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Asymmetric Catalysis

Phosphoramidites: Privileged Ligands in Asymmetric Catalysis

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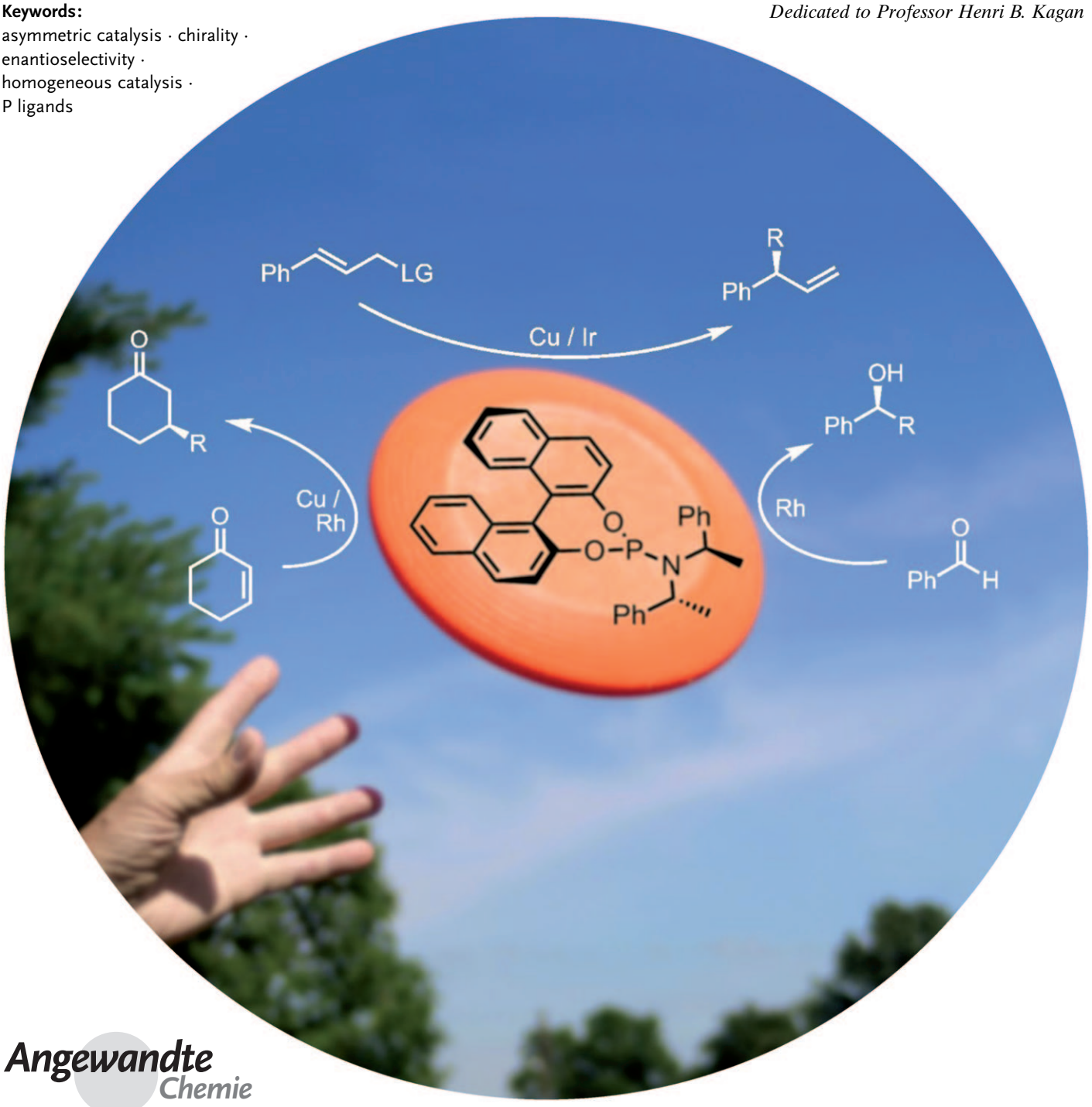
asymmetric catalysis · chirality · enantioselectivity · homogeneous catalysis · P ligands

Dedicated to Professor Henri B. Kagan



Asymmetric catalysis with transition-metal complexes is the basis for a vast array of stereoselective transformations and has changed the face of modern synthetic chemistry. Key to this success has been the design of chiral ligands to control the regio-, diastereo-, and enantioselectivity. Phosphoramidites have emerged as a highly versatile and readily accessible class of chiral ligands. Their modular structure enables the formation of ligand libraries and easy fine-tuning for a specific catalytic reaction. Phosphoramidites frequently show exceptional levels of stereocontrol, and their monodentate nature is essential in combinatorial catalysis, where a ligand-mixture approach is used. In this Review, recent developments in asymmetric catalysis with phosphoramidites used as ligands are discussed, with a focus on the formation of carbon–carbon and carbon–heteroatom bonds.

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1. Introduction

In the intervening 135 years since van't Hoff[1–4] and Le Bel[5] introduced the tetrahedral model of the carbon atom to explain the optical activity of organic molecules and provide a structural basis for molecular stereochemistry, scientists have been fascinated by the challenge to achieve absolute stereocontrol in chemical transformations starting from achiral compounds.[6] Chirality has been denoted as "a signature of life", and it is not unexpected that questions on the origin, control, and amplification of homochirality are intimately associated with chemical evolution and the origin of life.[7,8] Efforts to control molecular chirality have resulted in major breakthroughs in chemical catalysis,[9] and have arguably dramatically enhanced our understanding of molecular recognition and information transfer in molecular systems.[10] The enormous economic and scientific impact resulting from the major efforts devoted to asymmetric synthesis can hardly be overestimated.[11–13] The development of numerous drugs as single enantiomers along with a variety of other biologically active compounds including agrochemicals, pheromones, flavors, and fragrances would not have been achieved without the fruits of fundamental studies in asymmetric catalysis in the past few decades.[14–16] However, despite these achievements, the number of catalytic transformations that have reached the stage of an industrial process remains limited.

Several challenges remain in developing the desired future fully catalytic and sustainable asymmetric syntheses. These include the design of inexpensive ligands and catalysts that are easy to prepare and allow for rapid fine-tuning for a specific chemical transformation. There are strong incentives to expand our catalytic toolbox and to design catalysts that can be optimized for highly enantioselective synthetic steps by automated (robotic) procedures that avoid tedious procedures. Practicability is another key issue, which goes beyond the common model substrates, especially in the contexts of total synthesis, process development, and medicinal chemistry. Chiral catalysts that work in concert and allow for tandem, cascade, or multistep conversions with exquisite stereocontrol, thus mimicking nature in some of its pathways in the preparation of complex chiral molecules, provide additional challenges. The integration of metal-based catalysis, organocatalysis, and/or biocatalysis offers further opportunities.

In the past few decades, a plethora of asymmetric catalytic transformations have been studied, mostly relying on multidentate chiral ligands as the origin of stereodiscrimination,[9,15–18] although some of the first examples were based upon monodentate ligands.[11,19–21] The introduction of the bidentate chiral phosphine DIOP by Kagan and Dang in 1971 marked the beginning of the era of bidentate ligands in asymmetric catalysis.[19–23] Their approach of reducing the many degrees of conformational freedom in the metal–ligand complexes resulted in excellent enantioselectivity in hydrogenation. Following the application of DiPAMP in the commercial process of L-DOPA, the dogma of the superiority of bidentate (phosphorus) ligands was established.[24] The tremendous success of the C_2-symmetric bidentate phosphorus ligands resulted in this dogma remaining unchallenged for

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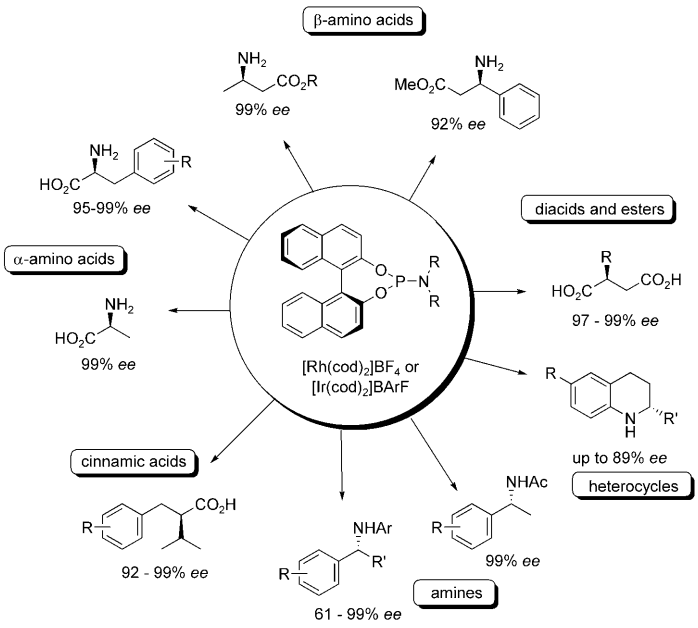
many years, although applications of monodentate ligands continued to emerge.[17,25]

When we introduced monodentate chiral phosphoramidites in 1994, we were surprised to find that these phosphorus compounds had apparently escaped the attention of the asymmetric catalysis community.[26,27] This is even more remarkable as phosphoramidites were long known as versatile reagents for oligonucleotide synthesis,[28–30] but the anticipated sensitivity of these phosphorus reagents might have hampered their introduction to the field of ligand design. A major breakthrough came in 1996/1997 with our enantioselective copper-catalyzed conjugate addition of dialkyl zinc reagents to enones in the presence of BINOL-based phosphoramidites.[31,32] The high enantioselectivity reached with a simple monodentate ligand in this key carbon–carbon bond formation set the stage for numerous asymmetric transformations based on monodentate chiral ligands, and challenged the notion that high flexibility in the metal–ligand complex is detrimental for high stereocontrol.

It is interesting that just at the start of the new millennium both Zhang and Kagan commented on the future of monodentate chiral ligands. Zhang[33] remarks: "*There have been only a limited number of monodentate chiral phosphines reported in the literature and high enantioselectivity with monodentate phosphines is difficult to obtain. However, there are many transition-metal-catalyzed reactions that do not work with chelating bidentate ligands. Efficient chiral monophosphines are clearly needed.*" Lagasse and Kagan[25] added: "*Chelating chiral diphosphines are often used as ligands of organometallic complexes. However, monophosphines or more generally ligands with one phosphorus linked to one or several heteroatoms, may also be useful.*" How drastically the scene has changed within one decade, and today numerous asymmetric transformations are known to work equally well when monodentate chiral ligands are used.

In 2000 the research groups of Reetz,[34] Pringle,[35] and Feringa and de Vries[36] independently reported the use of three new classes of chiral monodentate ligands for asymmetric hydrogenation. When chiral monodentate phosphorus ligands such as phosphoramidites,[31,32,36,37] phosphonites,[35] and phosphites[38] derived from a BINOL backbone were used, high enantioselectivity was reached that were comparable to the results obtained using the most selective bidentate phosphines in rhodium-catalyzed hydrogenation. Phosphoramidite ligands have proven to be particularly versatile in asymmetric hydrogenation, and the transformations summarized in Scheme 1 are illustrative of the broad scope and excellent *ee* values reached with these monodentate ligands.[37,39–41] Chiral product classes include α- and β-amino acids, diacids and esters, cinnamic acids, amines, and various heterocyclic compounds. Transition-metal-catalyzed hydrogenations with phosphoramidite ligands are covered elsewhere;[37,42–46] a selection of the various products available through this method can be found in Scheme 1.



Scheme 1. Phosphoramidites as ligands for asymmetric hydrogenation.

In this Review we discuss recent advances and applications of phosphoramidites, a class of privileged ligands,[26] in asymmetric catalysis, in particular the catalytic formation of carbon–carbon and carbon–heteroatom bonds.[47] The focus is on presenting an overview of the wide range of transformations where monodentate phosphoramidites have been applied with much success as new or alternative chiral ligands.

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Ben L. Feringa obtained his PhD in 1978 at the University of Groningen in the Netherlands under the guidance of Prof. Hans Wynberg. After working as a research scientist at Shell, he was appointed full professor at the University of Groningen in 1988 and named the distinguished Jacobus H. van't Hoff Professor of Molecular Sciences in 2004. He was elected honorary member of the American Academy of Arts and Sciences and member of the Royal Netherlands Academy of Sciences. His research interests include stereochemistry, organic synthesis, asymmetric catalysis, molecular switches and motors, self-assembly, and nanosystems.

Prior to illustrating the various reaction types, it is pertinent to briefly discuss the synthesis and selected features of these unique ligands.

2. Phosphoramidites: Structure, Synthesis, and Properties

Phosphoramidites **1** belong to the family of amides of trivalent phosphorus acid H_3PO_3.[48,49] Their structure is distinct from other trivalent phosphorus-based ligands **2**–**8** in that they contain one P–N and two P–O bonds (Figure 1). Three common types of phosphorus amides can be distinguished: phosphoramidites **1**, phosphordiamides **7**, and phosphortriamides **8**, although the latter two types of compounds as ligands for asymmetric catalysis has so far seen very limited use.[17,50,51] Both the phosphorus and the nitrogen atoms in **1** have an unshared pair of electrons which are potential metal-binding sites.

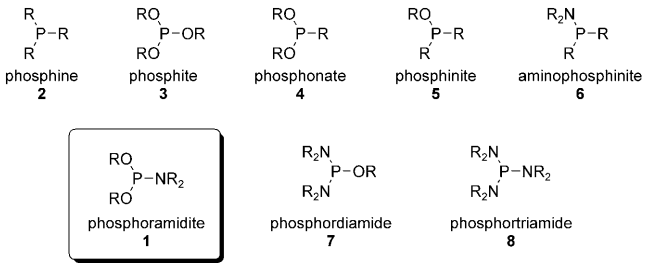
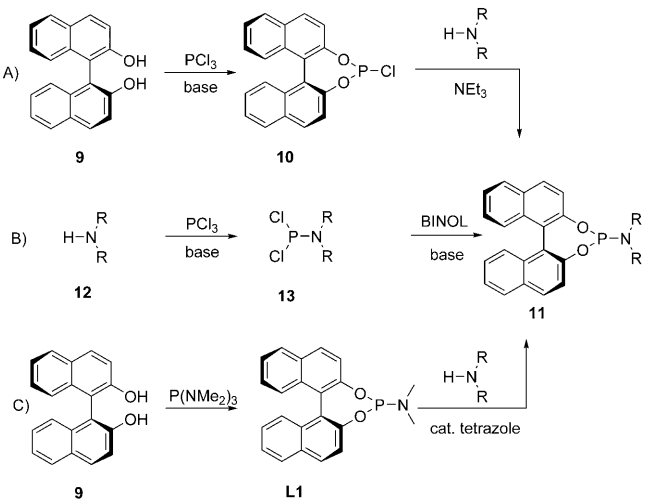


Figure 1. Some trivalent phosphorus compounds.

Two important general features of the structure of phosphoramidites have been revealed by X-ray analysis.[52] The phosphorus atom has a pseudotetrahedral geometry while the nitrogen atom is usually trigonal planar. This can be clearly seen in the structure of uncoordinated phosphoramidites[52] (Table 1, entries 1 and 2) and that of copper– and rhodium–phosphoramidite complexes[31,46,53] (Table 1 entries 3–5) as well as an iridium–phosphoramidite complex[54] (Table 1, entry 7), where the amine moiety of the ligand has an almost perfect trigonal configuration, thus indicating sp^2 hybridization. For phosphoramidite *ent*-**L2a** (Table 1, entry 1) and its isomers (see Figure 4), which have been the most employed ligands from this structural class, it is interesting to note that the solid state structure does not display C_2-symmetry, which has also been found for the lowest energy conformation by DFT calculations.[52b] Furthermore, this ligand has the ability to act both as a monodentate ligand via the phosphorus, as well as in a bidentate fashion either by cyclometalation (Section 4.2) or by additional coordination via the substituents of the amine moiety such as the phenyl rings (see Sections 6 and 7.1). In recent years, the structure of several metal–phosphoramidite complexes have been characterized by X-ray analysis (for selected examples, see Refs. [31,46,53,55–57]). Phosphoramidite ligands coordinated to copper, ruthenium, rhodium, iridium, palladium, platinum, and gold show several similarities, including a tetragonal phosphorus atom, an M-P-N angle in the range of 113 to 117°, and a nearly planar geometry for the amine group. Moreover, in the case of small substituents on the amine, there is an alignment of the dialkyl amine group with the phosphorus–metal bond, thus indicating some electronic interaction; however, no further studies on this topic have so far appeared. The X-ray structures of C_2-symmetric [Rh(cod)(phosphoramidite)$_2$]BF_4 and [Rh(MonoPhos)$_4$]BF_4[58] clearly show these geometrical features.[46,53] The same effects are observed with phosphoramidite ligands containing cyclic amines, such as morpholine and methylpiperazine, coordinated to gold (Table 1 entry 5).[59]

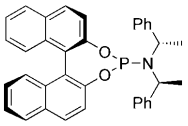
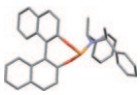
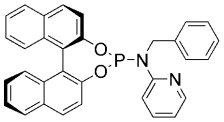
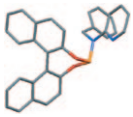
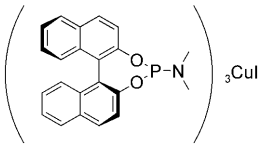
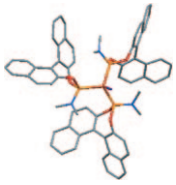
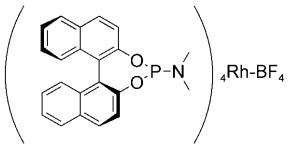
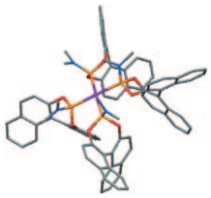
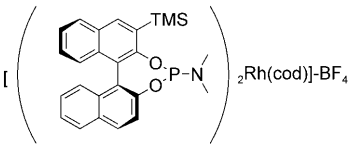
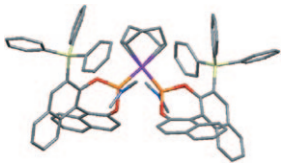
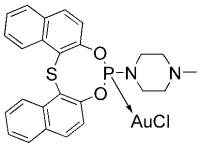
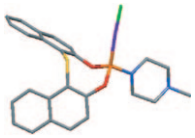
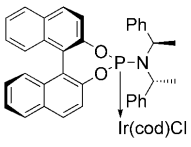
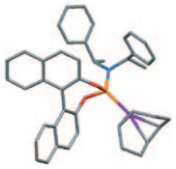
The electronic properties of phosphorus ligands can be characterized in terms of their π-accepting and σ-donating capabilities. Comparison of the frequencies of the C-O stretching vibration of their metal–carbonyl complexes allows the π-acceptor properties of the ligands to be deduced.[48,60,61] In general, it has been observed that the ability of phosphorus ligands to act as a π acceptor increases with the electronegativity of the substituents on the phosphorus atom. Thus, phosphoramidites (two P–O bonds, one P–N bond) lie between the weaker π acceptors such as phosphines (three P–C bonds) and the stronger π acceptors such as phosphites (three P–O bonds), likely with more resemblance to the latter class of ligands in terms of electronic properties. The facile modification of the substituents at both the oxygen and the nitrogen atoms in phosphoramidites allow for the fine-tuning of the donor properties of the ligand (and as a consequence the electronic properties at the metal center) for a specific catalytic application. Furthermore, the steric effects can readily be controlled as a result of the modular architecture of these ligands (see below).

Different routes allow for the synthesis of phosphoramidites, depending on which of the key P–O or P–N bonds are established first (Scheme 2).[26] Most frequently used is the synthesis via the chlorophosphite **10** (Route A, Scheme 2), where the appropriate diol **9** is treated first with phosphorus trichloride to yield **10**, and then the desired amine is subsequently added in the presence of a base.[26,31,32,62] For the more sterically hindered amines **12**, the initial synthesis of



Scheme 2. Syntheses of BINOL-based phosphoramidites.

Table 1: Selected X-ray structures of phosphoramidites and metal complexes.

Entry	Description	Structure	X-ray structure[a]
1	uncoordinated phosphoramidite *ent*-**L2a**[49c]		
2	uncoordinated phosphoramidite		
3	Cu–MonoPhos complex		
4	Rh–MonoPhos complex		
5	Rh–phosphoramidite complex		
6	Au–phosphoramidite complex		
7	Ir–phosphoramidite complex		

[a] Hydrogen atoms and counterions are omitted for clarity.

These complementary and high-yielding synthetic pathways towards phosphoramidites illustrate the modular framework of these ligands, a feature that has been applied to an easy and automated preparation of large ligand libraries (Figures 2 and 3).[76–84] Furthermore, the starting materials are cheap and available as enantiomerically pure compounds,[85] thus making the phosphoramidites easily accessible and low-priced chiral ligands. In terms of practicability it should be emphasized that many members of this ligand class are air-stable and do not require tedious procedures or handling under stringent inert conditions, as seen with several privileged phosphine ligands. The facile one- or two-step synthesis in combination with the use of various diols and amines greatly enhances the structural and stereochemical diversity (Figure 2). An important property of phosphoramidite ligands is that the chiral diol or the chiral amine can serve as the origin of the stereodiscrimination for the envisaged catalytic system. These features result in matched/mismatched effects of the different stereoisomers of one ligand frequently being observed with certain combinations of chiral diol and amine groups (for example, **L2** in Figure 4, see below)[32,86–88] and these effects can be exploited to optimize the enantioselectivity in a phosphoramidite-based asymmetric reaction. An illustrative example of this is the copper-catalyzed conjugate addition (see section 3), where (*S*,*R*,*R*)-**L2a** (Figure 4) is the ligand of choice in terms of stereoselectivity, whereas for the iridium-catalyzed allylic substitution reactions (see Section 4.2), the (*S*,*S*,*S*)-**L2b** isomer is the preferred ligand.

the dichloroaminophosphine **13** can provide an alternative;[63] in this case the amine is first treated with the phosphorus trichloride, and the appropriate diol is then added (Route B, Scheme 2). A third pathway starts with the reaction of BINOL with hexamethylphosphorus triamide (HMPT) to give the dimethylamine-derived phosphoramidite ligand **L1**, which is known as MonoPhos.[27] **L1** can either be applied itself as the chiral ligand in the catalysis or it can undergo subsequent amine exchange under basic conditions to give a number of other phosphoramidites (Route C, Scheme 2).[36,64,65] It should be noted that ligand **L1** is a cheap and readily accessible ligand that has found extensive application in enantioselective rhodium-catalyzed hydrogenation reactions, including in industrial processes for the synthesis of chiral amino acid derivatives, amines, alcohols, and itaconic acid derivatives.[36,46,66–75]

The success of the fully automated synthesis of ligand and catalyst libraries for a wide variety of asymmetric transformations is mainly due to the modular ligand architecture, the facile and short synthetic route, and the structural diversity that can be achieved. This approach enhances the discovery process for a suitable chiral catalyst for a particular asymmetric transformation and drastically reduces the time needed in the often highly labor-intensive process of further optimization of a lead catalyst toward a process suitable, for example, for the production of a chiral drug intermediate.[76–84]

Mixtures of chiral and achiral ligands can form heterocomplexes with transition metals and thus can have a favorable or detrimental influence on the asymmetric catal-

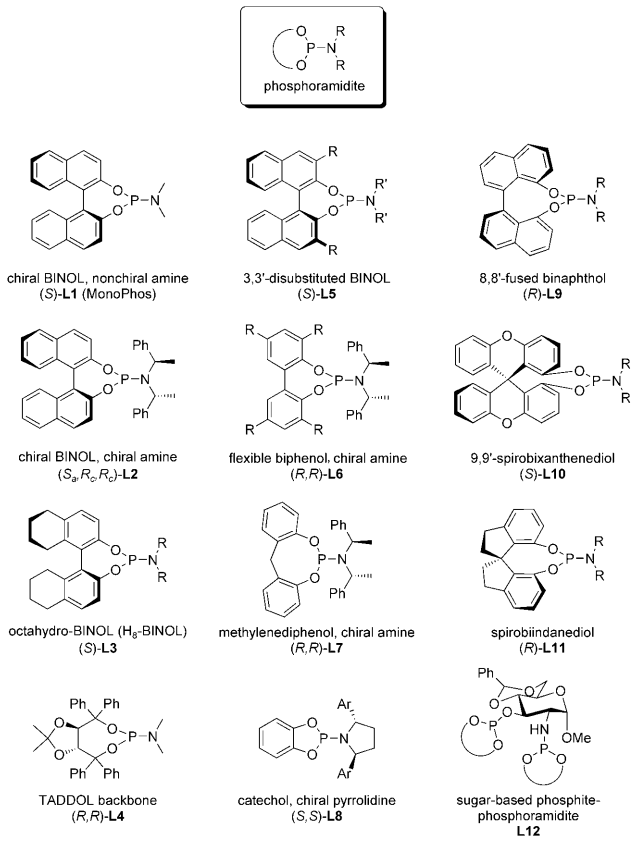


Figure 2. Modular chiral phosphoramidites: a selection of frequently used ligands.

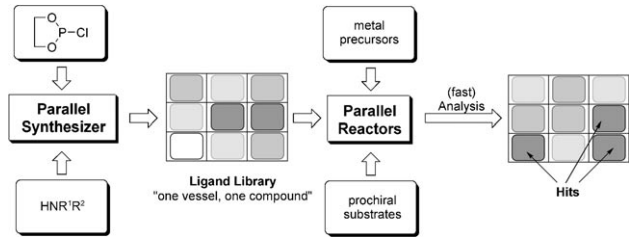


Figure 3. Automated parallel synthesis and screening of phosphoramidite ligands (adapted from Ref. [37]).

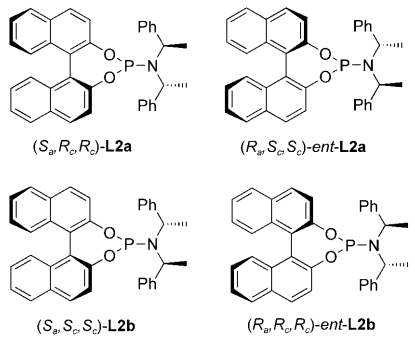
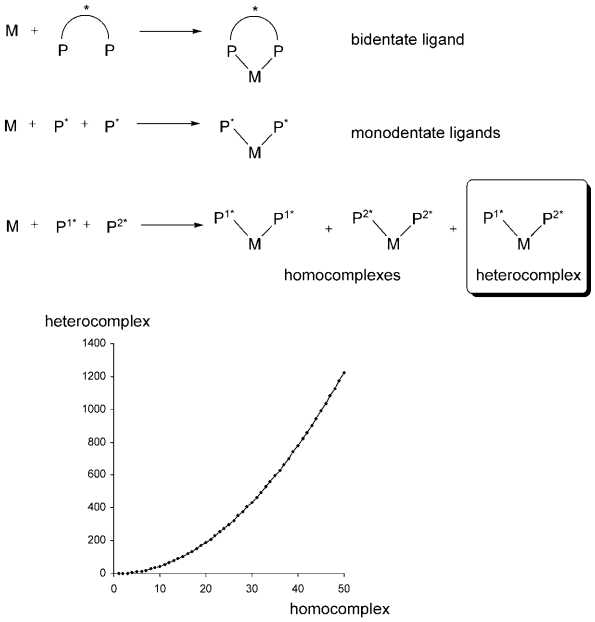


Figure 4. Phosphoramidite ligands with a chiral amine moiety.

ysis.[89–92] However, a new principle from the investigation of mixtures of different *chiral* monodentate ligands was introduced to asymmetric catalysis.[93–98] Commonly used bidentate phosphine and related privileged chiral bidentate ligands (bisoxazolines, diols, phosphine-oxazolines, etc.) normally provide active catalysts only when one ligand is coordinated to the metal center (Scheme 3). The same is usually true for

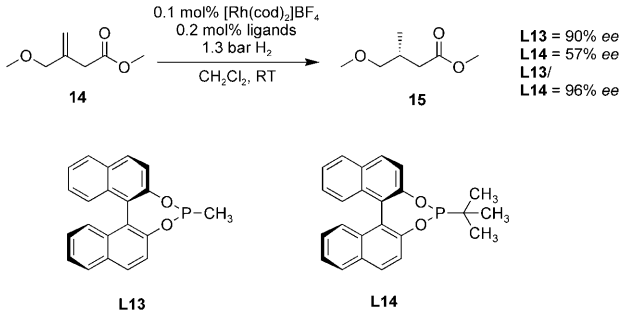


Scheme 3. Formation of heterocomplexes with two monodentate ligands and the number of combinations for heterocomplexes.

bidentate ligands bearing a weakly coordinating ancillary ligand, since the binding of several ligands block substrate or reagent binding sites, thereby resulting in inactive metal complexes.

The use of monodentate phosphoramidites (and monodentate ligands in general) allows for an approach based on mixed ligands or a combination of ligands (Schemes 3–5), as two monodentate ligands can be accommodated on a single metal center (Scheme 3). It was independently demonstrated that more-active and more-selective catalysts can be obtained by using a combination of chiral ligands.[92–95,97,99–101] Homochiral and heterochiral complexes are formed through self-assembly under equilibrium conditions, whereby the heterochiral complexes, which bear two non-identical chiral ligands, might be more active or selective (or both) than the commonly formed homochiral catalysts. The opposite effect is also frequently encountered when a single chiral ligand is applied.[102,103]

Better enantioselectivity was obtained in the rhodium-catalyzed hydrogenation of substituted olefins **14** with mixtures of different chiral monodentate phosphonites **L13** and **L14** compared to that achieved with only one chiral ligand (Scheme 4).[94,100] The conclusion drawn from these results was that heterocomplexes with different ligands coordinating to rhodium could serve as more active catalysts for the formation of the hydrogenated products **15** than could the related homocomplexes.

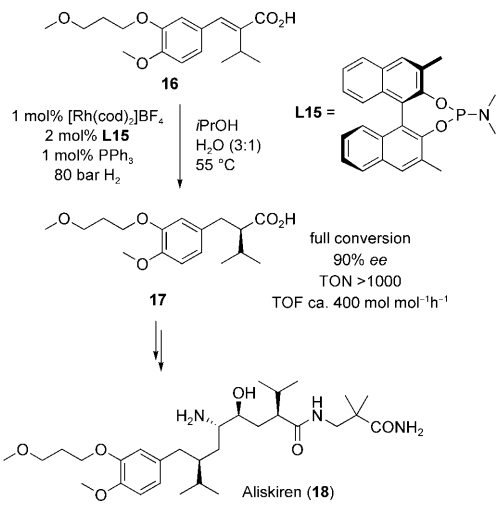


Scheme 4. Rhodium-catalyzed asymmetric hydrogenation using a combination of two chiral ligands.

Similarly, enhanced selectivity could be reached in several rhodium-catalyzed hydrogenations by using mixtures of different chiral monodentate phosphonites or phosphoramidites. In these transformations, the heterocomplexes with different ligands coordinated to the rhodium center proved to be more-active and more-selective catalysts than the corresponding homochiral complexes bearing two identical chiral ligands. It is evident that the "chiral catalytic space" can be drastically expanded through this self-assembly and self-selection process. The ability to form heterocomplexes results in the number of different heterocomplexes that are accessible expanding rapidly (Scheme 3). The same approach has been extended to other transformations, for example C–C bond formation (see below). An excellent and extensive discussion on combinatorial approaches in transition-metal catalysis in which monodentate ligands were used was recently presented.[96]

An important extension pertains to the use of mixtures of chiral monodentate phosphoramidites and achiral ligands, as we demonstrated for several hydrogenations.[92] This is particularly evident in the asymmetric hydrogenation of cinnamic acid **16**, one of an especially challenging class of substrates, that leads to chiral building block **17** for a wide variety of pharmaceutically important target compounds.[92,98] Whereas the exclusive use of homochiral phosphoramidite ligands resulted in low enantioselectivity (< 16% *ee*), the combination of achiral triphenylphosphine with **L15** boosted the activity and enantioselectivity (90% *ee*; Scheme 5).[98] This combination of an achiral and a chiral monodentate ligand approach is the basis for a multi-ton industrial production at DSM of a key intermediate for the renin inhibitor Aliskiren **18**.[98]

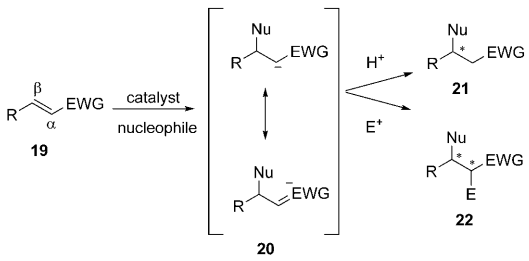
The immobilization of homogeneous catalysts for their application in a heterogenous fashion, thus allowing for easy and fast recovery of the catalyst, is an important field of research.[104,105] Phosphoramidite ligands have been immobilized on polystyrene and Merrifield resins by several research groups.[106–108] However, as frequently observed upon immobilization of homogeneous chiral catalysts, the enantioselectivity decreased when the benchmark reactions were carried out.



Scheme 5. Rhodium-catalyzed asymmetric hydrogenation by using a mixed-ligand approach with an achiral and a chiral ligand.

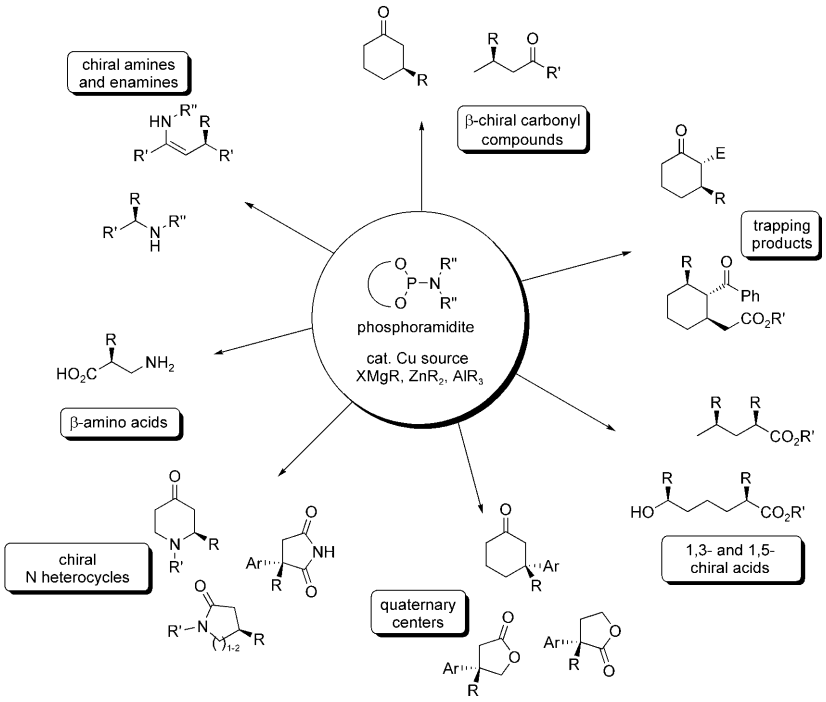
3. Transition-Metal-Catalyzed Asymmetric 1,4-Addition with Organometallic Nucleophiles

The asymmetric conjugate addition reaction is one of the most studied synthetic transformation of the last few decades.[109–113] In particular, the development of an effective enantioselective copper-catalyzed conjugate addition of organometallic reagents has for a long time been a major challenge in synthetic chemistry.[26,114–116] In this transformation, the nucleophile is transferred to the β position of an α,β-unsaturated system **19** (for example, an enone) to yield a stabilized carbanion **20** (Scheme 6). This intermediate can subsequently be protonated to yield the β-chiral product **21** or it can be quenched by addition of an electrophile to provide chiral compounds **22** with vicinal stereocenters.



Scheme 6. Conjugate addition.

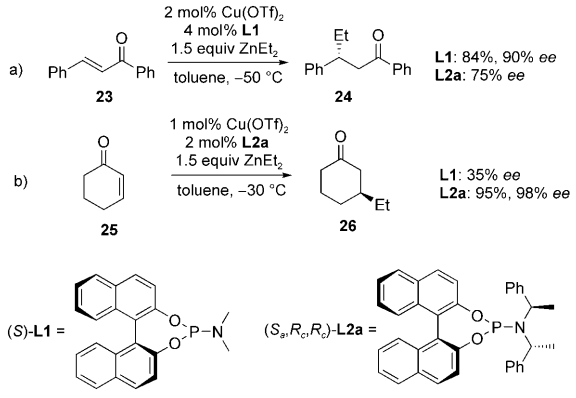
A well-known problem that had to be overcome was the high affinity of organometallic reagents to undergo direct 1,2-addition to the electron-withdrawing group. This catalytic asymmetric conjugate addition has successfully been developed with a wide variety of substrates (for example, enones, α,β-unsaturated esters, nitroalkenes, etc.) and organometallic nucleophiles (Grignard reagents, organozinc, and organoaluminum compounds), and furthermore has been applied to numerous natural product syntheses.[109–117] Scheme 7 illustrates a selection of chiral products accessible by this method.



Scheme 7. Chiral products accessible through copper/phosphoramidite-catalyzed asymmetric conjugate addition.

3.1. Asymmetric Copper-Catalyzed Conjugate Additions with Dialkyl Zinc Reagents

The copper-catalyzed conjugate addition of dialkyl zinc reagents to Michael acceptors[26,50,118,119] was introduced in 1996 and was the first reaction in which chiral phosphoramidite ligands were employed (Scheme 8).[31,32] Good yields and *ee* values as high as 90% were achieved for the addition of diethylzinc to chalcone (**23**) by using BINOL-based phosphoramidite ligand **L1** (MonoPhos: Scheme 8a). In most subsequent studies, a combination of simple monodentate chiral ligands and Cu^{II} salts in low catalyst loadings and optimal metal/ligand ratios (1:2) were used. The fact that both cyclic and acyclic enones could be converted with high levels of stereocontrol attracted much interest to this catalytic system.



Scheme 8. Copper-catalyzed asymmetric conjugate addition of diethylzinc to cyclic and acyclic enones.

A dramatic increase in the enantioselectivity of the addition reactions (Scheme 8) was observed when a chiral amine moiety was incorporated in these phosphoramidite ligands. Excellent yields (up to 95%) and *ee* values exceeding 98% *ee* were achieved in the addition to cyclochexenone **25** in the presence of the bis(1-phenylethyl)amine-derived ligand **L2** (Figure 4).[32]

These findings mark a breakthrough in asymmetric C–C bond formation and provide the first examples of catalytic enantioselective conjugate additions of organometallic reagents with absolute levels of stereocontrol. The easy synthesis of ligand **L2** (Figure 4) and its isomers, as well as the high levels of stereoselectivity have initiated numerous applications of phosphoramidite ligands, as well as a wealth of related chiral ligands, in catalysis.

Several reviews concerning earlier developments have appeared.[26,110–116,120–124] In the following sections we focus on progress in phosphoramidite-based asymmetric conjugate addition since 2002.

3.1.1. Recent Developments

The concept of asymmetric catalysis with flexible biphenyl ligands is well established.[90,91,125,126] This concept has been applied successfully to phosphoramidite ligands **L16** with an achiral, flexible biphenol unit as the diol and chiral amine moieties (Figure 5).[127,128] More recently, biphenol-based

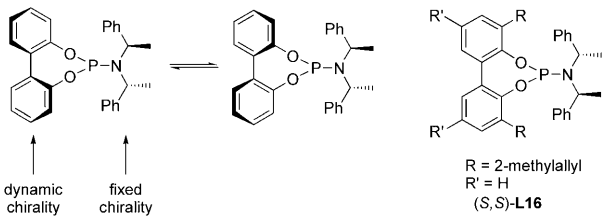
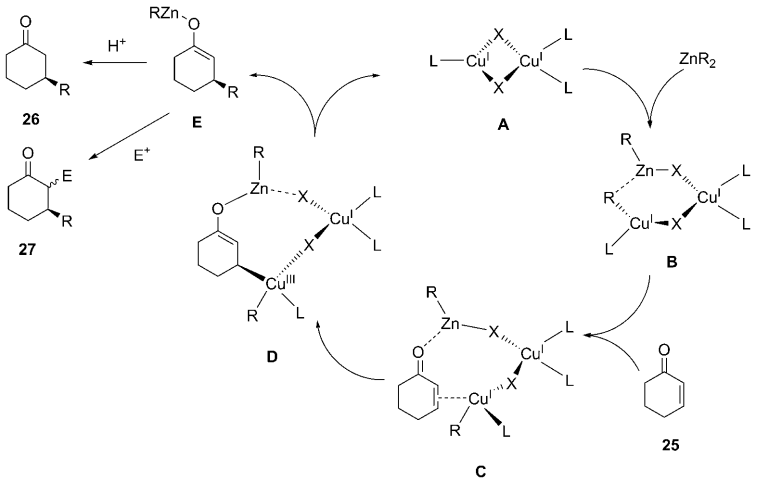


Figure 5. Biphenol-derived phosphoramidite ligands.

ligands with different substituents at the 2- and 4-positions were reported.[63] Variation of these substituents led to excellent *ee* values and yields in the addition of dialkyl zinc reagents to various Michael acceptors. The systematic variation of the substituents on the ligands showed no clear trend, but the best results were obtained with ligands **L16** (Figure 5).

The scope of the conjugate addition was expanded in various directions. Aryl zinc reagents were introduced as nucleophiles in 2004; previously only alkyl zinc reagents had been employed successfully in copper-catalyzed conjugate addition reactions to cyclohexenone.[129] The addition of diphenylzinc to cyclohexenone occurred in excellent yield and a selectivity of up to 94%. Furthermore, it was shown that a sequential asymmetric conjugate addition to dienones can be facilitated with the copper/phosphoramidite system.[130]

Following on from the early studies,[114,131–133] the nature of the phosphoramidite/copper catalyst for conjugate addition reactions was investigated by means of elaborate NMR and MS experiments (Scheme 9).[134–136] For these studies, phosphoramidite ligands **L4** (Figure 4) and **L5** (Figure 5) were employed. It was concluded that the precatalyst consists of a dimeric copper(I) complex **A**, wherein the two copper atoms are coordinated in a mixed trigonal/tetrahedral fashion. Based on this structural information, a catalytic cycle was proposed, starting with the alkyl transfer from the dialkyl zinc reagent to the copper atom to form trinuclear complex **B** (Scheme 9). The subsequent formation of complex **C** involves π coordination of the Cu^{I} center to the olefin moiety. The Zn^{II} center acts as a Lewis acid, thereby binding to the carbonyl group, with a second copper(I) halide acting as a bridging unit. Oxidative addition results in copper(III) intermediate **D**. The rate-determining step of this reaction was found to be the reductive elimination from **D**,[133] which restores the active catalyst **A** and the zinc enolate **E**. Intermediate **E** can subsequently be converted with various electrophiles to yield **27** (see Section 3.1.2) or be protonated to yield the simple conjugate addition product **26**.



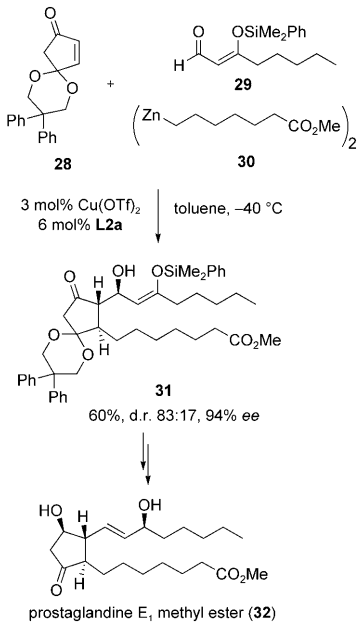
Scheme 9. Proposed catalytic cycle for the copper-catalyzed conjugate addition.

3.1.2. *Trapping of Reaction Intermediates with Electrophiles*

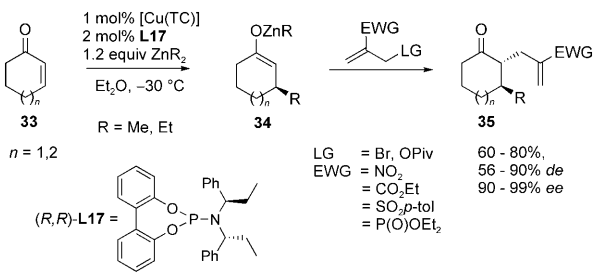
Several research groups had previously shown that the zinc enolate intermediates resulting from the copper-catalyzed conjugate addition reactions could be trapped with various electrophiles[32,137,138] or could be transferred in situ to the corresponding enol acetates.[139] This method was successfully applied in the key step of the synthesis of prostaglandine E_1 methyl ester (**32**).[140] When cyclopentenone **28** was subjected to the copper/phosphoramidite catalytic system with **L2a** in the presence of aldehyde **29** and dialkyl zinc reagent **30**, the corresponding aldol product **31**, which contains all the necessary structural and stereochemical elements of PGE_1, was obtained with high enantioselectivity (Scheme 10). This intermediate was used in a short total synthesis of prostaglandine **32**.

Following earlier reports on tandem copper-catalyzed conjugate addition/palladium-catalyzed allylation,[141] the direct trapping of zinc enolates **34** with activated allylic electrophiles was demonstrated (Scheme 11).[142] α,β-Disubstituted cyclohexanones and cycloheptanones **35** were obtained with yields of up to 80% and excellent *ee* values (up to 99%) by using catalytic amounts of biphenol-based phosphoramidite ligand **L17** and [Cu(TC)] (TC = thiophene carboxylate). The *trans*/*cis* ratios of **35** were high in most cases, with the *trans* products favored. This development marks an important alternative to the enantioselective palladium-catalyzed allylation reactions,[143–145] where mainly unsubstituted allyl moieties can be introduced at the α position of a ketone.

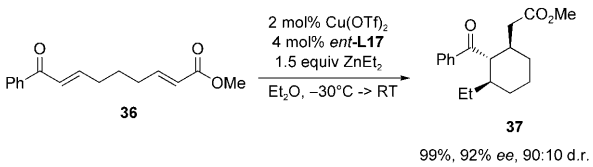
A related tandem copper/phosphoramidite-catalyzed conjugate addition with subsequent ring closure was also reported (Scheme 12).[146,147] The linear bis-α,β-unsaturated compound **36** was subjected to conjugate addition of diethylzinc, and the intermediate zinc enolate was trapped by an intramolecular Michael reaction, which resulted in



Scheme 10. Copper-catalyzed conjugate addition as a key step in the synthesis of prostaglandines.



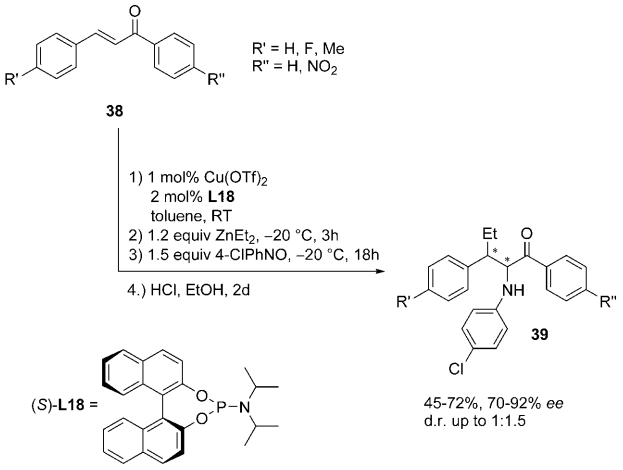
Scheme 11. Trapping of zinc enolates with activated allylic electrophiles.



Scheme 12. Tandem conjugate addition/cyclization reaction.

trisubstituted cyclohexane **37** in excellent yield (99%), high diastereoselectivity, and very good enantioselectivity. The outcome of this reaction with respect to the diastereo- and enantioselectivity is strongly dependent on the phosphoramidite ligand applied. The best results were obtained with flexible biphenol-based phosphoramidite (*S*,*S*)-*ent*-**L17** (see Scheme 11).

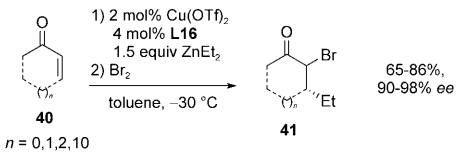
The trapping of intermediate chalcone-derived zinc enolates with 4-chloronitrosobenzene yields chiral α-amino ketones **39** through a formal tandem conjugate addition/*N*-nitroso aldol reaction to chalcone **38** (Scheme 13).[148] The



Scheme 13. Asymmetric tandem conjugate addition/*N*-nitroso aldol reaction.

diisopropylamine-based ligand **L18** afforded the desired products **39** in good yield and enantioselectivity (up to 92% *ee*). However, the diastereoselectivity remained low.

The use of a conjugate addition/halogenation method in the copper-catalyzed reaction of enones **40** with diethylzinc afforded α,β-disubstituted ketones **41** (Scheme 14).[149] In the case of biphenol-derived phosphoramidite **L16** (see Figure 5), the addition products **41** were formed with mostly excellent *ee* values (exceeding 90%). Both cyclic and acylic enones **40** were investigated, but a drawback was that in most cases the diastereoselectivity was low.



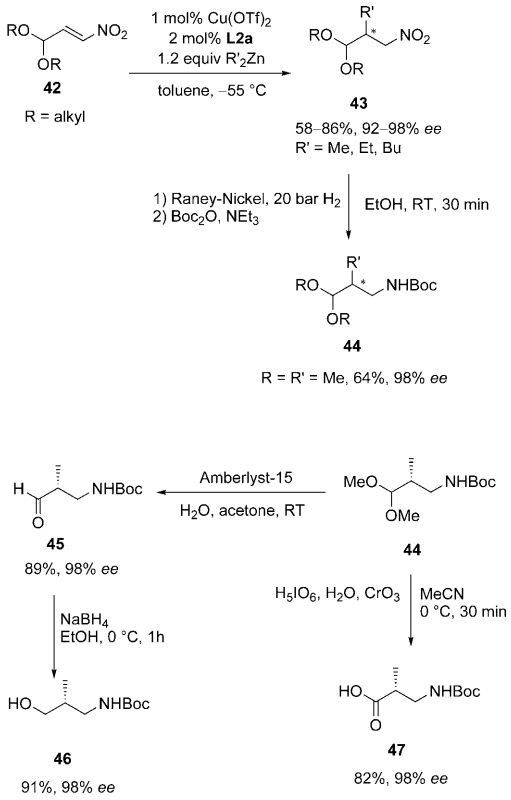
Scheme 14. Tandem conjugate addition/halogenation reaction.

3.1.3. Alternative Phosphoramidite Ligands for Conjugate Additions

Numerous chiral diol moieties have been used for the synthesis of chiral phosphoramidites.[111–113] These include ligands based on octahydro-BINOL **L3**,[150] TADDOLs **L4**,[137,151] 8,8′-fused binaphthols **L9**,[152] spirobiindane-diols **L11**,[153,154] sugar-based phosphoramidite-phosphites **L12**,[155] and 9,9′-spirobixanthene derivatives **L10**[156] (Figure 2). However, only a few of the newly developed ligands could compete with the phosphoramidites reported earlier[31,32,63,112,127] (see Figures 4 and 5) or the catalytic system based on N-heterocyclic carbenes and peptide-derived ligands[138,157,158] in terms of yield and enantioselectivity in the copper-catalyzed conjugate addition of dialkyl zinc reagents to enones.

3.1.4. Other Michael Acceptors

Shortly after the introduction of the copper/phosphoramidite system for conjugate addition to enones **23** and **25** (Scheme 8), studies were carried out on related Michael acceptors such as nitroolefins.[159–161] Acetal-substituted nitroalkenes **42** provide particularly attractive precursors for the synthesis of β-amino acids through a two-step procedure. The high reactivity of substrates **42** led to the development of a successful highly enantioselective method (Scheme 15).[162,163] Catalytic amounts of $Cu(OTf)_2$ and phosphoramidite **L2a** (Figure 4) led to the addition products **43** in moderate to good

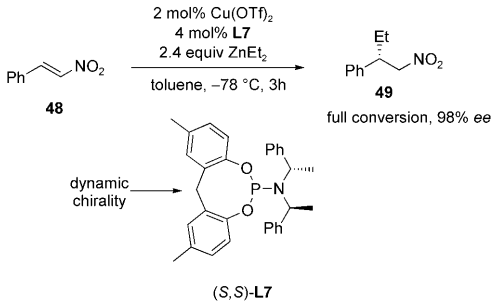


Scheme 15. Copper-catalyzed enantioselective conjugate addition to nitroolefins.

yield and excellent enantioselectivity (up to 98% *ee*). The *N*-Boc-protected acetal **44** could be readily converted into chiral amino alcohols **46** or carbonyl compounds such as amino aldehydes **45** and β^2-amino acids **47**.

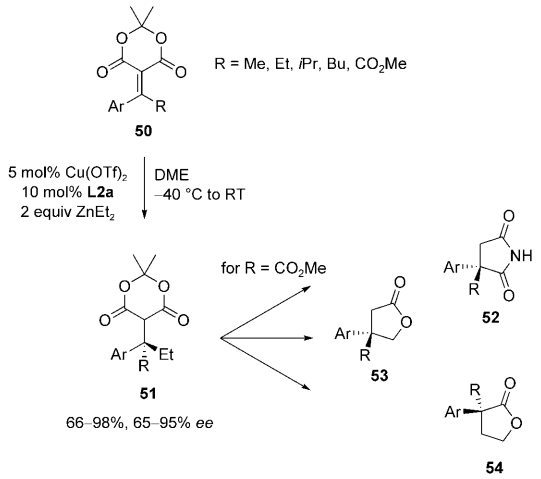
The conjugate addition to nitroolefins was also examined by using flexible biphenol-based phosphoramidite ligands **L16** (see Figure 5) carrying bulky substituents on the amine moiety.[164] In a related study, derivatives of the biphenol-based ligand **L16** with different substitutions on the biphenol unit were employed.[165] For example, the use of a 3,5,6-trimethylbiphenol backbone for the the phosphoramidite ligand led to the addition product of diethylzinc to nitrostyrene **48** being isolated with 94% *ee*.

Recently, it has been shown that *tropos*-diphenylmethane-based phosphoramidite **L7**, which has a more flexible backbone, outperforms the previously mentioned ligands in terms of enantioselectivity (Scheme 16).[126] The reaction of nitrostyrene **48** with diethylzinc gave nitroalkane **49** with 98% *ee*. It was argued that the more dynamic backbone of these ligands allows for easier self-adaption to the spacial demands of the catalyst, thereby enhancing the enantioselectivity of the asymmetric transformation (see also Section 3.1.1).

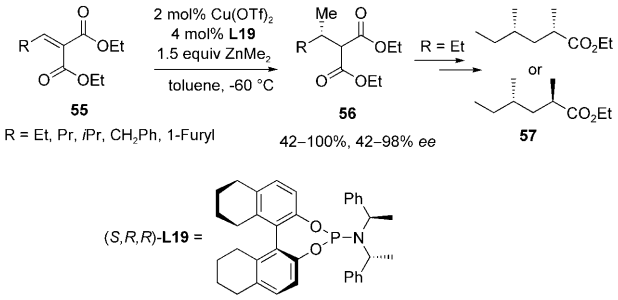


Scheme 16. Copper-catalyzed conjugate addition to nitrostyrene with a diphenylmethane-based ligand.

The copper-catalyzed conjugate addition of diethylzinc was also applied to derivatives of Meldrum's acid, which yielded derivatives of β-substituted carboxylic acids.[166] This transformation was extended to aryl alkylidene derivatives of Meldrum's acid **50**, which in the presence of phosphoramidite ligand **L2a** (see Figure 4) afforded the addition products **51** in excellent yields and *ee* values up to 95% (Scheme 17).[167] This reaction is an attractive route for the synthesis of stereogenic quaternary carbon atoms,[168–174] and has recently been applied to the asymmetric synthesis of chiral succinimides **52** as well as chiral γ-butyrolactones **53** and **54**.[175]



Scheme 17. Conjugate addition to derivatives of Meldrum's acid.

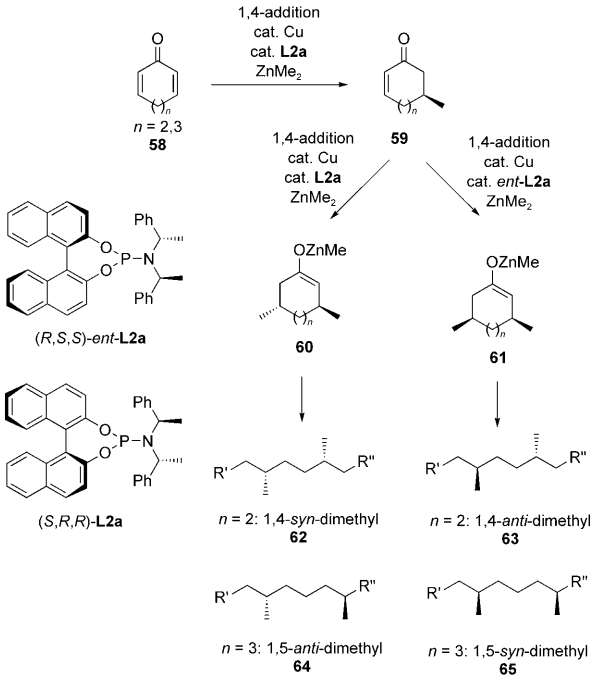


Scheme 18. Conjugate additions to unsaturated malonate esters.

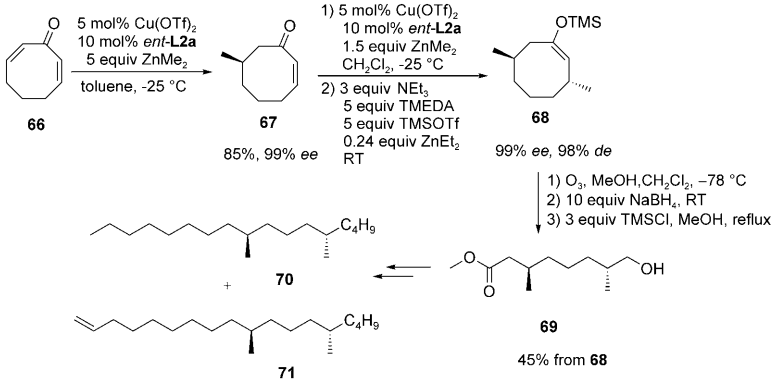
The related addition reaction to unsaturated malonate esters **55** allows the synthesis of acyclic deoxypropionate building blocks, key structural features of numerous natural products (Scheme 18).[176] The use of catalytic amounts of copper salt and octahydrobinaphthol-based phosphoramidite ligand **L19** enabled the products **56** to be isolated often in excellent yield and enantioselectivity (up to 98% *ee*). Since this reaction could be carried out in an iterative manner, it furnishes an enantio- and diastereoselective pathway towards chiral 1,3-dimethyl carboxylic acid derivatives **57**, which are important building blocks in the synthesis of deoxypropionate natural products.

In 2005, the copper-catalyzed asymmetric conjugate addition of dialkyl zinc reagents was extended to a general method for acyclic chiral building blocks with *syn*- and *anti*-1,4- and 1,5-dimethyl arrays.[177] By carrying out a double asymmetric conjugate addition on dienones **58** with a copper/phosphoramidite system and subsequent oxidative ring opening, both *syn* and *anti* products carrying the methyl-substituted stereogenic centers either in a 1,4- or 1,5-relationship (**62–65**) were accessible by judicious choice of the chiral ligands and trapping reagents for the enolate (Scheme 19).

These methods were applied in the enantioselective synthesis of isoprenoid building block **69** (Scheme 20). A double conjugate addition of $ZnMe_2$ to dienone **66** was carried out with ligand *ent*-**L2a** (see Figure 4) to yield TMS-enolate **68** in excellent yield, 98% *de*, and 99% *ee*. The isoprenoid building block **69** was obtained in a few steps after ozonolysis. The *anti*-dimethyl-substituted compound **69** was subsequently employed in the total synthesis of apple leaf-miner pheromones **70** and **71**.[177] A further example of the versatility of this catalytic method is the total synthesis of two naturally occuring compounds from *mycobacterium tuberculosis*.[178,179]

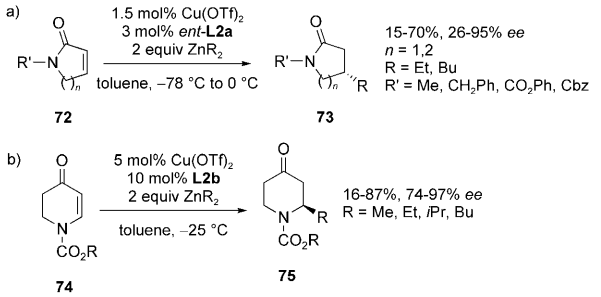


Scheme 19. General scheme for the construction of 1,4- and 1,5-dimethyl arrays.



Scheme 20. Enantioselective synthesis of isoprenoid building blocks.

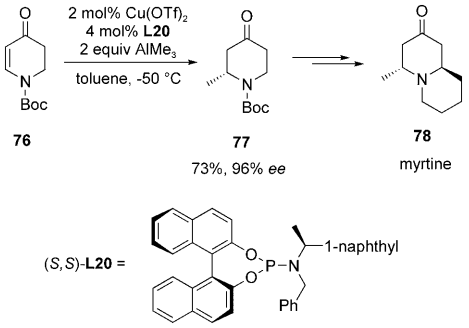
Conjugate addition reactions of dialkyl zinc reagents to cyclic nitrogen-containing Michael acceptors, such as lactams **72** and piperidones **74**, have recently been disclosed (Scheme 21).[180,181] The addition products **73** and **75** are important intermediates in alkaloid syntheses. The reaction of diethylzinc and α,β-unsaturated lactams in the presence of



Scheme 21. Conjugate addition to lactams and piperidones.

phosphoramidite ligand *ent*-**L2a** (see Figure 4) gave the heterocyclic products **73** with *ee* values of up to 95% (Scheme 21a). Although the addition to N-substituted-2,3-dehydro-4-piperidones **74** (Scheme 21b) required higher loadings of catalyst and phosphoramidite ligand **L2b** (see Figure 4), these reactions provided the products **75**, with few exceptions, in high yield and excellent enantioselectivity (up to 97% *ee*).

This method was applied in the first catalytic asymmetric synthesis of the naturally occurring alkaloid myrtine (**78**; Scheme 22).[182] For the key step, the introduction of the first



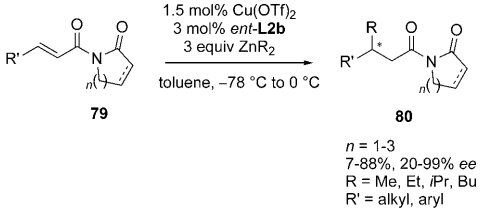
Scheme 22. Catalytic enantioselective synthesis of myrtine.

stereogenic center, an improved copper-catalyzed addition of trimethylaluminum to **76** in the presence of phosphoramidite ligand **L20** was employed to achieve higher yields (see Section 3.4). The conjugate addition product **77** was formed with excellent enantioselectivity.

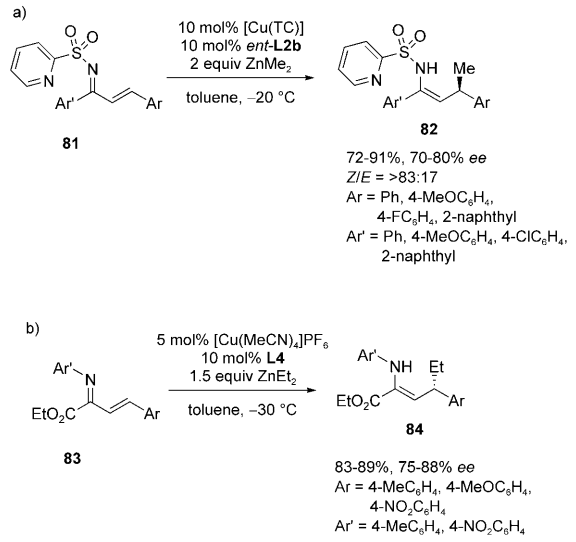
A synthetic route towards β-substituted chiral carboxylic acid derivatives **80** by a catalytic conjugate addition was reported in 2006. The transformation involved the reaction of alkyl zinc reagents with acyclic α,β-unsaturated imides **79** (Scheme 23)[183] in the presence of phosphoramidite ligand *ent*-**L2b** (see Figure 4), which led to the desired products **80** with excellent *ee* values (up to 99%).

The addition of the less-reactive dimethylzinc to α,β-unsaturated (pyridyl)sulfonylimines **81**, derived from chalcone, was also investigated (Scheme 24a).[184] By using a catalyst based upon phosphoramidite ligand *ent*-**L2b** (see Figure 4), the enamides **82** were obtained in good yields (up to 91%), *ee* values up to 80%, and *Z*/*E* ratios exceeding 83:17.

The scope of this reaction was subsequently expanded to α,β-unsaturated aryl imines **83** derived from α-keto acids,



Scheme 23. Addition to α,β-unsaturated imides.

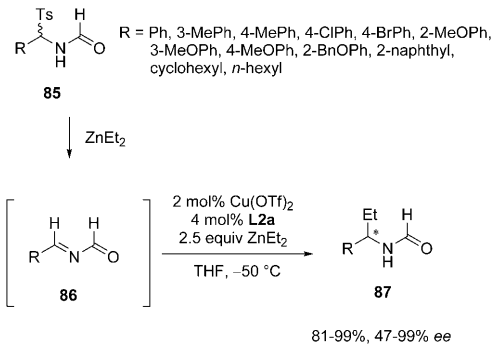


Scheme 24. Enantioselective conjugate addition to α,β-unsaturated imines.

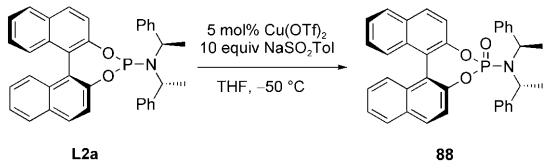
thereby opening up a route to interesting γ-chiral unsaturated amino acid derivatives **84** (Scheme 24b).[185,186] The addition products **84** were formed with good selectivity (up to 88% *ee*) by using TADDOL-based phosphoramidite ligands **L4** (see Figure 2). This method has recently been applied to the copper-catalyzed addition of dialkyl zinc reagents to maleimides, with subsequent trapping of the intermediate enolate.[187] However, only a single example showing modest enantioselectivity was reported.

A related reaction has been disclosed in which an in situ formed *N*-formylimine **86** acts as the electrophilic partner in the copper-catalyzed enantioselective addition of organometallic reagents. These include dialkyl zinc and trialkyl aluminum reagents, with the former giving rise to higher enantioselectivity.[188] Imines **86** are formed in situ from α-amidosulfones **85** by deprotonation with an extra equivalent of the dialkyl zinc reagent (Scheme 25). The use of phosphoramidite **L2a** (Figure 4) led to the chiral *N*-formyl amines **87** being obtained in excellent yield and enantioselectivity (up to 99% *ee*).

Remarkably, an in situ ligand oxidation of **L2a** to the corresponding phosphorus amide **88** was observed (Scheme 26). It was found that this oxidation was catalyzed



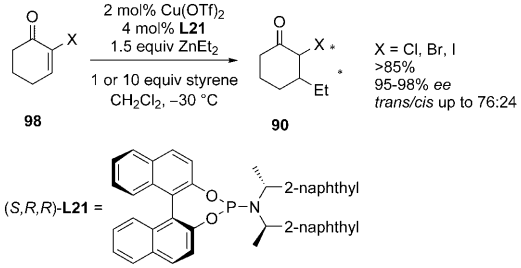
Scheme 25. Copper-catalyzed addition to *N*-formylimines.



Scheme 26. Copper-catalyzed oxidation of **L2a**.

by copper and involved the sulfinate from the reaction mixture. In some cases the presence of **88** in the reaction mixture led to higher enantioselectivity, however, the exact role of **88** is as yet not known. These findings could be related to the deterioration of **L2a** in other reactions (see Section 3.4, Scheme 40). A similar study with *N*-Boc-protected imines was recently disclosed.[189]

The conjugate addition of diethylzinc reagents to α-halo-substituted cyclohexenones **89** has also been described.[190] Remarkably, it was found that the addition of an excess of styrene could dramatically improve the enantioselectivity (Scheme 27). The use of binaphthol-based phosphoramidite

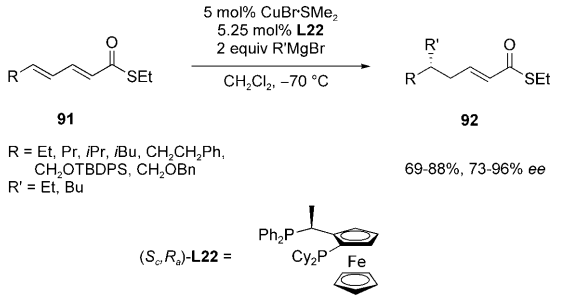


Scheme 27. Conjugate addition to α-halocyclohexenones in the presence of styrene as an additive.

ligand **L21** led to α,β-substituted cyclohexanones **90** being isolated with excellent *ee* values (exceeding 95%) and moderate diastereomeric ratios around 70:30 in favor of the *trans* products. The role of styrene as an additive remains unclear; however, it might be acting as a radical scavenger or as an auxiliary nonchiral ligand (see also Section 4.2.3).

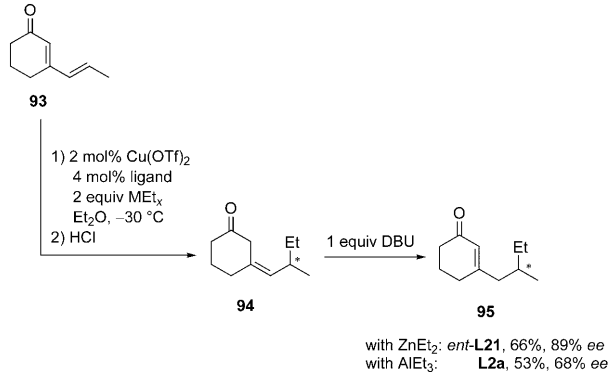
The influence of the double-bond geometry of the Michael acceptor on the enantioselectivity was recently examined in detail.[191] It was found that the substituents in the β position can influence the facial selectivity of the nucleophilic attack through a possible d–π* interaction with the copper atom (see also Section 4.1.2). However, no clear trend has yet been presented.

A number of studies on the catalytic asymmetric 1,6-conjugate addition of organometallic reagents have been carried out recently.[192,193] The 1,6-conjugate addition of Grignard reagents to dienoates **91** in the presence of a copper catalyst with ferrocenyl-based bisphosphine **L22** provided the 1,6-adducts **92** in good yield and excellent enantioselectivity (up to 96% *ee*; Scheme 28).[192] Phosphoramidites, however, gave low enantioselectivity in the 1,6-conjugate addition to acyclic substrates.



Scheme 28. Copper-catalyzed 1,6-addition of Grignard reagents.

In contrast, when propenyl-substituted cyclohexenone **93** was used as a substrate, phosphoramidite ligands **L2a** and *ent*-**L21** (compare Figure 4 and Scheme 27) gave the 1,6-addition product **95**, after isomerization of the olefin, in modest yields and *ee* values up to 89% (Scheme 29).[193] It was found in the same study that N-heterocyclic carbene ligands direct the C–C bond formation towards the 1,4-conjugate addition product, thus providing a viable synthesis of stereogenic quaternary carbon atoms.

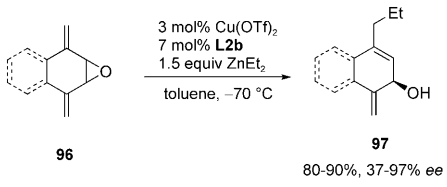


Scheme 29. Copper-catalyzed 1,6-conjugate addition.

3.2. Related Copper-Catalyzed Reactions with Organozinc Reagents

3.2.1. Desymmetrization Reactions

Shortly after the first copper/phosphoramidite-catalyzed conjugate addition reaction of dialkyl zinc reagents was reported (see Section 3.1), this method was used for desymmetrization reactions of *meso* compounds. After the addition of dialkyl zinc reagents to vinyloxiranes,[194] the desymmetrization of cylic *meso*-divinyloxiranes **96** was investigated (Scheme 30).[195] In the presence of phosphoramidite ligand

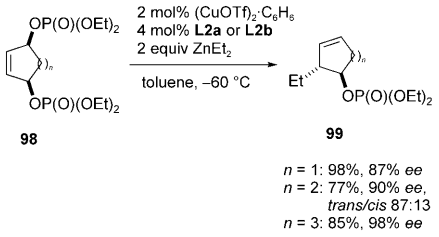


Scheme 30. Desymmetrization of divinyloxiranes.

L2b (see Figure 4) the resulting allylic alcohol **97** was formed with moderate to excellent enantioselectivity (up to 97% *ee*). The yield of these transformations reached 90%, and only traces of products resulting from direct attack on the epoxide were observed.

A related desymmetrization reaction involves the addition of dialkyl zinc reagents to cyclooctatetraene monoepoxide, which yields optically active substituted cyclooctatrienols.[196]

Furthermore, the desymmetrization of cyclic allyl phosphates by copper/phosphoramidite-catalyzed allylic alkylation in the presence of dialkyl zinc reagents was reported (Scheme 31).[197,198] Homoallylic phosphates **99** were obtained

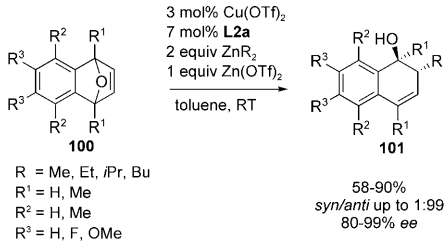


Scheme 31. Desymmetrization of allylphosphates.

from five- to seven-membered cyclic allylphosphates **98** in moderate to excellent yields and *ee* values exceeding 90% by employing ligands **L2a** or **L2b** (Figure 4). Remarkably, the addition to the five- and seven-membered allylic phosphates only gave the *trans* products **99**, whereas the addition to the six-membered allylic phosphates yielded diastereoisomers with a maximum diastereomeric ratio of 87:13 in favor of the *trans* product.

3.2.2. Ring-Opening Reactions

The copper/phosphoramidite-catalyzed conjugate addition reactions were extended to ring-opening reactions in 2002 (Scheme 32).[199] The addition and ring-opening reac-



Scheme 32. Ring opening of oxabenzonorbornadienes.

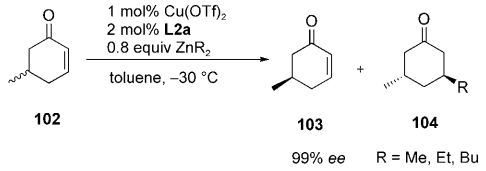
tions of oxabenzonorbornadienes **100** with dialkylzinc reagents to yield dihydrobinaphthols **101** were found to proceed with a high level of *anti* selectivity with respect to the alcohol and the newly introduced alkyl substituent. The substituted *anti*-dihydronaphthols **101** were obtained in moderate to good yields in a highly diastereo- and enantio-

selective transformation by using phosphoramidite ligand **L2a** (see Figure 4), $Cu(OTf)_2$, and one equivalent of $Zn(OTf)_2$. The copper/phosphoramidite-catalyzed *anti*-selective ring opening provides a complementary method to palladium-catalyzed ring opening, which results in the selective formation of the corresponding *syn* products.[200]

This method was subsequently extended to other heterobicyclic compounds.[201]

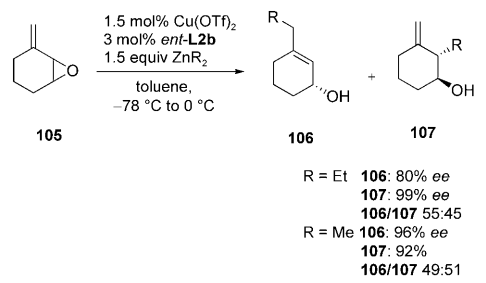
3.2.3. Kinetic Resolution Reactions

The first application of the copper/phosphoramidite catalytic system to kinetic resolution reactions was reported in 2001 (Scheme 33).[202,203] One enantiomer of methylcyclohexenone (**102**) was selectively converted under the conjugate addition conditions with dialkyl zinc reagents by using phosphoramidite **L2a** (see Figure 4), and allowed the isolation of the unreacted enantiomer of methylcyclohexenone **103** with an excellent *ee* value. In practical terms, it is noteworthy that the reaction virtually stops after one half of the racemic mixture is converted, thus making it easy to achieve the maximum yield.



Scheme 33. Kinetic resolution of methylcyclohexenone.

Building on this method, the kinetic resolution of racemic vinyloxiranes was studied.[204] Only one enantiomer of cyclic vinyloxirane **105** was found to undergo an S_N2'-type reaction under conjugate addition conditions to yield allylic alcohol **106**; the other enantiomer reacted in an S_N2 fashion to give cyclohexanol **107** (Scheme 34). When phosphoramidite *ent*-**L2b** (see Figure 4) was used as the ligand, the S_N2' (**106**) and S_N2 products (**107**) of the dialkyl zinc addition were obtained with up to 96% and 99% *ee*, respectively. Hence, this doubly selective reaction consisting of a regioselective addition and a kinetic resolution represents a remarkable and rare example of a stereodivergent and parallel kinetic resolution reaction.[205–207] In this transformation, the catalyst discriminates between the two enantiomers of the starting material **105** and selectively converts the enantiomers into two different products **106** and **107** under identical reaction conditions. Such a reaction is complementary to most kinetic resolution reactions, where only one of the two enantiomers of the starting material is converted, while the other remains unreacted (see Scheme 33).

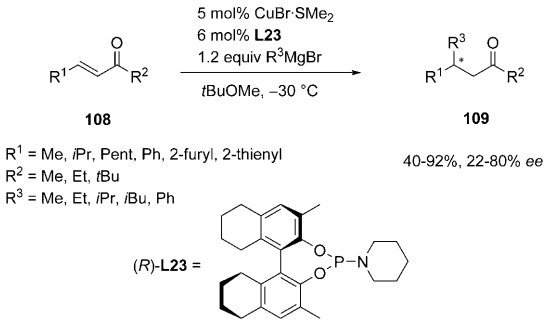


Scheme 34. Stereodivergent kinetic resolution and regioselective addition of diethylzinc.

3.3. Copper-Catalyzed Conjugate Additions with Grignard Reagents

Even though enantioselective conjugate additions of Grignard reagents have been studied extensively in the past years,[111,115,208–211] there have been few reports on the application of monodentate phosphoramidite ligands for this transformation. In 2005, the ring opening of oxabenzonorbornadienes **100** (Scheme 32) with spiro-phosphoramidite ligands **L11** (see Figure 2) and various Grignard reagents was reported.[212] The substituted dihydronaphthols **101** were obtained in yields of 54–90% and 42–88% *ee*. A related copper-catalyzed kinetic resolution of cyclohexadiene monoepoxide with Grignard reagents has been disclosed. However, in this case, ferrocenyl-derived bisphosphines proved to be superior chiral ligands.[213]

Recently, investigations on the conjugate additions of Grignard reagents to linear enones **108** in the presence of phosphoramidite ligands were reported.[214] Moderate to good yields and *ee* values were reported for the formation of 1,4-adducts **109** (Scheme 35) by using octahydrobinaphthol-derived ligand **L23**; however, further improvement on the level of enantiocontrol is required.

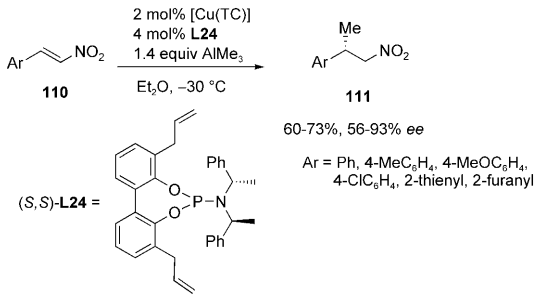


Scheme 35. Copper-catalyzed conjugate addition of Grignard reagents.

3.4. Copper-Catalyzed Conjugate Additions with Trialkyl Aluminum Reagents

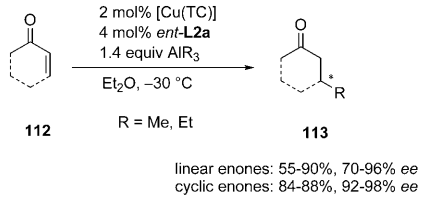
The enantioselective copper-catalyzed conjugate addition of trialkyl aluminum reagents[215] to cyclic enones **25**, linear α,β-unsaturated ketones **23** (Scheme 8), and nitroolefins (see Section 3.1.4) are important synthetic transformations,[216–222] and phosphoramidite ligands were recently applied to these reactions. Following on from early investigations on the addition of alkyl aluminum reagents to nitropropionic acid derivatives by employing phosphoramidite ligands,[223] the

asymmetric addition of trimethylaluminum to nitrostyrenes **110** was reported in 2005 (Scheme 36).[224] By using biphenol-derived phosphoramidite ligand **L24**, the chiral nitro compounds **111** were isolated in usually moderate yields, but with *ee* values reaching 93%.



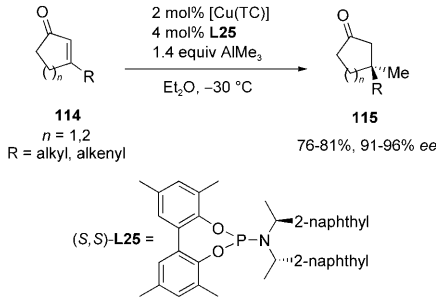
Scheme 36. Conjugate addition of trimethylaluminum to nitrostyrenes.

High yields (up to 90%) and excellent *ee* values (up to 98% *ee*) were reported for the "classic" conjugate addition to cyclic and linear enones **112** with trialkyl aluminum reagents (Scheme 37) by using binaphthol-derived phosphoramidite ligands *ent*-**L2** (see Figure 4).[225] The best results were obtained with cyclic substrates, while the addition of $AlEt_3$ generally led to higher yield and enantioselectivity compared to $AlMe_3$.



Scheme 37. Copper-catalyzed conjugate addition of trialkyl aluminum reagents.

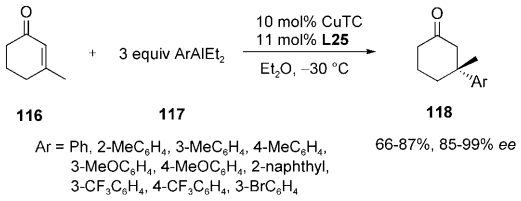
In an extension of these methods, the conjugate addition of trimethylaluminum to 3-substituted cylohexenones **114** was studied (Scheme 38).[226,227] Ketones **115**, which feature stereogenic quaternary carbon atoms,[168–174] were isolated with *ee* values of up to 96%. The best results were obtained with



Scheme 38. Copper-catalyzed conjugate additions of trialkyl aluminum reagents.

methyl-, as well as unsaturated butenyl- or propenyl-substituted cyclic enones by employing sterically demanding biphenol-based phosphoramidite ligands **L25**. This method could be extended to cyclopentenones.[228]

The abovementioned additions of trialkyl aluminum reagents are valuable methods for the generation of chiral all-carbon-quaternary centers,[229] including those with aryl substituents (Scheme 39).[230] The copper-catalyzed conjugate

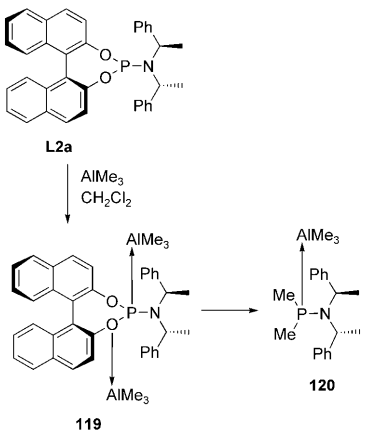


Scheme 39. Copper-catalyzed formation of aryl-substituted quaternary centers.

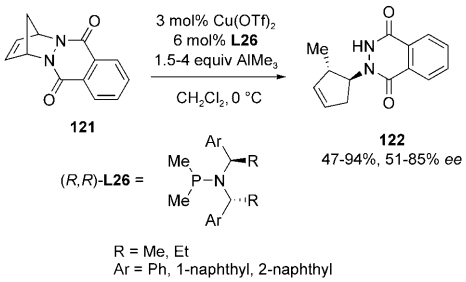
addition to 3-methylcyclohexenone (**116**) could successfully be carried out in the presence of phosphoramidite **L25** by employing in situ prepared diethyl-aryl-alane reagents **117** (compare Scheme 38). The resulting aryl-substituted cyclohexanones were obtained in good yields and with excellent *ee* values. Remarkably, the quality of aluminum reagent **117** proved to be crucial: any presence of lithium salts had a detrimental effect on the catalytic system in terms of conversion.

Recently, the ring-opening reaction of bicylic hydrazines **121** (see also Ref. [201]) by using trimethylaluminum species as nucleophiles was reinvestigated (Scheme 41).[231] Remarkably, ^{31}P NMR spectroscopy provided evidence that the employed phosphoramidite ligand **L2a** (see Figure 4) reacted in situ with trimethylaluminum to form aminophosphine **120** by cleavage of the binaphthol moiety from the phosphoramidite ligand. Aminophosphine **L26** itself can act as a ligand for copper and can also coordinate to trimethylaluminum (Schemes 40 and 41).

Even though the yield, stereoselectivity, and scope have not yet reached those of the dialkyl zinc reagents, the



Scheme 40. Formation of aminophosphines from phosphoramidite **L2a**.



Scheme 41. Ring-opening reactions with aminophosphines **L26**.

asymmetric transformations with trialkyl aluminum reagents in the presence of phosphoramidite ligands have seen remarkable developments in recent years. In particular, the facile highly enantioselective formation of quaternary carbon centers comprises a major advance. As the last example illustrates (Schemes 40 and 41), mechanistic studies need to be carried out to gain further insight into the actual catalytically active species involved.

In conclusion, the introduction of phosphoramidite ligands marks a major breakthrough in the copper-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds, and this transformation has become a powerful tool for the synthesis of chiral building blocks. A variety of substrates are tolerated and in many cases can be converted with unprecedented high yield and enantioselectivity. As a consequence of their facile and straightforward preparation, a large number of fine-tuned phosphoramidite ligands have been reported as the chiral ligand of choice for specific substrate classes or the formation of particular C–C bonds.

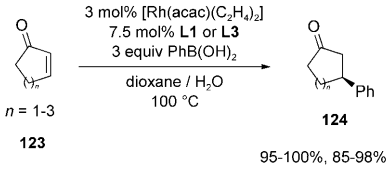
3.5. Rhodium-Catalyzed Conjugate Additions of Boronic Acids

The rhodium-catalyzed conjugate addition reaction is a highly versatile and widely used method for the stereoselective formation of carbon–carbon bonds.[233,234] Recently, monodentate phosphoramidite ligands have been applied to this important transformation.

3.5.1. General Considerations

The rhodium-catalyzed conjugate addition of boronic acids to enones in the presence of bidentate phosphorus ligands is a powerful method for introducing a variety of aryl substituents to α,β-unsaturated carbonyl compounds.[235] In 2003, monodentate phosphoramidite ligands were introduced for this transformation.[236,237] The addition of phenylboronic acid to cyclic enones **123** resulted in excellent yields (95–100%) and *ee* values being achieved (up to 98% *ee* for **124**) when elevated temperatures were employed (Scheme 42). Catalysts based upon binaphthol- and octahydrobinaphthol-derived phosphoramidite ligands **L1** and **L3** were used (see Scheme 8 and Figure 2).

The reaction conditions were later optimized and the transformations could be carried out at room temperature with similar *ee* values, although the yields were slightly

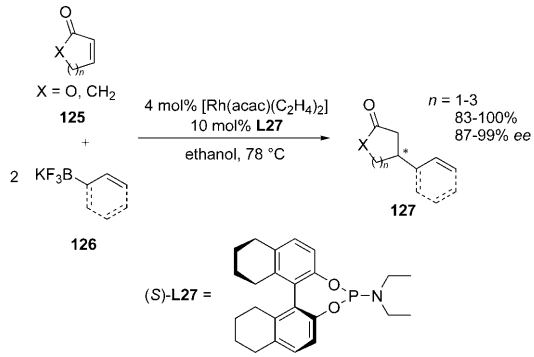


Scheme 42. Rhodium-catalyzed conjugate addition of phenylboronic acid to enones.

lower.[238] The range of aryl boronic acids applicable to this reaction was extended,[239] and it was found that rhodium complexes based on bidentate phosphoramidite ligands resulted in higher catalytic activity.[240] In all cases, better results in terms of chemical yield and enantioselectivity were obtained with cyclic enones than with linear ones. Similar results could be obtained with biphenol-derived phosphonites and phosphoramidites.[241,242] Further studies with dibenzazepine-based phosphoramidites were conducted, although lower selectivity was found.[243] A related tandem conjugate addition/allylation reaction in aqueous media was also described.[244]

3.5.2. New Reagents/Substrate Scope

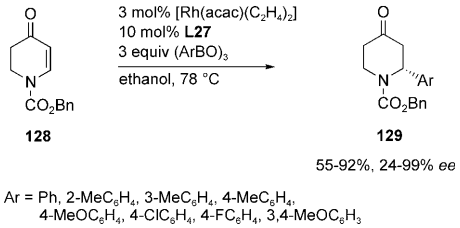
In 2004, the application of potassium trifluoroborates **126** as nucleophiles for the rhodium/phosphoramidite-catalyzed conjugate addition to different cyclic enones and unsaturated



Scheme 43. Rhodium-catalyzed conjugate additions with potassium organofluoroborates.

lactones **125** was reported (Scheme 43).[245] Trifluoroborates circumvent three problems encountered with boronic acids: They are moisture-stable, are easy to purify, and do not form trimers. A screening of phosphoramidite ligands was carried out to optimize the yield and enantioselectivity; the highest selectivity was achieved with octahydrobinaphthol-derived phosphoramidite ligand **L27**. Very good to excellent yields and *ee* values (up to 99% *ee*) were achieved by using various unsaturated trifluoroborates **126** and an optimized catalytic system.

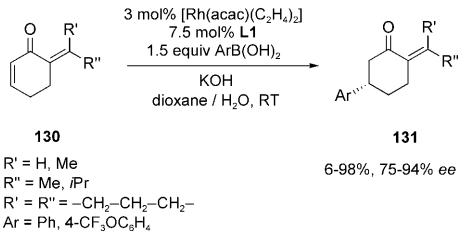
Recently, this method was extended to nitrogen-containing α,β-unsaturated carbonyl compounds, such as piperidones **128**, and yielded attractive chiral heterocyclic building blocks **129** for the synthesis of natural products (Scheme 44).[246] The



Scheme 44. Rhodium-catalyzed conjugate addition to piperidones.

use of phosphoramidite ligand **L27** (Scheme 43) led to addition products **129** in good yields and, with a few exceptions, excellent *ee* values of up to 99%.

A rhodium-catalyzed conjugate addition to substituted dienones **130** in the presence of phosphoramidite ligand **L1** was also reported (Scheme 45).[247] The products **131** of the addition to the least substituted Michael acceptor moiety in **130** were formed under basic conditions at room temperature in many cases in excellent yields and *ee* values (up to 98% yield and 94% *ee*).



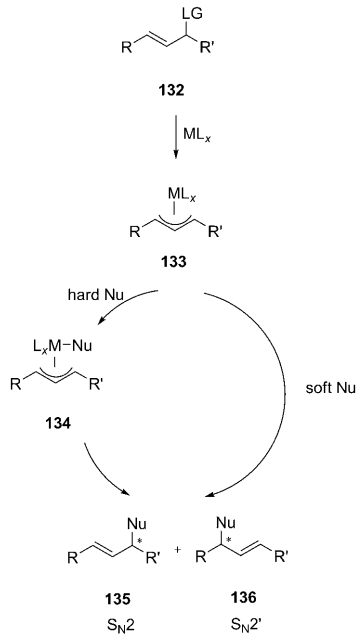
Scheme 45. Rhodium-catalyzed conjugate addition to dienones.

The mixed-ligand approach (see also Section 2) was also applied to the rhodium/phosphoramidite-catalyzed conjugate additions of boronic acids to nitrostyrenes **110** and cyclohexen-2-one **25** (see Schemes 8 and 36).[102,103] Mixtures of phosphoramidite ligands with chiral and achiral ligands were investigated. In these cases the heterocomplexes of different ligands showed higher activity; however, the results in terms of yield and enantioselectivity could not rival those reported previously with homocomplexes (see Section 3.5.1). The use of simple phosphoramidites in the rhodium-catalyzed conjugate addition of aryl boronic acids in the presence of monodentate ligands has become a very powerful method in recent years to prepare chiral building blocks for synthesis, and is complementary to the catalytic systems based on bidentate ligands. The versatility lies in the arylation of cyclic Michael acceptors; however, a highly enantioselective arylation of acylic substrates by using phosphoramidites remains a challenge.

In summary, the recent developments in the area of the conjugate additions based on the use of phosphoramidite ligands illustrate that these ligands have paved the way for a variety of new, high-yielding, and selective catalytic C–C bond-forming reactions.[112] Dialkyl zinc, alkyl magnesium, and trialkyl aluminum as well as aryl boronic reagents have been used successfully in highly enantioselective alkyl and aryl transfer reactions to a wide range of α,β-unsaturated compounds. Both cyclic and linear unsaturated systems can be employed as substrates for conjugate additions, depending on the catalytic system. For many conjugate addition reactions, phosphoramidites give rise to highly versatile catalytic systems in terms of scope and stereoselectivity.

4. Allylic Substitutions

The allylic substitution, particularly the palladium-catalyzed variant, is a reaction of major significance for the generation of chiral, multifunctional building blocks, and ranks among the key transformations for organic synthesis.[144,145,248–252] One of the typical features of the palladium-catalyzed reaction is that "soft" nucleophiles such as malonates are transferred directly to the allyl complex **133**, whereas "hard" nucleophiles such as organozinc or Grignard reagents are proposed to transmetalate to palladium to give allyl–palladium complex **134** prior to formation of a C–C bond (Scheme 46).[144,145] Thus, the different types of nucleophiles give a different ratio of the products **135**/**136** in the substitution reaction. In contrast to the conjugate addition reactions (see Section 3), the phosphoramidite/metal ratio required for the best enantioselectivity is 1:1, irrespective of which metal is employed.



Scheme 46. Allylic substitution.

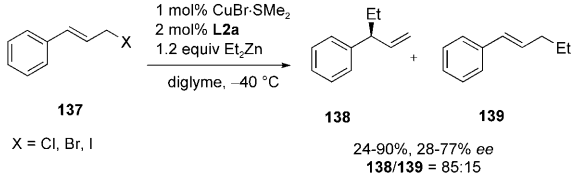
4.1. Copper-Catalyzed Allylic Substitutions

The copper-catalyzed allylic substitution, in contrast to the corresponding palladium-catalyzed reactions (see above), generally yields the branched chiral substitution products,[111–113,208,253–255] which makes this transformation very attractive for a stereoselective approach. Moreover, "hard"

organometallic nucleophiles in general are better tolerated by the copper catalyst system than by the palladium variant (for the palladium system, see Refs. [144, 145]). Shortly after the first reports of asymmetric copper-catalyzed allylic substitutions with Grignard[256,257] and organozinc[258,259] reagents, phosphoramidite ligands were applied to this transformation.

4.1.1. Copper-Catalyzed Allylic Substitution Reactions with Dialkyl Zinc Reagents

The application of phosphoramidite ligands for the copper-catalyzed allylic substitution was reported in 2001.[260] The branched product **138** was obtained in up to 77% *ee* (Scheme 47) in the asymmetric allylic alkylation of



Scheme 47. Copper-catalyzed allylic alkylation of diethylzinc with cinnamyl halides.

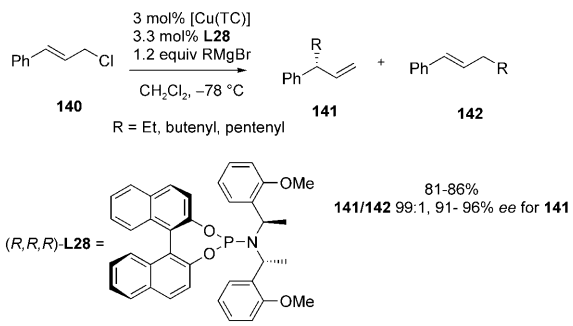
cinnamyl halides **137** with dialkyl zinc reagents in the presence of phosphoramidite ligand **L2a** (see Figure 4). However, the branched/linear ratios and yields were usually moderate.

Subsequent studies revealed similar results with spirophosphoramidite ligands **L11** (see Figure 2).[261] Extensive optimization of the reaction conditions, which included an elaborate ligand screening,[88] led to a dramatic improvement of the chemical yields (up to 98%) and enantioselectivity for **138** (up to 88% *ee*). An improvement of the regioselectivity (up to 97:3) in favor of the branched product **138** was also achieved. The best results were obtained with octahydrobinaphthol-derived phosphoramidite ligand **L3** (see Figure 2).

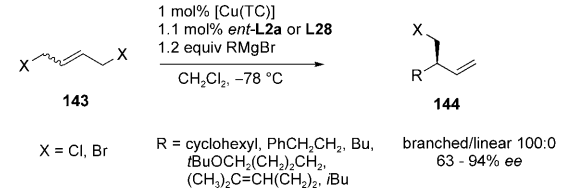
4.1.2. Copper-Catalyzed Allylic Substitution Reactions with Grignard Reagents

Following on from the early investigations of copper-catalyzed allylic substitutions of cinnamyl chloride with Grignard reagents,[262,263] this transformation was further optimized by using phosphoramidites as the chiral ligands (Scheme 48).[264,265] The *ortho*-methoxy substituents in the binaphthol-based phosphoramidite ligand **L28** were shown to be essential to achieve high selectivity. The reaction of alkyl Grignard reagents with cinnamyl chloride (**140**) yielded the branched allylic substitution product **141** with excellent *ee* values (up to 96%) and regioselectivity (branched/linear ratios of 99:1).

Recently, this methodology was extended to β-alkyl-substituted cinnamyl halides, endocyclic allylic chlorides, and 1,4-dihalobutenes.[266–269] The highest selectivity with 1,4-dichlorobutene **143** was obtained using phosphoramidite *ent*-**L2a** (see Figure 4), while **L28** (see Scheme 48) proved to be the best ligand for 1,4-dibromobutene **143** (Scheme 49). In



Scheme 48. Copper-catalyzed allylic alkylation with Grignard reagents.

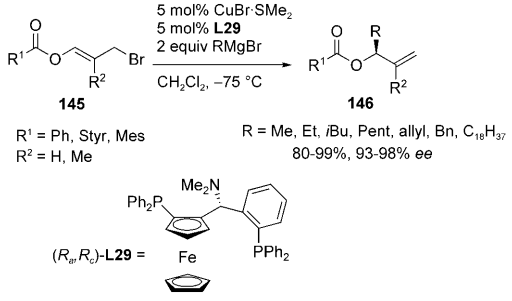


Scheme 49. Copper-catalyzed allylic alkylation of dihalobutenes.

all cases, excellent regioselectivity and high enantioselectivity were reported. It was shown that the chiral products **144** are versatile starting materials in a variety of transformations. Different substitution patterns at the olefin moiety of the starting materials **143** were also investigated, but significantly lower enantioselectivity was observed.

Remarkable results were obtained in studies on the influence of the *E*/*Z* geometry of the double bond of difunctional substrates such as dihalobutenes **143**.[268] In general, *E* substrates give higher enantioselectivity, whereas the regioselectivity towards the branched product **144** stays the same. Furthermore, both *E*/*Z* isomers of the starting material **143** give the same enantiomers when cyclohexylmagnesium bromide is used as the nucleophile. This finding is in contrast to that with phenethylmagnesium bromide, where *E* and *Z* isomers of the starting material **143** were converted into the different enantiomers of **144**. It was noted that the oxidative addition to the substrate determines the stereochemical outcome of the reaction, and not the approach of the catalyst to one of the two π faces of the olefinic double bond.

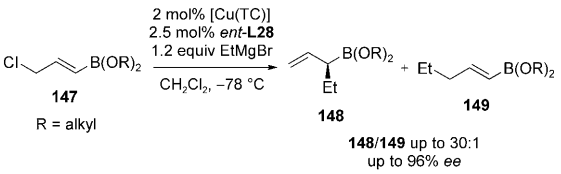
Excellent results have also been reported in the copper-catalyzed allylic substitution of various ester-substituted allyl bromides **145** (Scheme 50).[270,271] The remarkable feature of



Scheme 50. Copper-catalyzed allylic substitutions with Grignard reagents.

this transformation is that despite the presence of an enol ester moiety, branched substitution products, for example, chiral protected allylic esters, are formed exclusively. Homoallylic esters **146** were obtained in excellent yield and enantioselectivity by using ferrocenyl-based bidentate ligand **L29**[272–274] and $CuBr{\cdot}SMe_2$ as the catalyst.

A related method was recently used to prepare chiral allyl boronate reagents (Scheme 51), which were subsequently used in well-known allylation reactions of carbonyl compounds.[275] When the allylic substitution was carried out on different chloroallyl boronates **147** in the presence of phosphoramidite *ent*-**L28** (Scheme 48), the α-chiral allylboronates **148** were formed with moderate to very good regioselectivity (up to 30:1) and high enantioselectivity (96% *ee*).



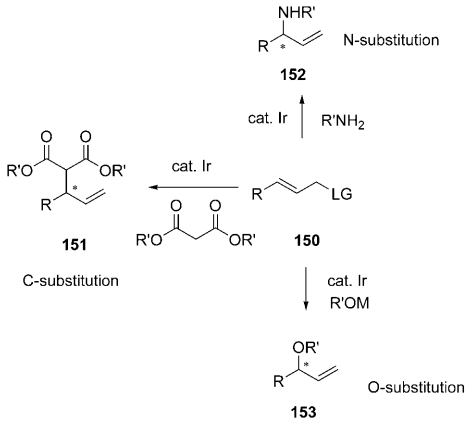
Scheme 51. Copper-catalyzed preparation of chiral borane reagents.

In summary, the copper-catalyzed asymmetric allylic substitution of hard organometallic nucleophiles has emerged in recent years as a highly useful reaction for the formation of C–C bonds that is complementary to the palladium-catalyzed allylic substitution with soft carbon nucleophiles. In particular, it allows for the preparation of numerous optically active allylic compounds, including allylic ester and allylic boranes with excellent enantioselectivity.

4.2. Iridium-Catalyzed Allylic Substitution Reactions

Iridium-catalyzed substitution reactions have gained much attention over the last years.[276–279] In fact, besides the copper-catalyzed conjugate addition, the iridium-catalyzed allylic substitution has been one of the most prominent reactions in which phosphoramidite ligands have been applied. As major developments in this field have been reviewed recently,[280] the focus in the following discussion is on demonstrating the potential of these transformations.

The first appearance of this reaction in which phosphoramidites were used as chiral ligands was as early as 1999, when the iridium-catalyzed allylic alkylation of allylic acetates **150** (LG = OAc) with sodium malonates to form **151** was reported (Scheme 52).[281] Although, with some exceptions, low enantioselectivity was observed at that time, the transformation set the stage for the numerous important iridium-based methods that were developed in recent years. One important feature of the iridium-catalyzed allylic substitution is that it allows for the application of carbon-, oxygen-, as well as nitrogen-based nucleophiles, thus providing access to a wide range of allylic products **151**–**153**.

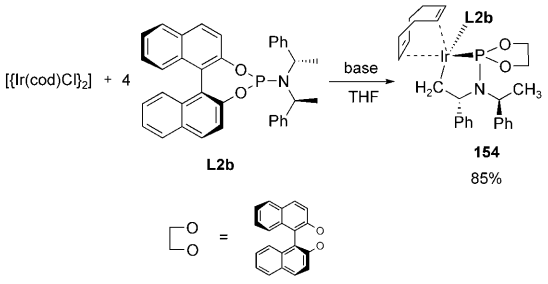


Scheme 52. Iridium-catalyzed allylic substitution.

4.2.1. Mechanistic Studies

Elaborate studies focussing on the origin of regio- and stereoselectivity as well as on the influence of different phosphoramidite ligands were carried out on this transformation.[55,282] However, the reaction mechanism and the active species involved remained largely unclear, and the desired optically active products were only obtained when LiCl was employed as an additive.

It was not until 2003 that the non-innocence of the amine moiety of the phosphoramidite ligand was discovered during the study of the related allylic amination and etherification reaction,[87,283] thus paving the way for the design of more sophisticated catalysts.[54] These investigations showed that, under basic conditions, phosphoramidite ligand (*S*,*S*,*S*)-**L2b** (see Figure 4) forms iridacycle **154** from the iridium(I) precursor through C–H activation of a methyl group in the amine moiety of the phosphoramidite (Scheme 53). In terms of later research in this area, it is remarkable that only the **L2b** diastereoisomer undergoes this activation, and can thus serve as a good catalyst for the iridium-catalyzed allylic substitution reaction. This finding is in contrast to the conjugate addition reactions (see Section 3), where the **L2a** isomer was the preferred ligand.

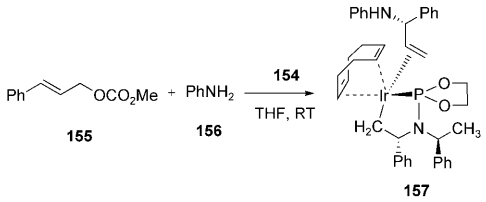


Scheme 53. Cyclometalation of ligand **L2b**.

Iridacycle **154**, when isolated and used as the catalyst in the allylic amination and etherification, provided generally good yields (up to 85%) and excellent *ee* values (94–98% *ee*), while giving the same high regioselectivity as observed before.

In contrast to reactions in which the in situ prepared catalyst from the phosphoramidite ligand and iridium precursor was used, no induction period was seen. Even faster catalysts were obtained when [{Ir(cod)Cl}$_2$] was added to the reaction mixture to decoordinate the second monodentate phosphoramidite ligand from iridacycle **154** to furnish a free coordination site at the iridium center.[54]

A recent investigation on the resting state of the iridium catalyst for the allylic amination of cinnamyl carbonate **155** with aniline (**156**) allowed for the isolation and identification of iridacycle **157** (Scheme 54). In this complex, one molecule of the desired product is coordinated to the iridium center.[284] Furthermore, kinetic investigations led to the conclusion that the addition of the allylic carbonate to the iridium catalyst is reversible.



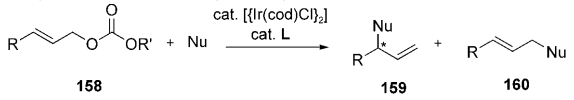
Scheme 54. Structure of the resting state of Ir/phosphoramidite catalyst **154**.

Further investigations showed that air-stable iridium catalysts could be synthesized when iridium precursors based on substituted cyclooctadienes were employed.[285] A salt-free method has also been developed.[286] Phosphoramidites bearing an amide functionality were also used; however, the catalysts based on these ligands could not compete with the aforementioned ones in terms of enantioselectivity.[287]

4.2.2. *Asymmetric Allylic Alkylations*

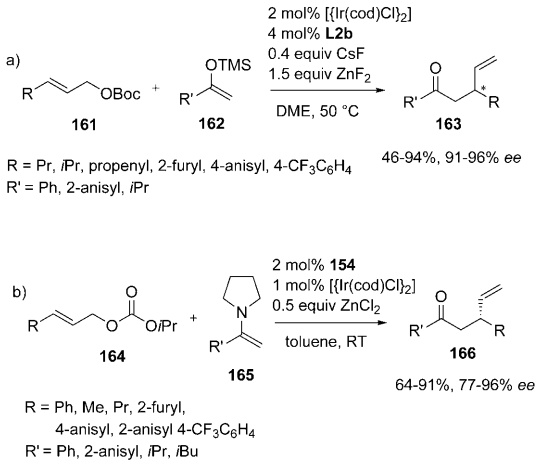
The earlier iridium-catalyzed allylic alkylation with malonates[280,288] was significantly improved in 2004 by employing allylic carbonates **158**. The results are summarized in Table 2. The use of phosphoramidite ligand *ent*-**L28** (see Scheme 48) resulted in the substitution product **159** usually being formed in good yields, excellent branched/linear ratios, and excellent *ee* values (Table 2, entries 1 and 2).[86] Remarkably, when the additive LiCl was omitted, the regioselectivity dropped significantly. In the same year, excellent results were obtained for the allylic alkylation of alkyl- and alkenyl-substituted allylic carbonates, under optimized conditions with tetrahydrothiophene (THT), 1,5,7-triazabicyclo[4.4.0]undecene (TBD,; Table 2, entries 3 and 4), and CuI as additives.[289] The application of phosphoramidite ligand **L2b** (see Figure 4) led to excellent yields, as well as with excellent regio-, and enantioselectivity.

Table 2: Selected examples of iridium-catalyzed allylic substitutions.



Entry	R (in **158**)	Nu	L	Additives	Yield [%]	**159**/**160**	*ee* [%]	Ref.
C nucleophiles								
1	Ph	NaHC(CO$_2$Me)$_2$	*ent*-**L28**	LiCl	82	99:1	98	[86]
2	4-MeOPh	NaHC(CO$_2$Me)$_2$	*ent*-**L28**	LiCl	99	99:1	97	[86]
3	Ph	NaHC(CO$_2$Me)$_2$	**L2b**	THT, TBD, CuI	88	99:1	96	[289]
4	4-MeOPh	NaHC(CO$_2$Me)$_2$	**L2b**	THT, TBD, CuI	95	99:1	97	[289]
N nucleophiles								
5	Ph	H$_2$NPh	**L2b**	–	81	99:1	97	[54]
6	Ph	H$_2$NCH$_2$Ph	**L2b**	–	81	98:2	97	[54]
7	Ph	H$_2$NCHPh$_2$	**L2b**	–	85	97:3	98	[54]
8	Ph	H$_2$N-Ph-4Me	*ent*-**L2b**	DABCO	76	99:1	94	[290]
9	Ph	H$_2$N-Ph-4MeO	*ent*-**L2b**	DABCO	91	98:2	95	[290]
10	Ph	H$_2$N-mesityl	*ent*-**L2b**	DABCO	82	97:3	96	[290]
O nucleophiles								
11	Ph	NaOPh	**L2b**	–	76	99:1	94	[54]
12	Ph	LiOPh-4Me	*ent*-**L2b**	–	91	98:2	95	[283]
13	Ph	LiOPh-4MeO	*ent*-**L2b**	–	88	98:2	97	[283]
14	4-MeOPh	LiOPh	*ent*-**L2b**	–	70	97:3	86	[283]

An important extension of the iridium-catalyzed allylic substitution in which silyl enol ethers **162** (Scheme 55a) and enamines **165** (Scheme 55b) were used as nucleophiles in the reaction with protected cinnamyl alcohols **161** was reported more recently.[291,292] In both cases, the corresponding chiral ketones **163** were obtained in excellent yield, regioselectivity, and enantioselectivity. The addition of 0.4 equivalents of CsF and 1.5 equivalents of ZnF_2 was needed to achieve the best results in the reaction of silyl enol ethers **162** with Boc-

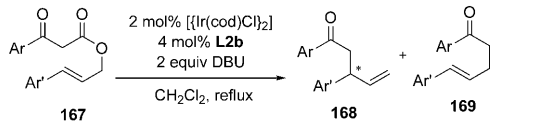


Scheme 55. Iridium-catalyzed allylation of ketone enolates and enamines.

protected allylic alcohols **161**. The role of the additives in the catalytic cycle is not clear so far; omission of either one of them led to lower or no turnover in this catalytic conversion. The preformed iridacycle **154** (see Scheme 53) was employed for the transformation of enamines **165**, which allowed the products **166** to be isolated in up to 91% yield and 96% *ee*.

This method was also applied in the allylic substitution of dienyl esters.[293] A further extension involves the use of aliphatic nitro compounds as nucleophiles in the substitution reaction with cinnamyl carbonates **158**.[294]

Investigations on the related iridium-catalyzed Carroll rearrangement were recently disclosed.[295] With catalytic amounts of $[\{Ir(cod)Cl\}_2]$ and ligand **L2b** (see Figure 4), the transformation of a variety of allyl-β-ketocarboxylates **167** to the branched ketones **168** was achieved in moderate yields but with excellent regio- and enantioselectivity (Scheme 56).



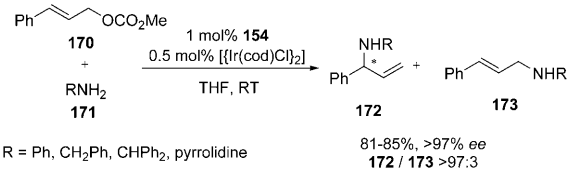
Scheme 56. Iridium-catalyzed asymmetric Carroll rearrangement.

4.2.3. ***Asymmetric Allylic Aminations/Etherifications***

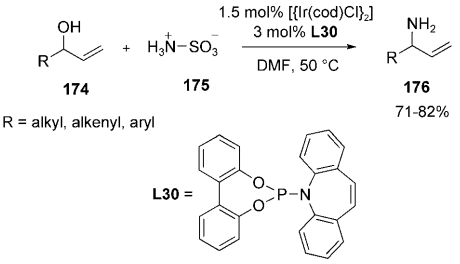
The catalytic enantioselective allylic substitution with oxygen and nitrogen nucleophiles in the presence of phosphoramidite ligands has attracted considerable interest in the past years, not least because the chiral products are highly valuable building blocks. Several studies towards the extension of allylic amination and etherification reactions to a variety of anilines, phenoxides, alkoxides, and recently alcohols as nucleophiles and different allylic carbonates have been reported.[290,296–301] Iridacycles prepared from ligands *ent*-**L2b** and **L21** (Figure 4 and Scheme 27) were used as catalysts, which led to significantly better results than those in the presence of in situ formed catalyst. Recent studies in which the biphenol-based phosphoramidite ligands with only one chiral substituent at the amine moiety was used show that the stereodiscrimination in these transformations can be attributed to the central chirality at the carbon atom located in the iridacycle.[56]

The asymmetric allylic amination of cinnamyl carbonate **170** with amines **171** catalyzed by preformed iridacycle **154** (Scheme 53) provided chiral allylic amines **172** in good yield and with excellent regio- and enantioselectivity (Scheme 57).[54]

Subsequent to the application of nosylamide as an ammonia equivalent for the allylic amination reaction,[302] sulfamic acid (**175**) was used as a cheap and versatile ammonia equivalent in allylic amination reactions (Scheme 58).[303] Remarkably, various allylic alcohols **174** could be used directly without prior transformation to



Scheme 57. Iridium-catalyzed asymmetric allylic amination.



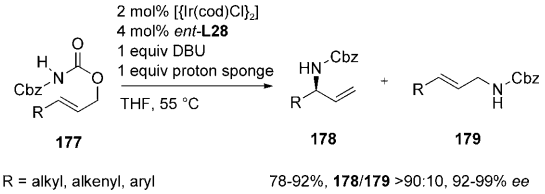
Scheme 58. Iridium-catalyzed direct amination of allylic alcohols.

generate a leaving group. The branched allylic amines **176** were reported as the only products formed in good yields when biphenol-derived phosphoramidite **L30** was used. In one case, an asymmetric version was described which reached 70% *ee* (which could be enhanced to 93% *ee* after trituration). The influence of the olefin moiety in **L30** is remarkable: The conversion dropped significantly in experiments with the saturated analogous ligand. This finding indicates an important role of the olefin in the actual catalyst. This direct formation of unprotected allylic amines shows promise as a highly valuable method for organic synthesis.

Recently, the use of various other nitrogen nucleophiles was disclosed.[304,305] Potassium trifluoroacetamide and lithium salts of di-*tert*-butylimidocarboxylate as well as amines with functionalized side chains were successfully applied to iridium-catalyzed allylic amination reactions.

Furthermore, a direct asymmetric amination of allylic alcohols with catalytic amounts of BPh_3 as an activator was demonstrated.[306] The products were obtained in moderate to excellent yields and with excellent regio- and enantioselectivity (branched/linear 97:3, 94% *ee*).

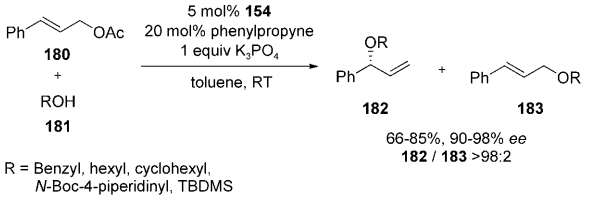
In this context, an intramolecular decarboxylative allylic amidation[298,307–309] based on the iridium/phosphoramidite catalytic system (Scheme 59) should be noted.[310,311] Chiral branched *N*-Cbz-protected allylic amines **178** were obtained from the reaction of a variety of allylic imidodicarbonates **177** in excellent yield, regioselectivity, and stereoselectivity by employing ligand ent-**L28** (see Scheme 48). An extension of



Scheme 59. Iridium-catalyzed allylic amidation.

this method to an intermolecular variant was also reported.[312] Protected primary and secondary amines could be used as nucleophiles in the reaction with ethyl allyl carbonates to yield the branched product **178** with excellent regio- and enantioselectivity.

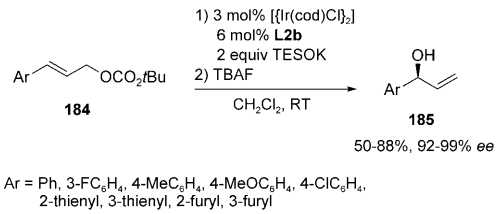
The recently discovered direct iridium/phosphoramidite-catalyzed allylic etherification with alcohols marks a major breakthrough in this area, since the oxygen-based nucleophiles commonly had to be deprotonated prior to use in allylic etherification reactions (Scheme 60).[297] Furthermore, the



Scheme 60. Iridium-catalyzed asymmetric allylic etherification.

high basicity of alkoxides poses problems with catalyst deactivation or reaction with the products. In the presence of preformed iridacycle **154** (Scheme 53), cinnamyl acetate (**180**) reacted with various alcohols **181** to give the chiral allylic ethers **182** in good yield (up to 85%) and excellent regio- and enantioselectivity. The addition of phenylpropyne proved to be necessary to prevent the isomerization of the products **182** to enol ethers. These findings mark a highly versatile system in terms of selectivity for direct allylic etherification with alcohols. In terms of stereoselectivity, they can compete with the palladium-based systems.[248,249,313]

Cleavage of protecting groups under mild conditions without racemization is a key issue for the synthesis of allylic alcohols by asymmetric allylic substitution. The first enantioselective method to give direct access to unprotected allylic alcohols was reported in 2006. By using potassium triethylsilylalcoholate (TESOK) as a nucleophile (Scheme 61)[314] and

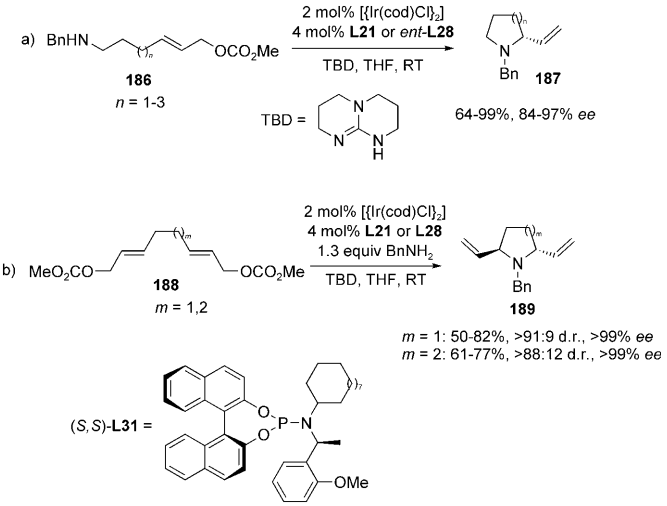


Scheme 61. Iridium-catalyzed direct synthesis of allylic alcohols.

ligand **L2b** (see Figure 4), allylic alcohols **185** were obtained with excellent enantioselectivity (up to 99% *ee*) from a wide variety of aryl-substituted allylic carbonates **184** after in situ cleavage of the silyl ethers with TBAF. The allylic alcohols **185** are very important chiral building blocks for organic synthesis.

4.2.4. *Further Applications of Iridium-Catalyzed Asymmetric Allylic Substitution*

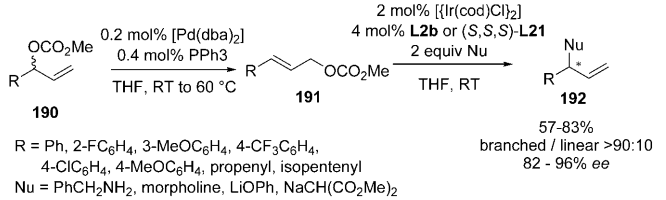
The scope of the iridium-catalyzed allylic substitution was expanded in 2004 to the synthesis of optically active nitrogen-containing heterocycles. An intramolecular asymmetric amination of benzylamine-substituted allylic carbonates **186** to yield α-vinyl-substituted pyrrolidines, piperidines, and azepanes **187** (Scheme 62a) was described.[315,316] Excellent yields and *ee* values could be achieved (up to 97% *ee*) when 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was added as a base in the presence of phosphoramidite ligands **L21**, *ent*-**L28** (see Schemes 27 and 48), or **L31**.



Scheme 62. Ring-closing reactions based on iridium-catalyzed allylic substitution.

This asymmetric substitution was subsequently extended to a double, inter- and intramolecular, allylic amination procedure.[315] The iridium-catalyzed reaction between **188**, which features two allylcarbonate moieties, and benzylamine led to divinylpyrrolidines and -piperidines **189** (Scheme 62b) with excellent *ee* values and high diastereomeric ratios in favor of the *trans* products.

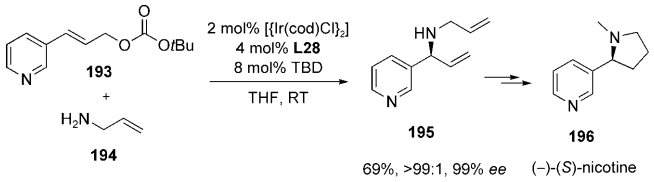
Further extensions of the iridium-catalyzed allylic substitution reaction were based on the use of sulfonamides as nucleophiles.[317] The method has also been applied to a sequential isomerization/allylic substitution reaction of allylic carbonates (Scheme 63).[318] Isomerization of the branched allylic carbonates **190** with a palladium catalyst gave the linear carbonates **191**, which are suitable starting materials for the



Scheme 63. Sequential catalytic isomerization/allylic substitution.

iridium-catalyzed asymmetric allylic substitution. The branched allylic products **192** were obtained in high regio- and enantioselectivity from reactions with a variety of nucleophiles. Catalysts derived from phosphoramidites **L2b** (Figure 4) and (*S*,*S*,*S*)-**L21**[319] (Scheme 27) were found to give the highest selectivity and yield.

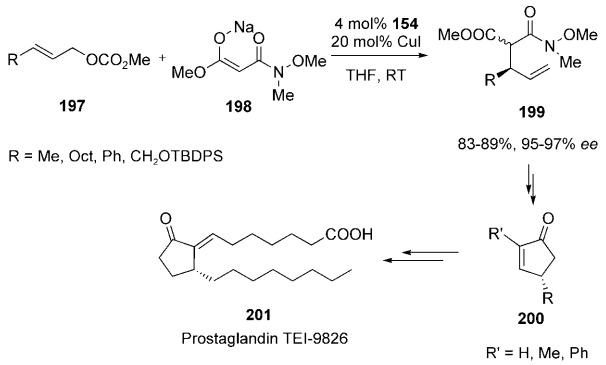
A total synthesis of nicotine **196** was reported based on an allylic amination as the key step to introduce the desired chiral amine (Scheme 64).[320] In this synthetic route allylic



Scheme 64. Total synthesis of (−)-(*S*)-nicotine.

carbonate **193** was treated with allylamine (**194**) in the presence of an iridium/phosphoramidite catalyst system. The allylic amine **195** was formed in moderate yield, but with excellent regio- and stereoselectivity when ligand **L28** was used (Scheme 48).

The application of the iridium-catalyzed allylic substitution in the syntheses of a variety of natural products, including target molecules such as prostaglandin **201**, demonstrates the synthetic utility of this method.[305,321–324] Treatment of allylic carbonates **197** with Weinreb amide **198** led to the desired products **199** in very good yields and with excellent *ee* values (Scheme 65). The malonate derivatives could subsequently be converted into chiral cyclopentenones **200**, which served as precursor compounds for the synthesis of prostaglandin **201**.



Scheme 65. Synthesis of a prostaglandin with allylic alkylation as a key step.

An iridium/phosphoramidite-catalyzed etherification was used as one of the key steps in a total synthesis of centrolobine.[325] Another related application involves an iridium-catalyzed allylic amination in combination with a ring-closing metathesis to furnish cyclic β-amino alcohol derivatives.[326] A selection of these and other target molecules accessible by application of the iridium-catalyzed substitution are shown in Figure 6.[305,321,323]

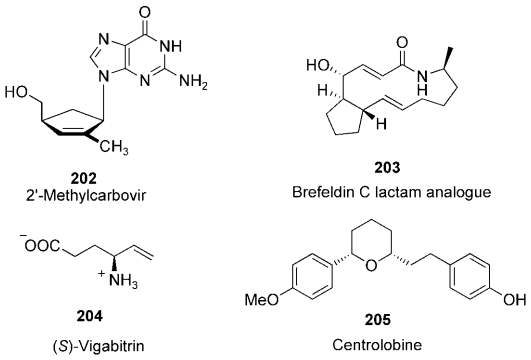
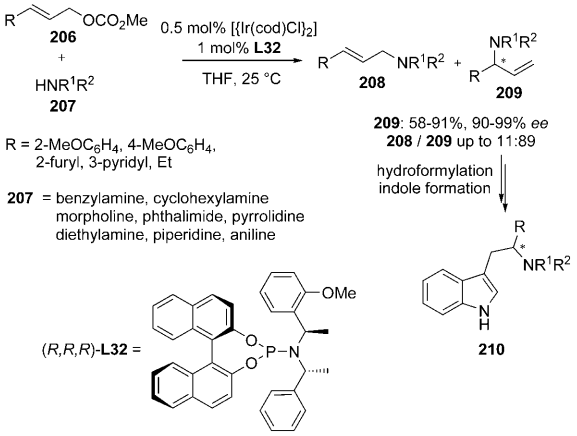


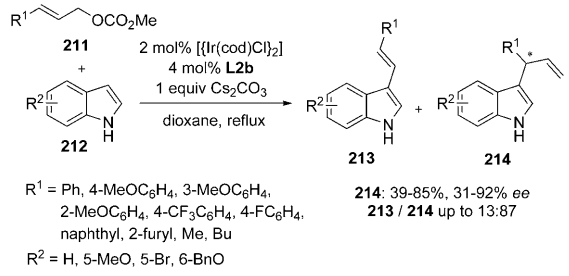
Figure 6. Target molecules obtained by routes involving iridium-catalyzed asymmetric allylic substitutions.

The iridium-catalyzed allylic substitution was also applied in the synthesis of chiral substituted indoles. The allylic amination was the key step in the synthesis of branched allylic amines **209** in good yield and excellent enantioselectivity (Scheme 66).[327] Allylamines **209** could be converted into substituted indoles **210** by a hydroformylation/Fischer indole synthesis to provide the indole derivatives **210**.



Scheme 66. Synthesis of substituted chiral indoles.

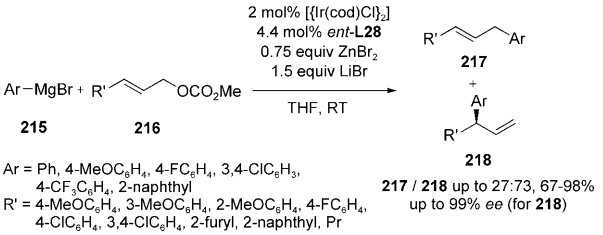
A related yet complementary synthesis of indoles was also disclosed, in which a direct Friedel–Crafts-type allylic allylation of indoles **212**, catalyzed by an iridium/phosphoramidite **L2b** (see Figure 4) complex, was used.[328] The products **213** and **214** were obtained as a mixture, but with a high preference for the branched product **214** (Scheme 67). In most cases, good yields and *ee* values were found.



Scheme 67. Iridium-catalyzed Friedel–Crafts-type allylic substitution.

4.2.5. Allylic Arylations

Efforts towards the development of an iridium-catalyzed allylic arylation method have recently been successful.[329,330] The method is based on diaryl zinc reagents, which were formed in situ from the corresponding Grignard reagents **215** and zinc bromide in the presence of lithium bromide (Scheme 68). These diaryl zinc species were shown to transfer



Scheme 68. Iridium-catalyzed allylic arylation.

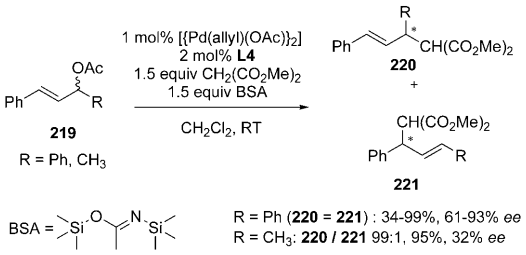
both aryl substituents to a variety of allylic carbonates **216** in high yields, and with excellent enantioselectivity observed in several cases. Unfortunately, the branched to linear ratio **218**/**217** could not be controlled satisfactorily. The best results were found with phosphoramidite *ent*-**L28** (see Scheme 48). This development marks a significant extension of the allylic substitution method for the formation of C–C bonds, since there had previously been few methods that facilitated the introduction of an aryl substituent.

In summary, the iridium-catalyzed allylic substitution has become a powerful synthetic method in the past decade. The introduction of chiral phosphoramidite ligands has resulted in major advances in regard to yield and enantioselectivity. Carbon-, nitrogen-, as well as oxygen-containing nucleophiles have successfully been used for these transformations, in most cases with excellent regioselectivity observed. Both inter- as well as intramolecular versions have been developed, and this asymmetric transformation has already found application in the synthesis of several natural products.

4.3. Palladium-Catalyzed Allylic Substitution Reactions

The palladium-catalyzed Tsuji–Trost allylic substitution is a well-established transformation to yield important, multifunctional chiral building blocks for organic synthesis, and has been the key step in numerous total syntheses.[144,145,248,249,251,252] In recent years, phosphoramidite ligands have been used in these palladium-catalyzed reactions. The palladium-catalyzed allylic substitution has also been used as a benchmark reaction for testing a variety of phosphorus-based monodentate ligands (see below and Ref. [331–334]).

The effect of phosphoramidite ligands on the palladium-catalyzed allylic substitution of diphenyl allylacetate (**219**) with malonates was reported (Scheme 69).[335] By using mainly TADDOL-derived phosphoramidites **L4** (see Figure 2), it was concluded that only one phosphoramidite ligand coordinates to the palladium center in the catalytically



Scheme 69. Palladium-catalyzed allylic substitution.

active species. The best results in the formation of products **220**/**221** (99% yield, up to 93% *ee*) were obtained with symmetric starting materials **219** (R = Ph) and phosphoramidite ligands carrying bulky amine moieties. Substitutions involving unsymmetric allyl acetates **219** with various R groups led in most cases to products **220** with low *ee* values.

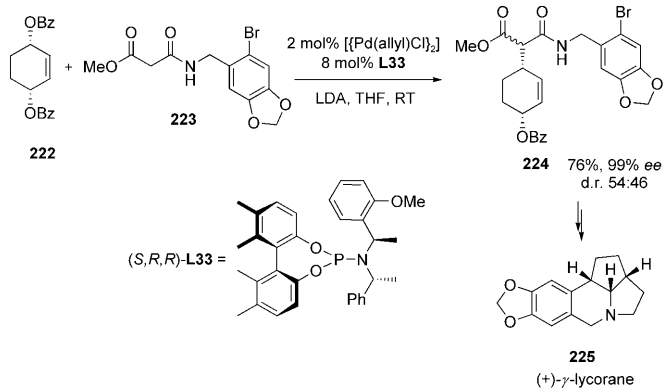
The influence of other phosphoramidite ligands on the allylic substitution and the related allylic sulfonylation and amination reactions of **219** was recently investigated;[336,337] however, no significant improvement to the previously reported method was obtained. The palladium-catalyzed allylic substitutions of cyclohexenyl acetate and cyclopentenyl acetate with various binaphthyl- and biphenol-based phosphoramidite ligands **L2** and **L16** were also studied (see Figures 4 and 5), but only poor enantioselectivity was found.[338]

D-Xylose and D-glucosamine were also used as the diol backbone for bidentate phosphoramidite-phosphonite ligands in the palladium-catalyzed asymmetric allylic alkylation of **219**.[339,340] In most cases only moderate yield and enantioselectivity were obtained; however, 98% *ee* was reached in a single case. An extension of this method through application of phosphate-phosphoramidite ligands derived from chiral amino alcohols was recently reported.[341–343]

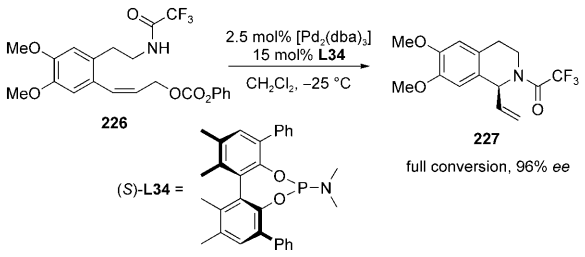
Phosphoramidite-oxazoline ligands were also used in the reaction depicted in Scheme 69, but could not match the previously reported results in terms of yield and enantioselectivity.[344] Finally, the application of polymer-supported phosphoramidites to this reaction resulted in a significant drop in the enantioselectivity.[345]

The highest *ee* values attained so far with the phosphoramidite/palladium catalytic system in allylic substitutions were obtained in the desymmetrization reactions of dibenzoylcyclohexene (**222**; Scheme 70).[346] The use of malonate derivative **223** was used as the carbon nucleophile and phosphoramidite ligand **L33** resulted in excellent *ee* values of up to 99% for cyclohexene **224**, a key precursor to γ-lycorane (**225**).

Phosphoramidites have been shown to be highly versatile ligands in an intramolecular palladium-catalyzed allylic amination,[347] and provided a synthetic pathway to the biologically important class of tetrahydroisoquinolines **227** (Scheme 71). The desired product **227** was formed with excellent enantioselectivity when allylic carbonates **226** were subjected to a catalyst system consisting of $[Pd_2(dba)_3]$ and highly substituted biphenyl-based phosphoramidite ligand **L34**.[348]



Scheme 70. Desymmetrization based on palladium-catalyzed allylic substitution.



Scheme 71. Palladium-catalyzed intramolecular allylic amination.

In summary, the useful applications of phosphoramidite ligands in the field of palladium-catalyzed asymmetric allylic substitutions are so far limited compared to the wide range of excellent available methods based on other chiral ligands that show high enantioselectivity. Acceptable results have mainly been reached with symmetric starting materials; however, the level of stereocontrol with other substrates is promising.

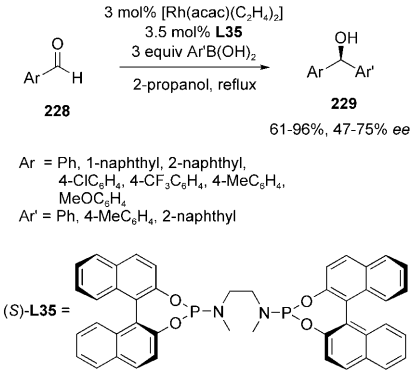
5. Metal-Catalyzed Arylation and Addition of Nucleophiles to Aldehydes

In addition to the well-established reactions described before, numerous efforts have been made to apply the phosphoramidite ligands to several other transition metal-catalyzed asymmetric transformations.

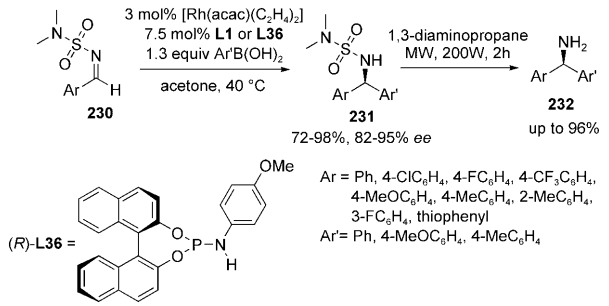
5.1. Rhodium-Catalyzed Arylation Reactions

Following on from the rhodium-catalyzed conjugate addition of boronic acids (see Section 3.5), studies on the rhodium-catalyzed enantioselective 1,2-addition of boronic acids to aromatic aldehydes **228** were reported.[349] The corresponding chiral diaryl alcohols **229** were obtained in up to 94% yield and 75% *ee* by using bidentate phosphoramidite ligand **L35** (Scheme 72). These products are very interesting synthons for the preparation of natural products and pharmaceuticals.[350]

This method was extended to the synthesis of chiral diaryl amines from *N*,*N*-dimethylsulfamoyl-protected aldimines **230** (Scheme 73).[77,351] The best results were obtained with



Scheme 72. Rhodium-catalyzed arylation of aldehydes.



Scheme 73. Rhodium-catalyzed asymmetric arylation of protected aldimines.

phosphoramidites **L1** (see Scheme 8) and aniline-based ligand **L36**. The latter had been identified by automated screening methods as a privileged ligand for this transformation (see also Section 2). The addition products **231** could be isolated with high yields and *ee* values (up to 95% *ee*). As the deprotection of the chiral amines was occuring with racemization (a common problem with protected diaryl methylamines), a new microwave-assisted transamination of the *N*,*N*-dimethylsulfamoyl protecting group was developed to yield the corresponding benzhydrylamines **232**, which are important chiral building blocks for organic synthesis. Similar results were obtained with tosyl-protected imines.[352]

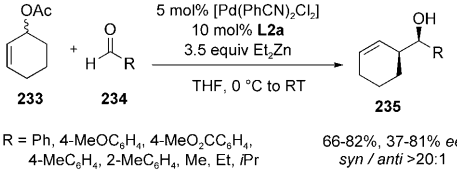
The related rhodium-catalyzed addition reaction of aryl boronic acids to *N*-tosylaryl imines in the presence of spirophosphoramidites **L11** (see Figure 2) provided the protected amines in moderate yields and variable *ee* values of up to 84%.[353] However, spirophosphonites turned out to be superior ligands in terms of enantioselectivity in this case.

The rhodium/phosphoramidite catalytic system for the 1,2-addition of boronic acids has been expanded to different substrate categories, including trifluoromethyl ketones and isatins.[354,355]

5.2. Allylation and Related Metal-Catalyzed Reactions

The aforementioned palladium-catalyzed allylic substitution (see Section 4.3) formed the basis for a diethylzinc-mediated umpolung of palladium–allyl complexes.[356–360]

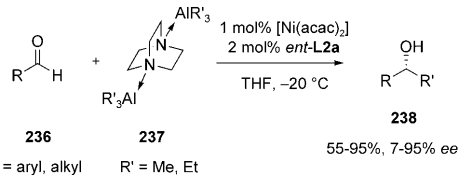
Accordingly, aldehydes **234** were treated with cyclohexyl acetate **233** and palladium catalysts based on phosphoramidite ligands (Scheme 74).[361] The proposed intermediate allylzinc species derived from the palladium–allyl complex



Scheme 74. Palladium-catalyzed allylation of aryl aldehydes.

was trapped with different aldehydes **234** to give *syn*-homoallylic alcohols **235** in yields of up to 82% and *ee* values up to 81%. In all cases, excellent diastereoselectivity (>20:1) was found. The highest selectivity so far was seen with phosphoramidite ligand **L2a** (see Figure 4).

The 1,2-addition of dialkyl zinc reagents to aldehydes to furnish chiral secondary alcohols is among the most frequently studied asymmetric transformations in which a large variety of chiral ligands are used.[362] A notably distinct 1,2-addition has been reported, which involved the enantioselective alkylation of aldehydes **236** with DABCO–trialkyl aluminum complexes **237** (DABCO: 1,4-diazabicylco-[2.2.0]octane), catalyzed by a nickel/phosphoramidite system (Scheme 75).[363] Chiral secondary alcohols **238** were

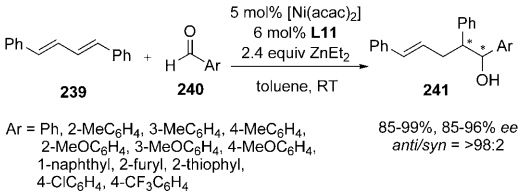


Scheme 75. Nickel-catalyzed asymmetric synthesis of secondary alcohols.

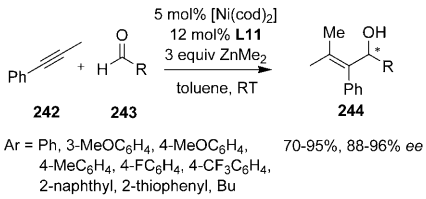
obtained in yields of up to 95% and high *ee* values (up to 95%) by using *ent*-**L2a** (Figure 4). Reactions carried out in the absence of DABCO gave high enantiomeric excess (up to 98%) for some products; however, the DABCO–trialkyl aluminum complex led to higher enantioselectivity for most substrates. Recently, bidentate phosphite-phosphoramidite ligands have been applied to this reaction, although significantly lower yields and *ee* values were found.[364]

Very recently, the application of spirophosphoramidites **L11** (see Figure 2) in a nickel-catalyzed addition of dienes to aldehydes (Scheme 76) was reported.[365] By using diethylzinc as the reducing agent, 1,4-phenylbutadiene (**239**) was coupled to a variety of aromatic aldehydes **240** in excellent yield and enantioselectivity to give the *anti* products **241**.

This method was extended to an enantioselective three-component coupling reaction of dimethylzinc, internal alkynes **242**, and aldehydes **243** to yield chiral allylic alcohols **244** with a tetrasubstituted olefin moiety (Scheme 77).[366]



Scheme 76. Nickel-catalyzed reductive coupling reactions.



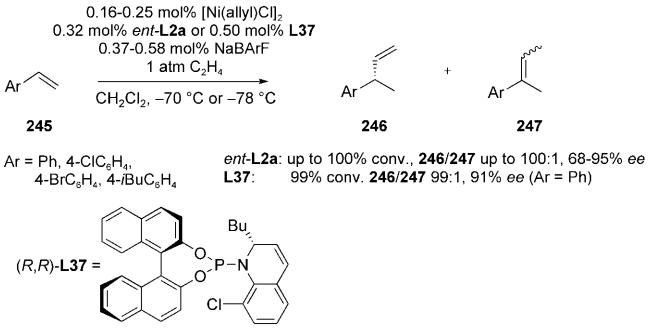
Scheme 77. Nickel-catalyzed reductive coupling of alkynes and aldehydes.

Again, phosphoramidites **L11** (see Figure 2) with a spirobiindane backbone were used in this transformation.

6. Hydrovinylations

The field of asymmetric nickel-catalyzed hydrovinylation of styrene derivatives has been dominated by phosphorus-containing ligands,[57,367,440] and remarkable progress was made with the introduction of monodentate azaphospholene ligands in the late 1990s.[368,369] However, it was not until 2002 that phosphoramidite ligands were introduced for this transformation.

The nickel-catalyzed hydrovinylations of styrene derivatives **245** with ethene using various phosphoramidite ligands provided the alkenes **246** and **247** (Scheme 78).[52b,370] When phosphoramidite *ent*-**L2a** (Figure 4) was employed, excellent regioselectivities (**246**/**247**: up to 100:1) in favor of the branched product and modest to excellent *ee* values (up to 95%) for **246** were obtained, albeit with often moderate yields. The hydrovinylation of styrene was also investigated with quinoline-derived phosphoramidite ligands, which led to equally good results.[372] Phosphoramidite **L37** was found to give the best results in terms of enantioselectivity. In this context, studies towards the catalytic cycle and the origin of enantioselectivity were carried out on the basis of DFT

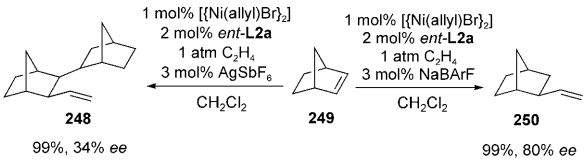


Scheme 78. Nickel-catalyzed hydrovinylations.

calculations.[52b] It was found that temporary coordination of the nickel to one of the phenyl rings in *ent*-**L2a** is crucial for the performance of the nickel catalyst. This marks a further example of noninnocent behavior of the amine moiety of phosphoramidites in catalysis

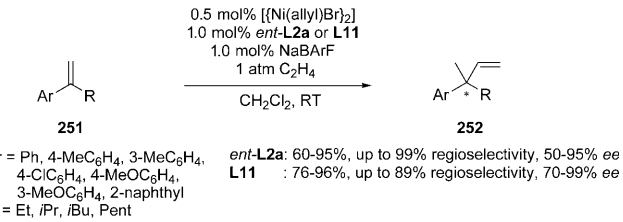
More recently, efforts were made to improve the yield and selectivity for more demanding substrates, including a number of substituted styrenes and precursors for drugs, such as Naproxen and Ibuprofen, as well as steroid derivatives.[373,374] Here, the easy-to-modify modular phosphoramidite ligands demonstrated their versatility. A wide screen of different binaphthol backbones as well as amines identified phosphoramidite ligand (R_a,S_c)-**L20** (Scheme 22) as resulting in a drastic improvement of both the regio- as well as the enantioselectivity in the hydrovinylation of styrenes (up to 98% yield, 99% *ee* for **246**).

The nickel-catalyzed hydrovinylation of norbornene **249** with phosphoramidite ligands (Scheme 79) was also investigated.[375,376] Even though the reported screening of phosphoramidite ligands did not lead to an increase in enantioselectivity, this particular catalytic hydrovinylation generates, depending on the additive used in the experiments, either the simple hydrovinylation product **250** or a hydrovinylated norbornene dimer **248** in a highly selective manner. With $AgSbF_6$, **248** was obtained with a low *ee* value, whereas with NaBArF as an additive, product **250** was formed selectively with up to 80% *ee*. The distinct role of the two different anions has not yet been elucidated.



Scheme 79. Anion-controlled chemoselective transformation in the nickel-catalyzed hydrovinylation of norbornene.

The nickel-catalyzed hydrovinylation of α-alkyl styrenes **251** opens up routes for the enantioselective synthesis of products **252** with quaternary stereogenic centers (Scheme 80).[377,378] Binaphthol-based *ent*-**L2a** (see Figure 4)[378] or spirophosphoramidite ligands **L11** (see Figure 2)[377] were identified as the preferred ligands. Treatment of branched α-allylstyrenes **251** with ethene in the presence of a catalyst comprising [{Ni(allyl)Br}$_2$] and phosphoramidite ligand *ent*-**L2a** resulted in a strong preference for the hydrovinylation products **252**, and in most cases *ee* values exceeding 90% were achieved. In terms of yields and enantioselectivity, the spirophosphoramidite ligands **L11** proved to be superior, although both methods give styrene isomers as by-products.



Scheme 80. Nickel-catalyzed hydrovinylation of α-alkyl styrenes.

The nickel-catalyzed hydrovinylation of 1,3-dienes by using phosphoramidite ligands was also investigated.[379] In an asymmetric version of this reaction, the hydrovinylation products of a variety of cyclic and acyclic 1,3-dienes were accessible in excellent yields and enantioselectivity.

In summary, the versatility of the nickel/phosphoramidite catalytic system has been well established for hydrovinylation reactions in the past few years. High regio- and enantioselectivity have been achieved, and after the recent improvements the phosphoramidite-based method will be able to compete favorably with the performance of related catalytic systems.[367]

7. Cycloadditions

In recent years, a series of investigations were reported in which phosphoramidites were used as ligands for metal-catalyzed cycloaddition reactions. A variety of ring sizes and structures are accessible by these catalytic routes as summarized below.

7.1. Ruthenium-Catalyzed Cyclopropanations

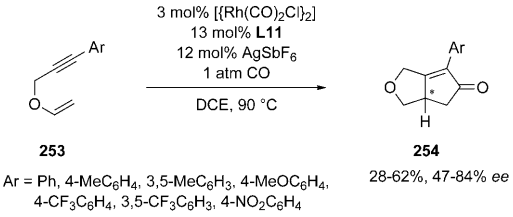
The application of phosphoramidite ligands in enantioselective cyclopropanation reactions was disclosed for the first time in 2004.[380,381] The cyclopropanation reaction of styrene and α-methylstyrene with ethyl diazoacetate to furnish substituted cyclopropane carboxylic acids was investigated by employing a ruthenium–phosphoramidite complex as the catalyst. However, the yield and enantioselectivity were in most cases low, and the *cis*/*trans* ratios did not exceed 61:39. A ruthenium complex was identified as a catalytically active species which has additional coordination to the metal center through one of the phenyl rings of the amine moiety of phosphoramidite ligand **L2** (see Figure 4).[382]

7.2. Rhodium-Catalyzed [2+2+1] Pauson–Khand Cycloadditions

Following the finding of a noncatalytic intermolecular [2+2+1] Pauson–Khand cycloaddition with a phosphoramidite-containing cobalt complex in 2004,[383] rhodium-catalyzed intramolecular [2+2+1] Pauson–Khand reactions were recently published.[384] The stereoselective ring-closing reaction of a variety of 1,6-enynes **253** under a carbon monoxide atmosphere and in the presence of spirophosphoramidite ligand **L11** (see Figure 2) provided the bicyclic products **254** with up to 84% *ee* (Scheme 81).

7.3. Palladium-Catalyzed [3+2] Cycloaddition Reactions

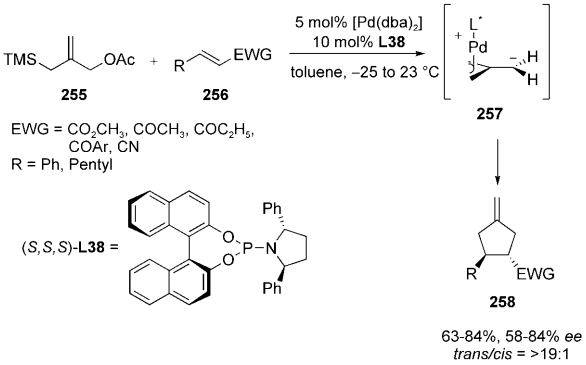
A palladium-catalyzed [3+2] cycloaddition reaction that leads to five-membered carbocyclic products was published in



Scheme 81. Rhodium-catalyzed [2+2+1] Pauson–Khand reaction.

2005.[385] Although a palladium/phosphoramidite catalytic system was shown to facilitate the anticipated cycladditions, it was established that bulky phosphites were the ligands of choice for this transformation.

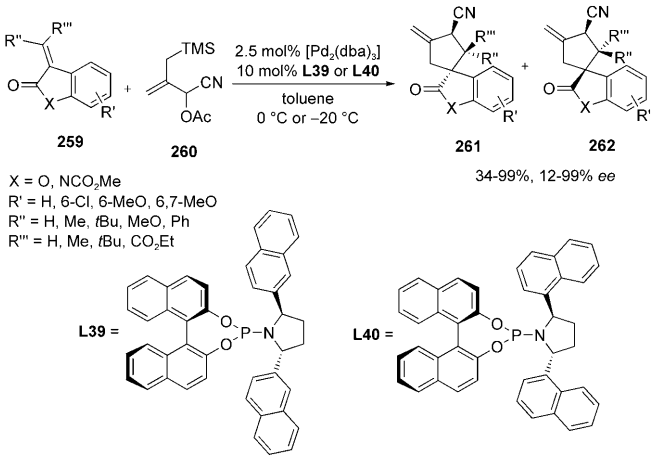
The palladium-catalyzed [3+2] cycloaddition of a trimethylenemethane unit is a marvellous and extremely useful transformation to provide five-membered carbocyclic compounds, and the development of an asymmetric variant has long been a highly desired goal.[386] Recently, a palladium-catalyzed [3+2] trimethylenemethane cycloaddition of 3-acetoxy-2-trimethylsilylmethylpropene (**255**) to various Michael acceptors **256** in the presence of phosphoramidite ligands was disclosed.[387] This reaction gave important multifunctionalized, chiral cylopentanes **258** in good overall yield and enantioselectivity (up to 84%, 84% *ee*), with **L38** proving to be the preferred ligand for this transformation (Scheme 82). The choice of ligand proved to be crucial to



Scheme 82. Palladium-catalyzed [3+2] trimethylenemethane cycloaddition.

create the steric constraints at the palladium catalyst required for high selectivity (see also Section 7.10) in the outer-sphere addition[386] distal from the coordinating ligand of the intermediate **257** to the olefin. Equally good results were obtained for the reaction with aryl and alkylidene tetralones as Michael acceptors as well as with imines.[388]

This method was successfully extended to accomplish the synthesis of important intermediates, including spirocyclic oxindole cyclopentanes.[389] The reaction of oxindoles **259** with allylic acetate **260** yielded the spirocyclic compounds **261** and **262** in excellent yield and stereoselectivity (up to 99% *ee*; Scheme 83). As in the aforementioned example, the choice of the phosphoramidite ligand proved to be critical: With 1-naphthylpyrrolidine-derived **L40**, compound **261** was the favored product, whereas with the 2-naphthyl-derived

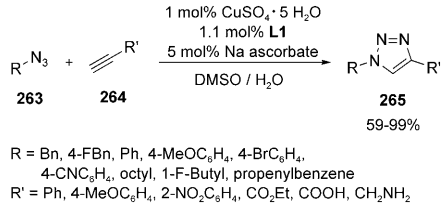


Scheme 83. Palladium-catalyzed [3+2] trimethylenemethane cycloaddition with oxindole substrates.

ligand **L39** a stereoisomer **262** was obtained. The authors claim that the origin of this selectivity lies in the different steric demands of the two ligands, which results in **259** approaching the intermediate palladium complex from either the *re* or the *si* side.

7.4. Copper-Catalyzed [3+2] Cycloadditions of Azides with Alkynes

Very recently, investigations on the effect of phosphoramidite ligands on the [3+2] cycloaddition of azides with alkynes[390] have been disclosed (Scheme 84).[391] A variety of

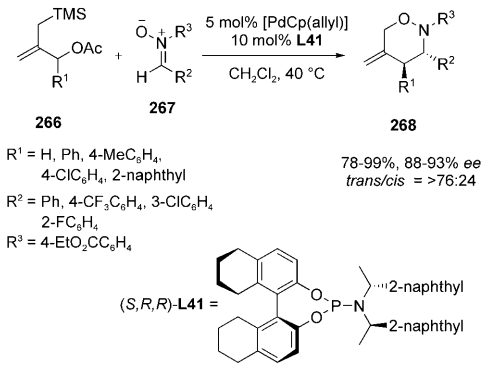


Scheme 84. Copper-catalyzed [3+2] cycloadditions of azides with alkynes.

azides **263** were treated with alkynes **264** to yield the substituted 1,2,3-triazoles **265**. The influence of the phosphoramidite **L1** on the reaction rate is remarkable. The reaction was tenfold faster than with phosphines and phosphates, thus making this [3+2] cycloaddition catalyst one of the fastest for this transformation.

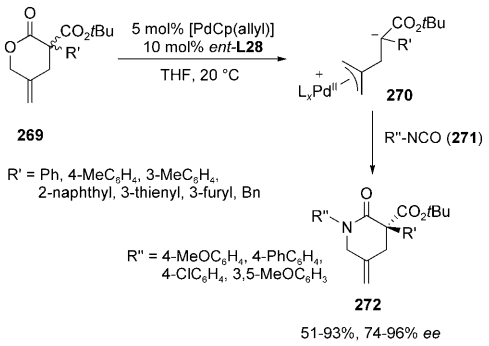
7.5. Palladium-Catalyzed [3+3] Cycloadditions and Related Reactions

The use of phosphoramidite ligands has been extended to other palladium-catalyzed cycloadditions. These studies can be seen as further developments emerging from the [3+2] trimethylenemethane cycloaddition (compare Section 7.3), as illustrated in the examples shown in Scheme 85. The two

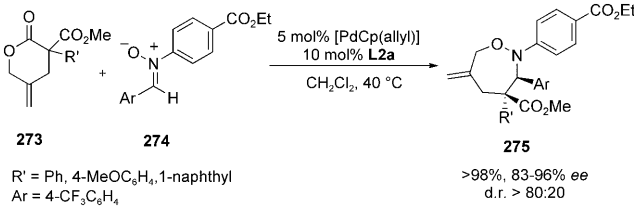


Scheme 85. Palladium-catalyzed [3+3] cycloaddition.

subsequent transformations discussed in this section, however, imply complementary approaches. In contrast to the trimethylenemethane reaction, which furnishes a formal C_3 reaction partner, the carbon framework was extended in these reactions to a C_4 moiety by a decarboxylative reaction pathway (Schemes 86 and 87).



Scheme 86. Palladium-catalyzed decarboxylative lactam formation.



Scheme 87. Palladium-catalyzed [4+3] cycloaddition.

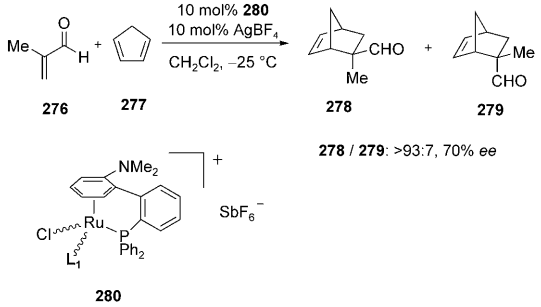
It was found by employing catalytic amounts of a palladium–allyl complex and octahydrobinaphthol-derived phosphoramidite ligand **L40** that trimethylenemethane precursors **266** reacted with a variety of aromatic nitrones **267** in a palladium-catalyzed asymmetric [3+3] cycloaddition to provide chiral six-membered heterocycles **268** efficiently (Scheme 85).[392]

In an interesting recent extension of these palladium-catalyzed reactions, γ-methylidene-δ-valerolactones **269** were subjected to a palladium/phosphoramidite catalytic system in the presence of an isocyanate **271**.[393] The formal exchange of the lactone oxygen atom of **269** with a substituted nitrogen atom in **272** involves decarboxylation to provide palladium–allyl species **270**, which reacts with the isocyanates to provide the ring-closed lactams **272** (Scheme 86). The best results were obtained with phosphoramidite *ent*-**L28** (see Scheme 48).

The same concept has been applied in the reaction of lactones **273** with aromatic nitrones **274**, thus rendering this a formal [4+3] cycloaddition.[394] In the presence of a palladium/phosphoramidite catalytic system, an initial decarboxylative reaction takes place to ultimately provide 1,2-oxazepines **275** in high yields and *ee* values (Scheme 87). The highest selectivity for this transformation was achieved with ligand **L2a** (see Figure 4).

7.6. Ruthenium-Catalyzed [4+2] Diels–Alder Cycloadditions

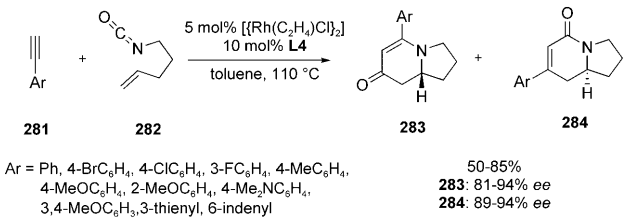
A chiral cationic ruthenium-phosphoramidite complex proved to be a suitable catalyst for the [4+2] Diels–Alder cycloaddition of methacrolein (**276**) and cyclopentadiene (**277**; Scheme 88).[395] The preformed chiral cationic ruthenium complex **280**, derived from **L1** (see Scheme 8), was used in relatively high amounts (10 mol%) to yield the cycloaddition product **278** with excellent *exo*/*endo* selectivity; however, only a modest 70% *ee* was achieved.



Scheme 88. Ruthenium-catalyzed Diels–Alder reaction.

7.7. Rhodium-Catalyzed [2+2+2] Cycloaddition Reactions

A new intermolecular rhodium-catalyzed [2+2+2] cycloaddition of a variety of aryl acetylenes **281** and alkenyl isocyanates **282** was discovered in 2006 (Scheme 89).[396] The transformation with the TADDOL-derived phosphoramidite ligand **L4** (see Figure 2) afforded the nitrogen-bridged bicyclic enones **283** and **284** with up to 94% *ee*. The

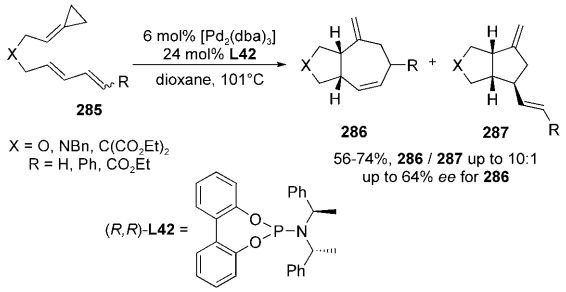


Scheme 89. Rhodium-catalyzed [2+2+2] cycloadditon.

predominant product **283** was obtained exlusively when donor-substituted aryl acetylenes **281** were used. This method has been extended recently to geminal disubstituted olefins, thereby rendering this method suitable for the preparation of quaternary stereogenic centers.[397] Furthermore, it was shown that carbodiimides could be employed instead of isocyanates.[398]

7.8. Palladium-Catalyzed [4+3] Cycloadditions

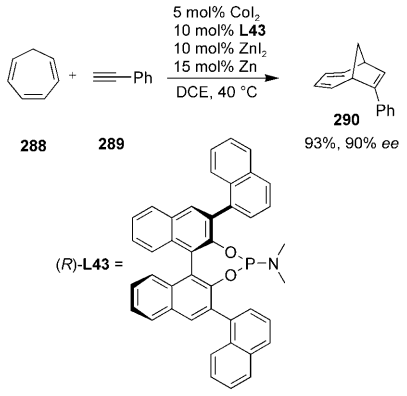
A palladium-catalyzed intramolecular [4+3] cycloaddition of alkylidenecyclopropanes and dienes was studied with the aim of developing a catalytic asymmetric synthesis of cycloheptane compounds.[399] When substrate **285** was subjected to a catalyst system comprising palladium and biphenol-derived phosphoramidite ligand **L42**, the corresponding bicyclic products **286** were obtained with moderate to good chemoselectivity and yield (Scheme 90). However, the enantioselectivity was in most cases rather modest (up to 64% *ee*).



Scheme 90. Palladium-catalyzed intramolecular [4+3] cycloaddition.

7.9. Cobalt-Catalyzed [6+2] Cycloadditions

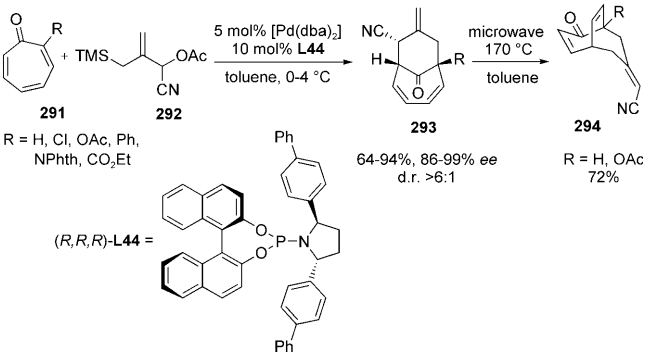
An enantioselective cobalt-catalyzed [6+2] cycloaddition of cycloheptatriene (**288**) and phenylacetylene (**289**) has also been reported (Scheme 91).[400,401] The cycloaddition product **290** was obtained in excellent yield and high enantioselectivity by using phosphoramidite ligand **L43**, which had been identified based on an extensive ligand screening.



Scheme 91. Cobalt-catalyzed [6+2] cycloaddition.

7.10. Palladium-Catalyzed [6+3] Cycloadditions

Investigations towards a new [6+3] trimethylenemethane cycloaddition with tropones was recently disclosed (see also Section 7.3).[402] The palladium-catalyzed cycloaddition of **291** with donor **292** in the presence of phosphoramidite ligand **L44** led to bicyclo[4.3.1]decadienes **293** in good yields and with excellent diastereo- and enantioselectivity (Scheme 92). Furthermore, it was found that the products **293** could be transformed by a microwave-assisted Cope rearrangement to bicyclo[3.3.2]decadienes **294**, thus rendering this a versatile method for the construction of sophisticated carbon frameworks. The development of the trimethylenemethane-based transformations[388,389,402] has demonstrated that phosphoramidites substituted with chiral pyrrolidines lead to a superior yield and enantioselectivity compared to the "classic" phosphoramidites with chiral secondary amines such as **L2** (see Figure 4).



Scheme 92. Palladium-catalyzed [6+3] trimethylenemethane cycloaddition.

From the enantioselective transformations discussed above, it is evident that chiral phosphoramidite ligands show excellent performance in a number of transition-metal-catalyzed cycloaddition reactions. Most of these transformations are based upon palladium– and rhodium–phosphoramidite catalysts, and the highly promising results obtained so far have paved the way for the catalytic asymmetric synthesis of a variety of chiral cyclic compounds.

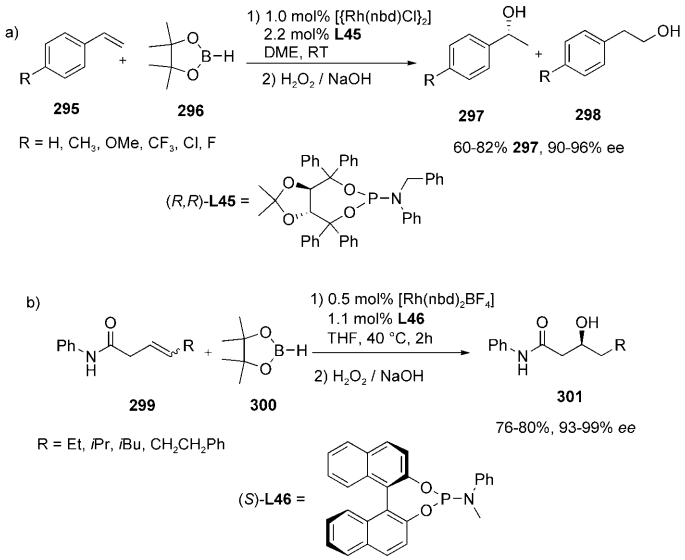
8. Hydroboration/Hydrosilylation Reactions

Transition-metal-catalyzed additions to olefins are among our most powerful synthetic tools,[403] and during the past few years monodentate phosphoramidite ligands have been applied successfully in several of these reactions.

8.1. Rhodium-Catalyzed Hydroboration Reactions

The rhodium-catalyzed hydroboration represents a highly versatile methodology for the enantioselective functionalization of olefins.[404–407] A rhodium/phosphoramidite-catalyzed hydroboration of *para*-substituted styrenes **295** with pinacol-

borane has been reported (Scheme 93a).[408] By using TADDOL-derived phosphoramidites **L45** carrying a bulky amine moiety, the corresponding chiral benzyl alcohols **297** were obtained with excellent yields (up to 96%) and *ee* values



Scheme 93. Rhodium-catalyzed hydroboration of styrene derivatives.

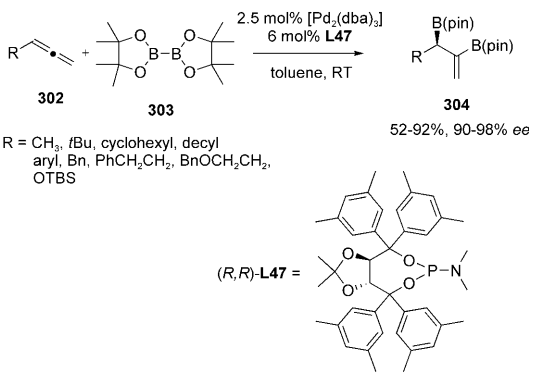
(96%) after oxidation. However, only moderate to good regioselectivity (**297**/**298**) was found. Nevertheless, in comparison to previously investigated systems, the *ee* values reported are among the highest reached.[404] This method was recently extended to the hydroboration of β,γ-unsaturated amides to furnish a pathway to chiral β-hydroxy amides **301**.[409] The use of lower catalyst loadings and phosphoramidite **L46** led to the formation of products in good yield and excellent enantioselectivity (up to 99% *ee*; Scheme 93b). Interestingly, the geometry of the olefin in the starting material **299** did not affect the selectivity.

A related iridium-catalyzed hydroboration of *meso*-bicyclic hydrazines (see Scheme 41) in the presence of biphenyl-derived phosphoramidite ligands **L16** (see Figure 5) provided the corresponding alcohols in moderate yields and *ee* values.[410]

8.2. Palladium-Catalyzed Diboration of Allenes

A palladium-catalyzed asymmetric diboration of prochiral allenes **302** with pinacolborane dimer **303**, catalyzed by a palladium/phosphoramidite complex, provided the di-boron-substituted products **304** with excellent levels of stereocontrol (up to 98% *ee*; Scheme 94).[411,412] The TADDOL-based phosphoramidite **L47** proved to be the most successful ligand in this transformation.

It was demonstrated that the chiral boron products **304** can be readily transformed into a variety of synthetically versatile building blocks including chiral *syn*-1,2-diols, aldol products, and β-amino ketones.[413–415]

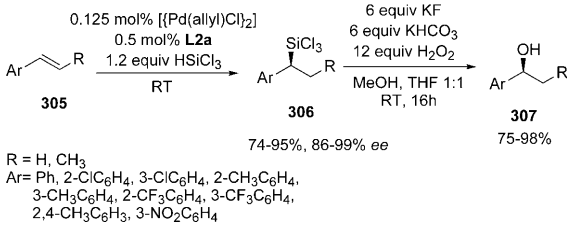


Scheme 94. Palladium-catalyzed diboration of allenes.

The catalyst system depicted in Scheme 94 was also used in an asymmetric silaboration of allenes.[416] However, in this case monodentate phosphine ligands provided higher enantioselectivity than did phosphoramidites.

8.3. Palladium-Catalyzed Hydrosilylation Reactions

Following on from earlier reports on palladium-catalyzed asymmetric hydrosilylation,[417,418] a palladium/phosphoramidite catalytic system for these transformations of styrene derivatives **305** was reported (Scheme 95).[419] The hydro-



Scheme 95. Palladium-catalyzed hydrosilylation of styrenes.

silylation products **306** were obtained in good to excellent chemical yields (up to 95%) and *ee* values reaching 99% by using a remarkably low catalyst loadings of 0.125 mol% [{Pd(allyl)Cl}$_2$] and 0.5 mol% phosphoramidite ligand **L2a** (see Figure 4). These are the best results in terms of enantioselectivity for this substrate class. Furthermore, the products **306** could readily be converted into the corresponding benzylic alcohols **307** in high yields and retention of configuration upon subsequent oxidation.

The yields in this hydrosilylation reaction were further improved by employing spirobiindane-derived phosphoramidites **L11** (see Figure 2).[420]

8.4. Platinum-Catalyzed Silaboration of 1,3-Dienes

Binaphthol-derived phosphoramidites have recently been applied to the platinum-catalyzed silicon–boron addition reaction of diphenylsilylpinacolborane to 1,3-cyclohexadiene. This interesting transformation provides the corresponding

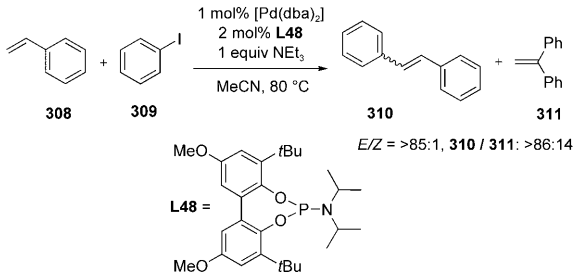
disubstituted cyclohexenes, although the yields and *ee* values are so far only moderate.[421,422]

9. Cross-Coupling Reactions

Metal-catalyzed cross-coupling reactions are among the most important synthetic methods available to form carbon–carbon bonds.[423,424] Palladium-catalyzed coupling reactions, in particular, have changed the face of numerous organic syntheses in the past decades and significantly contributed to the expansion of the transformations available in synthetic chemistry.[423–427] Soon after the first appearance of monodentate phosphoramidites, these ligands were also used in cross-coupling reactions.

9.1. Palladium-Catalyzed Heck Reactions

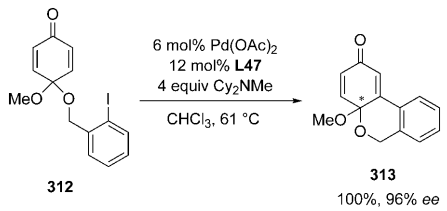
In 1999, the application of several achiral monodentate phosphorus ligands to the arylation of styrene (**308**) with iodobenzene (**309**) was reported (Scheme 96).[428] Stilbene (**310**) was formed with excellent *E/Z* selectivity, with 1,1-



Scheme 96. Palladium-catalyzed arylation of styrene.

diphenylethylene **311** as a by-product; however, the chemical yields were often poor. The best results were obtained with sterically hindered biphenol-based phosphoramidite ligand **L48**. The use of monodentate phosphoramidites represents the first application of easily tunable ligands, with respect to their electronic and steric parameters, to this type of reaction.[426]

The first asymmetric Heck reaction with phosphoramidite ligands was reported in 2002 (Scheme 97).[429] Prochiral cyclohexadienone derivative **312** was used in a formal desymmetrization Heck-type ring-closing reaction with TADDOL-derived phosphoramidite ligand **L47** (see

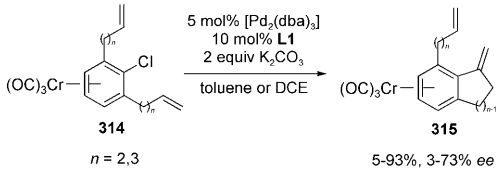


Scheme 97. Palladium-catalyzed asymmetric Heck reaction.

Scheme 94), which led to the formation of the heterocyclic product **313** in excellent yield and enantioselectivity (96% *ee*).

The scope of this reaction was significantly broadened,[430] since five-membered rings could be prepared and several substituents on the aromatic ring were accepted in this transformation. The products are usually isolated in very good yields and with high *ee* values (up to 92%).

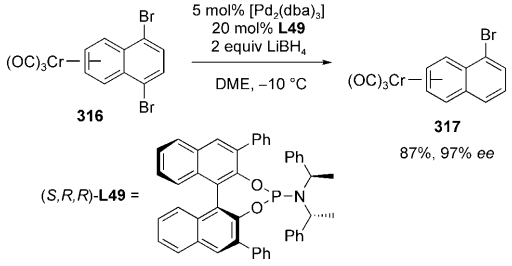
The palladium/phosphoramidite catalytic system for asymmetric Heck reactions has also been applied for the enantioselective synthesis of planar chiral chromium(arene) complexes **315** (Scheme 98).[431] Phosphoramidite ligand **L1**



Scheme 98. Asymmetric synthesis of planar chiral chromium complexes by a Heck reaction.

(see Scheme 8) was used in an intramolecular Heck reaction that led to the desymmetrization of the chromium-coordinated bis-*ortho*-substituted chlorobenzene derivative **314.** The indane-derived chromium complexes **315** were obtained with yields of up to 93%; the highest *ee* value of 73% was so far only observed in a single case.

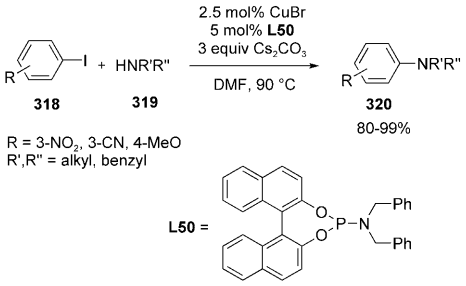
An excellent alternative method for preparing chiral chromium complexes was developed (Scheme 99).[432] A palladium/phosphoramidite system was used to perform an enantioselective catalytic partial hydrogenolysis of chromium–dibromonaphthalene complexes **316**. The use of 3,3′-diphenyl-substituted phosphoramidite **L49** led to the reduced monobromonaphthalene-chromium complex **317** with excellent enantioselectivity (97% *ee*).



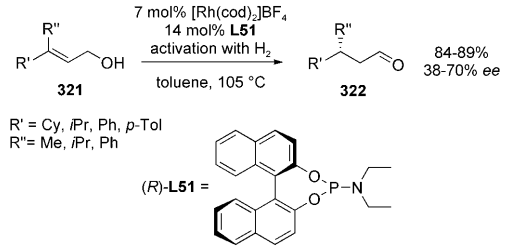
Scheme 99. Palladium-catalyzed desymmetrization of chromium complexes.

9.2. Copper-Catalyzed N-Arylation and Related Reactions

Phosphoramidite ligands have also been used in the copper-catalyzed arylation of aryl halides **318** with a variety of cyclic and acyclic amines **319** (Scheme 100).[433] The coupling products **320** were usually obtained in very good yields by using racemic biphenol-based phosphoramidite ligand **L50**.



Scheme 100. Copper-catalyzed arylation of amines.



Scheme 101. Rhodium-catalyzed isomerization of allylic alcohols.

This method was extended to the coupling of several aryl iodides, bromopyridines, and 5-bromopyrimidine with alkyl amines, aryl amines, and N heterocycles.[434] However, higher amounts of CuBr and phosphoramidite ligand **L50** were required for the coupling of heterocycles to provide the products in good yields.

A palladium/phosphoramidite-catalyzed Suzuki coupling of a variety of substituted bromobenzenes with phenylboronic acid was also developed recently.[435] The coupling products were isolated in excellent yields, and remarkably low catalyst loadings of 0.05 mol% palladium and 0.1 mol% phosphoramidite ligand were sufficient to achieve high conversion of most substrates.

In terms of catalyst loading and yields, the two aforementioned coupling reactions based on phosphoramidite ligands are state-of-the-art systems.[436–438]

The recent developments in the field of cross-coupling reactions show that monodentate phosphoramidite ligands can be applied to these transformations, thus showcasing their applicability to a variety of catalytic transformations. The modular structure of these ligands allows them to be custom-fit to many reactions, and it is envisioned that broad substrate classes might be accepted. Although examples of successful asymmetric reactions have been reported, the use of phosphoramidites as ligands in asymmetric cross-coupling reactions has so far been limited.

10. Miscellaneous Reactions

10.1. Nickel-Catalyzed Cycloisomerization of Diethyl Diallylmalonate

A nickel-catalyzed cycloisomerization of diethyl diallylmalonate in the presence of phosphoramidite ligands to form chiral cyclopentanes was also investigated.[439] However, phosphoramidites give low *ee* values, of only up to 48% *ee*, and these ligands can not so far compete with the azaphospholene ligands introduced earlier, which provide the products with much higher enantioselectivity (up to 80% *ee*).[370]

10.2. Rhodium-Catalyzed Isomerization of Allylic Alcohols

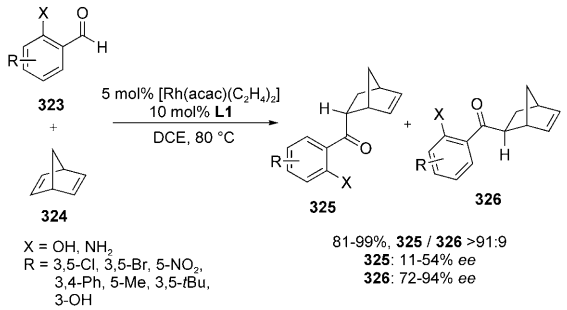
A rhodium/phosphoramidite catalytic system was used for the enantioselective isomerization of allylic alcohols[15,441,442] **321** to chiral aldehydes **322** (Scheme 101).[443] Aldehydes **322** were isolated in high yields and moderate *ee*' values (up to 70%) by using phosphoramidite ligand **L51**. The catalyst for this isomerization reaction requires prior activation by stirring in a H_2 atmosphere; however, the exact nature of this activation has not been elucidated yet.

10.3. Rhodium-Catalyzed Hydroformylation Reactions

So far the hydroformylation reaction has seen only very limited success with phosphoramidite ligands. Following earlier studies on non-asymmetric hydroformylations with phosphoramidite ligands,[443] the use of a rhodium/phosphoramidite catalytic system for the hydroformylation of allyl cyanide was reported.[444] However, the reaction did not give satisfactory results as only modest yields, regioselectivity as well as poor enantioselectivities were reached. The same conclusion can be drawn from a study of indole-substituted phosphoramidite ligands which were applied to the same reaction.[445]

10.4. Rhodium-Catalyzed Hydroacylation Reactions

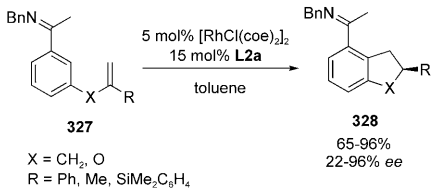
Salicylaldehydes **323** and norbonadiene (**324**) were converted into the corresponding ketones **325**/**326** in a rhodium-catalyzed hydroacylation reaction, with a catalyst comprising rhodium(I) and phosphoramidite **L1** (Scheme 102).[446] The products were isolated in high yields; however, the enantioselectivity for the formation of the *endo* product **325** was low. Remarkably, the minor *exo* diastereoisomer **326** was obtained with a much higher enantioselectivity.



Scheme 102. Rhodium-catalyzed hydroacylation of norbornadiene.

10.5. Rhodium-Catalyzed C–H Activation Reactions

Transition-metal-catalyzed C–H bond activation is a topic of great current interest.[447–452] In this context, a rhodium/phosphoramidite-catalyzed cyclization of aromatic imines **327** (Scheme 103) is particularly noteworthy.[453,454] Activation of the aromatic C–H bond, with the aid of an imine moiety as an

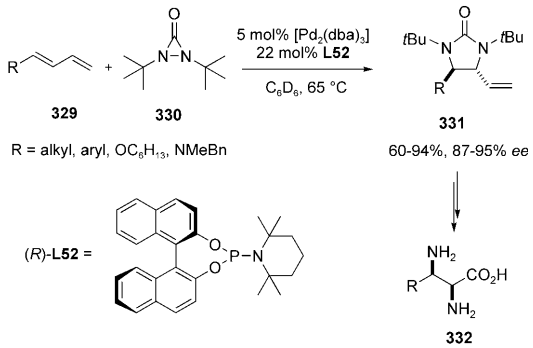


Scheme 103. Rhodium-catalyzed cyclization of aromatic imines.

ortho-directing group, followed by cyclization led to indane- and dihydrobenzofuran compounds **328**. By using phosphoramidite ligand **L2a** (see Figure 4), the products **328** were obtained in most cases in excellent yield (up to 96%) and enantioselectivity (up to 96% *ee*).

10.6. Palladium-Catalyzed Diamination of Dienes

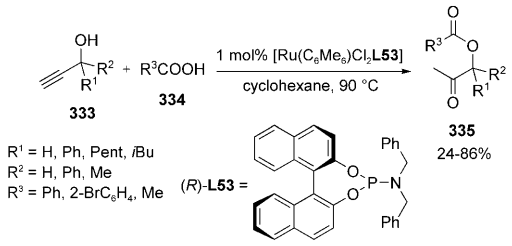
Following the recent development of a palladium-catalyzed diamination procedure for dienes,[455] an asymmetric variant was disclosed, in which a variety of phosphorus-based ligands were used.[456] The best results in terms of enantioselectivity were achieved with binaphthol-based phosphoramidite **L52**. Several dienes **329** were converted with di-*tert*-butylaziridinone (**330**) into the corresponding chiral imidazolidinones **331**, generally in high yields and *ee* values (Scheme 104). The products **331** could then be converted into chiral 2,3-diamino acids **332** in a few steps. This method was recently extended to the diamination of terminal non-conjugated olefins.[457]



Scheme 104. Palladium-catalyzed asymmetric diamination of dienes.

10.7. Ruthenium-Catalyzed Formation of Keto Esters

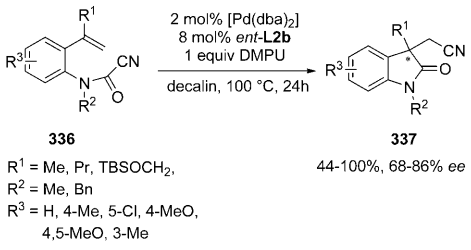
Air- and moisture-stable half-sandwich hexamethylbenzene–ruthenium–phosphoramidite complexes were used recently in the transformation of propargylic alcohols **333** to keto esters **335**.[458] Complexes derived from dibenzylamine-phosphoramidite **L53** resulted in the products **335** being obtained with yields of up to 86% (Scheme 105). No new stereocenter is generated in this reaction; however, it was demonstrated that the reaction occurs with full retention of configuration at the propargylic position.



Scheme 105. Ruthenium-catalyzed formation of keto esters.

10.8. Palladium-Catalyzed Cyanoamidation

Very recently, a phosphoramidite-based method for the catalytic asymmetric synthesis of biologically relevant oxindoles was disclosed.[459] Cyanoformamide **336** was converted in the presence of one equivalent of DMPU (dimethyltetrahydropyrimidinone) and a palladium/phosphoramidite catalytic system. The substrate undergoes an intramolecular cyanoamidation to provide the substituted chiral oxindoles **337** with *ee* values reaching 86% (Scheme 106). The highest selectivity so far was obtained using phosphoramidite *ent*-**L2b** (see Figure 4).

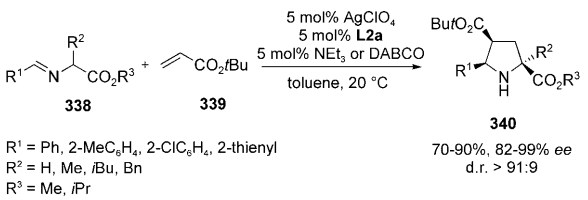


Scheme 106. Palladium-catalyzed asymmetric cyanoamidation.

10.9. Silver-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylide and Alkenes

The first successful catalytic application of a silver–phosphoramidite complex was also recently reported.[460] A silver-catalyzed 1,3-dipolar cycloaddition of aryl-substituted iminoglycinates **338** and activated olefins such as *tert*-butyl acrylate (**339**)[461] furnished proline derivatives **340**. The use of

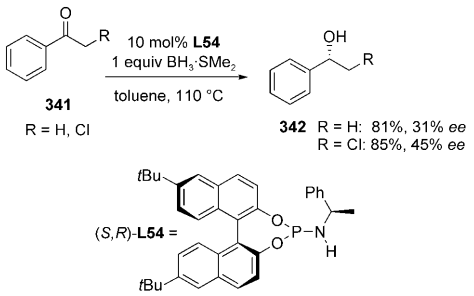
phosphoramidite **L2a** enabled a variety of pyrrolidines **340** with multiple stereogenic centers to be obtained, generally in good yield and excellent stereoselectivity (Scheme 107).



Scheme 107. Silver-catalyzed 1,3-dipolar cycloaddition.

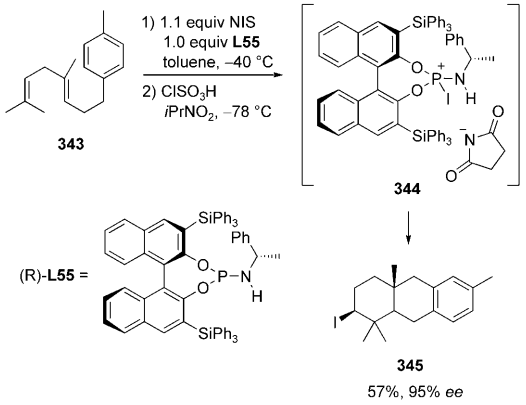
11. Phosphoramidites as Chiral Promotors

Phosphoramidite **L54** has been used as a chiral promotor in the asymmetric reduction of acetophenones **341** with borane (Scheme 108);[462] however, only modest enantioselectivity was attained.



Scheme 108. Asymmetric reduction of acetophenones with phosphoramidites.

The first application of phosphoramidites as chiral promotors in organic reactions was reported in 2007.[463] Phosphoramidite **L55** was used to conduct enantioselective halocyclizations of geranyl derivative **343** with *N*-iodosuccinimide (NIS) as the iodine source to yield polycyclic compound **345** with 95% *ee* (Scheme 109). The highest *ee* values were obtained by using a stoichiometric amount of phosphoramidite; however, even catalytic amounts of **L55** gave rise to enantioselectivity in the halocyclization. The mechanism was proposed to involve coordination of the iodonium ion to the phosphoramidite to give intermediate **344**, followed by a transfer of the iodine to the terminal double bond of **343** and subsequent stereocontrolled cyclization.



Scheme 109. Enantioselective halocyclization with a phosphoramidite as a chiral promotor.

12. Conclusion and Outlook

Phosphoramidites are still "infant" members among the ever-growing family of privileged chiral ligands, but have rapidly emerged as extremely potent ligands in enantioselective transition-metal catalysis. Following the introduction of phosphoramidites for asymmetric hydrogenation in 2000, it took only three years for the implementation of MonoPhos as a ligand in an industrial process for the production of a pharmaceutical intermediate—the hydrogenation of a cinnamic acid to afford a key component of the renin inhibitor aliskiren.[98] A unique feature of monodentate ligands proved essential in the development of this process: high enantioselectivity was only reached in a mixed-ligand approach in which a combination of chiral and achiral monodentate phosphorus ligands were used. In a field so far dominated by bidentate phosphines, the use of monodentate phosphoramidites and related phosphites and phosphonites has been extremely successful in numerous hydrogenations. In fact, as recently emphasized by Reetz:[96] "*These early studies opened a new chapter in asymmetric hydrogenation.*"

We introduced the concept of monodentate phosphoramidite ligands in 1996, and it was shown to be the key to success in the development of the first highly enantioselective copper-catalyzed conjugate addition of organozinc reagents. In these catalytic systems, two phosphoramidites take the role of a single bidentate ligand, but have greater "adaptive" behavior during the catalytic cycle.

The versatility of phosphoramidites is arguably most evident from the numerous highly enantioselective conjugate addition and allylic substitution methods that are now part of the toolbox of the synthetic organic chemist. Recent developments include cross-coupling, arylation, and cycloaddition reactions with excellent regio-, enantio-, or diastereoselectivity. Phosphoramidites also show promising stereoselectivity in numerous other transformations, although in many cases further ligand optimization is needed. In this context, perhaps the most attractive feature of this class of ligands is that they are readily accessible from cheap starting materials and, therefore, the structure can be easily optimized for a specific transformation. The automated synthesis of large libraries of phosphoramidite ligands and the use of combinatorial ligand approaches are particularly attractive for the exploration of chiral space in the generation of suitable leads for new ligands and catalysts.

It should be noted that, in some cases, the phosphoramidites are non-innocent, and ligand transformations prior to the formation of the actual catalyst has been observed. The use of bidentate phosphoramidites, phosphoramidites with auxiliary metal-binding P, N, O, or S units, or ligands that show

adaptive or responsive behavior, as well as phosphoramidites in organocatalysis remain largely unexplored.

Extensive structural and mechanistic studies are necessary for the majority of the transformations discussed here to elucidate the nature of the active transition-metal complex as well as the origin of the stereocontrol by the monodentate phosphoramidite ligands. Detailed insight into the dynamics and "chiral communication" in these catalytic systems offers exciting opportunitites to design future generations of ligands and catalysts.

Abbreviations

acac	acetylacetonate
BArF	tetrakis-[3,5-bis(trifluoromethyl)phenyl]-borate anion
BINOL	1,1′-binaphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bz	benzoyl
Cbz	carbobenzyloxy
cod	cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicylco[2.2.0]octane
dba	*trans*,*trans*-dibenzylideneacetone
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DME	dimethoxyethane
DMPU	dimethyltetrahydropyrimidinone
EWG	electron-withdrawing group
LDA	lithium diisopropylamide
nbd	norbornadiene
NIS	*N*-iodsuccinimide
Piv	pivaloyl
TBAF	*tert*-butylammonium fluoride
TBD	1,4,7-triazabicyclo[4.4.0]undecene
TBDMA	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TC	thiophene carboxylate
TESOK	potassium triethylsilyl alcoholate
Tf	trifluormethansulfonyl
THF	tetrahydrofuran
THT	tetrahydrothiophene
tol	tolyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
Ts	*p*-toluolsulfonyl

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