UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

1. Introduction

The growing demand for enantiomerically pure compounds for the development of pharmaceuticals, agrochemicals and flavors has captured the interest of the chemist in the last few decades. Of the various methods for producing enantiopure compounds, enantioselective homogeneous metal catalysis is an attractive one, as is reflected by the many publications in this field and the award of the Nobel Prize in 2001 to W.S. Knowles, R. Noyori and K. B. Sharpless.[1] One of the main advantages of asymmetric catalysis over other methods used in asymmetric synthesis is that products can be selectively synthesized from cheap, commercially available prochiral starting materials without undesirable products being formed. Usually with this strategy, a transition-metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate to one enantiomer as major product.

To reach the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters must be optimized. Of these, the selection and design of the chiral ligand is perhaps the most crucial step. One of the simplest ways to obtain chiral ligands is to transform or derivatize natural chiral compounds, thus making tedious optical-resolution procedures unnecessary. Carbohydrates have many advantages: they are readily available, are highly functionalized and have several stereogenic centers. This enables series of chiral ligands to be synthesized and screened in the search for high activities and selectivities for each particular reaction. This tuning of the ligand structure allows for a rational design of ligands, which provides valuable information about the origin of the selectivity. One of the main limitations of using natural products as precursors for ligands is that often only one of the enantiomers (in the case of carbohydrates, the D-series) is readily available. However, this limitation can be overcome by using pseudo-enantiomer ligands or by suitable ligand tuning.[2]

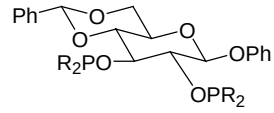
In this context, this thesis focuses on the development of new chiral ligand libraries derived from carbohydrates, the synthesis of new catalyst precursors and their application in the Pd-catalyzed asymmetric allylic substitution, Pd-catalyzed asymmetric Heck reactions, Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes, and Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones. In next section, we collect the most important carbohydrate-derivative ligand families developed for metal-catalyzed asymmetric reactions. The following sections describe the background of each of the asymmetric catalytic reactions studied in this thesis.

1.1. Carbohydrate ligands' background in asymmetric catalysis

Despite the advantages of carbohydrates, their systematic use as chiral auxiliaries in asymmetric catalysis has not been considered until recently. Nowadays, many type of carbohydrate ligands have been successfully applied in several catalytic asymmetric reactions (mainly in asymmetric hydrogenation).[2] A review of the research into carbohydrate ligands highlighted four main carbohydrate derivative ligand families:

- The first important family is the pyranoside diphosphinite ligands **1** derived from D-glucose (Figure 1) mainly developed by the groups of Selke and Rajanbabu. These ligands were the first successful application of diphosphinite ligands in asymmetric catalysis. They were applied with excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of dehydroaminoacids (ee's up to 99%)[3] and in the Ni-catalyzed asymmetric hydrocyanation of vinylarenes (ee's up to 91%).[4]

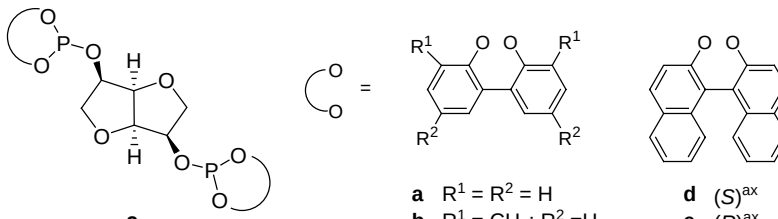
UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007



1

Figure 1. Diphosphinite pyranoside ligands.

- The second family is the C_2-diphosphite ligands **2** derived from D-mannitol. These ligands, developed by Reetz and coworkers, were successfully applied in the asymmetric hydrogenation of dehydroaminoacid derivatives (ee's up to 98%).[5]



2

a $R^1 = R^2 = H$
b $R^1 = CH_3$; $R^2 = H$
c $R^1 = R^2 = {}^tBu$
d $(S)^{ax}$
e $(R)^{ax}$

Figure 2. Diphosphite ligands derived from D-mannitol.

- The third important series of sugar derivative ligands in asymmetric catalysis is the 1,2-protected furanoses derived from D-(+)-xylose and D-(+)-glucose (Figure 3). These ligands were successfully applied in several asymmetric catalytic processes. It is to note the diphosphine ligand **3**[6], the phosphine-phosphite **4**[7] and phosphite-phosphoroamidite ligand **5**[8], derived from D-(+)-xylose and the diphosphite ligands **6**[9] and **7**[10] derived from D-(+)-glucose.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0175-0/DL:T-2193-2007

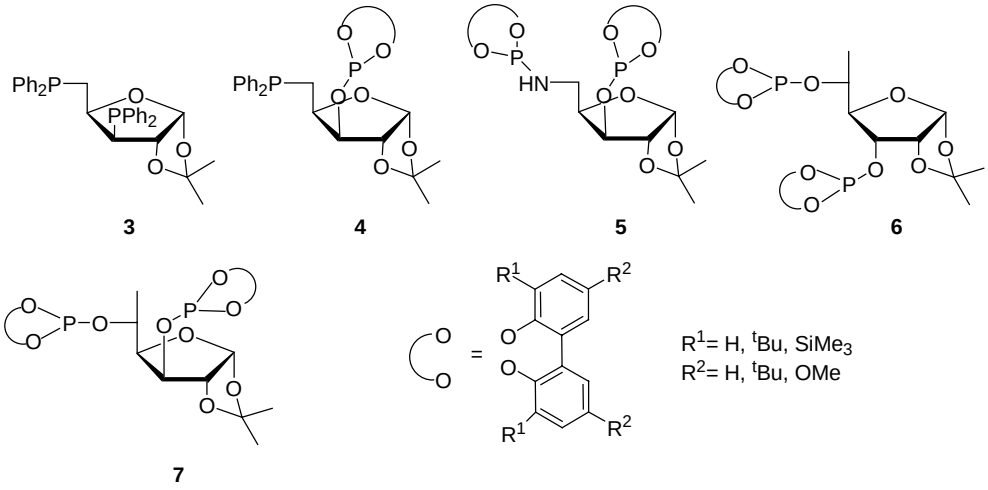


Figure 3. Carbohydrate ligands with furanoside backbone.

- The last important family of carbohydrate ligands are the phospholane ligands derived from D-mannitol **8-13** (Figure 4). In the last few years, these ligands have emerged as a powerful new class of ligands for asymmetric hydrogenation (ee's up to 99%)[11] and for asymmetric allylic substitution (ee's up to 99%)[12] reactions.

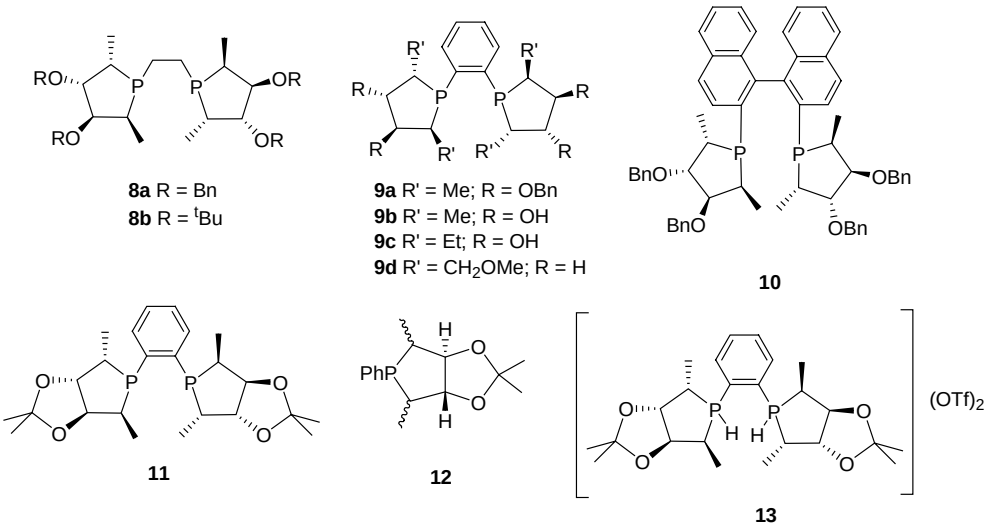


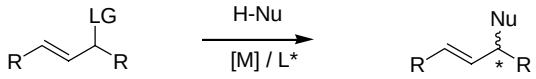
Figure 4. Phospholane ligands derived from D-mannitol.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

1.2. Asymmetric allylic substitution

Palladium-catalyzed asymmetric allylic substitution is one of the catalytic homogenous reactions that have attracted most attention in recent decades. This is mainly because this process is an efficient synthetic tool for the formation of carbon-carbon and carbon-heteroatom bonds. The mild reaction conditions, the compatibility with many functional groups and the often high enantioselectivities make this method attractive for application in the synthesis of complex natural products or pharmaceuticals.[1c,13]

In this process, an allyl acetate or carbonate is attacked by a nucleophile (typically, a carbon or nitrogen nucleophile). Therefore, a nucleophilic substitution takes place and either a new carbon-carbon bond (allylic alkylation, Scheme 1(a)) or a new carbon-nitrogen bond is generated (allylic amination, Scheme 2(b)).[1c,13]



(a) H-Nu= H-CH(COOMe)$_2$
(b) H-Nu= H-NHCH$_2$Ph

Scheme 1. Asymmetric allylic substitution reactions: (a) Dimethyl malonate (alkylation) and (b) Benzylamine (amination). LG = leaving group.

The range of substrates (linear and cyclic) tested is quite wide. However, *rac*-(*E*)-1,3-diphenylprop-2-enyl (Figure 5, R = Ph, LG = OAc) has been the substrate of choice for testing a new ligand. With regard to the metal source, a variety of transition metal complexes derived from Pd, Ni, Ru, Rh, Ir, Mo, W and other elements are known to catalyze allylic substitutions.[1c] However, the most widely used catalysts are palladium complexes. A wide range of carbon and heteroatom *soft* nucleophiles (those derived from conjugate acids with pKa < 25) have been employed in this process. Besides dimethyl malonate, which has become

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0175-0/DL:T-2193-2007

the standard nucleophile for testing new catalysts, many other stabilized carbanions bearing carbonyl, sulfone, nitrile or nitro groups have also been used. There are only a few examples of enantioselective reactions with *hard* nucleophiles such as diorganozinc or Grignard reagents.[1c]

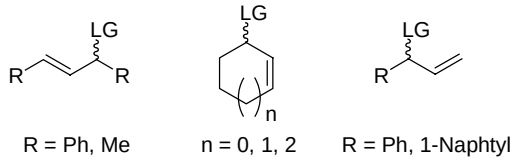


Figure 5. The most common substrates for the enantioselective allylic substitution.

1.2.1. Mechanism

The mechanism of the palladium-catalyzed asymmetric allylic substitution, with *soft* nucleophiles, is well established (Figure 6).[1c] This is partly due to the relative ease of isolating catalytic intermediates, especially the palladium allylic species **17**, although some related Pd(0) species **18** have also been characterized in solution.

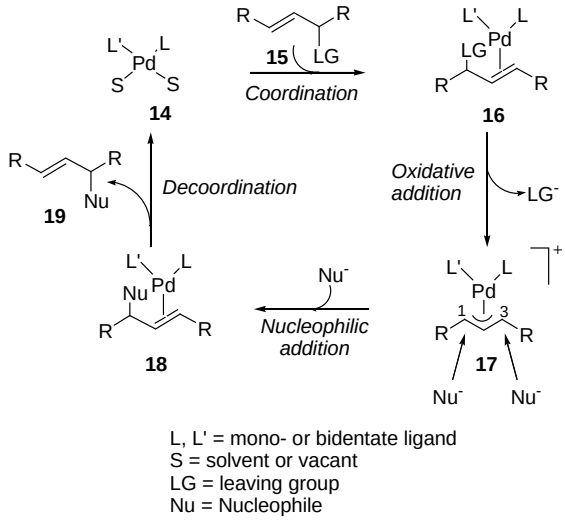


Figure 6. Catalytic cycle for the Pd-catalyzed allylic substitution with *soft* nucleophiles.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

The first step in the catalytic cycle is the coordination of an allylic substrate **15** to the catalyst precursor **14**, which enters the cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes (e.g. $Pd_2(dba)_3$, $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$, dba= dibenzylideneacetone) can be used as precatalysts because Pd(II) is easily reduced *in situ* by the nucleophile to the Pd(0) form. In the next step, the cationic π-complex **16** eliminates LG^- to produce the (η^3-allyl)palladium(II) complex **17**. This is the rate-determining step of the reaction. The product of this oxidative addition has two susceptible positions for receiving nucleophilic attack (C-1 and C-3). After nucleophilic addition, an unstable Pd(0)-olefin complex **18** is produced, which readily releases the final product **19**.

It is generally accepted that the enantioselectivity of the process is controlled by the external nucleophilic attack on the more electrophilic terminal allylic carbon of **17**. Therefore, the allyl complex **17** plays a central role as a key intermediate in the catalytic cycle, which can be isolated in the absence of nucleophiles. Allyl complexes can show dynamic behavior in solution, which results in a mixture of isomers (Figure 7).

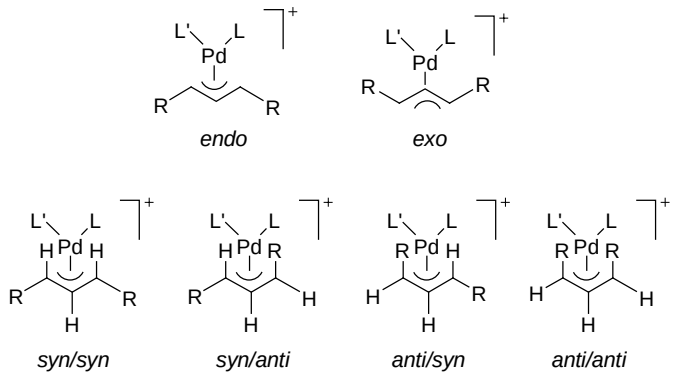


Figure 7. Possible isomers adopted by the Pd-allyl complexes.

To achieve high ee's, the formation of a single isomer is necessary if we assume that the reaction rates are similar for all possible isomers.[1c,13] Both the

oxidative addition leading to **17** and the subsequent nucleophilic attack normally occur stereoselectively with inversion of configuration at the reacting allylic carbon atoms. Therefore, if the intermediate allyl complex does not undergo any isomerization that changes its configuration, the overall process **14** to **19** proceeds with the retention of configuration, i.e. the nucleophile is introduced at the same side of the allyl plane that was occupied by the leaving group LG.

1.2.2. Ligands

Since the first enantioselective catalytic process described by Trost in 1977, with moderate enantioselectivity,[14] many catalytic systems have been tested. These have provided excellent enantiomeric excesses.[1c,13]

Unlike asymmetric hydrogenation process, few diphosphines have provided good enantioselectivities in allylic substitutions. Though high ee's could be obtained in certain cases for instance, with BINAP and CHIRAPHOS (Figure 8), the scope of standard diphosphines in this process seems limited.[1c,13]

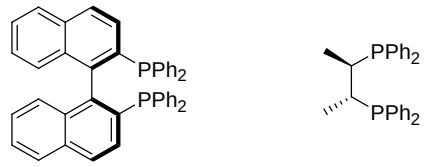


Figure 8. BINAP and CHIRAPHOS ligands.

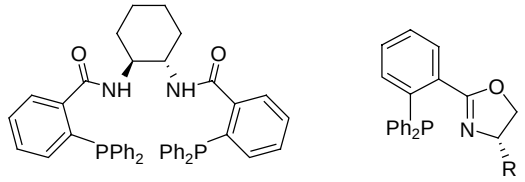
However, one of the most versatile ligands for this process is a diphosphine **20** developed by Trost (Figure 9).[13b,15] The remarkable properties of this ligand are related to the bite angle, which is larger than in unstrained Pd-diphosphine complexes. Consequently, the P-aryl groups generated a chiral cavity, in which the allyl system is embedded, that provides high ee's for several sterically

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

undemanding substrates. For diphosphines and other homodonor systems, the chiral discrimination is therefore induced by the C_2 or C_1 backbone of the ligand.

The selection of chiral ligands for highly enantioselective allylic substitution has mainly focused on the use of mixed bidentate donor ligands such as phosphorus-nitrogen, phosphorus-sulfur and sulfur-nitrogen.[1c,16] In this context, the phosphinooxazoline PHOX ligands represent, together with Trost's ligand, one of the most representative ligands developed for this process (Figure 9).[17] The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms that predominantly produced the nuclephilic attack at one of the allyl carbon atoms (the one located *trans* to the best π-acceptor).

Other ligands, such as bidentate nitrogen and sulfur, have also exhibited very good catalytic behavior.[1c,16]



20

Trost's ligand PHOX ligands

Figure 9. Two of the most representative ligands developed for the Pd-catalyzed allylic substitution reactions.

Carbohydrate ligands have only recently shown their huge potential as a source of highly effective chiral ligands in this process. Several types of ligands, mainly heterodonors, have been developed for this process and some of the results are among the best ever reported.[2]

In the next section we summarize the most relevant catalytic data published for the Pd-catalyzed allylic substitution with carbohydrate ligands.

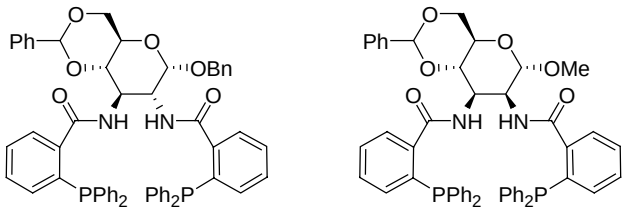
UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0175-0/DL:T-2193-2007

1.2.2.1. P-donor ligands

Phosphine Ligands

The most successful carbohydrate family of phosphine ligands was developed by RajanBabu and Zhang. These authors have independently reported the use of diphospholanes ligands **10** and **11** and monophospholane ligand **12**, derived from D-mannitol, in the Pd-catalyzed allylic alkylation of dimethyl malonate to (*E*)-1,3-diphenylprop-2-enyl acetate (ee's up to 99%, Figure 4).[12] In general, high enantioselectivies have been achieved. Interestingly, the sense of asymmetric induction appears to be dictated by the absolute stereochemistry of the P-carrying carbons. Both enantiomers of the product can therefore be obtained.

In 2006, Ruffo and coworkers developed a modification of the Trost-bis(phosphinoamides) ligands[15] using diamines based on glucose and mannose as chiral auxiliaries (Figure 10, ligands **21** and **22**) for the highly enantioselective Pd-catalyzed desymmetrization of meso-cyclopenten-2-ene-1,4-diol biscarbamate (ee's up to 97%). Interestingly both enantiomers of the product can be obtained in high enantioselectivities by switching from glucose (**21**) to mannose (**22**) derivative ligands.[18]



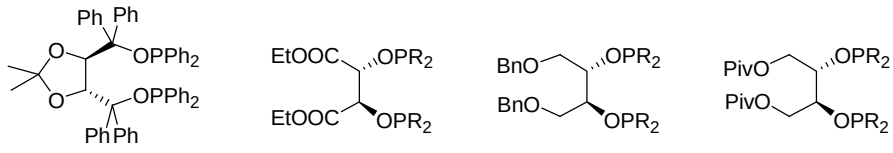
21 (97% (-)) **22** (97% (+))

Figure 10. Bis(phosphinoamides) **21** and **22** developed by Ruffo and coworkers.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Phosphinite Ligands

In 1995, Seebach and coworkers first prepared C_2-symmetric diphosphinite **23** from TADDOL, tested it in the asymmetric allylic substitution and obtained enantiomeric excesses of up to 76% (Figure 11).[19] Subsequently, RajanBabu and coworkers tested the previously mentioned ligands **1** (Figure 1) and ligands **24-26** (Figure 11), derived from tartaric acid, in the Pd-catalyzed asymmetric allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate with low-to-good enantioselectivities.[20] For ligands **1**, the best enantioselectivity (59% ee) was achieved with the ligand containing cyclohexenyl as substituent R.[20a] Interestingly, electron-withdrawing and electronic-rich diphosphinite ligands lead to products with opposite stereochemistry. Moreover, sterically bulky substituents have the same effect as electron-rich ones. For diphosphinite ligands **24-26**, the electronic effects were similar to those with ligands **1**, but enantioselectivities were up to 77% (Figure 11).[20b]



23 **24** **25** **26**

Figure 11. Diphosphinite **23-26** ligands applied in asymmetric allylic substitution.

Phosphite Ligands

In 2001, it has been reported the first diphosphite ligands family applied to Pd-catalyzed asymmetric allylic substitution reactions (Figure 12).[10d,e,21] These furanoside diphosphite ligands **27-33** (Figure 12) were successfully applied in the Pd-catalyzed allylic substitution of diethyl malonate and benzylamine to several acyclic and cyclic allylic esters (Figure 13).

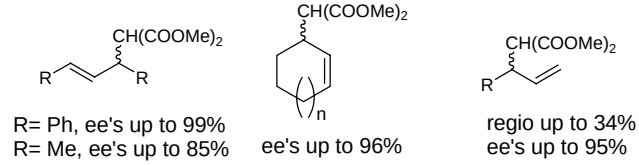


Figure 13. Acyclic and cyclic allylic esters tested with ligands **27-33**.

Results indicated that activities were best when the substituent at C-5 was Me and when the ligand contained bulky substituents at the *ortho* positions and electrodonating substituents at the *para* positions of the biphenyl moieties (i.e., **b**~**c**>**d**>**a**). Enantioselectivities were affected by the substituent at C-5 and the phosphite moieties and by the configuration of carbon atoms C-3 and C-5 and the configurations of the biaryl moieties. Enantioselectivities were best with ligand **30c**, which has a glucofuranoside backbone and bulky *tert*-butyl substitutents at both *ortho* and *para* positions of the biphenyl moieties. The results also indicated that the nucleophilic attack takes place *trans* to the carbon atom C-5. Ligand **27c** was also used to stabilize Pd-nanoparticles. These particles catalyzed the allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate leading to an almost total conversion of the (*R*) enantiomer and almost no reaction with the (*S*). This gives rise to 97% ee for the alkylation product and a kinetic resolution of the substrate recovered with ca. 90% ee.[22]

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

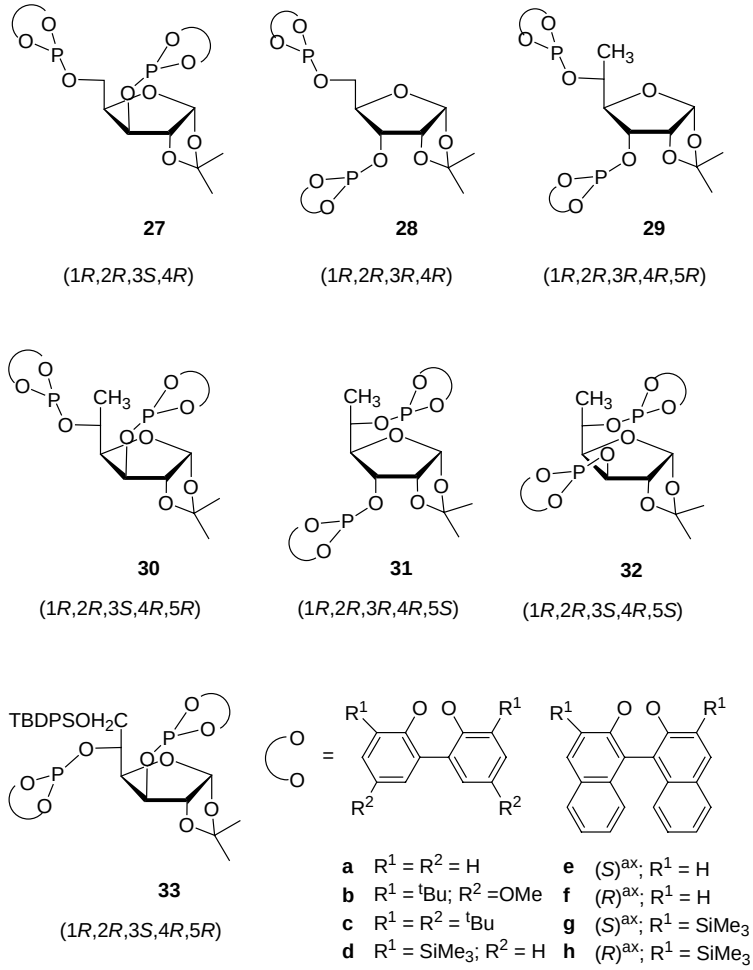


Figure 12. Furanoside diphosphite ligands **27-33**.

Phosphoroamidite Ligands

During the last decades, there has been a huge advance in the use of phosphoroamidite ligands for several asymmetric processes.[23] However, to best our knowledge only one family of diphosphoroamidite ligands **34** based on carbohydrates has been successfully applied in asymmetric catalysis (Figure 14).[24] Good-to-excellent activities (TOF's up to 850 mol substrate x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 95%) have been obtained in the Pd-catalyzed allylic alkylation for several di- and monosubstituted linear and cyclic substrates. The

results indicate that catalytic performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. The study of the 1,3-diphenyl and cyclohexenyl Pd-π-allyl intermediates indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety attached to C-5.

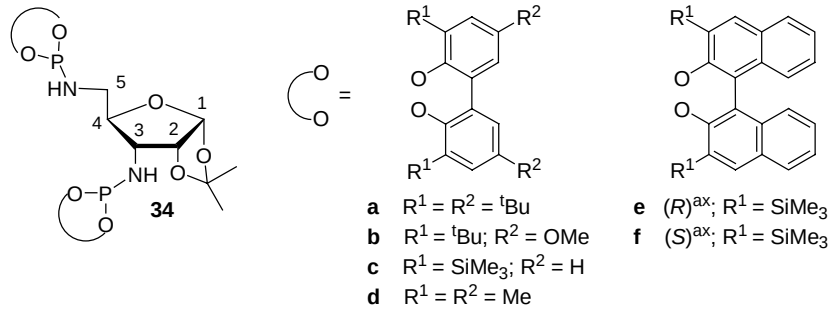


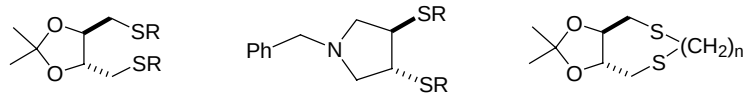
Figure 14. Diphosphophoroamidite ligands **34**.

1.2.2.2. S-donor ligands

Sulfur donor ligands have been used much less than phosphorus ligands in this process because a mixture of diastereomers can be obtained upon coordination of the thioether ligand to the metal, which can lead to a decrease in stereoselection if the relative rates of the intermediates are similar. Despite this, high enantiomeric excesses have been achieved.[16]

Among ligand backbones based on tartaric acid **35-37** (Figure 15), the five-membered ligand **36a** afforded the best enantioselectivity 81% (*S*) in the allylic substitution of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[25]

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007



35 R = ^{i}Pr (27% (*S*)) **36a** R = Ph (81% (*S*)) **36b** R = ^{i}Pr (30% (*S*)) **37a** n = 2 (13% (*S*)) **37b** n = 3 (42% (*S*))

Figure 15. Dithioether ligands **35**-**37**.

Recently, Khiar and coworkers used a combinatorial approach to find the best dithioether ligand **38** (Figure 16) from a library of 64 potential ligands (four linkers x four sugar residues x four protective groups) for the Pd-catalyzed allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate (ee's up to 90%).[26a] In the search for both enantiomers of the alkylation product, the authors successfully prepared pseudo-enantiomers **39** and **40** derived from D-galactose and D-arabinose, respectively (Figure 16).[26b]

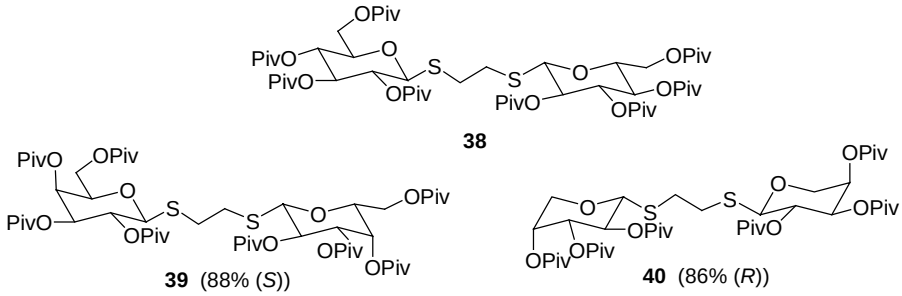


Figure 16. Dithioether ligands **38**-**40**.

1.2.2.3. Heterodonor Ligands

P-S ligands

Several combinations of P,S-donor ligands such as phosphine-thioether, phosphinite-thioether, phospholane-thioether, phosphine-oxathiane and phosphite-thioether have been studied. In particular, the phosphine-thioether, phosphinite-

thioether and phosphine-oxathiane have proven to be effective in enantioselective Pd-catalyzed allylic substitutions.

The ferrocenylphosphine-thiosugar ligand **41** (Figure 17) with multiple stereogenic units afforded an ee of 88% in the palladium allylic substitution of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[27a] However, when the thiosugar moiety was the sole stereogenic unit on ligand **42** (Figure 17), enantioselectivities were only moderate (ee's up to 64%).[27b]

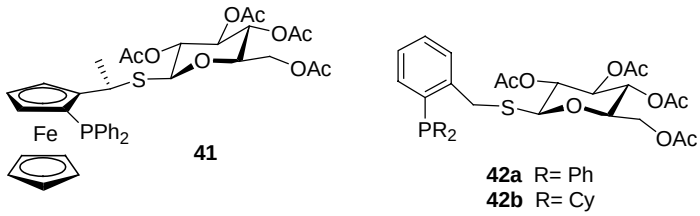
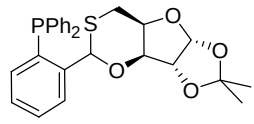


Figure 17. Thiother-phosphine ligands **41** and **42**.

In 2003, a phosphine-oxathiane ligand **43**, derived from D-(+)-xylose, has been developed for the Pd-catalyzed allylic substitution reactions (Figure 18). Good enantioselectivities have been obtained in the addition of dimethyl malonate and benzylamine to 1,3-diphenylprop-2-enyl acetate (ee's up to 91% and 94%, respectively).[28]



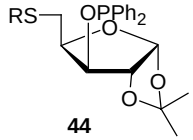
43

Figure 18. Phosphine-oxathiane ligand **43**.

More recently, a series of phosphinite-thioether ligands with furanoside backbone **44a-g** (Figure 19) were applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates (ee's up to 95%).[29] These

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

ligands contained several thioether substituents with different electronic and steric properties. The authors found that this group had an important effect on catalytic performance. Thus, enantioselectivities were best when the bulkiest ligands **44c-d** were used.

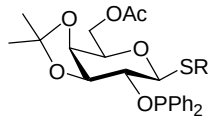


44

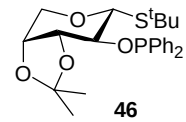
a R = Ph; **b** R = Me; **c** R = ^{i}Pr; **d** R = ^{t}Bu;
e R = 4-Me-C_6H_4; **f** R = 4-CF_3-C_6H_4;
g R = 2,6-di-Me-C_6H_3

Figure 19. Phosphinite-thioether ligands **44**.

At the same time, simple phosphinite-thioether ligands **45** and **46** with pyranoside backbones (Figure 20) were successfully applied in Pd-catalyzed allylic substitution of 1,3-diphenyl-prop-2-enyl acetate (ee's up to 96%). Enantioselectivities were best when bulky *tert*-butyl substituents were present in the thioether moiety. Both enantiomers of the products were obtained by using pseudo-enantiomeric ligands **45a** and **46**.[30]



45



46

a R = ^{t}Bu; **b** R = 2-OMe-C_6H_4;
c R = 4-Me-C_6H_4

Figure 20. Phosphinite-thioether ligands **45**-**46**.

P-N ligands

Several types of P,N-donor carbohydrate ligands have been developed for use in Pd-asymmetric allylic substitutions.[31,32] In particular, many phosphorus-oxazoline ligands have produced excellent results.

Kunz and coworkers developed a phosphine-oxazoline ligand **47** derived from D-glucosamine for the Pd-catalyzed allylic alkylation of dimethyl malonate to symmetrically and non-symmetrically substituted allyl acetates with high enantioselectivities (ee's up to 98%) (Figure 21).[32e] These results are in line with a nucleophilic attack *trans* to the phosphorus atom.

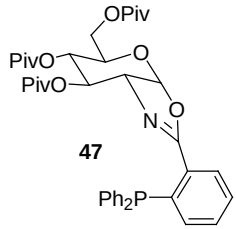
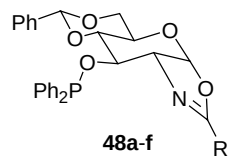


Figure 21. Phosphine-oxazoline ligand **47** developed by Kunz and coworkers.

Uemura and coworkers developed a series of phosphinite-oxazoline ligands **48** also derived from D-glucosamine for the Pd-catalyzed allylic substitution reactions (Figure 22).[32f,g] These ligands showed high enantioselectivity in the 1,3-diphenylprop-2-enyl acetate, but enantioselectivites were low-to-moderate for unhindered linear and cyclic substrates. The results of the allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate indicated that the best enantioselectivity was obtained with the smallest substituent on oxazoline (R= Me, ligand **48a**). Their results also indicate that the nucleophilic attack took place *trans* to the phosphorus atom thought and *endo* π-allyl Pd-intermediate.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

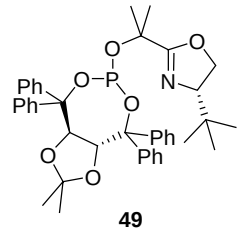


48a-f

	R	%ee
a	Me	96 (*S*)
b	^{i}Pr	90 (*S*)
c	^{i}Bu	95 (*S*)
d	^{t}Bu	83 (*S*)
e	Ph	94 (*S*)
f	Bn	78 (*S*)

Figure 22. Phosphinite-oxazoline ligands **48**. This figure shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.

Pfaltz and coworkers used the phosphite-oxazoline ligand **49** (Figure 23) for the Pd-catalyzed allylic alkylation of several substrates.[31] This ligand showed good enantioselectivities in the reaction of 3-aryl-2-propenyl acetates (ee's up to 94%), whereas enantioselectivity was low in the reaction of 1,3-diphenylprop-2-enyl acetate (ee's up to 20%).



49

Figure 23. Phosphite-oxazoline ligand **49**.

In 2005 Framery and coworkers developed phosphine-amide ligands **50**-**52** (Figure 24) derived from D-glucosamine for the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The results clearly showed a cooperative effect between stereocenters that resulted in a matched combination for ligand **51** (ee's up to 86%).[33]

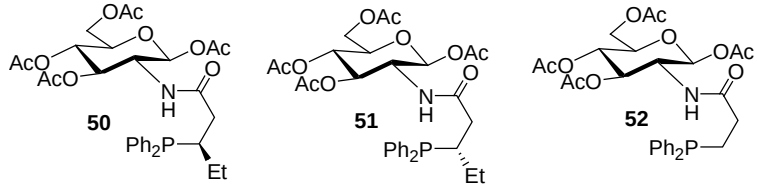


Figure 24. Phosphite-oxazoline ligand **50**-**52**.

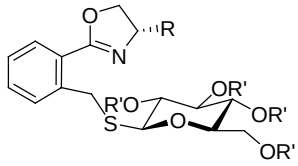
P-P' ligands

The first successful family of P-P' carbohydrate ligands were the phosphite-phosphoroamidite ligands **5**, derived from D-xylose (Figure 3).[8b] They were successfully applied in the Pd-asymmetric allylic substitution (ee's up to 98%). Interestingly, this ligand family also provides high activity (because of the high π-acceptor capacity of the phosphoroamidite moiety) and enantioselectivities in different substrate types (mono- and disubstituted linear and cyclic substrates), which overcomes the most important limitations of the most successful catalytic systems for this process such as, low reaction rates and the high substrate specificity.

N-S ligands

Thioglucose-derived ligands **53a-d**, containing a chiral oxazoline moiety (Figure 25), used as ligands in the palladium-catalyzed allylic alkylation of diphenylprop-2-enyl acetate have provided some of the best results achieved in this reaction with mixed N,S-donor ligands.[34] The effects of the thiosugar substituents on enantioselectivity were mild. The success of this kind of system seems to lie in the combination of thiosugar function and the proximity of all stereogenic units to the palladium allylic fragment, because the Pd-N distance is shorter than the Pd-P distance in related phosphino-thiosugar palladium complexes.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007



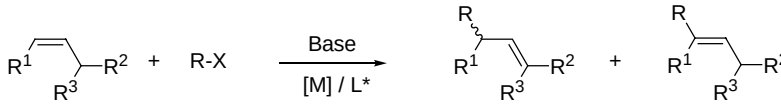
53a-d

	R	R'	% ee
a	^{i}Pr	C(O)Me	93 (*S*)
b	^{i}Pr	C(O)^{t}Bu	97 (*S*)
c	Ph	C(O)Me	90 (*S*)
d	Ph	C(O)^{t}Bu	96 (*S*)

Figure 25. Phosphinite-oxazoline ligands **53**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.

1.3. Asymmetric Heck reaction

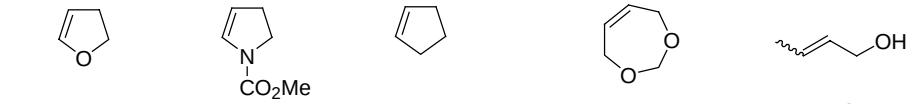
The asymmetric Heck reaction generally referred to the palladium mediated coupling of aryl or vinyl halides or triflates with alkenes in the presence of base has become one of the most versatile methods for C-C bond formation (Scheme 2). This process has found extensive applications in asymmetric synthesis. Shibasaki and Overman have convincingly demonstrated the value of such transformation in the synthesis of complex natural molecules.[1c,35]



Scheme 2. Pd-catalyzed Heck reaction. X= Halide or triflate.

Heck reaction has been know to synthetic chemists since the late 1960's. However, reports of successful examples of the asymmetric Heck reaction were published at the end of the 1980's. The bulk of the reported examples involve intramolecular reactions, which have the advantage of allowing easy control of alkene regiochemistry and geometry in the product.[1c] In contrast, successful intermolecular reactions have until very recently been limited to quite reactive substrates, principally O-,N- heterocycles, which again simplifies the question of alkene regiochemistry.[1c,35] Nowadays several substrates have been applied in the

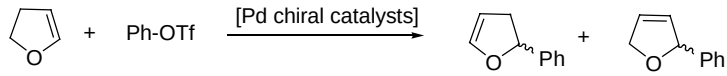
intermolecular asymmetric Heck reactions. Most of them are cyclic substrates, such as, enol ethers, dihydropyrroles, dihydrodioxepins and alkenes (Figure 26). Traditionally, 2,3-dihydrofuran has been the substrate of choice for testing a new ligand. With regard to aryl or vinyl source, a variety of triflate compounds have been applied. However, the most widely used is phenyltriflate. The base is also an important parameter for high catalytic activity and enantioselectivity. A wide range of base have been employed in this process, being *N*,*N*-diisopropylamine and proton sponge the standard bases for testing new catalysts.[1c,35]



54 2,3-dihydrofuran; **55** 2,3-dihydropirrol; **56** cyclopentene; **57** 4,7-dihydro-1,3-dioxepin; **58** crotyl alcohol

Figure 26. The most common substrates for the intermolecular asymmetric Heck reaction.

It should be noted that in the asymmetric intermolecular Heck reaction it is not only the enantioselectivity of the process that needs to be controlled, the regioselectivity is also a problem, because a mixture of regioisomers can be obtained. So, for example, in the Heck reaction of 2,3-dihydrofuran **54** with phenyl triflate, a mixture of two products is obtained - product 2-phenyl-2,3-dihydrofuran (**59**) and the expected 2-phenyl-2,5-dihydrofuran (**60**; Scheme 3). The former is formed due to an isomerization process (see Section 1.2.1.).[1c,35]



54 **59** **60**

Scheme 3. Model Pd-catalyzed intermolecular Heck reaction.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

1.3.1. Mechanism

Figure 27 illustrates a proposed catalytic cycle for the phenylation reaction of 2,3-dihydrofuran.[1c,35,36] The catalytic cycle starts with the oxidative addition of the organic triflate to a Pd(0)-complex **61** to produce compound **62**. Since the triflate ligand in **62** is a good leaving group, coordination of 2,3-dihydrofuran on **62** induces dissociation of the triflate ligand to give the cationic phenylpalladium olefin species **63**, which has a 16-electron square-planar structure convenient for the subsequent enantioselective insertion of olefin. The resulting alkyl palladium (II) complex **64** undergoes β-hydride elimination leading to a hydrido-palladium olefin complex **65**. Dissociation of this π-complex leads to the product **60** and a hydrido-palladium species **68**. Finally, the catalytic Pd(0) complex **61** is regenerated by reductive elimination of HOTf. Depending on the ligand, catalyst precursor and reaction parameters, the palladium complex **65** can also undergo re-insertion of the hydride, which leads to the alkyl palladium (II) complex **66**. β-hydride elimination of **66** followed by dissociation of the resulting π-complex **67** lead to isomer **59** and hydride **68**. Reductive elimination of HOTf in **68** regenerates active species **61**.

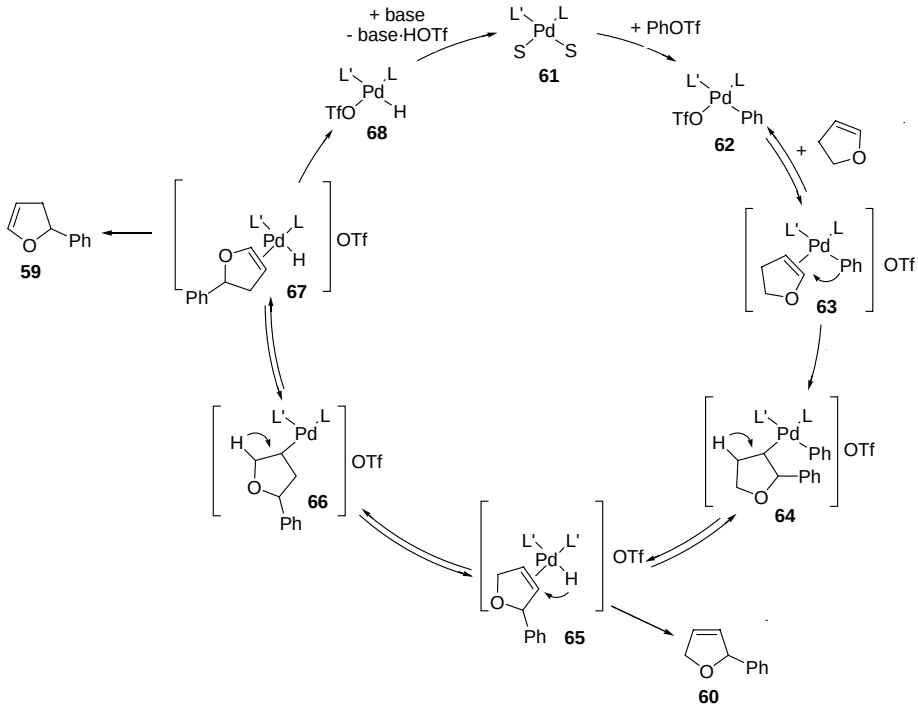


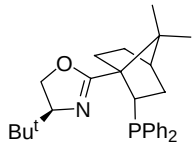
Figure 27. Proposed mechanism for the catalytic Pd-catalyzed arylation of 2,3-dihydrofuran with phenyl triflate.

1.3.2. Ligands

In 1991, Ozawa and Hayashi reported the first example of the intermolecular version of the Heck reaction using 2,3-dihydrofuran and phenyl triflate (Scheme 3).[37] Since then, this chemistry has been extensively studied using various chiral bidentate ligands. Diphosphines, which have played a key role in the success of the intramolecular version, were early applied. Among these, the Pd-BINAP were the first catalytic system that offered good regio- (in favour to product **59**) and enantiocontrol.[1c,35] In the last few years, a class of heterodonor ligands - the phosphine-oxazoline - have emerged as suitable ligands for the intermolecular Heck reaction of several substrate types and triflates sources.[38] Two of the most representative examples of this type of ligands are the PHOX ligands developed by

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Pfaltz[38a,b] and coworkers (Figure 9) and the phosphine-oxazoline based on ketopinic acid developed by Gilberston and coworkers[38e] (Figure 28). In contrast to Pd-BINAP systems, they offer preferentially isomer **60** in high enantioselectivities.



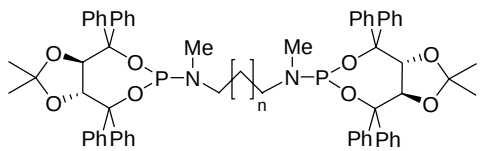
Gilbertson's Ligand

Figure 28. Phosphine-oxazoline ligand for asymmetric Pd-catalyzed Heck reactions.

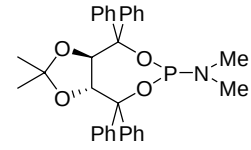
Although carbohydrate-based ligands have been successfully used in other enantioselective reactions,[2] there are only two reports on the highly enantioselective palladium-catalysed asymmetric Heck reaction using this type of ligand.[39]

The first succesfull application of carbohydrate-ligands in this process used the previously reported pyranoside phosphinite-oxazoline ligands **48** (Figure 22) in the Pd-catalyzed enantioselective arylation of 2,3-dihydrofuran (ee's up to 96%). This set of ligands were also applied in the phenylation of *trans* and *cis*-crotyl alcohols with low enantioselectivity (ee's up to 17%).[39a]

Phosphoroamidite ligands **69** and **70** (Figure 29) were applied in the Pd-catalyzed intramolecular Heck reaction of cyclohexadienone monoacetals with high enantioselectivities (ee`s up to 96%). Results indicate that the extra flexibility and rotational freedom obtained by using monodentate ligand **70** instead of bidentate ligand **69** has a beneficial effect on enantioselectivity.[39b]



69

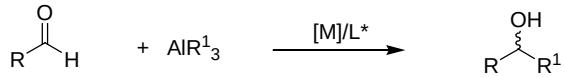


70

Figure 29. Ligands **69** and **70** derived from TADDOL.

1.4. Asymmetric 1,2-addition of organometallic reagents

Nucleophilic 1,2-addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of secondary alcohols, which are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products. In this context, the catalytic addition of dialkylzincs to aldehydes as a route to chiral alcohols has attracted much attention.[40] For alkylation reagents, trialkylaluminium compounds are more interesting than other organometallic reagents because they are economically obtained in industrial scale from aluminium hydride and olefins.[41] Despite this advantage their use is rare.[23f,42] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminium to aldehydes can be grouped in two types (Scheme 4). The first group are the titanium complexes that usually afford high enantioselectivities, but the high catalyst loadings (10-20 mol %) and the slow turnover rate hamper their potential utility.[42] The second ones are the recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (1 mol %).[23f,43]



Scheme 4. Metal-catalyzed 1,2-addition of trialkylaluminium to aldehydes

Several aldehydes, such as aryl-, alkyl- and vinylaldehydes, have been tested as substrates. However, benzaldehyde has been the substrate of choice for testing a new ligand. The aluminium source is also an important parameter for high catalytic activity and enantioselectivity. Traditionally, commercially available trialkylaluminium reagents have been widely used. However, these reagents are often contamined with oxo-containing by-products formed through accidental

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

exposure to traces of air and moisture, such impurities modify the reactivity of the reagent.[44] Recently, the group of Woodward reported the preparation of DABAL-Me_3 (Figure 30) as a new air-stable solid $AlMe_3$ adduct that is easily form from the exposure of neat $AlMe_3$ to DABCO (1,4-diazobicyclo[2,2,2]octane).[23f]

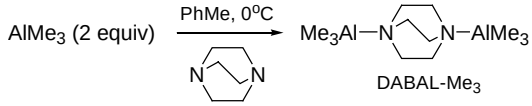


Figure 30. Formation of DABAL-Me_3.

1.4.1. Mechanism

Figure 31 shows the tentative mechanism proposed for the Ni-catalyzed 1,2-addition of trimethylaluminium reagents to aryl aldehydes.[43] The reductive generation of the active Ni(0)-catalyst **71** is followed by the formation of a π-aldehyde complex **72**, as showed possible by the seminal work of Walther who crystallized $Ni(\eta^2\text{-}O{=}CHAr)(PCy_3)_2$ (Ar= Ph, 2,4-$(MeO)_2C_6H_3$).[45] Aluminium lewis acid promoted oxidative addition of the ketone complex **72** and produces Ni(II)-complex **73**. By reductive elimination, they generated product **74** and regenerate the catalytically active species **71**.

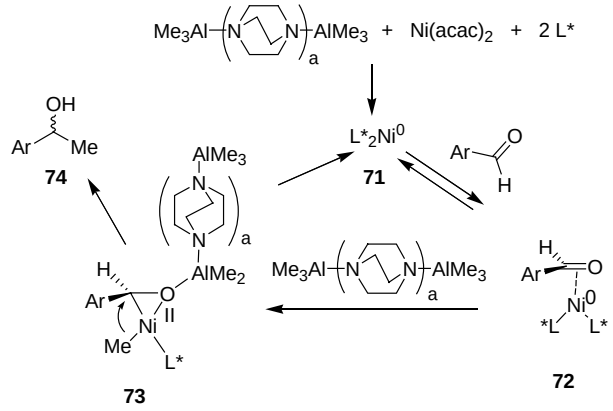
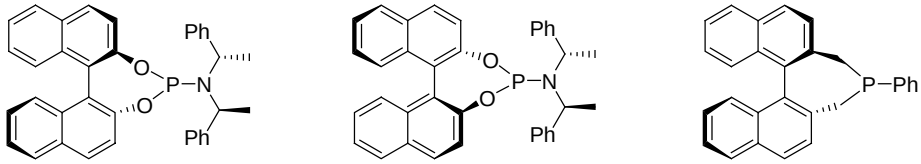


Figure 31. Proposed catalytic cycle for the 1,2-addition of DABAL-Me_3 (a = 1) or $AlMe_3$ (a = 0) to aromatic aldehydes.

1.4.2. Ligands

For the Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes, only the group of Woodward have recently reported the successful use of phosphoroamidite and monophosphine ligands as chiral auxiliares (Figure 32).[23f,43] High enantioselectivities (up to 95%) were obtained using monophosphoramidite ligands **75** and **76**.

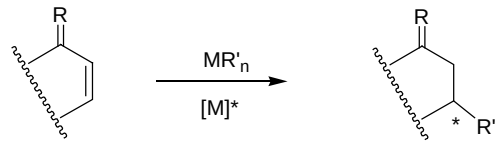


75 **76** **77**

Figure 32. Monophosphoroamidite and monophosphine ligands **75-77**.

1.5. Asymmetric 1,4-addition of organometallic reagents

The enantioselective conjugate addition (also called enantioselective Michael addition) of organometallic reagents to α,β-unsaturated compounds catalyzed by chiral transition metal complexes is a useful synthetic process for asymmetric carbon-carbon bond formation (Scheme 5).[1c,46] This process is important in the synthesis of many biologically active compounds such as steroids and terpens.



Scheme 5. Metal-catalyzed asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated compounds (R= O and NO_2).

Michael additions of organolithium, Grignard, diorganozinc and triorganoaluminium reagents to α,β-unsaturated compounds can be catalyzed by

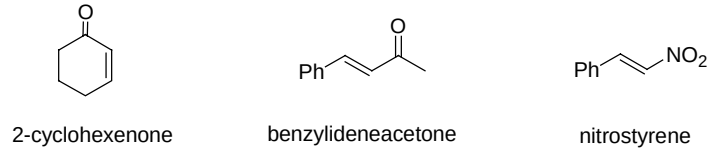
UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

nickel, cobalt and copper-complexes.[46] The best results have been achieved with Cu(I)-catalysts, especially those in which copper is bound to a *soft* center (sulphur or phosphorus).[46] Initially, Grignard reagents were the first species to be applied in this process. However, in 1993 Alexakis and coworkers introduced the use of dialkylzinc reagents for this enantioselective reaction and found them to be more appropriate than the classical use of Grignard reagents. Trialkylaluminum reagents have been tested in only a few cases but these represented an interesting alternative since they can be easily attained by technically simple hydro- and carboalumination and because they allow to undergo Cu-catalyzed 1,4-addition of more challenging substrates (i.e. β-trisubstituted enones).[46,47] Nowadays, the copper-catalyzed asymmetric 1,4-addition of organozinc reagents has been adopted as standard procedure for testing new ligands.[46]

In the copper-catalyzed asymmetric 1,4-addition, the copper salt is also important for high catalytic activity and enantioselectivity. Copper (I) and copper (II) salts have been used. The true catalytic species is Cu(I), so the reduction of Cu(II) is the first step in the process. The copper (II) triflate is usually the salt of choice, though many other copper salts have demonstrated their power in this reaction.[46]

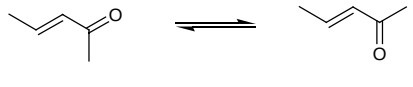
Cyclic and acyclic enones have been used as substrates in enantioselective copper-catalyzed conjugate addition (Figure 33). Traditionally, 2-cyclohexenone has been the substrate of choice for testing a new ligand. This cyclic enone avoids the *s-cis*/*s-trans* interconversion of acyclic substrates (Scheme 6).[46] For acyclic enones, the most widely studied substrate is benzylideneacetone (Figure 33). To achieve a high catalytic performance with this acyclic substrate, the class of ligands usually has to be different from those with cyclic substrates. Nitro-olefins are another class of excellent Michael acceptors for this reaction.[46] Again, the efficient ligands are different from the previous ones (Figure 33).

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0175-0/DL:T-2193-2007



2-cyclohexenone benzylideneacetone nitrostyrene

Figure 33. The most common substrates in the copper-catalyzed asymmetric 1,4-addition.



s-trans *s*-cis

Scheme 6. *S-cis* and *S-trans* conformational interconversion.

1.5.1. Mechanism.

The tentative catalytic cycle proposed for the Cu-catalyzed asymmetric 1,4-addition of diorganozinc to 2-cyclohexenone is illustrated in Figure 34.[23a,46] Starting from a Cu(I), or preferably a Cu(II) species, an alkyl fragment is transferred from ZnR_2 to the copper center. Complexation of the alkylzinc fragment to the enone carbonyl and formation of the π-complex of the copper alkyl species with the enone results in complex **78**. Subsequent alkyl transfer generates zinc enolate **79**, which upon protonation may afford the β-substituted cycloalkanone **80** (E= H) or be trapped by an electrophile reagent (E).

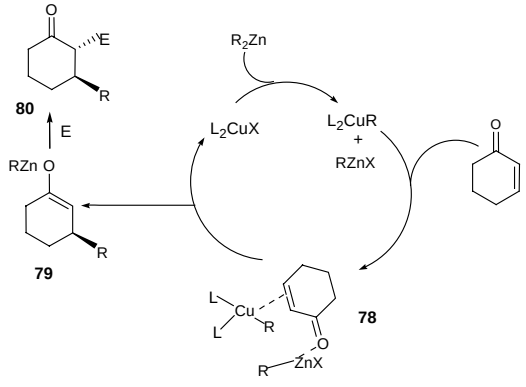
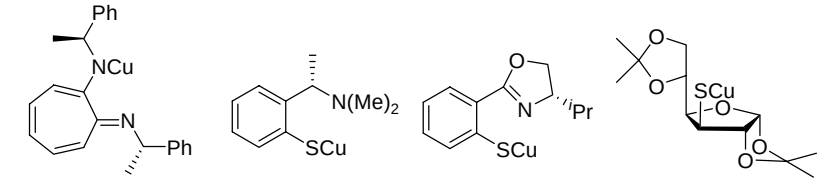


Figure 34. Proposed catalytic cycle for the Cu-catalyzed asymmetric 1,4-addition.

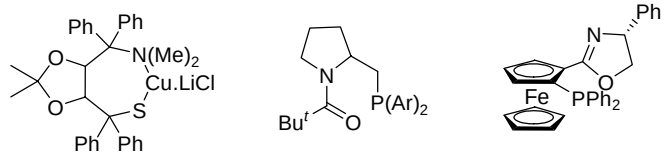
UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

1.5.2. Ligands

The first enantioselective copper catalysts were reported by Lippard and coworkers in 1988.[48] The reaction of 2-cyclohexenone with Grignard reagents in the presence of the chiral aminotroponeimine copper complex as catalyst (Figure 35) gave the 1,4-adducts with low enantioselectivity (up to 14%).[48] Selectivity increased to 74% ee with the addition of hexamethylphophoric triamide (HMPA) and silyl halides.[49] Later, various copper thiolates gave moderate-to-good results on cyclic and acyclic enones (Figure 35).[50] However, the best results were obtained with external ligands developed by Tomioka and Sammakia (Figure 35).[50e,f]



Lippard, 74 % ee van Koten, 76 % ee Pfaltz, 72 % ee Spescha, 60 % ee



Seebach, 84 % ee Tomioka, 90 % ee Sammakia, 98 % ee

Figure 35. Heterocuprate-based ligand and chiral ligands using Grignard reagents.

Since the late 1990s all authors have focused on the dialkylzinc procedure. The selection of chiral ligands for the highly enantioselective conjugate addition of organozinc reagents to α,β-unsaturated compounds has mainly focused on P-donor and mixed P,N-donor ligands (Figure 36).[46,51] Most phosphorus ligands are of the phosphite (mainly monophosphite) and phosphoramidite type. Non-phosphorus

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0175-0/DL:T-2193-2007

ligands have scarcely been used with dialkylzinc reagents.[46] Some of the most representative phosphorus ligands are shown in Figure 36.

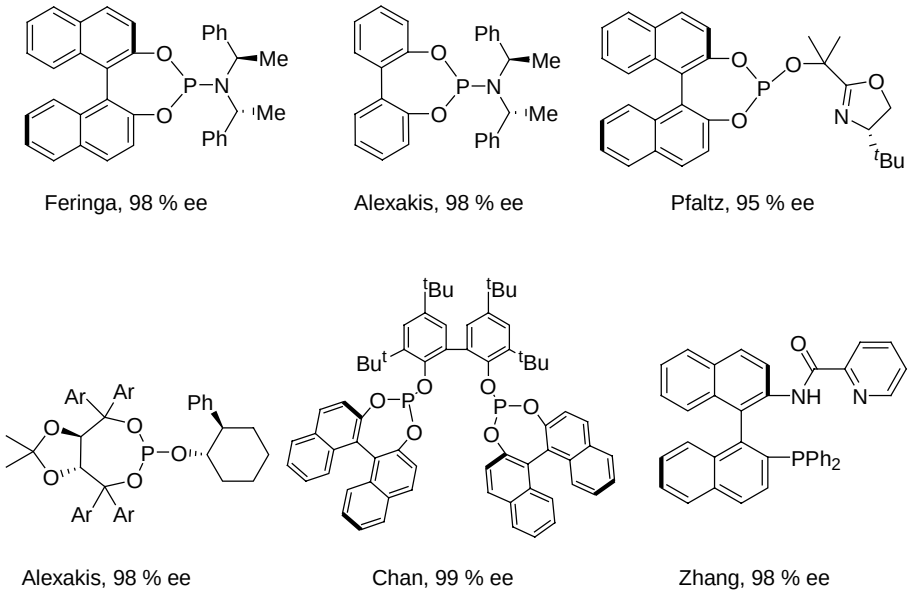


Figure 36. Representative phosphorus chiral ligands for 1,4-addition of organozinc reagents to α,β-unsaturated compounds.

Although carbohydrate ligands have been successfully used in other enantioselective reactions,[2] there have been few reports on the highly enantioselective 1,4-addition using these systems. Notable examples, however, include monophosphonite,[52] monophosphite,[51,53] and mixed amino-thiolate.[50d,54] ligands derived from TADDOL, and furanoside diphosphite ligands.[55] Other carbohydrate ligands, such as phosphoroamidite[51d,52,53,56] and mixed S-O,[57] N-P,[58] S-P[59] and P-P'[59] heterodonor ligands, have also been tested with low-to-moderate enantioselectivities.

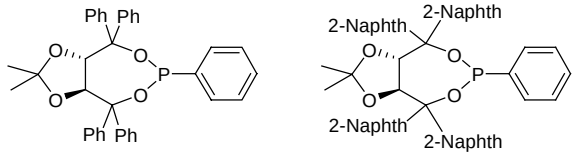
Here we present the most relevant catalytic data on the copper-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds with carbohydrate ligands.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

1.5.2.1. P-ligands

Phosphonite ligands

Alexakis used phosphonite ligands **81** and **82** (Figure 37), derived from (+)-TADDOL, in the asymmetric conjugate addition of diethylzinc to nitro-olefins[52] and alkylidene malonates[60] with good-to-moderate enantioselectivities. Ligand **81** appears to be the optimal choice for the diethylzinc addition to aryl nitro-olefins (ee's up to 86%).



81 **82**

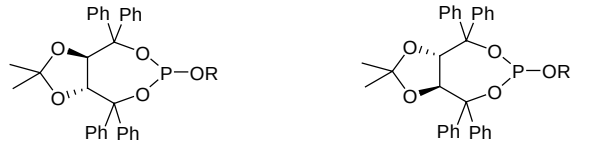
Figure 37. Phosphonite ligands **81** and **82** derived from (+)-TADDOL.

Phosphite ligands

Phosphite furanoside ligands **27-33** (Figure 12) were also applied in the Cu-catalyzed 1,4-addition of diethylzinc to cyclohexenone.[55] Results show that enantioselectivity depends strongly on the absolute configuration of the C-3 stereogenic center and on the biaryl substituents, while the sense of enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. The best enantioselectivites were obtained with ligands **27h** and **29g** with ee's of 81% (*R*) and 84% (*S*), respectively. Interestingly, both enantiomers of the product can be obtained. Introducing a stereogenic center in C-5 had a positive effect on activity but did not affect enantioselectivity.

Alexakis and coworkers have developed a series of phosphite ligands **83** and **84**, derived from (-)-TADDOL and (+)-TADDOL (Figure 38). These ligands were applied in the Cu-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone (ee's up

to 96%),[53] benzalacetone (ee's up to 35%),[51d,53] chalcone (ee's up to 50%),[51d,53] nitro-olefins (ee's up to 96%)[52] and alkylidene malonates (ee's up to 73%)[60] (Figure 38).



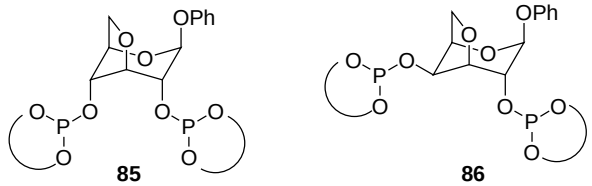
83 **84**

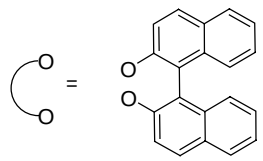
R = alkyl, cyclohexanyl, substituted cyclohexanyl, aryl

R= substituted cyclohexanyl

Figure 38. Basic structure of phosphite ligands **83** and **84**.

Recently, Chan and coworkers reported the synthesis of chiral pyranoside diphosphites **85** and **86**, derived from D-glucose and D-galactose, for application in the Cu-catalysed 1,4-addition of cyclic enones (Figure 39).[61] The enantioselectivity depends on the absolute configuration of the C-4 stereogenic center of the ligand backbone, while the sense of enantioselectivity is mainly controlled by the configuration of the binaphthyl moieties. Therefore, the results were best with ligand **85b** (ee's up to 88%).





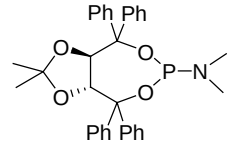
a (*S*)^{ax}
b (*R*)^{ax}

Figure 39. Pyranoside diphosphite ligands **85** and **86**.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Phosphoroamidite ligands

In the last few years several mono- and diphosphoroamidite ligands, derived from TADDOL, have been developed for the Cu-catalyzed 1,4-addition of diethylzinc to several substrates with poor-to-moderate enantioselectivity.[51d,52,53] However, Feringa and coworkers observed an unexpected improvement in enantioselectivity in the Cu-**87** (Figure 40) catalyzed addition of diethylzinc to cyclohexenone when they used powdered molecular sieves (ee's up to 71%).[56b]



87

Figure 40. Phosphoroamidite ligand **87** derived from TADDOL.

1.5.2.2. Heterodonor ligands

The groups of Seebach and Alexakis have developed a series of heterodonor O-S, N-S and N-P ligands derived from TADDOL for the Cu-catalyzed 1,4-addition of organometallic reagents to cyclic and lineal enones.[50d,51d,53,54] The best enantioselectivities were obtained with the previously mentioned N-S ligand (Figure 35) developed by Seebach and coworkers in the Cu-catalyzed addition of butylmagnesium cloride to cycloheptanone (ee's up to 84%).[50d,54]

1.6. References

[1] See for example: a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**. b) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley: New York, **2000**. c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, **1999**.

[2] See for example: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev*. **2004**, *104*, 3189. b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev*. **2004**, *248*, 2165. c) Castillón, S.; Díaz, Y,; Claver, C.; Chem. *Soc. Rev.* **2005**, *34*, 702. d) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* in press.

[3] a) Jackson, R.; Thompson, D. J. J. *Organomet. Chem*. **1978**, *159*, C29. b) Selke, R.; Pracejus, H. *J. Mol. Catal*. **1986**, *37*, 213. c) Selke, R. *J. Prakt. Chem.* **1987**, *329*, 717. d) Selke, R. *J. Organomet. Chem.* **1989**, *370*, 249. e) Selke, R.; Schwarze, M.; Baudisch, H.; Grassert, I.; Michalik, M.; Oehme, G.; Stoll, N.; Costisella, B. *J. Mol. Catal.* **1993**, *84*, 223. f) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, T. V. *J. Am. Chem. Soc.* **1994**, *116*, 4101. g) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012.

[4] a) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc*. **1992**, *114*, 6265. b) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869.

[5] Reetz, M. T.; Neugebauer, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 179.

[6] Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Eur. J. Inorg. Chem.* **2000**, 2011.

[7] a) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Chem. Commun*. **2000**, 2383. b) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Org. Chem*. **2001**, *66*, 8364.

[8] a) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun*. **2001**, 2702. b) Raluy, E. ; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49.

[9] a) Diéguez, M.; Ruiz, A.; Claver, C. *J. Org. Chem*. **2002**, *67*, 3796. b) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans*. **2003**, 295.

[10] a) Diéguez, M.; Pàmies, O.; Ruiz, A.; Castillón, S.; Claver, C. *Chem. Commun*. **2000**, 1607. b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. *New J. Chem*. **2002**, *7*, 827. c) Diéguez, M.; Pàmies, O.; Ruiz, A.; Castillón, S.; Claver, C *Chem. Eur. J*. **2001**, 3086. d) Diéguez, M. ; Jansat, S. ; Gomez, M. ; Ruiz, A. ;

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Muller, G. ; Claver, C. *Chem. Commun.* **2001**, 1132. e) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1257.

[11] a) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H. J.; Heller, D.; Krimmer, H. P.; Börner, A. Eur. *J. Org. Chem.* **2001**, 4615. b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.

[12] a) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471. b) Zhang, X. Patent WO 03/040149 A2, **2003**. c) Yan, Y. Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199.

[13] a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, **1995**. b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1869. d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 292.

[14] Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649.

[15] Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

[16] a) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M.; *Coord. Chem. Rev.* **2003**, *242*, 159. b) Martin, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188.

[17] Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

[18] Ruffo, F.; Del Litto, R.; De Roma, A.; D'Errico, A.; Magnolia, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2265

[19] Seebach, D.; Devaquet, E.; Ernst, A.; Hayakawa, M.; Kühnle, F.N.M.; Schweizer, W.B.; Weber, B.*; Helv.Chim.Acta* **1995**, *78*, 1638.

[20] a) Nomura, N.; Mermet-Boubier, Y.C.; RajanBabu, T.V. *Synlett* **1996** , 745. b) Clyne, D.S.; Mermet-Bouvier, Y.C. Nomura, N.; RajanBabu, T.V. *J. Org. Chem.* **1999**, *64*, 7601

[21] Pàmies, O.; van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 8867.

[22] Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.* **2004**, *126*, 1592.

[23] See for instance: a) Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346. b) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2789. c) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426. d) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Angew. Chem. Int. Ed.* **2006**, *12*, 3596. e) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Chem. Eur. J*. **2004**, *10*, 6232. f) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2232. g) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.

[24] Raluy, E.; Diéguez, M.; Pàmies, O. *J. Org. Chem.* **2007**, *72*, 2842.

[25] a) Jansat, S.; Gómez, M.; Muller, G.; Diéguez, M.; Aghmiz, A.; Claver, C.; Masdeu-Bultó, A. M.; Flores Santos, L.; Martín, E.; Maestro, M.A.; Mahía, J. T. *Tetrahedron: Asymmetry* **2001**, *12*, 1469. b) Fernández, F.; Gómez, M.; Jansat, S.; Muller, G.; Martín, E.; Flores Santos, L.; García, P. X.; Acosta, A.; Aghmiz, A.; Jiménez-Pedrós, M.; Masdeu-Bultó, A. M.; Diéguez, M.; Claver, C.; Maestro, M.A. *Organometallics* **2005**, *24*, 3946.

[26] a) Khiar, N.; Araújo, C. S.; Alvarez, E.; Fernández, I. *Tetrahedron Lett.* **2003**, *44*, 3401. b) Khiar, N.; Araújo, C. S.; Suárez, B.; Fernández, I. *Eur. J. Org. Chem.* **2006**, 1685.

[27] a) Albinati, A.; Pregosin, P.S.; Wick, K. *Organometallics* **1996**, *15*, 2419. b) Barbaro, P.; Currao, A.; Herrmann, J.; Nesper, R.; Pregosin, P.S.; Salzmann, R. *Organometallics* **1996**, *15*, 1879.

[28] Nakano, H.;Yokohama, J.; Okuyama, Y.; Fujita R.; Hongo H. *Tetrahedron: Asymmetry* **2003**, *14*, 2361.

[29] a) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959. b) Diéguez, M.; Pàmies, O.; Claver, C. *J. Organomet. Chem.* **2006**, *691*, 2257.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

[30] a) Khiar, N.; Suárez, B.; Stiller, M.; Valdivia, V.; Fernández, I. *Phosphorus, Sulfur and Silicon* **2005**, *180*, 1253. b) Khiar, N.; Suárez, B.; Valdivia, V.; Fernández, I. *Synlett* **2005**, 2963.

[31] Hildraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.

[32] a) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Basoli, C.; Marchetti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 885. b) Robert, F.; Gaillard, N.; Sinou, D. *J. Mol. Catal. A-Chem.* **1999**, *144*, 473. c) Borriello, C.; Cucciolito, M. E.; Panunzi, A.; Ruffo, F. *Inorg. Chim. Acta* **2003**, *353*, 238. d) Brunner, H.; Schönherr, M.; Zabel, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1115. e) Gläser, B.; Kunz, H. *Synlett* **1998**, 53. f) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *Chem. Commun*. **1999**, 415. g) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374.

[33] Konovets, A.; Glegola, K.; Penciu, A.; Framery, E.; Jubault, P.; Goux-Henry, C.; Pietrusiewicz, K. M.; Quirion, J. C.; Sinou, D. *Tetrahedron: Asymmetry* **2005**, *16*, 3183.

[34] Boog-Wick, K.; Pregosin, P.S.; Trabesinger, C. *Organometallics* **1998**, *17*, 3254.

[35] For recent reviews, see: a) Tietze, L. T.; Ila, H.; Bell, H. P. *Chem Rev.* **2004**, *104*, 3453. b) Dai, L.X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659. c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *44*, 3284. d) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schemees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16. e) Beller, M.; Riermeier, T. H.; Stark G. *in Transition Metals for Organic Synthesis* (Eds. Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **1998**. f) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945

[36] Ozawa F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188.

[37] Ozawa F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 1417.

[38] See for instance: a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200. b) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A.

Synthesis **1997**, 1338. c) Tu, T.; Hou, X.L.; Dai, L.X. *Org. Lett.* **2003**, *5*, 3651. d) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240. e) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161. f) Tu, T.; deng, W.P.; Hou, X.L.; Dai, L.X.; Dong, X.C. *Chem. Eur. J.* **2003**, *9*, 3073. g) Gilberston, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885. h) Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205. i) Hou, X. L.; Dong, D. X.; Yuan, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2189. j) Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460.

[39] a) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K. G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40. b) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc*. **2002**, *124*, 184.

[40] Pu. L; Yu, H. B. *Chem. Rev*. **2001**, *101*, 757.

[41] Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988; p. 224.

[42] a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc*. **1997**, *119*, 4080. b) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593. c) Lu, J.-F.; You, J.-S.; Gau, H.-M. *Tetrahedron: Asymmetry* **2000**, *11*, 2531. d) You, J.-S.; Hsieh, S.-H.; Gau, H.-M. *Chem. Commun*. **2001**, 1546.

[43] Biswas, K.; Chapron, A.; Cooper, T.; Fraser, P. K.; Novak, A.; Prieto, O.; Woodward, S. *Pure Appl. Chem.* **2006**, *78*, 511.

[44] Fraser, P. K.; Woodward, S. *Chem. Eur. J.* **2000**, *9*, 776

[45] a) Walther, D. *J. Organomet. Chem.* **1980**, *190*, 393. b) Kaiser, J.; Sieler, J.; Walther, D.; Dinjus, E.; Golic, L. *Acta Cryst. Sec. B* **1982**, *B38*, 1548.

[46] For reviews, see: a) Rossiter, B. E.; Swingle, H. M. *Chem. Rev.* **1992**, *92*, 771. b) Alexakis, A. *In Organocopper Reagents, A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, **1994**; Chapter 8. c) Krause, N. *Angew. Chem., Int. Ed.* **1998,** *37*, 283. d) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393. e) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. f) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002,** 3211. g) Alexakis, A. in *Methodologies in Asymmetric*

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Catalysis; Chapter 4, American Chemical Society, Washington DC, 2004. h) Krause, N. *Modern Organocopper Chemistry*; Wiley-VCH, Weinheim, 2002.

[47] Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1376 and references therein.

[48] Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.

[49] Ahn, K. H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.

[50] a) Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Speck, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1992**, *114*, 3400. b) Zhou, Q. L.; Pfaltz, A. *Tetrahedron Lett.* **1993**, *34*, 7725. c) Spescha, M. Rihs, G.; *Helv. Chim. Acta* **1993**, *76*, 1219. d) Seebach, D.; Jaeschke, G.; Pichota, A.; Audergon, L. *Helv. Chim. Acta* **1997**, *80*, 2515. e) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843. f) Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503.

[51] For some succesfull ligands see: a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem. Int. Ed.* **1997**, *36*, 2620. b) Alexakis, A.; Rosset, S.; Allamand, J.; March, S. Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375. c) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429. d) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett*. **1998**, *39*, 7869. e) Yan, M.; Yang, L. W.; Wong, K. Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11. f) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem. Int. Ed.* **1999**, *38*, 3518. g) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843.

[52] Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579.

[53] Alexakis, A.; Burton, J.; Vastra, J.; Benhaim,C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem*. **2000**, 4011.

[54] Pichota, A.; Pregosin, P. S.; Valentín, M.; Wörle, M.; Seebach, D. *Angew. Chem. Int. Ed.* **2000**, *39*, 153.

[55] a) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 4377. b) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2895.

[56] a) Mandoli, A.; Arnold, L. A.; de Vries, A. H. M.; Salvadori, P.; Feringa, B. L. *Tetrahedron: Asymmetry* **2001**, *12*, 1929. b) Kelle, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron Asymmetry* **1998**, *9*, 2409. c) Duursma, A; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, 58, 5773.

[57] Pàmies, O.; Net, G.; Ruiz, A.; Claver, C.; Woodward, S. *Tetrahedron: Asymmetry* **2000**, *11*, 871.

[58] Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2861.

[59] Diéguez, M.; Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *J. Mol. Catal. A: Chem.* **2002**, *185*, 11.

[60] Alexakis, A.; Benhaim, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1151.

[61] Wang, L.; Li, Y.-M.; Yip, C.-W.; Qiu, L.; Zhou, Z.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 947.