)_2$ in THF (30 mL) were added dropwise 15 mL (50 mmol, 1.5 equiv.) of $HSnBu_3$. The dark solution was stirred at rt for 10 min. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (pentane/Et_2O, 8/2). It yielded 15 g (90%) of the desired compound as a yellow oil.

N.M.R.: This compound was observed as a mixture of 2 diastereoisomers. Atropoisomerism is confirmed by temperature-dependent NMR experiments: coalescence is observed at 350K.

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.57-7.52 (m, 1H); 7.29-7.21 (m, 1H); 7.04-6.99 (m, 1.3H); 6.89-6.86 (m, 0.7H); 5.85 (d, J = 8.4 Hz, $^3J_{H\text{-}Sn}$ = 60 Hz, 0.7H); 5.82 (d, J = 8.4 Hz, $^3J_{H\text{-}Sn}$ = 60 Hz, 0.3H); 4.21-4.11 (m, 1H); 1.80 (br. s., 1H); 1.56-1.20 (m, 15H); 0.95.0.66 (m, 15H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 147.5; 146.9; 145.7; 145.4; 145.3; 145.2; 132.8; 132.7; 128.5; 127.7; 127.1; 121.8; 121.0; 66.3; 66.1; 29.2; 27.7; 23.1; 22.9; 14.0; 11.0; 10.9.

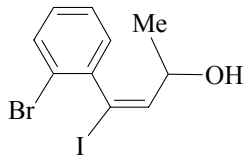
I.R. (film, cm^{-1}): 3350; 2960; 1460.

MS (EI, 70 eV): 459 ($[M\text{-}Bu]^+$, 100); 403 (15); 177 (15); 128 (19); 103 (15).

$C_{22}H_{19}O_2P$ **HRMS**: Calcd. 515.0111 ($[M\text{-}H]^+$).

Found 515.0991 ($[M\text{-}H]^+$).

(*E*)-1-(2-Bromophenyl)-1-iodo-but-1-en-3-ol **(32)**



This procedure was carried out in the dark and all the glassware was protected from light by aluminium foil. All the solvents were evaporated at room temperature to avoid isomerization and decomposition of the final alkenyl iodide.

To a precooled (0 °C) solution of 5.2 g (10 mmol, 1 equiv.) of **31** in CH_2Cl_2 (10 mL) were added in one portion 2.9 g (12 mmol, 1.2 equiv.) of iodine. The mixture was warmed to rt and stirred for 30 min. It was quenched with 50 mL of a 1 M aqueous solution of KF. It was stirred for 30 min, then filtered. It was washed with 30 mL of an aqueous, saturated solution of sodium thiosulfate. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (CH_2Cl_2). It yielded 2.6 g (80%) of the desired product as a light yellow solid.

m.p.: 72-74 °C.

N.M.R.: This compound was observed as a mixture of 2 diastereoisomers.

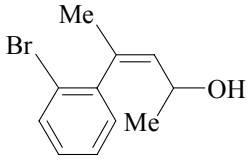
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.33-7.29 (m, 1.5H); 7.13-7.10 (m, 0.5H); 6.96-6.80 (m, 1.5H); 6.67-6.51 (m, 1.5H); 3.97-3.84 (m, 1H); 1.68 (br. s., 1H); 1.08 (d, J = 6 Hz, 1.5H); 1.00 (d, J = 9 Hz, 1.5H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 149.0; 148.6, 142.7; 133.7; 130.5; 130.2; 130.1; 130.0; 123.0; 122.0; 95.2; 94.3; 67.7; 67.5; 22.9; 22.5.

I.R. (KBr, cm^{-1}): 3300; 2970; 1640; 1460.

MS (EI, 70eV): 354 (M^+, ^{81}Br, 0.3); 352 (0.3); 227 (37); 225 (38); 181 (100); 146 (39).

$C_{10}H_{10}BrIO$ **HRMS**: Calcd. 351.9028 (M^+, ^{79}Br).
Found 351.8994 (M^+, ^{79}Br).

(*Z*)-2-(2-Bromophenyl)-pent-2-en-4-ol (*Z*)**-(26)**



To a solution (protected from light) of 2.4 g (7 mmol, 1 equiv.) of **32** and 240 mg (0.35 mmol, 0.05 equiv.) of $PdCl_2(PPh_3)_2$ in THF (5 mL) were added 20 mL (0.75 M in THF, 15 mmol, 2 equiv.) of MeZnCl (prepared from MeLi and freshly dried $ZnCl_2$). It was stirred overnight. The mixture was quenched with 100 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 1/1). It yielded 1.5 g (90%) of the alcohol as a red oil.

N.M.R.: This compound was observed as a mixture of 2 diastereoisomers (^{13}C spectrum). Coalescence could be observed at 318K in $CDCl_3$.

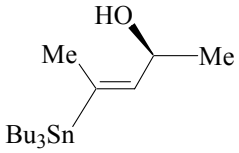
^{1}H (DMSO-*d6*, 300 MHz) δ(ppm): 7.66-7.63 (m, 1H); 7.41-7.38 (m, 1H); 7.29-7.21 (m, 2H); 5.53 (d, *J* = 9 Hz, 1H); 4.52 (m, 1H); 3.74 (br. s., 1H); 1.94 (s, 3H); 1.06 (d, *J* = 6.3 Hz, 3H). **^{13}C** (DMSO-*d6*, 75 MHz) δ(ppm): 141.9; 140.9; 134.6; 133.7; 132.7; 132.4; 131.4; 130.0; 129.7; 128.7; 128.1; 127.9; 127.5; 126.1; 121.7; 121.1; 63.9; 24.1; 23.8; 23.1.

I.R. (film, cm^{-1}): 3350; 3050; 1470; 1370.

MS (EI, 70eV): 239 (M^+, ^{79}Br, 14); 161 (100); 145 (33).

$C_{11}H_{12}BrO$ **HRMS**: Calcd. 239.0072 (M^+, ^{79}Br).
Found 239.0084 (M^+, ^{79}Br).

(4*S*)-(*E*)-2-Tributylstannyl-pent-2-en-4-ol **(35)**[109]



To a precooled (-80 °C) suspension of 5.5 g (60 mmol, 2 equiv.) of CuCN in THF (100 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 75 mL, 120 mmol, 4 equiv.). The dark yellow solution was stirred at –80 °C for 20 min. 40 mL (120 mmol, 4 equiv.) of $HSnBu_3$ were slowly added. The golden solution was stirred at –80 °C for 20 min, then MeOH (30 mL) was added. The dark red solution was warmed to –50 °C for 10 min, then cooled again to –80 °C. 2.52 g (30 mmol, 1 equiv.) of (*S*)-but-3-yn-2-ol in THF (30 mL) were added. The solution was warmed to -10°C and stirred overnight. It was quenched with 300 mL of water, filtered over celite and extracted with 3 x 50 mL of Et_2O. The organic layer was

[109] W. Adam, P. Klug, *Synthesis* **1994**, 567.

dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 100/0 to 1/1). It yielded 4.5 g (60%) of the desired stannane as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.78, CH_2Cl_2): -22

N.M.R.:

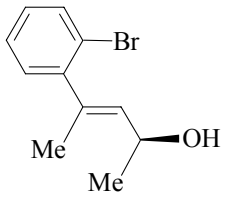
^1H ($CDCl_3$, 300 MHz) δ(ppm): 5.51 (dq, *J* = 1.8 Hz, *J* = 8.1 Hz, $^3J_{H\text{-}Sn}$ = 67 Hz, 1H); 4.70-4.63 (m, 1H); 1.83 (d, *J* = 1.8 Hz, $^3J_{H\text{-}Sn}$ = 48 Hz, 3H); 1.42-1.15 (m, 15H); 0.85-0.80 (m, 15H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 145.1; 140.6; 63.9; 29.5; 28.1; 23.7; 19.7; 14.4; 9.6.

I.R. (film, cm^{-1}): 3330; 2960; 1460.

MS (EI, 70 eV): 319 ($[M\text{-}Bu]^+$, 100); 263 (71); 207 (52); 177 (48).

$C_{17}H_{36}OSn$	Calcd.:	C: 54.42%	H: 9.67%
	Found:	C: 54.36%	H: 9.70%

(4*S*)-(*E*)-2-(2-Bromophenyl)-pent-2-en-4-ol (*E*)**-(26)**



To a precooled (-50 °C) solution of 20 g (54 mmol, 1 equiv.) of enantiomerically pure **35** in THF (100 mL) was added over 40 minutes *n*-BuLi (1.6 M in hexanes, 70 mL, 110 mmol, 2 equiv.). The yellow solution was warmed to rt and stirred for 1 h. The resulting yellow suspension was cooled to –50 °C and 110 mL (110 mmol, 2 equiv.) of a 1M solution of freshly dried $ZnCl_2$ in THF were added. The solution was warmed to rt and stirred for 20 min. The solution turned colourless. It was then added to a mixture of 6 g (5.5 mmol, 0.1 equiv.) of $Pd(PPh_3)_4$ and 30 g (110 mmol, 2 equiv.) of 2-bromoiodobenzene. The solution was refluxed for 40 h. It was quenched with 300 mL of water and extracted with 3 x 100mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 6.1 g (50%) of the alcohol as a yellow oil.

$[\alpha]_D^{20}$ (c = 0.2, CH_2Cl_2): -10

N.M.R.:

^1H ($CDCl_3$, 300 MHz) δ(ppm): 7.45-7.42 (m, 1H); 7.18-6.97 (m, 3H); 5.33 (dq, *J* = 1.5 Hz, *J* = 8.4 Hz, 1H); 4.68-4.58 (m, 1H); 2.08 (br. s., 1H); 1.91 (d, *J* = 1.5 Hz, 3H); 1.25 (d, *J* =

6.3 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 144.3; 136.8; 133.7; 131.7; 128.7; 127.3; 126.2, 121.0; 63.8; 22.2; 16.8.

I.R. (film, cm^{-1}): 3350; 2970; 1470; 1430.

MS (EI, 70 eV): 239 (M^+, ^{79}Br, 0.3); 225 (17); 161 (100).

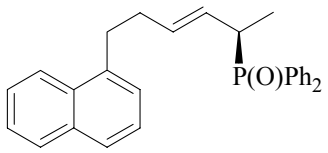
$C_{11}H_{12}BrO$ **HRMS**: Calcd. 239.0096 (M^+, ^{79}Br).

Found 239.0084 (M^+, ^{79}Br).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 95/5, 0.6 mL/min): 14.3 min(*S*); 20.9 min (*R*).

2.1.2. Preparation of the allylic phosphine oxides

(5*R*)-(*E*)-5-Diphenylphosphinoyl-1-(naphth-1-yl)- hex-3-ene **(5a)**



To a solution of 560 mg (4.6 mmol, 1.1 equiv.) of DMAP and 950 mg (4.2 mmol, 1 equiv.) of **2** in Et_2O (20 mL) were added 970 mg (4.4 mmol, 1.05 equiv.) of distilled PPh_2Cl. A white precipitate was instantaneously formed. The mixture was stirred for a further 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were evaporated *in vacuo* and toluene (30 mL) was added. The solution was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1), yielding 1.3 g (75%) of the pure phosphine oxide as a colourless, viscous oil.

$[\alpha]_D^{20}$ (c = 0.8, CH_2Cl_2): +3

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.95-7.68 (m, 7H); 7.40-7.31 (m, 9H); 7.05 (m, 1H); 5.44-5.41 (m, 2H); 3.06-3.03 (m, 1H); 2.82 (m, 2H); 2.31-2.24 (m, 2H); 1.18 (dd, *J* = 7.5 Hz; *J* = 16.5 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.0; 134.2; 134.2 (d, *J* = 15 Hz); 133.0 (d, *J* = 15 Hz); 132.6-131.8 (m); 131.7; 131.6; 129.5; 129.3; 129.1; 129.0; 128.9; 128.8; 128.6; 127.0; 126.85 (d, *J* = 4 Hz); 126.8 (d, *J* = *7* Hz); 126.2 (d, *J* = *7* Hz); 124.1; 38.3 (d, *J* = 68 Hz); 34.0; 33.0; 13.8. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 35.4.

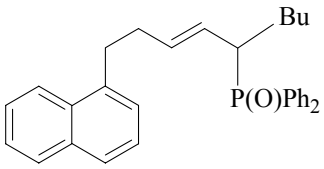
I.R. (film, cm^{-1}): 3435; 3055; 1595; 1440; 1185.

MS (EI, 70 eV): 410 (M^+, 17); 269 (100); 256 (70); 1414 (35).

$C_{28}H_{27}OP$ **HRMS**: Calcd. 410.1778 (M^+).

Found 410.1789 (M^+).

(*E*)-5-Diphenylphosphinoyl-1-(naphth-1-yl)-non-3-ene **(5b)**



To a solution of 160 mg (1.3 mmol, 1 equiv.) of DMAP and 340 mg (1.3 mmol, 1 equiv.) of **4b** in Et_2O (10 mL) were added 290 mg (1.3 mmol, 1equiv.) of PPh_2Cl. A white precipitate was instantaneously formed. The solution was stirred for 30 min. At this point, no residual chlorophoshine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were removed *in vacuo* and toluene (10 mL) was added. The solution was stirred at 80 °C for 3 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 330 mg (60%) of the pure phosphine oxide as a colourless, viscous oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.80-7.52 (m, 7H); 7.38-7.21 (m, 9h); 7.03-7.01 (m 1H); 5.32 (m, 2H); 2.85-2.75 (m, 3H); 2.28 (m, 2H); 1.55 (m, 2H); 1.26-1.07 (m, 4H); 0.71 (t, J = 6 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.0; 136.1; 134.3; 132.1; 132.0; 131.9; 131.8; 131.6; 131.5; 129.2; 129.1; 128.9; 128.7; 128.5; 127.0; 126.2; 126.1; 125.9; 125.8; 125.5; 124.1; 44.5 (d, J = 68 Hz); 34.0; 33.0; 30.3 (d, J = 15 Hz); 27.3; 22.6; 14.3. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 30.9.

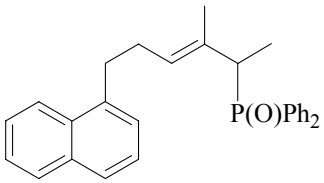
I.R. (film, cm^{-1}): 3400; 3060; 2220; 1440.

MS (EI, 70 eV): 452 (M^+, 18); 311 (100); 298 (15); 201 (83); 141 (66).

$C_{31}H_{33}OP$ **HRMS**: Calcd. 452.2269 (M^+).

Found 452.2271 (M^+).

(*E*)-5-Diphenylphosphinoyl-4-methyl-1-(naphth-1-yl)-hex-3-ene **(5c)**



To a solution of 122 mg (1 mmol, 1 equiv.) of DMAP and 240 mg (1 mmol, 1 equiv.) of **4c** in Et_2O (10 mL) were added 220 mg (1 mmol, 1 equiv.) of PPh_2Cl. A white precipitate was instantaneously formed and the solution was stirred for 30 min. At this point, no residual chlorophosphine could be detected in ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were evaporated *in vacuo* and toluene (15 mL) was added. The solution was stirred at 80 °C for 20 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 200 mg (50%) of the phosphine oxide as a courless, viscous oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.81-7.76 (m, 7H); 7.41-7.26 (m, 9H); 7.09 (m, 1H); 5.28 (m, 1H); 2.97 (m, 1H); 2.75-2.70 (m, 2H); 2.25-2.19 (m, 2H); 1.53 (d, *J* = 1 Hz, 3H); 1.24 (dd, *J* = 7.2 Hz; *J* = 16.5 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.4; 134.2; 133.0; 132.9; 132.2; 131.9 (2C); 131.6 (2C); 131.5; 131.4; 129.8; 129.7; 129.2; 129.1; 128.9; 128.6; 128.4; 127.0; 126.1; 125.9; 125.8; 124.1; 43.8 (d, *J* = 67 Hz); 32.8; 29.5; 15.7; 13.5 (d, *J* = 7 Hz). **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 34.8.

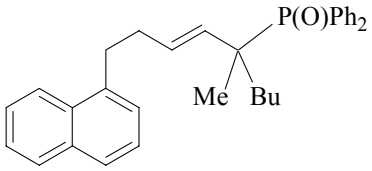
I.R. (film, cm^{-1}): 3410; 3060; 2220; 1440.

MS (EI, 70 eV): 424 (M^+, 21); 283 (97); 201 (100); 141 (54).

$C_{29}H_{29}OP$ **HRMS**: Calcd. 424.1956 (M^+).

Found 424.1942 (M^+).

(*E*)-5-Diphenylphosphinoyl-5-methyl-1-(naphth-1-yl)- non-3-ene **(5d)**



To a solution of 350 mg (1.2 mmol, 1 equiv.) of **4d** and 166 mg (1.3 mmol, 1.1 equiv.) of DMAP in Et_2O (7 mL), were added dropwise 287 mg (1.25 mmol, 1.05 equiv.) of chlorodiphenylphosphine. A white precipitate was instantaneously formed. It was stirred for 30 min at rt. At this point, no residual peak of PPh_2Cl could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were evaporated *in vacuo* and toluene (10 mL) was added. The resulting solution was heated at 80 °C for 3 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 280 mg (50%) of the phosphine oxide as a colourless, viscous oil.

N.M.R.:

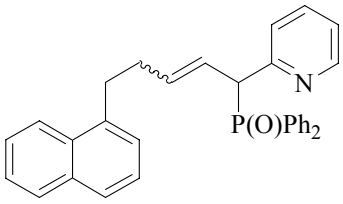
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.89-7.85 (m, 3H); 7.78-7.74 (m, 1H); 7.38-7.18 (m, 13H); 5.40-5.34 (m, 2H); 3.06-2.98 (m, 2H); 2.49-2.44 (m, 2H); 1.72-1.65 (m, 1H); 1.47-1.43 (m, 1H); 1.15 (d, J = 9 Hz, 3H), 1.13-0.99 (m, 6H); 0.70 (t, J = 6 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 136.4; 132.9; 131.5; 131.4; 131.3; 130.9; 130.7 (2C); 130.3 (2C); 129.7; 129.5; 127.8; 127.4; 127.1; 127.0; 126.9 (2C); 125.7; 124.9; 124.8; 124.4; 122.6; 42.5 (d, J = 68 Hz); 32.8 (d, J = 30 Hz); 31.5 (d, J = 3 Hz); 22.1; 16.0; 13.0. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 35.9.

I.R. (film, cm^{-1}): 3060; 2215; 1440.

MS (EI, 70 eV): 466 (M^+, 5); 325 (22); 312 (38); 202 (72); 141 (100).

$C_{32}H_{35}OP$ **HRMS**: Calcd. 466.2447 (M^+).
Found 466.2436 (M^+).

(*E*)-1-Diphenylphosphinoyl-5-(naphth-1-yl)-1-(2-pyridyl)-pent-2-ene **(5f)**



To a solution of 180 mg (1.5 mmol, 1 equiv.) of DMAP and 434 mg (1.5 mmol, 1 equiv.) of **4f** in Et_2O (10 mL) were added dropwise 320 mg (1.5 mmol, 1 equiv.) of PPh_2Cl. A white precipitate was formed. The mixture was stirred for 30 min at rt. At this point, no residual peak of PPh_2Cl could be detected by ^{31}P N.M.R. spectroscopy. The precipitate was filtered off under argon through a short pad of dry silica gel. The solvents were evaporated *in vacuo* and toluene (10 mL) was added. It was heated to 80 °C for 3 h. The solvents were

removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2/MeOH, 50/50/2). It gave 350 mg (50%) of the compound as an 85/15 mixture of (*E*) and (*Z*) isomers as a light yellow, viscous oil.

N.M.R.:

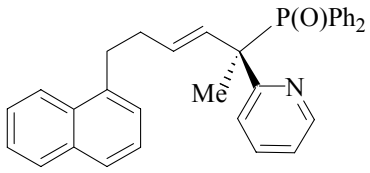
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.23 (m, 1H); 7.75-7.14 (m, 18H); 7.00-6.6.80 (m, 2H); 6.00-5.85 (m, 1H); 5.50-5.35 (m, 1H); 4.52 (t, *J* = 9.3 Hz, 1H); 2.76-2.71 (m, 2H); 2.25-2.20 (m, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 156.9; 149.4; 137.9; 137.1; 134.2; 132.1; 132.0; 131.9; 131.8; 131.7; 129.1; 128.9; 128.7; 128.5; 127.0; 126.2; 125.9; 125.8; 124.7; 124.6; 124.3; 124.2; 124.0; 122.4; 55.0 (d, *J* = 60 Hz); 33.9; 32.9. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 33.1 (*E* isomer); 32.2 (*Z* isomer).

I.R. (film, cm^{-1}): 3410; 3060; 2220; 11590; 1440.

MS (EI, 70 eV): 473 (M^+, 2); 332 (64); 319 (100); 272 (92); 201 (96); 141 (58); 130 (35).

$C_{32}H_{28}NOP$ **HRMS**: Calcd. 473.1815 (M^+).
Found 473.1841 (M^+).

(5*R*)-(*E*)-5-Diphenylphosphinoyl-1-(naphth-1-yl)-5-(2-pyridyl)-hex-3-ene **(5g)**



To a solution of 122 mg (1mmol, 1 equiv.) of DMAP and 303 mg (1mmol, 1 equiv.) of **4g** in Et_2O (15 mL) were slowly added 220 mg (1 mmol, 1 equiv.) of Ph_2PCl. A white precipitate was formed. It was stirred for 30 min. At this point, no more chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered off under argon through a short pad of dry silica gel. The solvents were evaporated *in vacuo* and toluene (5 mL) was added. It was heated to 80 °C for 3 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 470 mg (90%) of the pure phosphine oxide as a colourless, viscous oil.

$[\alpha]_D^{20}$ (c = 0.8, CH_2Cl_2): +5

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.36-8.34 8m, 1H); 7.92-7.15 (m, 19H); 7.04-6.97 (m, 1H); 6.43 (ddt, *J* = 15 Hz; *J* = 6 Hz; *J* = 1 Hz, 1H); 5.58-5.46 (m, 1H); 3.03-2.97 (m, 2H); 2.51-2.47 (m, 2H); 1.70 (d, *J* = 15 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 159.1 (d, *J* = 4 Hz); 147.1; 136.7; 135.0; 132.8; 131.9; 131.8; 131.5; 131.4; 131.0; 130.9; 130.7; 130.4; 130.0; 129.9; 129.6; 127.7; 126.9; 126.8; 126.7; 126.6; 125.6; 124.9; 124.7; 124.5; 124.4; 123.1 (d, *J* = 3 Hz); 122.8; 120.7; 50.7 (d, *J* = 60 Hz); 33.1; 31.6 (d, *J* = 2 Hz); 18.7. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 37.3.

I.R. (film, cm^{-1}): 3400; 3060; 2220; 1590; 1440.

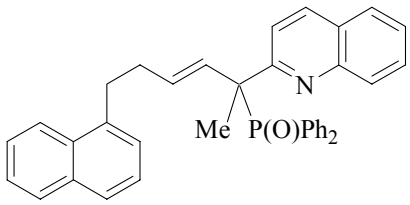
MS (EI, 70 eV): 487 (M^+, 3); 346 (49); 286 (100); 201 (62); 144 (74); 141 (51).

$C_{33}H_{30}NOP$ **HRMS**: Calcd. 487.2065 (M^+).

Found 487.2078 (M^+).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 88/12, 0.9 mL/min): 19.1 min (*S*); 24.2 min (*R*).

(*E*)-5-Diphenylphosphinoyl-1-(naphth-1-yl)-5-(2-quinolyl)-hex-3-ene **(5h)**



To a solution of 200 mg (0.6 mmol, 1 equiv.) of **4h** and 72 mg (0.6 mmol, 1 equiv.) of DMAP in Et_2O (5 mL) were added 132 mg (0.6 mmol, 1 equiv.) of Ph_2PCl. A white precipitate was formed. It was stirred for 30 min at rt. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica. The solvents were removed *in vacuo* and toluene (5 mL) was added. The mixture was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 120 mg (30%) of the pure phosphine oxide as a viscous, slightly yellow oil.

N.M.R.:

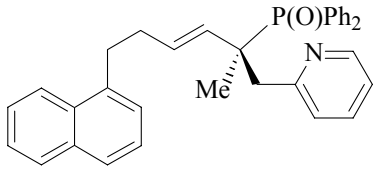
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.91-7.87 (m, 2H); 7.78-7.71 (m, 4H); 7.67-7.64 (m, 1H); 7.60-7.54 (m, 6H); 7.42-7.15 (m, 10H); 6.50 (dd, *J* = 6 Hz, *J* = 15 Hz, 1H); 5.58-5.46 (m, 1H); 3.03-2.98 (m, 2H); 2..5-2.43 (m, 2H); 1.80 (d, *J* = 15 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 159.6 (d, *J* = 3 Hz); 146.0; 136.7; 134.7; 132.8; 132.0; 131.9; 131.7; 131.6; 1313.5; 131.4; 131.3; 130.8; 130.3; 130.1; 130.0; 128.1 (d, *J* = 3 Hz); 127.7; 126.8; 126.7; 126.65; 126.6; 126.3; 125.7; 125.6; 125.3; 124.9; 124.7; 124.5; 124.4; 122.7; 120.5 (d, *J* = 3 Hz); 51.7 (d, *J* = 62 Hz); 33.1; 31.5 (d, *J* = 2 Hz); 19.0. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 37.7.

I.R. (film, cm^{-1}): 3400; 3060; 2220; 1600; 1500; 1440; 1260.

MS (EI, 70 eV): 537 (M^+, 1); 396 (24); 336 (100); 309 (20); 201 (32); 194 (58); 141 (29).

$C_{37}H_{32}NOP$ **HRMS**: Calcd. 537.2142 (M^+).
Found 537.2182 (M^+).

(2*S*)-(*E*)-2-Diphenylphosphinoyl-2-methyl-6-(naphth-1-yl)-1-(2-pyridyl)-hex-3-ene **(5i)**



To a solution of 330 mg (1.05 mmol, 1 equiv.) of **4i** and 140 mg (1.1 mmol, 1.05 equiv.) of DMAP in Et_2O (5 mL) were added 240 mg (1.1 mmol, 1.05 equiv.) of Ph_2PCl. A white precipitate was formed. It was stirred for 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica. The solvents were evaporated *in vacuo* and toluene (5 mL) was added. It was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2/MeOH, 1/1/0 to 1/1/0.5). It yielded 220 mg (48%) of the pure phosphine oxide as a viscous, slightly yellow oil.

$[\alpha]_D^{20}$ (c = 0.75, MeOH): -13.9

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.36-8.34 (m, 1H); 7.93-7.83 (m, 6H); 7.58 (m, 1H); 7.40-7.31 (m, 10H); 7.05-6.95 (m, 3H); 5.90 (dd, *J* = 5.1 Hz, *J* = 10 Hz, 1H); 5.13-5.07 (m, 1H); 3.18-3.14 (m, 2H); 2.90-2.83 (m, 2H); 2.42-2.37 (m, 2H); 1.17 (d, *J* = 15 Hz, 3H). **^{13}C**

($CDCl_3$, 75 MHz) δ(ppm): 156.3 (d, *J* = 15 Hz); 147.6; 136.5; 134.3; 132.8; 131.6-131.4 (m); 130.7; 130.6; 129.9 (d, *J* = 4 Hz); 129.2 (d, *J*= 24 Hz); 127.8; 127.3-127.0 (m); 124.7 (d, *J* = 2 Hz); 124.5; 124.4; 122.6; 120.4; 43.8 (d, *J* = 68 Hz); 41.6; 32.9; 31.6 (d, *J* = 3 Hz); 16.2. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 35.6.

I.R. (film, cm^{-1}): 3410; 3060; 2220; 1590.

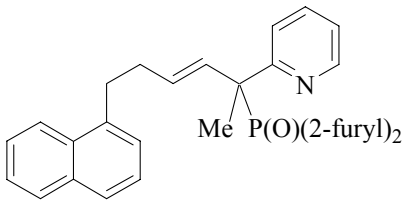
MS (EI, 70 eV): 502 ($[M+H]^+$, 4); 360 (53); 300 (100); 201 (36); 158 (62); 141 (86).

$C_{34}H_{32}NOP$ **HRMS**: Calcd. 502.2352 ($[M+H]^+$).

Found 502.2326 ($[M+H]^+$).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 85/15, 0.9 mL/min): 3.2 min (*R*); 13.5 min (*S*).

(*E*)-5-[Di-(2-furyl)-phosphinoyl]-1-(naphth-1-yl)-5-(2-pyridyl)-hex-3-ene **(12)**



To a solution of 120 mg (1mmol, 1 equiv.) of DMAP and 303 mg (1 mmol, 1 equiv.) of **4g** in Et_2O (10 mL) were added dropwise 200 mg (1 mmol, 1 equiv.) of bis(2-furyl)chlorophosphine. A white precipitate was formed. It was stirred at rt for 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were removed *in vacuo* and toluene (10 mL) was added. It was heated to 110 °C for 2 h. It was quenched with 50 mL of water and extracted with 3 x 20 mL of Et_2O. The combined organic extracts were washed with 5 x 50 mL of water. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 120 mg (30%) of the phosphine oxide as a slightly yellow solid.

m.p.: 108-110 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.36-8.34 (m, 1H); 7.92-7.88 (m, 1H); 7.77-7.73 (m, 1H); 7.62-7.32 (m, 7H); 7.31-7.25 (m, 1H); 7.20-7.18 (m, 1H); 7.03-6.95 (m, 3H); 6.36-6.30 (m, 3H); 5.59 (m, 1H); 3.02-2.97 (m, 2H); 2.50-2.44 (m, 2H); 1.75 (d, *J* = 15 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 159.6 (d, *J* = 5 Hz); 148.8; 148.2; 148.1; 148.0; 147.4 (d, *J* = 16

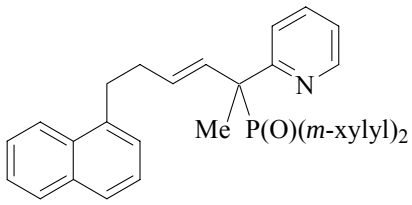
Hz); 145.6 (d, *J* = 17 Hz); 138.1; 136.5; 134.3; 133.2; 133.1; 132.2; 129.4; 129.2; 127.0; 126.3; 126.2; 125.9; 125.8; 124.2; 124.1-124.0 (m); 123.8; 123.6; 122.2; 111.1; 11.0 (d, *J* = 2 Hz); 110.9; 52.5 (d, *J* = 79 Hz); 34.5; 33.2 (d, *J* = 3 Hz); 18.8. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 19.9.

I.R. (KBr, cm^{-1}): 3430; 3050; 2230; 1590; 1460; 1200.

MS (EI, 70 eV): 467 (M^+, 1); 326 (10); 286 (100); 141 (40).

$C_{29}H_{26}NO_3P$ **HRMS**: Calcd. 467.1638 (M^+).
Found 467.1644 (M^+).

(*E*)-5-[Di-(3,5-dimethylphenyl)-phosphinoyl]-1-(naphth-1-yl)-5-(2-pyridyl)-hex-3-ene **(13)**



To a stirred solution of 120 mg (1 mmol, 1 equiv.) of DMAP and 303 mg (1 mmol, 1 equiv.) of **4g** in Et_2O (10 mL) were added 276 mg (1 mmol, 1 equiv.) of bis(3,5-dimethylphenyl)chlorophosphine. A white precipitate was formed. It was stirred for 30 min at rt. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon and the solvents were removed *in vacuo*. Toluene (10 mL) was added. It was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 170 mg (30%) of the phosphine oxide as a viscous, slightly yellow oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.40 (m, 1H); 7.91-7.88 (m, 1H); 7.78-7.73 (m, 1H); 7.62 (m, 1H); 7.57-7.47 (m, 2H); 7.42-7.35 (m, 2H); 7.32-7.22 (m, 3H); 7.19 (m, 2H); 7.10-6.94 (m, 4H); 6.45 (dd, *J* = 6 Hz, *J* = 15.5 Hz, 1H); 5.54 (ddt, *J* = 4.2 Hz, *J* = 6.6 Hz, *J* = 15.5 Hz, 1H); 3.02 (dt, *J* = 4.2 Hz, *J* = 16.8 Hz, 2H); 2.54-2.45 (m, 2H); 2.19 (d, *J* = 8 Hz, 6H); 1.70 (d, *J* = 15 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 160.8 (d, *J* = 4 Hz); 148.4; 138.3; 137.7; 137.6 (d, *J* = 2Hz); 136.2; 134.2; 133.5 (d, *J* = 2 Hz); 132.2; 132.1; 132.0; 131.8; 131.6; 131.5; 131.0; 130.9; 130.7; 130.6; 129.1; 127.0; 126.3; 126.1; 125.9; 125.8124.9 (d, *J*

= 3 Hz); 124.1; 122.1; 52.0 (d, *J* = 60 Hz); 34.7; 33.2 (m); 21.7 (d, *J* = 3 Hz); 20.1. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 37.8.

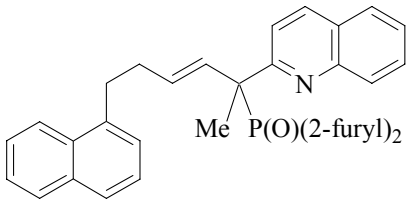
I.R. (film, cm^{-1}): 3400; 3050; 1600; 1430; 1180.

MS (EI, 70 eV): 543 (M^+, 4); 402 (33); 286 (33); 257 (100); 144 (32).

$C_{37}H_{38}NOP$ **HRMS**: Calcd. 544.2769 ($[M+H]^+$).

Found 544.2743 ($[M+H]^+$).

(*E*)-5-[Di-(2-furyl)-phosphinoyl]-1-(naphth-1-yl)-5-(2-quinolyl)-hex-3-ene **(14)**



To a stirred solution of 120 mg (1 mmol, 1 equiv.) of DMAP and 353 mg (1 mmol, 1 equiv.) of **4h** in Et_2O (10 mL) were added 200 mg (1 mmol, 1 equiv.) of bis(2-furyl)chlorophoshine. A white precipitate was formed. It was stirred at rt for 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were evaporated *in vacuo* and toluene (10 mL) was added. It was heated to 110 °C for 3 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 360 mg (70%) of the phosphine oxide as a viscous, slightly yellow oil.

N.M.R.:

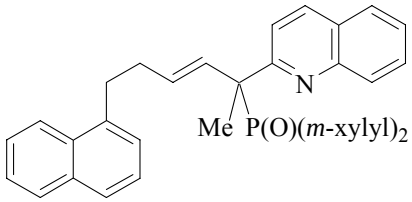
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.87-7.82 (m, 2H); 7.76-7.72 (m, 1H); 7.68-7.63 (m, 1H); 7.58-7.38 (m, 8H); 7.35-7.08 (m, 6H); 6.94-6.91 (m, 1H); 6.85-6.81 (m, 1H); 6.39 (dd, *J* = 7 Hz, *J* = 15 Hz, 1H); 6.24-6.16 (m, 1H); 5.61-5.48 (m, 1H); 2.96-2.92 (m, 2H); 2.44-2.42 (m, 2H); 1.80 (d, *J* = 16 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 160.0 (d, *J* = 14 Hz); 148.2; 148.1; 148.0; 147.8; 147.6; 146.0 (d, *J* = 5 Hz); 138.1; 136.3; 134.3; 133.6 (d, *J* = 9 Hz); 132.3; 129.9; 129.6; 129.5; 129.2; 127.8; 127.3; 127.1; 126.8; 126.4; 126.2; 126.0; 125.9; 124.2; 123.9; 123.8; 123.6; 121.5 (d, *J* = 3 Hz); 111.2-111.0 (m); 53.5 (d, *J* = 75 Hz); 34.6; 33.2 (d, *J* = 3 Hz); 18.9. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 19.7.

I.R. (film, cm^{-1}): 3410; 3130; 3060; 2230; 1600; 1500; 1460; 1210.

MS (EI, 70 eV): 517 (M^+, 0.5); 336 (100); 194 (45); 141 (41).

$C_{33}H_{28}NO_3P$ **HRMS**: Calcd. 517.1825 (M^+).
Found 517.1805 (M^+).

(*E*)-5-[Di-(3,5-dimethylphenyl)-phosphinoyl]-1-(naphth-1-yl)-5-(2-quinolyl)-hex-3-ene **(15)**



To a stirred solution of 122 mg (1 mmol, 1 equiv.) of DMAP and 350 mg (1 mmol, 1 equiv.) of **4h** in Et_2O (10 mL) were added 276 mg (1 mmol, 1 equiv.) of bis(3,5-dimethylphenyl)chlorophosphine. A white precipitate was formed. It was stirred at rt for 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel and the solvents were removed *in vacuo*. Toluene (10 mL) was added and the mixture was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 200 mg (30%) of the phosphine oxide as a viscous, slightly yellow oil.

N.M.R.:

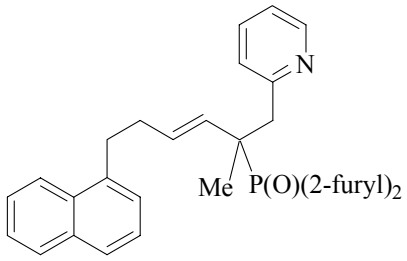
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.91-7.84 (m, 2H); 7.76-7.72 (m, 1H); 7.69-7.66 (m, 1H); 7.60-7.53 (m, 3H); 7.43-7.35 (m, 6H); 7.28-7.26 (m, 1H); 7.23-7.08 (m, 3H); 6.96-6.94 (m, 2H); 6.59 (dd, *J* = 6 Hz, *J* = 15.9 Hz, 1H); 5.62-5.51 (m, 1H); 3.07-2.99 (m, 2H); 2.51-2.48 (m, 2H); 2.15 (s, 6H); 2.08 (s, 6H); 1.81 (d, *J* = 15 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 161.1 (m); 147.5; 138.3; 137.7; 137.6; 137.5; 135.8; 134.3; 133.4; 132.4; 132.3; 132.2; 131.7; 131.6; 131.1; 131.0; 130.8; 130.6; 129.6; 129.4; 129.1; 127.7; 127.2; 127.0; 126.6; 126.3; 126.1; 125.9; 125.8; 124.1; 122.4; 56.7 (d, *J* = 60 Hz); 34.8; 33,3; 21.6 (d, *J* = 6 Hz); 20.4. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 38.2.

I.R. (film, cm^{-1}): 3320; 3060; 1600; 1500; 1430.

MS (EI, 70 eV): 593 (M^+, 3); 452 (58); 336 (85); 309 (37); 257 (100); 194 (82); 181 (49); 141 (33).

$C_{41}H_{40}NOP$ **HRMS**: Calcd. 593.2844 (M^+).
Found 593.2830 (M^+).

(*E*)-2-[Di-(2-furyl)-phosphinoyl]-2-methyl-6-(naphth-1-yl)-1-(2-pyridyl)-hex-3-ene **(16)**



To a stirred solution of 120 mg (1 mmol, 1 equiv.) of DMAP and 317 mg (1 mmol, 1 equiv.) of **4i** in Et_2O (10 mL) were added 200 mg (1 mmol, 1 equiv.) of bis(2-furyl)chlorophosphine. A white precipitate was formed. It was stirred for 30 min at rt. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel and the solvents were removed *in vacuo*. Toluene (10 mL) was added and it was heated to 110 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 160 mg (30%) of the phosphine oxide as a viscous, slightly yellow oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.41-8.38 (m, 1H); 7.83-7.78 (m, 1H); 7.76-7.72 (m, 1H); 7.65-6.57 (m, 3H); 7.28-7.21 (m, 1H); 7.13-6.97 (m, 5H); 6.45-6.39 (m, 2H); 5.85 (dd, *J* = 5.7 Hz, *J* = 15.7 Hz, 1H); 5.26-5.12 (m, 1H); 3.35 (dd, *J* = 7.7 Hz, *J* = 12.7 Hz, 1H); 3.10 (dd, *J* = 8 Hz, *J* = 12.7 Hz, 1H); 2.86-2.78 (m, 2H); 2.38-2.27 (m, 2H); 1.23 (d, *J* = 19.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 156.1 (d, *J* = 17 Hz); 147.8; 147.2; 147.1; 147.0; 146.0 (d, *J* = 7 Hz); 144.2 (d, *J* = 7 Hz); 136.7; 134.4; 132.8; 132.6; 132.5; 130.7; 127.7; 127.6; 127.5; 125.6; 124.7-124.4 (m); 123.0-122.6 (m); 120.5; 109.8 (d, *J* = 8 Hz); 44.0 (d, *J* = 78 Hz); 41.0; 32.9 (d, *J* = 3 Hz); 31.9 (d, *J* = 3 Hz); 15.1. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 22.0.

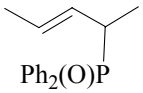
I.R. (film, cm^{-1}): 3440; 3050; 2230; 1590; 1460; 1200.

MS (EI, 70 eV): 481 (M^+, 2); 340 (98); 300 (64); 158 (80); 141 (100).

$C_{30}H_{28}NO_3P$ **HRMS**: Calcd. 481.1789 (M^+).

Found 481.1809 (M^+).

(*E*)-2-Diphenylphosphinoyl-pent-3-ene **(21)**



To a solution of 244 mg (2 mmol, 1 equiv.) of DMAP and 170 mg (2 mmol, 1 equiv.) of pent-3-en-2-ol (*E*/*Z* = 96/4) in Et_2O (10 mL) were added 440 mg (2 mmol, 1 equiv.) of chlorodiphenylphosphine. A white precipitate was formed. It was stirred at rt for 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel and the solvents were evaporated *in vacuo*. Toluene (10 mL) was added and the mixture was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 200 mg (40%) of the phosphine oxide as a colourless oil.

N.M.R.:

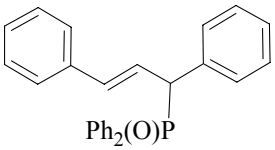
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.74-7.63 (m, 4H); 7.40-7.30 (m, 6H); 5.37-5.31 (m, 2H); 3.11-2.98 (m, 1H); 1.47 (dd, *J* = 5.5 Hz, *J* = 0.8 Hz, 3H); 1.18 (dd, *J* = 7.2 Hz, *J* = 16.3 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 133.0 (d, *J* = 22 Hz); 131.9-131.7 (m); 1331.6; 131.5, 129.6 (d, *J* = 12 Hz); 128.8 (d, *J* = 12 Hz); 128.6 (d, *J* = 12 Hz); 126.8 (d, *J* = 7 Hz); 38.0 (d, *J* = 81 Hz); 18.4 (d, *J* = 2 Hz); 13.6 (d, *J* = 3 Hz). **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 35.0.

I.R. (film, cm^{-1}): 3430; 3060; 2220; 1440.

MS (EI, 70 eV): 270 (M^+, 26); 201 (100).

$C_{17}H_{19}OP$ **HRMS**: Calcd. 270.1248 (M^+).
Found 270.1211 (M^+).

(*E*)-1,3-Diphenyl-1-diphenylphosphinoyl-prop-2-ene **(23)**



To a solution of 210 mg (1 mmol, 1 equiv.) of **22** and 122 mg (1mmol, 1 equiv.) of DMAP in Et_2O (10 mL) were added dropwise 220 mg (1 mmol, 1 equiv.) of Ph_2PCl. A white precipitate was formed. It was stirred for 30 min at rt. At this point, no residual

chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were removed *in vacuo* and toluene (10 mL) was added. The solution was warmed to 80 °C for 1.5 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 170 mg (40%) of the desired product as a white solid.

m.p.: 195-198 °C.

N.M.R.:

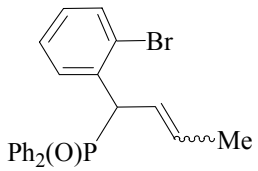
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.82-7.73 (m, 2H); 7.54-7.07 (m, 18H); 6.59-6.46 (m, 1H); 6.28-6.15 (m, 1H); 4.32-4.28 (m, 1H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 135.7; 134.9 (d, *J* = 6 Hz); 133.3 (d, *J* = 11 Hz); 130.7-130.2 (m); 128.4 (d, *J* = 5 Hz); 127.5-127.1 (m); 127.0; 126.7; 126.6; 126.1; 125.8; 125.6; 125.3; 123.6 (d, *J* = 7 Hz); 51.3 (d, *J* = 67 Hz). **^{31}P** ($CDCl_3$, 82 MHz): 32.4.

I.R. (KBr, cm^{-1}): 3420; 3060; 2910; 1440.

MS (EI, 70 eV): 394 (M^+, 100); 268 (11); 201 (42); 165 (42).

$C_{27}H_{23}OP$ **HRMS**: Calcd. 394.1486 (M^+).
Found 394.1509 (M^+).

(*E*) and (*Z*)-1-(2-Bromophenyl)-1-diphenylphosphinoyl-but-2-ene **(25)**



To a solution of 454 mg (2 mmol, 1 equiv.) of **24** and 244 mg (2 mmol, 1 equiv.) of DMAP in Et_2O (10 mL) were added 440 mg (2 mmol, 1 equiv.) of Ph_2PCl. A white precipitate was formed. It was stirred for 30 min. At this point, no residual chlorophosphine was detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel and the solvents were evaporated *in vacuo*. Toluene (10 mL) was added and the mixture was heated to 80 °C for 3 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 400 mg (50%) of the phosphine oxide as a a colourless solid.

m.p.: 114-116 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.95-7.92 (m, 1H); 7.82-7.78 (m, 2H); 7.50-7.14 (m, 10H); 6.92-6.90 (m, 1H); 5.69-5.64 (m, 1H); 5.37-5.35 (m, 1H); 4.84 (t, *J* = 8.7 Hz, 1H); 1.49-1.45 (m, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 136.6 (d, *J* = 4 Hz); 133.3-132.9 (m); 132.1-131.3 (m); 128.9; 128.8; 128.5; 128.3; 125.2 (d, *J* = 9 Hz); 124.7 (d, *J* = 8 Hz); 50.0 (d, *J* = 22 Hz); 18.5. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 33.6.

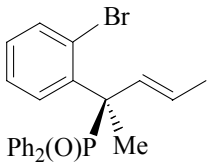
I.R. (KBr, cm^{-1}): 3440; 3060; 1470; 1200.

MS (EI, 70 eV): 412 (M^+, ^{81}Br, 2); 410 (2); 331 (22); 201 (100).

$C_{32}H_{20}BrOP$ **HRMS**: Calcd. 410.0435 (M^+, ^{79}Br).

Found 410.0406 (M^+, ^{79}Br).

(2*R*)-(*E*)-2-(2-Bromophenyl)-2-diphenylphosphinoyl-pent-3-ene **(36)**



To a solution of 1.2 g (5 mmol, 1 equiv.) of *trans*-**26** and 610 mg (5 mmol, 1 equiv.) of DMAP in Et_2O (20 mL) were added 1.1 g (5 mmol, 1 equiv.) of Ph_2PCl. A white precipitate was formed. It was stirred at rt for 30 min. At this point, no residual chlorophosphine could be detected by ^{31}P N.M.R. spectroscopy. It was filtered under argon through a short pad of dry silica gel. The solvents were removed *in vacuo* and toluene (20 mL) was added. It was heated to 110 °C overnight. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 1.35 g (75%) of the pure phosphine oxide as a white solid.

m.p.: 100-102 °C.

$[\alpha]_D^{20}$ (c = 0.36, CH_2Cl_2): +98

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.31 (m, 1H); 7.69 (m, 4H); 7.52-7.27 (m, 8H); 7.06 (dt, *J* = 1.8 Hz, *J* = 7.5 Hz, 1H); 6.95 (dt, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H); 5.87-5.79 (m, 1H); 5.02-4.89 (m, 1H); 1.83 (d, *J* = 15 Hz, 3H); 1.59 (dt, *J* = 6.6 Hz, *J* = 1.8 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 141.5; 136.5; 134.2 (d, *J* = 8 Hz); 133.3 (d, *J* = 8 Hz); 133.1 (d, *J* = 8 Hz);

131.7 (m); 130.3 (d, *J* = 11 Hz); 128.7; 128.6; 128.4; 127.7 (d, *J* = 12 Hz); 127.3; 123.4 (d, *J* = 10 Hz); 51.5 (d, *J* = 68 Hz); 21.8; 18.7. **^{31}P** ($CDCl_3$, 82 MHz): 41.4.

I.R. (KBr, cm^{-1}): 3430; 3050; 1440; 1180.

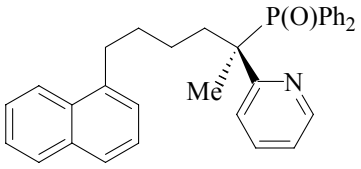
MS (EI, 70 eV): 426 (M^+, ^{81}Br, 4); 424 (4); 345 (15); 202 (100); 144 (35); 129 (36).

$C_{23}H_{22}BrOP$ **HRMS**: Calcd. 424.0616 (M^+, ^{79}Br).

Found 424.0604 (M^+, ^{79}Br).

2.1.3. Further functionalization of allylic phosphine oxides

(5*R*)-5-Diphenylphosphinoyl-1-(naphth-1-yl)-5-(2-pyridyl)-hexane **(19)**



To a precooled (0 °C) solution of 2 g (4 mmol, 1 equiv.) of **5i** in methanol (5 mL) were added 3.2 g (80 mmol, 20 equiv.) of sodium borohydride. 500 mg (4 mmol, 1 equiv.) of nickel chloride hexahydrate were added by small portions. H_2 evolved. After the end of the addition, it was warmed to rt and stirred for 30 min. It was quenched with 50 mL of water and extracted with 3 x 30 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_2O/CH_2Cl_2/MeOH, 1/1/0.1). It yielded 65 mg (30%) of the desired product as a yellow, very viscous oil.

$[\alpha]_D^{20}$ (c = 10, MeOH): -22

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.35 (m, 1H); 7.77-7.73 (m, 1H); 7.67-7.43 (m, 7H); 7.34-7.06 (m, 9H); 7.00 (m, 1H); 6.93-6.89 (m, 2H); 2.79-2.73 (m, 2H); 2.53-2.45 (m, 1H); 1.95-1.89 (m, 1H); 1.58 (d, *J* = 15.5 Hz, 3H); 1.54-1.46 (m, 1H); 1.33-1.20 (m, 1H); 0.89-0.82 (m, 1H); 0.78-0.71 (m, 1H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 158.6 (m); 147.3; 137.3; 134.7; 132.7; 131.5; 131.4; 1331.3; 130.7; 130.4 (d, *J* = 2 Hz); 130.3; 129.3 (m); 127.6; 126.9 (d, *J* = 4 Hz); 126.7 (d, *J* = 4 Hz); 125.3; 124.6; 124.5; 124.3; 124.2; 123.0 (d, *J* = 3 Hz); 122.6; 120.6 (d, *J* = 2 Hz); 47.8 (d, *J* = 63 Hz); 34.0, 31.6; 29.9, 22.2 (d, *J* = 11 Hz); 17.9. **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 38.6.

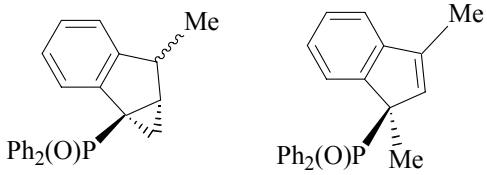
I.R. (film, cm^{-1}): 3350; 3060; 2220; 1590; 1440.

MS (EI, 70 eV): 489 (M^+, 28); 307 (65); 288 (100); 201 (40); 141 (22).

$C_{33}H_{32}NOP$ **HRMS**: Calcd. 489.2222 (M^+).

Found 489.2213 (M^+).

(1*R*)-1,3-Dimethyl-1-diphenylphosphinoyl-indene **(38)** and (1*R*, 8*S*, 9*S*) and (1*R*, 8*R*, 9*S*)-8-methyl-1-diphenylphosphinoyl-tricyclo[7.1.0.$0^{2,7}$]deca-2(7),3,5-triene **(37)**



To a mixture of 8 mg (0.04 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 26 mg (0.1 mmol, 0.5 equiv.) of PPh_3, 125 mg (0.4 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 150 mg (1.1 mmol, 5 equiv.) of K_2CO_3 were added 106 mg (0.25 mmol, 1 equiv.) of **36** in DMF (4 mL). It was heated to 120 °C overnight. The mixture turned red. Heating was continued overnight. It was quenched with 30 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 50 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_2O/CH_2Cl_2, 1/1). It yielded 15 mg (20%) of **38** as a red wax and 40 mg (50%) of **37** as a yellow solid (diastereomeric ratio: 70/30).

Data for **38**:

[α]$_D^{20}$ (c= 0.7, CH_2Cl_2): +148

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.41-7.13 (m, 14H); 6.19-6.18 (m, 1H); 1.90 (m, 3H); 1.61 (d, *J* = 15 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 146.2; 145.8 (d, *J* = 3 Hz); 142.2 (d, *J* = 8 Hz); 133.4 (d, *J* = 3 Hz); 132.2; 132.1 (d, *J* = 5 Hz); 132.0; 131.8 (d, *J* = 3 Hz); 131.7; 130.5 (d, *J* = 16 Hz); 128.4 (d, *J* = 10 Hz); 127.9; 127.8; 127.7; 56.2 (d, *J* = 60 Hz); 17.6 (d, *J* = 5 Hz); 13.1 (d, *J* = 1 Hz). **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 35.6.

I.R. (film, cm^{-1}): 3440; 3060; 1610; 1440; 1260.

MS (EI, 70 eV): 344 (M^+, 100); 343 (48); 329 (20); 201 (40).

$C_{23}H_{21}OP$ **HRMS**: Calcd. 344.1330 (M^+).

Found 344.1357 (M^+).

Data for 37:

m.p.: 106-108 °C.

N.M.R.: Compound isolated as a mixture of diastereoisomers (d.r.= 70/30).

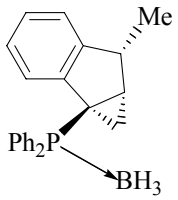
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.71-7.57 (m, 4H); 7.47-7.34 (m, 7H); 7.09-6.96 (m, 2H); 6.89-6.85 (m, 1H); 3.59 (m, 1H); 2.19 (m, 1H); 1.52 (m, 1H); 1.26 (d, *J* = 6.9 Hz, 3H); 0.71-0.66 (m, 1H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 145.5 (d, *J* = 8 Hz); 142.1 (d, *J* = 8 Hz); 131.2; 1313.0; 130.9; 130.8; 127.6; 127.55; 127.5, 127.4; 127.2; 127.1; 125.5 (d, *J* = 17 Hz); 123.7 (d, *J* = 17 Hz); 37.8; 28.7 (d, *J* = 105 Hz); 27.6 (d, *J* = 2 Hz); 17.7; 16.1 (d, *J* = 3Hz). **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 32.7 (major diastereoisomer); 30.2 (minor diastereoisomer).

I.R. (KBr, cm^{-1}): 3430; 3060; 1600; 1440; 1190.

MS (EI, 70 eV): 344 (M^+, 100); 343 (80); 329 (25); 201 (25).

$C_{23}H_{21}OP$ **HRMS**: Calcd. 344.1330 (M^+).
Found 344.1353 (M^+).

(1*R*, 8*R*, 9*S*)-8-Methyl-1-diphenylphosphinyl-tricyclo[7.1.0.0^{2,7}]deca-2(7),3,5-triene borane complex **(39)**



To a solution of 1.5 g (4.5 mmol, 1 equiv.) of **37** in toluene (15 mL) were added 1.5 mL (4.5 mmol, 1 equiv.) of Ti(O-*i*Pr)$_4$ and 2.7 g (45 mmol, 10 equiv.) of polymethylhydrosiloxane. The solution was refluxed for 2 days. The mixture was cooled to rt and 1.5 mL (10 M, 15 mmol, 3 equiv.) of neat BH_3·Me_2S was added. It was stirred for 4 h, then carefully poured onto ice. The mixture was extracted with 3 x 30 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 8/2). The residue was dissolved in isohexane. Recrystallization in the fridge afforded 230 mg of triphenylphosphine-borane complex as colourless needles. The filtrate was concentrated *in vacuo* and the residue was recrystallized from pentane at –40 °C. It afforded 400 mg (30%) of the diastereo- and enantiomerically pure phosphine-borane complex as a white powder.

m.p.: 98-100 °C.

$[\alpha]_D^{20}$ (c = 0.82, CH_2Cl_2): +89

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.61-7.51 (m, 4H); 7.46-7.40 (m, 1H); 7.35-7.15 (m, 8H); 6.95-6.85 (m, 2H); 6.75-6.70 (m, 2H); 3.47 (m, 1H); 2.20-2.10 (m, 1H); 1.57-1.47 (m, 1H); 1.17 (d, *J*= 6.6 Hz, 3H); 0.63 (m, 1H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 145.4 (d, *J* = 5Hz); 142.6 (d, *J* = 2 Hz); 132.1 (d, *J* = 2 Hz); 131.7 (d, *J* = 2 Hz); 130.2; 130.15; 130.1; 130.05; 130.0; 128.8; 128.5; 128.0; 127.8; 127.7; 127.65; 127.6; 126.9; 125.6; 125.1; 123.8; 123.5; 37.8; 27.9; 24.5 (d, *J* = 57 Hz); 18.6; 16.0 (d, *J* = 2 Hz). **^{31}P** ($CDCl_3$, 82 MHz) δ(ppm): 25.3 (m).

I.R. (KBr, cm^{-1}): 3440; 3060; 2380; 2350; 1440.

MS (EI, 70 eV): 328 ($[M\text{-}BH_3]^+$, 100); 313 (82); 183 (53); 143 (57).

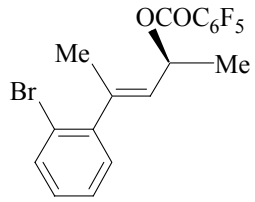
$C_{23}H_{24}BP$ **HRMS**: Calcd. 328.1385 ($[M\text{-}BH_3]^+$).

Found 328.1366 ($[M\text{-}BH_3]^+$).

2.2. Asymmetric Cu-mediated allylic substitution reactions

2.2.1. Preparation of the substrates

(2*S*)-(*E*)-[4-(2-Bromophenyl)-pent-3-en-2-yl]-pentafluorobenzoate **(41)**



To a precooled (-50°C) solution of 120 mg (1mmol, 0.3 equiv.) of DMAP, 0.4 mL (5 mmol, 1.6 equiv.) of pyridine and 710 mg (2.8 mmol, 1 equiv.) of (*E*)-**26** in CH_2Cl_2 (5 mL) were added 1.15 g (5 mmol, 1.6 equiv.) of pentafluorobenzoylchloride. The mixture was stirred at –20 °C overnight. It was quenched with 10 mL of water and extracted with 3 x 10 mL of Et_2O. The organic layer was concentrated *in vacuo* at rt. The residue was dissolved in 5 mL of pentane and washed with 3 x 20 mL of an aqueous saturated solution of $NaHCO_3$. The organic extract was dried over Na_2SO_4 and concentrated *in vacuo* at rt. It yielded 1.15 g (97%) of the compound as an orange solid. It was used without further purification.

m.p.: 41-43 °C.

$[\alpha]_D^{20}$ (c = 1.11, CH_2Cl_2): -8

N.M.R.:

^{1}H (C_6D_6, 300 MHz) δ(ppm): 7.48-7.45 (m, 1H); 7.07-7.04 (m, 1H); 7.00-6.97 (m, 1H); 6.81-6.78 (m, 1H); 6.02 (m, 1H); 5.49 (m, 1H); 2.12 (d, *J* = 1.5 Hz, 3H); 1.38 (d, *J* = 6.3 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 157.3; 145.0 (m, 2CF); 143.8; 142.9 (m, CF); 140.3 (m, 2CF); 140.0; 131.8; 128.5; 127.9; 127.6; 126.5; 120.8; 70.1; 19.3; 13.0.

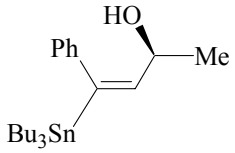
I.R. (KBr, cm^{-1}): 3060; 2980; 1730; 1650; 1500; 1240.

MS (EI, 70 eV): 434 (M^+, ^{79}Br, 0.27), 241 (11); 239 (11); 224 (21); 222 (21); 195 (60); 143 (100); 128 (61).

$C_{18}H_{22}BrF_5O_2$ **HRMS**: Calcd. 433.9917 (M^+, ^{79}Br).

Found 433.9929 (M^+, ^{79}Br).

(3*S*)-(*E*)-1-tributylstannyl-1-phenyl-but-1-en-3-ol **(46)**



To a solution of 7 g (45 mmol, 1 equiv.) of (3*S*)-1-phenyl-but-1-yn-3-ol, 300 mg (0.5 mmol, 0.01 equiv.) of bis(triphenylphosphine)palladium chloride in THF (50 mL) were added dropwise 15 mL (55 mmol, 1.2 equiv.) of $HSnBu_3$. The mixture was stirred at rt for 30 minutes. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (pentane/Et_2O, 9/1). It yielded 14 g (80%) of the desired stannane as a single regio and stereoisomer as a colourless oil.

$[\alpha]_D^{20}$ (c = 1.03, CH_2Cl_2): -18

N.M.R.:

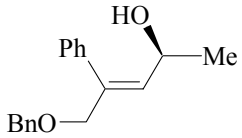
^{1}H (CDCl3, 300 MHz) δ(ppm): 7.21-7.14 (m, 2H); 7.07-7.02 (m, 1H); 6.87-6.82 (m, 2H); 5.72 (d, *J* = 8.4 Hz, $^3J_{H\text{-}Sn}$ = 63 Hz, 1H); 4.34-4.27 (m, 1H); 1.40-1.33 (m, 6H); 1.23-1.13 (m, 9H); 0.84-0.76 (m, 15H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 147.3; 145.2; 144.7; 128.5; 126.8; 125.5; 65.5; 29.3; 27.6; 23.9; 14.0; 10.3.

I.R. (film, cm^{-1}): 3340; 2960; 2930; 1460.

MS (EI, 70 eV): 381 ([M-Bu]$^+$, 100); 325 (19); 307 (14); 249 (38); 177 (34); 147 (39); 131 (67).

$C_{22}H_{38}OSn$ **HRMS**: Calcd. 381.1240 ([M-Bu]$^+$).
Found 381.1243 ([M-Bu]$^+$).

(4*S*)-(*E*)-1-benzyloxy-2-phenyl-pent-2-en-4-ol **(44)**



To a cooled (-50 °C) solution of 4.4 g (10 mmol, 1 equiv.) of **46** in THF (20 mL) were added 14 mL (1.5 M in hexanes, 20 mmol, 2 equiv.) of *n*-BuLi. The first equivalent was added very slowly to deprotonate selectively the alcohol without carring out the Sn-Li exchange reaction. After the end of the addition, the mixture was warmed to rt and stirred for 1 h. It was cooled again to –50 °C and 2 g (12 mmol, 1.2 equiv.) of benzyl(chloromethyl)ether was added. The solution was warmed to rt and stirred overnight. It was quenched with 50 mL of water and extracted with 3 x 15 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 1.28 g (48%) of the pure product as a yellow oil.

$[\alpha]_D^{20}$ (c = 1.05, CH_2Cl_2): -13

N.M.R.:

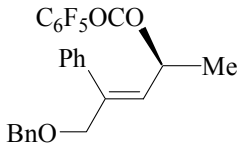
^{1}H (CDCl3, 300 MHz) δ(ppm): 7.34-7.18 (m, 10H); 5.91 (dd, *J* = 0.3 Hz, *J* = 8.1 Hz, 1H); 4.64 (m, 1H); 4.49 (s, 2H); 4.42 (d, *J* = 10.2 Hz, 1H); 4.31 (d, *J* = 11.1 Hz, 1H); 2.00 (br. s., 1H); 1.26 (d, *J* = 6.3 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 141.1; 138.3; 138.1; 137.7; 128.9; 128.7; 128.4; 128.3; 127.9; 126.7; 73.1; 68.0; 64.7; 23.7.

I.R. (film, cm^{-1}): 3400; 2970; 1490; 1450; 1370; 1090.

MS (EI, 70 eV): 265 ([M-3H]$^+$, 0.03); 159 (43); 145 (19); 131 (26); 91 (100).

$C_{18}H_{20}O$ **HRMS**: Calcd. 265.1229 ([M-3H]$^+$).
Found 265.1242 ([M-3H]$^+$).

(4*S*)-(*E*)-[1-benzyloxy-2-phenyl-pent-2-en-4-yl] pentafluorobenzoate **(47)**



To a precooled (-50°C) solution of 20 mg (0.14mmol, 0.1 equiv.) of DMAP, 0.2 mL (2.1 mmol, 1.5 equiv.) of pyridine and 380 mg (1.4 mmol, 1equiv.) of **44** in CH_2Cl_2 (3 mL) were added 460 mg (2 mmol, 1.4 equiv.) of pentafluorobenzoylchloride. The mixture was stirred at –20 °C overnight. It was quenched with 10 mL of water and extracted with 3 x 10 mL of Et_2O. The organic layer was concentrated *in vacuo* at rt. The residue was dissolved in 5 mL of pentane and washed with 3 x 20 mL of an aqueous saturated solution of $NaHCO_3$. The organic extract was dried over Na_2SO_4 and concentrated *in vacuo* at rt. It yielded 480 mg (95%) of the compound as an orange oil. It was used without further purification.

$[\alpha]_D^{20}$ (c = 0.7, CH_2Cl_2): +8

N.M.R.:

^{1}H ($CDCl_3$, 400 MHz) δ(ppm): 7.44-7.41 (m, 2H); 7.36-7.26 (m, 8H); 6.12-6.05 (m, 1H); 5.94 (m, 1H); 4.66 (m, 1H); 4.56 (m, 1H); 4.46 (d, *J* = 11.6 Hz, 1H); 1.52 (d, *J* = 6.4 Hz, 3H). **^{13}C** ($CDCl_3$, 100 MHz) δ(ppm): 157.3; 145.0 (m, 2CF); 142.9 (m, CF); 140.3 (m, 2CF); 140.3; 140.2; 137.9; 130.4; 128.4 (2 x 2C); 127.9; 127.8; 127.7; 126.6; 72.5; 70.9; 67.4; 20.9.

I.R. (film, cm^{-1}): 3060; 2870; 1740; 1650; 1520; 1500; 1340; 1230.

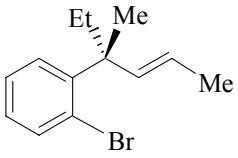
MS (EI, 70 eV): 462 (M^+, 0.06); 194 (66); 159 (23); 144 (30); 129 (22); 91 (100).

$C_{24}H_{19}F_5O_3$ **HRMS**: Calcd. 462.1255 (M^+).

Found 462.1270 (M^+).

2.2.2. Enantioselective Cu-mediated allylic substitution reactions

(4*R*)-(*E*)-4-(2-Bromophenyl)-4-methyl-hex-2-ene **(42a)**



To a precooled (-30 °C) solution of 120 mg (1.3 mmol, 1.3 equiv.) of CuCN and 100 mg (2.6 mmol, 2.6 equiv.) of LiCl in THF (2 mL) were added 0.25 mL (10 M, 2.4 mmol, 2.4 equiv.) of Et_2Zn. The resulting orange solution was stirred for 30 min at –30 °C. Then a solution of 435 mg (1 mmol, 1 equiv.) of **41** in THF (1 mL) were added. It was stirred at –10 °C overnight. The mixture was quenched with 20 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane). It yielded 135 mg (90%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.46, pentane): -4

N.M.R.:

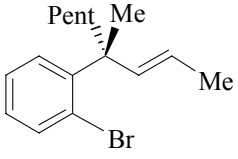
^{1}H ($CDCl_3$, 600 MHz) δ(ppm): 7.61-7.60 (m, 1H); 7.44-7.43 (m, 1H); 7.29-7.26 (m, 1H); 7.08-7.05 (m, 1H); 5.82 (d, *J* = 15.6 Hz, 1H); 5.36-5.30 (m, 1H); 2.37-2.34 (m, 1H); 1.88-1.85 (m, 1H); 1.76-1.74 (m, 3H); 1.51 (m, 3H); 0.76-0.72 (m, 3H). **^{13}C** ($CDCl_3$, 150 MHz) δ(ppm): 146.2; 139.6; 135.9; 130.1; 127.8; 127.2; 123.9; 123.2; 45.8; 32.0; 26.4; 18.6; 9.7.

I.R. (film, cm^{-1}): 2960; 1460; 1260.

MS (EI, 70 eV): 254 (M^+, ^{81}Br, 5); 252 (M^+, ^{79}Br, 5); 225 (15); 223 (15); 144 (100); 129 (42).

$C_{13}H_{17}Br$ **HRMS**: Calcd. 252.0477 (M^+, ^{79}Br).
Found 252.0495 (M^+, ^{79}Br).

(4*R*)-(*E*)-4-(2-Bromophenyl)-4-methyl-non-2-ene **(42b)**



To a precooled (-30 °C) solution of 120 mg (1.3 mmol, 1.3 equiv.) of CuCN and 100 mg (2.6 mmol, 2.6 equiv.) of LiCl in THF (2 mL) were added 0.4 mL (4.6 M, 2.4 mmol, 2.4 equiv.) of $Pent_2Zn$. The resulting orange solution was stirred for 30 min at –30 °C. Then a solution of 435 mg (1 mmol, 1 equiv.) of **41** in THF (1 mL) was added. It was stirred at –10 °C overnight. The mixture was quenched with 20 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane). It yielded 200 mg (70%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.52, pentane): +15

N.M.R.:

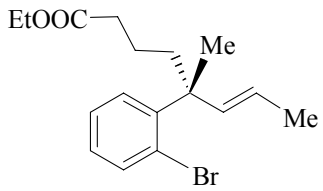
^{1}H ($CDCl_3$, 600 MHz) δ(ppm): 7.60-7.56 (m, 1H); 7.42-7.41 (m, 1H); 7.27-7.25 (m, 1H); 7.07-7.05 (m, 1H); 5.81 (d, *J* = 18.6 Hz, 1H); 5.35-5.30 (m, 1H); 2.28-2.26 (m, 1H); 1.79-1.78 (m, 1H); 1.77-1.73 (m, 3H); 1.51 (s, 3H); 1.29-1.18 (m, 5H); 0.99-0.87 (m, 4H). **^{13}C** ($CDCl_3$, 150 MHz) δ(ppm): 146.5; 139.9; 135.9; 129.9; 127.8; 127.2; 123.8; 122.9; 45.5; 39.5; 32.9; 24.7; 23.0; 18.5; 14.5.

I.R. (film, cm^{-1}): 3060, 2960; 2930; 2870; 1700; 1470.

MS (EI, 70 eV): 296 (M^+, ^{81}Br, 7); 294 (M^+, ^{79}Br, 5); 225 (5); 223 (5); 144 (100); 129 (40).

$C_{16}H_{23}Br$ **HRMS**: Calcd. 294.1035 (M^+, ^{79}Br).
Found 294.1009 (M^+, ^{79}Br).

(4*R*)-(*E*)-Ethyl-5-(2-bromophenyl)-5-methyl-oct-6-enoate **(42c)**



To a precooled (-30 °C) solution of 120 mg (1.3 mmol, 1.3 equiv.) of CuCN and 100 mg (2.6 mmol, 2.6 equiv.) of LiCl in THF (2 mL) were added 1.9 mL (1.3 M, 2.4 mmol, 2.4 equiv.) of bis(3-ethoxycarbonylprop-1-yl)zinc. The resulting orange solution was stirred for 30 min at –30 °C. Then a solution of 435 mg (1 mmol, 1 equiv.) of **41** in THF (1 mL) was added. It was stirred at –10 °C overnight. The mixture was quenched with 20 mL of water and

extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 100/0 to 95/5). It yielded 230 mg (68%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.3, pentane): +5

N.M.R.:

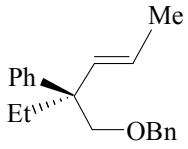
^1H ($CDCl_3$, 300 MHz) δ(ppm): 7.49-7.47 (m, 1H); 7.33-7.30 (m, 1H); 7.19-7.16 (m, 1H); 6.96-6.95 (m, 1H); 5.70 (m, 1H); 5.28-5.16 (m, 1H); 4.06-4.00 (m, 2H); 2.22-2.15 (m, 2H); 1.74 (m, 1H); 1.64 (m, 4H); 1.58 (s, 3H); 1.28-1.14 (m, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 172.7; 144.4; 137.9; 134.5; 128.5; 126.6; 125.9; 122.3; 121.9; 59.2; 44.0; 37.4; 33.8; 25.6; 19.3; 17.1; 13.2.

I.R. (film, cm^{-1}): 3060; 1740; 1460; 1260.

MS (EI, 70 eV): 338 (M^+, ^{79}Br, 1); 223 (24); 144 (100); 129 (38).

$C_{17}H_{23}BrO_2$ **HRMS**: Calcd. 338.0839 (M^+, ^{79}Br).
Found 338.0855 (M^+, ^{79}Br).

(4*R*)-(*E*)-4-benzyloxymethyl-4-phenyl-hex-2-ene **(48a)**



To a precooled (-30 °C) solution of 480 mg (5.2 mmol, 1.3 equiv.) of CuCN and 420 mg (10 mmol, 2.6 equiv.) of LiCl in THF (5 mL) were added 1 mL (10 M, 10 mmol, 2.4 equiv.) of Et_2Zn. The resulting orange solution was stirred for 30 min at –30 °C. Then a solution of 1.8 g (4 mmol, 1 equiv.) of **47** in THF (3 mL) were added. It was stirred at –10 °C overnight. The mixture was quenched with 50 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 690 mg (69%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.69, CH_2Cl_2): -13

N.M.R.:

^{1}H ($CDCl_3$, 400 MHz) δ(ppm): 7.36-7.20 (m, 10H); 5.68 (dq, *J* = 1.6 Hz, *J* = 15.6 Hz, 1H); 5.48 (dq, *J* = 6.4 Hz, *J* = 16 Hz, 1H); 4.51 (s, 2H); 3.73 (d, *J* = 9.6 Hz, 1H); 3.65 (d, *J* = 9.2 Hz, 1H); 1.99-1.86 (m, 2H); 1-77 (dd, *J* = 1.6 Hz, *J* = 6.8 Hz, 3H); 0.78 (t, *J* = 7.2 Hz, 3H). **^{13}C** ($CDCl_3$, 100 MHz) δ(ppm): 145.0; 138.7; 136.2; 128.2; 127.8; 127.7; 127.4; 127.3; 125.8; 124.2; 75.5; 73.3; 48.4; 28.9; 18.5; 8.7.

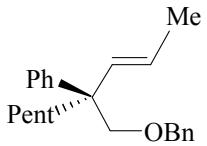
I.R. (film, cm^{-1}): 3030; 2960; 2930; 2860; 1740; 1500; 1450; 1100.

MS (EI, 70 eV): 280 (M^+, 0.02); 159 (100); 132 (14); 117 (39); 91 (35).

$C_{20}H_{24}O$ **HRMS**: Calcd. 280.1823 (M^+).

Found 280.1825 (M^+).

(4*R*)-(*E*)-4-benzyloxymethyl-4-phenyl-non-2-ene **(48b)**



To a precooled (-30 °C) solution of 120 mg (1.3 mmol, 1.3 equiv.) of CuCN and 100 mg (2.6 mmol, 2.6 equiv.) of LiCl in THF (2 mL) were added 0.5 mL (4.5 M, 2.4 mmol, 2.4 equiv.) of $Pent_2Zn$. The resulting orange solution was stirred for 30 min at –30 °C. Then a solution of 430 mg (1 mmol, 1 equiv.) of **47** in THF (3 mL) were added. It was stirred at –10 °C overnight. The mixture was quenched with 20 mL of water and extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 290 mg (90%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.68, CH_2Cl_2): -9

N.M.R.:

^{1}H ($CDCl_3$, 400 MHz) δ(ppm): 7.25-7.10 (m, 10H); 5.57 (dq, *J* = 1.5 Hz, *J* = 15.9 Hz, 1H); 5.35 (dq, *J* = 6.3 Hz, *J* = 15.9 Hz, 1H); 4.40 (s, 2H); 3.61 (d, *J* = 8.7 Hz, 1H); 3.54 (d, *J* = 9.0 Hz, 1H); 1.76-1.71 (m, 2H); 1.66 (dd, *J* = 1.5 Hz, *J* = 6.3 Hz, 3H); 1.18-0.93 (m, 6H); 0.76 (t, *J* = 6.6 Hz, 3H). **^{13}C** ($CDCl_3$, 100 MHz) δ(ppm): 145.3; 138.7; 136.5; 128.2; 127.8; 127.5; 127.4; 127.3; 125.8; 123.9; 75.9; 73.3; 48.1; 36.5; 32.7; 23.7; 22.6; 18.5; 14.1.

I.R. (film, cm^{-1}): 3030; 2960; 2860; 1740; 1500; 1450; 1100.

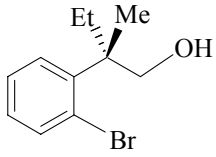
MS (EI, 70 eV): 322 ([M^+, 0.02); 201 (100); 145 (33); 131 (100); 91 (91).

$C_{23}H_{30}O$ **HRMS**: Calcd. 322.2297 (M^+).

Found 322.2317 (M^+).

2.2.3. Derivatization of the alkenes

(2*S*)-2-(2-Bromphenyl)-2-methyl-butan-1-ol **(43a)**



A solution of 253 mg (1 mmol, 1 equiv.) of **42a** in CH_2Cl_2 (20 mL) was cooled to –78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 0.4 mL (10 M, 4 mmol, 4 equiv.) of neat $BH_3{\cdot}Me_2S$ were added. The solution was stirred at rt for 24 h, then carefully quenched with 20 mL of water. The mixture was extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 150 mg (60%) of the desired compound as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.2 ,CH_2Cl_2): +14

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.53-7.51 (m, 1H); 7.33-7.30 (m, 1H); 7.22-7.17 (m, 1H); 7.01-6.98 (m, 1H); 4.32 (d, *J* = 11.1 Hz, 1H); 3.59 (d, *J* = 11.1 Hz, 1H); 2.37-2.30 (m, 1H); 1.56-1.46 (m, 1H); 1.43 (s, 3H); 1.30 (br. s., 1H); 0.60 (t, *J* = 7.5 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 142.3; 136.2; 131.8; 128.4; 127.7; 122.6; 69.3; 46.6; 28.3; 23.7; 8.9.

I.R. (film, cm^{-1}): 3370; 2970; 1470; 1020.

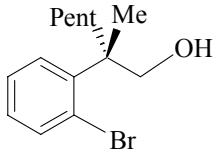
MS (EI, 70 eV): 242 (M^+, ^{79}Br, 0.1); 213 (56); 211 (53); 171 (100); 169 (100); 163 (21); 115 (19).

$C_{11}H_{15}BrO$ **HRMS**: Calcd. 242.0282 (M^+, ^{79}Br).

Found 242.0294 (M^+, ^{79}Br).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 97/3, 0.6 mL/min): 13.8 min (*R*); 15.1 min (*S*).

(2*S*)-2-(2-Bromophenyl)-2-methyl-heptan-1-ol **(43b)**



A solution of 100 mg (0.3 mmol, 1 equiv.) of **42b** in CH_2Cl_2 (10 mL) was cooled to – 78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 0.4 mL (10 M, 4 mmol, 4 equiv.) of neat $BH_3{\cdot}Me_2S$ were added. The solution was stirred at rt for 24 h, then carefully quenched with 50 mL of water. The mixture was extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 200 mg (70%) of the desired compound as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.69, CH_2Cl_2): +11

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.53-7.50 (m, 1H); 7.32-7.30 (m, 1H); 7.19-7.18 (m, 1H); 6.98 (m, 1H); 4.33 (d, *J* = 10.8 Hz, 1H); 3.57 (d, *J* = 10.8 Hz, 1H); 2.28 (m, 1H); 1.44 (s, 3H); 1.44 (m, 1H); 1.27 (br. s., 1H); 1.19-1.12 (m, 4H); 1.07-0.98 (m, 1H); 0.91-0.81 (m, 1H); 0.75 (m, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 142.7; 136.2; 131.6; 128.4; 127.6; 122.6; 69.6; 46.3; 35.8; 32.9; 24.4; 22.9; 14.4.

I.R. (film, cm^{-1}): 3370; 2960; 1470; 1020.

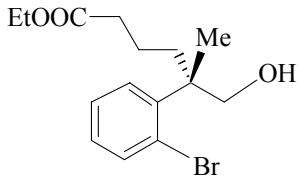
MS (CI, isobutane): 283 ($[M-H]^+$, ^{79}Br, 3); 269 (86); 267 (92); 255 (30); 253 (26); 227 (28); 225 (35); 213 (53); 211 (62); 197 (74); 185 (100); 183 (100); 169 (37).

$C_{14}H_{21}BrO$ **HRMS**: Calcd. 283.0698 ($[M-H]^+$, ^{79}Br).

Found 283.0713 ($[M-H]^+$, ^{79}Br).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 97/3, 0.6 mL/min): 14.7 min (*R*); 16.8 min (*S*).

(2*S*)-5-Ethoxycarbonyl-2-(2-bromophenyl)-2-methyl-pentan-1-ol **(43c)**



A solution of 100 mg (0.3 mmol, 1 equiv.) of **42c** in CH_2Cl_2 (15 mL) was cooled to – 78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 0.12 mL (10 M, 1.2 mmol, 4 equiv.) of neat $BH_3 \cdot Me_2S$ were added. The solution was stirred at rt for 24 h, then carefully quenched with 20 mL of water. The mixture was extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 1/1). It yielded 75 mg (80%) of the desired compound as a colourless oil.

$[\alpha]_D^{20}$ (c = 1, CH_2Cl_2): + 4

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.53-7.50 (m, 1H); 7.36-7.33 (m, 1H); 7.21-7.19 (m, 1H); 7.01-6.99 (m, 1H); 4.22 (d, *J* = 11.1 Hz, 1H); 4.02 (q, *J* = 6.9 Hz, 2H); 3.67 (d, *J* = 11.1 Hz, 1H); 2.33-2.22 (m, 1H); 2.18 (t, *J*= 7.2 Hz, 2H); 1.60 (m, 2H); 1.44 (s, 3H); 1.41-1.20 (m, 2H); 1.16 (t, *J* = 7.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 172.7; 141.0; 134.8; 130.1; 127.1; 126.4; 121.2; 68.1; 59.3; 44.6; 33.6; 33.5; 22.6; 18.8; 13.2.

I.R. (film, cm^{-1}): 3440; 2970; 1730; 1470; 1260; 1190; 1020.

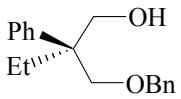
MS (EI, 70 eV): 313 ($[M\text{-}CH_3]^+$, 0.1); 253 (32); 219 (89); 173 (100); 145 (28); 130 (43); 115 (33).

$C_{15}H_{21}BrO_3$ **HRMS**: Calcd. 311.0647 ($[M\text{-}OH]^+$).

Found 311.0641 ($[M\text{-}OH]^+$).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 97/3, 0.6 mL/min): 30.9 min (*R*); 34.5 min (*S*).

(2*S*)-2-benzyloxymethyl-2-phenyl-butan-1-ol **(49a)**



A solution of 280 mg (1 mmol, 1 equiv.) of **48a** in CH_2Cl_2 (15 mL) was cooled to –78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 0.4 mL (10 M, 4 mmol, 4 equiv.) of neat $BH_3{\cdot}Me_2S$ were added. The solution was stirred at rt for 24 h, then carefully quenched with 30 mL of water. The mixture was extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 190 mg (66%) of the desired compound as a colourless solid.

m.p. : 56-58 °C.

$[\alpha]_D^{20}$ (c = 1, CH_2Cl_2): -10

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.29-7.15 (m, 10H); 4.50 (d, *J* = 2.7 Hz, 1H); 3.95-3.80 (m, 3H); 3.67 (d, *J* = 9 Hz, 1H); 2.39 (m, 1H); 1.71 (dq, *J* = 2.1 HZ, *J* = 7.5 Hz, 2H); 0.59 (t, *J* = 7.5 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 142.2; 138.3; 128.9; 128.8; 128.2; 128.0; 127.3; 126.7; 76.1; 74.1; 69.4; 47.4; 27.3; 8.3.

I.R. (KBr, cm^{-1}): 3430; 3030; 2960; 2880; 1500; 1450; 1090.

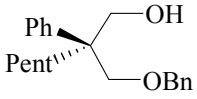
MS (EI, 70 eV): 271 ($[M+H]^+$, 0.3); 149 (13); 132 (76); 147 (14); 91 (100).

$C_{18}H_{22}O_2$ **HRMS**: Calcd. 271.1607 ($[M+H]^+$).

Found 271.1653 ($[M+H]^+$).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 97/3, 0.6 mL/min): 28.7 min (*S*); 34.5 min (*R*).

(2*S*)-2-benzyloxymethyl-2-phenyl-butan-1-ol **(49b)**



A solution of 342 mg (1 mmol, 1 equiv.) of **48b** in CH_2Cl_2 (10 mL) was cooled to –78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 0.4 mL (10 M, 4 mmol, 4 equiv.) of neat $BH_3 \cdot Me_2S$ were added. The solution was stirred at rt for 24 h, then carefully quenched with 30 mL of water. The mixture was extracted with 3 x 10 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 7/3). It yielded 230 mg (66%) of the desired compound as a colourless oil.

$[\alpha]_D^{20}$ (c = 1, CH_2Cl_2): -13

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.30-7.12 (m, 10H); 4.50 (d, *J* = 4.2 Hz, 2H); 3.93-3.79 (m, 3H); 3.65 (d, *J* = 9.0 Hz, 1H); 2.60 (br. s., 1H); 1.66-1.61 (m, 2H); 1.14-1.08 (m, 4H); 0.94-0.90 (m, 2H); 0.73 (t, *J* = 6.9 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 142.6; 138.3; 128.9; 128.8; 128.2; 128.0; 127.1; 126.7; 76.4; 74.1; 69.8; 47.2; 34.8; 32.9; 23.4; 22.8; 14.4.

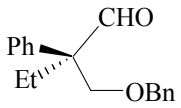
I.R. (film, cm^{-1}): 3440; 2950; 1500; 1450; 1100.

MS (EI, 70 eV): 312 (M^+, 0.08); 191 (14); 174 (20); 118 (92); 91 (100).

$C_{21}H_{28}O_2$ **HRMS**: Calcd. 312.2139 (M^+).
Found 312.2114 (M^+).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 97/3, 0.6 mL/min): 18.8 min (*S*); 24.1 min (*R*).

(2*R*)-2-benzyloxymethyl-2-phenyl-butanal **(50a)**



A solution of 660 mg (2.4 mmol, 1 equiv.) of **48a** in CH_2Cl_2 (20 mL) was cooled to –78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 780 mg (3 mmol, 1.3 equiv.) of PPh_3 were added. The solution was stirred at rt for 24 h, then quenched with 30 mL of water. The mixture was extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 365 mg (58%) of the desired compound as a colourless oil.

$[\alpha]_D^{20}$ (c = 1, CH_2Cl_2): +18

N.M.R.:

^1H ($CDCl_3$, 300 MHz) δ(ppm): 9.52 (s, 1H); 7.29-7.17 (m, 8H); 7.11-7.08 (m, 2H); 4.46 (s, 2H); 3.96 (d, *J* = 9.3 Hz, 1H); 3.79 (d, *J* = 9.3 Hz, 1H); 2.00 (dq, *J* = 1.8 Hz, *J* = 7.5 Hz, 2H); 0.66 (t, *J* = 7.5 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 202.4; 138.3; 137.5; 129.1; 128.8; 128.1; 128.0; 127.9; 127.8; 73.9; 70.6; 59.0; 24.5; 8.4.

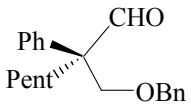
I.R. (film, cm^{-1}): 3030; 2970; 2860; 2710; 1730; 1500; 1450.

MS (EI, 70 eV): 268 (M^+, 0.11); 238 (13); 132 (35); 117 (11); 91 (100).

$C_{18}H_{20}O_2$ **HRMS**: Calcd. 268.1463 (M^+).

Found 268.1522 (M^+).

(2*R*)-2-benzyloxymethyl-2-phenyl-butanal **(50b)**



A solution of 800 mg (2.5 mmol, 1 equiv.) of **48b** in CH_2Cl_2 (20 mL) was cooled to – 78 °C and ozone was bubbled through it until the solution turned blue. N_2 was then bubbled to remove the excess ozone. The colourless solution was then warmed to rt and 760 mg (3 mmol, 1.2 equiv.) of PPh_3 were added. The solution was stirred at rt for 24 h, then quenched with 30 mL of water. The mixture was extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 520 mg (66%) of the desired compound as a colourless oil.

$[\alpha]_D^{20}$ (c = 1.05, CH_2Cl_2): +15

N.M.R.:

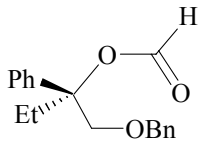
^1H ($CDCl_3$, 300 MHz) δ(ppm): 9.51 (s, 1H); 7.30-7.08 (m, 10H); 4.45 (s, 2H); 3.95 (d, *J* = 9.3 Hz, 1H); 3.79 (d, *J* = 9.3 Hz, 1H); 1.92 (t, *J* = 6.0 Hz, 2H); 1.17-1.15 (m, 4H); 1.00-0.96 (m, 2H); 0.75 (m, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 202.4; 138.3; 137.8; 129.1; 128.7; 128.1; 127.9; 127.8; 127.7; 73.9; 71.0; 58.7; 32.7; 23.6; 22.8; 14.4.

I.R. (film, cm^{-1}): 3030; 2930; 2710; 1730; 1450.

MS (EI, 70 eV): 310 (M^+, 0.05); 118 (39); 91 (100).

$C_{18}H_{20}O_2$ **HRMS**: Calcd. 310.1919 (M^+).
Found 310.1926 (M^+).

(1*R*)-[1-benzyloxymethyl-1-phenyl-propan-1-yl] formate **(52a)**



A solution of 210 mg (0.8 mmol. 1 equiv.) of **50a** in CH_2Cl_2 (10 mL) were added to dried *m*-CPBA (420 mg, 2.5 mmol, 3 equiv.). The reaction was stirred at rt for 40 hours. It was quenched with 30 mL of water and extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 150 mg (73%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 0.64, CH_2Cl_2): -26

N.M.R.:

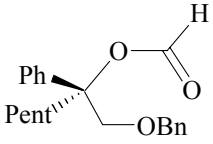
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.20 (s, 1H); 7.28-7.14 (m, 10H); 4.45 (s, 2H); 3.97 (d, *J* = 9.0 Hz, 1H); 3.90 (d, *J* = 9.0 Hz, 1H); 2.25-2.18 (m, 1H); 2.02-1.95 (m, 1H); 0.70 (t, *J* = 6.0 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 160.3; 139.5; 136.6; 127.4; 127.3; 126.8; 126.5; 124.7; 85.3; 72.5; 65.7; 29.3; 6.4.

I.R. (film, cm^{-1}): 3030; 2960; 2930; 2870; 1730; 1450; 1180; 1110.

MS (FAB, Xe, 8 kV): 239 ($[M\text{-}COOH]^+$, 3); 135 (11); 105 (14); 91 (100).

$C_{18}H_{20}O_3$ **HRMS**: Calcd. 239.1436 ($[M\text{-}COOH]^+$).
Found 239.1442 ($[M\text{-}COOH]^+$).

(1*R*)-[1-benzyloxymethyl-1-phenyl-hexan-1-yl] formate **(52b)**



A solution of 310 mg (1 mmol, 1 equiv.) of **50b** in CH_2Cl_2 (10 mL) were added to dried *m*-CPBA (550 mg, 3.3 mmol, 3.3 equiv.). The reaction was stirred at rt for 40 hours. It

was quenched with 30 mL of water and extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 225 mg (68%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 2.0, CH_2Cl_2): -22

N.M.R.:

^1H ($CDCl_3$, 300 MHz) δ(ppm): 8.49 (s, 1H); 7.49-7.25 (m, 10H); 4.55 (s, 2H); 4.05 (d, *J* = 10.2 Hz, 1H); 4.00 (d, *J* = 10.2 Hz, 1H); 2.27-2.22 (m, 1H); 2.05-2.02 (m, 1H); 1.26-1.15 (m, 6H); 0.84 (t, *J* = 6.6 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 169.8; 141.3; 138.0; 128.9; 128.8; 128.2; 128.1; 128.0; 126.1; 86.6; 74.0; 73.7; 37.9; 32.3; 23.0; 22.8; 14.4.

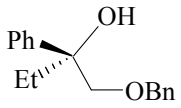
I.R. (film, cm^{-1}): 3030; 2960; 2930; 2870; 1730; 1450; 1180; 1110.

MS (FAB, Xe, 8 kV): 281 ($[M\text{-}COOH]^+$, 9); 161 (5); 105 (10); 91 (100).

$C_{21}H_{26}O_3$ **HRMS**: Calcd. 281.1905 ($[M\text{-}COOH]^+$).

Found 281.1914 ($[M\text{-}COOH]^+$).

(1*R*)-1-benzyloxy-1-phenyl-propan-1-ol **(51a)**



To a solution of 110 mg (0.4 mmol, 1 equiv.) of **52a** in MeOH (1 mL) were added 60 mg (1.1 mmol, 3 equiv.) of KOH dissolved in water (0.6 mL). The reaction mixture was stirred at rt for 2 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (pentane/Et_2O, 8/2). It yielded 70 mg (70%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 1.02, CH_2Cl_2): -14

N.M.R.:

^1H ($CDCl_3$, 300 MHz) δ(ppm): 7.34-7.15 (m, 10H); 4.45 (s, 2H); 3.58 (d, *J* = 9.0 Hz, 1H); 3.53 (d, *J* = 9.0 Hz, 1H); 2.64 (br. s., 1H); 1.92-1.80 (m, 1H); 1.77-1.68 (m, 1H); 0.67 (t, *J* = 7.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 144.1; 138.3; 128.8; 128.4; 128.1; 128.0; 127.1; 125.9; 77.9; 76.8; 73.9; 32.2; 7.9.

I.R. (film, cm^{-1}): 3560; 2930; 1450; 1100.

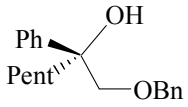
MS (EI, 70 eV): 256 (M^+, 0.04); 135 (100); 91 (25).

$C_{17}H_{20}O_2$ **HRMS**: Calcd. 256.1464 (M^+).

Found 256.1485 (M^+).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 98/2, 0.2 mL/min): 49.0 min (*R*); 53.3 min (*S*).

(1*R*)-1-benzyloxy-1-phenyl-heptan-hexan-1-ol **(51b)**



To a solution of 220 mg (0.6 mmol, 1 equiv.) of **52b** MeOH (1 mL) were added 60 mg (1.1 mmol, 3 equiv.) of KOH dissolved in water (0.6 mL). The reaction mixture was stirred at rt for 4 h. The solvents were evaporated *in vacuo* and the residue was purified by flash chromatography (pentane/Et_2O, 8/2). It yielded 140 mg (77%) of the desired product as a colourless oil.

$[\alpha]_D^{20}$ (c = 1.1, CH_2Cl_2): -8

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.34-7.14 (m, 10H); 4.45 (s, 2H); 3.57 (d, *J* = 9.0 Hz, 1H); 3.52 (d, *J* = 9.0 Hz, 1H); 2.73 (br. s., 1H); 1.84-1.68 (m, 2H); 1.29-1.05 (m, 3H); 1.00-0.89 (m, 1H); 0.73 (t, *J* = 6.6 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 144.5; 138.3; 128.8; 128.4; 128.1; 128.0; 127.0; 125.8; 78.1; 76.6; 73.9; 39.6; 32.6; 23.2; 22.9; 14.4.

I.R. (film, cm^{-1}): 3560; 3480; 2930; 1450.

MS (EI, 70 eV): 298 (M^+, 0.1); 177 (100); 91 (45).

$C_{20}H_{26}O_2$ **HRMS**: Calcd. 298.1933 (M^+).

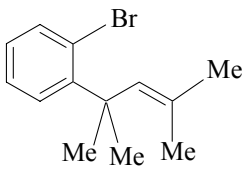
Found 298.1957 (M^+).

Chiral HPLC (OD-H column, *n*-heptane/*i*-propanol, 98/2, 0.2 mL/min): 40.0 min (*S*); 42.8 min (*R*).

2.3. Intramolecular Heck reaction/C-H activation cascades

2.3.1. Preparation of the substrates

(*E*)-2-(2-Bromophenyl)-2,4-dimethylpent-3-ene **(54)**



To a suspension of 4.3 g (10 mmol, 1 equiv.) of isopropyltriphenylphophonium iodide in toluene (40 mL) was added at rt *n*-BuLi (1.5 M in hexanes, 7 mL, 10 mmol, 1 equiv.). The resulting red solution was stirred at rt for 2.5 h. The solution was cooled to –80 °C and 1.8 g (8 mmol, 0.8 equiv.) of 2-(*o*-bromophenyl)-2-methylpropanal were added. The mixture was warmed to rt and stirred overnight. It was quenched with 100 mL of water and extracted with 3 x 20 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane). It yielded 1.3 g (70%) of the pure alkene as a colourless oil.

N.M.R.:

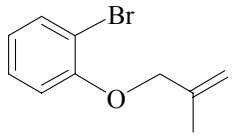
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.60-7.51 (m, 2H); 7.32-7.26 (m, 1H); 7.07-7.02 (m, 1H); 5.56 (m, 1H); 1.69 (d, *J* = 1.5 Hz, 3H); 1.54 (s, 6H); 1.08 (d, *J* = 1.2 Hz, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 148.8; 135.5; 134.2; 134.1; 130.1; 128.0; 127.4; 123.5; 40.9; 30.3; 26.9; 18.4.

I.R. (film, cm^{-1}): 2970; 2930; 1470; 1020.

MS (EI, 70 eV): 254 (M^+, ^{81}Br, 7); 252 (M^+, ^{79}Br, 7); 158 (100); 143 (60).

$C_{13}H_{17}Br$ **HRMS**: Calcd. 252.0514 (M^+, ^{79}Br).
Found 252.0514 (M^+, ^{79}Br).

(2-Bromophenyl)-(2-methyl-prop-2-en-1-yl) ether **(57)**[110]



To a suspension of 500 mg (60% in oil, 10 mmol, 1 equiv.) of NaH in DMF (10 mL) were added 1.7 g (10 mmol, 1 equiv.) of 2-bromophenol in DMF (10 mL). When evolution of H_2 has ceased, 2 mL (20 mmol, 2 equiv.) of methallyl chloride were added. The reaction mixture was heated to 80 °C overnight. It was quenched with 50 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 50 mL of water. The organic extract was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It gave 2.2 g (85%) of the desired compound as a colourless oil.

N.M.R.:

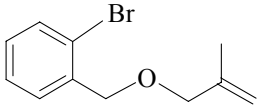
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.39-7.36 (m, 1H); 7.09-7.03 (m, 1H); 6.73-6.63 (m, 2H); 5.00 (m, 1H); 4.84 (m, 1H); 4.32 (m, 2H); 1.69 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 155.4; 140.7; 133.8; 128.7; 122.3; 113.9; 113.3; 112.7; 72.9; 19.8.

I.R. (film, cm^{-1}): 3080; 2920; 1480; 1660; 1590.

MS (EI, 70 eV): 228 (M^+, ^{81}Br, 52); 226 (M^+, ^{79}Br, 52); 174 (28); 172 (28); 147 (100); 133 (28).

$C_{10}H_{11}BrO$ **HRMS**: Calcd. 225.9992 (M^+, ^{79}Br).
Found 203.1327 (M^+, ^{79}Br).

(2-Bromophenyl)methyl-(2-methyl-prop-2-en-1-yl) ether **(58)**



To a suspension of 500 mg (60% in oil, 11 mmol, 1.1 equiv.) of NaH were added 1.9 g (10 mmol, 1 equiv.) of *o*-bromobenzylalcohol in DMF (10 mL). When H_2 evolution has ceased, 2 mL (20 mmol, 2 equiv.) of methallylchloride were added and the solution was

[110] P. Stanetty, H. Koller, G. Puerstinger, *Monatsh. Chem.* **1990**, *121*, 883.

warmed to 80 °C for 2 h. The reaction was quenched with 30 mL of water and extracted with 3 x 5 mL of Et_2O. The combined organic layers were washed with 5 x 20 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 9/1). It afforded 2 g (80%) of the pure ether as a colourless oil.

N.M.R.:

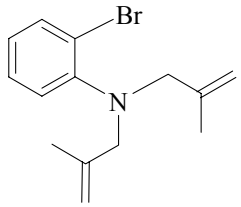
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.47-7.42 (m, 2H); 7.28-7.21 (m, 1H); 7.09-7.03 (m, 1H); 4.97-4.96 (m, 1H); 4.88-4.87 (m, 1H); 4.49 (s, 2H); 3.94 (s, 2H); 1.72 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 142.8; 138.6; 133.2; 129.7; 129.5; 128.1; 123.3; 113.2; 75.1; 71.6; 19.9.

I.R. (film, cm^{-1}): 3070; 2920; 2850; 1440.

MS (EI, 70 eV): 240 (M^+, ^{79}Br, 0.08); 198 (15); 196 (14); 185 (33); 171 (100); 169 (98); 90 (31).

$C_{11}H_{13}BrO$ **HRMS**: Calcd. 240.0150 (M^+, ^{79}Br).
Found 240.0175 (M^+, ^{79}Br).

N,*N*-Bis(2-methyl-prop-2en-1-yl)-2-bromoaniline **(59)**



To a suspension of 2 g (60% in oil, 40 mmol, 2 equiv.) of NaH were addded 3.4 g (20 mmol, 1 equiv.) of 2-bromoaniline in DMF (10 mL). When the evolution of H_2 has ceased, 10 mL (100 mmol, 5 equiv.) of methallylchloride were added. The mixture was heated to 80 °C overnight. The mixture was quenched with 50 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 30 mL of Et_2O, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 5.2 g (90%) of the pure desired product as a colourless oil.

N.M.R.:

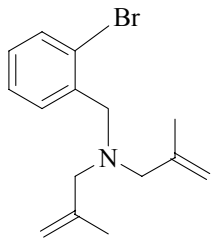
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.49-7.46 (m, 1H); 7.15-7.10 (m, 1H); 7.03-7.00 (m, 1H); 6.83-6.77 (m, 1H); 4.85 (br. s., 2H); 4.77 (br. s., 2H); 3.48 (s, 4H); 1.66 (s, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 149.3; 142.7; 133.9; 127.4; 124.4; 123.9; 121.0; 113.3; 59.0; 20.7.

I.R. (film, cm^{-1}): 3070; 2970; 2820; 1580; 1470.

MS (EI, 70 eV): 281 (M^+, ^{81}Br, 7); 279 (M^+, ^{79}Br, 9); 238 (74); 200 (37); 144 (59); 55 (100).

$C_{14}H_{18}BrN$ **HRMS**: Calcd. 279.0622 (M^+, ^{79}Br).
Found 279.0626 (M^+, ^{79}Br).

N,*N*-Bis(2-methyl-prop-2-en-1-yl)-2-bromobenzylamine **(61)**



To a suspension of 1.7 g (60% in oil, 33 mmol, 3.3 equiv.) of NaH were added 2.3 g (10 mmol, 1 equiv.) of *o*-bromobenzylamine hydrochloride in DMF (20 mL). When H_2 evolution has ceased, 4 mL (40 mmol, 4 equiv.) of methallylchloride were added and the solution was heated to 80 °C overnight. The mixture was quenched with 50 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 50 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 9/1). It afforded 2.25 g (80%) of the pure product as a colourless oil.

N.M.R.:

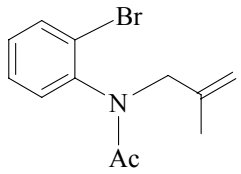
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.60-7.56 (m, 1H); 7.45-7.42 (m, 1H); 7.24-7.21 (m, 1H); 7.03-6.97 (m, 1H); 4.90-4.89 (m, 2H); 4.79-4.77 (m, 2H); 3.50 (s, 2H); 2.85 (s, 4H); 1.69 (s, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 144.1; 139.6; 132.9; 130.3; 128.3; 127.6; 124.5; 113.1; 61.3; 57.7; 21.3.

I.R. (film, cm^{-1}): 3070; 2920; 1650; 1440; 1370.

MS (EI, 70 eV): 295 (M^+, ^{81}Br, 7); 293 (M^+, ^{79}Br, 10); 254 (98); 252 (100); 214 (7); 171 (57); 169 (56).

$C_{15}H_{20}BrN$ **HRMS**: Calcd. 293.0779 (M^+, ^{79}Br).
Found 293.0741 (M^+, ^{79}Br).

N-(2-Methylprop-2-en-1-yl)-2-bromoacetanilide **(64)**[111]



To a solution of 1.9 g (9 mmol, 1 equiv.) of *N*-acetyl-2-bromoaniline, water (1.5 mL), 1.25 g (30 mmol, 3 equiv.) of NaOH and 35 mg (0.1 mmol, 0.1 equiv.) of *n*-Bu_4NHSO_4 were added 8 mL (80 mmol, 9 equiv.) of methallylchloride. The mixture was refluxed under vigourous stirring overnight. The reaction was quenched with 50 mL of water and extracted with 3 x 15 mL of Et_2O. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and distilled in the Kugelrohr ($b.p._{.20}$ = 250 °C). It yielded 1.7 g (66%) of the pure compound as a colourless oil.

N.M.R.:

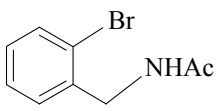
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.61-7.58 (m, 1H); 7.28-7.23 (m, 1H); 7.19-7.10 (m, 2H); 4.84 (d, *J* = 15 Hz, 1H); 4.73 (m, 1H); 4.57 (m, 1H); 3.37 (d, *J* = 15 Hz, 1H); 1.74 (s, 3H); 1.70 (m, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 169.0; 140.2; 139.3; 132.6; 129.6; 128.4; 127.1; 122.4; 112.8; 52.4; 21.2; 19.3.

I.R. (film, cm^{-1}): 3080; 2970; 1670; 1470; 1380; 1280.

MS (EI, 70 eV): 269 (M^+, ^{81}Br, 4); 267 (M^+, ^{79}Br, 3); 227 (55); 225 (55); 188 (100).

$C_{12}H_{14}BrNO$ **HRMS**: Calcd. 267.0234 (M^+, ^{79}Br).
Found 267.0243 (M^+, ^{79}Br).

N-Acetyl-2-bromobenzylamine **(63)**[98]



[111] J. P. Dittami, H. Ramanathan, *Tetrahedron Lett.* **1988**, *29*, 45.

To a solution of 600 mg (3.3 mmol, 1 equiv.) of 2-bromobenzylamine in Et_3N (1 mL) and CH_2Cl_2 (10 mL) were added 240 mg (3.3 mmol, 1 equiv.) of acetyl chloride. A precipitate was formed and the reaction mixture was stirred at rt for 2 h. It was quenched with 30 mL of water and extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. It yielded 600 mg (80%) of the crude product as a yellow solid. It was used without further purification.

m.p. : 64-66 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.49-7.46 (m, 1H); 7.33-7.30 (m, 1H); 7.24-7.19 (m, 1H); 7.10-7.04 (m, 1H); 5.97 (br. s., 1H); 4.44 (s, 1H); 4.42 (s, 1H); 1.94 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 170.3; 137.7; 133.2; 130.8; 129.6; 128.1; 124.1; 44.3; 23.6.

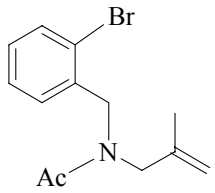
I.R. (KBr, cm^{-1}): 3260; 3060; 1630; 1440; 1030.

MS (EI, 70 eV): 227 (M^+, ^{81}Br, 0.09); 186 (0.6); 184 (0.9); 148 (100); 107 (39).

C_9H_9BrNO **HRMS**: Calcd. 227.9960 (M^+, ^{81}Br).

Found 227.9992 (M^+, ^{81}Br).

N-Acetyl-*N*-(2-methyl-prop-2-en-1-yl)-2-bromobenzylamine **(65)**



To a solution of 600 mg (2.7 mmol, 1 equiv.) of **63**, 600 mg (15 mmol, 5, equiv.) of NaOH, 120 mg (0.3 mmol, 0.1 equiv.) of *n*-Bu_4NHSO_4 in water (1.2 mL) were added 2mL (20 mmol, 7 equiv.) of methallyl chloride. It was refluxed overnight under vigourous stirring. It was quenched with 30 mL of water and extracted with 3 x 10 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 1/1). It gave 600 mg (70%) of the pure compound as a yellow oil.

N.M.R.: This compound was observed as a mixture of rotamers around the amide bound.

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.61-7.52 (m, 1H); 7.37-7.09 (m, 3H); 4.98-4.76 (m, 2H); 4.70 (s, 1.3 H); 4.49 (s, 0.7H); 4.00 (s, 0.5H); 3.76 (s, 0.5H); 2.18 (s, 1.7H); 2.11 (s,

1.3H); 1.73 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 171.9; 171.7; 140.7; 139.9; 136.9; 135.9; 133.6; 133.2; 129.4; 129.1; 128.3; 128.0; 127.1; 124.1; 123.1; 112.9; 111.6; 53.9; 51.6; 51.2; 48.8; 21.82; 21.75; 21.65; 21.55; 20.5.

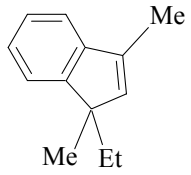
I.R. (film, cm^{-1}): 3080; 2920; 1650; 1440.

MS (EI, 70 eV): 283 (M^+, ^{81}Br, 2); 281 (M^+, ^{79}Br, 2); 202 (100); 186 (24); 184 (24); 171 (19); 169(18).

$C_{13}H_{16}BrNO$ **HRMS**: Calcd. 281.0366 (M^+, ^{79}Br).
Found 281.0391 (M^+, ^{79}Br).

2.3.2. Preparation of carbocycles

1,3-Dimethyl-2-ethylindene **(53)**[112]



To a mixture of 20 mg (0.1 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 75 mg (0.25 mmol, 0.4 equiv.) of PPh_3, 23 mg (0.7 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 350 mg (2.5 mmol, 5 equiv.) of K_2CO_3 were added 120 mg (0.5 mmol, 1 equiv.) of **42a** dissolved in DMF (15 mL). The mixture was heated to 120 °C overnight. The dark mixture was quenched with 50 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 50 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane). It yielded 70 mg (80%) of the pure desired product as a colourless oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.22-7.01 (m, 4H); 5.89-5.88 (m, 1H); 2.02 (d, *J* = 1.5 Hz); 1.76-1.53 (m, 2H); 1.18 (s, 3H); 0.56 (t, *J* = 7.5 Hz). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 151.8; 143.9; 139.0; 135.7; 125.2; 123.8; 119.9; 117.9; 51.1; 30.3; 22.0; 11.9; 8.6.

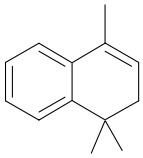
I.R. (film, cm^{-1}): 2960; 2920; 1460; 1380; 1260.

MS (EI, 70 eV): 172 (M^+, 26); 157 (23); 143 (100); 128 (40).

[112] R. Gelin, A. Chantegrel, *Bull. Soc. Chim. Fr.* **1971**, 2527.

$C_{13}H_{16}$ **HRMS**: Calcd. 172.1252 (M^+).
Found 172.1286 (M^+).

1,1,4-Trimethyl-dihydronaphthalene **(56)**[113]



To a mixture of 80 mg (0.4 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 262 mg (1 mmol, 0.5 equiv.) of PPh_3, 920 mg (2.6 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 1.4 g (10 mmol, 5 equiv.) of K_2CO_3 were added 500 mg (2 mmol, 1 equiv.) of **54** dissolved in DMF (5 mL). The mixture was warmed to 120 °C overnight. The black solution was quenched with 10 mL of water and extracted with 3 x 10 mL of Et_2O. The organic layer was washed with 5 x 30 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane). It yielded 140 mg (40%) of the title compound as a colourless oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.28 (m, 1H); 7.15-7.02 (m, 3H); 5.27 (m, 1H); 3.19 (m, 2H); 1.70 (s, 3H); 1.23 (s, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 144.1; 134.0; 128.9; 128.5; 128.4; 126.5; 126.1; 125.9; 36.4; 35.2; 32.3; 23.4.

I.R. (film, cm^{-1}): 2970; 1660; 1450.

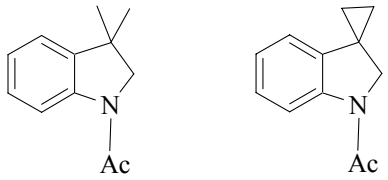
MS (EI, 70 eV): 172 (M^+, 60); 157 (25); 144 (19); 129 (100); 115 (51); 101 (22).

$C_{13}H_{16}$ **HRMS**: Calcd. 172.1252 (M^+).
Found 172.1259 (M^+).

[113] M. F. Ansell, S. A. Mahmud, *J. Chem. Soc., Perkin Trans. 1* **1973**, 2789.

2.3.3. Preparation of N-containing heterocycles

N-Acetyl-3,3-dimethylindoline **(66b)** and *N*-acetyl-1′,2′-dihydrospiro [cyclopropane-1,3′-indoline] **(66a)**



To a mixture of 160 mg (0.8 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 520 mg (2 mmol, 0.5 equiv.) of PPh_3, 1.2 g (5 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 2.8 g (20 mmol, 5 equiv.) of K_2CO_3 were added 1 g (4 mmol, 1 equiv.) of **64** dissolved in DMF (100 mL). The reaction was heated to 120 °C overnight. The mixture was quenched with 200 mL of water and extracted with 3 x 100 mL of Et_2O. The combined organic layers were washed with 5 x 300 mL of water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/Et_2O, 1/1 to 0/100). It yielded 150 mg (25%) of **66b** and 300 mg (50%) of **66a** as light yellow solids.

Data for **66b**:

m.p.: 96-98 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.10 (m, 1H); 7.11-7.03 (m, 2H); 6.98-6.95 (m, 1H); 3.69 (s, 2H); 2.13 (s, 3H); 1.27 (s, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 167.7; 140.5; 139.4; 126.7; 122.8; 120.8; 115.9; 62.6; 39.2; 27.6; 23.2.

I.R. (KBr, cm^{-1}): 2970; 1660; 1480; 1410.

MS (EI, 70 eV): 189 (M^+, 44); 147 (19); 132 (100); 117 (14).

$C_{12}H_{15}NO$ **HRMS**: Calcd. 189.1154 (M^+).
Found 189.1163 (M^+).

Data for **66a**:

m.p.: 97-99 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 8.13-8.10 (m, 1H); 7.06-7.00 (m, 1H); 6.90-6.85 (m, 1H); 6.54-6.52 (m, 1H); 3.88 (s, 2H); 2.06 (s, 3H); 0.97-0.91 (m, 4H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 169.0; 143.7; 136.9; 127.3; 124.1; 118.4; 116.9; 57.8; 24.5; 23.0; 18.0.

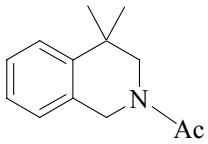
I.R. (KBr, cm^{-1}): 3060; 2990; 2890; 1660; 1480; 1400.

MS (EI, 70 eV): 187 (M^+, 35); 159 (14); 144 (18); 130 (46); 117 (100).

$C_{12}H_{13}NO$ **HRMS**: Calcd. 187.0997 (M^+).

Found 187.0986 (M^+).

N-Acetyl-4,4-dimethyl-tetrahydroisoquinoline **(67)**[114]



A mixture of 40 mg (0.2 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 120 mg (0.4 mmol, 0.4 equiv.) of PPh_3, 450 mg (1.3 mmol, 1.3 equiv.) of *n*-Bu_4NBr, 700 mg (5 mmol, 5 equiv.) of K_2CO_3 and 270 mg (1 mmol, 1 equiv.) of **65** in DMF (5 mL) was heated to 120 °C overnight. It was quenched with 30 mL of water and extracted with 3 x 5 mL of Et_2O. The combined organic layers were washed with 5 x 50 ml of water. The organic extract was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 1/1). It yielded 80 mg (50%) of the desired compound as a colourless oil.

N.M.R.: This compound is observed as a mixture of rotamers around the amide bound.

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.29-6.97 (m, 4H); 4.69 (s, 1.3H); 4.59 (s, 0.7H); 3.53 (s, 0.7 H); 3.35 (s, 1.3H); 2.13 (s, 1H); 2.11 (s, 2H); 1.23 (s, 4H); 1.20 (s, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 170.1; 169.9; 144.5; 143.0; 132.2; 131.4; 127.8; 127.1; 126.9; 126.8; 126.4; 126.2; 126.0; 125.5; 56.8; 51.3; 49.1; 45.5; 35.9; 35.4; 28.8; 27.9; 27.8; 22.1; 22.0; 21.9; 21.8.

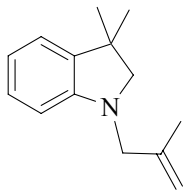
I.R. (film, cm^{-1}): 2960; 1650; 1450.

MS (EI, 70 eV): 203 (M^+, 100); 160 (36); 144 (33); 132 (81); 117 (49).

[114] S. M. Bromidge, S. F. Moss, PCT Int. Appl. **2002**, WO 2002042293 A1 20020530.

$C_{13}H_{17}NO$ **HRMS**: Calcd. 203.1310 (M^+).
Found 203.1327 (M^+).

N-(2-Methyl-prop-2-en-1-yl)-3,3-dimethyl-indoline **(68b)**



A mixture of 230 mg (0.4 mmol, 0.2 equiv.) of $Pd(dba)_2$, 1 g (3 mmol, 1.3 equiv.) of *n*-Bu_4NBr, 1.4 g (10 mmol, 5 equiv.) of K_2CO_3 and 560 mg (2 mmol, 1 equiv.) of **59** in DMF (5 mL) was heated to 120 °C overnight. It was quenched with 50 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 30 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 200 mg (50%) of the desired product as a yellow oil.

N.M.R.:

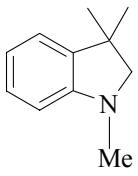
^{1}H ($CDCl_3$, 400 MHz) δ(ppm): 7.15-7.08 (m, 2H); 6.77-6.73 (m, 1H); 6.55-6.53 (m, 1H); 5.05 (m, 1H); 4.96 (m, 1H); 3.65 (s, 2H); 3.16 (s, 2H); 1.86 (s, 3H); 1.38 (s, 6H). **^{13}C** ($CDCl_3$, 100 MHz) δ(ppm): 151.2; 142.4; 138.8; 127.4; 121.7; 117.4; 112.0; 106.7; 67.8; 55.4; 40.1; 22.7; 20.4.

I.R. (film, cm^{-1}): 2960; 1610; 1460.

MS (EI, 70 eV): 201 (M^+, 83); 186 (100); 160 (59); 144 (45); 130 (49).

$C_{14}H_{19}N$ **HRMS**: Calcd. 201.1423 (M^+).
Found 201.1470 (M^+).

N-Methyl-3,3-dimethyl-indoline **(70)**[115]



[115] T. Nishio, N. Okuda, C. Kashima, Y. Omote, *Chem. Commun.*, **1988**, 572.

A mixture of 230 mg (0.4 mmol, 0.2 equiv.) of $Pd(dba)_2$, 1 g (3 mmol, 1.3 equiv.) of *n*-Bu_4NBr, 1.4 g (10 mmol, 5 equiv.) of K_2CO_3 and 480 mg (2 mmol, 1 equiv.) of **60** in DMF (5 mL) was heated to 120 °C overnight. It was quenched with 30 mL of water and extracted with 3 x 10 mL of Et_2O. The combined organic layers were washed with 5 x 30 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5). It yielded 150 mg (50%) of the desired compound as a yellow oil.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.26-7.21 (m, 1H); 7.15-7.14 (m, 1H); 6.86-6.83 (m, 1H); 6.63-6.61 (m, 1H); 3.19 (s, 2H); 2.88 (s, 3H); 1.44 (s, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 152.1; 139.3; 127.6; 121.6; 118.0; 107.4; 70.5; 40.4; 36.1; 27.5.

I.R. (film, cm^{-1}): 2960; 1610; 1490.

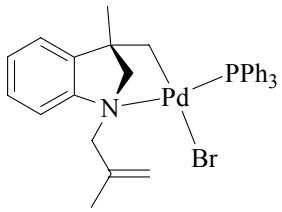
MS (EI, 70 eV): 161 (M^+, 20); 146 (100); 131 (35).

$C_{11}H_{15}N$ **HRMS**: Calcd. 161.1200 (M^+).

Found 161.1202 (M^+).

2.3.4. Preparation of complexes

Bromo (*N*-allyl-3-methyl-indolin-3-yl-methyl-C,N) triphenylphosphine palladium **(68a)**



To a mixture of 40 mg (0.2 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 130 mg (0.5 mmol, 0.5 equiv.) of PPh_3, 460 mg (1.3 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 700 mg (5 mmol, 5 equiv.) of K_2CO_3 were added 280 mg (1 mmol, 1 equiv.) of **59** dissolved in DMF (10 mL). The mixture was heated to 120 °C for 36 h. It was quenched with 30 mL of water and extracted with 3 x 15 mL of Et_2O. The organic layer was washed with 5 x 30 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 95/5 to 1/1). It yielded 210 mg (75%) of unreacted starting material and 110 mg (15%) of the complex as a light yellow cristalline solid.

m.p.: 168-175 °C.

N.M.R.:

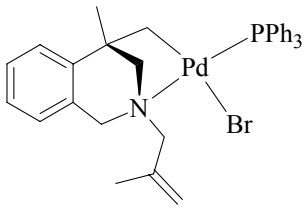
^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.38-7.12 (m, 16H); 7.00-6.98 (m, 2H); 5.10 (d, *J* = 12.6 Hz, 1H); 5.01 (m, 2H); 3.40 (dd, *J* = 6.3 Hz, *J* = 12.6 Hz, 1H); 3.31 (d, *J* = 7.5 Hz, 1H); 2.76-2.73 (m, 1H); 2.19 (s, 3H); 1.54 (dd, *J* = 1.8 Hz, *J* = 9.3 Hz, 1H); 1.26-1.18 (m, 1H); 1.22 (s, 3H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 148.8; 143.4; 139.4; 133.6 (d, *J* = 7.5 Hz); 130.0 (d, *J* = 53 Hz); 129.2; 126.8 (d, *J* = 7.5 Hz); 126.4; 121.9; 119.0; 116.2; 113.1; 73.0; 58.6; 56.6; 46.2; 22.5; 15.5.

I.R. (KBr, cm^{-1}): 3440; 3050; 2950; 1650; 1430; 1090.

MS (EI, 70 eV): 648 ($[M+H]^+$, ^{79}Br, 2); 568 (41); 262 (100); 200 (53); 183 (65); 144 (29).

$C_{32}H_{33}BrNPPd$ **HRMS**: Calcd. 647.0568 (M^+, ^{79}Br).
Found 647.0568 (M^+, ^{79}Br).

Bromo (*N*-allyl-4-methyl-tetrahydroisoquinolin-4-yl-methyl-C,N) triphenylphosphine palladium **(69)**



To a mixture of 120 mg (0.5 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 420 mg (1.5 mmol, 0.4 equiv.) of PPh_3, 1.38 g (4 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 2.1 g (15 mmol, 5 equiv.) of K_2CO_3 were added 900 mg (3 mmol, 1 equiv.) of **61** dissolved in DMF (5 mL). The solution was heated to 120 °C overnight. It was quenched with 20 mL of water and extracted with 3 x 5 mL of Et_2O. The combined organic layers were washed with 5 x 20 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane/Et_2O, 100/0 to 1/1). It afforded 720 mg (80%) of unreacted starting material and 230 mg (15%) of the complex as a light yellow solid.

m.p.: 220-225 °C (dec.).

N.M.R.:

^{1}H ($CDCl_3$, 600 MHz) δ(ppm): 7.27-7.15 (m, 18H); 7.10-7.08 (m, 1H); 5.22 (s, 1H); 5.11 (d, *J* = 14.4 Hz); 5.09 (s, 1H); 4.69 (d, *J* = 12.6 Hz, 1H); 3.60 (dd, *J* = 5.4 Hz, *J* = 15 Hz, 1H); 3.01-2.99 (m, 1H); 2.88 (dd, *J* = 5.4 Hz, *J* = 6.6 Hz, 1H); 2.45 (s, 3H); 2.20 (dt, *J* = 3 Hz, *J* = 10.8 Hz, 1H); 1.48 (m, 2H); 1.14 (s, 3H). **^{13}C** ($CDCl_3$, 150 MHz) δ(ppm): 143.7; 139.2; 133.4 (d, *J* = 12 Hz); 132.0; 130.8; 130.5; 128.9; 126.9 (d, *J* = 10.5 Hz); 126.1; 125.5; 125.0; 123.4; 117.1; 65.3; 65.1; 61.4; 51.2; 44.8; 22.9; 21.4. **^{31}P** ($CDCl_3$, 81 MHz) δ(ppm): 31.7

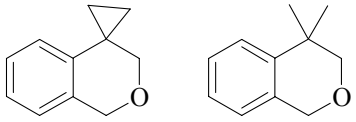
I.R. (KBr, cm^{-1}): 3440; 3050; 2960; 1640; 1440; 1100.

MS (FAB, 20 kV): 662 ($[M+H]^+$, ^{79}Br, 1); 582 (100); 367 (12); 263 (11); 214 (64); 198 (19).

$C_{33}H_{35}BrNPPd$ **HRMS**: Calcd. 661.0725 (M^+, ^{79}Br).
Found 661.0733 (M^+, ^{79}Br).

2.3.5. Preparation of O-containing heterocycles

1′,2′-Dihydrospiro-[cyclopropane-1,3′-benzo[*c*]pyrane] **(71a)** and 4,4-dimethyl-benzo[*c*]pyrane **(71b)**



To a mixture of 120 mg (0.5 mmol, 0.2 equiv.) of $Pd(OAc)_2$, 420 mg (1.5 mmol, 0.4 equiv.) of PPh_3, 1.38 g (4 mmol, 1.3 equiv.) of *n*-Bu_4NBr and 2.1 g (15 mmol, 5 equiv.) of K_2CO_3 were added 720 mg (3 mmol, 1 equiv.) of **58** dissolved in DMF (5 mL). The solution was heated to 120 °C overnight. It was quenched with 20 mL of water and extracted with 3 x 5 mL of Et_2O. The combined organic layers were washed with 5 x 20 mL of water, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (pentane). It yielded 360 mg (50%) of unreacted starting material, 160 mg (30%) of **71a** as a colourless solid and 80 mg (15%) of **71b** as a colourless oil.

Data for **71a**:

m.p.: 32-34 °C.

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.06-7.00 (m, 2H); 6.89-6.86 (m, 1H); 6.64-6.61 (m, 1H); 4.80 (s, 2H); 3.62 (s, 2H); 0.95-0.92 (m, 2H); 0.83-0.79 (m, 2H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 138.7; 135.2; 127.4; 125.6; 124.4; 121.7; 74.4; 69.7; 18.9; 16.2.

I.R. (KBr, cm^{-1}): 3070; 2940; 2870; 1460.

MS (EI, 70 eV): 160 (M^+, 43); 131 (100); 117 (20); 104 (54); 101 (62).

$C_{11}H_{12}O$ **HRMS**: Calcd. 160.0889 (M^+).

Found 160.0878 (M^+).

Data for **71b**:

N.M.R.:

^{1}H ($CDCl_3$, 300 MHz) δ(ppm): 7.26-7.23 (m, 1H); 7.15-7.01 (m, 2H); 6.89-6.84 (m, 1H); 4.71 (s, 2H); 3.54 (s, 2H); 1.20 (s, 6H). **^{13}C** ($CDCl_3$, 75 MHz) δ(ppm): 143.3; 133.8; 127.1; 126.1; 126.0; 124.4; 77.3; 69.4; 33.9; 27.8.

I.R. (film, cm^{-1}): 2930; 2880; 1720; 1610; 1490.

MS (EI, 70 eV): 162 (M^+, 57); 147 (41); 132 (100); 117 (37); 103 (37).

$C_{11}H_{14}O$ **HRMS**: Calcd. 162.1045 (M^+).

Found 162.1053 (M^+).

3. Cristallographic Data for Complex 68a

Colour, habitus	Slightly yellow, plates	
Crystal size	0.13 x 0.43 x 0.50 mm^3	
Crystal system	monoclinic	
Space group	$P2_1/C$	
Unit cell dimensions	a = 18.547(5) Å	α = 90.00(0)°
	b = 10.5065(14) Å	β = 114.54(2)°
	c = 16.146(3) Å	γ = 90.00(0)°
Volume	2862.2(10) $Å^3$	
Z	4	
Empirical formula	$C_{32}H_{33}BrNPPd$	
Molecular weight	648.87	
Density (calculated)	ρ = 1.506 $g.cm^{-3}$	
Absorption coefficient	μ = 2.121 mm^{-1}	
F(000)	1312	
Diffractometer type	Nonius Mach3	
Wavelength	λ = 0.71073 Å	
Temperature	22(2) °C	
Theta range for data collection	2.40 to 23.97°	
Index ranges	$-21 \leq h \leq 0$; $0 \leq k \leq 12$; $-16 \leq l \leq 18$	
Scan method	ω-scans	
Scan angle	0.88 + 0.47 tan θ	
Scan time	Max. 60 s	
Reflections collected	4629	
Independent reflections	4466	
Observed reflections	3823 [$I > 2\sigma I$]	
Absorption correction	Semi-empirical from psi-scan	
Refinment method	Full-matrix least squares	
Programs used	SHELXL-93	
	SHELXL-86	
Goodness of fit	1.087	
R index (all data)	ωR2 = 0.0606	
R index conventional [$I>2\sigma I$]	R1 = 0.0269	

Name : Frédéric Liron
Date of Birth: January, 14th 1976
Citizenship: French

EDUCATIONAL BACKGROUND

Since 2000: Ph.D. Thesis at the Ludwig-Maximilians-University (Munich) under the supervision of Prof. KNOCHEL

1998-1999: D.E.A. (Diplomarbeit) in Organic and Bioorganic Chemistry at the University Pierre-et-Marie-Curie (Paris VI) under the supervision of Prof. CAHIEZ and Dr. ALAMI

1993-1998: Chemistry Studies at ESCOM (Ecole Supérieure de Chimie Organique et Minérale), a French "Grande Ecole" in Chemistry.
Degree: Chemical Engineer

1993: End of Secondary School.

RESEARCH AND WORKING EXPERIENCE

Since 2000: Ph.D. under the supervision of Prof. KNOCHEL
Topic: Chirality Transfer in Acyclic Allylic Systems and New Pd-Catalyzed Heck Reaction/C-H Activation Cascades.
Assistant in the Organic Chemistry practical course for undergraduate students at the LMU University Munich.

1999-2000: Research Engineer under the supervision of Prof. CAHIEZ
Topic: Synthesis of Unnatural Aminoacids.

1998-1999: D.E.A. in Organic and Bioorganic Chemistry under the supervision of Prof. CAHIEZ and Dr. ALAMI
Topic: New Palladium / Metal Couples in Organic Synthesis.

1997-1998: 8 month-trainee under the supervision of Prof. CAHIEZ and Dr. ALAMI
Topic: Stereoselective Synthesis of Trisubstituted Olefins.

PUBLICATIONS

1. F. Liron; P. Le Garrec; M. Alami: " Regiochemical Control in the Hydrostannylation of Aryl-Substituted Alkynes. A Stereoselective Synthesis of Disubstituted Vinylstannanes" *Synlett* **1999**, 246.
2. M. Alami; F. Liron; M. Gervais; J.-F. Peyrat; J.-D. Brion: " Ortho Substituents Direct Regioselective Addition of Tributyltin Hydride to Unsymmetrical Diaryl (or Heteroaryl) Alkynes: an Efficient Route to Stannylated Stilbene Derivatives" *Angew. Chem*. **2002**, *114*, 1648; *Angew. Chem. Int. Ed.* **2002**, *41*, 1578.

3. F. Liron; M. Gervais; M. Alami; J.-F. Peyrat;J.-D. Brion: " Palladium-Catalyzed Stereoselective Synthesis of (E)- and (Z)- 1,1- Diaryl or Triarylolefins" *Tetrahedron Lett*. **2003**, *44*, 2789.
4. F. Liron; P. Knochel: " Stereoselective [2,3] Sigmatropic Rearrangement of acyclic Allylic Phosphinites " *Chem. Commun*., **2004**, 304.

POSTERS

1. M. Alami; F. Ferri; F. Liron; M. Gervais; J.-F. Peyrat; J.-D. Brion, Journées de Chimie Organique (Palaiseau, France, **2001**) Poster A3: " Recent Advances on Regioselective Hydrostannation of Unsymmetrical Alkynes".
2. P. Knochel; F. Liron; A. Gavriouchine, Annual Congress of the GDCh (Munich, **2003**) Poster ORG-ALL 006:" Enantioselective [2,3] Sigmatropic Rearrangement of Allylic Phosphinites".
3. H. Leuser; F. Liron; F. F. Kneisel; P. Knochel, Annual Congress of the GDCh (Munich, **2003**) Poster ORG-ALL 137:" Enantioselective Copper-Mediated Allylic Substitutions: An Efficient Method for the Preparation of Enantiomerically Enriched Quaternary Centers".

LANGUAGES

French: mother tongue
English: fluent
German: basic level

München, den 15.06.2004