Asymmetric catalysis for the construction of quaternary carbon centres: nucleophilic addition on ketones and ketimines

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There is a growing need in organic synthesis for efficient methodologies for the asymmetric synthesis of quaternary carbon centres. One of the most attractive and straightforward methods focuses on the use of asymmetric catalysis for the addition of various types of nucleophiles on prochiral ketones and ketimines. A view of the literature from this growing area of research will be presented in this review, with an emphasis on the pioneer works and milestones brought by the main players in this field.

Introduction

One of the major challenges in organic methodology focuses on the enantioselective construction of quaternary carbon centres. Indeed, there is a growing need for efficient methods as there are many examples of naturally occurring and pharmaceutical drugs (such as Efavirenz and Tripanavir, two enzyme inhibitors used in the treatment of AIDS) that display one or more tetrasubstituted centres in their structures (Fig. 1).

This need for new methodologies has already been well-fulfilled by many groups of chemists through the applications of classical reactions such as the Diels–Alder reaction, the Heck reaction or palladium catalyzed allylic alkylation.[1] One straightforward access to chiral quaternary centres that adds nicely to the existing methods relies on the asymmetric addition of nucleophiles on ketones and ketimines and will be described here. However, the goal of this article is not to review the full literature of this area of research, but to highlight the concepts, milestones and most efficient methods developed over recent years.

The nucleophilic addition of organometallic reagents on ketones has always been a major challenge in organic synthesis methodology as this class of substrates suffers from many drawbacks such as the poor electrophilic character of the carbonyl group. Furthermore, competitive enolisation and reduction of the ketones are often encountered as main side reactions, especially in the case of sterically hindered substrates. The problem becomes even more challenging when chirality has to be introduced as the binding properties of ketones to the Lewis acidic atom of the

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Olivier Riant (born in Boulogne Billancourt, France, in 1964) graduated in 1989 from the Ecole Normale Supérieure de Saint-Cloud Lyon. He carried out a PhD under the supervision of Professor Henri B. Kagan at Université Paris-Sud and earned his PhD degree in 1992 before starting post-doctoral research at Imperial College (London, UK) with Professor Susan Thomas. He was appointed as a CNRS fellow researcher in 1994 at Université Paris-Sud, followed by a new professorship position in Louvain la Neuve in 2000. His research interests focus on various aspects of asymmetric catalysis, including the use of chiral metal hydrides in asymmetric reduction and C–C bond formation, the use of low valent chiral metal complexes in asymmetric redox catalysis and the design of new chiral ligands for various applications in asymmetric catalysed transformations.

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Jérôme Hannedouche

Jérôme Hannedouche was born 1976 in the North of France. After studying chemistry at the Université des Sciences et Technologies de Lille (France), he undertook a PhD degree at the University of Warwick (UK) under the supervision of Professor Martin Wills. In 2003, he completed his PhD on the development of new ruthenium(II) catalysts for asymmetric transfer hydrogenation of ketones. After 2 years of post-doctoral training with Professor O. Riant (Université catholique de Louvain, Belgium), he joined the CNRS as Chargé de Recherches in October 2006 and was appointed at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (Université Paris-Sud) in the group of Professor J.-C. Fiaud. His research interests lie in the development of novel synthetic methodologies in asymmetric catalysis, mainly for C–N bond formation via *asymmetric hydroamination reaction.*

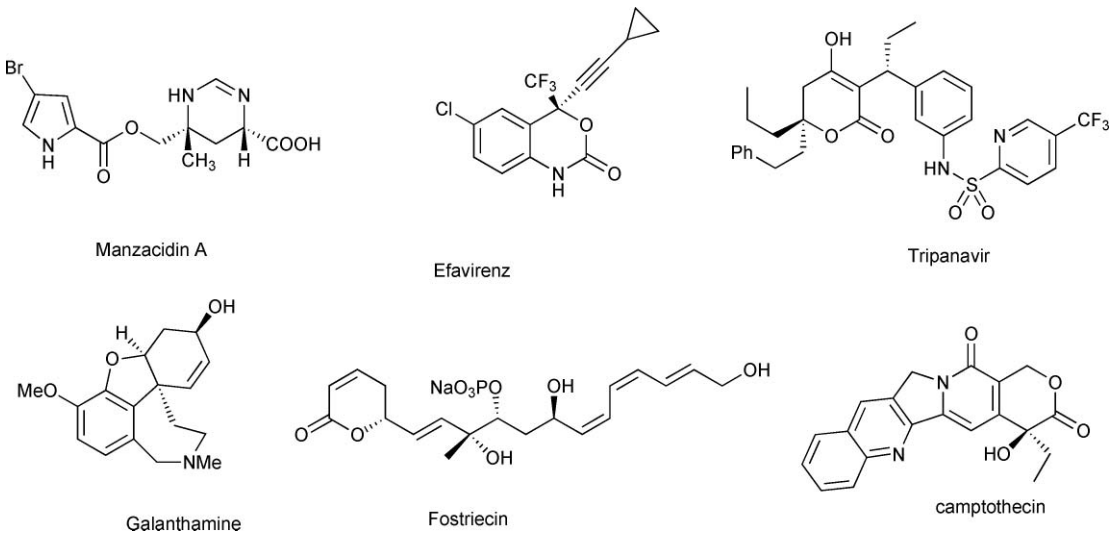


Fig. 1 Selected examples of molecules (naturally occurring and artificial) bearing a chiral quaternary centre.

organometallic reagent are usually poor, and also by the fact that discrimination between the two prochiral faces of the carbonyl is made more challenging due to the greater similarity of the two substituting groups on the carbonyl compared to aldehydes (Fig. 2).

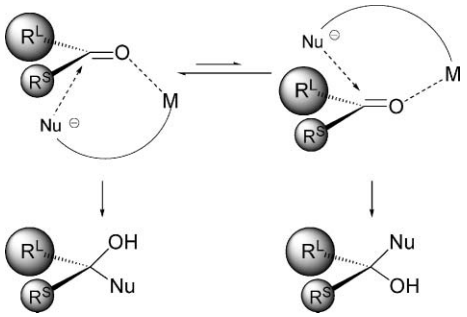
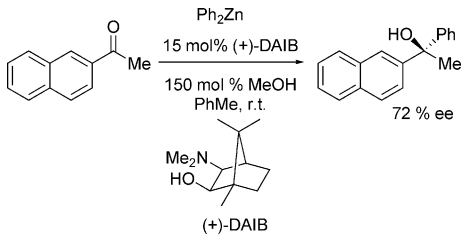


Fig. 2 Schematic representation of the addition of a nucleophile on the prochiral faces of a ketone.

From those basic considerations, it is not surprising to see that although various catalytic systems have been designed during the past 25 years for the enantioselective addition of organometallic reagents on aldehydes, the development of such methodology for the case of ketones and ketimines became an emerging area of research only recently. However, it will be shown that the accumulated experience on the asymmetric addition of organometallic reagents on aldehydes has finally opened new successful routes for the introduction of ketones and ketimine substrates in this class of reactions.

Asymmetric addition of carbon-based organometallic nucleophiles on ketones and ketimines

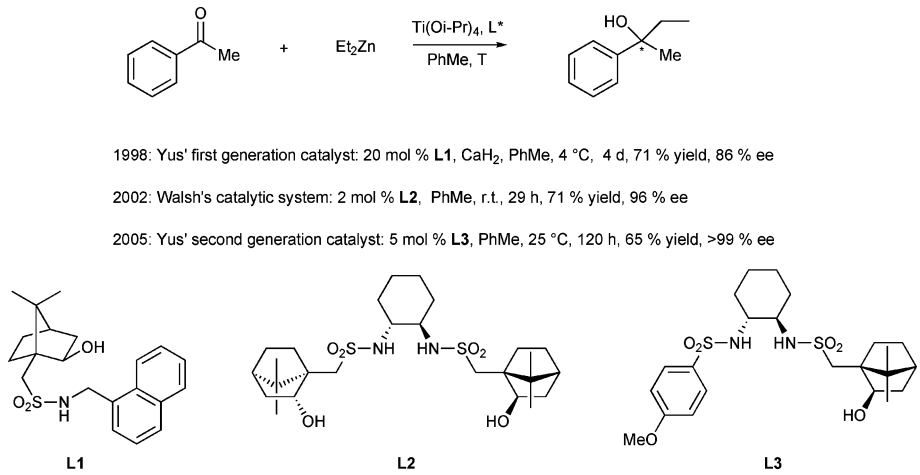
The breakthrough in this area came in 1998 when Dosa and Fu reported the first example of the asymmetric addition of diphenyl zinc to ketones (Scheme 1).[2] The modification of Noyori's catalytic system with an excess of methanol allowed the addition of diphenyl zinc to aromatic and aliphatic ketones with fair to excellent enantioselectivities (up to 91% ee). It was postulated that



Scheme 1 Dosa and Fu's breakthrough in the asymmetric addition of organometallic reagents on ketones.

a mixed aryl alkoxide reagent was formed as the active nucleophile and reacted to the ketone *via* a similar mechanism demonstrated by Noyori in the case of aldehydes.

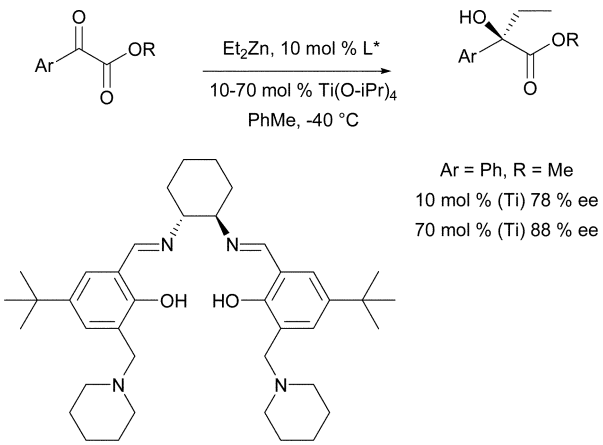
Another milestone in this area was published in the same year by the group of Yus who reported the first addition of dialkylzinc reagents to ketones promoted by a hydroxysulfonamide–titanium catalyst.[3] This type of titanium-based catalyst was also already well-known for the asymmetric addition of diorganozinc reagents to aldehydes but a careful optimisation of the structure of the chiral ligand and the reaction parameters allowed enantioselectivities over 90% ee on model ketones to be reached (Scheme 2). A catalytic cycle based on similar catalytic systems designed for aldehydes was proposed in the initial report and relies on the formation of an alkyl dititanium as the active species, one titanium acting as a Lewis acid to bind the ketone and the second bearing the alkyl group to be transferred on the carbonyl. This first generation of catalytic system soon inspired other groups for the design of improved ligands and the major amelioration was reported in 2002 by the group of Walsh[4] and in 2005 by the group of Yus.[5] The most successful ligand **L2** was designed in order to bring an increased constrained geometry and showed in most cases improved reactivity as the ligand loading could be reduced down to 2 mol% while retaining high enantioselectivity for the addition of diorganozinc reagents to ketones. This bissulfonamide structure was also used by Yus and co-workers to study various chiral ligands,[5,6] which finally gave an optimised second generation catalyst with ee's >90% for the alkylation reaction. The latter



Scheme 2 Asymmetric alkylation of ketones with diethylzinc developed by the groups of Yus and Walsh.

was also successfully applied to the asymmetric vinylation and phenylation of ketones.

The concept of bifunctional catalysis[34] developed by Noyori *et al.* for the enantioselective addition of dialkylzinc to aldehydes was used by the group of Kozlowski for the design of new ligands for the asymmetric addition of diethylzinc to α-ketoesters (Scheme 3).[7] The new salen ligand bearing amines as pendants were used in combination with titanium(IV) isopropoxide to generate a titanium salen complex which is postulated to act as a Lewis acid for the activation of the ketone while the amine pendant would activate the organometallic nucleophile. Good enantioselectivities were obtained for a range of α-ketoesters and it was also noticed that the use of an excess of titanium isopropoxide (70 mol%) allowed an increase in the ee's in most cases. This notion of multimetallic catalysis for the asymmetric addition of diorganozinc to α-ketoesters was also used by the groups of Shibasaki,[8] Pedro[9] and Hoveyda[10] using the following chiral ligands (Fig. 3).



Scheme 3 Kozlowski's conception of chiral bifunctional ligands.

Only one example of the asymmetric alkylation of ketimine has been reported and it is based on the use of a family of diphosphine mono oxide–copper catalysts developed by the group of Charette (Scheme 4).[11] The catalytic system previously used for the enantioselective addition of diorganozinc reagents on activated

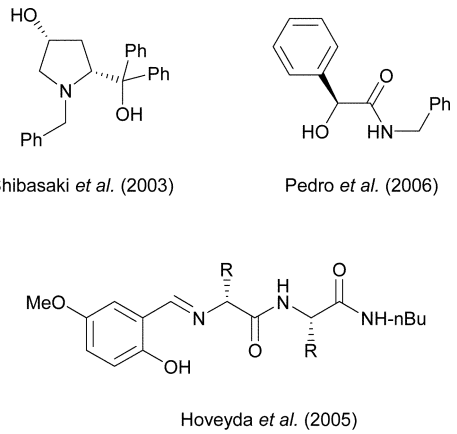
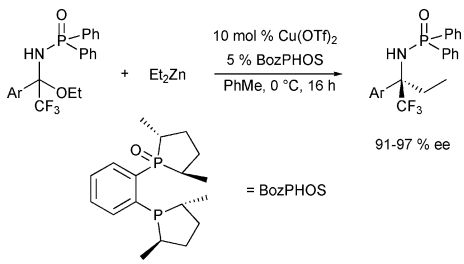


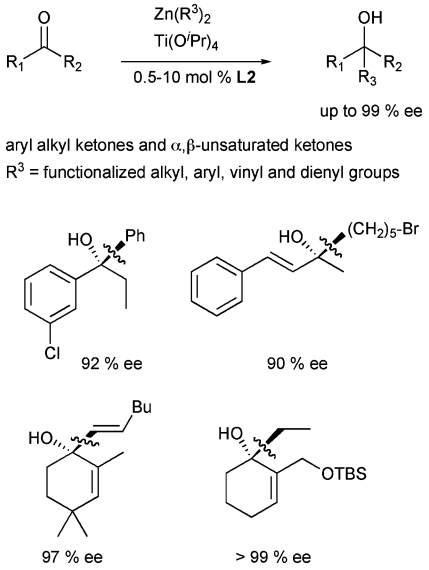
Fig. 3 Chiral ligands developed for enantioselective alkylation of ketones.



Scheme 4 Charette's asymmetric alkylation of trifluoromethyl ketimines with diethylzinc.

aldimines[12] did not give any addition products when it was tested on simple aryl methyl ketimines. However, the more reactive trifluoromethyl ketimines bearing a diphenylphosphinoyl group, generated *in situ* from the corresponding ethoxy hemiaminal, gave the corresponding addition adducts with high enantioselectivities.

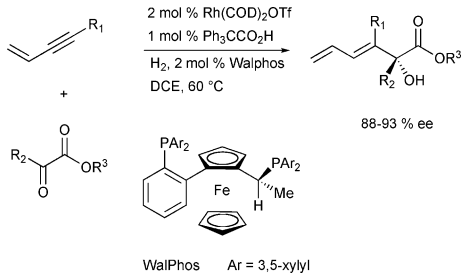
Extensive applications of ligand **L2** were also reported by Walsh's group for the asymmetric addition of various classes of carbon-based nucleophiles on ketones.[13] Some representative examples are displayed in Scheme 5. The catalytic system using **L2** is especially reactive toward aryl alkyl ketones and α,β-unsaturated ketones. The range of nucleophile was also extended from simple ethyl and methyl groups to functionalised alkyl groups, aryl,



Scheme 5 Walsh's catalytic method for the asymmetric addition of functionalised organometallics to ketones.

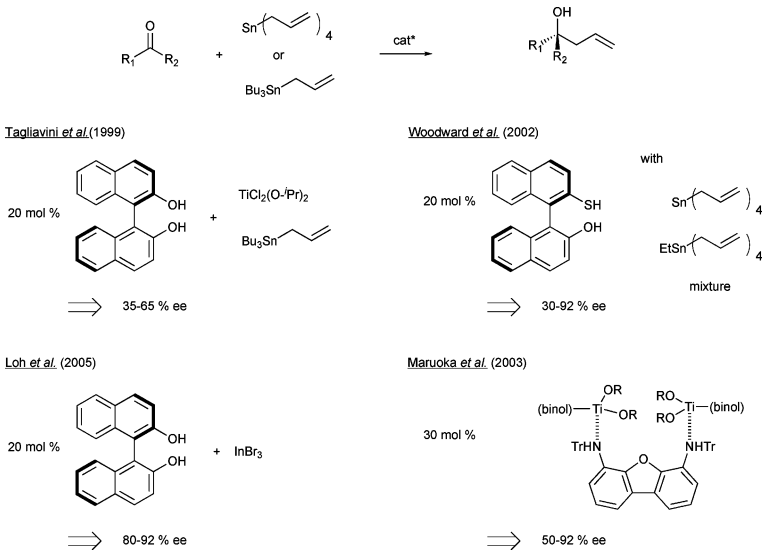
vinyl and dienyl groups with high enantioselectivities. A recent report from the group was focused toward the optimisation of the catalytic systems and showed that concentrated or solvent-free conditions allowed the use of only 1 mol% of the chiral ligand while retaining reasonable reaction times and high enantioselectivities.[13j]

An elegant strategy for the asymmetric rhodium catalyzed dienylation of α-ketoesters was also recently reported by the group of Krische (Scheme 6).[14a] Conjugated enynes are used as pronucleophiles for the introduction of the dienyl group in the presence of a Walphos rhodium(I) catalyst for the hydrogen mediated coupling on ketones. The adducts are isolated with high enantiomeric excesses and can be easily transformed by simple reactions to yield chiral α-hydroxy esters bearing a chiral tertiary alcohol centre. This catalytic method was later applied to heteroaromatic aldehydes and ketones with high (>90%) enantioselectivities.[14b]



Scheme 6 Krische's asymmetric dienylation of α-ketoesters.

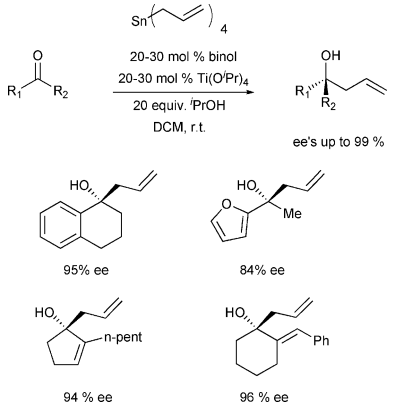
Another classical class of carbon-based nucleophiles for the addition on carbonyls and imines, allyl metal reagents, have been widely used in asymmetric synthesis due to the ease of preparation of the reagents and the high value in synthesis of the homoallylic alcohols and amines resulting from such processes.[15] During the past 6 years, several groups reported the adaptation of classical catalytic systems originally designed for the enantioselective allylation of aldehydes to the case of ketones with moderate to high enantioselectivities. Most of the catalyst reagents are based on the use of binol and its derivatives as the chiral ligand and some selected examples are represented in Scheme 7. An early report from the group of Tagliavini showed that one of the oldest chiral Lewis acid catalysts initially designed for the asymmetric allylation of aldehydes with allylstannane reagents could be used for ketones with moderate enantioselectivities.[16] The use of the more reactive tetraallyl tin allowed high conversions of the starting ketones to the chiral tertiary homoallyl alcohols to be achieved in fair to good yields. A metal-free procedure was later reported by Woodward *et al.* who used monothio binol as a soft chiral base to promote the direct allyl transfer of mixtures of tetraallyl stannanes and triallyl stannanes (bearing either alkyl or chloride substituents) to ketones with fair to high enantioselectivities.[17] The optimised procedure involves the addition of 0.4 equivalent of water, which inhibits side reactions leading to the racemic adducts. Loh *et al.* reported the preparation of a chiral binol–indium(III)



Scheme 7 Catalytic strategies developed for asymmetric allyl nucleophile transfer on ketones with binol type ligands.

bromide Lewis acid which gave fair to high enantioselectivities (up to 92%) for the asymmetric transfer of allyltributyl stannane on various ketones, including one example on an aliphatic ketone.[18] A bis titanium chiral Lewis acid was also described by the group of Maruoka for the same reaction.[19] In that case, two titanium atoms, each bearing a binol ligand, are brought together by an assembling ligand to give a bimetallic chiral catalyst. This chiral complex gave high enantioselectivities for simple aromatic ketones but gave somewhat lower efficiencies when simple unsaturated and aliphatic ketones were tested (ee up to 54%).

An optimisation of Tagliavini's titanium–binol catalyst was recently reported by Walsh *et al.* for the asymmetric transfer of tetraallyl stannane to ketones (Scheme 8).[20] The authors observed the beneficial effect of added isopropanol on the catalytic efficiency (enantioselectivity) of the chiral complex prepared by mixing the binol ligand and titanium isopropoxide. The role of isopropanol has not been yet elucidated but the new procedure could be generalised to various families of prochiral substrates, including aliphatic, aromatic, heteroaromatic and unsaturated ketones, yielding the corresponding homoallylic alcohols with high enantioselectivities. This strategy was recently applied with success to the asymmetric methallylation of ketones using H_8-binol as a chiral ligand.[21]

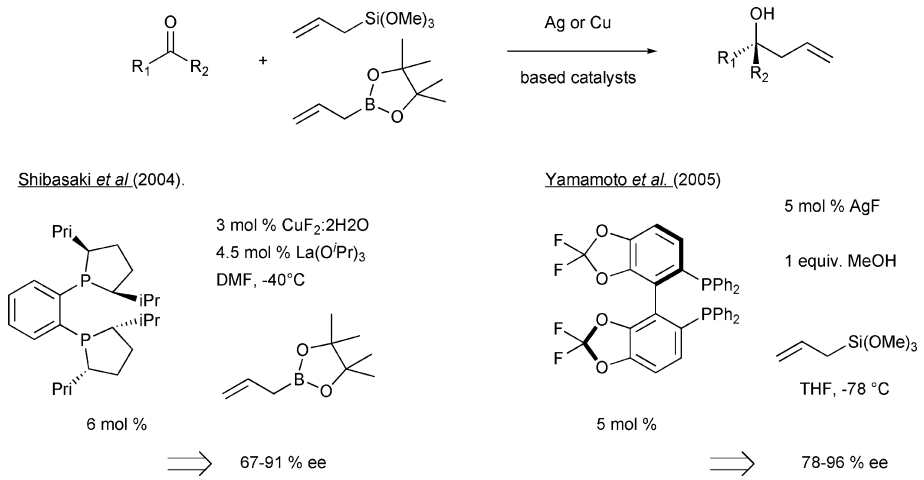


Scheme 8 Walsh's optimised procedure for the asymmetric allylation of ketones with tetraallyl stannane.

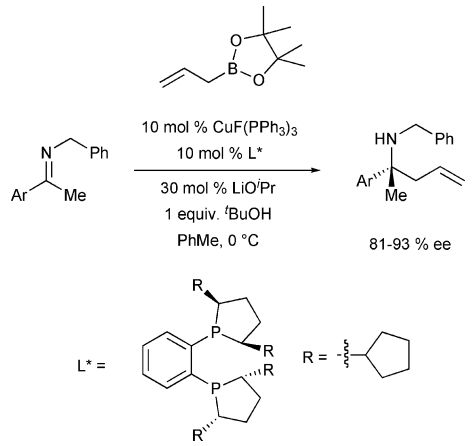
The asymmetric allylation of ketones was also recently studied by the groups of Shibasaki[22] and Yamamoto[23] using soft transition metal–chiral diphosphine complexes as catalysts (Scheme 9). Shibasaki *et al.* used allyl boronates as nucleophiles for the allyl transfer on aliphatic and aromatic ketones with fair to high enantioselectivities when a chiral copper complex was used as a catalyst. Intensive optimisation on the catalytic system led the authors to select ^{i}Pr-DuPHOS as a chiral ligand and a diphosphine copper(I) fluoride complex is supposed to be generated as the active catalytic species in the reaction mechanism. The fluoride ligand on copper is also essential for catalytic activity and is supposed to activate the nucleophile by formation of a boronate complex, which will in turn allow the transfer of the allyl group to the copper atom. The addition of La(O^{i}Pr)$_3$ as a Lewis acid accelerates the reaction, presumably by participation in the transmetallation step that leads to the active allylcopper species. This catalytic system was also applied to the first example of crotylation of ketones with modest *syn–anti* diastereoselectivities and high ee's for the isomers (ee's up to 93%). Yamamoto *et al.* later reported the application of a chiral silver catalyst, previously optimised for the asymmetric allylation of aldehydes, to the enantioselective allyl transfer to ketones. Reactive trimethoxy allyl siloxane nucleophiles were used with a difluorphos–silver(I) fluoride catalyst and could be used on a wide range of prochiral ketones, yielding the corresponding homoallylic alcohols with high enantioselectivities, and could also be applied to crotyl siloxane nucleophiles.

The copper-based chiral catalyst devised by Shibasaki *et al.* for the asymmetric allylation of ketones was recently adapted to ketimines and represents the first example of asymmetric catalysed allylation of this class on unreactive substrates.[24] High enantioselectivities were reached with a cyclopentyl derivative of the DuPHOS family and the use of LiO^{i}Pr and *t*-BuOH as additives proved necessary to reach good reactivity (Scheme 10). Mechanistic studies showed that the lithium alkoxide played an important role in the catalytic cycle by participating in the transmetallation step and thus increasing the concentration of the allyl copper nucleophile in the reaction media.

The synthesis of propargyl tertiary alcohols by direct nucleophilic addition of metal acetylides to ketones was pioneered by the group of Thompson and Corley from the Merck company who



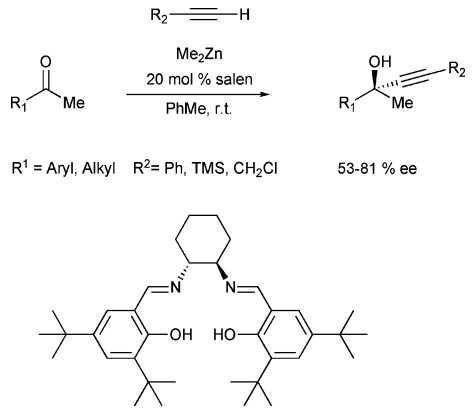
Scheme 9 Shibasaki's and Yamamoto's stategies for asymmetric allyl transfer on ketones.



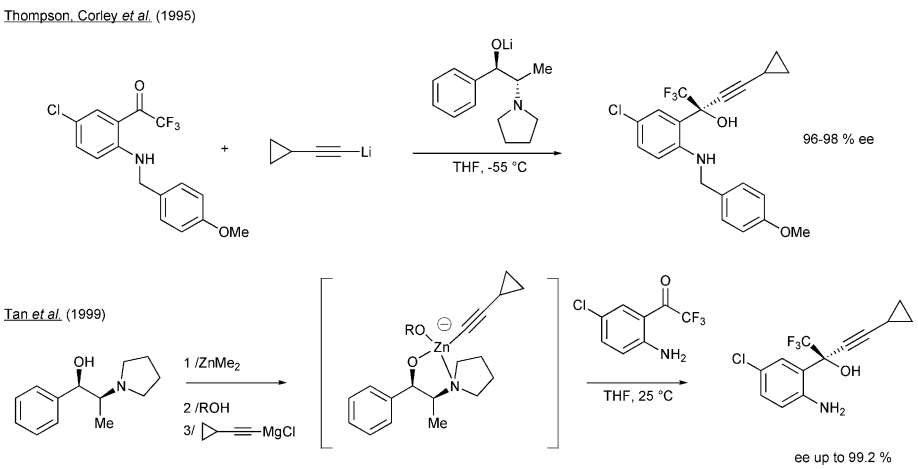
Scheme 10 Shibasaki's catalytic procedure for the asymmetric allylation of ketimines.

reported an efficient stoichiometric system for the preparation of a precursor of Efavirenz (Scheme 11). The addition of the lithium anion of cyclopropyl acetylene mediated by a stoichiometric amount of the lithium salt of a *nor*-ephedrine ligand derivative on a PMB protected trifluoromethyl ketone, gave the corresponding tertiary alcohol with enantioselectivities reaching 98% after optimisation and gave a straightforward access to Efavirenz.[25] The reaction mechanism and the nature of the active nucleophilic species was investigated by NMR spectroscopy and gave evidence for the involvement of a mixed 2 : 2 ligand–acetylide tetramer in the reaction pathway leading to the chiral tertiary alcohol.[26] An improved procedure involving organozincate nucleophiles was later reported by a group from the same company.[27] They generated the zinc aminoalkoxide nucleophile by reacting dimethylzinc, an alcohol and the magnesium halide acetylide on the chiral ligand. This procedure allowed them to use the unprotected anilino ketone and only a stoichiometric amount of the cyclopropylacetylide. It was successfully scaled up to multi-kilogram scale and was applied to the production of Efavirenz. Although those two examples are not catalytic in both metal and ligand, they represent a major milestone for the asymmetric addition of acetylenes to ketones and most probably inspired the following research in this field for the discovery of efficient catalytic systems.

The use of substoichiometric amounts of chiral ligands for the asymmetric alkynylation of ketones was pioneered in 2003 by Cozzi (Scheme 12).[28,29] An excess of dimethylzinc was added to a mixture of the ketone substrate, an alkyne pronucleophile and a catalytic amount of a chiral salen ligand to generate the zinc acetylide nucleophile and a zinc salen catalyst. The author reasoned that the zinc salen complex could act as a bifunctional catalyst by activating the ketone through coordination to the zinc atom and also by activating the zinc alkynide by coordination to the oxygen atom of the zinc bisphenolate complex. Good reactivity was reached with a 20 mol% amount of the salen ligand with enantioselectivities up to 81%. Moreover, this catalytic system could be used with both aromatic and aliphatic ketones. This first example was soon followed by many other examples which used similar concepts (chiral ligands such as binol, amino alcohols and amino alcohol derivatives in combination with a metal source based on zinc, aluminium, and titanium).[30] Those works will not be discussed here but often gave high enantioselectivities for the corresponding propargyl tertiary alcohols arising from the addition of the metal acetylide to various ketones.



Scheme 12 Cozzi's pioneer work on alkynation of ketones.



Scheme 11 Strategies developed by Merck groups for the asymmetric synthesis of Efavirenz precursors by asymmetric addition of chiral metal acetylides to prochiral trifluoromethyl ketones.

Asymmetric addition of cyanide-based nucleophiles to ketones

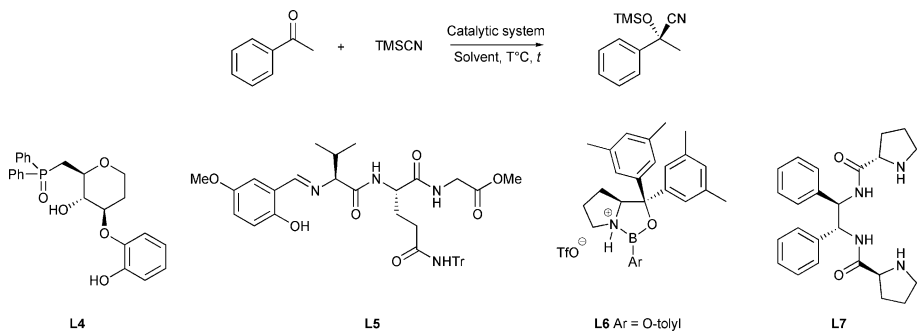
In regard to the synthetic utility of chiral tertiary cyanohydrin compounds to access a number of key chiral building blocks, time and effort have been dedicated to the development of efficient asymmetric and catalytic cyanosilylation methodologies applicable to ketones.[31] Despite pioneer work by the group of Belokon using a bimetallic titanium salen complex,[32] the first useful catalytic system for the asymmetric cyanosilylation of prochiral ketones with a broad application was masterfully developed by Shibasaki *et al.* in 2000.[33] Based on studies on the asymmetric addition of trimethylsilylcyanide on aldehydes, it was proposed that $Ti(O^iPr)_4$ in combination with the D-glucose derived ligand **L4** as a chiral scaffold was an efficient catalyst system for this transformation. A range of aliphatic and aromatic chiral tertiary cyanohydrins with enantioselectivities of up to 92% were indeed obtained with 10 mol% of the 1 : 1 metal–ligand complex $Ti(O^iPr)_4$–**L4** (Table 1, entry 1). From NMR studies and labelling experiments, it was deduced that the actual catalyst bears one cyanide ligand bound to the metal and that the cyanide unit is transferred from TMSCN itself. Control experiments revealed that the presence of the phosphine oxide moiety of **L4** plays a primordial role on the activity and enantioselectivity of the process. From these observations, it was therefore postulated that this transformation proceeds *via* a bifunctional mechanism in which the ketone and TMSCN are respectively activated by the Lewis acid nature of the titanium metal and the Lewis base character of the phosphine oxide entity. The particular efficiency of the catalyst system relies on its ability to simultaneously activate both the nucleophile and the electrophile in a high enantiofacial discriminative manner.[34]

Working on the synthesis of (*S*)-camphothecin and its analogues, potential agents for the treatment of solid tumors, the groups of Curran and Shibasaki further improved the activity and enantioselectivity of the catalytic system by switching the early transition metal for a lanthanide.[35] The best results for a variety of aromatic and α,β-unsaturated ketones were obtained with a 1 : 2 combination of $Gd(O^iPr)_3$ and chiral ligand **L4** (Table 1, entry 2). On the basis of mechanistic studies, the active catalytic species was proposed to be bimetallic in which 2 gadolinium metals were linked through one chiral ligand **L4**. Contrary to the previous $Ti(O^iPr)_4$–**L4** complex, one of the lanthanide metal cyanides was the actual nucleophile, the secondary lanthanide centre acting as a Lewis acid. In this case, the role of the phosphine oxide was to increase the nucleophilic character of the metallic cyanide. It is worth mentioning that these 2 catalysts are complementary: both enantiomers of the chiral tertiary cyanohydrins can be obtained using either $Ti(O^iPr)_4$ or $Gd(O^iPr)_3$ in conjunction with the single enantiomer of chiral ligand **L4**. Theses methodologies were applied to the preparation of key intermediates in the synthesis of pharmaceutical compounds such as (*S*)-oxybutynin, fostriecin or triazole antifungal agents.[36]

In 2002, the groups of Snapper and Hoveyda reported an efficient aluminium-based catalyst associated to a modular peptidic chiral ligand such as **L5** for the catalytic asymmetric addition of trimethylcyanide to ketone substrates.[37] Stimulated by their works on the development of efficient catalytic asymmetric carbon–carbon bond formation reactions, promoted by peptide based chiral ligands ligated to transition metal, a variety of peptide ligand–metal combinations were screened. Ligand **L5**–$Al(O^iPr)_3$ was identified as the best combination. Using 10 to 20 mol% of $Al(O^iPr)_3$ and **L5** with 20 mol% of MeOH, a wide range of aromatic, aliphatic, unsaturated and even propargylic ketones were indeed converted into tertiary cyanohydrins in high chemical yields and with enantiomeric excesses reaching 95% (Table 1, entry 3). The presence and the stereochemistry of the glutamine-derived moiety as well as the addition of MeOH were essential for the high efficiency of the system.

Inspired by the effectiveness of chiral oxazaborolidinium salts to catalytically promote the enantioselective addition of TMSCN to aldehydes, Corey and Ryu successfully extended the application of these salts to the asymmetric cyanosilylation of methyl ketones.[38] The employment of 10 mol% of chiral salt **L6** and 10 mol% of $MeP(O)Ph_2$ as a co-reactant allowed the preparation of aromatic

Table 1 Enantioselective cyanosilylation of a model substrate, acetophenone catalysed by metal-based catalytic systems



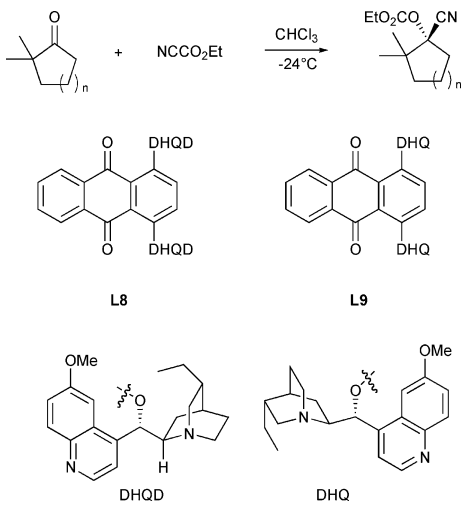
Entry	Year	Research group	Catalytic system	Solvent	T/°C	t	Yield (%)	Ee (%) (conf.)
1	2000	Shibasaki *et al.*	10 mol% $Ti(O^iPr)_4$ + 10 mol% **L4**	THF	−30	36 h	85	92 (*R*)
2	2001	Curran and Shibasaki *et al.*	5 mol% $Gd(O^iPr)_3$ + 10 mol% **L4**	THF	−40	2 h	92	92 (*S*)
3	2002	Hoveyda *et al.*	10 mol% $Al(O^iPr)_3$ + 10 mol% **L5** + 20 mol% MeOH	Toluene	−78	48 h	84	91 (*R*)
4	2005	Corey *et al.*	10 mol% **L6** + 10 mol% $MeP(O)Ph_2$	Toluene	25	14 d	77	83 (*R*)
5	2006	Feng *et al.*	30 mol% $Ti(O^iPr)_4$ + 30 mol% **L7**	CH_2Cl_2	−45	100 h	77	92 (*R*)

and aliphatic ketone cyanohydrins with moderate to high yields and ee values despite long reaction times (Table 1, entry 4). The success of these catalysts relied on a well-organised transition state involving 1) a strong attractive interaction between one of the electron-rich methyl substituents of **L6** and the carbonyl bond of the ketone substrate, and 2) a stabilising hydrogen bond between the oxygen of **L6** and a α-hydrogen atom of the substrate. As in the case of the aldehydes, the role of $MeP(O)Ph_2$ is to generate a more reactive intermediate ($MePh_2P(OTMS)(NC)$) than TMSCN itself.

Encouraged by their early works on the use of chiral bifunctional titanium-based catalysts for the asymmetric cyanosilylation of ketones,[39] Feng *et al.* developed a new titanium–chiral ligand **L7** combination to access chiral tertiary cyanohydrins (up to 94% ee) in a catalytic manner (Table 1, entry 5).[40] The new ligand is easily accessible *via* a 2-step synthesis from commercially available reactants. Mechanistically, the authors proposed a dual activation mode similar to the one observed with Shibasaki's catalyst ($Ti(O^iPr)_4$–**L4**). In this case, the nitrogen functionality of one of the proline entities plays the role of the phosphine oxide.

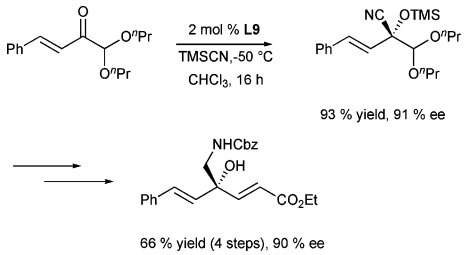
In 2001, Deng and Tian applied for the first time the concept of chiral Lewis-base catalysis to the enantioselective cyanosilylation of ketones.[41a] Using readily available modified cinchona alkaloids as chiral base ligands, they reached tremendous results (up to 97% ee) for the asymmetric addition of methyl cyanoformate to a wide range of acyclic and cyclic dialkyl ketones. Both enantiomers of the corresponding product could be obtained in high ee values from either dihydroquinidine or dihydroquinine-based modified cinchona alkaloids (Table 2). The remarkable feature of this chiral catalytic system is its singular capacity to transform cyclic and sterically hindered dialkyl ketones into tertiary cyanohydrins in an enantioselective manner. Two years later, the same research group broadened the substrate scope of these catalysts to aromatic, conjugated and unconjugated acetal ketones to afford the corresponding compounds with 90–97% ee.[41b] An example of the application of this methodology to the construction of a useful building block bearing a tetrasubstituted carbon centre is represented in Scheme 13. The usefulness of this approach was also illustrated in target-oriented synthesis.[41c]

Table 2 Modified cinchona-alkaloid-catalysed enantioselective cyanation of cyclic dialkyl ketones developed by Deng *et al.* (2001)



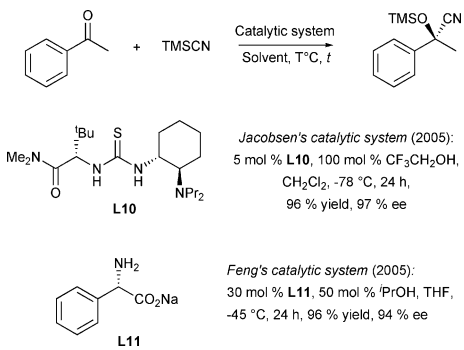
n	Catalyst	Mol (%)	*t*/d	Yield (%)	Ee (%)
1	L6	15	4	76	95 (−)
1	L7	15	2	66	97 (+)
2	L6	30	5[a]	53	92 (−)
2	L7	20	4	62	91 (+)

[a] $T = -12$ °C



Scheme 13 Example of a useful chiral building block synthesised by asymmetric Lewis base-catalysed cyanosilylation (Deng *et al.* 2003).

Recently, the group of Jacobsen exploited an alternative approach to the well-known metal-based Lewis acid for the activation of the electrophilic ketones towards asymmetric trimethylsilylcyanation addition (Scheme 14). This approach relied on a hydrogen bonding activation mode[42] similarly found in enzymatic systems. After careful optimisation of the catalyst structure and reaction parameters (solvent, temperature, additive), a variety of aromatic, heteroaromatic and unsaturated ketones were converted in high yields (87–96%) and enantioselectivities (89–98% ee) into the corresponding cyanohydrin trimethylsilyl ethers with 5 mol% of chiral thiourea catalyst **L10** in the presence of alcohol additive (100 mol%) and TMSCN.[43] In these conditions, dialkyl ketones were however obtained in low yields and enantiomeric excesses. The authors noted that the presence of the Brønsted basic tertiary amine functionality in **L10** is essential for the activity of the present system and therefore suggested a dual activation mechanism.



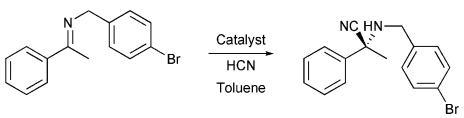
Scheme 14 Enantioselective cyanosilylation of acetophenone catalysed by chiral thiourea and organic salt catalysts.

Simultaneously to the Jacobsen's report, Feng and co-workers disclosed the asymmetric cyanosilylation of ketones catalysed by a chiral organic salt (Scheme 14).[44] Screening experiments revealed that L-phenylglycine sodium salt **L11** (30 mol%) was an efficient catalyst to promote the formation of tertiary cyanohydrins in high yields (77–96%) and enantiomeric excesses (90–97%) from aromatic, heteroaromatic and unsaturated ketones. Moderate ee

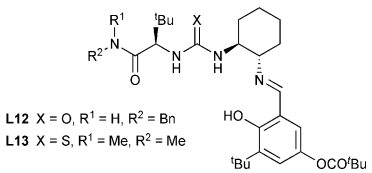
values were nonetheless observed with aliphatic substrates as in the case of Jacobsen's system. It is worth noting that the lithium and potassium analogues of **L11** gave both racemic products and that the primary amine entity of the salt was essential to achieve high chemical yields and ee's. A hypervalent silicon intermediate *via* coordination of the chiral organic salt to TMSCN was proposed as an active species.

Asymmetric addition of cyanide-based nucleophiles on ketimines

Despite intensive research into the development of highly efficient processes for the catalytic asymmetric Strecker-type reaction of aldehydes,[45] only few reports have been devoted to ketimine substrates.[46] This is unanticipated considering the potential of this approach for the preparation of chiral α,α-disubstituted α-amino acids, important building blocks for the pharmaceutical industry. Nevertheless, the breakthrough in this area came in 2000 from the group of Jacobsen which described for the first time, a highly enantioselective addition of HCN to ketimines.[47] This reaction was catalysed by readily accessible and recyclable Schiff base catalysts discovered earlier for the asymmetric Strecker-type reaction of aldehyde through a lead optimisation strategy by a parallel library synthesis.[48] With 2 mol% of chiral urea catalyst **L12**, aryl methyl ketimines and *tert*-butyl ketimine were converted into the corresponding Strecker adducts in high yields and enantioselectivities (up to 95% ee) (Scheme 15). In some cases, simple recrystallisation techniques afforded the product with ee up to >99.9%. The catalyst can be easily recovered by chromatography and reused without significant loss of selectivity. Studies into the nature of the catalyst–substrate interaction revealed that the two hydrogen atoms on the urea moiety were essential for catalyst activity and that the substrate was bound to **L12** *via* its *Z*-isomer. Fine-tuning of the electronic properties of the active site as well as the steric bulk of the amide functionality led to the development of the second generation of catalyst **L13**.[49] On the two-reported substrates, phenyl methyl and *tert*-butyl methyl ketimines, better enantioselectivities were observed with the second generation of catalyst.



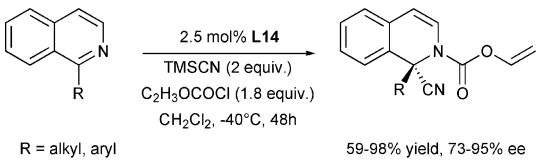
First generation catalyst (2000): 2 mol % **L12**, -75 °C, 97 % yield, 92 % ee
Second generation catalyst (2002): 1 mol % **L13**, -78 °C, 96 % ee



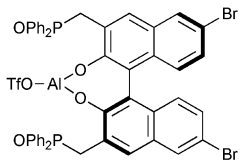
L12 X = O, R^1 = H, R^2 = Bn
L13 X = S, R^1 = Me, R^2 = Me

Scheme 15 Enantioselective Strecker-type reaction catalysed by Jacobsen's first and second generations of chiral Schiff base catalysts.

In 2001, Shibasaki *et al.* described the first catalytic and highly enantioselective Reissert-type reaction of 1-substituted isoquinolines.[50] For this purpose, a bifunctional catalyst based on early findings on the asymmetric catalytic cyanosilylation of aldehydes was investigated. Fine-tuning of the Lewis acid character of the catalyst (counterion TfO^- and bromide substituents at the 6,6′-positions) allowed **L14** to be identified as an efficient chiral Lewis acid catalyst for the Reissert-type reaction of a variety of 1-alkyl and 1-aryl isoquinolines into the corresponding products with yields and ee's ranging from 59 to 98% and 73 to 95%, respectively (Scheme 16).



R = alkyl, aryl — 59-98% yield, 73-95% ee



L14

Scheme 16 First report of a catalytic enantioselective Reissert-type reaction from Shibasaki *et al.* (2001).

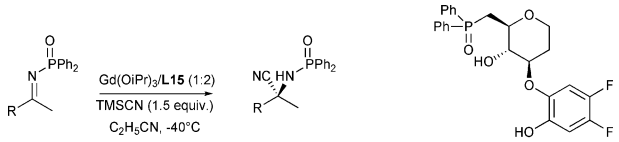
In view of the success of the $Gd(O^iPr)_3$–**L4** combination as an efficient catalytic system for the enantioselective cyanosilylation of ketones, the group of Shibasaki proposed to apply this system to the asymmetric addition of trimethylsilylcyanide onto ketimines. Screening experiments (imine protecting group, lanthanide metals, ligands, metal–ligand ratios), led to the discovery of a general catalytic method in terms of substrate generality for the enantioselective Strecker-type reaction of ketimines. Indeed, a catalytic amount of $Gd(O^iPr)_3$ in conjunction with **L15**, bearing electron-withdrawing substituents on the catechol allowed the transformation of aryl methyl, alkyl methyl and α,β-unsaturated *N*-diphenylphosphinoyl ketimines into the corresponding adducts in high to moderate yields and enantioselectivities (up to 95% ee) (Table 3, entries 1–3).[51] Significant improvement in terms of enantioselectivity, yield, catalyst activity and substrate scope were accomplished with the addition of a stoichiometric quantity of 2,6-dimethylphenol as a protic source.[52a] Representative examples are displayed in Table 3 (entries 4–7). The authors analysed the structure of the catalyst by ESI-MS technique and proposed that the role of the protic additive was to tune the structure of the catalytic species into one more active and enantioselective. This improved catalytic system was also applied to the catalytic total synthesis of (+)-lactacystin, a potent and selective proteasome inhibitor.[53] The use of a catalytic amount of TMSCN in combination with a stoichiometric amount of HCN allowed a decrease in catalyst loading as low as 0.1 mol%.[52b]

The group of Vallée also reported the asymmetric addition of TMSCN to acetophenone-derived ketimine catalysed by a $Sc(Binol)_2Li$ heterobimetallic complex (10 mol%) with high enantioselectivity (95% ee).[54]

Asymmetric addition of nitromethane to ketones

The catalytic asymmetric Henry-type reaction (nitroaldol reaction) is a powerful method to straightforwardly access key intermediates for the preparation of valuable chiral buiding blocks such

Table 3 Enantioselective Strecker-type reaction of *N*-diphenylphosphinoyl ketimines catalysed by Shibasaki's bifunctional Lewis acid/Lewis base catalyst



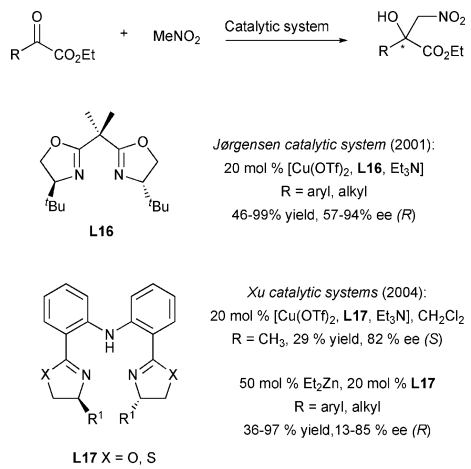
L15

	Entry	R	$Gd(O^iPr)_3$ (mol%)	*t*/h	Yield (%)	Ee (%)
Initial catalytic system (2003): $Gd(O^iPr)_3$–**L15** (1 : 2)	1	Ph	2.5	24	94	95
	2	C_5H_{11}	5	65	73	72
	3	$C_5H_{11}CHCH$	5	52	99	88
Improved catalytic system (2004): $Gd(O^iPr)_3$–**L15** (1 : 2) + 2,6-dimethylphenol (100 mol%)	4	Ph	2.5	2	98	97
	5	C_5H_{11}	5	2	96	93
	6	$C_5H_{11}CHCH$	5	2	94	94
	7	3-Thienyl	2.5	1.3	98	99

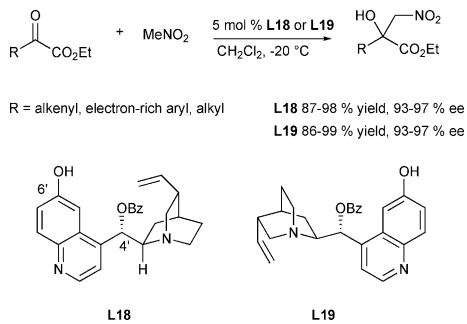
as α-hydroxy-carboxylic acids or 1,2-amino-alcohols. In the last few years, significant progress in the field of catalytic asymmetric Henry-type reactions of aldehydes has been achieved.[55] So far, and to the best of our knowledge, only three research groups have however reported the application of such a reaction to ketones, essentially α-ketoesters.

In 2001, the group of Jørgensen described the first catalytic enantioselective Henry-type reaction to α-ketoesters. The reaction was catalysed by $Cu(OTf)_2$ in conjunction with chiral bis(oxazoline) ligand **L16** and in the presence of Et_3N as a Brønsted base.[56] A variety of aryl and alkyl α-ketoesters were converted into β-nitro-α-hydroxyesters in high yields and with ee values of up to 94% with 20 mol% of the combination [$Cu(OTf)_2$, **L16**, Et_3N] (Scheme 17). β,γ-Unsaturated α-ketoesters were poor substrates in terms of enantioselectivity. It was shown that the enantioselectivity was dependent on the amount of base. Three years later, Xu *et al.* replaced the ligand **L16** by C_2-symmetric tridentate bis(oxazoline) or bis(thiazoline) ligand **L17** and observed a decrease in yield and ee in the addition of nitromethane to ethyl pyruvate.[57a] This group also reported an interesting inversion of the absolute configuration of the product governed by the metal. Using either $Cu(OTf)_2$ or $ZnEt_2$ in conjunction with the same (*S*,*S*)-bis(oxazoline) or bis(thiazoline) ligand, both enantiomers of the Henry-type adducts can be obtained (ee <85%) (Scheme 17).[57b]

In terms of enantioselectivity and substrate generality, the true breakthrough in this area came from the group of Deng in 2006, who reported the first efficient and highly enantioselective Henry-type reaction on ketones catalysed by cinchona alkaloid ligands.[58] In light of the successes achieved earlier with chiral C6′-OH cinchona alkaloid ligands in diverse asymmetric Michael-type addition reactions,[59] Deng *et al.* investigated this class of organic catalysts in the asymmetric Henry-type reaction of α-ketoesters. Remarkable yields (87–98%) and enantioselectivities (93–97% ee) were attained for a wide range of aryl, alkyl and alkenyl α-ketoesters with only 5 mol% of catalyst **L18** or **L19** (Scheme 18). Worth noting were the high results obtained with challenging substrates such as alkenyl α-ketoesters (92–99% yield, 95–97% ee) and electron-rich α-ketoesters (Scheme 18, R = 4-MeO, 85% yield, 97% ee). The authors observed that the enantioselectivity was dependent on the substituent of the oxygen at the C4′ position and that a free-hydroxyl moiety at the C6′ was necessary to reach high enantiomeric excesses.



Scheme 17 Copper(II)-based catalytic systems developed for the enantioselective Henry-type reaction to α-ketoesters.



Scheme 18 Cinchona alkaloid-catalysed enantioselective Henry reaction of α-ketoesters developed by Deng *et al.* (2006).

Asymmetric addition of silyl/metal enol(ate) to ketones

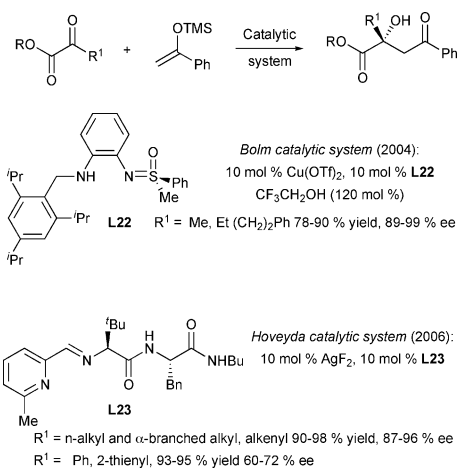
The asymmetric aldol addition reaction is one of the most fundamental carbon–carbon bond-forming reactions for the stereoselective construction of chiral alcohols. Despite an array of catalytic asymmetric aldol processes targeting aldehydes as acceptors,[60] not many reports have been devoted to ketones as precursors for the construction of chiral tertiary alcohols.

Seminal work in this research domain appeared in 1997 from the group of Evans, which published the first catalytic enantioselective Mukaiyama-type aldol reaction between α-ketoesters and enolsilanes (Scheme 19).[61] Encouraged by their earlier findings on the use of C_2-symmetric bis(oxazoline) copper(II) complexes as efficient chiral Lewis acid catalysts for the asymmetric aldol reaction of aldehydes, Diels–Alder and ene reactions,[61] the Evans group explored the potential of these complexes to catalyse the Mukaiyama-type aldol reaction of chelating substrates, α-ketoesters. Chiral bis(oxazoline) ligands, copper counterions, solvents and reaction temperature were surveyed to identify the best parameters for this transformation. From these screenings, a 10 mol% amount of copper(II) complex **L20** was found to catalyse the aldol reaction between alkyl-substituted α-ketoesters and substituted ($R^2 \neq H$) and non-substituted silyl thioketene acetals ($R^2 = H$) in high yields and enantioselectivity (93–99% ee) (Scheme 19). The best results were respectively obtained in THF and CH_2Cl_2 for substituted and non-substituted silyl thioketene acetals. With the latter, the process was highly diastereoselective in favour of the *syn* isomer for a range of substrates (d.r. ranging from 90 : 10 to 98 : 2). Both (*E*) and (*Z*)-silyl ketene acetal isomers afforded the same *syn* product isomer.

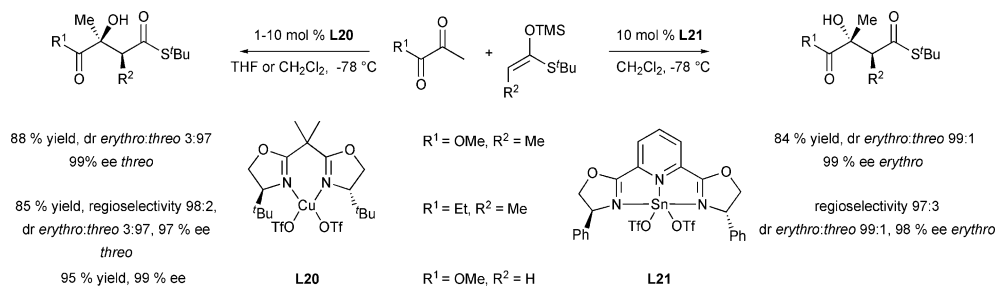
Based upon silyl cross-over experiments that highlight the intermolecular nature of the silyl transfer step, the authors discovered that the reaction rate was considerably increased by the addition of a stoichiometric amount of TMSOTf. Mechanistically, the stereochemical induction can be rationalised by nucleophilic attack of the silyl ketene acetal to a distorted square planar copper–substrate complex *via* an open transition state. This catalytic system was also efficient for the enantioselective Mukaiyama-type aldol reaction of a challenging substrate such as a prochiral diketone ($R^1 = Et$, Scheme 19). For both classes of substrates, α-ketoesters and diketones, the *anti* aldol adduct could be obtained using (pybox) tin(II) complex **L21** instead of **L20** (Scheme 19).[62]

Pagenkopf *et al.* replaced the *tert*-butyl susbtituents of **L20** by *o*-alkoxyaryl group and developed a new class of chiral bis(oxazoline)–copper(II) complexes.[63] These new complexes provided higher enantioselectivities than **L20** for the aldol reaction between silyl dienolate and aryl- and alkyl-substituted α-ketoesters (up to 91% ee compared to 74% ee with **L20**).

In 2004, the group of Bolm described a highly enantioselective copper(II)-catalysed Mukaiyama-type aldol reaction between *n*-alkyl substituted α-ketoesters and enolsilanes using C_1-symmetric benzene-bridged aminosulfoximines as chiral ligands.[64a] Optimisation of the ligand structure and the reaction conditions revealed that a 10 mol% mixture of $Cu(OTf)_2$ and **L22** in THF allowed the reaction to perform in high yields (up to 90%) and with excellent ee values (up to 99%) in the presence of a fluorinated alcohol as an additive (Scheme 20).[64b] The additive increases significantly the rate of the reaction with no effect on the enantioselectivity. These results were of the same order of magnitude as those obtained with C_2-symmetric bis(oxazoline) copper(II) complexes ($R^2 = OMe$, $R^1 = Me$, Scheme 19). More recently, Snapper and Hoveyda *et al.* disclosed the successful use of highly modular amino acid-based chiral ligands in the silver(II)-catalysed enantioselective Mukayaima-type aldol reaction between ketone-derived enolsilanes and α-ketoesters.[65] The [AgF_2–**L23**] catalytic system was highly efficient, in terms of yield and enantioselectivity, for *n*-alkyl, α-branched alkyl and alkenyl substituted ketoesters, and less effective for aryl substituted substrates (Scheme 20). Contrary to the copper(II)-based catalytic systems developed by the groups of Evans and Bolm, this silver(II)-based system requires simple laboratory techniques without air and moisture exclusion.

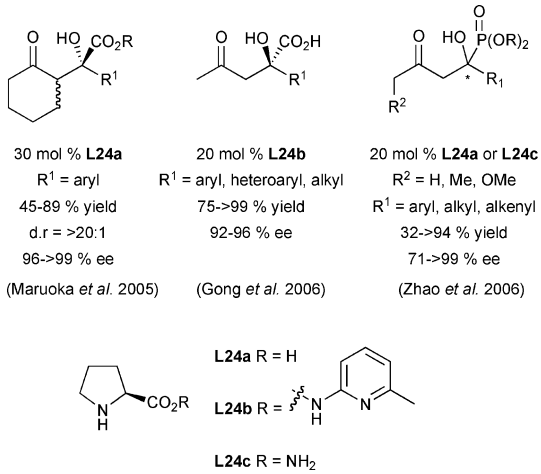


Scheme 20 Copper(II) and silver(II)-catalysed enantioselective Mukaiyama-type adol reaction between α-ketoesters and enolsilanes.



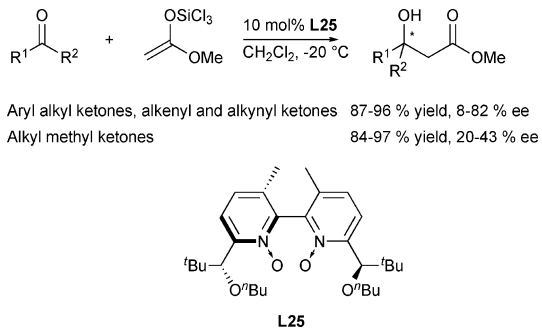
Scheme 19 Diastereoselectivity switch in the enantioselective Mukaiyama-type aldol reaction on α-ketoesters and diketones controlled by chiral Lewis acid catalysts.

Recently, organocatalysed asymmetric direct aldol reactions of α-keto esters,[66a] acids[66b] and phosphonates[66c] with ketones were also reported.[67] These successful accounts, catalysed by L-proline **L24a** and L-proline-derived molecules **L24b–c** afforded the corresponding chiral tertiary α-hydroxy esters, acids or phosphonates in moderate to high yields and enantioselectivities (Scheme 21).



Scheme 21 Chiral tertiary α-hydroxy esters, acids and phosphonates prepared by enantioselective direct aldol reactions catalysed by L-proline and L-proline-based molecules.

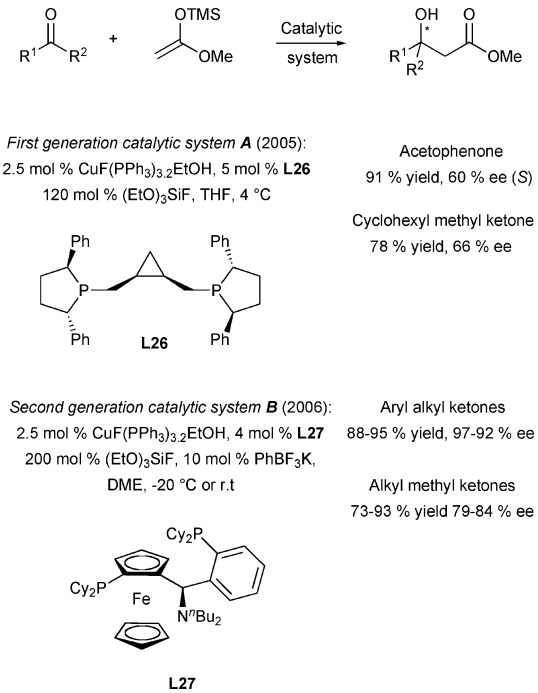
In 2002, Denmark *et al.* focused on an alternative approach to develop a general method for the catalytic asymmetric aldol reaction to unactivated ketones.[68] This approach relied on the use of chiral Lewis base catalysts to promote the reaction, a concept that the same group previously employed in the enantioselective allylation and aldolisation reactions of aldehydes.[69] Screening experiments with different chiral Lewis basic promoters brought into light chiral bis *N*-oxide **L25** as a competent catalyst for the catalytic asymmetric aldol reaction between the highly reactive trichlorosilyl ketene acetal of methyl acetate and ketones. Excellent yields (84–97%) of aldol adducts were obtained from aryl, alkyl, alkenyl and alkynyl substituted ketones. Better asymmetric inductions were however observed with aryl, alkenyl and alkynyl substituted ketones (up to 82% ee) than with alkyl, methyl ketones (up to 43% ee) (Scheme 22). The authors reasoned that 2 molecules of Lewis base catalyst coordinate to the silicon atom to generate a reactive hypervalent silicate intermediate, which can then activate



Scheme 22 Enantioselective aldol reaction between trichlorosilyl ketene acetal and ketones catalysed by a chiral bis *N*-oxide Lewis base catalyst developed by Denmark *et al.* (2002).

the ketone. Due to the similarity with the Lewis base-catalysed aldol reaction of aldehydes, this reaction was proposed to proceed through a closed transition-state.

The first report of a catalytic enantioselective Mukaiyama-type aldol reaction to simple ketones appeared from the group of Shibasaki in 2005.[70] Preliminary work on the development of a general method for the catalytic aldol reaction between trimethylsilyl ketene acetates and ketones showed that $CuF(PPh_3)_3{\cdot}2EtOH$ and a stoichiometric amount of $(EtO)_3SiF$ additive was an efficient catalytic system to promote this transformation.[71] From this observation, Shibasaki *et al.* investigated a series of chiral diphosphine ligands to turn this system into an asymmetric version. Nevertheless, disappointing outcomes with available diphosphine-type ligands led the research group to design new chiral C_2-symmetric bidentate phosphine ligands. Even so, the best enantiomeric excess reported was 66% with the bis(diphenylphospholane) ligand **L26** bearing a wide bite angle and the cyclohexyl methyl ketone as a substrate (Scheme 23). Mechanistic studies pointed out that the copper enolate intermediate, generated by dynamic ligand exchange between silicon and copper, was the reactive nucleophile in this process.

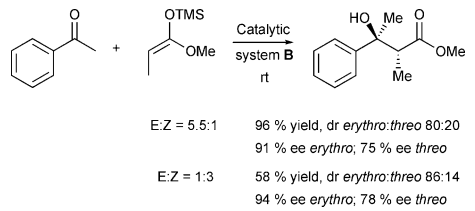


Scheme 23 Enantioselective Mukaiyama-type aldol reaction of ketones catalysed by Shibasaki's first and second generation catalytic systems.

Later on, the same research group improved the efficiency of the methodology in terms of yield, enantioselectivity and substrate scope.[72] For this, Shibasaki *et al.* performed a screening of diverse taniaphos-based ligands bearing cyclohexyl moieties at the phosphorus atoms and different alkyl substituents on the amine entity. Various additives and ratios of $(EtO)_3SiF$ were also tested. From these studies, it was identified that **L27**, with 10 mol% of $PhBF_3K$ and 200 mol% of $(EtO)_3SiF$ as additives, was the best ligand for the copper(I) fluoride-catalysed aldol reaction between trimethylsilyl ketene acetal of methyl acetate and cyclohexyl methyl ketone, affording aldol adduct in 89% yield and

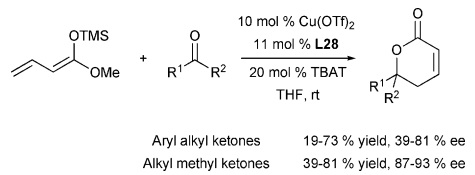
77% ee. Under these optimised conditions, an array of tertiary β-hydroxy esters were synthesised in high yields (88–95%) and enantioselectivites (97–92% ee) from aryl alkyl ketones. Adducts from alkyl methyl ketones, that were poor substrates for the chiral bis *N*-oxide Lewis base catalysed aldol reaction (Scheme 22), were even achieved with practical ee values (79–84%) (Scheme 23).

This second generation of catalytic system (**B**) was also highly efficient for the diastereo- and enantioselective Mukaiyama-type aldol reaction between propionate-derived enol silane and acetophenone (Scheme 24). It is worth noting that the diastereomeric ratio and the enantiomeric excesses of both *erythro* and *threo* isomers were weakly sensitive to the ratio of (*E*) and (*Z*)-silyl ketene acetals.



Scheme 24 Diastereo- and enantioselective Mukaiyama-type aldol reaction between propionate-derived enol silane and acetophenone catalysed by Shibasaki's second generation catalytic system (2006).

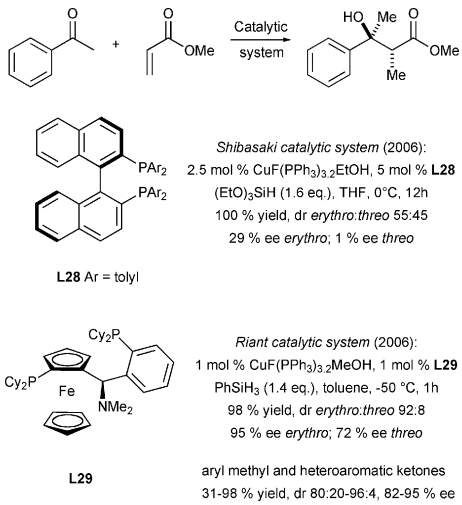
Early in 2005, the group of Campagne published the first examples of the application of vinylogous Mukaiyama-type aldol reaction on ketones in a catalytic and asymmetric manner (Scheme 25).[73] In this report, the use of Cu(OTf)$_2$–**L28**–TBAT as a catalytic system was stimulated by the excellent results achieved earlier on aldehyde substrates from Carreira and co-workers initially,[74] and Campagne *et al.* later.[75] As in the case of aldehydes with γ-substituted silyl dienolates,[75b] the reaction of linear silyl dienolate with ketones afforded the corresponding α,β-unsaturated lactones in moderate to high yields. The process was highly efficient for the preparation of enantiomerically enriched chiral lactones bearing a tetrasubstituted carbon centre from alkyl methyl ketones (yields and ee's ranging from 39 to 81% and 87 to 93% respectively). Aryl methyl ketones were however poorer substrates in this process (Scheme 25). As evidenced by Carreira *et al.* in the case of aldehydes,[74b] a copper enolate intermediate might be speculated as the reactive species.



Scheme 25 Enantioselective copper-catalysed vinylogous Mukaiyama–type aldol reaction between silyl dienolate and ketones developed by Campagne *et al.* (2005).

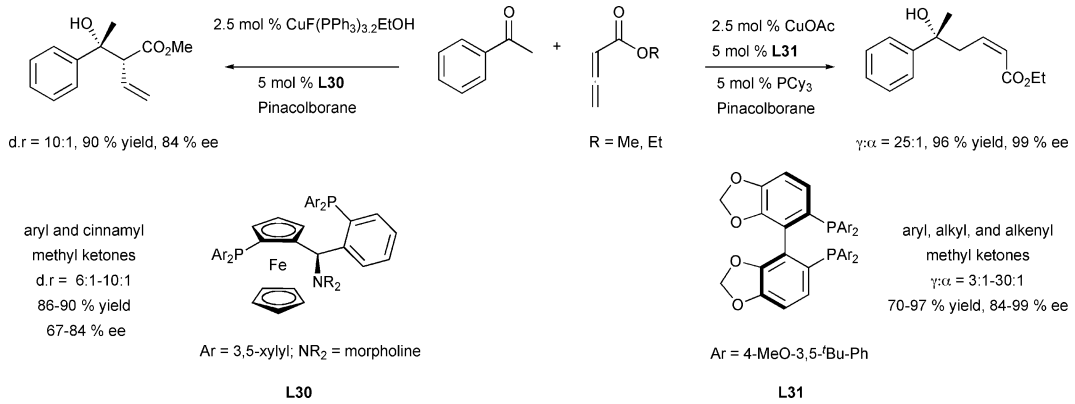
The catalytic systems reported so far for the aldol-type reaction to ketones involve pre-activation of the nucleophilic partners in an independent step, under the form of a silyl enolate derivative. An alternative strategy to this two-step procedure is to generate *in situ* the silyl or metal enolate *via* a tandem conjugate reduction–aldolisation reaction between α,β-unsaturated carbonyl compounds and ketones with hydrosilane as the reducing agent. This approach was successfully employed in the catalytic asymmetric reductive aldol reaction between α,β-unsaturated esters and aldehydes.[76] In 2005, the first disclosure of the use of such a strategy to construct chiral tertiary β-hydroxy esters was made by the group of Lam.[77] This group reported a diastereo- and enantioselective intramolecular reductive aldol reaction between α,β-unsaturated esters, ketones and hydrosilane catalysed by a copper complex[78] with axially chiral biaryl diphosphine ligands. Despite high diastereoselectivities, yields and ee values were moderate (51–79% and 49–83% respectively). Soon after, the groups of Shibasaki[79] and Riant[80] independently reported the first asymmetric intermolecular version of this three-component strategy[81] on ketonic acceptors.

Shibasaki *et al.* examined the asymmetric reductive aldol reaction between methyl acrylate and acetophenone catalysed by a catalytic amount of CuF(PPh$_3$)$_3$·2EtOH associated to 3 different chiral diphosphine ligands, in the presence of (EtO)$_3$SiH as a reducing agent.[79] The best combination of yield, diastereo- and enantioselectivity was obtained with tol-BINAP ligand **L28** (Scheme 26). Switching the hydride source (EtO)$_3$SiH for pinacolborane led to similar results. This observation suggests that the actual nucleophile was a copper enolate intermediate rather than a silyl enolate.



Scheme 26 Diastereo- and enantioselective copper-catalysed domino reduction–aldol reaction between methyl acrylate and acetophenone.

The group of Riant investigated the use of chiral diphosphine-modified copper fluoride as a catalyst for the stereoselective reductive aldol reaction between methyl acrylate and aromatic ketones with phenylsilane as a reducing agent.[80] After optimisation of the parameters of the reaction (copper(I) source, solvent, temperature) between methyl acrylate and acetophenone using a chiral Roche ligand, a screening of diverse chiral biaryl and ferrocenyl-based diphosphine ligands was performed under the optimised conditions (CuF(PPh$_3$)$_3$·2MeOH, toluene, −50 °C). Among them, taniaphos-type ligands, and particularly **L29**, were the most efficient in terms of diastereo- and enantioselectivities. Indeed, the domino process between methyl acrylate and acetophenone catalysed by 1 mol% of CuF(PPh$_3$)$_3$·2MeOH–**L29**, in the presence of phenylsilane, afforded the aldol adduct in a high



Scheme 27 Copper source/ligand effect on the regioselectivity of the asymmetric copper(I)-catalysed reductive aldol reaction of allenic esters to ketones (Shibasaki *et al.* 2006).

diastereomeric ratio of 92 : 8 in favor of the *erythro* isomer and with a high enantiomeric excess of 95% for the major isomer (Scheme 26). The catalyst loading can be reduced to 0.1 mol% without a significant variation of the level of diastereocontrol, despite a slight decrease in the enantioselectivity (to 87% ee). The authors noted an inversion of absolute configuration for the *erythro* isomer when the groups on the phosphorus atoms of **L29** were changed from cyclohexyl to phenyl substituents. A variety of aromatic and heteroaromatic ketones participate successfully in the tandem reaction with methyl acrylate. For the range of substrates considered, the diastereo- and enantioselectivtity of the reaction were moderate to high with dr and ee for the *erythro* compound ranging from 80 : 20–96 : 4 and 82–95% respectively.

In a preliminary study, Shibasaki *et al.* had extended the potential of the copper(I) fluoride-catalysed tandem methodology, described previously, to allenic esters as pre-nucleophiles and pinacolborane as a reducing agent.[79] Despite moderate γ–α regioselectivity, excellent enantioselectivity and acceptable diastereoselectivity were however obtained for the γ and α isomers respectively, using $CuF(PPh_3)_3{\cdot}2EtOH$–**L31** as a catalyst. Very recently, the regioselectivity was improved for the reductive aldol reaction between allenic ester (R = Et) and acetophenone by employing CuOAc as a copper source and adding achiral basic phosphine PCy_3 (Scheme 27, right side).[82] Indeed, a γ–α regioselectivity of 25 : 1 was obtained for the predominant *cis* isomer, isolated in 96% yield and with an enantiomeric excess of 99%. Similar trends were observed for a variety of aryl, alkenyl and alkyl methyl ketones: range values of yields, regioselectivities and enantioselectivities are displayed in Scheme 27. During the optimisation stage, a change in the regioselectivity in favour of the α isomer was noted when taniaphos-type ligands were employed. Fine-tuning of the ligand structure led to the synthesis of ligand **L30** with a morpholine moiety and xylyl groups on the phosphorus atoms. This ligand in combination with $CuF(PPh_3)_3{\cdot}2EtOH$ catalysed the tandem reaction between acetophenone and allenic ester (R = Me) in high yield (90%), good ee value (84%) and moderate diastereoselectivity (dr = 10 : 1) (Scheme 27, left side). This change of regioselectivity, controlled by the ligand, was also observed with other aryl and cinnamyl methyl ketones (Scheme 27). Under these catalytic conditions, these substrates gave the corresponding adducts with excellent stereoinduction. No account to rationalise this behaviour has yet been provided.

Conclusion

This short review emphasizes the milestones and recent developments in the fascinating and highly challenging area of asymmetric catalysis. An obvious observation shows that the expertise gained in the field of asymmetric addition of nucleophiles to aldehydes has often guided the researchers to apply such successful catalytic systems to the cases of ketones and ketimines. This often resulted in good enantioselections, albeit poor catalytic efficiencies. More recent reports show that the design of new chiral catalysts has become more and more targeted toward ketonic substrates and, thus shows a fast evolution in this area of catalysis. However, this review also shows that, regardless of all the work already performed, there is much room for further improvement and new discoveries. One aspect concerns for instance the high catalyst loading still required in much of the reported systems, although a few very active catalytic systems have yet been optimised. Another aspect concerns the most challenging substrates, such as ketimines, for which there are still very few successful examples in the literature.

Note added in proof: as this field of research is rapidly expanding, some relevant work regarding asymmetric allylboration[83] and nitroaldol (tertiary nitroaldol resolution[84]) reactions on ketones, Mannich[85] and Strecker[86] type reactions on ketimines, alkenylation and arylation of trifluoromethylketones[87] and isatins[88] have been reported since the completion of this manuscript.

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