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Copper-Catalyzed Asymmetric Allylic Alkylation

Caroline A. Falciola[a] and Alexandre Alexakis*[a]

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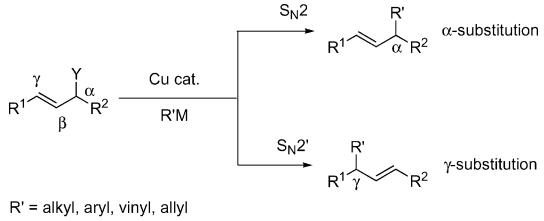
Over the past decade, much effort has been put on designing efficient chiral ligands and screening of the different parameters that govern the main challenges of asymmetric S_N2' reactions, namely chemo-, regio- and enantioselectivity. This review traces the evolution of the methodologies for creating stereogenic centers through asymmetric copper-catalyzed allylic alkylation with the use of different organometallic reagents and their subsequent applications.

Introduction

Among the fundamental transformations and C–C bond formations, the asymmetric allylic alkylation (AAA) has been extensively studied with a wide spectrum of metals, such as Pd, W, Mo, Ir, Ni, Rh and Ru.[1,2] The most common one, palladium, has been used with considerable success using soft stabilized nucleophiles for the eponym Tsuji–Trost reaction.[2b] However, the poor regioselectivity observed in non-symmetrical allylic substrates has hampered the general use of this methodology. Complementary to it, copper tolerates the use of hard non-stabilized nucleophiles, such as small alkyl groups in the form of organometallic species, including organolithium, magnesium or zinc reagents.[3]

One key feature of allylic substitution is controlling the regiochemistry. The displacement of an allylic leaving group can involve two distinct pathways: one resulting from a direct attack on the carbon bearing the leaving group at α-position, formally known as S_N2 reaction, and the second γ-substitution, also referred to as S_N2', displaces the leaving group whilst involving an allylic shift of the double bond (Scheme 1). Thus, a substrate bearing two distinct substituents at the α and γ positions of the allylic moiety ($R^1 \neq R^2$) can give rise to two different products according to each pathway. One should keep in mind that many parameters dictate the regioisomeric outcome of the reaction, such as



Scheme 1.

[a] Department of Organic Chemistry, University of Geneva
30 quai E. Ansermet, 1211 Geneva 4 (Switzerland)
E-mail: alexandre.alexakis@chiorg.unige.ch

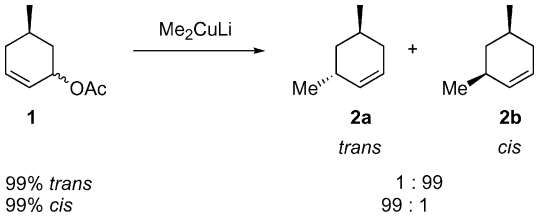
Caroline A. Falciola, born in Geneva (Switzerland) in 1978, studied chemistry at the University of Geneva. After a one-year experience at the SPRI research institute of Serono International in Geneva, she completed her master degree at the Polytechnical School in Paris while starting her Ph.D. in 2003 under the supervision of Professor A. Alexakis at the University of Geneva, Switzerland. Her doctoral research was directed to broadening the scope of allylic substitution reactions.

Alexandre Alexakis graduated from Paris VI University in 1970 and received his PhD in 1975. After a postdoctoral stay at Johns Hopkins University, he joined the CNRS at Pierre et Marie Curie University in 1977, being appointed Directeur de Recherche in 1985. In 1994 he was awarded the Silver Medal of the CNRS. In 1996 he moved from CNRS to Pierre et Marie Curie University as full Professor (1st class), then to the University of Geneva in 1998. In 2002 he was awarded the Novartis Lectureship Award. His research focuses on asymmetric synthesis and methodologies, using both metal catalysts, particularly copper reagents, and non-metallic catalysts (organocatalysis).

the substrate (structural and electronic features), leaving group, solvent, temperature, organometallic source, etc. Fine tuning of the conditions allow for control, at will, of the regioselectivity.

Mechanism

As for the S_N2 displacements, the copper-catalyzed allylic-S_N2' reaction usually takes place with highly *anti* stereochemistry with respect to the leaving group, affording inversion at the reaction center (Scheme 2).[4]



Scheme 2. A selective *anti*-substitution.

Indeed, in 1984, Corey et al. rationalized this highly *anti*-diastereoselectivity for incoming organocuprates by stereoelectronic effects based on frontier molecular orbitals considerations. They suggested a concerted, asynchronous mechanism involving a bidentate overlap of the diffuse d^{10}-orbital of the reacting copper with the allylic system, inducing a partial S_N2 character to the S_N2' reaction. More precisely, the d^{10}-orbital simultaneously coordinates with both the π* (LUMO) of the olefin, and to a minor extent with the antibonding σ*-orbital of the leaving group (α-carbon), as depicted in Figure 1.[5]

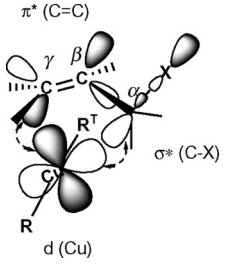


Figure 1. Corey's model for orbital overlap of d(Cu) and an allylic system.

A prerequisite for the reaction requires that the leaving group is orthogonal to the double bond (i.e. coplanar orbitals π* and σ*). However, the intrinsic stereoelectronic control over the allylic substitution can be overridden. Some examples will present specific *syn*-selectivities, owed in part to steric constraints[4,6] or to the chelating nature of the leaving group (Figure 2).[7]

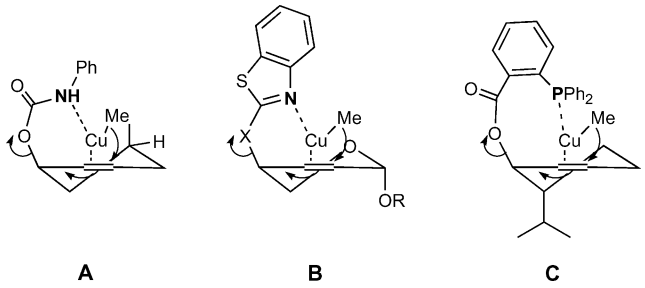
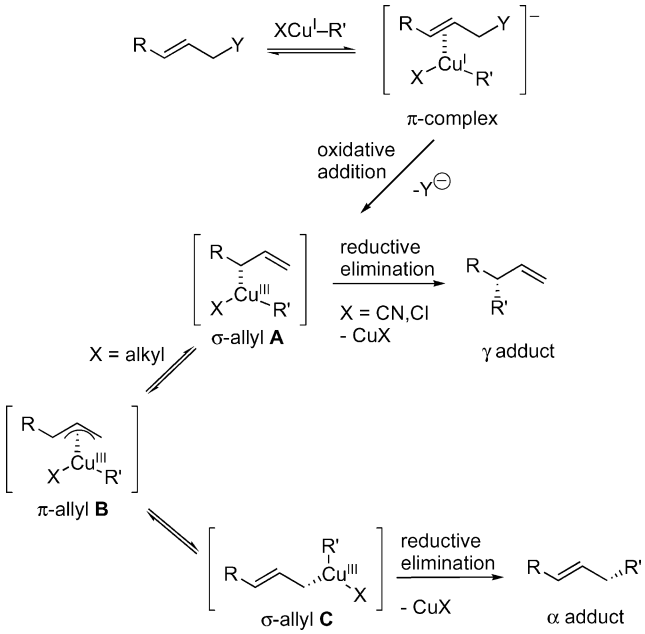


Figure 2. *syn*-Directing carbamate (A), benzothiazoles (B) and *o*-(diphenylphosphanyl)benzoyl (C).

In the past decades, many mechanisms for the copper-catalyzed allylic substitution have been proposed.[8] However, the commonly accepted one today, as shown in Scheme 3, was postulated by Bäckvall and van Koten, and proceeds via a transient Cu^{III} intermediate.[9]



Scheme 3. Cu-mediated allylic substitution mechanism.

In this mechanism, the stereo- and regiochemistry are established at different stages of the reaction. Initial formation of the π-copper(I) complex leads to the subsequent stereo-determining step, namely the oxidative addition of the copper, *anti* with respect to the leaving group, into **A** the σ-allyl Cu^{III} species. The regiochemistry is decided upon the relative kinetics of reductive elimination of the species **A** and/or isomerization into the π-allyl Cu^{III} **B**, later leading to the σ complex **C**. Indeed, the kinetic γ adduct may be formed preferentially when the copper salt's counterion is electron-deficient (X = CN, Cl), thus inciting a rapid reductive elimination of species **A**. In contrast, under reaction conditions that favor the formation of a more electron-rich Cu^{III} intermediate (X = alkyl, as in R_2CuLi), the Cu^{III} transient species is stabilized and proceeds to equilibration through π-allyl Cu^{III} **B**, thus favoring the least sterically

hindered carbon.[10] Despite the regiochemical loss, the stereochemistry is maintained in complex **C**.

Although the copper(III) intermediates predicted in the mechanism have not been isolated or detected spectroscopically, a study by Bäckvall and co-workers has given indirect evidence of their existence,[11] concomitant with the computational results of Nakamura.[12]

Enantioselective Copper-Catalyzed S_N2' Substitution

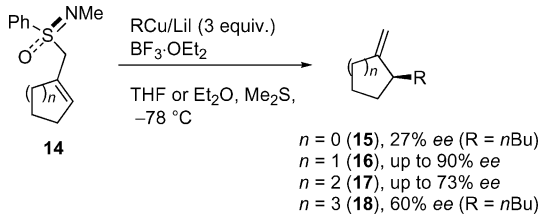
With simple substrates, such as the ones shown in Scheme 3, a γ-insertion could generate a new stereogenic center. Two general methodologies to do so have been developed over the past decades, chiral auxiliaries in place of the leaving group, or asymmetric catalytic protocols.

Diastereoselective Procedures

Asymmetric induction exerted by a chiral leaving group is an attractive method for creating a chiral C–C bond, more importantly when the chirality is contained in the nucleofuge. The first instances of Cu-catalyzed diastereoselective allylic alkylation were reported with the use of chiral acetals (mostly of C_2 symmetry). At the time, these chiral auxiliaries were popular enantio-inducing agents for asymmetric synthesis.[13] The chiral acetals could be used in the vicinity of a prochiral center and induce stereolectivity to the reaction taking place at the sp^2 center. When adding vinyl or phenyl organocopper reagents to the chiral ethylenic acetal **4**, the facial approach of the reagent is specifically *anti* to the equatorial or pseudo-equatorial substituent activated by the Lewis acid (BF_3) (Scheme 4).[14] This methodology was later applied in the asymmetric synthesis of a California Red Scale pheromone.[14b]

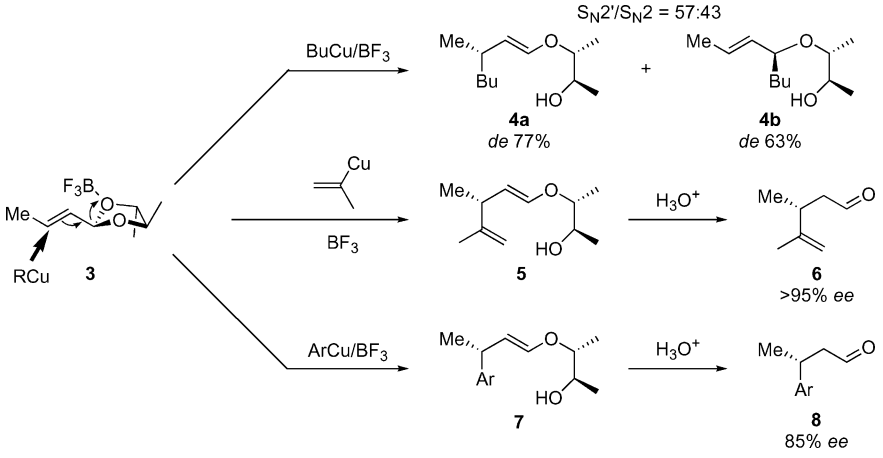
Denmark et al. reported on **10** as the first stereodirecting leaving group that affords a new C–C chiral bond without subsequent treatment.[15] This procedure affords chiral branched adducts with a complete S_N2' regiocontrol, and good to very good enantioselectivities for the addition of alkyl- and arylcopper reagents (up to 95% *ee*) (Scheme 5).

In the course of their research on a stereoselective synthesis of isocarbacyclin-derived drugs, Gais and co-workers designed an efficient asymmetric system, making use of optically active allylic sulfoximines.[16] When subjecting chiral allylic sulfoximines **14** to treatment with homocuprate reagents (R_2CuLi/LiI), the conditions would favor the α-selective allylation adduct, whereas tuning of the reaction parameter with an organocopper reagent in the presence of $BF_3{\cdot}OEt_2$, would yield regio- and enantioselective exocyclic alkenes with a maximum of 90% *ee* for the cyclopentenyl substrate (Scheme 6).

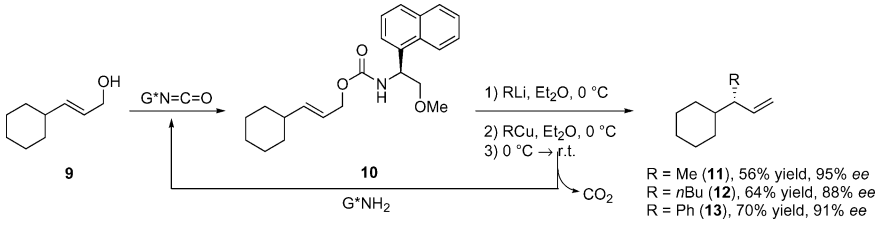


Scheme 6. Enantioselective allylic substitution of endocyclic allylic sulfoximines.

Another set of chiral leaving groups in the form of heterocyclic moieties was first described by Caló and co-

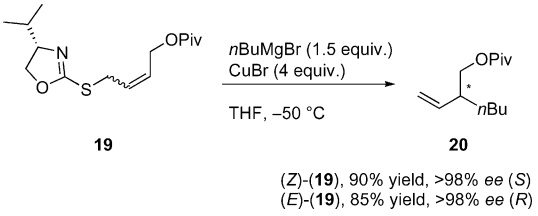


Scheme 4. Addition of different organocopper reagents to crotonaldehyde acetal.



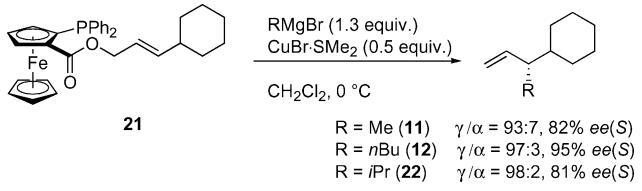
Scheme 5.

workers. Upon thorough investigation of the parameters that govern the regioselectivity of the S_N2' displacement of the benzothiazole leaving group in THF, they concluded, like others, that organocuprates (R_2CuMgX) were S_N2-selective.[17,18] They later developed allylic substrates containing dihydrooxazoles and thioazoles **19** (with the chiral source α to the coordinating nitrogen), which underwent the copper-mediated substitution with very high enantioselectivity on either configuration of the olefin (>98% *ee*) (Scheme 7).



Scheme 7. Enantioselective substitution of allylic sulfide.

The most recently published diastereoselective procedure. involving a chiral nucleofuge, was reported by Breit and coworkers in 2005.[19] By grafting their highly *syn*-directing *o*-DPPB leaving group upon a chiral planar ferrocenyl moiety (*o*-DPPF) (**21**), they induced the asymmetric S_N2' displacement with high chimio-, regio- and enantioselectivities (see Schemes 8 and 19).



Scheme 8.

A Copper-Catalyzed System

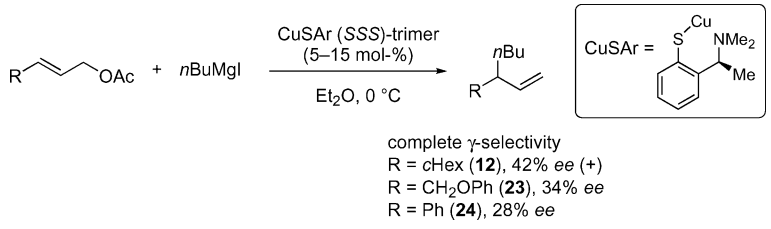
A catalytic procedure has many advantages from an atom economy viewpoint: only small amounts of copper are required, and only a catalytic amount of the potentially precious alkyl group is lost as an unreactive alkylcopper. Thus, the chiral ligand, also present in substoichiometric quantities, induces the stereochemistry upon the metal, which will necessarily lay closer to the reacting center than a chiral auxiliary grafted upon the substrate.

Organomagnesium Reagents

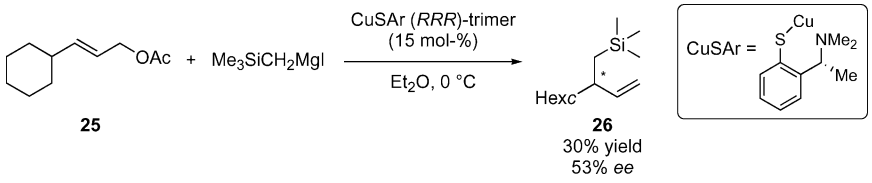
The first catalytic process of a copper-catalyzed asymmetric allylic alkylation was reported in 1995 by Bäckvall and van Koten.[20] The non-transferable arenethiolate was used in place of the chiral ligand to copper(I) in combination with Grignard reagents. Through an extensive analysis of leaving groups, R-substituents, temperatures and methods of addition of the organometallic reagent, they highlighted the inherent difficulty of controlling the asymmetric S_N2' reaction. Nevertheless, arenethiolato–copper(I) complex (CuSAr) promoted the regiospecific γ-allylation of allylic acetates with butylmagnesium iodide, affording *ee* values ranging from 28% to 42% (Scheme 9). Their observations underscored that slow and simultaneous additions of the Grignard reagent and the substrate were essential for a selective outcome, and that temperatures below 0 °C adversely affected the enantioselectivity.

Further detailed investigations of the reaction parameters increased the *ee* to 50% for the addition of brominated Grignard reagents, namely *n*-butylmagnesium bromide to the cyclohexyl-substituted allylic acetate **25**.[21] A more hindered organomagnesium reagent, Me_3SiCH_2MgI, resulted in the γ adduct **26** with 53% *ee*, albeit in a low yield (Scheme 10).

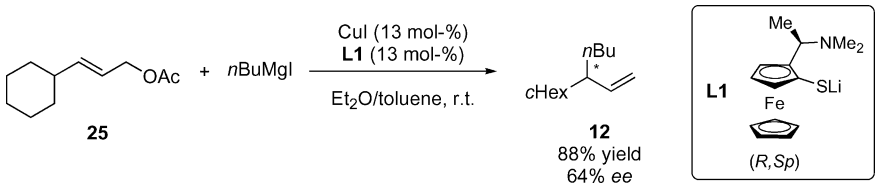
After failed attempts of structural modifications brought to the "non-transferable" chiral ligand in the copper(I) complex, Bäckvall and co-workers transposed the framework of their precedent chiral complex onto a ferrocene backbone (**L1**).[22] The new ferrocene-thiolatocopper(I) brought added selectivity to the allylic reaction and induced



Scheme 9. Asymmetric allylic alkylation catalyzed by a chiral arenethiolato-copper(I) complex.



Scheme 10.



Scheme 11.

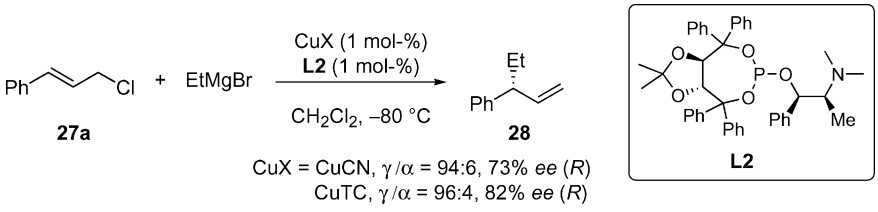
up to 64% *ee* for the addition of *n*-butylmagnesium iodide to the cyclohexyl allylic acetate (**25**), as illustrated in Scheme 11. Furthermore, the reaction was carried out in new sets of conditions (in a 3:1 mixture of Et_2O/toluene at room temperature).

Parallel to these studies, Alexakis et al. developed the first allylic substitution of organomagnesium reagents in the presence of chiral external ligands.[23] After a high-throughput screening of many phosphorus ligands, they made note of enantioselectivities reaching 73% *ee* for the addition of ethylmagnesium bromide to cinnamyl chloride (**27**) with a TADDOL-derived phosphite (**L2**) and CuCN (Scheme 12). Slow addition of the organomagnesium reagent was crucial for enantioselectivity of the substitution reaction.

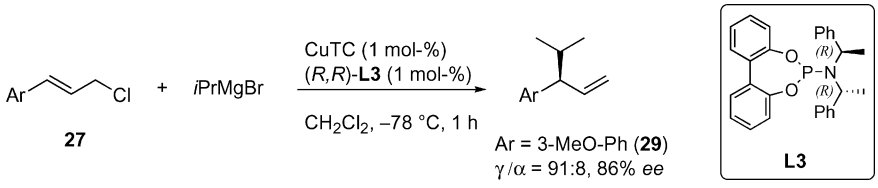
In a second-generation system, Alexakis et al. replaced the copper source by copper thiophene carboxylate (CuTC), which increased the selectivity of the ethyl adduct **28** from 73% *ee* to 82% *ee* in the presence of **L2** (Scheme 12).[24] Interestingly, in the absence of a chiral phosphorus ligand, the latter copper salt catalyzed an exclusive α-alkylation. This observation would suggest a strong accelerating effect produced by the phosphorus ligand, favorably affecting the rate of reductive elimination. Moreover, the typically monodentate biphenol-based ligand (*RR*)-**L3** afforded up to 86% *ee* (for **29**) for the addition of *i*PrMgBr to the cinnamyl derivative bearing an electron-donating group, with a good γ-selectivity of 91% (Scheme 13).

Under the more recent set of conditions, the copper-catalyzed S_N2' process, which previously limited asymmetric induction to aryl allylic halides **27**, now promoted the asymmetric addition of *i*PrMgBr to aliphatic substrates **30**. With the binaphthyl phosphoramidite ligand (*R*,*SS*)-**L4**, the highly regiocontrolled branched alkylation reached 74% *ee* (Scheme 14).

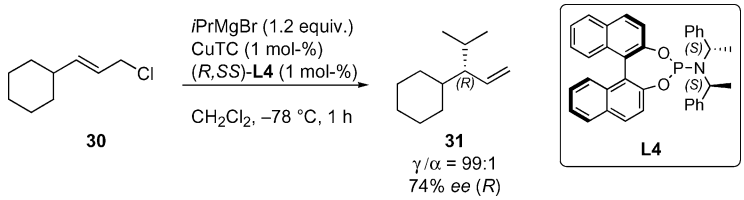
More importantly, these new sets of conditions were compatible with a one-pot double process, namely the allylic alkylation followed by a ruthenium-catalyzed metathesis reaction. In the presence of the second- or the first-generation Grubbs catalysts and copper and magnesium salts, either cross- (**32**) or ring-closing metathesis (**34**) (RCM) were achieved, respectively, with complete stereoretention (Scheme 15).



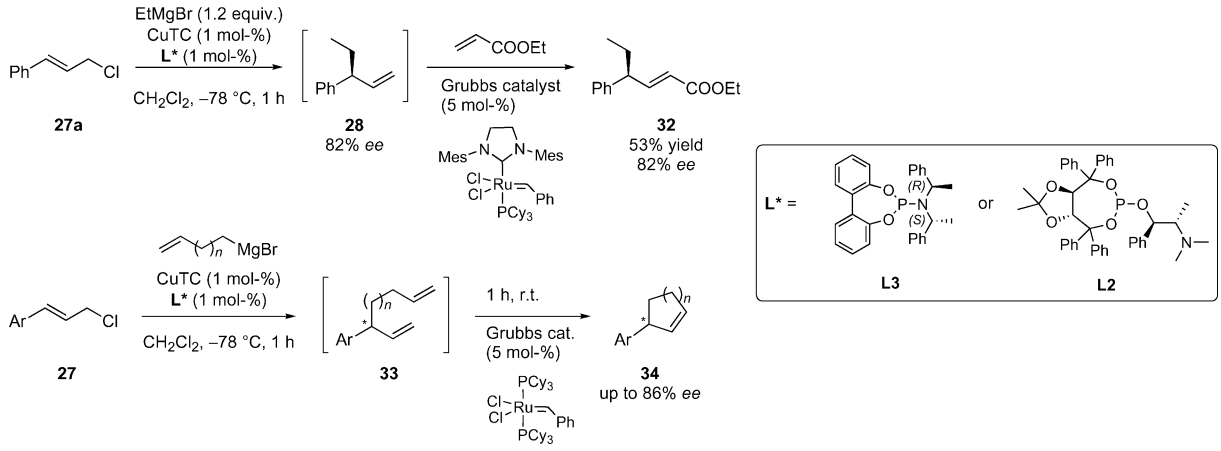
Scheme 12.



Scheme 13.

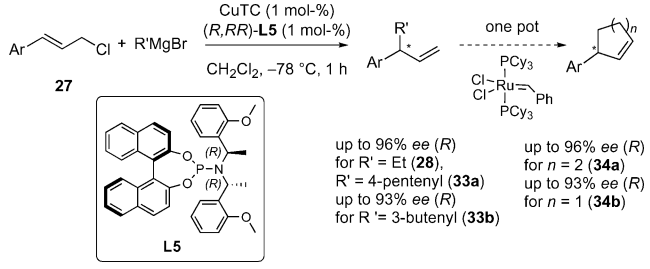


Scheme 14.



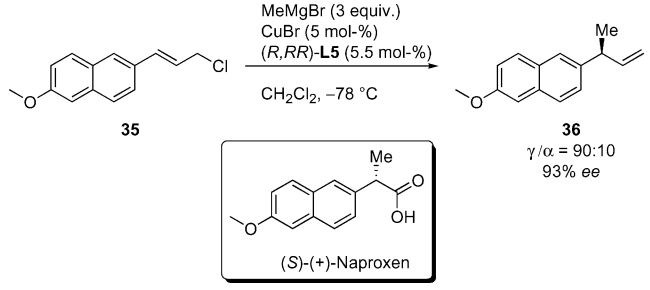
Scheme 15. One-pot asymmetric allylic substitution and cross- or ring-closing metathesis.

More recently, a third-generation chiral phosphoramidite ligand (*R*,*RR*)-**L5** was disclosed with outstanding results in terms of regio- and enantioselectivity.[25] The ligand is composed of a matched combination of an *o*-methoxy-substituted amine moiety and a binaphthol unit of similar stereogenic nature. This hemilabile P,O-bidentate ligand provided (*R*)-**33a** with high enantioselectivity of 96% *ee*, which again could be coupled to RCM without any loss of *ee* (Scheme 16). This ligand was also suitable for the asymmetric allylic substitution with diethylzinc [91% *ee* for **28**, starting from cinnamyl bromide (**63**) at –40 °C].



Scheme 16.

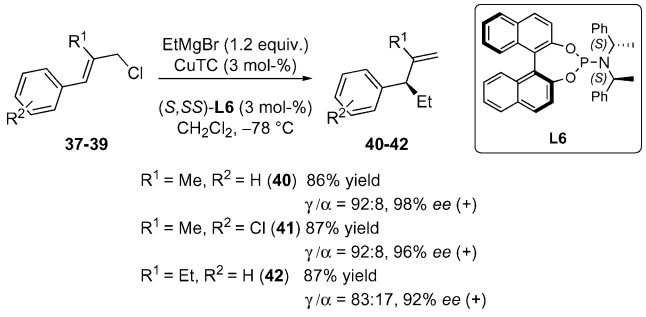
Thereafter, the highly asymmetric inducing catalytic set CuTC/**L5** was used successfully for the methylation of different allylic chlorides (generally > 90% *ee*).[26] This methodology was applied for the short synthesis of the precursor **36** of chiral naproxen, the familiar *anti*-inflammatory drug (Scheme 17).



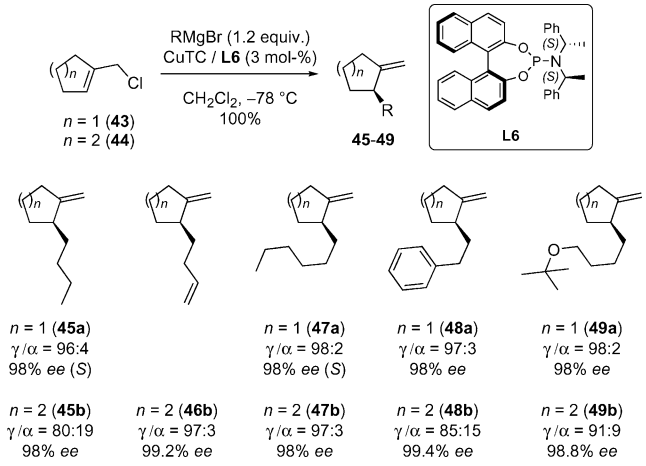
Scheme 17.

It was shortly after, that Alexakis found a new application of his methodology to more substituted allylic frameworks, namely the β-disusbtituted allylic electrophiles.[27] By changing the diastereomeric nature of the phosphoramidite ligand to an (*S*,*SS*) configuration, both cinnamyl and aliphatic β-disusbtituted allylic chlorides afforded excellent regio- and enantioselectivities for the formation of the new stereogenic centers.

The model reaction would function invariably on electron-rich or -poor aromatic systems **37**–**39** (*ee* values up to 98%; Scheme 18), as well as on different ring-sized aliphatic endocyclic allylic chlorides **43**,**44** (up to >99% *ee*; Scheme 19).



Scheme 18.

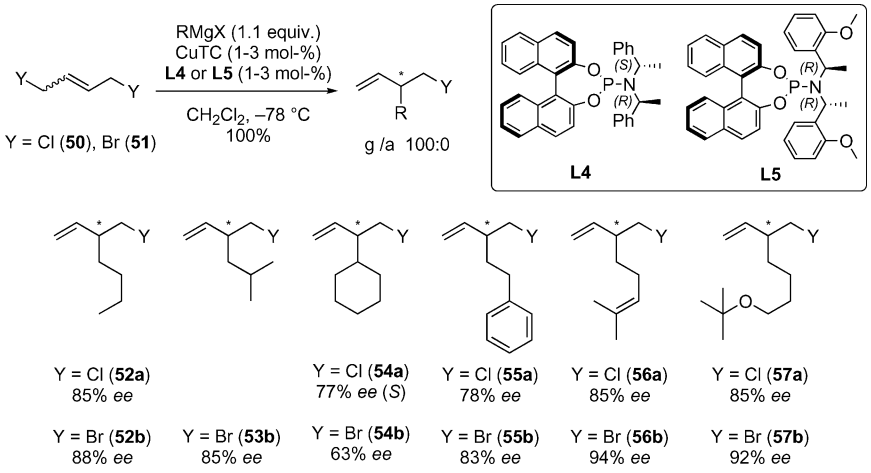


Scheme 19.

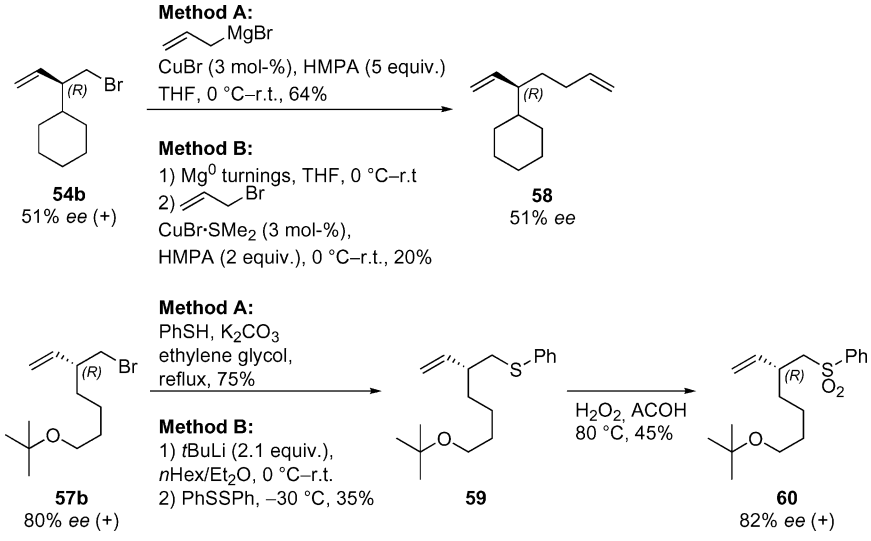
Later on, a similar procedure was applied to commercially available 1,4-dihalo-2-butene substrates **50**,**51** with impressive complete regiocontrol,[28] imputed to the intramolecular stabilisation of the intermediate copper(III)–allyl complex. Such reactions afforded highly tunable substrates with up to 94% *ee* (Scheme 20).

Both electrophilic (Method B) or nucleophilic (Method A) procedures could further be performed on the remaining halide present in the homo-allylic chiral adducts **54b** and **57b** with a complete retention of the optical purity (Scheme 21).

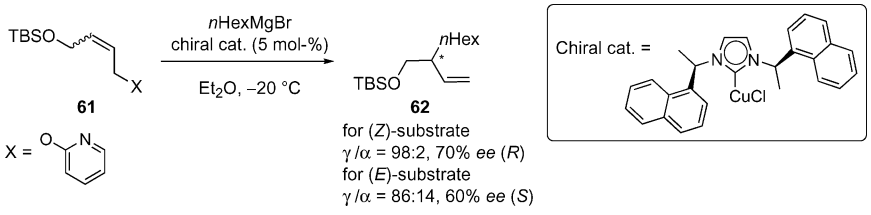
Other than the largely used phosphorus ligands, Okamoto and co-workers introduced the use of *N*-heterocyclic diaminocarbenes (NHC) in a new catalytic asymmetric protocol.[29a] The C_2-symmetric carbene–copper complex, bearing the sterically demanding 2-naphthyl group, would yield allylic branched adducts **62** with moderate *ee* of 70% on (*Z*)-configured difunctionalized substrate **61** (Scheme 22). Interestingly though, the *trans*-isomer would afford the opposite enantiomer, albeit in lower optical purity (60% *ee*). The 2-pyridyloxy group as well as the acetate were suitable leaving groups, the latter affording slightly



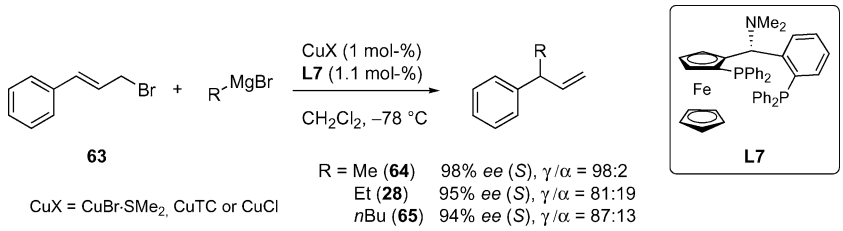
Scheme 20.



Scheme 21. Stereoretentive derivatization of homoallylic halides trough nucleophilic (Method A) or electophilic (Method B) pathways.



Scheme 22.

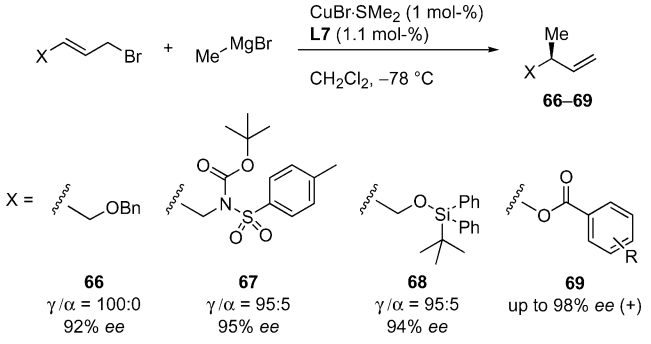


Scheme 23.

lower enantioselectivities [60% *ee* on (*Z*)-configured substrate].[29b]

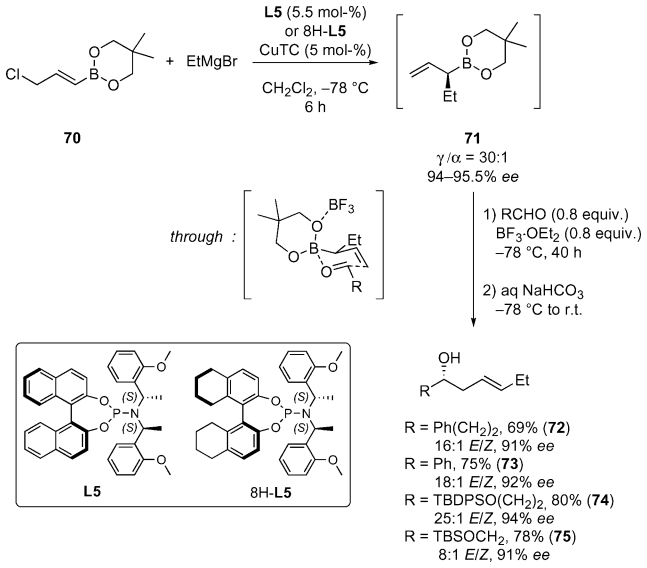
More recently, the research group of Feringa showed that the ferrocenyl-based (*R*,*S*)-taniaphos (**L7**) could induce high selectivities for the addition of different organomagnesium reagents in dichloromethane at –78 °C (Scheme 23).[30] In this set of conditions close to those used previously by Alexakis et al.,[26] they found that the bidentate ligand (*R*,*S*)-**L7** could promote asymmetric allylic substitutions with up to 98% *ee* for the addition of a methylmagnesium reagent to different allylic bromides, coupled with very high S_N2' selectivities.

More recent publications of Feringa's group describe the application of the catalytic mixture of CuBr·SMe_2/**L7** to more functionalized aliphatic allylic ethers like **66**, **68** or carbamates **67**,[31] as well as different vinylic esters **69** (Scheme 24).[32] As in the aforementioned study, enantioselectivities were very high for the new set of methylated versatile adducts, *ee* values generally > 92%. Traditional oxidative treatment of the terminal olefins (hydroboration, Wacker oxidation, ozonolysis, etc.) were performed with retention of the starting optical purity.



Scheme 24.

In the end, the highly efficient *o*-methoxy-bearing ligand **L5** and its semi-saturated counterpart 8H-**L5** were applied successfully by Hall and co-workers in the asymmetric allylic alkylation of vinylic boronates **70** with ethylmagnesium bromide (Scheme 25).[33] Without isolation of intermediate chiral adducts, these allylic boronates (**71**, up to 95.5% *ee*) would further undergo one-pot boron-mediated aldehyde allylation, rendering the homoallylic alcohols **72**–**75** with almost complete transfer of chirality.

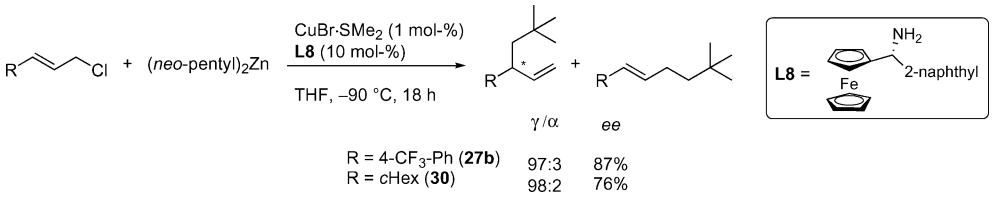


Scheme 25.

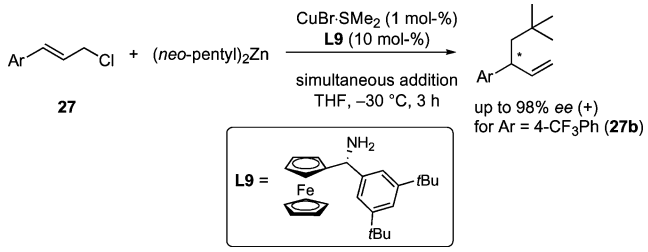
Organozinc Reagents

The pioneering results from Bäckvall and van Koten (in organomagnesium allylic alkylation) were followed soon after by the diorganozinc equivalent disclosed in 1999 by Dubner and Knochel.[34] This breakthrough copper-catalyzed reaction afforded up to 87% *ee* for copper(I)-catalyzed allylic substitution reactions of allylic chlorides in the presence of a ferrocenyl-based chiral amine (**L8**) (Scheme 26). The reaction yielded good γ-selectivities (up to 98%), but stayed limited to the addition of the highly sterically hindered dineopentylzinc reagent for a 72% yield on the *p*-(trifluoromethyl)cinnamyl chloride (**27b**). The selectivity was furthermore highly dependent upon the temperature: a reaction carried out at room temperature caused the *ee* value to diminish from 87% to 25% *ee*.

For the same reaction, more adequate conditions were found ulteriorly by structural modifications of the chiral ligand (**L9**) and by changing to a simultaneous addition of substrate and zinc reagent over a period of three hours.[35] These new parameters led to a S_N2'-selective displacement with 98% *ee* (Scheme 27). This increase of selectivity was also perceived for the addition of *n*-alkylzinc reagents to cinnamyl chloride (**27a**), yielding moderate *ee* values of 52% and 65% *ee* for the ethyl-[36] (**28**) and the pentyl adducts, respectively.



Scheme 26.

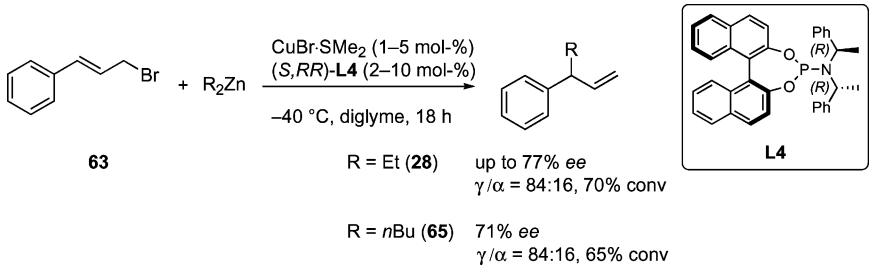


Scheme 27.

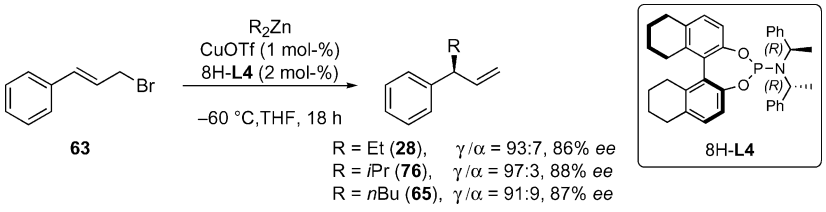
In the line of work undertaken by Knochel, accessing highly enantioselective allylic substitutions with linear alkylzinc reagents remained a major challenge. In view of increasing the moderate enantioselectivities obtained with small alkylzinc reagents, Feringa and co-workers published in 2001 their findings in the presence of chiral phosphoramidite ligands (**L4**) (Scheme 28).[37] After comparing the inherent effects of leaving groups, temperature, ligands and solvent, the optimal conditions used in Scheme 28 promoted the allylic substitution of cinnamyl bromide (**63**) with diethylzinc to 77% *ee*. Nevertheless, an objectionable feature resided in the necessity of using a highly polar solvent to succeed in promoting a selective reaction.

These last results were later improved by changing the copper source to CuOTf, through the use of tetrahydrofuran, and by inducing chirality through a new phosphoramidite ligand 8H-**L4** (Scheme 29).[38] Consequently, the allylic substitution proceeded with enantioselectivities reaching 86% to 88% *ee* for the addition of dialkylzinc compounds to cinnamyl bromide (**63**).

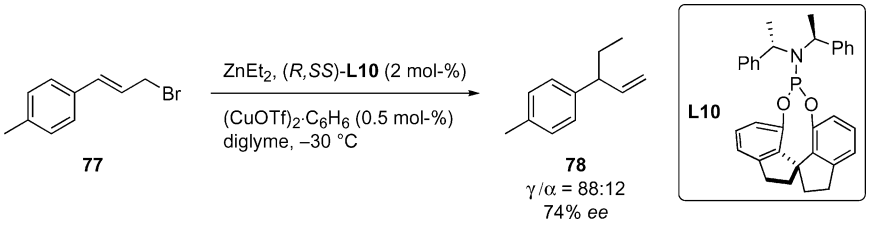
In parallel to the work disclosed by Feringa, the research group of Zhou and co-workers applied their original spiro phosphoramidite **L10** and phosphate ligands under similar reaction conditions (diglyme at –30 °C) to cinnamyl-type



Scheme 28. With the use of phosphoramidite ligands for the addition of alkylzinc reagents.



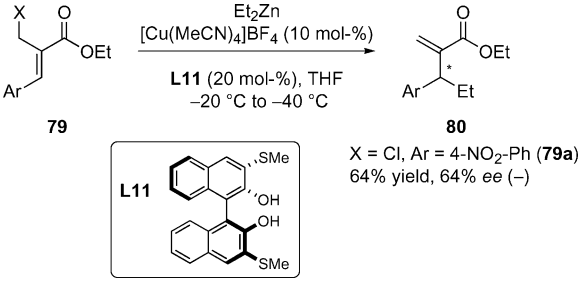
Scheme 29.



Scheme 30. Spiro phosphoramidite ligand **L10** in the Cu-catalyzed AAA.

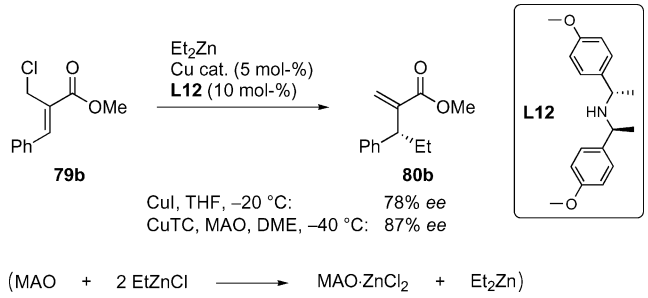
bromides **77**.[39] The branched adducts **78** were produced in moderate selectivities in terms of *ee* values (74%) and γ/α ratios (88:12). Notably, a crystal structure of the complex between $CuBr{\cdot}SMe_2$ and the spiro-phosphoramidite **L10**, pictured in Scheme 30, was successfully isolated and its dimeric structure [{$CuBrL_2$}$_2$] validated by X-ray analysis.

Woodward and co-workers developed the addition of diethylzinc to substrates derived from the Morita–Baylis–Hillmann chemistry for the asymmetric allylic substitution reaction.[40] After having efficiently used the binaphthol ligand **L11** illustrated in Scheme 31 in the conjugate addition,[41] the authors selected it as an initial candidate for their prelimary test for asymmetric induction on **79**. However, the moderate enantioselectivity was limited to a *para*-nitro substituent on the aryl moiety and to the chloride leaving group **79a** with 64% *ee*. Moreover, a rather large quantity of catalyst (10 mol-%) and of ligand (20 mol-%) were necessary to maximize the asymmetric induction.



Scheme 31.

However, during their investigations on the use of phosphoramidite ligands for the reaction, Woodward and coworkers discovered that the sole C_2-symmetrical amine **L12** enabled the asymmetric induction.[42] Their study also highlighted that, when using dialkylzinc reagents, the enantiomeric excess would decreased as the reaction proceeded, allowing an 80% *ee* at its onset and falling to 74% *ee* after one hour. This observation inferred that the progressive formation of the EtZnCl species in the reaction media impaired the selectivity.[43] Thus, a halide scavenger used in the reaction could drive the zinc-Schlenk equilibrium in favor of the dialkylzinc species. After a screening of different candidates, they found that the addition of methylaluminoxane {MAO; [–Al(Me)O-]$_n$} enabled higher anticipated enantioselectivities, increasing the *ee* from 78% to 87% (Scheme 32). In these conditions, the more electron-donating groups in the substrate (4-MeO–Ph) allowed *ee* values up to 90%.



Scheme 32.

In 2001, Hoveyda and co-workers applied peptide-based ligands **L13**, free of any C_2-symmetry, to promote asymmetric S_N2' substitution reactions under copper catalysis.[44] Accordingly, diethylzinc reagents alkylated cinnamyl phosphates with selectivities ranging from 66% to 90% *ee* (Scheme 33). As Knochel had underlined previously, they observed that electron-withdrawing functionalities of the aryl moiety allowed higher enantioselective γ-substitutions. These were also the first published highly enantioselective substitution reactions of γ-disubstituted allylic substrates **82**, affording chiral quaternary centers with up to 90% *ee* for **84a**. Furthermore, this was the first instance of an asymmetric use of allylic phosphates **81**,**82**.

The synthetic utility of their methodology was further illustrated by the enantioselective synthesis of (*R*)-(–)-sporochnol (**85**), a fish repellant, yielding a product in 82% *ee* and 82% yield (Figure 3). With the different results obtained in the presence of their library of ligands, Hoveyda et al. underscored the important advantage on a practical level of this class of versatile chiral ligands, which are readily tunable and adaptable to combinatorial chemistry.

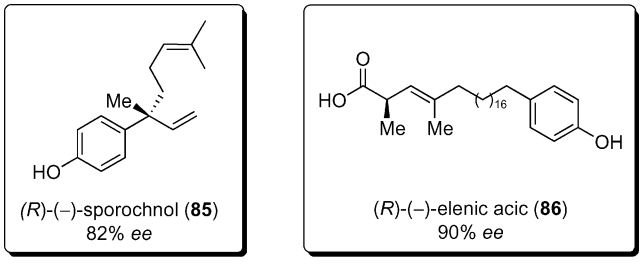
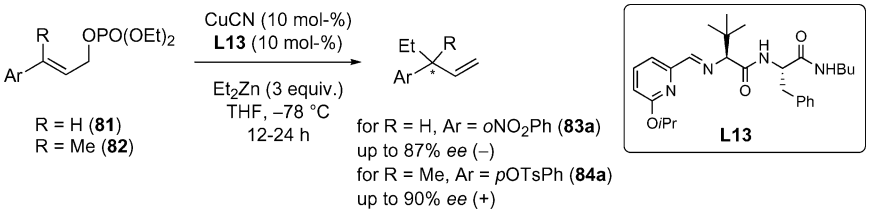


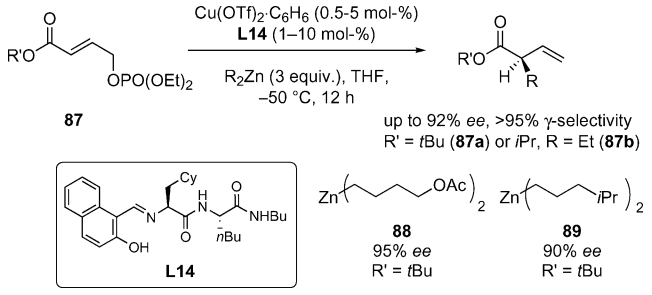
Figure 3. Natural products synthesized through AAA on allylic phospates.

Soon after, by small structural modifications brought to their Schiff peptidic base, they managed to induce copper-catalyzed asymmetric allylic alkylations on unsaturated



Scheme 33.

esters possessing a primary phosphate at a γ-position (Scheme 34).[45] This efficient synthesis is an alternative to the alkylation of enolates, and afforded homoallylic α-alkylated esters ranging from 87% to 97% *ee*. For these substrates, a new optimum set of conditions was identified, by changing the ligand to **L14** and the copper salt to $(CuOTf)_2 \cdot C_6H_6$. Their observations further aimed at the ester's substituents, which influenced the regiochemical outcome of the reaction. Indeed, encumbering functionalities [*tert*-butyl (**87a**) or isopropyl (**87b**)] afforded higher γ-selectivities (up to >95%), while the regioselectivity dropped to a S_N2'/S_N2 ratio of 7:1 for the allylic alkylation of the unsaturated methylic esters. In addition, the synthetic utility of their chiral synthons was again exemplified by the total synthesis of the topoisomerase II inhibitor, the (*R*)-elenic acid (**86**), with a final chiral outcome of 90% *ee* (Figure 3).



Scheme 34.

The results presented in Scheme 34 were later improved, and the methodology developed by Hoveyda and co-workers was generalized by using another chiral promoter, the state-of-the-art dipeptidic Schiff base **L15**, illustrated in Figure 4.[46] In the presence of the latter, enantioselectivities for the allylic alkylation of disubstituted olefins reached 96% *ee* (in place of a previous 87% *ee*), albeit with a dramatic loss of regioselectivity (S_N2'/S_N2 ratio of 1:1). The same ligand afforded similar good *ee* values for the formation of quaternary centers starting from trisubstituted olefins.

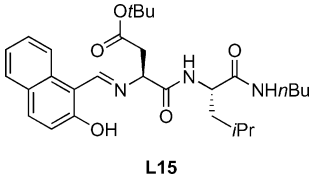


Figure 4. Improved peptidic ligand for Scheme 34.

Interestingly, by the knowledge gained with their combinatorial approach to ligand synthesis, the authors managed to propose a transition state for the copper–ligand-substrate-reagent cluster (Figure 5).

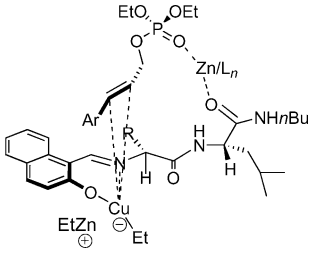
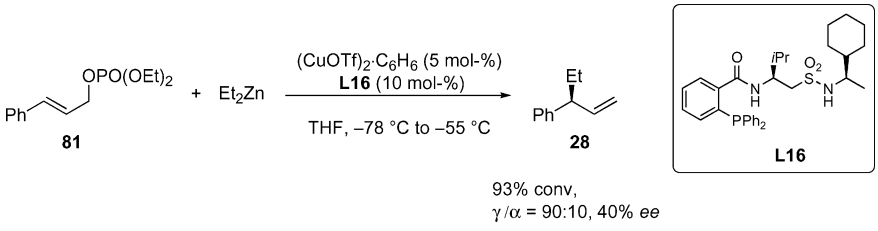


Figure 5. Proposed transition state for the Cu^I peptide-based complex.

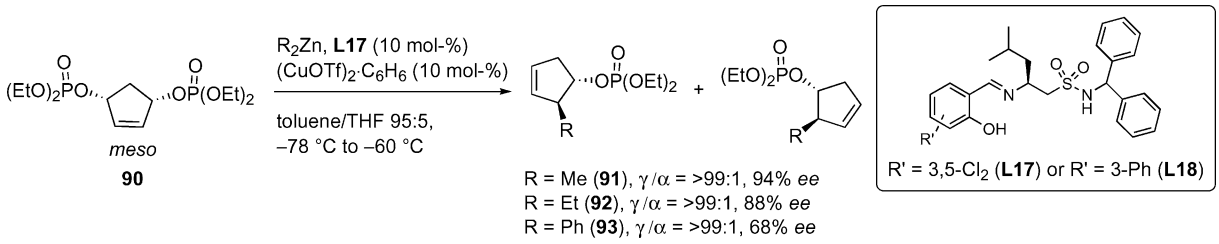
Comparatively to Hoveyda's work, the research group of Piarulli and Gennari based their studies on the family of Schiff base chiral ligands and their use for the copper-catalyzed allylic substitution. Their preliminary assays in 2002 would deliver only poor enantiomeric excesses.[47] Indeed, after an intensive screening of their library of ligands and of different copper salts, 40% *ee* was the best enantiomeric outcome for the addition of diethylzinc to cinnamyl phosphates **81**, in spite of a good regiocontrol (Scheme 35).

Thereafter, Gennari and co-workers exploited their ligand library in the catalytic desymmetrization of cyclic *meso* compounds **90** with dialkylzinc reagents (Scheme 36).[48] The chiral copper(I) complex with the Schiff base promoted the asymmetric addition of diethylzinc to cyclic allylic bisdiethylphosphates with a high control over the regio-, diastereo- and enantioselectivity. As illustrated in Scheme 36, the reaction upon the cyclopentene substrate **90** produced a specific S_N2' adduct with an *anti* stereochemical mechanism. The best enantioselective result was enabled by the addition of Me_2Zn, yielding 94% *ee* in favour of the (*S*,*S*) enantiomer **91**. The ethyl (**92**) and phenyl (**93**) adducts were produced in lower *ee* values with 88% and 68%, respectively. Shortly thereafter, the same authors published, in collaboration with Feringa, new results on the subject in the presence of phosphoramidite ligands inducing enantioselectivities of 87%, 94% and >98% *ee* for the addition of Et_2Zn to the derivatives of cyclopentene **90**, cyclohexene and cycloheptene, respectively.[49]

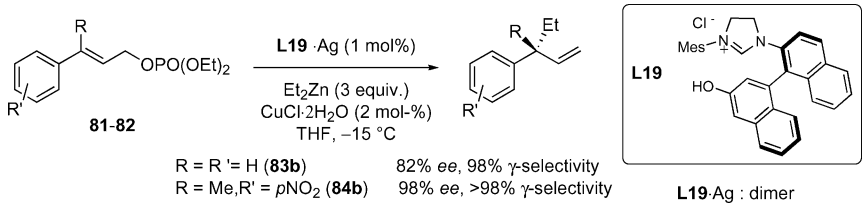
Besides the oligopeptide-based ligands, Hoveyda disclosed bidentate diaminocarbene-based ligands (NHC, **L19**) as efficient chiral promoters for the copper-catalyzed allylic substitution (Scheme 37).[50] This new set of catalyst



Scheme 35.



Scheme 36.



Scheme 37.

was significantly more effective than the above-mentioned peptide-based ligands, allowing highly selective substitutions of di- or trisubstituted olefins to arise with catalyst loading as low as 2 mol-% of chiral NHC. To increase the efficacy and the selectivity of the process, the dinuclear silver(I) complex of the same NHC ligand (**L19**) was prepared, and upon treatment with copper salts a facile exchange of the silver-based carbene complex generated highly effective copper complexes. Indeed, these ligands induced enantioselectivities up to 98% *ee* for quaternary center formation.

The results presented in Scheme 37 were soon after improved by the new chiral NHC ligand **L20**, with the chirality induced to the biphenyl-core by the carbene diphenyl-backbone (Figure 6).[51]

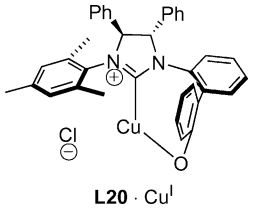
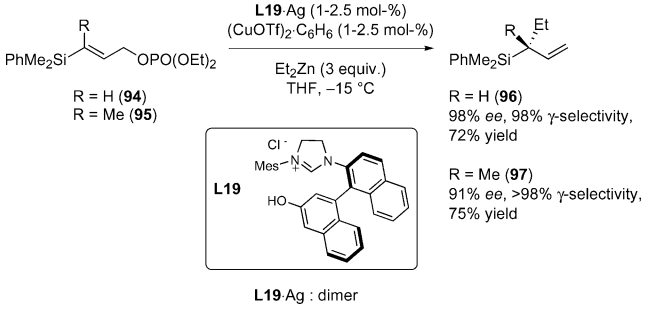


Figure 6. Improved carbene ligand for Scheme 37.

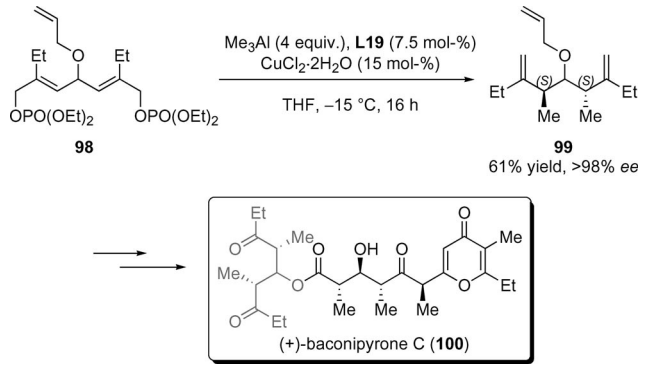
Very recently, Hoveyda et al. disclosed the allylic substitution of difunctionalized vinylsilanes **94**, **95** (Scheme 38).[52] The addition of diethylzinc to di- or trisubstituted olefins afforded chiral allylic silanes with 98% *ee* (for **96**) and 91% *ee* (for **97**), respectively. Furthermore, these specific substrates promoted an efficient arylation using Ph_2Zn, affording highly selective S_N2'-displacement (>98%) with high asymmetric outcomes (up to 92% *ee*).



Scheme 38.

Alkylaluminum Reagents

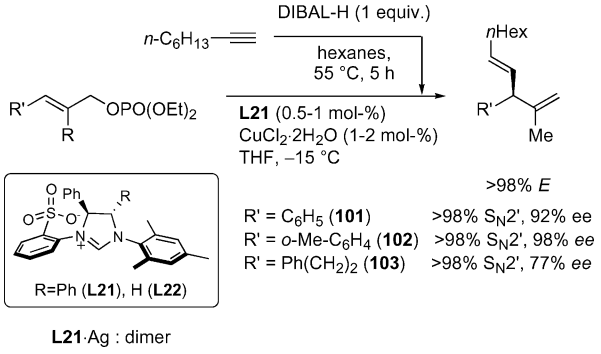
The first reported uses of trialkylaluminum reagents for the copper-catalyzed allylic substitution by Woodward were poorly successful.[40] Finally, further contributions from Hoveyda and co-workers disclosed the asymmetric total synthesis of Baconipyrone C through a double allylic substitution of a β-disubstituted olefin using a N-heterocyclic carbene (NHC) as chiral ligand (Scheme 39).[53] After test-



Scheme 39.

ing different conditions with dialkylzinc reagents, a trimethylaluminum reagent stood out as better suited for a regio- (γ/α = 20:1), diastereo- (*dr* 20:1) and enantiocontrolled allylic substitution reaction on the analogous mono allylic substrate (up to 98% *ee*). These new conditions applied to the bis-allylic diphosphate afforded an analogous high enantioselectivity (98% *ee*) in a diastereomeric mixture 8:1 in favor of the catalyst-controlled C_2-symmetrical double adduct (*S*,*S*).

Most recently, this newly developed methodology was used with vinylaluminum reagents (generated in situ from alkyne and DIBAL-H) on different β-disubstituted cinnamyl derivatives affording diene adducts **101**–**103** in a range of 77% to 98% *ee* (Scheme 40).[54]



Scheme 40.

Ring-Opening of Allylic Oxiranes

Kinetic Resolution for the Opening of Racemic Monoepoxide

Allylic monoepoxide can be used as substrates for chiral organocopper reagents. More importantly, a racemic mixture of cyclic monoepoxides can react kinetically with half an equivalent of organometallic reagent, thus enriching the optical purity of starting material. This principal was first illustrated by the research group of Feringa.[63] Half an equivalent of dimethylzinc in the presence of $Cu(OTf)_2$ (3 mol-%) and (*S*,*RR*)-**L4** (6 mol-%) could selectively alkylate cyclic epoxides **104**–**106** with good regio- and enantiocontrol in favour of the S_N2' adducts (Scheme 41).

This latter reaction was performed in a similar fashion by the research group of Alexakis,[55] who deracemized cycloalkene oxiranes [five- (**104**) to eight-membered (**110**) ring substrates] with commercially available trimethylaluminum reagent, affording chiral allylic and homo-allylic alcohols with up to 93% *ee* and 99% *ee* respectively (Scheme 42). However, regioselectivities in favor of the S_N2' adduct were not optimal for each ring-size (at the best 94:6 on the six-membered ring alkene **108**).

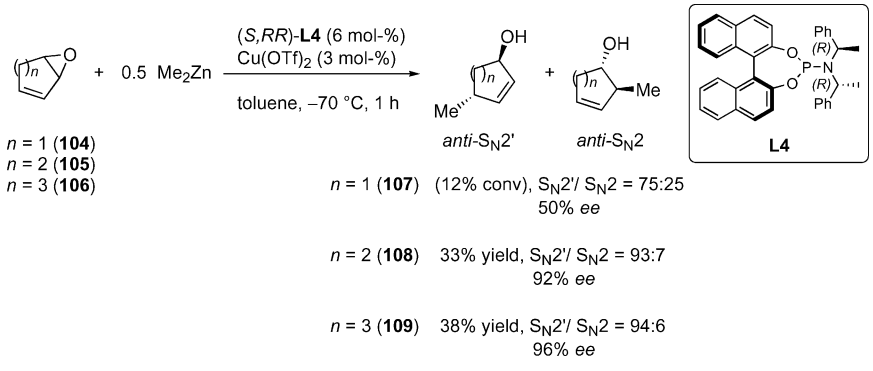
Soon after, this methodology was improved in a further contribution by Alexakis and co-workers, by using a broad range of organomagnesium reagents and commercially available ferrocene-based ligands **L22**,**L23**.[56] This version enabled highly regioselective alkylation into allylic alcohols (up to S_N2'/S_N2 = 99:1) with good enantioselectivities (up to 90% *ee*) (Scheme 43).

Desymmetrization of *meso*-Bicyclic Substrates

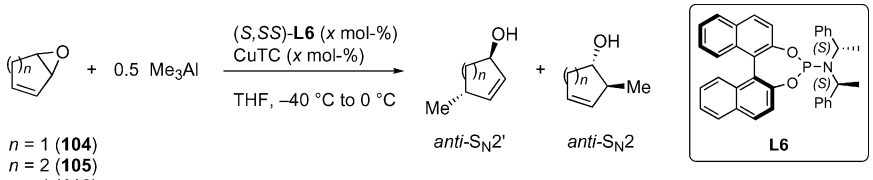
As regards symmetrical substrates, reports from Pineschi and co-workers stated that 1,3,5,7-cyclooctatetraene-monoepoxide (**116**) could be regio- and enantioselectively alkylated using diethylzinc and $Cu(OTf)_2$/(*R*,*RR*)-**L6** to afford (1*R*,4*R*)-4-ethyl-2,5,7-cyclooctatrienol (**117**) with 94% *ee* (Scheme 44).[57]

In the continuation of these preliminary studies Pineschi et al. desymmetrized oxanorbornadiene-type substrates using diorganozinc reagents with a stoichiometric amount of zinc triflate.[58] Although reactions were quite slow (up to 70 hours reaction time), single S_N2' adducts were observed with enantioselectivities > 90% *ee* (Scheme 45). However, limitations occurred when using dimethylzinc (**120**) or substrates containing electron-withdrawing groups (**118**, R′ = 6,7-F_2), lowering both reactivity (17–58% yield) and enantiomeric excess of the *anti* adducts (80–88% *ee*).

Organomagnesium reagents were also described for such ring-opening reaction.[59] Zhou and co-workers showed that under these conditions the reaction was slightly faster (15 hours). However, in the presence of their spiro-ligand (*S*,*SS*)-**L24**, the catalytic procedure would enable lower enantioselectivities [up to 88% *ee* (**123**)] (Scheme 46).



Scheme 41.



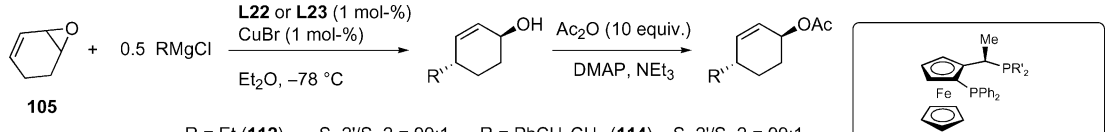
n = 1 (**104**)
n = 2 (**105**)
n = 4 (**110**)

n = 1, *x* =3 (**107**) 10% yield, S_N2'/S_N2 = 61:39, 87% *ee* (99% *ee*)

n = 2, *x* =1 (**108**) 44% yield, S_N2'/S_N2 = 94:6, 82% *ee* (–)

n = 4, *x* =3 (**111**) 59% yield, S_N2'/S_N2 = 58:42, 93% *ee* (99% *ee*)

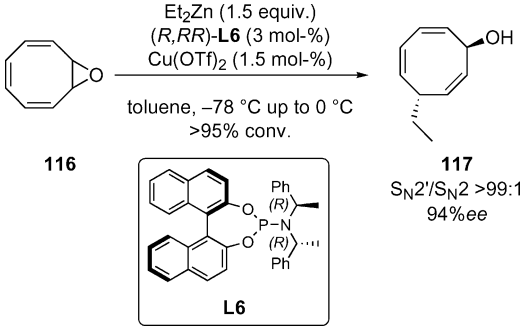
Scheme 42.



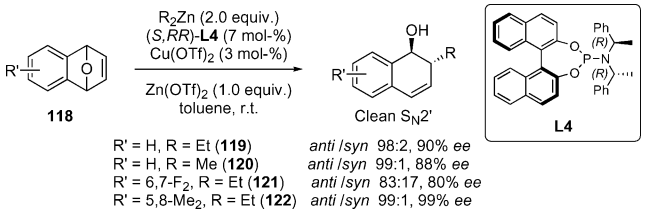
R = Et (**112**) S_N2'/S_N2 = 99:1, 84% *ee*
R = *n*Bu (**113**) S_N2'/S_N2 = 99:1, 90% *ee*
R = $PhCH_2CH_2$ (**114**) S_N2'/S_N2 = 99:1, 84% *ee*
R = *i*Pr (**115**) S_N2'/S_N2 = 99:1, 74% *ee*

R' = 3,5-$Me_2C_6H_3$ (**L22**)
R' = 3,5-Me_2-4-OMe-C_6H_2 (**L23**)

Scheme 43.

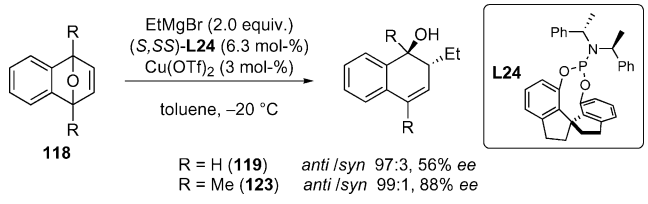


Scheme 44. Catalytic enantioselective desymmetrization of 1,3,5,7-cyclooctatetraene-monoepoxide (**116**).



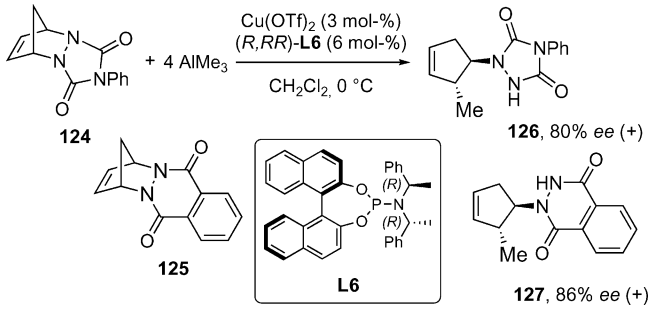
R' = H, R = Et (**119**) *anti* /*syn* 98:2, 90% *ee*
R' = H, R = Me (**120**) *anti* /*syn* 99:1, 88% *ee*
R' = 6,7-F_2, R = Et (**121**) *anti* /*syn* 83:17, 80% *ee*
R' = 5,8-Me_2, R = Et (**122**) *anti* /*syn* 99:1, 99% *ee*

Scheme 45.



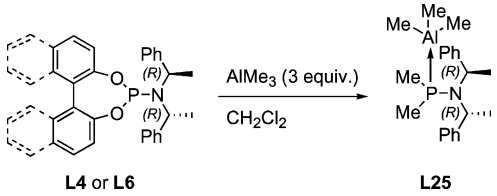
R = H (**119**) *anti* /*syn* 97:3, 56% *ee*
R = Me (**123**) *anti* /*syn* 99:1, 88% *ee*

Scheme 46.

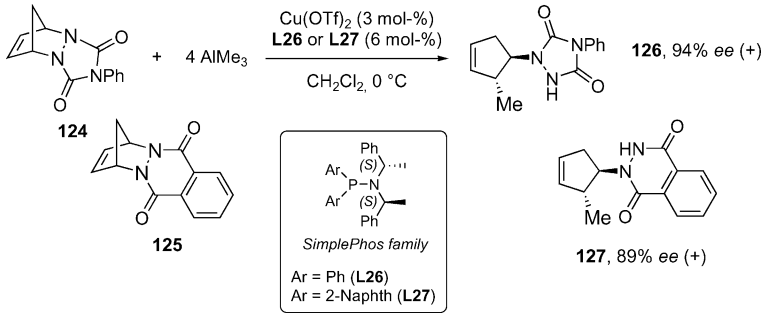


Scheme 47.

More recently, Pineschi and co-workers published a copper-catalyzed desymmetrization of polycyclic hydrazines **124**,**125** using large excesses of trialkylaluminum reagents in apolar solvents, such as dichloromethane.[60] The use of binaphtol-based phosphoramidite chiral ligands (**L6**) enabled enantioselectivities up to 86% *ee* for the methyl adducts (Scheme 47).



Scheme 48.



Scheme 49.

Oddly when the diastereomeric ligand **L4** was used, combining both (*R*)-binapthol and (*S*,*S*)-amine, the enantiomeric nature of the resulting products **126**,**127** was opposite to the one obtained with the ligand (*R*,*RR*)-**L6**. This last observation was soon after explained by Micouin and Alexakis, who discovered that in non-coordinating solvents, such as toluene or dichloromethane, an aluminum reagent generates phosphinamines (*RR*)-**L25** by in situ reaction with the chiral phosphoramidite ligands (*S*,*RR*)-**L4** or (*R*,*RR*)-**L6** (Scheme 48).[61]

Shortly after, the ring-opening of *meso* polycyclic hydrazines **124** and **125** was improved with the use of a novel class of monodentate phosphorus ligands described by Alexakis and co-workers.[62] A new generation of phosphinamine ligands **L26**,**L27**, termed SimplePhos, untouched by the aluminum reagent, would enable higher enantioselectivities than previously reported with *ee* values up to 94% (Scheme 49).

Conclusions

In conclusion, over the past five years, the field has grown considerably. The copper-catalyzed reaction proceeds with generally high regioselectivity with inversion at the reaction center. Moreover, in comparison to the palladium analogous reaction, the metal source for copper salts is generally less expensive. Many types of chiral inducers have emerged for efficient enantioselective procedure, such as classical phosphorus-based ligands, peptides and, more recently, diaminocarbenes (NHC). Subsequently, the different organometallic reagents used, namely organomagnesium, -zinc or -aluminum reagents, are complementary to one another on a variety of parameters: the tolerance to functionalities, the price, the reactivity, commercial availability and ease of handling. Following the primary model based upon cinnamyl substrates, lots of effort has been put into broadening the scope of the reaction to more functionalized substrates, containing different heteroelements. However, the mechanistic issues are still widely unexplored and the allylic arylation remains a largely unexploited field.

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