Formation of quaternary centres by copper catalysed enantioselective conjugate addition reaction

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List of acronyms:

ECA – Enantioselective Conjugate Addition

ECB – Enantioselective conjugate Borylation

*c*Hex – cyclohexyl

*c*Pent – cyclopentyl

CuTC – Copper(I)-thiophene-2-carboxylate

DCM – Dichloromethane

DME – Dimethoxyethane

TMSOTf – Trimethylsilyl trifluoromethanesulfonate

NHC – *N*-heterocyclic carbene

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 summarizes the developments in the area.

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 [4,5,6,7], 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 an 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-90s, metal catalysed enantioselective conjugate addition (ECA) reactions have evolved as an important tool for the synthetic chemist to access to enantiopure molecules [14,15,16], such as the natural products and biologically active compounds represented in Figure 1 [17,1819,20,21,22,23,24].

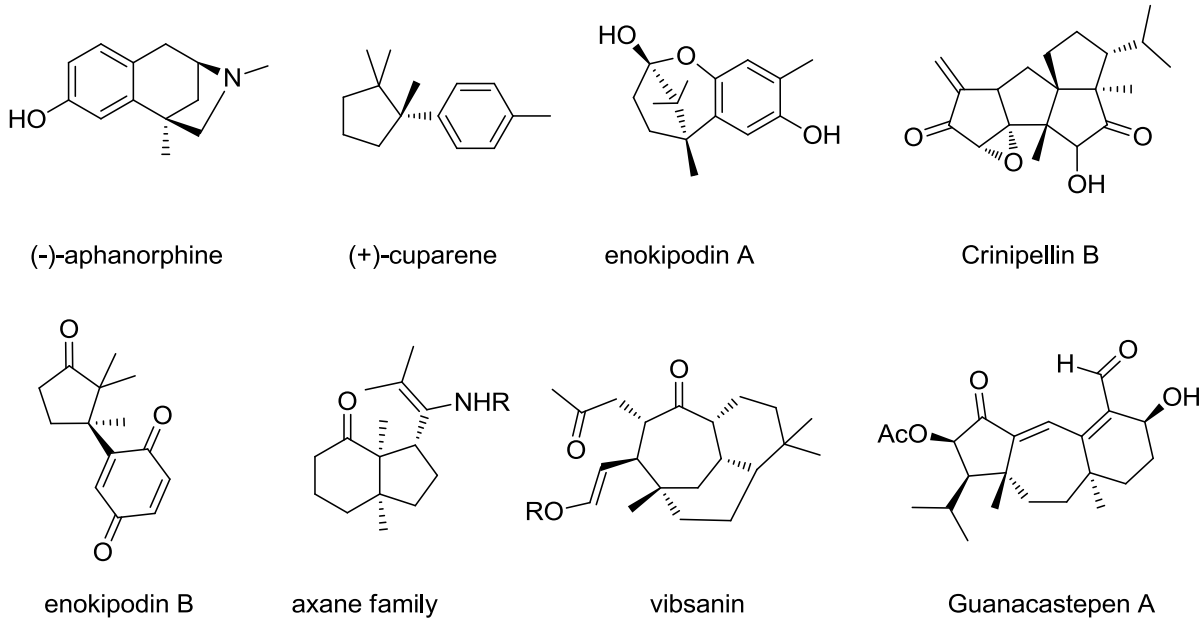


Figure 1. Examples of natural products and biologically active compounds containing chiral quaternary centres, synthesised by copper catalysed ECA.

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 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 [29,30,31]. 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, Section 2 covers carbon nucleophiles, including organoaluminium (section 2.1), Grignard (section 2.2), organozinc (section 2.3) and organozirconium reagents (section 2.4). Next, Section 3 reviews the use of organoboron reagents, to form boron containing quaternary centres. And last, Section 4 presents the use of organosilicon reagents, to form silicon containing quaternary centres.

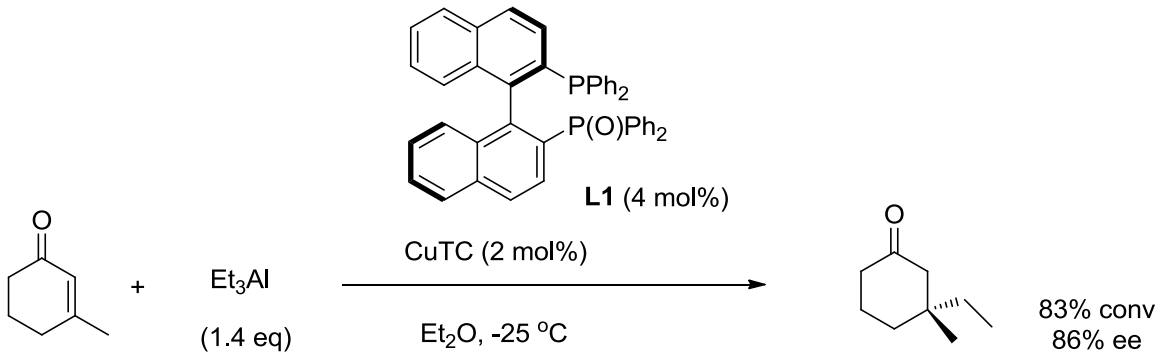
After the ECA reaction step, the generated enolate requires protonation to generate the corresponding enol, which rapidly tautomerises to the ketone product. Protonation is typically carried out by addition of water, aqueous NH_4Cl or aqueous HCl. For simplicity, this step has been omitted in all schemes, 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-trisubstituted substrate. 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-trisubstituted 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 triethyl aluminium in diethyl ether at -25 °C gives 86% enantiomeric excess (Scheme 1).



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

Phosphoramidite ligands are more efficient in the generation of stereogenic quaternary centres by copper-catalysed addition of aluminium organyls to cyclic enones. Alexakis has demonstrated that excellent enantiomeric excesses can be achieved with catalytic amounts of **L2-3** (Figure 2) and CuTC, for a range of commercially available nucleophiles and β-trisubstituted 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. 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.

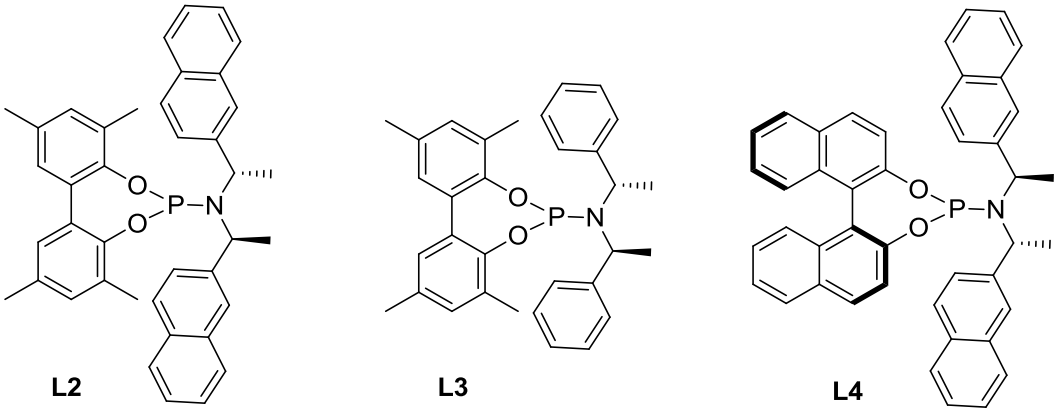
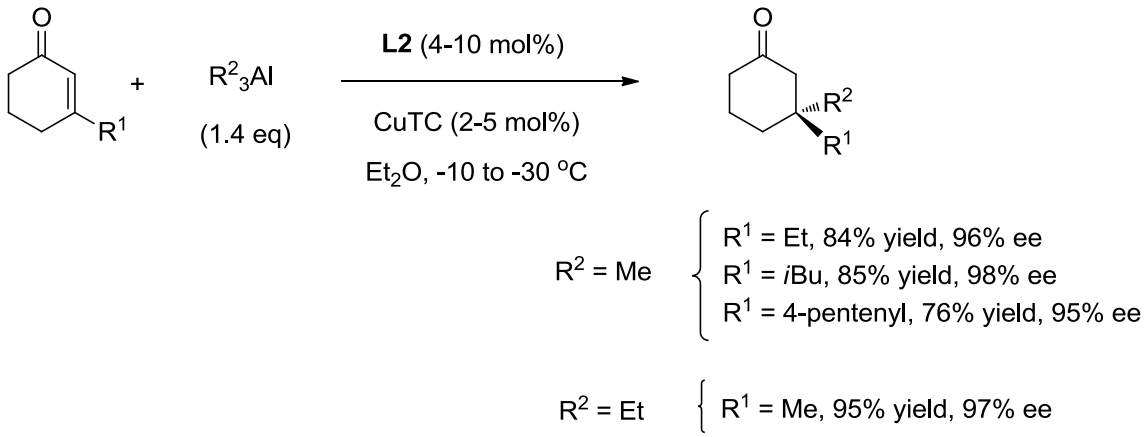


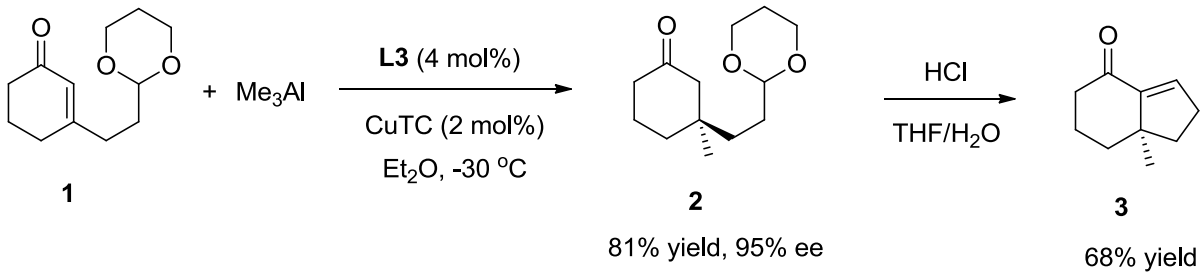
Figure 2. Effective phosphoramidite ligands for the copper catalysed ECA of organoaluminium reagents to enones.

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



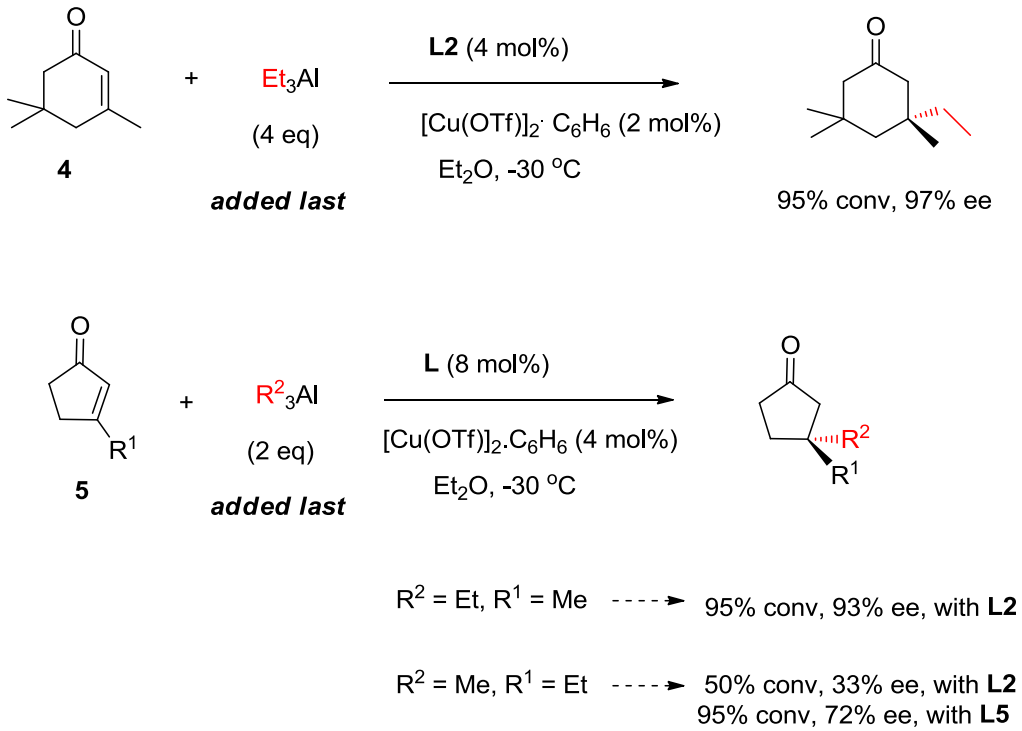
Scheme 2. Copper-phosphoramidite catalysed ECA to β-substituted cyclohexenones by Alexakis [35].

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 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 (iBu_3Al), which often lead to complex reaction mixtures.



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

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 organoaluminun reagent the 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** (Figure 3) provides slightly better results than the phosphoramidite ligands [37].



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

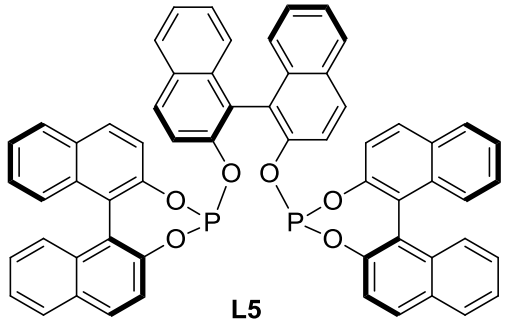
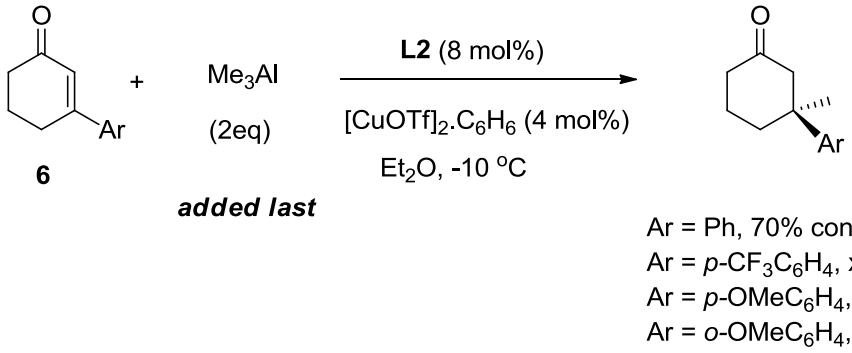


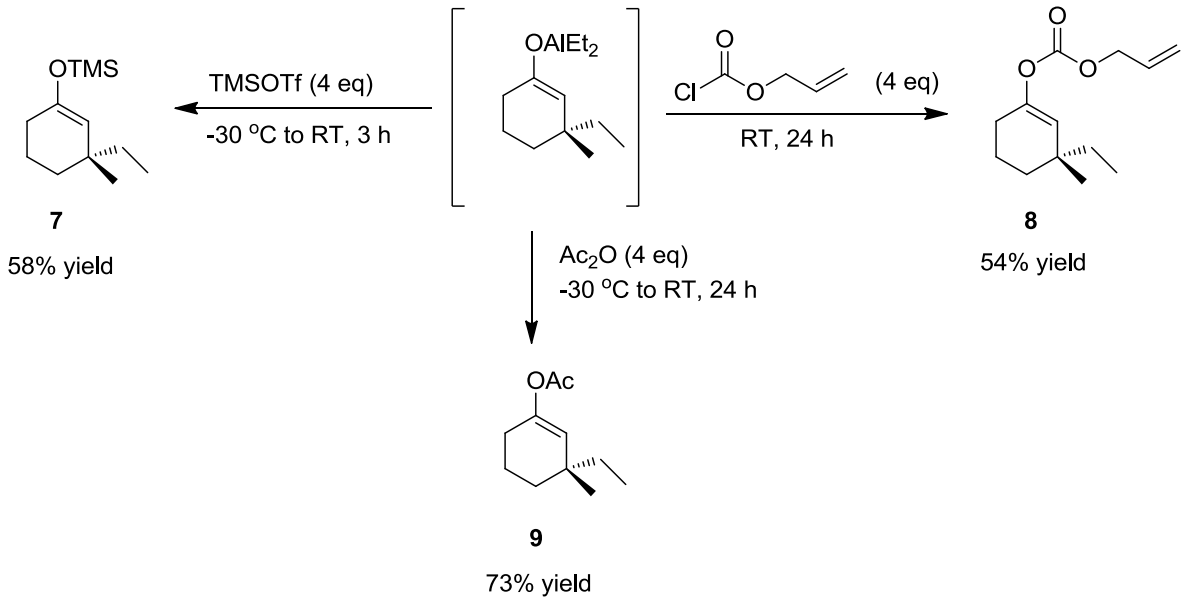
Figure 3. Chiral diphosphite ligand for the addition of organoaluminium reagents to β-substituted cyclopentenones by Alexakis [37].

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 steric and electronic effects are observed. For example, the addition of Me_3Al to 3-phenyl cyclohexenone gives 72% ee, while functionalised aromatic groups give up to 66% ee. If the substituent of the phenyl group is in the *ortho*-position, racemic product is obtained.



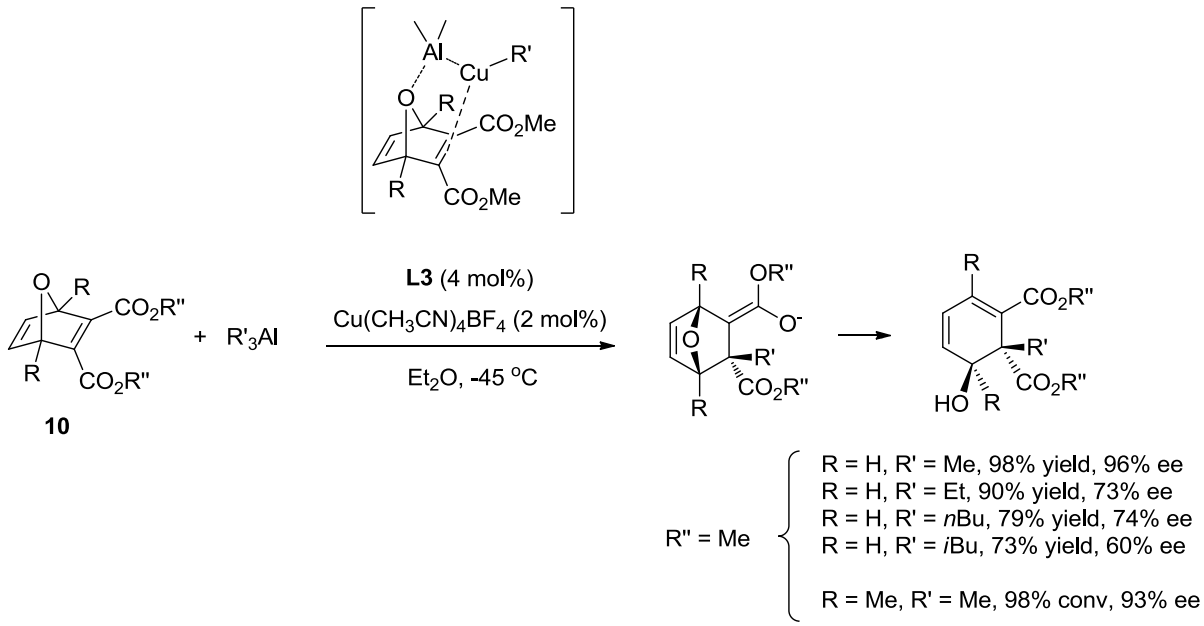
Scheme 5. Copper-phosphoramidite catalysed ECA to β-aryl cyclohexenones by Alexakis [38].

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].



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

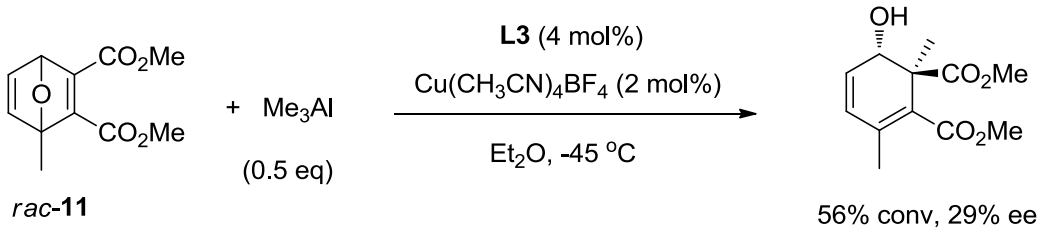
Trialkylaluminium reagents have been shown to undergo copper-phosphoramidite-catalysed ECA reaction with oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates **10**, with the simultaneous creation of up to two adjacent quaternary stereocentres (Scheme 7) [39]. The conjugate addition occurs from the *exo* side, probably due to coordination by the bridging oxygen atom. 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].

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 = H, R'' = *i*Pr).

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

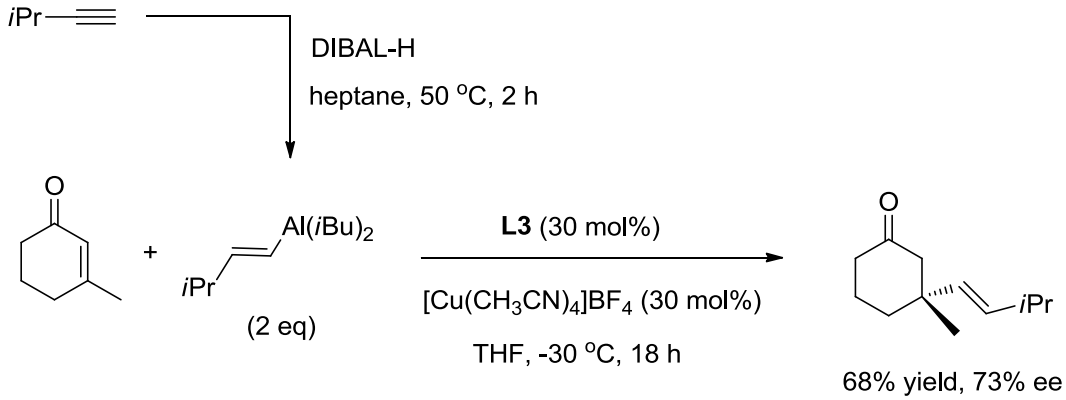


Scheme 8. Copper-phosphoramidite catalysed ECA to racemic 1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates by Alexakis [39].

Phosphoramidite ligands are also suitable for the challenging enantioselective addition of alkenyl aluminium reagents to trisubstituted 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.

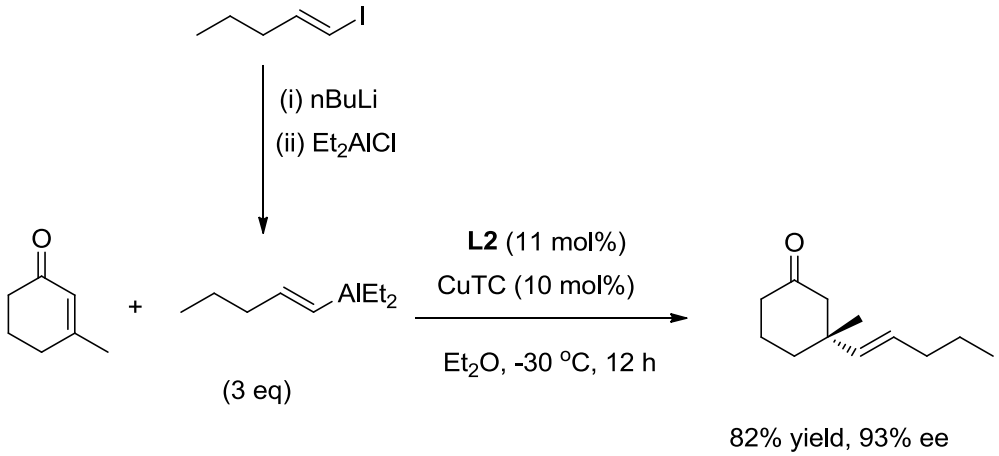
Alkenyl aluminium reagents can be easily generated by hydroalumination of the corresponding alkynes with DIBAL-H, under Zweifel conditions (Scheme 9) [42]. Interestingly, the use of the "standard" conditions (CuTC, Et_2O), optimal for the ECA of alkyl aluminium reagents with phosphoramidite ligands, only leads to the 1,2-addition–dehydration product when alkenyl

aluminium reagents are used as nucleophiles. However, the use of THF as solvent supresses 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]



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

Alkenyl aluminium reagents can be also prepared by halogen/lithium exchange from the corresponding iodo alkene, 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) [44,45].

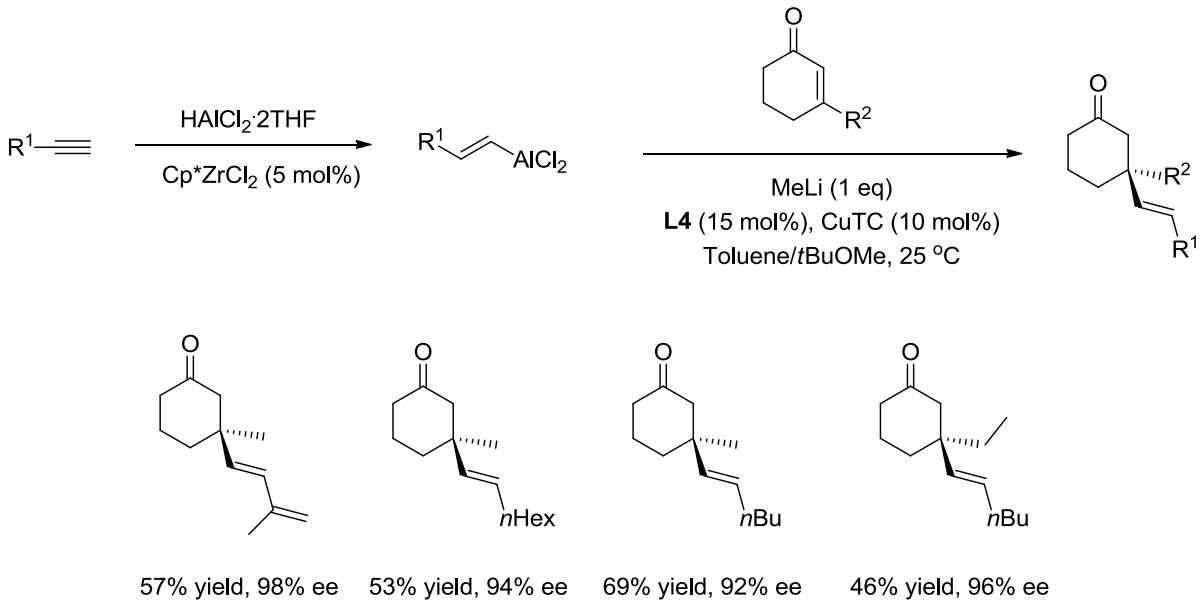


Scheme 10. Copper-phosphoramidite catalysed ECA of alkenyl aluminium reagents (prepared from iodoalkenes) to β-substituted cyclohexenones by Alexakis [44,45].

Recently, Woodward et al. have described the synthesis of alkenylaluminium reagents from their corresponding alkynes and $HAlCl_2{\cdot}2THF$, using $Cp^*_2ZrCl_2$ as catalyst. The initially obtained aluminium species can be activated with MeLi (1 equiv)[*] 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) [46]. This process shows good generality for 1,4-additions to a wide variety of β-substituted cyclohexenones. The alkenyl aluminium reagents

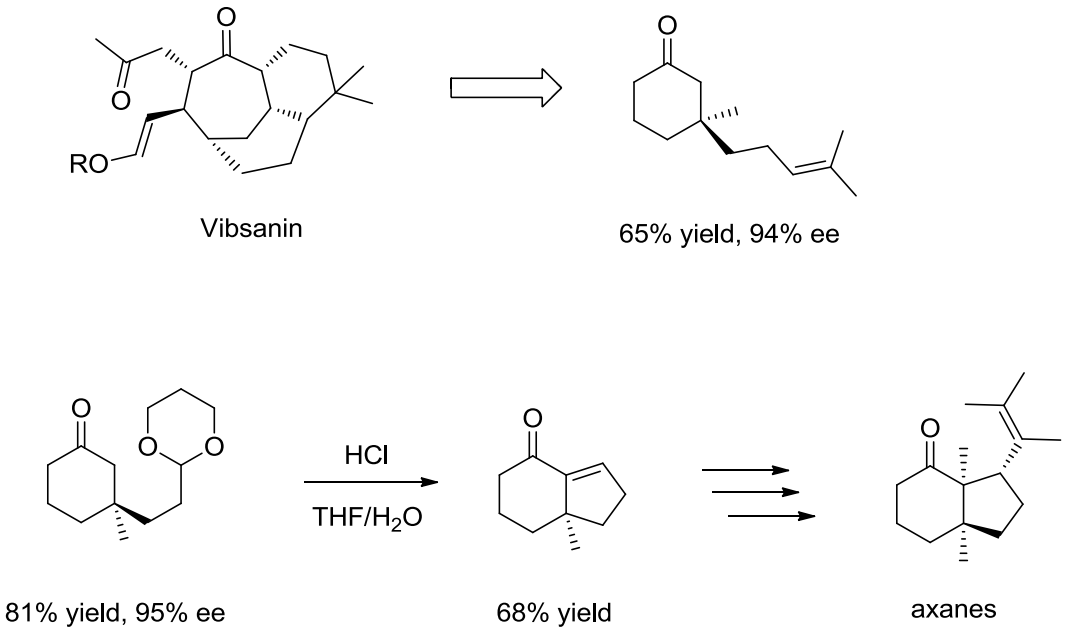
[*] Strangely, the use of two equivalents of MeLi gave poor processes – despite the known efficacy of $Me_2AlCH{\equiv}CHR$ species in related processes.

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.



Scheme 11. Copper-phosphoramidite catalysed ECA of alkenyl aluminium reagents (prepared *via* zirconium catalysed hydroalumination) to β-substituted cyclohexenones by Woodward [46].

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 [36,47].



Scheme 12. Copper-phosphoramidite catalysed ECA of organoaluminium reagents in the synthesis of some key intermediates from natural products by Alexakis [36,47].

Introduced by Alexakis et al., copper-phosphinamine systems also stand out as effective catalysts for the addition of organoaluminium reagents to cyclic enones [47,48]. In many cases, and in particular with challenging substrates, phosphinamine ligands (Figure 5) outperform the phosphoramidite counterparts.

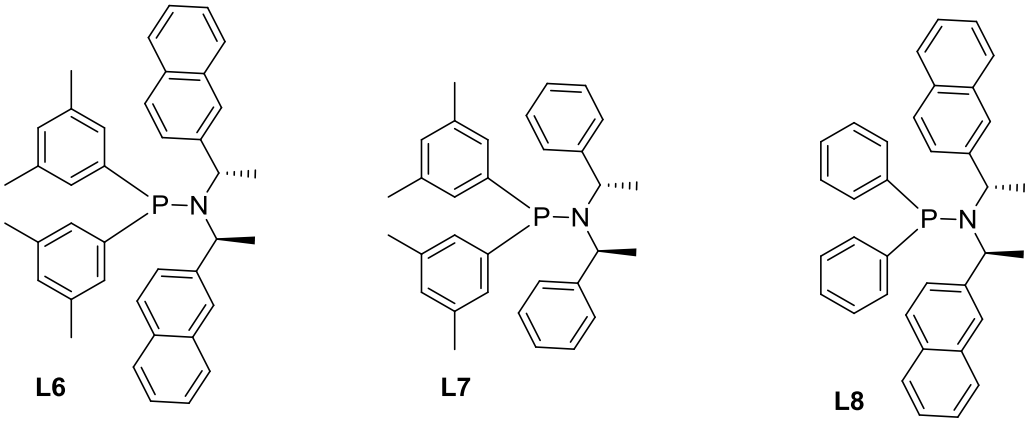
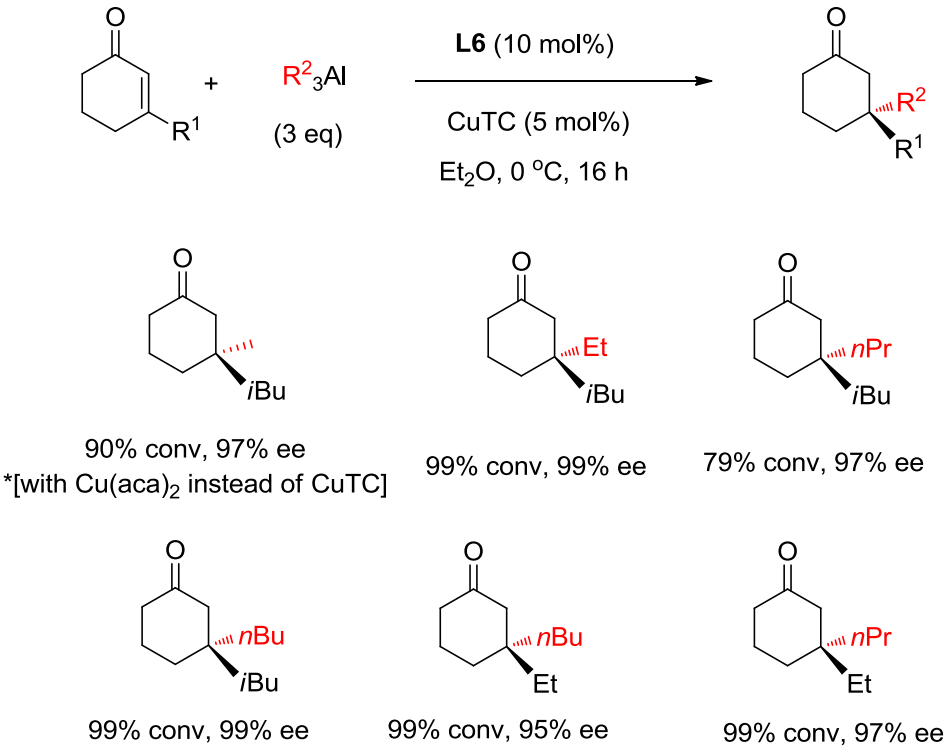
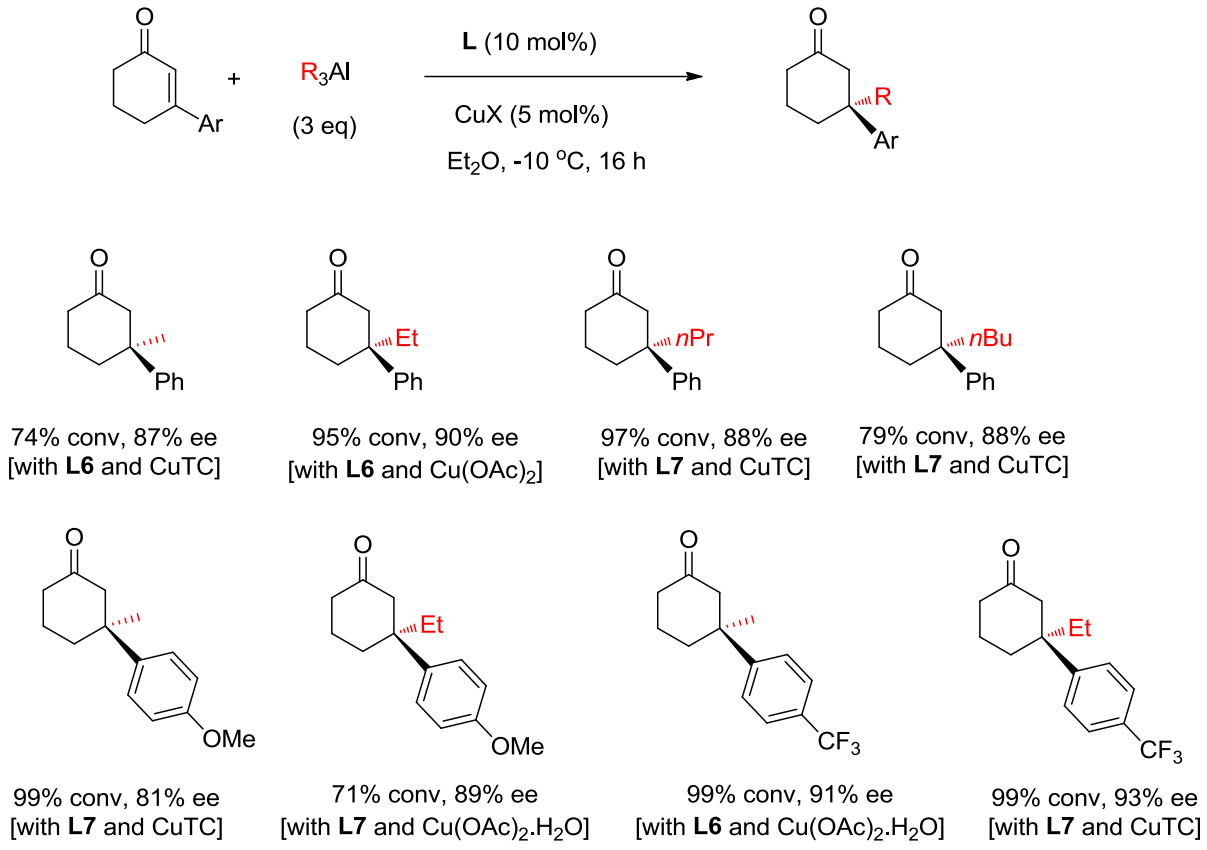


Figure 4. Effective phosphinamine ligands for the copper catalysed ECA of organoaluminium reagents to β-trisubstituted enones.

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).

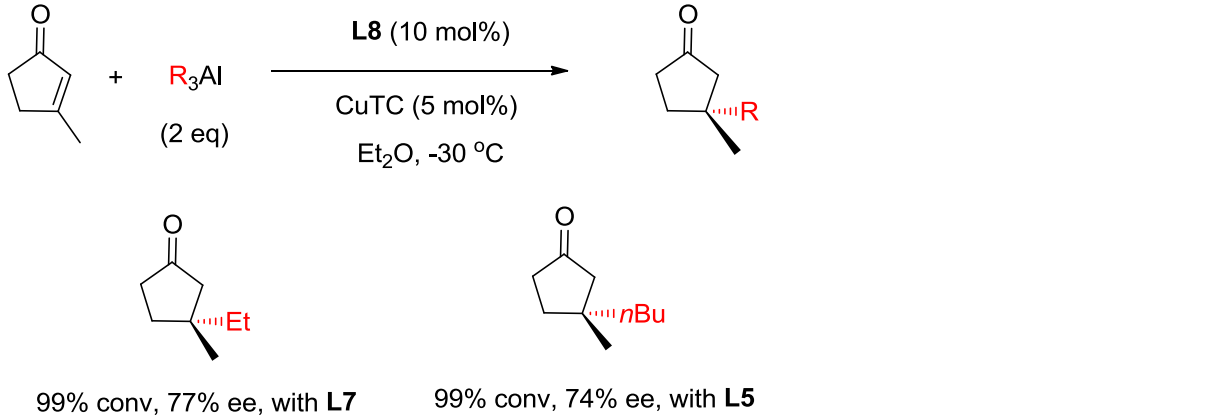


Scheme 13. Copper-phosphinamine catalysed ECA of organoaluminium reagents to β-substituted cyclohexenones by Alexakis [47,48].



Scheme 14. Copper catalysed ECA of organoaluminium reagents to β-aryl cyclohexenones by Alexakis [47,48].

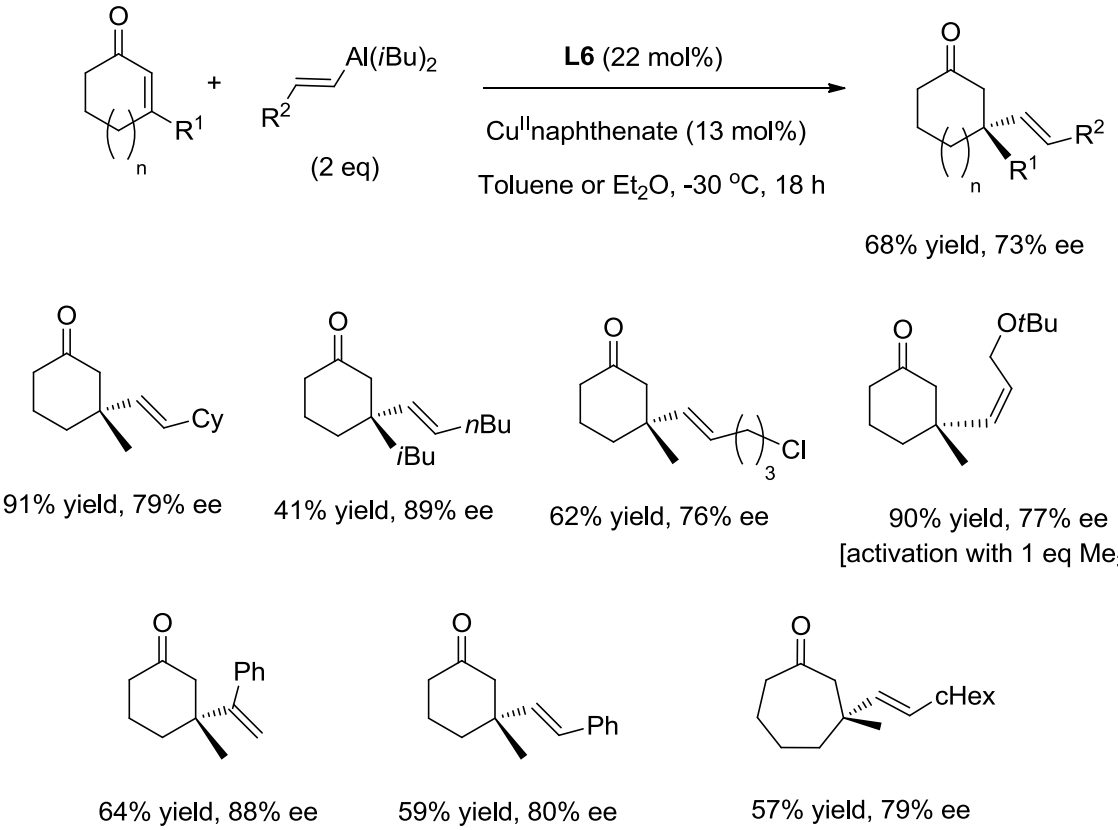
Regarding the challenging β-substituted cyclopenten-2-one substrates, phosphinamine ligands give moderate, comparable enantioselectivities to phosphoramidites, as shown in Scheme 15.



Scheme 15. Copper-phosphinamine catalysed ECA of organoaluminium reagents to β-substituted cyclopentenones by Alexakis [47,48].

The tandem hydroalumination–ECA process to β-substituted cyclic enones with phosphinamine ligands also works very efficiently (Scheme 16) [49,50]. 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

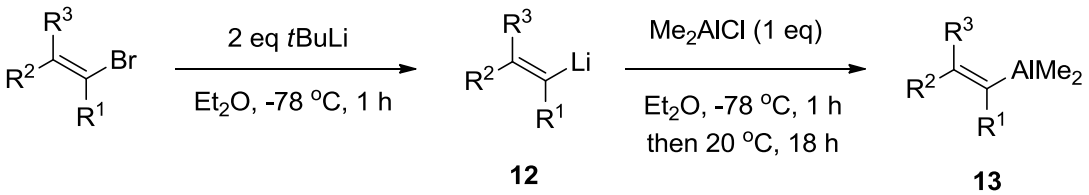
very good levels of enantioselectivity, including (*Z*)-nucleophiles, halogen containing alkenes, conjugated alkenes, protected alcohols and α-substituted alkenes, which might be difficult to achieve using other organometallic species. Furthermore, this methodology allows high levels of enantioselectivity for sterically hindered substrates, although further activation with 1 equivalent of Me_3Al is required to obtain high conversion (see example in Scheme 16). Cycloheptenones substrates can be also used (see example in Scheme 16) but, unfortunately, the cyclopentenone analogues give low levels of enantioselectivity with this method.



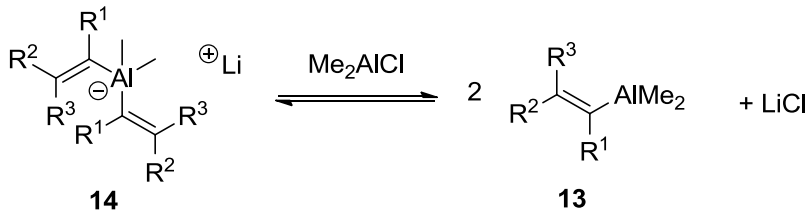
Scheme 16. Copper-phosphinamine catalysed ECA of alkenyl aluminium reagents (prepared by hydroaluminations with DIBAL-H) to β-substituted cyclic enones by Alexakis [49,50].

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*BuLi), followed by transmetalation with dimethylaluminium chloride provides the desired alkenyl aluminium reagent (Scheme 17) that can be used directly in the ECA reaction [50,51]. 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).



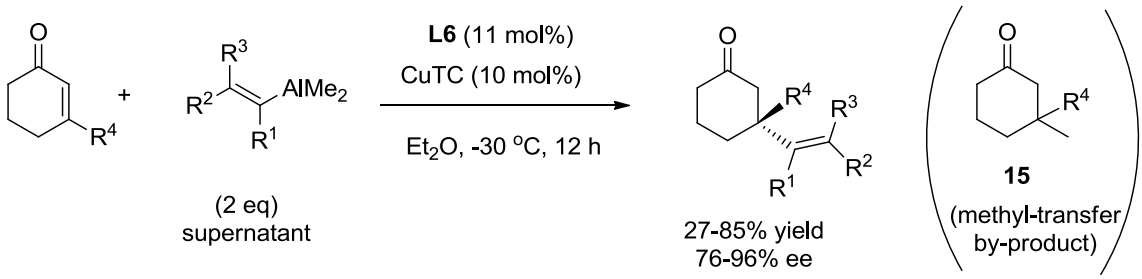
Scheme 17. Preparation of alkenyl aluminium reagents from bromoalkenes by Alexakis [50,51].

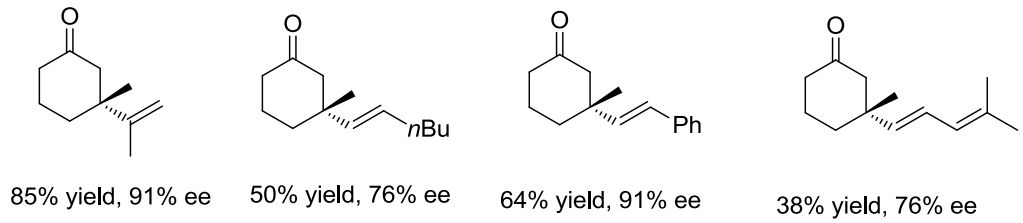


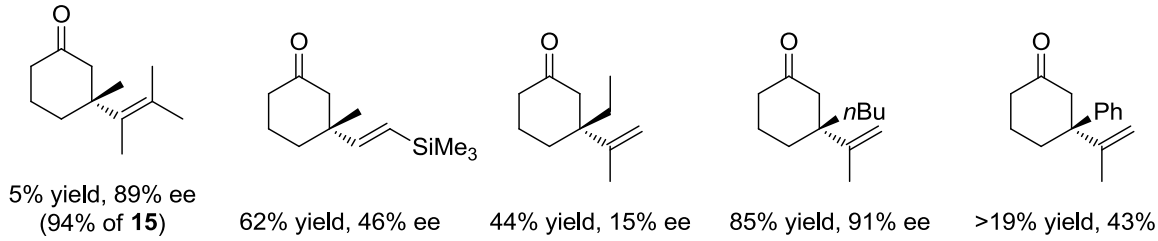
Scheme 18. Equilibrium reaction between alkenyl organoaluminium species generated from bromoalkenes [51].

Bromoalkenes are the preferred starting material for the generation of the corresponding nucleophile **13**, since many are commercially available or readily prepared [52,53,54,55,56]. Whilst the methodology is also efficient when iodo-alkenes 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 [44,45].

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 very good yields and enantioselectivities with only 10 mol% of the Cu-phosphinamide catalyst. The enantioselectivity of the process varies with the equivalents of alane 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 equivalents of **13** leads to a drop in enantioselectivity, probably due to contamination of the alane with traces of lithium salts, which might perturb the structure of the chiral copper complex.





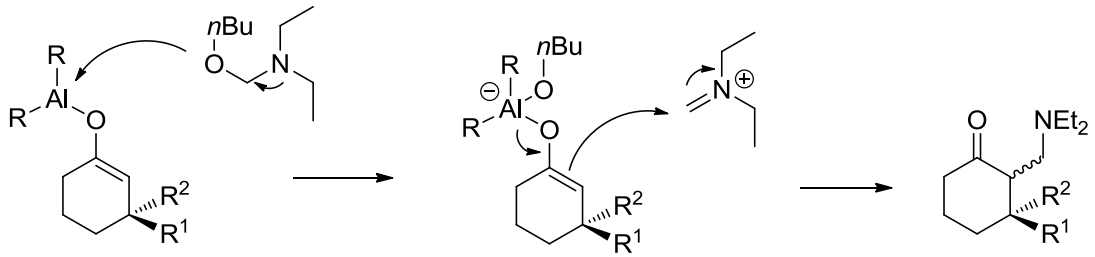


Scheme 19. Copper-phosphinamine catalysed ECA of alkenyl aluminium reagents (prepared by Br/Li exchange) to β-substituted cyclic enones by Alexakis [50,51]

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

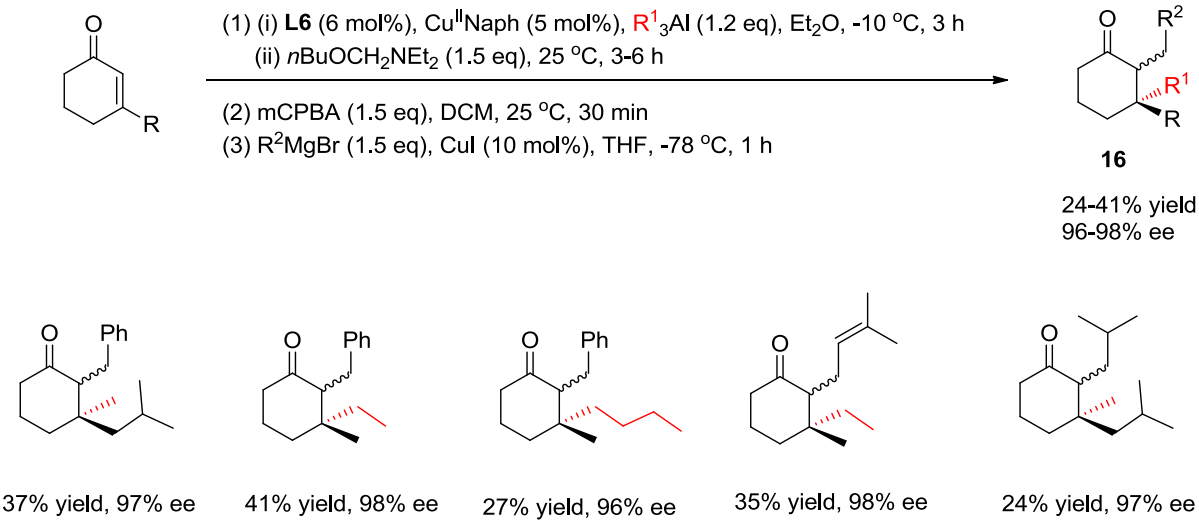
1. Hindered alkenylaluminiums reagents produce higher amounts of the methyl transfer by-product **15**.
2. Alkenylaluminiums reagents where R^2 = aryl group provide higher enantioselectivities than when R^2 = alkyl group (see Scheme 17 and examples in Scheme 19).
3. Silyl-protected vinyl aluminiums give 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.

Phosphinamide 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) [57]. 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 enolate in the same step. The formation of a reactive electrophile and reactive nucleophile in close proximity explains the high efficiency of this transformation.



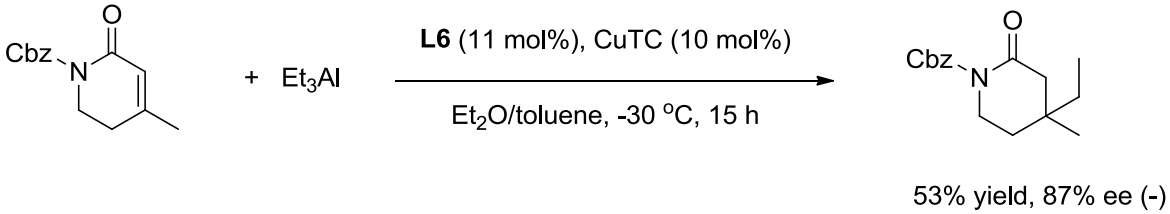
Scheme 20. Mechanism for the direct trapping of sterically encumbered aluminium enolates by Alexakis [57].

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).



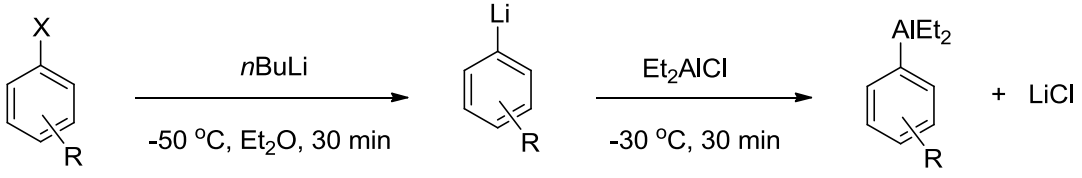
Scheme 21. Tandem copper-phosphinamine catalysed ECA / direct trapping by Alexakis [57].

The versatile phosphinamide 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 [58].



Scheme 22. Copper-phosphinamine catalysed ECA of organoaluminium reagents to β-methyl-substituted δ-lactams by Alexakis [58].

Regarding the use of aryl aluminium reagents as nucleophiles in the copper catalysed ECA, both phosphoramidites and phosphinamide ligands have demonstrated to be effective. Only one triaryl aluminium compound is commercially available (Ph_3Al), 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 alanes 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 Et_2AlCl (Scheme 23) [44].

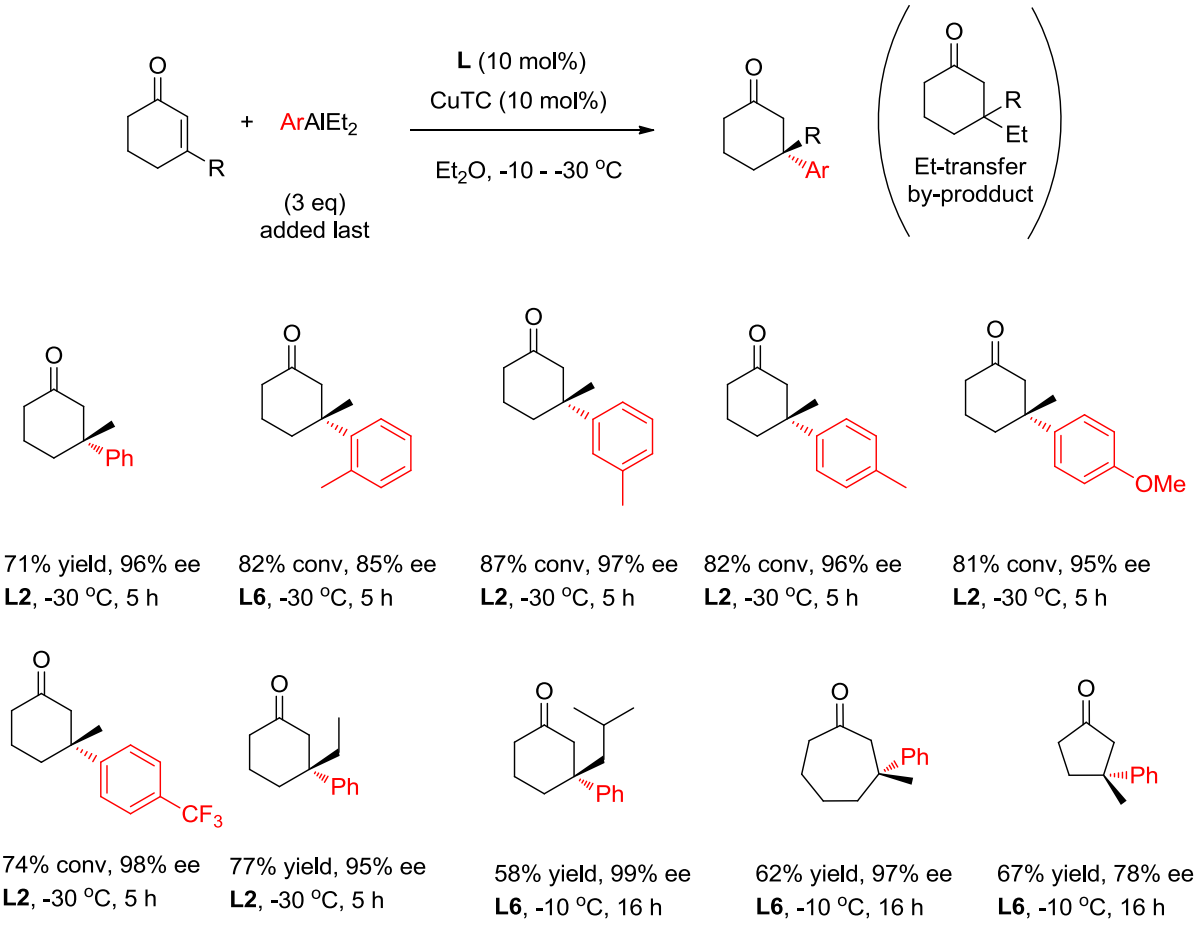


X = I, Br

Scheme 23. Preparation of dialkyl aryl aluminium species from aryl halides by Alexakis [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 the β-position of the enone is always preferred to the ethyl-transfer. The addition of a wide variety of aryl alanes proceeds with

enantioselectivities up to 99%, using 10 mol% of ligand (note this catalyst loading is slightly higher than when alkyl alanes are used as nucleophiles) and 10 mol% of the copper salt with both 6 and 7 membered ring cyclic enones (Scheme 24). Three equivalents of the alane 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 5-membered cyclic enones (see example in Scheme 24).



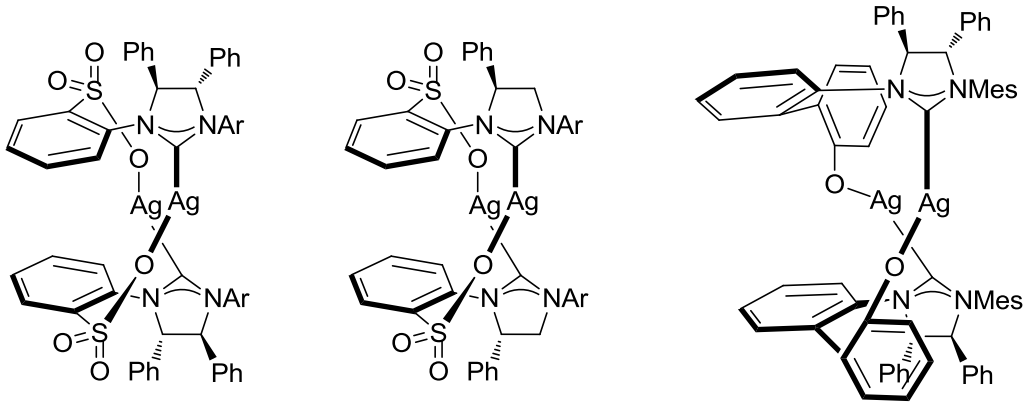
Scheme 24. Copper-phosphinamine catalysed ECA of arylaluminium reagents to β-substituted cyclic enones by Alexakis [44].

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**-**14** developed by Hoveyda and co-workers (Figure 5) [59].

Since their discovery in 1968 by Öfele [60] and Wanzlick [61], and their first isolation in the free state by Arduengo [62] in the early 1990s, NHC have received a growing attention as catalysts in many organic transformations [63]. 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 [64]. 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 NCHs have a planar chelation site.

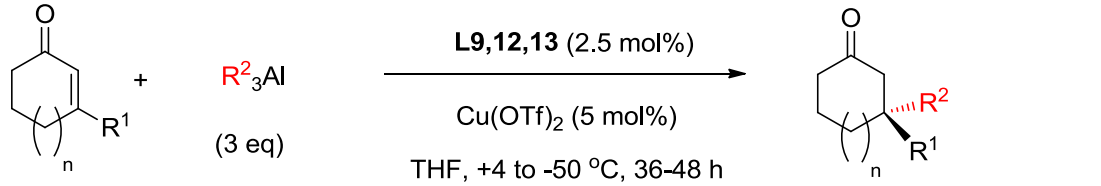
The copper-NHC catalysed addition of organoaluminium reagents to cyclohexenones and cycloheptenones reported by Hoveyda [59] is, in some cases, slightly less selective than those performed in the presence of phosphoramidites or phosphinamide catalysts (≤90% ee for the imidazolium ligands, *versus* ≤99% ee that the phosphoramidites and phosphinamides 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).



L9, Ar = 2,4,6-$Me_3C_6H_2$ (Mes)
L10, Ar = 2-*i*PrC_6H_5
L11, Ar = 2,4,6-*i*$Pr_3C_6H_2$ (Mes)

L12, Ar = 2,4,6-MeC_6H_2 (Mes)
L13, Ar = 2,6-EtC_6H_3
L14, Ar = 2,6-(*i*Pr)$_2C_6H_3$

Figure 5. Effective NHC ligands for the ECA of organoaluminium reagents to β-trisubstituted enones.



up to 97% ee and 97% conv

R^1 = Me, Et, *n*Bu, alkynyl, aryl, CO_2R^3
R^2 = Me, Et, *i*Bu

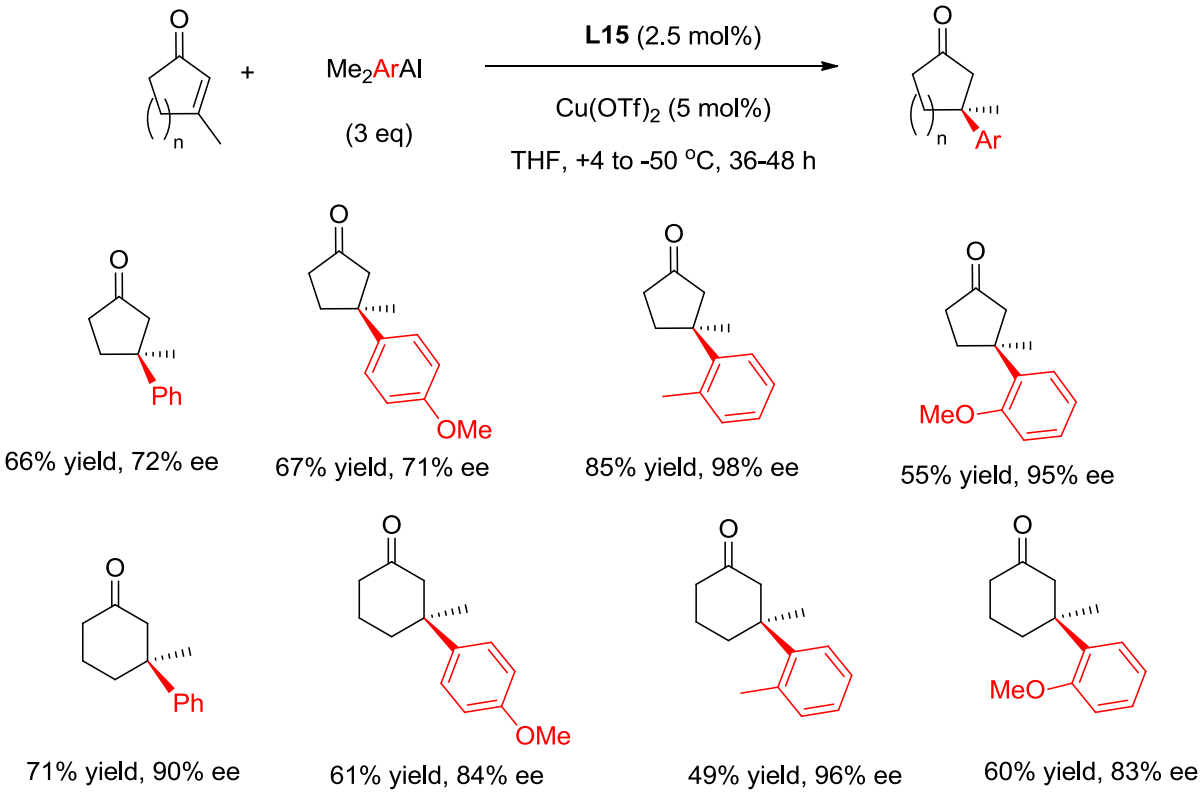
Scheme 25. Copper-NHC catalysed ECA of organoaluminium reagents to β-substituted cyclohexenones by Hoveyda [59].

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 one equivalent of commercially available Me_2AlCl in pentane (-78 to 22 °C, 12 h)[†]. The resulting solution of Me_2PhAl, containing LiCl, can be used directly—without filtration or purification—in the copper catalysed ECA

[†] Note that when Et_2AlCl is used as transmetallating agent (see reference 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).

reactions of β-substituted cyclic enones (Scheme 26) and can be also stored under N_2 for more than two 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 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 5-membered rings are remarkable, considering that they are usually challenging substrates in the ECA.

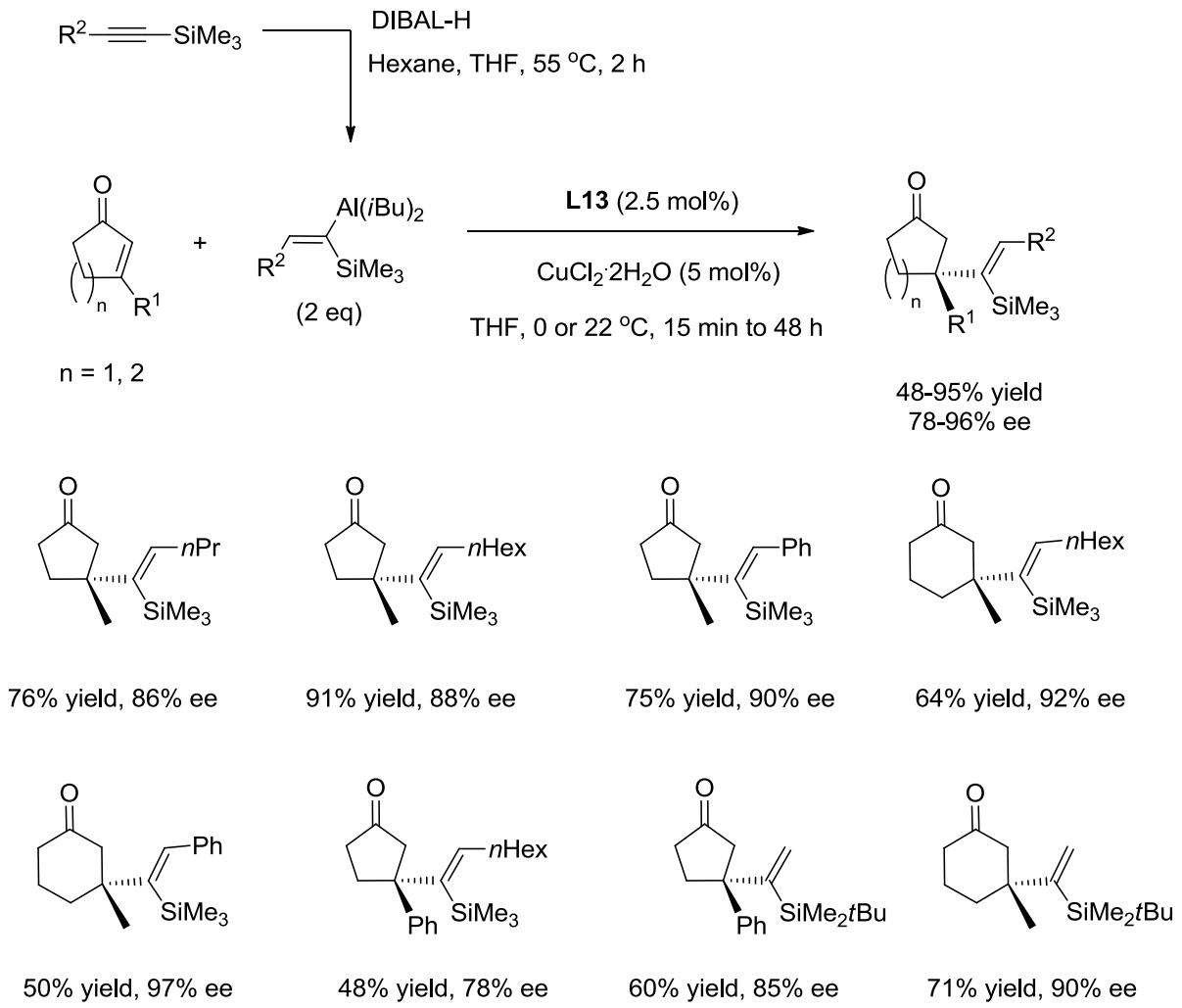


Scheme 26. Copper-NHC catalysed ECA of aryl aluminium reagents to β-substituted cyclic enones by Hoveyda [59].

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) [65].

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 $CuCl_2 \cdot 2H_2O$ 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 additions of alkenyl aluminium reagents to cycloheptenones under these reaction conditions are, however, inefficient.

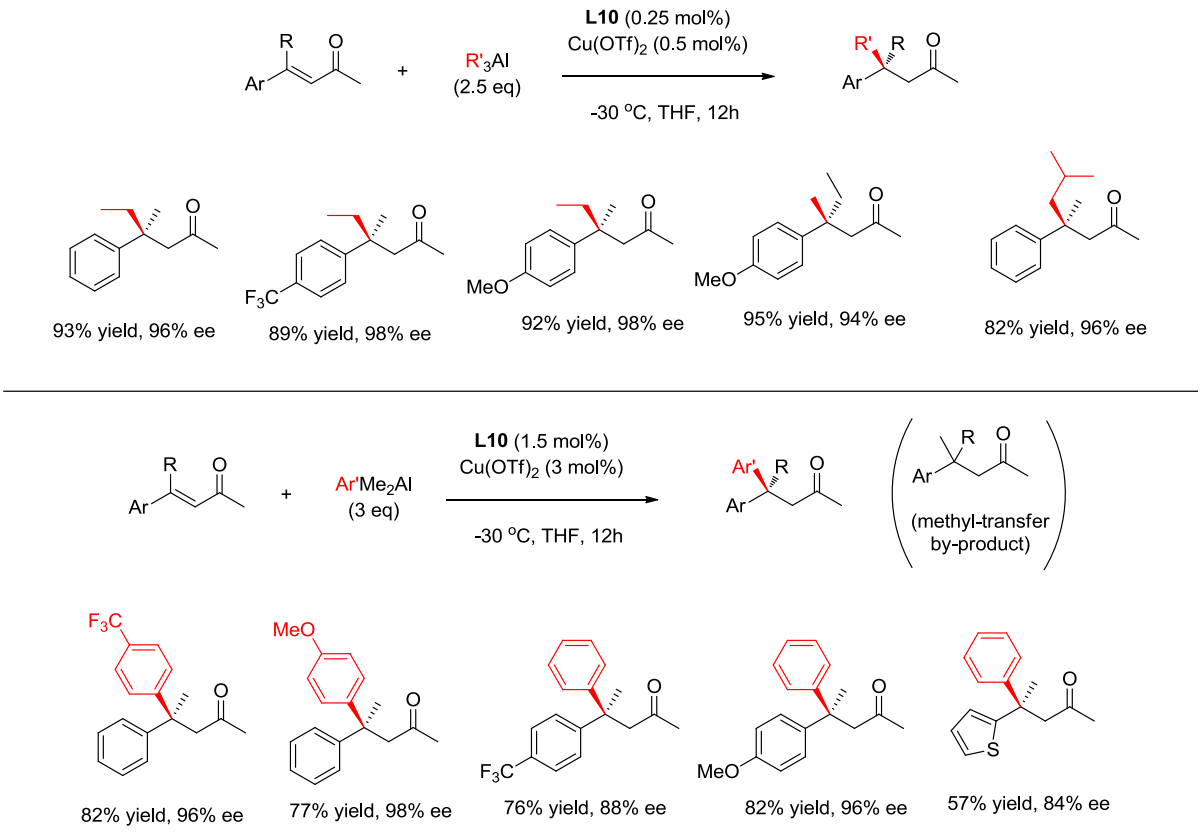
As represented in the last 2 examples in Scheme 27, vinylaluminium reagents bearing a more hindered silyl unit (*t*BuMe$_2$Si vs SiMe$_3$) also provide high enantioselectivities. The vinylsilane moiety within the products can be functionalised to afford acyl, vinyliodide, or desilylated alkenes in 67% to >98%yield and with >90% retention of the alkene's stereochemical identity [65].



Scheme 27. Copper-NHC catalysed ECA of alkenyl aluminium reagents (prepared by hydroaluminations with DIBAL-H) to β-substituted cyclic enones by Hoveyda [65].

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 Cu(OTf)$_2$ [66].

A wide range of acyclic trisubstituted enones readily undergo ECA with both commercially available trialkylaluminium reagents or 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) [66].



Scheme 28. Copper-NHC catalysed ECA of organoaluminium reagents to β,β-disubstituted linear enones by Hoveyda [66].

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 alkylaluminium reagents to bulky substrates and non-aromatic enones proceeds with very high enantioselectivity, as exemplified in Figure 6.

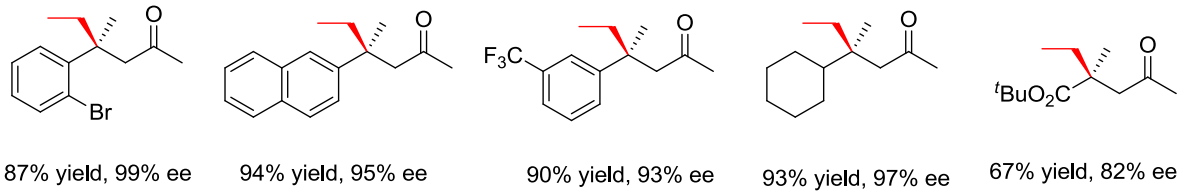
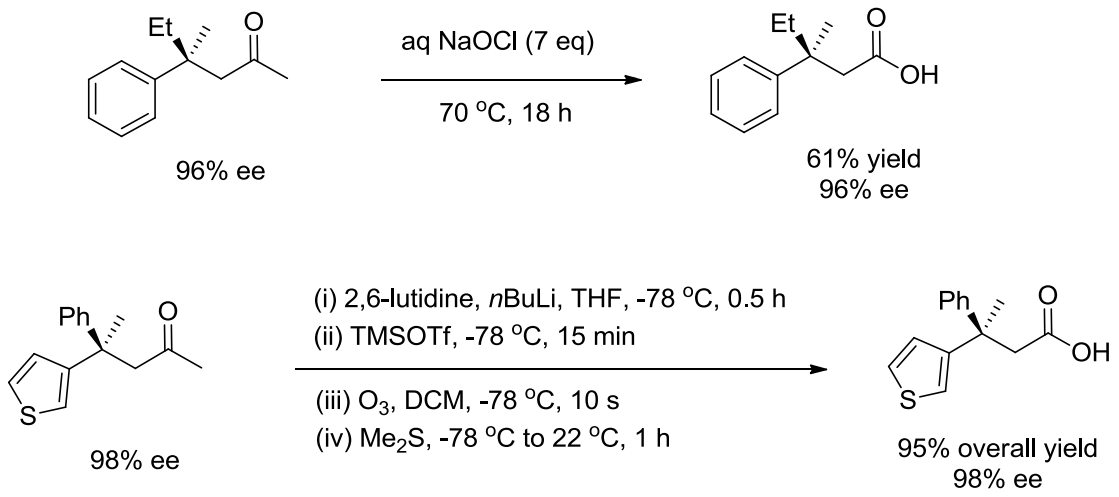


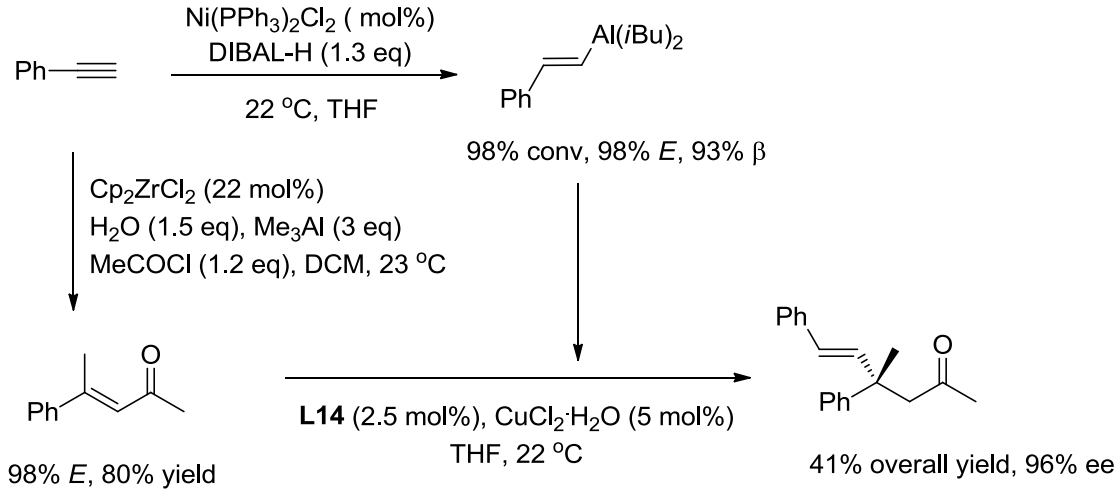
Figure 6. Copper-NHC catalysed ECA of organoaluminium reagents to both bulky and aliphatic β,β-disubstituted linear enones by Hoveyda [66].

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).



Scheme 29. Oxidation of chiral ketones to versatile carboxylic acids by Hoveyda [66].

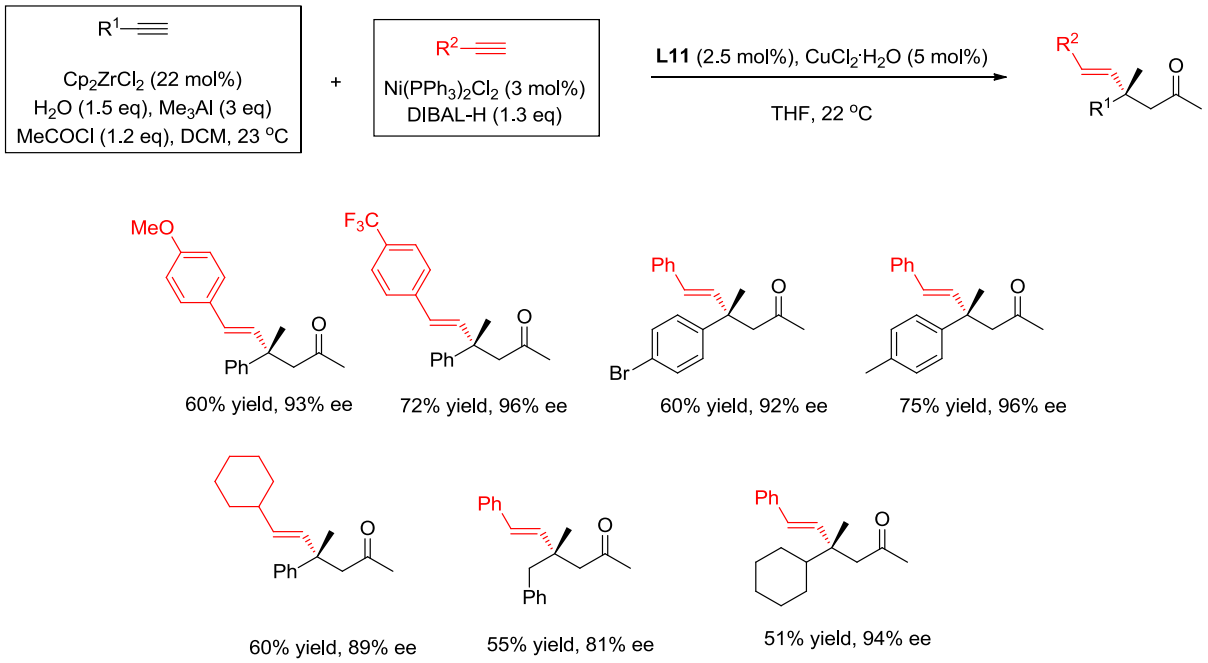
The addition of alkenyl aluminium nucleophiles to linear β,β-disubstituted enones to give all-carbon quaternary stereogenic centres can be also achieved with consistently high yields and enantioselectivities (up to 99% ee) by copper-NCH catalysed ECA, using very low catalyst loadings at room temperature (Scheme 30) [67].



Scheme 30. Multicomponent Ni-, Zr-, and Cu-catalysed strategy for ECA of alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [67].

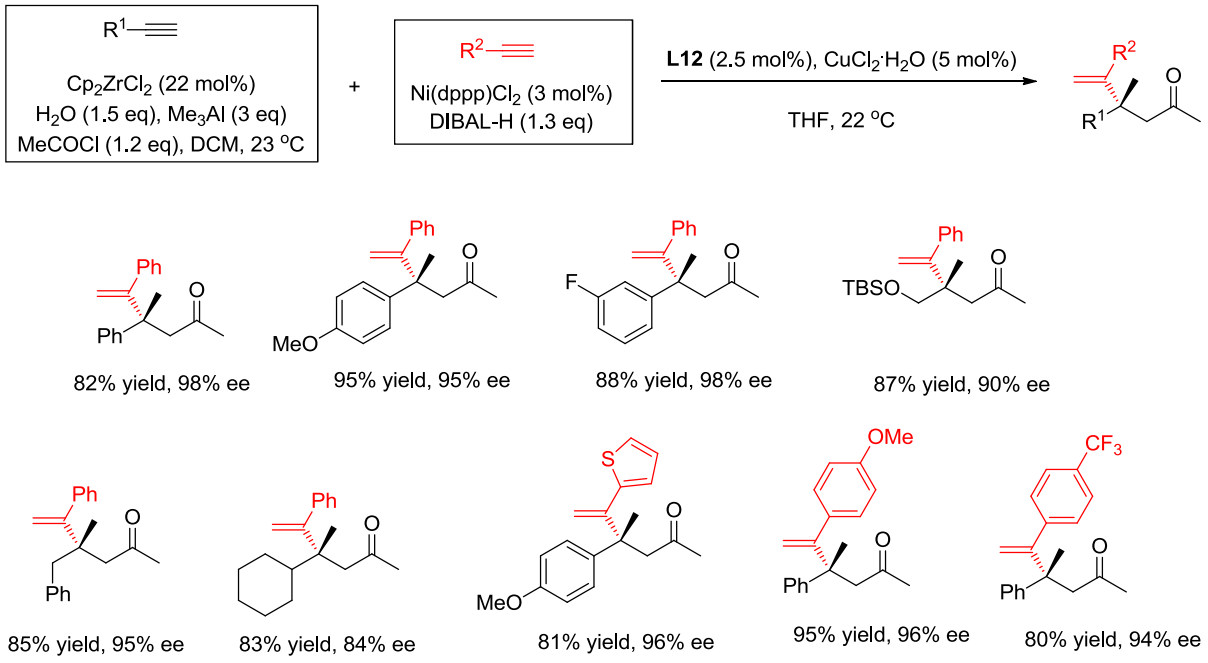
In this work, Hoveyda et al. synthetise alkenyl aluminium reagents with exceptional site- and/or stereoselectivity using a Ni-catalysed hydroalumination process and use them directly. Unlike the methodology previously described for β-substituted cyclic enones, silyl-substituted alkenyl aluminium species 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 3 steps) and

high enantioselectivities (>90%), using the NHC silver complexes **L11** (Scheme 30) or **L14** (Scheme 31) as pre-catalyst, in combination with $CuCl_2.H_2O$.



Scheme 31. Multicomponent Ni-, Zr-, and Cu-catalysed strategy for ECA of linear alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [67].

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 very good yields and enantioselectivities when a **L12**/$CuCl_2{\cdot}H_2O$ mixture is used as catalyst (Scheme 32).



Scheme 32. Multicomponent Ni-, Zr-, and Cu-catalysed strategy for ECA of branched alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [67].

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

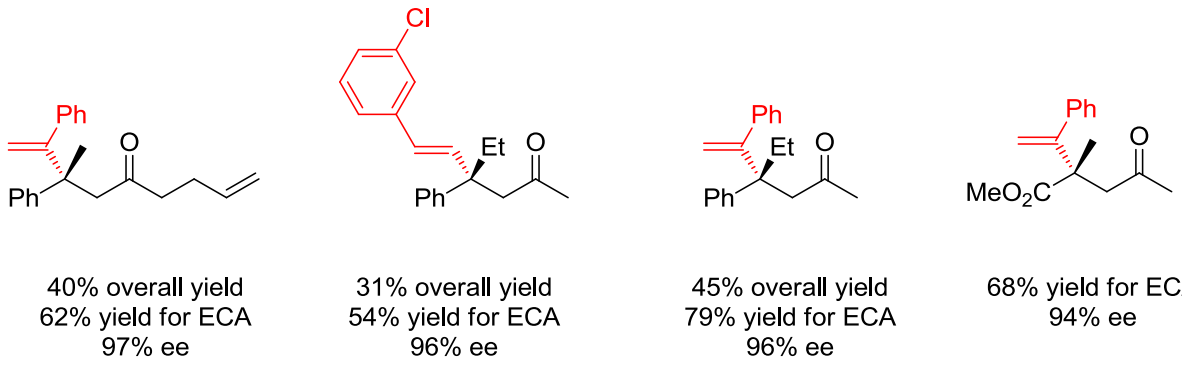


Figure 7. Examples on the multicomponent Ni-, Zr-, and Cu-catalysed strategy for ECA of alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [67].

The utility of this method has been demonstrated with the enantioselective synthesis of antimicrobial enokipodin B (Figure 1) [67].

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** (Figure 8) represents the lowest energy pathway, consistent with the identity of the major isomers; whilst complex **B** (Figure 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.

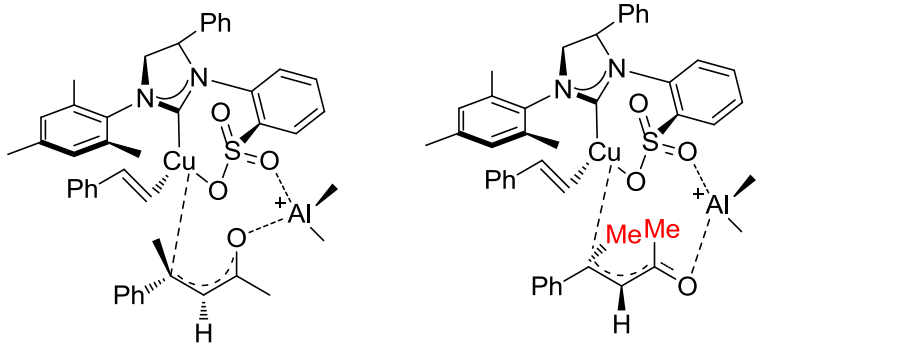


Figure 8. Proposed transitions states for the copper-NCH catalysed ECA or alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [67].

Phosphine ligands such as **L16** and **L17** (Figure 9), based on either a spinol or binol architecture, are also suitable ligands for the copper catalysed ECA of 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) [68].

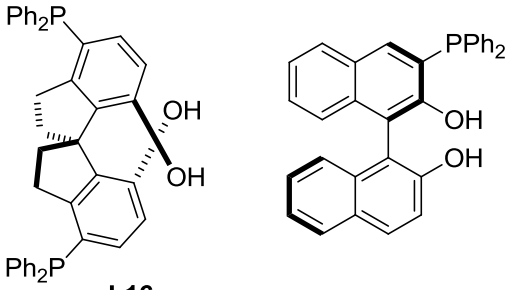
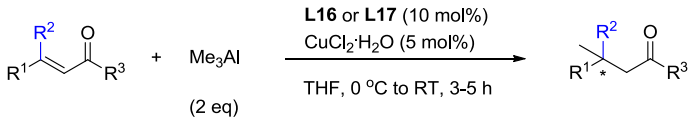
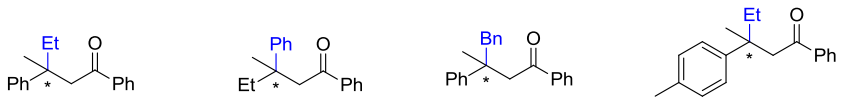
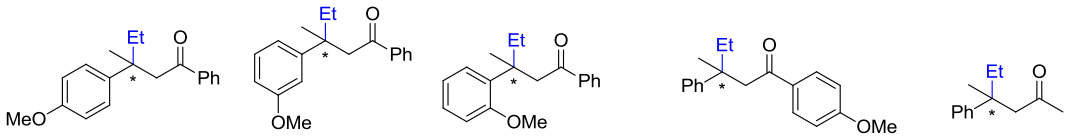


Figure 9. Effective phosphine ligands for the ECA of organoaluminium reagents to β-trisubstituted enones.





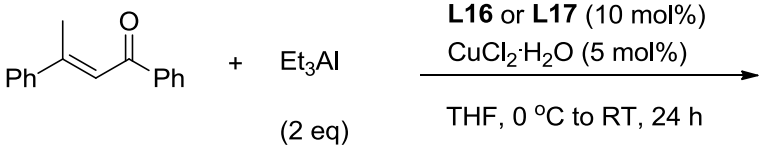
L16	98% yield, 98% ee (+)	98% yield, 35% ee (-)	80% yield, 97% ee (+)	95% yield, 98% ee (+)
L17	98% yield, 95% ee (-)	98% yield, 75% ee (-)	72% yield, 94% ee (-)	97% yield, 98% ee (-)



L16	98% yield, 98% ee (+)	93% yield, 98% ee (+)	93% yield, 94% ee (+)	97% yield, 98% ee (*R*)	97% yield, 93% ee (-)
L17	86% yield, 98% ee (-)	60% yield, 95% ee (-)	89% yield, 98% ee (-)	98% yield, 98% ee (*S*)	76% yield, 98% ee (+)

Scheme 33. Copper-phosphine catalysed ECA of trimethylaluminium to β,β-disubstitued linear enones by Endo [68].

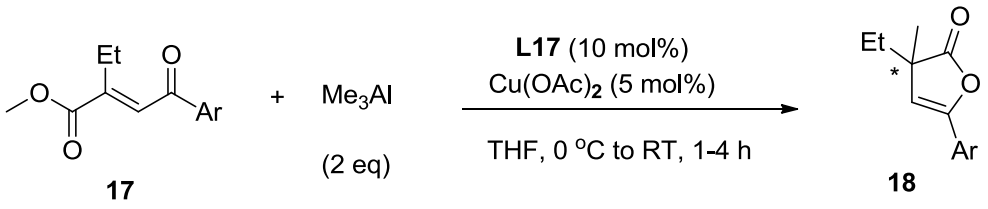
The addition of other alkylaluminium reagents, such as Et_3Al, with phosphine ligands **L16** and **L17**, provides good enantioselectivities but moderate yields, due to low conversions (Scheme 34).



L16	53% yield, 90% ee (-)
L17	70% yield, 98% ee (+)

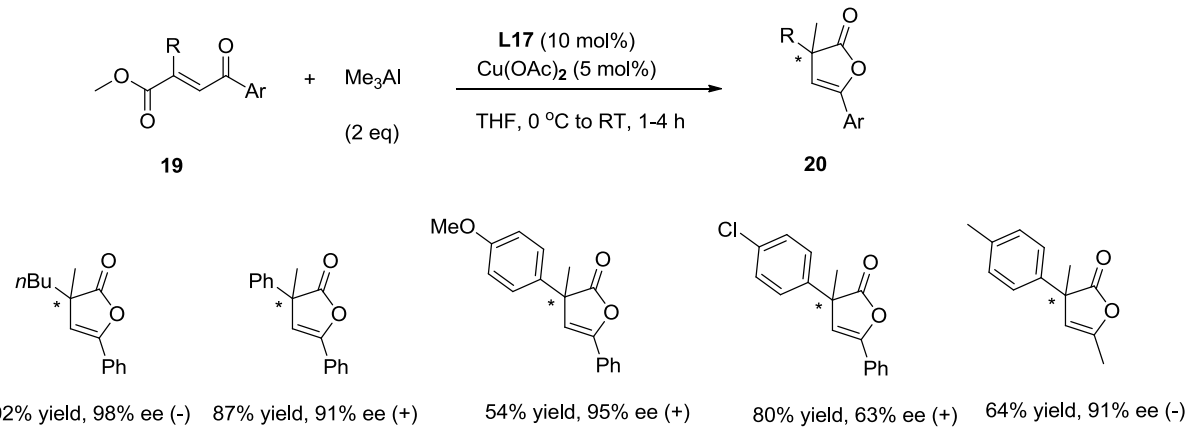
Scheme 34. Copper-phosphine catalysed ECA of triethylaluminium to β,β-disubstitued linear enones by Endo [68].

When unsaturated ketoesters **17** or **19** are used as substrates, the copper catalysed addition of Me_3Al in the presence of **L16** or **L17** provides, after subsequent lactonization, chiral furanones **18** and **20**, respectively, bearing quaternary stereogenic centres (Schemes 35 and 36) [69]. The optimised reaction conditions are applicable to a wide variety of benzyl ketoesters and all products can be 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.



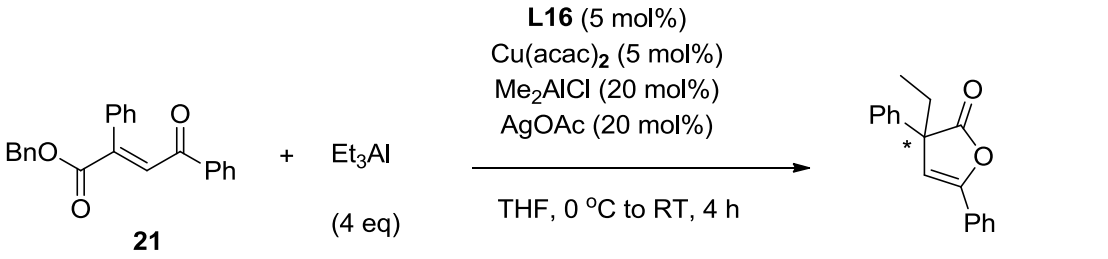
Ar	Ph	*p*-FC_6H_4	*p*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	2-naphthyl
yield (%)	88	94	92	92	95
ee (%)	97 (-)	98 (-)	98 (-)	98 (-)	96 (-)

Scheme 35. Synthesis of α,α-disubstituted furanones by copper-phosphine catalysed ECA of trimethylaluminium by Endo [69].



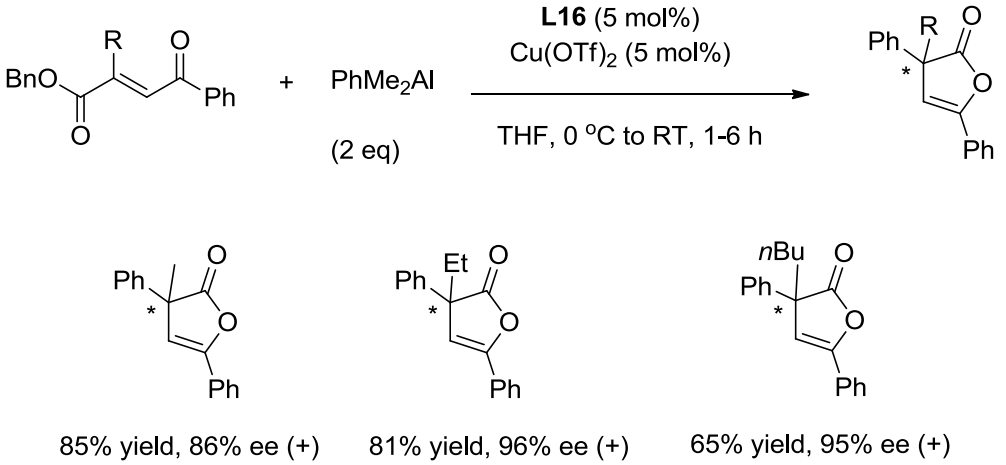
Scheme 36. Synthesis of α,α-disubstituted furanones by copper-phosphine catalysed ECA of trimethylaluminium by Endo [69].

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



Scheme 37. Benzyl ketoesters as substrates for the synthesis of α,α-disubstituted furanones by copper-phosphine catalysed ECA of triethylaluminium by Endo [69].

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, as exemplified in Scheme 38.



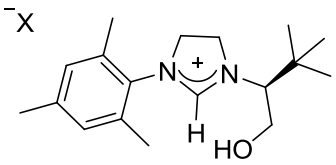
Scheme 38. Aryl aluminium reagents as nucleophiles for the synthesis of α,α-disubstituted furanones by copper-phosphine catalysed ECA by Endo [69].

2.2. Grignard reagents as nucleophiles

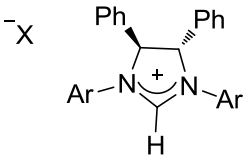
The copper-catalysed ECA of Grignard reagents has been extensively studied with a variety of phosphorous ligands [70]. Some of the interesting economical aspects of these nucleophiles, as compared to their zinc or aluminium counterparts, include:

(i) they are more reactive (less excess needed to complete the addition).
(ii) they are readily accessible and highly tunable.
(iii) all R groups from the nucleophile are transferred to the substrate.

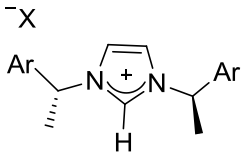
In 2006, Alexakis and Mauduit demonstrated that NHC ligands derived from C2-symmetric imidazolidinium salts (**L18**-**25**, Figure 10) were superior to phosphoramidite and ferrocene-based ligands when used for the copper catalysed ECA of Grignard reagents to trisubstituted enones [71]. They also observed that these ligands give better results with Grignard reagents than with any other organometallic compound.



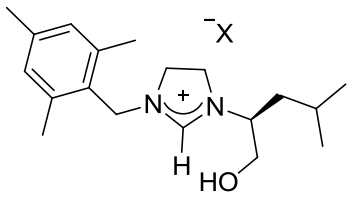
L18, X = PF_6
L19, X = Cl



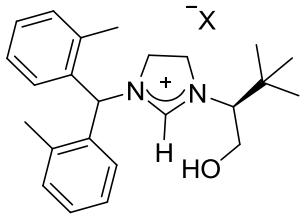
L20, Ar = *o*-$MeOC_6H_5$, X = BF_4
L21, Ar = 1-naphthyl, X = BF_4
L22, Ar = 8-MeO-1-naphthyl, X = Cl



L23, Ar = *o*-$MeOC_6H_5$, X = BF_4



L24, X = PF_6



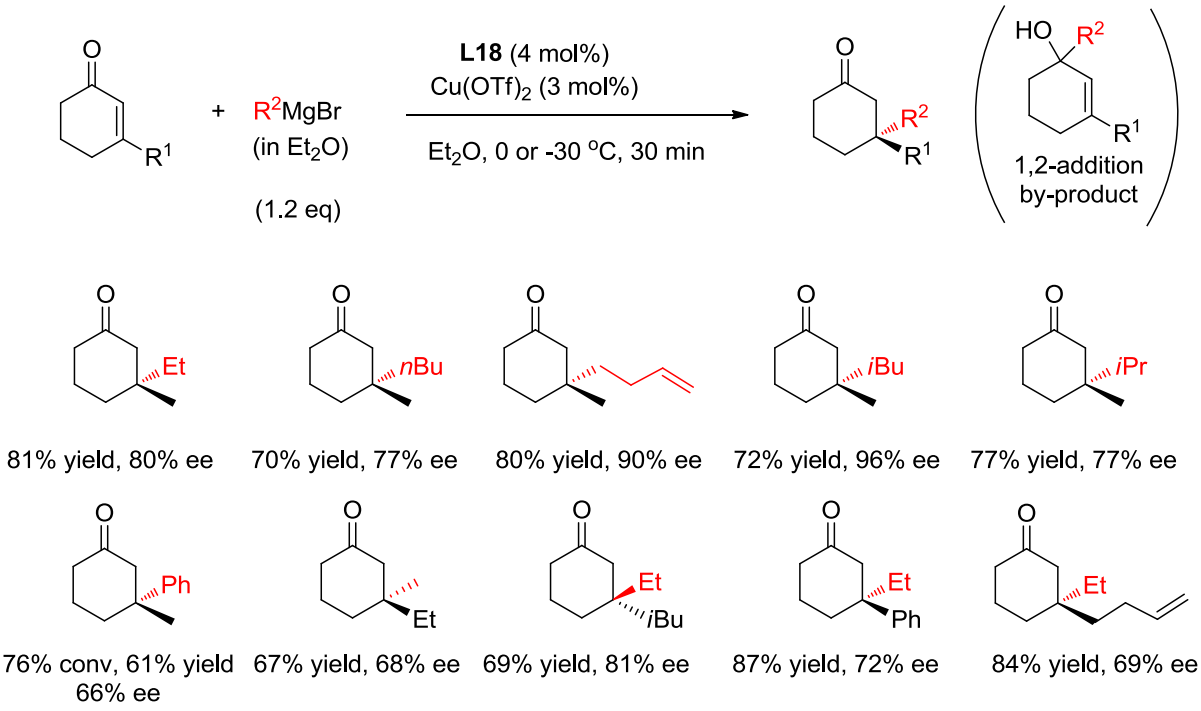
L25, X = PF_6

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

In particular, imidazolium salt **L18** (Figure 10) shows very high efficiency for the copper catalysed ECA of Grignard reagents to β-substituted cyclohexenones (Scheme 39) [71].71 A very low catalyst loading is needed to achieve moderate to good enantioselectivity, and the reaction proceeds in 30 minutes, working at 0 or -30 °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 member ring enones, as exemplified in Figure 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.



Scheme 39. Copper-NCH catalysed ECA of Grignard reagents to β-substituted cyclic enones by Alexakis [71].

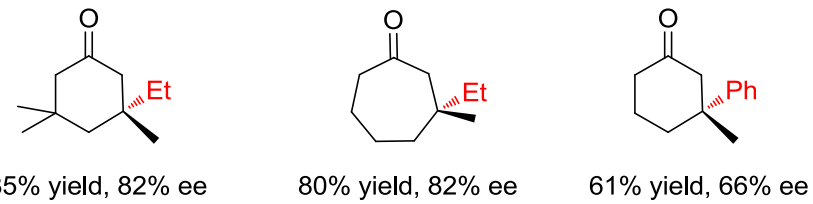
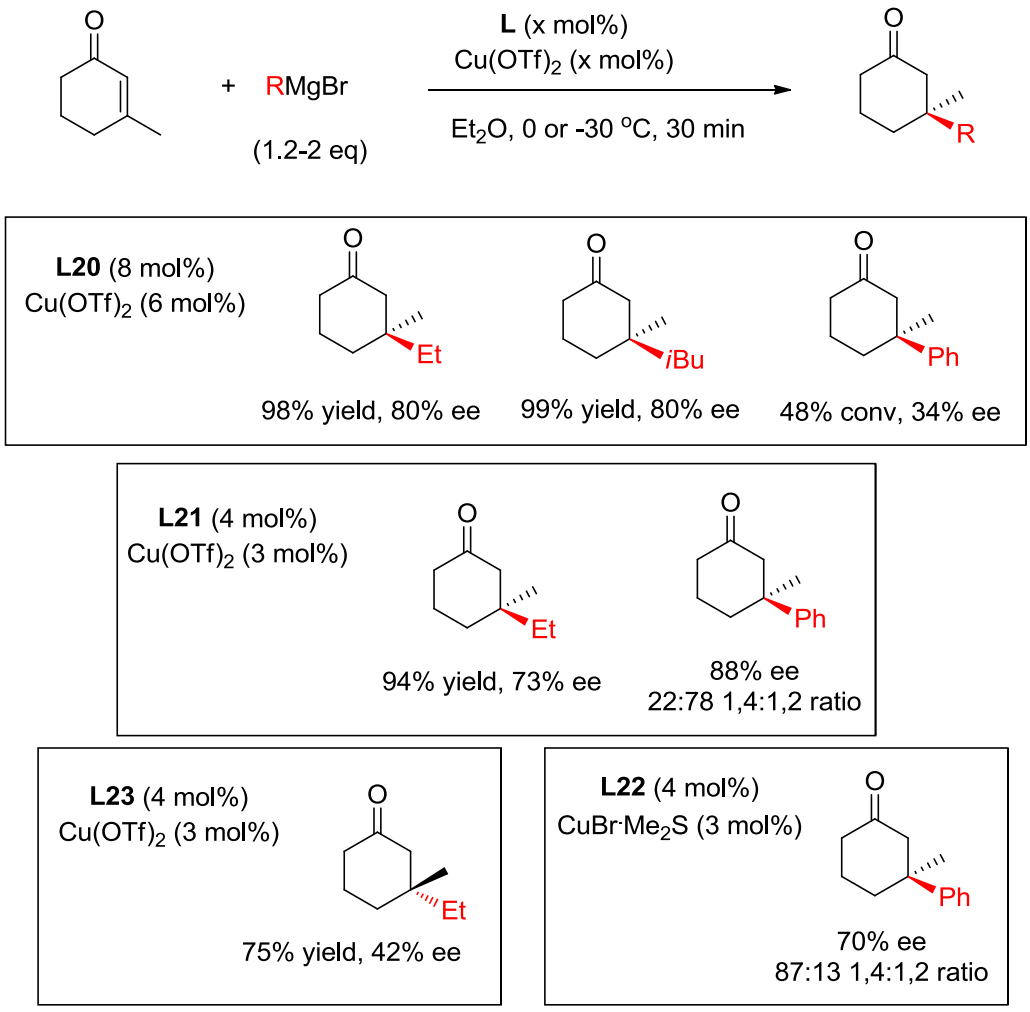


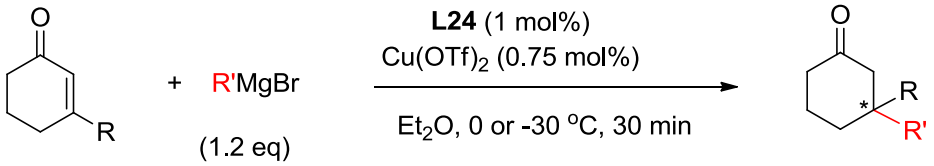
Figure 11. Synthesis of chiral bulky cyclohexanones and cycloheptanones *via* copper-NCH catalysed ECA of Grignard reagents by Alexakis [71].

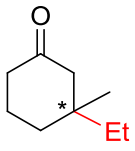
Although salts **L18**-**19** are superior and provide the best results in terms of conversions and enantiomeric excesses (with their main limitations mentioned above), other C_2-symmetric [72] and nonsymmetric [73] imidazolium salts, such as **L20-23**, are able to induce the copper catalysed ECA of alkyl Grignard reagents to 3-methylcyclohex-2-enone in moderate to good enantioselectivities, as exemplified in Scheme 40. Unfortunately, none of these ligands as **L20-23** provides better results for the addition of PhMgBr or *t*BuMgBr than the hydroxyl containing ligands **L18**-**19**.



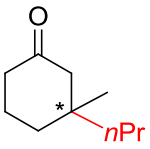
Scheme 40. Copper-NCH catalysed ECA of Grignard reagents to β-substituted cyclic enones by Alexakis [73] and Tomioka [72].

The imidazolium salt **L24**, bearing an additional methylene spacer to increase the flexibility on that side of the carbene, and thus occupy 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 [74]. 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 0.75 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-ethylcyclohexenone); this is certainly due to the well-known lack of reactivity and specific behaviour of this nucleophile.

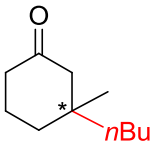




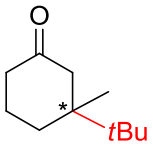
75% yield, 93% ee



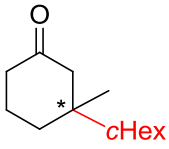
47% yield, 87% ee



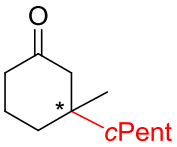
71% conv, 89% ee



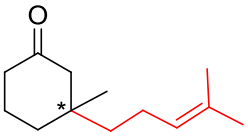
90% conv, 73% ee



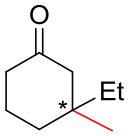
46% yield, 86% ee



43% yield, 60% ee

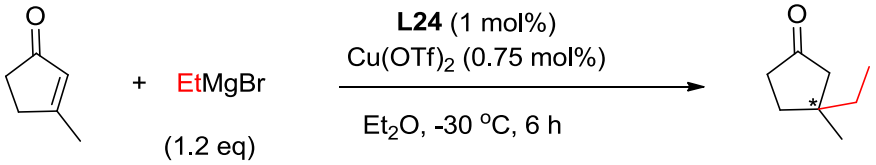


56% yield, 89% ee



49% yield, 40% ee

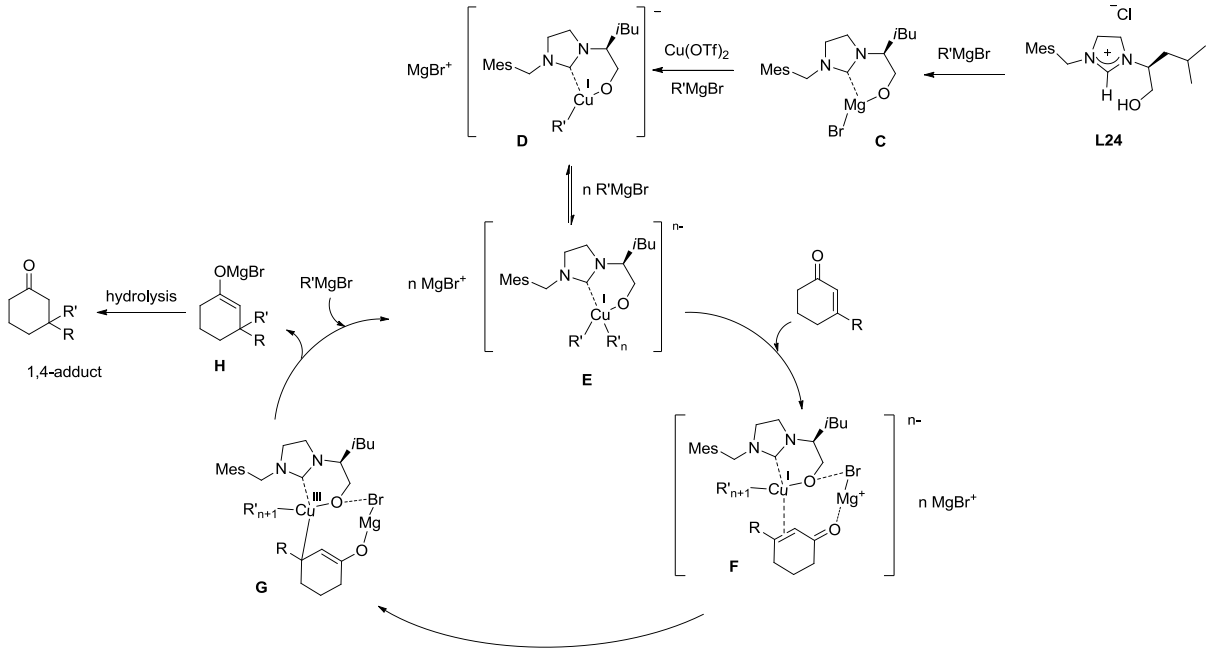
Scheme 41. Copper-NCH catalysed ECA of Grignard reagents to β-substituted cyclohexenones by Alexakis [74].



48% yield, 86% ee

Scheme 42. Copper-NCH catalysed ECA of Grignard reagents to β-substituted cyclopentenones by Alexakis [74].

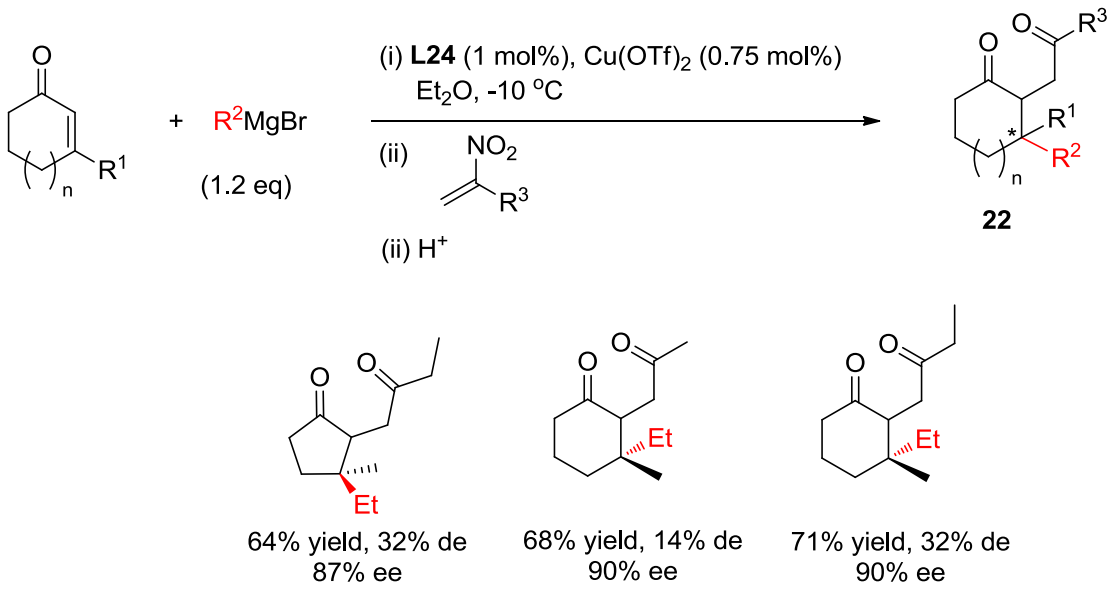
Alexakis et al. have proposed a catalytic cycle for the ECA with imidazolium ligands and Grignard reagents (Scheme 43) [74].



Scheme 43. Proposed catalytic cycle for the copper-NHC catalysed ECA of Grignard reagents to cyclic enones by Alexakis [74].

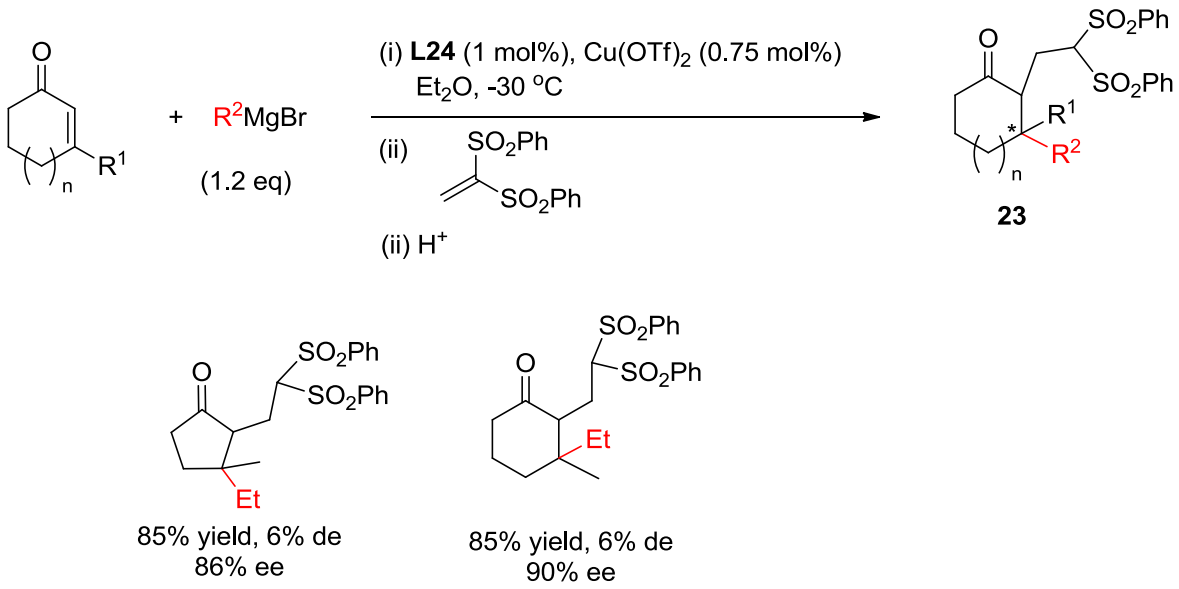
Acting as a base, the Grignard reagent deprotonates first the hydroxyl group in the side-chain, and then the imidazolium, leading to the NHC coordinated alkoxymagnesium compound **C**. Copper triflate, which is reduced *in situ* by 1 equivalent of the Grignard reagent to give a copper(I) species, is 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** [75]. 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'MgX 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 or chloride are undesirable counterions [76]. The following steps in the catalytic cycle correspond to the classical mechanistic pathway of a copper-mediated conjugate addition [77]. 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) [78]. After the trapping, an in situ Nef reaction [79] takes place, generating the corresponding 1,4-diketones **22**. These Michael adducts **22** can be then derivatised toward notable bicyclic structures, with relevance in natural products.



Scheme 44. Domino copper-NHC catalysed ECA of Grignard reagents / CA trapping with 1-alkyl-1-nitroolefins by Alexakis [78]. All ee´s measured before trapping.

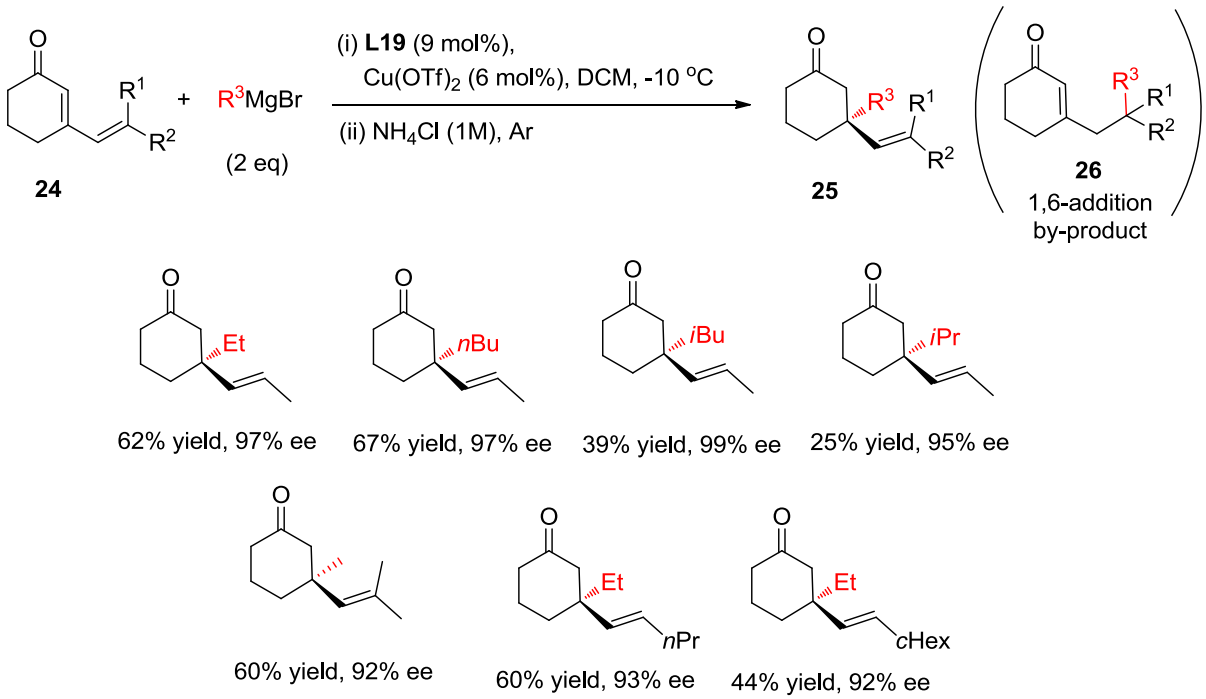
The same tandem procedure can be carried out using vinyl disulfones as electrophiles to provide the corresponding γ-sulfonylated ketones **23** in high yields and diastereo- and enantioselectivities (Scheme 45) [78]. Sulfones derivatives are tunable synthetic entities [80]. For example, the homolytic cleavage of disulfones through lithium naphthalenide or samarium iodide methodologies are well-established procedures for their corresponding derivatisation [81].



Scheme 45. Domino copper-NHC catalysed ECA of Grignard reagents / CA trapping with vinyl disulfones by Alexakis [78]. All ee´s measured before trapping.

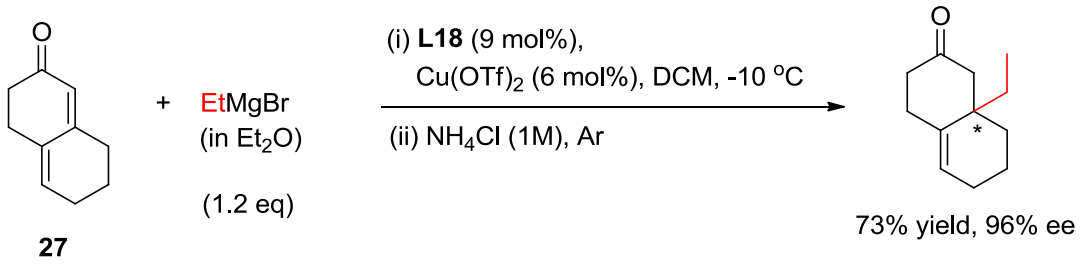
NHC ligands bearing an hydroxyl group (such as the ones derived from the imidazolium salts **L18**-**19**) also allow a high regio- and enantioselective CA reaction to conjugated dienones **24** (Scheme 46) [82,83]. Primary and secondary Grignard reagents provide the corresponding 1,4 adducts **25** 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 equivalents 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.



Scheme 46. Copper-NHC catalysed ECA of Grignard reagents to conjugated dienones by Alexakis [82,83].

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 47. Copper-NHC catalysed ECA of ethylmagnesium bromide to the bycyclic conjugated dienone **27** by Alexakis [83].

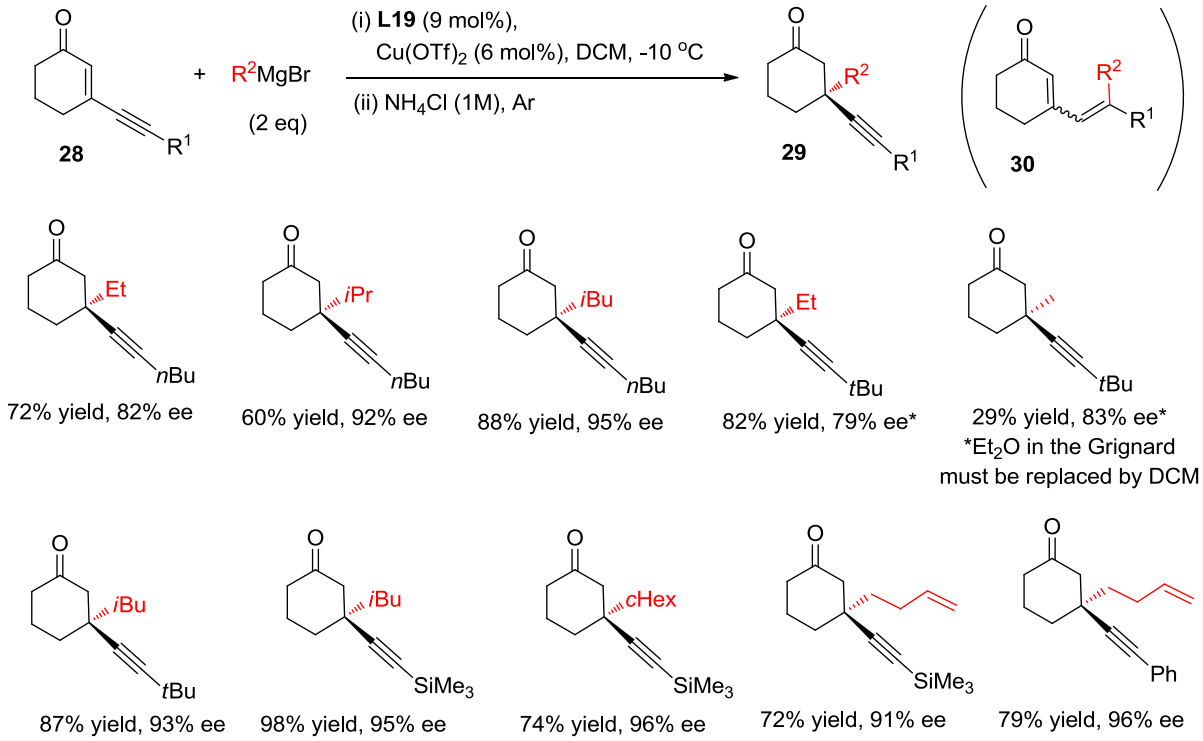
Unsuitable nucleophiles for this methodology are PhMgBr, which gives complex reaction mixtures, and MeMgBr, which only provides the corresponding 1,6-addition product **26** when the substituent R^1 in the dienone **24** (Scheme 46) is a hydrogen atom. The addition of MeMgBr is not always problematic; γ,δ-trisubstituted 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 carbine [84]) 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 [85].

In terms of synthetic applications, the remaining C=C double bond in the 1,4 adducts **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 [82,83].

This methodology also allows very good regio- and enantioselectivities when cyclic enynones such as **28** are used as substrates [82,86]. 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 [59,87].



Scheme 48. Copper-NHC catalysed ECA of Grignard reagents to cyclic enynones by Alexakis [82,86].

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 Et_2O 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.* R^1 = *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 (Figure 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 Figure 12.

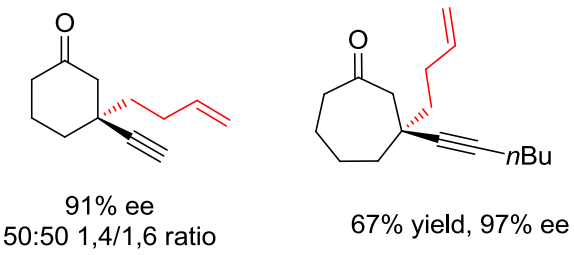
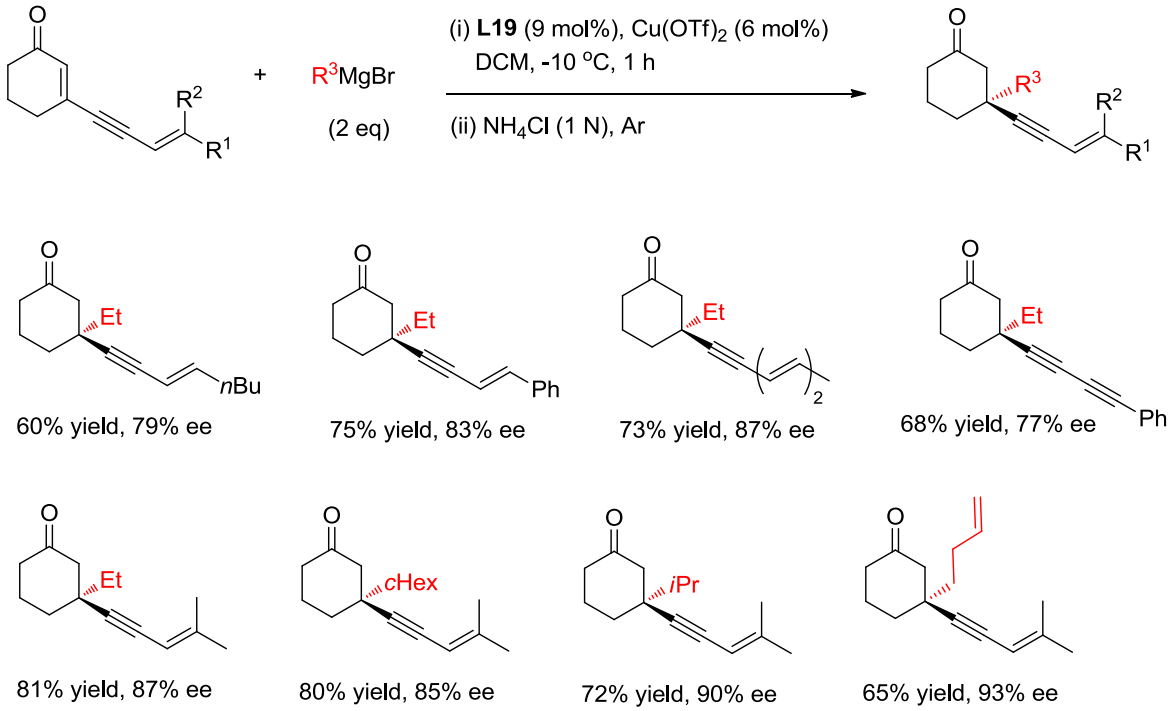


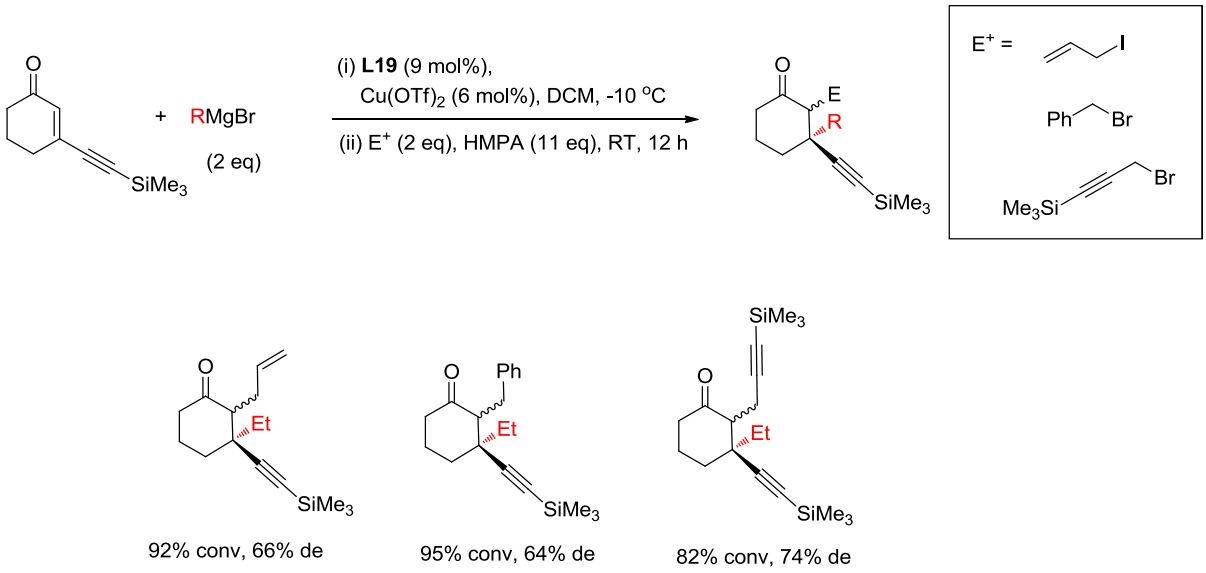
Figure 12. Synthesis of chiral cyclohexanone bearing a terminal alkyne and chiral cycloheptanone by copper-NHC catalysed ECA of Grignard reagents to cyclic enynones by Alexakis [8286].

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 49. Copper-NHC catalysed ECA of Grignard reagents to cyclic enynones that bear additional unsaturations by Alexakis [86].

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.



Scheme 50. Tandem copper-NHC catalysed ECA of Grignard reagents to cyclic enynones / enolate trapping by Alexakis [86].

Several experimental observations have been taken into account to propose a plausible structure of the catalytic system (Figure 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 transcient complex **I0**, followed by the formation of the heterocuprate complex. Based on the characterization of a magnesium organocuprate complex by Davies et al. [88], Alexakis proposes the dimeric heterocuprate **I1** 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 **I2**. Presumably, the addition of the dienone to complexes **I1** or **I2** leads to 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 disfavors the migration to the 1,6 position.

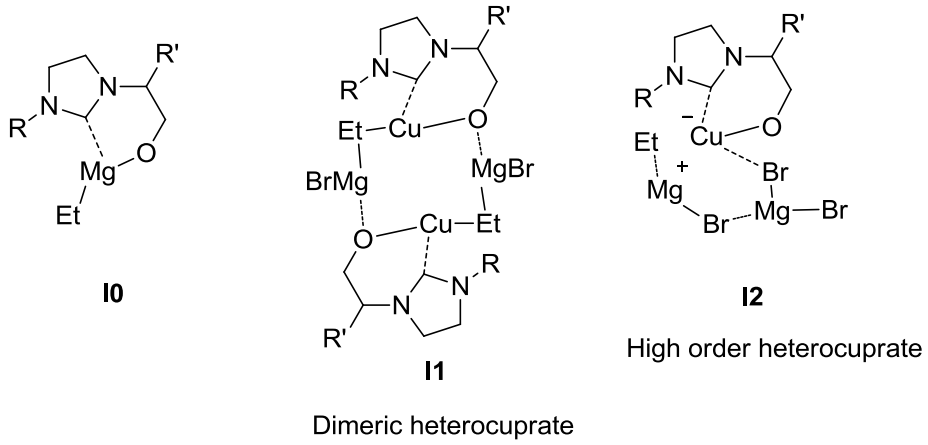
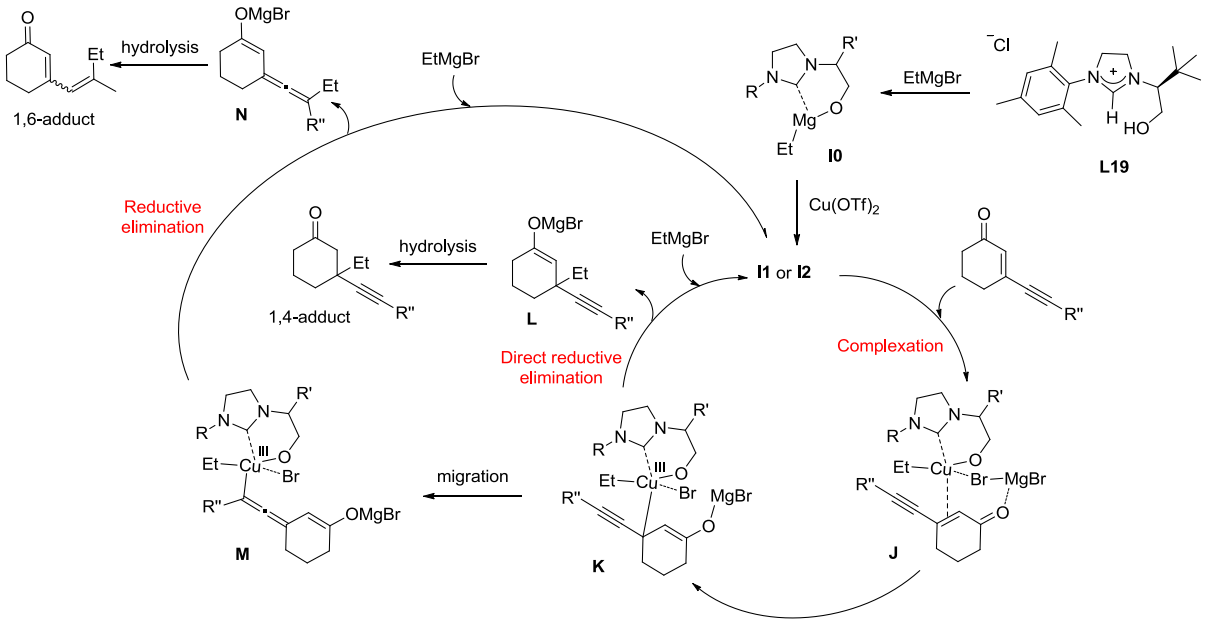
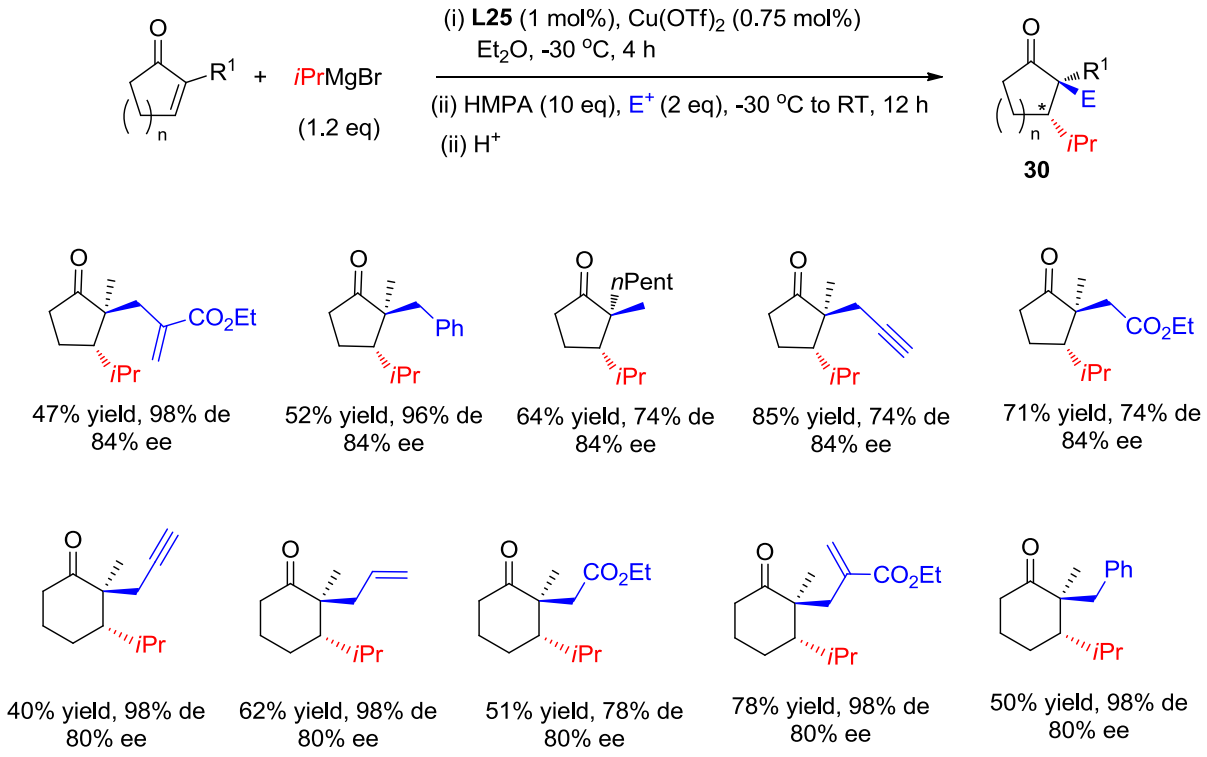


Figure 13. Proposed carbenoid metal complexes for the copper-NHC catalysed ECA reaction with Grignard reagents by Alexakis [86].



Scheme 51. Proposed catalytic cycle for the ECA reaction to polyconjugated cyclic enones by Alexakis [86].

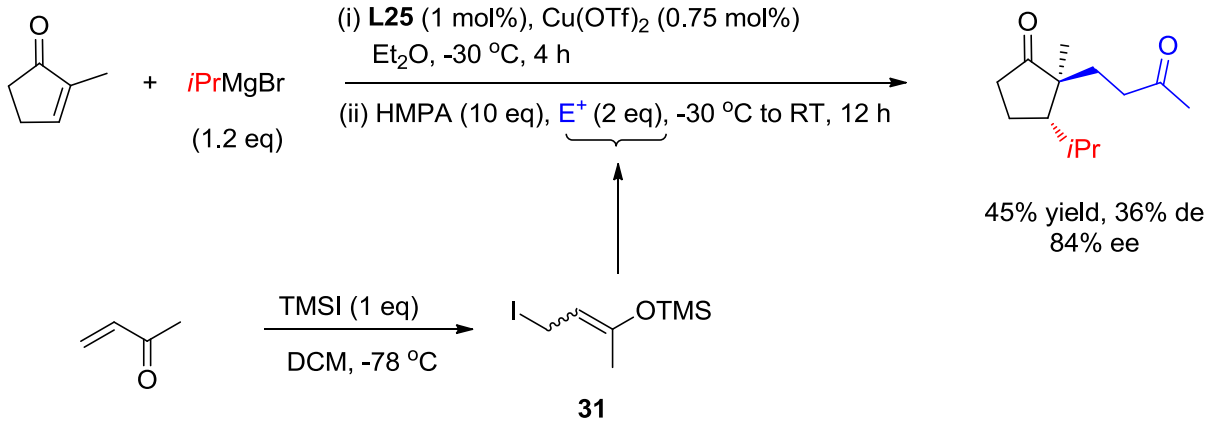
The enantioselective generation of quaternary centres *via* copper catalysed CA can be also achieved through a tandem ECA-enolate trapping process on α-substituted enones (Schemes 52 to 57). In this case, the quaternary centre is generated at the α position of the carbonyl, contiguous to a β-tertiary centre. The imidazolium ligand **L25** is able to catalyse such a transformation, using Grignard reagents as nucleophiles in the presence of $Cu(OTf)_2$, giving very good enantio- and diastereoselectivities with both α-substituted cyclopentanones and cyclohexanones (Scheme 52) [89,90]. Alkyl, propargyl, allyl and benzyl halides have been used as electrophiles, all providing ketones **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 enones / enolate trapping by Alexakis [89,90] (all ee measured after recrystallisation).

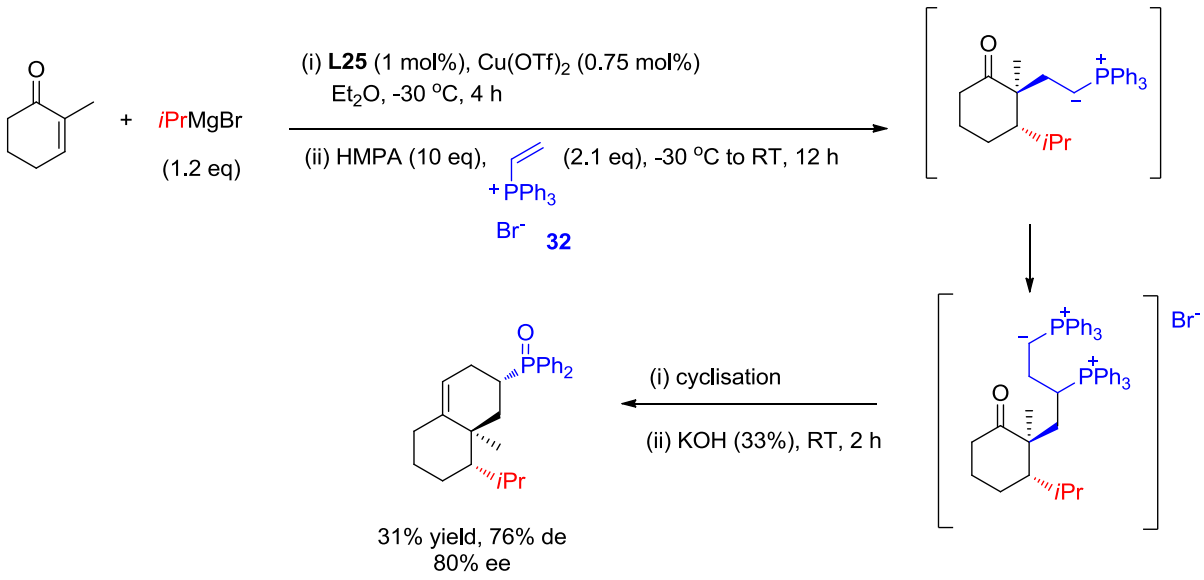
It is worth highlighting that this methodology brings a new approach to versatile terpenoid-like skeletons of bioactive natural products and it has been applied to the formal synthesis of crinipellin B and guanacastepene A (Figure 1) [89].

Other electrophiles, such as derivative **31** (Scheme 53),‡ triphenylvinylphosphonium bromide **32** (Scheme 54), *N*-halosuccinimides (Scheme 55) and tosyl cyanide (Scheme 56) have been also evaluated in this tandem ECA-enolate trapping methodology [90]. Lower regio- and enantioselectivities are obtained in these cases than when the trapping is carried out with alkyl, propargyl, allyl or benzyl halides.

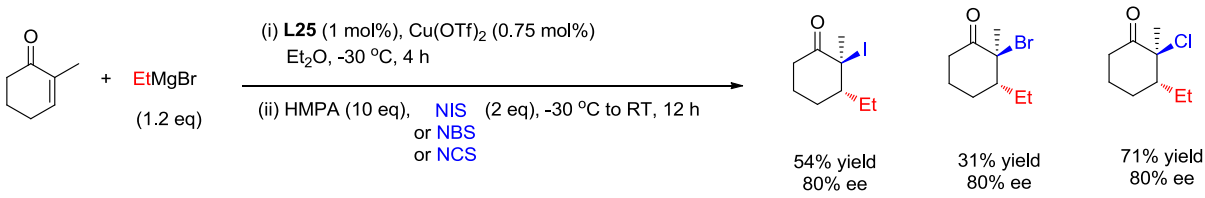


Scheme 53. Tandem copper-NHC catalysed ECA of Grignard reagents to α-substituted cyclic enones / enolate trapping with **31** by Alexakis [90].

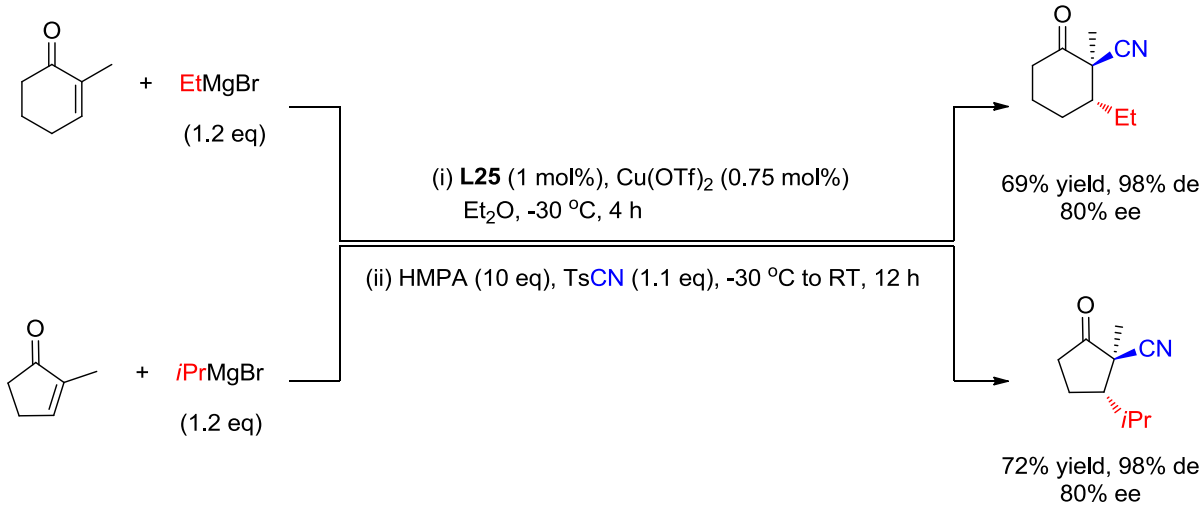
‡ The direct trapping with methylvinyl ketone (MVK) gives a complex mixture of oligomers.



Scheme 54. Tandem copper-NHC catalysed ECA of Grignard reagents to α-substituted cyclic enones / enolate trapping with triphenylvinylphosphonium bromide **32** by Alexakis [90].



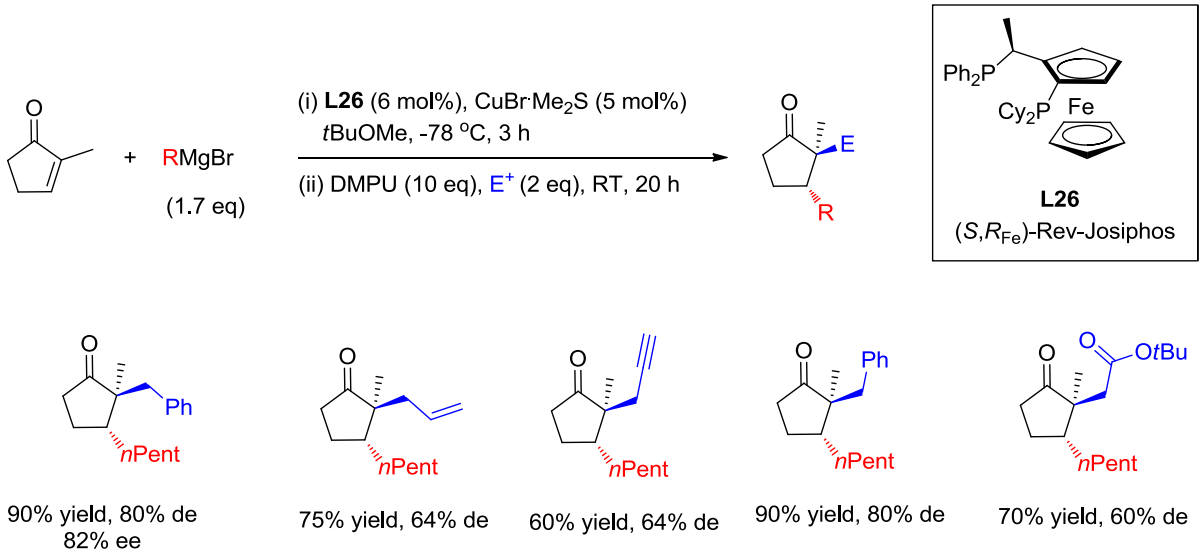
Scheme 55. Tandem copper-NHC catalysed ECA of Grignard reagents to α-substituted cyclic enones / enolate trapping with *N*-halosuccinimides by Alexakis [90].



Scheme 56. Tandem copper-NHC catalysed ECA of Grignard reagents to α-substituted cyclic enones / enolate trapping with tosyl cyanide by Alexakis [90].

Interestingly, a complementary methodology that allows the addition of linear Grignard reagents to α-substituted 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 distereoselectivities, especially when cyclopentenones are used as substrates (Scheme 57) [91].



Scheme 57. Tandem copper-diphosphine catalysed ECA of Grignard reagents to α-substituted cyclopentenones / enolate trapping by Minnaard [91].

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, trisubstituted 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** (Figure 14 and Scheme 58) [92].

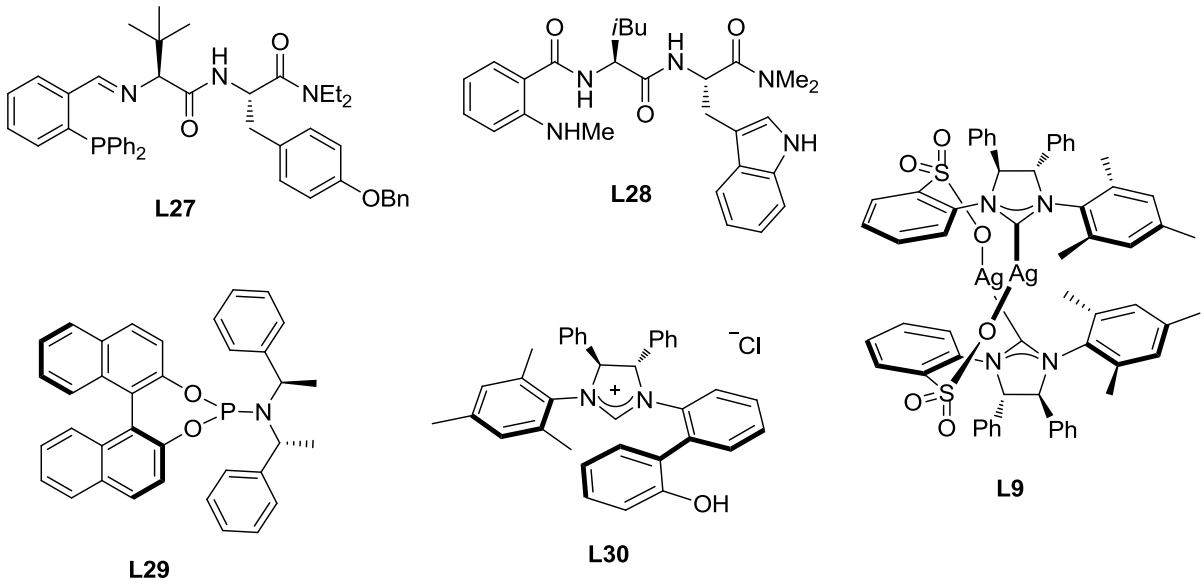
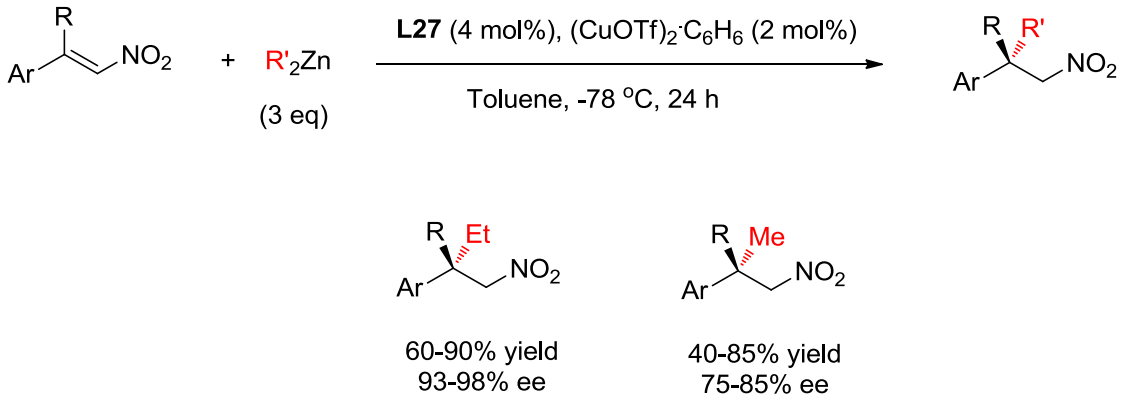
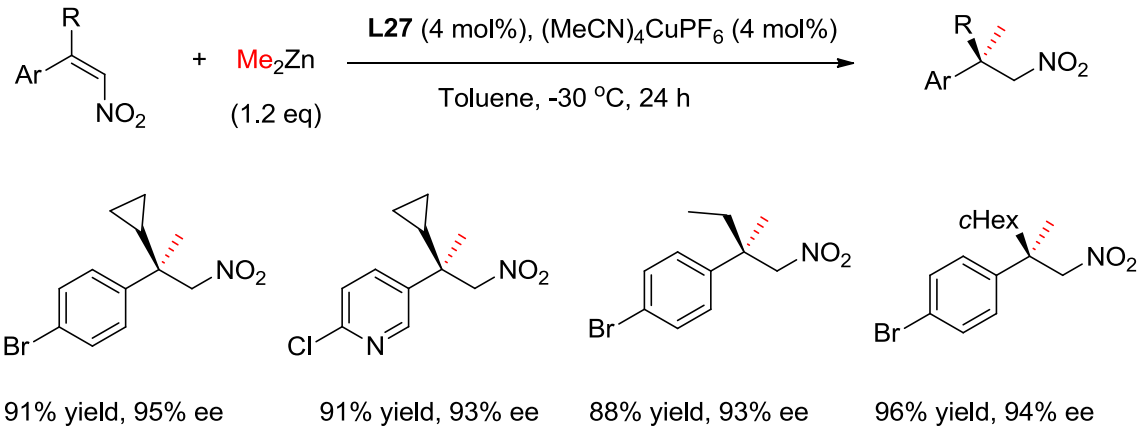


Figure 14. Efficient ligands for the copper catalysed ECA of organozinc reagents to β,β-disubstituted α,β-unsaturated systems.



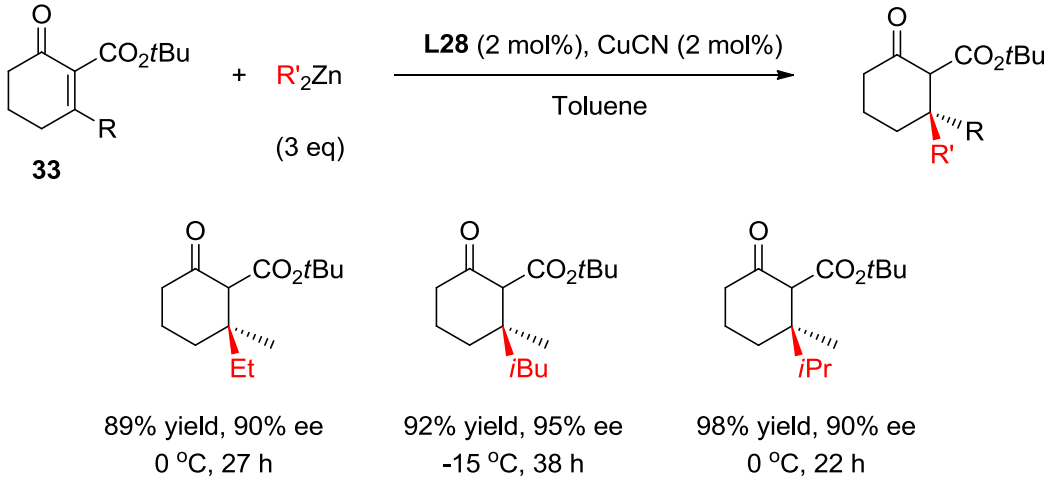
Scheme 58. Copper-peptide catalysed ECA of organozinc reagents to β,β-disubstituted (*E*)-nitroalkenes by Hoveyda [92].

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 $[(MeCN)_4Cu]PF_6$ as the copper source [93]. By using the (*Z*) isomer, the undesired nitroalkene isomerization is minimized and the enantioselectivity of the process is enhanced dramatically, as shown in the examples in Scheme 59.



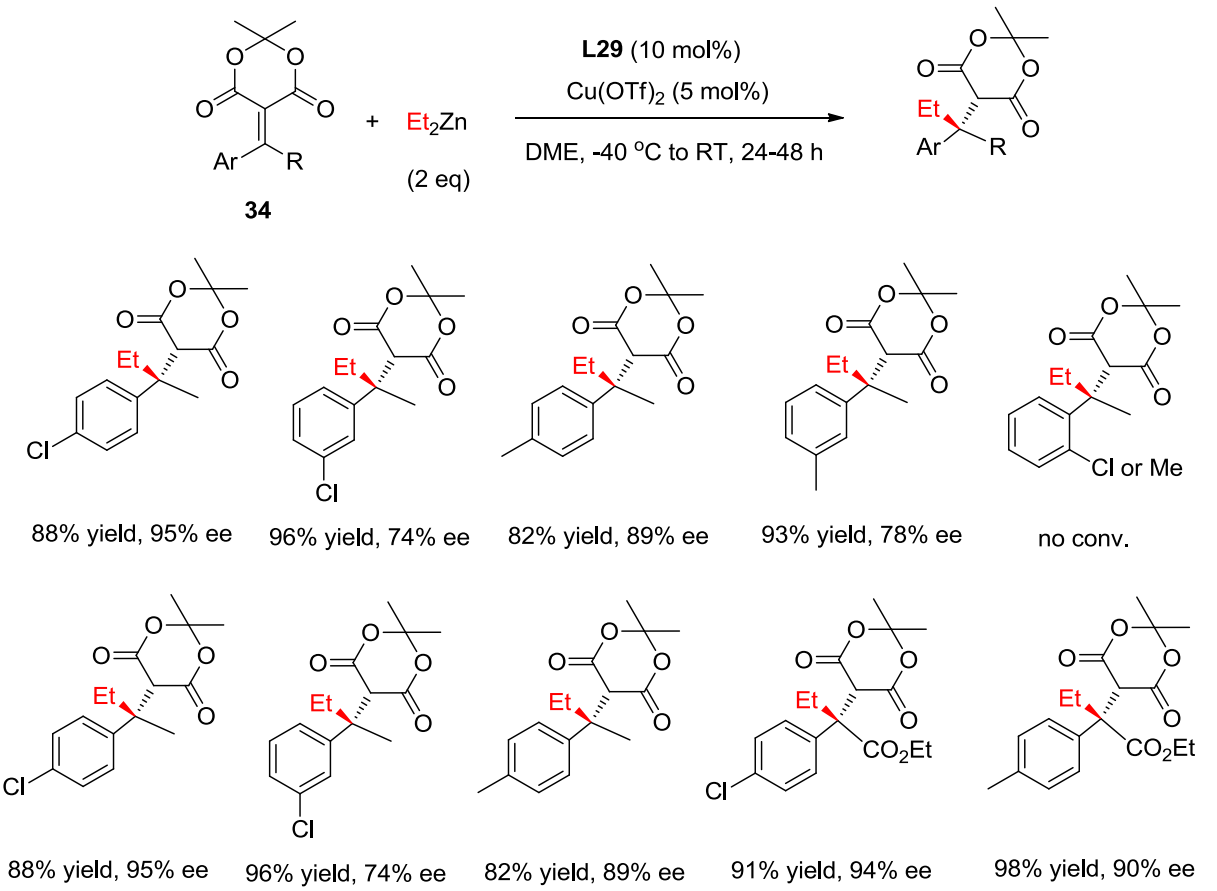
Scheme 59. Copper-peptide catalysed ECA of organozinc reagents to β,β-disubstituted (*Z*)-nitroalkenes by Zeng [93].

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 [94]. Cyclic 6-membered substrates provide higher yields and enantioselectivities than the 5-membered counterparts. Although variation of the α-ester is tolerated in the reaction, bulky esters lead to the highest enantioselectivities.



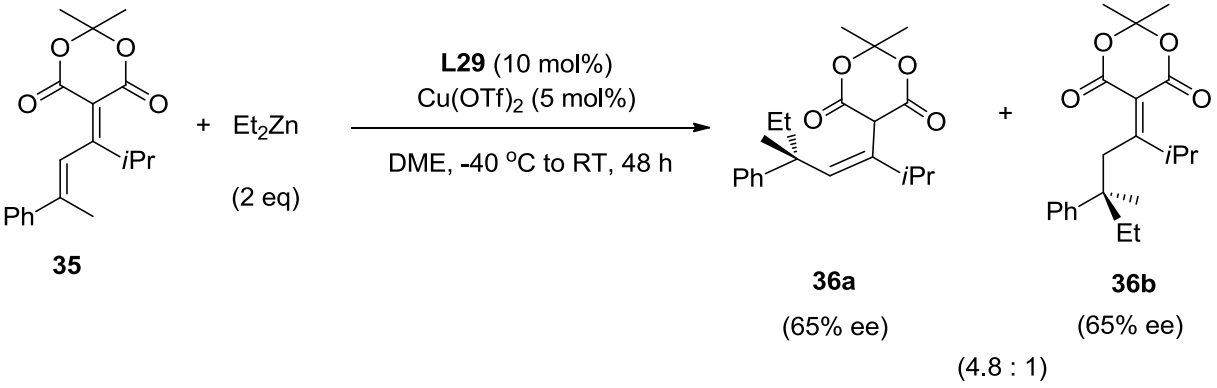
Scheme 60. Copper-peptide catalysed ECA of organozinc reagents to activated cyclic ketoesters by Hoveyda [94].

The doubly activated Meldrum's acids 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 **L29** (Scheme 61) [95,96,97,98]. 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 subsequent transformations, leading to the expedient preparation of succinimides, succinate esters and succinic acids, γ-butyrolactones, and β-amino acid derivatives [96].



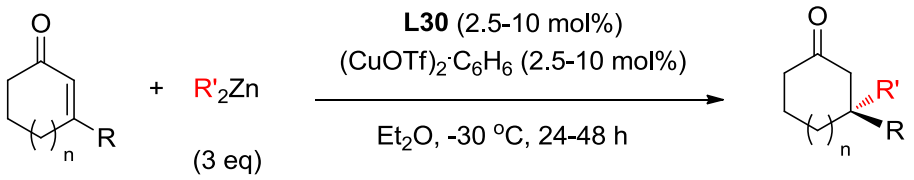
Scheme 61. Copper-phosphoramidite catalysed ECA of organozinc reagents to Meldrum's acids derivatives by Fillion [95,96,97,98].

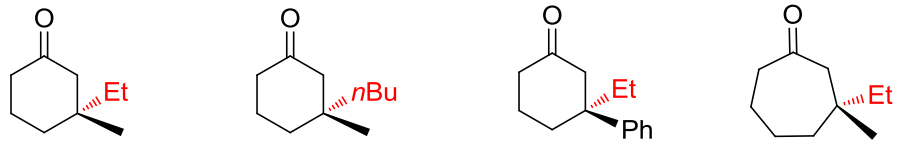
The formation of quaternary stereogenic centres via 1,6-conjugate addition of dialkylzinc reagents to Meldrum's acid derived acceptors has also been reported [99]. Thus, **35** reacts with Et_2Zn in the presence of $Cu(OTf)_2$ (5 mol %), and phosphoramidite ligand **L29** (10 mol %) to afford exclusively 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).



Scheme 62. Copper-phosphoramidite catalysed enantioselective 1,6-CA of organozinc reagents to Meldrum's acids derivatives by Fillion [99].

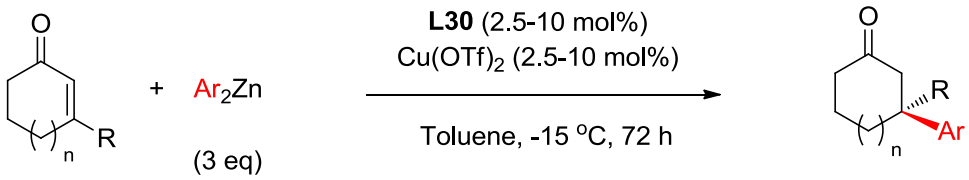
The more recent development of NHC-ligands, such as those derived from the imidazolium salt **L30**, has allowed the addition of dialkylzinc (Scheme 63) and diarylzinc reagent[§] (Scheme 64) to simple unactivated β-substituted cyclic enones [100]. Very good yields and enantioselectivities are obtained with a wide variety of organozinc compounds; only the less reactive Me_2Zn does not provide any conversion.

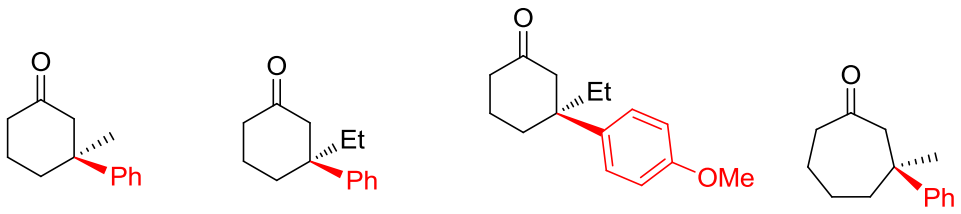




92% yield, 93% ee 83% yield, 86% ee 85% yield, 90% ee 83% yield, 85% ee

Scheme 63. Copper-NHC catalysed ECA of dialkylzinc reagents to β-substituted cyclic enones by Hoveyda [100].



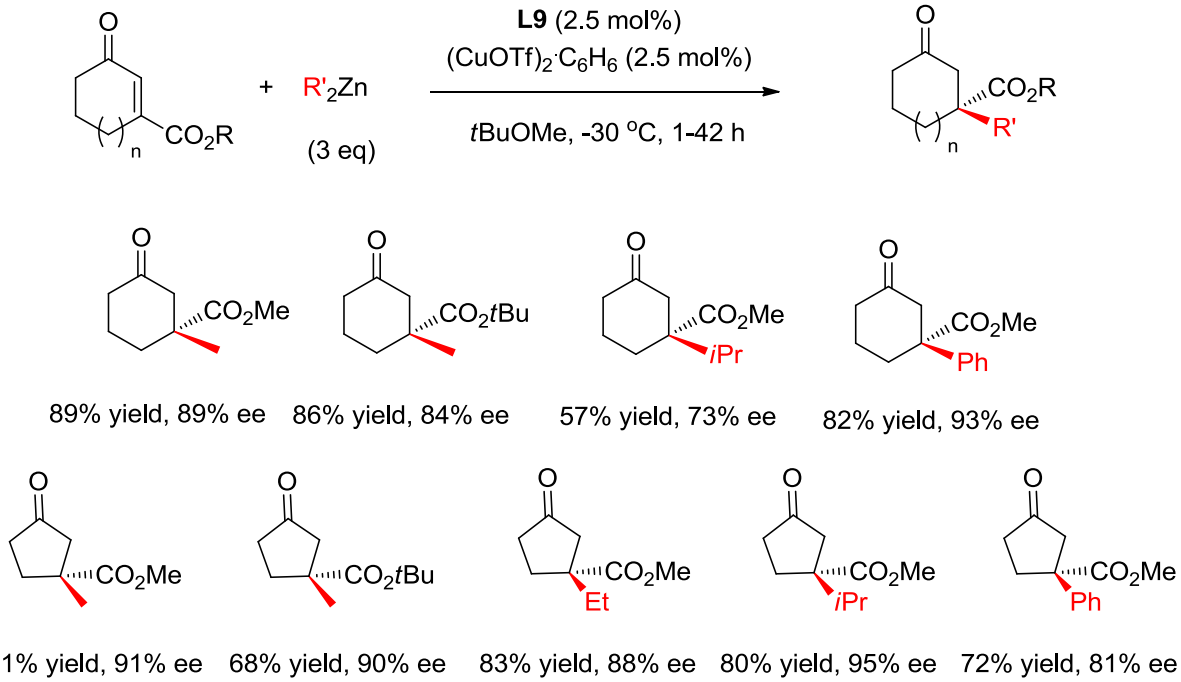


95% yield, 97% ee 89% yield, 94% ee 89% yield, 90% ee 88% yield, 96% ee

Scheme 64. Copper-NHC catalysed ECA of diarylzinc reagents to β-substituted cyclic enones by Hoveyda [100].

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) [101]. The scope of this reaction includes both alkyl (including methyl) and aryl dialkylzinc reagents as nucleophiles and methyl and more sterically 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.

[§] The 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.



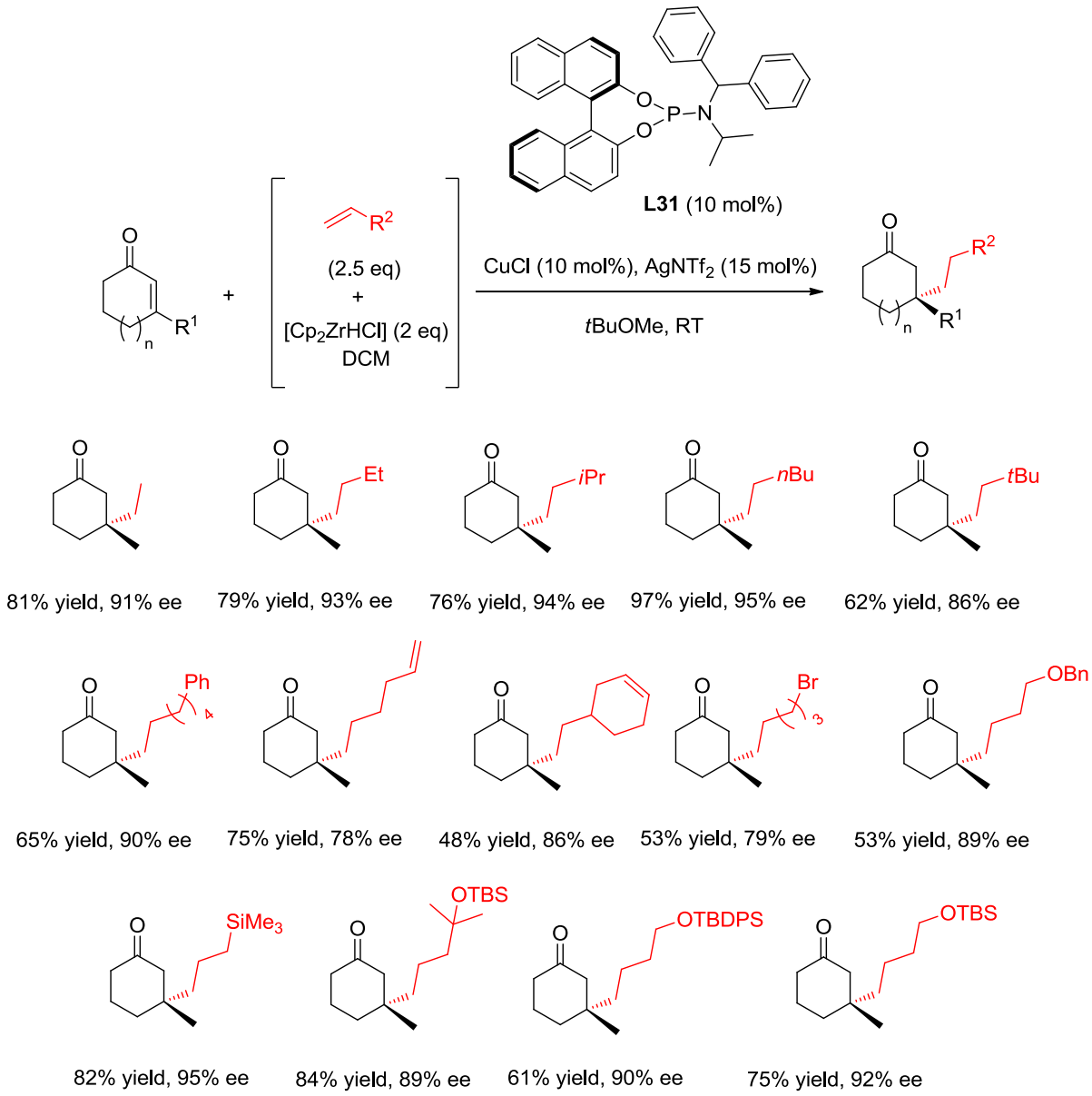
Scheme 65. Copper-NHC catalysed ECA of dialkylzinc reagents to cyclic ketoesters by Hoveyda [101].

Zirconium

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) [102,103].

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

Alkylzirconium reagents are prepared *in situ* by hydrometalation from the corresponding alkenes [104,105,106] 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 organozirconiun 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.



Scheme 66. Copper catalysed ECA of organozirconium reagents to β-substituted cyclic enones by Fletcher [102].

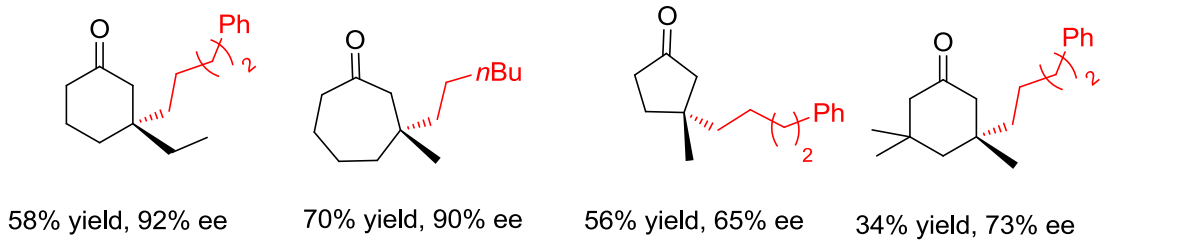
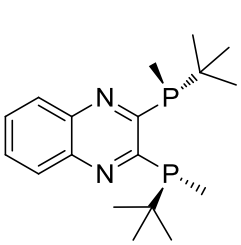


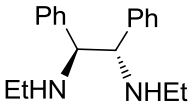
Figure 15. Chiral ketones prepared by copper catalysed ECA of organozirconium reagents to β-substituted cyclic enones by Fletcher [102].

3. Formation of boron-containing quaternary centres by copper catalysed ECA

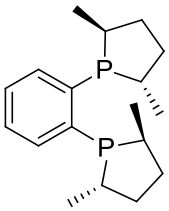
Chiral organoboron compounds are versatile synthetic intermediates due to the convertibility of C-B bonds to a variety of functional groups [107,108]. Furthermore, chiral organoboron molecules exhibiting unique biological activities have been recently identified, such as potent inhibitors of the proteasome, thrombin, and histone deacetylases [109]. 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.



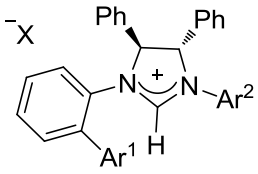
(*R*,*R*)-QuinoxP
L32



L33



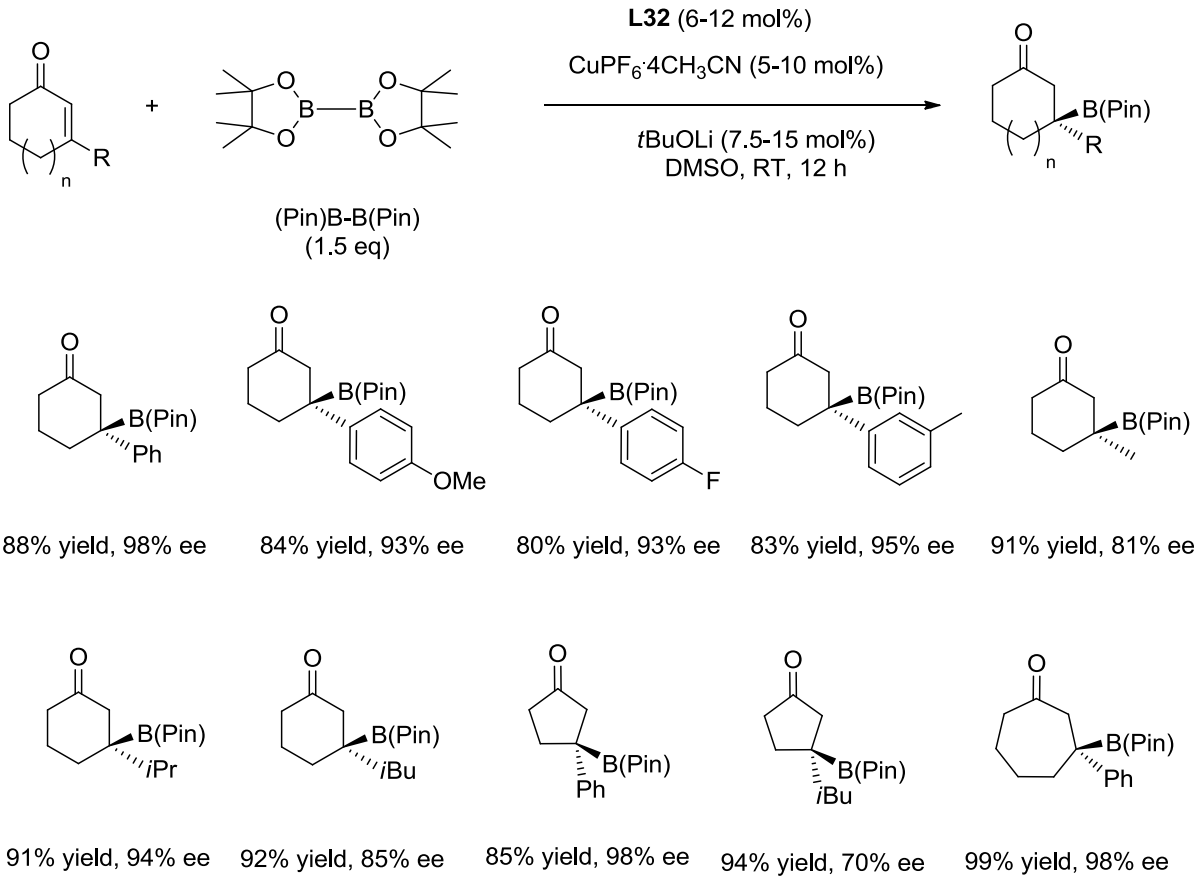
(*S*,*S*)-MeDuPhos
L34



L35, Ar^1 = Ph, Ar^2 = o-$MeOC_6H_4$, X = BF_4
L36, Ar^1 = Mes, Ar^2 = 2-Me,6-*i*Pr-C_6H_3, X = BF_4

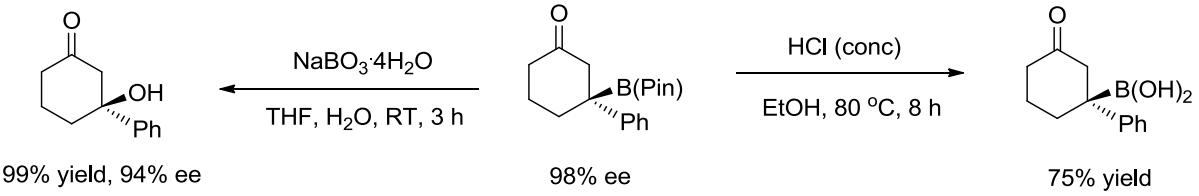
Figure 16. Effective ligands for the enantioselective conjugate boration (ECB) to β,β-disubstituted α,β-unsaturated compounds.

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 $CuPF_6{\cdot}4CH_3CN$. Commercially available bis(pinacolato)diboron [(Pin)B-B(Pin)] is the borylating reagent that provides the best results in this transformation (Scheme 67) [110]. The reaction generally proceeds with high enantioselectivity for both aromatic and aliphatic β-substituted cyclic enones, including 5-, 6- and 7-membered rings (Scheme 67).



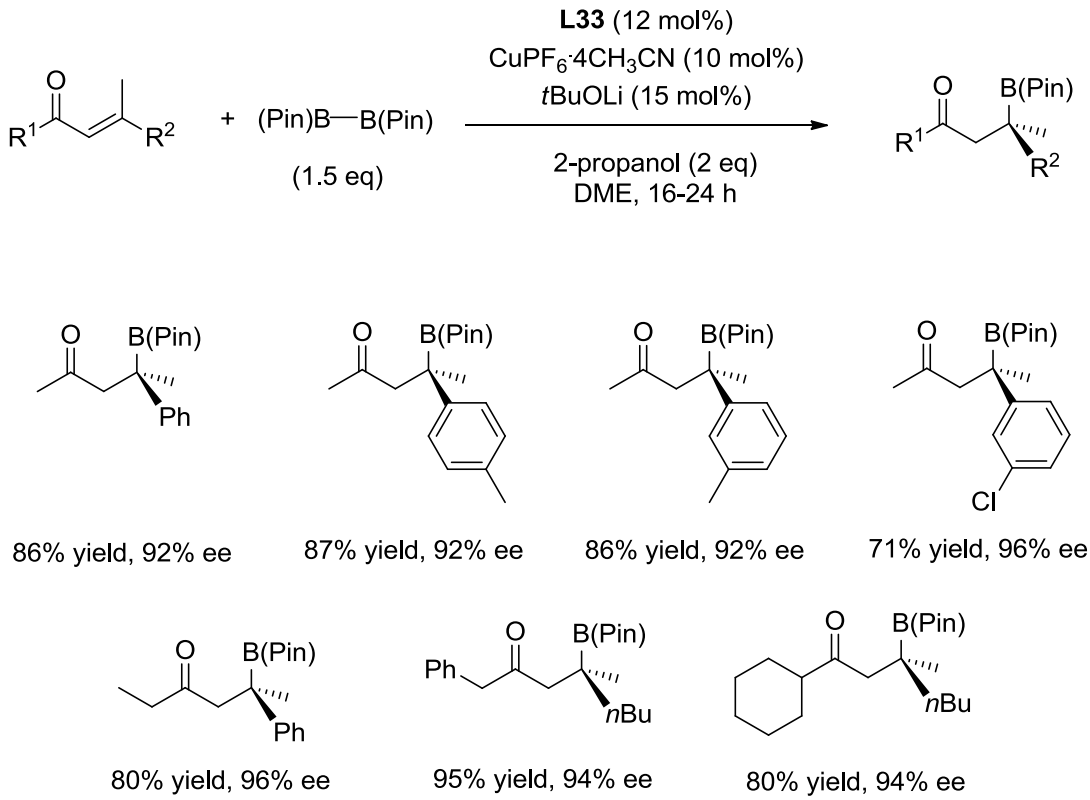
Scheme 67. Copper-phosphine catalysed ECB of β-substituted cyclic enones by Shibasaki [110].

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.



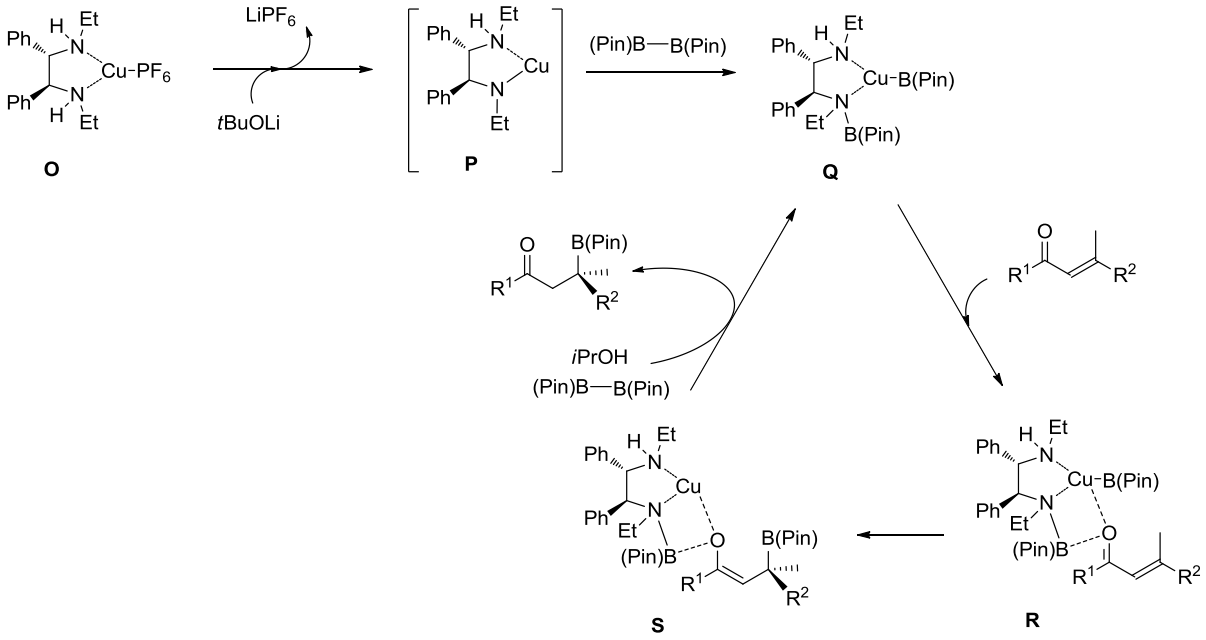
Scheme 68. Derivatisation of chiral organoboron compounds by Shibasaki [110].

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) [111]. 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 equivalents 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).



Scheme 69. Copper-diamine catalysed ECB of β,β-disubstituted enones by Shibasaki [111].

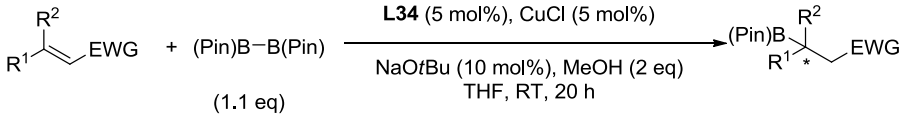
When the reaction is carried out with *t*BuOCu, in the absence of a lithium salt, yields and enantioselectivities are not affected. This indicates that the diamine coordinates to the copper atom at the enantio-differentiating step, even in the presence of the cationic lithium atom. In addition, ESI-MS 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 (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)-BB(Pin). This proposed mechanism is in accordance with the low enantioselectivity observed when using diamine ligands without an ability to form copper amides.

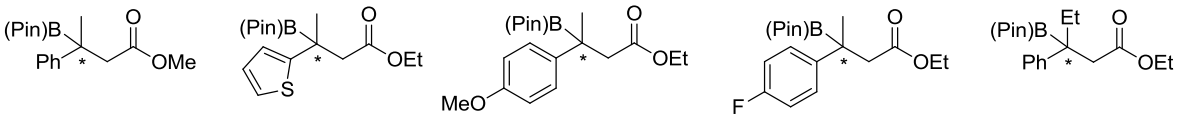


Scheme 70. Proposed mechanism for the copper-diamine catalysed ECB of β,β-disubstituted enones by Shibasaki [111].

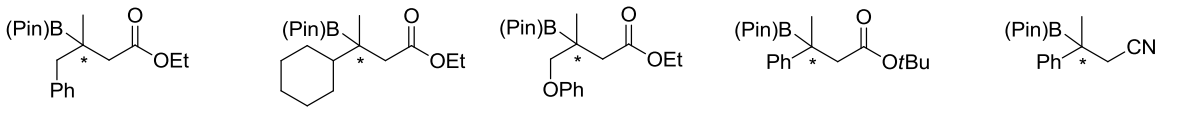
Yung et al. have demonstrated that for acyclic β,β-disubstituted α,β-unsaturated esters, the phosphine ligand **L34** provides high yields and enantioselectivities in the copper catalysed ECB reaction (Scheme 71) [112]. Again, the inclusion of proton accelerators (2 eq of MeOH – in contrast to the aprotic DMSO used with cyclic enones; see Scheme 67 and reference 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-dialkylsubstituted esters give good to modest results. Also, bulkier conjugated EWG groups such as *tert*-butyl esters or nitriles, provide lower enantioselectivities.





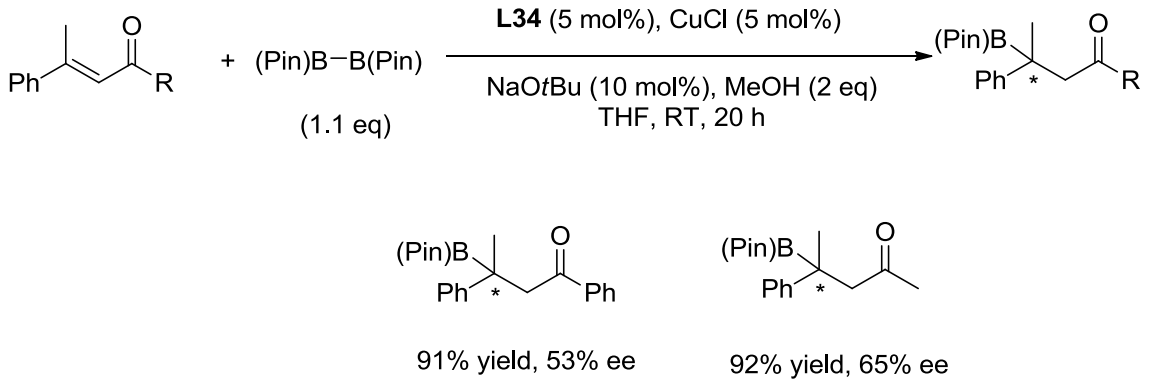
91% yield, 94% ee (*S*) | 91 yield, 92% ee | 85% yield, 88% ee | 95% yield, 94% ee | 85% yield, 91% ee (*S*)



90% yield, 84% ee | 88% yield, 92% ee | 95% yield, 69% ee | 85% yield, 88% ee (*S*) | 90% yield, 84% ee (*S*)

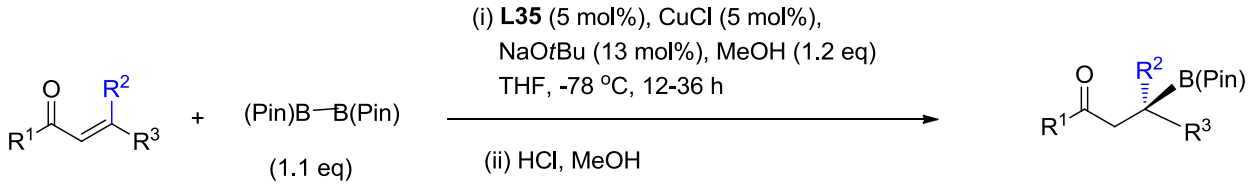
Scheme 71. Copper-phosphine catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated esters by Yung [112].

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).



Scheme 72. Copper-phosphine catalysed ECB of acyclic β,β-disubstituted enones by Yung [112].

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 [113]. The transformations proceed with high yields and enantioselectivities, using bis(pinacolato)diboron as the nucleophile and the readily accessible 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.



Scheme 73. Copper-NHC catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated systems by Hoveyda [113].

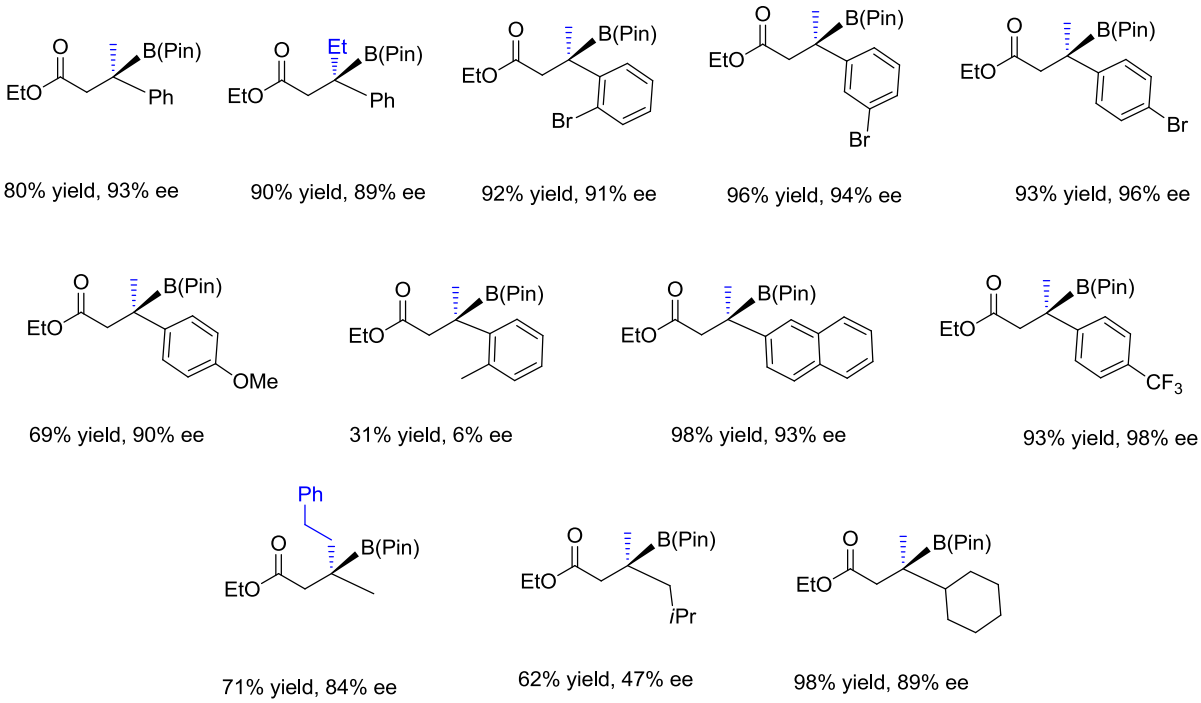


Figure 17. Representative examples for the copper-NHC catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated esters by Hoveyda [113].

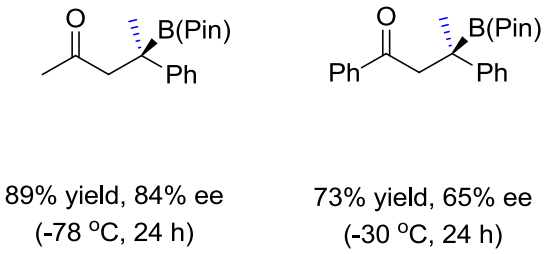


Figure 18. Representative examples for the copper-NHC catalysed ECB of acyclic β,β-disubstituted enones by Hoveyda [113].

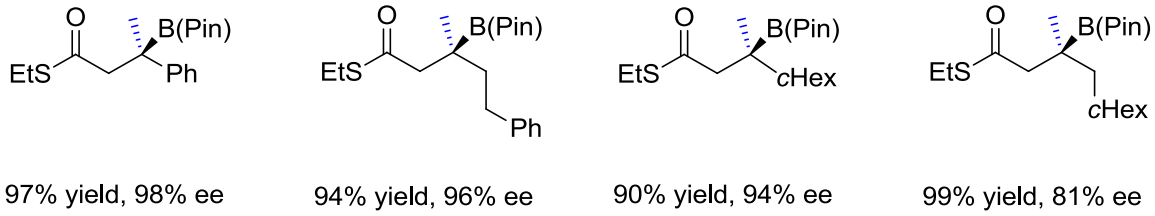


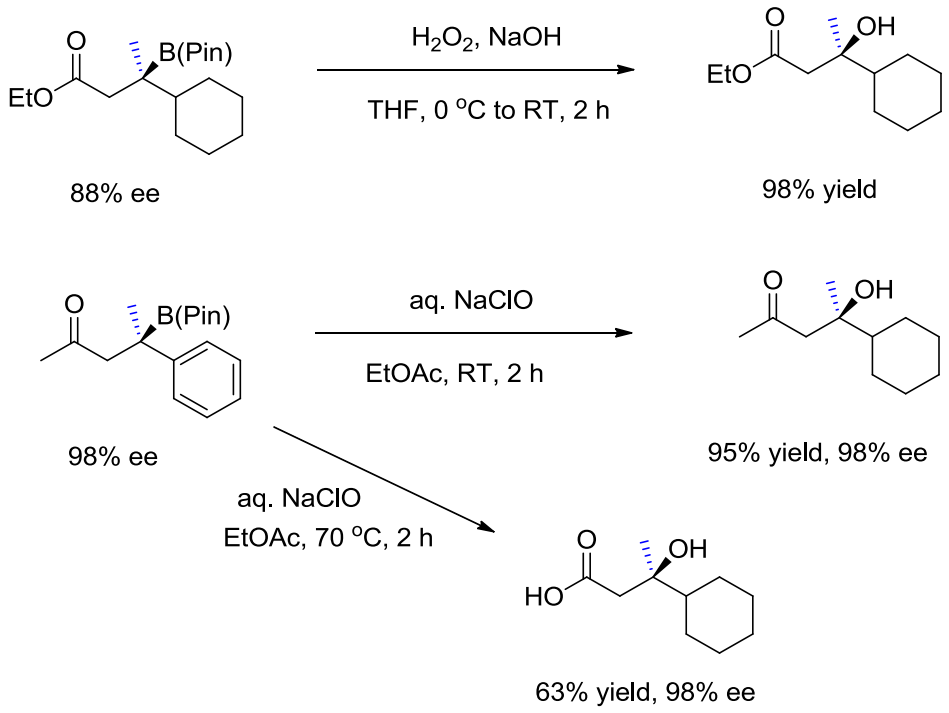
Figure 19. Representative examples for the copper-NHC catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated thioesters by Hoveyda [113] (all reactions carried out at -50 °C for 18 h).

As represented in Figure 17, β-aryl substituted esters (R^1 = OEt, R^3 = 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 substrate electrophilicity. β,β-Dialkyl substituted esters afford slightly lower yields and enantioselectivities (especially when R^3 = CH_2*i*Pr) than the aromatic substrates.

In the case of β,β-disubstituted unsaturated ketones (R^1 = 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 (Figure 18).

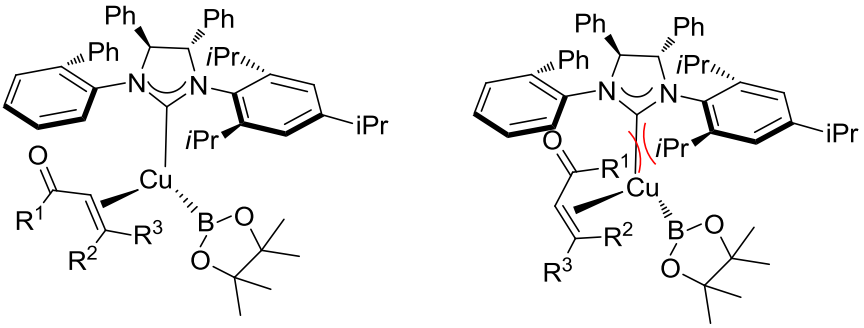
Lastly, the methodology gives excellent yields and enantioselectivities when β,β-disubstituted unsaturated thioesters are used as substrates (R^1 = SEt, Scheme 73), regardless of whether an aromatic β substituent is present (Figure 19). The thioester functionality allows easy conversion to the corresponding unsaturated carboxylic ester or ketones through Ag mediated and Pd-catalysed procedures, respectively [113].

Chiral boron containing adducts are versatile building blocks which can be derivatized easily. For example, oxidation of the C-B bond of the chiral 1,4-adduct with H_2O_2/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).



Scheme 74. Derivatisation of chiral organoboron compounds by Hoveyda [113].

The proposed model that explains the results for the NHC-copper catalysed boronate conjugate addition reaction is represented in Figure 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^*, while the carbonyl moiety resides proximal to the NHC's monosubstituted *N*-Ar unit (vs **U**).

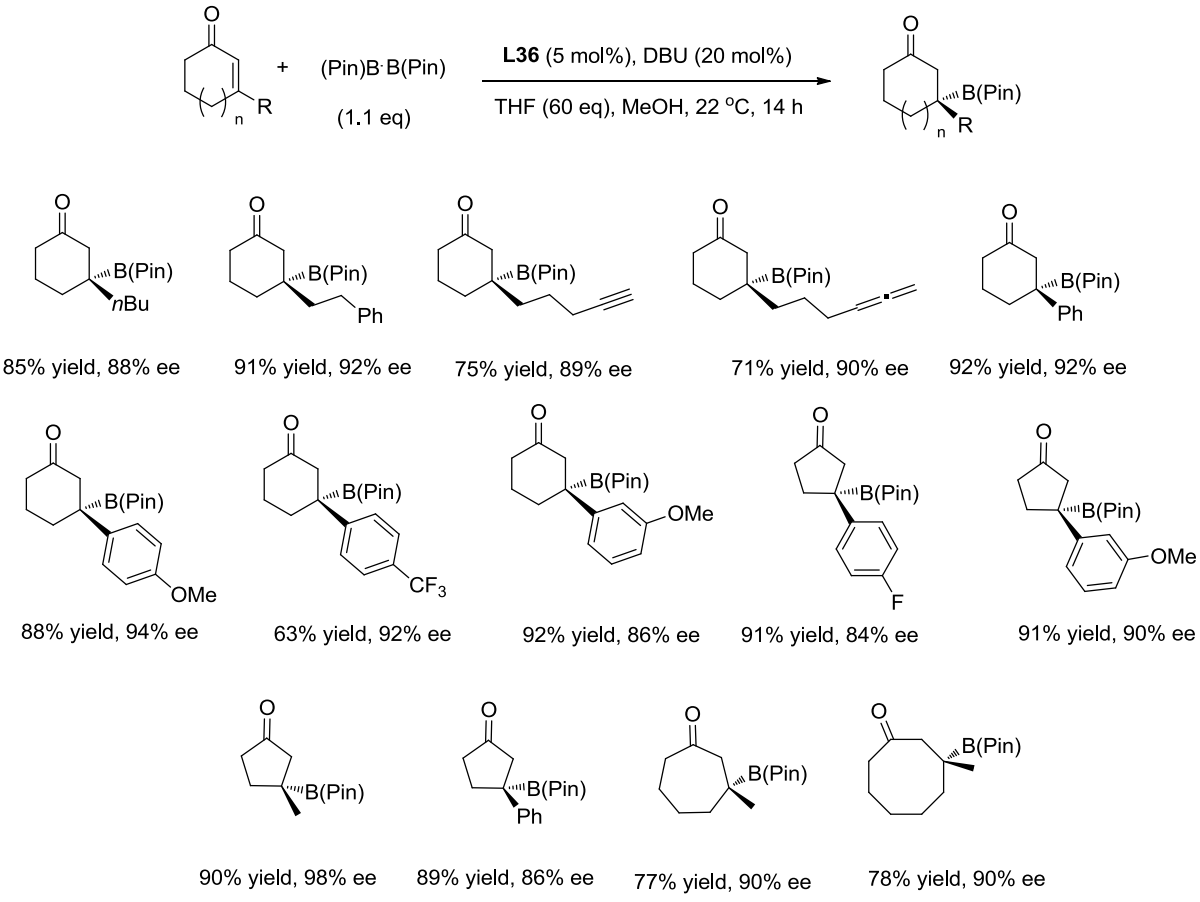


Complex **T** (favoured)

Complex **U** (unfavoured)

Figure 20. Proposed transition states for the copper-NHC catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated systems by Hoveyda [113].

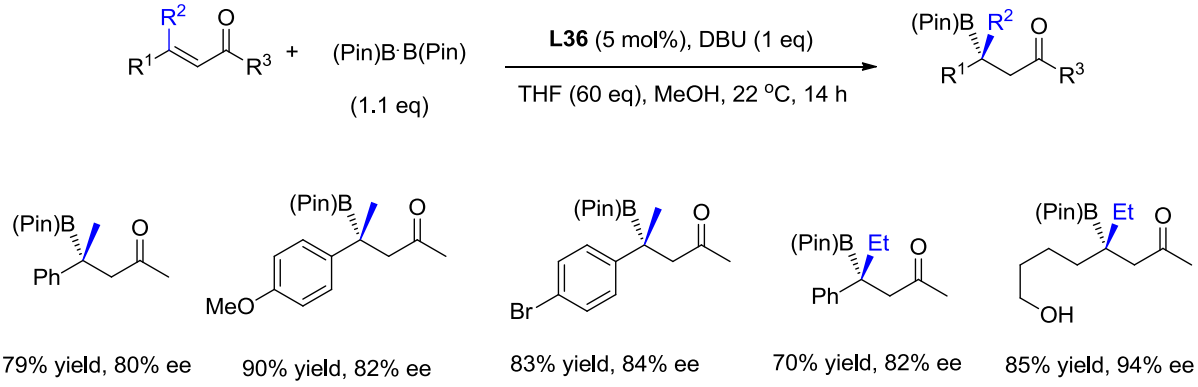
Very recently, Hoveyda et al. have demonstrated that the conjugate addition of organoboron reagents to β,β-disubstituted cyclic enones, catalysed by the readily accessible imidazolium ligand **L36** and in the *absence of any transition metal*, gives excellent selectivities in the formation of boron-substituted quaternary carbon stereogenic centres (63–95% yield and 82 to >98% ee, Scheme 75) [114].



Scheme 75. Transition metal free-NHC catalysed ECB of β-substituted cyclic enones by Hoveyda [114].

Both yields and enantioselectivities obtained with this methodology are comparable to the copper catalysed reaction with (*R*,*R*)-QuinoxP **L32** [110]. 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 56–94% yield and >98% ee (Scheme 76).



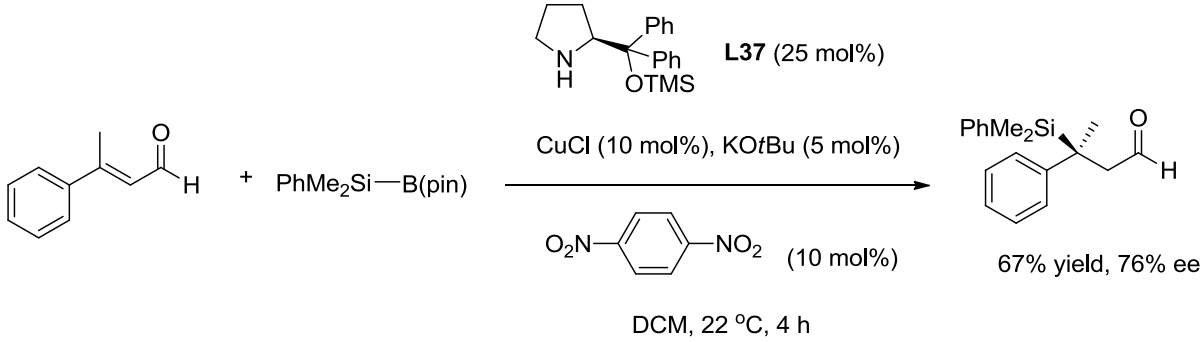
Scheme 76. Transition metal free-NHC catalysed ECB of β,β-disubstituted linear enones by Hoveyda [114].

The mechanism of these NHC-catalysed boryl conjugate addition reaction in the absence of transition-metal complexes [115] will not be discussed here, as it is outside of the scope of this chapter.

4. Formation of silicon-containing quaternary centres by copper catalysed ECA

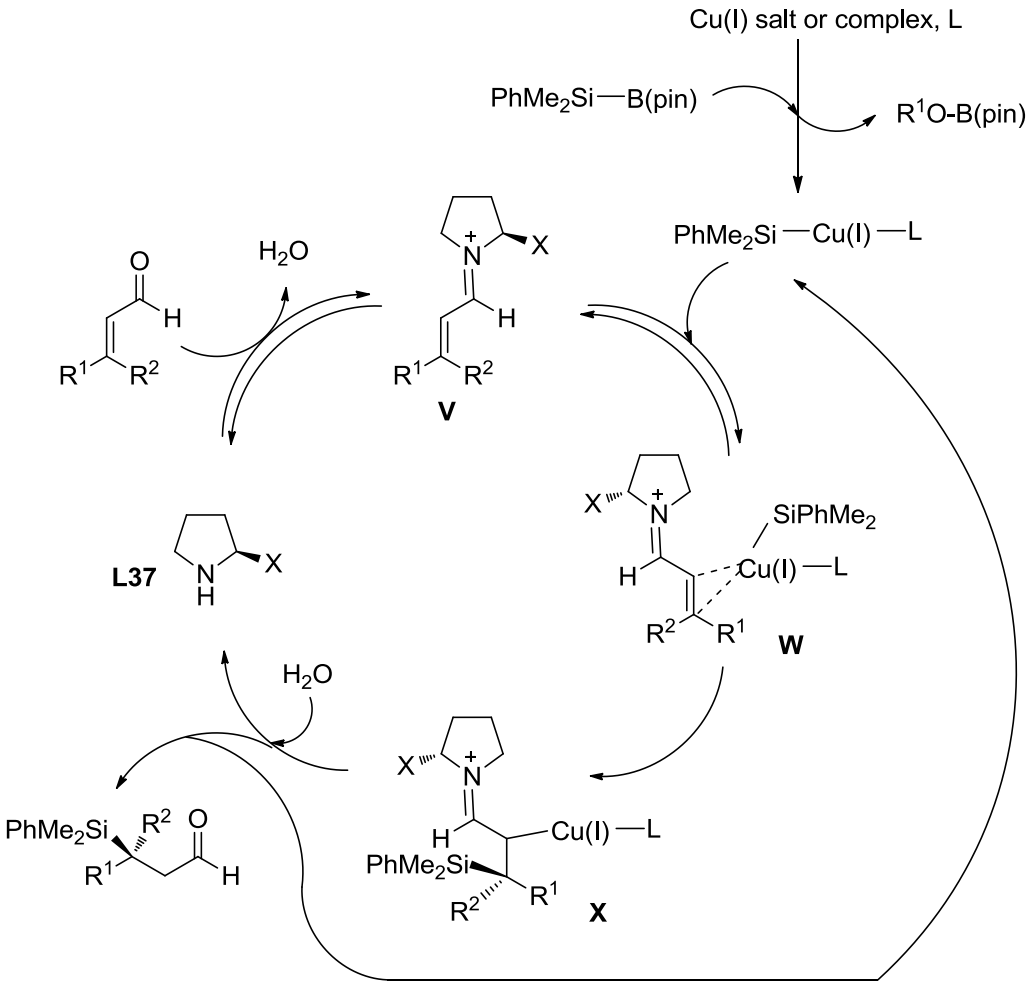
The development of methods for the catalytic enantioselective formation of C-Si bonds is an important challenge in organic synthesis [116]. In this context, the transition metal-catalysed enantioselective conjugate addition (ECA) of *in situ* generated Si nucleophiles derived from readily available sources [e.g., $Cl_2PhSi\text{-}SiMe_3$ and $Me_2PhSi\text{-}B(pin)$] to α,β-unsaturated acceptors with a substituent in the 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 [117] 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.



Scheme 77. Copper and amine catalysed ECS of β,β,-disubstituted linear enals by Cordova [117].

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.



Scheme 78. Proposed catalytic cycle for the ECS of enals catalysed by combination of copper and chiral amine catalysts by Hoveyda [117].

The copper salt (or copper complex) reacts with Me_2PhSi-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 iminum intermediate **V** *via* a possible intermediate **W** to form a C-Si bond in intermediate **X**. Subsequent hydrolysis of imiunium ion **X** gives the corresponding β-silyl aldehyde product as well as regenerate the Cu(I)-silane and the chiral catalyst **L37** [117].

It is worth mentioning that other methodologies for the asymmetric silyl addition to α,β-unsaturated systems [118] do not allow the formation of quaternary centres.

6. 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 [119,120]. 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. [113], 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 [121,122].

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, synthesized and evaluated in the near future.

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