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Chiral *N*-heterocyclic carbene ligands with additional chelating group(s) applied to homogeneous metal-mediated asymmetric catalysis

Christophe Fliedel,^{a*} Agnès Labande,^{a**} Eric Manoury,^a Rinaldo Poli,^{a,b}

Affiliations.

^a LCC-CNRS, Université de Toulouse, CNRS, INPT, Toulouse, France
205 Route de Narbonne, Toulouse F-31077 Cedex 4, France

^b Institut Universitaire de France, 1 Rue Descartes, 75231 Paris Cedex 05, France

Corresponding authors.

* christophe.fliedel@lcc-toulouse.fr (C. Fliedel).

** agnes.labande@lcc-toulouse.fr (A. Labande)

Dedicated to Professor Armando J.L. Pombeiro for his outstanding achievements in Coordination Chemistry and Catalysis

Abstract

Since their early development, *N*-heterocyclic carbene (NHC) ligands and their related metal complexes have attracted much attention, due to their high performances in many catalytic processes. Structural variations on the heterocycle allowed to fine tune their steric and electronic properties. Introduction of one (or more) additional donor group(s) on the *N*-side arm(s) opened the possibility to transform classical monodentate NHCs into bi- or tridentate ligands with different metal-donor affinities for binding. The additional donor may be a neutral donor, *e.g.* phosphine, (thio)ether, or anionic, *e.g.* alkoxide, offering of myriad of possibilities for the resulting polyfunctional NHC ligands. Another development of importance in the field of the NHC chemistry was the introduction of chirality, which can be either 1) central, located on an *N*-side arm and/or on the ligand backbone, 2) axial or 3) planar, opening the door to the application of NHC metal complexes to asymmetric catalysis. The present review summarizes the examples of chiral NHC ligands, functionalized by an additional donor group, which were successfully applied to metal-mediated asymmetric catalysis. When possible, the beneficial (or detrimental) effect of the NHC-functionalization will be discussed, along with the influence of the nature of the additional function, *e.g.* -OH *vs.* -OMe.

Keywords

N-heterocyclic carbene (NHC) – chiral ligands – polyfunctional ligands – transition metals – asymmetric catalysis

Highlights

1. Use of chiral functionalized N-heterocyclic carbenes (NHCs) in metal-mediated asymmetric catalysis
2. Exhaustive description of chiral NHC ligands as a function of the additional chelating donor group
3. Comparison of the functionalized ligands performances according to the nature and/or location of the chiral element
4. Identification of possible trends between ligands architecture and selectivity

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Abbreviations

AAA: asymmetric allylic addition

ACA: asymmetric conjugate addition

Ad: adamantyl

BAr_F: tetrakis[3,5-bis(tri-fluoromethyl)phenyl]borate

Bn: benzyl (CH₂Ph)

COD: 1,5-cyclooctadiene

c-Pentyl: cyclopentyl

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

Dipp: 2,6-di*iso*propylphenyl

ee: enantioselectivity

ⁱPent: *iso*-pentyl ((CH₂)₂CHMe₂)

KHMDS: potassium bis(trimethylsilyl)amide ((Me₃Si)₂NK)

Mes: 2,4,6-trimethylphenyl

Ms: methanesulfonyl (SO₂Me)

Napht: 1-naphthyl

NBD: 2,5-norbornadiene

Pin: pinacolato

RT: room temperature

OAc: acetate (CH₃COO⁻)

OTf: trifluoromethanesulfonate (CF₃SO₃⁻)

TBDMS: *tert*-butyldimethylsilyl (Si(Me)₂^tBu)

TC: thiophene-2-carboxylate

Ts: Tosyl (SO₂*p*-MeC₆H₄)

1. Introduction

N-heterocyclic carbenes (NHCs) are electron-rich neutral ligands, the coordination chemistry of which has been widely studied over the last 25 years [1,2,3]. Rapidly, NHCs were considered as an alternative to phosphine ligands for applications in metal-mediated homogeneous catalysis [4,5,6], and were also used as organocatalysts [4,7,8]. Considerable efforts have been dedicated to the understanding of the stereo-electronic properties of NHCs [9,10] and how the latter influence the M-C_{NHC} bond [11]. Unique donor properties allow these ligands to stabilize a wide range of metal centers, from soft late transition metals [1,2,12,13] to highly Lewis acidic metals such as Group 1-2 and early transition metals [14,15], f-block metals [16] or Group 13 metals [17].

The synthetic routes to NHC precursors are now well-established and allow high degrees of variations both in the nature of the heterocycle (imidazole, oxazole, thiazole-based rings...) and the *N*-substituents [18]. These peculiarities have led to several sub-classes of NHCs; for instance, metal complexes of poly-NHC ligands, obtained by connecting two or more carbene centers, have been synthesized and applied to catalytic transformations [19,20]. On the other hand, the introduction of an additional chemical function, such as amine, alcohol, phosphine or thioether on the *N*-side arm led to NHC-based chelating or pincer ligands, commonly referred to as *N*-C_{NHC} [21,22], *O*-C_{NHC} [23,22], *P*-C_{NHC} [24] and *S*-C_{NHC} [25,26], respectively. The influence of the presence of anionic *N*-functionalities in NHC-metal complexes in catalytic reactions was also recently reviewed [27]. Noteworthy, chiral NHC ligands were also accessible; the chiral element being possibly located 1) on the ligand backbone *via* endocyclic asymmetric carbon(s) (Chart 1-1, A-type) or, 2) on the *N*-side arm *via* the presence of a stereogenic center, an axially chiral or planar chiral group (Chart 1-1, B, C and D-type, respectively). Many efforts have been devoted to the development of chiral NHCs and their metal complexes for various application in asymmetric synthesis/catalysis, and several reviews have already summarized the most relevant results in this challenging area [28,29,30,31,32,33]. We are interested in the development of poly-functional NHC-based ligands and asymmetric catalysis, and therefore we aimed at providing a literature survey of the performances of chiral NHCs (restricted to diaminocarbenes), incorporating additional chelating *N*-, *O*-, *P*-, or *S*-donor group(s), in metal-mediated asymmetric catalysis. Our objective is also, whenever possible, to compare the performances of these chiral *N*-functionalized NHC ligands as a function of the nature and/or the location of the chiral element, and with the performances of their non-functionalized analogs, to point out possible trends between ligands architectures and selectivity. NHC (pro)ligands in which the additional functional group is not well-oriented for chelation, *e.g.* a *para*-OMe group on an *N*-aryl substituent, are outside the scope of this review.

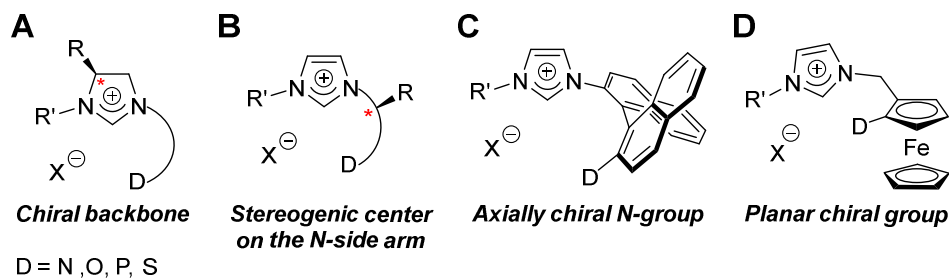


Chart 1-1. Schematic view of the different classes of precursors of chiral *N*-functionalized NHCs treated in this review. Note: some compounds may present more than one chiral element, *e.g.* chiral backbone and stereogenic center(s) on the *N*-side arm(s).

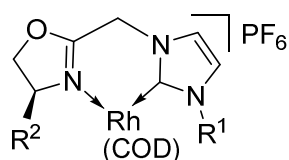
2. Nitrogen-functionalized NHC ligands

2.1. Oxazoline- and thiazoline-groups

Chiral oxazoline-carbene ligands constitute one of the first and most successful families of mixed *N,C*_{NHC} ligands [34].

2.1.1. NHC-oxazoline mixed ligands with central chirality only

To the best of our knowledge, the first ligands of this type were described by Herrmann and coworkers, who developed complexes **2.1-2.4** (Scheme 2-1) [35]. These rhodium complexes were tested in the hydrosilylation of acetophenone providing the chiral secondary alcohols with moderate enantiomeric excesses (*ee* up to 70%) [36].



2.1: R¹ = Me, R² = Bn

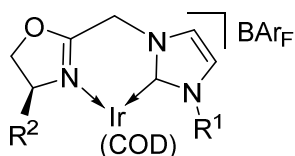
2.2: R¹ = Me, R² = *i*Pr

2.3: R¹ = *t*Bu, R² = Bn

2.4: R¹ = *t*Bu, R² = *i*Pr

Scheme 2-1. Rhodium complexes described by Herrmann *et al.* [35,36].

Pfalz *et al.* developed iridium complexes with similar ligands **2.5-2.11** but also with other ligands where the chiral centre is bonded to the methylene linker **2.12-2.28** [37]. These modular iridium complexes were used in the asymmetric hydrogenation of alkenes giving the corresponding alkanes with low to high enantiomeric excesses (Scheme 2-2).



2.5: R¹ = Me, R² = *t*Bu

2.6: R¹ = Me, R² = *i*Pr

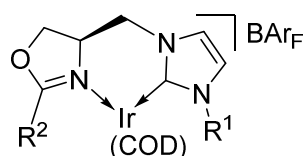
2.7: R¹ = *i*Pr, R² = *t*Bu

2.8: R¹ = Mes, R² = *t*Bu

2.9: R¹ = neopentyl, R² = *t*Bu

2.10: R¹ = isobutyl, R² = *t*Bu

2.11: R¹ = *t*Bu, R² = *t*Bu



2.12: R¹ = Me, R² = *t*Bu

2.13: R¹ = *i*Pr, R² = *t*Bu

2.14: R¹ = Mes, R² = *t*Bu

2.15: R¹ = neopentyl, R² = *t*Bu

2.16: R¹ = *t*Bu, R² = *t*Bu

2.17: R¹ = Me, R² = 1-Ad

2.18: R¹ = *i*Pr, R² = 1-Ad

2.19: R¹ = Mes, R² = 1-Ad

2.20: R¹ = neopentyl, R² = 1-Ad

2.21: R¹ = *t*Bu, R² = 1-Ad

2.22: R¹ = Me, R² = 2,4-Me₂C₆H₃

2.23: R¹ = *i*Pr, R² = 2,4-Me₂C₆H₃

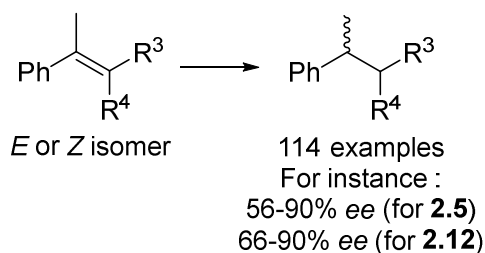
2.24: R¹ = Mes, R² = 2,4-Me₂C₆H₃

2.25: R¹ = neopentyl, R² = 2,4-Me₂C₆H₃

2.26: R¹ = *t*Bu, R² = 2,4-Me₂C₆H₃

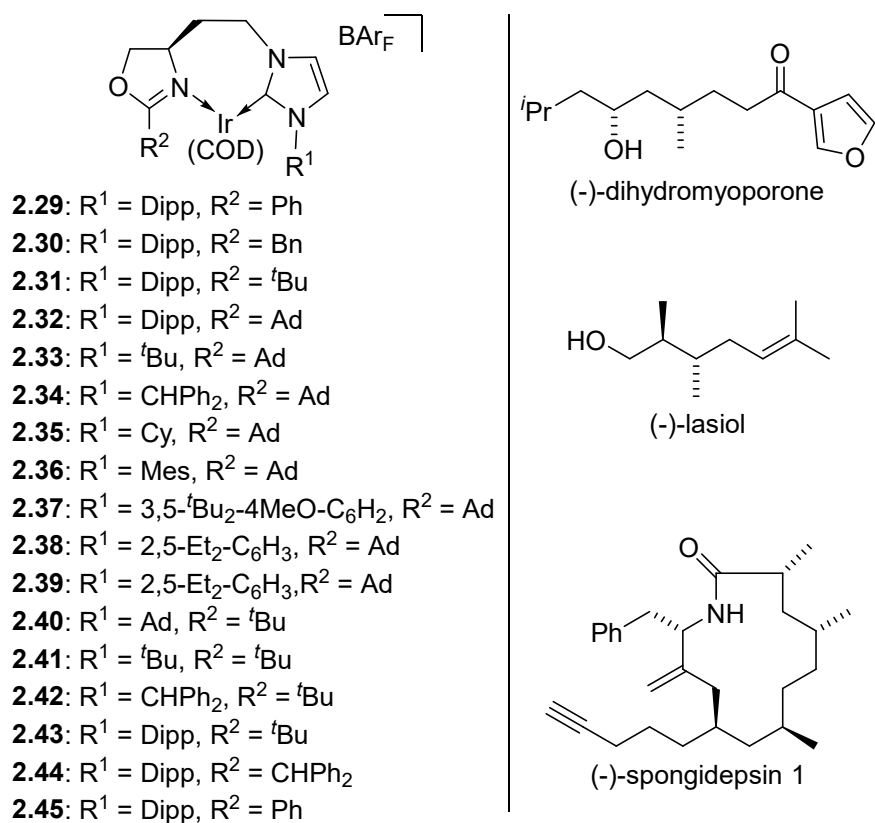
2.27: R¹ = *t*Bu, R² = 2,4-Me₂C₆H₃

2.28: R¹ = Mes, R² = Ph



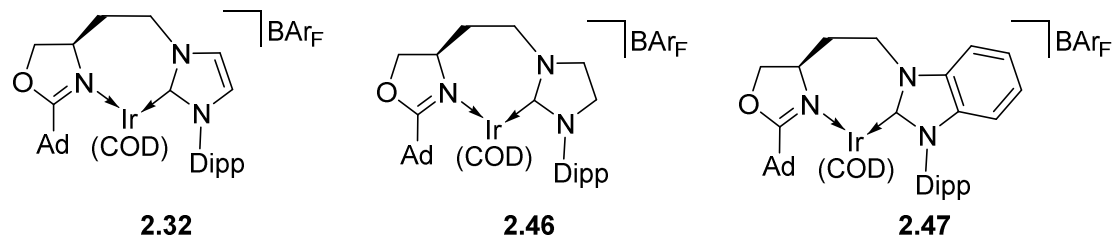
Scheme 2-2. Iridium complexes described by Pfaltz *et al.* [37].

Burgess and coworkers developed a large family of iridium complexes of chiral NHC-oxazoline **2.29-2.45**, R¹ and R² being alkyl or aryl substituents (Scheme 2-3) [38,39]. These iridium complexes, which are analogues of Crabtree's catalyst, have been tested in the hydrogenation of various alkenes. In particular, complex **2.32** (Scheme 2-3) with large steric hindrance around the iridium center, proved to be not only often more efficient than the *P,N* analogues but also to provide catalytic systems of high enantioselectivities in the asymmetric hydrogenation of various trisubstituted unfunctionalized alkenes [38,39, 40], aryl-substituted dienes [41,42], α,β -unsaturated esters and amides [42], α -methyl γ -amino acid derivatives [43], vinyl ethers [44,45], etc. **2.32** was also used to synthesize various synthons and molecules of interest [46,47,48,49,50,51,52] such as (-)-dihydromyoporone, (-)-lasiol or (-)-spongidepsin 1 (Scheme 2-3).



Scheme 2-3. Iridium complexes **2.c-2.d** described by Burgess *et al.* and selected examples of chiral molecules synthesized using such complexes [38-51].

Burgess and coworkers studied in details, both experimentally and computationally, the mechanism of hydrogenation with complex **2.32** [53,54,55]. In particular, they showed that the hydride derivative obtained from complex **2.32** is much less acidic (7 order of magnitude!) than its analogues obtained from corresponding oxazoline-phosphinite ligands and therefore the product distribution could be very different with acid-sensitive substrates [56]. The same authors also studied analogues of **2.32** with an imidazolylidene (**2.46**) or a benzimidazolylidene (**2.47**) ring instead of an imidazolidene ring: the catalytic performances of the three iridium complexes are in fact very similar [57] (see scheme 2-4).

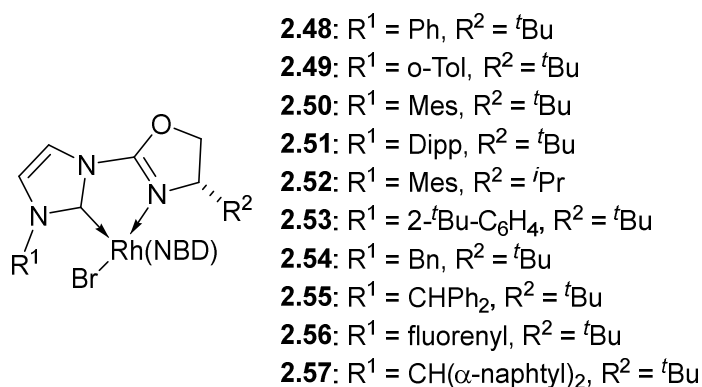


Scheme 2-4. Analogues of iridium complex **2.32** [57].

The efficiency of Burgess' system for the asymmetric hydrogenation of olefins was higher than Pfaltz's (complexes **2.5-2.28**) when bulky R¹ and R² substituents were used (complex **2.32**). Conversely,

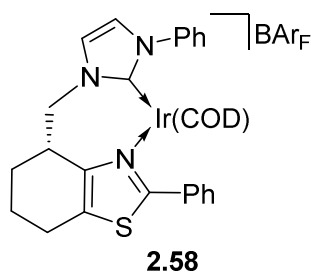
2.5-2.28 bearing 6-membered metallacycles performed better when small R¹ and R² groups were present. This trend, however, was only verified for the cited reaction.

Gade, Bellemin-Lapponnaz and coworkers developed a family of rhodium complexes **2.48-2.57** with a direct link between the NHC and the oxazoline ring (Scheme 2-5), R¹ and R² being an aryl and an alkyl group, respectively [58,59]. These complexes were tested in the hydrosilylation of aryl alkyl ketones (80-99% *ee* with **2.50**) and dialkyl ketones (53-98% *ee* with **2.50**). A comparative study between complexes **2.48-2.57** and their analogues with CH₂ or CMe₂ linkers clearly showed that complexes **2.48-2.57** are more active and more enantioselective and can work at low temperature giving rise to high enantioselectivities [60]. Following an experimental and theoretical study of the hydrosilylation of ketones by complexes **2.48-2.57**, a new mechanism through silylene intermediates was proposed [61].



Scheme 2-5. Rhodium complexes described by Bellemin-Lapponnaz, Gade *et al.* [58,59].

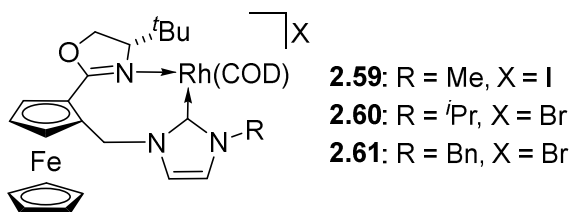
Andersson and coworkers developed an iridium complex **2.58** (Scheme 2-6) of a related NHC-thiazoline ligand which showed good catalytic activities and low to good enantioselectivities (0-90% *ee*) in the hydrogenation of various trisubstituted alkenes [62].



Scheme 2-6. NHC-thiazoline iridium complex described by Andersson *et al.* [62].

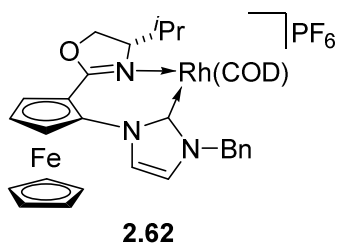
2.1.2. NHC-oxazoline mixed ligands with central and planar chirality

Bolm and coworkers described the synthesis of the first ferrocene-based chiral NHC-oxazoline proligands and their rhodium complexes **2.59-2.61** (Scheme 2-7) [63]. These complexes bear the planar chirality of the 1,2-substituted derivatives and the central chirality of the oxazoline parts. They were used as catalysts in the hydrosilylation of acetophenone by diphenylsilane but the enantioselectivities were very low (up to 6% *ee*). Compared to Gade and Bellemin-Laponnaz's [58,59,60] and Herrmann's [35] systems, respectively based on 5-membered and 6-membered metallacycles, the complex described by Bolm *et al.* possesses a large 8-membered metallacycle. We can observe a correlation ring size/level of enantioselectivity in the hydrosilylation of aryl alkyl ketones with these three systems, where the best *ees* were obtained with the 5-membered metallacycle. In the present case, the low *ees* can tentatively be explained by an excessive flexibility of the metallacycle and a limited influence of planar chirality due to the lack of proximity of the ferrocenyl unit to the metal center.



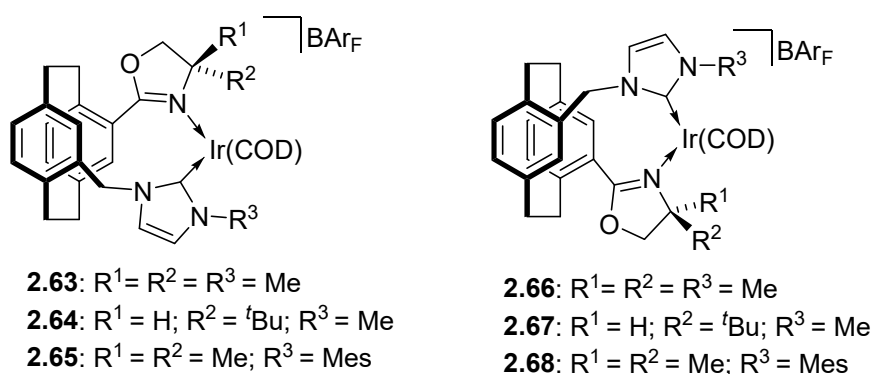
Scheme 2-7. Rhodium complexes of ferrocene-based NHC-oxazoline described by Bolm *et al.* [63].

In 2009, Kuang and coworkers described the synthesis of the rhodium complex **2.62** containing a chiral ferrocenyl carbene-oxazoline ligand (Scheme 2-8) [64]. The latter was tested in the asymmetric transfer hydrogenation of aryl alkyl ketones in isopropanol at 75°C in presence of KOH: good yields and moderate enantiomeric excesses (39-67% *ee*) could be obtained. This complex presents a 7-membered metallacycle, probably more rigid than Bolm's system, which could partly explain the better *ees*, even though the reaction is different (hydrosilylation vs transfer hydrogenation of aryl alkyl ketones). One should note, however, that the substituent on the oxazoline ring is different in both cases and could also have an effect on enantioselectivity, therefore the influence of planar chirality alone is difficult to assess.



Scheme 2-8. Rhodium complex of ferrocene-based NHC-oxazoline described by Kuang *et al.* [64].

Bolm and coworkers described the synthesis of five new cationic iridium complexes of NHC-oxazoline ligands built on the planar chiral paracyclophane scaffold **2.63-2.65** and **2.66-2.68** (Scheme 2-9) [65]. These complexes were used in the asymmetric hydrogenation of alkenes. The best enantioselectivities were obtained using complex **2.65** with planar chirality only (0-46% *ee*). Once again, the influence of planar chirality is difficult to evaluate but appears moderate since the metallacycle is rather flexible and not close to the metal center. The authors, on the other hand, underline the important role of the oxazoline and imidazole ring substituents.

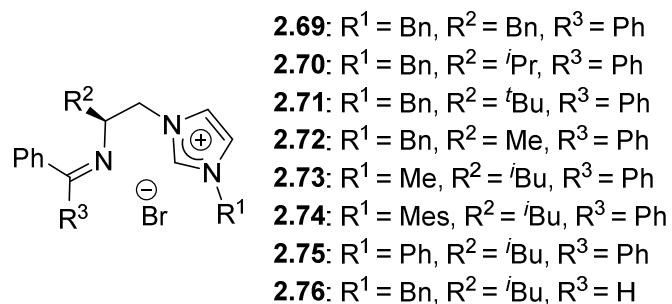


Scheme 2-9. Rhodium complexes of paracyclophane-based NHC-oxazoline described by Bolm *et al.* [65].

2.2. NHC-Imine and amine mixed ligands

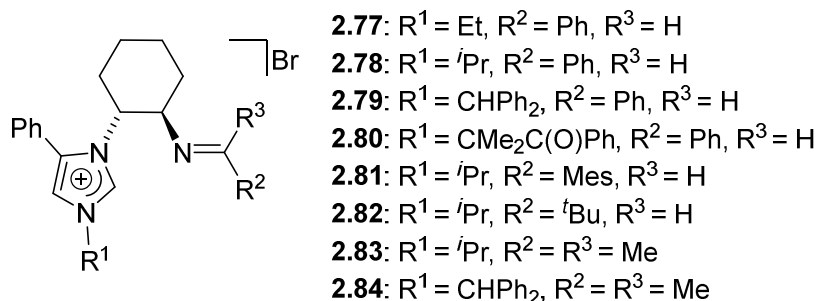
2.2.1. NHC-imine mixed ligands

Williams and coworkers developed a family of chiral NHC-imine ligands from amino acids [66]. The palladium complexes obtained *in situ* from the imidazolium pro-ligands **2.69-2.76** (Scheme 2-10) were tested in the asymmetric allylic substitution of 1,3-diphenylpropenyl acetate giving rise to low to moderate enantiomeric excesses (7-53% *ee*).



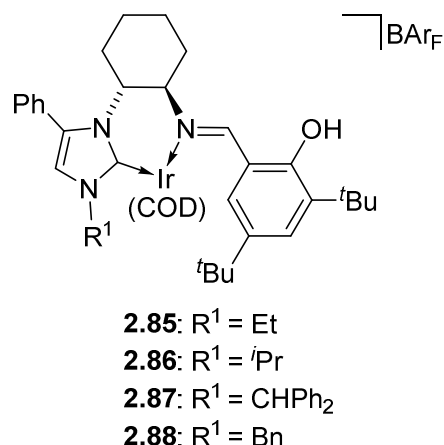
Scheme 2-10. NHC-imine pro-ligands developed by Williams *et al.* [66].

Douthwaite *et al.* developed chiral NHC-imine pro-ligands from 1,2-diaminocyclohexane **2.77-2.84** [67]. Palladium complexes generated from these ligands were used in the asymmetric allylic substitution of 1,3-diphenylpropenyl acetate. Although the use of these catalysts required higher temperatures (50°C) to reach good conversions compared to pro-ligands **2.69-2.76**, they allowed reaching higher *ees* (up to 92%). The closer proximity of the chirality source in the present case may explain these results.



Scheme 2-11. NHC-imine pro-ligands developed by Douthwaite *et al.* [67].

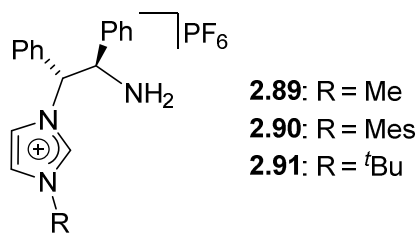
Iridium complexes **2.85-2.88** also generated from the same kind of pro-ligands (Scheme 2-12) were used in the asymmetric transfer hydrogenation of aryl ketones but only low to moderate enantiomeric excesses could be obtained (0-43% *ee* with **2.86**) [68].



Scheme 2-12. Iridium complexes of NHC-imine ligands developed by Douthwaite *et al.* [68,67].

2.2.2. NHC-amine mixed ligands

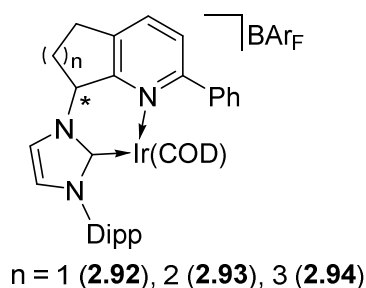
Recently, Morris and coworkers developed NHC-amine pro-ligands incorporating two asymmetric carbon atoms on the *N*-side arm, R being an alkyl or an aryl group (Scheme 2-13) [69,70]. This ligand family has been named kaibene. A ruthenium complex (**2.89-Ru**) of the kaibene with R = Me was tested as an inseparable 1/1 mixture of diastereoisomers with an uncontrolled chirality at metal in the asymmetric transfer hydrogenation of acetophenone but a racemic alcohol was obtained [69]. Iridium complexes of kaibene R = Mes or *t*Bu were also used in the asymmetric transfer hydrogenation of aryl ketones but low enantioselectivities were observed (< 30% *ee*) [70].



Scheme 2-13. Precursors of NHC-amine ((*S,S*)-kaibene) ligands used by Morris *et al.* in asymmetric transfer hydrogenation [69,70].

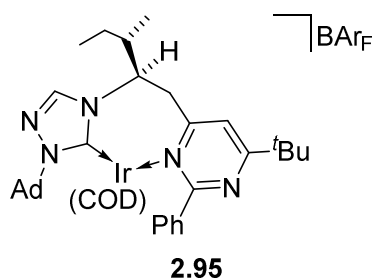
2.2.3. NHC-heterocycle mixed ligands

Pfaltz and coworkers synthesized a series of iridium complexes **2.92-2.94** of NHC-pyridine ligands (Scheme 2-14) [71]. Complexes **2.92-2.94** were tested in the asymmetric hydrogenation of trisubstituted alkenes. Excellent yields and moderate to excellent enantioselectivities (37-97% *ee*), usually slightly lower than those obtained using the pyridine-phosphinite analogues, were observed. The enantioselectivities were shown to depend on the saturated ring size ($n = 1, 2$ or 3).



Scheme 2-14. Iridium complexes of NHC-pyridine ligands described by Pfaltz *et al.* [71].

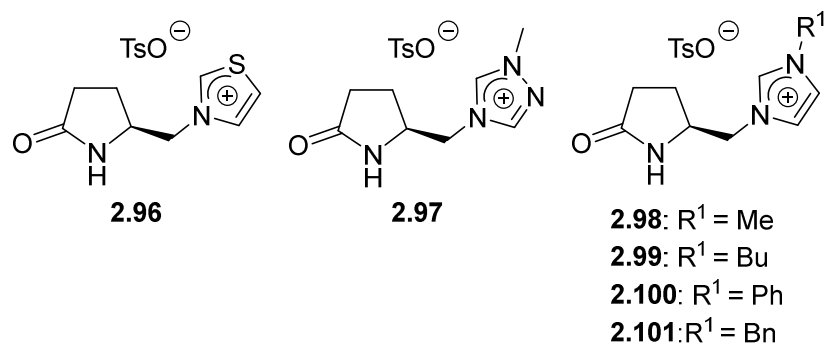
Burgess *et al.* synthesized an iridium complex **2.95** of a NHC-pyrimidine ligand which can efficiently catalyze the hydrogenation of *E*-1,2-diphenylpropene under mild conditions but with low enantiomeric excesses (12% *ee*) (Scheme 2-15) [72].



Scheme 2-15. Iridium complex of a NHC-pyrimidine ligand described by Burgess *et al.* [72].

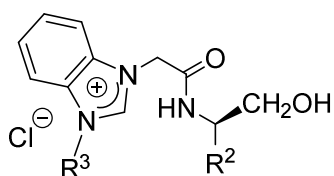
2.3. NHC-amide mixed ligands

More recently, a few chiral NHC-amide ligands have been used in asymmetric catalysis. In particular, Vo-Thanh and coworkers developed a family of amide-azolium precursor salts **2.96**, **2.97** and **2.98-2.101** (Scheme 2-16) [73]. *In situ* synthesized rhodium complexes were tested in the asymmetric transfer hydrogenation of aryl ketones. The best results were obtained with **2.98** (50-80% *ee*).



Scheme 2-16. NHC-amide pro-ligands developed by Vo-Thanh *et al.* [73].

Sakaguchi and coworkers synthesized various chiral benzimidazoliums bearing one (**2.102-2.131**) or two (**2.132-2.136**) substituents containing an asymmetric carbon atom from amino acid derivatives (Scheme 2-17) [74,75,76,77,78]. Ruthenium complexes were synthesized from the corresponding NHC precursors and tested in the transfer hydrogenation of acetophenone: low yields and *ee*'s were obtained (best *ee* up to 41% with **2.104**) [74]. Copper complexes were synthesized *in situ* from the corresponding NHC precursors and were tested in the copper-catalyzed asymmetric conjugate addition (ACA) of dialkylzinc on enones. Good yields and enantioselectivities could be obtained in particular with compound **2.124** (R¹ = CH₂OH and R² = COOMe) (51-93% *ee*) [76]. Compounds **2.102-2.123** and **2.124-2.128** were also used to prepare *in situ* iridium complexes that were applied to the asymmetric hydrosilylation of ketones. Yields and enantioselectivities are highly dependent on the structure of the NHC ligand, and good results could be obtained in particular with benzimidazolium **2.115** (30-96% *ee* for aryl alkyl ketones) [77] and **2.127** (30-96% *ee* for aryl alkyl ketones) [78] (Scheme 2-17).



2.102: $R^2 = \text{COOMe}$, $R^3 = \text{Me}$

2.103: $R^2 = \text{COOMe}$, $R^3 = \text{Bn}$

2.104: $R^2 = i\text{Pr}$, $R^3 = \text{Me}$

2.105: $R^2 = i\text{Pr}$, $R^3 = \text{Et}$

2.106: $R^2 = i\text{Pr}$, $R^3 = n\text{Bu}$

2.107: $R^2 = i\text{Pr}$, $R^3 = i\text{Pr}$

2.108: $R^2 = i\text{Pr}$, $R^3 = \text{allyl}$

2.109: $R^2 = i\text{Pr}$, $R^3 = \text{Bn}$

2.110: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(2-Me-C}_6\text{H}_4\text{)}$

2.111: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(3-Me-C}_6\text{H}_4\text{)}$

2.112: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(4-Me-C}_6\text{H}_4\text{)}$

2.113: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(3-CF}_3\text{-C}_6\text{H}_4\text{)}$

2.114: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(4-Ph-C}_6\text{H}_4\text{)}$

2.115: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(1-naphtyl)}$

2.116: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(2-naphtyl)}$

2.117: $R^2 = i\text{Pr}$, $R^3 = \text{CH}_2\text{-(5-anthracenyl)}$

2.118: $R^2 = i\text{Pr}$, $R^3 = \text{Ph}$

2.119: $R^2 = \text{Me}$, $R^3 = \text{Me}$

2.120: $R^2 = \text{Et}$, $R^3 = \text{Me}$

2.121: $R^2 = i\text{Pr}$, $R^3 = \text{Me}$

2.122: $R^2 = s\text{Bu}$, $R^3 = \text{Me}$

2.123: $R^2 = t\text{Bu}$, $R^3 = \text{Me}$

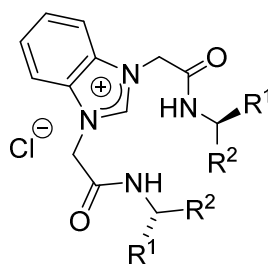
2.124: $R^2 = \text{Ph}$, $R^3 = \text{Me}$

2.125: $R^2 = \text{Bn}$, $R^3 = \text{Me}$

2.126: $R^2 = i\text{Bu}$, $R^3 = \text{Bn}$

2.127: $R^2 = t\text{Bu}$, $R^3 = \text{Bn}$

2.128: $R^2 = t\text{Bu}$, $R^3 = \text{CH}_2\text{-(1-naphtyl)}$



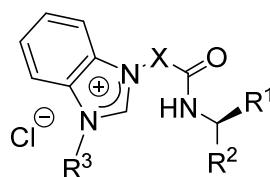
2.132: $R^1 = \text{CH}_2\text{OH}$, $R^2 = \text{COOMe}$

2.133: $R^1 = \text{CH}_2\text{OH}$, $R^2 = \text{COOEt}$

2.134: $R^1 = i\text{Bu}$, $R^2 = \text{COOMe}$

2.135: $R^1 = t\text{Bu}$, $R^2 = \text{COOMe}$

2.136: $R^1 = t\text{Bu}$, $R^2 = \text{CH}_2\text{OH}$



2.129: $R^1 = \text{CH}_2\text{OMe}$,

$R^2 = \text{Me}$, $R^3 = \text{Bn}$, $X = \text{CH}_2$

2.130: $R^1 = t\text{Bu}$, $R^2 = \text{CH}_2\text{OH}$,

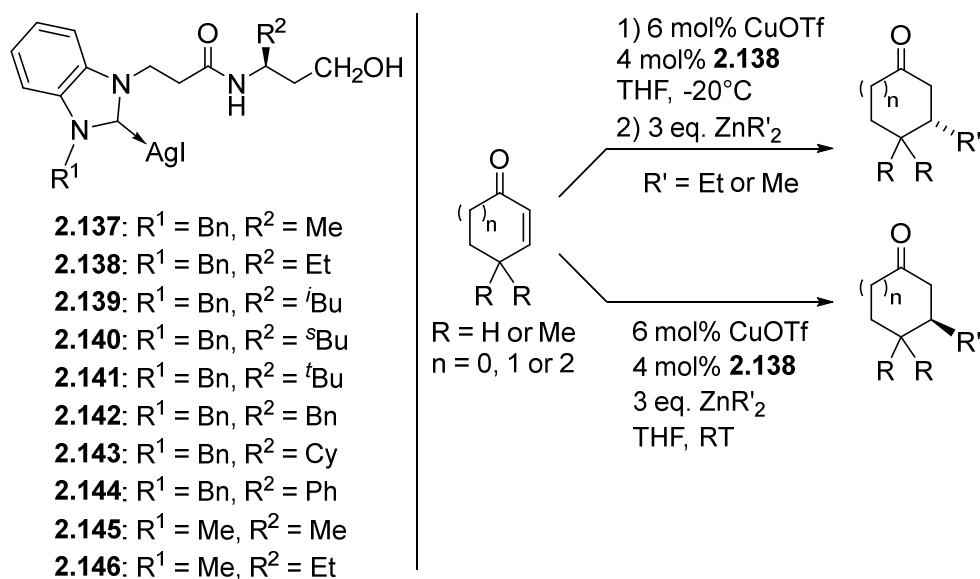
$R^3 = \text{Bn}$, $X = \text{CH}_2$

2.131: $R^1 = \text{CH}_2\text{OH}$,

$R^2 = t\text{Bu}$, $R^3 = \text{Bn}$, $X = \text{CMe}_2$

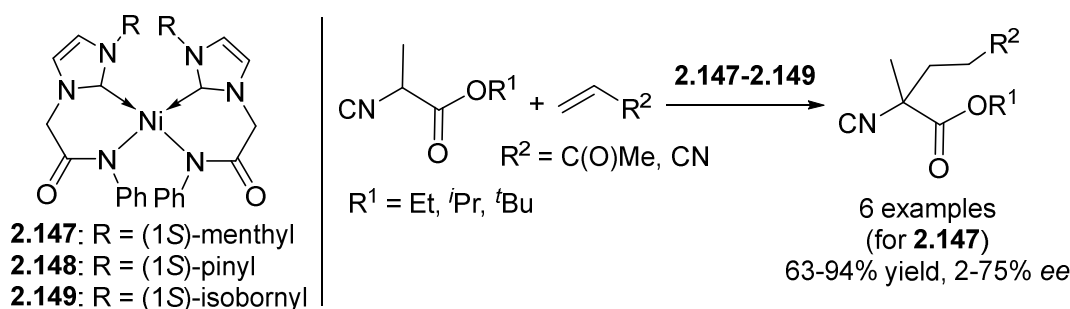
Scheme 2-17. Chiral benzimidazolium salts obtained from amino acids by Sakaguchi *et al.* [74,77].

More recently, Sakaguchi and coworkers synthesized silver complexes of a new family of NHC-amide ligands (Scheme 2-18) [79]. Their silver(I) complexes (**2.137-2.146**) have been used as pre-catalysts in the Cu-catalyzed ACA of dialkylzinc on cyclic enones. When the enone was added first to the catalytic system followed by the dialkylzinc (Scheme 2-18), good enantioselectivities could be obtained for 6-membered rings (up to 74% *ee* with **2.138**) and for 7-membered rings (up to 83% *ee* with **2.138**). When the dialkylzinc was added first to the catalytic system, before the substrate, the addition products could still be obtained in good yields, but with opposite enantioselectivities (Scheme 2-18). Again the best silver complex is **2.138**, and with this other procedure very good yields could be obtained (up to 80% for 5-membered rings, up to 96% for 6-membered rings, up to 95% for 7-membered rings).



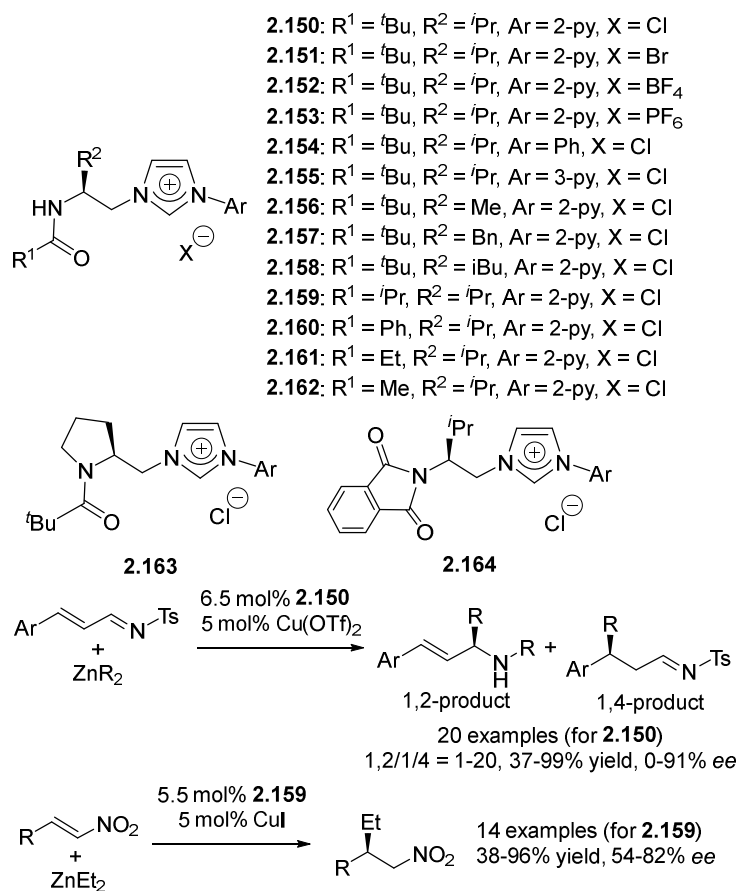
Scheme 2-18. Silver complexes of NHC-amide ligands developed by Sakaguchi *et al.* and their use in the Cu-catalyzed ACA of alkylzinc on cyclic enones [79].

Ghosh and coworkers developed, from natural terpenes, chiral nickel(II) complexes **2.147-2.149** of NHC-amide ligands (Scheme 2-19) [80]. Complexes **2.147-2.149** catalyze asymmetric Michael reaction of racemic 2-cyanopropanoates (Scheme 2-19). No enantioselectivities were observed for **2.148** and **2.149**, but good enantiomeric excesses could be obtained with **2.147**, in particular with methylvinylketone (50-75% *ee*).



Scheme 2-19. Nickel complexes of NHC-amide ligands developed by Ghosh *et al.* [80].

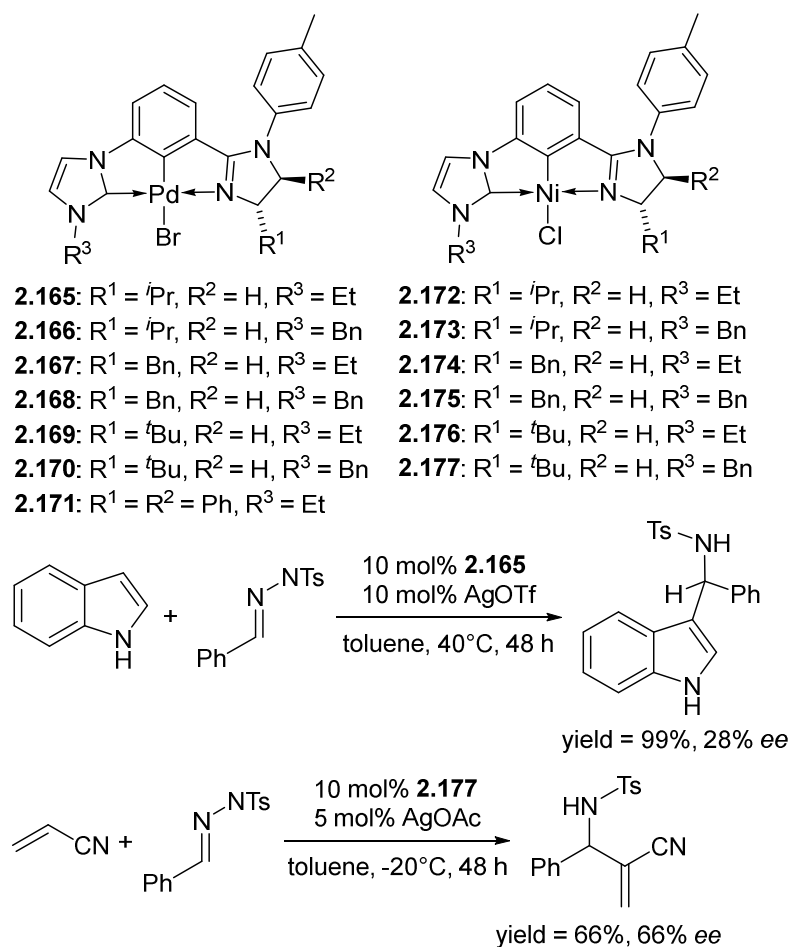
Ukaji and coworkers synthesized several chiral NHC-amide precursors **2.142-2.156** where R¹ and R² are alkyl groups and Ar are aryl or heteroaryl groups (Scheme 2-20) [81]. These salts were tested in the presence of [Cu(OTf)₂] in the asymmetric ethylation of α,β -unsaturated aldimines. The best results were obtained with **2.142**: 1,2/1,4 product ratios up to 20, *ees* for the 1,2 product up to 91% (Scheme 2-20). The same ligands were used in the asymmetric copper-catalyzed addition of diethylzinc to various nitroalkenes (R being alkyl, aryl or heteroaryl substituents, Scheme 2-20) [82]. The best results were obtained with **2.159**: yields up to 94%, *ee* up to 82%.



Scheme 2-20. NHC-amide pro-ligands developed by Ukaji *et al.* and their use in the asymmetric addition of dialkylzinc on α,β -unsaturated aldimines and nitroalkenes [81,82].

2.4. Miscellaneous

Recently, Zhu, Song and coworkers described chiral N,C,C_{NHC} pincer Pd(II) and Ni(II) complexes **2.165-2.177** from (imidazolyl)arylNHC pro-ligands (Scheme 2-21) [83]. The palladium complexes were tested as catalysts for asymmetric Friedel-Crafts and asymmetric aza-Morita-Baylis-Hillman reactions. The best results were obtained with **2.165** for the Friedel-Crafts reaction and with **2.170** for the aza-Morita-Baylis-Hillman reaction (Scheme 2-21).



Scheme 2-21. Chiral N,C,C_{NHC} pincers developed by Zhu, Song *et al.* [83].

3. Oxygen-functionalized NHC ligands

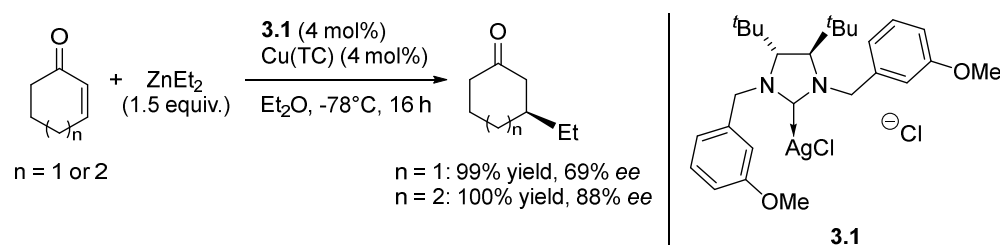
3.1. Central chirality

The (pro)ligands described in this section may present; 1) a chiral backbone (asymmetric endo-cyclic carbon(s)), 2) one or two N -substituent containing an asymmetric carbon or 3) both chiral elements.

3.1.1. Copper-catalyzed asymmetric conjugate addition (ACA)

In 2002, Alexakis and Benhaim summarized the work done in the field of copper-catalyzed asymmetric conjugate addition (Cu-ACA), also called Michael addition, revealing at that time the supremacy of chiral P-based ligands [84]. Organometallic species, such as dialkylzinc, trialkylaluminum or Grignard reagents are the typical nucleophiles for this reaction. The first use of a chiral NHC (pro)ligand in this reaction was reported at the same time, independently, by Alexakis *and coll.* [85] and Roland *and coll.* [86] in 2001. The significant breakthroughs achieved in the field of Cu-ACA were recently discussed by Mauduit *and coll.* [87], and a review specially devoted to the results obtained with chiral O,C_{NHC} ligands is also available [88].

With organozinc reagents. A couple of years later, Alexakis, Roland *and coll.* studied the impact of several parameters on the ACA of ZnEt_2 to cyclohex-2-enone [89]. First, the authors highlighted that replacing the usual $[\text{Cu}(\text{OTf})_2]$ precursor by $[\text{Cu}(\text{OAc})_2]$ or the copper(I) thiophene-2-carboxylate precursor $[\text{Cu}(\text{TC})]$ was beneficial to the efficiency (+28% yield) and enantioselectivity (+13% *ee*) of the reaction, for one specific (non-functionalized) chiral imidazolium salt. Subsequently, the authors pointed out that the results could be improved by using isolated silver(I) NHC complexes instead of the NHC precursors. In particular, complex **3.1** afforded (*S*)-3-ethylcyclohexanone in 99% yield and 69% *ee* (Scheme 3-1). The *ee* value obtained with **3.1** is slightly higher (69 vs. 58% *ee*) than that obtained with its non-functionalized analog (*N*-benzyl substituent), and this represents the first report of the use of an *O,C*_{NHC} ligand in ACA. The feasibility of the reaction towards various substrates was investigated and complex **3.1** was found to be one of the best performing catalysts for the ACA of ZnEt_2 to cyclohept-2-enone (100% yield, 88% *ee*, Scheme 3-1).



Scheme 3-1. Copper-catalyzed asymmetric conjugate addition of diethylzinc to cyclohex- and cyclohept-2-enone using NHC-Ag complexes [89].

Arnold *and coll.* developed an efficient route to unprecedented chiral alkoxide-functionalized NHC copper(II) complexes (Chart 3-1), that readily mediate the ACA of ZnEt_2 to cyclohex-2-enone (toluene, -30°C , 2 h, 60-100% conv.). Complex **3.2** performed the best, leading to 3-ethylcyclohexanone with 51% *ee* (*S*-configuration) [90].

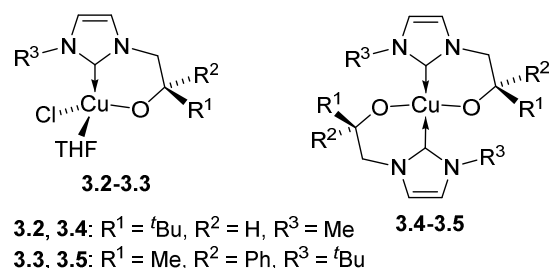


Chart 3-1. Chiral copper(II) alkoxy-*N*-heterocyclic carbene complexes [90].

Following these pioneering work, Mauduit *and coll.* developed a large library of *N*-alkoxy-functionalized imidazolium salts, the chiral *N*-alkoxy group originating from the use of enantiopure

amino-alcohols in the four-step synthesis (**3.6-3.26**, 33-83% overall yield, Chart 3-2) [91,92]. The library was extended a few years later, following the same strategy, by similar chiral *O,C_{NHC}* pro-ligands with different, an generally bulkier, non-functionalized *N*-substituents (**3.30-3.37**, 34-62% overall yield, Chart 3-2) and/or benzimidazolium rings (**3.38-3.42**, 17-38% overall yield, Chart 3-2) instead of imidazolinium ones [93]. More recently, the authors reported a one-pot multicomponent synthesis to access the chiral pro-ligands **3.45-3.51** (15-59% yield, Chart 3-2) from the corresponding enantiopure amino alcohols or amino acids [94]. The *O,C_{NHC}* precursors **3.6-3.44** were evaluated in the copper-catalyzed ACA of ZnEt₂ to cyclohex-2-enone and the scope of the reaction could be extended to various cyclic enones, to other Michael acceptors (5 examples, >99% conv., 5-37% *ee*) and to different organozinc reagents for the best performing imidazolinium salt **3.6** within the **3.6-3.26** series (Scheme 3-2). Use of the analogous protected pro-ligands **3.27-3.29** led to a loss of enantioselectivity, especially for the bulkier groups (*ees*: TBDMS-**3.27** 24%, Ts-**3.27** 21%, Ms-**3.29** 80% *vs.* **3.6** 86%) [91,95]. Noteworthy, pro-ligand **3.26**, the opposite enantiomer of **3.6**, afforded the alkylated product with identical *ee*, however with opposite configuration. The introduction of bulkier groups in **3.30**, **3.32** and **3.34** led to slightly improved enantioselectivity (89-92% *ee*), while all other *O,C_{NHC}* precursors from the series **3.28-3.44** led to lower *ees* [93]. In their recent report Baslé, Mauduit *and coll.* compared the unsaturated imidazolium salt **3.45** to its saturated imidazolinium analog **3.6**; the two ligands performed similarly for the Cu-ACA of ZnEt₂ to 3-methyl-2-cyclohexen-1-one (84-85% yield, 98-99% *ee*, 0.5 mol% Cu, 1 mol% Lig., 2.5 mol% *n*BuLi, EtOAc, RT, 16 h). Comparable results were also obtained with **3.46** and **3.47**. However, the “amino acids versions” of these pro-ligands (**3.48-3.50**) were much less efficient (10-43% yield, 66-82% *ee*) [94].

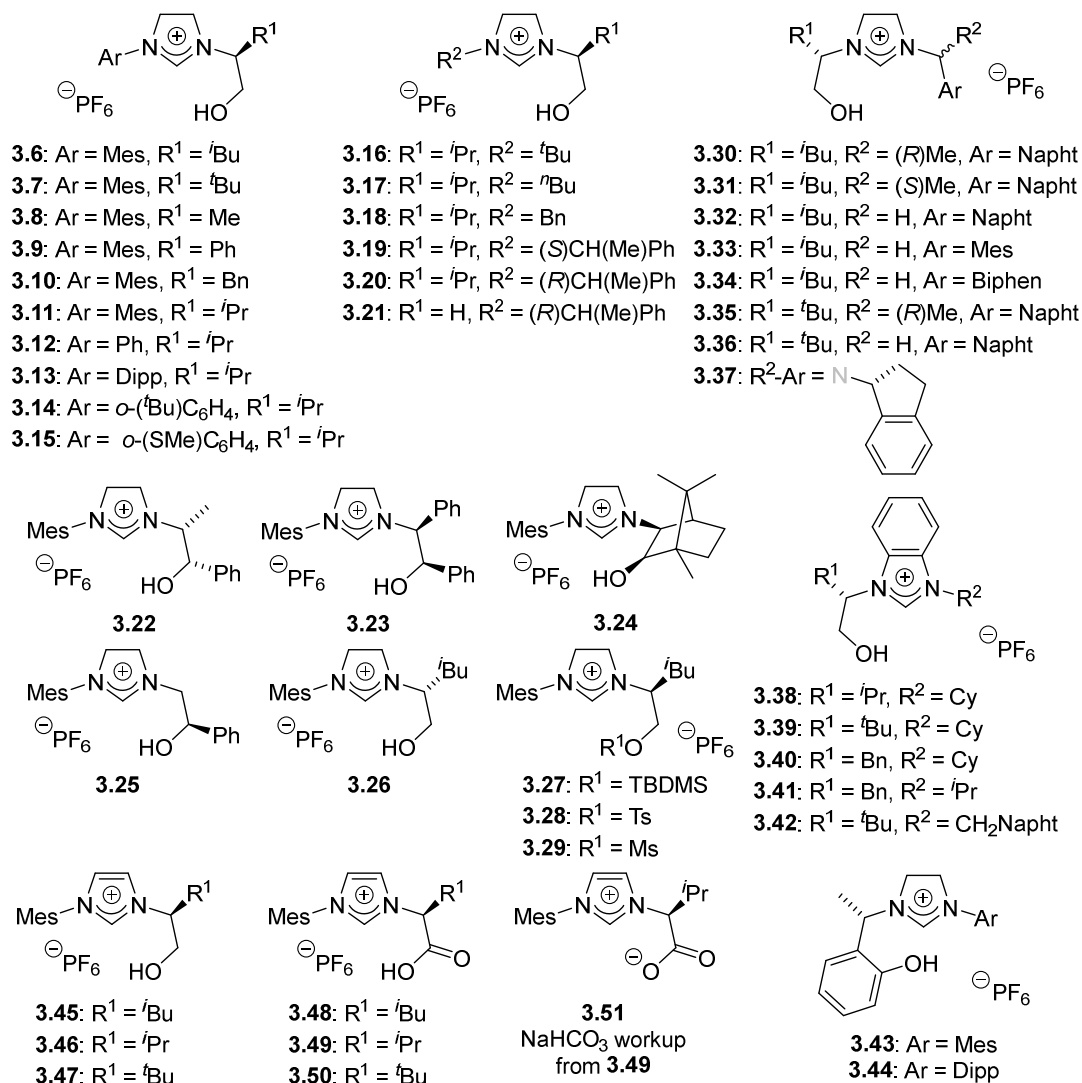
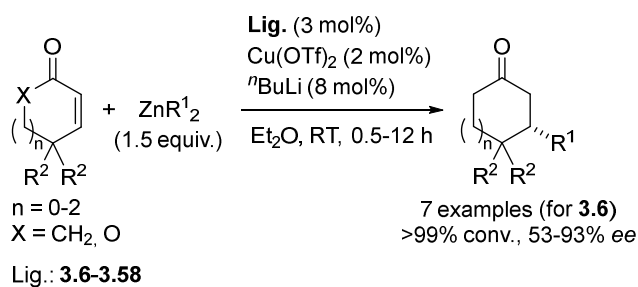


Chart 3-2. Hydroxyl-, carboxyl- and ether-(benz)imidazol(in)ium salts with chiral *N*-side arm developed by Mauduit *and coll.* for the copper-catalyzed asymmetric conjugate addition of organozinc reagents [91-95].

Crévisy, Mauduit *and coll.* reported the synthesis of imidazolium salts **3.52-3.57** (14-52% overall yields, Chart 3-3), starting from amino-acid derivatives, which are closely related to the best **3.6** and **3.45** pro-ligands, except for having the chiral element located on the ligand backbone [93]. The best results in the Cu-ACA of ZnEt₂ to cyclohex-2-enone were obtained with **3.55** bearing the bulkiest ^tBu group (full conv., 66% *ee*), although still inferior to those of **3.6** under similar conditions (see above and Scheme 3-2). The presence of ^tBu groups on the non-functionalized *N*-aryl group in **3.56** or in close proximity of the *O*-donor in **3.58** was detrimental for the enantioselectivity of the process (41 and 20% *ee*, respectively) [93].



Scheme 3-2. Scope of the Cu-ACA of ZnEt₂ using *O*,C_{NHC} precursors [91-93].

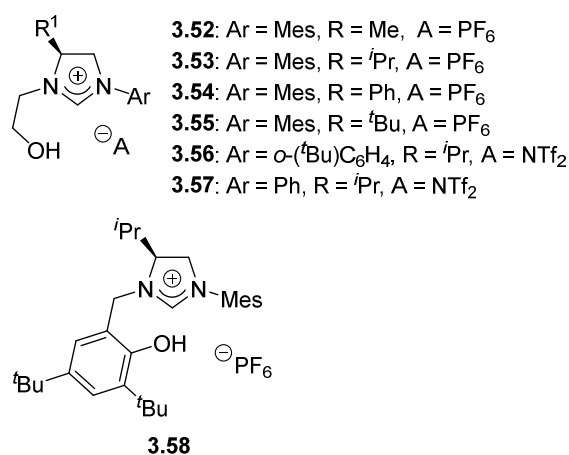


Chart 3-3. Hydroxyl-imidazolinium salts with chiral backbone developed by Mauduit *and coll.* for the copper-catalyzed asymmetric conjugate addition of organozinc reagents [93].

Li *and coll.* developed another series of C₂-symmetric chiral NHC precursors containing two hydroxyl or ether groups, readily accessible in two or three steps from commercially available enantiopure β-amino alcohols (Chart 3-4) [96]. A few of these imidazolinium salts had in fact already been reported by Wilhelm and coworkers (see Section 3.1.4). The influence of several reaction parameters, such as copper source, base, solvent and temperature on the Cu-ACA of ZnEt₂ to cyclohex-2-enone were studied, but these systems never outperformed those of Mauduit *and coll.* (best run: **3.181**, 95% conv., 76% ee, see Chart 3-10 for the structure of **3.181**). The reaction also worked on cyclohex-2-enone (3 mol% **3.181**, 4 mol% [Cu(OTf)₂], 18 mol% KHMDS, Et₂O, -30 °C, 2 h), affording the corresponding adduct with 65% ee (96% conv.).

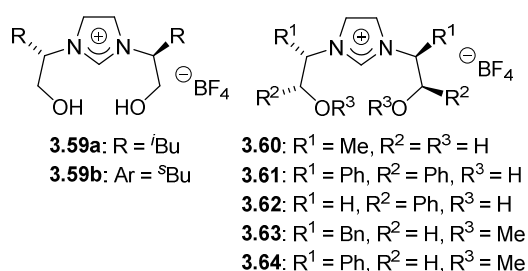
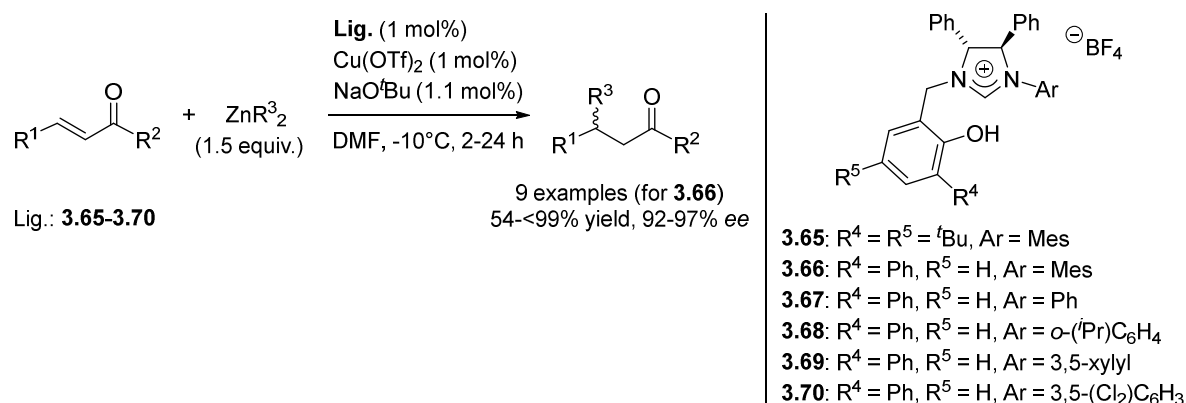


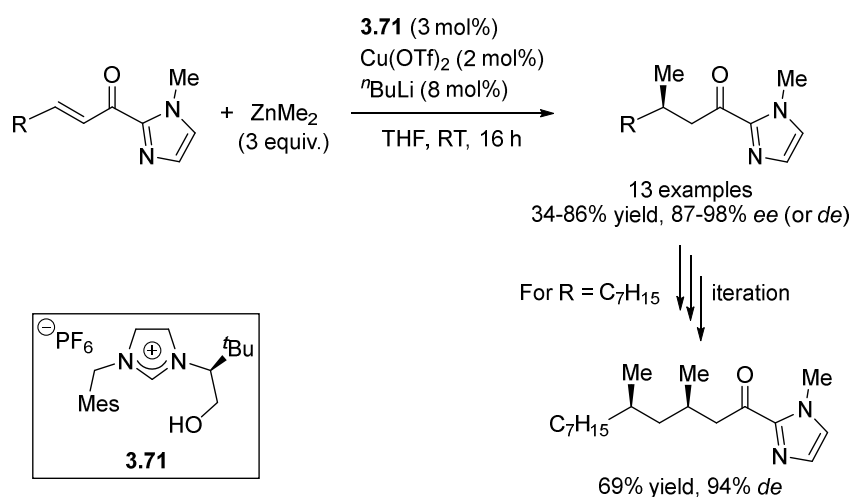
Chart 3-4. C_2 -symmetric bis-hydroxyl and bis-ether chiral imidazolium salts applied to the Cu-ACA of $ZnEt_2$ to cyclohex- or cyclopent-2-enone [96].

Uchida and Katsuki reported the synthesis of a series of imidazolium salts (**3.65-3.70**) containing a chiral backbone and functionalized on one nitrogen atom by an *o*-hydroxybenzyl derived substituent and applied them to the Cu-ACA of $ZnEt_2$ to chalcone (Scheme 3-3) [97]. Within the series of NHC precursors studied, **3.66** performed the best, reaching 99% yield of the desired product with 97% *ee* (see Scheme 3-3 for reaction conditions). Several substitution patterns were investigated for the acyclic enone derivatives, including substituted aryls and alkyl groups on R^1 , as well as diverse dialkylzinc reagents. In all cases, the products were formed with average to excellent yields and very high enantioselectivity. The sole limitation in term of enantioselectivity was the introduction of an alkyl group as R^2 substituent (2% *ee*). A test reaction with cyclohex-2-enone as substrate was performed, leading to very poor selectivity (Fig. **3.70**, 54% yield, 3% *ee*) like for the related imidazolium **3.58** (see above).



Scheme 3-3. Cu-ACA of $ZnEt_2$ to acyclic enones [97].

Recently, Mauduit, Campagne *and coll.* reported the efficient insertion of methyl groups on α,β -unsaturated acyl-*N*-methylimidazole derivatives *via* Cu-ACA (Scheme 3-4), with high yields and enantioselectivities, using chiral hydroxyl-functionalized imidazolium salts (**3.7**, **3.33** and **3.71**) [98]. Pro-ligand **3.71**, initially designed for the Cu-ACA of Grignard reagents (see below and [99]), led to the best results and was applied to a wide range of substrates, including a polyenic substrate that was transformed with excellent regio-selectivity (1,4:1,6 ratio = 96/4). Moreover, the 1,4-ACA products can be converted into the corresponding aldehydes (esters or ketones) and subsequently used in an iterative process, leading to 1,3-desoxypropionate skeletons (Scheme 3-4).



Scheme 3-4. Cu-ACA of ZnMe₂ to α,β -unsaturated acyl-*N*-methylimidazole and iterative process [98].

Imidazolium salt **3.45** (3 mol%), and its saturated analog **3.6**, in combination with [Cu(OTf)₂] (2 mol%) and ⁿBuLi (8 mol%) were the first reported examples of *O,C*_{NHC} to mediate the Cu-ACA of dialkylzinc reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated six-membered cyclic dienones. Both pro-ligands performed similarly and afforded exclusively the 1,6-adducts in moderate to good yields (44-76%) and enantioselectivities (93-95.5% *ee*) [94].

Fiksdahl and coworkers reported the synthesis of chiral symmetrical and unsymmetrical imidazolium salts derived from the L-proline and L-phenylalanine amino acids (Chart 3-5) [100]. A few of these NHC pro-ligands were evaluated in the Cu-catalyzed ACA of ZnEt₂ to cyclohexen-2-one. Although complete conversion was observed in nearly all cases, only low to moderate *ee* values (8.5-57%) were obtained.

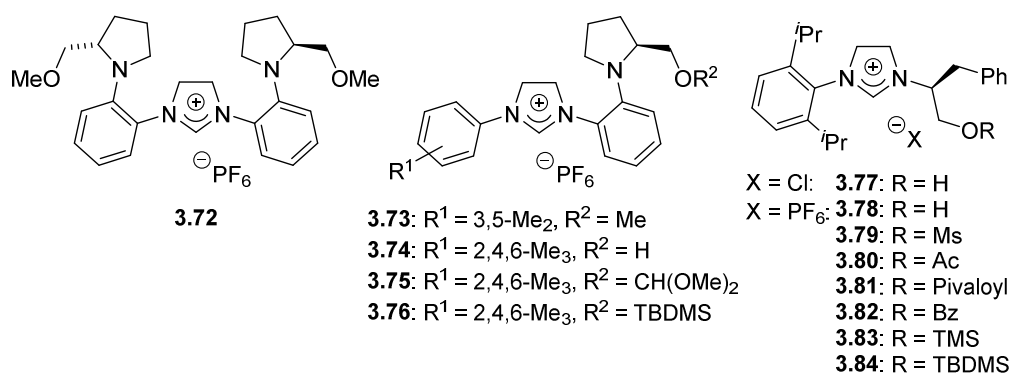
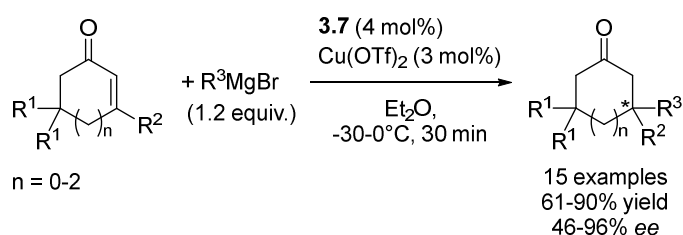


Chart 3-5. Chiral *O*-functionalized NHC precursors developed by Fiksdahl and coworkers [100].

With Grignard reagents. In 2006, Mauduit, Alexakis and coll. reported the first use of chiral NHC pro-ligands for the Cu-ACA of Grignard reagents to cyclic enones. *O*-functionalized imidazolium salts incorporating an asymmetric carbon on the *N*-side arm exhibited the best performances (**3.6-3.11**, Chart

1-1) [101]. After optimization of the reaction conditions with 3-methylcyclohexenone as substrate and EtMgBr as Grignard reagent, the authors highlighted that the enantioselectivity increased with the substituent size on the chiral center, **3.7** (^tBu-substituent) giving the (*R*)-3-ethyl-3-methylcyclohexanone product in 99% yield with 81% *ee*. The scope of the reaction could be extended to various Grignard reagents; primary and secondary alkyls worked well, with up to 96% *ee* (^tBu), whereas PhMgBr gave lower yield and *ee* (61 and 66%, respectively) and ^tBuMgBr was inactive. The system could be applied to a variety of 5-, 6- and 7-membered cyclic enones and afforded the corresponding products in good yields and with moderate to good *ees* (Scheme 3-5). Later, the authors compared the performances of **3.7** with imidazolium salts incorporating other chiral substituents, namely **3.23**, **3.24**, **3.44**, **3.58**, **3.99-3.101** but none of them outperformed **3.7**, leading to no or poor enantioselectivity in all cases (0-25% *ee*) and nearly no regioselectivity for **3.24** and **3.58** (50:50 of 1,2/1,4-adduct) [102]. In this study, the authors also successfully extended the scope of the reaction, especially to cyclic enones substituted by various aromatic rings (*R*² position in Scheme 3-5) and several aromatic Grignard reagents ([Cu(OAc)•H₂O] as copper source).



Scheme 3-5. Cu-ACA of Grignard reagents to 5-, 6- and 7-membered cyclic enones [101].

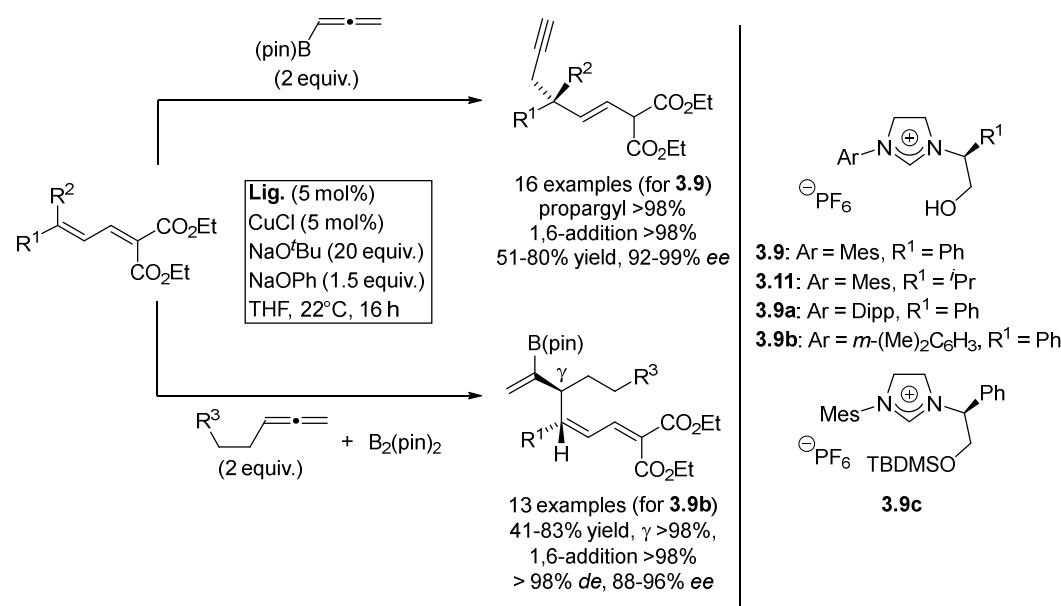
Following their initial work, Alexakis *and coll.* further developed the family of hydroxyl-imidazolium salts, with chiral *N*-side arm (**3.85-3.98**) for the Cu-ACA of Grignard reagents to cycloenones, as depicted in Chart 3-6 [99]. Pro-ligands **3.91-3.92** were initially developed by Crévisy, Mauduit *and coll.* for the Cu-AAA of allylic phosphates with organozinc reagents (see Section 3.1.2) [103]. Along this study, the authors could highlight that the bulkiness of the non-functionalized *N*-substituent plays a crucial role, because NHC pro-ligands **3.31**, **3.88-3.90** and **3.94-3.96**, bearing bulky groups, gave rise to high enantioselectivities (90-93% *ee*), but too sterically demanding substituents (**3.72**, **3.92**, **3.98**) led to lower *ee* values (26-40% *ee*). However, the former pro-ligands led to incomplete conversions and to non-negligible amounts of the 1,2-adduct (up to 14%). The diastereomeric NHC precursors **3.30** and **3.31** (Chart 3-2) afforded the same enantiomer product, indicating that only the chiral chelating moiety is responsible for the product absolute configuration. Therefore, there is no need to introduce two chiral groups in the ligand scaffold. Finally, the *N*-CH₂-Mes derivatives (**3.33**, **3.71**, **3.86**, **3.87**) appeared to give the best results for the benchmark reaction (3-methylcyclohexenone and EtMgBr substrates), affording solely the 1,4-product in good yields with high enantioselectivity (88-

similar non-functionalized analogs (42% vs. 9-17% *ee*), but this value remained modest in comparison to the systems based on *O,C*_{NHC} ligands in which the chiral center is located on the *O*-chelate side arm (e.g. **3.7**, **3.33**, Chart 3-2 or **3.89**, **3.96**, Chart 3-6). Within the *C*₂-symmetric pro-ligands, **3.101** and its non-functionalized analog (incorporating *N*-1-naphtyl groups) performed the best, with similar efficiencies in the alkylation of 3-methylcyclohexenone with several alkylmagnesium reagents (Scheme 3-5). However, the *ee* value obtained for the more bulky ⁱPrMgBr reagent drastically increased with the introduction of the *ortho*-methoxy groups (70% for **3.101** vs. 39% for the non-functionalized analog), the latter preventing the “opening” of the chiral reaction pocket by chelation. The *ee* values obtained for the addition of the ⁱPr- and EtMgBr nucleophile to 3-methylcyclohexenone with pro-ligand **3.101** (67-70% *ee*) were slightly lower than those obtained with the very similar imidazolium salt **3.103** (71-80% *ee*) developed by Tomioka *and coll.* [104].

Further studies were devoted to the copper-catalyzed enantioselective 1,4-, 1,6- or sequential 1,6/1,4-conjugate addition of Grignard reagents on polyconjugated cyclic enones or enynones, with various chiral ligands, including *O,C*_{NHC} [105,106,107,108]. These works were well summarized and discussed in a recent review by Mauduit *and coll.* [87], and therefore they will not be detailed here.

With other nucleophiles. Very recently, Hoveyda *and coll.* reported the Cu-catalyzed enantioselective 1,6-conjugate additions of propargyl and 2-boryl-substituted allyl groups to acyclic dienoates with high regio- and enantioselectivity [109]. Initially, the authors investigated the reaction between allenyl-B(pin), diethyl cinnamylidenemalonate and NaOPh in the presence of a catalytic mixture composed of a chiral ligand and CuCl (1:1, 5 mol%) (Scheme 3-6, top). While chiral phosphines gave unsatisfactory results (complicated mixture of products and/or low *ees*), NHC precursors **3.9**, **3.11** and **3.9a-3.9c** afforded exclusively the awaited 1,6-propargyl adduct with variable *ees*. While pro-ligand **3.9** delivered the product with 74% yield and 97.5% *ee*, an increase of steric bulk on the *N*-aryl group in **3.9a** (Dipp vs. Mes) led to a significant decrease in enantioselectivity (67.5% *ee*). The very similar pro-ligands **3.9b** and **3.11** led to only slightly lower *ee* values than **3.9** (92 and 91% *ee*, respectively). These observations again highlight how subtle changes in the ligand scaffold strongly affect the enantioselectivity in such processes. The beneficial effect of the chelating hydroxyl group was further emphasized by the nearly racemic formation of the 1,6-adduct with the silyl-protected analog **3.9c** (Scheme 3-6). The scope of the reaction was explored with **3.9**, and the protocol was found tolerant to various aryl groups, whether containing electron-donating or electron-withdrawing groups, heterocycles, alkenyl and linear or branched aliphatic groups. All-carbon quaternary centers were also readily formed and with remarkable group-, site- and enantioselectivity (*R*² = Me, 3 examples, 72-80% yield, 95% *ee*, in Scheme 3-6, top). The authors further applied their catalytic system to the multicomponent mixture composed of a dienoate, a mono-substituted allene and B₂(pin)₂, expecting the enantioselective 1,6- (to dienoate), and γ -addition (to the allene) to form 2-B(pin)-substituted allyl products (Scheme 3-6, bottom). For this reaction, the enantioselectivity decreased with increasing the

bulkiness of the *N*-aryl group (*i.e.* from *m*-(Me)₂C₆H₃ to Mes and Dipp) and the silyl-protected derivative (**3.9c**) led again to nearly racemic mixture. However, in all cases exceptional site- and diastereoselectivity was observed. The scope of the reaction was then explored with the best **3.9b** NHC precursor. This system allows diene functionalization with various aryl-, heteroaryl- and alkyl-substituents, while the allenes containing alkene, alkyne or Weinreb amide were also tolerated (Scheme 3-6, bottom).



Scheme 3-6. Cu-catalyzed enantioselective 1,6-conjugate additions of propargyl and 2-boryl-substituted allyl groups to acyclic dienoates [109].

Organoboronic esters have been shown over the past decade to be a viable alternative to highly reactive organometallic reagents (Grignard, organozinc, organoaluminum reagents) as nucleophiles in NHC-copper-catalyzed enantioselective conjugate addition reactions. The use of chiral *O*-functionalized imidazolium salts (**3.91**, **3.107-3.108**, Chart 3-7), in combination with a copper(I) salt and a base, allowed the efficient (up to 93% yield) 1,4-addition of organoboronic acids to various aryl-, heteroaryl-, and alkenyl-substituted methylidenecyanoacetate substrates with good to excellent enantioselectivity (up to 95% *ee*) [110]. Very recently, similar systems have been applied to the copper-catalyzed asymmetric conjugate addition of alkenyl-B(pin) reagents to α,β -unsaturated substrates with a good tolerance to many functional groups, affording the desired compounds in good yields and enantioselectivities (up to 98% yield and 99.5% *ee*) [111] (imidazolium salts used were reported in [91], Chart 3-1 and Scheme 3-6).

The BF₄ salt of imidazolium **3.13** (Chart 3-2) was evaluated, as part of a larger study using chiral imidazoli(ni)um salts without additional donor groups, in the Cu-catalyzed ACA of an alkylborane to the *trans*-cinnamyl 1-methylimidazol-2-yl ketone, but led to modest results (24% yield, 30% *ee*) [112].

The performances of the bis-methoxy functionalized salt **3.109** will be discussed along with its phosphate analogue in Section 3.3.1 (Scheme 3-25).

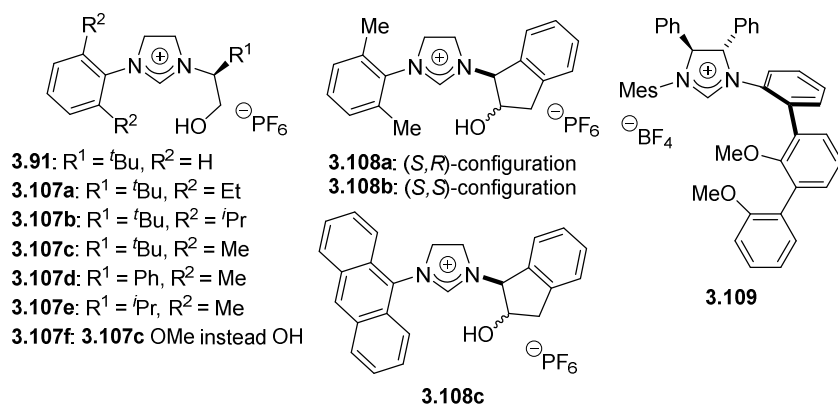


Chart 3-7. Chiral *O*-functionalized imidazolium salts used in copper-catalyzed ACA of organoboronic acids [110].

The group of Hoveyda has been very active in the fields of Cu-catalyzed asymmetric conjugate addition (ACA) or (allylic) addition (AAA) reactions (see Section 3.1.2 for the latter), using the chiral bidentate *O*-functionalized imidazolium salt **3.110** or its dimeric silver(I) counter-part **3.111** in combination with a copper precursor, or (less frequently) the isolated CuCl complex **3.112** (Chart 3-8). However, in most cases these catalysts were less efficient than the sulfoxide-functionalized NHC system developed in the same group, and therefore the results will be discussed in Section 3.3. Nevertheless, pioneering publications reporting the synthesis of compounds **3.110-3.112** and their initial evaluation in Cu-AAA and Cu-ACA are cited here [113,114].

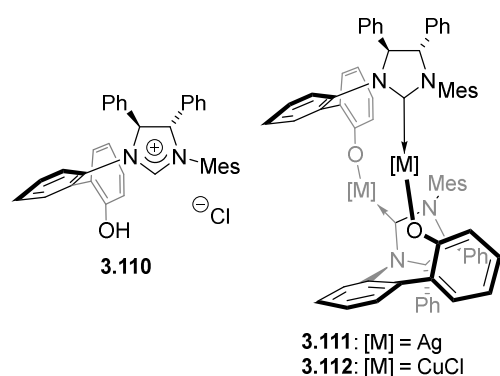
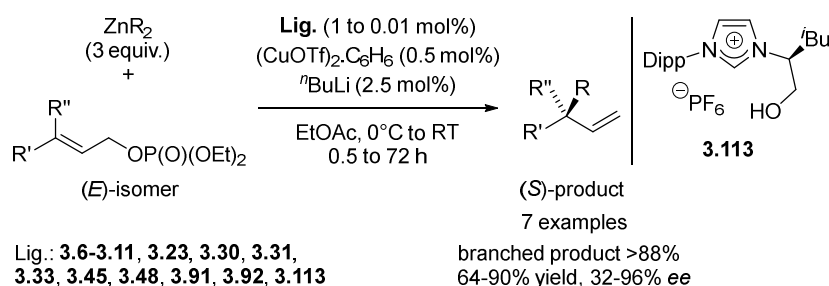


Chart 3-8. Chiral imidazolium salt (**3.110**) and its related metal complexes (**3.111-3.112**) incorporating a biphenol moiety as additional *O*-function developed by Hoveyda *and coll.* [113,114].

3.1.2. Copper-catalyzed asymmetric allylic alkylation (AAA) / substitution reactions

The group of Mauduit demonstrated the potential of their chiral bidentate hydroxyalkyl NHC precursors in the Cu-catalyzed asymmetric allylic alkylation (Cu-AAA) to form all-carbon quaternary centers (Scheme 3-7) [94,103,115]. The catalysts, which were generated *in-situ* by deprotonation of the imidazolium salts using ⁿBuLi in the presence of copper(I) triflate, efficiently promoted the reaction between dialkylzinc reagents and allylphosphate substrates to form the desired products with very good regioselectivity (S_N2' product vs. linear product) and in most cases high enantioselectivities (Scheme 3-7).

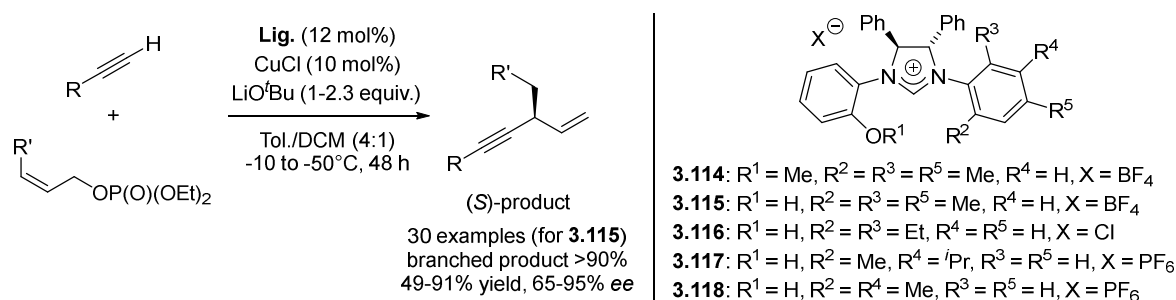


Scheme 3-7. Cu-AAA to form all-carbon quaternary centers [94,103,115].

Recently, Xiao, Fu and coworkers reported the copper-catalyzed S_N2'-selective and asymmetric substitution of an allylic phosphate substrate with diborylmethane (CH₂(BX₂)₂ with X = pinacol or pinanediol) reagents, using the hydroxyl-functionalized imidazolium salt **3.107e** (see Chart 3-7), leading to the corresponding chiral alcohol (after work-up) in good yields (76-85%) and moderate enantioselectivities (64% ee, with the bulkier diborylalkane) [116].

Over the last few years, Ohmiya, Sawamura *and coll.* demonstrated that a combination of a chiral O,C_{NHC} ligand (*in situ* generated), a copper(I) precursor and a base readily mediates various enantioselective transformations [117-120]. Thus, the association of CuCl, pro-ligands **3.114-3.118** and LiO^tBu, catalyzes the regio- and enantioselective allylic alkylation of terminal alkynes with (*Z*)-allylic substrate (Scheme 3-8) [117]. The initial catalysts screening (toluene, 40°C), with triisopropylsilylacetylene and the (*Z*)-5-phenyl-2-pentenol phosphate derivative (R' = (CH₂)₂Ph, Scheme 3-8) as reagents, revealed that **3.115** performed the best, affording the corresponding chiral enynes ((*S*)-product) in 96% yield, with >99% selectivity for the branched product (*vs.* linear), and 65% ee. Modification of the non-functionalized *N*-substituent on the NHC ligand in **3.116-3.118** did not affect the product yield and branched/linear (b/l) ratio, but the ee drastically dropped by removing one *ortho* substituent on the aryl ring in **3.117** and **3.118**. In contrast, no improvement was observed by changing the *o*-Me substituents in **3.115** by *o*-Et in **3.116**. Both the nature of the chirality on the NHC ligand and the chelating group affected the catalytic process. Indeed, pro-ligand **3.9** (see Chart 3-2), in which the chiral element is located on one *N*-substituent (*vs.* on the NHC backbone in **3.114-3.118**), exhibited the

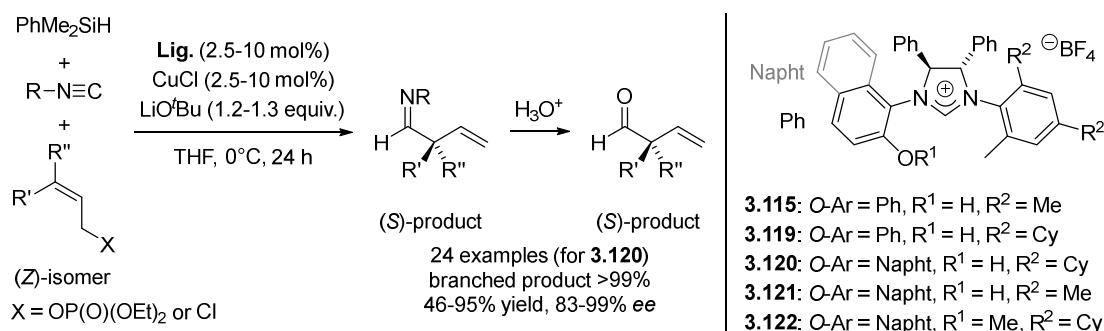
lowest enantioselectivity (7% *ee*), and pro-ligand **3.114**, incorporating an *o*-OMe group in place of an *o*-OH group in **3.116-3.118**, displayed a lower regioselectivity (b/l 83:17). The beneficial effect of the chelating phenol moiety was clearly highlighted by the lower yield, regio- and enantioselectivity when using a pro-ligand closely related to **3.115** (chiral backbone) but incorporating two *N*-mesityl groups instead of one mesityl and one hydroxyphenyl. Various terminal alkynes, including silyl, aliphatic and aromatic alkynes could be used. Phosphates with variable steric demands at the γ position and diverse functional groups (silyl ether, pivalate, THP ether, *p*-toluenesulfonate, benzoate moiety with various *para*-substituents...) were compatible with the reported method. A reaction pathway involving 1,3-allylic migration of Cu in a ($[\sigma+\pi]$ -allyl)copper(III) species was proposed.



Scheme 3-8. Copper-catalyzed regio- and enantioselective allylic alkylation of terminal alkynes with (*Z*)-allylic phosphates [117].

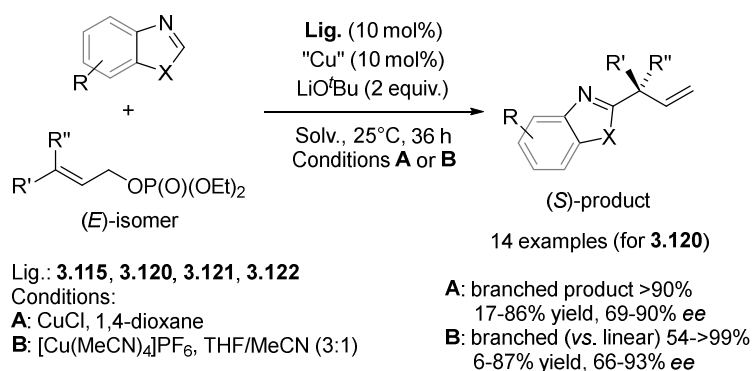
The three-component (isocyanides, hydrosilanes and γ,γ -disubstituted allylic phosphates/chlorides) coupling to form α -quaternary aldehydes ((*S*)-product), via α -quaternary *N*-cyclohexylformimide intermediates, occurred efficiently in the presence of a LiO^tBu and a catalytic amount of CuCl and the chiral pro-ligands **3.115**, **3.119-3.121** (10 mol% each, Scheme 3-9) [118]. The γ -regioselectivity, affording the γ,γ -disubstituted allylic aldehyde over the achiral linear product, was exclusive (>99%). The initial catalyst screening (THF, 25 °C), using dimethylphenylsilane, cyclohexyl isocyanide and (*Z*)-3-phenyl-2-buten-1-ol phosphate derivative (R' = Ph, R'' = Me, Scheme 3-9) as reagents, clearly highlighted the beneficial effect of a *N*-phenol or *N*-naphthol group on the NHC ligand and bulky *ortho*-substituents on the other *N*-aryl group, because **3.119-3.120** gave the best results with 90-93% yield and 81-96% *ee*. The less sterically congested analogues **3.115** and **3.121**, with R² = Me, afforded lower *ee* values (32-72%). Other chiral NHC precursors with a *N*-(*o*-OMe)naphthyl group (**3.122**), without additional donor or with the chiral information placed on a flexible *N*-substituent (**3.9**, see Chart 3-2), were found poorly active and selective or completely inactive. The scope of the reaction was extended, with the most efficient chiral imidazolium **3.120**, to other aliphatic and aromatic isocyanides and to a large variety of allylic phosphates with alkyl and aryl (*m*- or *p*-functionalized) substituents on the γ -position. The reaction was applicable to allylic phosphates with two alkyl substituents (R' and R''), albeit with decreased enantioselectivity (83-84% *ee*). Also, allylic chlorides could be used in place of

the allylic phosphates. However, both yield and *ee* were lowered (46-60% and 84-88%, respectively). Interestingly, reaction of the (*E*)-isomer of the allylic phosphate reagent, instead of (*Z*)-isomer, under optimized conditions led to the antipode (*R*)-product, however in lower yield (86% *vs.* 94%) and *ee* (66% *vs.* 99%) than those of the (*S*)-product.



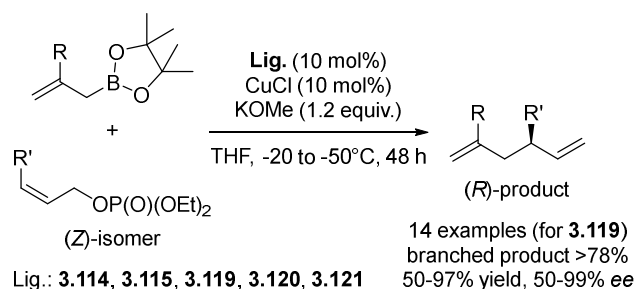
Scheme 3-9. Copper-catalyzed regio- and enantioselective coupling of isocyanides, hydrosilanes and γ,γ -disubstituted allylic phosphates/chlorides [118].

Catalyst screening for the regio- and enantioselective allylic alkylation of benzothiazole with the (*E*)-allylic phosphate derivative to form the chiral (*S*)-functionalized azole product ($\text{R}' = (\text{CH}_2)_2\text{Ph}$, $\text{R}'' = \text{Me}$, Scheme 3-10) revealed a similar trend as for the aforementioned coupling of isocyanides, hydrosilanes and allylic phosphates, with the most sterically encumbered NHC precursor **3.120** (in combination of CuCl and LiO^tBu) achieving the reaction with the best selectivity (>99% branched product and 88% *ee*) [119]. Again, the OMe-functionalized analog (**3.122**) and non-functionalized NHC precursors exhibited poor or no activity. The less sterically congested imidazolium salt **3.121** afforded a slightly higher yield (77% *vs.* 60%) while the *ee* value dropped markedly from 88% to 68%, highlighting how subtle changes on the NHC ligand can strongly affect both activity and selectivity of the catalytic system. The studied reaction can be performed either using CuCl in 1,4-dioxane or $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ in THF/MeCN (3:1), with the former conditions generally leading to higher yields, while the latter gave better *ees*. Various substitution patterns on the allylic phosphate reagent were compatible with the reaction, including bulkier aliphatic R' and R'' groups, alkenes or silyl ethers. Functionalization on the benzothiazole ring and (benz)oxazole derivatives were also tolerated, however the specific 5-chlorobenzoxazole and 4-phenyloxazole led respectively to low yield and moderate (regio- and enantio-)selectivity.



Scheme 3-10. Copper-catalyzed regio- and enantioselective allylic alkylation of azoles with (*E*)-allylic phosphates [119].

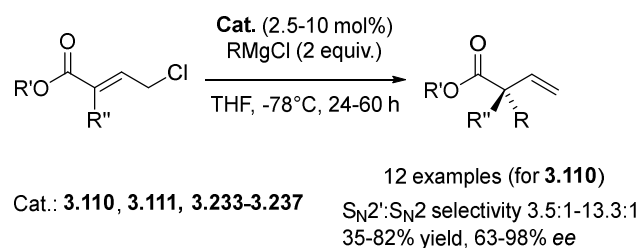
The beneficial effect of an *N*-phenol or *N*-naphthol additional donor on a chiral NHC pro-ligand was also well illustrated in the allyl-allyl coupling between allylic boronates and phosphates [120]. Thus, while a combination of the phenoxy-functionalized imidazolium salt **3.119**, CuCl and KOMe readily mediates the transformation of allylboronic acid pinacol ester and the (*Z*)-5-phenyl-2-penten-1-ol phosphate derivative ($R' = (\text{CH}_2)_2\text{Ph}$, Scheme 3-11) to the corresponding branched γ -substituted ((*R*), $\gamma/\alpha >99:1$) 1,5-diene product with good yield (83%) and excellent enantioselectivity (92% *ee*), non-functionalized imidazolium salts gave very poor yields or *ees*. Notably, the NHC precursor **3.114**, with an ether-group in place of the alcohol-group in **3.119**, exhibited very low activity (10% yield) and moderate enantioselectivity, highlighting the crucial role of the OH group in the reaction pathway. Reduced steric hindrance on the *N*-aryl group in **3.115** or **3.121** led in both cases to reduced activity and selectivity in comparison with **3.119** and the switch from an *N*-phenol (**3.119**) to an *N*-naphthol (**3.120**) substituent was not beneficial to the catalytic activity or enantioselectivity. The scope of the reaction was therefore evaluated with **3.119** and the authors could point out that by changing the phosphate leaving group by a halogen atom (Cl or Br) led to a significant drop of both regio- and enantioselectivity. The nature of the base also impacted the reaction, because replacing KOMe by NaOMe or the more bulky KO^tBu reduced both regio- and enantioselectivity, while LiOMe resulted in no reaction. This was attributed to a catalyst deactivation by the soluble LiCl or LiOP(O)(OEt)₂ salts. Concerning the allylic phosphate substrate, various aliphatic γ -substituents (octyl, benzyl, cyclohexyl) were tolerated and led to good *ee* values (80-86%). Furthermore, various functional groups such as THP-, benzyl- or silyl-ethers, pivalate, *p*-toluenesulfonate, and a series of *para*-substituted benzoates were tolerated and afforded the corresponding 1,5-diene products with good yields (61-87%) and high enantioselectivities (85-97% *ee*). While the β -substitution of the allylboronate substrate with methyl or ethyl groups did not affect either regio- or enantioselectivity, introduction of bulkier groups such as *n*-hexyl, benzyl or phenyl led to moderate regioselectivity (chiral branched vs. achiral linear product) although the *ee* values remained high (> 80%). In a recent report, the same authors further examined the effect of the different reaction parameters and extended the scope of the allylic phosphate and allylboronate substrates [121].



Scheme 3-11. Copper-catalyzed regio- and enantioselective allyl-allyl coupling between allylic boronates and phosphates [120].

3.1.3. Copper-free asymmetric allylic alkylation (AAA)

Hoveyda *and coll.* first reported the possible copper-free asymmetric allylic alkylation (AAA) in 2006 using Grignard reagents [122]. In their initial studies, the authors compared the chiral *N*-biphenol (**3.110**, Chart 3-8) and *N*-binol-substituted imidazolium salts (**3.233-3.237**, see Section 3.2) and the silver(I) complex (**3.111**, Chart 3-8) towards α -alkyl- γ -chloro- α,β -unsaturated esters and i PrMgCl reagents. The imidazolium salt **3.110** was found to have the best performance (Scheme 3-12). The scope of the reaction could therefore be extended for **3.110** to various alkylmagnesium chlorides and different α -alkyl (R'') groups, yielding regioselectivities (in favor of S_N2' product) in the 3.5:1-13.3:1 range and generally very good enantioselectivities (*ees* up to 98%) (Scheme 3-12). The crucial role of the pendant OH group was demonstrated by the inefficiency of the -OMe and -H analogues (<2% AAA) of **3.110**.



Scheme 3-12. Cu-free enantioselective addition to α -alkyl- γ -chloro- α,β -unsaturated esters [122].

Alexakis and coworkers further investigated the transition metal-free AAA on allyl bromide substrates (*e.g.* cinnamyl bromide), with various Grignard reagents and using a large library of NHC precursors incorporating an hydroxyl (or ether) function (Chart 3-9) [123,124,125]. The formation of stereogenic quaternary centers was highly regioselective for both aromatic and aliphatic derivatives and the products were obtained with good to excellent enantioselectivities (*ee* up to 96%). Several combination of *N*-substituents (non-functionalized moiety) and substitution patterns on the *O*-containing *N'*-group were tested (see Chart 3-9) and among them **3.132**, **3.135** and **3.136** led to the best results (also

combined to the “easiest” synthetic accessibility). Mechanistic studies, using NMR spectroscopy, allowed the authors to conclude that the catalytically active species is a magnesium complex supported by a chelating monoanionic *O*-C_{NHC} ligand.

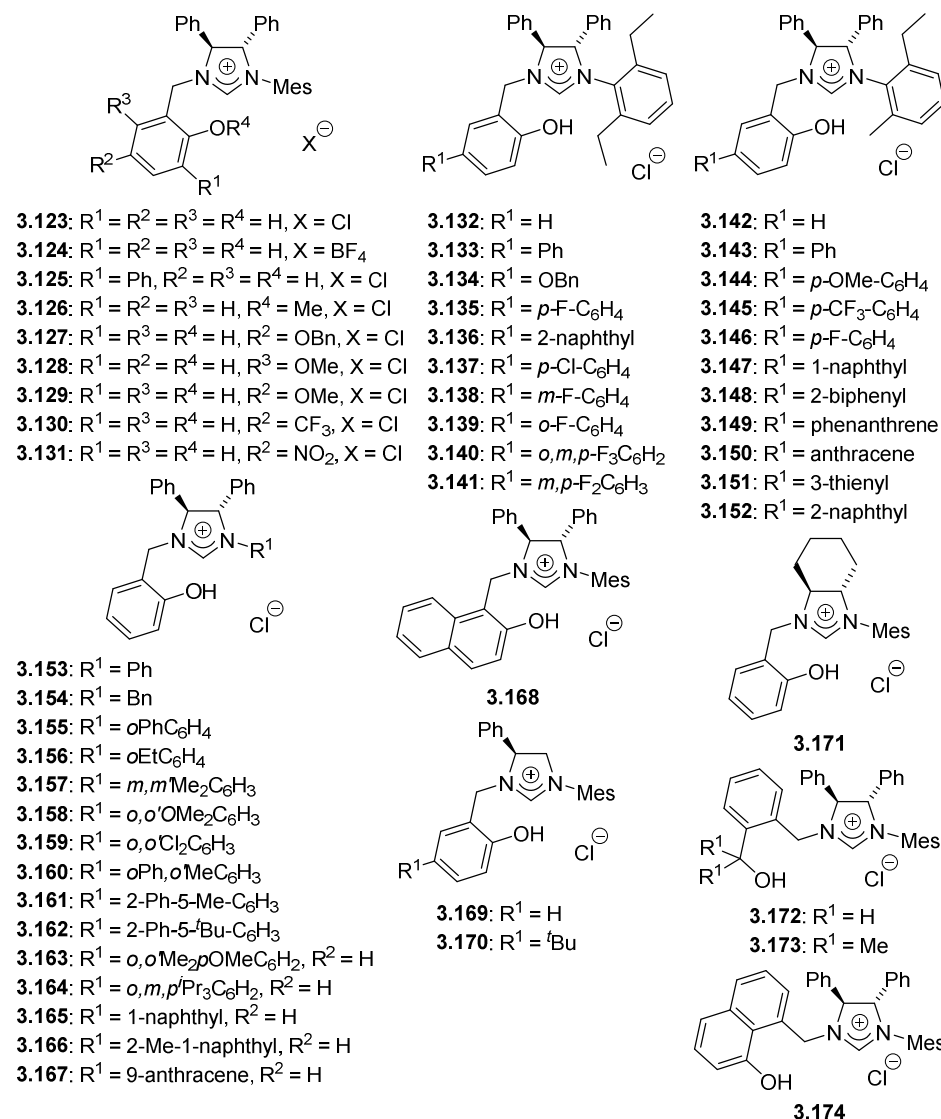


Chart 3-9. *O*-functionalized imidazolium salts used by Alexakis and coworkers for the copper-free AAA [123,124,125].

3.1.4. Copper-catalyzed other asymmetric addition reactions

Wilhelm *and coll.* synthesized a library of chiral imidazolium salts functionalized with two alcohol (Chart 3-10) or silylated alcohol groups (see Section 3.1.5 for the latter) for various applications, including asymmetric catalysis. All the hydroxyl-functionalized imidazolium salts were evaluated, as part of a tri-component catalytic mixture further composed of a metal precursor and a base, in the

asymmetric addition of diethylzinc to benzaldehyde or 1-naphthaldehyde for form the corresponding chiral alcohol [126,127]. Several reaction conditions, *i.e.* metal precursors (Cu, Fe, Ti...), base (KO^tBu, KHMDS) and solvent, were investigated. However, the performances of these systems remained moderate (yield and *ee*).

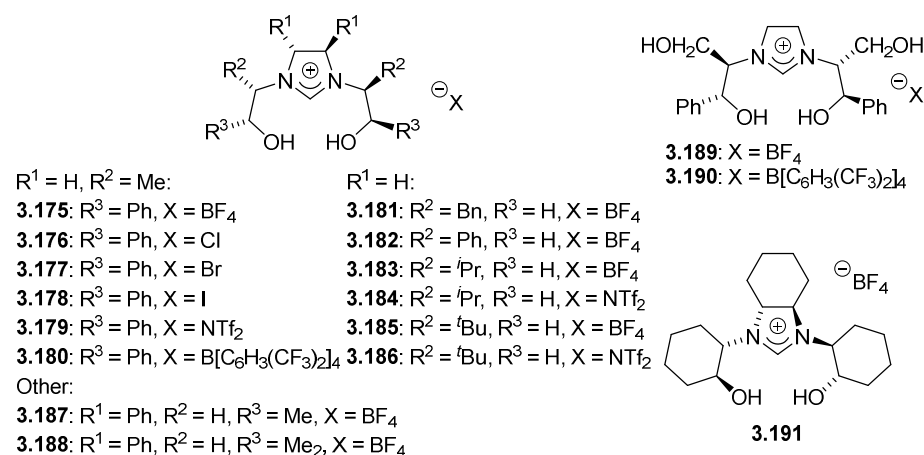
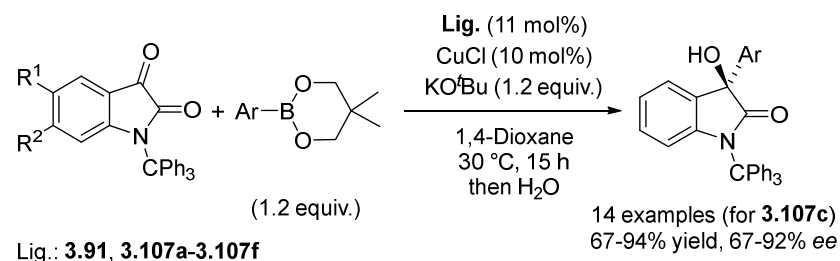


Chart 3-10. Chiral hydroxyl-functionalized imidazolium salts used in the copper-catalyzed addition of diethylzinc to benzaldehyde and 1-naphthaldehyde [126,127].

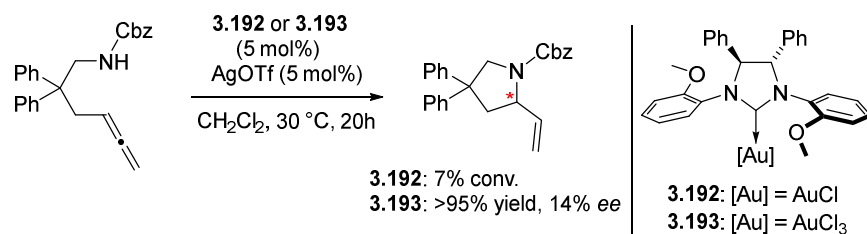
Chiral *O*-functionalized NHC precursors have been employed in the copper-catalyzed asymmetric addition of arylboronates to isatin derivatives to give 3-aryl-3-hydroxy-2-oxindoles in good yields and with high *ee* values (Scheme 3-13) [128]. Pro-ligand **3.107c**, which bears the bulkier ^tBu group on the chiral center and Me groups on the aryl (*vs.* H, Et, Ph) exhibited the best compromise between yield and selectivity and was applied to various substrates and boronic acids. Again, the replacement of the OH group on the ligands by H or OMe led to much lower *ees*. Stoichiometric reactions allowed the authors to propose a catalytic cycle based on the formation of an NHC-Cu-O^tBu complex (from KO^tBu) as key intermediate, which then undergoes transmetalation with boronic acid, leading to an NHC-Cu-Ar complex. Insertion of isatin to the latter leads to an alkoxo-copper complex that further reacts with KO^tBu to generate the NHC-Cu-O^tBu catalyst and the product.



Scheme 3-13. Copper-catalyzed asymmetric addition of arylboronates to isatin derivatives [128]. Structures of the pro-ligands are depicted in Chart 3-7.

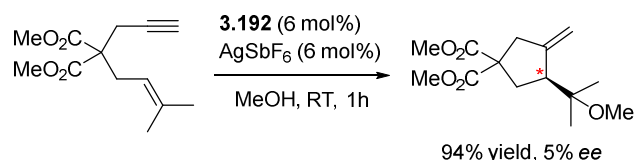
3.1.5. Intramolecular hydroamination and arylation/cyclization reactions

Michon and Agbossou-Niedercorn evaluated a large library of chiral monodentate (essentially phosphoramidites) and bidentate ligands for the gold-catalyzed asymmetric intramolecular hydroamination of allenes [129]. In a preliminary screening, the authors investigated well-defined NHC-Au^I and NHC-Au^{III} complexes, **3.192** and **3.193** and their non-functionalized counter-parts (*N*-CHPh₂ substituents). However, only **3.193** exhibited a reasonable conversion (>95%) but with a very poor enantiomeric excess (*ee* 14%, Scheme 3-14) and therefore the authors concentrated their efforts towards more efficient phosphoramidite ligands. Nevertheless, these studies highlighted a beneficial effect of the additional *ortho*-methoxy donor in **3.193** compared to the non-functionalized complex, which was found completely inactive, and such effect was already mentioned for an *ortho*-methoxy functionalized phosphine ligand in gold-catalyzed hydrofunctionalization of allenes [130].



Scheme 3-14. Gold-catalyzed asymmetric intramolecular hydroamination of allenes [129].

Chiral NHC-AuCl complexes, in combination with a silver salt, could accomplish the asymmetric cyclization of 1,6-enynes in good yields (>93%) and under mild conditions (RT, 1-2.5 h), although with low to moderate *ee* (4-56%, Scheme 3-15) [131]. The functionalized NHC-AuCl complex **3.192** led to a very poor *ee* (5%), which was attributed to the orientation of the *N*-aryl groups perpendicularly to the Au-Cl bond [104], while the most selective catalyst (*N*-(2,5-dimethylphenyl)methyl substituents, *ee* 56%) presents bulky stereo-directing groups pointing towards the Au center.

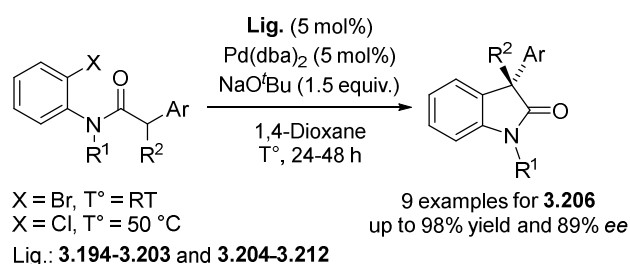


Scheme 3-15. Gold-catalyzed asymmetric cyclization of 1,6-enynes [131].

The NHC-AuCl complex of pro-ligand **3.77** (see Chart 3-5, no details about the synthesis or characterization were provided), in combination to AgNTf₂ (5 mol% each), was applied to a reaction of

olefin cyclopropanation and led to a mixture of products (38:62 *trans:cis*) with only poor enantioselectivity ($\approx 10\%$ *ee* for each isomer) after complete conversion [100].

Chiral (silyl)ether-functionalized NHC precursors **3.194-3.212** (Chart 3-11) were successfully applied to the palladium-catalyzed asymmetric intramolecular α -arylation of amides (Scheme 3-16) [132,133,134]. Within the silylether-functionalized imidazolium salts, **3.195** proved to be the most effective one, leading to the corresponding indole derivative ($R^1 = R^2 = \text{Me}$, $\text{Ar} = \text{Ph}$) in up to 95% yield and 72% *ee* [132]. The ether-functionalized pro-ligands developed by Kündig and coworkers, with the exception of the less encumbered **3.204**, afforded the expected indole products in high yields (57-99%) and with good to high *ee* values (57-94%) [133,134].



Scheme 3-16. Palladium-catalyzed asymmetric intramolecular α -arylation of amides [132,133,134].

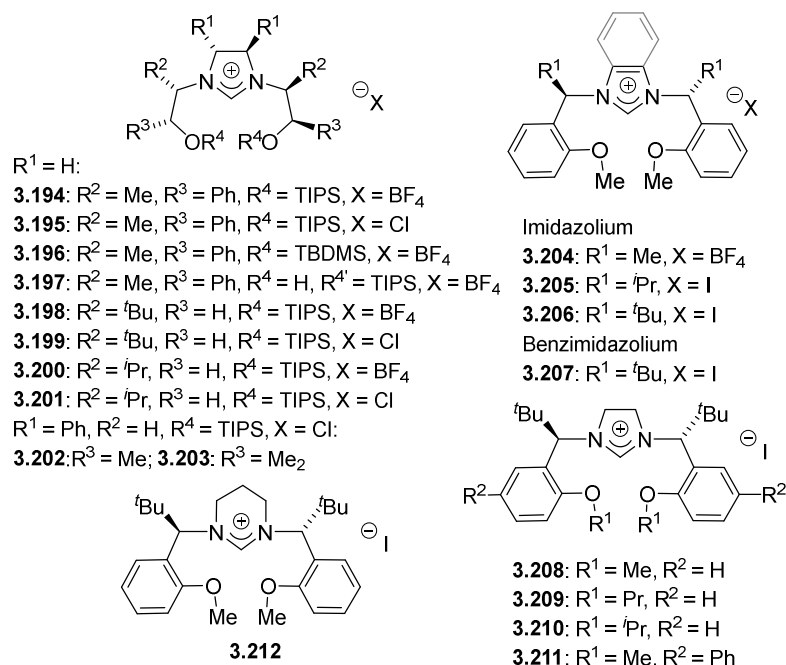
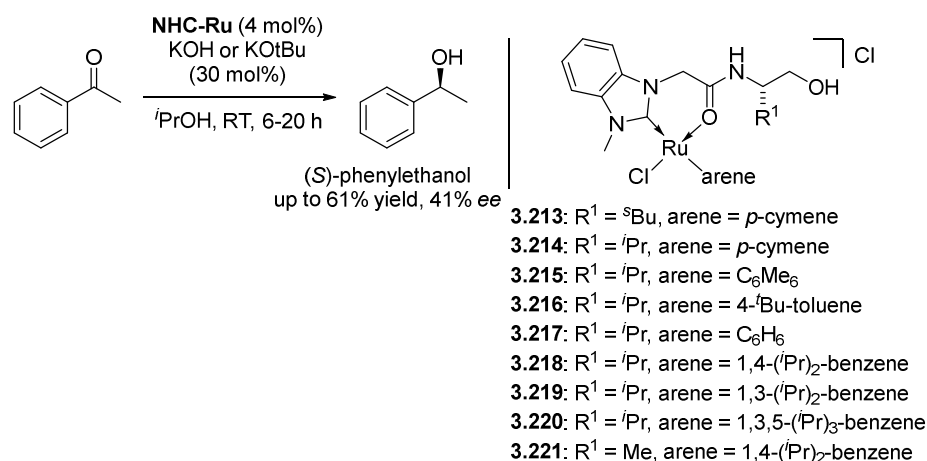


Chart 3-11. Chiral (silyl)ether-functionalized NHC precursors applied to palladium-catalyzed asymmetric intramolecular α -arylation of amides [132,133,134].

3.1.6. Asymmetric hydrogenation reactions

Chiral NHC-based metal complexes are privileged compounds to mediate asymmetric hydrogenation reactions [135]. The chiral ether-functionalized imidazolium salt **3.204** (Chart 3-11) was used by Glorius and coworkers in ruthenium-catalyzed asymmetric hydrogenation of a quinoxaline derivative and exhibited a high regioselectivity towards the hydrogenation of positions 5-8 (99%), however the enantiomeric ratio (64:36 *er*) remained moderate in comparison to other non-functionalized chiral NHC precursors evaluated in this study [136].

Piano-stool cationic ruthenium(II) complexes supported by chiral NHC ligands (**3.213-3.221**) incorporating both an amide and terminal alcohol functions were evaluated in enantioselective transfer hydrogenation and afforded the expected secondary chiral alcohol in modest yields and in general with relatively low *ee* values (Scheme 3-17) [137]. The authors could highlight that the terminal hydroxyl function of the NHC ligand is crucial for the catalytic activity (no reaction with OMe derivative).

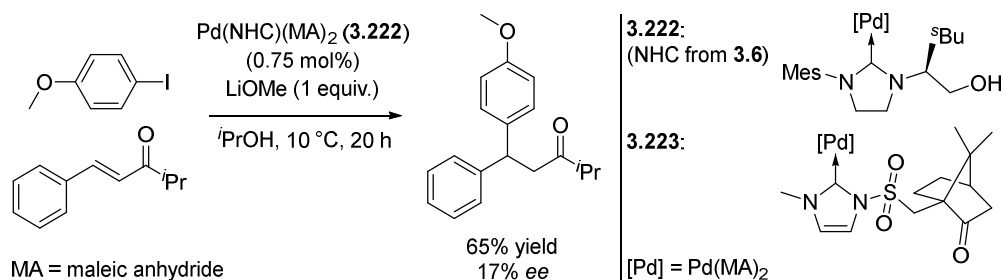


Scheme 3-17. Asymmetric transfer hydrogenation mediated by chiral NHC-Ru catalysts [137].

Two publications reported the synthesis of metal complexes supported by a chiral *N*-functionalized NHC ligand and their use in catalysis, however the process is not enantioselective or the selectivity is not mentioned and therefore they will not be discussed in the present contribution [138,139].

3.1.7. Asymmetric reductive Heck reaction

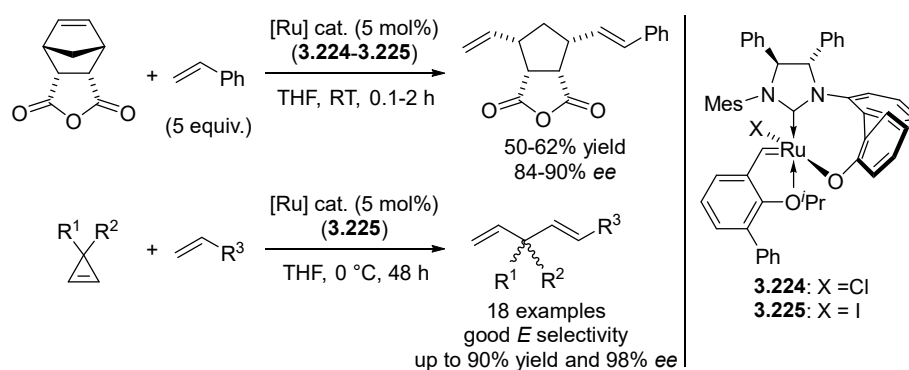
Palladium(0) complexes of chiral NHC ligands, including the corresponding carbene ligand of imidazolium **3.6** (Chart 3-2), were used as catalysts for the asymmetric reductive Heck reaction (Scheme 3-18) [140]. Within all the catalysts tested, those incorporating an additional *O*-function (**3.222-3.223**) performed very well (47-65% yield, 17% *ee*) in comparison with the non-functionalized NHC ligands).



Scheme 3-18. Palladium mediated asymmetric reductive Heck coupling [140].

3.1.8. Ruthenium-catalyzed asymmetric olefin metathesis reactions

As already mentioned in Section 3.1.1, the group of Hoveyda developed in 2005 a chiral NHC precursor *N*-functionalized with a hydroxybiphenyl moiety. This NHC ligand could be successfully coordinated to ruthenium, affording complexes **3.224** and **3.225** in good yields [113]. The authors applied these compounds to enantioselective ring-opening metathesis/cross-metathesis (AROM/CM) reactions on various substrates and generally obtained very good enantioselectivities [113,141,142]. Hoveyda published an excellent review that recounts the evolution of the olefin metathesis catalyst design and discusses the performance of the chiral *O*,*C*_{NHC}-Ru catalysts (**3.224-3.225**, see Scheme 3-19 and **3.226-3.232**, see Section 3.2) [143].

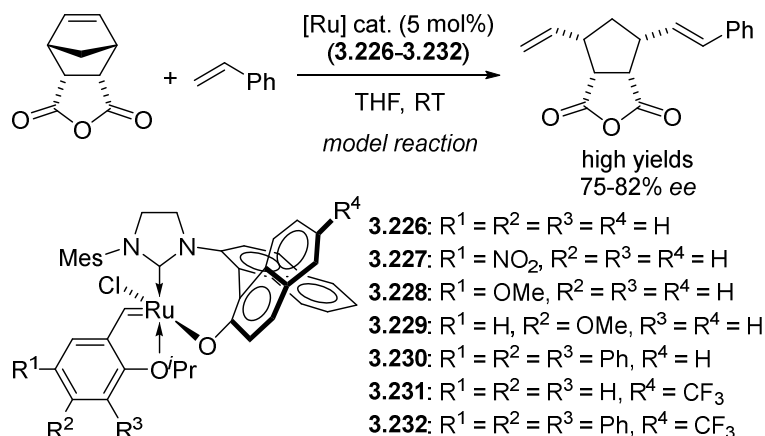


Scheme 3-19. Enantioselective ring-opening metathesis/cross-metathesis (AROM/CM) catalyzed by chiral *O*,*C*_{NHC}-Ru catalysts developed by Hoveyda and coworkers [113,141,142].

3.2. Axial chirality

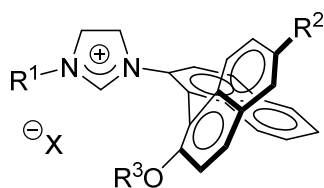
In 2002, the Hoveyda group reported the synthesis of a chiral NHC precursor incorporating a Binol moiety as *N*-substituent and its coordination to ruthenium to afford original catalysts for asymmetric ring-opening/cross-metathesis (Scheme 3-20) [144]. Further variations on the ligand skeleton were reported and the scope of the reaction could be extended to various substrates in the following years [145]. A useful review highlights the unique properties of the chiral *O*_{Binol},*C*_{NHC}-Ru catalysts and

compares their performance to that of other Ru-based catalysts in olefin metathesis [146,143]. Catalysts **3.226-3.232** were effective and the substitution pattern was shown to affect the rate of AROM/CM reaction.



Scheme 3-20. Enantioselective ring-opening/cross-metathesis catalyzed by chiral *O*-Binol, *C*-NHC-Ru catalysts developed by Hoveyda and coworkers [144,145].

The imidazolium precursors of the Binol-functionalized NHC ligands were also used, in combination with a copper salt, in Cu-catalyzed asymmetric allylic alkylation of dialkylzinc to allylic phosphate substrates (Chart 3-12) [147]. The best results were obtained with pro-ligand **3.233** with >98% conversion, >98% S_N2' product selectivity and up to 82% ee. The OMe (*vs.* OH) derivative, as well as the *N*-Dipp-substituted imidazolium led only to poor conversions <21%. The authors observed that the preformed corresponding dimeric Ag(I) complex of **3.233** was also very effective and they extended the scope of substrate with the latter.

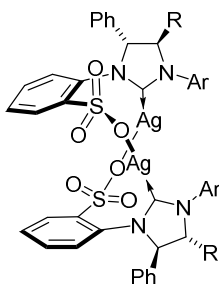
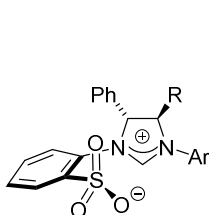


- 3.233:** R¹ = Mes, R² = R³ = H, X = Cl
3.234: R¹ = Mes, R² = CF₃, R³ = H, X = Cl
3.235: R¹ = Mes, R² = H, R³ = Me, X = BF₄⁻
3.236: R¹ = Dipp, R² = R³ = H, X = Cl
3.237: R¹ = Ad, R² = R³ = H, X = Cl

Chart 3-12. Binol-functionalized NHC precursors [147].

3.3. Sulfonate- and phosphate-functionalized NHC ligands

Although the field of asymmetric catalysis using chiral *O*,*C*_{NHC} ligands has been largely devoted to *alkoxide*-functionalized NHC ligands, Hoveyda and coll. developed in 2007 a new class of chiral functionalized NHC ligands bearing a chelating *sulfonate* moiety (Chart 3-13) [148]. The introduction of this functional group gives unique properties to the related Cu-NHC complexes that allowed reaching unprecedented efficiencies and selectivities, particularly in the areas of asymmetric copper-catalyzed conjugate addition and asymmetric allylic alkylation/substitution.



3.238: Ar = Mes; R = H

3.239: Ar = 2,6-(Et)₂C₆H₃; R = H

3.240: Ar = 2,6-(*i*-Pr)₂C₆H₃ (Dipp); R = H

3.241: Ar = 2,4,6-(*i*-Pr)₃C₆H₂; R = H

3.242: Ar = Mes; R = Ph

3.243: Ar = 2,6-(*i*-Pr)₂C₆H₃ (Dipp); R = Ph

3.244: Ar = 2,4,6-(*i*-Pr)₃C₆H₂; R = Ph

3.245: Ar = 2-PhC₆H₄; R = Ph

3.246: Ar = 2-Ph-5-*t*BuC₆H₃; R = Ph

3.247: Ar = 2-Ph-5-(2,4,6-(*i*-Pr)₃C₆H₂)C₆H₃; R = Ph

3.248: Ar = 2-Ph-6-MeC₆H₃; R = Ph

3.249: Ar = 2-Ph-naphthyl; R = Ph

3.250: Ar = 3,5-(*t*Bu)₂C₆H₃; R = Ph

3.251: Ar = 3,5-(2,4,6-(*i*-Pr)₃C₆H₂)₂C₆H₃; R = Ph

3.238-Ag: Ar = Mes; R = H

3.239-Ag: Ar = 2,6-(Et)₂C₆H₃; R = H

3.240-Ag: Ar = 2,6-(*i*-Pr)₂C₆H₃ (Dipp); R = H

3.241-Ag: Ar = 3,5-(*t*Bu)₂C₆H₃; R = H

3.242-Ag: Ar = Mes; R = Ph

3.243-Ag: Ar = 2-(*i*-Pr)C₆H₄; R = Ph

3.244-Ag: Ar = 2,4,6-(*i*-Pr)₃C₆H₂; R = Ph

3.245-Ag: Ar = 3,5-(*t*Bu)₂C₆H₃; R = Ph

3.246-Ag: Ar = 3,5-(2,4,6-(*i*-Pr)₃C₆H₂)₂C₆H₃; R = Ph

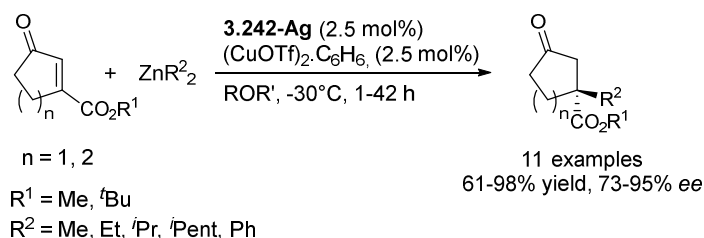
Chart 3-13. Chiral sulfonate-imidazolium salts and chiral sulfonate-NHC silver complexes developed by Hoveyda and coll. for copper-catalyzed reactions [141, 142-149,151-164,166-171].

3.3.1. Copper-catalyzed nucleophilic asymmetric conjugate addition

The use of sulfonate-NHC pro-ligands or sulfonate-NHC silver complexes in Cu-catalyzed ACA allowed removing bottlenecks and solving a number of challenges usually associated with the addition of functionalized substrates. By careful association of NHC ligand and nucleophilic reagent (metal-based, borane), Hoveyda and coll. were able to significantly widen the range of substrates involved in ACAs and obtain the expected products very efficiently and with very high selectivities.

With organozinc reagents. The first copper-catalyzed ACA with sulfonate-NHC silver complexes deals with the addition of organozinc reagents to cyclic γ -ketoesters [148]. A preliminary ligand screening showed the superiority of silver complex **3.242-Ag** compared to aryloxy-NHC complexes **3.111** and **3.233-Ag** (see Sections 3.1 and 3.2): **3.242-Ag** allowed obtaining the addition products with complete conversions and, except in one case, *ees* superior to 73%; dialkyl- and diarylzinc reagents were

equally used (Scheme 3-21). On the contrary, aryloxy-NHC complexes **3.111** and **3.233-Ag** furnished the products with variable conversions and low *ees* (less than 33% except in one case). The authors postulated that the use of sulfonate-functionalized NHCs gives rise to a seven-membered chelate with copper, which should be more sterically constrained than the eight-membered metallacycle formed with alkoxy-based NHC ligands. Furthermore, the chelating O-atom is less basic with sulfonate-based ligands. This postulate was reinforced by the fact that the related NHC-silver complex bearing a carboxylate group in place of a sulfonate is ineffective in promoting this class of ACA reactions (<30% *ee*). Silver(I) complexes of NHC-amide ligands (**2.137-2.146**, part 2.3) developed by Sakaguchi and coworkers [79] were used for the ACA of similar substrates, i.e. cyclic enones, with diethylzinc: *ees* are in the same range as those obtained with sulfonate-based ligands, although the substitution at the substrate β carbon atom may influence their reactivity. The formation of a seven-membered chelate with Cu may contribute in both cases to the good levels of enantioselectivity.



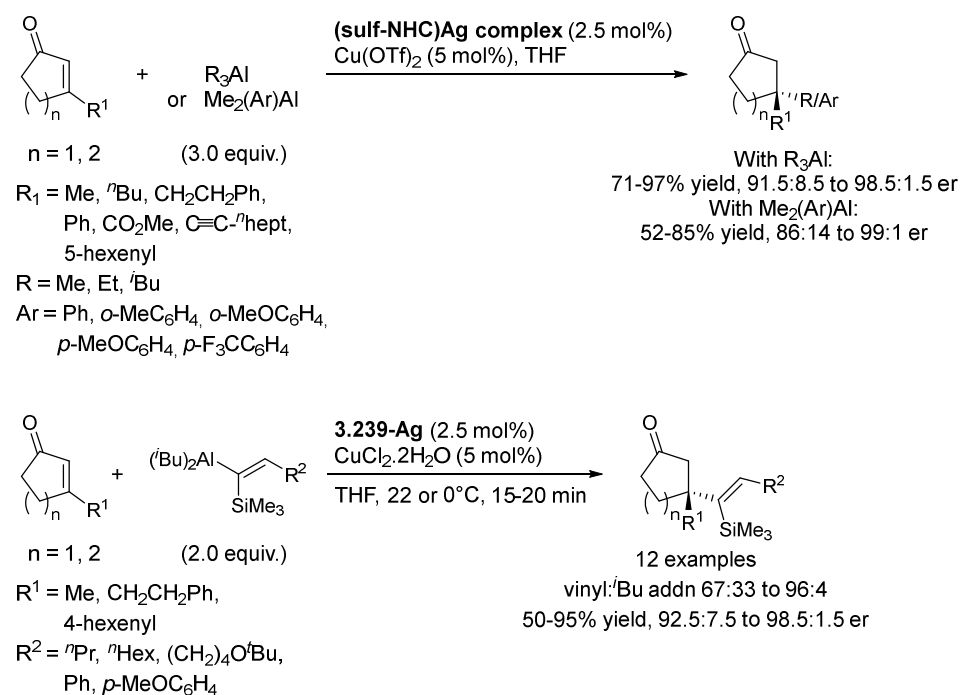
Scheme 3-21. Enantioselective addition of organozinc reagents to cyclic γ -ketoesters catalyzed by chiral (sulfonate-NHC)-Cu complexes [148].

This reactivity has also been exploited by Peese and Gin as a mean to carry out a concise total synthesis of alkaloid (+)-nominine [149]. Thus a six-membered γ -ketoenoate (where $R^1 = \text{Me}$, Scheme 3-21) has been treated with ZnMe_2 in the presence of silver complex **3.242-Ag** and $[\text{Cu}(\text{OTf})_2]$ in C_6H_6 at -30°C , followed by trapping of the nucleophilic addition product by Tf_2O at 0°C , to give the enol triflate in 88% yield and 92:8 *er*.

With organoaluminum reagents. The first report of Cu-catalyzed ACA involving NHC-sulfonate silver complexes with alkyl- and arylaluminum reagents was disclosed in 2008 by Hoveyda and coll. [150]. Although efficient systems with zinc-based reagents were developed for cyclic enones, they only work for five-membered-ring substrates that bear an activating substituent. Organoaluminum reagents allowed the introduction of a quaternary carbon stereogenic centre onto a range of non-activated β -substituted cyclic enones. The developed method presents the advantage of being more general, if not as efficient as other catalytic systems in some cases (cyclohexenones and -heptenones) (Scheme 3-22). Thus silver complexes **3.238-Ag**, **3.239-Ag** and **3.242-Ag**, associated to $[\text{Cu}(\text{OTf})_2]$, were very efficient with trialkylaluminum reagents (up to 97% yield and 97% *ee* with cyclopentenones, 89% yield and 90% *ee* with cyclohexenones), whereas aryloxy-NHC **3.111** remained more efficient in the presence of

aryldialkylaluminum reagents. The same year, Hoveyda and coll. used this methodology to complete the first enantioselective total synthesis of Clavirolide C [151]. In this case, the addition of AlMe₃ to a β -substituted cyclopentenone in the presence of [Cu(OTf)₂] and sulfonate-NHC silver complex **3.239-Ag** furnished the desired cyclic silyl enol ether in 72% yield and 84% *ee*.

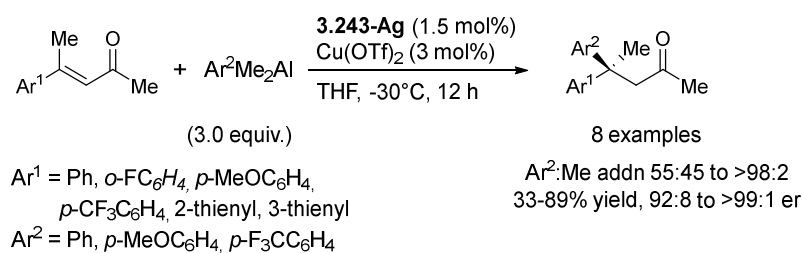
The development of an efficient and stereoselective synthesis of silyl-containing vinylaluminum reagents also allowed the addition of a range of alkyl- as well as aryl-substituted 1-trimethylsilyl-vinylaluminums to unactivated β -substituted cyclic enones [152]. The methodology worked particularly well with cyclopentenones, usually challenging substrates for ACA reactions. Among the sulfonate-NHC silver complexes tested (**3.238-Ag**-**3.240-Ag** and **3.242-Ag**), catalyst **3.239-Ag** furnished the best levels of chemo- and enantioselectivity (Scheme 3-22), while the aryloxy-NHC complex and monodentate NHCs gave very low conversions. This catalyst was also applied in the enantioselective synthesis of Riccardiphenol B [152].



Scheme 3-22. Enantioselective addition of alkyl- and arylaluminum [150] or silyl-containing vinylaluminum reagents [152] to unactivated β -substituted cyclic enones catalyzed by chiral (sulfonate-NHC)-Cu complexes.

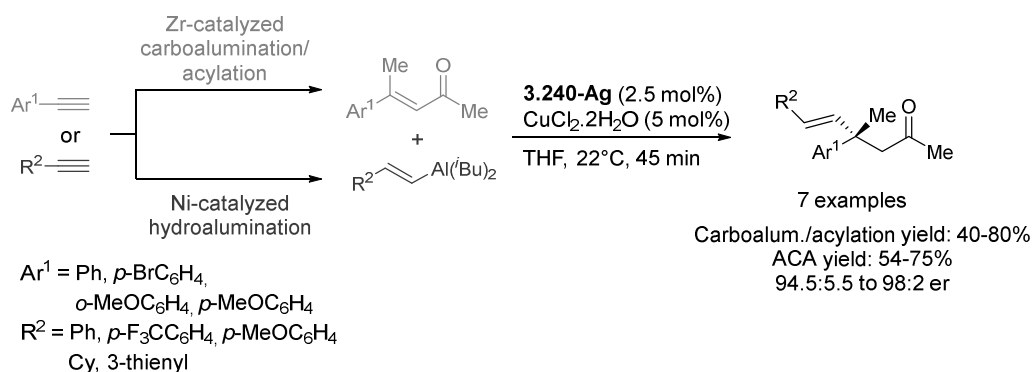
Acyclic enones are usually regarded as more challenging than their cyclic counterparts and have been relatively rarely investigated. Hoveyda and coll. have once again evaluated their sulfonate-NHC silver complexes in the Cu-catalyzed ACA of alkyl- and arylaluminum reagents to acyclic trisubstituted enones (Scheme 3-23) [153]. Although several chiral monodentate NHC pro-ligands proved effective, the best results were obtained in most cases with silver complex **3.243-Ag**, associated to [Cu(OTf)₂]. Most addition products, bearing quaternary carbon stereogenic centres, were obtained with very high levels of enantioselectivity (*er* > 92:8). Excellent chemoselectivities were also reached since Ar vs Me

addition ratios were greater than 92:8 with aryl(dimethyl)aluminum reagents (except in one isolated case).



Scheme 3-23. Enantioselective addition of aryl- and alkylaluminum to acyclic trisubstituted enones [153].

Finally, a multi-component strategy was used to allow the addition of alkenylaluminum reagents to acyclic trisubstituted enones to afford all-carbon quaternary stereogenic centres [154]: alkynes were used to prepare both the alkenylaluminum reagents – via a Ni-catalyzed hydroalumination reaction – and the enones – using a Zr-catalyzed carboalumination/acylation reaction (Scheme 3-24). Silver complexes of chiral monodentate NHCs or O,C_{NHCs} were totally inefficient, whereas the use of several sulfonate-NHC silver complexes allowed the formation of the addition products with greater than 90.5:9.5 er.



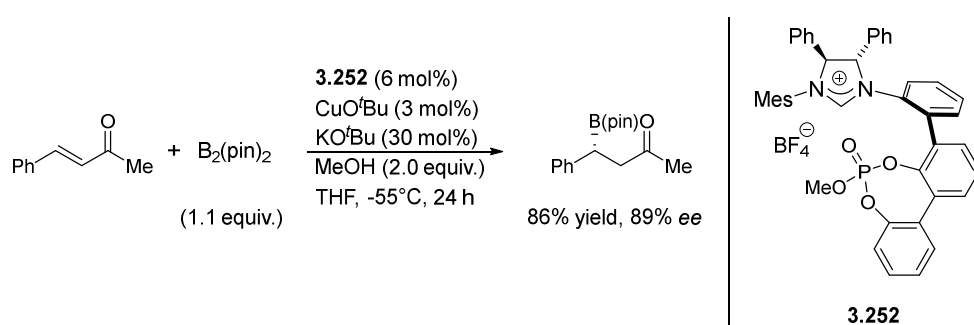
Scheme 3-24. Multi-component strategy for the synthesis of acyclic trisubstituted enones [154].

With other nucleophiles. Sulfonate-NHC pro-ligands or silver complexes were evaluated by Hoveyda and coll. in the copper-catalyzed ACA of $\text{PhMe}_2\text{SiB}(\text{pin})$ to cyclic and acyclic unsaturated carbonyls [155] and of $\text{B}_2(\text{pin})_2$ to trisubstituted alkenes of acyclic α,β -unsaturated esters, ketones and thioesters [156]. In the case of $\text{PhMe}_2\text{SiB}(\text{pin})$, sulfonate-NHC silver complex **3.242-Ag**, however competent, proved slightly less efficient than the silver complexes of monodentate NHCs in terms of enantioselectivity (89:11 er with **3.242-Ag** and >90:10 er with monodentate NHCs). For the addition of $\text{B}_2(\text{pin})_2$ to trisubstituted alkenes, an initial evaluation of various NHC pro-ligands was carried out with α,β -unsaturated esters. The copper complexes obtained from sulfonate-imidazolium salts **3.242** and

3.244 furnished higher enantioselectivities (up to 88:12 er) than the complex of aryloxy-substituted imidazolium salt, but suffered from a relatively low catalytic activity compared to copper complexes of monodentate NHCs.

Recently, Hoveyda and coll. investigated the reactivity of a multicomponent mixture composed of easily accessible butadiene or isoprene, an enoate and $B_2(\text{pin})_2$, in the presence of CuCl (5 mol%), a chiral ligand (5 mol%) and NaOPh as base [157]. The formation of two possible intermediate allylcopper species from the 1,3-diene could furnish either the α - or γ -addition products on the unsaturated diester, which raised many selectivity issues. Many chiral ligands or pro-ligands were evaluated (phosphines, bisphosphines, functionalized and non-functionalized imidazolium salts) and the only sulfonate-imidazolium salt used (**3.244**) gave mostly the γ -addition product with very low levels of enantio- and diastereoselectivity.

A rare example of chiral imidazolium salt bearing a phosphate moiety as anionic N-substituent, in place of a sulfonate, has been described by Sawamura and coll. in 2013 [158]. They envisioned that this ligand could be an interesting candidate for the copper-catalyzed conjugate addition of bis(pinacolato)diboron to an α,β -unsaturated ester. Indeed, the *m*-terphenyl-based phosphate moiety could work as an anionic coordination site, resulting in bidentate coordination, and the steric environment around the NHC is easily tunable. The reaction was carried out in the presence of CuO^tBu as catalyst and MeOH as proton source (Scheme 3-25). The use of phosphate-imidazolium salt **3.252** gave an excellent yield (86%) and enantioselectivity (89% *ee*), much better than the non-functionalized chiral imidazolium salt tested for comparison (83% yield, 32% *ee*). Results were even better in the case of the dimethoxy-substituted analogue that does not possess the anionic phosphate substituent (94% yield, 96% *ee*, Chart 3-7). The phosphate-NHC ligand can thus be considered as a good choice for the copper-catalyzed enantioselective synthesis of an enantioenriched β -boryl ester. However, given the efficiency of the dimethoxy-substituted NHC ligand, the role of the phosphate moiety is still unclear.

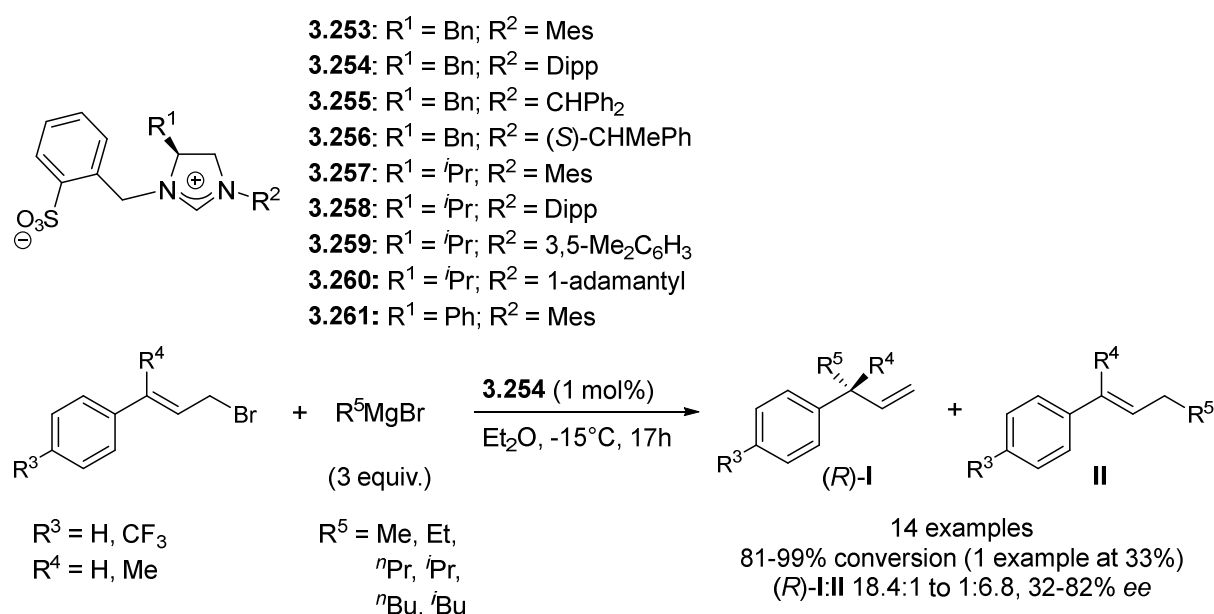


Scheme 3-25. Chiral phosphate-imidazolium salt for the copper-catalyzed conjugate addition of bis(pinacolato)diboron to an α,β -unsaturated ester [158].

3.3.2. Copper-free asymmetric conjugate addition (ACA)

Most of the chiral sulfonate-based NHC proligands or related silver complexes have been developed and exploited by Hoveyda and coll. in copper-catalyzed ACA reactions with a wide range of substrates. Woodward and coll. noticed however that some of these sulfonate-imidazolium salts required lengthy syntheses. As an example, eight steps were needed to obtain imidazolium salt **3.238** from mesitylamine. Based on these considerations, they successfully developed a general method that allowed the short preparation of a wide range of chiral sulfonate-based imidazolium salts, bearing hindered, aromatic or non-aromatic substituents (R^2) on the heterocycle (Scheme 3-26) [159]. These pro-ligands differ slightly from those of Hoveyda in that they possess a methylene linker between the arylsulfonate substituent and the heterocycle, and were prepared in three steps from commercially available BOC-protected amino-alcohols.

Following the work of Hoveyda and Alexakis on copper-free additions of Grignard reagents to allylic halides [122,123,160], Woodward and coll. evaluated their pro-ligands in the conjugate addition of alkyl Grignard reagents to various (*E*)-cinnamyl electrophiles [159]. Among the various tested electrophiles, (*E*)-cinnamyl bromide gave the best results. A pro-ligand screening was carried out for the addition of EtMgBr to (*E*)-cinnamyl bromide, suggesting that the size and nature of the R^2 substituent have a large influence on the regio- (S_N2'/S_N2 ratio) and enantioselectivity. Pro-ligand **3.254**, bearing a relatively large aryl group with two *i*Pr substituents in the 2- and 6- positions, proved the best candidate and was investigated further with other electrophiles and Grignard reagents (Scheme 3-26).



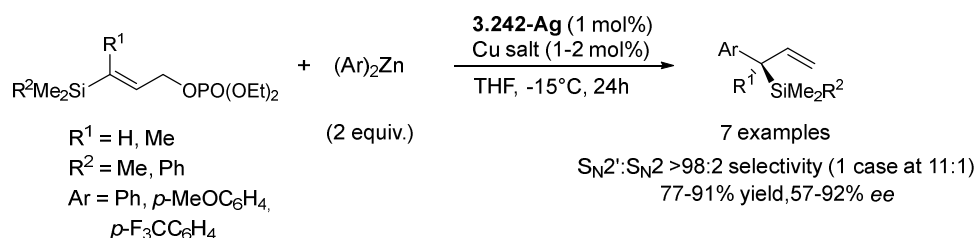
Scheme 3-26. Chiral sulfonate-imidazolium salts evaluated in the copper-free ACA of alkyl Grignard reagents to (*E*)-cinnamyl bromides [159].

Contrarily to what was observed by Alexakis and coll. with *O*-substituted imidazolium salts [123], methyl-(*E*)-cinnamyl bromide provided a very low regioselectivity in favor of conjugate addition product (*R*)-**II**, and the introduction of an electron-withdrawing CF₃ on the aryl group (R³) slightly improved the enantioselectivity (up to 82% *ee*) but not the regioselectivity. This clearly shows that *O*-substituted NHCs and sulfonate-substituted NHCs are complimentary and can both catalyze efficiently ACA reactions according to the type of substrate used.

3.3.3. Copper-catalyzed asymmetric allylic alkylation (AAA)

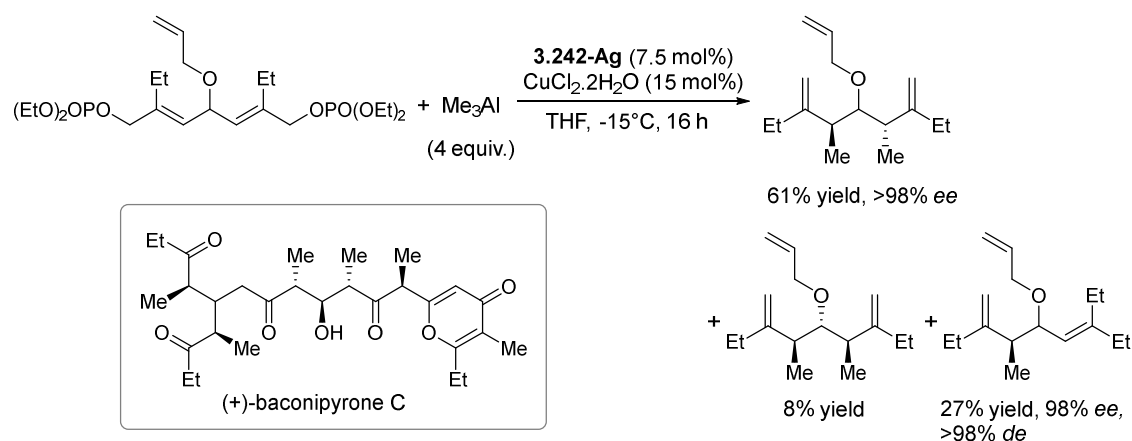
Chiral sulfonate-NHC pro-ligands and silver complexes have been successfully used by Hoveyda and coll., in the presence of a copper salt, to catalyze asymmetric allylic alkylations of unsaturated phosphates. The structure of these sulfonate-bearing NHC-copper catalysts gives them unique properties that allowed them to surpass copper complexes based on monodentate NHC ligands or bidentate *O,C*_{NHC} ligands. Indeed, the ability of the catalyst to accommodate a metal bridge between the sulfonate group and the phosphate leaving group seems to be the key factor to reach high efficiency, excellent site- (*S*_N2') mode of addition preferred over *S*_N2) and enantioselectivity in most cases. This has been observed whatever the nature of the organometallic nucleophile engaged in the reaction.

With organozinc and organoaluminum reagents. In 2007, Hoveyda and coll. realized the copper-catalyzed AAA of Si-substituted unsaturated phosphates in the presence of dialkyl- and diarylzinc reagents [161]. Before this report, all catalyzed enantioselective syntheses of allylsilanes were Pd-based and often afforded the enantioenriched products in less than 90% *ee*. The combined use of a chiral NHC silver complex, a Cu salt and zinc reagents enabled the enantioselective synthesis of allylsilanes bearing tertiary or quaternary Si-substituted carbons, with a strong *S*_N2' selectivity and good to excellent *ees* (Scheme 3-27). Whereas *O*-based NHCs **3.111** and **3.233-Ag** proved the best choice with dialkylzinc reagents, **3.242-Ag** outperformed all other ligands in the case of diarylzinc nucleophiles. In the latter case, 90-92% *ee* were obtained with disubstituted vinylsilanes, whereas trisubstituted vinylsilanes afforded slightly lower *ees* (76-90%).



Scheme 3-27. Copper-catalyzed AAA of Si-substituted unsaturated phosphates with diarylzinc reagents [161].

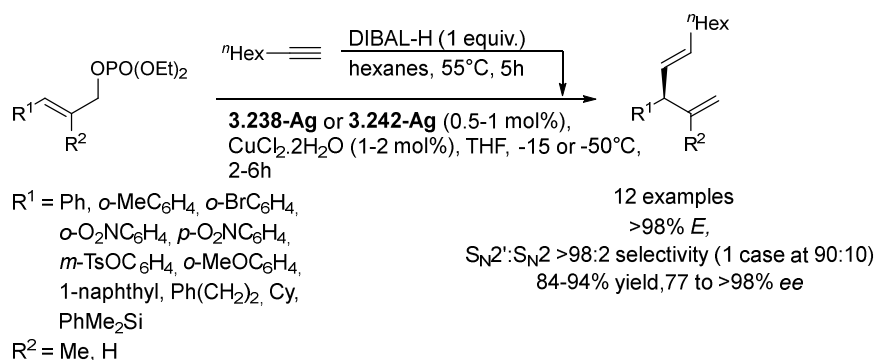
Organozinc reagents, however, proved totally ineffective in the more challenging double AAA of an unsaturated diphosphate, which was involved in the total synthesis of baconipyronone C [162]. This transformation was accomplished with the more Lewis acidic and nucleophilic trimethylaluminum species, in the presence of a chiral silver-NHC complex and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (Scheme 3-28). Sulfonate-NHC complex **3.242-Ag** showed a better activity than the *O*-functionalized NHCs **3.111** and **3.233-Ag** and allowed establishing two stereogenic centres in one step, in 61% yield and >98% *ee*.



Scheme 3-28. Copper-catalyzed AAA of an unsaturated diphosphate with trimethylaluminum [162].

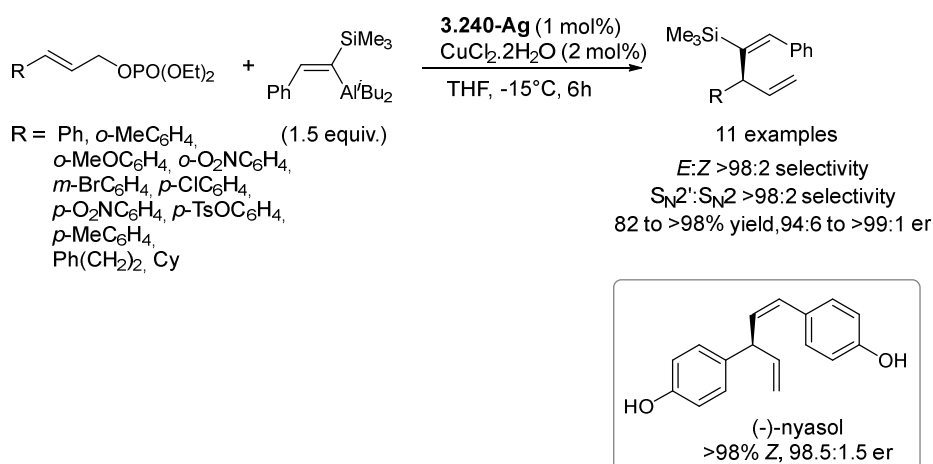
The use of arylaluminum reagents, prepared from aryllithium and aluminum chlorides, allowed tackling the issue of aryl additions to form all-carbon quaternary centres [163]. The copper-catalyzed allylic substitution of these reagents on allylic phosphates occurred with complete site selectivity (>98% $\text{S}_{\text{N}}2'$) and high enantioselectivity (up to >98:2 *er*) with most substrates when silver complexes of chiral sulfonate-NHC ligands (**3.238-Ag**, **3.242-Ag** or **3.244-Ag**) were used. The *O*-functionalized NHC complex **3.111** also offered a complete site selectivity but a lower enantioselectivity, whereas the $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$ ratio was much lower with monodentate NHCs.

The superiority of sulfonate-NHC-based ligands over other types of NHC ligands was demonstrated in the copper-catalyzed AAA of vinylaluminum reagents with allylic phosphates (Scheme 3-29) [164]: no reaction occurred with monodentate or *O*-functionalized NHCs, whereas total conversions of the trisubstituted olefins bearing an aryl substituent were obtained with silver complexes **3.238-Ag** and **3.242-Ag**. Again, a strong site selectivity (>98% $\text{S}_{\text{N}}2'$) was observed, as well as total selectivity in favour of the *E* isomer and high enantioselectivities (77 to >98% *ee*).



Scheme 3-29. Copper-catalyzed AAA of a vinylaluminum reagent with an allylic phosphate [164].

The use of vinylaluminum reagents in copper-catalyzed AAAs was developed further by Hoveyda and coll. [165]: aryl- and alkyl-substituted phosphates were subjected to stereoisomerically pure vinylaluminum reagents in the presence of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and sulfonate-NHC silver complexes **3.240-Ag** and **3.244-Ag**. A simple solvent switch allowed obtaining either pure *Z*- or pure *E*-silyl-containing vinylaluminum reagents from a silyl-substituted alkyne. The AAA reaction of the *E*-isomer furnished almost exclusively the *E*-isomer of the product, while a total site selectivity (>98% S_N2') was observed (Scheme 3-30). No addition of an *t*Bu group *vs* the vinyl group was detected either. Yields of 82% to >98% and 94:6 to >99:1 *er* were obtained with aryl-substituted phosphates, and alkyl-substituted phosphates could also be used with somewhat lower enantioselectivities (94:6 *er*). The first enantioselective synthesis of niasol was thus realized. Interestingly, complex **3.240-Ag** performed better with *E*-vinylaluminums, whereas **3.244-Ag** was preferred with *Z*-vinylaluminums, giving better enantioselectivities.

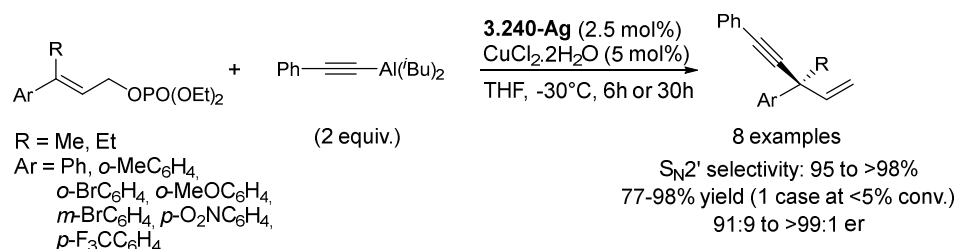


Scheme 3-30. Copper-catalyzed AAA of an *E*-silyl-containing vinylaluminum reagent with an allylic phosphate [165].

Aryl- and alkyl-substituted vinylaluminum reagents were finally used in the synthesis of 1,4-dienes containing a quaternary carbon stereogenic center at their C-3 site [166]. Once again, chiral sulfonate-

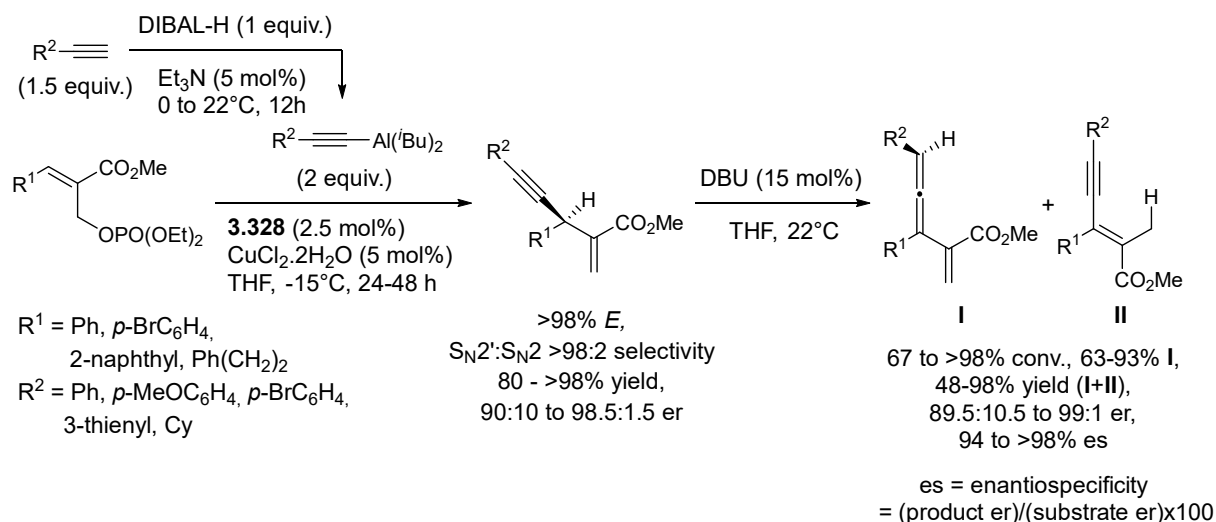
NHC silver complexes **3.238-Ag**, **3.240-Ag** and **3.242-Ag** furnished the desired products efficiently (66-97% yield of isolated products) and in high site (>98% S_N2') and enantioselectivity (up to 99:1 er).

The development of a simple preparation procedure for alkynylaluminum reagents further widened the scope of copper-catalyzed AAA. Hoveyda and coll. thus described the formation of alkyne-substituted all-carbon quaternary stereogenic centres through the addition of alkynylaluminum reagents to variously substituted allylic phosphates (Scheme 3-31) [167]. The use of chiral sulfonate-NHC silver complexes **3.240-Ag** and **3.242-Ag** provided the products with excellent site selectivity (>98% S_N2') and er values ranging from 91:9 to 99:1. Monodentate NHCs were totally inefficient (<10% conversion) and *O*-substituted NHCs furnished good er values but poor activities (ca. 30% conversion). **3.240-Ag** generally gave the best results, often showing a subtle influence of the ligand sterics on the catalytic results.



Scheme 3-31. Copper-catalyzed AAA of alkynylaluminum reagents with allylic phosphates [167].

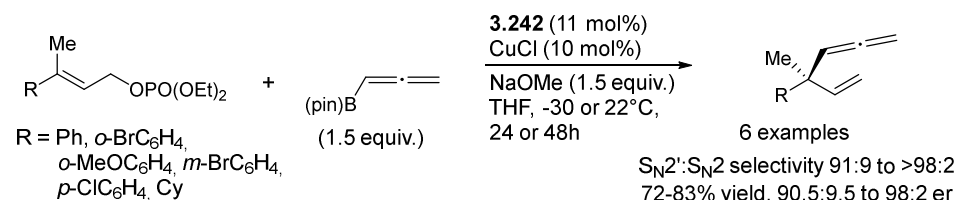
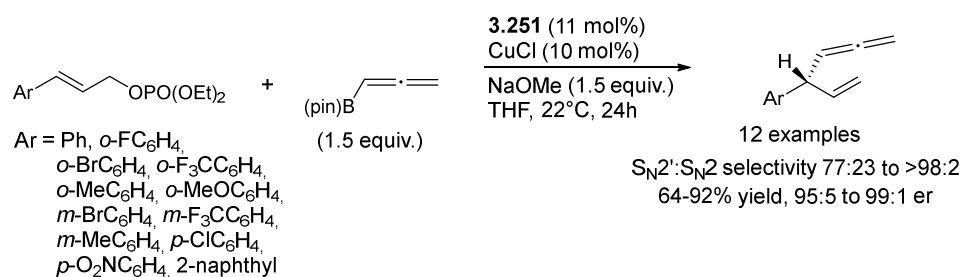
Hoveyda and coll. subsequently showed that the addition of a catalytic amount of base (15 mol% of DBU), after the copper-catalyzed AAA of alkynylaluminum reagents with trisubstituted allylic phosphates containing a C2 carboxylic ester, allowed a clean and stereospecific isomerization of the alkyne-substituted product to give trisubstituted allenes Scheme 3-32 [168]. Although similar alkynylaluminums to those described earlier [167] were used, different sulfonate-NHC silver complexes, i.e. **3.238-Ag** and **3.241-Ag**, proved the most efficient and selective in this case: the alkyne-substituted unsaturated esters were obtained in 58–98% yield and 90:10–98.5:1.5 e.r. Excellent S_N2' selectivities were also observed (>98%, except for one case with 95:5).



Scheme 3-32. Enantioselective AAA with alkynylaluminum reagents and stereospecific isomerization of the products to trisubstituted allenes [168].

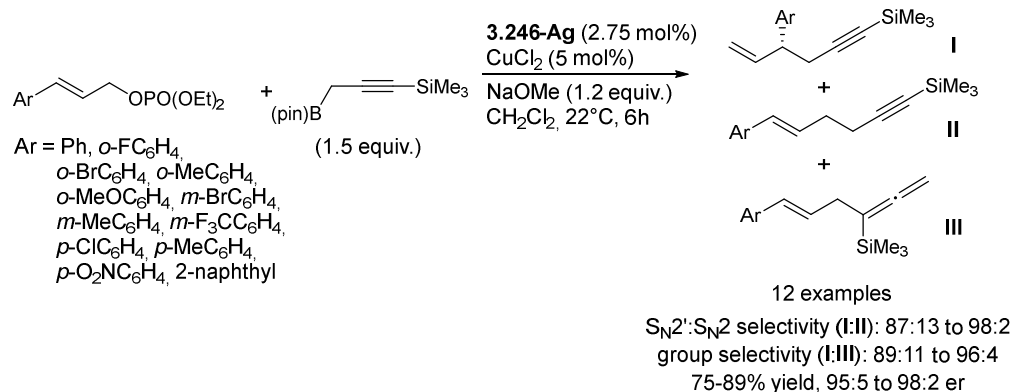
With other nucleophiles. Unlike what was observed in copper-catalyzed ACA, chiral sulfonate-NHC ligands appeared very efficient for the copper-catalyzed AAA of boron-based nucleophiles. They were first evaluated by Hoveyda and coll. in the enantioselective synthesis of allylboronates, using commercially available $B_2(\text{pin})_2$ and alkyl- or aryl-trisubstituted allylic carbonates [169]. Among the different tested pro-ligands, sulfonate-imidazolium salts **3.240** and **3.242** showed the best efficiency/enantioselectivity compromise, whereas *O*-substituted imidazolium salts and non-functionalized imidazolium salts gave lower levels of enantioselectivity (less than 63:37 er). Thus allylboronates possessing a tertiary or a quaternary α carbon stereogenic centre were produced in $>98\%$ S_N2' site selectivity and up to 99:1 er.

Hoveyda and coll. next investigated the copper-catalyzed reaction of allenyl-B(pin) onto allylic phosphates with exclusive addition of an allenyl unit ($<2\%$ propargyl addition) [170]. Contrary to organometallic nucleophiles, where the catalyst can accommodate a metal bridge between the sulfonate group and the phosphate unit, Lewis acidic metal activation and organization is absent with an organoboron reagent. The addition of NaOMe solved the problem and allowed the (sulfonate-NHC)-Cu-allene to be formed by transmetalation via the allenylboronate. Thus the products of the AAA reaction, containing allenyl-substituted tertiary or quaternary stereogenic centres, were obtained in high yields, high site selectivity (S_N2' over S_N2) and enantioselectivity (90.5:9.5 to 99:1 er) in the presence of imidazolium salt **3.251**, except in the case of trisubstituted alkenes where **3.242** gave better results (Scheme 3-33).



Scheme 3-33. Reaction of allenyl-B(pin) onto disubstituted or trisubstituted allylic phosphates [170].

A thorough examination of the ligand properties showed that there is a strong influence of the *N*-aryl substituents (steric bulk and position) on enantioselectivity. On the other hand, *O*-substituted imidazolium salts and non-functionalized imidazolium salts gave almost exclusively an achiral product, arising from the S_N2 addition. Copper-catalyzed AAA involving a propargylic nucleophile were also reported between a silyl-containing propargylic organoboron substrate and an allylic phosphate, leading to products bearing tertiary as well as quaternary carbon stereogenic centres (Scheme 3-34) [171]. The addition of a propargylic group represents a challenge since the incorporation of the propargylic group can compete with allenyl addition, additionally to the S_N2'/S_N2 selectivity issue.



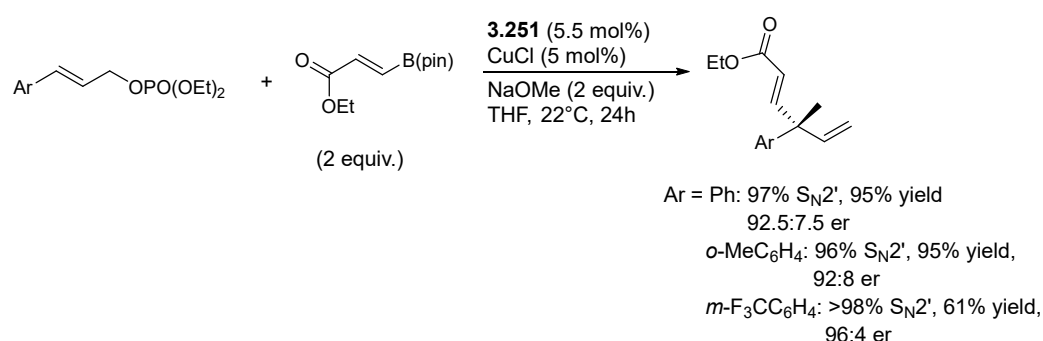
Scheme 3-34. Reaction of silyl-containing propargyl-B(pin) onto aryl-disubstituted allylic phosphates [171].

A thorough mechanistic study has been carried out by Hoveyda and coll. to understand the origin of the selectivity: DFT calculations have shown that the Cu(I)-propargyl and Cu(I)-allenyl species could interconvert via a π -allyl transition state, but the latter, although of slightly higher energy, is more reactive than the Cu(I)-allenyl species, leading predominantly to the propargyl-containing product. The high site selectivity has been explained by the possibility for the sulfonate moiety to participate in an

interaction with the phosphate leaving group, mediated by the Na⁺ cation (from NaOMe), thus directing the approach of the allylic phosphate. Finally, the role of the sulfonate ligand substituents were highlighted. The stereochemical outcome is different depending on whether the N-aryl substituents are situated in a *meta* position (**3.245-Ag/3.250** and **3.246-Ag/3.251**), leading to preferential addition to the disubstituted phosphates from the *si* face, or in *ortho/para* positions (**3.238**, **3.239**, **3.242** and **3.243**), leading to preferential *re* face addition.

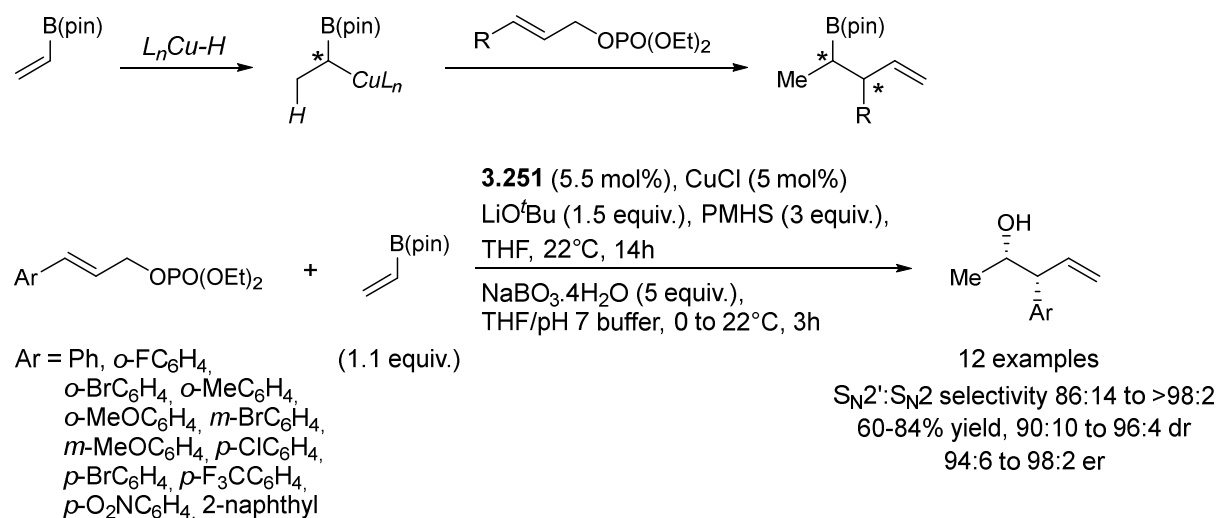
The introduction of vinylic units possessing a heteroatom in the allylic position by copper-catalyzed AAA is only possible via organoboron reagents, since the aluminum analogues are not accessible. Based on their previous reports, Hoveyda and coll. successfully developed the allylic substitution of *n*-hexyl(pinacolato)vinylboron reagents on aryl-substituted allylic phosphates, catalyzed by CuCl and a chiral sulfonate-imidazolium salt in the presence of a base (NaOMe) [172]. Among the various NHC precursors tested, **3.240** and **3.241** showed the best efficiency, site- and enantioselectivity, and were used with carbonyl- and acetal-functionalized vinylboron reagents (51-90% yield, >98% S_N2' and 84:16 to >98:2 er). This strategy has been used as a starting point for the synthesis of the Pummerer ketone, intermediate in morphine biosynthesis.

The use of boron-based nucleophiles also allowed expanding the scope of alkenyl groups introduced by copper-catalyzed AAA. Indeed, the methodology developed earlier by Hoveyda and coll. with organoaluminum reagents [164,165,166] is not typically applicable to carbonyl-functionalized reagents. The use of a B(pin)-based reagent provided the desired 1,4-dienes in good yields and high enantioselectivities (>93% S_N2', >83:17 er), despite the presence of a sensitive, possibly epimerizable stereogenic centre [173]. Several NHC precursors were examined: chiral monodentate and *O*-substituted NHC precursors were not efficient; chiral sulfonate-based imidazolium salts **3.240**, **3.242** and **3.250**, **3.251** showed better activity, but only **3.251** gave good enantioselectivities (Scheme 3-35). Large *Z*-alkenyl-B(pin) reagents required a different catalytic system (with **3.246**) to improve selectivity. The catalytic system was also used for several substrates leading to the synthesis of natural products.



Scheme 3-35. Reaction of a carboxylic ester-substituted alkenyl-B(pin) with aryl-substituted allylic phosphates [173].

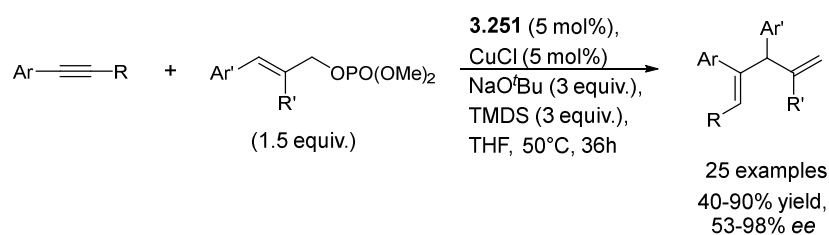
In order to gain access to enantioenriched homoallylic boronates, Hoveyda and coll. developed a sequential Cu-H addition to vinyl-B(pin)/Cu-catalyzed allylic substitution on allylic phosphates (Scheme 3-36) [174].



Scheme 3-36. Top: sequential enantioselective Cu-H addition to vinyl-B(pin) / S_N2'-allylic substitution. Bottom: Cu addition / allylic substitution on aryl-substituted phosphates, then C-B bond oxidation [174].

As confirmed by DFT calculations, chiral sulfonate-imidazolium salts showed a unique selectivity compared to bisphosphines or *O*-substituted imidazolium salts, in that they allowed avoiding competing routes (reaction of Cu-alkoxide complex with vinyl-B(pin) to give a Cu-vinyl complex, or direct reaction of the copper hydride with the allylic phosphate). The effectiveness of imidazolium salt **3.251**, compared to **3.242**, was explained by the limited steric repulsion between the *N*-aryl substituents and the approaching vinyl-B(pin) group in the Cu-H addition step and by a better positioning of the allylic phosphate during the diastereoselective allylic substitution.

The same year, Xiong and coll. described the sequential Cu-H addition to alkynes/Cu-catalyzed allylic substitution with allylic phosphates and a hydrosilane as reductant (Scheme 3-37) [175]. 1,4-skipped dienes were obtained, and again the careful choice of imidazolium salts associated to the copper salt allowed to orient the reaction regioselectivity. Thus branched, chiral skipped dienes were predominantly obtained via an S_N2'-type of addition in the presence of sulfonate-based imidazolium salts **3.242** and **3.251**, whereas the use of non-functionalized imidazolium salts favoured the linear 1,4-skipped dienes via an S_N2 addition. The use of **3.251** yielded the dienes in 53-98% *ee* (most examples above 90% *ee*).

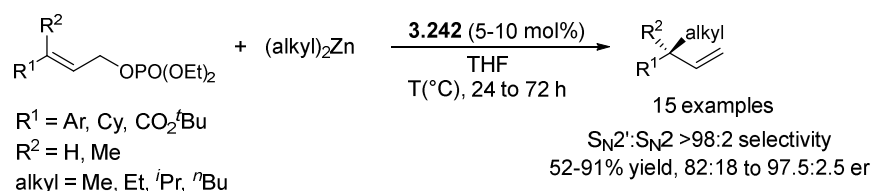


Scheme 3-37. Sequential enantioselective Cu-H addition to alkynes / S_N2'-allylic substitution [175].

Finally, chiral sulfonate-imidazolium salts enabled the copper-catalyzed AAA of organoboron reagents on variously substituted penta-2,4-dienyl phosphates and cyclic dienyl phosphates, giving functionalized 1,3-dienes with good to excellent S_N2'' selectivity (84–97% for propargyl-containing products and 69-96% for silyl-allenyl products) [176]. Again, among the various ligands used (bisphosphines, *O*-functionalized and sulfonate-functionalized imidazolium salts), the sulfonate-based pro-ligands showed unique efficiency in terms of enantioselectivity, and **3.247** proved the most efficient in terms of combined S_N2''-, *E:Z*- and enantioselectivity in dichloromethane.

3.3.4. Copper-free asymmetric allylic alkylation (AAA)

The exceptional ability of sulfonate-based NHC ligands to promote allylic alkylations of allylic phosphates has also been demonstrated without addition of a copper salt. Hoveyda and coll. examined allylic alkylations of allylic phosphates with organometallic reagents in the presence of various ligands or pro-ligands, namely phosphines, phosphine oxides and imidazolium salts [160]. In the presence of diethylzinc, the reaction occurred efficiently only with the sulfonate-based salt **3.242** (>98% conversion, >98:2 S_N2':S_N2 selectivity). *O*-functionalized imidazolium salts worked very sluggishly, while ethylsulfonate **3.262** (Chart 3-14) and sulfonate-NHC silver complex **3.242-Ag** did not furnish any of the expected product. The reaction worked well with di- or trisubstituted olefins, in the presence of various alkylzinc reagents (52-91% yield, >98:2 S_N2':S_N2 selectivity and 89.5:10.5 to 97.5:2.5 er) (Scheme 3-38).



Scheme 3-38. Copper-free AAA of di- and tri-substituted allylic phosphates with dialkylzinc reagents [160].

The rationale for such efficiency is the formation of a Zn-(sulfonate-NHC) complex **3.263** (Chart 3-14), that serves as an allylic alkylation catalyst itself. Its high reactivity can be explained by the enhanced Lewis basicity of the sulfonate, due to strong donation of the NHC relayed by the metal centre:

this allows for a good interaction with the approaching diethylzinc reagent. The phosphate group can also coordinate to the metal centre (cf. **3.264**), which places the allylic substrate in a favorable position to react with Et_2Zn and explains the high $\text{S}_{\text{N}}2'$ selectivity observed in all cases.

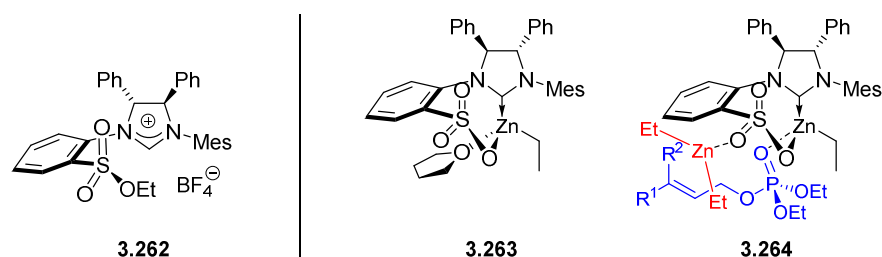


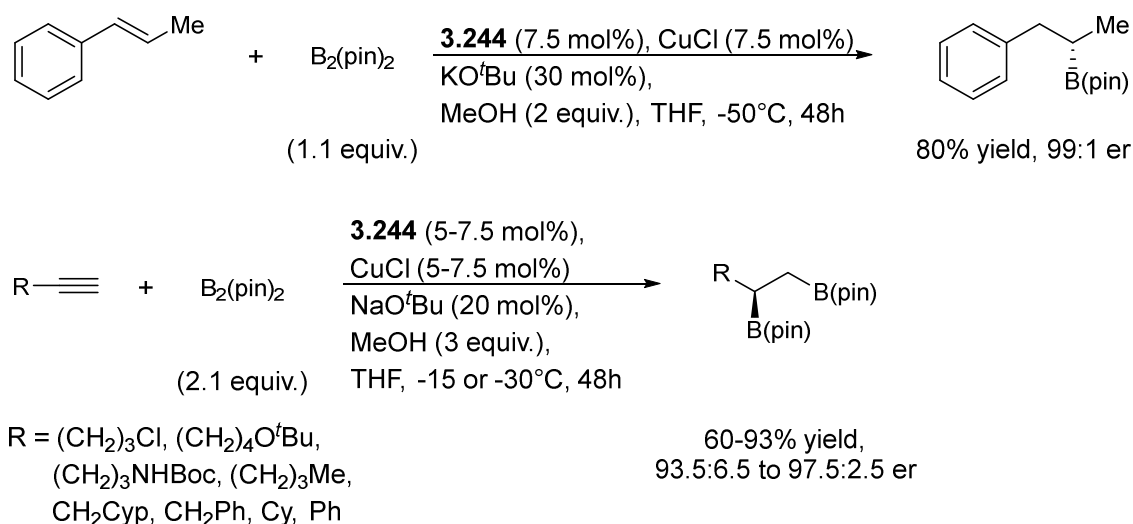
Chart 3-14. Left: ethylsulfonate **3.262**; right: Zn-(sulfonate-NHC) complex **3.263** and supposed reaction intermediate **3.264** [160].

The reaction does not work well with carboxylate-based NHC ligands because, in this case, the Lewis basic oxygen is not in a correct position to assist the addition of Et_2Zn . The reaction with sulfonate-based salt **3.242** works less efficiently than alkoxy-based salt **3.110** for the addition of α,β -unsaturated esters with alkylmagnesium halides, because the oxygen atom is not positioned correctly relative to the substrate to deliver the alkyl group from the alkylmagnesium halide. It is also less efficient with trimethylaluminum alone because the NHC-aluminum complex forms sluggishly, even though enantioselectivity is high. The reaction, however, goes to completion when Zn-NHC complex **3.263** is used in association with AlMe_3 as a more nucleophilic alkylating agent.

3.3.5. Copper-catalyzed enantioselective hydroboration

The development of efficient methods for enantioselective hydroboration reactions is synthetically very useful, as organoboranes can easily be further functionalized. Classical methods involving transition metals may be based on rhodium or iridium catalysts and copper-catalyzed hydroboration is a complementary method, as it can grant access to different regioisomers. Hoveyda and coll. capitalized on their experience in copper-catalyzed enantioselective transformations to investigate the hydroboration of aryl-substituted alkenes [177]. The use of NHC-Cu complexes indeed gave access to boronate isomers that complement those obtained with borohydride reagents or rhodium/iridium catalysts. An enantioselective version was successfully developed using sulfonate-functionalized imidazolium salt **3.244**. The reaction of (*E*)- β -methylstyrene furnished the boronate, after methanolic work-up to protonate the Cu-C bond, in 99:1 er, >98:2 site selectivity and 80% yield (Scheme 3-39). For cyclic olefins, however, better results were obtained with chiral monodentate NHC pro-ligands. The same strategy was applied to terminal alkynes. Thus vicinal diboronates were obtained with exceptional site selectivity (down to <2% of gem-diboronates) by a double copper-catalyzed hydroboration, using two equivalents of $\text{B}_2(\text{pin})_2$ [178]. Once again, the introduction of a chiral sulfonate-NHC ligand,

derived from **3.244**, on the copper complex induced a high selectivity for the formation of *terminal* vinylboronates, whereas secondary vinylboronates were formed preferentially with copper complexes bearing monodentate NHCs. The use of **3.244** as pro-ligand also allowed the reactions to proceed with high enantioselectivities (>93.5:6.5 er) (Scheme 3-39). Finally, the copper-catalyzed reaction enabled chemoselective diboration of alkynes in the presence of a halogen atom or an O- or N-based substituent, and more interestingly in the presence of an olefin (<2% reaction on the alkene).

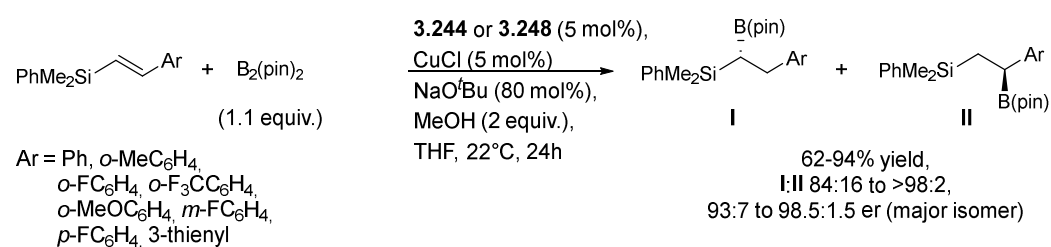


Scheme 3-39. Copper-catalyzed enantioselective hydroboration of (E)-β-methylstyrene (top) [177] and of terminal alkynes (bottom) [178].

Hoveyda and coll. then tackled the problem of 1,1-disubstituted aryl alkenes, for which classical hydroboration conditions (stoichiometric reagents, Rh- and Ir-catalyzed processes) allowed reaching good levels of enantioselectivity in very limited cases. Thus the enantioselective hydroboration of α-methylstyrene was investigated in the presence of CuCl and ^tBuOK, and several chiral NHC precursors [179]. Non-functionalized and O-functionalized imidazolium precursors yielded the expected product, albeit with very low levels of enantioselectivity. Sulfonate-containing imidazolium salts gave better results, **3.246** and **3.249** proving the best candidates with complete conversions and greater than 82:18 er. The dissymmetric substitution pattern on the N-aryl group, together with the presence of an *ortho*-phenyl substituent, gives enhanced flexibility to these two imidazolium salts so as to limit the steric repulsion between the substrate and the NHC backbone: this explains their better reactivity compared to **3.244**. Hydroboration of more sterically demanding and heterocyclic or carbocyclic 1,1-disubstituted aryl olefins performed better in the presence of **3.249**, where the N-aryl substitution pattern favors a more important tilt of the N-Ar moiety, with 57-90% yield and 91.5:8.5 to 96.5:3.5 er.

Following their work on copper-catalyzed hydroboration of aryl-substituted alkenes [177] and tandem double hydroboration of terminal alkynes to give vicinal diboronates [178], Hoveyda and coll. investigated the sequential copper-catalyzed protosilylation of terminal alkynes and enantioselective copper-catalyzed protoboration of the ensuing vinylsilanes [180]. The protosilylation was efficiently

and selectively carried out with Me₂PhSi-B(pin) in the presence of a monodentate Cu-NHC complex to give (*E*)-β-vinylsilanes. The latter were then converted into borosilanes with B₂(pin)₂ in the presence of a chiral copper-NHC complex. Although it was predicted from previous studies that alkyl-substituted substrates would preferentially furnish vicinal borosilanes for electronic reasons, the outcome was less obvious for aryl-substituted vinylsilanes. Copper-NHC complexes bearing chiral monodentate ligands indeed allowed the selective formation of vicinal borosilanes from *alkyl*-substituted vinylsilanes in 30–94% yield and 84:16 to 96.5:3.5 er. However in the case of aryl-substituted vinylsilanes, where either the silyl or the aryl group is capable of influencing site selectivity, the use of sulfonate-based NHC-Cu complexes proved essential to discriminate the different modes of Cu-B addition and to obtain predominantly geminal borosilanes (Scheme 3-40). Monodentate or *O*-functionalized NHC ligands gave low levels of selectivity, with only up to 70:30 in favor of the geminal borosilane. In the presence of bidentate sulfonate-NHC copper complexes formed from **3.244** or **3.248**, only one among all the possible addition modes seemed to limit the steric repulsion between the substrate and the NHC backbone to yield borosilanes in good yields, high *gem/vic* selectivities (84:16 to >98:2) and high enantioselectivities (93:7 to 98.5:1.5 er). As in the case of 1,1-disubstituted alkene hydroboration [179], a subtle variation in the substitution pattern on the *N*-aryl group induced high changes in selectivity, as the use of **3.242** gave equal amounts of geminal and vicinal borosilane.



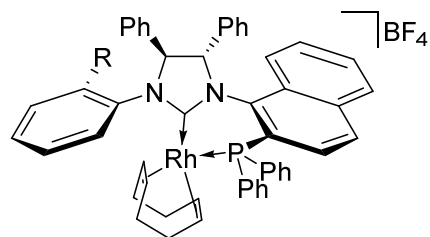
Scheme 3-40. Copper-catalyzed enantioselective synthesis of geminal borosilanes from aryl-substituted vinylsilanes [180].

4. Phosphorus-functionalized NHC ligands

Although *N*-heterocyclic carbenes are still often considered as phosphine analogues, their stronger σ-donor and somewhat weaker π-acceptor capacities, coupled with their fan-like geometry (in opposition to the cone-like geometry of phosphines), put them definitely in a category of their own [181,182,183]. Both phosphines and NHCs are among the most useful ligand families for catalytic applications and their association to form strongly coordinating, polydentate ligands with complimentary properties has rapidly been considered by chemists [184]. The origin of chirality for ligands falling into this category is varied – central (on carbon), planar and axial chirality, but also central chirality at the phosphorus atom, which brings the source of chiral information close to the catalytic center.

4.1. Central chirality

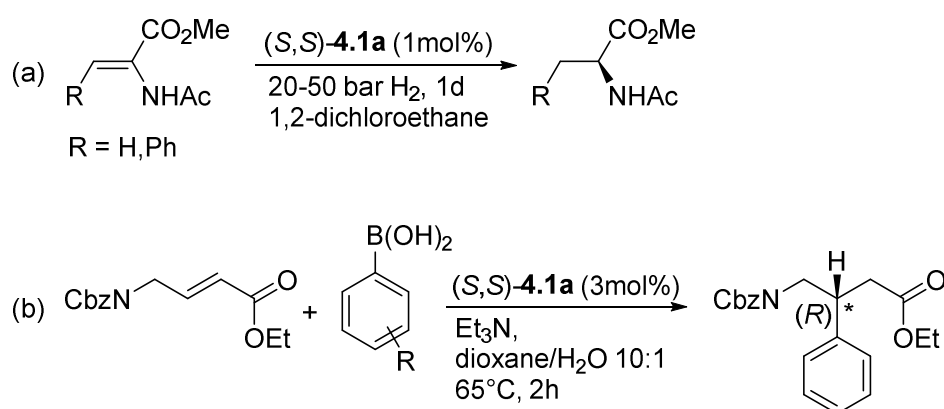
In 2004, the Helmchen group reported chiral bidentate NHC-phosphine ligands where the two chiral centres are contained in the heterocycle (Chart 4-1) [185]. These imidazolin-2-ylidenes are related to Grubbs' monodentate ligands [186], where one aryl group at nitrogen has been replaced by a naphthylphosphine. One interest of complex **4.1a** is the relay role of the *i*Pr group on the aryl moiety, which is placed *anti* to the phenyl group on the backbone. Transmetalation via silver complexes afforded air-stable rhodium complexes **4.1**. In **4.1a**, the association of the NHC with the naphthyl moiety led to a mixture of configurationally stable atropisomers in a 2:1 ratio, thus adding axial chirality.



R = *i*Pr (**4.1a**), H (**4.1b**)

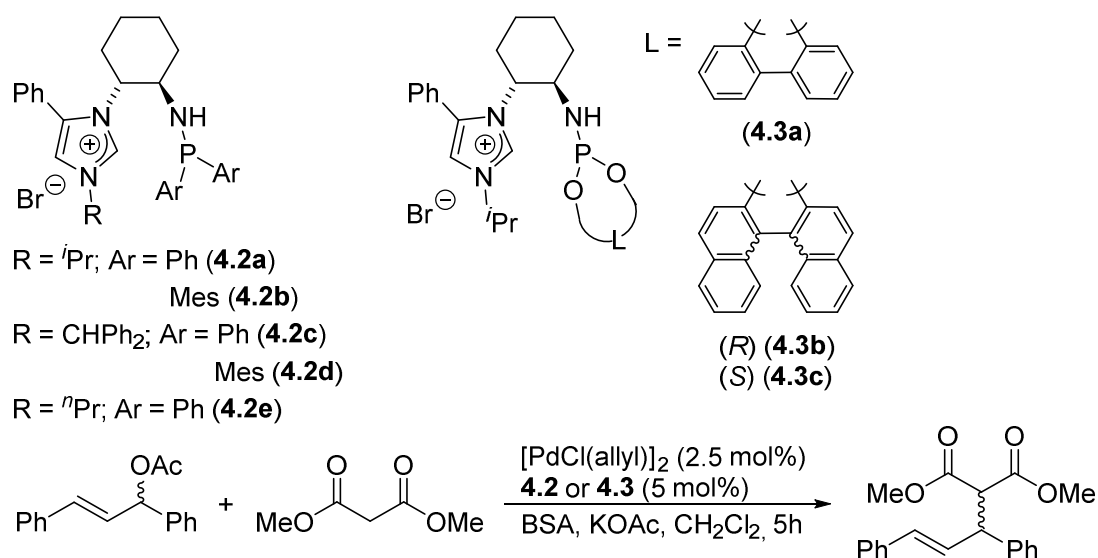
Chart 4-1. Rhodium complex described by Helmchen and coll. [185].

Rhodium complex **4.1a** proved to be active for the asymmetric hydrogenation of substituted acrylic acid derivatives, even if its activity was somewhat lower than that of phosphine-based systems. Enantioselectivity levels, however, were very high (Scheme 4-1 (a), up to 99% *ee* with R = Ph). The same complex was tested for asymmetric conjugate additions of arylboronic acids (Scheme 4-1 (b)) [187]. Compared to their previously reported results, where (*R*)- or (*S*)-BINAP were used in the presence of a rhodium precursor, both activities and enantioselectivities were greatly improved with rhodium complex **4.1a** (>99% *ee* in 2 h at 65°C vs. 86% *ee* in 24-48 h at 100°C for the conjugate addition to an α,β -unsaturated ester) and were among the best results reported in the literature at that time for α,β -unsaturated esters and, less overwhelmingly, for cyclic enones.



Scheme 4-1. (a) Asymmetric hydrogenation of *N*-acetamidoacrylate (R=H) or cinnamate (R=Ph); (b) Asymmetric conjugate addition of phenylboronic acid to an α,β -unsaturated ester [187].

Mixed P,C_{NHC} ligands bearing centers of chirality have also been described by Douthwaite and coll. in 2005 [188]. They are based on (1*R*,2*R*)-*trans*diaminocyclohexane, a frequently used building block in asymmetric catalysis. Thus, a series of imidazolium-aminophosphines (**4.2**) and imidazolium-phosphoramidates (**4.3**) have been prepared in good yields (Scheme 4-2). In the latter case, the use of (*R*)- and (*S*)-binaphthol-derived phosphoramidates allowed assessing the implication of the second source of chirality (here, axial chirality) in asymmetric catalysis.



Scheme 4-2. Imidazolium-aminophosphines (**4.2**) and imidazolium-phosphoramidates (**4.3**) developed by Douthwaite and coll. [188].

The precursors of NHC-aminophosphine and NHC-phosphoramidate ligands have been deprotonated *in situ* in the presence of palladium precursor [Pd(η^3 -C₃H₅)Cl]₂ and the resulting species were active in asymmetric allylic substitution (Scheme 4-2) [188]. Compared to analogous chiral di-NHC and NHC-imine ligands [67], the mixed P,C_{NHC} ligands proved to be more active: whereas reactions required typically 15 h at 50°C to obtain good yields with the former, P,C_{NHC} ligands furnished the products in moderate to excellent yields (64-98%) after 5 h at 0 or 25°C. The authors attributed this higher reactivity to the phosphine potential to act as a π -acid relieving charge build-up at the palladium center. Lower yields were obtained with phosphines bearing mesityl groups (70% with **4.2b** and 64% with **4.2d**), probably due to their higher steric hindrance compared to phenyl groups. Phosphoramidate-based ligands gave similar yields, although **4.3c** showed a lower activity compared to the phosphine analogue **4.2a**, especially at low temperature. Conversely, the *ee* values were significantly lower with P,C_{NHC} ligands than with NHC-imines (up to 42% vs. up to 92%, respectively).

The same imidazolium-P salts were then engaged in the transfer hydrogenation of acetophenone in the presence of iridium precursor [Ir(COD)Cl]₂. No positive effect of the phosphorus atom was observed since the reaction rates were similar to those reported for other NHC-Ir complexes, with a preference for phosphoramidates **4.3** over phosphines **4.2**. *Ee* values were low (up to 37%) and comparable to those

obtained with other P- or S-functionalized NHC ligands for hydrogenation reactions. (Note: this was the only point of comparison for the authors at that time).

A different approach has been developed by several groups, *i.e.* introduction of a chiral center on the tether between the NHC and the P donor. The first to envisage this strategy in 2006 was the group of Pfaltz [189]. They designed mixed phosphine-NHC ligands structurally related to their successful pyridylalkyl phosphinite ligands, as well as chiral phosphinoxy-NHCs issued from chiral epoxides. Iridium complexes of these ligands were obtained in classical conditions and analysis of the NMR and X-Ray data of **4.4c** indicated a similar *trans* influence for the phosphine and the NHC donors (Chart 4-2).

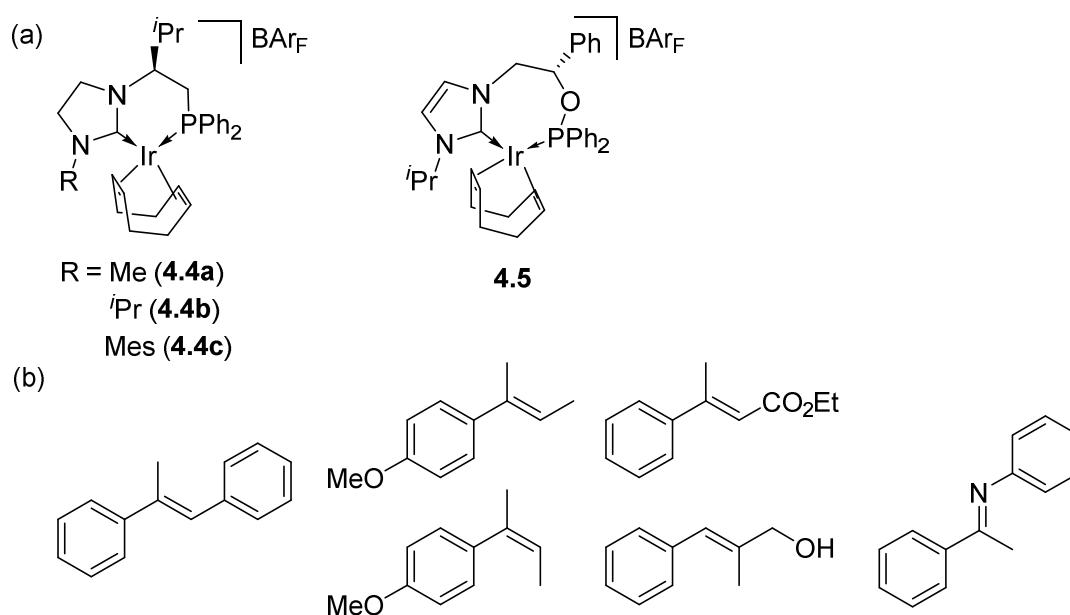
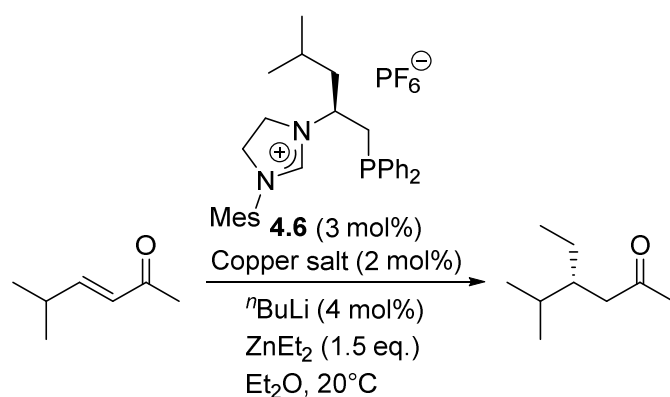


Chart 4-2. (a) Iridium complexes bearing mixed phosphine-NHC (**4.4**) and phosphinoxy-NHC (**4.5**) ligands; (b) substrates for asymmetric hydrogenation (conditions: 1 mol% **4.4** or **4.5**, CH₂Cl₂, RT, 50 bars H₂) [189].

All complexes were evaluated as catalysts for the hydrogenation of various olefins and one imine. With unfunctionalized olefins, *P,C*_{NHC} ligands (**4.4**) gave lower activities and enantioselectivities than their *P,N* or (dihydrooxazole)-NHC counterparts (10-95% yield in 12 h and 0-63% *ee* for **4.4** and **4.5** vs. >99% yield in 2 h and 41-90% *ee* for other ligands). On the other hand, they were better with the α,β -unsaturated ester and allylic alcohol tested and even allowed to hydrogenate an imine, which was not possible with the (dihydrooxazole)-NHC analogue. However, the enantioselectivities stayed moderate for all *P,C*_{NHC} complexes (up to 60% *ee*).

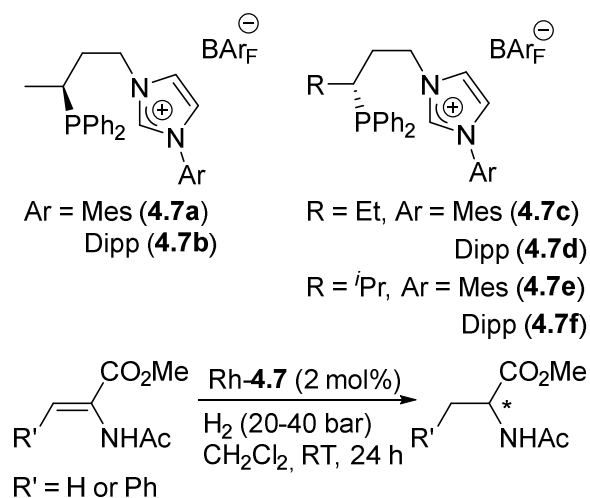
Soon after, the Mauduit group described a similar phosphine-NHC ligand for applications in copper catalysis [95]. The phosphine-imidazolium pro-ligand **4.6** was synthesized in two steps from their previously reported hydroxy-functionalized imidazolium salt [92] and used in the enantioselective copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone and 5-methylhex-3-en-2-one

(Scheme 4-3). Moderate to good conversions and modest enantioselectivities were obtained with the phosphine-NHC ligand. Longer reaction times were required to reach good conversions compared to other ligands (particularly the mesylate-functionalized analog **3.29** (Chart 3-2, OMs instead of PPh₂) and a non-functionalized bis-NHCs) and, in the case of the reaction on 2-cyclohexenone, enantioselectivities were lower than that obtained with **3.29** (41% *ee* with **4.6** vs. 80% *ee* with **3.29**). This was attributed to the steric bulk of the PPh₂ moiety, situated too close to the asymmetric center.



Scheme 4-3. Copper-catalyzed conjugate addition of diethylzinc to 5-methylhex-3-en-2-one with ligand **4.6** [95].

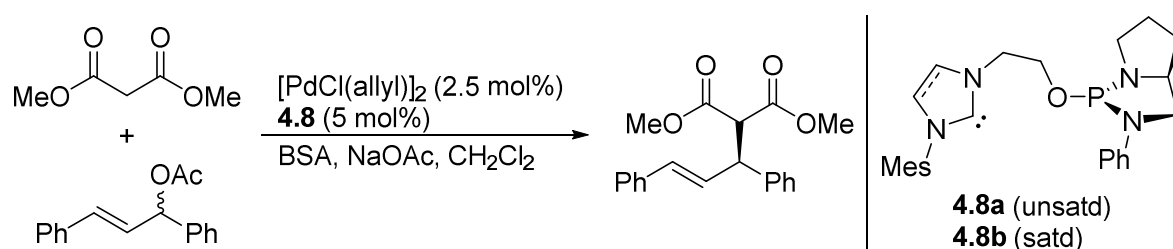
In 2011, Jubault, Leclerc and coll. described the synthesis of chiral phosphine-imidazolium salts **4.7**, precursors of phosphine-NHC ligands, with the chiral center α to the phosphino group (Scheme 4-4), in contrast with ligands **4.4** and **4.6**, where the chiral center is α to the NHC [190]. The second difference is that in the present case, the unsaturated version of the NHC was used. A series of iridium(I) complexes were prepared and tested in the asymmetric hydrogenation of various olefins. Only methylstilbene gave encouraging results, however 40-50 bars of H₂ at 50°C were required to reach complete conversions. The best results in terms of activity and enantioselectivity (up to 63% *ee*) were obtained with the most sterically demanding ligand (**4.7f**).



Scheme 4-4. Hydrogenation of dehydroamino acids catalyzed by chiral Rh complexes **4.7** [190].

Rhodium(I) complexes were also evaluated in the asymmetric hydrogenation of dehydroamino acids (Scheme 4.4) [190]. In this case, the ligands bearing a mesityl group on the NHC (**4.7a**, **c** and **e**) gave more efficient catalysts than those bearing a DIPP and allowed modest to good conversions and up to 61% *ee* (**4.7e**).

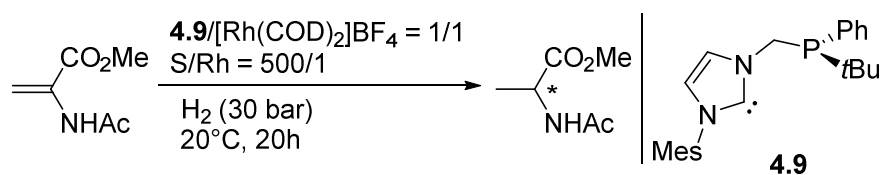
The use of a P-coordinating atom has the advantage of offering the possibility to introduce the chirality directly on the phosphorus atom, therefore very close to the metal centre. Thus Martin, Buono and coll., relying on their experience in the design of P-chiral ligands, reported the synthesis of bidentate NHC-diazaphospholidine ligands, bearing either unsaturated (**4.8a**) or saturated (**4.8b**) NHCs (Scheme 4-5) [191].



Scheme 4-5. Bidentate NHC-diazaphospholidine ligands bearing chirality at phosphorus [191].

The ligands were then engaged in Pd-catalyzed asymmetric allylic alkylation reactions [191]. Use of a monodentate NHC was detrimental to the catalytic activity, but a bidentate NHC-diazaphospholidine was active for the aforementioned reaction. Although the reaction rates were inferior to those observed with diazaphospholidines alone, the enantioselectivities were the highest with the mixed *P,C*_{NHC} ligands (up to 89% *ee*), especially with the unsaturated version (**4.8a**). The best results, however, were obtained by mixing monodentate NHCs and monodentate diazaphospholidines. This could be explained by a lower tunability of the P-functionalized NHC ligand, as the steric bulk can only be changed on one side of the NHC.

In a patent dating from 2008, Jäkel *et al.* described the synthesis of bidentate NHC-phosphine (**4.9**) or NHC-phosphite ligands, bearing the chirality on the phosphorus atom only [192]. Many transition metal salts have been evaluated for coordination studies, but only one application in asymmetric catalysis was described, i.e. the rhodium-catalyzed hydrogenation of methyl α -acetamidoacrylate (Scheme 4-6). The efficiency of the chiral NHC-phosphine ligand compares well with those of previously reported P-chiral diphosphines, since 99.9% *ee* were obtained (98 to 99.9% *ee* with diphosphines).



Scheme 4-6. Chiral-at-phosphorus bidentate NHC-phosphine ligand used in the rhodium-catalyzed hydrogenation of methyl α -acetamidoacrylate [192].

4.2. Planar chirality

Planar chirality was also used frequently to produce chiral bidentate P,C_{NHC} ligands. Most often, the ferrocenyl unit was used as a mean to introduce planar chirality, with reports by the groups of Chung [193] and Togni [194,195,196] as early as 2003-2004. In their case, Ugi's amine was used as a starting block, therefore adding a centre of chirality to the plane of chirality. Chung *et al.* reported a coordinatively saturated rhodium(I) complex (**4.10**, Chart 4-3) that proved inactive in the asymmetric hydrogenation of dimethyl itaconate at 50°C under 10 atm of H₂ [193]. An *in-situ* generated version, bearing only one P,C_{NHC} ligand on rhodium, was highly active in the same reaction, with a complete conversion in 4 h (RT, 4 atm H₂) but poorly enantioselective (13% *ee*).

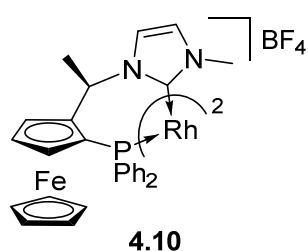


Chart 4-3. Rhodium(I) complex bearing planar chiral ferrocenyl phosphine-NHC ligands [193].

Togni *et al.* first proposed in 2004 a C_2 -symmetrical, tridentate P,C_{NHC},P ligand based on Ugi's amine (Chart 4-4). Preliminary catalytic tests were carried out with a palladium complex of this ligand (**4.11a**), with the enantioselective addition of morpholine to methacrylonitrile (Scheme 4-7) [194]. The *ee* of 37% and a good activity were judged encouraging, even though the enantioselectivity was lower than that observed with a Pigiphos-containing Ni(II) complex (69% *ee* under the same conditions). After modification of the phosphine substituents, the palladium complex of the bulkier, more electron-rich ligand (**4.11b**) furnished the addition products with better *ees* (up to 75% at -80°C) [195]. However, once again these systems did not offer any real advantage over the Pigiphos-based Ni(II) complexes for the catalyzed addition of amines to acrylonitriles.

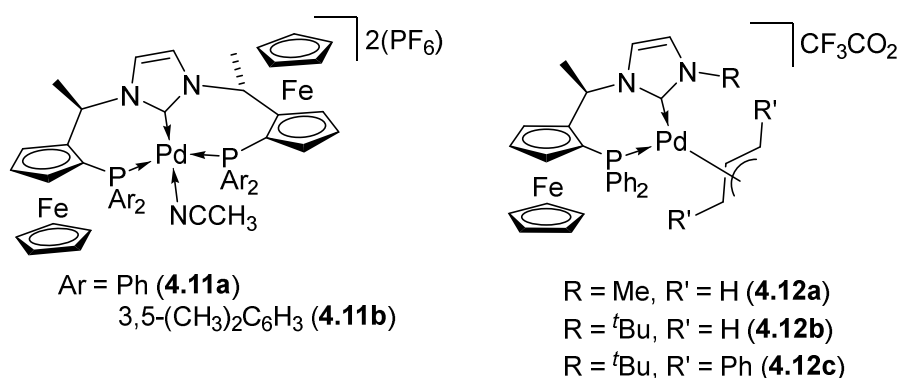
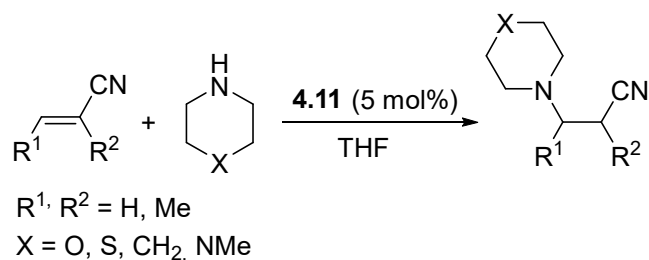
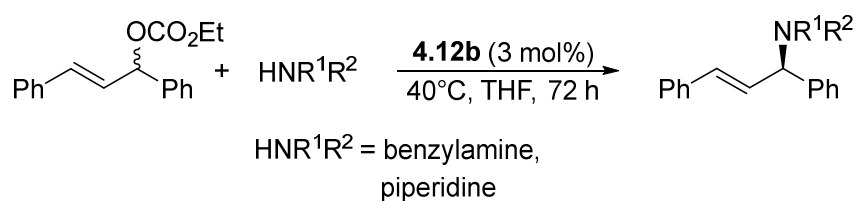


Chart 4-4. Palladium(II) complexes bearing tridentate (**4.11**) or bidentate (**4.12**) planar chiral ferrocenyl phosphine-NHC ligands [194,195,196].



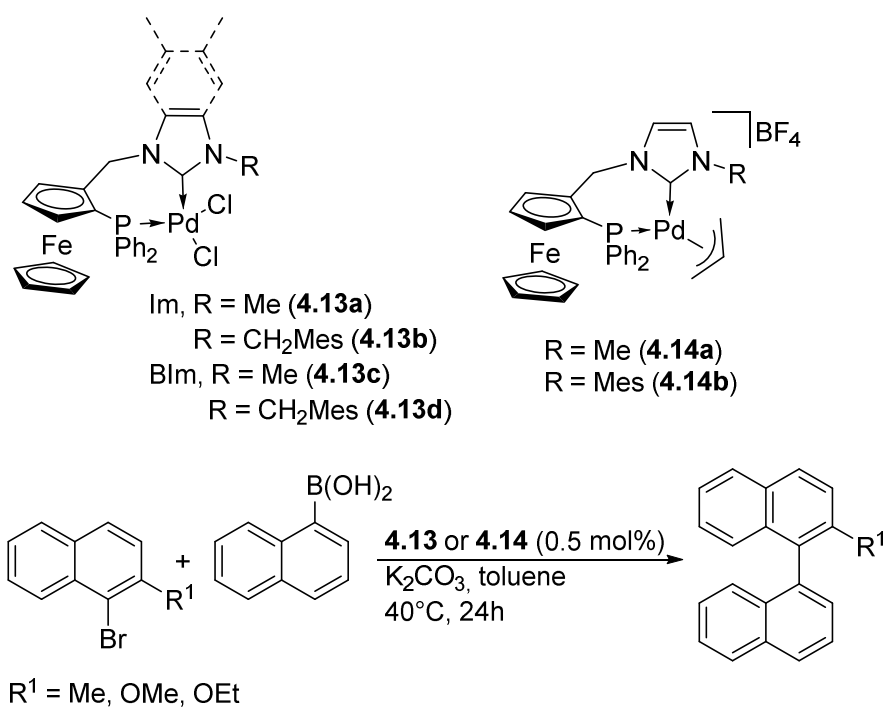
Scheme 4-7. Asymmetric hydroamination of cyano olefins with palladium complexes **4.11** [194, 195].

In 2007, Togni designed bidentate ligands similar to those of Chung and used them to generate Pd(II)-allyl complexes (**4.12**) [196]. Palladium complex **4.12b** was evaluated in asymmetric allylic amination reactions (Scheme 4-8) and proved moderately active (32% conversion of the starting allylic carbonate with benzylamine, 58% with piperidine) and poorly selective (5% *ee* for both). The authors attributed these disappointing results to electronic effects. Indeed, phosphine and NHC donors have similar *trans* effects, resulting in a non-selective nucleophilic attack; the use of a related mixed phosphine-pyrazole ligand, on the other hand, induces an exclusive attack *trans* to phosphorus and leads to very high enantioselectivities (97.7 and 97.2% *ee*, respectively).



Scheme 4-8. Asymmetric allylic amination with palladium complex **4.12b** [196].

In 2010, Labande and coll. reported ferrocenyl NHC-phosphine ligands related to those of Chung and Togni, but bearing only planar chirality [197]. Pd(II) complexes of these ligands (**4.13** and **4.14**) were generated and were the first complexes with chiral NHCs evaluated in the asymmetric Suzuki-Miyaura reaction (Scheme 4-9). Very good activities (86 to 95% yield with complex **4.13a**) were obtained with low catalyst loadings, however with moderate *ees* (up to 41%). Changing the substituents around the NHC did not drastically improve the enantioselectivity, since only 46% *ee* were reached with **4.13b**, and the complexes proved inactive for the transformation of sterically demanding substrates (*e.g.* $R^1 = P(O)(OEt)_2$), probably because of the strongly chelating nature of the ligands and their steric bulk [198].



Scheme 4-9. Asymmetric Suzuki-Miyaura reaction with palladium complexes bearing planar chiral ferrocenyl NHC-phosphine ligands [197,198].

Planar chiral ligands are mostly but not exclusively based on the ferrocenyl unit. Thus in 2004, the Bolm group reported the synthesis of planar chiral NHC-phosphine ligands taking advantage of the paracyclophane backbone (Chart 4-5) [199]. Iridium(I) complexes of these ligands (**4.15**) were prepared and evaluated as catalysts in the asymmetric hydrogenation of simple or functionalized alkenes (Scheme 4-10). All proved to be active and the products were obtained with moderate to good enantioselectivities (up to 82% for simple alkenes and 89% for functionalized ones). Activity and enantioselectivity levels appear to be dependent on the nature and steric bulk of the imidazole substituent.

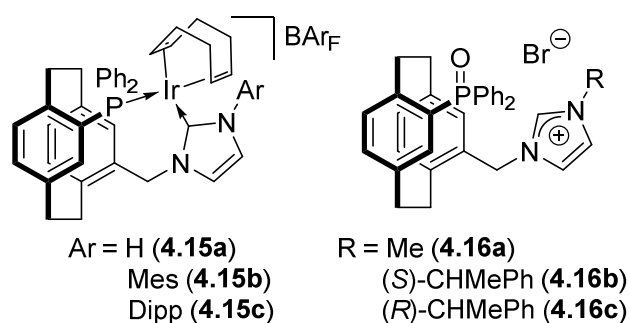
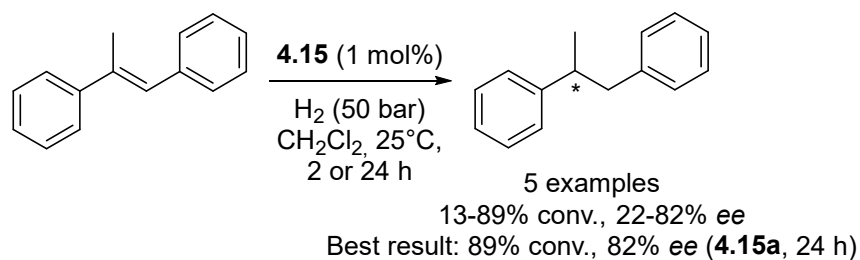
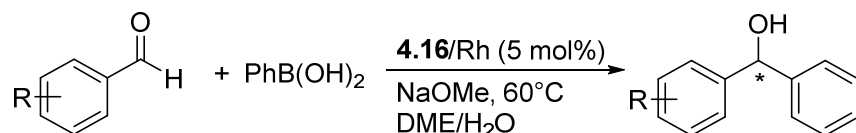


Chart 4-5. Left: iridium(I) complexes (**4.15**) bearing planar chiral NHC-phosphine ligands based on the paracyclophane backbone [199]; right: planar chiral imidazolium-phosphinoxy pro-ligands based on the paracyclophane backbone [200].



Scheme 4-10. Hydrogenation of (*E*)-1,2-diphenyl-1-propene catalyzed by chiral iridium(I) complexes **4.15** [199].

The same group subsequently described the synthesis of planar chiral imidazolium salts bearing a phosphine oxide moiety (**4.16**) [200]. Their deprotonation in the presence of a rhodium precursor presumably afforded the NHC complexes (neither isolated nor characterized in solution), which were evaluated as catalysts for the addition of arylboronic acids to aromatic aldehydes. According to the nature of the imidazole substituent, *ees* up to 38% were obtained. The phosphinoxy-derived imidazolium salts performed better than the methoxy-substituted or, even more, the phosphine-substituted ones. For the imidazolium salts possessing both planar and central chirality, planar chirality was the stereo-determining element.



Scheme 4-11. Asymmetric addition of arylboronic acids to aldehydes [200].

4.3. Axial chirality

Almost ten years after the work of Helmchen and coll. on centrally and axially chiral P,C_{NHC} ligands (see Section 4.1) [185,187], the Shi group described in 2013 a series of chiral NHC-phosphine ligands based on a 1,1'-binaphthyl scaffold, therefore uniquely based on axial chirality (Chart 4-6) [201]. Their previous work, based on bis(NHC) ligands derived from BINAM and H8-BINAM, allowed them to obtain efficient catalysts in terms of yields and enantioselectivities [202,203,204,205,206]. In order to widen the range of catalysts, they exchanged one of the NHC moieties for a phosphine. Thus iridium(I) and rhodium(I) complexes were prepared with these ligands and evaluated as catalysts for the asymmetric hydrogenation of functionalized olefins (Scheme 4-12).

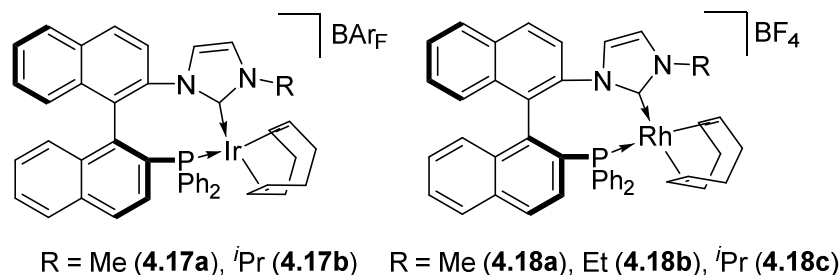
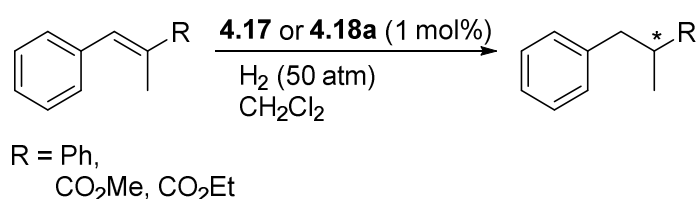
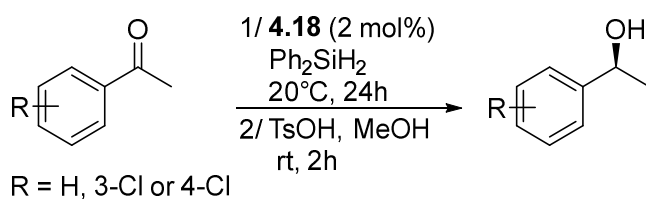


Chart 4-6. Complexes of chiral NHC-phosphine based on the 1,1'-binaphthyl scaffold [201,207].



Scheme 4-12. Hydrogenation of alkenes catalyzed by chiral complexes **4.17** and **4.18a** [201].

The iridium complexes **4.17** gave a complete conversion of acrylates at 25°C, however with much lower enantioselectivities than those obtained by the Pfaltz group with N,P-iridium complexes (up to 38% *ee* with **4.17** vs. 97% *ee* with N,P-Ir complexes). They gave instead moderate conversions for the hydrogenation of (*E*)-1,2-diphenyl-1-propene at 50°C (35% conv. and 61% *ee*), whereas the rhodium complex **4.18a** showed a very poor activity whatever the olefin used. However, **4.18a** and other rhodium(I) complexes (Chart 4-6) showed good activities in the asymmetric hydrosilylation of acetophenone and a few of its derivatives (Scheme 4-13) [207]. Thus up to 91% yield and 72% *ee* were obtained with the least encumbered ligand. The authors explained this trend on the basis of the structure of the different complexes, where increasing the steric hindrance on the ligands pushes the rhodium away from the chelate, and thus from the chiral source.



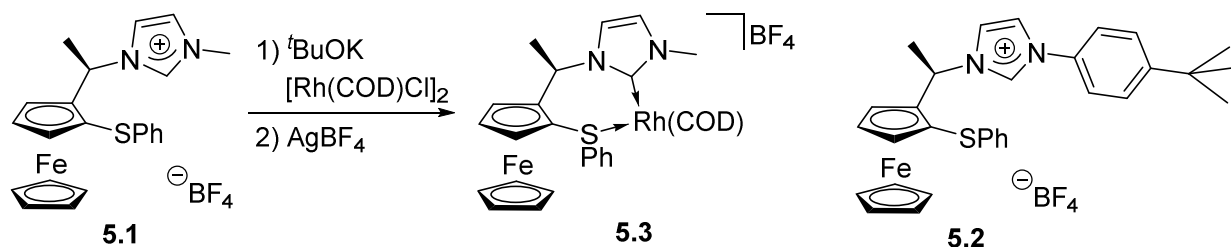
Scheme 4-13. Hydrosilylation of acetophenone catalyzed by chiral complexes **4.18** [207].

Chiral palladium(II) complexes were also reported but were only investigated in Suzuki-Miyaura or Heck reactions with model substrates generating no chiral products; no asymmetric version was reported.

5. Sulfur-functionalized NHC ligands

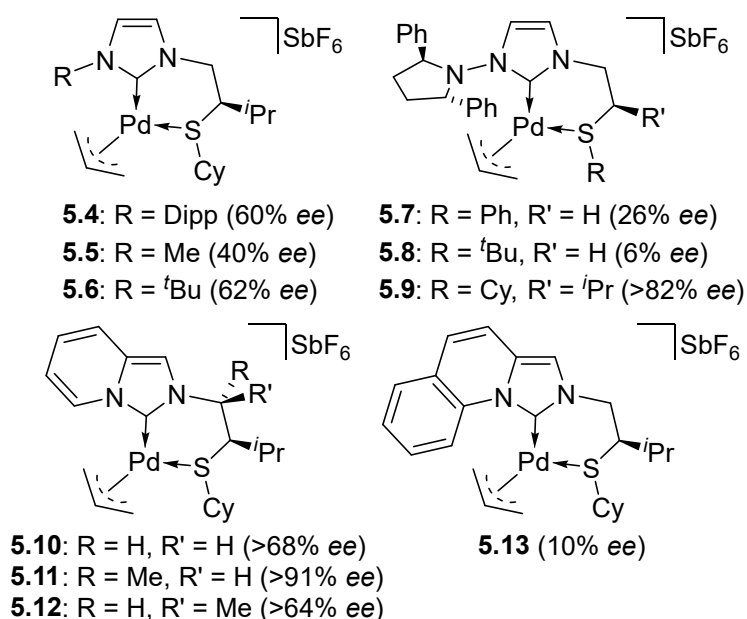
Although many sulfur functionalized NHCs have been described [25,26], only few of them have been used in asymmetric catalysis. In this field, only thioether-functionalized NHCs exhibit a direct interaction between the sulfur atom and the metal center. Chiral sulfoxide-functionalized NHC ligands were also widely and successfully studied in asymmetric catalysis, however in the latter class the oxygen atom is interacting with the metal center and therefore the related compounds/results are discussed in Section 3.3.

To the best of our knowledge, the first chiral NHC-thioether ligands used in asymmetric catalysis were described by Chung *et al.* [208]. Imidazolium salts **5.1** and **5.2** could be efficiently obtained from commercially available Ugi's amine. Rhodium complex **5.3** (Scheme 5-1) showed only moderate catalytic activities and low enantioselectivities (18% *ee*) in the hydrogenation of dimethyl itaconate.



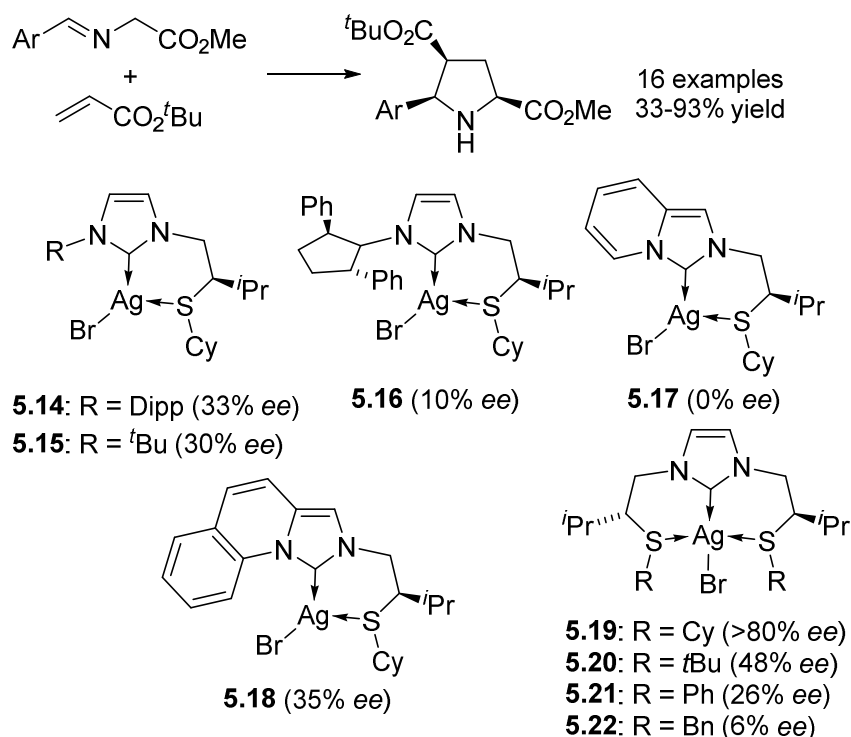
Scheme 5-1. Chiral NHC-thioether ligand developed by Chung *et al.* [208].

Fernandez and coworkers synthesized a family of palladium complexes of chiral NHC-thioether ligands (**5.4-5.13**, Scheme 5-2) which were tested in the asymmetric allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate with low to very good enantioselectivities (*ee* up to 91% with **5.11**) [209,210]. These complexes generally proved more efficient than those described by Williams [66] or Douthwaite [67] based on NHC-imine ligands. Indeed, **5.4-5.13** displayed similar reactivity as Pd complexes with proligands **2.69-2.76** [66], but gave higher *ees*. Pd complexes made with proligands **2.77-2.84**, developed by Douthwaite [67], necessitate higher temperatures compared to **5.4-5.13** but gave similar levels of enantioselectivity. Although the metallacycle size is the same in all cases, it is difficult to correlate activity and heteroatom nature. In terms of enantioselectivity, the better proximity of the chirality source in **2.77-2.84** and **5.4-5.13** may explain their efficiency.



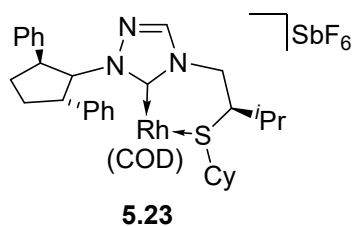
Scheme 5-2. Palladium complexes of chiral NHC-thioether ligand developed by Fernandez *et al.* [209,210]. The *ee* obtained for the asymmetric allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate is given in parentheses for each complex.

Silver complexes of a few NHC-thioether ligands presented in Scheme 5-2 were used by the same team in the enantioselective 1,3-dipolar cycloaddition of azomethine ylides with *tert*-butyl acrylate (**5.14-5.18**, Scheme 5-3). Good yields could be obtained but with moderate enantiomeric excesses (up to 35% *ee*) [211]. Silver complexes of new tridentate NHC-bis-thioether ligands **5.19-5.22** were also tested for the same reaction, complex **5.19** proving to be the most efficient catalyst (76% *ee* (**5.19**) vs. 6-48% *ee* (**5.20-5.22**) with Ar = 2-tolyl) (Scheme 5-3).



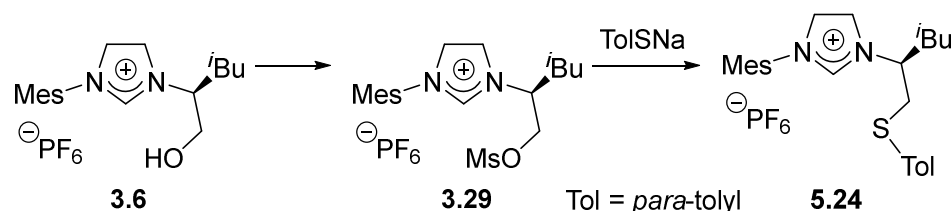
Scheme 5-3. Silver complexes of chiral NHC-thioether ligand developed by Fernandez *et al.* [211].

Fernandez, Lassaletta and coworkers synthesized the rhodium(I) complex **5.23** (Scheme 5-4) obtained from a chiral triazolium-thioether salt [212]. This complex was used in the asymmetric hydrosilylation of acetophenone: good yields could be obtained but with moderate enantiomeric excesses (up to 62% *ee*).



Scheme 5-4. Rhodium complex of a chiral NHC-thioether ligand developed by Fernandez, Lassaletta *et al.* [212].

From a readily available hydroxyl-imidazolium salt [92], Mauduit *et al.* synthesized the imidazolium-thioether salt **5.24** which was used in the asymmetric copper-catalyzed addition of dialkylzinc on enones, however only very low enantioselectivities could be obtained (<6% *ee*) [95].



Scheme 5-5. Synthesis of imidazolium-thioether salt **5.13** by Mauduit *et al.* [95].

6. Conclusions

The present review summarizes the chiral functionalized NHC (pro)ligands and complexes that were applied to metal-mediated asymmetric catalysis. It can be observed that *N*-, *O*-, *P*- and *S*-additional functions are all represented, as well as all types of chirality, *i.e.* central, axial and planar. Noteworthy, within the compounds of interest here, central chirality located either on the *N*-side arm or on the ligand backbone is dominant. While *P*- and *S*-groups are exclusively present as additional neutral donors, *O*-functionalized species are in most cases acting in their deprotonated forms as anionic donors, *i.e.* alkoxides and sulfonates. While chiral *N*,*C*_{NHC}-metal complexes were mostly applied to asymmetric hydrogenation and hydrosilylation reactions, the field of applications of *O*,*C*_{NHC} derivatives is clearly dominated by asymmetric conjugate or allylic alkylation reactions. Several efforts have been devoted to the mechanistic understanding of many of these reactions, as well as to the identification of key intermediates. NHC-complexes presenting an additional *P*-donor function were applied to a wide scope of catalytic reactions, such as hydrogenation, allylic alkylation, hydroamination, C-C coupling, but no clear specific target reaction could be privileged. The joint presence of a *P* and an NHC coordinating units, both strong σ -donors, may have a beneficial effect for certain reactions but can be detrimental to activity for others (such as the Suzuki-Miyaura cross-coupling), where coordinative flexibility rather than strong chelates are required. NHC-metal complexes functionalized with *S*-donors were much less studied than *O*-functionalized ones. Considering the richness of sulfur-based synthetic and coordination chemistry, further development of chiral *S*,*C*_{NHC} (pro)ligands and metal complexes is expected. Evaluation of thiolate-NHC analogues of performant alkoxide-NHC systems to Cu-ACA or Cu-AAA would be of great interest.

Because of the wide range of investigated reactions and many parameters that may vary from one study to the other, general trends on the influence of the additional donor nature (N, O, P, S) or type of chirality (central, axial and planar) do not clearly emerge. However, when available, the catalytic

performances of different systems for a similar reaction were discussed in their dedicated sections. These analyses allowed highlighting a few interesting features. For the catalytic reactions performed with *O*-functionalized NHC species, the –OH derivatives were shown to be in most cases much more effective than their –OMe (or non-functionalized) analogues. Sulfonate-based NHCs almost systematically performed better than alkoxy-functionalized NHCs in copper-catalyzed ACA and AAA reactions in terms of chemo-, regio- and enantioselectivity. They are only seldom surpassed by their *O*-functionalized counterparts. Also, as a representative example, an NHC-phosphinite (P, C_{NHC}) performed better than similar NHC-pyridine (N, C_{NHC}) systems in asymmetric hydrogenation of trisubstituted alkenes with cationic Ir^I complexes. A clear chelate ring-size effect could be observed in the Rh-catalyzed hydrosilylation of aryl alkyl ketones, for which reaction 5-membered metallacycles gave rise to the best *ee* values.

7. Acknowledgments

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8. References

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