Enantioselective Copper-Catalysed Conjugate Addition

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Dedicated to Professor Jean F. Normant, a pioneer in organocopper chemistry

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The review covers the efforts made over the last decade towards designing efficient copper-catalysed systems for the asymmetric conjugate addition reaction.

1. Introduction

The conjugate addition reaction, also called Michael addition, is a major synthetic transformation and has been employed in numerous total syntheses.[1] Although several soft carbon nucleophiles (such as malonates) easily undergo this reaction, harder carbon nucleophiles (such as classical organometallic reagents) need the presence of a transition metal to avoid direct attack on the carbonyl group of the Michael acceptor. Traditionally, copper has found the broadest application, and various organocopper species have been widely used.[2]

Four decades ago, when organocopper chemistry took off, it was already obvious that an asymmetric version could be of great interest. Early attempts were quite discouraging, however, the main reason being the lack of knowledge of the intrinsic mechanistic pathway. There are several ways to tackle the problem (Scheme 1). Until the mid 1990s, the stoichiometric approach with covalent auxiliaries was the most successful, with diastereoselectivities reaching $> 99\%$. All these results are summarized in several review articles.[3] A catalytic approach can only be envisioned by Method 3: heterocuprates and external chiral ligands. We focus here only on the copper-catalysed approaches, which have attracted exponential interest over the last 5−6 years.[4]

Copper-catalysed conjugate addition has its background in the first example described by Kharash, in 1941.[5] Stoichiometric organocopper reagents are usually prepared by transmetallation of an organolithium or a Grignard reagent. The catalytic process, however, is usually performed with Grignard reagents, organolithium reagents being too reactive towards the carbonyl functionality. Therefore, all

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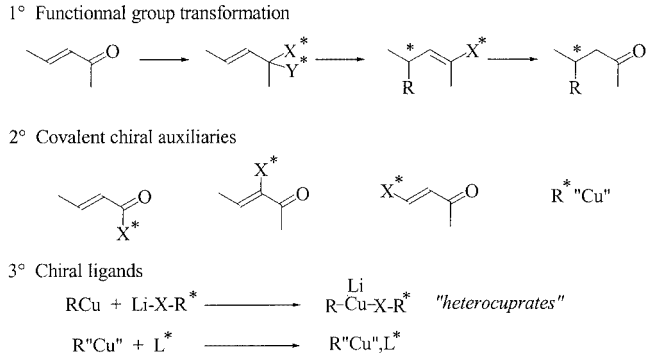
Prof. Alexandre Alexakis graduated from Paris VI University in 1970 and received his Ph.D. in 1975. After a postdoctoral stay at Johns Hopkins University, he joined the CNRS at Pierre et Marie Curie University in 1977, being appointed Directeur de Recherche in 1985. In 1994 he was awarded the Silver Medal of the CNRS. In 1996 he was appointed full professor at Pierre et Marie Curie University, then moved in 1998 to his present position at the University of Geneva. His research focuses on asymmetric synthesis, particularly in organocopper chemistry.

Dr. Cyril Benhaim was born in 1975 in Bourg-la-Reine, France. He did his undergraduate studies at the University of Toulon and Paris VI. He obtained his Ph.D. in 2002 at the University of Geneva under the direction of Prof. Alexakis. His work dealt with the copper-catalysed asymmetric conjugate addition reaction. He is now set to join the group of Prof. P. D. Magnus, Texas, as a postdoctoral fellow.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1

the enantioselective catalytic approaches were based on the use of Grignard reagents as primary organometallics. In 1993, however, we introduced dialkylzinc reagents for this enantioselective reaction,[6] and this procedure has since then been adopted by most chemists. In addition, in 1991, we had also introduced the use of chiral phosphorus ligands,[7] in contrast to most of the previous approaches, which had been based on heterocuprates.[3a]

This review summarizes the efforts of the last few years (until April 2002) in the identification of new chiral ligands with increased efficiency and with more general applicability. Since the classes of ligands are very different, depending on the primary organometallics, this review is subdivided by metals and not by chronological order.

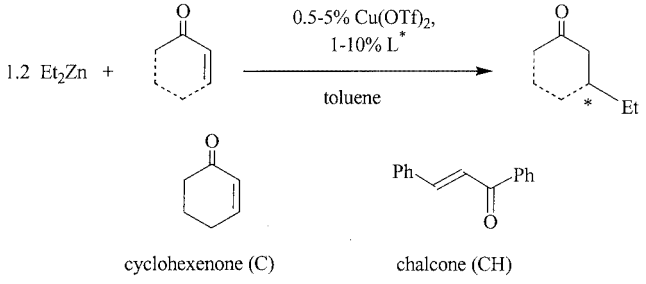
2. Dialkylzinc Reagents

Although dialkylzinc reagents add to Michael acceptors such as cyclohexenone, they do so in highly polar solvent mixtures with TMSCl as an additive.[8] Ni,[9] Co,[10] and Cu,[11] however, have been found to catalyse the reaction efficiently even in apolar solvents such as toluene. In asymmetric conjugate addition, the first reports dealt with Ni-based catalysts.[12] Despite high enantioselectivities, however, the reaction was restricted to chalcone-type enones: acyclic enones with two aryl substituents.

In 1993, we found that the Cu-catalysed asymmetric conjugate addition of dialkylzinc reagents is a viable approach, using chiral trivalent phosphorus ligands.[6] Since then, most work in this area has focused on improvements to this basic system, with some efforts based on changing the Cu source, but most focussed on the design of more efficient chiral phosphorus ligands.

The exact mechanistic pathway is believed to follow the usually accepted mechanism of cuprate conjugate addition: oxidative addition to a Cu^{III} intermediate, followed by reductive elimination.[13] Although a radical pathway for diethylzinc addition is known,[4c,14] copper-catalysed experiments in the presence of added isopropyl iodide do not show any trace of isopropyl adduct, thus ruling out such a mechanism.[15]

The typical experiment in most studies is the reaction, in toluene, between diethylzinc and cyclohexenone or chalcone – taken as representatives of cyclic and acyclic enones, respectively – in the presence of 0.5–5% $Cu(OTf)_2$ and 1–10% chiral ligand (Scheme 2).



Scheme 2

Each of the parameters of this reaction is carefully examined, and the variations are discussed in detail.

2.1. The Solvent

This Cu-catalysed reaction is very sluggish without ligands,[11b,16] whatever the solvent used. It is therefore a typical ligand-accelerated reaction, amenable to being tuned according to the nature of the chiral ligand. Among the different reported solvents (toluene, dichloromethane, diethyl ether, *tert*-butyl methyl ether, THF, ethyl acetate, acetonitrile), the usual trend is of a deceleration of the reaction in coordinating solvents.[16,17]

Thus, in toluene and dichloromethane, addition to cyclohexenone is usually complete in 2 h at −30 °C (depending on the experimental conditions). In the weakly coordinating solvent Et_2O, the reaction is almost as fast. In the stronger coordinating solvents THF and EtOAc, however, the reaction time is longer (5 h), and the reaction in acetonitrile is so sluggish that it seems no faster than the uncatalysed one. The enantioselectivities vary according to the solvent, but it may be considered that high levels are obtainable in all of these solvents (except acetonitrile).[17] With some ligands, dichloromethane seems more appropriate,[18–20] whereas toluene is the more favoured solvent for others. Recently, Et_2O in combination with Cu carboxylates has been shown to be an excellent solvent for higher enantioselectivities.[17]

It should be concluded that toluene, dichloromethane and Et_2O are the best choices for this reaction.

2.2. The Copper Salt

The copper salt is essential for high catalytic activity and high enantioselectivity. There are no examples of the use of chiral copper thiolates for an heterocuprate approach, as is the case in catalysed Grignard reactions. Copper halides are not usually the best choice. For some particular ligands, some isolated examples exhibit better enantioselectivities than the most commonly used $Cu(OTf)_2$ salt. It has been demonstrated that the copper salt alone does catalyse the

reaction, albeit at a very low rate.[16] Addition of 2 equiv. of $ArSO_2NHR$ per CuCN strongly accelerates the rate of the reaction.[11b,11c] Similarly, addition of 2 equiv. of a trivalent phosphorus ligand per $Cu(OTf)_2$ allows the reaction to go to completion in a very short time.[16]

Both Cu^I and Cu^{II} salts have been used equally successfully (Scheme 3). Cu^I triflate, for example, has been extensively tested, and shows catalytic activity equal to that of Cu^{II} triflate. Some authors report higher enantioselectivity, but most often Cu^{II} triflate is better and more convenient. Indeed, Cu^I triflate is very sensitive to oxidation and should be handled with care.[21−24] This is not the case with Cu^{II} triflate, which is easily handled in the open air. It should be pointed out that the Cu^{II} salt is reduced in situ to the Cu^I salt, which is the true catalytic species. This reduction is effected by the dialkylzinc reagent and not by the phosphorus ligand.

CuCl	CuCN
CuBr	CuSPh
$CuBr \cdot Me_2S$	$[(CuOTf)_2 \cdot benzene]$
CuI	$Cu(OTf)_2$
$CuCl_2$	CuOAc
$CuBr_2$	$Cu(OAc)_2$
$CuSO_4$	$Cu(OAc)_2 \cdot H_2O$
$CuSO_4 \cdot 5H_2O$	$Cu(acac)_2$
$Cu(ClO_4)_2 \cdot 6H_2O$	$Cu(trifluoroacetonyl\ acetate)_2$
$Cu(BF_4)_2 \cdot 6H_2O$	$Cu(cyclohexanebutyrate)_2$
$CuBF_4 \cdot 4CH_3CN$	$Cu(2\text{-}ethylhexanoate)_2$
$Cu(SbF_6)_2$	$Cu(naphthenate)_2$
$CuPF_6 \cdot 4CH_3CN$	Cu-thiophene-2-carboxylate

Scheme 3

An important aspect was consideration of the Lewis acidity of the copper salt, believed to explain the higher catalytic activity of $Cu(OTf)_2$ over copper halides. Another indication of the higher effectiveness of Lewis acidic Cu salts was shown by the use of $Cu(SbF_6)_2$, which gives slightly higher enantioselectivity than $Cu(OTf)_2$.[25] However, addition of $Zn(OTf)_2$ to the reaction mixture did not show any acceleration.[26] In addition, the high effectiveness of copper carboxylates [even better than $Cu(OTf)_2$] points to the lipophilicity of the Cu salt. Among Cu carboxylates, the best enantioselectivities and reaction rates are found with copper thiophene-2-carboxylate (CuTC) and copper naphthenates, the latter being quite soluble in organic solvents.[17]

Another aspect was the water content of the Cu salt. It has been reported that improved enantioselectivities can in some cases be attained by addition of small amounts of H_2O to the reaction mixture.[27] Although this is not general, it could explain the better *ee* values obtained with $Cu(OAc)_2 \cdot H_2O$ than with $Cu(OAc)_2$ alone.[17] The small quantity of water (0.5−10%) is neutralised by an equivalent excess of dialkylzinc.

To conclude, although $Cu(OTf)_2$ is the copper source most widely used, $Cu(OAc)_2 \cdot H_2O$, CuTC, or Cu naphthenate are better choices, the last of these also being the least expensive organic copper salt.[17]

2.3. The Chiral Ligand

The chiral ligand is the centrepiece of this reaction, the degree of enantioselectivity being entirely due to it. The exponential growth of articles on this topic is mainly due to chiral phosphorus ligands. Other ligands, such as sulfonamides or bis(oxazolines), have been studied, however, with the latter being more efficient.

2.3.1. Phosphorus Ligands

Phosphorus ligands are by far the most widely used chiral source. Together with the use of dialkylzinc reagent, it is this combination that has made this enantioselective methodology so successful. Any source of trivalent phosphorus ligands (phosphanes, phosphites, phosphoramidites, phosphonites) strongly accelerates the reaction.[16] The phosphorus ligand may be monodentate or bidentate. The best ratio has been found to be 2 equiv. of P per Cu.[6] Thus, bidentate ligands are usually used in a 1:1 ratio with respect to Cu.[18]

In the catalytic cycle, only 1 equiv. of phosphorus ligand is needed. The second one is replaced by π complexation of the enone to the Cu^I intermediate species. Nonlinear effects have been examined to address this question: slightly positive[27b] or moderately negative[28−30] effects were found, depending on the ligand used. In practice, the ligand/Cu ratio may be lowered to 1.5:1 without loss of enantioselectivity, but lower ratios are usually detrimental. However, the 2:1 ratio has most often been used.

All the ligands reported in the literature are summarized in Figures 1−12, and all substrates are found in the Tabular Survey.

As stated above, phosphane ligands (Figure 1) do accelerate the reaction rate. However, most of the well-known chiral diphosphane ligands give disappointingly low enantioselectivities. The best *ee* values have been found with NORPHOS **L2** and CHIRAPHOS **L6** (both 44% *ee*)[18] and particularly with MiniPHOS **L12**−**14** (up to 97% *ee* on **S16**).[31] Obviously diphosphanes are not adequate for the copper-catalysed conjugate addition. That does not mean that bidentate ligands per se are not suited for this reaction. Bidentate P,N arylphosphane ligands (Figure 2) have been found to be very efficient in this enantioselective conjugate addition. Many ligands of this type have been described, affording high *ee* values, despite the aromatic substitution of the P atom. The N atom is often included in a ring, such as an oxazoline, oxazine, imidazolidine, pyridine or

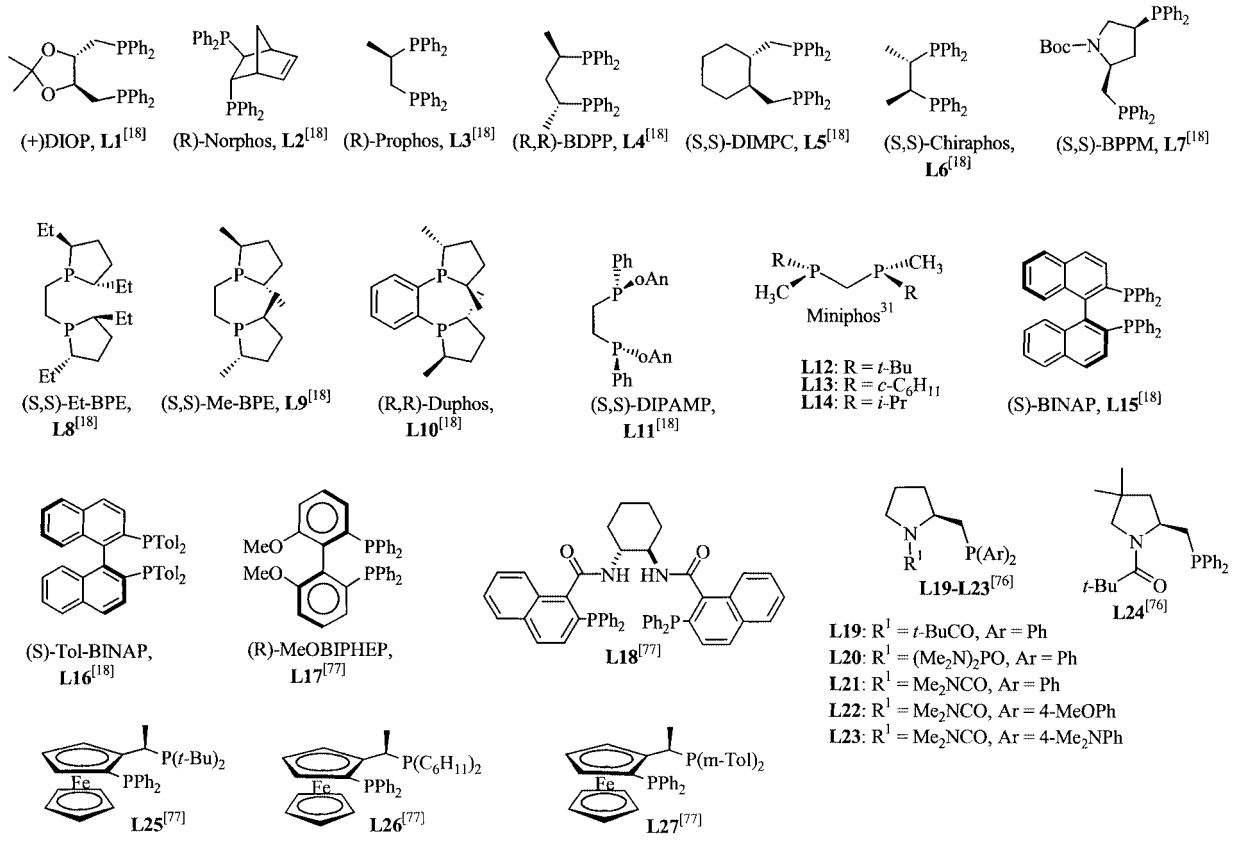
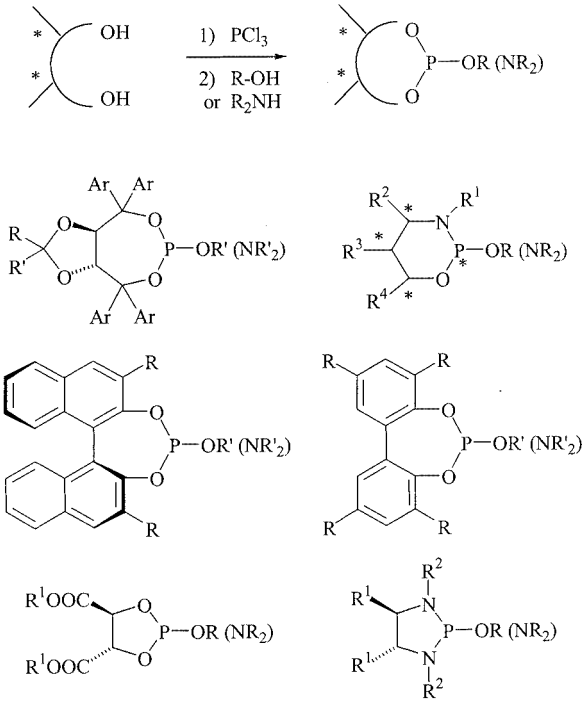


Figure 1. Phosphane-based ligands

imidazole moiety. Tridentate ligands (P,N,N or P,N,S) have also been described. Among the most efficient, we should cite ligands **L33**,[19] **L40**,[20] **L47**[21a] (for cyclic enones) or **L45**[21b] (for acyclic enones), obtained through combinatorial screening.

Phosphinite- (Figure 3) and phosphonite-type ligands (Figure 4) (one carbon atom on P, and two heteroatoms) are scarce. Such ligands bear a TADDOL (**L65**−**71**),[15,32] a binaphthol (**L51**−**60**)[33] or a chiral diamine (**L72**,**73**)[34] unit. The TADDOL-based ligand (R = Ph) **L65** gave the best reported *ee* values with aryl nitro olefins,[32] although its behaviour with cyclic or acyclic enones is poor to moderate.[15] On the other hand, the binaphthol-based phosphonites (R = Ph) **L51** gave poor results with cyclic enones but moderate *ee* values with chalcone.[33] However, the bidentate diphosphonite **L63** (Reetz) was reported to afford a 96% *ee* on cyclohexenone.[35]

By far the most studied ligands are those bearing three heteroatoms around the phosphorus atom: phosphites and phosphoramidites. 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 last case, a matched or mismatched relationship may exist, with different catalytic behaviour for each of the two diastereomeric ligands. Most favoured for the cyclic moiety are C_2-symmetrical diols such as tartrate derivatives, TADDOL-type diols



Scheme 4

or variously substituted binaphthols or biphenols (Scheme 4).

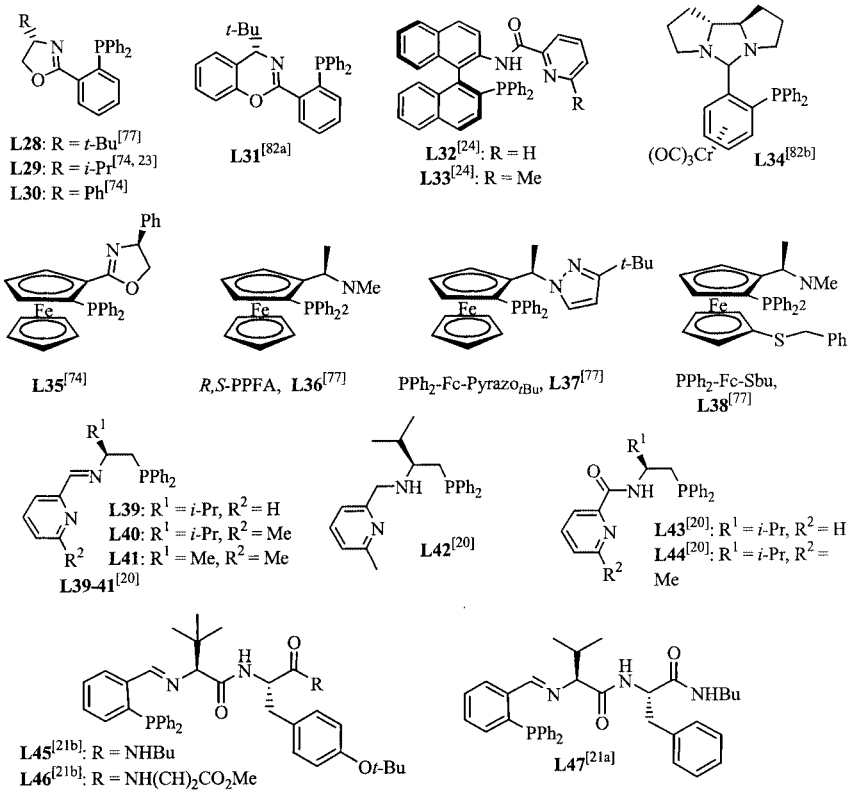


Figure 2. Phosphane P,N ligands

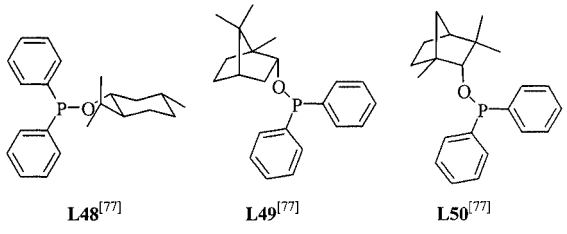


Figure 3. Phosphinite ligands

In tartrate-based ligands the phosphorus atom is incorporated in a five-membered ring (Figure 5). Despite the variety of structures tested, only low to moderate *ee* values have been attained.[36] The best result was obtained with benzalacetone **S27** and the most hindered ligand **L79** (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 incorporate the phosphorus atom in a seven-membered ring (Figure 6). Many ligands of this type have been prepared and tested in the conjugate addition.[15,27a,37] 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 induces low to moderate enantioselectivity on enones (up to 71% *ee* on cyclohexenone).[27a] When an exocyclic chiral alcohol is attached, however, high enantioselectivity has been attainable. With 2-phenylcyclohexanol **L108**, for example, a 96% *ee* was obtained with cyclohexenone **S6**,[15,37] whilst a 73% *ee* − the highest so far reported for these substrates − was obtained with 2-[2-naphthyl]cyclohexanol **L112** and alkylidenemalonates.[38] These ligands with two chiral moieties (the TADDOL part and the exocyclic part) show strong matched/mismatched character. For example, ligand **L108** affords a 96% *ee* with cyclohexenone, whereas its diastereomer **L107** affords a racemic product.[15] Finally, as in the case of phosphanes, bidentate TADDOL ligands with two phosphorus atoms **L121**,**122** are less efficient than monodentate ligands.[39]

Binaphthol-based ligands are the most intensely studied (Figure 7). The chirality of the binaphthol backbone alone is efficient enough to induce high levels of asymmetric induction, particularly on chalcone-type substrates **S21**−**S26** (*ee* values as high as 83%).[25,29] 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.[40] 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.

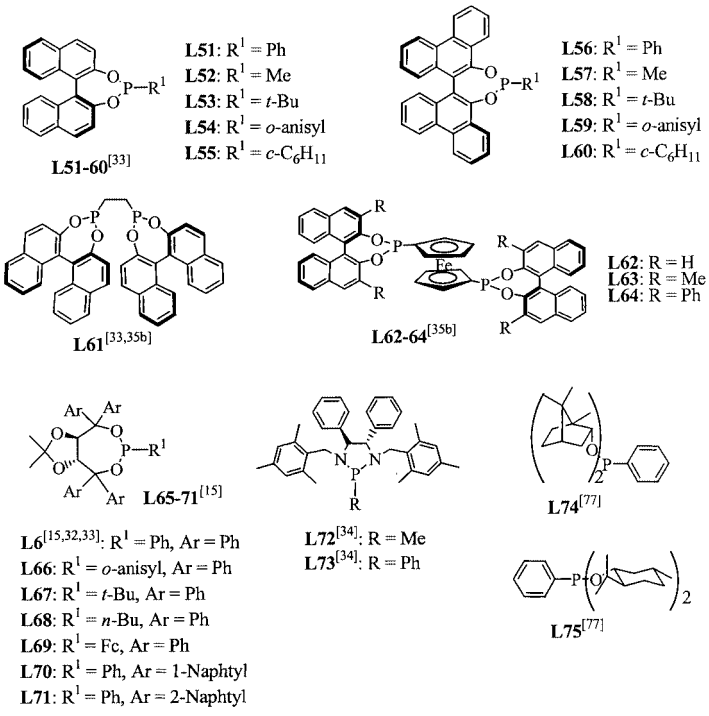


Figure 4. Phosphonite ligands

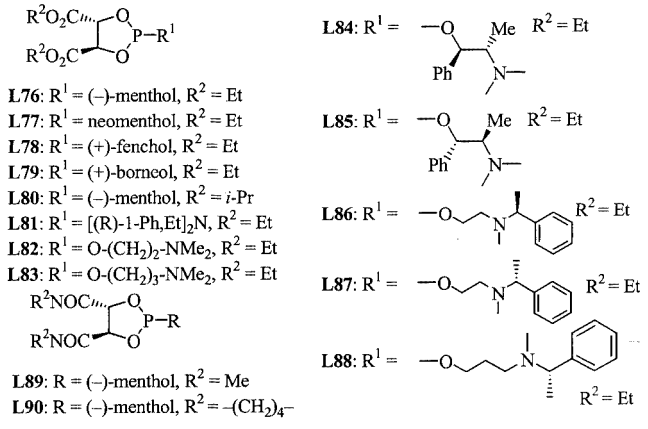


Figure 5. Tartrate-based ligands[36,71]

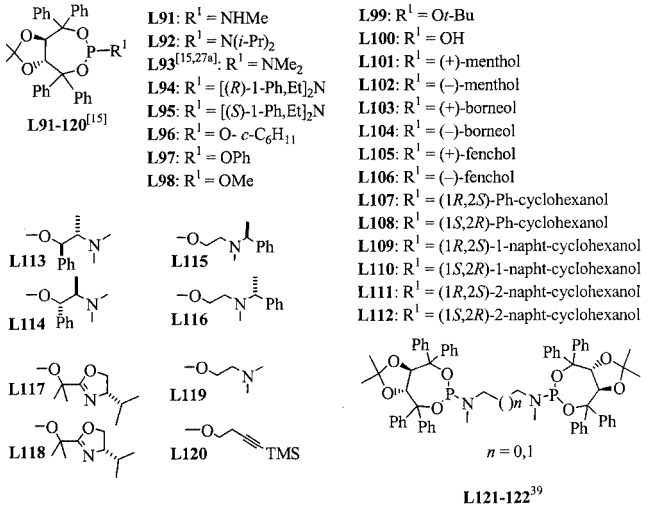


Figure 6. TADDOL-based ligands

For example, ligand **L128**, with a chiral amine attached, has found several applications both on cyclic and on acyclic enones.[40,64,65b] Ligand **L147**,[41] with phenylcyclohexanol in the exocyclic position, gives the highest *ee* value with cyclopentadecenone **S18**, for the synthesis of (*R*)-muscone, a valuable fragrance. Other ligands (**L155**−**173**) may bear an alcohol associated with a chiral oxazoline.[42] These kinds of bidentate ligands perform very well on cyclopentenone **S1**, one of the most demanding substrates (see below). Many variations on these ligands have also been designed by incorporation of *ortho* substituents in the binaphthol part.[29,42] In some cases, such a modification brings higher levels of enantioselectivity. Finally, bidentate ligands with two binaphthol and two phosphorus atoms have been tested (Figure 8).[39,43−45] Excellent enantioselectivities have been attained in some cases (ligand **L186**), particularly on lactone-type substrates.[44]

Biphenol-type ligands are similar to the binaphthol-based ones, but with the advantage of being much less expensive (Figure 9).[17,45−47] Unlike the binaphthol moiety, the biphenol unit is not atropoisomerically stable

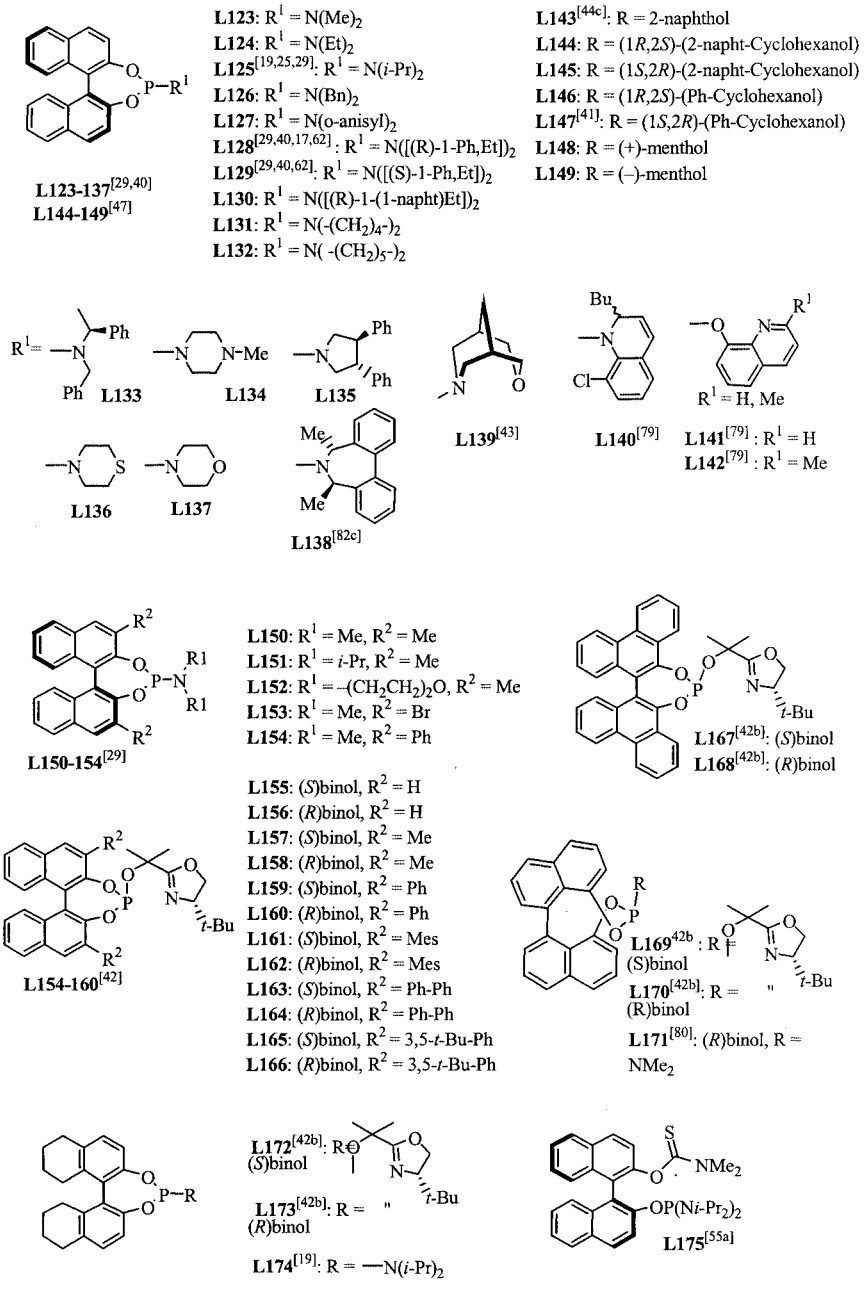
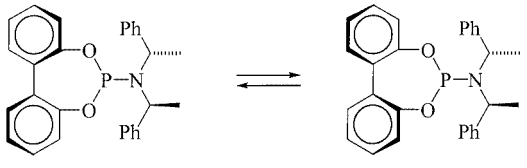


Figure 7. Binaphthol-based ligands



Scheme 5

(Scheme 5). However, the chirality of the exocyclic part induces a favourable atropoisomerism, which in turn controls the enantioselectivity.[47] Thus, the matched/mismatched problem is avoided.

Several ligands of this class have been tested. They afford among the best enantioselectivities (> 99% *ee*) on a variety of Michael acceptors, particularly when used with Cu carboxylates and in Et_2O as solvent.[17]

In all the above phosphorus ligands, the P atom was not a stereogenic centre. Only a few examples of ligands in which P is a stereogenic centre have been described, and the P atom in such cases is always incorporated in a ring (see **L252** for example, Figure 10).[6,7,27b,48,49] However, the obtained enantioselectivities have been modest at best.

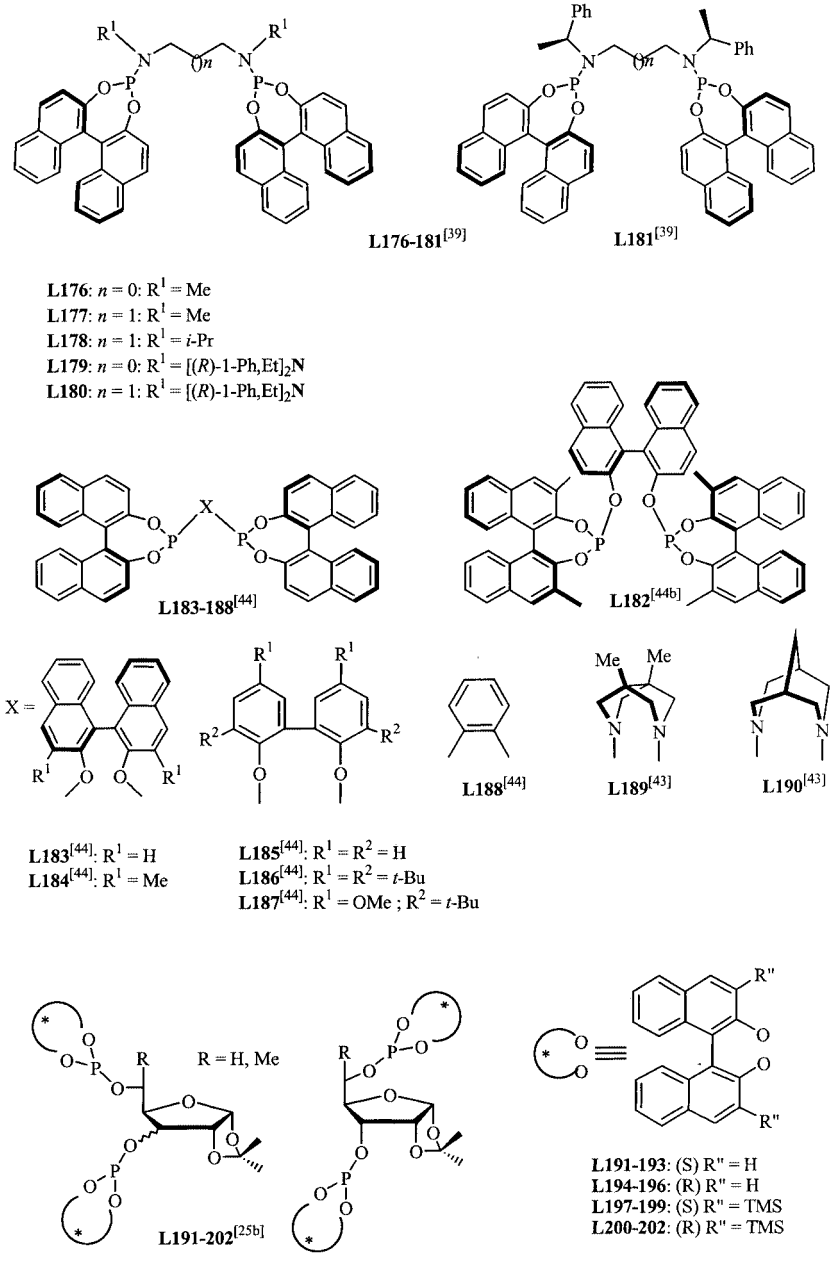


Figure 8. Binaphthol/diphosphorus-based ligands

2.3.2. Other, Non-Phosphorus Ligands

Non-phosphorus ligands have scarcely been used with dialkylzinc reagents, (Figure 11), but new fields of investigation on different classes of ligands are now opening up. Sulfonamides have been reported to accelerate the conjugate addition of dialkylzinc.[11b,11c] Several chiral sulfonamides have been tested with various copper salts.[50−52] The enantioselectivities with cyclic enones and nitro olefins are moderate to good (max. 90% *ee* with **L261**).[22] Similarly, diaminocarbenes are good phosphane-like ligands.[53] Again, the *ee* values are moderate (51% at best, with **L270**).[54] Modified binaphthols (**L272**−**291**)[55,67,68] and sugar-derived ligands (**L292**−**295**)[56] have been tested on cyclic and acyclic enones with moderate success (up to 62% *ee* with **L294**). Finally, chiral heterocyclic ligands (**L296**−**324**) such as thiazolidines (**L296**−**299**),[57] oxazoline (**L300**−**310**)[23] or bis(oxazolines) (**L311**−**323**)[23] should be mentioned. The last class seems very efficient with cyclohexenone (94% *ee*) but behaves poorly with other enones.[58]

2.4. The Michael Acceptor

From the start, the most widely studied substrate for copper-promoted asymmetric conjugate addition has been cyclohexenone **S6**. This enone is very reactive and has the advantage of being cyclic. Thus, the problem of *s-cis* and *s-*

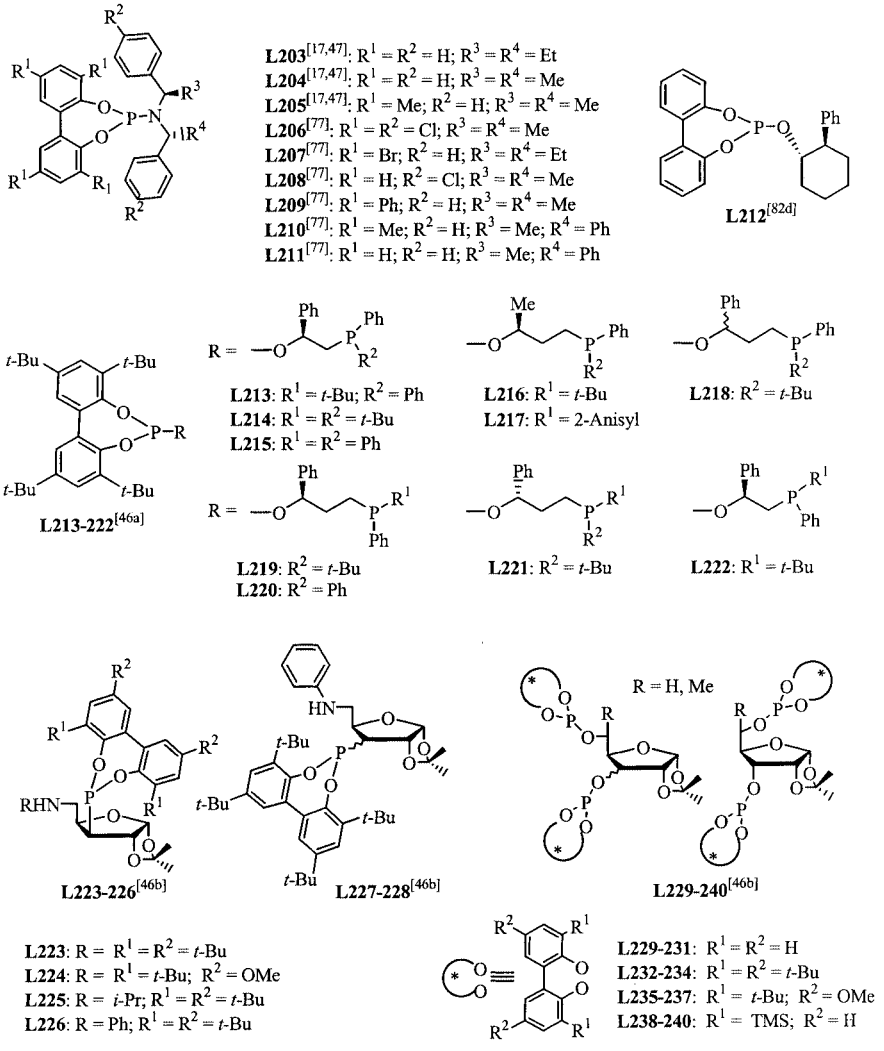


Figure 9. Biphenol-based ligands

Scheme 6

trans conformational interconversion (Scheme 6) is avoided. In many articles, this is the only enone screened against several ligands. However, not all enones behave similarly, to say nothing of other Michael acceptors. The Tabular Survey summarizes all the substrates tested in the literature, with the best enantioselectivities.

2.4.1. Cyclic Enones

In the cyclic enone series, cyclopentenone **S1** 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 conjugate adduct. The enantioselectivity may also be altered by kinetic resolution during this process. 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 with the same ligand. However, very good enantioselectivities have been obtained with specifically designed ligands (**L164**[42b] and **L47**[21a]), or with substituted cyclopentenones, such as **S2**−**4**.[21a,39] The alkylidenecyclopentanone **S5** has been reported in one case, with 72−86% *ee*.[55b] In this case, the *s-cis* conformation is secured by its structure.

Cycloheptenone **S16** and cyclooctenone **S17**, when tested, gave levels of enantioselectivity similar to those found with cyclohexenone. Dienones such as cycloheptadienone **S15**, as well as substituted cyclohexadienones **S12**−**14**, reacted smoothly to give high *ee* values. Cyclopentadecenone **S18**, the precursor of muscone, is a large enough ring to allow *s-cis* and *s-trans* conformational interconversion, and so is discussed with the acyclic substrates.[41]

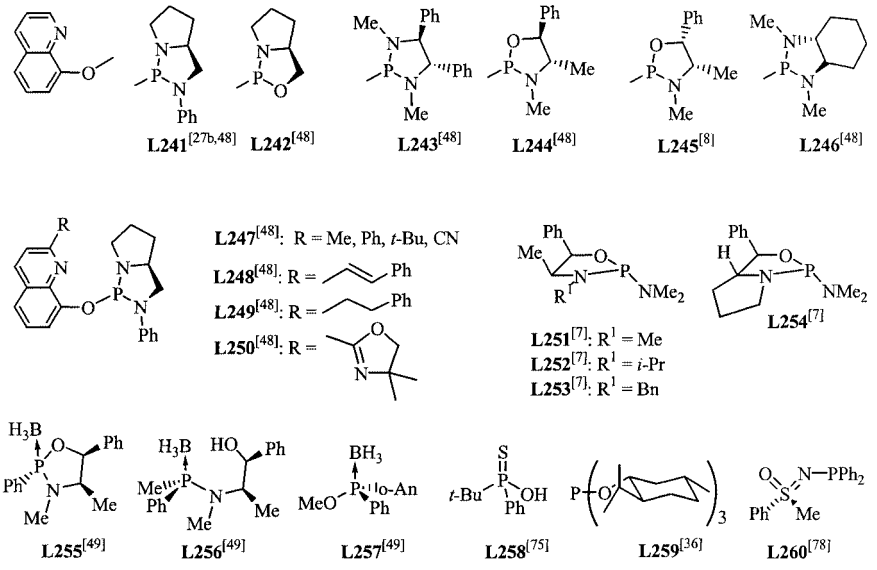


Figure 10. Various phosphorus ligands

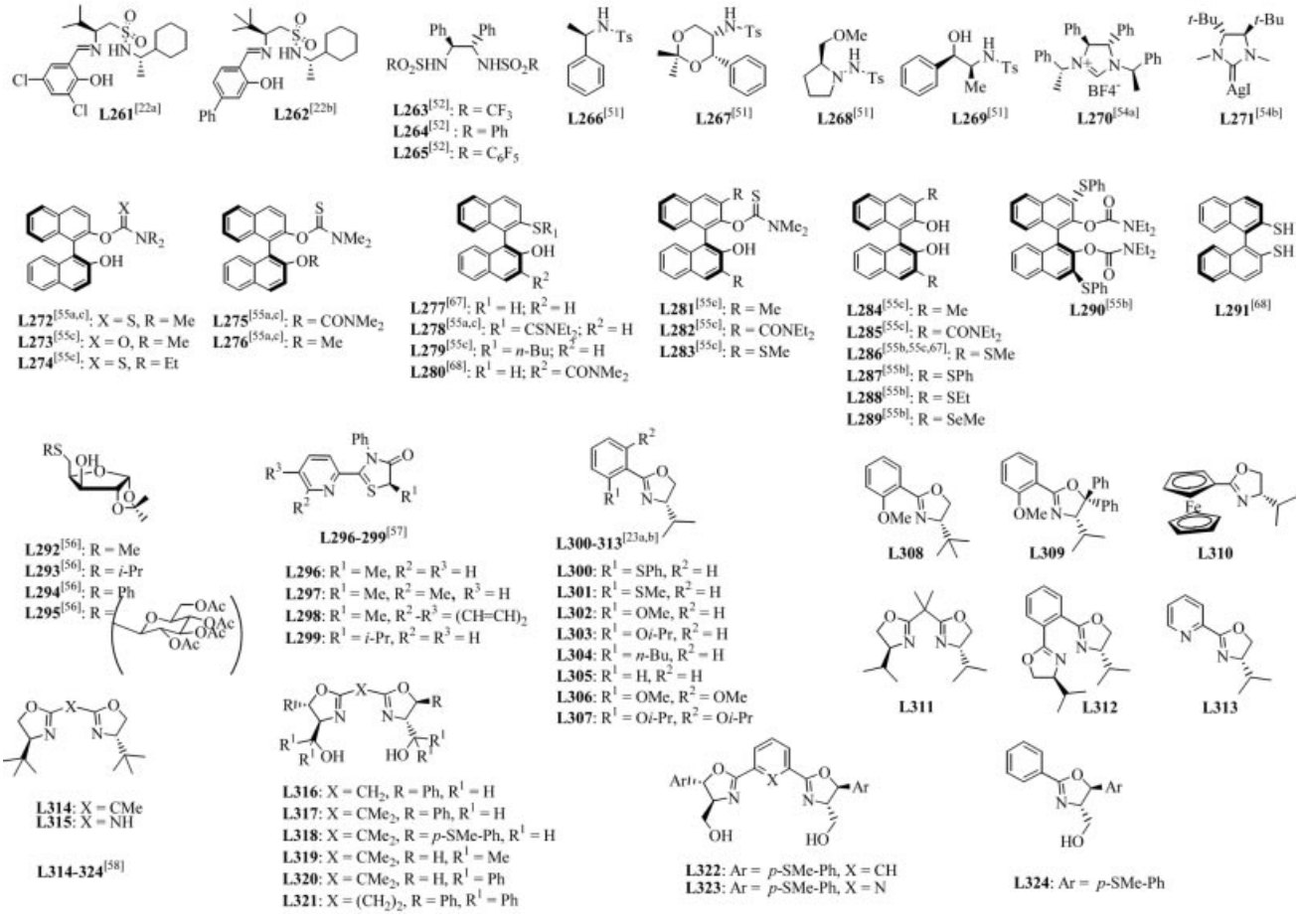


Figure 11. Various ligands without P

Other cyclohexenones substituted in the 4- or 5-position and without stereogenic centres, such as **S9**−**11**, gave high *ee* values (84−98%).[59−60] Substrates **S7** and **S8**, with stereogenic centres, give rise to kinetic resolution.[61] At slightly over 50% conversion, **S7** affords conjugate adducts with > 99% *ee*,[61] whereas **S8** affords lower *ee* values (85% at best). Excellent kinetic resolutions were also obtained with dienones **S13**.

In summary, small-ring cyclic enones appear to be among the best substrates in terms of enantioselectivities.

2.4.2. Acyclic Enones

Because of *s-cis* and *s-trans* conformational interconversion, acyclic enones are more demanding substrates. The most widely studied structural type is chalcone **S21** and the related substrates **S22**−**26**, bearing two aryl groups. Many ligands afford good enantioselectivities, but only a few are very efficient, the best results being for chalcone itself (96% with **L33**).[19] The Ni-catalysed reaction is also very efficient, but only on chalcone-type substrates.[12]

More generally, alkyl-substituted acyclic enones have been studied much less, although they provide wider structural variation. Good to excellent enantioselectivies were obtainable with phosphites **L145** and **L147**[41] and phosphoramidite ligands (**L128**, **L204**, **L205**).[17] The P,N bidentate ligand **L45** has recently given some excellent results with many acyclic enones.[21b]

A particular case is that offered by cyclopentadecenone **S18**, the precursor of muscone. As mentioned above, the size of the ring allows for *s-cis* and *s-trans* conformational interconversion, and so it behaves like the acyclic enones. The best ligand, for *ee* values of up to 87%, was **L147**.[41] It should be pointed out that the addition of dimethylzinc gives slightly lower enantioselectivity.

2.4.3. Other Michael Acceptors

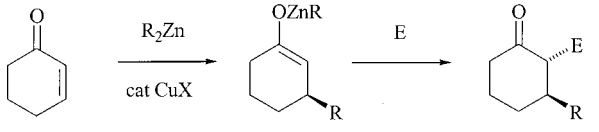
As well as enones, other Michael acceptors have also been tested in the enantioselective conjugate addition. These include lactones, nitro olefins, and alkylidenemalonates. The six-membered ethylenic lactone **S20**, structurally related to cyclohexenone, gave up to 92% *ee* with **L185**, whereas the five-membered **S19** gave only 56% *ee*.[44a] Several structurally different nitro olefins have been tested with various ligands. Phosphonite ligand **L65** seems very efficient for nitroalkenes **S34**−**37**,[32] bearing aromatic substituents, whereas phosphoramidite ligands and **L128**[17,62] are more efficient with the alkyl-substituted **S38**−**39** and the cyclic **S40**−**41**. Finally, alkylidenemalonates are also excellent substrates. However, the enantioselectivities are good to moderate **(L112)**, due to the high rate of the uncatalysed reaction.[38]

2.5. The Dialkylzinc Reagent

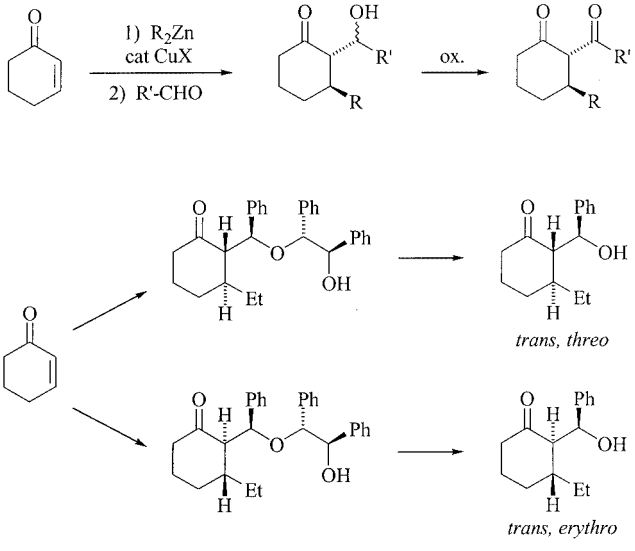
Only a few dialkylzinc reagents (Me_2Zn, Et_2Zn, Bu_2Zn, Ph_2Zn) are commercially available, but the most widely used is diethylzinc. Dibutylzinc usually affords similar results to diethylzinc. Dimethylzinc has seldom been used; it is 10 times less reactive and the reaction temperature is usually higher, with longer reaction times. The enantioselectivities are fairly similar to those obtained with diethylzinc, sometimes slightly lower. Although diphenylzinc is known to undergo copper-catalysed conjugate addition,[11b] only one enantioselective example has been reported (74% *ee* with cyclohexenone with **L317**[58]). Other diorganozinc reagents have been also used with degrees of success equivalent to those obtained with diethylzinc. Thus, diisopropylzinc affords high enantioselectivities,[21a,21b,40] as do reagents bearing an ester or acetal functionality.[21a,40,42a,42b] Indeed, one of the major advantages of dialkylzinc reagents is their functional compatibility. These functionalized reagents may be prepared by RI/Et_2Zn exchange or by a hydroboration/transmetallation sequence.[63] This variation of the diorganozinc reagent allows for high synthetic versatility.

2.6. Reactions of Zinc Enolates

All conjugate additions result in the formation of enantioenriched zinc enolates. When this zinc enolate is quenched with an electrophile (other than water), more elaborated synthons may be accessed (Scheme 7).



Scheme 7



Scheme 8

The reactivity of pure zinc enolates (without additional salts) has not previously been studied. However, some reactions were found to occur readily with the homochiral zinc enolate resulting from the conjugate addition. Thus, alkylations have been performed with alkyl halides (tenfold excess and 10 equiv. HMPA as additive),[21a,21b] and allylations with allyl acetate and Pd catalysis.[11b,11c,62] Both afford the *trans* diastereomer. The reaction with aldehydes gives the aldol adduct, albeit with low stereoselectivity. Oxidation of the alcohol allows the obtention of a single diketone.[11b,11c,27a,39,65] A fully controlled aldol reaction (*syn* or *anti*) may be obtained through the use of chiral acetals and a Lewis acid (Scheme 8).[66] Orthoesters react similarly.[66]

3. Triorganoaluminium Reagents

In analogy with dialkylzinc reagents, some attempts have been made with trialkylaluminium reagents, particularly with Me_3Al. These reagents react better in THF as solvent. The chiral ligand may be an oxazoline (**L300−313**),[23a,23b] a thioether (**L277−280**, **291−295**)[30,56,65,68] or a phosphite **L112**.[38] The substrates were cyclic or acyclic enones, as well as alkylidenemalonates. Recent results show that Me_3Al affords among the best *ee* values on acyclic enones with **L292−294**.[83] This interesting variation of the organometallic reagent allows for potential use of other structural types of R group.

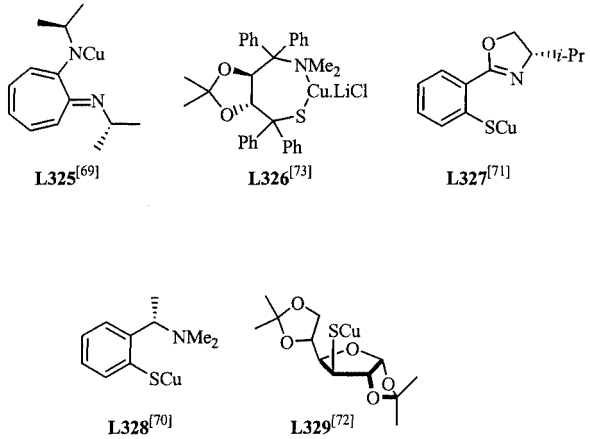
4. Grignard Reagents

Historically, Grignard reagents were the first species to be tested in enantioselective conjugate additions.[3a] Most work has been directed on the use of chiral stoichiometric heterocuprates, using easily available chiral alcohols, amines, or thiols. Successful catalytic reactions were first reported with the chiral amide **L325**,[69] and then with several copper thiolates (**L326−329**).[70−73] External chiral ligands, all of them bearing a phosphorus atom, have been introduced only in the last decade.[49,74−76] One of the main problems associated with Grignard reagents is the control of the Schlenk equilibrium, which affects the true nature of the reactive species.

The solvent in Grignard additions has most often been diethyl ether. THF has also been used, mainly in reactions involving a heterocuprate approach. Several additives, such as HMPA, LiBr, or silyl halides or triflates, may improve the enantioselectivity.

The copper source in the heterocuprate approach is the chiral copper thiolate. When an external ligand has been used, CuI, CuBr, and CuCN have been the most usual copper salts. There is no general trend, as seen with dialkyl zincs. It should be pointed out that the catalyst loading is usually much higher, varying from 5 to 25%.

In the heterocuprate approach (Figure 12), the chiral source is a structurally variable thiol. It always bears additional heteroatoms, to allow better coordination of the organometallic cluster. One example with a chiral amide has also been described,[69] as has one with a thiophosphinic acid.[75] In the external ligand approach, two classes of ligands have been extensively studied. These derive either from proline (**L19−24**)[76] or from chiral ferrocenes (**L35**).[74] The enantioselectivities with cyclohexenone may reach up to 92% with 8% CuI and 32% ligand loading.



L325[69] **L326**[73] **L327**[71]

L328[70] **L329**[72]

Figure 12. Heterocuprate-based ligands

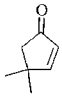
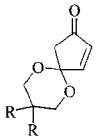
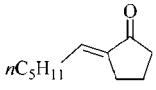
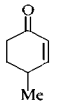
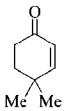
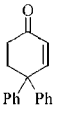
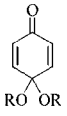
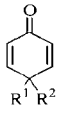
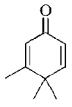
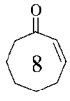
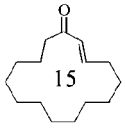
The substrates tested with Grignard reagents have mainly been cyclic enones. Addition to cyclopentenone usually affords better chemical yields than with dialkylzinc reagents. Some acyclic substrates have also been tested, most often chalcone **S21** and benzalacetone **S27**. Lactone **S20** afforded a 91% *ee* with **L21**.[76]

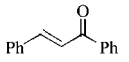
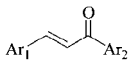
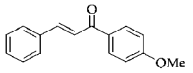
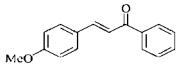
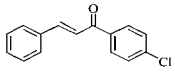
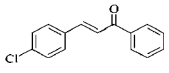
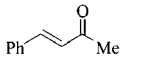
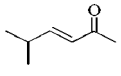
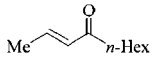
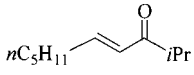
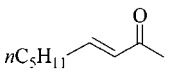
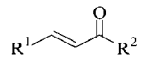
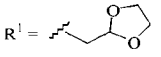
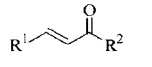
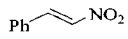
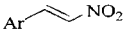
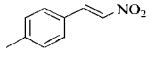
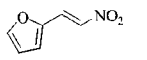
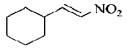
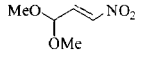
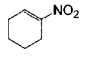
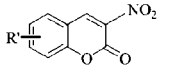
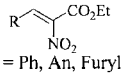
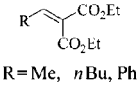
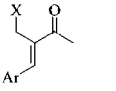
All types of Grignard reagents − Me, Bu, Hex, *i*Pr, *t*Bu, Ph, vinyl etc. − have been represented with variable success. Trapping of the magnesium enolate with reagents other than water has not been reported.

5. Conclusion and Perspectives

The asymmetric conjugate addition has a long historical background. Although Grignard reagents were the first species to be used, the success of this copper-catalysed reaction lies in the breakthrough brought about by the combined use of dialkylzinc reagents and chiral phosphorus ligands. New chiral ligands to improve enantioselectivities with specific classes of substrates are continuously being designed; indeed, there is as yet no ligand of general applicability. It is also important to bring the focus back onto Grignard reagents, as they still are among the cheapest primary organometallic sources. Despite the synthetic advantages of dialkylzinc reagents, their cost and/or commercial availability are limiting factors in large-scale reactions.

Tabular Survey

Substrates		Tabular Survey
	**S1**	L47 (79-98 % ee) ref. [21a] L164 (7-94 % ee) ref. [42b] L181 (83 % ee) ref. [39] L183 (76.6 % ee) ref. [44a]
	**S2**	L47 (>98 % ee) ref. [21a]
	**S3**	L47 (97 % ee) ref. [21a]
 R = Me, Ph	**S4**	L128 (87-97 % + D24) ref. [65b]
	**S5**	L290 (72-86 % ee) ref. [55b]
	**S6**	L22 (92 % ee) ref. [76a] L33 (92 % ee) ref. [24] L47 (98 % ee) ref. [21a] L63 (99 % ee) ref. [35b] L128 (98 % ee) ref. [40] L158 (90 % ee) ref. [42b] L182 (82 % ee) ref. [44b] L183 (90.2 % ee) ref. [44] L203 (99.1 % ee) ref. [17,47] L317 (94 % ee) ref. [58]
 R = Me, *i* Pr, Ph, TMS	**S7**	L128 (12-99 % ee) ref. [61]
	**S8**	L128 (10-85 % ee) ref. [61]
	**S9**	L128 (98 % ee) ref. [40] L174 (88 % ee) ref. [19]
	**S10**	L128 (98 % ee) ref. [40]
	**S11**	L128 (84-88 % ee) ref. [40]
 R = Me, Et R = -(CH$_2$)$_2$ R = -(CH$_2$)$_3$ R = -CH$_2$C(Me)$_2$CH$_2$	**S12**	L128 (85-99 % ee) ref. [40]
 R^1 = OMe; R^2 = Me R^1 = OMe; R^2 = CH$_2$Ph R^1 = R^2 = -(CH$_2$CH$_2$CH$_2$O)- R^1 = OMe; R^2 = OCH$_2$Ph R^1 = R^2 = Ph	**S13**	L128 (65-98 % ee) ref. [40]
	**S14**	L306 (68 % cc) ref. [23]
	**S15**	L128 (>99 % ee) ref. [59]
	**S16**	L12 (97 % ee) ref. [31] L21 (83 % ee) ref. [76] L47 (62-98 % ee) ref. [21a] L62 (93 % ee) ref. [35b] L128 (>98 % ee) ref. [40] L167 (94 % ee) ref. [42b] L190 (82 % ee) ref. [43a] L261 (81 % ee) ref. [22a]
	**S17**	L128 (97 % ee) ref. [40]
	**S18**	L147 (87 % ee) ref. [41]
	**S19**	L186 (56 % ee) ref. [44]
	**S20**	L21 (91 % ee) ref. [76] L63 (88 % ee) ref. [35b] L186 (92 % ee) ref. [44]

	**S21**	L12 (71 % ee) ref. [31] L33 (96 % ee) ref. [24] L62 (71 % ee) ref. [35b] L125 (89 % ee) ref. [29] L139 (58-82 % ee) ref. [43]
	**S22**	L125 (15-89 % ee) ref. [29]
Ar_1 = Furyl , Ar_2 = 2'Me-Furyl Ar_1 = thienyl , Ar_2 = thienyl Ar_1 = C(O)thienyl , Ar_2 = thienyl Ar_1 = Ph , Ar_2 = pyr. Ar_1 = Ph , Ar_2 = *p*-NO_2-C_6H_4 Ar_1 = *p*-Br-C_6H_4 , Ar_2 = *p*-Br-C_6H_4		
	**S23**	L33 (97 % ee) ref. [24] L125 (80 % ee) ref. [29]
	**S24**	L33 (98 % ee) ref. [24] L45 (94 % ee) ref. [21b] L125 (70 % ee) ref. [29]
	**S25**	L33 (95 % ee) ref. [24] L125 (75 % ee) ref. [29]
	**S26**	L33 (95 % ee) ref. [24] L125 (88 % ee) ref. [29]
	**S27**	L33 (90 % ee) ref. [24] L45 (93 % ee) ref. [21b] L165 (87 % ee) ref. [42b] L205 (93 % ee) ref. [17]
	**S28**	L33 (86 % ee) ref. [24] L45 (91 % ee) ref. [21b] L128 (80 % ee) ref. [17] L290 (77 % ee) ref. [55b]
	**S29**	L45 (90 % ee) ref. [21b] L128 (92 % ee) ref. [47]
	**S30**	L45 (90 % ee) ref. [21b] L290 (39 % ee) ref. [55b]
	**S31**	L45 (95 % ee) ref. [21b] L204 (81 % ee) ref. [17] L286 (77 % ee) ref. [55c]
	**S32**	L290 (18-79 % ee) ref. [55b]
R^1 = nC_5H_{11}, R^2 = CH_2OMe R^1 = CH_2-*i*Pr, R^2 = Me R^1 = $CH(OMe)_2$, R^2 = Me R^1 = $CH_2CH(OEt)_2$, R^2 = Me R^1 = $CH_2CH_2CH(OEt)_2$, R^2 = Me R^1 =  , R^2 = Me		
	**S33**	L45 (58-92 % ee) ref. [21b]
R^1 = $(CH_2)_3OAc$, R^2 = Me R^1 = nC_5H_{11}, R^2 = *t*Bu R^1 = *p*-NO_2-C_6H_4, R^2 = Me R^1 = *p*-CF_3-C_6H_4, R^2 = Me		
	**S34**	L65 (82 % ee) ref. [32] L128 (48 % ee) ref. [51] L205 (82 % ee) ref. [17] L262 (54 % ee) ref. [22b]
	**S35**	L262 (23-57 % ee) ref. [22b]
Ar = -OMe-C_6H_4, Thienyl, *o*-OMe-C_6H_4, Mesityl		
	**S36**	L65 (86 % ee) ref. [32] L262 (52 % ee) ref. [22b]
	**S37**	L65 (78 % ee) ref. [32]
	**S38**	L128 (94 % ee) ref. [32]
	**S39**	L128 (86 % ee) ref. [51]
	**S40**	L205 (95 % ee) ref. [17]
	**S41**	L128 (30-92 % ee) ref. [81]
R' = H, 8-OMe, 6-OMe, 6-Br, 6Me		
	**S42**	L128 (2-26 % ee) ref. [81]
R = Ph, An, Furyl		
	**S43**	L112 (64-73 % ee) ref. [38]
R = Me, *n*Bu, Ph		
	**S44**	L286 (2-64 % ee) ref. [67]
Ar = Ph, 4-NO_2-C_6H_4, 4-Cl-C_6H_4 Ar = 4-Me-C_6H_4, 1-Napht X = Br, Cl, OCHO, OSO_2Me		

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