Review

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Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions

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1. Introduction

In the past decades there has been a dramatic increase in the demand for enantiopure compounds for fine-chemicals (i.e., agrochemicals and pharmaceuticals) and material science (i.e., liquid crystals and polymers). In response to this need, enantioselective catalysis has experienced an unprecedented advance, as has been reflected by the many publications in this field and the 2001 Nobel Prize in Chemistry awarded to W. S. Knowles, R. Noyori, and K. B. Sharpless.[1] One of the main advantages of asymmetric catalysis over other methods used in asymmetric synthesis is that products can be selectively synthesized from cheap, commercially available prochiral starting materials without undesirable products being formed. Usually with this strategy, a transition-metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate to one enantiomer as major product.[1]

Enantioselective copper-catalyzed conjugate addition and allylic substitution are two of the most powerful carbon−carbon bond-forming reactions for construction of enantioenriched synthons for biological active and natural compounds.[2] Significant advantages of these processes are the high compatibility with many functional groups, low cost of the copper salts, and the often high regio- and enantioselectivities. In the copper-catalyzed asymmetric conjugate addition an α,β-unsaturated compound is attacked by a carbon nucleophile (nonstabilized, Scheme 1a, or stabilized, Scheme 1b) to form a new stereogenic carbon center. In the copper-catalyzed asymmetric allylic substitution the new stereogenic carbon center is formed by the attack of a nonstabilized carbon nucleophile to an allylic substrate (Scheme 1c). In the past few years impressive results have been obtained in the development of highly efficient new copper catalytic systems by exploring several ligand types, copper sources, and reaction conditions. Remarkable efforts have been made to enlarge the scope of substrates and nucleophiles, increasing the possibilities for their use in the synthesis of more complex chiral organic molecules.

Despite the large amount of relevant literature on enantioselective copper-catalyzed conjugate additions and allylic substitution reactions (we can easily count more than 200 research papers in the past few years), there are only a few recent reviews that deal with the copper-catalyzed conjugate additions and allylic substitution reactions.[2] However, these reviews are mainly microreviews or book chapters that either cover mainly narrow-specific areas (i.e., one type of ligand or one type of substrate or only describe mechanistic aspects) or describe only one of the reactions. In addition, the reviews that deal with the copper-catalyzed conjugate additions usually cover either the use of organometallic reagents (nonstabilized nucleophiles) or the use of organic nucleophiles (stabilized nucleophiles). In summary, there is no review that discusses the mechanism, catalysis, and application in total synthesis of both Cu-catalyzed conjugate additions reactions and the allylic substitution reactions with the same perspective and gives a global view of the research done and the possibilities of future research.

This review covers the literature reports on enantioselective copper-catalyzed conjugate additions and allylic substitution reactions in the most emerging period in these areas of

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Alexandre Alexakis graduated from Paris VI University in 1970 and received his Ph.D. 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 (first 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 nonmetallic catalysts (organocatalysis).

Jan-Erling Bäckvall was born in Malung, Sweden, in 1947. He received his Ph.D. from the Royal Institute of Technology, Stockholm, in 1975 under the guidance of Prof. B. Åkermark. After postdoctoral work (1975−1976) with Prof. K. B. Sharpless at Massachusetts Institute of Technology he joined the faculty at the Royal Institute of Technology. He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997 he moved to Stockholm University, where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences and the Finnish Academy of Science and Letters. His current research interests include transition-metal-catalyzed organic transformations, biomimetic oxidations, and enzyme chemistry. Recently efficient systems for dynamic kinetic resolution of alcohols and amines based on combined ruthenium and enzyme catalysis were developed in his laboratory.

research. Particular emphasis is given to the results published in the last five years (2002−2007).

The review is organized as follows. In section 2 we present the results obtained in the asymmetric conjugate addition reaction. In this part the catalytic data are grouped according to the type of nucleophiles. For each nuclephile we present an overview of the state of the art and then focus on the catalytic data reported. In section 3 the results obtained in the asymmetric allylic substitution reaction are covered. For each reaction we also discuss mechanistic and practical aspects as well as their application to the synthesis of more complex molecules.

Norbert Krause graduated from Technical University of Braunschweig in 1984 and received his Ph.D. in 1986. After postdoctoral stays at the ETH Zürich and Yale University, he joined the Technical University of Darmstadt and obtained his Habilitation in 1993. In 1994, he moved to the University of Bonn as Associate Professor, before being appointed to his present position at Dortmund University of Technology as Full Professor in 1998. He was a Fellow of the Japan Society for the Promotion of Science (2003) and Guest Professor at the Université Catholique de Louvain (2007). Since 2006, he is a member of the Editorial Board of the *European Journal of Organic Chemistry*. His review on "Recent Advances in Catalytic Enantioselective Michael Additions" was the World's Most Cited Chemistry Paper in Nov 2002. His research focuses on stereoselective syntheses and reactions of allenes, taking advantage of copper and gold catalysis.

Oscar Pàmies was born in Reus, Spain, in 1972. After receiving his Ph.D. in Prof. Carmen Claver's group in 1999 at Universitat Rovira i Virgili, he spent three years as a postdoc in the group of Prof. J.-E. Bäckvall at the Department of Organic Chemistry (Stockholm University), where he was involved in the study of the mechanism of the hydrogen transfer reactions and in the development of new protocols for chemoenzymatic dynamic kinetic resolution. He is actually working in Universitat Rovira i Virgili toward his habilitation. His research interests are asymmetric catalysis, organometallic chemistry, and combinatorial synthesis.

2. Asymmetric Conjugate Addition Reaction

2.1. Using Nonstabilized Nucleophiles (Organometallic Reagents)

The past decade has seen dramatic breakthroughs in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones.[2a–k] These addition reactions have been used as key steps in the synthesis of numerous biologically active compounds and show a broad scope because of the large variety of donor and acceptor compounds that can be employed (see section 2.1.6 below). Most of the successful asymmetric versions of this chemistry have made use of oganozinc reagents, especially $ZnEt_2$, a trend started by Alexakis (Cu catalysis)[3] and Soai (Ni catalysis).[4]

Montserrat Diéguez studied chemistry at the Rovira i Virgili University in Tarragona (Spain), where she received her Ph.D. in 1997 working in the group of Prof. C. Claver. After a year as posdoctoral fellow with Prof. R. H. Crabtree at Yale University, in New Haven, CT, she returned to Tarragona in 1999. She is currently working as an Associate Professor at the Rovira i Virgili University. Her present research is focused on organometallic chemistry, mainly the synthesis of chiral ligands and asymmetric catalysis.

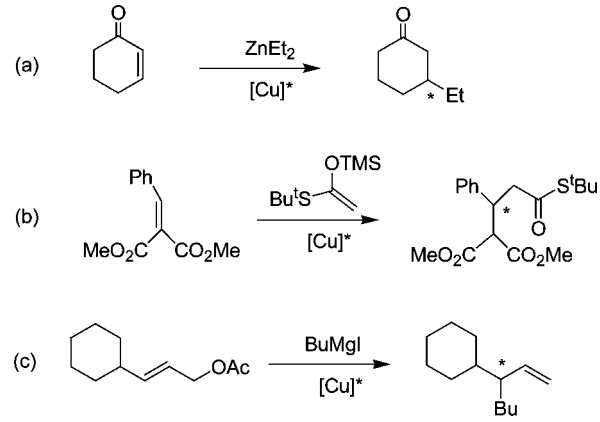
The inherently low reactivity of organozinc reagents toward unsaturated carbonyl compounds has facilitated the development of a plethora of chiral phosphorus-based ligands (i.e., phosphoroamidites, phosphites, phosphonites, phosphines) capable of providing highly efficient ligand-accelerated catalysis with excellent enantioselectivities over a broad range of substrates. Therefore, viable ligand classes affording >95% enantiomeric excess for the addition of ZnR_2 to disubtituted cyclic and acyclic enones, lactones or lactams, nitro-olefins, amides, and malonates are now available.

Trialkylaluminum reagents have recently appeared as an interesting alternative to organozinc reagents since they are also readily available and also offer additional hydro- and carboalumination possibilities for their preparation. Additionally, due to their higher reactivity, they allow Cu-catalyzed 1,4-addition to very challenging substrates (i.e., β,β'-disubstituted enones), which are inert to organozinc methodologies. Nowadays, very successful examples with cyclic and acyclic enones and nitro-olefins have been described.

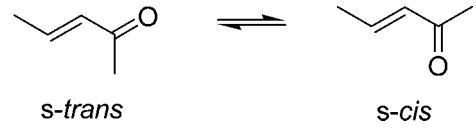
Although Grignard reagents were the first species to be used, their higher reactivity leads to uncatalyzed 1,2- and 1,4-additions, which limited their early application. Grignard reagents are cheaper, more readily available, and easier to handle than diorganozinc. Considerable effort has therefore been undertaken in order to replace zinc reagents by Grignards in this process. It has turned out that ligand structures favorable for diethyl zinc additions are not effective for magnesium compounds. There have been recent breakthroughs that opened up the use of Grignard reagents for the highly active and enantioselective Cu-catalyzed conjugate addition of a wide range of substrates. Therefore, in addition to cyclic and acyclic enones, the less reactive α,β-unsaturated esters and thioesters can be transformed with good enantioselectivities.

In this section we compile the catalytic data reported using nonstabilized nucleophiles. First, we present several types of Michael acceptors that have been used as substrates in this process. Then, we group the catalytic data according to the type of nucleophiles. Due to the prominent position of the use of diorganozinc reagents in this process, hundreds of chiral ligands have been developed. To better compare their results, we present them grouped by ligand types.

Scheme 1. Typical Examples of Enantioselective Copper-Catalyzed Conjugated Addition (a and b) and Allylic Substitution Reactions (c)



Scheme 2. *s-cis* and *s-trans* Conformational Interconversion



Finally, we also discuss mechanistic and practical aspects as well as the application of this process to the synthesis of more complex molecules.

2.1.1. The Michael Acceptor

2.1.1.1. Cyclic Enones. Most of the cyclic enones are shown in Figure 1. In the cyclic enone series, cyclohexenone **S1** has been the most widely studied substrate for copper-promoted asymmetric conjugate addition. It has been the substrate of choice for testing a new ligand. This enone is very reactive and has the advantage of being cyclic. Thus, the problem of *s-cis* and *s-trans* conformational interconversion of acyclic substrates (Scheme 2) is avoided. In many articles, this is the only enone screened against several ligands. Cyclopentenone **S2** is a special case. It is the most reactive substrate, and the resulting enolate is reactive enough to undergo Michael addition to unreacted cyclopentenone, thus lowering the isolated yield of the reaction. The other problem with this substrate is the flatness of the molecule, which is less sensitive to the steric requirements of the chiral ligand. As a result, cyclopentenone generally affords lower ee values than cyclohexenone. Specific ligands have been developed to circumvent this problem. Cycloheptenone **S3** and cyclooctenone **S4** behave exactly as cyclohexenone but usually provide higher ee's with the same ligands. Other cyclic enones include substituted cyclohexenones **S5**, **S11**, and **S12**, substituted cyclopentenones **S6**, and cyclodienones **S15**. They give rise to efficient kinetic resolution, depending on the position of the substituent in the ring. More recently, the conjugate addition of less reactive β,β'-disubstituted cyclic enones **S12**, which allows the construction of quaternary chiral centers, has been achieved using either organoaluminum reagents or Grignard reagents. Trisubstituted exocyclic unsaturated enones **S13** and **S14** have also been successfully alkylated using organozinc reagents. Other cycloenones and cyclodienones substituted in the 4- or 5-position and without stereogenic centers, such as **S7**-**S10** and **S16**-**S17**, gave also high ee values (ee's up to 98%). Finally, cyclopentadecenone **S18**, the precursor of muscone (a fragrance), is a large enough ring to allow *s-cis* and *s-trans*

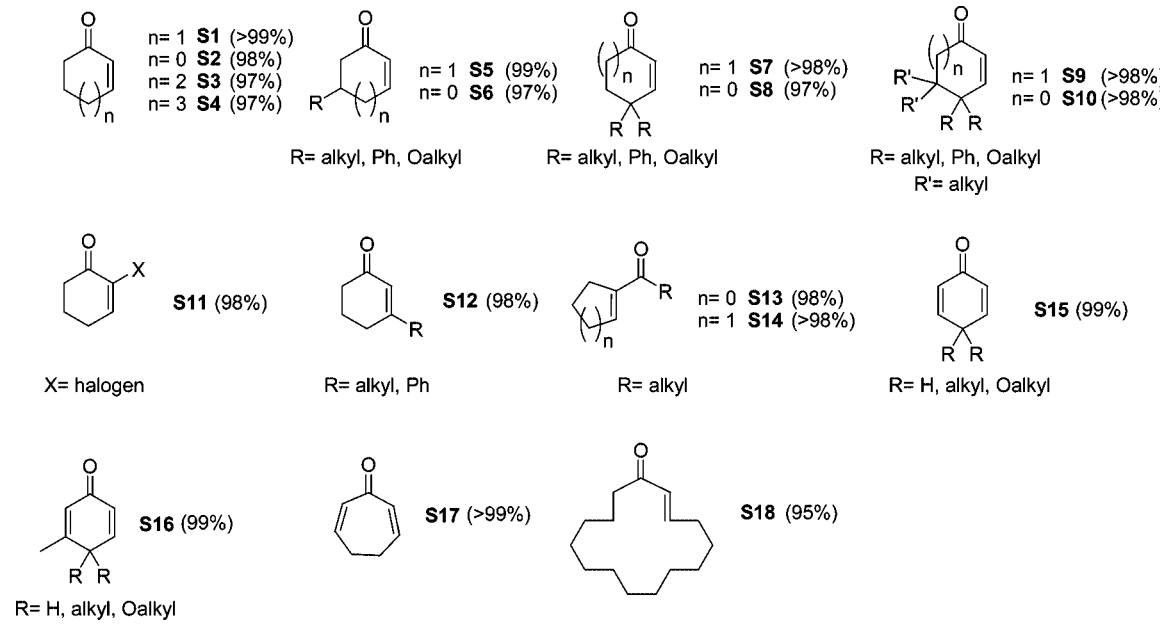


Figure 1. The most representative cyclic enones studied. The maximum ee values reached for each substrate type are also shown in parentheses.

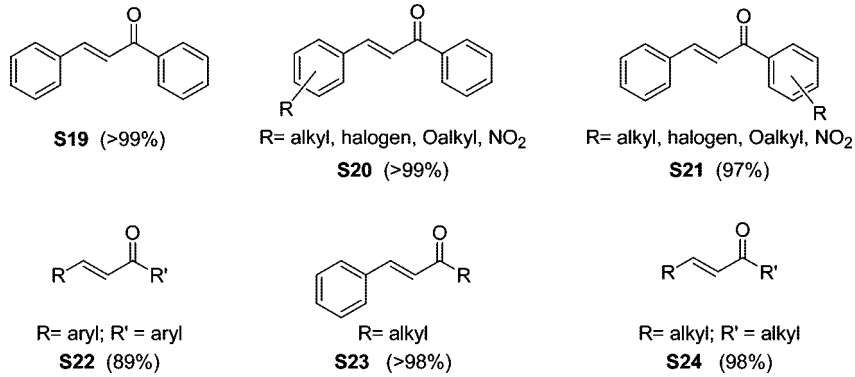


Figure 2. The most representative acyclic enones studied. The maximum ee values reached for each substrate type are also shown in parentheses.

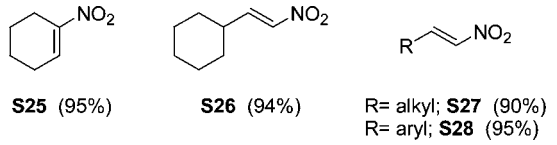


Figure 3. The most representative nitro-olefins studied. The maximum ee values reached for each substrate type are also shown in parentheses.

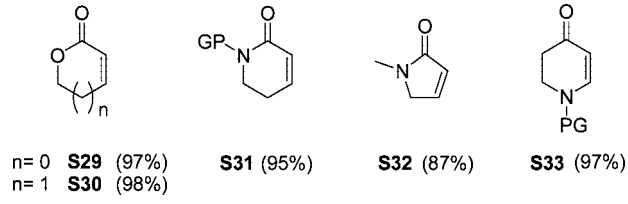


Figure 4. The most representative lactones, lactams, and piperidines studied. The maximum ee values reached for each substrate type are also shown in parentheses.

conformational interconversion, and so it behaves like the acyclic enones.

2.1.1.2. Acyclic Enones. Because of the *s-cis* and *s-trans* conformational interconversion, acyclic enones (Figure 2) are more demanding substrates. In general, they need different ligands than those required for cyclic enones. For

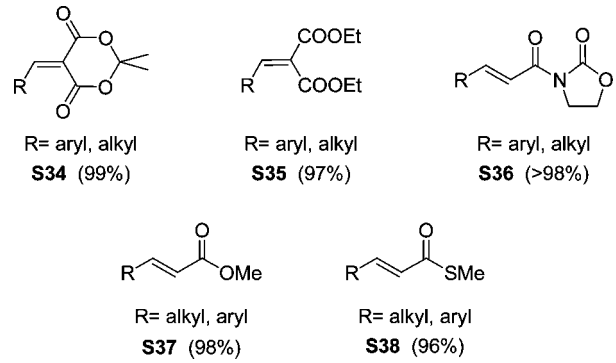


Figure 5. The most representative α,β-unsaturated esters, thioesters, and imides studied. The maximum ee values reached for each substrate type are also shown in parentheses.

this type of substrates, the use of organoaluminum reagents has been very useful for obtaining high levels of enantioselectivity. The most widely studied structural type is chalcone **S19** and the related substrates **S20**−**S22**, bearing two aryl groups. Alkyl-substituted acyclic enones **S23**−**S24** have been less studied, although they provide a wider structural variation.

2.1.1.3. Other Michael Acceptors. Other Michael acceptors have also been tested in the enantioselective conjugate

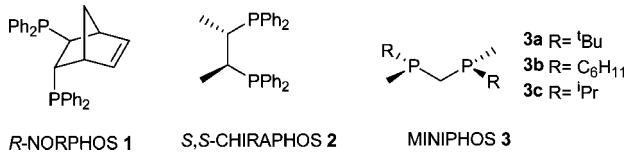


Figure 6. Phosphine ligands most successfully applied.

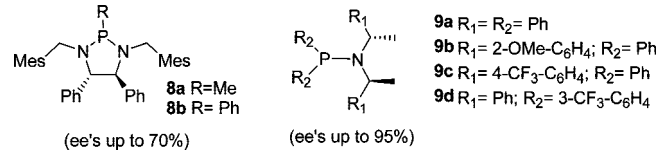


Figure 8. Aminophosphine ligands **8** and **9**. In parentheses, the best enantioselectivities obtained in the Cu-catalyzed addition of diorganozinc to **S1** for each ligand series are shown.

addition. These mainly include nitro-olefins, lactones, lactams, piperidines, alkylidenemalonates and α,β-unsaturated imides, esters, and thioesters.

Several types of nitro-olefins **S25**−**S28** have been tested (Figure 3). Their chiral adducts are valuable synthons, since the nitro group has successfully been transformed to a variety of valuable organic compounds such as aldehydes, carboxylics acids, nitriles, nitrile oxides, and amines.[2d] The latter are of great importance with respect to the preparation of biologically active compounds. Significant results on the conjugate addition of diorganozinc reagents and more recently using trialkylaluminum have been achieved.

Lactones **S29**−**S30**, lactams **S31**−**S32**, and piperidinones **S33** have also been successfully used as Michael acceptors (Figure 4). These compounds are important building blocks for total synthesis and fine-chemical production.

Another type of Michael acceptor of interest is the α,β-unsaturated esters (Figure 5). The first attempts were done using diorganozinc reagents, and they were unsuccessful due to low reactivity of this type of substrate. A good alternative was the enantioselective conjugate addition of more reactive akylidene malonates **S34** and **S35** and *N*-acyloxazolidinones **S36** using diorganozinc reagents. Recently, Feringa and co-workers have reported the asymmetric conjugated addition of Grignard reagents to α,β-unsaturated esters **S37** and thioesters **S38** with high enantioselectivities and regioselectivity.

2.1.2. Diorganozinc as Nucleophiles

Ever since the discovery in the early 1990s by Alexakis and co-workers that the Cu-catalyzed asymmetric conjugated addition of dialkylzinc reagents is a viable approach,[3] considerable progress has been made in this area during the past decade focused mainly on the design of more effective catalysts. As a consequence, diorganozinc reagents have taken a prominent position in this field, and they have been successfully applied to many substrates.

One of the major advantages of the diorganozinc reagents is their compatibility with many functional groups. These functional reagents may be prepared by RI/Et_2Zn exchange or by hydroboration/transmetalataion sequence. Only a few diorganozinc reagents are commercially available. Among them, diethylzinc (Et_2Zn) is by far the most used. Dibutylzinc usually provides similar results to diethylzinc. Dimethylzinc has been rarely used, and despite that it usually provides similar enantioselectivities to diethylzinc, it is much less reactive and therefore longer reaction times are required. Although diphenylzinc is known to undergo copper-catalyzed conjugated addition, only recently have high enantiomeric excesses been obtained.[5] Other diorganozinc reagents (i.e., diisopropylzinc, reagents bearing an ester or acetal functionality) have also been used with high degrees of success.

2.1.2.1. Ligands. The design of chiral ligands together with the reaction conditions (see section 2.1.5) is perhaps the key to attaining high asymmetric induction in this process. Subtle changes in the conformational, steric, and/or electronic properties of the chiral ligand have led to dramatic variation of the reactivity and enantioselectivity. As a result of strong substrate dependence in most cases, tunable and readily synthesized ligand series are desirable to obtain high enantioselectivities for a wide range of substrates. The initially

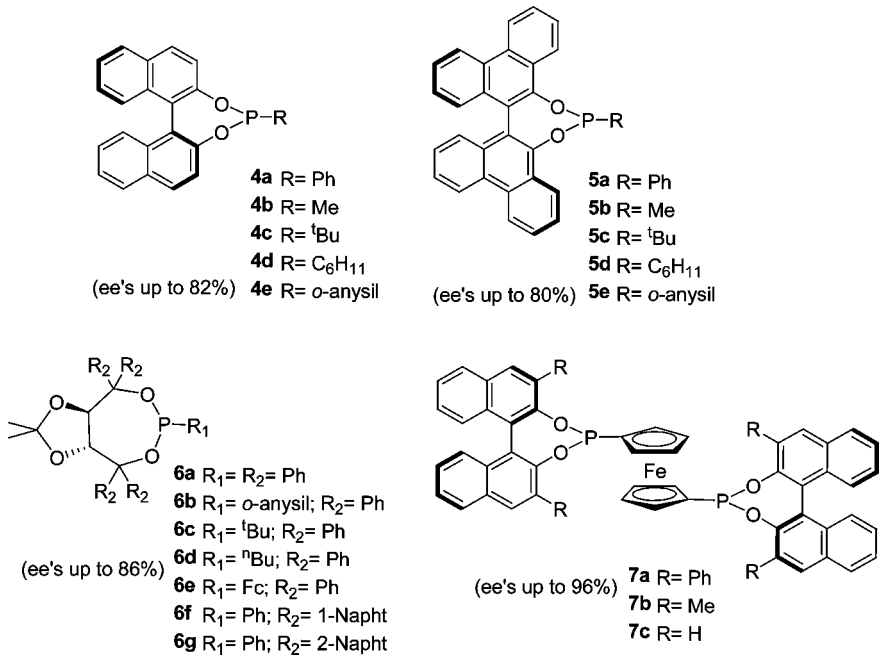
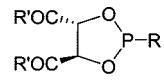


Figure 7. Families of the most successful phosphonite ligands. In parentheses, the best enantioselectivities obtained for each ligand series are shown.



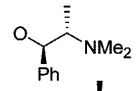
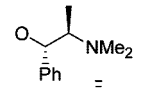
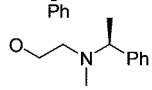
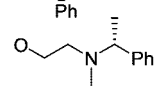
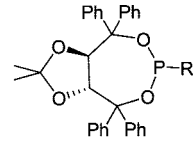
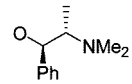
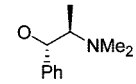
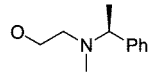
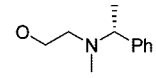
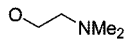
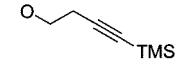
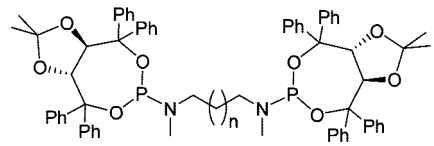
	R	R'	% ee		R	R'	% ee
10a	(-)-menthyloxy	OEt	62	**10b**	neomenthyloxy	OEt	63
10c	(+)-fenchyloxy	OEt	65	**10d**	(+)-borneyloxy	OEt	63
10e	O-$(CH_2)_2$-NMe_2	OEt	37	**10f**	O-$(CH_2)_3$-NMe_2	OEt	41
10g		OEt	28	**10h**		OEt	22
10i		OEt	43	**10j**		OEt	29
10k	(-)-menthyloxy	O^{i}Pr	53	**10l**	N[(*R*)-1-Ph,Et]$_2$	OEt	22
10m	(-)-menthyloxy	NMe	28	**10n**	(-)-menthyloxy	N-$(CH_2)_4$-N	0

Figure 9. Representative tartrate-based ligands **10**. The ee's shown are the best ones obtained regardless of the substrate used.



	R	% ee		R	% ee
11a	OPh	5	**11b**	OMe	4
11c	O^{t}Bu	16	**11d**	O-c-C_6H_{11}	18
11e	(+)-menthyloxy	20	**11f**	(-)-menthyloxy	50
11g	(+)-borneyloxy	32	**11h**	(-)-borneyloxy	11
11i	(+)-fenchyloxy	34	**11j**	(-)-fenchyloxy	28
11k	(1*R*,2*S*)-2-Ph-cyclohexyloxy	0	**11l**	(1*S*,2*R*)-2-Ph-cyclohexyloxy	96
11m	(1*R*,2*S*)-1-Napht-cyclohexyloxy	17	**11n**	(1*S*,2*R*)-1-Napht-cyclohexyloxy	82
11o	(1*R*,2*S*)-2-Napht-cyclohexyloxy	25	**11p**	(1*S*,2*R*)-2-Napht-cyclohexyloxy	86
11q		16	**11r**		29
11s		5	**11t**		38
11u		15	**11v**		12
12a	NHMe	49	**12b**	N[(*R*)-1-Ph,Et]$_2$	17
12c	NMe_2	35	**12c**	N[(*S*)-1-Ph,Et]$_2$	15
12e	N^{i}Pr$_2$	17			

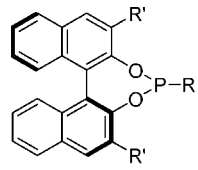


13a n= 0; ee's up to 18%
13b n= 1; ee's up to 2%

Figure 10. Representative TADDOL-based phosphite (**11**) and phosphoroamidite (**12**, **13**) ligands. The ee's shown are the best ones obtained regardless of the substrate used.

explored chiral ligands were trivalent phosphorus ligands.[3,6] Although other ligand types have been disclosed, those based on phosphorus are the most effective (>350 phosphorus-based catalysts reported). Most ligands are monodentate, but some are bidentate, either homodonor or heterodonor. Most phosphorus ligands are of the phosphite and phosphoroamidite type. Aryl phosphines are scarce and successful only when associated with another coordination site. The usual chiral diphosphines are ineffective in this reaction. Other classes of ligands, without a phosphorus atom (such as sulfonamides, diaminocarbenes, oxazolines, and heterodonor S,O and N,S ligands), have also been studied. However, they are not yet as efficient, although ee's as high as 98% have been achieved. Below, we present in more detail several effective ligands applied in this process. First, we cover the results using mono- and bidentate homodonor phosphorus ligands. Then, we compile the results using heterodonor phosphorus-containing ligands. Finally, we review the catalytic data using nonphosphorus ligands.

2.1.2.1.1. Mono- and Bidentate Homodonor Phosphorus Ligands. Despite the large amount of diphosphine ligands used, only a few provided good to high enantioselectivities.[2a] The best ee values (Figure 6) have been obtained with NORPHOS **1**, CHIRAPHOS **2**, and particularly MINIPHOS **3a**−**c**. The former ligands (**1** and **2**) both gave 44% ee with cyclohexenone **S1**,[7] whereas the ligands **3** afforded up to 97% ee on cycloheptanone **S3**.[8]



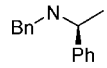
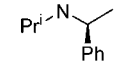
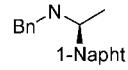
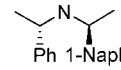
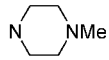
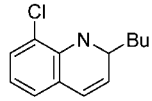
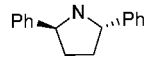
	R	R'	% ee		R	R'	% ee
14a	(+)-menthyloxy	H	19	**14b**	cyclohexyloxy	H	32*
14c	(1*R*,2*S*)-2-Ph-cyclohexyloxy	H	33*	**14d**	(1*S*,2*R*)-2-Ph-cyclohexyloxy	H	87**
14e	(1*R*,2*S*)-2-Napht-cyclohexyloxy	H	8*	**14f**	(1*S*,2*R*)-2-Napht-cyclohexyloxy	H	66*
15a	NMe_2	H	65	**15b**	NEt_2	H	27
15c	$NiPr_2$	H	83	**15d**	$N(o\text{-anisyl})_2$	H	48
15e	$N[(R)\text{-}CH(Ph)Me]_2$	H	>99	**15f**	$N[(S)\text{-}CH(Ph)Me]_2$	H	72
15g	$N[(R)\text{-}CH(1\text{-napht})Me]_2$	H	98	**15h**	$N[(S)\text{-}CH(2\text{-napht})Me]_2$	H	94
15i	$N(\text{-}(CH_2)_4\text{-})$	H	40	**15j**	$N(\text{-}(CH_2)_5\text{-})$	H	43
15k	NMe_2	Me	52	**15l**	N^iPr_2	Me	81
15m	NMe_2	Ph	35	**15n**	NMe_2	Br	51
15o		H	72	**15p**		H	86*
15q		H	71*	**15r**		H	80*
15s		H	0	**15t**		H	71
15u		H	70	**15v**	$N[(S)\text{-}CH(Cy)Me]_2$	H	99***
15w		H	95**				

Figure 11. Representative monodentate binaphthol-based phosphite (**14**) and phosphoroamidite (**15**) ligands. Unless otherwise noted, enantioselectivities obtained with cyclic substrates are shown. *ee's on linear substrates. **ee's on 15-membered-ring enone **S18**. ***ee's on malonates.

Phosphinite- and phosphonite-type ligands (one carbon atom on P, and two heteroatoms) are scarce. Phosphinite ligands have been less studied[9] and provided lower enantioselectivities than the phosphonite-type ligands.[9a,10] Figure 7 shows the most successful phosphonite ligands applied in this process. Most of them are derived from TADDOL or binaphthol (Figure 7). The TADDOL-based ligand ($R_1 = R_2 =$ Ph) **6a** gave among the best reported ee values with aryl nitro-olefins **S28** (ee's up to 86%),[10c,d] although its behavior with cyclic or acyclic enones is poor to moderate (ee's up to 54% and 8%, respectively).[10b] On the other hand, in general, the binaphthol-based monophosphonites **4** and **5** gave poor results with cyclic enones (ee's up to 41%) but moderate ee values (up to 82% using ligand **4c** ($R = {}^tBu$)) with chalcone **S19**.[10a] However, the bidentate diphosphonites **7**, which combine two binaphthol units on a ferrocene backbone, provided good enantioselectivities (ee's up to 96%) for cyclic enones.[10e]

In 1998, Tomioka and co-workers reported the application of aminophosphine **8** (Figure 8) in the Cu-catalyzed conjugate addition of diorganozinc to cyclic enones, which afforded ee's up to 70%.[11a] Recently, Alexakis and co-workers developed phosphinoamine ligands **9**, containing two phenyl groups on the phosphorus atom (Figure 8).[11b] These simple ligands, based on the successful monophosphoroamidite-related ligands **17** (see below), have provided enantioselectivites up to 95% for cyclohexenone **S1**.

By far the most studied ligands are phosphites and phosphoramidites. These ligands have in common the presence of three heteroatoms around the phosphorus atom. In all cases the phosphorus atom is incorporated in a ring, formed from a diol or an amino alcohol. The chirality is introduced through the diol unit or by an exocyclic alcohol or amine, or by both. In the latter case, a matched or mismatched relationship may exist, with different catalytic behavior for each of the two diastereomeric ligands. A review of the research into phosphite and phosphoroamidite ligands reveals four main trends: tartrate-based ligands, TADDOL derivatives, binaphthol-based ligands, and biphenol-type ligands.

In tartrate-based ligands the phosphorus atom is incorporated in a five-membered ring (Figure 9). Despite the variety of structures tested, only low to moderate ee values have been attained.[3,12,13] The best result was obtained with benzalacetone (**S23**; R = Me) and the most hindered ligand **10c** (65% ee), bearing fenchol as the chiral exocyclic component. These ligands do not show any matched or mismatched effects, both diastereomeric ligands being equal. In contrast to most ligands, it seems that the ester functionality of the tartrate part of the ligand also participates in the coordination of the organometallic species.

TADDOL ligands **11** and **12**, which are readily accessible from tartaric acid, incorporate the phosphorus atom in a seven-membered ring (Figure 10). Many ligands of this type have been prepared and tested in the conjugate addition.[10b,14] This family includes both ligands that possess an additional exocyclic chiral group and those that do not. In the absence of exocyclic chirality, the TADDOL part of the ligand

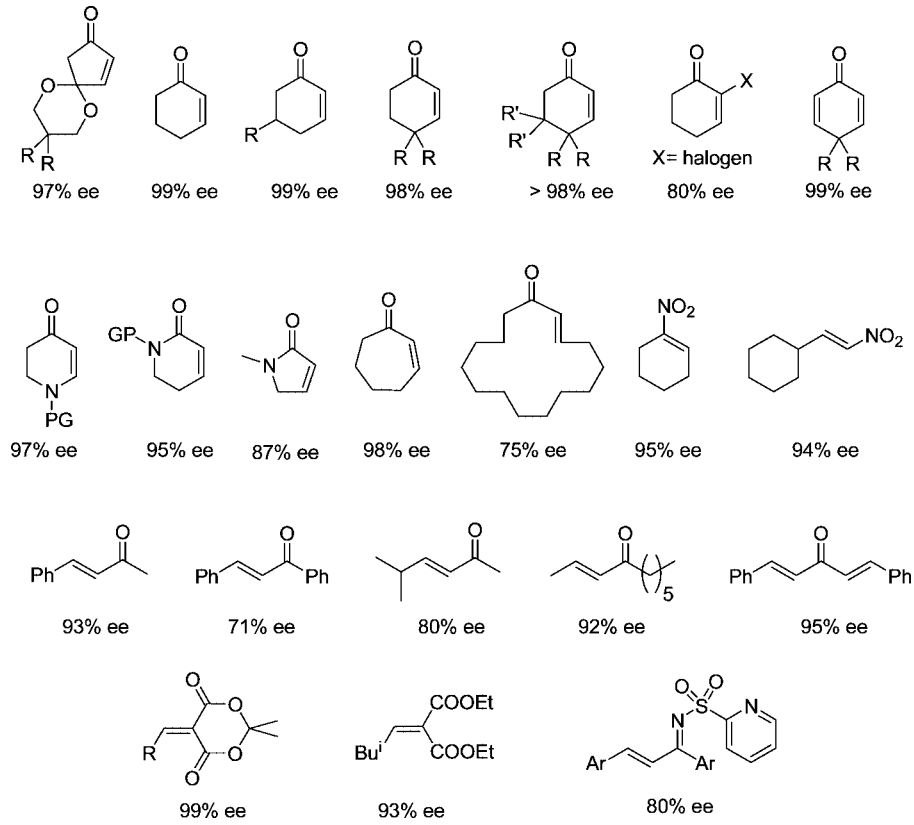


Figure 12. Representative results obtained with several enones using ligand **15e** with diethylzinc as a nucleophile.

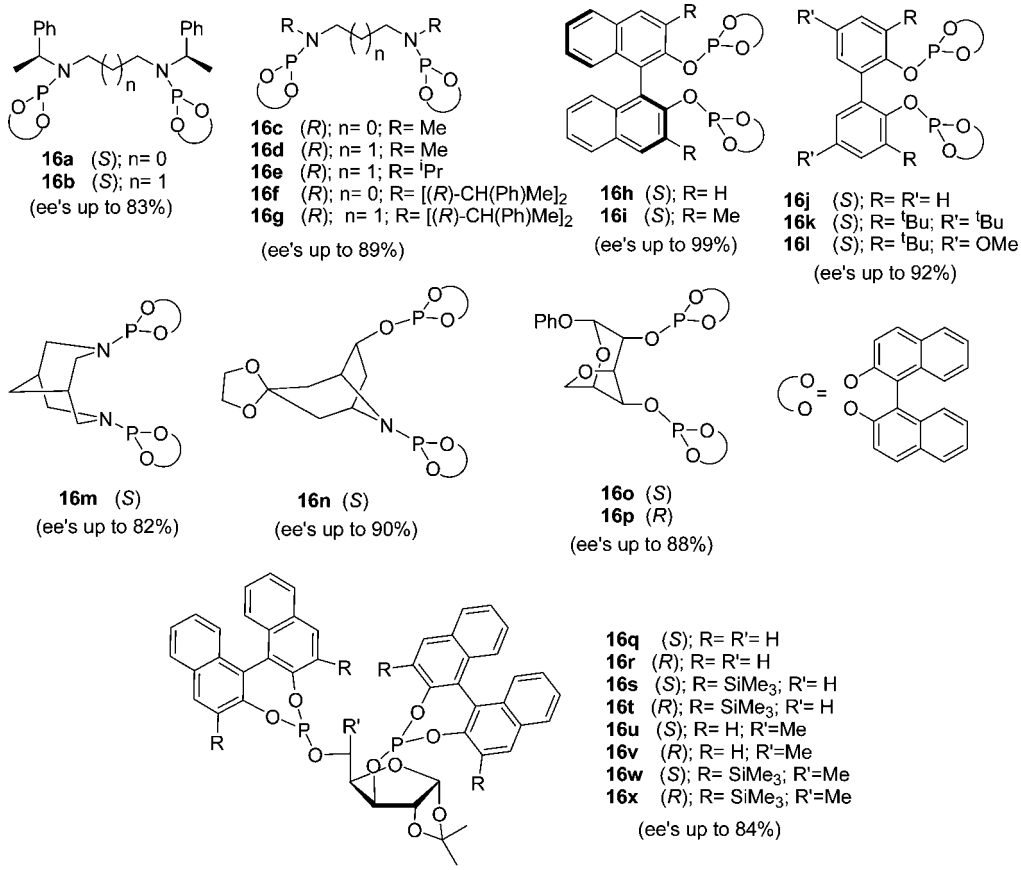
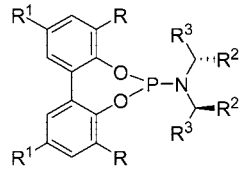


Figure 13. Representative bidentate binaphthol-based ligands **16**. In parentheses are shown the ee values obtained with cyclohexenone **S1**.

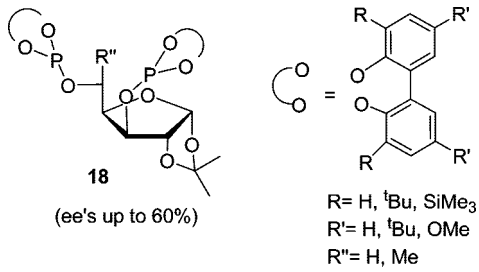
induces low to moderate enantioselectivity on enones (up to 71% ee on cyclohexenone **S1**).[14a] When an exocyclic chiral alcohol is attached, however, high enantioselectivity has been achieved. Thus, for instance, using 2-phenylcyclohexanol derivative **11l**, a 96% ee was obtained with cyclohexenone **S1**,[10b,14b] while a 73% ee was obtained using 2-[2-naphthyl]-



17a-z

	R	R^1	R^2	R^3		R	R^1	R^2	R^3
a	H	H	Me	Ph	**b**	H	H	Et	Ph
c	Me	Me	Me	Ph	**d**	Me	Me	Et	Ph
e	Cl	Cl	Me	Ph	**f**	Cl	Cl	Et	Ph
g	Br	Br	Me	Ph	**h**	Br	Br	Et	Ph
i	Ph	Ph	Me	Ph	**j**	Ph	Ph	Et	Ph
k	OMe	Me	Me	Ph	**l**	OMe	Me	Et	Ph
m	^{t}Bu	^{t}Bu	Me	Ph	**n**	^{t}Bu	^{t}Bu	Et	Ph
o	$SiMe_3$	H	Me	Ph	**p**	$SiMe_3$	H	Et	Ph
q	allyl	H	Me	Ph	**r**	allyl	H	Et	Ph
s	methally	H	Me	Ph	**t**	methally	H	Et	Ph
u	^{n}Pr	H	Me	Ph	**v**	^{n}Pr	H	Et	Ph
w	H	H	Me	2-Napht	**x**	Me	Me	Me	2-Napht
y	allyl	H	Me	2-Napht	**z**	Ph	Ph	Me	2-Napht

Figure 14. Representative biphenol-based phosphoroamidite ligands **17**.

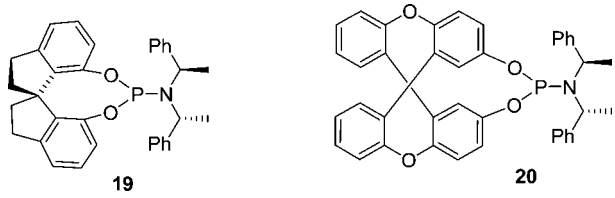


18

(ee's up to 60%)

R= H, ^{t}Bu, $SiMe_3$
R'= H, ^{t}Bu, OMe
R"= H, Me

Figure 15. Biphenol-based diphosphite ligands **18**. In parentheses are shown the ee values obtained with cyclohexenone **S1**.



19 20

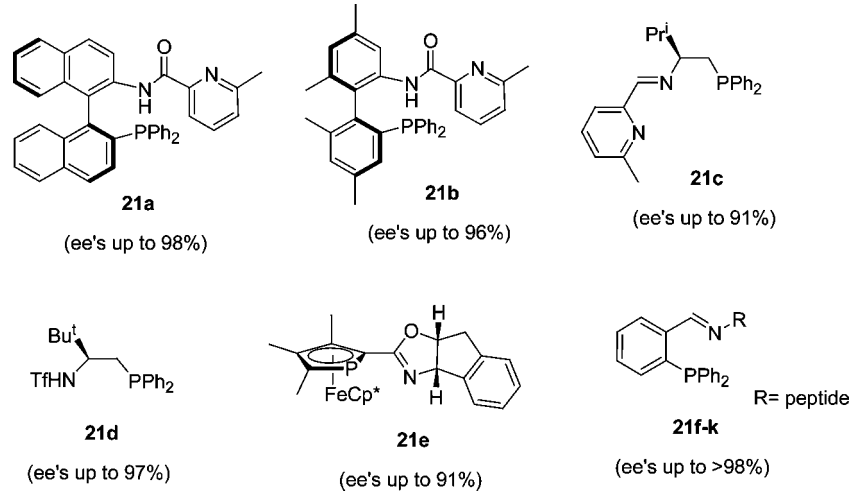
Figure 16. Spiro phosphoroamidite ligands **19** and **20**.

cyclohexanol derivative **11p** with alkylidenemalonates **S35** (R = Ph).[14c] These ligands with two chiral moieties (the TADDOL part and the exocyclic part) show strong matched/mismatched character. For example, ligand **11l** affords a 96% ee with cyclohexenone, whereas its diastereomer **11k** affords a racemic product.[10b] Finally, as in the case of phosphines, bidentate TADDOL ligands **13**, with two phosphorus atoms, are less efficient than monodentate ligands.[14d]

Binaphthol-based ligands are one of the most intensely studied (Figures 11 and 13). Many modifications on the binaphthol backbone and especially on the exocyclic amine or alcohol have been developed.[3,14c,d,15–17] These ligands have provided excellent enantioselectivities with a wide range of substrates (ee's for cyclic substrates up to >99%; ee's for linear substrates up to 95%; ee's for nitro-olefins up to 95%; and ee's for alkylidenemalonates up to 99%). Interestingly, the chirality of the binaphthol backbone alone is efficient enough to induce high levels of asymmetric induction, particularly on chalcone-type substrates **S19**−**S22** (ee values as high as 90%).[15a–c] By far the most efficient ligands of this class, however, are those bearing a chiral exocyclic moiety, an alcohol for phosphites or an amine for phosphoramidites.[15c] Such diastereomeric ligands show strong matched/mismatched character, but the absolute stereochemistry of the conjugate adduct is imposed by the chirality of the binaphthol component. Several dozen ligands of this kind have been tested, the most successful being those bearing a hindered exocyclic amine or alcohol. For example, monophosphoroamidite ligand **15e** (Figure 11), with a chiral amine attached, has found several applications both on cyclic and on acyclic enones, unsaturated nitro-olefins, unsaturated piperidones, malonates, and unsaturated imines and amides (Figure 12).[5,10c,d,16] It should be noted that so far this ligand is the only one that provided high enantioselectivities in the diphenylzinc addition to cyclohexenone.[5] A polymer-supported version of this ligand has been developed, allowing the recycling of the catalyst, but with lower asymmetric induction.[16j]

Recently, monophosphoroamidite ligand **15g** (Figure 11), related to **15e**, provided excellent enantioselectivities in the Cu-catalyzed asymmetric conjugate addition to cyclic α-haloenones **S11** (ee's up to 98%)[16k] and in the tandem conjugated addition/cyclization of several linear enones for the synthesis of functionalized chiral cyclic compounds (ee's up to 94%).[15j,k]

Regarding monophosphite-binaphthol-based ligands, it is to be noted that ligand **14d** (Figure 11),[15d] with (1*S*,2*R*)-2-phenylcyclohexanyloxy in the exocyclic position, gives the



21a

(ee's up to 98%)

21b

(ee's up to 96%)

21c

(ee's up to 91%)

21d

(ee's up to 97%)

21e

(ee's up to 91%)

21f-k

R= peptide

(ee's up to >98%)

Figure 17. Representative heterodonor phosphine−nitrogen ligands **21**. The ee's shown are the best ones obtained regardless of the substrate used.

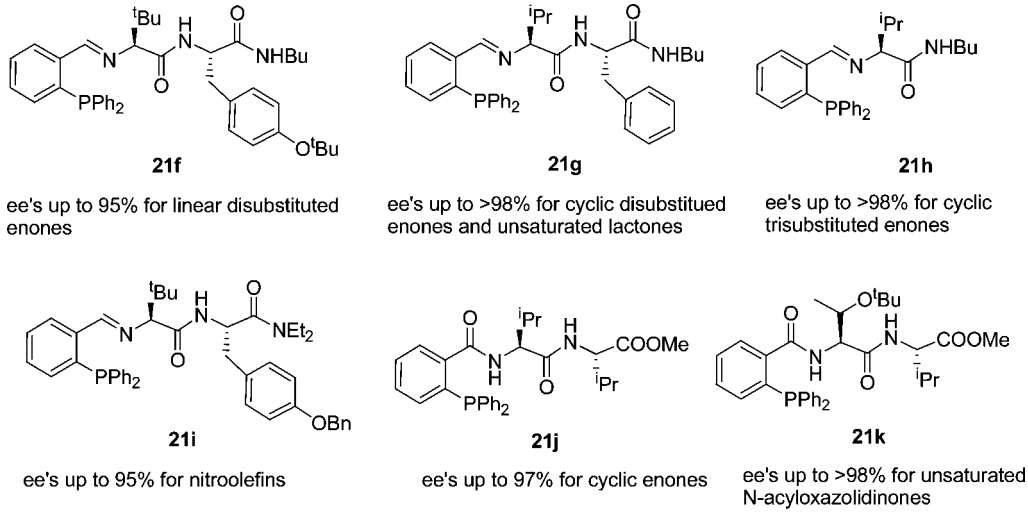


Figure 18. Most successful heterodonor phosphine−nitrogen ligands **21e**−**i**.

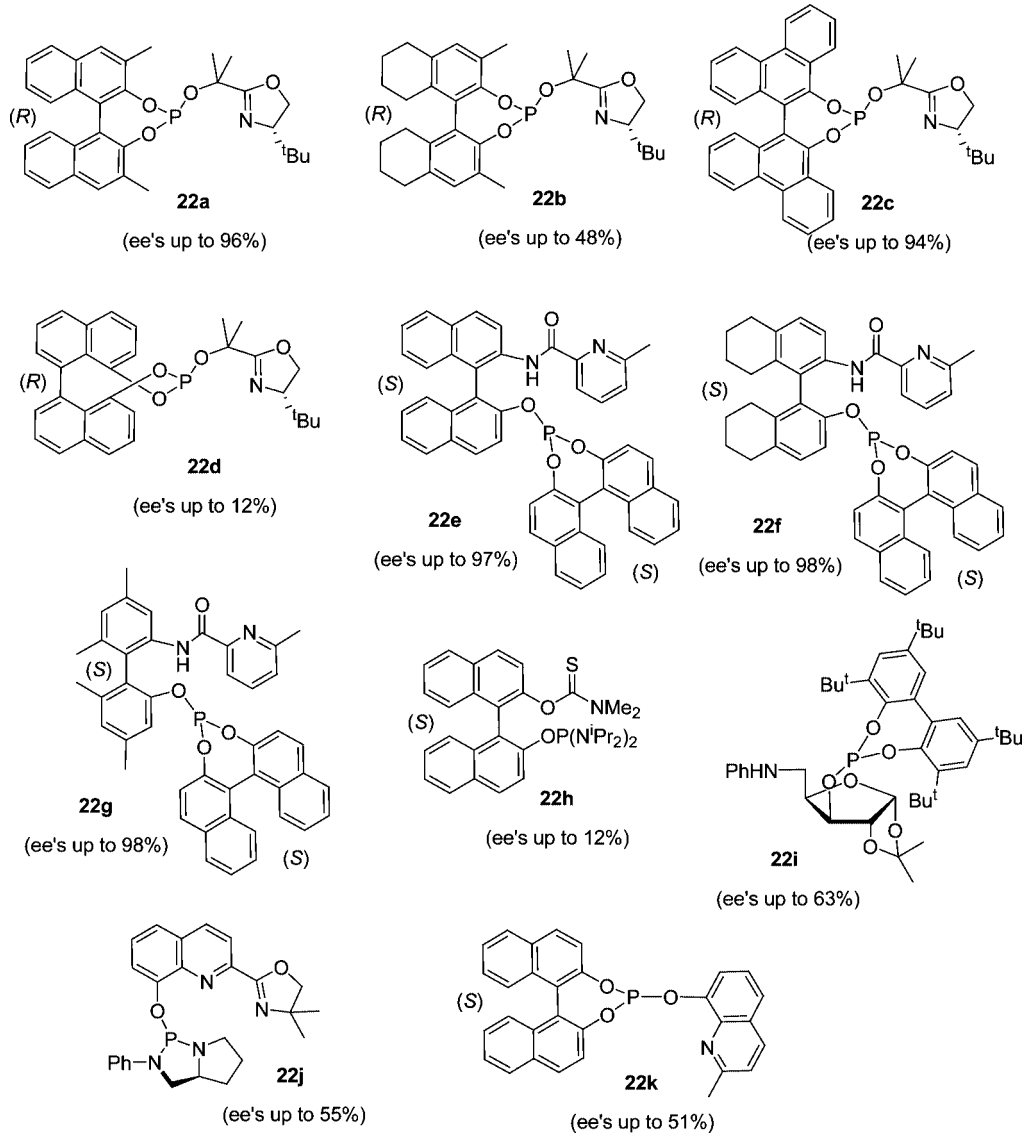


Figure 19. Representative heterodonor phosphite/phosphoroamidite−nitrogen ligands **22**. The ee's shown are the best ones obtained regardless of the substrate used.

highest ee value with cyclopentadecenone **S18**, for the synthesis of (*R*)-muscone, a valuable fragrance.

Finally, bidentate ligands with two binaphthol and two phosphorus atoms have also been developed and tested in this reaction (Figure 13).[14d,15h,i,17] It is interesting to note the excellent enantioselectivities obtained in the Cu-catalyzed conjugate addition to cyclic enones **S1**−**S3** and lactones **S30** with ligands **16h** and **16l**.[15h,17a,h,f]

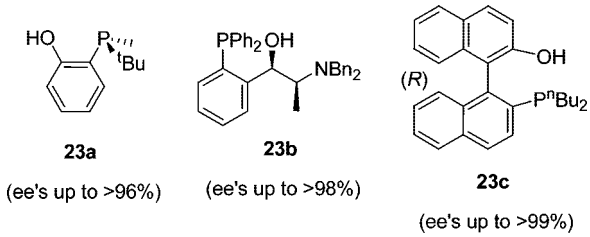


Figure 20. Representative heterodonor P,O ligands **23**. The ee's shown are the best ones obtained regardless of the substrate used.

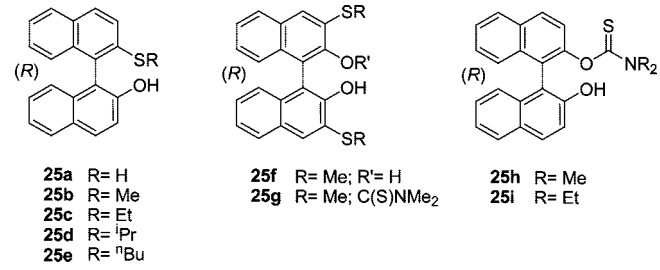


Figure 22. Representative binaphthol heterodonor S,O ligands **25.**

More recently, biphenol-type ligands have appeared as a successful alternative to the related binaphthol-based ones. They have the advantage of being much less expensive (Figures 14 and 15).[10d,15e,g,j–l,16i,k,l,o,p,17c,d,18] Unlike the binaphthol moiety, the biphenol unit presents atropoisomerism. However, the chirality of the exocyclic part induces the preferential formation of one of the atropoisomers, which in turn controls the enantioselectivity.[15e] Thus, the matched/mismatched problem is avoided. Several ligands of this class have been tested. Among them there is a large series of monophosphoroamidites **17** (Figure 14). In many cases these new ligands afforded much better results than the parent ligands based on chiral binapthol **15** and sometimes the best reported in the literature. They afford excellent enantioselectivities in cyclic (ee's up to >99%)[15g,16l,18a–c] and linear enones (ee's up to 95%),[15g,18a,c] α-haloenones (ee's up to 90%),[16k] unsaturated nitro-olefins (ee's up to 96%),[15g,10d,16i,18a] and unsaturated malonates (ee's up to 93%)[16p] and also in the tandem conjugated addition/cyclization of several linear enones for the synthesis of functionalized chiral cyclic compounds (ee's up to 98%).[15l,j] The high modularity of these ligands has allowed studies of the effect of different substituents in the biphenyl group and in the amino moiety. This has resulted in an easy and cheap "fine-tuning" of the ligand structure, affording the highest levels of enantioselectivity for a given substrate class. However, no ligand showed general enantioselectivity on every substrate. From the exhaustive study a few general trends have been observed: (1) the presence of bulky substituents in the biphenyl moiety were unfavorable for catalytic activity and enantioselectivity, (2) the presence of methyl groups in the *ortho* and *para* positions of the biphenyl moiety is favorable for the conjugate addition to cyclic enones, (3) the presence of allyl groups at the *ortho* position of the biphenyl moiety is favorable for the conjugate addition to linear enones and nitro-olefins, and (4) the presence of phenyl or 2-naphthyl groups in the amino part is highly advantageous in many cases; remarkably, the latter group usually provides better results on nitro-olefins. Therefore, ligands **17c** have provided excellent enantioselectivities with cyclic enones (ee's up to >99%).[18a] Ligands **17q**,[18a] **17r**,[10d] and **17x**[18c] afforded high to excellent enantioselectivities for cyclic (ee's up to 99%) and linear (ee's up to 95%) enones and nitro-olefins (ee's up to 96%).

As for the binapthol-type ligands, bidentate diphosphite ligands with two biphenol and two phosphorus atoms have also been developed and tested in this reaction (Figure 15, ligands **18**).[17d,18e] However, the obtained enantioselectivities

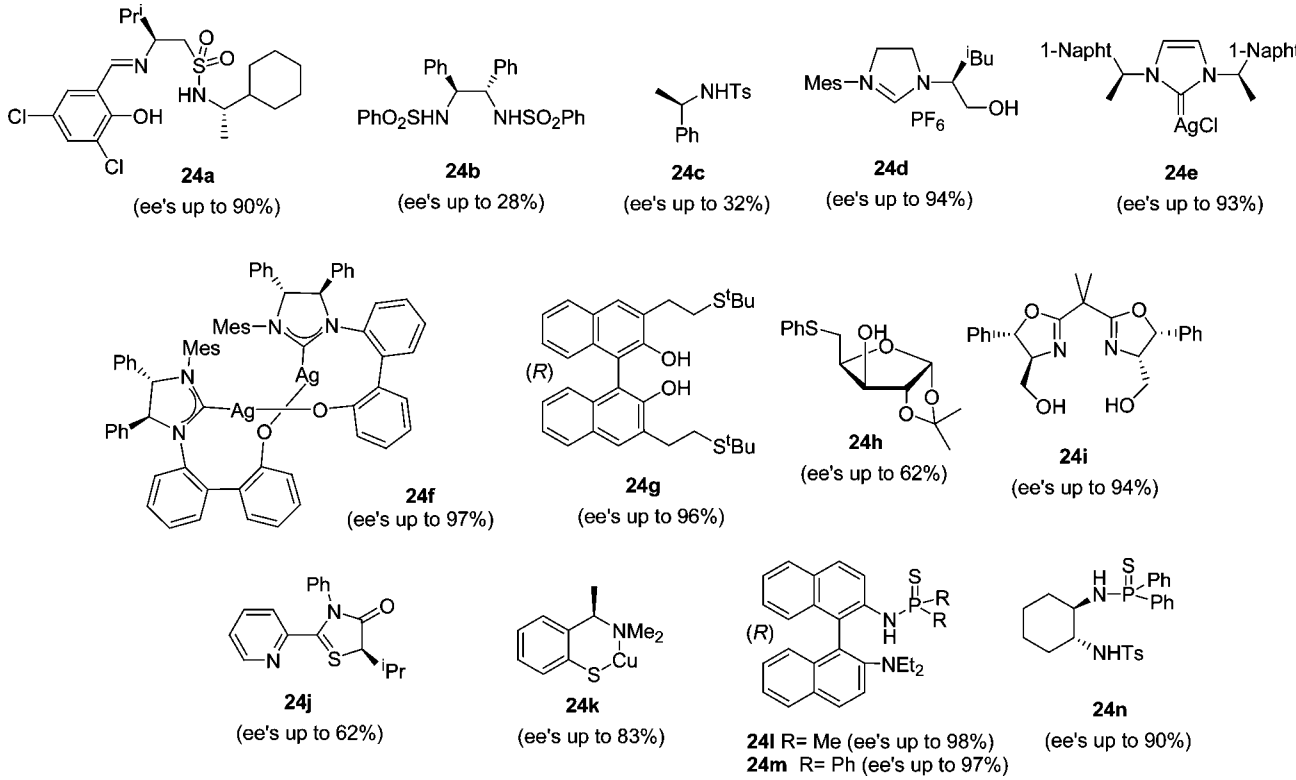


Figure 21. Nonphosphorus ligands. Most representative of each ligand's families developed for conjugated addition of diorganozinc reagents to enones are shown. The ee's shown are the best ones obtained regardless of the substrate used.

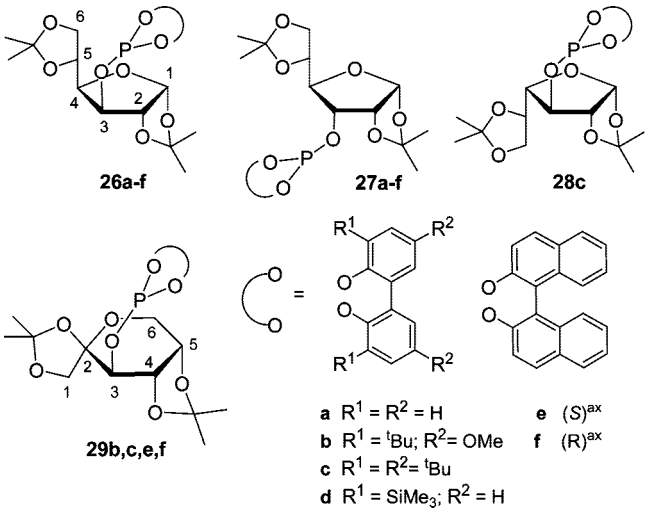


Figure 23. Library of sugar-based monophosphite ligands **26**−**29**.

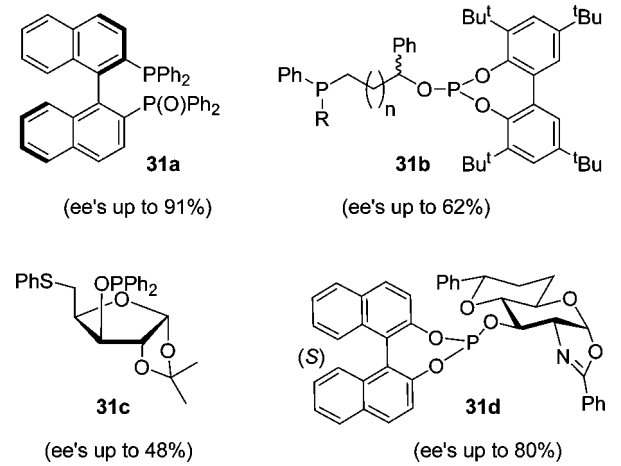


Figure 25. Representative heterodonor P,O, P,N, P,S, and P−P′ ligands **31**.

have been modest and showed much lower enantioselectivities than their binaphthol-based counterparts **16q**−**x**.

Other phosphite and phosphoroamidite ligands not based on the above-mentioned basic structures have also been described.[3,19] To all of them, the spiro phosphoroamidite ligands **19**[19a] and **20**[19b] (Figure 16) have been successfully applied to the diethyl zinc addition to cyclic enones (ee's up to 98% and 99%, respectively). Ligands **19** afforded also enantioselectivities up to 76% for chalcone-type substrates **S19**−**S22**.[19a]

2.1.2.1.2. Heterodonor Phosphorus-Containing Ligands. ***2.1.2.1.2.1. Heterodonor P,N Ligands.*** Many types of heterodonor bi- and tridentate phosphorus−nitrogen ligands have been described and found to be very efficient in this enantioselective conjugate addition (Figures 17–19).[15q,20–22] Most of the ligands are phosphine−nitrogen- and phosphite−nitrogen-based ligands. The nitrogen atom is often included in a ring, e.g., an oxazoline, oxazine, imidazolidine, pyridine, or imidazole moiety. Among the most efficient phosphine−nitrogen ligands, one finds ligands **21a**−**k** (Figure 17).[20,21] Ligands **21a**,[20a,b] **21b**,[20c] and **21e**[20f] have provided good to excellent enantioselectivities for disubstituted linear enones, while ligands **21a**,[20a,b] **21c**,[20d] and **21d**[20e] have proved to be efficient for cyclic enones. However, the best family of phosphine−nitrogen compounds is ligands **21f**−**k**, with modular peptide structure, mainly developed by Hoveyda and co-workers.[21] These ligands, which were synthesized using a combinatorial approach, are among the most versatile for this process (Figure 18). Therefore, ligand **21f** has proved to be highly efficient in the conjugate addition to linear disubstituted enones[21a,b] and cylic nitro-olefins.[21c] The related ligands **21g**[21d,e] and **21j**[21i] provided excellent results for cyclic disubstituted enones and cyclic lactones. Ligand **21h** has been highly effective for trisubstituted enones.[21f] Ligands **21i**[21g,h] and **21k**[21j] have been successfully applied to dialkylzinc addition to several linear nitro-olefins and unsaturated *N*-acyloxazolidinones, respectively.

Concerning the phosphite−nitrogen ligands (Figure 19),[15q,20c,22] the best ligands for the conjugate addition on cyclic enones are the phosphite−oxazoline ligands **22a**[22a] and **22c**[22b] (ee's up to 96%), but they behave poorly in disubstituted linear enones. On the other hand, phosphite−pyridine ligands **22e**−**g** have provided excellent results for several linear enones, but only moderate enantioselectivities for cylic enones.[22c–e]

2.1.2.1.2.2. Other Heterodonor P-Containing Ligands. Few heterodonor P,O-ligands have been developed for this process.[15i,23] However, ligands **23** have recently provided excellent levels of enantioselectivity in the conjugate addition of dialkylzinc to linear disubstitued enones (Figure 20).[23]

Other heterodonor P−P′[22i,24] and P,S[9b] ligands have also been developed. However, they have provided low to moderate enantioselectivities (up to 72% ee).

2.1.2.1.3. Nonphosphorus Ligands. Nonphosphorus ligands have been less used than P-containing ligands with dialkylzinc reagents (Figure 21). In this context, several chiral sulfonamides have been tested with various copper salts.[25] The best enantioselectivities have been obtained with sulfonamide **24a**, which provided ee's up to 90% in the conjugate addition of cyclic enones.[25a–c] Another type of ligands is the diaminocarbenes.[26] Recently, the diaminocarbene **24d** and silver carbenes **24e** and **24f** afforded enantioselectivities up to 97% with several cyclic enones.[26c,d,f] Several thioether−hydroxyl ligands have been developed.[22g,27] Most of them are based on a binaphthol scaffold.[27a–c,e,f] However, only ligand **24h** has provided high enantioselec-

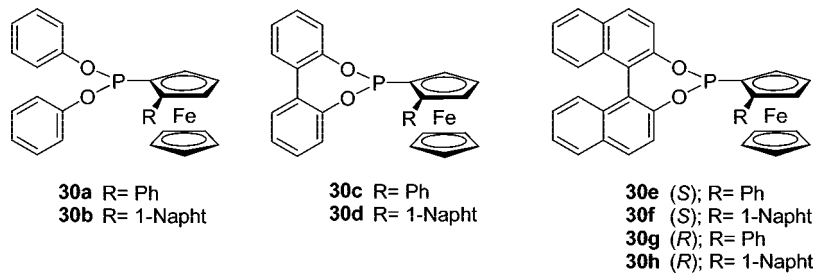
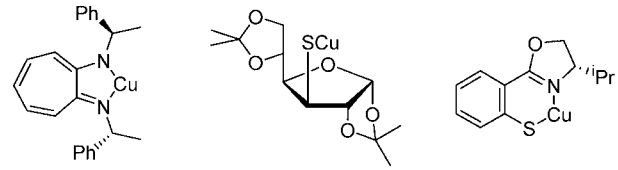
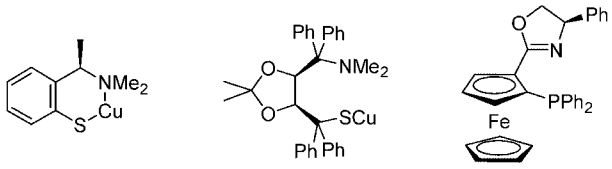


Figure 24. Phosphonite aryl ferrophite ligands **30**.

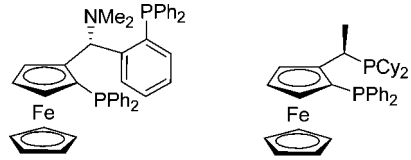


32a (ee's up to 74%) 32b (ee's up to 60%) 32c (ee's up to 87%)



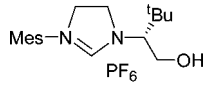
32d (ee's up to 76%) 32e (ee's up to 84%) 32f (ee's up to 92%)

Figure 26. Selected catalytic systems developed between 1988 and 1997 for the conjugate addition of Grignard reagents to enones.



33a 33b

Figure 27. Diphosphine Taniaphos (**33a**) and Josiphos (**33b**) ligands.



34

Figure 28. Diaminocarbene ligand **34**.

tivites (up to 96% ee) with linear disubstituted enones.[27e] Several types of oxazoline-based ligands have also been studied.[28] Among them, it is interesting to note the bis-oxazoline ligand **24i**, which provided enantioselectivities up to 94% with cyclic enones but behaved poorly with other enones.[28a] Binaphthyl diamines have also been used in this process but with moderate success.[29] Finally, N,S ligands should also be mentioned.[30] In this respect ligands **24l** and **24m** have provided high enantioselectivities in cyclic enones (ee's up to 98%) and disubstitued linear enones (ee's up to 97%).[30c]

2.1.3. Triorganoaluminum as Nucleophiles

Less attention has been paid to trialkylaluminum reagents. However, they have recently appeared as interesting alternatives to organozinc reagents since they are also readily available and offer additional hydro- and carboalumination possibilities for their preparation and therefore high potential for use in synthesis. Therefore, for example, Woodward and Alexakis have exploited this advantage in the asymmetric conjugate addition of vinylalanes to α,β-unsaturated enones. Additionally, organoaluminum reagents allow Cu-catalyzed 1,4-addition to very challenging substrates that are inert to organozinc methodologies.[31d] For example, these reagents provided a new efficient way to build chiral quaternary centers. Due to their stronger Lewis acidity, a better activation of the substrates is reached, overcoming the steric hindrance of β,β'-disubstituted enones **S12**. Nowadays, very successful examples with various cyclic and acyclic enones and nitro-olefins have also been described.

2.1.3.1. Ligands. Compared to the conjugate addition of diorganozinc reagents, the number of ligands applied in this process using trialkylaluminum nucleophiles has been lower.[9b,10d,11b,15m,16m,22h,23c,24,27b–d,31]

The first family of ligands extensively studied on the conjugate addition of trialkylaluminum reagents was the binaphthol heterodonor S,O ligands **25** (Figure 22).[22h,27b–d,31a] These ligands were designed to contain both *hard* and *soft* donors groups to easily accommodate bimetallic aluminum−cuprate species, which are responsible for the catalytic activity in these type of reactions (see section 2.1.5). These ligands were mainly applied to disubstituted linear substrates. The sulfur moiety in these ligands can be either thiol, thioether, or thiourethane. Nevertheless, the best results were obtained for the Cu-catalyzed trimethylaluminum addition to *trans*-3-nonen-2-one (ee's up to 86%, **S24**; R = C_5H_{11} and R′ = CH_3) using the thioether−hydroxyl ligand **25e**.[31a] Other heterodonor S,O ligands early applied in the conjugate addition using trialkylaluminum reagents were the previously mentioned xylofuranoside thioether−hydroxyl **24g** (Figure 21). However, they provided low enantioselectivities for *trans*-3-nonen-2-one (ee's up to 34%, **S24**; R = C_5H_{11} and R′ = CH_3).[27c]

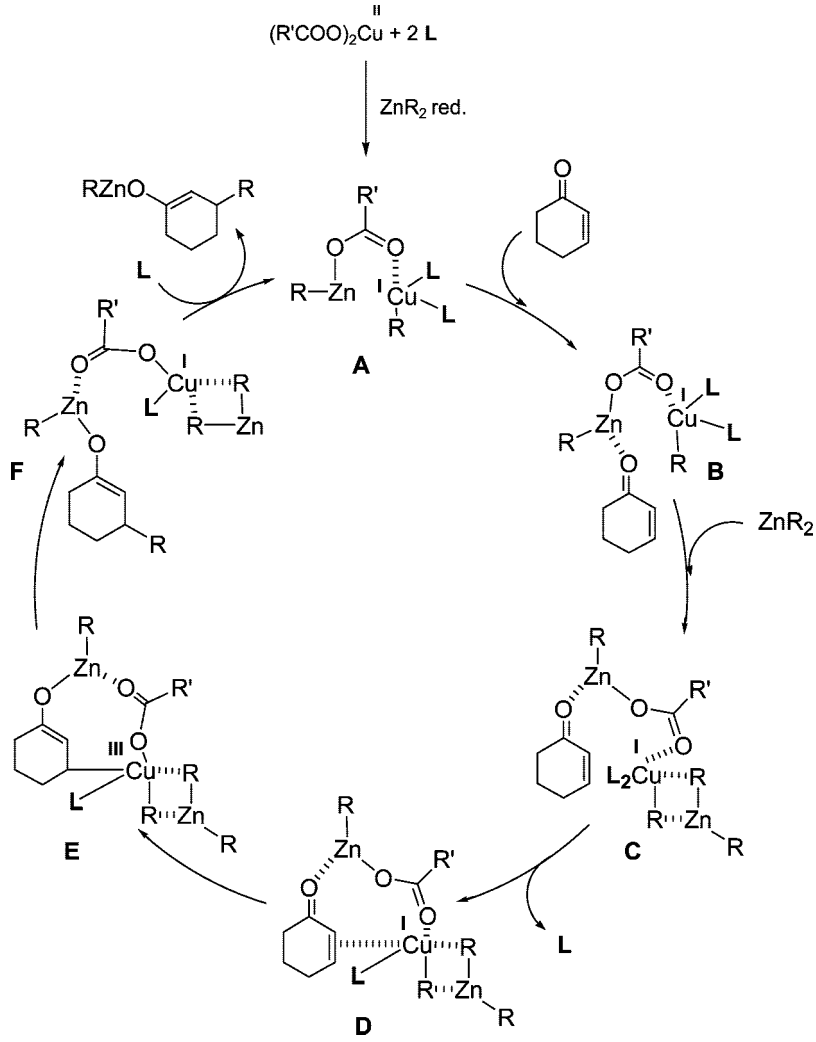
Other most studied ligand's classes are the previously mentioned phosphoroamidite ligand families **15** and **17** (Figures 11 and 14).[10d,11b,15m,16m,31c,d,e,k] Several examples of their use in a wide range of substrates and under several reaction conditions have recently been described. They afforded better enantioselectivities for disubstituted linear enones than with diorganozinc reagents (i.e., using ligand **15e** the ee's increased from 80% to 90% by replacing diethylzinc by triethylaluminum in the conjugate addition of *trans*-5-methyl-3-hexen-2-one **S24**; R = ^{i}Pr and R′ = CH_3)[31d] and similar enantioselectivites for cyclic enones (**S1**−**S3**, **S7**, **S12**), nitro-olefins (**S25**−**S28**), and *N*-acyloxazolidinones (**S36**). For example, ligand **15e** was successfully applied in the conjugate addition to cyclic (ee's up to >98%) and linear (ee's up to 96%) enones and nitro-olefins (ee's up to 92%).[31d,e] Ligand **17r** also provided excellent enantioselectivities for nitro-olefins (ee's up to 93%).[10d] In addition, these families of ligands have provided excellent results with 2- and 3-trisubstituted cyclic enones. For example, ligands **17a** and **17x** have been successfully applied in the conjugate addition of 2-trisubstituted (ee's up to 93%) and 3-trisubstituted (ee's up to 98%) cyclohexenones, respectively.[31c,k]

The above-mentioned binaphthol-based diphosphite ligands **16h** and **16k** (Figure 13)[31g,h] and a library of monophosphite ligands **26**−**29** (Figure 23)[31f] have also been applied to this process. Ligands **16h** and **16k** provided enantioselectivities up to 96% in the conjugate addition of trimethylaluminum to cyclic enones. The use of the monophosphite ligand library afforded enantioselectivitites up to 57% for **S1** (ligand **25e**) and 51% for linear substrates **S24** (ligand **29f**).

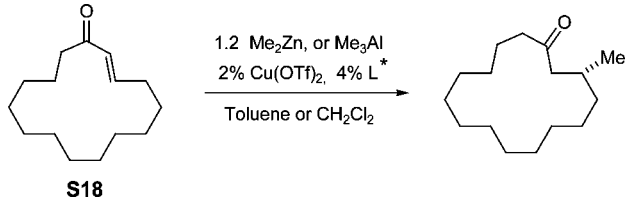
Recently, a new class of ferrocenyl-based phosphonite ligands, the aryl ferrophites (Figure 24), has provided better enantioselectivities than phosphoroamidite ligand **15e** in the trimethylaluminum addition of cyclic enones (ligand **30g**, 92% ee vs 88% ee).[31i]

Finally, a few heterodonor ligands such as P,O,[23c] P,N,[31j] P,S,[9b] and P−P′[24] have also been applied using trialkylaluminum reagents but with moderate success (Figure 25).

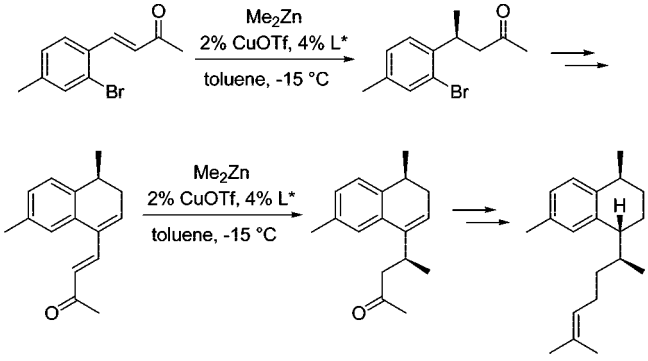
Scheme 3. Tentative Catalytic Cycle



Scheme 4. Synthesis of (*R*)-Muscone



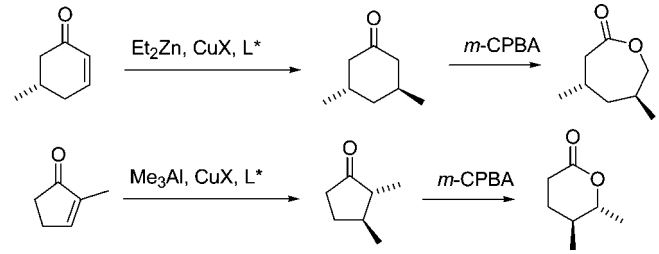
Scheme 5. Conjugate Addition for the Synthesis of Erogorgiaene



2.1.4. Other Nucleophiles

Another source of alkylating reagent is Grignard compounds. In contrast to organozinc reagents, the application

Scheme 6. Baeyer-Villiger Oxidations



of Grignard compounds in the copper-catalyzed asymmetric conjugated addition to α,β-unsaturated carbonyl systems has received less attention. This is mainly due to the higher reactivity of Grignard reagents, which leads to uncatalyzed 1,2- and 1,4-additions. However, due to their advantage, such as ready availability, the transfer of many alkyl groups of the organometallic compound, and the higher reactivity of the magnesium enolates obtained, considerable effort has been undertaken to use Grignards in the copper-catalyzed asymmetric conjugated addition. It has turned out that ligand structures favorable for organozinc reagents additions are not effective for magnesium compounds.

2.1.4.1. Ligands. In 1988, Lippard and co-workers reported the first enantioselective conjugate addition of a Grignard reagent to an enone, using a catalytic amount of Cu-amide complex **32a** (Figure 26).[32] Subsequently, a variety of catalytic systems, mainly based of Cu-thiolates **32b**−**e**[33]

and phosphine−oxazoline ligand **32f**,[34] were introduced for the conjugate addition of Grignard reagents (Figure 26). Although the scope remained limited and ee's infrequently reached the 90% level (Figure 26), high enantioselectivity (ee 92%) was obtained in two examples.[33b,34]

A breakthrough came in 2004 when Feringa and co-workers were able to identify the ligands Taniaphos **33a** and Josiphos **33b** as chiral diphosphines suitable for the above-mentioned purpose (Figure 27).[2i,35] These ferrocene-based ligands provided high enantioselectivities with cyclic enones (**S1**−**S3**, **S30**; ee's up to 96%)[35c] and linear enones (**S23**−**S24**; ee's up to 98%),[35b] α,β-unsaturated esters (**S37**; ee's up to 98%),[35d] and thioesters (**S38**; ee's up to 96%).[35e,f]

Recently, Alexakis and co-workers described the successful application of a diaminocarbene, **34** (Figure 28), in the Cu-catalyzed asymmetric conjugate addition of Grignard reagents to several β,β′-disubstituted enones **S12** (ee's up to 96%).[36] Interestingly, the higher reactivity of the Grignard reagents has improved the catalytic activity compared to the use of trialkylaluminum reagents.

These catalytic results opened up the use of Grignard reagents for the highly active and selective copper-catalyzed conjugate addition of a wide range of substrates.

2.1.5. Mechanistic and Practical Aspects

The conjugate addition of stoichiometric organocopper reagents has been the focus of many experimental and theoretical studies.[2k,n] Most often they deal with standard R_2CuLi reagents. Few such in-depth studies have been done on the catalytic processes, not even talking about the change of metal counterion (Zn and Al in this case, instead of Li).[37]

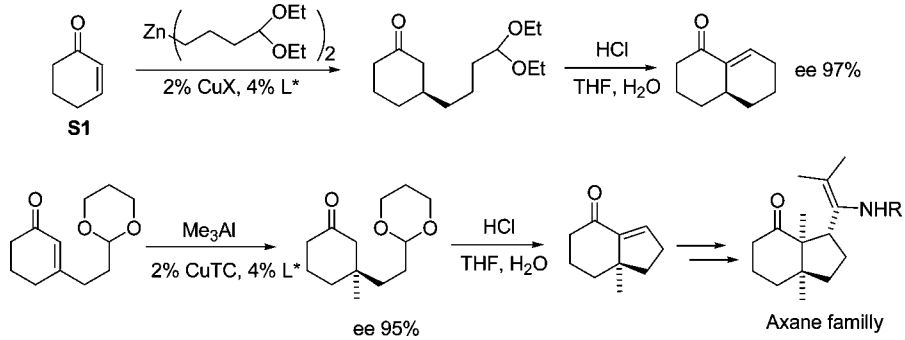
The conjugate addition of diorganozinc and triorganoaluminum reagents fits in the generally accepted mechanism of cuprate reactions.[2o] The difference lies in the nature of the reactive species, which involve a bimetallic cluster, where copper and the other metal (Li, Mg, Zn, or Al) are intimately associated. To make things even more complex, it is well known that several species (with different stoichiometries) are in equilibrium and that the degree of enantioselectivity they provide may also be different. Nevertheless, a general scheme could be drawn, although no intermediate has been characterized (Scheme 3).[15g]

The usual Cu(II) salt is first reduced to Cu(I) by R_2Zn or R_3Al. This Cu(I) salt reacts with the primary organometallic reagent to form an organocopper reagent **A**. The latter reagent strongly coordinates to the oxygen atom of the enone (**B**) by the most oxophilic metal (Zn or Al). However, since stoichiometric reagents of this type have been shown to be unable to react further, complex **B** must be transformed to a higher order cuprate reagent **C**. This could also occur before the coordination to the oxygen atom of the enone. The first step toward the conjugate addition is the formation of a π complex **D**. This is also the step that determines the absolute configuration of the adduct. At this stage, only 1 equiv of the ligand remains, although the ratio of Cu to ligand is generally 1:2. Nonlinear effects have been examined to address this question:[15b,27b,30b,33a] slightly positive or moderately negative effects were found, depending on the ligand used. In practice, the Cu-to-ligand ratio may be lowered to 1:1.5 without loss of enantioselectivity. Lower ratios are usually detrimental. Following this π complexation, the oxidative addition occurs to give Cu(III) intermediate **E**. Such a copper(III) intermediate was recently characterized by rapid injection NMR (RI-NMR) at −100 °C in the analogous conjugate addition of Me_2CuLi to 2-cyclohexenone triggered by Me_3SiCN.[38,39] The reductive elimination step provides the zinc (or Al) enolate **F**, where the oxophilic metal is bound to the oxygen atom. The Cu species is then released to enter in a new catalytic cycle.

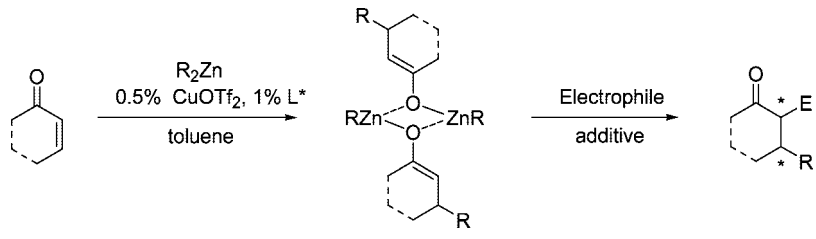
Detailed studies have been done by Schrader on many aspects of the conjugate addition of diethylzinc to cyclohexenone.[37a] It is clear that the reductive elimination is the rate-determining step. The nature of the substituents on the phosphorus ligand plays a key role in this step: the higher the number of P−O bonds (versus P−N), the higher the rate of addition.[40]

This schematic view accounts for most of the experimental facts. A strongly coordinating solvent (THF or more polar) slows the reaction due to competing coordination to the oxophilic metal (Zn or Al).[15g,40] In the case of aluminum reagents, Et_2O allows the formation of more reactive

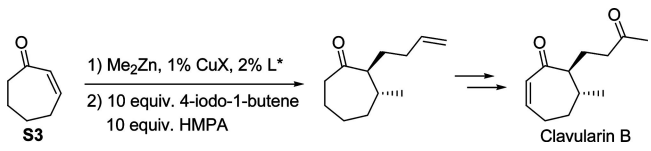
Scheme 7. Aldolization−Cyclization of Acetals



Scheme 8. Trapping of Enolate



Scheme 9. Synthesis of Clavularin B



monomeric species, thus explaining why this is the best solvent for these reagents. In addition, because Al is a better Lewis acid, it becomes understandable why this metal allows the conjugate addition to hindered trisubstituted enones by lowering the LUMO.[31c,k]

The nature of the Cu salt plays an important role. Most often, Cu halides are not the best choice. Cu carboxylates, sulfonates, or triflates usually afford better results.[15g] This is probably due to the aggregation state of the Cu/Zn (or Al) reagent **C**, where several species are in equilibrium. It has been reported that the same ligand may afford opposite enantiomers depending on the Cu salt.[25d] Even more puzzling is the fact that the enantioselectivity varies with the temperature.[2g] Low reaction temperature often does not correspond to an increase of the enantioselectivity, with sometimes inversion of the absolute configuration! CuX tend to form dimers, coordinated by only three ligands.[37b,41] This may account for the 1:1.5 Cu-to-ligand ratio.

Most often Cu(II) salts are used for practical reasons. They are less hygroscopic, not sensitive to oxidation, and cheaper. Since Cu(II) is reduced in situ to Cu(I) by the organometallic reagent employed, it was believed that this was of no consequence. However, some substrates, such as α-halogenated enones, are prone to single electron transfer processes. The Et radical generated during the reduction of Cu(II) to Cu(I) may itself add in a conjugate fashion to the substrate, thus allowing an achiral pathway to take place. It was found that addition of styrene to the reaction mixture (0.5−5 equiv) can stop this radical process with a dramatic increase of the observed enantioselectivity.[31c]

2.1.6. Application in Organic Synthesis

The asymmetric conjugate addition, and the exploitation of the resulting enolates, has already found many applications in the synthesis of natural products. One frequent target is (*R*)-Muscone, a natural valuable fragrance. Several reports show high levels of enantioselectivity using cyclopentadecanone **S18** as substrate (ee's up to 95%; Scheme 4).[15d,23c,31a,42] When cyclopentadeca-2,14-dienone was used instead of **S18**, 98% ee could be attained.[43]

A short synthesis of Erogorgiaene, an inhibitor of *Mycobacterium tuberculosis*, has, as key steps, two asymmetric conjugate additions to acyclic enones (Scheme 5).[21b]

Another simple reaction that can be performed on the hydrolysis product is a regioselective Baeyer−Villiger oxidation (Scheme 6).[42f,44] This methodology gives access to chiral lactones, which are key intermediates in organic synthesis.

Functionalization can be introduced by reacting either a functionalized zinc reagent[16b] or a built-in function on the substrate itself.[31c,k] Commonly, acetals are used as functions, because, upon hydrolysis, they allow an intramolecular aldolization−cyclization (Scheme 7). For instance, this procedure has been used in the synthesis of axane derivatives isolated from the marine sponge *Axinella cannabia*.

The in situ trapping of the enolate allows the formation of a second stereogenic center, usually in a stereocontrolled manner (Scheme 8). These enolates have been shown to be dimeric, with the Zn atom at the oxygen.[45]

Simple alkylation with benzyl[21a] or homoallyl iodide[21d] have been reported, although a large excess of electrophile was needed. The latter allowed a short synthesis of anticancer clavularin B (Scheme 9). Intramolecular alkylations of acyclic enones having a terminal tosylate functionality are more facile; they form five- or six-membered rings.[21a]

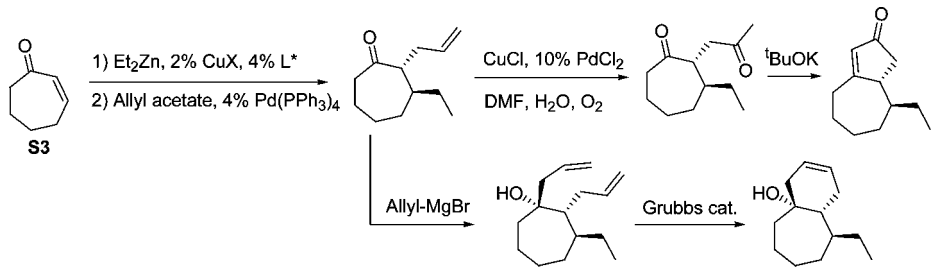
Allylation reactions have also been reported. Allyl acetate reacted, under Pd catalysis, with enolates resulting from the conjugate addition to cyclic enones (Scheme 10).[46,16a,b,h] The resulting disubstituted cyclic ketone may, then, be submitted to further transformations, such as Wacker oxidation or ring-closing metathesis.[16a,b,h]

More reactive and functionalized allylic derivatives do not require palladium catalyst.[18b] The α-allylated product may be reacted further, as in the short synthesis of (−)-pumiliotoxin C, a potent neurotoxin isolated from *Dendrobates pumilio* (poison dart frogs) that acts as a noncompetitive blocker for acetylcholine receptor channels (Scheme 11).[47]

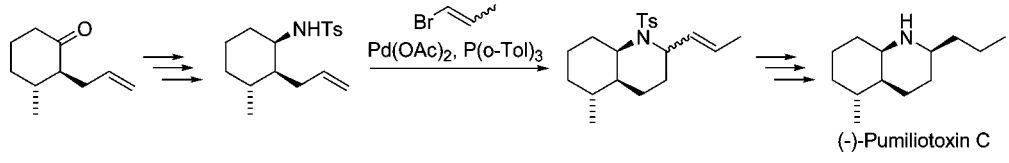
The zinc enolates are excellent reagents to undergo aldol reactions. However, the diastereoselectivity could not be controlled (Scheme 12).[45,46] This problem can be circumvented by oxidation of the aldol product[45,14a] or by using chiral acetals instead of free aldehyde.[48]

Another interesting application of the aldol condensation leads to a synthesis of (−)-prostaglandin E_1, which belongs

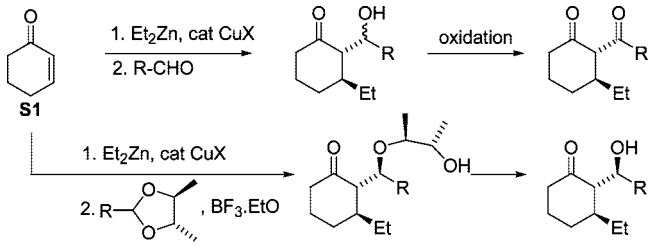
Scheme 10. Allylation−Cyclization



Scheme 11. Synthesis of Pumiliotoxin C



Scheme 12. Aldol Reactions



to the family of polyoxygenated fatty acids that are produced by a cyclooxygenase enzyme system widely distributed in mammalian tissue (Scheme 13).[16d,49]

Other trapping reactions have been described with *N*-nitrosobenzene, leading to α-hydroxylamino ketones and, after reduction, to α-amino ketones.[50] These aldol reactions can also be done in an intramolecular fashion, with high enantioselectivity, albeit with moderate diastereoselectivity (Scheme 14).[51]

The resulting zinc enolates are prone to undergo Michael addition with α,β-unsaturated compounds (Scheme 15). However, only the intramolecular version is synthetically useful. It should be pointed out that the Michael addition is so fast that no double conjugate addition of R_2Zn could be observed.[15j,k] The reaction is both highly enantioselective and diastereoselective.

The halogenation (Cl, Br, and I) of the zinc or aluminum enolate is possible. This allows further reactions through radical pathways (Scheme 16).[151]

A more general way to trap the enolate for further transformations is to quench it as an enol acetate[15m] or triflate[52] or, more generally, as silyl enol ethers.[53] Therefore all the known reactions of silyl enol ethers are possible. Some of them are shown in Scheme 17.

Zinc enolates have also been trapped by in situ formed cyclopropanating reagent, in a one-pot reaction. These cyclopropanes are useful synthetic intermediates, particularly for ring expansion (Scheme 18).[54] For instance, this approach has been used in the preparation of clavukerin A, a sesquiterpene isolated from the Okinawan soft coral *Clavularia koellikeri*.

In summary, the conjugate addition products can be versatile synthetic intermediates. Combined with the in situ trapping of the zinc or aluminum enolates, this methodology provides a powerful synthetic tool for the synthesis of enantiopure complex natural compounds. Many other applications are expected in the forthcoming years.

2.2. Using Stabilized Nucleophiles

The C_2-symmetrical bisoxazoline copper(II) complexes **35** are the catalysts of choice for enantioselective Michael additions of stabilized nucleophiles (e.g., enolsilanes, indoles) (Figure 29).[2c,e,h] These chiral Lewis acids have been introduced by Evans et al.[55] for Diels−Alder reactions and various other transformations. Enantioselective conjugate addition catalyzed by chiral copper complexes **35** are normally used for C−C bond formation, but also result in enantioselective aminations, which afford a new C−N bond.

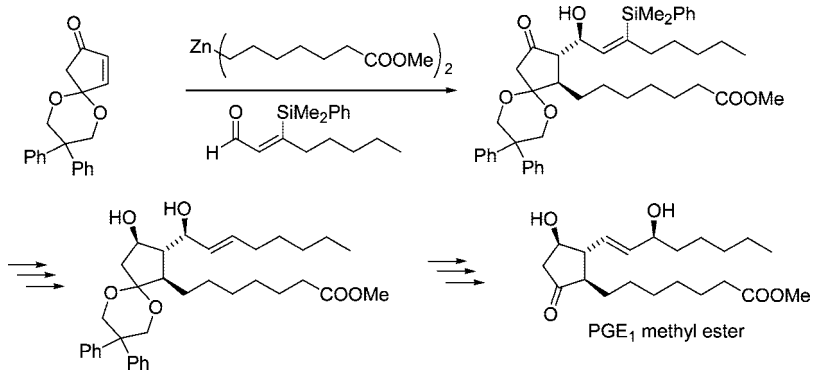
2.2.1. Enolsilanes as Nucleophiles

The first use of complexes of the type **35** for enantioselective conjugate additions was reported by Scolastico et al.,[56] who observed enantiomeric excesses of up to 66% ee in Mukaiyama−Michael additions of silyl ketene acetals to 2-methoxycarbonylcyclopent-2-enone. Preparative useful levels of stereodiscrimination were later achieved by Katsuki and co-workers,[57] in addition to reactions of trimethylsilyloxyfurans **36** to unsaturated oxazolidinone **37** catalyzed by **35a** (Scheme 19). In the presence of molecular sieves and hexafluoroisopropanol (which strongly accelerates the reaction), adducts **38** were obtained with high enantiomeric excesses and *anti*-diastereoselectivities.

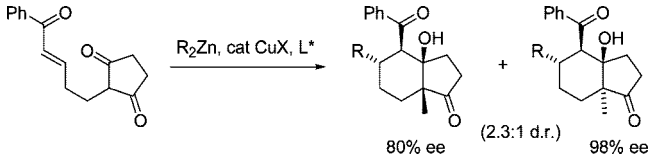
The chiral Lewis acids **35** were employed extensively by Evans and co-workers[55,58] in enantioselective Michael additions of enolsilanes to alkylidene malonates and fumaroyl oxazolidinones. Thus, treatment of alkylidene malonates **39** with silyl ketene acetal **40** in the presence of **35b** gave the desired adducts **41** with at least 93% ee and high chemical yields (Scheme 20). Likewise, the corresponding additions of silyl enol ethers **43** to fumaroyl oxazolidinone **42** furnished products **44** with high degrees of diastereo- and enantioselection. In a similar fashion, Jørgensen and co-workers[59] realized enantioselectivities of up to 92% ee in 1,4-addition reactions of 4-hydroxycoumarins to 2-oxo-3-butenoates, catalyzed by bisoxazoline copper(II) complex **35a**.

The extension of the copper-catalyzed enantioselective Michael additions described so far to the stereoselective formation of a C−N bond by reaction of azodicarboxylate **45** with enolsilanes **43** was successful using triflate **35a** as Lewis-acidic catalyst, giving rise to the formation of hydrazines **46** with extraordinarily high enantiomeric excesses (Scheme 21).[58c] Jørgensen and co-workers[60] used α-/β-ketoesters or 1,3-diketones as the nucleophile and the corresponding phenyl-substituted bisoxazoline copper(II) triflate to obtain amination products of azodicarboxylates, also with very high enantioselectivity. More recently, the

Scheme 13. Synthesis of Prostanglandin PGE_1



Scheme 14. Tandem Intramolecular Conjugate Addition−Aldol Reaction



scope of the copper-catalyzed enantioselective C−N bond formation was extended to the 1,4-addition of carbamates **48** to hydroxyenones **47**, which afford the β-aminoketones **49** with excellent yield and enantiomeric excess in the presence of copper complex **35a**.[61] These adducts can be further elaborated into enantiomerically pure N-protected β-amino acids by oxidation with sodium periodate.

2.2.2. Indoles as Nucleophiles

Another important application of the copper catalysts **35** is the enantioselective Friedel−Crafts alkylation of aromatic or heteroaromatic compounds with Michael acceptors (Scheme 22).[62] Whereas the reaction of various indoles **50** with 2-oxobutenoate **51** afforded the products **52** with very high enantioselectivities in the presence of catalytic amounts of **35a**,[63] inferior stereoselectivities were observed with alkylidene malonates as the Michael acceptor.[64] With hydroxyenones **47** as the Michael acceptor, the scope of the copper-catalyzed Friedel−Crafts alkylation was recently extended to pyrroles.[65]

In some cases, the enantioselectivity of the Friedel−Crafts alkylation of indoles can be improved by using trisoxazoline copper complexes instead of the classical bisoxazoline catalysts **35**.[66] For example, reaction of indoles **53** with benzylidene malonate **54** in the presence of a chiral copper catalyst generated from trisoxazoline **55** and copper(II) triflate afforded the adducts **56** with high yield and enantioselectivity (Scheme 23). In the case of the unsubstituted indole, the catalyst **35a** gave only 48% ee,[66c] indicating the importance of the additional coordination site in the tridentate ligand **55** for attaining high levels of stereoselection.

2.2.3. Mechanistic and Practical Aspects

Mechanistic investigations on the Michael addition of enolsilanes catalyzed by bisoxazoline copper(II) complexes **35** have been reported by Evans and co-workers.[58] Monitoring of the reaction of fumarate **42** with enolsilane **43a** (R = Me) and **35b** by in situ IR spectroscopy in the absence of hexafluoroisopropanol showed coordination of the Lewis-acidic Cu(II) to the carbonyl oxygen atoms of the oxazolidinone and adjacent ester group,[67] followed by a rapid accumulation of an intermediate; isolation confirmed this to be dihydropyran **58** (Scheme 24). An analogous intermediate was observed in the corresponding amination of azodicarboxylate derivatives.[58c] Thus, these transformations can be viewed as hetero Diels−Alder reactions. In the presence of an alcohol, which serves as proton source and silicon acceptor, the catalyst turnover is facilitated.

The same authors also noted that the starting enolsilane can undergo hydrolysis in the reaction mixture (probably by hexafluoroisopropanol coordinated to the copper complex **35b**), leading to unsatisfactory product yields. A fine-tuning of the solvent polarity served to prevent this destructive enolsilane hydrolysis. By using a mixture of dichloromethane and toluene, the concentration of hexafluoroisopropanol (which is sparingly soluble at low temperature) was kept rather low, favoring the productive Michael addition pathway.[58d]

2.2.4. Applications in Organic Synthesis

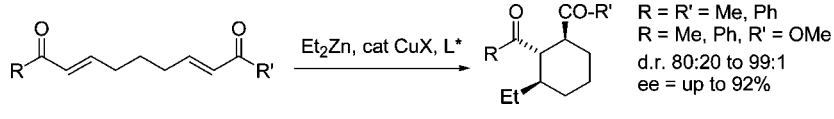
Even though enantioselective Michael additions of stabilized nucleophiles catalyzed by bisoxazoline copper(II) complexes **35** are well established, applications in target-oriented synthesis are still scarce. Katsuki and co-workers[68] used the adduct **38a** (Scheme 19, R = H) as starting material for a stereoselective synthesis of the *trans*-whisky lactone **61**, which is found in many liquors stored in oak barrels (Scheme 25). Titanium-mediated alcoholysis of the oxazolidinone, followed by reduction of the double bond and the lactone, afforded the lactol **59**, which was subjected to a Wittig olefination, giving the γ-lactone **60** by spontaneous cyclization of the intermediate γ-hydroxy ester. Finally, hydrogenation of the double bond provided diastereo- and enantiomerically pure *trans*-whisky lactone **61**.

3. Asymmetric Allylic Substitution Reaction

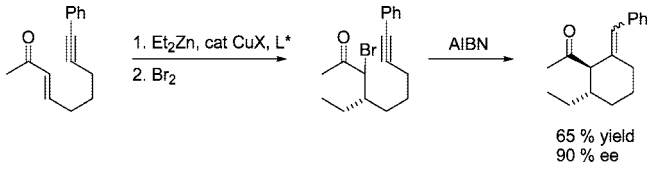
Asymmetric allylic substitution is also a potentially powerful method for creating chiral centers in readily available starting materials (Scheme 1c). Great efforts have been made to control the chemo-, regio-, and enantioselectivities of the reaction products.[1] In contrast to other metals (Pd, Mo, and Ir, for example),[1,69] copper allows nonstabilized nucleophiles to be used. Increasing interest is being shown in catalytic systems employing Grignard, organozinc, and organoaluminum reagents as the carbon nucleophiles and diboron as noncarbon nucleophile.

The first successful attempts were made with a chiral leaving group and a stoichometric organocopper reagent.[70] It was only in 1995 that a catalytic process was disclosed by Bäckvall and van Koten, which gave a moderate ee of 42% in Grignard reactions with allylic acetates.[71a] This was later improved to 64% with a new chiral catalyst.[71b] The catalytic system involved a Grignard reagent as primary organometallic, a chiral copper thiolate, and an allylic acetate substituted by an alkyl group. A few years later, in 1999 and 2000, Dubner and Knochel disclosed a different system, based on dialkylzinc reagents as primary organometallics, an amine as chiral ligand to copper bromide, and an allylic chloride.[72] The results are better when the allylic chloride is substituted by an aryl group and when the zinc reagent is a hindered one, such as a neopentyl group. These two catalytic systems are complementary. The dialkylzinc systems needs a polar solvent, whereas the Grignard system works better in the least polar solvent. With Grignard reagents, allylic acetates afford higher stereoselectivity than halides; the reverse is true with dialkylzinc reagents. An alkyl substituent works better than an aryl one on the allylic

Scheme 15. Tandem Intramolecular Conjugate Addition−Michael Reaction



Scheme 16. Halogenation of Enolates Followed by Radical Cyclization



substrate with Grignard reagents. With dialkylzincs, aryl substituents are preferred; in addition, an electron-withdrawing group affords higher enantioselectivity. Recently, triorganoaluminum reagents have also been successfully applied in this process.[11b,73] More recently, the use of boryl nucleophiles has also been described, allowing the preparation of chiral allylboronates in high enantioselectivitites.[74]

In this section we present the results obtained in the copper-catalyzed asymmetric allylic substitution reaction. First, we group the catalytic data according to the type of nucleophile. Then, we also discuss mechanistic aspects as well as the application of this process to the synthesis of more complex molecules.

3.1. Grignard as Nucleophiles

A review of the most successful catalytic systems with the use of Grignard reagents as nucleophiles revealed three main trends: thiolatocopper(I) compounds, phosphorus, and carbene ligands.

The use of Grignard reagents was first reported by Bäckvall, van Koten, and co-workers with chiral copper thiolate **32d** (Figure 26), yielding moderate ee values (up to 42%) for alkyl allylic acetates.[71a] Later, they also developed a second- (**62a**)[71b] and third-generation (**62b**)[71c] copper−thiolates, based on a ferrocene backbone, which provided higher enantioselectivities (ee's up to 64%; Figure 30>). They found that enantiomeric excesses depended strongly on the temperature, the coordination ability of the leaving group in the substrate, and the method of addition of the substrate and the Grignard reagent.

The first report on phosphorus ligands was introduced by Alexakis and co-workers. They first applied TADDOL-based phosphites for cinnamyl chloride-type substrates. The best

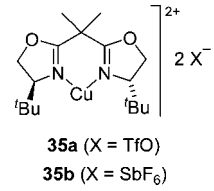


Figure 29. Copper catalysts used for enantioselective 1,4-additions of stabilized nucleophiles.

enantioselectivities (up to 73% ee) were obtained with the above- mentioned ligand **11q** (Figure 10) for cinnamyl chloride and EtMgBr.[75a] Subsequently, they found that the previously mentioned phosphoroamidite **17a** (Figure 14) improved enantioselectivities up to 79%. They also allowed a wider scope of applicability in terms of magnesium sources and substrate types.[75b] More recently, they found that ligand **63** (Figure 31), containing methoxy groups at the 2-positionof the aryl amine groups, provided outstanding results in terms of both regio- and enantioselectivity. Ligand **63** afforded enantioselectivities of >91% and regioselectivities of >97%. It works with several Grignard reagents and with various di- and trisubstituted and endocyclic allylic chlorides and also for 1,4-halo-2-butene substrates.[75c−f]

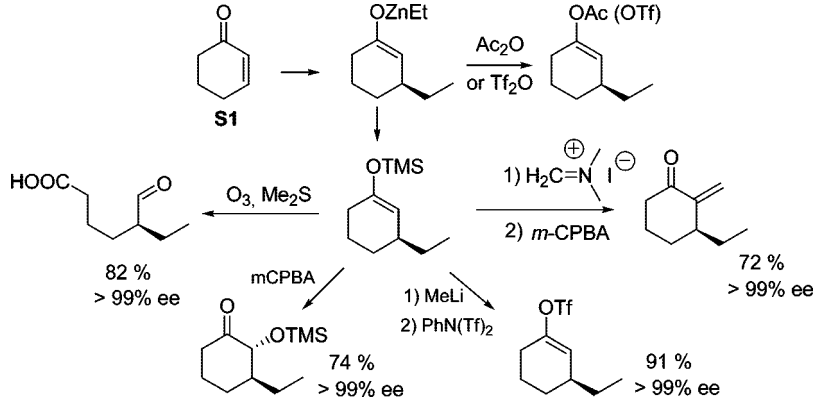
Recently, Feringa and co-workers successfully applied the previously mentioned diphosphine ligand **33a** (Figure 27) in the allylic alkylation of various allylic bromide derivatives using several Grignard sources (ee's up to 98%).[76]

The use of diaminocarbenes in this reaction was introduced by Okamoto and co-workers. Diaminocarbene **64** (Figure 32) provided the best enantioselectivities (up to 70%) for difunctionalized substrates with *Z* double-bond stereochemistry. It should be pointed out that the *E* isomer afforded the opposite enantiomer, but in lower ee's (up to 60%).[77]

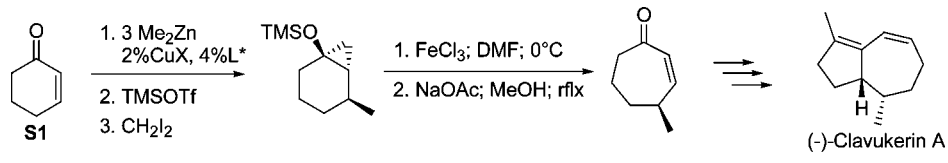
3.2. Diorganozinc as Nucleophiles

A review of the most successful ligands used in the asymmetric allylic substitution with diorganozinc reagents as nucleophiles revealed five main trends: amines, phosphorus, sulfonamides, peptides with an imine core, and carbene ligands.

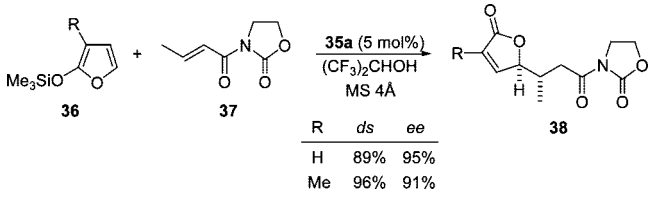
Scheme 17. Silylation of Zinc Enolates



Scheme 18. Cyclopropanation of Zinc Enolates

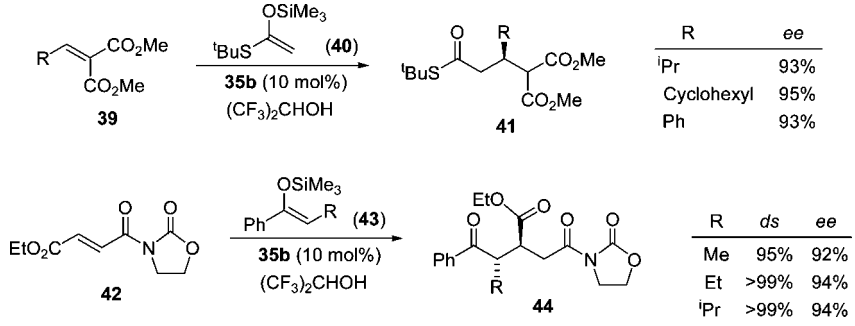


Scheme 19. Enantioselective Michael Addition of Trimethylsilyloxyfurans 36 to Unsaturated Oxazolidinone 37 in the Presence of Copper Catalyst 35a

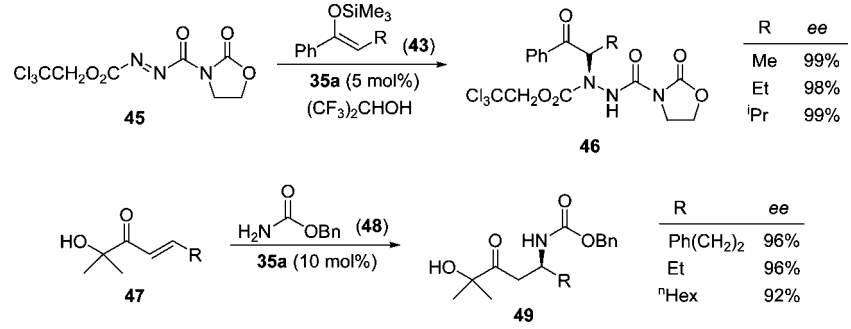


In 1999, Dubner and Knochel reported the first allylic substitution using diorganozinc reagents with the amine **65a** as chiral ligand (Figure 33). To attain a high enantioselectivity, the system required a high ratio of ligand to copper, very low temperatures, and the presence of bulky alkyl groups on zinc. For example, the reaction of cinnamyl chloride with dineopentylzinc at −90 °C afforded 82% ee. In subsequent studies, ligand **65b** (Figure 33) was found to be more effective in this reaction, providing 96% ee.[72] Later, Woodward and co-workers identified ligand **65c** (Figure 33), from a series of amines, that provided enantioselectivities up to 90% using simple linear dialkylzinc species, such as $ZnEt_2$.[78] They also found that the enantioselectivity was higher in the beginning of the reaction. The formation of $ZnCl_2$ during the reaction shifted the Schlenk equilibrium (Scheme 26) toward EtZnCl, a nonselective reagent. To solve this, they added polymeric methylaluminoxide, MAO-([−Al(Me)O]$_n$), which shifted back the Schlenk equilibrium to $ZnEt_2$.

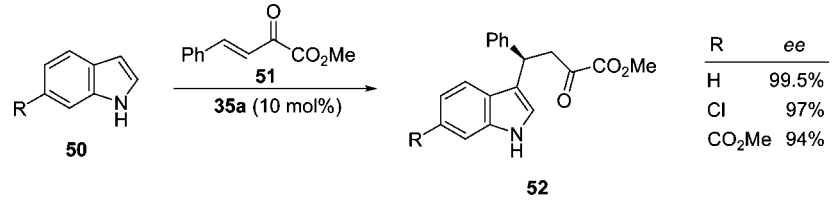
Scheme 20. Enantioselective Michael Addition of Enolsilanes in the Presence of Copper Catalyst 35b



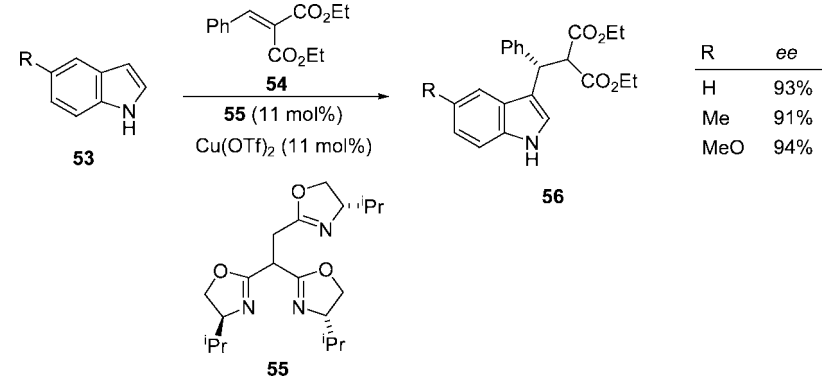
Scheme 21. Enantioselective C−N Bond Formation in the Presence of Copper Catalyst 35a



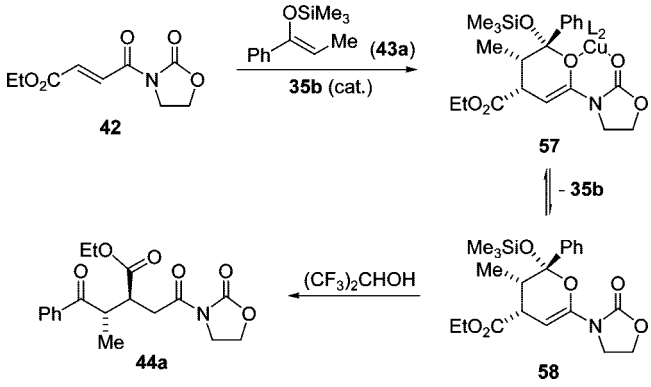
Scheme 22. Enantioselective Friedel-Crafts Alkylation of Indoles in the Presence of Copper Catalyst 35a



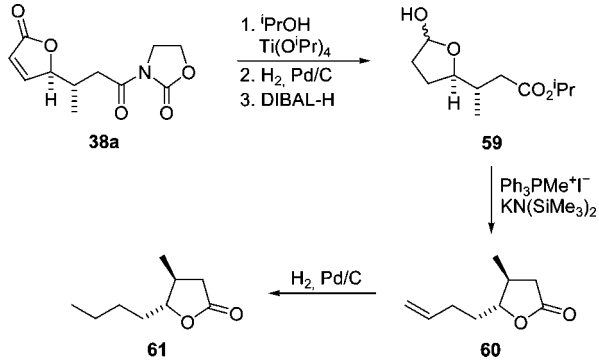
Scheme 23. Copper-Catalyzed Enantioselective Friedel−Crafts Alkylation of Indoles in the Presence of Trisoxazoline 55



Scheme 24. Mechanism of the Michael Addition of Enolsilane 43a to Fumarate 42 in the Presence of Copper Catalyst 35b



Scheme 25. Conversion of the Michael Adduct 38a into *trans*-Whisky Lactone 61



Feringa and co-workers screened a wide range of TADDOL- and binaphthol-based phosphoroamidites in this process. They discovered that phosphoroamidite ligand **66** (Figure 34), H8 analogue to **15e** (Figure 11), provided the best enantioselectivies (up to 88%) on cinnamyl-type substrates.[79a] Similarly, Alexakis and co-workers reported

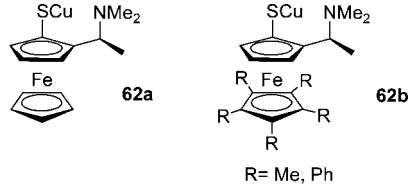


Figure 30. Ferrocene-based copper−thiolate compounds **62**.

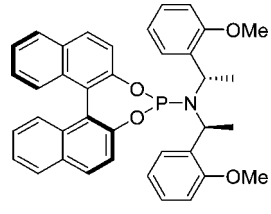


Figure 31. Phosphoroamidite ligand **63**.

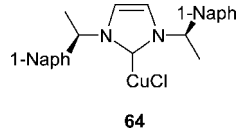


Figure 32. Diaminocarbene **64**.

higher ee's (up to 91%) in this reaction using binaphthol-based phosphoroamidite **63** (Figure 31), containing methoxy groups.[75c] Phosphoroamidite **15e** (Figure 11) was also successfully used in the desymmetrization of *meso* cyclic allylic bis(diethylphosphates) with high ee's (up to 94%, Scheme 27)[79bc] and in the allylic alkylation of dialkylzinc reagents to vinyloxiranes (ee's up to 96%).[79e]

On the other hand, Zhou and co-workers applied phosphoroamidite **19** (Figure 16) with moderate success (ee's up to 71%).[79d]

Another group of ligands also applied in this process is the sulfonamides. Gennari and co-workers tested a combinatorial library of 125 chiral sulfonamide ligands. These catalytic systems provided low enantioselectivities for cinnamyl-type substrates (ee's up to 30%). However, they found that sulfonamides **67** (Figure 35) and **24a** (Figure 21) provided high enantioselectivities (up to 94%) in the desymmetrization of *meso* cyclic allylic bis(diethylphosphates).[80]

Hoveyda and co-workers developed a series of peptide ligands bearing a hydroxynaphthimine core. Using a combinatorial approach, they successfully applied ligand **68** (Figure 36) to the allylic substitution of aryl-, alkyl-, and vinyl- allylic phosphates and trisubstituted allylic systems, which allows the formation of chiral quaternary centers.[81]

Hoveyda and co-workers also disclosed new bidentate carbene chiral ligands, related to the previoulsy mentioned **24f**, for an efficient copper-catalyzed allylic substitution reaction. The best results were obtained with carbenes **69** (Figure 37), which provided excellent enantioselectivities (up to 98%) with trisubstituted allylic phosphonates.[82]

3.3. Triorganoaluminum as Nucleophiles

Up to now, there are only a few recent papers on the use of triorganoaluminum reagents as nucleophiles in this process.[11b,73] Recently, the application of the previously mentioned ligands **9a** (Figure 8) and **15e** (Figure 11) in the copper-catalyzed nucleophilic ring opening of bicyclic hydrazines using trialkylaluminum as reagent has been reported (ee's up to 94%, Scheme 28).[11b,73a,c]

Very recently, Hoveyda and co-workers have reported the successful application of diaminocarbene **70** (Figure 38) in the asymmetric copper-catalyzed allylic alkylation of several allylic phosphates (ee's up to 98%).[73b] Interestingly, this is the first report of catalytic allylic alkylation reagents involving vinylmetal reagents.

3.4. Diboronas Nucleophiles

In 2007, Ito, Sawamura, and co-workers successfully reported the use of boryl nucleophiles in this process using ligand **71** (ee's up to 96%, Scheme 29).[74] This constitutes the first example of a copper-catalyzed asymmetric allylic substitution with a noncarbon nucleophile.

3.5. Mechanistic and Practical Aspects

The copper-catalyzed allylic substitution reactions proceed via initial formation of an organocopper(I) species, which is formed by transmetalation between the organometallic compound (RMgX or Et_2Zn) and the copper catalyst. Since most copper-catalyzed allylic substitution reactions employ a primary allylic compound

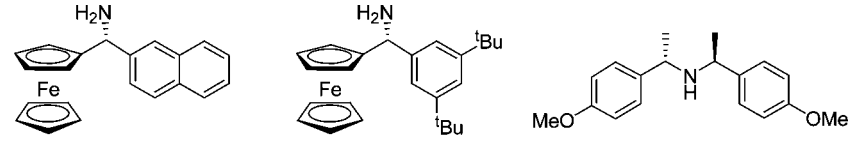


Figure 33. Amine ligands **65**.

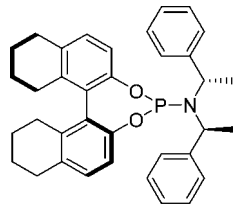
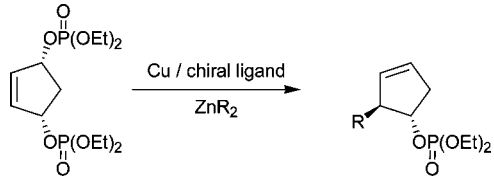


Figure 34. Phosphoroamidite ligand **66**.

Scheme 26. Schlenk equilibrium

Scheme 27. Desymmetrization of *meso* Cyclic Allylic Bis(diethylphosphates)



as the substrate, a highly selective S_N2' substitution is required to obtain a chiral product. Mechanistic studies have been carried out on copper-catalyzed allylic substitutions,[2n,83] and it is commonly believed that monoalkylcopper species favor S_N2' attack, while dialkylcuprates favor S_N2 attack. In a copper-catalyzed allylic substitution

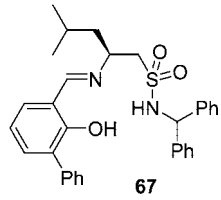


Figure 35. Sulfonamide ligand **67**.

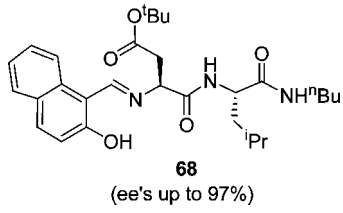


Figure 36. Peptide-based ligand **68**.

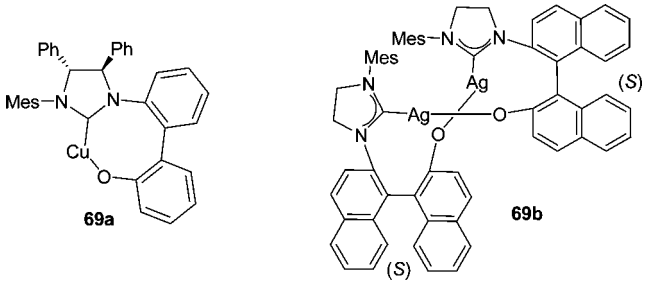


Figure 37. Bidentate carbene ligand **69**.

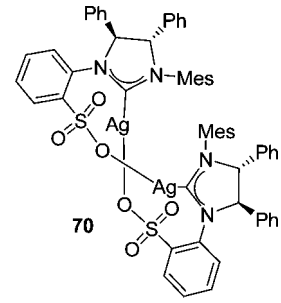
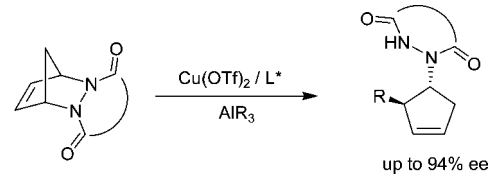
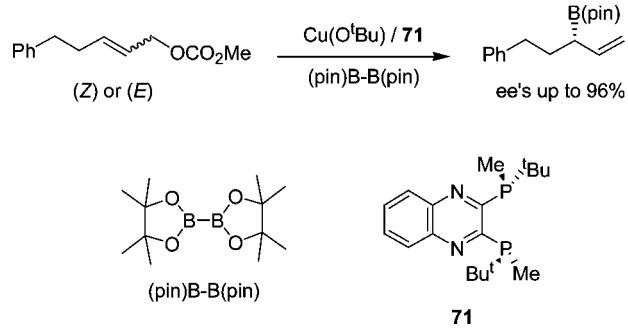


Figure 38. Diaminocarbene **70**.

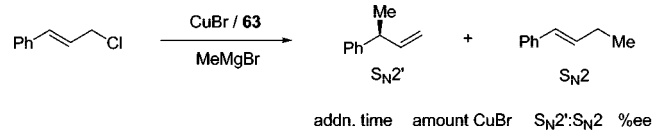
Scheme 28. Desymmetrization via Ring Opening of Bicyclic Hydrazines



Scheme 29. Enantioselective Cu-Catalyzed Substitution of Allylic Carbonates with Diboron Nucleophiles

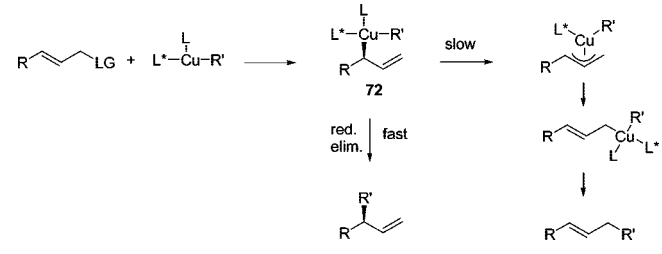


Scheme 30. Allylic Substitution of Cinnamyl Chloride Using Ligand 63: Effect of the Addition Time and Catalyst Loading



addn. time	amount CuBr	$S_N2':S_N2$	%ee
40 min	1 mol%	38 : 62	94
4 h	1 mol%	83 : 17	96
4 h	3 mol%	89 : 11	96

Scheme 31



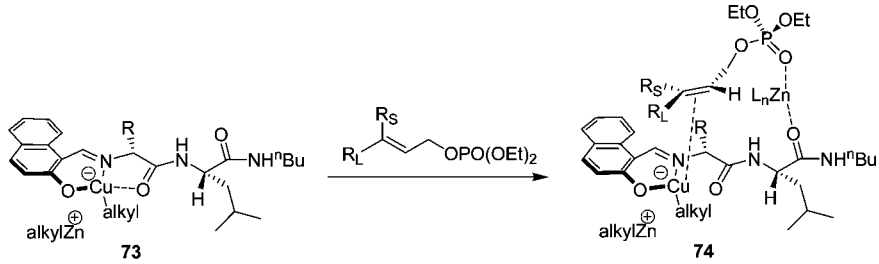


Figure 39. Cu intermediates **73** and **74**, containing chiral amino acid-based type ligands **68**.

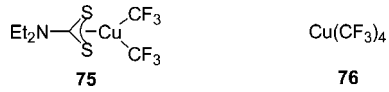
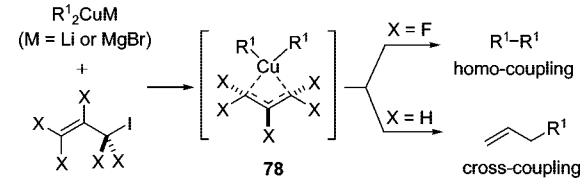


Figure 40. Organocopper(III) complexes **75** and **76**.

the rate of addition of the organometallic compound employed, e.g., a Grignard reagent, will therefore be of importance for the regiochemical outcome. A fast addition will allow formation of a dialkylcuprate, whereas slow addition will prevent formation of the dialkylcuprate by letting the monoalkylcuprate species react with the allylic substrate.[83c] Also an increased temperature and an increased amount of catalyst will favor the monoalkylcopper species (and hence S_N2' attack) by accelerating the reaction, since a faster reaction of the monoalkylcopper species will prevent its transformation to the dialkylcuprate. The effect of all three parameters (addition time, catalyst amount, reaction temperature) on the regioselectivity has been demonstrated.[83b,c] Variation of the rate of addition and amount of catalyst was used by Alexakis to optimize the copper-catalyzed enantioselective allylic substitution by MeMgX.[75d,e] An increased addition time from 40 min to 4 h reversed the regioselectivity from mainly S_N2 to predominantly S_N2' attack (Scheme 30). An increase of the catalyst loading further increased the relative amount of S_N2' attack.

The copper-catalyzed asymmetric allylic substitutions most likely proceed through a Cu^{III} intermediate (Scheme 31). Oxidative addition of the allylic substrate to the organocopper(I) complex leads to Cu^{III} intermediate **72**. If the Cu^{III} intermediate is formed from a monoalkylcopper(I) species, there will be only one R′ group on copper and a fast reductive elimination takes place. Electron-withdrawing ligands will increase the rate of reductive elimination, whereas electron-donating ligands slow the reductive elimination.[83c] Rearrangement to allyl- and finally primary σ-allylcopper should be slow compared to reductive elimination. With two R′ groups on copper, reductive elimination from Cu^{III} intermediate **72** is slowed and rearrangement to the primary σ-allylcopper species is favored.[84]

Scheme 33



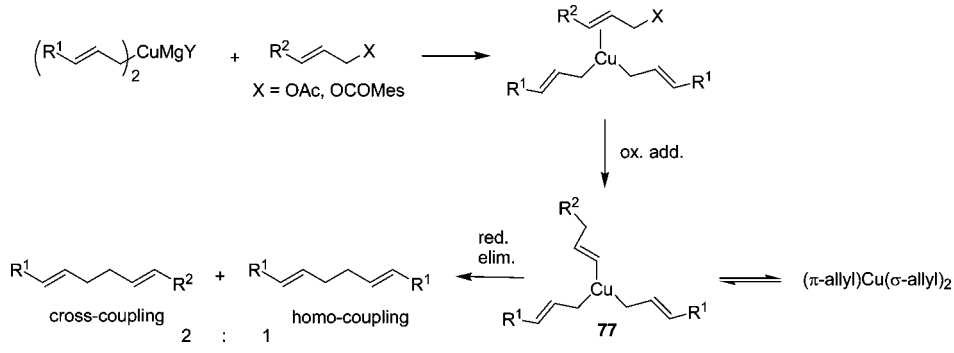
An interesting observation supporting the mechanism in Scheme 31 is that in copper-catalyzed allylic substitution of 3-phenyl-2-propenyl chloride with EtMgBr (cf. Scheme 30), gamma attack is favored in the presence of a chiral ligand, whereas the alpha product is obtained without the ligand.[75b] This shows that reductive elimination from the γ-copper intermediate is accelerated by the ligand.

In the copper-catalyzed asymmetric allylic alkylation of aromatic and aliphatic phosphates with dialkylzinc reagents using chiral amino acid-based ligands Hoveyda proposed the intermediates shown in Figure 39.[81c] The pseudotetrahedral copper(I) complex **73** represents the resting state of the chiral complex. Coordination of the allylic substrate produces **74**. Oxidative addition of the allylic substrate to copper would produce a Cu^{III} intermediate, which on reductive elimination would give the product.

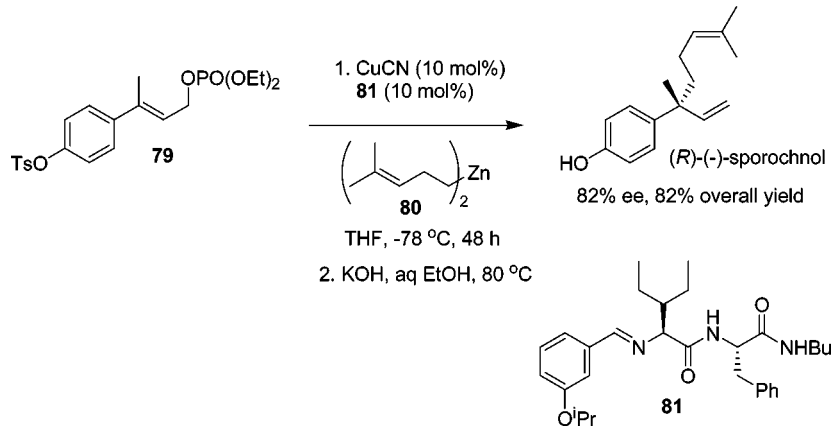
Although copper(III) intermediates have not yet been isolated from allylic substitution reactions, there is ample evidence for their existence. Two organocopper(III) complexes that have been isolated and characterized are shown in Figure 40.[84] Complexes **75**[85a] and **76**[85b] were unambiguously characterized by their X-ray structures. Furthermore, copper(III) intermediates from conjugative addition of dimethylcuprate were recently observed (vide supra).[38,39]

In 2001 Karlström and Bäckvall provided experimental evidence supporting a Cu^{III} intermediate in cross-coupling reactions of allylic substrates and diallylcuprates (Scheme 32).[86] Reaction of the diallylcuprate with the allylic substrate will produce a triallylCu^{III} intermediate, in which the three allyl groups can be considered as equivalent. Therefore

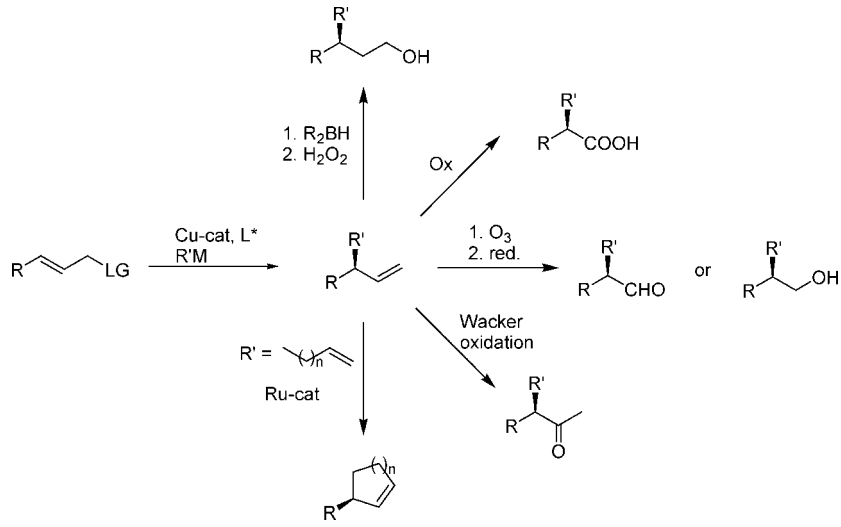
Scheme 32. Experimental Evidence Supporting a Cu^{III} Intermediate in Cross-Coupling Reactions of Allylic Substrates and Diallylcuprates



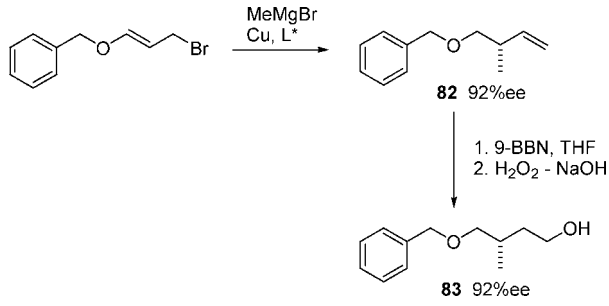
Scheme 34. Synthesis of (*R*)-Sporochnol



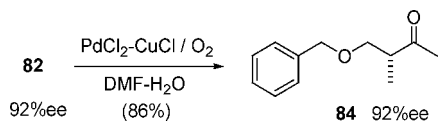
Scheme 35



Scheme 36. Synthesis of Monoprotected Diol 83



Scheme 37. Synthesis of Ketone 84



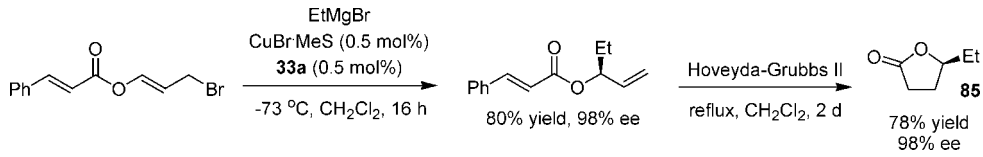
the probability of forming a cross-coupling product should be twice as high as forming a homocoupling product in the reductive elimination from tris(*σ*-allyl))copper(III) complex **77**. The results from the catalytic reaction between an allyl Grignard reagent and the allylic ester as well as from the stoichiometric reaction between diallylcuprate and the allylic ester are in good agreement with the predicted ratio between cross-coupling and homocoupling products. The catalytic reaction is complicated by the fact that homocoupling from the triallylcopper(III) intermediate produces Cu^{I} complex $Cu(CH_2CH{=}CHR^2)$, which goes back into the catalytic cycle and gives a new type of homocoupling product, $(R_2CH{=}CHCH_2)_2$. A mathematical expression was provided to predict the distribution between the cross-coupling and homocoupling products in the catalytic reaction. The experimental results were in close agreement with the predicted distribution.

The stability of the Cu^{III} complexes **75** and **76** in Figure 40 is explained by the electronegative carbons of the CF_3 groups, which are less prone to undergo reductive elimination. The reluctance of a perfluorinated carbon to participate in reductive elimination was used in mechanistic studies of the copper-catalyzed allylic substitution to obtain support for a Cu^{III} intermediate.[87] For Ph_2CuLi and Hex_2CuLi the fluorinated substrate (X = F) gave exclusively homocoupling, whereas the parent allyl substrate (X = H) afforded exclusively the cross-coupling product. These results are nicely explained by the intermediacy of Cu^{III} complex **78** (Scheme 33). DFT calculations supported this mechanism and gave a high barrier for reductive elimination between the perfluorinated allyl group and the R^1 group on copper. Recently, Gschwind and co-workers were able to detect Cu^{III} intermediates by NMR from the reaction of alkyl halides and Gilman cuprates.[88]

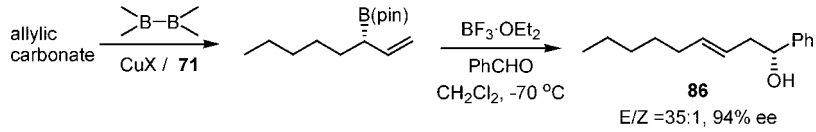
3.6. Application in Organic Synthesis

The enantioselective copper-catalyzed allylic substitution has been used in a number of synthetic applications. A few

Scheme 38. Synthesis of Lactone 85



Scheme 39. Synthesis of Homoallylic Alcohol 86



examples are reviewed in this section. Hoveyda employed the enantioselective copper-catalyzed reaction of allylic phosphate **79** with organozinc compound **80** for the synthesis of (*R*)-sporochnol (Scheme 34), a fish deterrent from the Caribbean marine alga *Sporochnus bolleanus*.[81a] This demonstrates the usefulness of the allylic alkylation for the synthesis of chiral compounds with quaternary carbons.

Since many of the enantioselective copper-catalyzed allylic substitutions give terminal olefins with a chiral carbon in the 3-position, further functionalization of the carbon−carbon double bond is an attractive approach to obtain new chiral compounds of interest. A few examples used in the literature are shown in Scheme 35.[75bd−f,76a,b,81d]

Hydroboration−oxidation was used to transform allylic substitution product **82** to monoprotected diol **83** (Scheme 36).[76a] Compound **83** is an important imtermediate in vitamin K_1 and vitamin E total synthesis.

The synthesis of optically active α-methyl carboxylic acids is readily achieved by oxidation ($RuCl_3$−$NaIO_4$ or ozonolysis) of the products from the enantioselective copper-catalyzed allylic substitution and has been demonstrated.[75e,76a] These acids are of pharmaceutical interest (i.e., (+)-naproxen).

Ozonolysis of the allylic substitution product followed by either oxidative or reductive workup has been used for the synthesis of chiral aldehydes[81d] and chiral alcohols,[76a] respectively.

Palladium-catalyzed oxidation of the terminal double bond (Wacker oxidation) has also been used. Thus, the intermediate **82** in Scheme 35 was oxidized to ketone **84** without loss of chiral information (Scheme 37).[76a] Ketone **84** is an important synthetic intermediate in natural product synthesis.

The combination of enantioselective copper-catalyzed allylic substitution and ring-closing methathesis (RCM) has been used to prepare optically active substituted cyclopentenes and cyclohexenes.[76a,b] An efficient example of the allylic substitution in combination with RCM for the synthesis of the naturally occurring lactone **85** is shown in Scheme 38.

An elegant application of an allylic boranate, obtained from copper-catalyzed allylic substitution, was demonstrated by Ito and Sawamura (Scheme 39).[74]

4. Concluding Remarks and Perspectives

The enantioselective copper-catalyzed conjugate addition and allylic substitution reactions have become two of the most powerful approaches for the formation of new stereogenic C−C bonds. Impressive results have been obtained in the development of highly efficient new copper catalytic systems by exploring several ligand types, copper sources, and reaction conditions. Remarkable efforts have been made to enlarge the scope of substrates and nucleophiles, increasing the possibilities for their use in the synthesis of more complex chiral organic molecules. However, the full potential of these methodologies as powerful synthetic tools remains to be exploited. This will lead to many other applications in the forthcoming years. Another important remaining objective is to enhance the efficiency of the known copper-catalyzed conjugate addition and allylic substitution processes. More efforts in the search for new efficient catalytic systems and nucleophiles that provide higher activities at milder temperatures (closer to room temperature) are necessary. Moreover, additional efforts are needed to obtain more information about the reaction mechanisms and enantiodiscriminating steps.

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