

Formation of Quaternary Stereocentres by Copper-Catalysed Enantioselective Conjugate Addition Reaction

Beatriz Maciá

Abstract Remarkable progress in copper-catalysed enantioselective conjugate addition (ECA) reactions has been made over the past decade. This enantioselective transformation now allows the challenging formation of chiral quaternary centres by addition of different nucleophiles to trisubstituted α,β -unsaturated systems. This chapter summarises the developments in the area.

Keywords Conjugate addition · Copper catalysis · Enantioselective catalysis · Quaternary centres

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Abbreviations

CA	Conjugate addition
CBz	Carboxybenzyl

B. Maciá (✉)

Division of Chemistry and Environmental Science, Faculty of Science and Engineering,
Manchester Metropolitan University, John Dalton East, Oxford Road, M1 5GD Manchester, UK
e-mail: B.Macia-Ruiz@mmu.ac.uk

cHex	Cyclohexyl
cPent	Cyclopentyl
CuTC	Copper(I)-thiophene-2-carboxylate
DCM	Dichloromethane
DME	Dimethoxyethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	Dimethylsulfoxide
ECB	Enantioselective conjugate borylation
HMPA	Hexamethylphosphoramide
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NIS	<i>N</i> -Iodosuccinimide
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

1 Introduction

Quaternary stereocentres, which bear four different carbon or heteroatom substituents at the four vertices of a tetrahedron, add greatly to the three dimensionality and novelty of molecules [1]. Three-dimensional structures represent a much larger fraction of the chemical space and often have superior properties compared to flat aromatic compounds [2], since they can interact better with the target protein, which has a three-dimensional structure as well. Several recent studies have suggested that drug candidates with a larger fraction of sp^3 carbons and chiral centres have a lower rate of attrition in the clinic [3]. However, building quaternary stereocentres is challenging [4–7], which has hampered their implementation in the synthesis of medicines, agriculturals and potentially other areas such as flavouring, fragrances and materials [8]. One of the difficulties of constructing quaternary centres in a stereoselective manner is their congested nature [9]. Remarkable advances have been made during the last decade in the stereocontrolled construction of quaternary stereocentres using chemical catalysis [10, 11]. Catalytic asymmetric transformations, including Diels Alder, Heck, conjugate additions and allylic substitution reactions, allow the synthesis of quaternary stereocentres [12, 13].

Since the initial reports in the mid-1990s, metal-catalysed enantioselective conjugate addition (ECA) reactions have evolved as an important tool for the synthetic chemist to access to enantiopure molecules [14–16], such as the natural products and biologically active compounds represented in Fig. 1 [17–24].

Most of the research efforts in the field of ECA involve the use of rhodium [25], palladium [26] and copper catalysis [27]. From all these transition metals able to catalyse an ECA reaction, copper is probably the most versatile [28]. Copper is not only one of the cheapest transition metals used in asymmetric catalysis, but it is also

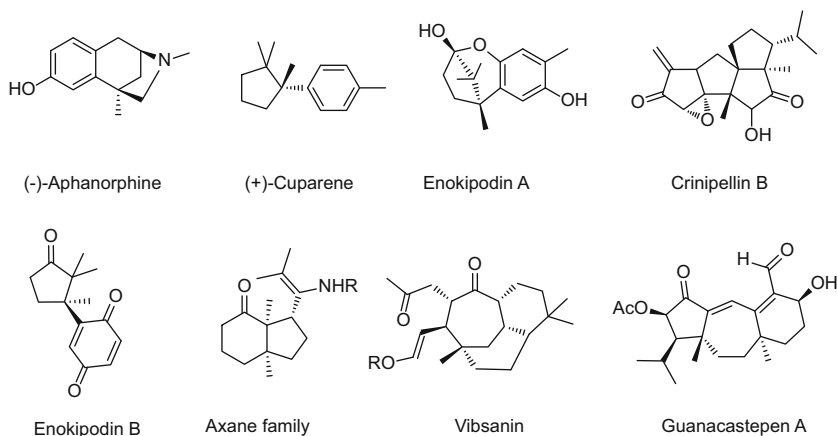


Fig. 1 Examples of natural products and biologically active compounds containing chiral quaternary centres, synthesised by copper-catalysed ECA

easily transmetalated from many organometallic reagents, such as organoaluminium, magnesium and zinc. Rhodium and palladium were initially preferred for the ECA reaction with aryl and alkenyl nucleophiles, but nowadays the copper-catalysed ECA is not restricted anymore to alkyl nucleophiles, and aryl/alkenyl counterparts give comparable levels of enantiocontrol to the other metals.

Over the past two decades, the copper-catalysed ECA of nitroalkenes and Meldrum acid derivatives and, more recently, simple cyclic and acyclic enones and other α,β -unsaturated systems, with different organometallic reagents, has emerged as a powerful approach to access chiral molecules [29–31]. Two substituents in the β -position of an α,β -unsaturated system hamper the conjugate addition of the nucleophile; however, several highly efficient copper-based catalytic systems are able to overcome this barrier and allow the synthesis of quaternary stereogenic centres with very good selectivities [32, 33], as it will be presented in the following pages of this chapter. Alternative strategies to facilitate the copper-catalysed formation of quaternary chiral centres include the activation of the β,β -disubstituted α,β -unsaturated systems (by making the β -position more electrophilic) by using Lewis acidic nucleophiles or by the implementation of additional electron-withdrawing functionalities in the substrate.

This chapter is an overview of the copper-based catalytic systems that enable the formation of chiral quaternary centres through conjugate addition reactions. The existing methodologies have been classified in three main sections, according to the nature of the nucleophile that participates in the ECA reaction. Thus, Sect. 2 covers carbon nucleophiles, including organoaluminium (Sect. 2.1), Grignard (Sect. 2.2), organozinc (Sect. 2.3) and organozirconium reagents (Sect. 2.4). Next, Sect. 3 reviews the use of organoboron reagents, to form boron-containing quaternary centres. And last, Sect. 4 presents the use of organosilicon reagents, to form silicon-containing quaternary centres.

After the ECA reaction step, the generated enolate requires protonation to generate the corresponding enol, which rapidly tautomerises to the ketone product.

Protonation is typically carried out by the addition of water, aqueous NH_4Cl or aqueous HCl . For simplicity, this step has been omitted in all schemes, and only the conditions for the ECA have been presented.

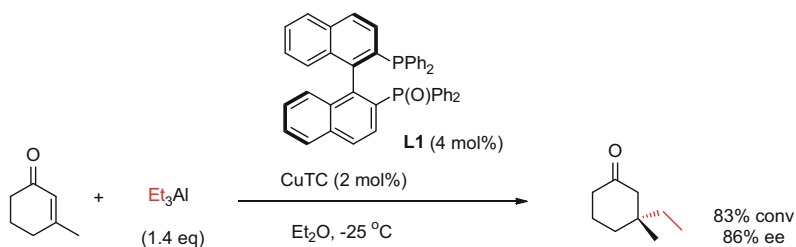
2 Formation of All Carbon Quaternary Centres by Copper-Catalysed ECA

2.1 Organoaluminium Reagents as Nucleophiles

Aluminium reagents are strong Lewis acids that can coordinate to the oxygen atom of the enone and thus render the substrate more electrophilic. For this reason, these organometallic reagents were the first to be successfully utilised for the formation of quaternary centres by reaction with a β,β -disubstituted enone. Enantioselective conjugate addition reactions with organoaluminium reagents are usually carried out in coordinating solvents such as Et_2O or THF, as this allows the cleavage of the AlR_3 dimeric species, thus increasing its reactivity.

Initial attempts at copper-catalysed conjugate addition with organoaluminium reagents and β -substituted cyclic enones utilised the hemilabile P,O-heterobidentate and axially chiral (*R*)-BINPO (**L1**, Scheme 1) [34]. The presence of a soft phosphorous centre which could bind to copper and also a hard oxygen centre that could potentially coordinate to aluminium was thought to lead to a highly organised, asymmetric transition state. Although not reaching full conversion (83%), the addition of triethylaluminium in diethyl ether at -25°C gives 86% enantiomeric excess (Scheme 1).

Phosphoramidite ligands are more efficient in the generation of stereogenic quaternary centres by copper-catalysed addition of aluminium organyls to β -substituted cyclic enones. Alexakis has demonstrated that excellent enantiomeric excesses can be achieved with catalytic amounts of **L2-3** (Fig. 2) and CuTC, for a range of commercially available nucleophiles and β -substituted cyclic enones (Schemes 2 and 3) [35, 36]. In general, ‘simple’ substrates give excellent conversions, isolated yields and enantioselectivities, whereas Michael acceptors such as five-membered ring systems and highly hindered substrates need carefully optimised conditions.



Scheme 1 Copper-catalysed ECA to β -substituted cyclohexenones by Alexakis [34]

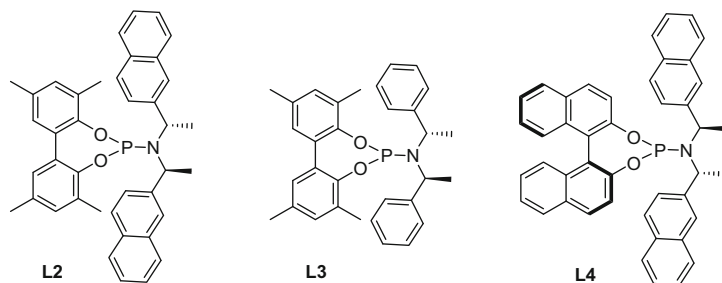
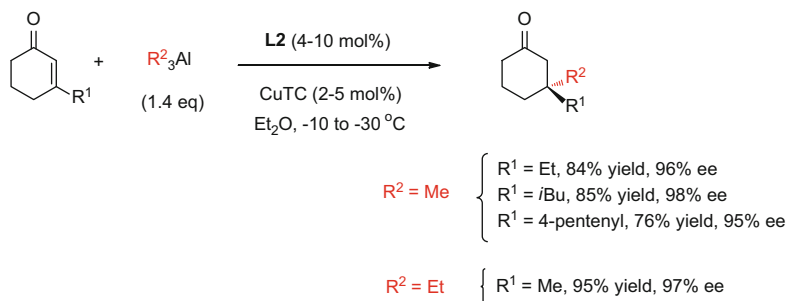
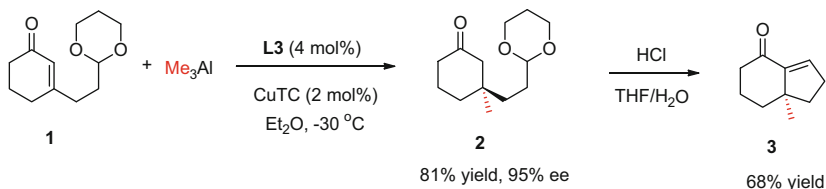


Fig. 2 Effective phosphoramidite ligands for the copper-catalysed ECA of organoaluminium reagents to enones



Scheme 2 Copper-phosphoramidite-catalysed ECA to β -substituted cyclohexenones by Alexakis [35]

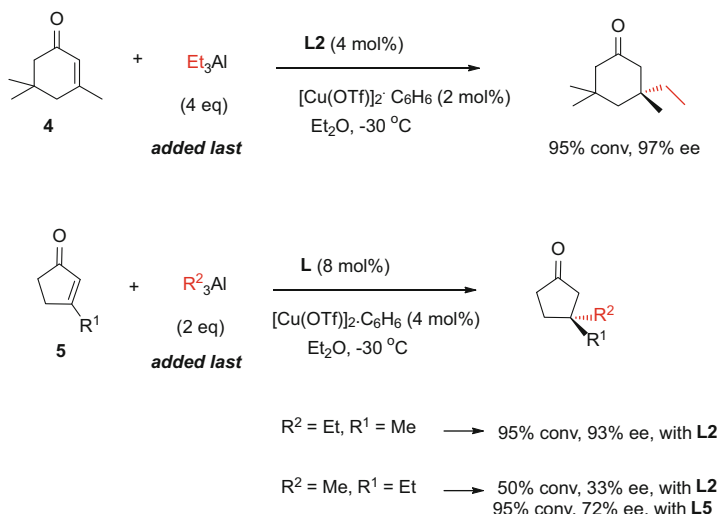


Scheme 3 Copper-phosphoramidite-catalysed ECA to functionalised β -substituted cyclohexenones by Alexakis [36]

With this catalytic system, the order of addition of the reagents is crucial for the outcome of the reaction, and better results are normally achieved when the enone is added last to the reaction mixture, after the addition of the organoaluminium reagent.

In general, both Me_3Al and Et_3Al work well with this methodology, and high yields and enantioselectivities can be achieved in the addition to β -substituted cyclohexenones, as represented by the key examples in Scheme 2 [35].

Functionalised enones are also compatible with this methodology and easily undergo stereoselective copper-catalysed conjugate addition with trimethylaluminium reagents in the presence of phosphoramidite ligand **L3**. Thus, **1** can be converted by treatment with Me_3Al into the chiral ketone **2** (95% ee), which can be



Scheme 4 Copper-catalysed ECA to bulky β -substituted cyclohexenones and β -substituted cyclopentenones by Alexakis [37]

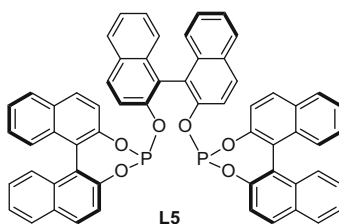
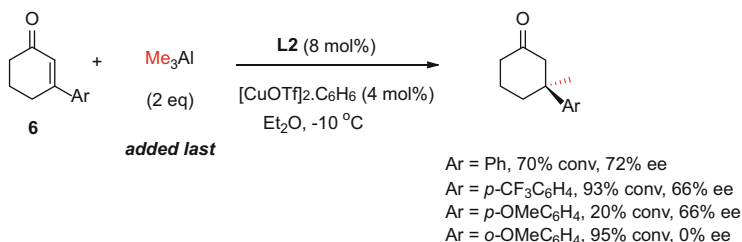


Fig. 3 Chiral diphosphite ligand for the addition of organoaluminium reagents to β -substituted cyclopentenones by Alexakis [37]

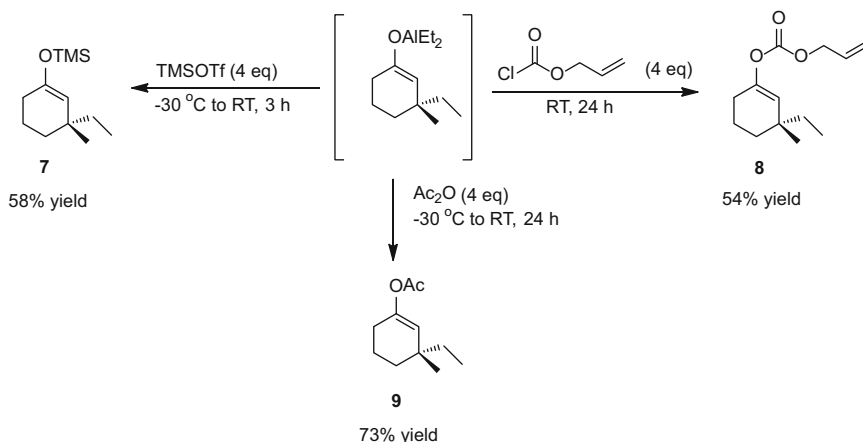
transformed into the bicyclic product **3** under acidic conditions. This method is also suitable for the generation of quaternary stereogenic centres at the β position of cyclopentanones [36]. The main limitation of this methodology is the performance of bulky nucleophiles, such as triisobutylaluminium (*i*Bu₃Al), which often lead to complex reaction mixtures.

Similarly, sterically demanding substrates, such as the isophorone **4** and β -substituted cyclopentenones **5**, also proved challenging, but moderate to good enantioselectivities can be achieved when a ‘reverse’ addition protocol (i.e. adding the organoaluminium reagent last to the reaction mixture, after the addition of the enone, Scheme 4) is conducted. For the addition of organoaluminium reagents to β -substituted cyclopentenones **5**, the chiral diphosphite ligand **L5** (Fig. 3) provides slightly better results than the phosphoramidite ligands [37].

Phosphoramidite ligands are also able to promote the addition of organoaluminium reagents to aromatic cyclohex-2-en-1-ones **6**, using again a reverse addition protocol (Scheme 5) [36, 38]. Only moderate yields and enantioselectivities are reached for these substrates with this methodology, and detrimental



Scheme 5 Copper–phosphoramidite-catalysed ECA to β-aryl cyclohexenones by Alexakis [38]

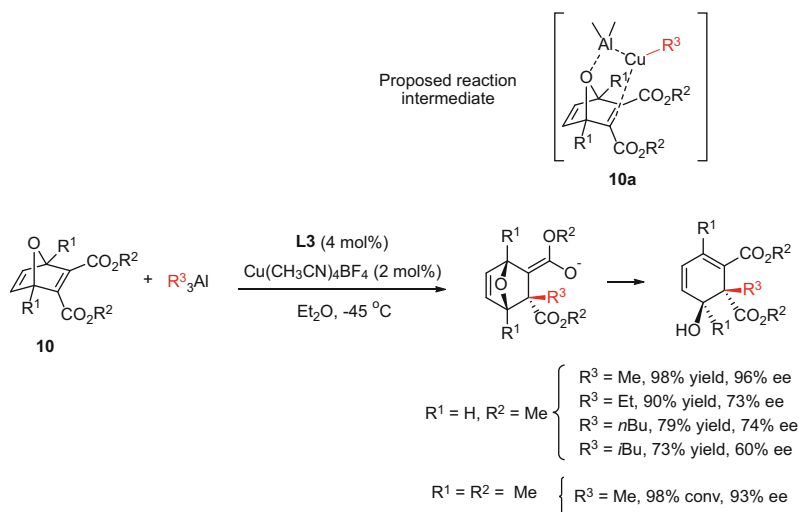


Scheme 6 In situ trapping of aluminium enolates by Alexakis [36]

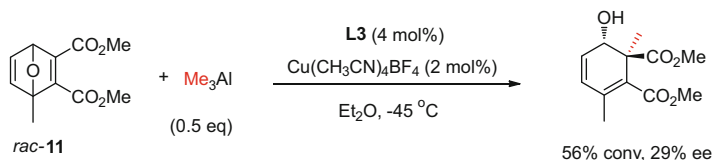
steric and electronic effects are observed. For example, the addition of Me₃Al to 3-phenyl-cyclohexenone gives 72% *ee*, whilst functionalised aromatic groups give up to 66% *ee*. If the substituent of the phenyl group is in the *ortho*-position, racemic product is obtained.

The aluminium enolates generated after ECA do not react directly with electrophiles, probably due to their high stability. However, they can be trapped in situ by silylation, carbonation and *O*-acylation in good yields (Scheme 6). These intermediates 7–9 can eventually be used in Tsuji reactions or ozonolysis, for example, to generate more elaborated adducts [36].

Trialkylaluminium reagents have been shown to undergo copper–phosphoramidite-catalysed ECA reaction with oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates **10**, with the simultaneous creation of up to two adjacent quaternary stereocentres (Scheme 7) [39]. The conjugate addition occurs from the *exo*-side, probably due to coordination by the bridging oxygen atom (see intermediate **10a**). The intermediate enolate subsequently undergoes β-elimination opening the ring. The *syn*-relative stereochemistry of the products indicates a conjugate addition/elimination mechanism rather than an allylic substitution, which would have afforded the *endo*-addition product.



Scheme 7 Copper–phosphoramidite-catalysed ECA to oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates by Alexakis [39]



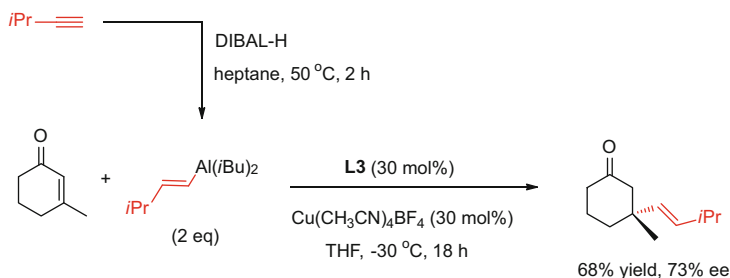
Scheme 8 Copper–phosphoramidite-catalysed ECA to racemic dimethyl 1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate by Alexakis [39]

The best enantiomeric excesses on this type of oxabicyclic substrates are obtained with Me_3Al . The addition of Et_3Al , nPr_3Al , nBu_3Al and iBu_3Al gives good yields (70–92%) but moderate enantioselectivities (55–73%). When bulkier isopropyl esters are used, instead of methyl esters, both yield and enantioselectivity of the reaction drop (73% yield and 67% ee for the addition of Me_3Al to the isopropyl esters analogue **10** where $R^1=H$, $R^2=iPr$).

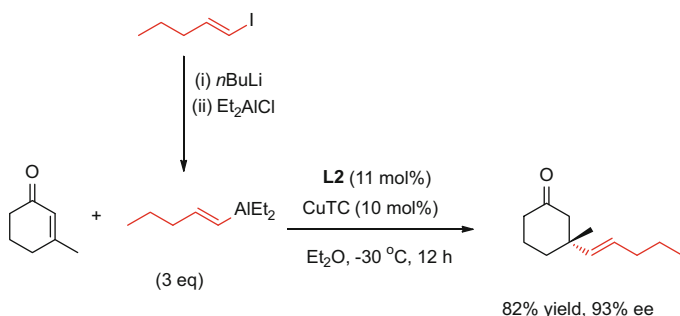
Unfortunately, this methodology does not allow kinetic resolution of racemic mixtures. When a racemic oxabicyclic substrate, such as **11**, is used with 0.5 equiv. of trimethylaluminium, only poor enantioselectivities are obtained (Scheme 8).

Phosphoramidite ligands are also suitable for the challenging enantioselective addition of alkenyl aluminium reagents to β -substituted cyclic enones [36]. Although the introduction of alkenyl groups to enones has been largely the domain of Rh catalysis [40, 41], the remarkable advances in copper-catalysed ECA have now made this transformation possible.

Alkenyl aluminium reagents can be easily generated by hydroalumination of the corresponding alkynes with DIBAL-H, under Zweifel conditions (Scheme 9)



Scheme 9 Copper-phosphoramidite-catalysed ECA of alkenyl aluminium reagents (prepared via hydroalumination) to β-substituted cyclohexenones by Alexakis [36]

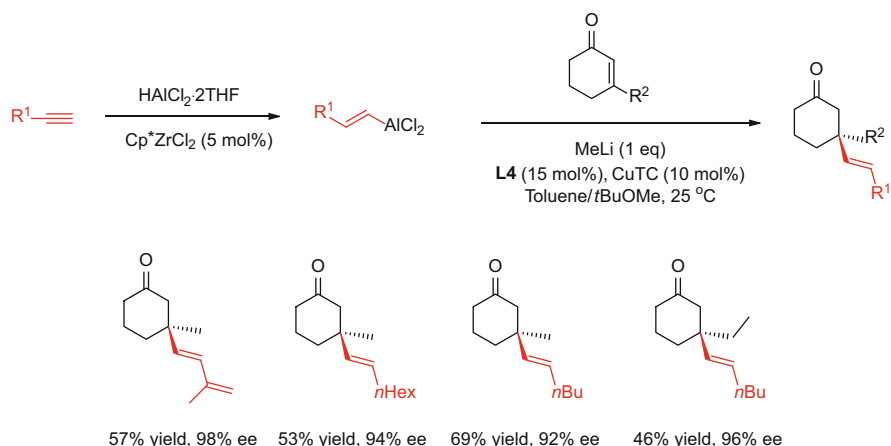


Scheme 10 Copper-phosphoramidite-catalysed ECA of alkenyl aluminium reagents (prepared from iodoalkenes) to β-substituted cyclohexenones by Alexakis [32, 44]

[42]. Interestingly, the use of the ‘standard’ conditions (CuTC , Et_2O), optimal for the ECA of alkyl aluminium reagents with phosphoramidite ligands, only leads to the 1,2-addition–dehydration product when alkenyl aluminium reagents are used as nucleophiles. However, the use of THF as solvent suppresses the 1,2-addition by-product and allows moderate yields and enantioselectivities, albeit at catalyst loadings up to 30 mol% (Scheme 9). A possible explanation for the need of such large amounts of catalyst might be that in the hydroalumination reaction, about 6% of Al acetylide is formed by deprotonation of the corresponding terminal alkyne. These Al acetylides are known to strongly bind to copper and act as non-transferable ligands in cuprate chemistry [43].

Alkenyl aluminium reagents can be also prepared by halogen/lithium exchange from the corresponding iodoalkene, followed by transmetalation with Et_2AlCl . In this way, the formation of Al acetylides is avoided and lower catalysts loading for the ECA are allowed (Scheme 10) [32, 44].

Recently, Woodward et al. have described the synthesis of alkenylaluminium reagents from their corresponding alkynes and $\text{HAlCl}_2 \cdot 2\text{THF}$, using $\text{Cp}^*_2\text{ZrCl}_2$ as



Scheme 11 Copper–phosphoramidite-catalysed ECA of alkenyl aluminium reagents (prepared via zirconium-catalysed hydroalumination) to β -substituted cyclohexenones by Woodward [45]

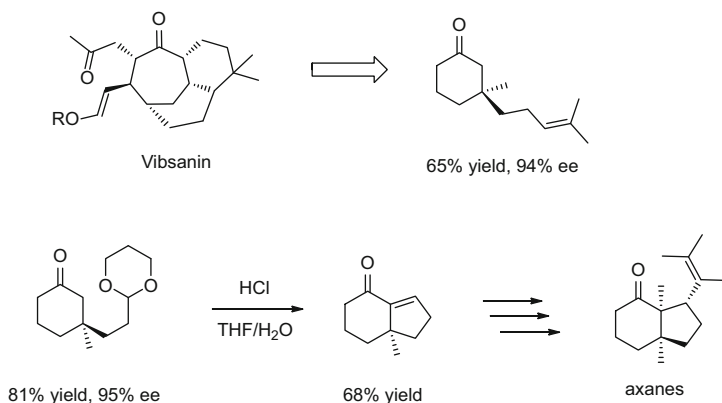
catalyst. The initially obtained aluminium species can be activated with MeLi (1 equiv.)¹ to generate the alane (*E*)- ClAlMeCH=CHR^1 which, under copper(I)–phosphoramidite catalysis with a cyclic enone, provides the corresponding 1,4-addition product with high enantioselectivity (Scheme 11) [45]. This process shows good generality for 1,4-additions to a wide variety of β -substituted cyclohexenones. The alkenyl aluminium reagents generated by this methodology are more reactive than those prepared by hydroalumination with DIBAL-H (which bear a bulky isobutyl substituent on the aluminium atom) and therefore lead to faster reactions and higher yields.

The synthetic utility of copper–phosphoramidite-catalysed conjugate additions as a means for generating quaternary stereocentres using organoaluminium reagents has been demonstrated with the synthesis of several key intermediates in natural product syntheses, as represented in Scheme 12 [36, 46].

Introduced by Alexakis et al., copper–phosphinamine systems also stand out as effective catalysts for the addition of organoaluminium reagents to cyclic enones [46, 47]. In many cases, and in particular with challenging substrates, phosphinamine ligands (Fig. 4) outperform the phosphoramidite counterparts.

For example, phosphinamine ligands are not only efficient in the addition of linear organoaluminium reagents to both bulky and non-bulky β -substituted cyclic enones (Scheme 13) but perform particularly well with β -aryl-substituted cyclic enones, giving higher yields and enantioselectivities than phosphoramidite ligands (Scheme 14 versus Scheme 5).

¹ Strangely, the use of two equivalents of MeLi gave poor processes – despite the known efficacy of $\text{Me}_2\text{AlCH=CHR}$ species in related processes.



Scheme 12 Copper-phosphoramidite-catalysed ECA of organoaluminium reagents in the synthesis of some key intermediates from natural products by Alexakis [36, 46]

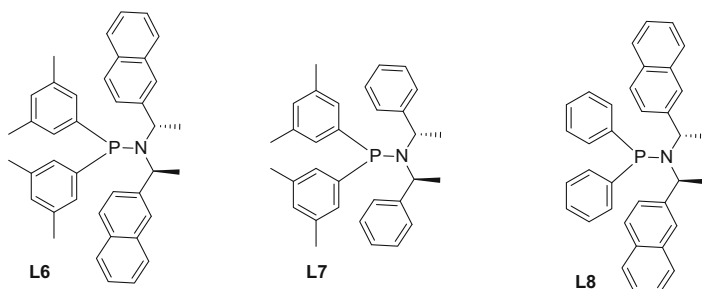
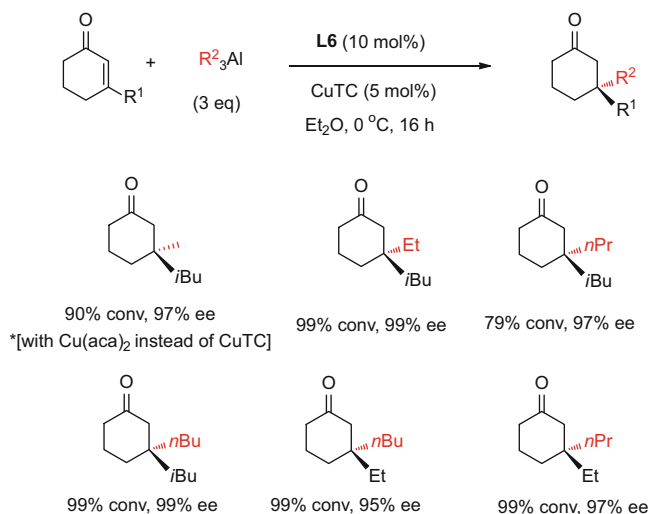


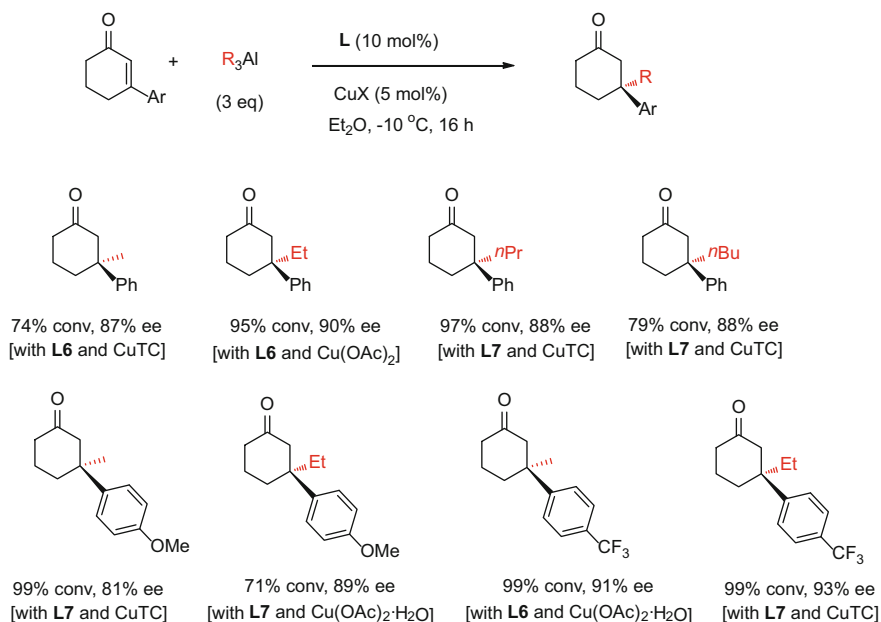
Fig. 4 Effective phosphinamine ligands for the copper-catalysed ECA of organoaluminium reagents to β,β -disubstituted enones

Regarding the challenging β -substituted cyclopenten-2-one substrates, phosphinamine ligands give moderate, comparable enantioselectivities to phosphoramidites, as shown in Scheme 15.

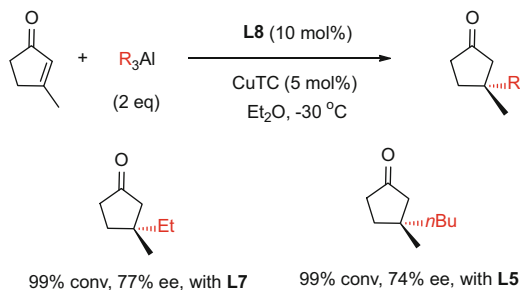
The tandem hydroalumination–ECA process to β -substituted cyclic enones with phosphinamine ligands also works very efficiently (Scheme 16) [48, 49]. The best copper source for this catalytic system is copper (II) naphthenate, which is cheaper than the CuTC used in previous methodologies and can be used as a stock solution. A wide range of alkenylaluminium reagents can be added with very good levels of enantioselectivity, including (*Z*)-nucleophiles, halogen-containing alkenes, conjugated alkenes, protected alcohols and α -substituted alkenes, which might be difficult to achieve using other organometallic species. Furthermore, this methodology allows high levels of enantioselectivity for sterically hindered substrates, although further activation with 1 equiv. of Me_3Al is required to obtain high conversion (see example in Scheme 16). Cycloheptenone substrates can be also used (see example in Scheme 16), but unfortunately, the cyclopentenone analogues give low levels of enantioselectivity with this method.



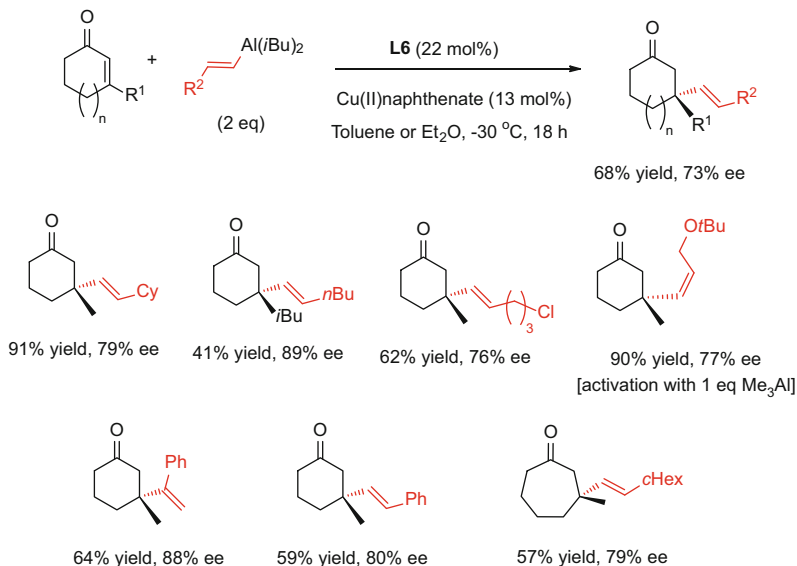
Scheme 13 Copper–phosphinamine-catalysed ECA of organoaluminium reagents to β -substituted cyclohexenones by Alexakis [46, 47]



Scheme 14 Copper-catalysed ECA of organoaluminium reagents to β -aryl cyclohexenones by Alexakis [46, 47]



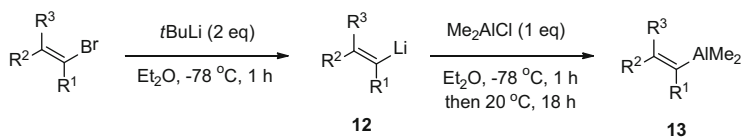
Scheme 15 Copper–phosphinamine-catalysed ECA of organoaluminium reagents to β -substituted cyclopentenones by Alexakis [46, 47]



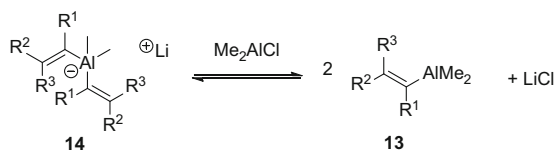
Scheme 16 Copper–phosphinamine-catalysed ECA of alkenyl aluminium reagents (prepared by hydroalumination with DIBAL-H) to β -substituted cyclic enones by Alexakis [48, 49]

It is worth mentioning that no transfer of the isobutyl group from the alkenyl aluminium reagents is observed in any case; the preferential transfer of the vinylic group occurred exclusively.

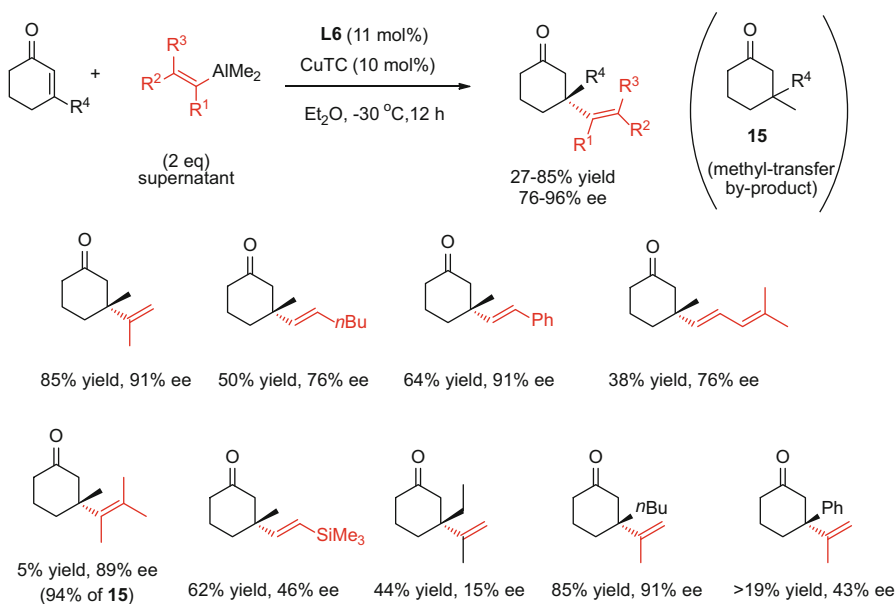
As mentioned before, the amounts of copper and ligand needed for the ECA of alkenyl aluminium reagents can be diminished if the nucleophile is prepared from the corresponding alkene halide instead of by a hydroalumination process. For example, a halogen/lithium exchange (using $t\text{BuLi}$), followed by transmetalation with dimethylaluminium chloride, provides the desired alkenyl aluminium reagent (Scheme 17) that can be used directly in the ECA reaction [49, 50]. It is important to stir the 2-alkenyl lithium **12** and the Me_2AlCl overnight, at room temperature, to cleanly obtain the desired alane **13** by allowing its equilibration from the initially formed alanate **14** (Scheme 18).



Scheme 17 Preparation of alkenyl aluminium reagents from bromoalkenes by Alexakis [49, 50]



Scheme 18 Equilibrium reaction between alkenyl organoaluminium species generated from bromoalkenes [50]



Scheme 19 Copper-phosphinamine-catalysed ECA of alkenyl aluminium reagents (prepared by Br/Li exchange) to β -substituted cyclic enones by Alexakis [49, 50]

Bromoalkenes are the preferred starting material for the generation of the corresponding nucleophile **13**, since many are commercially available or readily prepared [51–55]. Whilst the methodology is also efficient when iodoalkenes are used as the precursors for the organoaluminium reagent, a very precise temperature protocol must be followed and Et_2AlCl provides better results in the transmetalation process [32, 44].

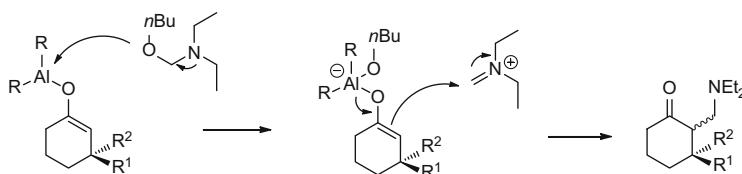
The supernatant solution of the generated alkenyl aluminium reagent **13** can be used directly in the ECA to β -substituted cyclohex-2-enones (Scheme 19), providing good yields and enantioselectivities with only 10 mol% of the Cu–

phosphinamine catalyst. The enantioselectivity of the process varies with the equivalents of organoaluminium reagent added. When decreased quantities of nucleophile **13** are used, the enantiomeric excess improves but the amount of methyl transfer also increases and more of the by-product **15** is obtained. Using more than 2.0 equiv. of **13** leads to a drop in enantioselectivity, probably due to contamination of the organoaluminium reagent with traces of lithium salts, which might perturb the structure of the chiral copper complex.

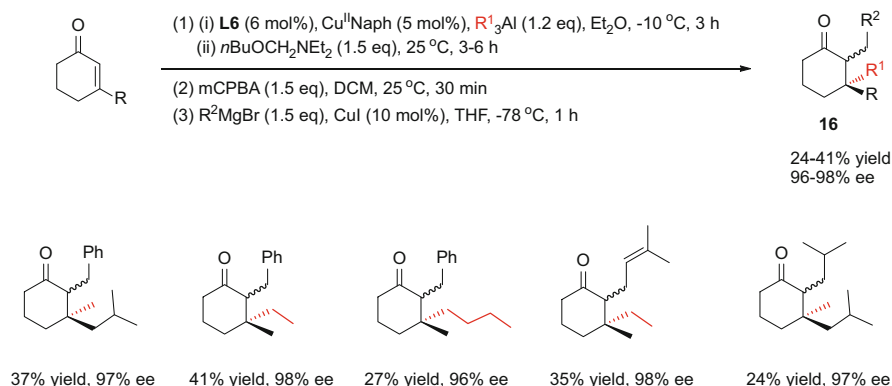
General observations and limitations on the copper–phosphinamine-catalysed CA of alkenyl aluminium reagents include:

1. Hindered alkenylaluminium reagents produce higher amounts of the methyl transfer by-product **15**.
2. Alkenylaluminium reagents where R^2 =aryl group provide higher enantioselectivities than when R^2 =alkyl group (see Scheme 17 and examples in Scheme 19).
3. Silyl-protected vinyl aluminiums give disappointing results (see example in Scheme 19).
4. Dimethylvinylaluminium (generated by either a bromine–lithium exchange from vinyl bromide and subsequent trapping with Me_2AlCl or by transmetalation of a vinyl Grignard reagent) gives low enantioselectivities.
5. Changing the substituent on the β -position of the cyclohexenone from methyl to ethyl, butenyl or phenyl leads to significant drops in conversion and enantioselectivity.
6. Five- and seven-membered substrates give lower enantioselectivities than cyclohexenones.
7. Conjugate addition to acyclic enones furnishes the product as racemic mixtures.

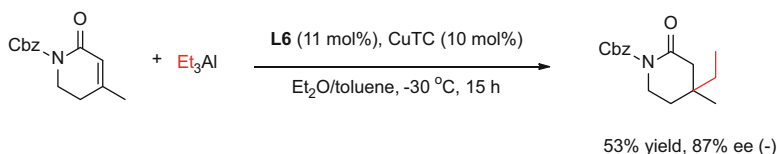
Phosphinamine ligands have also been applied to the formation of chiral and sterically congested cyclohexanone derivatives through a multistep sequence using (*n*-butoxymethyl)-diethylamine for the direct trapping of the aluminium enolate (Scheme 20) [56]. As mentioned before, aluminium enolates (and those adjacent to an all-carbon quaternary stereocentre in particular) are not very reactive towards most electrophilic species. However, when an α -aminoether is used as electrophile, the trapping process works efficiently. The (*n*-butoxymethyl)-diethylamine coordinates to the aluminium enolate, and a subsequent transfer of the *n*-butoxy group to the aluminium takes place, forming the desired electrophile, but also activating the



Scheme 20 Mechanism for the direct trapping of sterically encumbered aluminium enolates by Alexakis [56]



Scheme 21 Tandem copper-phosphinamine-catalysed ECA/direct trapping by Alexakis [56]



Scheme 22 Copper-phosphinamine-catalysed ECA of organoaluminium reagents to β-methyl-substituted δ-lactams by Alexakis [57]

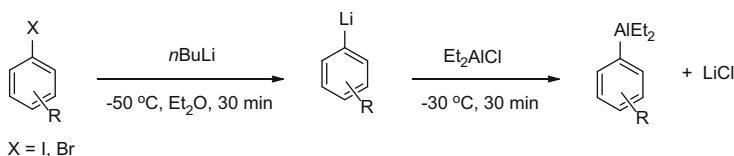
enolate in the same step. The formation of a reactive electrophile and reactive nucleophile in close proximity explains the high efficiency of this transformation.

After work-up and oxidation with *m*-CPBA, an elimination reaction takes place to generate a double bond. A second CA with a Grignard reagent can be then performed to provide products **16** in 27–41% overall isolated yields with good enantioselectivities (Scheme 21).

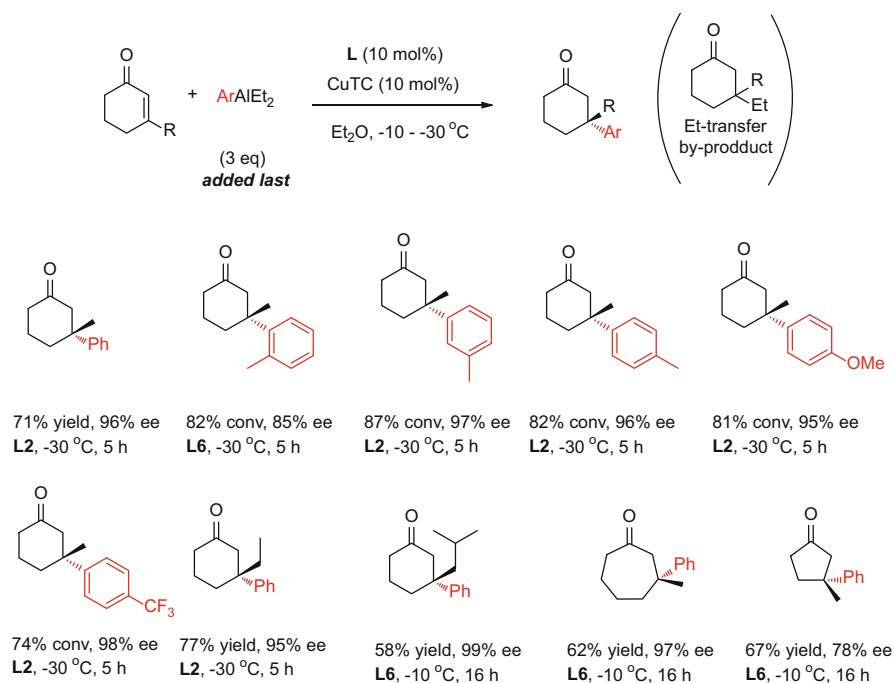
The versatile phosphinamine ligands are also suitable for the copper-catalysed ECA of organoaluminium reagents to α,β-unsaturated lactams, including β-methyl-substituted δ-lactams, whose reaction allows the formation of all-carbon quaternary stereogenic centres in moderate yields and good enantioselectivities, as exemplified in Scheme 22 [57].

Regarding the use of aryl aluminium reagents as nucleophiles in the copper-catalysed ECA, both phosphoramidites and phosphinamine ligands have demonstrated to be effective. Only one triaryl aluminium compound is commercially available (Ph₃Al), but its use as nucleophile would not be an atom-economical process. For this reason, readily available dialkyl aryl aluminium species are preferred. The preparation of these mixed aryl alkanes can easily be achieved from the corresponding aryl iodide or bromide through a halogen/Li exchange (with *n*BuLi) followed by a Li/Al transmetalation process with Et₂AlCl (Scheme 23) [44].

A suspension of an aryl aluminium reagent prepared with this method can be directly added to an enone without the need to remove the LiCl. The aryl transfer to



Scheme 23 Preparation of dialkyl aryl aluminium species from aryl halides by Alexakis [44]



Scheme 24 Copper-phosphinamine-catalysed ECA of aryl aluminium reagents to β -substituted cyclic enones by Alexakis [44]

the β -position of the enone is always preferred to the ethyl transfer. The addition of a wide variety of aryl organoaluminium reagents proceeds with enantioselectivities up to 99%, using 10 mol% of ligand (note that this catalyst loading is slightly higher than when alkyl organoaluminium reagents are used as nucleophiles) and 10 mol% of the copper salt with both six- and seven-membered ring cyclic enones (Scheme 24). Three equivalents of the organoaluminium reagent are needed, which must be added last to the reaction mixture, after the enone, in order to achieve good results. Reaction conditions and ligand may also need to be adapted for the more challenging, bulkier substrates. Higher temperatures and longer reaction times are usually needed in these cases in order to achieve satisfactory conversion, although, unfortunately, this leads to an increase of ethyl transfer. The main limitation of this methodology is the reduced enantioselectivity obtained with five-membered cyclic enones (see example in Scheme 24).

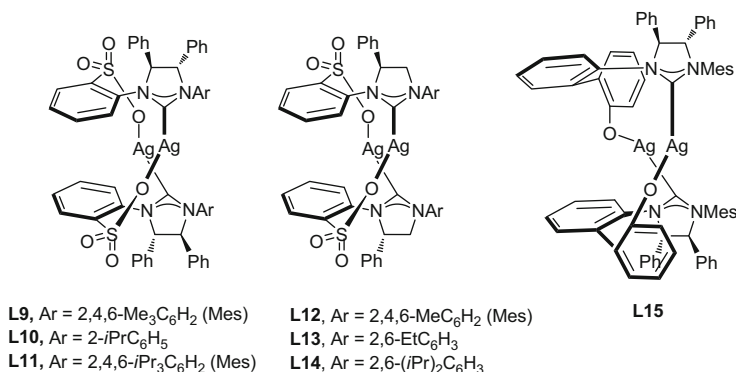


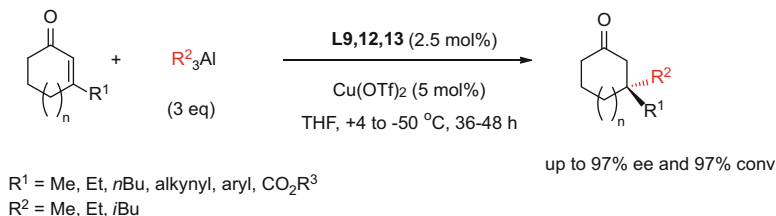
Fig. 5 Effective NHC ligands for the ECA of organoaluminium reagents to β,β -disubstituted enones

A different and very versatile class of catalysts for the addition of organoaluminium reagents to β -substituted cyclic enones are the silver-*N*-heterocyclic carbene (NHC) complexes **L9–L14** developed by Hoveyda and co-workers (Fig. 5) [58].

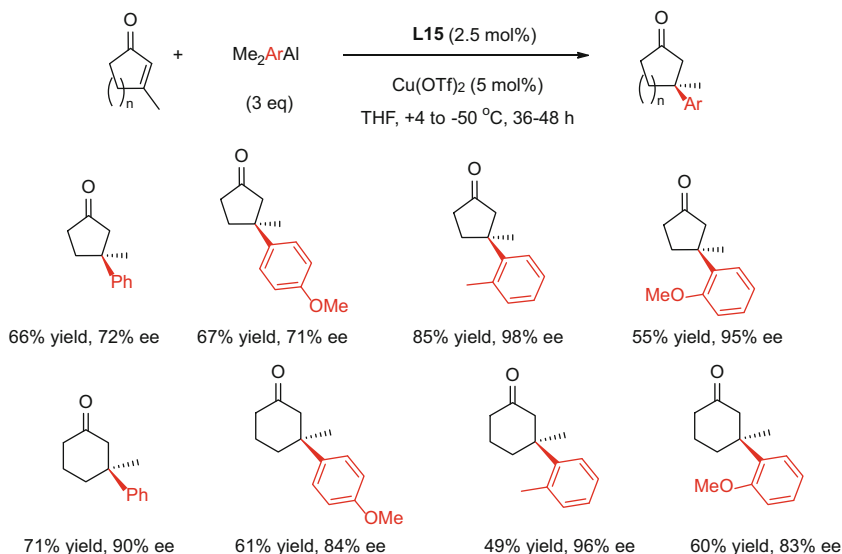
Since their discovery in 1968 by Öfele [59] and Wanzlick [60], and their first isolation in the free state by Arduengo [61] in the early 1990s, NHCs have received a growing attention as catalysts in many organic transformations [62]. These NHC ligands are likely to surpass in popularity well-known phosphorous-based ligands because of their remarkable ability to form strong bonds with metallic centres, allowing significant doping of catalytic activity in a wide range of chemical transformations, such as olefin metathesis, carbon–carbon and carbon–nitrogen cross-coupling reactions, hydrogenation and hydrosilylation reactions [63]. The electronic donating properties of NHCs are similar to those of their phosphine counterparts, but their topological features are quite different; phosphines produce a conical environment, whereas NHCs have a planar chelation site.

The copper–NHC-catalysed addition of organoaluminium reagents to cyclohexenones and cycloheptenones reported by Hoveyda [58] is, in some cases, slightly less selective than those performed in the presence of phosphoramidites or phosphinamine catalysts ($\leq 90\%$ *ee* for the imidazolium ligands versus $\leq 99\%$ *ee* that the phosphoramidites and phosphinamine can provide). However, NHC–Cu catalysis provides better results (up to 97% *ee* and 97% conv) when challenging cyclopentenones and bulky β -substituted cyclic enones (bearing *n*-butyl, alkynyl, aryl or an ester group as the β substituent) are used as substrates (Scheme 25).

Aryl-based aluminium reagents are also compatible with Cu–NHC catalysis. These nucleophiles can be prepared by the treatment of the corresponding aryl lithium compound (which can be easily obtained by treatment of commercially available aryl bromides with *n*BuLi) with 1 equiv. of commercially available



Scheme 25 Copper–NHC-catalysed ECA of organoaluminium reagents to β -substituted cyclohexenones by Hoveyda [58]

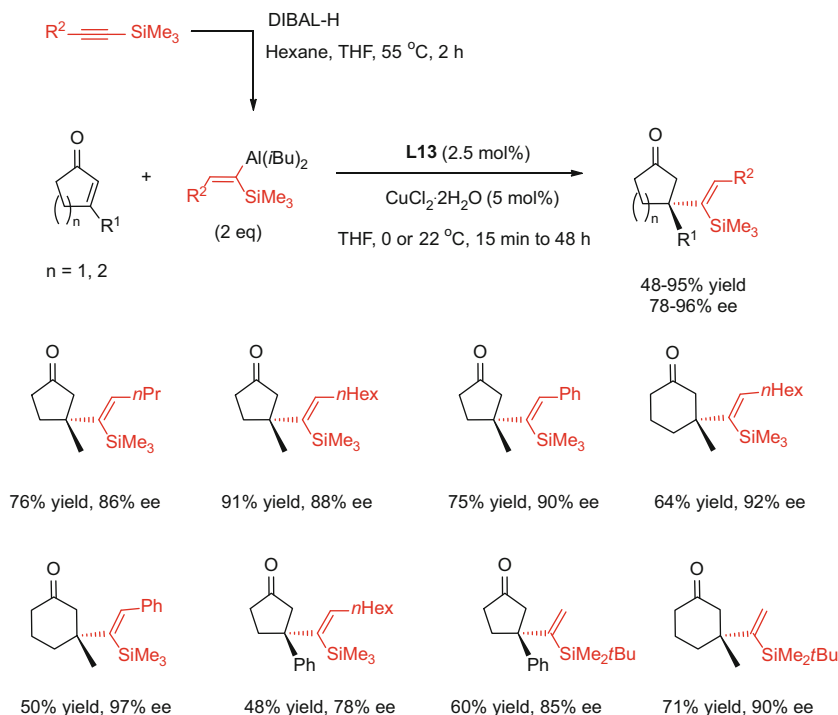


Scheme 26 Copper–NHC-catalysed ECA of aryl aluminium reagents to β -substituted cyclic enones by Hoveyda [58]

Me_2AlCl in pentane (-78 to 22 °C, 12 h).² The resulting solution of Me_2PhAl , containing LiCl , can be used directly – without filtration or purification – in the copper-catalysed ECA reactions of β -substituted cyclic enones (Scheme 26) and can be also stored under N_2 for more than 2 months without any noticeable diminution in efficiency.

As exemplified in Scheme 26, the reaction works well with five- and six-membered β -substituted cyclic enones, affording the desired products in up to

² Note that when Et_2AlCl is used as transmetalating agent (see [44]), instead of Me_2AlCl , shorter reaction times are needed for the transmetalation step (30 min at -30 °C for Et_2AlCl versus 12 h at -78 to 22 °C for Me_2AlCl).

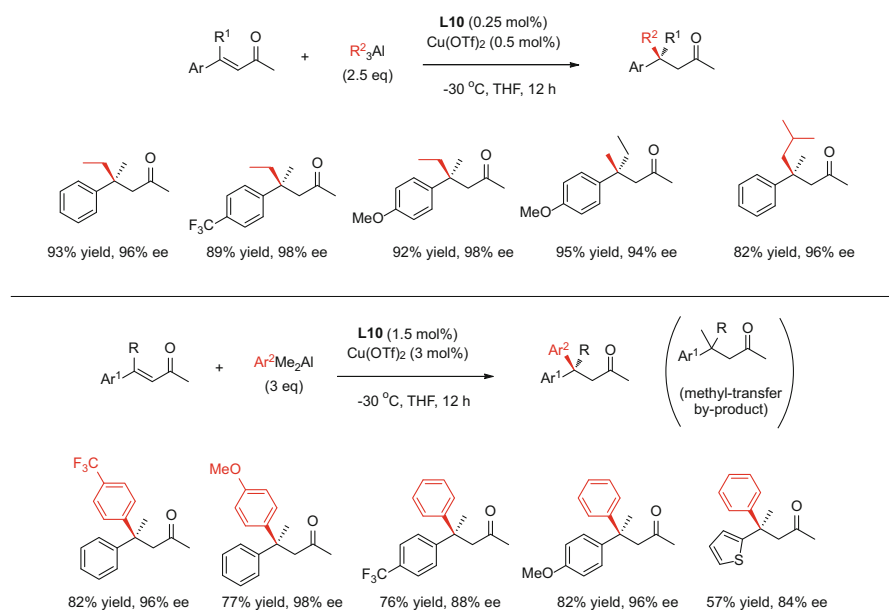


Scheme 27 Copper–NHC-catalysed ECA of alkenyl aluminium reagents (prepared by hydroalumination with DIBAL-H) to β -substituted cyclic enones by Hoveyda [64]

98% ee. Aryl lithium species bearing electron-donating and electron-withdrawing substituents can be used effectively, although enantioselectivities appear to be highest when the aryl unit is sterically more encumbered (i.e. carries an *ortho*-substituent); otherwise, levels below 90% ee are obtained. The moderate yields stated are ascribed to difficulties with the removal of biphenyl formed in the course of the transformation. Despite this, results for the five-membered rings are remarkable, considering that they are usually challenging substrates in the ECA.

The use of alkenyl aluminium reagents as nucleophiles for the copper–NHC-catalysed ECA has also been described through a tandem hydroalumination–CA process. To prevent the formation of aluminium acetylides during the hydroalumination reaction, which could perturb the chiral complex, Hoveyda and co-workers opt for the use of silyl-protected alkynes as starting material, which undergo clean *cis*-hydroalumination with DIBAL-H in coordinating solvents (Scheme 27) [64].

Although sterically congested, the resulting silicon-substituted alkenyl aluminium reagents undergo fast ECA using 1.0–5.0 mol% of a NHC–Cu complex, which is prepared from air-stable $\text{CuCl}_2\cdot 2\text{H}_2\text{O}$ and precursor **L13**. Both cyclopentenones and cyclohexenones are suitable substrates for this methodology, and only their β -aryl-substituted derivatives lead to diminished reaction rates. The challenging cyclopentenones generally react more efficiently than cyclohexenones. Catalytic



Scheme 28 Copper–NHC-catalysed ECA of organoaluminium reagents to β,β -disubstituted linear enones by Hoveyda [65]

additions of alkenyl aluminium reagents to cycloheptenones under these reaction conditions are, however, inefficient.

As represented in the last two examples in Scheme 27, vinyl aluminium reagents bearing a more hindered silyl unit ($t\text{BuMe}_2\text{Si}$ vs SiMe_3) also provide high enantioselectivities. The vinylsilane moiety within the products can be functionalised to afford acyl, vinyl iodide or desilylated alkenes in 67% to >98% yield and with >90% retention of the alkene's stereochemical identity [64].

The use of acyclic enones for ECA reactions is very challenging. They lack the ring strain of their cyclic counterparts, and most catalysts fail to differentiate the enantiotopic faces of the olefin. The 'privileged' silver–NHC complexes are effective, however, in combination with $\text{Cu}(\text{OTf})_2$ [65].

A wide range of acyclic trisubstituted enones readily undergo ECA with both commercially available trialkylaluminium reagents and the in situ-generated aryl (dialkyl)aluminium reagents. Very low catalyst loadings are sufficient (0.5–3.0 mol %) and products are formed in good yields (33–95%) and exceptional enantioselectivities (80 to 99%) (Scheme 28) [65].

The main limitations of the methodology are the low reactivity observed with *ortho*-substituted aryl(dimethyl)aluminium reagents and the competing methyl transfer-derived by-product which can be detected. Conversely, the addition of alkyl aluminium reagents to bulky substrates and non-aromatic enones proceeds with very high enantioselectivity, as exemplified in Fig. 6.

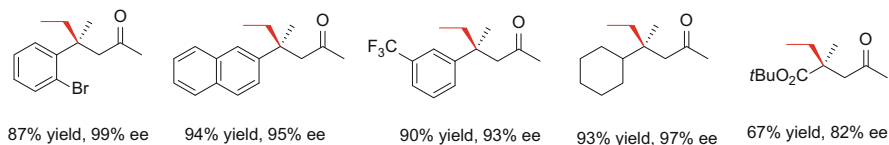
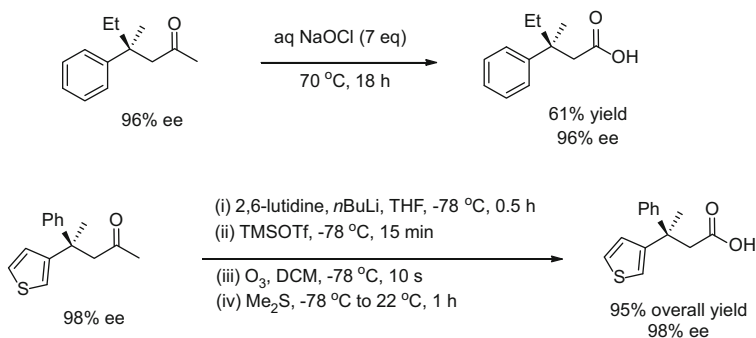


Fig. 6 Copper–NHC-catalysed ECA of organoaluminium reagents to both bulky and aliphatic β,β -disubstituted linear enones by Hoveyda [65]

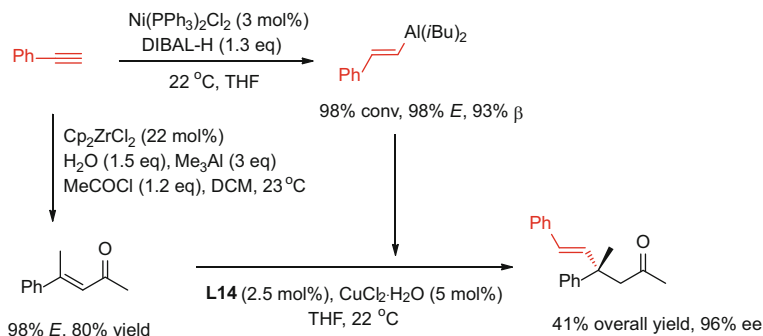


Scheme 29 Oxidation of chiral ketones to versatile carboxylic acids by Hoveyda [65]

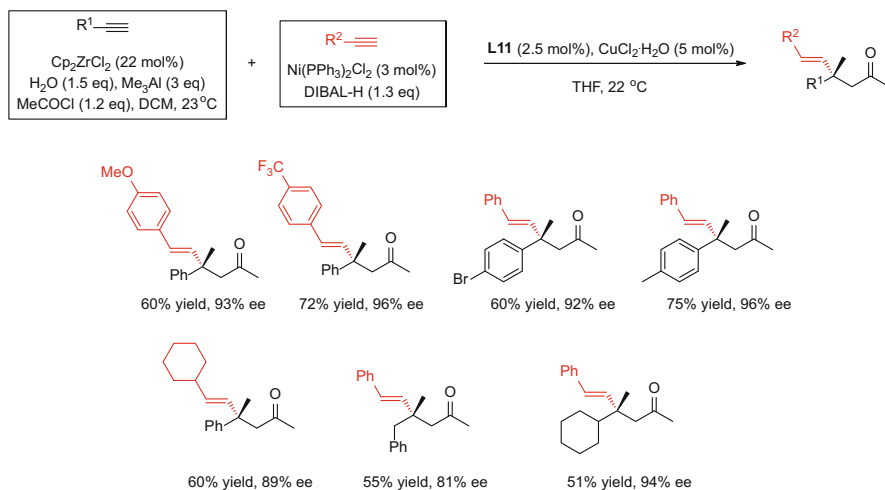
Although this methodology is not successful with acyclic carboxylic acid derivatives (e.g. Weinreb amides, *N*-acyloxazolidinones, carboxylic esters or thioesters), it is possible to reach this kind of valuable enantiomerically enriched products by a simple oxidation with commercial bleach from the corresponding ketone (Scheme 29, top). If the ketone possesses a substituent prone to oxidation, an alternative procedure, involving the formation of a silyl enol ether (which does not need isolation/purification), can be followed instead (Scheme 29, bottom).

The addition of alkenyl aluminium nucleophiles to linear β,β -disubstituted enones to give all-carbon quaternary stereogenic centres can be also achieved with consistently high yields and enantioselectivities (up to 99% ee) by copper–NHC-catalysed ECA, using very low catalyst loadings at room temperature (Scheme 30) [66].

In this work, Hoveyda et al. synthesise alkenyl aluminium reagents with exceptional site selectivity and/or stereoselectivity using a Ni-catalysed hydroalumination process and use them directly. Unlike the methodology previously described for β -substituted cyclic enones, silyl-substituted alkenyl aluminium species are not necessary to obtain high enantioselectivities with linear substrates. The overall process becomes highly efficient when the acyclic enone is also prepared through catalytic means, by a site- and stereoselective zirconocene-catalysed carboalumination/acylation reaction (Scheme 30). It is important to note that the acyclic enone prepared here must be purified by silica gel chromatography before the ECA reaction, to prevent loss of enantioselectivity. Thus, the addition of aryl- or heteroaryl-substituted β -alkenyl aluminium compounds to aryl- or alkyl-substituted substrates furnishes β -alkenyl ketones in moderate to good yields (24–60% after the



Scheme 30 Multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of alkenyl aluminium reagents to β,β -disubstituted linear enones by Hoveyda [66]



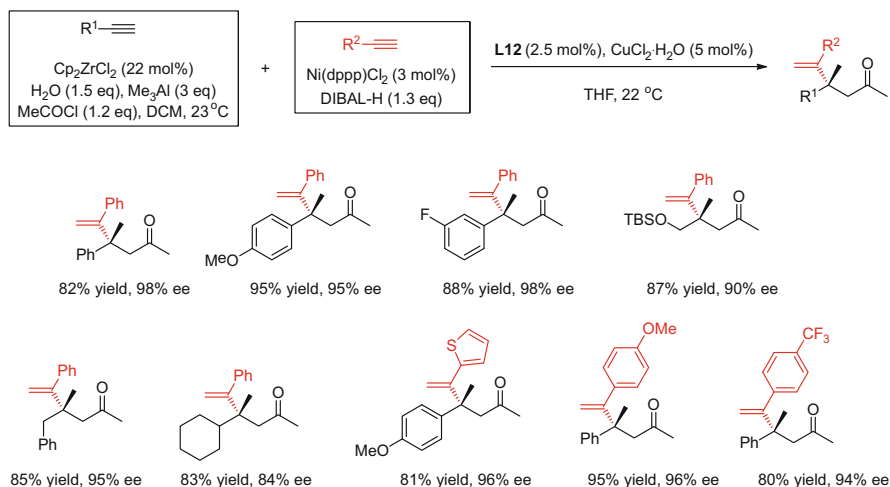
Scheme 31 Multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of linear alkenyl aluminium reagents to β,β -disubstituted linear enones by Hoveyda [66]

3 steps) and high enantioselectivities (>90%), using the NHC silver complexes **L11** (Scheme 30) or **L14** (Scheme 31) as precatalyst, in combination with $\text{CuCl}_2\cdot\text{H}_2\text{O}$.

Moreover, when the Ni-catalysed hydroalumination is carried out with Ni(dppp)Cl_2 , the α -substituted alkenylaluminium reagent is obtained, which can be also used in the ECA to acyclic enones, providing good yields and enantioselectivities when a **L12**/ $\text{CuCl}_2\cdot\text{H}_2\text{O}$ mixture is used as catalyst (Scheme 32).

Linear alkyl (vs methyl) ketones and unsaturated ketoesters are also tolerated with this methodology, as exemplified in Fig. 7.

The utility of this method has been demonstrated with the enantioselective synthesis of antimicrobial Enokipodin B (Fig. 1) [66].



Scheme 32 Multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of branched alkenyl aluminium reagents to β,β -disubstituted linear enones by Hoveyda [66]

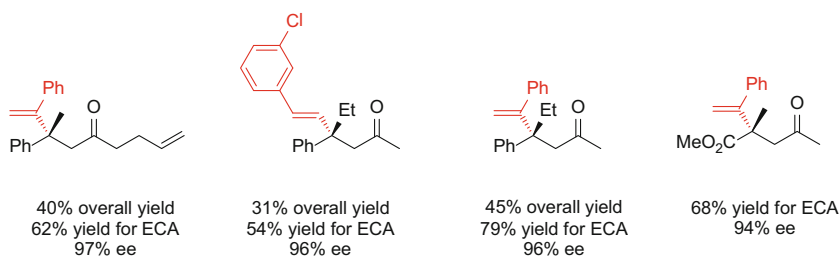


Fig. 7 Examples on the multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of alkenyl aluminium reagents to β,β -disubstituted linear enones by Hoveyda [66]

The DFT calculations carried out to gain insight on the origins of the enantioselectivity in this process indicate that an initial conjugate addition of the (alkenyl) Cu^{I} complex followed by a reductive elimination of the (alkenyl) Cu^{III} alkyl intermediate are the key steps involved in the catalytic cycle. Complex **A** (Fig. 8) represents the lowest energy pathway, consistent with the identity of the major isomers, whilst complex **B** (Fig. 8), leading to the minor enantiomers, is about 1.6 kcal/mol higher in energy. In the latter case, simultaneous coordination of the substrate to the Lewis acidic aluminium bridge atom and copper centre dictates that the enone binds in its energetically more demanding *s-trans* conformation (vs. *s-cis* in complex **A**), introducing severe A(1,3) strain between the ketone and alkene substituents. In the absence of an aluminium bridge atom, the transition state for addition to the same face as the complex is appreciably higher in energy.

Phosphine ligands such as **L16** and **L17** (Fig. 9), based on either a SPINOL or BINOL architecture, are also suitable ligands for the copper-catalysed ECA of

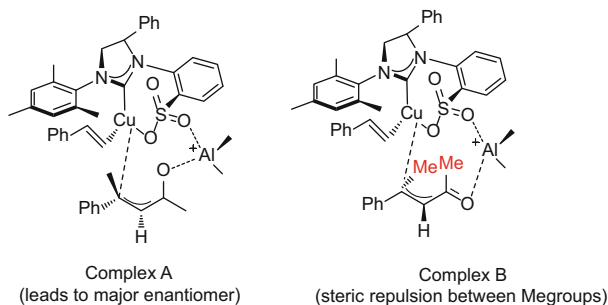


Fig. 8 Proposed transition states for the copper–NHC-catalysed ECA of alkenyl aluminium reagents to β,β -disubstituted linear enones by Hoveyda [66]

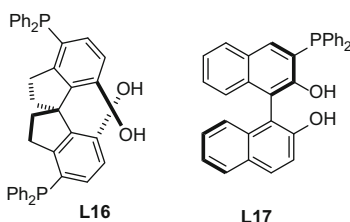
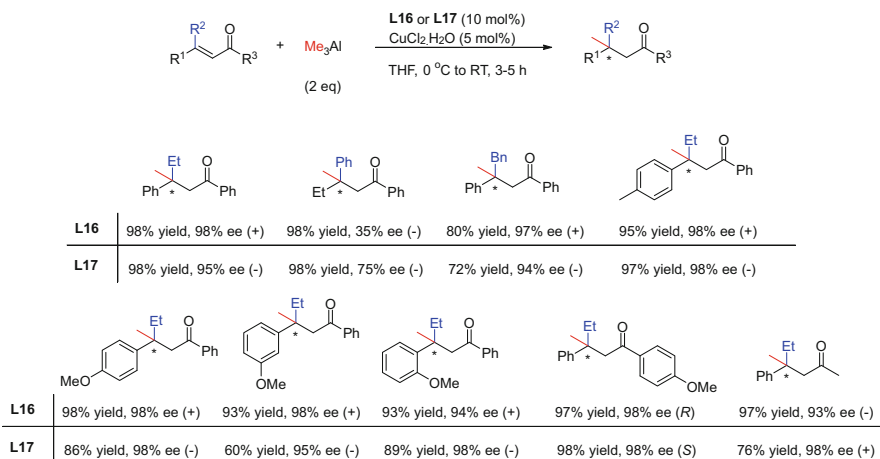
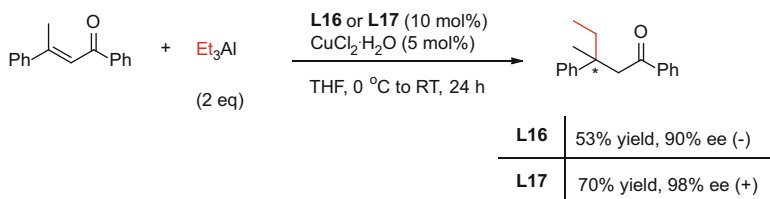


Fig. 9 Effective phosphine ligands for the ECA of organoaluminium reagents to β,β -disubstituted enones

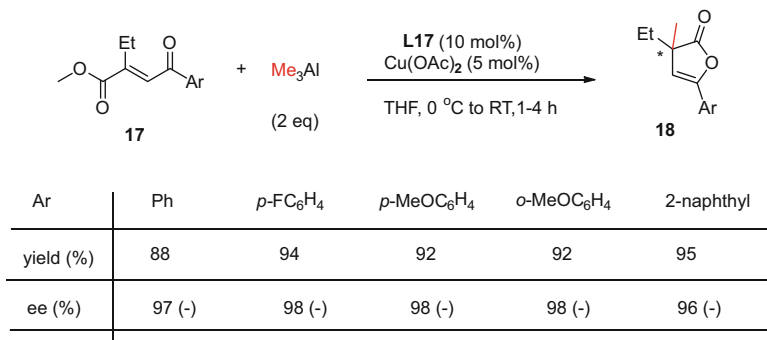


Scheme 33 Copper–phosphine-catalysed ECA of trimethylaluminium to β,β -disubstituted linear enones by Endo [67]

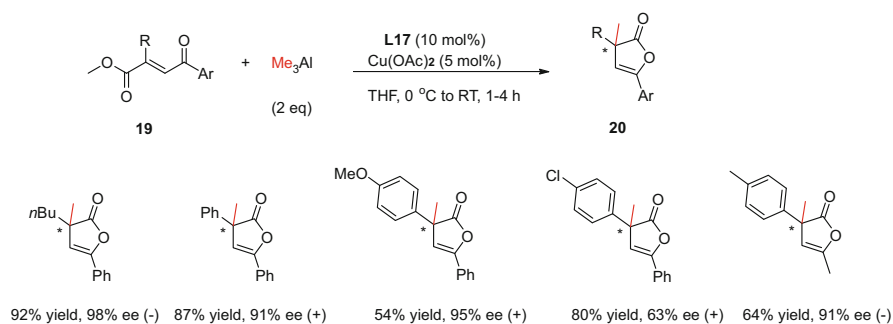
Me_3Al to β,β -disubstituted acyclic enones, giving the corresponding chiral quaternary carbon centres with enantioselectivities higher than 95% at room temperature (Scheme 33) [67].



Scheme 34 Copper–phosphine-catalysed ECA of triethylaluminium to β,β -disubstituted linear enones by Endo [67]



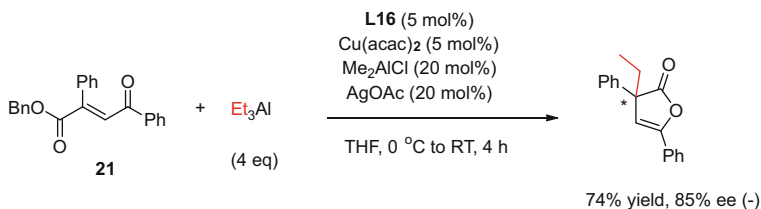
Scheme 35 Synthesis of α,α -disubstituted furanones by copper–phosphine-catalysed ECA of trimethylaluminium by Endo [68]



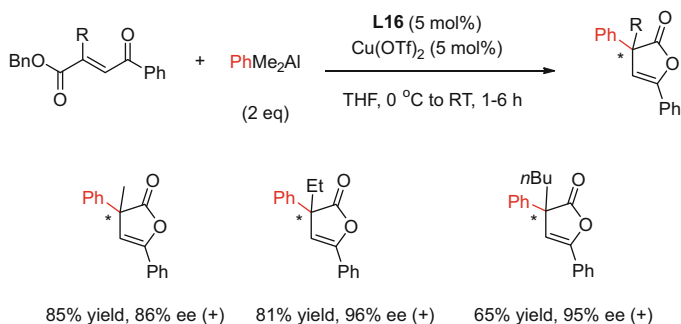
Scheme 36 Synthesis of α,α -disubstituted furanones by copper–phosphine-catalysed ECA of trimethylaluminium by Endo [68]

The addition of other alkyl aluminium reagents, such as Et₃Al, with phosphine ligands **L16** and **L17**, provides good enantioselectivities but moderate yields, due to low conversions (Scheme 34).

When unsaturated ketoesters **17** or **19** are used as substrates, the copper-catalysed addition of Me₃Al in the presence of **L17** provides, after subsequent lactonization, chiral furanones **18** and **20**, respectively, bearing quaternary stereogenic centres (Schemes 35 and 36) [68]. The optimised reaction conditions are applicable to a wide variety of benzyl ketoesters, and all products can be



Scheme 37 Benzyl ketoesters as substrates for the synthesis of α,α -disubstituted furanones by copper–phosphine-catalysed ECA of triethylaluminium by Endo [68]



Scheme 38 Aryl aluminium reagents as nucleophiles for the synthesis of α,α -disubstituted furanones by copper–phosphine-catalysed ECA by Endo [68]

obtained in high to excellent yields with high enantioselectivities. Furanones are versatile synthetic intermediates, which can be easily transformed into a variety of densely functionalised scaffolds.

Benzyl ketoesters, such as **21**, are also suitable substrates for this methodology and efficiently undergo ECA with $\text{Cu}(\text{acac})_2$ and **L16**, when Me_2AlCl and AgOAc are used as additives (Scheme 37).

Regarding the use of aryl aluminium reagents as nucleophiles for the copper-catalysed ECA with phosphines **L16** and **L17**, the reaction does not work with Ph_3Al , but the mixed aryl alane PhMe_2Al (or PhEt_2Al) provides good results with **L16**, as exemplified in Scheme 38.

2.2 Grignard Reagents as Nucleophiles

The copper-catalysed ECA of Grignard reagents has been extensively studied with a variety of phosphorous ligands [16]. Some of the interesting economical aspects of these nucleophiles, as compared to their zinc or aluminium counterparts, include the following:

1. They are more reactive (less excess needed to complete the addition).
2. They are readily accessible and highly tunable.
3. All R groups from the nucleophile are transferred to the substrate.

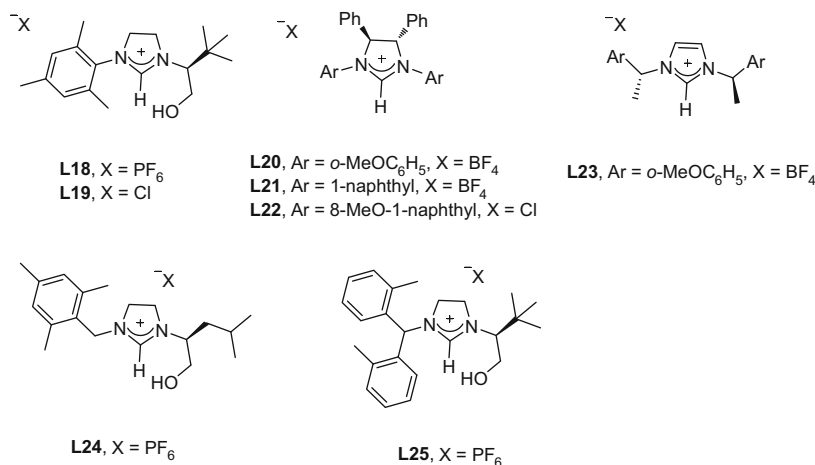


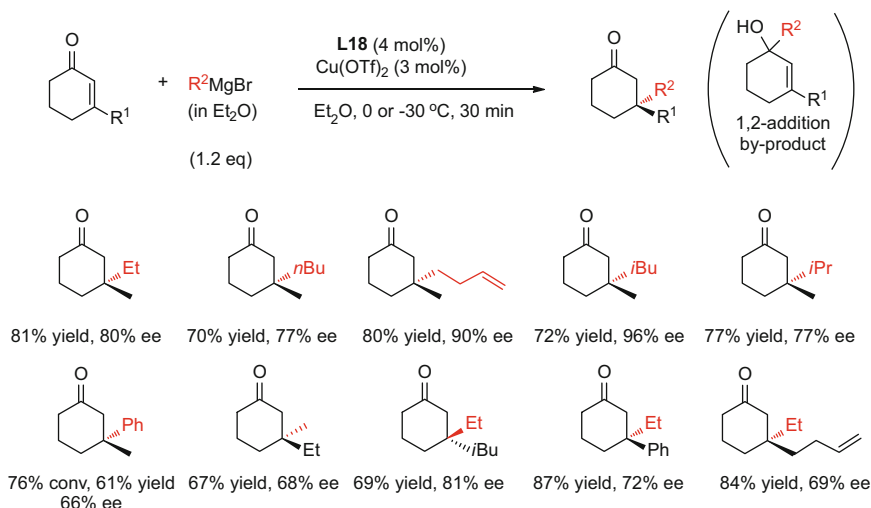
Fig. 10 Effective imidazolium salts for the copper-catalysed ECA of Grignard reagents to β -trisubstituted enones

In 2006, Alexakis and Mauduit demonstrated that NHC ligands derived from C2-symmetric imidazolidinium salts (**L18–25**, Fig. 10) were superior to phosphoramidite and ferrocene-based ligands when used for the copper-catalysed ECA of Grignard reagents to β,β -disubstituted enones [69]. They also observed that these ligands give better results with Grignard reagents than with any other organometallic compound.

In particular, imidazolium salt **L18** (Fig. 10) shows very high efficiency for the copper-catalysed ECA of Grignard reagents to β -substituted cyclohexenones (Scheme 39) [69]. A very low catalyst loading is needed to achieve moderate to good enantioselectivity, and the reaction proceeds in 30 min, working at 0 or $-30\text{ }^{\circ}\text{C}$. The slight excess of Grignard reagent employed is necessary for in situ deprotonation of the imidazolium salt (precatalyst) to form the NHC species. Slightly better conversions and enantioselectivities are obtained by adding the substrate last to the reaction mixture, after the addition of the Grignard reagent.

The scope of the reaction is wide, as represented in Scheme 39. Primary and secondary Grignard reagents give good to high enantioselectivities (up to 96%). The methodology is also applicable to more hindered substrates and seven-membered ring enones, as exemplified in Fig. 11. Unfortunately, the addition of aryl Grignard reagents proceeds with moderate regioselectivities (the 1,2-addition product is obtained in high percentages), and the sterically demanding *t*BuMgBr does not react, even at higher temperatures.

Although salts **L18–19** are superior and provide the best results in terms of conversions and enantiomeric excesses (with their main limitations mentioned above), other C2-symmetric [70] and nonsymmetric [71] imidazolium salts, such as **L20–23**, are able to induce the copper-catalysed ECA of alkyl Grignard reagents to 3-methylcyclohex-2-enone in moderate to good enantioselectivities, as



Scheme 39 Copper–NHC-catalysed ECA of Grignard reagents to β -substituted cyclic enones by Alexakis [69]

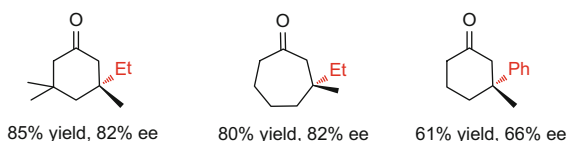
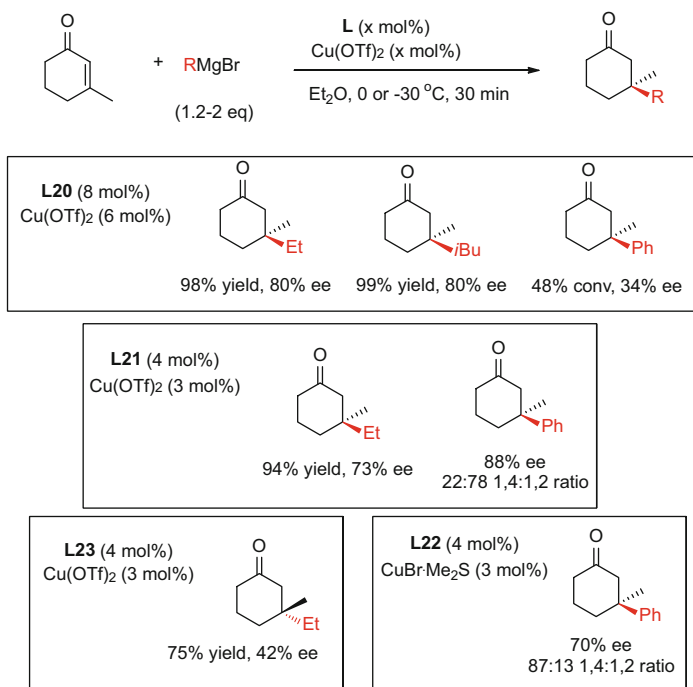


Fig. 11 Synthesis of chiral bulky cyclohexanones and cycloheptanones via copper–NHC-catalysed ECA of Grignard reagents by Alexakis [69]

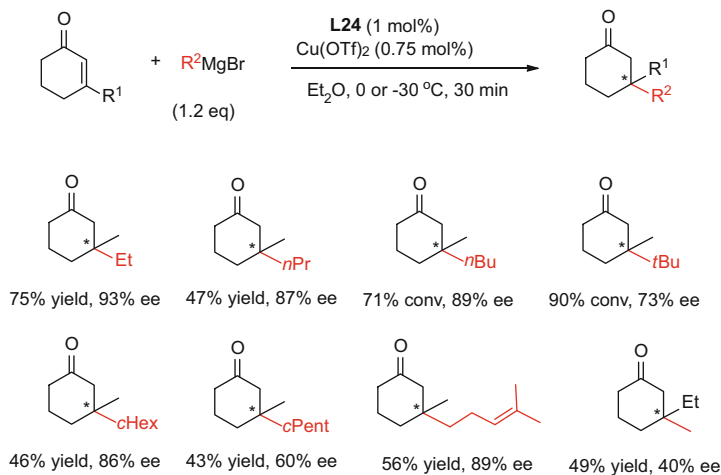
exemplified in Scheme 40. Unfortunately, none of these ligands as **L20–23** provides better results for the addition of PhMgBr or $t\text{BuMgBr}$ than the hydroxyl containing ligands **L18–19**.

The imidazolium salt **L24**, bearing an additional methylene spacer to increase the flexibility on that side of the carbene and thus occupying a larger space versus **L18–19**, gives very good results for the copper-catalysed ECA of Grignard reagents to β -substituted cyclic enones (Scheme 41). The challenging five-membered ring substrates, which are out of scope for ligands **L18–19** (Scheme 42), perform well in this example [72]. Thus, the ECA of a wide variety of Grignard reagents (both primary and secondary) to β -substituted cyclic enones allows the formation of quaternary centres with high levels of regio- and enantioselectivity with only 1 mol% of **L24**. One of the main drawbacks of this methodology is the moderate results obtained when methylmagnesium bromide is used as nucleophile (40% *ee* for the addition to 3-ethylcyclohex-2-enone); this is certainly due to the well-known lack of reactivity and specific behaviour of this nucleophile.

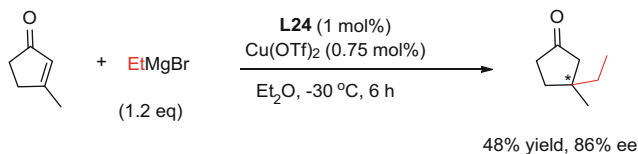
Alexakis et al. have proposed a catalytic cycle for the ECA with imidazolium ligands and Grignard reagents (Scheme 43) [72].



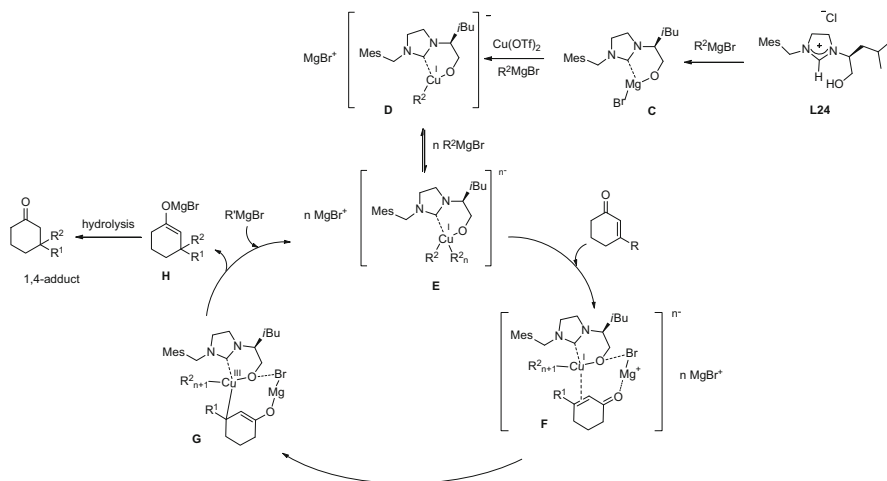
Scheme 40 Copper–NHC-catalysed ECA of Grignard reagents to β -substituted cyclic enones by Alexakis [71] and Tomioka [70]



Scheme 41 Copper–NHC-catalysed ECA of Grignard reagents to β -substituted cyclohexenones by Alexakis [72]

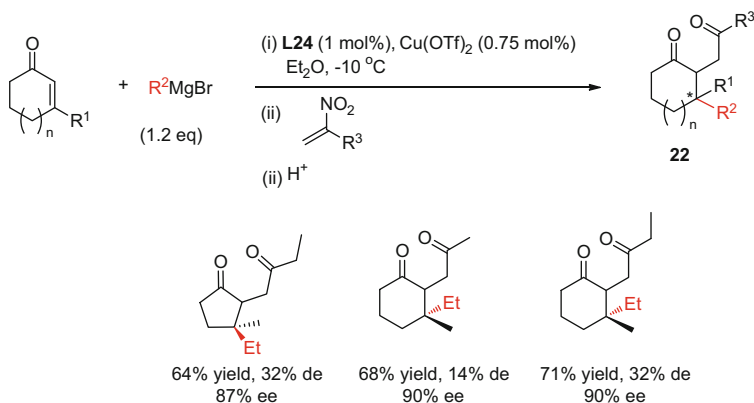


Scheme 42 Copper–NHC-catalysed ECA of Grignard reagents to β -substituted cyclopentenones by Alexakis [72]

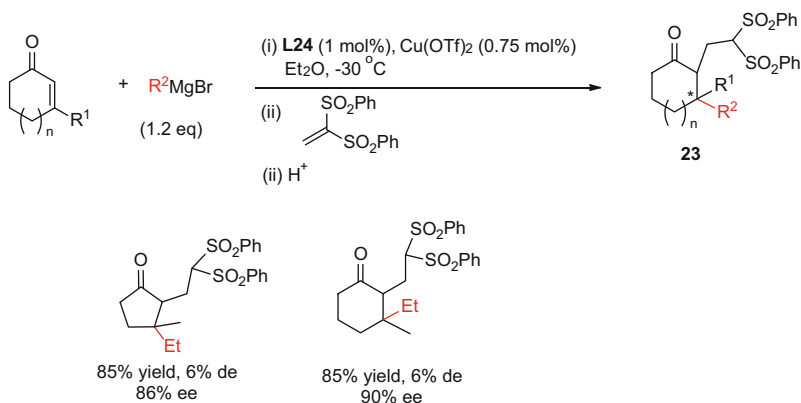


Scheme 43 Proposed catalytic cycle for the copper–NHC-catalysed ECA of Grignard reagents to cyclic enones by Alexakis [72]

Acting as a base, the Grignard reagent deprotonates first the hydroxyl group in the side chain, and then the imidazolium, leading to the NHC-coordinated alkoxy magnesium compound **C**. Copper triflate, which is reduced *in situ* by 1 equiv. of the Grignard reagent to give a copper(I) species, is involved in a transmetalation step to give the Cu–NHC complex, which upon addition of the Grignard reagent gives a heterocuprate **D**. In the presence of excess Grignard reagent, cuprate **D** probably forms higher-order aggregates **E** [73]. The equilibrium between heterocuprate **D** and higher-order heterocuprate **E** could be the key to understanding the following experimental fact: the slow addition of R^2MgBr generates heterocuprate **D**, which undergoes a non-enantioselective conjugate addition faster than forming the higher-order heterocuprate **E**. When the enone is added as the last component, the heterocuprate **D** has had time to equilibrate towards the highly efficient heterocuprate **E** and good enantioselectivities are obtained. The equilibrium between **D** and **E** could also be affected by the nature of the halogen present in the Grignard reagent, which explains why iodide and chloride are undesirable counterions [74]. The following steps in the catalytic cycle correspond to the classical mechanistic pathway of a copper-mediated conjugate



Scheme 44 Domino copper–NHC-catalysed ECA of Grignard reagents/CA trapping with 1-alkyl-1-nitroolefins by Alexakis [76]. All *ee*'s measured before trapping

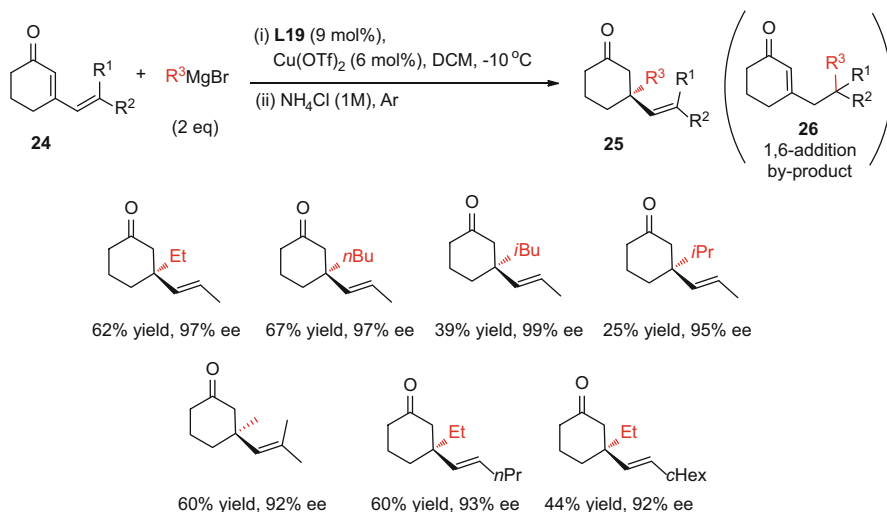


Scheme 45 Domino copper–NHC-catalysed ECA of Grignard reagents/CA trapping with vinyl disulfones by Alexakis [76]. All *ee*'s measured before trapping

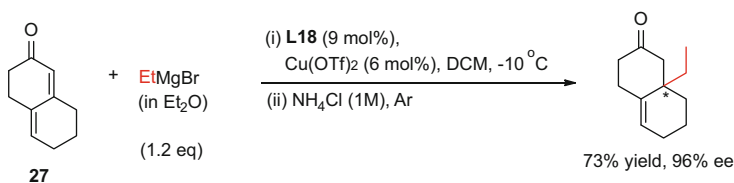
addition [75]. Thus, a reversible π complex **F** undergoes oxidative addition to a Cu^{III} intermediate **G**, which collapses by reductive elimination to give the magnesium enolate **H**.

The magnesium enolates generated by ECA using the copper–**L24** catalytic system can be easily trapped with 1-alkyl-1-nitroolefins (Scheme 44) [76]. After the trapping, an in situ Nef reaction [77] takes place, generating the corresponding 1,4-diketones **22**. These Michael adducts **22** can be then derivatised towards notable bicyclic structures, with relevance in natural products.

The same tandem procedure can be carried out using vinyl disulfones as electrophiles to provide the corresponding γ -sulfonylated ketones **23** in high yields and diastereo- and enantioselectivities (Scheme 45) [76]. Sulfone derivatives are tunable synthetic entities [78]. For example, the homolytic cleavage of disulfones



Scheme 46 Copper–NHC-catalysed ECA of Grignard reagents to conjugated dienones by Alexakis [80, 81]

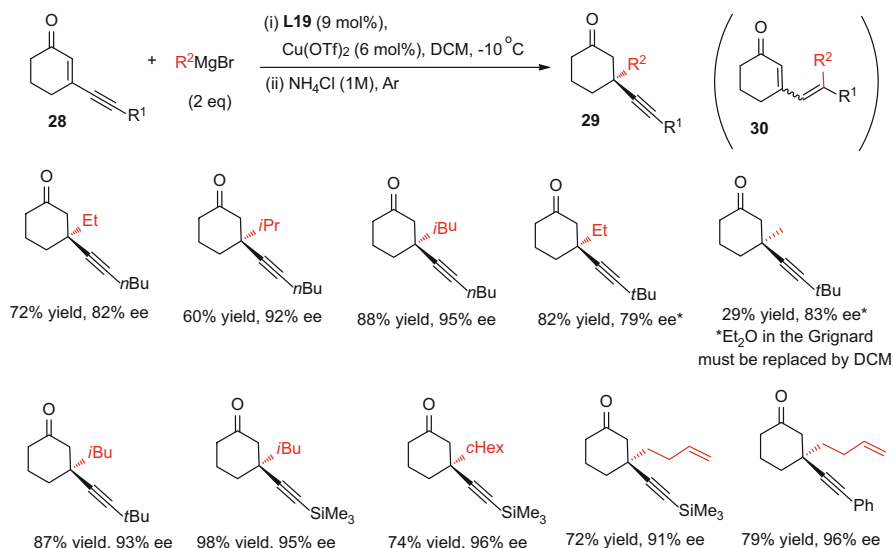


Scheme 47 Copper–NHC-catalysed ECA of ethylmagnesium bromide to the bicyclic conjugated dienone **27** by Alexakis [81]

through lithium naphthalenide or samarium iodide methodologies are well-established procedures for their corresponding derivatisation [79].

NHC ligands bearing a hydroxyl group (such as the ones derived from the imidazolium salts **L18–19**) also allow a high regio- and enantioselective CA reaction to conjugated dienones **24** (Scheme 46) [80, 81]. Primary and secondary Grignard reagents provide the corresponding 1,4-adduct **25** with greater than 95% selectivity (less than 5% of 1,6- and/or 1,2-addition regioisomers is observed) and enantioselectivity values as high as 99%. To prevent the formation of oxidative by-products, hydrochloric acid or NH_4Cl – which must be degassed with argon – are used to quench the reaction. The methodology demands the use of 2 equiv. of Grignard reagent, to compensate the reduced reactivity that these species display in DCM, the optimal solvent for this transformation. Also, the presence of Et_2O has negative effects on the regiocontrol; replacing the Et_2O Grignard solvent with DCM provides higher regioselectivity towards the desired 1,4-adducts.

Bicyclic substrates, such as **27**, also give excellent regio- and enantioselectivity in the conjugate addition reaction of EtMgBr promoted by the copper–NHC system derived from **L18** (Scheme 47).



Scheme 48 Copper-NHC-catalysed ECA of Grignard reagents to cyclic enynones by Alexakis [80, 84]

Unsuitable nucleophiles for this methodology are $PhMgBr$, which gives complex reaction mixtures, and $MeMgBr$, which only provides the corresponding 1,6-addition product **26** when the substituent R^1 in the dienone **24** (Scheme 46) is a hydrogen atom. The addition of $MeMgBr$ is not always problematic; γ,δ -disubstituted dienones **24** ($R^1, R^2 \neq H$) allow the formation of the 1,4-adduct exclusively, with high enantioselectivities (92% ee when $R^1 = R^2 = Me$).

This regiodivergent ECA is quite intriguing. Experiments with simpler NHC's (Arduengo's carbene [82]) and Grignard reagents give exclusively the 1,6-adduct **26**. The pendant hydroxyl group in the imidazolium ligand is essential to obtain good 1,4-selectivity. Also, other ligands, such as phosphoramidites, Josiphos and BINAP derivatives, only lead to the corresponding 1,6-addition product **26** in moderated to low enantioselectivities [83].

In terms of synthetic applications, the remaining $C=C$ double bond in the 1,4-adduct **25** allows useful transformations, affording interesting bicyclic building blocks. In addition, the corresponding magnesium enolate intermediate can be trapped with different electrophiles, allowing for the formation of useful synthons [80, 81].

This methodology also allows very good regio- and enantioselectivities when cyclic enynones such as **28** are used as substrates [80, 84]. The use of $Cu(OTf)_2$ and imidazolium ligand **L19** as catalysts in DCM leads to the unique formation of the 1,4-adduct **29** (Scheme 48). Again, this selectivity does not follow the general trend observed when extended Michael acceptors are used with phosphoramidites or phosphine ligands, which provide the 1,6-adduct **30** as the major regioisomer [58, 85].

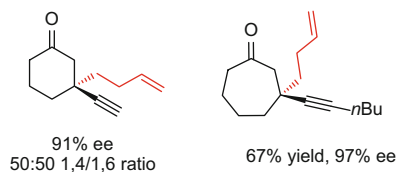
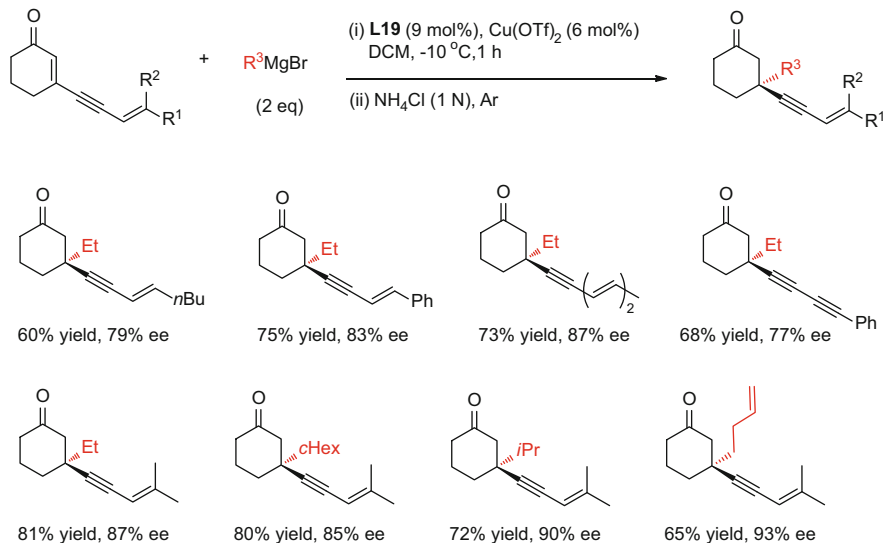


Fig. 12 Synthesis of chiral cyclohexanone bearing a terminal alkyne and chiral cycloheptanone by copper–NHC-catalysed ECA of Grignard reagents to cyclic enynones by Alexakis [84]

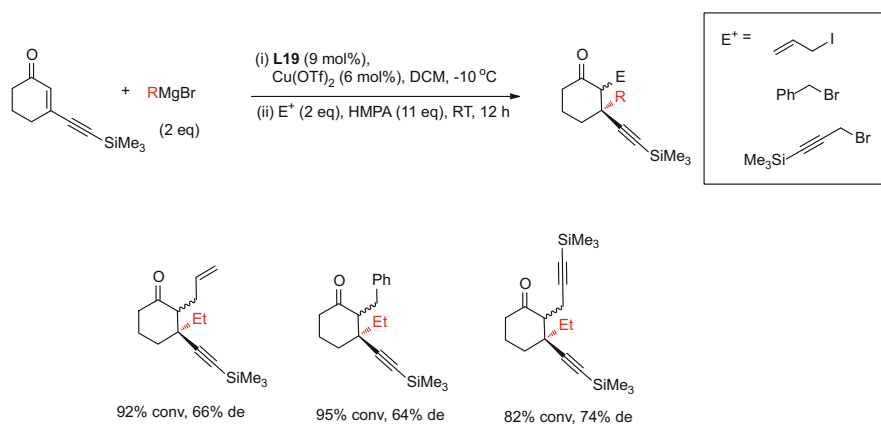


Scheme 49 Copper–NHC-catalysed ECA of Grignard reagents to cyclic enynones that bear additional unsaturations by Alexakis [84]

The ECA to cyclic enynones provides good selectivities and enantioselectivities in most cases with ethyl, isopropyl and *n*-butyl Grignard reagents. In some cases, the Et₂O Grignard solvent has to be replaced by DCM, to avoid low 1,4-regioselectivity. The addition of MeMgBr is again problematic regarding regioselectivity; the corresponding 1,6-adduct **30** is obtained as the major isomer unless a bulky substituent is placed at the alkyne position (e.g. R¹=*t*Bu), in which case the 1,4-adduct **29** is favoured and obtained with good enantioselectivity (Scheme 48).

The scope of the methodology includes seven-membered cyclic enynones (Fig. 12), whereas the five-membered rings give complex reaction mixtures, with very poor regioselectivity control. Enynones possessing a terminal alkyne give low regioselectivity but high enantioselectivity for the 1,4-addition product, as exemplified in Fig. 12.

Challenging substrates possessing additional unsaturated units also give good to moderate results with this methodology (Scheme 49). Primary and secondary Grignard reagents add with high regio- and enantioselectivity (up to 90%). Unfortunately, MeMgBr remains problematic.



Scheme 50 Tandem copper-NHC-catalysed ECA of Grignard reagents to cyclic enynones/enolate trapping by Alexakis [84]

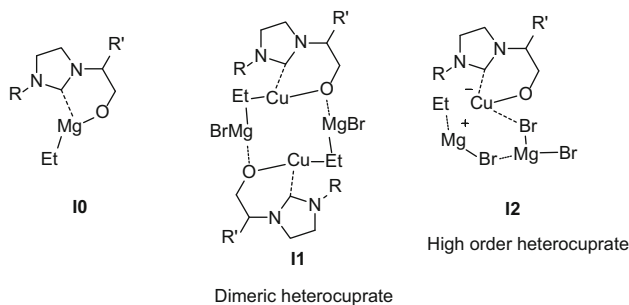
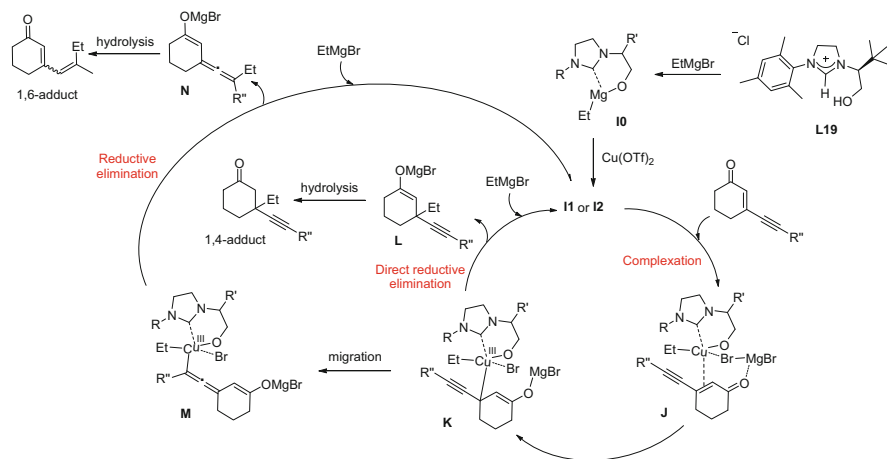


Fig. 13 Proposed carbenoid metal complexes for the copper-NHC-catalysed ECA reaction with Grignard reagents by Alexakis [84]

The catalytic system copper/**L19** gives moderate diastereoselectivities (see examples in Scheme 50) in a tandem CA electrophilic trapping process, using allyl, benzyl and propargyl halides as electrophiles.

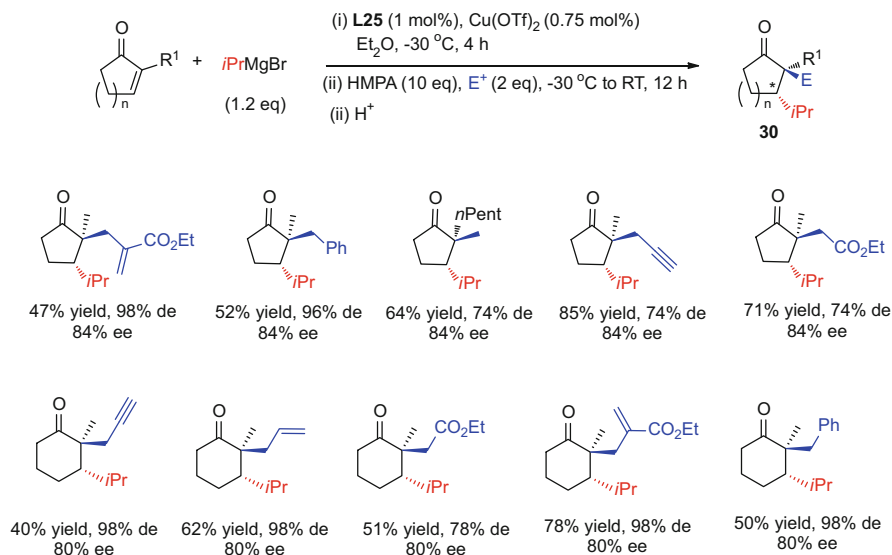
Several experimental observations have been taken into account to propose a plausible structure of the catalytic system (Fig. 13) and mechanism for the ECA reaction to polyconjugated cyclic enones (Scheme 51). Better enantioselectivities are obtained when the substrate is added last to the reaction mixture, after the addition of the Grignard reagent. This means that the hydroxy group of the NHC is deprotonated by the Grignard reagent, leading to the formation of a transient complex **10**, followed by the formation of the heterocuprate complex. Based on the characterisation of a magnesium organocuprate complex by Davies et al. [86], Alexakis proposes the dimeric heterocuprate **11** as the copper complex in the reaction with the polyconjugated cyclic enones. However, the large excess of Grignard reagents employed cannot exclude the presence of a high-order heterocuprate **12**. Presumably, the addition of the dienone to complexes **11** or **12** leads to



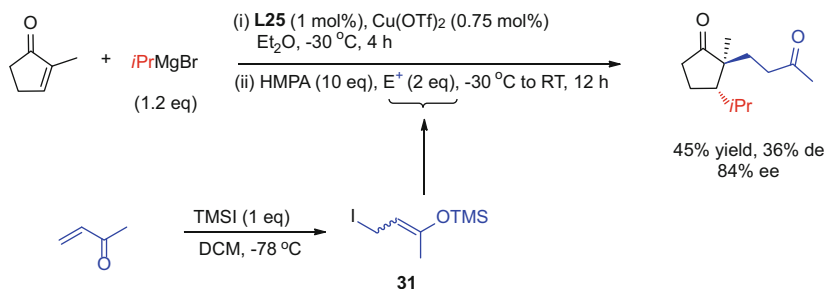
Scheme 51 Proposed catalytic cycle for the ECA reaction to polyconjugated cyclic enones by Alexakis [84]

the formation of a π complex **J** followed by the generation of a β -cuprio(III) enolate intermediate **K**. At this point, two pathways can be envisaged: complex **K** can reductively eliminate to afford the 1,4-adduct, enolate **L**, or the heterocuprate complex can migrate to the triple bond to form a new organocopper(III) intermediate **M**, followed by reductive elimination to afford the 1,6-adduct, enolate **N**. Both enolate species **M** and **N** can be transformed upon hydrolysis into the corresponding 1,4- and 1,6-adducts, respectively. In this case, the 1,4-addition trend observed with the above-discussed catalytic system implies that the 1,4-reductive elimination is faster than the migration to form complex **M**. It has been postulated that the copper complex derived from **L19** lowers the activation barrier of this 1,4-reductive elimination step and thus disfavours the migration to the 1,6-position.

The enantioselective generation of quaternary centres via copper-catalysed CA can be also achieved through a tandem ECA–enolate trapping process on α -substituted cyclic enones (Schemes 52, 53, 54, 55, 56 and 57). In this case, the quaternary centre is generated at the α -position of the carbonyl, contiguous to a β -tertiary centre. The imidazolium ligand **L25** is able to catalyse such a transformation, using Grignard reagents as nucleophiles in the presence of $\text{Cu}(\text{OTf})_2$, giving very good enantio- and diastereoselectivities with both α -substituted cyclopentanones and cyclohexanones (Scheme 52) [87, 88]. Alkyl, propargyl, allyl and benzyl halides have been used as electrophiles, all providing ketone derivatives **30** in high diastereoselectivity and good enantioselectivity when the secondary and bulky Grignard reagent *i*PrMgBr is used as nucleophile. Primary Grignard reagents are inferior to their branched counterparts in the addition to α -substituted cyclic enones. The maximum enantioselectivities for the addition of ethylmagnesium bromide to α -substituted cyclohexenones and cyclopentenones are 80 and 60%, respectively. The reaction with MeMgBr does not proceed, due probably to the lower reactivity of this species.



Scheme 52 Tandem copper–NHC-catalysed ECA of Grignard reagents to α -substituted cyclic enone/enolate trapping by Alexakis [87, 88] (all *ee*'s measured after recrystallisation)

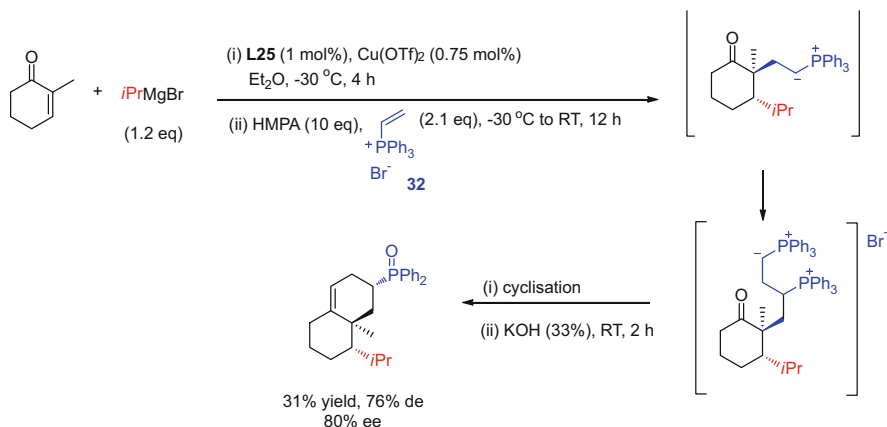


Scheme 53 Tandem copper–NHC-catalysed ECA of Grignard reagents to α -substituted cyclic enone/enolate trapping with **31** by Alexakis [88]

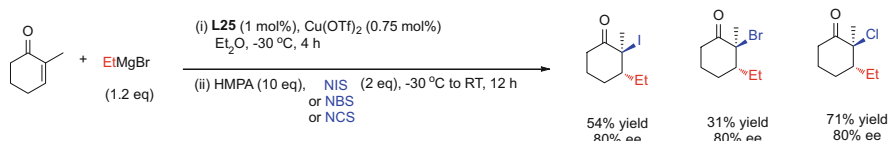
It is worth highlighting that this methodology brings a new approach to versatile terpenoid-like skeletons of bioactive natural products, and it has been applied to the formal synthesis of Crinipellin B and Guanacastepene A (Fig. 1) [87].

Other electrophiles, such as derivative **31** (Scheme 53),³ triphenylvinyl-phosphonium bromide **32** (Scheme 54), *N*-halosuccinimides (Scheme 55) and tosyl cyanide (Scheme 56), have been also evaluated in this tandem ECA–enolate trapping methodology [88]. Lower regio- and enantioselectivities are obtained in these cases than when the trapping is carried out with alkyl, propargyl, allyl or benzyl halides.

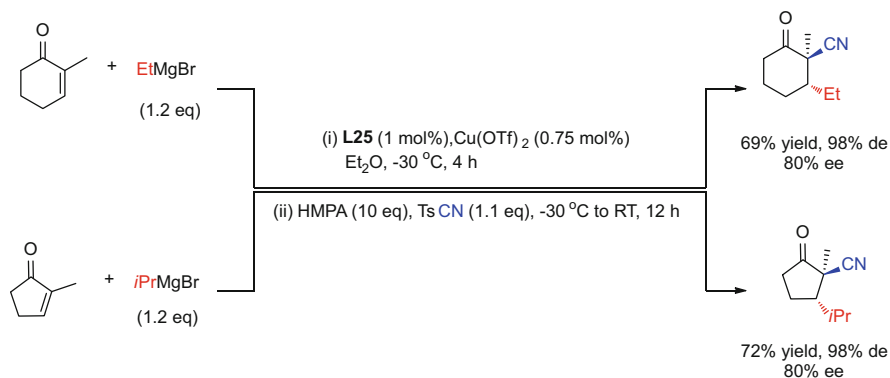
³The direct trapping with methylvinyl ketone (MVK) gives a complex mixture of oligomers.



Scheme 54 Tandem copper–NHC-catalysed ECA of Grignard reagents to α -substituted cyclic enone/enolate trapping with triphenylvinylphosphonium bromide **32** by Alexakis [88]

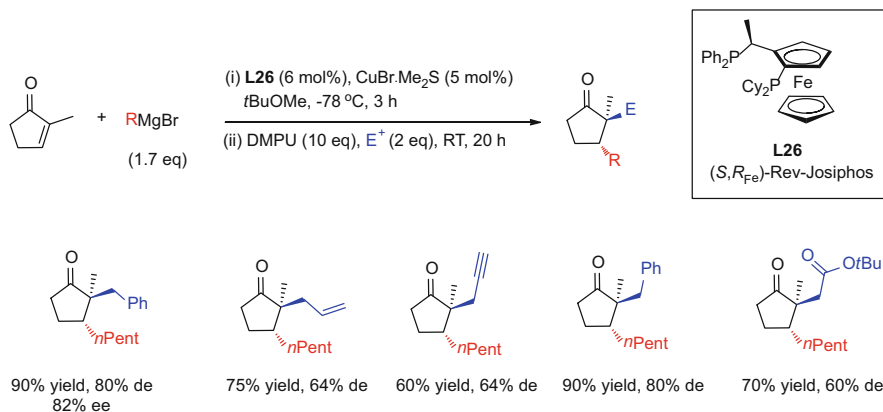


Scheme 55 Tandem copper–NHC-catalysed ECA of Grignard reagents to α -substituted cyclic enone/enolate trapping with N -halosuccinimides by Alexakis [88]



Scheme 56 Tandem copper–NHC-catalysed ECA of Grignard reagents to α -substituted cyclic enone/enolate trapping with tosyl cyanide by Alexakis [88]

Interestingly, a complementary methodology that allows the addition of linear Grignard reagents to α -substituted cyclic enones has been recently developed. It includes the use of copper/Rev-Josiphos (**L26**) for the ECA reaction, followed by in situ trapping of the magnesium enolate with various alkylating reagents, in the presence of DMPU. This strategy provides α -quaternary centres contiguous to β -tertiary centres with very good enantio- and diastereoselectivities, especially when cyclopentenones are used as substrates (Scheme 57) [89].



Scheme 57 Tandem copper–diphosphine-catalysed ECA of Grignard reagents to α-substituted cyclopentenones/enolate trapping by Minnaard [89]

2.3 Organozinc Reagents as Nucleophiles

Although zinc reagents are very popular nucleophiles in the copper-catalysed conjugate addition reaction, their relatively low reactivity makes the formation of quaternary stereocentres via addition to unactivated β,β-disubstituted enones very challenging. Nitroolefins, a class of especially reactive substrates, are, however, suitable substrates for this transformation, and their corresponding trisubstituted derivatives display good reactivity towards the addition of dialkylzinc reagents catalysed by copper and chiral peptide-based ligand **L27** (Fig. 14 and Scheme 58) [90].

One way to enhance the enantioselectivity of this transformation when dimethylzinc is used as nucleophile consists on employing (*Z*)-nitroalkenes instead as starting materials and [(MeCN)₄Cu]PF₆ as the copper source [91]. By using the (*Z*) isomer, the undesired nitroalkene isomerisation is minimised and the enantioselectivity of the process is enhanced dramatically, as shown in the examples in Scheme 59.

Another class of activated α,β-unsaturated compounds that is effective towards the ECA with organozinc reagents is the enone **33** (Scheme 60). The ester group at the α-position renders the substrate more electrophilic and, therefore, more prone to attack by dialkylzinc reagents. The peptide-based ligand **L28**, in combination with CuCN, successfully catalyses this process [92]. Cyclic six-membered substrates provide higher yields and enantioselectivities than the five-membered counterparts. Although variation of the α-ester is tolerated in the reaction, bulky esters lead to the highest enantioselectivities.

The doubly activated Meldrum's acid derivatives **34** also undergo copper-catalysed ECA with diorganozinc reagents, to provide all-carbon quaternary centres in moderated to good yields and enantioselectivities with phosphoramidite ligand

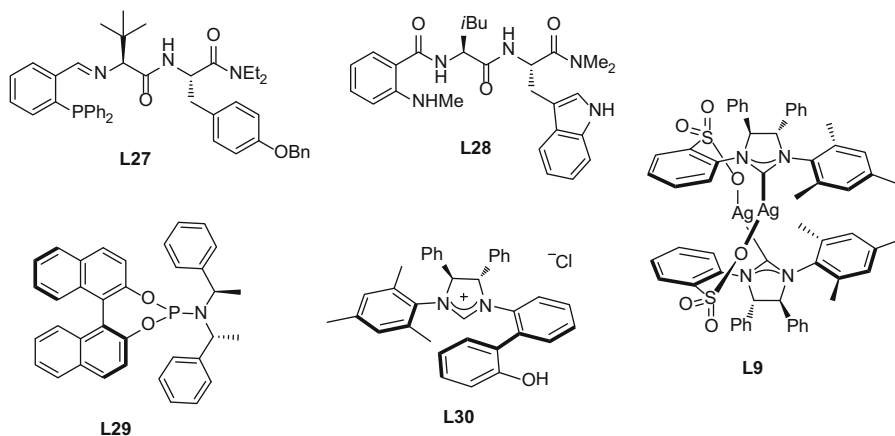
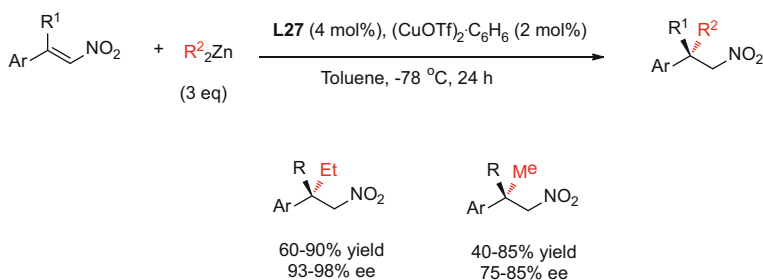
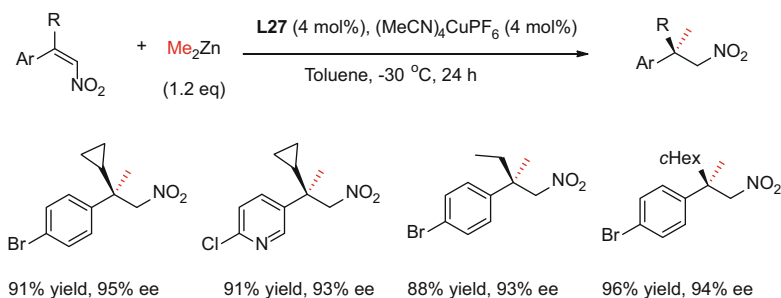


Fig. 14 Efficient ligands for the copper-catalysed ECA of organozinc reagents to β , β -disubstituted α,β -unsaturated systems

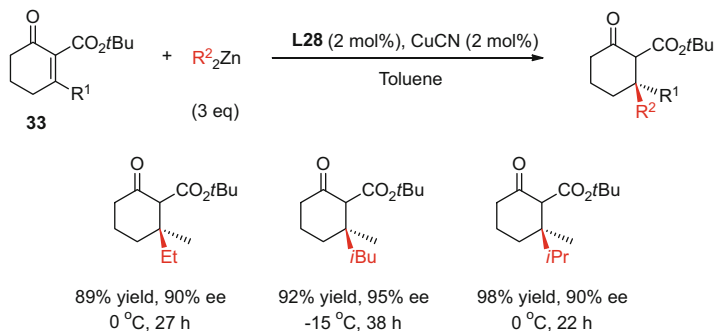


Scheme 58 Copper-peptide-catalysed ECA of organozinc reagents to β,β -disubstituted (*E*)-nitroalkenes by Hoveyda [90]

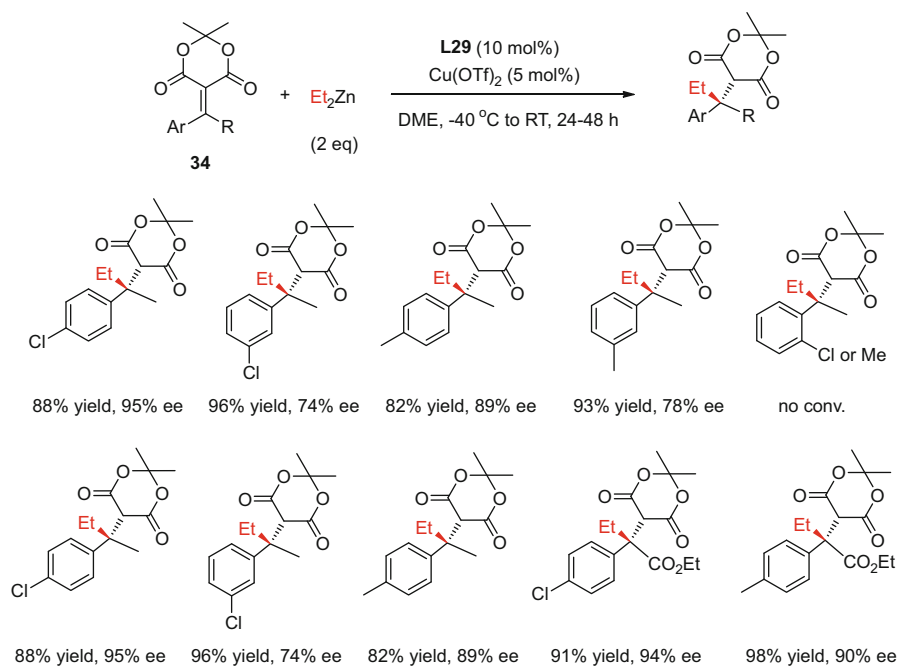


Scheme 59 Copper-peptide-catalysed ECA of organozinc reagents to β,β -disubstituted (*Z*)-nitroalkenes by Zeng [91]

L29 (Scheme 61) [93–96]. The scope of the reaction excludes *ortho*-substituted aromatic derivatives, which do not react under these conditions. The acid and ester moieties present on the all-carbon quaternary centre allow for a wide variety of



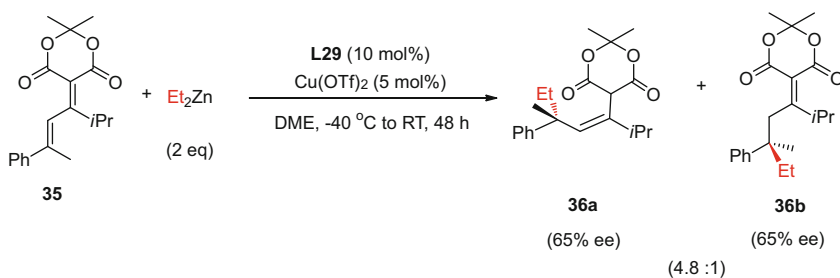
Scheme 60 Copper–peptide-catalysed ECA of organozinc reagents to activated cyclic ketoesters by Hoveyda [92]



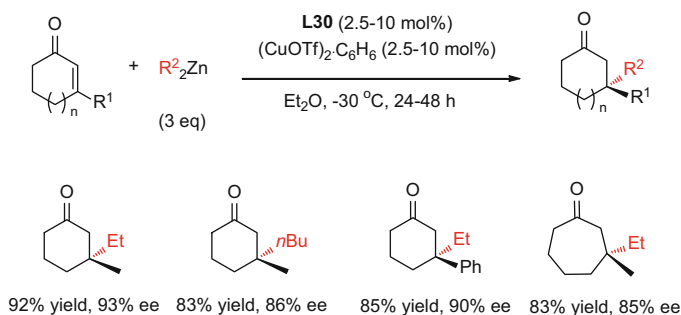
Scheme 61 Copper–phosphoramidite-catalysed ECA of organozinc reagents to Meldrum's acids derivatives by Fillion [93–96]

subsequent transformations, leading to the expedient preparation of succinimides, succinate esters and succinic acids, γ -butyrolactones and β -amino acid derivatives [94].

The formation of quaternary stereogenic centres via 1,6-conjugate addition of dialkylzinc reagents to Meldrum's acid derived acceptors has also been reported [97]. Thus, **35** reacts with Et₂Zn in the presence of Cu(OTf)₂ (5 mol%) and



Scheme 62 Copper–phosphoramidite-catalysed enantioselective 1,6-CA of organozinc reagents to Meldrum's acids derivatives by Fillion [97]



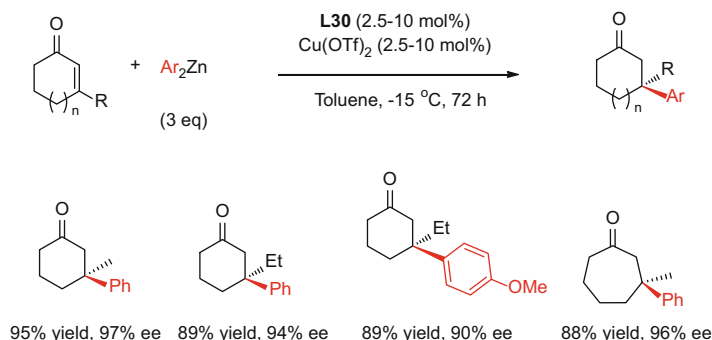
Scheme 63 Copper–NHC-catalysed ECA of dialkylzinc reagents to β -substituted cyclic enones by Hoveyda [98]

phosphoramidite ligand **L29** (10 mol%) to afford exclusively 1,6-adducts **36a** and **36b** in a 4.8:1 ratio, 81% combined isolated yield and 65% enantiomeric excess (Scheme 62). It is noteworthy that **Z**-olefin **36a** was obtained as a single isomer (determined by NOE experiments).

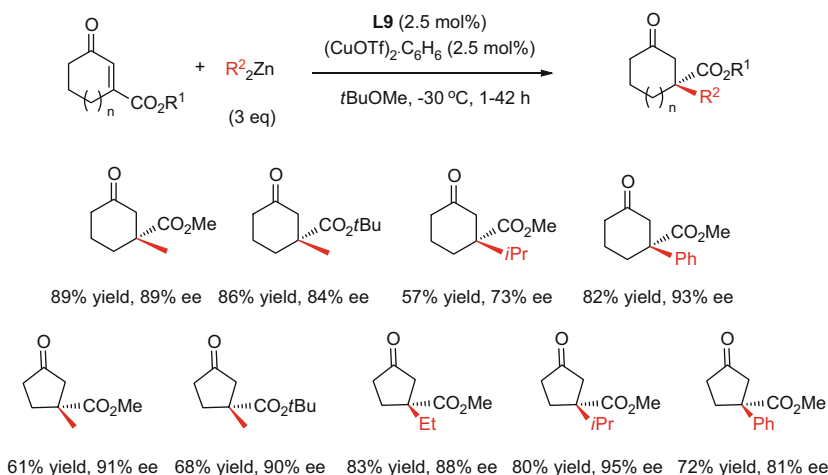
The more recent development of NHC ligands, such as those derived from the imidazolium salt **L30**, has allowed the addition of dialkylzinc (Scheme 63) and diarylzinc reagent⁴ (Scheme 64) to simple unactivated β -substituted cyclic enones [98]. Very good yields and enantioselectivities are obtained with a wide variety of organozinc compounds; only the less reactive Me_2Zn does not provide any conversion.

When the β -substituent in the cyclic enone is an ester group, the enantioselective formation of the quaternary stereogenic centre is very effective using ligand **L9** (Scheme 65) [99]. The scope of this reaction includes both alkyl (including methyl) and aryl dialkylzinc reagents as nucleophiles and methyl and more sterically

⁴The generation of the diarylzinc reagents can be carried out by transmetalation from the corresponding Grignard reagent using ZnCl_2 , requiring subsequent filtration over Celite under argon to remove the magnesium salts.



Scheme 64 Copper–NHC-catalysed ECA of diarylzinc reagents to β -substituted cyclic enones by Hoveyda [98]

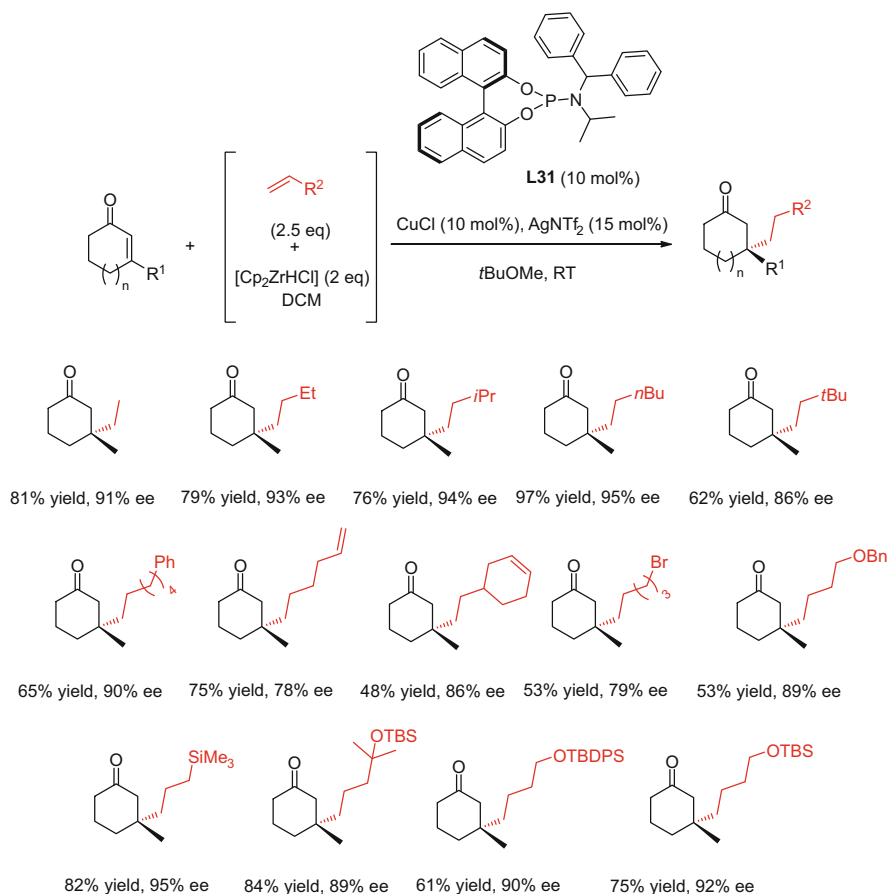


Scheme 65 Copper–NHC-catalysed ECA of dialkylzinc reagents to cyclic ketoesters by Hoveyda [99]

hindered *tert*-butyl esters as substituents in the substrates. Under the optimal conditions, cyclopentenone substrates provide higher enantiomeric purity than cyclohexenones. The enantiomerically enriched products obtained by this protocol are very versatile, since the carboxylic ester unit provides a convenient handle for further manipulations.

2.4 Organozirconium Reagents as Nucleophiles

Recently, Fletcher et al. have demonstrated that the formation of all-carbon quaternary centres can be carried out by copper-catalysed ECA of alkylzirconium reagents to β -substituted cyclic enones (Scheme 66) [100, 101].



Scheme 66 Copper-catalysed ECA of organozirconium reagents to β -substituted cyclic enones by Fletcher [100]

The reaction proceeds in high yields and very good enantioselectivity under mild conditions (i.e. room temperature) when phosphoramidite ligand **L31** and CuNTf_2 (prepared in situ from CuCl and AgNTf_2) are used as catalyst. β -Substituted cyclohexenone and cycloheptenone substrates provide higher enantioselectivities than cyclopentenones analogues, as long as the β -substituent is not too sterically demanding (Fig. 15).

Alkylzirconium reagents are prepared in situ by hydrometalation from the corresponding alkenes [102–104] which, conceptually, act as the equivalent to premade organometallic nucleophiles. The mild reaction conditions in which the reaction takes place, together with the low reactivity that the in situ-prepared organozirconium reagents display, lead to several advantages for this methodology: (1) it allows the preparation and use of more complex nucleophiles, (2) more functional groups are compatible, and (3) alkenes are easier to handle, compared to the air- and moisture-sensitive often pyrophoric organometallic reagents.

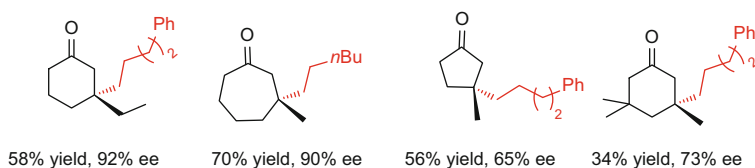


Fig. 15 Chiral ketones prepared by copper-catalysed ECA of organozirconium reagents to β -substituted cyclic enones by Fletcher [100]

3 Formation of Boron-Containing Quaternary Centres by Copper-Catalysed ECA

Chiral organoboron compounds are versatile synthetic intermediates due to the convertibility of C–B bonds to a variety of functional groups [105, 106]. Furthermore, chiral organoboron molecules exhibiting unique biological activities have been recently identified, such as potent inhibitors of the proteasome, thrombin and histone deacetylases [107]. The formation of boron-containing quaternary centres via copper-catalysed ECA of organoboron reagents to β,β -disubstituted α,β -unsaturated systems is challenging (due both to the low reactivity and smaller steric and electronic differences between two substituents on the β -prochiral carbon of the substrate), but very impressive contributions have appeared in the literature over the past 10 years (Fig. 16).

As described by Shibasaki et al., the formation of quaternary centres via enantioselective conjugate boration (ECB) to β -substituted cyclic enones can be efficiently catalysed by the phosphine ligand **L32** and $\text{CuPF}_6 \cdot 4\text{CH}_3\text{CN}$. Commercially available bis(pinacolato)diboron [(Pin)B–B(Pin)] is the borylating reagent that provides the best results in this transformation (Scheme 67) [108]. The reaction generally proceeds with high enantioselectivity for both aromatic and aliphatic β -substituted cyclic enones, including five-, six- and seven-membered rings (Scheme 67).

This reaction is a useful platform for the synthesis of various chiral building blocks that are otherwise difficult to access, as exemplified in Scheme 68.

For acyclic β,β -disubstituted α,β -unsaturated substrates, the copper(I)–chiral diamine **L33** complex catalyses the enantioselective conjugate boration (ECB) in high yields and enantioselectivity (Scheme 69) [109]. Amine ligands have a weaker affinity for Cu(I) compared to phosphine ligands, and for this reason, there are not many efficient asymmetric reactions to date using a nucleophilic Cu(I)–chiral amine complex as a catalyst. However, in this case, very good yields and enantioselectivities are achieved under the optimised reaction conditions for a wide range of substrates, including methyl, linear and branched alkyl-substituted enones. Both aromatic and aliphatic organoboron compounds are effective. The addition of 2 equiv. of *i*PrOH as additive in the reaction allows a substantial improvement on the yield, since it promotes the conversion of the enolate intermediate to the corresponding borylated product (see mechanism of the reaction in Scheme 70).

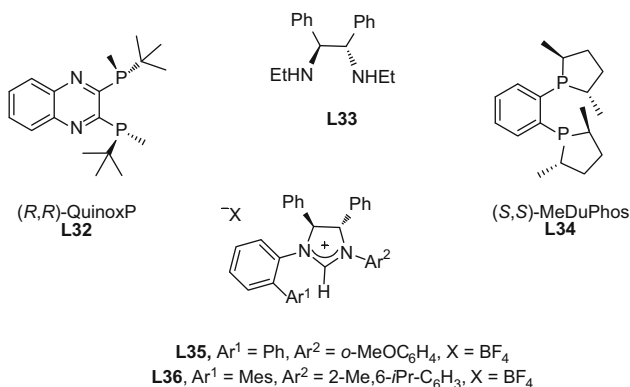
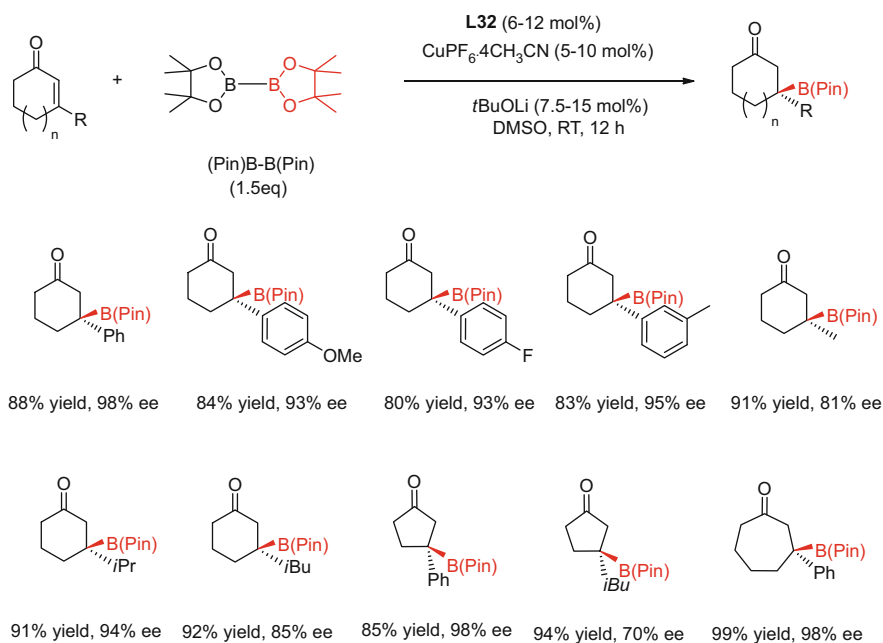
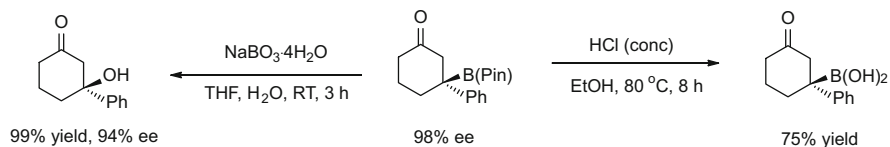


Fig. 16 Effective ligands for the enantioselective conjugate boration (ECB) to β,β -disubstituted α,β -unsaturated compounds

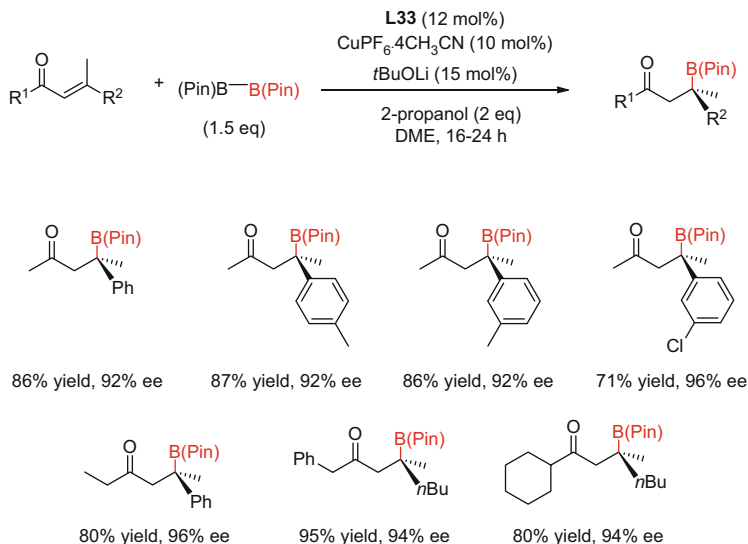


Scheme 67 Copper–phosphine-catalysed ECB of β -substituted cyclic enones by Shibasaki [108]

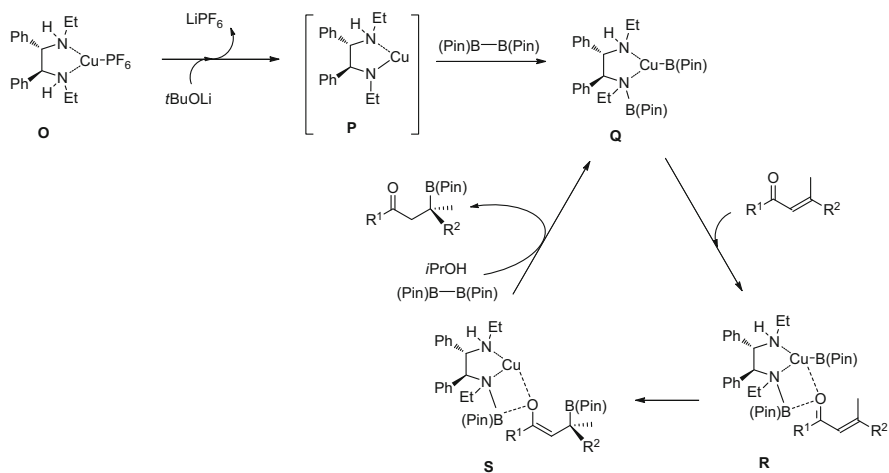
When the reaction is carried out with *t*BuOCu, in the absence of a lithium salt, yields and enantioselectivities are not affected. This indicates that the diamine coordinates to the copper atom at the enantio-differentiating step, even in the presence of the cationic lithium atom. In addition, ESI-MS experiments support the presence of complex **O** (Scheme 70). Shibasaki et al. have proposed a working hypothesis for the catalytic cycle, as shown in Scheme 70. Copper amide **P** is generated from **O** and *t*BuOLi, and next, the copper–nitrogen bond cleaves



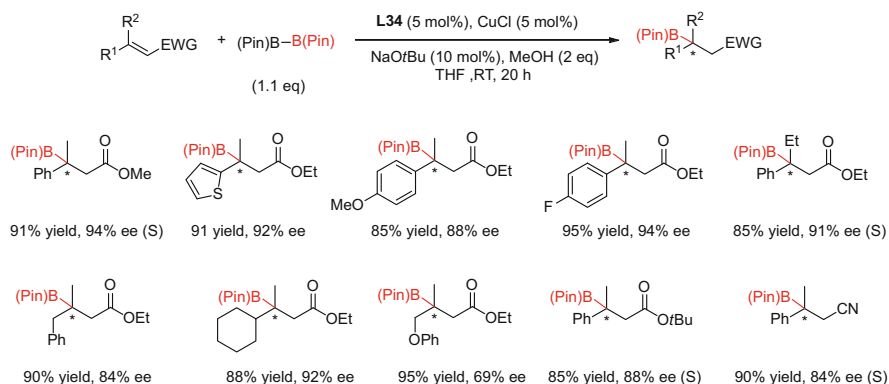
Scheme 68 Derivatisation of chiral organoboron compounds by Shibasaki [108]



Scheme 69 Copper-diamine-catalysed ECB of β,β -disubstituted enones by Shibasaki [109]



Scheme 70 Proposed mechanism for the copper-diamine-catalysed ECB of β,β -disubstituted enones by Shibasaki [109]



Scheme 71 Copper-phosphine-catalysed ECB of acyclic β,β -disubstituted α,β -unsaturated esters by Yung [110]

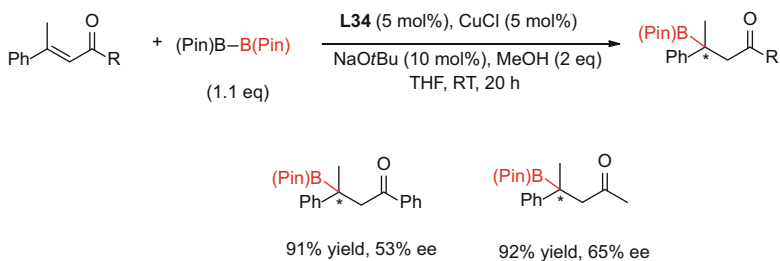
(Pin)B–B(Pin) through metathesis, generating the copper boronate complex **Q**, which contains a *N*-borylated ligand. Next, the carbonyl oxygen atom of the substrate coordinates to the Lewis acidic boron atom of the aminopinacolyl boronate part of the catalyst, generating a pre-transition state complex **R**. ECB from **R** produces boron enolate complex **S** (or a copper enolate complex, alternatively), which is protonated by 2-propanol, and reactive species **Q** is regenerated by reaction with (Pin)B–B(Pin). This proposed mechanism is in accordance with the low enantioselectivity observed when using diamine ligands without an ability to form copper amides.

Yung et al. have demonstrated that for acyclic β,β -disubstituted α,β -unsaturated esters, the phosphine ligand **L34** provides high yields and enantioselectivities in the copper-catalysed ECB reaction (Scheme 71) [110]. Again, the inclusion of proton accelerators (2 equiv. of MeOH – in contrast to the aprotic DMSO used with cyclic enones; see Scheme 67 and [110]) is necessary to promote the conversion of the enolate intermediate to the corresponding borylated product.

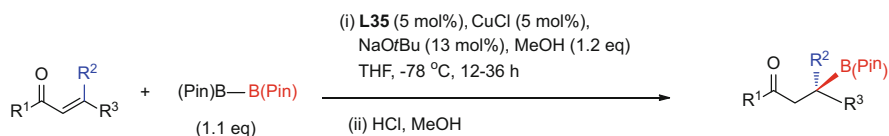
Under the optimised conditions (see Scheme 71), a wide range of β,β -disubstituted α,β -unsaturated substrates afford the corresponding borylated products with high enantioselectivity. The electronic nature of the aromatic substituent in the β position does not affect the yield nor enantioselectivity; however, β,β -dialkyl-substituted esters give good to modest results. Also, bulkier conjugated EWG groups such as *tert*-butyl esters or nitriles provide lower enantioselectivities.

Unfortunately, this methodology only provides moderate levels of enantiomeric excess when acyclic β,β -disubstituted α,β -unsaturated ketones are used as substrates (Scheme 72).

In contrast, the catalytic methodology reported by Hoveyda et al. allows the enantioselective synthesis of boron-substituted quaternary carbons units by copper-catalysed addition of boronate to unsaturated carboxylic esters, ketones and thioesters [111]. The transformations proceed with high yields and enantioselectivities, using bis(pinacolato)diboron as the nucleophile and the readily accessible



Scheme 72 Copper-phosphine-catalysed ECB of acyclic β,β -disubstituted enones by Yung [110]



Scheme 73 Copper-NHC-catalysed ECB of acyclic β,β -disubstituted α,β -unsaturated systems by Hoveyda [111]

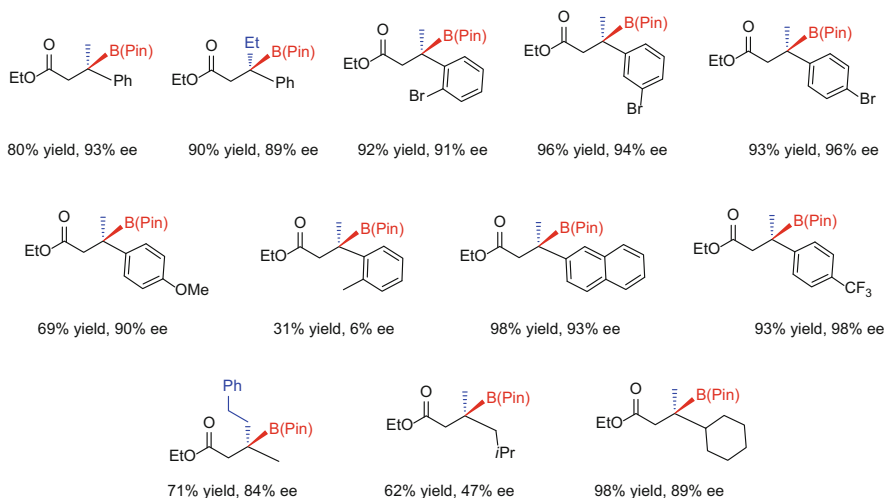


Fig. 17 Representative examples for the copper-NHC-catalysed ECB of acyclic β,β -disubstituted α,β -unsaturated esters by Hoveyda [111]

chiral imidazolium ligand **L35** (Scheme 73). Once again, the presence of MeOH as additive in the reaction is necessary to achieve good conversions, but it does not affect the enantioselectivity of the process.

As represented in Fig. 17, β -aryl-substituted esters ($R^1 = \text{OEt}$, $R^3 = \text{aryl}$, Scheme 73) give, in general, very good yields and enantioselectivities, except when the β -substituent is an *o*-tolyl group, in which case the corresponding boron adduct is obtained as a near racemate. A *p*-methoxyphenyl substituent in the β -position affords the desired β -boryl ester in moderate yield, due to diminished

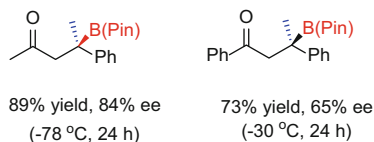


Fig. 18 Representative examples for the copper–NHC-catalysed ECB of acyclic β,β -disubstituted enones by Hoveyda [111]

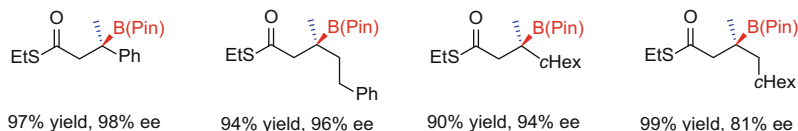


Fig. 19 Representative examples for the copper–NHC-catalysed ECB of acyclic β,β -disubstituted α,β -unsaturated thioesters by Hoveyda [111] (all reactions carried out at -50 °C for 18 h)

substrate electrophilicity. β,β -Dialkyl-substituted esters afford slightly lower yields and enantioselectivities (especially when $R^3 = \text{CH}_2\text{iPr}$) than the aromatic substrates.

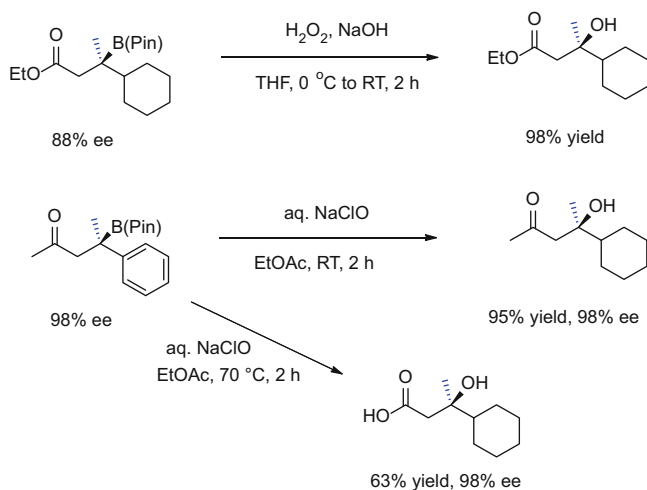
In the case of β,β -disubstituted unsaturated ketones ($R^1 = \text{Me}$, Ph , Scheme 73), reactions are, as expected, less enantioselective than with the analogous and less reactive unsaturated esters. However, moderate to good enantioselectivities and yields are reached, taking into account the challenging nature of this type of acyclic substrates (Fig. 18).

Lastly, the methodology gives excellent yields and enantioselectivities when β,β -disubstituted unsaturated thioesters are used as substrates ($R^1 = \text{SEt}$, Scheme 73), regardless of whether an aromatic β -substituent is present (Fig. 19). The thioester functionality allows easy conversion to the corresponding unsaturated carboxylic ester or ketones through Ag-mediated and Pd-catalysed procedures, respectively [111].

Chiral boron-containing adducts are versatile building blocks which can be derivatised easily. For example, oxidation of the C–B bond of the chiral 1,4-adduct with $\text{H}_2\text{O}_2/\text{NaOH}$ (at 0 °C) or common household bleach (at RT) delivers the corresponding tertiary alcohols in high yield. If the bleach-assisted oxidation is carried out at 70 °C, the methyl ketone will be transformed into a carboxylic acid as well during the process (Scheme 74).

The proposed model that explains the results for the NHC–copper-catalysed boronate conjugate addition reaction is represented in Fig. 20. Complex **T** provides a rationale for the levels and trends in selectivity. Alkene coordination likely occurs such that the Cu–B bond is aligned with the substrate π^* , whilst the carbonyl moiety resides proximal to the NHC's monosubstituted $N\text{-Ar}$ unit (vs **U**).

Very recently, Hoveyda et al. have demonstrated that the conjugate addition of organoboron reagents to β -substituted cyclic enones, catalysed by the readily accessible imidazolium ligand **L36** and in the *absence of any transition metal*,



Scheme 74 Derivatisation of chiral organoboron compounds by Hoveyda [111]

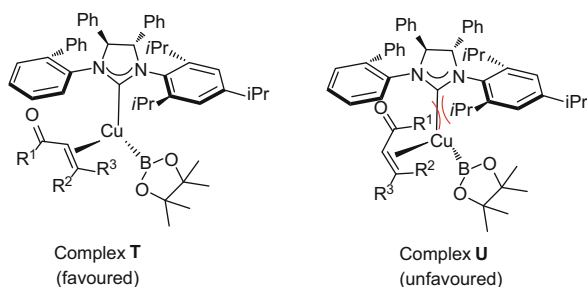


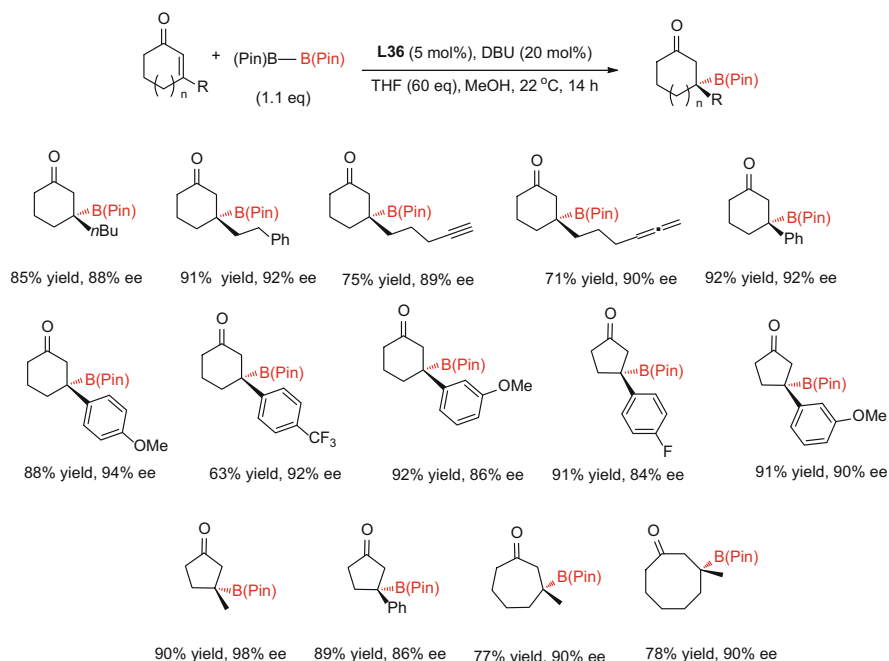
Fig. 20 Proposed transition states for the copper-NHC-catalysed ECB of acyclic β,-β-disubstituted α,β-unsaturated systems by Hoveyda [111]

gives excellent selectivities in the formation of boron-substituted quaternary carbon stereogenic centres (63–95% yield and 82 to >98% *ee*, Scheme 75) [112].

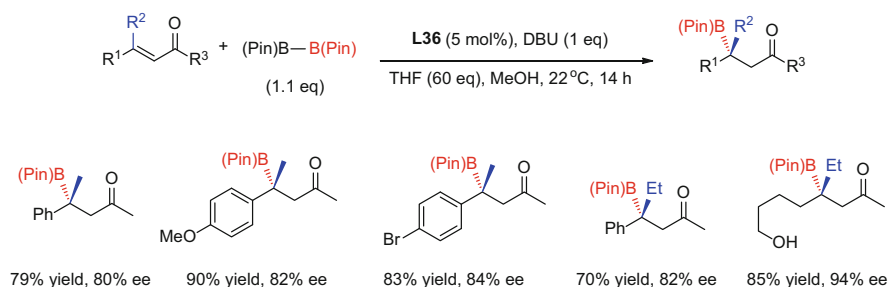
Both yields and enantioselectivities obtained with this methodology are comparable to the copper-catalysed reaction with (*R,R*)-QuinoxP **L32** [108]. However, when the enone is provided with β-substituents that contain multiple bonds, the reaction is more efficient with **L36** in the absence of a copper salt, probably because competitive reactions of the Cu–B(pin) complex with the alkyne or alkene moieties are avoided this way.

The imidazolium salt **L36** is also effective when acyclic, aryl- or alkyl-substituted enones are used as substrates. The corresponding linear β-boryl ketones can be obtained from 56 to 94% yield and >98% *ee* (Scheme 76).

The mechanism of these NHC-catalysed boryl conjugate addition reaction in the absence of transition metal complexes [113] will not be discussed here, as it is outside of the scope of this chapter.



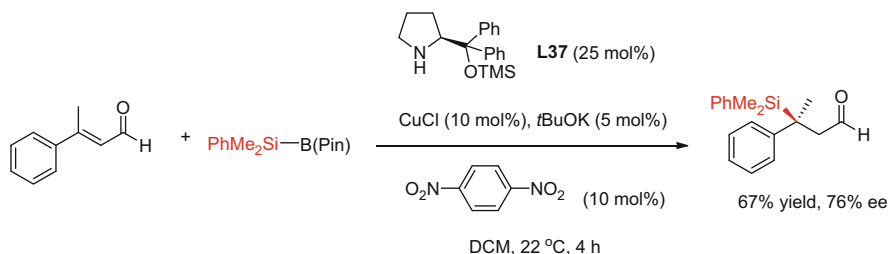
Scheme 75 Transition metal-free NHC-catalysed ECB of β -substituted cyclic enones by Hoveyda [112]



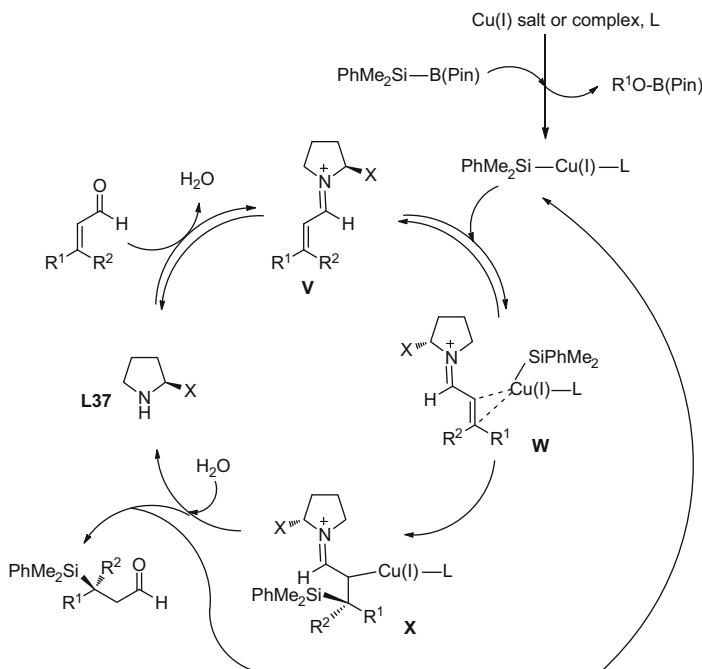
Scheme 76 Transition metal-free NHC-catalysed ECB of β,β -disubstituted linear enones by Hoveyda [112]

4 Formation of Silicon-Containing Quaternary Centres by Copper-Catalysed ECA

The development of methods for the catalytic enantioselective formation of C–Si bonds is an important challenge in organic synthesis [114]. In this context, the transition metal-catalysed enantioselective conjugate addition (ECA) of in situ-generated Si nucleophiles derived from readily available sources [e.g. $\text{Cl}_2\text{PhSi}-\text{SiMe}_3$ and $\text{Me}_2\text{PhSi}-\text{B}(\text{Pin})$] to α,β -unsaturated acceptors with a substituent in the



Scheme 77 Copper- and amine-catalysed ECS of β,β -disubstituted linear enals by Cordova [115]



Scheme 78 Proposed catalytic cycle for the ECS of enals catalysed by combination of copper and chiral amine catalysts by Hoveyda [115]

β -position is particularly attractive, as it provides direct access to synthetically useful β -silyl quaternary centres.

As described by Cordova et al., the strategy of combining transition metal-catalysed nucleophilic activation with chiral amine-catalysed iminium activation allows the enantioselective conjugate silyl addition to α,β -unsaturated aldehydes [115]. The reaction proceeds with good 1,4-selectivity and moderate enantioselectivity when β,β -disubstituted unsaturated aldehydes are used as substrates, as exemplified in Scheme 77. The silylated products are versatile adducts that can be easily converted to protected 1,3-diols and β -functionalised esters.

Supported by DFT calculations, the proposed catalytic cycle for this transformation is presented in Scheme 78. The origin of the enantioselectivity is attributed to the steric repulsion between the nucleophile and the bulky group of the catalyst.

The copper salt (or copper complex) reacts with $\text{Me}_2\text{PhSi-B(Pin)}$ to deliver the corresponding L-Cu(I)-silane . In parallel, the chiral amine forms the iminium intermediate **V** with the α,β -unsaturated aldehyde. Next, the catalytic cycles merge and the L-Cu-silane complex stereoselectively reacts with the chiral iminium intermediate **V** via a possible intermediate **W** to form a C-Si bond in intermediate **X**. Subsequent hydrolysis of iminium ion **X** gives the corresponding β -silyl aldehyde product as well as regenerate the Cu(I)-silane and the chiral catalyst **L37** [115].

It is worth mentioning that other methodologies for the asymmetric silyl addition to α,β -unsaturated systems [116] do not allow the formation of quaternary centres.

5 Perspective

The amount of methodologies available to synthetic chemists for incorporating quaternary stereocentres in organic molecules with high enantioselectivity has substantially increased in the past decade, especially in the area of conjugate addition reactions.

Although a diverse range of chemical transformations are now available to meet this formidable challenge, there are limitations and challenges to overcome. Not only is the development of alternative catalytic methods, based on readily available and less expensive complex catalysts, highly desirable, but also other particular issues need to be addressed. For example, the formation of quaternary stereocentres in acyclic molecules or acyclic molecular fragments is still in its early stage and needs further development [117, 118]. Also, efficient methodologies are needed for the ECA to β,β -disubstituted α,β -unsaturated carboxylic acid derivatives (e.g. ester, thioesters, amides etc.); except for the ECB procedure developed by Hoveyda et al. [111], none of the reported methodologies allows the formation of chiral quaternary stereocentres on any substrate different from an enone. Lastly, and of particular interest, is the development and/or improvement of existing methodologies for the ECA of the less reactive methyl nucleophiles that provide an easy approach to methyl-substituted quaternary stereogenic centres, ubiquitous in natural products [119, 120].

The methods now available for the copper-catalysed enantioselective formation of quaternary stereocentres remove many of the previous barriers to incorporating such fragments in organic molecules. These enantiomerically enriched building blocks can be used in the synthesis of natural products, medicines and agriculturals to polymers and advanced materials. We expect an increasing number of novel compounds containing quaternary stereocentres, including new drug candidates, being designed, synthesised and evaluated in the near future.

Acknowledgements BM thanks the European Commission for a Marie Curie Career Integration Grant, the EPSRC for a First Grant and G. P. Howell for helpful comments on the manuscript.

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Organometallic Flow Chemistry

Noël, T. (Ed.)

2016, VII, 267 p. 50 illus., 46 illus. in color., Hardcover

ISBN: 978-3-319-33241-3