

# Copper-NHC complexes in catalysis

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Although the chemistry of copper has a long history [1a-d], the relatively recent discovery of *N*-heterocyclic carbene (NHC) as transition-metal supporting ligands has permitted novel vistas to be explored in copper reactivity and catalysis [1e,f]. Shortly after the seminal discovery of Arduengo, Raubenheimer reported a neutral copper carbene complex [1e,1f,2]. However, the field remained dormant for almost ten years. In the early 2000s, new breakthroughs were achieved: first, the synthesis of NHC-copper using Cu<sub>2</sub>O was reported by Danopoulos and followed by the first application in catalysis by Woodward [3,4]. The work by Buchwald and Sadighi appeared next, where the first catalysis using a well-defined complex was described [5].

The first reports in this field were based on systems used to mimic their phosphine relatives. NHCs have become ligands of significant interest due to their steric and electronic properties [6,7,8]. Combining the NHC ligand family and copper became, for some, an obvious and productive area [6]. Over the last decade alone, numerous systems have been developed. Copper-NHC complexes can be divided into two major classes: neutral mono-NHC and cationic bis-NHC derivatives: [Cu(X)(NHC)] [9] (X = halide, acetate, hydroxide, hydride, etc.) and [Cu(NHC)(L)][Y] (L = NHC or PR<sub>3</sub>; Y = PF<sub>6</sub>, BF<sub>4</sub>) [10].

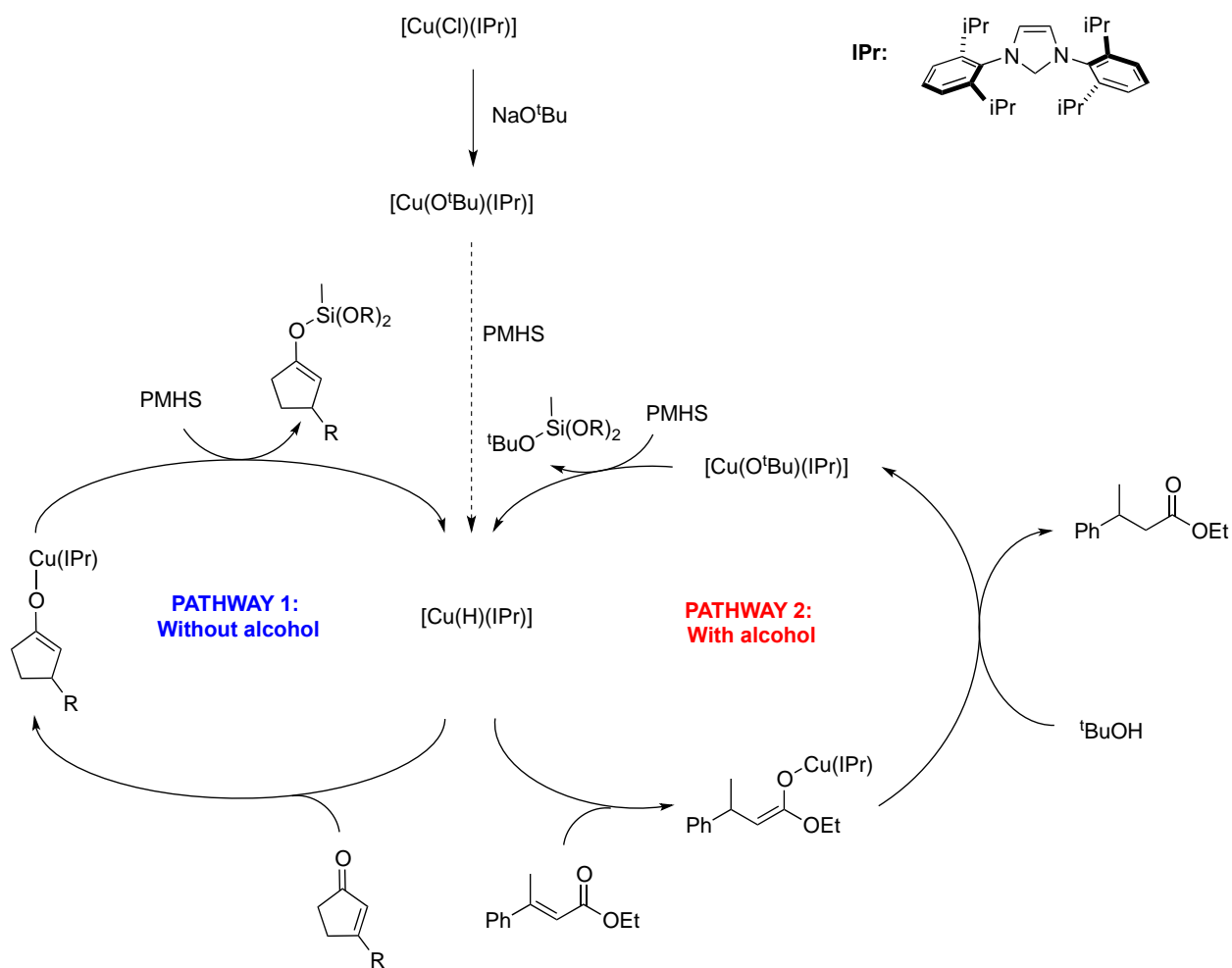
The neutral-halide-bearing complexes have been widely used in catalysis, mainly due to their ease of synthesis.<sup>9</sup> In addition to halide-bearing complexes, notable important related compounds have been reported: Nolan and co-workers disclosed the first hydroxide derivative [Cu(OH)(IPr)] (IPr = *N,N'*-bis(2,6-di-*isopropylphenyl*)imidazol-2-ylidene) and Sadighi published alkoxides, hydrides and borate species, which permitted novel reactivity to be explored [9g-i]. With respect to cationic derivatives, homoleptic and heteroleptic bis-NHC complexes have been reported and have been efficiently used in catalysis allowing important improvements [10]. In this review, an overview of the two classes and their respective catalytic performance will be presented.

## 1. Alkenes and allenes functionalization

### 1.1. 1,4-Reduction

One of the emblematic reactions catalyzed by copper is undoubtedly the 1,4-reduction of enones and enoates. After Arduengo's seminal work, NHC-copper complexes were successfully used in the conjugate additions of diethyl zinc to enones. In 2003, based on their previous report focusing on phosphine complexes, Buchwald and Sadighi published the conjugate reduction of  $\alpha,\beta$ -unsaturated

carbonyls using a Cu-NHC system (Scheme 1.1) [11]. In the primary investigation of cyclic enones, the silane sources presented no significant effect as approximately the same yields were obtained. In this transformation, THF or toluene can be used to efficiently perform the reaction with no loss of reactivity. Interestingly, with respect to the nature of the  $\alpha,\beta$ -unsaturated ester, the reactivity was completely different. After 20 hours, the reduction of ethyl *trans*- $\beta$ -methylcinnamate was incomplete, and addition of an alcohol solvent increased the reaction rate. In the presence of 4 equivalents of *tert*-butanol, full conversion was reached after only 1 h, with only 0.3 mol% of catalyst. A range of  $\alpha,\beta$ -unsaturated carbonyls were investigated. Tri-substituted cyclic enones were also converted in the presence of [Cu(Cl)(IPr)]. In the case of phosphine hydride complex, a high catalyst loading and long reaction time were required. A high tolerance to functional groups such as nitro was observed, without decomposition. The reaction was efficiently performed on tetra-substituted olefins.



Insight into the catalytic cycle supported an *in-situ* formation of a hydride species *via*  $\sigma$ -bond metathesis between [Cu(O<sup>t</sup>Bu)(IPr)] and the silane. The conjugate reduction formed a copper enolate intermediate

(Scheme 1.1.1). The process involving alcohol leads to the protonation of the copper enolate releasing the alkoxide intermediate and the product.

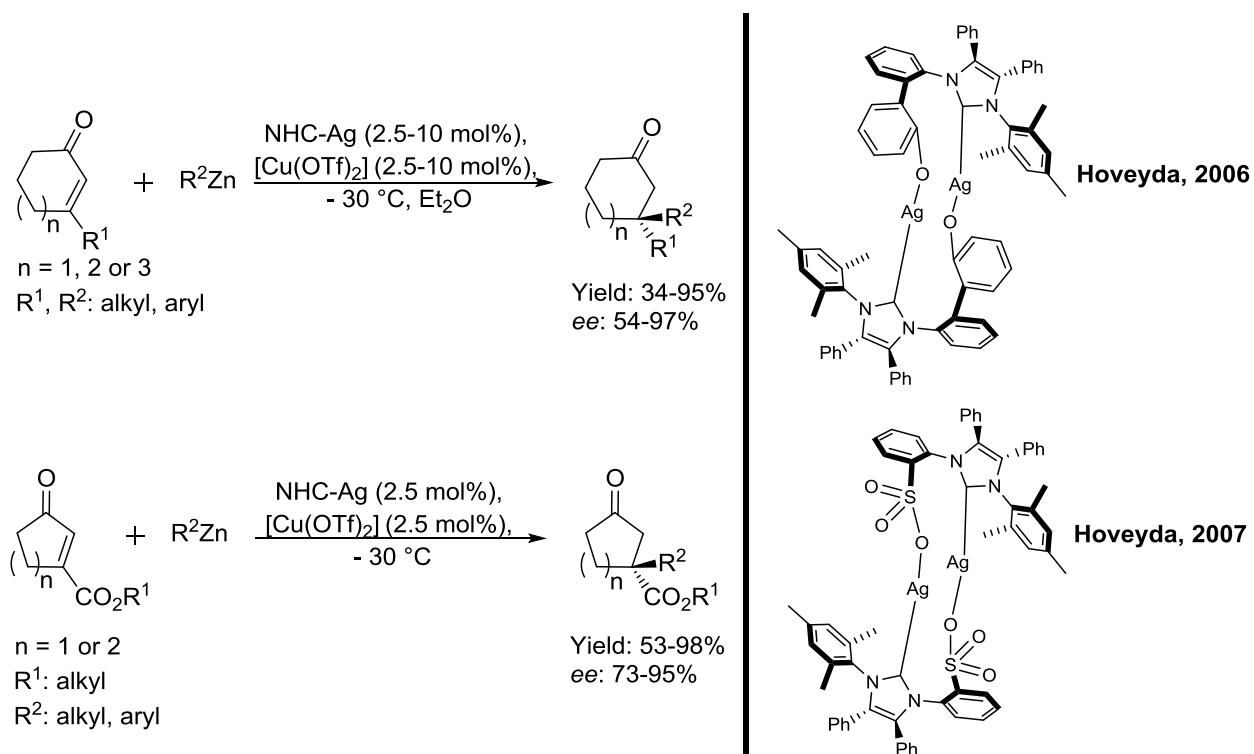
In 2013, a dual catalysis 1,4-reduction/allylation process involving copper and palladium was reported by Riant and Nahra. In this case, [Cu(Cl)(IMes)] was selected for the 1,4-reduction reaction [12]. In the presence of a palladium complex, the allylic alkylation occurred leading to an interesting range of functional molecules. A similar mechanism as for the conjugate reduction reaction was proposed also involving a hydride intermediate.

## 1.2. Conjugated additions

### 1.2.1. Zinc reagents

In the field of conjugate addition, the use of organozinc reagents is frequently encountered. In this context, Alexakis has made a seminal contribution by using a phosphoramidite copper-based system enabling an asymmetric conjugate addition. The first efficient copper-NHC system enabling 1,4-addition was reported by Woodward [4]. Indeed, rapid formation of the conjugate product was observed by exposing cyclohexenone to ZnEt<sub>2</sub>, a copper source and SIMes (SIMes = *N,N'*-bis[2,4,6-(trimethyl)phenyl]imidazolin-2-ylidene) ligand. This was the first step towards what became one of the most popular benchmark reactions in organocopper chemistry. Soon after, a chiral version was reported. However, poor enantioselectivities were obtained ranging from 23% to 50% *ee* [13]. The alternative protocol, reported by Alexakis, makes use of transmetalation from silver to copper. With only 4 mol% of copper salt and a silver complex, enantioselectivity of up to 93% were obtained. In 2005, Mauduit and Clavier reported a new class of chiral alkoxy-imidazolium salts.<sup>14</sup> Interestingly, an unexpected phenomenon was observed with Cu(OTf)<sub>2</sub> and Cu(eaa)<sub>2</sub> (eaa = ethylacetoacetate) in correlation with temperature. Indeed, lowering the temperature to -78 °C with Cu(eaa)<sub>2</sub> led to a slight decrease of the enantioselectivity, while a significant drop was monitored at room temperature. Curiously the opposite effect was obtained with Cu(OTf)<sub>2</sub>. A hypothesis to explain the phenomenon highlights the possible presence of two different intermediates depending on the temperature. Regarding the copper sources, CuX<sub>2</sub> types are the most efficient. By tuning the NHC ligands, the enantioselectivity was affected by the ligand side-chain. The presence of a hydroxyl group is required for good enantiocontrol and a slight excess of ligand enhanced the enantioselectivity. Most important is the correlation observed between the aromatic moiety and the *ee*. The absence of C<sub>2</sub>-symmetry in the ligand requires the presence of the mesityl group, which hinders one side and favours approach of the substrate from the other side. A less hindered aromatic group (phenyl) leads to a dramatic decrease in the *ee* from 85% to 54%. The presence of a stereogenic centre in the C<sub>2</sub>

position of the alkyl chain is also very favourable. Despite the contributions mentioned above, the scope remained limited to a number of organozinc reagents and simple enone substrates [13,14,15].



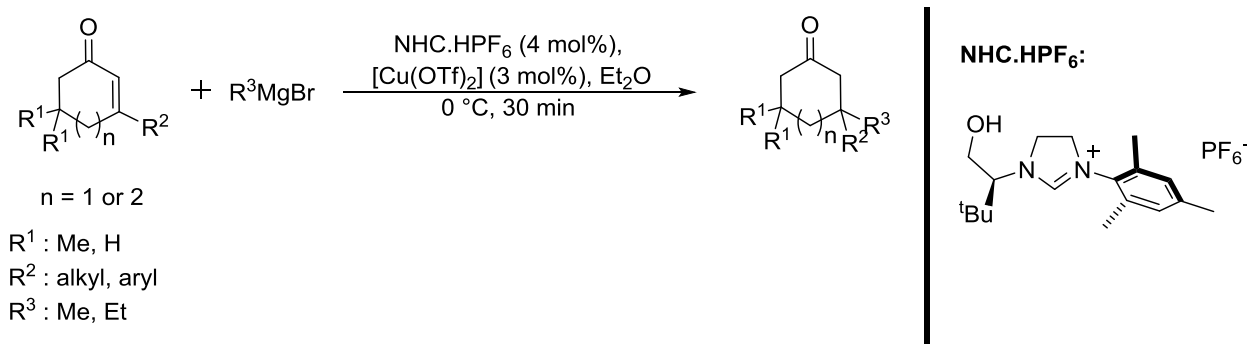
**Scheme 1.2.1.1: Asymmetric conjugated additions [16]**

In this area, a challenge remained in the formation of quaternary C-C centres. Hoveyda and co-workers efficiently overcame this problem by using Ag-NHC species as transfer reagents (Scheme 1.2.1.1) [16]. Inactive  $\beta$ -substituted cyclic enones were first explored. The complex investigation showed that using Ag-NHC with a copper salt led to a more efficient system than the well-defined Cu-NHC alone. Indeed the conversion and the *ee* increased significantly for reaction involving cyclohexenone and diethyl zinc (from 72% to 93% *ee* and 32% to 94% conversion). Based on these conditions, asymmetric conjugate additions (ACA) with alkyl and aryl zinc reagents were efficiently performed. However, for diaryl zinc reagents, the transformation proceeds slowly compared to dialkyl zinc, but with high enantioselectivity. Following this report, the scope was broadened to keto esters [17].

## 1.2.2. Grignard reagents

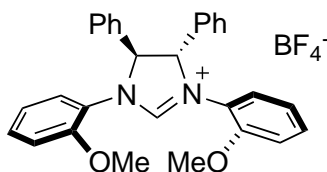
Grignard reagents are the logical alternative to organozincs as they are less expensive and more readily available. Alexakis and co-workers reported methodologies based on Grignard reagents [18]. Different ligand-types were tested such as  $C_2$  symmetric NHCs or unsymmetrical diaminocarbenes

(Scheme 1.2.2.1). Interestingly, the chirality can be efficiently transferred in this transformation. As with the organozincs, the unsymmetrical NHCs lead to efficient catalysts. No base was required as the Grignard reagent plays this role in the activation step. A large range of reactants was efficiently converted. Primary Grignard reagents give high *ees* (up to 96%) while secondary Grignard reagents required lower temperatures to provide similar results (-30 °C). Regarding enones, tri-substituted cyclohexenones were converted with moderate to good yields and even poorly reactive enones such as phenyl cyclohexenone presented good enantioselectivity.



**Scheme 1.2.2.1: Conjugated addition using Grignard reagents [18]**

Tomioka and co-workers achieved excellent regio- and enantio-selectivity using chiral NHCs bearing two methoxy moieties with  $C_2$  symmetry (Figure 1.2.2.2) [19].



Tomioka

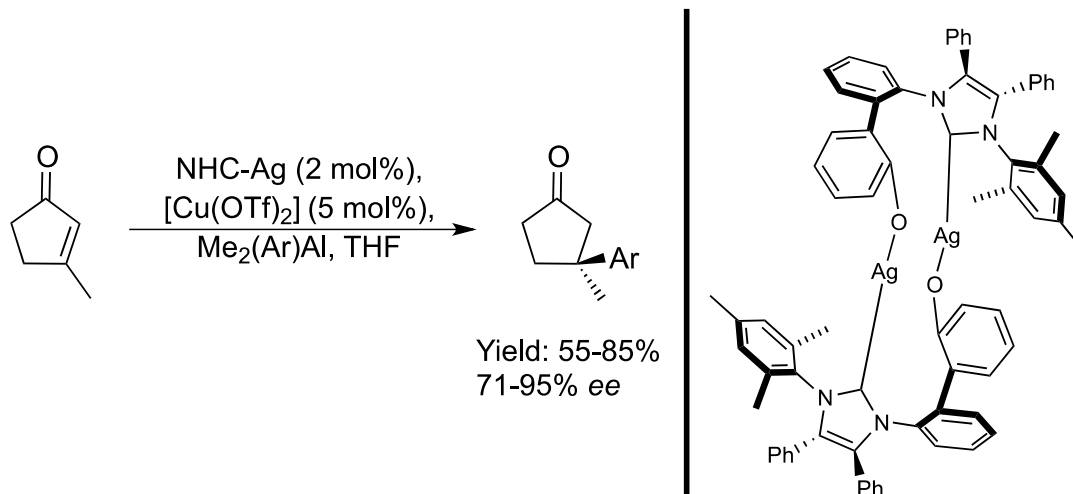
**Figure 1.2.2.2: The Tomioka complex [19]**

Alexakis and Mauduit extended the scope to poly-conjugated systems. The unusual 1,4-conjugate addition product was observed with chelated NHCs, while most other NHCs and other ligand classes favoured the 1,6-conjugate addition. Very desirable building blocks such as chiral alkenes and alkynes can be produced using this methodology [20].

### 1.2.3. Aluminium reagents

Organoaluminum reagents are an alternative class of substrates for conjugate additions, which has

been explored to a lesser extent. Using such reagents, poorly reactive substrates such as small cyclopentenones can efficiently be converted. However an activating functionality is required on the organoaluminium reagents. Aryl and alkyl silyl-fluorides were used with unsubstituted cyclic enones. A few reports based on organoaluminium reagents have been reported by the Hoveyda group (Scheme 1.2.3.1) [21].  $\beta$ -substituted cyclic enones are efficiently reacted with aryl and alkyl moieties. For the challenging  $\beta$ -substituted cyclopentanones, highly enantiopure compounds were obtained with *ee* of up to 98%.



**Scheme 1.2.3.1: Conjugated addition using aluminum reagents [21]**

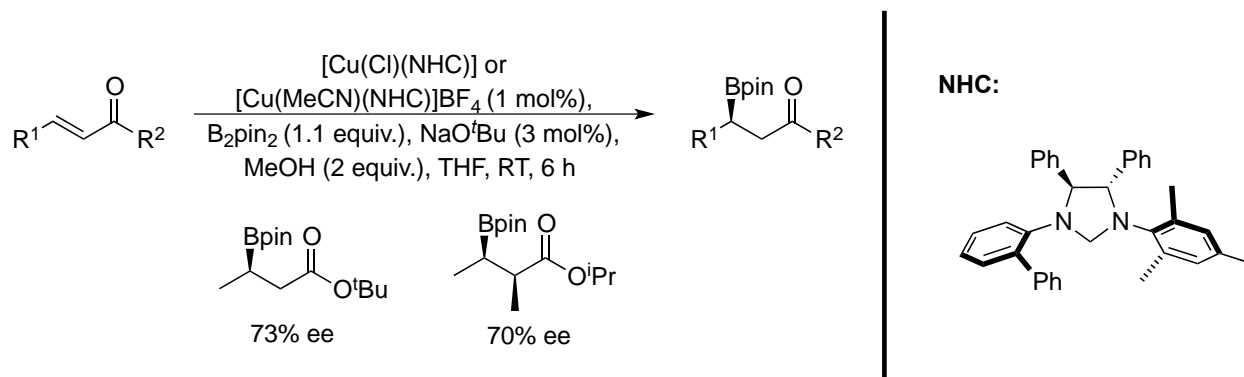
In addition, five- or six-membered cyclic enones can also be substituted with silane vinyl aluminum reagents. The presence of a silane moiety brings an additional opportunity for further functionalization [21].

#### 1.2.4. Boron reagents

During the last decade, new opportunities have been created with the utilisation of organoboron reagents. The  $\beta$ -boration of unsaturated carbonyl compounds was first investigated by Fernandez and co-workers (Scheme 1.2.4.1) [22]. Chiral cationic and neutral NHC complexes, such as  $[\text{Cu}(\text{NCMe})(\text{NHC})]\text{BF}_4$  and  $[\text{Cu}(\text{Cl})(\text{NHC})]$ , were compared using  $\text{B}_2\text{pin}_2$  as the boron reagent. Interestingly, the nature of the anion did not affect the enantioselectivity or the conversion. This observation was rationalised by the presumed formation of the same catalytic species  $[\text{Cu}(\text{NHC})]^+$ . However, the ligand symmetry appeared to impact the reactivity. Indeed,  $C_1$  symmetric ligands were slightly better than the  $C_2$  symmetric ones. Based on this methodology, the challenging  $\alpha,\beta$ -unsaturated aldehyde, cinnamaldehyde, was quantitatively



converted, but only in 40% *ee*. The *syn*-diastereomer was slightly favoured for substituted alkenes, such as  $\alpha$ -methyl ester.



In 2010, Hoveyda expanded the scope of the transformation to the formation of quaternary chiral centres for trisubstituted alkenes of acyclic  $\alpha,\beta$ -unsaturated carboxylic esters, ketones, and alkylthioesters [23,24]. In contrast with previously reported articles, the monodentate ligands were more active than bidentate ligands. Interestingly, various aryl-substituted unsaturated esters are converted. However, a decrease in the reactivity and enantioselectivity was monitored for the *ortho*-methyl substituted substrate. The presence of a halogenated group affected neither the reactivity nor the *ee* (93% to 96% yield with 97% to 98% *ee*). Alkyl-substituted esters were also efficiently transformed into boron reagents. However a dramatic drop in the conversion was observed for unsaturated ketones (73 to 89%), but the *er* remained good (82 to 92%). Thioesters presented surprising reactivity; all substrates were obtained with high enantiomeric purity (>99%).

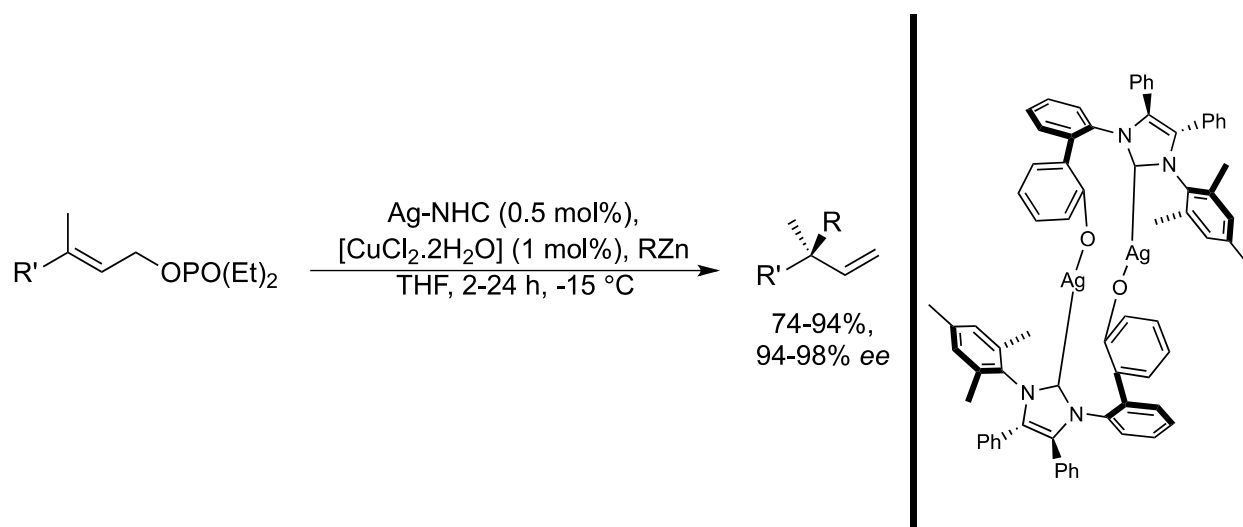
The methodology allowed for the formation of a large number of chiral  $\beta$ -boryl carbonyls with high *ees*. More recently, Sawamura has additionally developed a methodology for the enantioselective conjugate addition of alkylboranes using bulky NHC ligands [25].

## 1.3. Allylic substitution

### 1.3.1. Zinc reagents

Inspired by ruthenium systems, a new class of chiral NHCs was developed by Hoveyda. The optically pure NHC-Ag(I) complex was used as transfer reagent to synthesise an air-stable bidentate NHC copper complex (Scheme 1.3.1.1) [26]. The addition of alkylzinc reagents to di- and tri-substituted allylic phosphates was investigated. The reaction proceeds smoothly with high *ees* (up to 98%) and yields. By tuning the ligand backbone, the chirality induction of these ligands was improved [27]. The ligands show

similar results to those previously reported and the silyl-substituted allyl phosphates were efficiently converted [28].



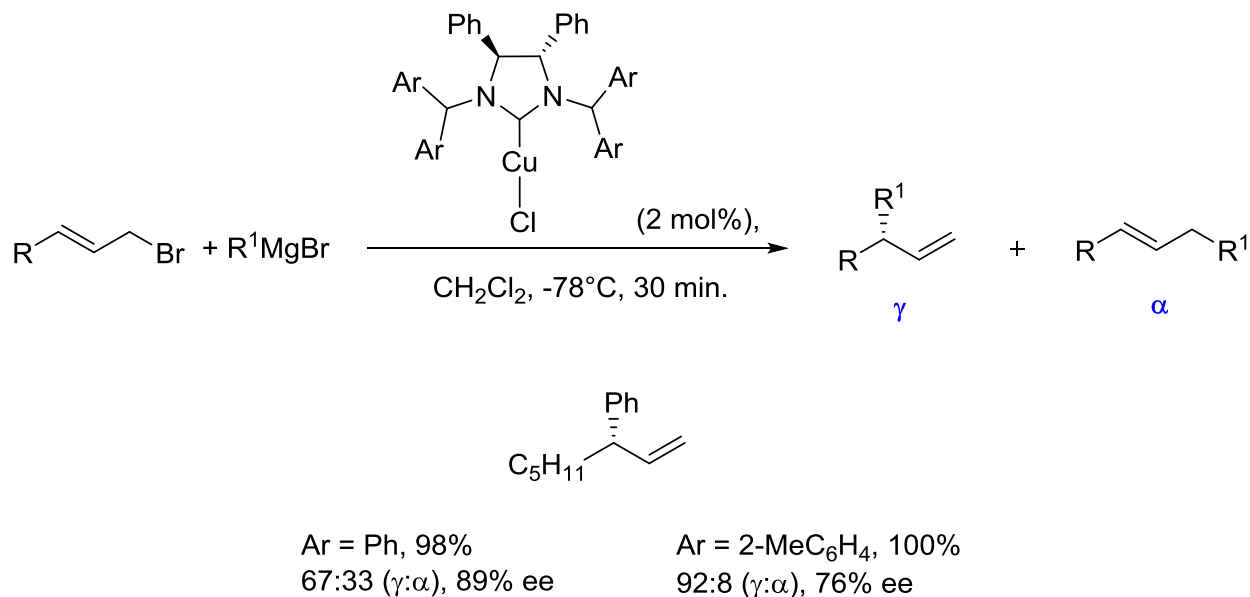
**Scheme 1.3.1.1: Use of zinc reagents in the allylic substitution [26]**

### 1.3.2. Grignard reagents

The alternative of using Grignard reagents is obviously attractive as accessibility is not an issue. The substitution's regioselectivity is dependent of various factors such as the structure of the allylic substrates, the Grignard reagents, the copper salt, solvent and temperature as well as the order of addition of reagents. However, further development of the ligand structures should enable catalyst-based control of the reaction, including enantioselectivity and regioselectivity. Okamoto reported a novel procedure for this transformation using copper-NHC complexes as well as an asymmetric version using chiral ligands [29]. Interestingly the steric bulk of the NHC affects the regioselectivity and the rate of the reaction. Alkenes bearing leaving groups such as carbonate, acetate, phosphate and chloride gave high  $\gamma$ -selectivity. However,  $\alpha$ -products are predominantly obtained with allylic carbonates in THF, while only  $\gamma$ -products were formed with allylic chlorides under similar conditions. Primary and secondary alkyl Grignard reagents provided  $\gamma$ -products in excellent yield and regioselectivity. In the case of aryl Grignard reagents, the  $\alpha$ -product was mainly obtained. Regarding allylic substrates, the reaction with di-substituted and tri-substituted alkenes having a variety of substituents such as alkyl, aryl, siloxy- and alkoxyethyl groups with *E*- or *Z*-geometry proceeded in a  $\gamma$ -selective manner.

In the presence of chiral NHCs, the reactions proceeded to give optically active  $\gamma$ -substituted products in low to moderate enantiopurity. Highest *ees* were obtained for catalysts bearing sterically demanding *N*-substituents. Interestingly, the introduction of additional *C*<sub>2</sub>-chirality into the NHC resulted in the

inversion or decrease of the enantioselectivity. Such phenomena were observed when *E*-allylic substrates were used instead of *Z*-isomers.



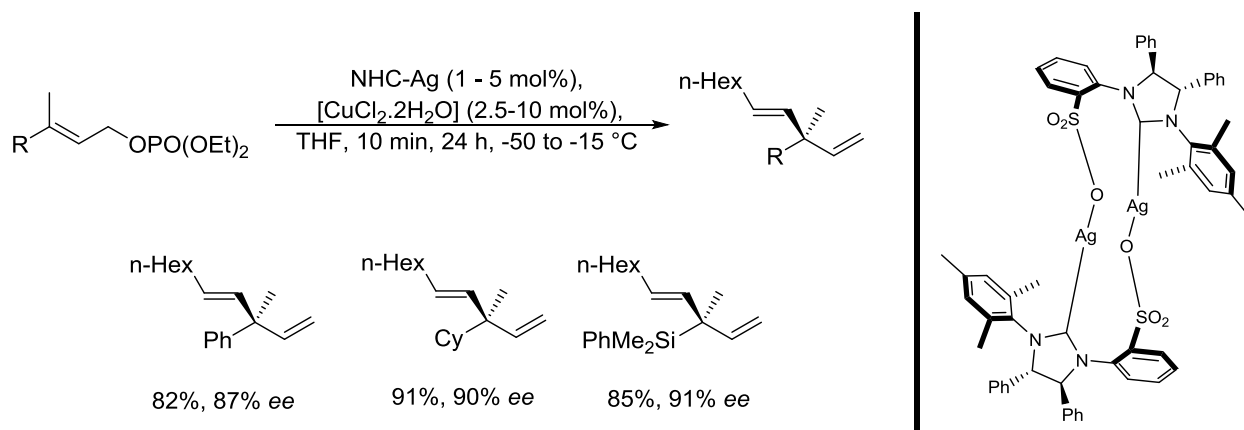
**Scheme 1.3.2.1: Allylic substitution using Grignard reagents [31]**

Tomioka reported an asymmetric version of this transformation using an air-stable complex [30]. Interesting activity was recorded with a  $\gamma/\alpha$  ratio of 67:33 and enantioselectivity of 96% (*ee*). The bulkiness of the ligand improved the regioselectivity. Indeed, introducing a methyl group in the *ortho*-position (aryl group on the *N*-substituent) increased considerably the regioselectivity (from 67:33 to 92:8) and the yield but decreased the enantioselectivity. The reaction conditions are compatible with more sterically demanding substrates. Based on these observations, the reaction was explored for aliphatic systems (Scheme 1.3.2.1) [31]. Investigations of the steric properties of NHC showed that the *ortho*-substitution (aryl group on the *N*-substituent) is key for  $\gamma$ -selectivity ( $\gamma/\alpha$  92:8) but not for the *ee*, which dropped considerably (76%). Other positions did not influence the reactivity. Concerning electronic effects in this reaction, EWG (electron-withdrawing groups) in *para*-position increased the  $\gamma$ -selectivity, while the bulkiness of the substituent led to a decrease in the enantioselectivity. Suitable catalysts can be found but this reaction remained dependent on the allylic substrates and the Grignard reagents. Catalysts bearing *N*-benzhydryl groups afforded good results for linear allylic substrates with Grignard reagents having an electron-deficient aryl group (up to 86% *ee*, 88%  $\gamma$ -product) and for branched allylic substrates with any Grignard reagents (up to 96% *ee*, 96%  $\gamma$ -product). Catalysts with *N*-(4,4'-difluorobenzhydryl) moiety performed well in the case of linear allylic substrates with magnesium compounds without electron-withdrawing group (up to 87% *ee*, 84%  $\gamma$ -product). All results highlighted that the  $\gamma$ -selectivity is impacted by the electron-deficiency and steric hindrance of the complex, Grignard reagents and allylic substrates. The  $\gamma$ -selectivity is likely to be governed by the relative rates of reductive elimination of the  $\gamma$ -

$\eta^1$ -allyl intermediate and isomerisation to the  $\eta^3$ -allyl intermediate, and the subsequent reductive elimination.

### 1.3.3. Aluminium reagents

Catalytic asymmetric allylic alkylation (AAA) has been performed by Hoveyda and co-workers in the presence of vinylaluminium reagents (Scheme 1.3.3.1) [32, 33]. Readily available DIBAL-H being added to terminal alkynes permits to deliver *in situ* the vinylmetals. Alkylation is promoted by 0.5 - 2.5 mol % of chiral copper-NHC complexes. Tri-substituted alkenes bearing sterically demanding groups, electron-withdrawing aryl units or an unsubstituted phenyl group undergo the transformation in 82-94% yield and 87 to >98% *ee*. Alkylations of di-substituted olefins proceed in high yield but are less selective unless a sterically demanding group, such as a silyl substituent, is present. The catalytic alkylation can be performed with vinyl bromides, cyclic alkenes or vinyl alkynes. This method was efficiently used for the synthesis of 1,4-dienes containing *Z,E*-alkenes [33]. Copper-NHC complexes were generated *in situ* by reacting silver-NHC complexes and a copper salt; high selectivity (98%) was observed, with high enantiomeric purity for all substrates (between 94:6 and >99:1). A large panel of vinylaluminum reagents were converted giving an interesting methodology for allylic alkylation.

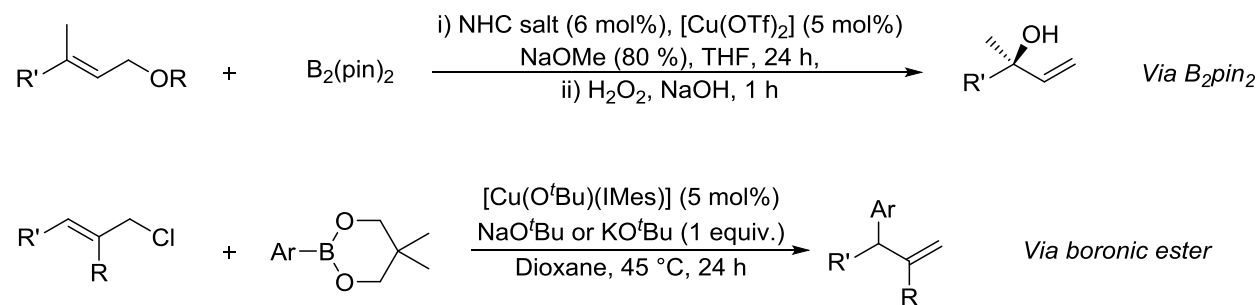


**Scheme 1.3.3.1: Asymmetric allylic substitution reported by Hoveyda [32, 33]**

### 1.3.4. Boron reagents

The most interesting alternatives as reducing reagents are boron derivatives as these permit milder reaction conditions. Commercially available B<sub>2</sub>pin<sub>2</sub> in reactions with chiral sulfonate-NHC afforded the formation of allylboronates with stereogenic centres (Scheme 1.3.4.1). High enantioselectivity (*E*- and *Z*-substrates favour *S*- and *R*-products, respectively) and yield (71 to 97 %)

were obtained based on this methodology. During the studies, the effect of the base (NaOMe) was monitored [34]. A similar reaction was reported by McQuade using 6-membered NHC copper complexes [35]. These systems reached higher conversion and enantioselectivity compared to their imidazole analogue ([Cu(Cl)(IMes)]). Interestingly, stereo-convergence was observed. Indeed both systems presented a preference for the same face of both *E*- and *Z*-alkenes. These observations were clearly in contrast with the Hoveyda report. It should be mentioned that McQuade only formed tertiary centres whereas Hoveyda formed quaternary centres.



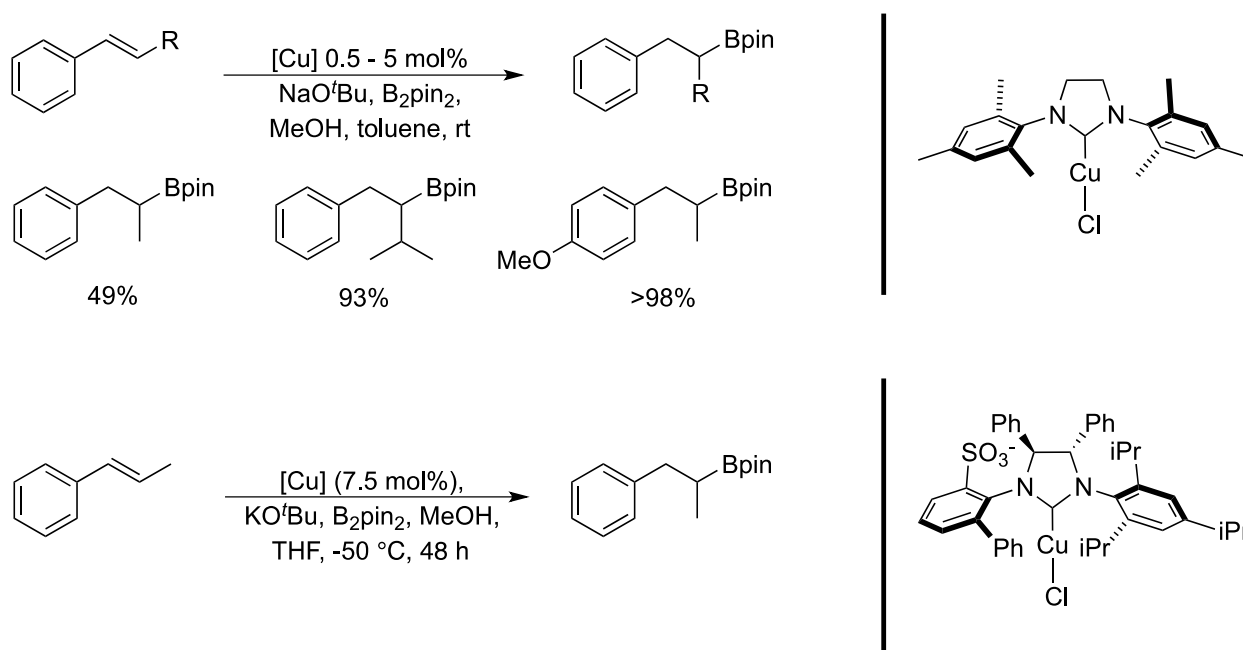
**Scheme 1.3.4.1: Allylic substitution *via* boronic ester or B<sub>2</sub>pin<sub>2</sub> [34, 36]**

Allylic substitution of aryl boronic esters was also reported. (Scheme 1.3.4.1) [36]. A trend was found between the reactivity and the NHC ligand. Indeed, the best selectivity was obtained with [Cu(Cl)(IMes)], while ICy and IAd provided a lower selectivity despite a higher reaction rate. The *tert*-butoxide analogue [Cu(O<sup>*t*</sup>Bu)(IMes)] was the most active catalyst. Regarding the base, two different systems were efficient. In the case of electron-poor species, high yield and selectivity were obtained using KO<sup>*t*</sup>Bu, meanwhile NaO<sup>*t*</sup>Bu was selected for electron-rich substrates. Steric bulk around the boronic ester did not influence the reaction outcome. *E*- and *Z*-substituted electrophiles as well as azides, cyanides, chlorides and protected alcohols are compatible with the reaction conditions. Hayashi described an asymmetric version for monosubstituted allyl phosphates [37]. The impact of the metal alkoxide was investigated and proved to be significant. Indeed, NaO<sup>*t*</sup>Bu gave high selectivity towards  $\gamma$ -substituted compounds with a lack of enantioselectivity, whereas NaOMe increased the *ees*. The *N*-substituents also affect the  $\gamma$ -selectivity and enantioselectivity. Various aryl groups are tolerated. However heteroaryl and alkenylboronate showed a loss in the regioselectivity and enantioselectivity but high yields. The methodology was successfully applied to the formation of quaternary carbon stereocentres [38].

## 1.4. Boration and carboboration of alkenes

### 1.4.1 Boration of alkenes

In 2006, Sadighi reported the first well-defined copper boryl complex  $[\text{Cu}(\text{Bpin})(\text{IPr})]$ . The insertion of alkene into the copper-boron bond was investigated. A rapid reaction toward the formation of a boron-alkyl was observed when  $[\text{Cu}(\text{Bpin})(\text{IPr})]$  was exposed to styrene [39]. Boration of substituted styrene was efficiently performed. Despite a slow reaction rate monitored for the alkyl derivatives, high yields were obtained (86%) [40]. This observation was a breakthrough, thus opening doors to novel chemistry. In 2009, a racemic version was developed by Hoveyda [41a], using  $[\text{Cu}(\text{Cl})(\text{NHC})]$  (NHC = e.g. SIMes, IMes or ICy), followed by an enantioselective version using chiral NHCs. The investigations on the nature of the ligand showed a trend (SIMes: 98%; IMes: 65%; ICy: 13%) with the saturated SIMes being the most efficient catalyst (Scheme 1.4.1.1). The presence of an alcohol is required to generate the alkoxide species. High regioselectivity (96%) and yield (80%) were observed for the enantioselective hydroboration. The boration of sterically hindered olefins was efficiently performed while that of cyclic olefins was obtained with lower selectivity (86%).



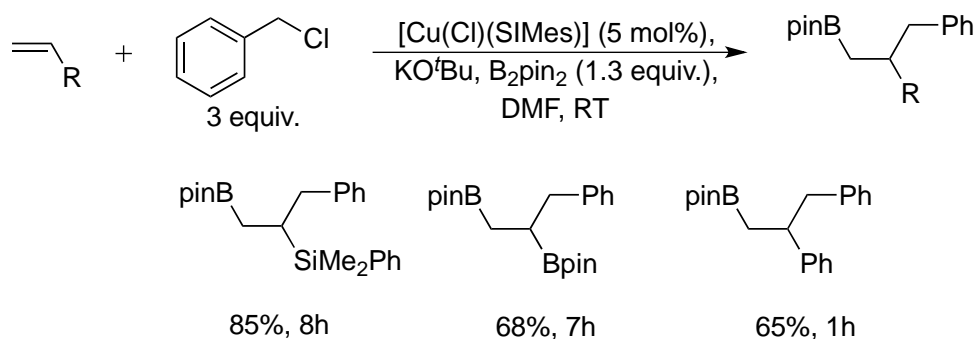
**Scheme 1.4.1.1: Alkenes boration [39, 40, 41]**

In 2011, Hoveyda reported on the enantioselective hydroboration of disubstituted aryl olefins [41b]. Once again these experiments were based on the previously described boryl copper complex. The ability of chiral NHC-copper complexes to undergo hydroboration was investigated on  $\alpha$ -methylstyrene. When monodentate complexes were used, almost no stereoselectivity was observed (59:41). However, with bidentate derivatives, an increase of the *e.r.* was recorded (75:25). Interestingly, chiral NHC bearing

sulfonate-moiety presented high activity and stereoselectivity (85.5:14.5). The authors argued that the flexibility of the *N*-substituent was the key factor for the transformation, allowing a more favorable conformation for the binding of the alkene to the metal center. Lowering the temperature of the reaction affected the selectivity (*er*: 93.5:6.5) without loss of reactivity (96%). Large numbers of  $\alpha$ -methylaryl olefins were converted with high stereoselectivity (> 98%). Despite these encouraging results, the 1,1-disubstituted aryl olefins did not proceed the same way and a change of catalyst was required to achieve this transformation. In the particular case of allylic alcohols, the 2-substituted allylboronates were formed, which is correlated to the fast rate of the Cu-alkoxide elimination *vs* the Cu-C protonation [42]. Recently, McQuade has reported on the reactivity of copper(I) fused NHC complex for the boration of styrenic and strained alkenes [43].

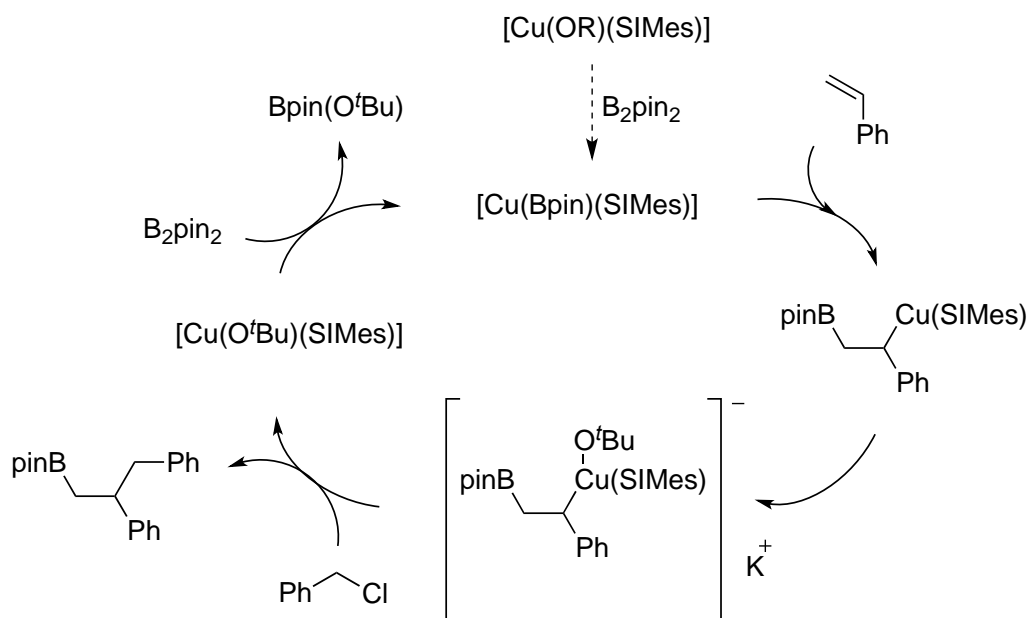
### 1.4.2. Carboboration of alkenes

The preparation of highly functionalized molecules is of significant interest. In this area, carboboration is an interesting method leading to substituted vinylboronic esters. In 2008, Suginome and co-workers reported a palladium and nickel catalyzed carboboration [44]. However, only functionalized alkynes (bearing hydroxyl group) were tolerated. Recently, the *syn*-carboboration of alkynes leading to tri- and tetra-substituted vinylboronates was reported based on copper-phosphines complexes [45]. In 2012, Tatakai reported the analogous transformation using copper-NHC systems [46a]. [Cu(Cl)(SIMes)] (SIMes = *N,N'*-bis[2,4,6-(trimethyl)phenyl]imidazolin-2-ylidene) was highly efficient in the formation of the vinylboronates in moderate to high yields. (Scheme 1.4.2.1).



**Scheme 1.4.2.1: Carboboration of alkenes [46a]**

Vinylboranes and styrenes derivatives were tolerated. Mechanistic studies supported the presence of a Cu-B species followed by the alkene insertion as part of the catalytic cycle (Scheme 1.4.2.2). Regarding the selectivity, a correlation was observed between the insertion of the copper moiety to the more substituted carbon and the electronic properties of the substituents.



**Scheme 1.4.2.2: Postulated mechanism for alkenes carboboration [46a]**

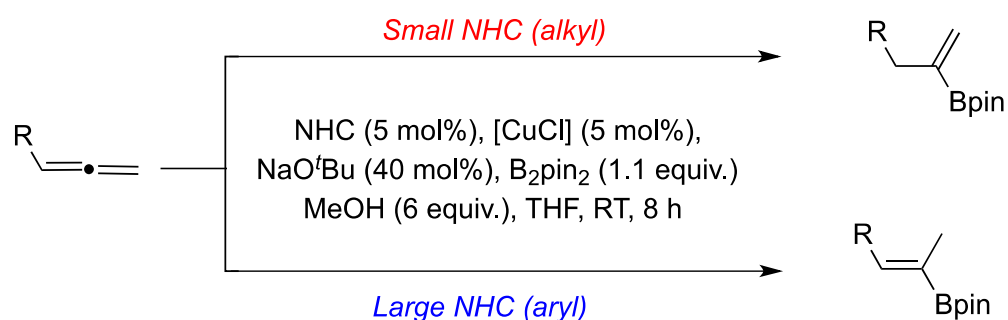
Recently with the development and progress made in the dual catalysis, a methodology was reported combining palladium/copper [46b]. The first evaluation was performed used as model styrene,  $B_2pin_2$ , phenyl bromide and as palladium source  $Pd(OAc)_2$ . Regarding the copper species,  $Cu(OtBu)(IPr)$  leads only to 82%. The chloride analogue in presence of  $NaOMe$  gave 95% with high regioselectivity. Unfortunately with the lithium base, no activity was recorded, whereas the  $LiOtBu$  gave identical results than  $NaOMe$ . Other carbenes were investigated:  $^ClIPr$  gave only moderate activity while the more electron donating  $^{Me}IPr$  showed better activity. The less sterically demanding  $IMes$  gave poor yield and regioselectivity. The scope of substrates showed that the reaction proceeds with an high regioselectivity and various functional groups were tolerated. Later on, Brown developed a similar strategy using  $SiMes$  as ligand [46c].

## 1.5. Boration of allenes

Due to the importance of boron species in organic chemistry, intensive studies have been reported leading to the formation of such substrates. In the case of hydroboration of allenes, systems based on metals have been reported with major drawbacks (low regioselectivity, formation of by-products and the need for unstable/reactive boron sources). Methodologies using  $HBpin$  or  $B_2pin_2$  (stable boron reagents) are highly attractive. In 2013, Hoveyda reported the protoboration of monosubstituted allenes [47]. It was demonstrated that the chemoselectivity of the reaction was dependent on the presence of alkyl or aryl *N*-

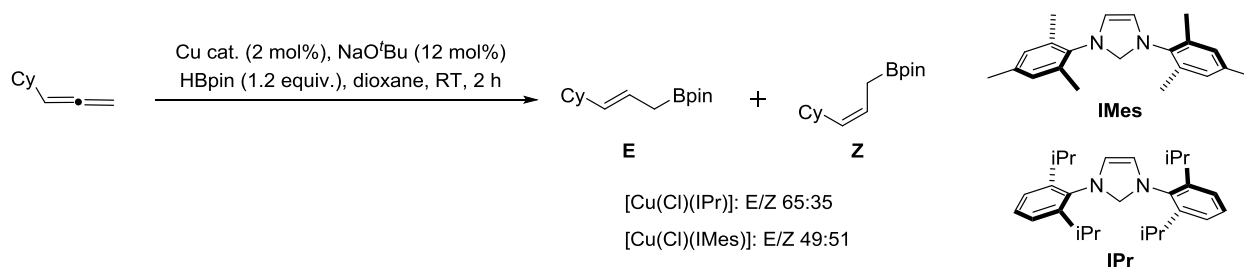


substituents on the NHC ligands. DFT calculations were undertaken to confirm and corroborate the observed trends (Scheme 1.5.1).



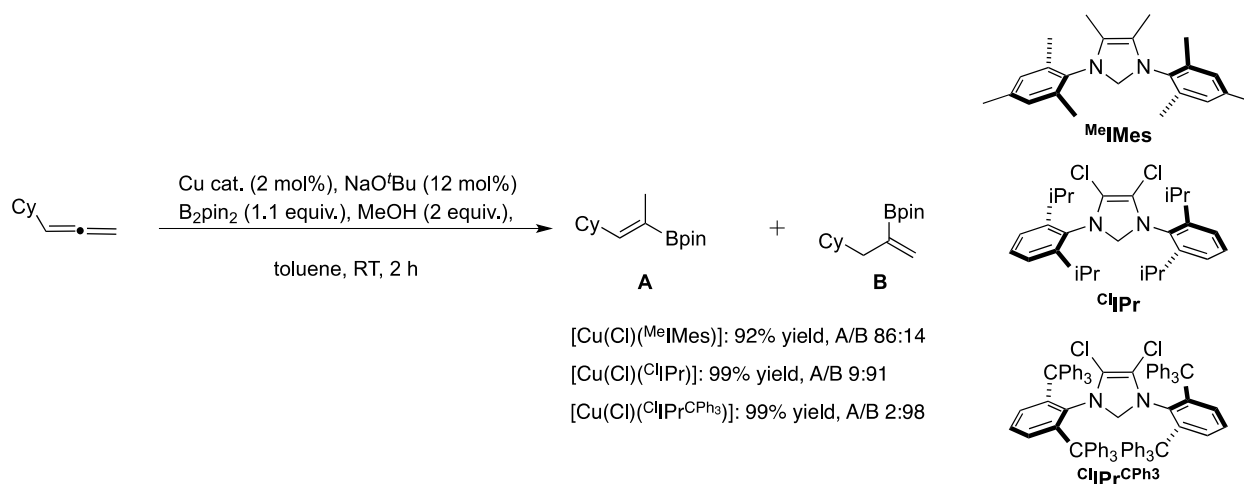
**Scheme 1.5.1: Effect of the NHC on allenes boration [47]**

Independently, Tsuji reported on the hydroboration of allenes [48a]. Using HBpin or B<sub>2</sub>pin<sub>2</sub>, the selectivity for allylboranes and alkenylboranes was controlled by the formation of the copper(I) hydride or copper(I) boryl intermediates (Scheme 1.5.2). Additionally, by varying the ligand, the selectivity can be tuned. In the presence of HBpin, the *E* and *Z* allylboranes were formed. However, the NHC copper(I) complexes showed lower catalytic activity than bidentate phosphine ligands.



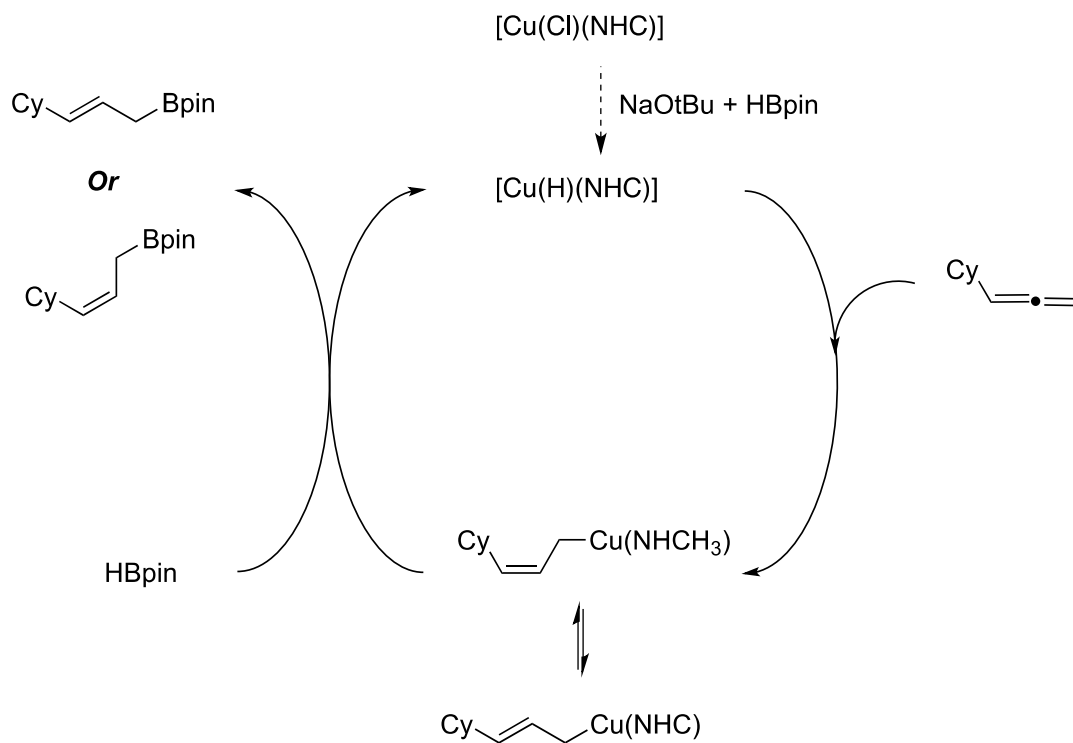
**Scheme 1.5.2: HBpin in allenes boration [48a]**

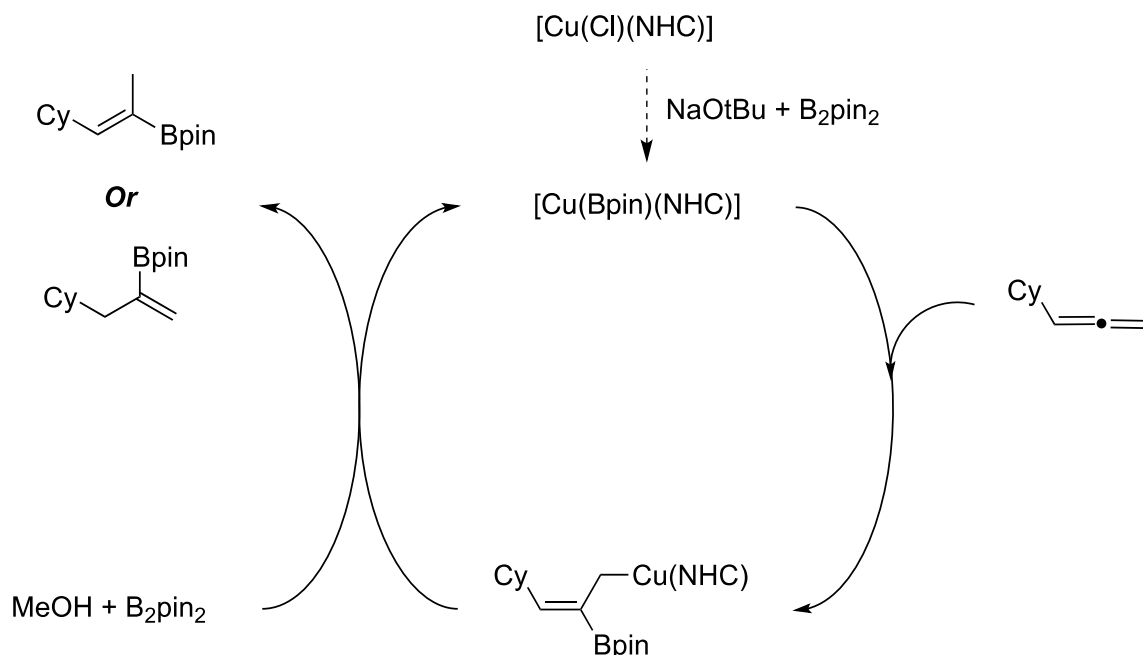
When B<sub>2</sub>pin<sub>2</sub> was used as the boron source, the regioselectivity switched to the *Z* isomers. Once again, the NHC ligand has a direct effect on the selectivity (Scheme 1.5.3). Lowering the temperature gave higher yields and selectivity. In light of these results, mono-substituted allenes bearing primary, secondary alkyls and aromatic groups were efficiently converted to the boron species. High tolerance of electron-donating and electron-withdrawing groups was observed.



### Scheme 1.5.3: HBpin in allenes boration [48a]

The proposed mechanism is similar to the one described for alkynes (Scheme 1.5.4).



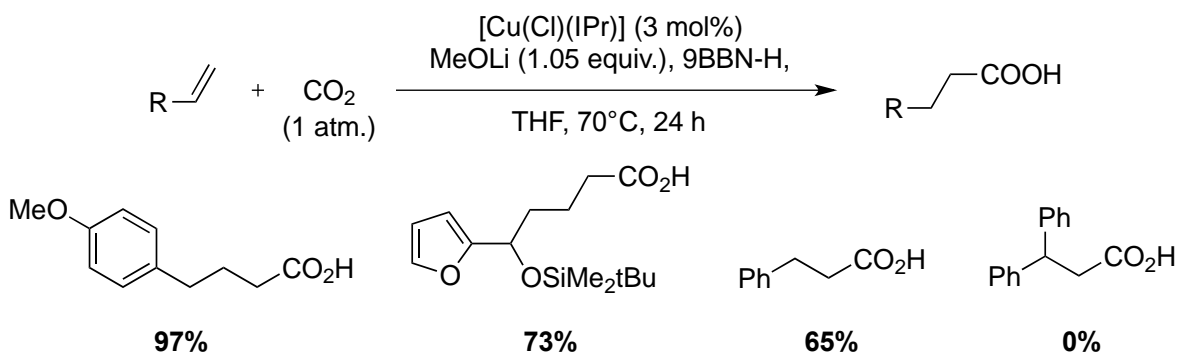


**Scheme 1.5.4: Proposed mechanisms for the boration of allenes [48a]**

Later that same year, Tsuji broadened the scope of this reaction by performing the borylation of alkoxyallenes to afford boryl butadiene [48b].

## 1.6. Carboxylation of alkenes

Copper-NHC systems have been involved in carboxylation catalysis. The use of  $\text{CO}_2$  as C1 source and chemical feedstock is of great interest. A number of processes have been reported allowing formation of carboxylic acids or esters. However, in the case of alkenes, a tandem reaction with *in situ* formation of alkylborane followed by the carboxylation has been reported [49]. Using  $[\text{Cu}(\text{Cl})(\text{IPr})]$ , only 35% of product was observed with potassium *tert*-butoxide under ambient atmosphere of  $\text{CO}_2$  at  $70^\circ\text{C}$ . By changing the base to  $\text{LiOMe}$ , which is less bulky, higher yield was reached and with 3 mol% of catalyst almost quantitative yield (97%) was obtained. The effect of the cation was investigated showing  $\text{KOMe}$  slightly less efficient than  $\text{NaOMe}$  or  $\text{LiOMe}$ . The less bulky  $[\text{Cu}(\text{Cl})(\text{IMes})]$  gave only 41% conversion, probably due to a lower stability of the intermediate. Interestingly, a wide range of functional groups are tolerated, such as propargyl, carbonyl, halides and vinyl bromide. Despite these encouraging results, diphenylethylene showed no reactivity. The plausible mechanism involves the formation of a boryl copper species followed by a  $\text{CO}_2$  insertion, which is similar to the proposed catalytic cycle for the carboxylation of boronic esters.



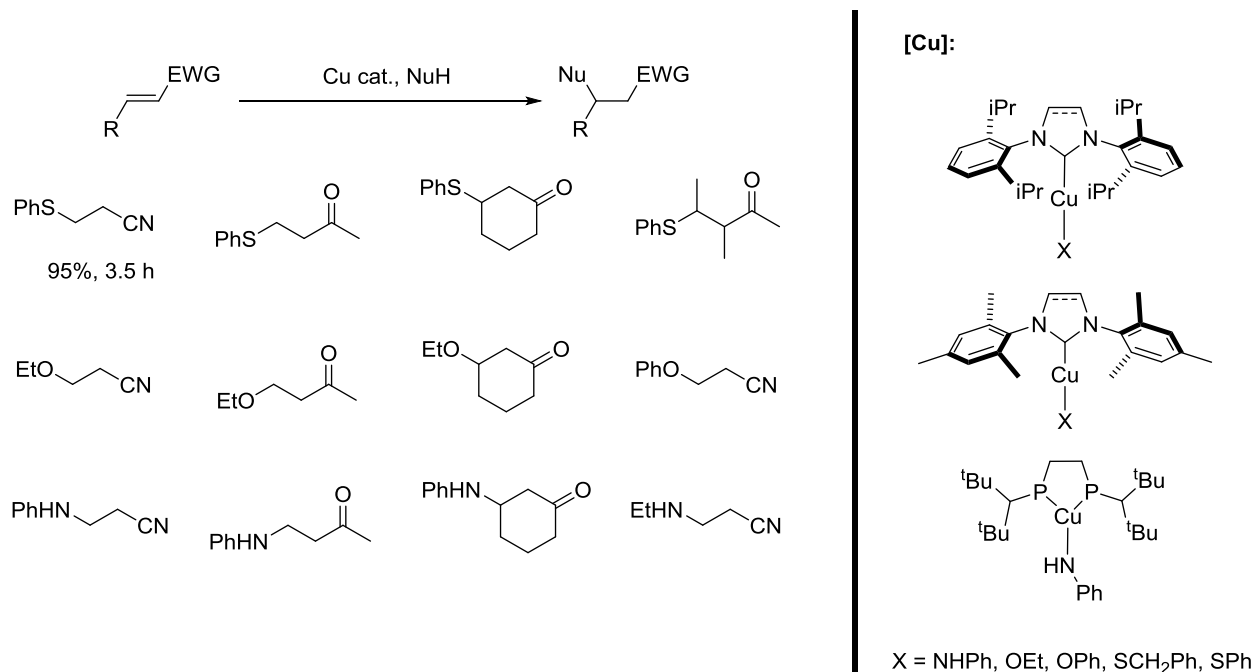
**Scheme 1.6.1: Carboxylation of alkenes [49]**

## 1.7. Hydrothiolation, hydroalkoxylation and hydroamination

The development of highly atom efficient processes is another grand challenge facing organic and organometallic chemistry. One successful example of such achievement is olefin functionalization. Indeed, formation of C-S or C-N bond *via* addition of thiols or amines remains a model of such accomplishments [50]. A series of articles from the Gunnoe group reported on such reactivity for Cu-NHC complexes. Based on previously described [Cu(NHR)(NHC)], [Cu(OR)(NHC)] and [Cu(SR)(NHC)], hydrothiolation, hydroamination and hydroalkoxylation were possible (Scheme 1.7.1). The anti-Markovnikov products were obtained, while other metal systems lead to the Markovnikov products. This unusual selectivity was observed in all examined reactions. In the case of the hydroamination, primary alkyl and aryl amines as well as sterically demanding alkynes were efficiently used. A blank reaction conducted in the absence of copper showed a decrease in the reaction rate by 1200-fold, highlighting the importance of the copper source. A comparison between the NHC complexes and the bis-phosphine copper species [Cu(NHPh)(dtbpe)] (dtbpe = 1,2-bis(di-*tert*-butylphosphino)ethane) showed that, in some cases, the latter outperformed the NHC analogues. Indeed, 95% conversion was observed for the aniline in the presence of acrylonitrile after 3 hours with dtbpe, compared to 12 hours for the [Cu(NHPh)(IPr)]. Despite this example, the [Cu(NHPh)(IPr)] outshone the other system for di-substituted cyclohexenones. In the case of *n*-propyl amine, the SIPr analogue was the most active species. The investigations showed the efficiency of all systems, but results were substrates dependent. The functional group tolerance for electron-deficient vinylarene remained limited. Meanwhile after 48 hours, no reaction was observed for *para*-substituted compound with EWG (CF<sub>3</sub> or Br). The transformation required the *in situ* formation of [Cu(NHBn)(NHC)] by reaction of benzylamine and [Cu(NHPh)(IPr)]. This intermediate is the key active species, which enters in the catalytic cycle even in the case of unactivated substrates.

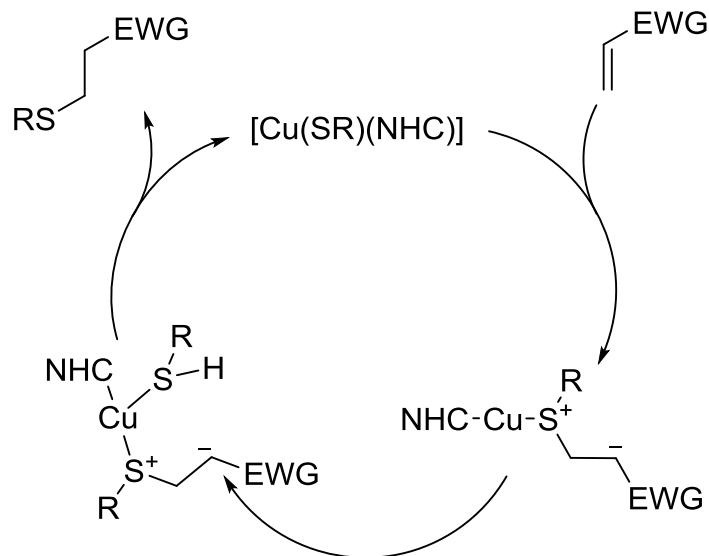
Regarding the hydroalkoxylation, the activity was limited to only a few compounds and long reaction

time. This phenomenon is due to the presence of a side-reaction: transesterification. The catalyst screening showed two efficient systems: [Cu(OEt)(IPr)] with ethanol and [Cu(OPh)(IPr)] for phenol derivatives.



**Scheme 1.7.1: Hydrothiolation, hydroalkoxylation and hydroamination catalyzed by Cu-NHC complexes [50]**

The last transformation studied was the hydrothiolation. Usually, the presence of sulfur derivatives is a serious drawback in catalysis due to catalyst poisoning. However, in Gunnoe's methodology, several thiols were efficiently converted in the presence of mono-, di- and tri-substituted alkenes and styrenes. Once again the Anti-Markovnikov regioselectivity was obtained using [Cu(SR)(IMes)] as the most active catalyst. For the reaction of benzenethiol with cyclohexenone, quantitative conversion was obtained after 5 min with the IMes complex vs 8 hours for the IPr analogue.



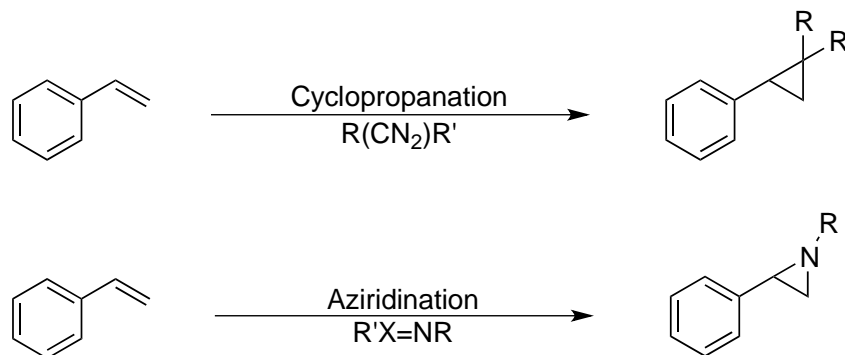
**Scheme 1.7.2: Proposed mechanism for the hydrothiolation [50]**

The decrease of the steric hindrance leads to higher activity (IMes > IPr > SIPr). The poor solubility of the SIPr explained the low activity measured. Different hypothesis have been developed concerning the catalytic pathway. A plausible mechanism was presented for the hydrothiolation (Scheme 1.7.2).

## 1.8. Carbene/Nitrene transfer

In the early 2000's, Pérez and Nolan reported a methodology for carbene and nitrene transfer based on copper systems. The preliminary work was focused on transfer to olefins, amines and alcohols using the well-known [Cu(Cl)(IPr)] complex [51]. The cyclopropanation of styrene in the presence of ethyl diazoacetate (EDA) was investigated and a fast formation of the product was recorded with 90% conversion after 6 hours. In the absence of styrene, no decomposition of EDA was observed (13 hours no decomposition). Regarding the stereoselectivity of the reaction, good *cis/trans* ratios were observed for styrene (32/68) and for cyclooctene (*exo/endo*: 73/27). The insertion of EDA into the C-H bonds of cyclohexane and 2,3-dimethylbutane was also attempted using the [Cu(Cl)(IPr)] complex and its gold analogue [52]. In the cyclohexane case, both gold and copper complexes were not active in the absence of NaBAR<sub>4</sub>, which indicates that a cationic complex is needed for this transformation. With 2,3-dimethylbutane, the gold congener was the most active catalyst with 90% conversion while the copper only led to a 48% conversion. Interestingly, a reversed regioselectivity was noticed: the insertion into tertiary C-H bond occurred with copper and into primary C-H bond with gold.

When the role and effect of halide and NHCs were examined for the C-H insertion reaction, the chemo- and the regioselectivity observed with 2,3-dimethylbutane highlighted the importance of the counter-anions. Indeed,  $\text{BAR}_4$  ( $\text{BAR}_4 = \text{tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate}$ ) showed a 48% conversion, while quantitative conversion was obtained for the  $\text{PF}_6$  derivative along with a higher regioselectivity towards the tertiary C-H insertion product.



**Scheme 1.8.1: Cyclopropanation and aziridination [51, 54]**

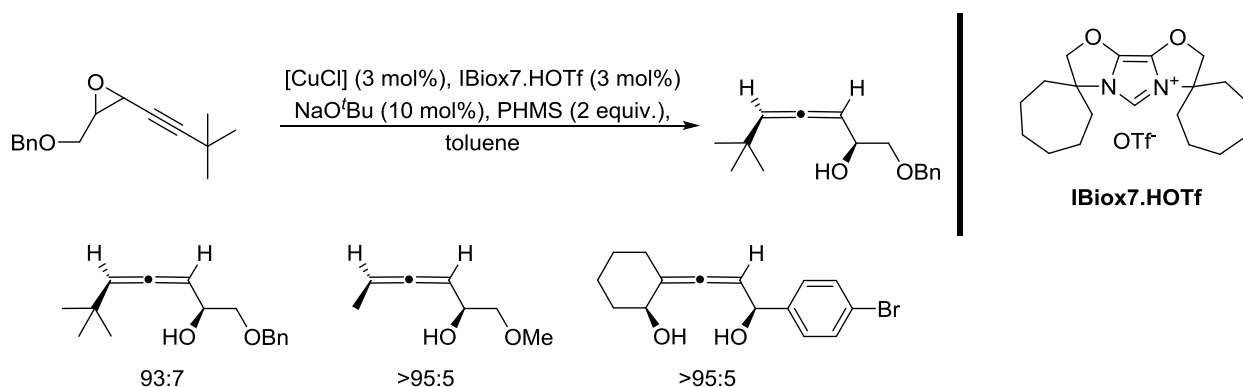
In 2005, the cyclopropanation on a wide range of substrates including substituted diazoacetates was reported by Narayan [53]. Later, Appella studied the aziridination reaction allowing nitrene transfer (Scheme 1.8.1) [54]. In this process, the halide abstraction reagent was no longer necessary. The investigation of the copper-carbene complexes highlighted  $\text{Cu(II)}$  species as the most efficient for such transformations. However, in the absence of NHC ligand, no product was detected. The optimal conditions were found in the presence of a 1,3-diketone specifically dibenzoylmethane (DBM). More recently, an extended scope to non-aliphatic alkenes and various functional groups was reported based on di- and tri-nuclear cationic  $\text{Cu}$  species [55]. Despite the ability to act as carbene transfer agents, the reactivity of tri-nuclear copper complexes remained inferior compared to the mono- and dinuclear analogues [56].

## 2. Reactivity of Alkynes

### 2.1. Formation of allenes

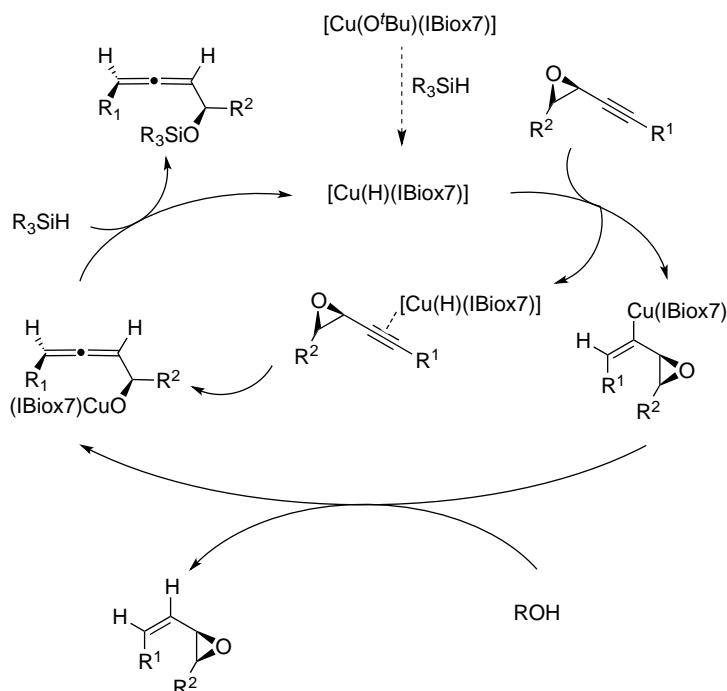
In organic chemistry, allenes are valuable reactive entities which can undergo several transformations [57]. In its copper incarnation, these are usually synthesised using Stryker's reagent [58], however an alternative was investigated by Krause and Lipshutz based on copper-NHC complexes (Scheme 2.1.1) [59]. The well-known IBiox class of ligands, developed by Glorius, as well as the most common NHCs were studied for the  $\alpha$ -hydroxyallene formation [60]. Regarding the NHC effect, ICy, SIMes and IBiox7 were the most active species in the allene formation, but poor results were measured with SIPr, IPr and

IMes analogues (ICy = *N,N'*-bis(cyclohexyl)imidazol-2-ylidene; SIMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene; SIPr = *N,N'*-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene; IMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene). In the absence of ligand, the  $S_N2'$  substitution product was observed as well as side-reactions, leading to a mixture of diastereoisomers. The chirality is dependent on the ligand and the copper source. The IBiox was the optimal ligand combining good yield and diastereoselectivity. The chirality transfer was monitored and highlighted the *anti*-selective  $S_N2'$  reduction. Electron-rich and electron-poor arenes, enynes and esters were converted with complete chemoselectivity. Regarding the catalytic cycle, two pathways were proposed. One based on the  $S_N2'$  substitution observed by Alexakis [61], the second involving the formation of a  $\pi$ -complex, usually observed for  $S_N2'$  substitution of allylic electrophiles. The latter justifies the *anti*-stereoselectivity.



**Scheme 2.1.1: Formation of allenes using IBiox7 [59]**

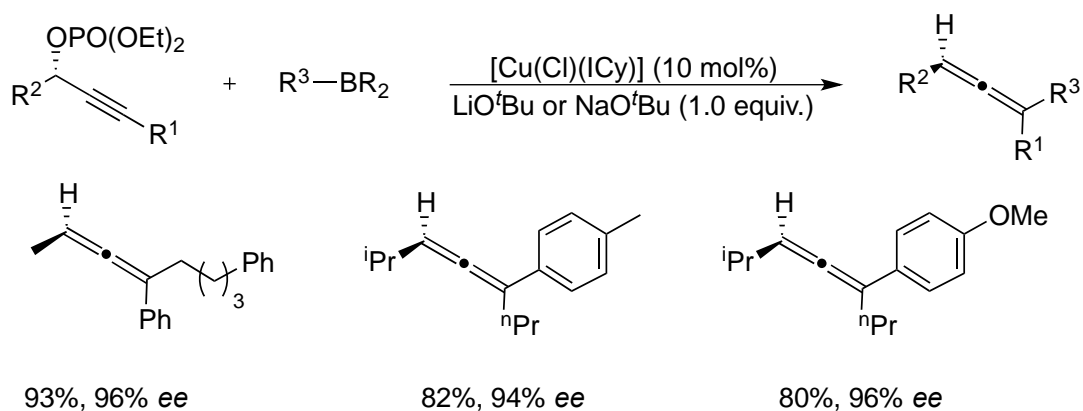




**Scheme 2.1.2: Proposed mechanisms for allenes formation [63]**

In 2009, Krause proposed a variant of this transformation allowing the formation of allenes from propargylic carbonates [62]. Once again, the IBiox-based systems outperformed the common NHCs. A DFT study was performed to probe the mechanism of this transformation (Scheme 2.1.2) [63].

Two years ago, Lalic reported an asymmetric version leading to chiral allenes using propargylic phosphates (Scheme 2.1.3) [64]. In this case, the investigations showed  $[\text{Cu}(\text{Cl})(\text{ICy})]$  (ICy = *N,N'*-dicyclohexylimidazol-2-ylidene) as the optimal catalyst for the arylation and alkylation of propargylic phosphates, *via* a  $\text{S}_{\text{N}}2'$  substitution. This reactivity was linked to the intrinsic selectivity during the substitution step. Indeed, no racemisation occurred with the phosphate and allene. The presence of lithium *tert*-butoxide was required to afford the allenes without side-reactions. Silyl and phenyl ethers, alkyl chlorides, thioacetals and aryl bromides proceed with high regioselectivity. Interestingly, no inhibition was observed with bulky substituents at the  $\gamma$ -position of propargylic phosphates. As for the alkylation, the arylation occurred *via*  $\text{S}_{\text{N}}2'$  substitution.

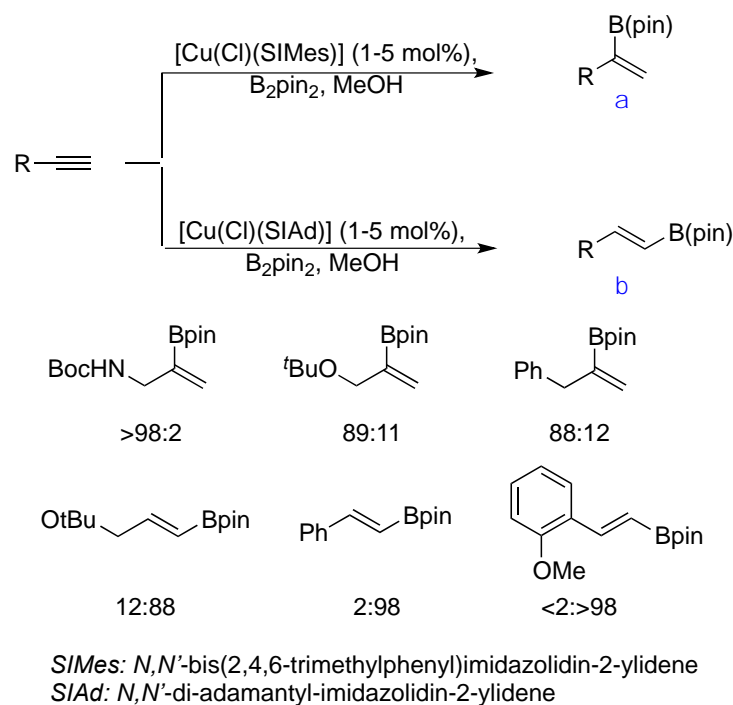


**Scheme 2.1.3: Asymmetric synthesis of allenes [64]**

A plausible mechanism was proposed involving a transmetalation step followed by an *anti*-selective substitution. Later on, Hoveyda successfully developed the enantioselective allylation of boroallenes to access enantiopure monosubstituted allenes [65].

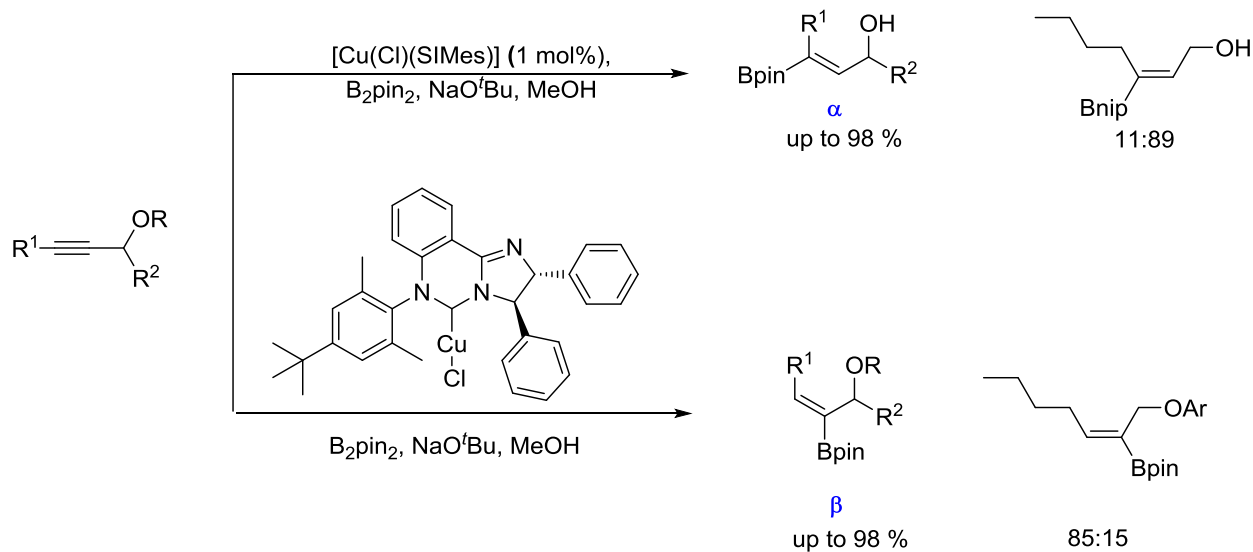
## 2.2. Boration of alkynes

As previously described, hydroboration of multiple carbon-carbon bond is a straightforward process to access organoboranes [66]. These potent reagents find many applications, such as in the Suzuki-Miyaura cross-coupling reaction. In 2011, Hoveyda and co-workers published a highly efficient and selective process for the hydroboration of terminal alkynes [67,68]. The *N*-substituents of NHC ligands allowed to control the selectivity. Indeed, the presence of aryl group favored the  $\alpha$ -vinylborane (up to >90%), while alkyl derivatives led predominantly to the  $\beta$ -product (up to >98%) (Scheme 2.2.1). Interestingly, [Cu(Cl)(SIMes)] was more selective catalyst at low temperature. During the investigation of the reaction scope, different behaviors were observed. For propargylic alcohols, the transformation occurred in the absence of additive (methanol). The low acidity of amines did not allow the deprotonation of the vinylcopper intermediate. The  $\alpha$ -vinylboranes were obtained in high selectivity and purity for aryl and heteroaryl-substituted terminal alkynes. EWG were tolerated leading to high selectivity, but the IPr catalyst is necessary in this case. The  $\beta$ -hydroboration product was obtained using the [Cu(Cl)(IAd)] catalyst. Regarding alkyl-substituted alkynes, moderate to good yields were observed (50-86%). Aryl-derivatives gave better selectivity. Insight into the mechanism identified several decisive factors for the formation of  $\alpha$ - or  $\beta$ -product. Indeed, the steric and electronic properties of the NHC and the alkyne substituents are two fundamental parameters affecting the selectivity. The more basic complex favours preferentially the  $\beta$ -product, whereas the less donating NHC promoted the  $\alpha$ -vinylboration.



**Scheme 2.2.1: Alkynes boration [67,68]**

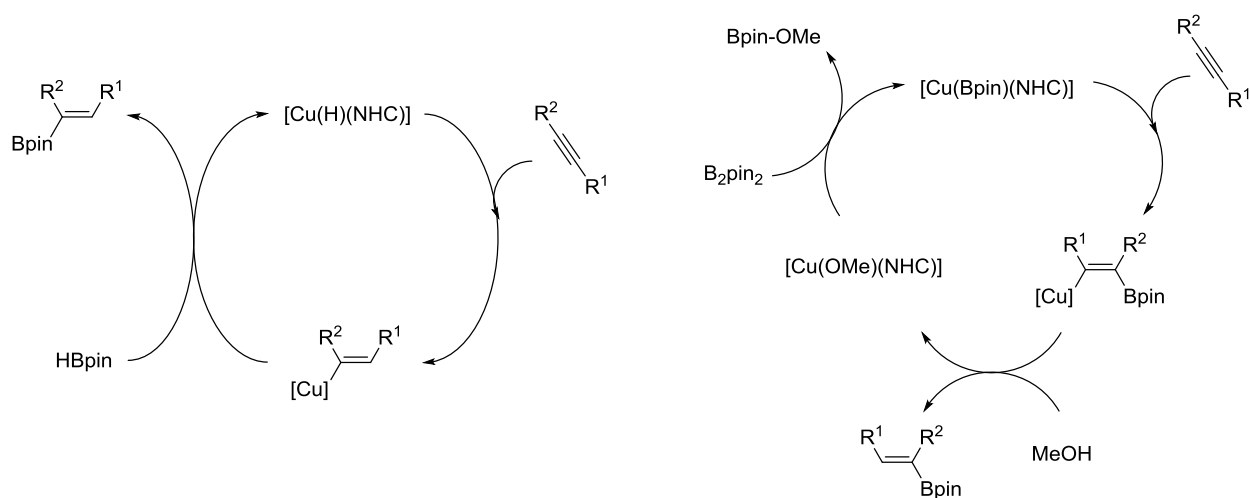
In 2012, Tsuji and McQuade independently published on the hydroboration of internal alkynes (Scheme 2.2.2) [69, 70]. In Tsuji's methodology, the  $\alpha$ -product was obtained using  $IPr^{Cl}$  ligand [69]. Aryl esters and amines were converted with high regioselectivity. Electron-withdrawing and electron-donating groups were tolerated. In the case of alkenyl derivatives, a drop in the selectivity was noticed. In parallel, McQuade's systems involved two types of NHC complexes with different selectivities [70]. The use of 5-membered-ring NHCs led to high selectivity for the  $\alpha$ -boration. Amines and silyl-protected alcohols were efficiently converted, while primary ethers resulted in poor selectivity (85/15). In the presence of the 6-membered NHC complex, the  $\beta$ -product was the major product.



**Scheme 2.2.2: Boration of alkynes reported by McQuade [70]**

Recently, Cazin and co-workers reported an aerobic version for the formation of tri- and tetra-substituted vinylboronates.  $[\text{Cu}(\text{Cl})(\text{IMes})]$  catalyzed the  $\alpha$ - and  $\beta$ -hydroboration as well as the carboboration. Indeed, using  $\text{B}_2\text{pin}_2$  as the boron source, the selectivity was enhanced towards the  $\beta$ -substituted derivative, while  $\text{HBpin}$  gave the  $\alpha$ -product [71].

Two mechanisms were proposed for the hydroboration as described below (Scheme 2.2.3).

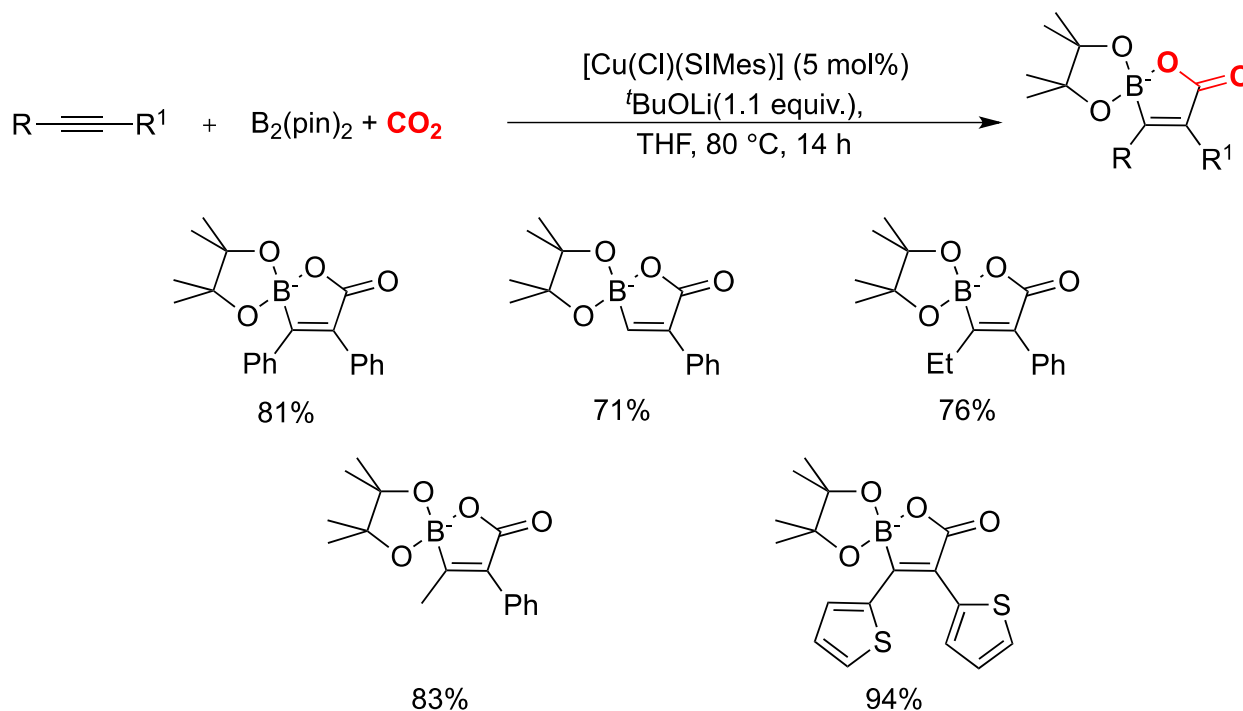


**Scheme 2.2.3: Proposed mechanisms for the hydroboration of alkynes [70]**

## 2.3. Carboxylation and boracarboxylation

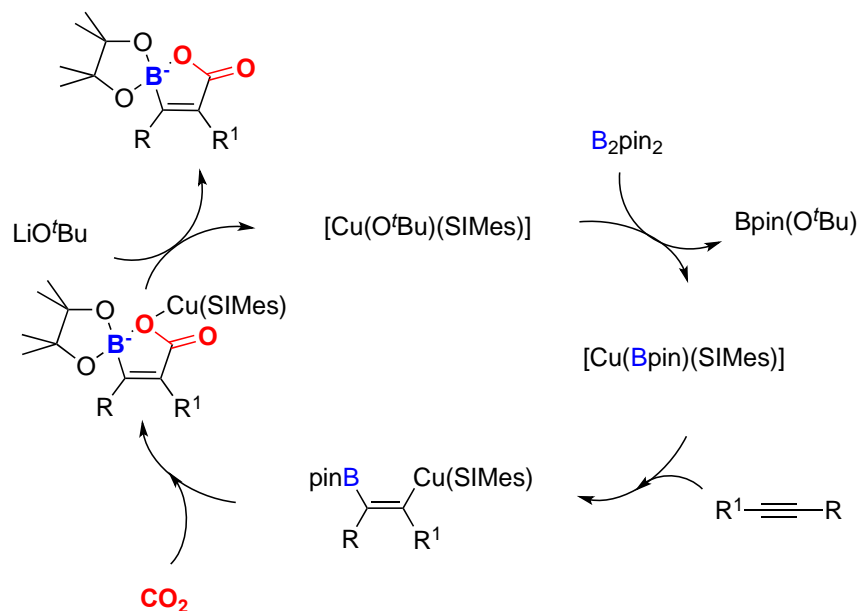
### 2.3.1. Boracarboxylation of alkynes

CO<sub>2</sub> is an abundant and nontoxic carbon source. The use of this renewable material as a building block in straightforward processes to access functionalised compounds is highly desirable and remains challenging [72]. Indeed, the heterocarboxylation in which CO<sub>2</sub> and a heteroatom are simultaneously introduced represents an extremely valuable and green method of molecular assembly. In 2012, Hou and co-workers reported a combination of carboxylation and borylation (Scheme 2.3.1.1) [73]. To study the boracarboxylation, different copper-NHC complexes were tested. Low conversions were observed using [Cu(Cl)(IPr)], whereas less sterically demanding NHC ligands such as IMes showed a significant increase in catalytic activity (73%). The saturated analogues presented better results with 81%. At room temperature, a loss of activity was observed (26%). Regarding the alkynes tolerance, all substrates afforded the cyclic compound in good to excellent yields. Different functionalities were transformed, such as esters or haloalkynes. However, in the case of unsymmetrical alkynes with alkyl and aryl moieties, the boryl group was exclusively set up on the carbon bearing the alkyl group, supposedly due to steric hindrance.



Scheme 2.3.1.1: Borocarboxylation of alkynes [73]

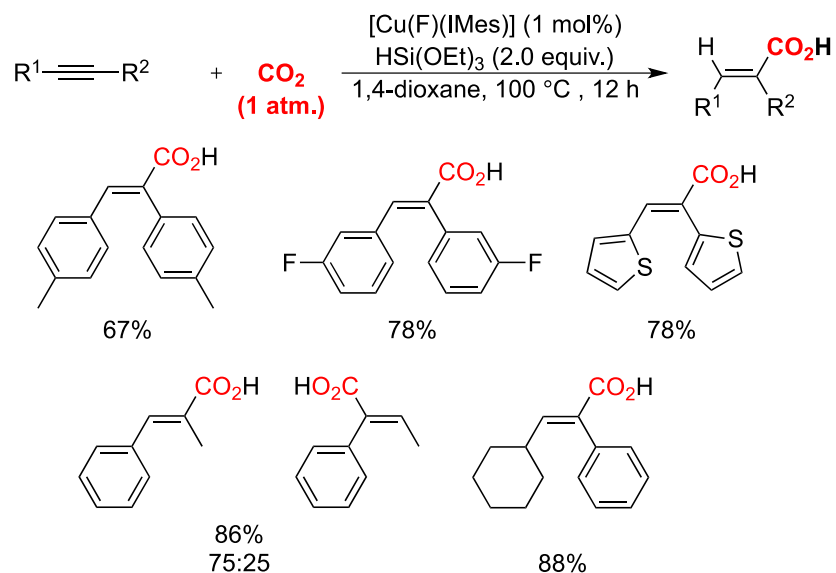
Insight into the catalytic cycle involved the *in situ* formation of the *tert*-butoxide copper catalyst (Scheme 2.3.1.2). The boron source  $B_2pin_2$  generated the borylcopper complex  $[Cu(Bpin)(SiMes)]$ . Then, the alkyne insertion into the Cu-B bond in a *syn* fashion affords the boryl alkenylcopper species. The nucleophilic attack of the alkenyl copper by  $CO_2$  is followed by the transmetalation to generate the final product.



**Scheme 2.3.1.2: Proposed mechanism for the boracarboxylation [73]**

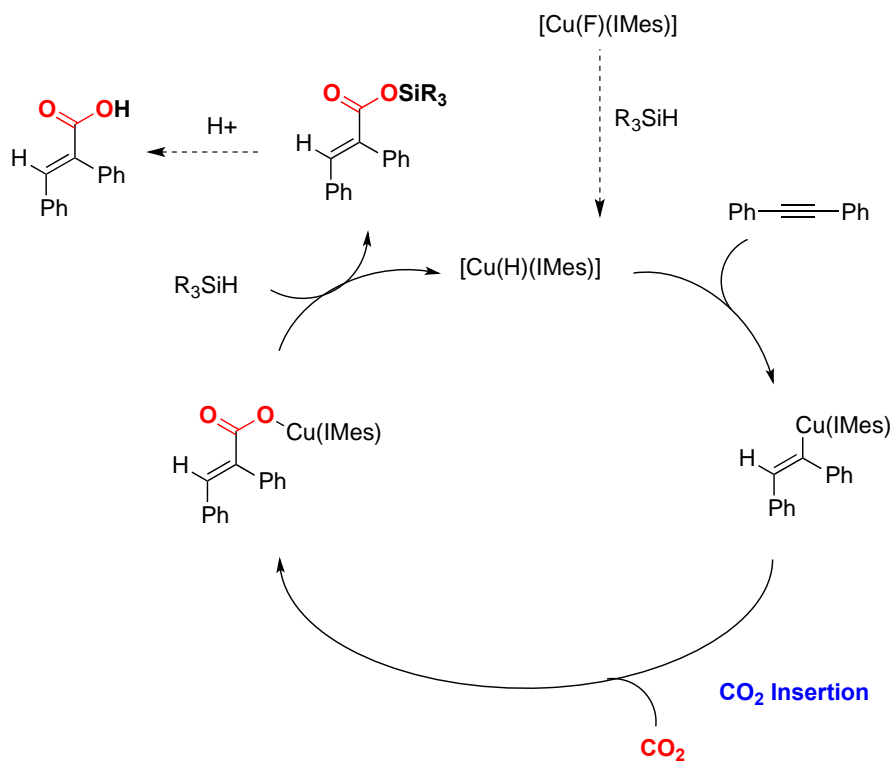
### 2.3.2. Hydrocarboxylation of alkynes

Although nickel has been extensively studied as catalyst for hydrocarboxylation of alkynes [74], and requires highly unstable reducing reagents such as zinc or aluminium, an alternative method with copper-NHC has been developed by Tsuji (Scheme 2.3.2.1) [75]. In the presence of silane, unsaturated carboxylic acids were formed. Internal alkynes were converted using the commercially available  $HSi(OEt)_3$ . In the presence of sodium *tert*-butoxide and  $[Cu(Cl)(IPr)]$ , only traces of the desired compound were obtained. Interestingly, the IMes ligand permitted a 49% conversion, but a significant amount of the hydrogenated derivative was observed. An important halide effect was measured. Indeed the  $[Cu(F)(IPr)]$  allowed an important decrease of the side-product with only 3% observed, but it is accompanied by a slight decrease of the conversion. However, a more effective species was obtained with IMes. The stereoselectivity was displaced toward the formation of the *E* isomer. The silane source was efficiently replaced by a more environmentally friendly reducing reagent, PMHS (polymethylhydrosiloxane). Regarding the scope investigation, alkynes bearing electron-poor and electron-rich aryl moieties were efficiently hydrocarboxylated.



**Scheme 2.3.2.1: Hydrocarboxylation of internal alkynes [75]**

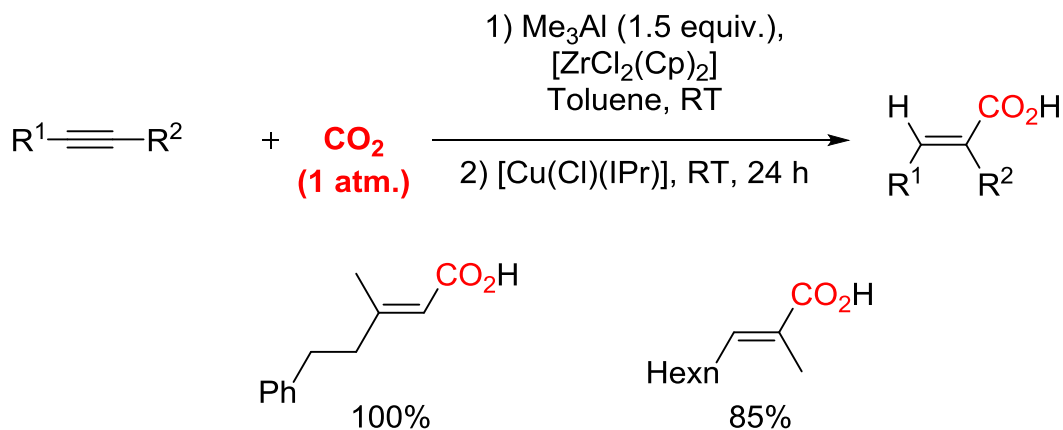
Studies toward understanding the catalytic cycle appear to confirm the formation of the hydride intermediate (Scheme 2.3.2.2). An alkenyl copper complex was obtained by reacting the  $[Cu(H)(NHC)]$  and the alkyne. The next step consists of the  $CO_2$  insertion into the Cu-C bond. More recently, DFT calculations studies undertaken by Lin and coworker supported this mechanism [76].



**Scheme 2.3.2.2: Hydrocarboxylation mechanism [76]**

### 2.3.3. Methylative and hydrogenative carboxylation of alkynes

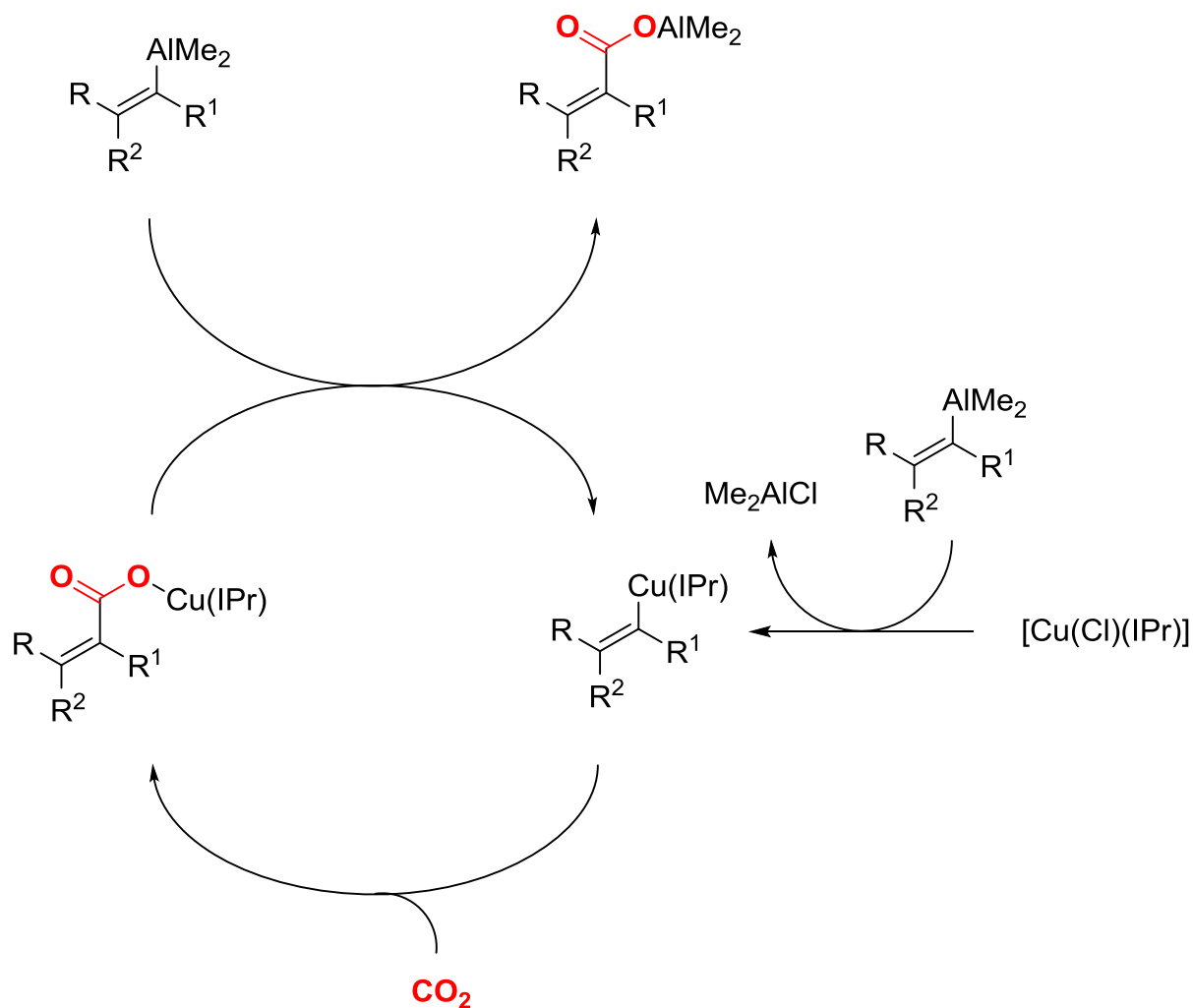
Catalytic functionalization in which CO<sub>2</sub> unit and another group are incorporated into alkynes is a powerful tool to access highly functionalized molecules using potentially simple synthetic steps. After the previously described reactions (hydrocarboxylation or boracarboxylation), it became of great interest to develop new methodologies based on CO<sub>2</sub> insertion and functionalization [77]. In 2013, Hou reported a copper catalyzed methylative and hydrogenative carboxylation (Scheme 2.3.3.1) [78]. First the examination of the alkenylaluminium intermediate in the absence of the copper source did not afford the carboxylate species. Interestingly, the presence of a catalytic amount of [Cu(Cl)(IPr)] leads to the formation of the desired product at ambient temperature under atmospheric pressure of CO<sub>2</sub>. At higher temperature, a significant drop in the conversion was observed (86%). Under similar conditions, CuCl and IPr salts gave a much lower yield (8 and 28%). Interestingly, retention of the stereoconfiguration of the alkenylaluminium was observed leading to the hypothesis that the regio- and stereoselectivity of the reaction is controlled by the methylalumination step. The methylative carbonylation of internal alkynes bearing ether groups was efficiently achieved in high yield using scandium as co-catalyst.



**Scheme 2.3.3.1: Hydrogenative and methylative carboxylation of alkynes [78]**

Interestingly, the *anti*-configuration was obtained when trimethylsilyl-substituted alkynes were used. In the case of terminal alkynes, the scandium was replaced by a zirconium catalyst, well-known for methylalumination [79]. For all products obtained, the CO<sub>2</sub> unit was introduced on the less hindered carbon. Finally, the hydrogenative carboxylation of terminal alkynes was studied. In this case, a nickel/copper system was required. Indeed, the nickel catalyst performed the hydroalumination, while the copper allowed the CO<sub>2</sub> insertion. For all reactions, the carboxylation occurred in a *cis*-fashion. However, when [Ni(Cl)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] was replaced by [Ni(Cl)<sub>2</sub>dppp] (dppp = 1,3-bis(diphenylphosphino)propane), the selectivity was switched and the branched carboxylation products were obtained.





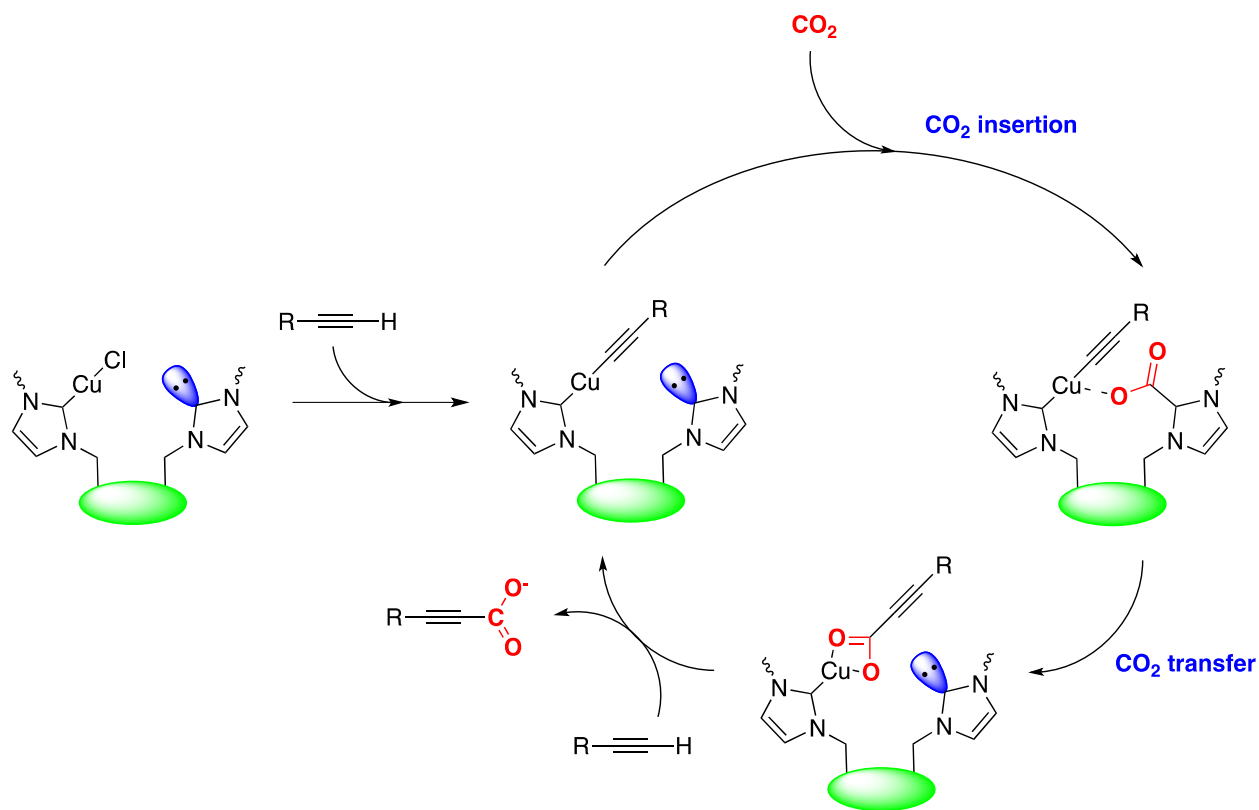
**Scheme 2.3.3.1: Plausible mechanism for carboxylation of alkynes [79]**

A plausible mechanism was described involving a transmetalation step between the Cu-NHC and the alkenylaluminium species (Scheme 2.3.3.2). Then, CO<sub>2</sub> insertion occurs into the M-C bond. A second transmetalation step releases the product as well as regenerates the alkenyl copper intermediate.

### 2.3.4. Carboxylation of alkynes

Carboxylation of terminal alkynes is an efficient method to access alkynyl carboxylic acids [80]. In 2010, Lu and co-workers reported a methodology for the carboxylative coupling using allylic chlorides. The well-defined [Cu(Cl)(IPr)] was highly active for the conversion of phenylacetylene with a 91% yield of the desired product. Interestingly, 92% of the catalyst was recovered at the end of the reaction. In the absence of CO<sub>2</sub>, no product was detected. The IMes derivative gave only 51% yield. Interestingly, an important requirement was noticed, the pressure of CO<sub>2</sub> had a profound effect on

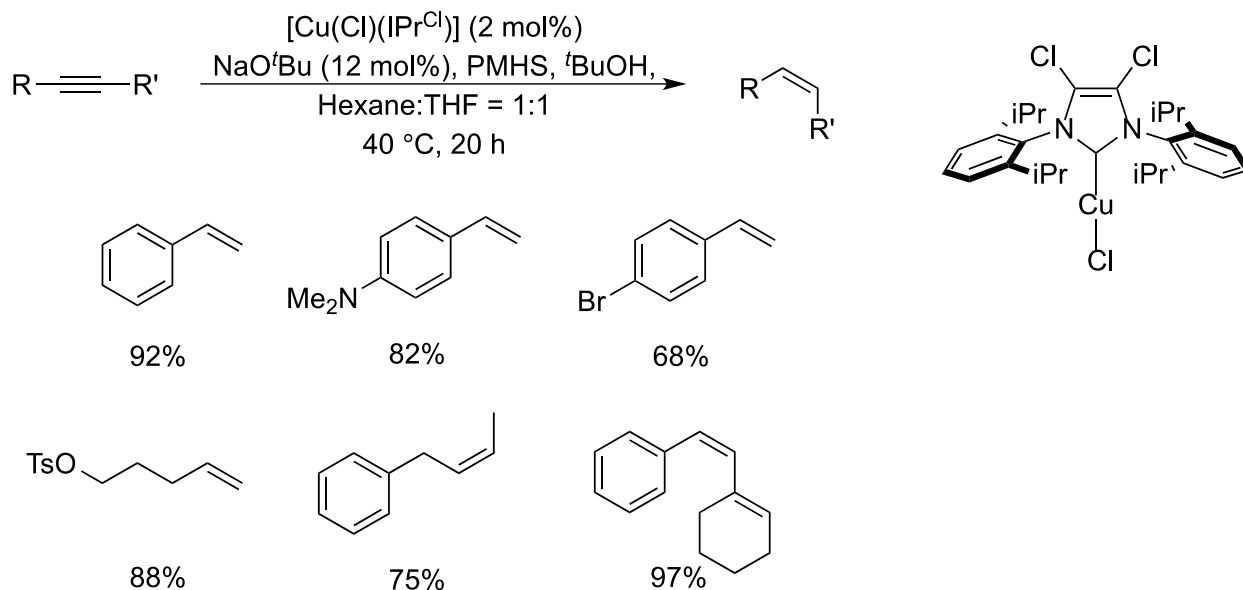
conversion. High pressure is beneficial avoiding any side-reaction and increases the reaction rate. A variety of alkyl and aryl alkynes in the presence of cinnamyl chloride were efficiently carboxylated with good to excellent yields. High tolerance toward functional groups such as ether, ester and cyano was observed. In the case of heteroaryl alkynes modest yields were obtained. Different allylic chlorides were efficiently transformed. Independently, Zhang reported an alternative methodology for the formation of propiolic acids based on copper-NHC complexes [81]. The catalyst system based on CuCl and TMEDA efficiently promotes the reaction at ambient temperature and atmospheric pressure of CO<sub>2</sub>. But a strong base such as Cs<sub>2</sub>CO<sub>3</sub> was required for alkyl substrates. The presence of EWG on the phenyl ring inhibits the reaction. To overcome this limitation, poly-*N*-heterocyclic carbenes (PNHC) were used. An increase in reactivity was monitored. Thus, with 10 mol% of poly-NHC ligand and CuCl, electron-deficient derivatives were carboxylated (RT and 1 bar of CO<sub>2</sub>). The reaction mechanism proposed involved a dual function of the PNHC ligand (Scheme 2.3.4.1). Indeed, the copper-PNHC allowed the formation of an acetylide, whereas the free ligand facilitated the CO<sub>2</sub> insertion leading to the formation of PNHC carboxylate. The proximity of these two species allowed the transfer of the CO<sub>2</sub> unit from the NHC to the metal center and the C-C bond formation. A metathesis step releases the final product [82].



**Scheme 2.3.4.1: Carboxylation of alkynes using copper poly-NHC complexes [82]**

## 2.4. Semi-hydrogenation of alkynes

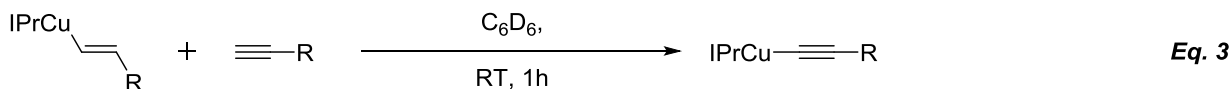
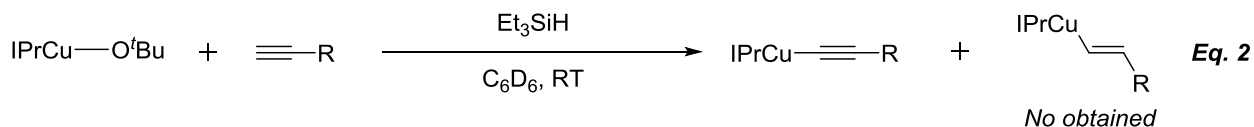
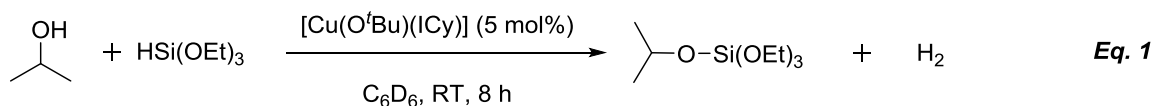
Semi-hydrogenation of alkynes is a worthwhile process leading to (*Z*)-alkenes. Heterogeneous catalysts have been widely used for this transformation. The most famous example remains the Lindlar catalyst (Pb-poisoned Pd) [83]. However, this system suffers from several drawbacks such as *Z/E* isomerisation, low chemoselectivity and lack of reproducibility. Few years ago, Tsuji published a Cu-NHC methodology for the semi-hydrogenation of non-polar carbon-carbon triple bonds (Scheme 2.4.1) [84]. Terminal alkynes were successfully reduced to alkenes. The NHC effect was evaluated based on IPr, IPr<sup>Me</sup> and IPr<sup>Cl</sup> ligands. When compared with the Xanphos ligand, the NHC-based complexes demonstrated higher activity, especially [Cu(Cl)(IPr<sup>Cl</sup>)], which afforded styrene (92% yield) without the formation of ethylbenzene. An over-reduced compound (89% yield) was observed in the presence of the Lindlar catalyst. Various substrates were efficiently converted to the alkenes without formation of the alkane derivatives.



**Scheme 2.4.1: Semi-hydrogenation of terminal alkynes [84]**

Independently, Lalic reported on a similar approach based on Sadighi's work (Scheme 2.4.2) [85]. Their initial investigations on the reduction of alkynes were unsuccessful. Indeed, when [Cu(O<sup>t</sup>Bu)(ICy)] was used as catalyst in the presence of triethoxysilane, *tert*-butanol and the alkyne, only an incomplete conversion toward the alkene was observed (19%). Three side-reactions were identified during the process. The first involved the reaction between the silane and the alcohol. Interestingly, changing ICy for IPr decreased the rate of this transformation. The second outcome was the fast formation of the copper acetylide complex, which is an inactive species for the hydrogenation. To overcome this phenomenon,

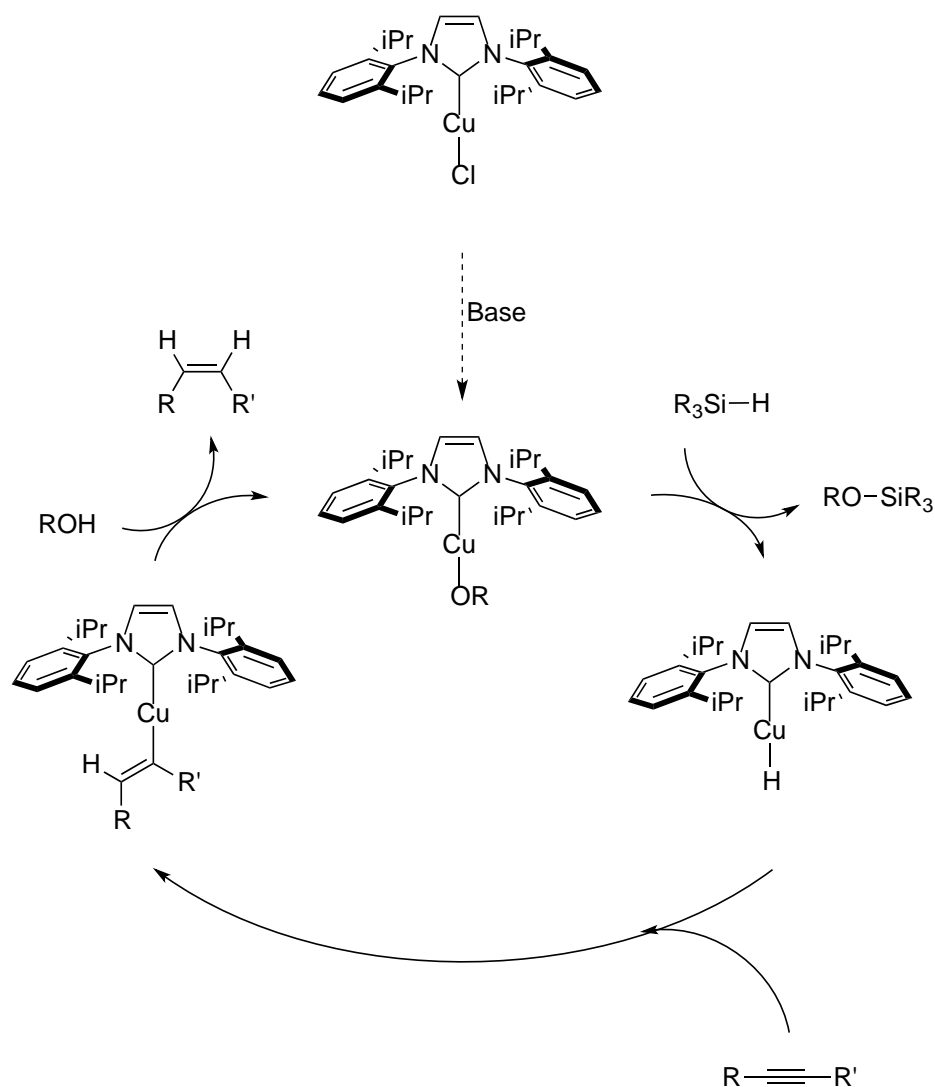
PMHS (polymethylhydrosiloxane) was used, which increases the rate of the silicon-copper hydride transmetallation allowing the formation of the alkenyl copper complex. However, this latest species might deprotonate the alkyne to favour once again the acetylide copper complex formation. Interestingly, the presence of a more acidic alcohol leads to higher conversions. Based on these observations, terminal alkynes were selectively converted to the desired alkene. A variety of functional groups were presented such as nitroarenes, sulfonates or ketones and no over-reduced product was detected. Nevertheless, in the case of internal alkynes, the previously described conditions were not efficient. However, when replacing *iso*-butanol by a less acidic alcohol such as *tert*-butanol, an increase of the conversion was observed. During examination of the scope, only the *Z*-isomer was detected. No presence of alkane derivatives was observed.



#### Scheme 2.4.2: Side-reactions observed by Lalic during alkyne semi-reduction [85]

Recently, a copper catalyst generated *in-situ* was reported [86]. Quantitative conversion was observed with the use of  $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$  and  $\text{IPr} \cdot \text{HCl}$  in the presence of potassium *tert*-butoxide. However, copper halide salts such as  $\text{CuI}$  or  $\text{CuCl}$  generated low to moderate yields (3 to 69%). Interestingly, a minimal impact was correlated to the silane source (with 96% and 100%, for the triethoxysilane and PMHS respectively). Despite these interesting results, some over-reduced product was identified for substrates bearing electron-withdrawing groups.

The plausible mechanism for semi-hydrogenation involves the formation of  $[\text{Cu(H)(NHC)}]$  (Scheme 2.4.3). Indeed, the copper-alkoxy species reacts with the silane and leads to the formation of the hydrido-copper(I) complex. The hydrocupration of the alkyne leads to an alkenyl copper intermediate, which in the presence of an alcohol releases the *Z*-alkene and regenerates the active species, the alkoxide copper complex.

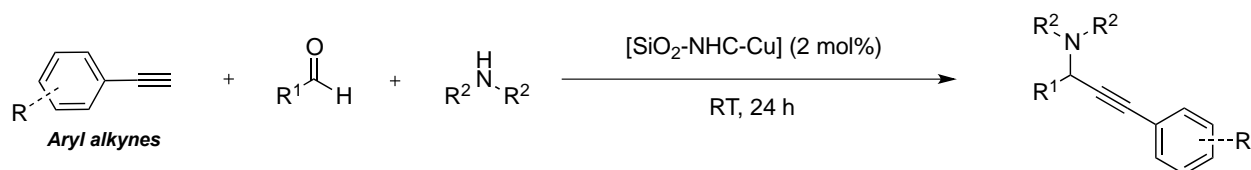


**Scheme 2.4.3: Postulated mechanism for the hydrogenation of alkynes [86]**

## 2.5. A<sup>3</sup> coupling

Multicomponent reactions are powerful tools allowing access to highly functionalized scaffolds. During the last decade, A<sup>3</sup> coupling (Amine - Alkyne - Aldehyde) has drawn significant attention and represents one of the most interesting examples of atom-efficient transformation. The reaction of an amine, alkyne and aldehyde favoured the formation of propargylamine derivatives, which are predominantly used as building blocks for biological molecules. Many groups have explored the chemistry of propargylamines using metal-based systems such as copper or silver salts. In 2008, Wang reported a silica-supported copper-NHC-catalyzed A<sup>3</sup> coupling (Scheme 2.5.1) [87a]. The comparison with the common neutral derivatives showed that both systems were highly active with 95% conversion after 24 hours under solvent-free conditions. Nonetheless, the following studies were conducted on the

SiO<sub>2</sub>-NHC-Cu complex. The catalytic activity was clearly influenced by the solvent. Polar solvents such as acetone or dichloromethane enhanced the reactivity leading to quantitative conversion, while toluene, acetonitrile and tetrahydrofuran (THF), previously reported as highly efficient in the presence of copper salts, gave low yields. The role of the solvent is unclear at this point. The reaction scope showed a high tolerance to functional groups. Cyclic/acyclic and heterocyclic amines were efficiently reacted under standard conditions. Nevertheless, moderate yields (43%) were observed for primary aliphatic amines, whereas aromatic analogues, such as anilines, provided the desired products in good yields. Regarding the aldehyde reactivity, aliphatic as well as cyclic/acyclic derivatives presented high reactivity. Besides the reactants, the catalyst remains the major variable. The heterogeneous nature of this specific system makes its recyclability without significant loss of catalytic activity a great contribution to the A<sup>3</sup> coupling reaction.



**Scheme 2.5.1: SiO<sub>2</sub>-NHC-Cu(I) system catalysing A<sup>3</sup> coupling [87a]**

More recently, Navarro and co-workers have reported on the synthesis of propargylamines, using [Cu(X)(NHC)] (X = Cl, NHC = IPr, SIPr, IMes and SIMes) (Scheme 2.5.2) [87b]. A significant effect of the *N*-substituent was observed. IPr and its saturated analogue (SIPr) produced the best results (82 and 94% conversion respectively), compared to IMes and SIMes, which almost showed no activity (4 and 7% conversion). A minimal impact was observed with the saturation of the NHC backbone. Additionally, a relatively small decrease in the reactivity is measured by replacing a chloride with an iodide. An attempt to rationalize the halide effect involves the first step of the proposed mechanism. The acetylide copper(I) formation will be favoured by the presence of chloride *vs.* iodide.

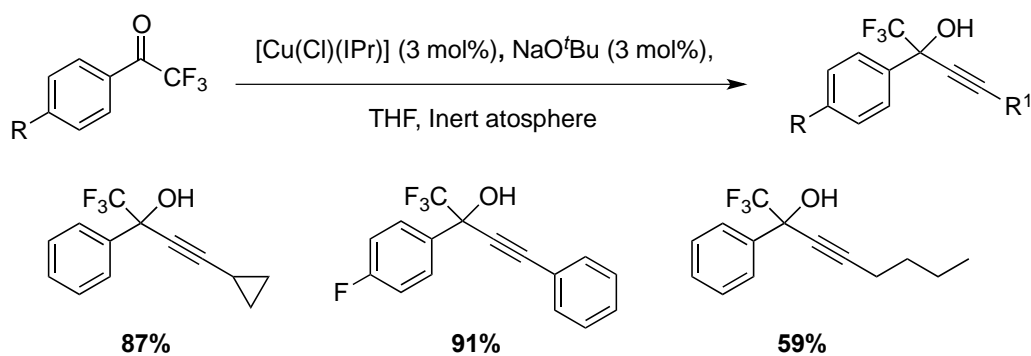


**Scheme 2.5.2: Neutral copper(I) complex efficient catalyst for the formation of propargylamines [87b]**

Overall, the copper-NHC complexes are efficient systems for this multicomponent coupling. The aliphatic aldehydes are efficiently converted to the corresponding propargylamines. Despite these good results, aromatic aldehydes showed a lack of reactivity, necessitating longer reaction times (1 to 2 days), a higher catalyst loading (3 mol%) and higher temperatures (50 to 70 °C vs. RT).

## 2.6. Alkynylation of ketones

The alkynylation of ketones represents a potentially very powerful synthetic method. Recently, Carreira described the alkynylation of ketones leading to the formation of Efavirenz, an anti-HIV drug [88]. McQuade and Seeberger have reported copper-NHC catalysis for alkynylation of ketones (Scheme 2.6.1) [89].  $[\text{Cu}(\text{Cl})(\text{IPr})]$  and  $[\text{Cu}(\text{Cl})(\text{IMes})]$  were compared. Despite the fact that both complexes catalyzed efficiently the transformation, the more hindered NHC (IPr) showed better catalytic activity. The comparison with CuCl salt highlighted the crucial importance of the presence of a ligand (CuCl = 0% conversion). In the absence of a base ( $\text{NaO}^t\text{Bu}$ ), no product was detected.



**Scheme 2.6.1: Hydrogenative carboxylation of alkynes [89]**

The formation of the copper(I) alkoxide is essential for the production of trifluoromethylpropargylic alcohols. Indeed, NaO<sup>t</sup>Bu has a double role: to favor the formation of this intermediate and also facilitate the proton transfer step. An excess of alkynes was required to achieve higher yields. Various terminal alkynes were converted with moderate to good yields. Interestingly the electronic properties of alkynes and ketones are a determining parameter. Indeed, when phenylacetylene was reacted with 2,2,2-trifluoroacetophenone a higher temperature was required to reach 86% yield. The system was tested under continuous flow conditions. The first issue encountered was the solubility of the additive (NaO<sup>t</sup>Bu) and that of the catalyst in tetrahydrofuran (THF). These problems were overcome by combining three solvent DMF, benzene and THF (2:3:1).

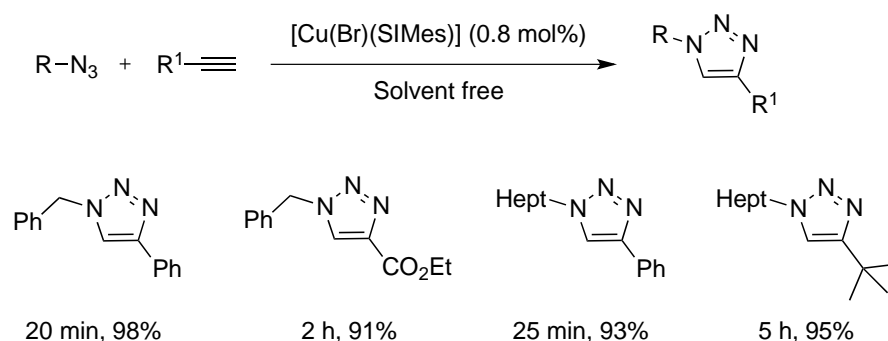
## 2.7. [3+2] Cycloaddition: Synthesis of triazoles

Since the seminal discovery of Huisgen, the 1,3 dipolar cycloaddition represents the most straightforward methodology for the formation of 1,2,3-triazoles. However, the process reported required harsh conditions and both regioisomer 1,5 and 1,4-disubstituted triazoles were initially formed. In 2002, Sharpless and Medal reported the first copper-catalyzed system for the [3+2] cycloaddition [90]. Interestingly, only the 1,4-disubstituted derivatives were formed. Since this report, the number of publications on this reaction grew exponentially, however, some major drawbacks still persisted and to circumvent these, copper-NHC complexes were employed.

The neutral copper complexes were the first investigated for this transformation (Scheme 2.7.1) [91,92]. Their efficiency was mainly proven on terminal alkynes, where low catalyst loadings were achieved. Testing different NHC highlighted an important effect of the ligand. Indeed, while [Cu(Cl)(IMes)] showed almost full conversion, a significant decrease in the conversion was recorded with [Cu(Cl)(IPr)]. The saturated analogues presented better catalytic activity on internal as well as terminal alkynes. *N*-moieties also affected the system. Indeed, the adamantyl species was the most effective compared to other

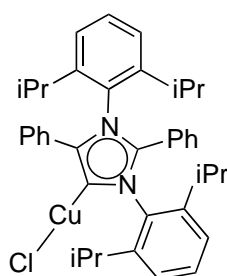


analogues. Nevertheless, the impact of the halide should not be ignored. A trend in the activity was observed as I > Br > Cl.



**Scheme 2.7.1: Formation of triazoles using neutral NHC copper(I) complexes [91,92]**

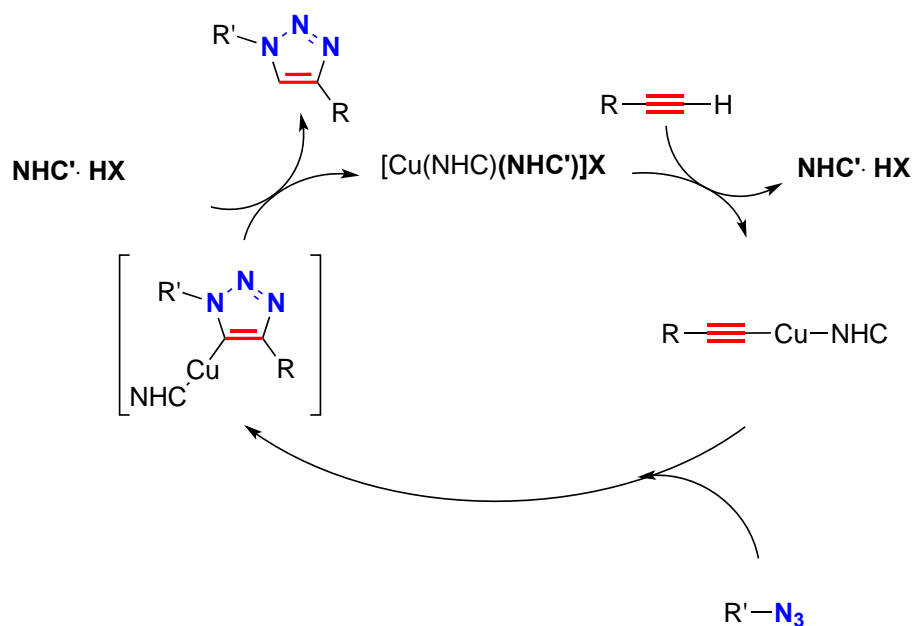
Recently, with the importance gained by abnormal NHCs, new evaluations of this NHC ligand motif were performed in the [3+2] cycloaddition reaction [93]. Mandal and co-workers reported the reaction using abnormal systems. These new abnormal Cu-NHC complexes showed high efficiency under similar conditions as those previously reported for the normal NHC species. Recycling tests showed a significant longevity with 10 successive catalytic runs performed before complete loss of reactivity. However, already after the 7<sup>th</sup> cycle an increase in the time reaction was observed. aNHC (aNHC = abnormal NHC) or NHC copper complexes catalyzed efficiently the [3+2] cycloaddition with high TON and low catalyst loading.



**Figure 2.7.1: aNHC copper(I) complex reported by Mandal [93a]**

In parallel to reports on neutral complexes, cationic bis-NHC copper species were also investigated [10]. In 2008, Nolan and Díez-González studied the effect of homoleptic cationic copper systems in the preparation of triazoles (Scheme 2.7.2) [10a]. Interestingly, the reactivity of such species proved higher than that of their neutral analogues. The SIMes derivative presented poor activity, which was in contrast with report on the neutral analogue.  $[\text{Cu}(\text{ICy})_2][\text{PF}_6]$  outperformed all other systems at low loadings and in the absence of solvent. The heteroleptic bis-NHC and the mixed NHC/phosphine derivatives developed



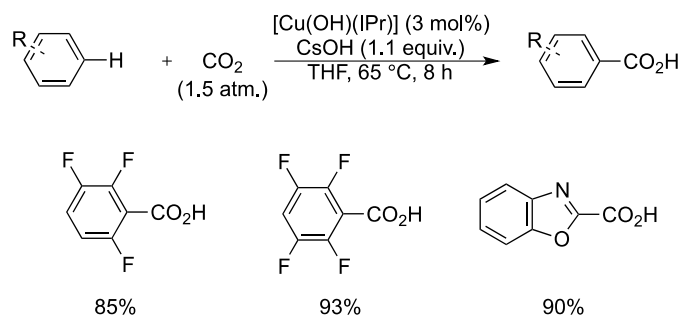


Scheme 7.2.3: Catalytic cycle for the formation of triazoles [10b]

### 3. C-H bond activation and functionalization of aryl and heterocyclic compounds

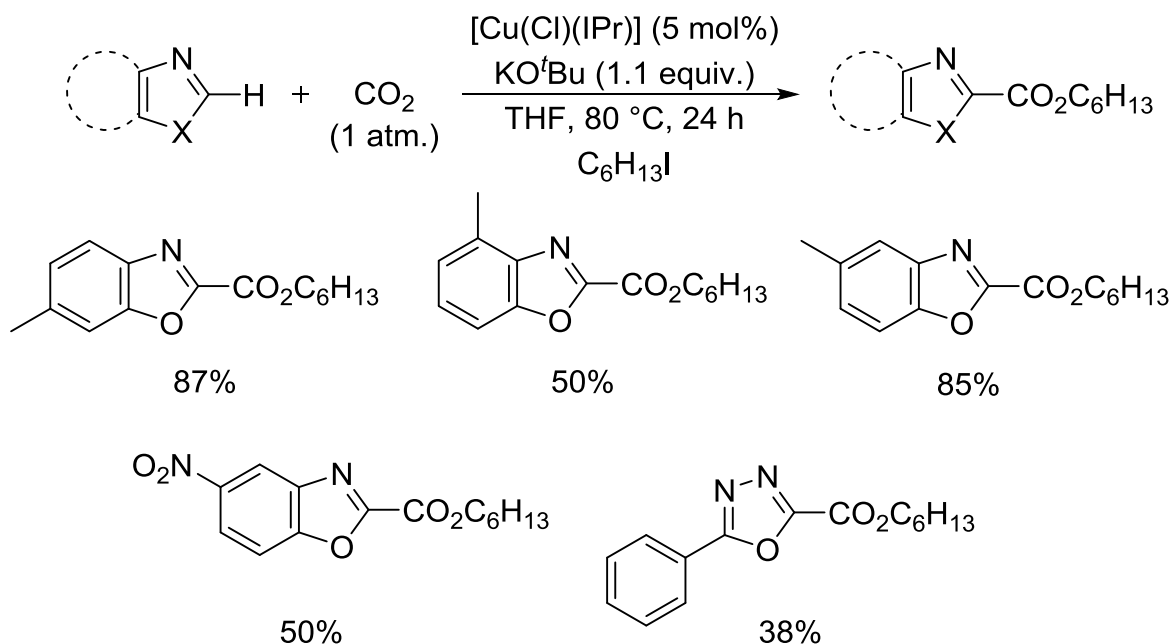
#### 3.1. Carboxylation and carbonylation (*via* boronic acids, C-H activation): CO<sub>2</sub> insertion

Commonly, methodologies to access carboxylic acids with CO<sub>2</sub> require the presence of organolithium or organomagnesium halides. However, these methods have a major drawback, which is their low functional group tolerance.



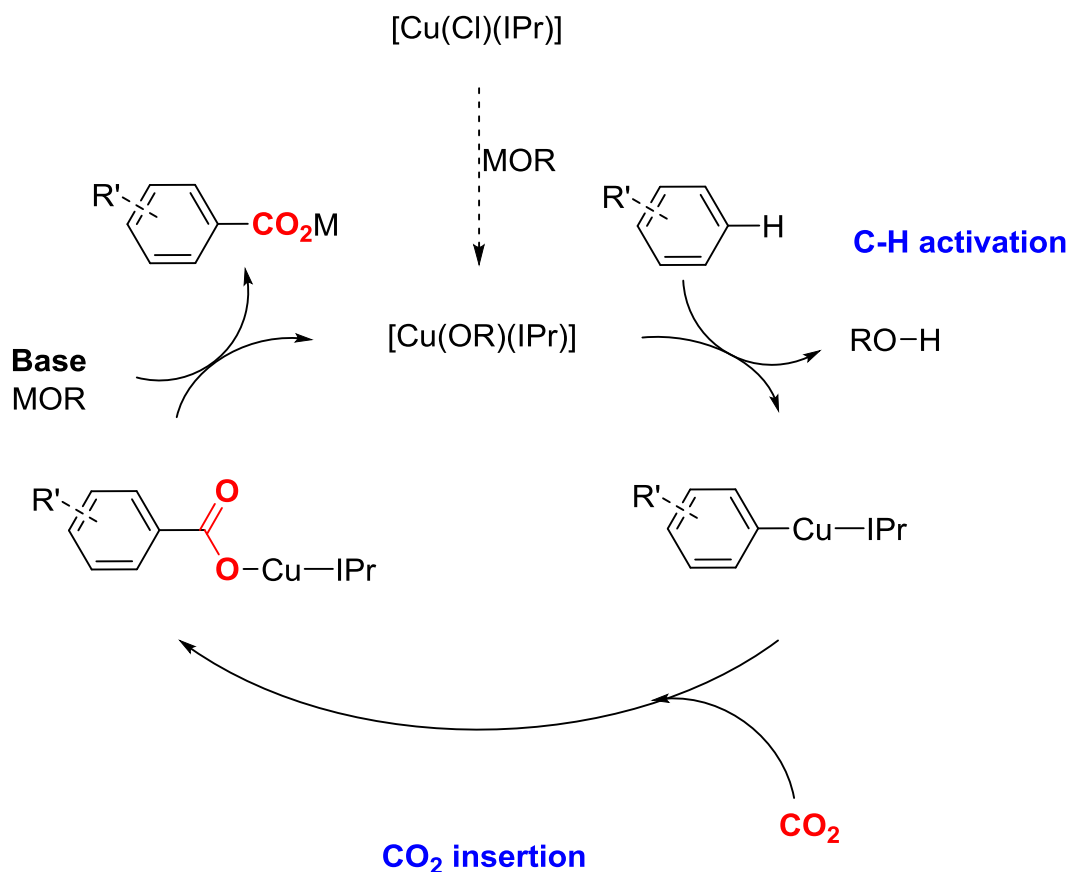
Scheme 3.1.1: Direct carboxylation [94]

Nolan and co-workers synthesized the first copper-NHC hydroxide complex [9g]. This new species was first used as a synthon for the synthesis of  $[\text{Cu}(\text{R})(\text{IPr})]$  derivatives via stoichiometric C-H activation. These initial studies were followed by the use of the hydroxide derivative as a powerful catalyst for direct carboxylation of N-H and C-H bonds (Scheme 3.1.1) [94]. The complex showed high selectivity for N-H and C-H bonds (with a  $\text{pK}_a$  below 27.7). A large panel of aryl carboxylic acids was prepared, as well as heterocyclic compounds. Independently, Hou developed a methodology leading to a range of heterocyclic esters (Scheme 3.1.2) [95].



**Scheme 3.1.2: Carboxylation system reported by Hou [95]**

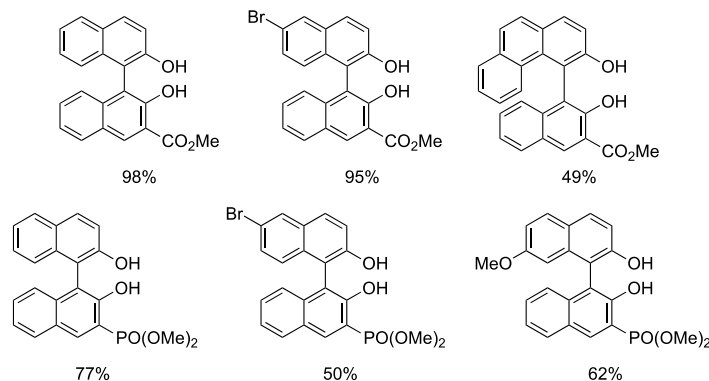
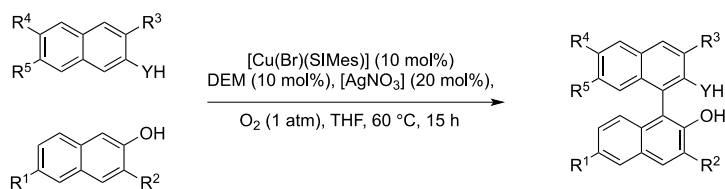
In both systems, the C-H bond activation is followed by  $\text{CO}_2$  insertion and an excess of a strong base is required (Scheme 3.1.3) [95]. The IPr ligand was the most efficient NHC-based ligand, with a high reactivity for boronic and aryl compounds. More recently, the carboxylation was conducted using abnormal NHC copper complexes [96]. The catalytic activity of copper (I) species proved interesting [97]. A plausible mechanism for this transformation was described involving C-H activation and  $\text{CO}_2$  insertion steps. This has great potential and much remains to be done in this area.



Scheme 3.1.3: Mechanism of the carboxylation of C-H bonds [95]

### 3.2. Oxidative coupling

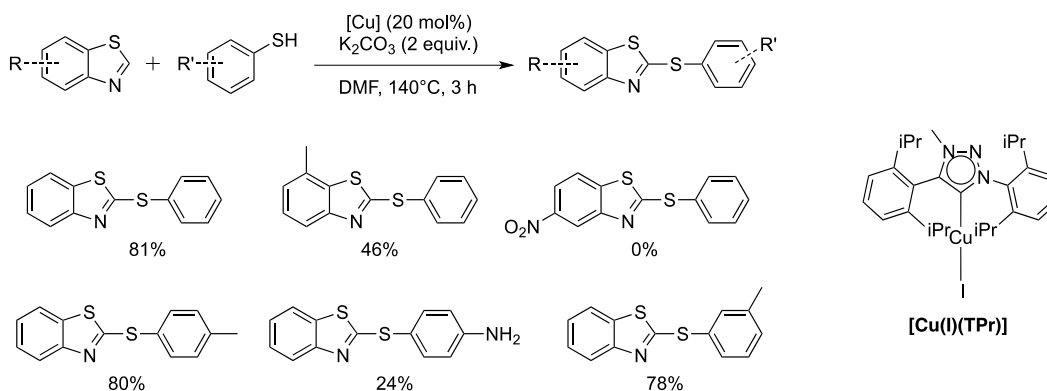
In Nature, large ranges of biaryl compounds are formed *via* oxidative coupling. To mimic Nature, metal complexes have been used, including ruthenium, iron or copper [98]. However, side-reactions leading to the formation of homocoupling or over-oxidised products are an issue. In 2013, copper-NHC complexes were used for the oxidative coupling of naphthols (Scheme 3.2.1). [Cu(Br)(IPr)] and [Cu(Br)(SIMes)] were used to perform the coupling of methyl esters and naphthols with Oxone [98g]. Good yields were obtained in both cases (63-67%). When Oxone was replaced by molecular oxygen, 77% yield was obtained. Adding diethyl malonate (DEM) (50 mol%) leads to quantitative conversion and excellent yield (98%). Different 1,3-dicarbonyls were tested, that led to similar or lower yields than with diethyl malonate. It is supposed that DEM acts as a ligand and slows the over-oxidation of 2-naphthol. C1-symmetric binols were prepared using these conditions. A large range of naphthols was efficiently converted to the binols.



**Scheme 3.2.1: Oxidative coupling leading to the formation of BINOLs [98]**

### 3.3. Thiolation

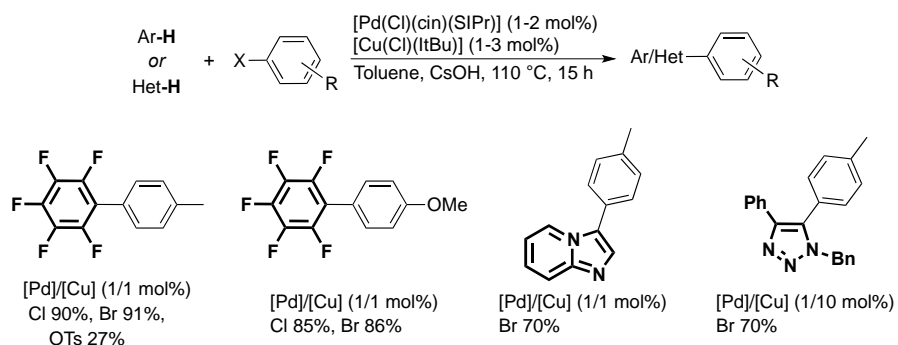
Recently, thiolation of benzothiazole and azole derivatives has been achieved using NHC and aNHC copper(I) complexes (Scheme 3.3.1) [99]. Cu(IPr) complexes was the most efficient complex leading to 95% yield after 3 h, while the IMes reached only 85% after 6 hours. The aNHC ligands were also quite efficient. Interestingly, the presence of oxygen was necessary for the reaction. Different thiol derivatives were tested. Depending on the functional group, moderate to good yields were obtained.



**Scheme 3.3.1: Thiolation of benzothiazole derivatives [99]**

### 3.4. C-H bond arylation

Cross-coupling reactions are the most common method to access highly valuable and functionalized molecules. With the new research based on the C-H activation, direct arylation of such bond became of great interest. Recently, Cazin and Lesieur reported cooperative palladium/copper catalysis [100]. A combination of Pd(Cl)(cin)(SIPr) and Cu(OH)(IPr) leads to 14% of the coupling product from pentafluorobenzene and 4-chlorotoluene. The chloride analogue gave identical result. By interchanging the carbene ligand with the Cu(Cl)(ItBu) in presence of CsOH gave 93% conversion and 90% isolated yield. In absence of one of the other catalyst, no activity was recorded. Under the optimized conditions, the system performed efficiently with aryl chlorides as well as bromides. These results support the fact that the oxidative addition is not the limiting step of the reaction. High activity was observed in the case of electro-donating and withdrawing aryl halides. Fluoroarenes were efficiently coupled to aryl halides. Interestingly the highly challenging and sterically hindered tetra-*ortho*-substituted compounds were efficiently observed while using the bulky IPr\* palladium complex. The C-H bond of various heterocyclic compounds were efficiently activated and functionalized.



**Scheme 3.4.1: Arylation developed by Cazin [100]**

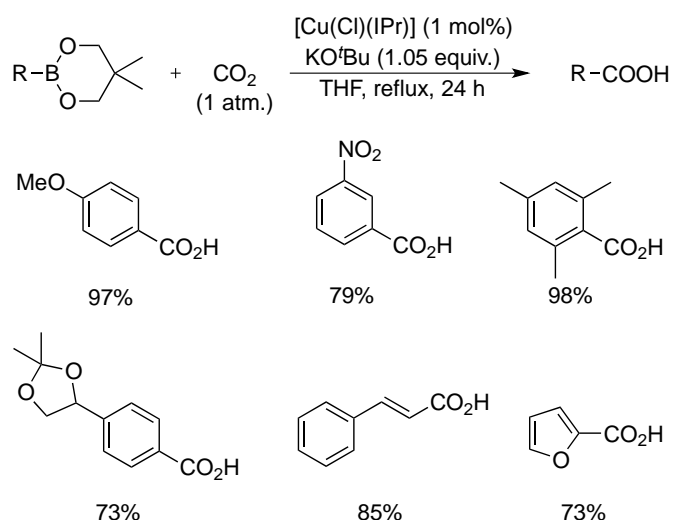
A proposed mechanism was described. Regarding the copper catalytic cycle, the first step involves the *in situ* formation of the hydroxyl synthon followed by the C-H activation leading to the formation of the copper-aryl complex. At this stage, the transmetalation with the palladium-aryl intermediate occurs.

## 4. Carbon-Heteroatom bond reactivity

### 4.1. Carboxylation of boronic esters

This area was greatly stimulated by reports from Sadighi and co-workers on the reactivity of copper-NHC complexes for the reduction of CO<sub>2</sub> to CO [101]. Subsequently, DFT studies undertaken by Marder showed that such reductions occur through CO<sub>2</sub> insertion into the Cu-B bond, to form a Cu-CO<sub>2</sub>-boryl species [102]. This is followed by boryl migration and CO release. Importantly, CO<sub>2</sub> insertion also occurred in copper-NHC alkyl systems, but the energy barrier does not favor the migration and the CO elimination.

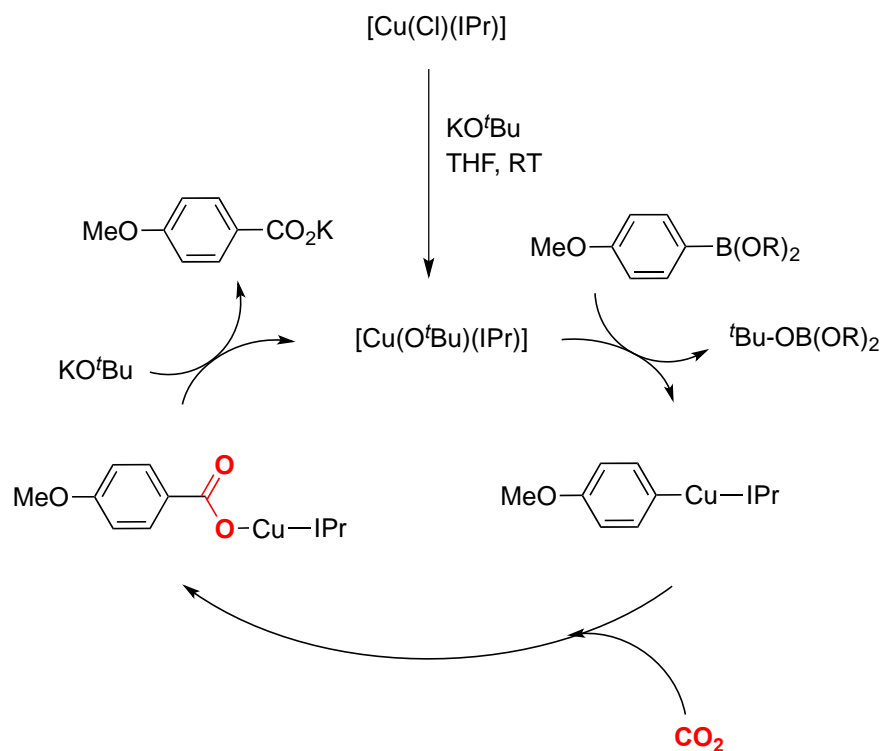
A few years ago, Hou and co-workers identified [Cu(Cl)(IPr)] as an active copper catalyst for the transformation of boronic esters into the corresponding carboxylic acids (Scheme 4.1.1) [103]. A wide range of aryl and alkenyl boronic esters were efficiently transformed with good to excellent yields.



**Scheme 4.1.1: Carboxylation of boronic esters [103]**

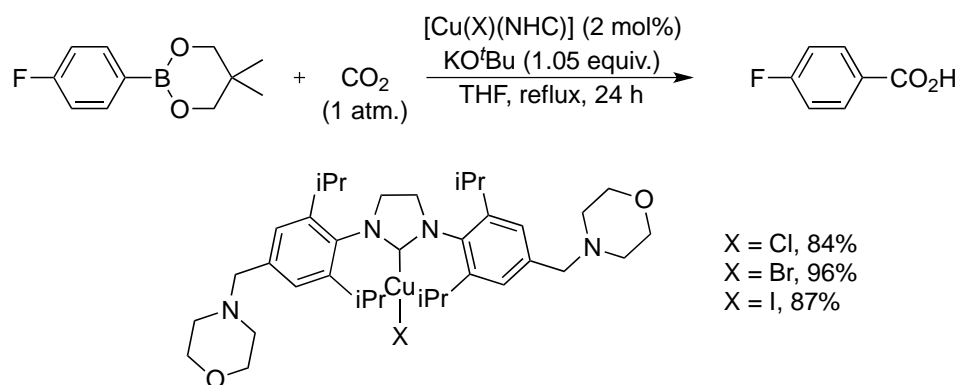
Stoichiometric reactions established the mechanism for this transformation (Scheme 4.1.2). A  $\sigma$ -bond metathesis step between [Cu(Cl)(IPr)] and potassium *tert*-butoxide formed the alkoxide derivative. [Cu(O<sup>*t*</sup>Bu)(IPr)] reacts with the boronic ester to give a [Cu(Aryl)(IPr)] intermediate which is followed by CO<sub>2</sub> insertion. A second  $\sigma$ -bond metathesis step regenerates the active species and releases the carboxylate.





**Scheme 4.1.2: Mechanism of carboxylation of boronic esters [103]**

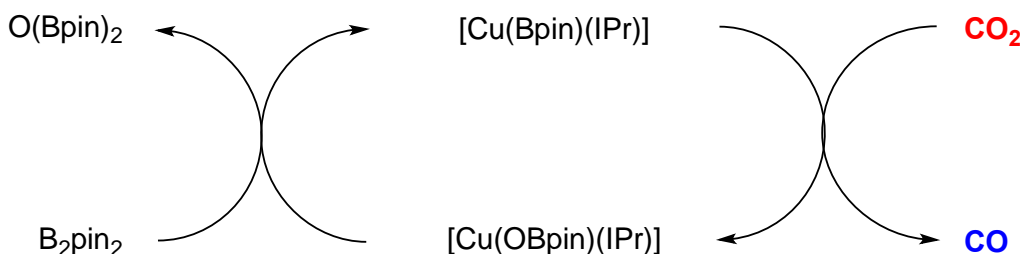
Recently, a pH responsive-NHC copper complex was reported (Scheme 4.1.3). Amine-functionalized [Cu(X)(SIPr)] complexes were synthesized, which will ideally allow the separation of the catalyst and the product at the end of the reaction. The presence of a morpholine group permits to switch from monophasic to biphasic conditions, by protonation, to form an ammonium salt. The insoluble catalyst can then be removed by centrifugation. The introduction of a fresh batch of substrate and base leads to catalyst regeneration, and thus allows further cycles. When compared, the chloro-derivative was more active than its I and Br analogues, and could undergo 4 cycles with a slight decrease in the catalytic activity [104].



**Scheme 4.1.3: Carboxylation using pH-responsive NHCs [104]**

## 4.2. Reactivity of CO<sub>2</sub>

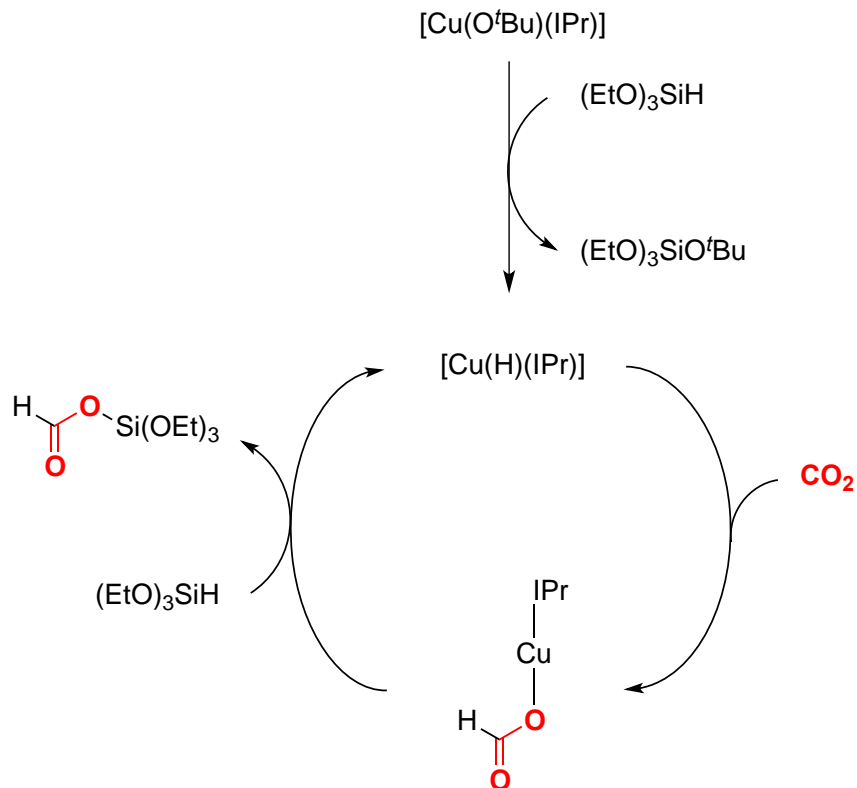
In 2005, Sadighi and co-workers showed copper-NHC complexes as efficient systems for the reduction of CO<sub>2</sub> to CO (Scheme 4.2.1). The [Cu(Bpin)(IPr)] complex, in the presence of CO<sub>2</sub>, formed a new complex identified as [Cu(OBpin)(IPr)]. During the reaction, an oxygen abstraction occurred leading to the release of CO gas. Interestingly, addition of B<sub>2</sub>pin<sub>2</sub> regenerates the boryl complex with concomitant formation of pinB-O-Bpin.



**Scheme 4.2.1: Reduction of CO<sub>2</sub> [101]**

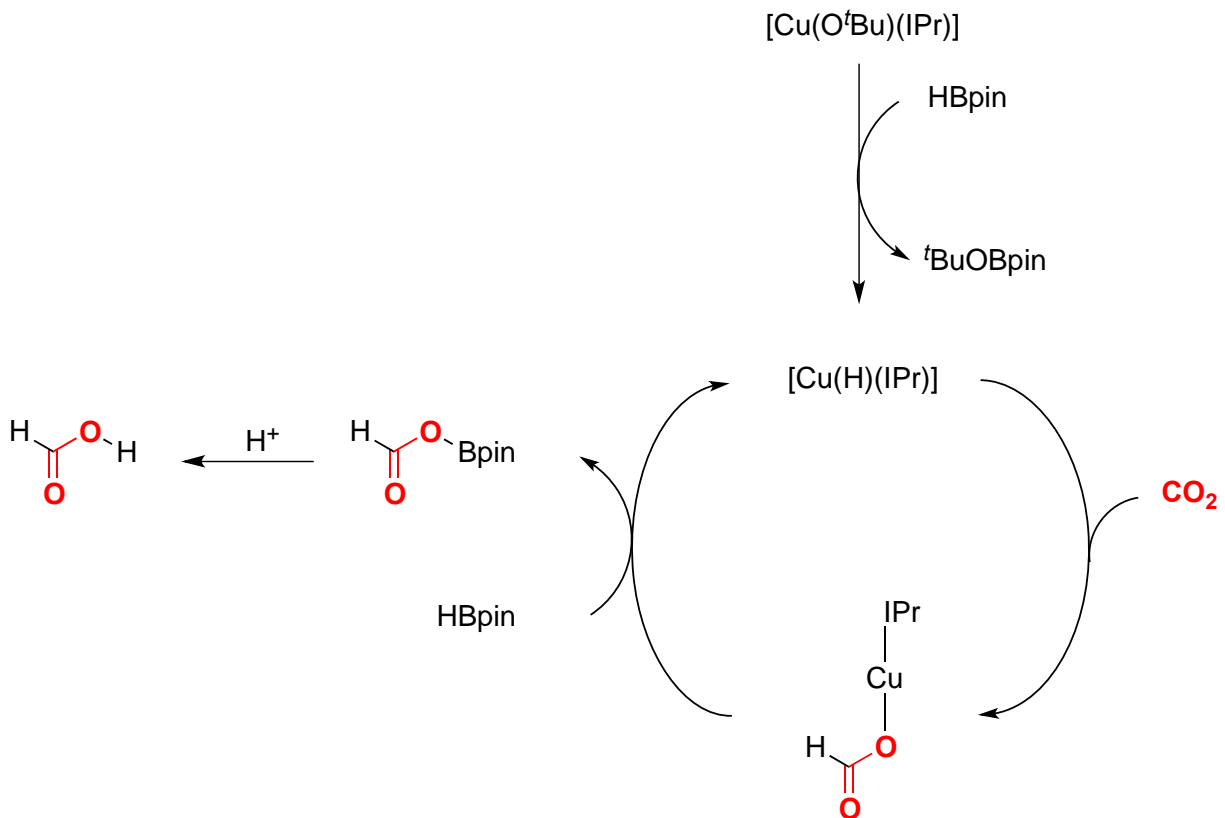
In the absence of copper, no transformation was observed. Higher turnover numbers were achieved by increasing the temperature. Indeed, with 0.1 mol% of [Cu(O<sup>t</sup>Bu)(IPr)], quantitative conversion was recorded after 20 hours at 100°C (1000 TONs). The use of a less sterically demanding ligand such as ICy leads to 81% conversion at room temperature after 1 hour due to the low stability of the boryl complex. However lowering the temperature to 0°C promoted efficiently the reaction with a turnover frequency of 100 turnovers per hour which is superior to that of the IPr analogue [101].

Recently, Hou and co-workers reported the hydrosilylation of carbon dioxide using a copper-alkoxide complex (Scheme 4.2.2). [Cu(O<sup>t</sup>Bu)(IPr)] was placed in the presence of CO<sub>2</sub> and triethoxysilane at 100°C. Full conversion toward the silyl formate was recorded after only 1 hour. Interestingly, the reaction proceeded even at lower temperatures. Indeed at room temperature, the methodology was still efficient but a longer reaction time was required (almost 10 hours). The presence of a less hindered NHC such as IMes involved a lower conversion but the complex remained effective. A plausible mechanism was proposed involving the formation of a hydride species. The CO<sub>2</sub> insertion promotes the formation of a copper formate complex, which by reaction with the silane releases the hydrosilylated product [105].



**Scheme 4.2.2: Hydrosilylation of CO<sub>2</sub> [105]**

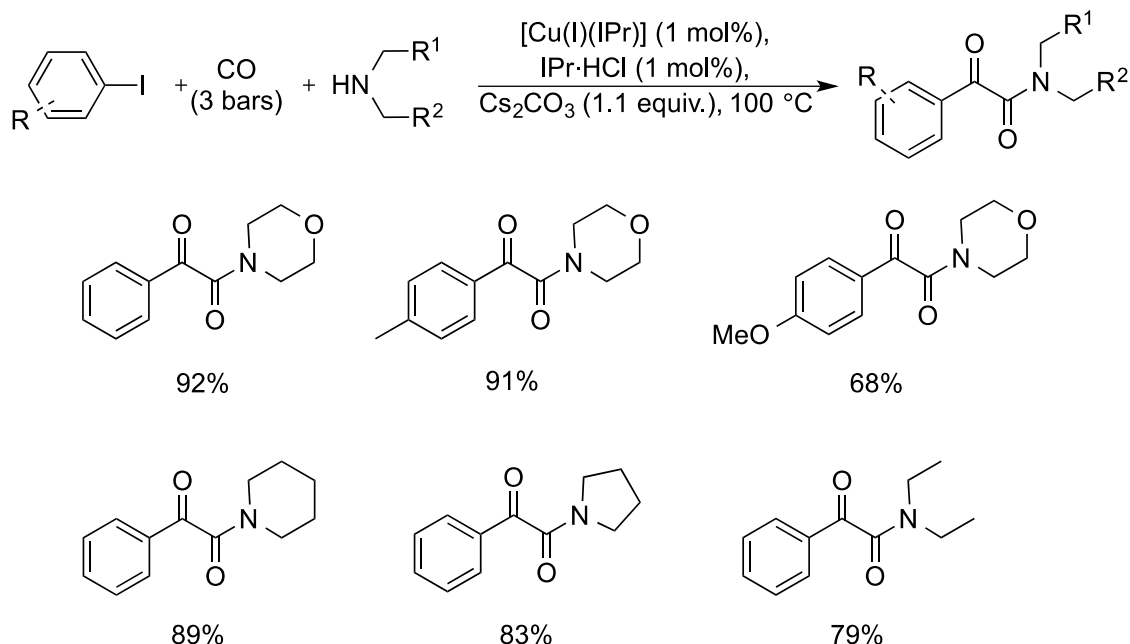
In parallel, Nozaki proposed a process for the hydroboration of CO<sub>2</sub>, which leads to the formation of formic acid, after protonolysis. [Cu(OtBu)(IPr)] was reacted with pinalcolborane (HBpin) under CO<sub>2</sub> atmosphere at 35°C. Under such conditions, an 85% yield of formic acid was obtained. Interestingly, the addition of an alkoxide base is not necessary in this system. When pinalcolborane was replaced by catecholborane, the formation of formic acid was not observed. The IMes analogue showed lower reactivity. Stoichiometric reactions were conducted to gain insights into the catalytic cycle. By reacting HBpin with [Cu(OtBu)(IPr)], [Cu(H)(IPr)] was generated despite its low stability in solution, along with tBuO-Bpin. Under CO<sub>2</sub> atmosphere, the hydride species was converted to a new complex identified as [Cu(CO<sub>2</sub>H)(IPr)]. Nevertheless, the copper formate in the presence of HBpin did not allow the observation of the first intermediate. Interestingly, [Cu(CO<sub>2</sub>H)(IPr)] was catalytically active for the hydroboration of CO<sub>2</sub>. These results lead to the proposed mechanism described in Scheme 4.2.3. This process was efficiently applied for the *N*-formylation of amines [106].



**Scheme 4.2.3: Hydroboration of CO<sub>2</sub> [106]**

### 4.3. Carbonylation

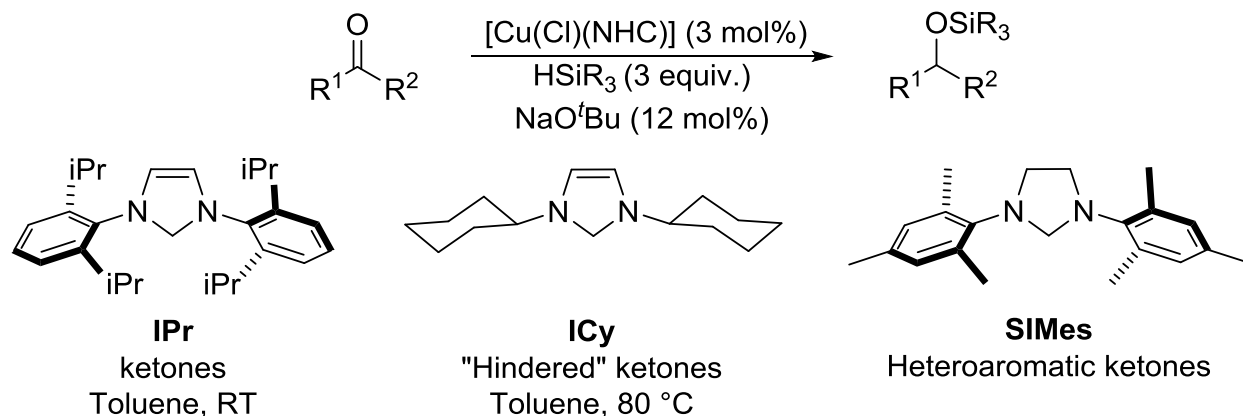
In 2007, Xia made a seminal contribution to the area of carbonylation catalysis by using a cheap metal and stable species:  $[\text{Cu}(\text{I})(\text{IPr})]$  (Scheme 4.3.1) [107]. Carbonylation of aryl iodides with amines was efficiently conducted. The investigation clearly showed the need for a NHC salt in addition to the copper complex for the success of the reaction. Interestingly, a trend was noticed regarding the halide; with reactivity observed in the following order  $\text{I} > \text{Cl} > \text{Br}$ . It was noticed that the presence of bulky NHCs enhanced the catalytic activity. When the cationic derivative  $[\text{Cu}(\text{IPr})_2][\text{BF}_4]$  was tested, a double carbonylation occurred [108]. The presence of  $\text{NaI}$  as additive leads to almost quantitative conversion. It was postulated that the bis-NHC copper(I) complex was the active species in the carbonylation. During examination of the reaction scope, various aryl iodides and amines were converted. Functional groups such as bromo- or nitro- were tolerated.



**Scheme 4.3.1: Double carbonylation [107]**

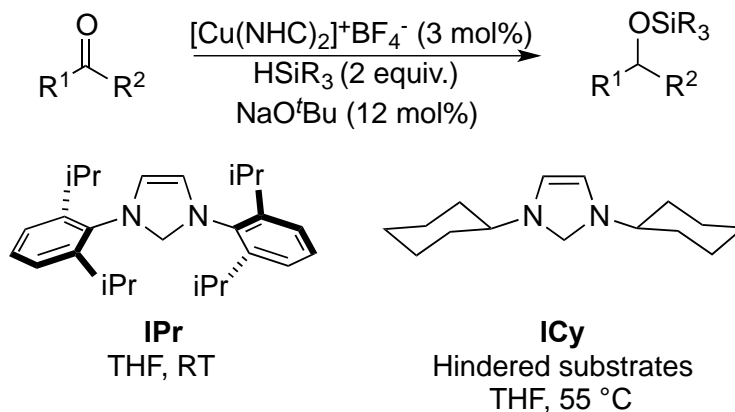
#### 4.4. Hydrosilylation

In organometallic chemistry, the reduction of ketones is an emblematic reaction, particularly with copper hydride species. In 1988, Stryker reported the first well-known hydride copper species, also known as the Stryker reagent  $[\text{Cu(H)(PPh}_3\text{)}]_6$  ( $\text{PPh}_3$  = triphenylphosphine) [109]. In a series of articles, this hexamer was utilized for the reduction of carbonyl derivatives [109b]. However, several drawbacks were noted mainly regarding the stability of the active species  $[\text{Cu(H)(PPh}_3\text{)}]$ . An excellent alternative to ‘Stryker’s reagent’ was found in copper-NHC complexes [109, 110, 111]. Nolan and co-workers first investigated the well-defined  $[\text{Cu(Cl)(IPr)}]$  for the hydrosilylation of simple ketones toward the formation of the silyl ethers (Scheme 4.4.1) [110]. High yields were obtained under mild conditions. Nonetheless, some limitations were noted especially for more hindered ketones, where harsher conditions were necessary. Tuning the NHC permitted the use of the optimal complex applicable to different classes of carbonyl substrates. The ICy ligand (ICy = *N,N'*-dicyclohexylimidazol-2-ylidene) was suitable for hindered ketones, whereas SIMes (*N,N'*-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene) proved appropriate for the hydrosilylation of heteroaromatic ketones (Scheme 4.4.1) [110].



**Scheme 4.4.1: Hydrosilylation of ketones [110]**

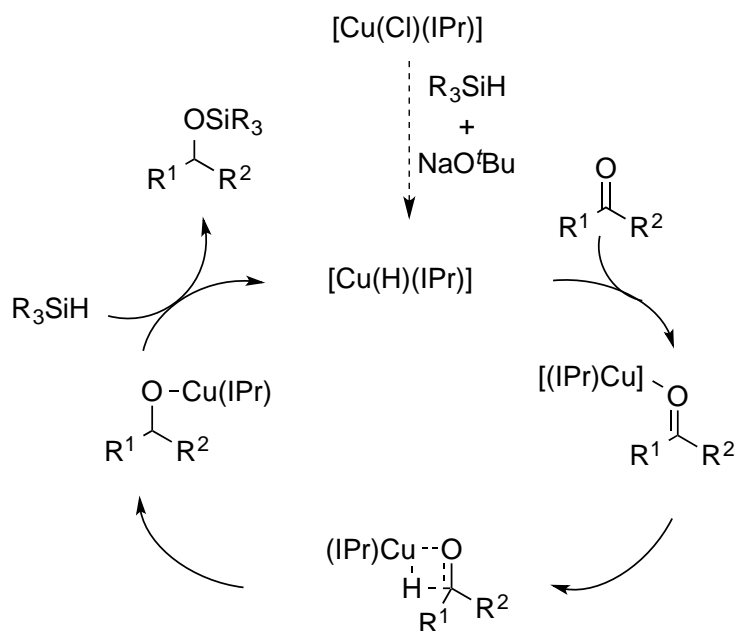
Later, a series of bis-NHC copper systems were developed and examined for the hydrosilylation of ketones [110c]. The catalytic activities showed the influence of the ligand but also that of the counteranion ( $\text{BF}_4^-$  and  $\text{PF}_6^-$ ) (Scheme 4.4.2). Interestingly, these cationic complexes were more efficient than their neutral analogues under similar conditions. Further studies showed that milder reaction conditions (lower temperature, reduced amount of silane, shorter reaction time) lead to the formation of the silylated compounds. Insight into the mechanism presented the dissociation of one NHC as a key catalytic step.



**Scheme 4.4.2: Hydrosilylation using cationic copper(I) complexes [110c]**

Mechanistic studies were carried out on neutral and cationic Cu systems [110, 111b]. Regarding  $[\text{Cu}(\text{Cl})(\text{NHC})]$  complexes, the proposed mechanism involves the *in situ* formation of  $[\text{Cu}(\text{O}^t\text{Bu})(\text{NHC})]$  (Scheme 4.4.3). The hydrido-copper(I) complex is then formed by  $\sigma$ -bond metathesis between the *tert*-butoxide copper complex and the hydrosilane. The active species  $[\text{Cu}(\text{H})(\text{NHC})]$  is highly unstable and quickly reacts with the carbonyl followed by a  $\sigma$ -bond metathesis with the silane, affording the expected silyl ether. In the case of the cationic analogues, the first step involves the dissociation of one NHC, which is displaced by the *tert*-butoxide moiety: the direct precursor for the active species. The hydrosilane

is activated by the nucleophilic NHC, allowing the formation of the silyl ether. The rate-determining step was the activation of the silane.



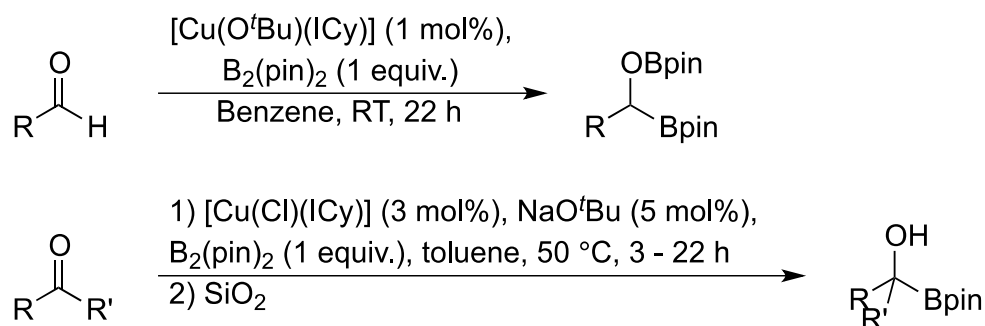
**Scheme 4.4.3: Proposed mechanism for the hydrosilylation of ketones [110]**

Later on, Riant and Leyssens reported on the hydrosilylation of ketones using their copper-NHC bifluoride complexes. Interestingly, these complexes readily catalyse the desired reaction without the requirement of any activating substances (e.g.,  $\text{MO}^t\text{Bu}$ ). The same group went on to fully disclose the mechanism of the hydrosilylation reaction of ketones *via* DFT, experimental and kinetic methods, using these bifluorides as probes [111c-e].

#### 4.5. Boration of ketones and aldehydes

Since the report by Sadighi of the synthetic feasibility of  $[\text{Cu}(\text{Bpin})(\text{IPr})]$  [101], the probable insertion into a metal-boron bond has become an attractive potential catalytic feature. To explore this reactivity, the boration of carbonyl substrates attracted significant attention. First, the reaction of aldehydes was examined using bis(pinacolato)diboron as a boron source and  $[\text{Cu}(\text{O}^t\text{Bu})(\text{IPr})]$  as the catalyst [112]. The evaluation of the carbene ligands influence pointed out that the steric hindrance considerably affected catalytic efficiency. Indeed, smaller NHCs such as ICy were more effective than larger congeners. As a result,  $[\text{Cu}(\text{O}^t\text{Bu})(\text{ICy})]$  was selected to examine the reaction scope. A large range of substrates was converted in high yields (Scheme 4.5.1). Aliphatic aldehydes bearing primary, secondary and tertiary alkyl substituents were efficiently converted. The presence of chloride and bromide did not interfere in

the formation of the diboronated compound and electron-withdrawing as well as electron-donating groups were tolerated.



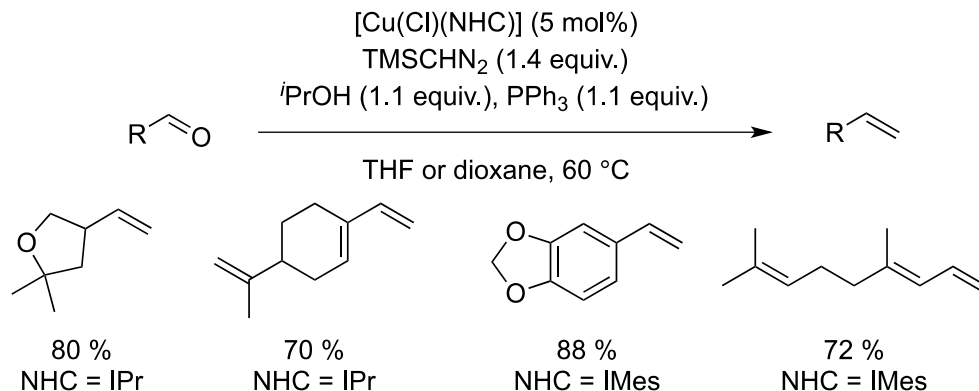
**Scheme 4.5.1: Boration of carbonyl derivatives [112, 113]**

Interestingly, for ketone derivatives, the chloride complex  $[\text{Cu}(\text{Cl})(\text{ICy})]$  was used. The reaction rate was improved by adding  $\text{NaO}^t\text{Bu}$ , which generates the *tert*-butoxide derivative *in situ* and thus complete conversions were reached. The complex being highly moisture sensitive, the addition of drying agents was an interesting solution to reach higher conversions. However, no improvement in the TON was observed and the combination of molecular sieves and  $\text{MgSO}_4$  inhibited the reaction. Other bases such as  $\text{NaHCO}_3$  increased the efficiency of the catalyst, however further optimisation did not result in full conversion. These observations suggested coordination of the diboron reagent by the base, which regenerates the active boryl-species. Boration of cyclic and dialkyl substrates gave moderate to high yields (51-81%). Various functional groups were tolerated: furans, alkenes, esters, and nitriles.

## 4.6. Olefination of carbonyl derivatives

For decades, the transformation of carbonyl compounds into olefins was based on rhodium catalyzed transformations [114]. The methodology developed by Lebel and Nolan was based on the use of  $[\text{Cu}(\text{Cl})(\text{NHC})]$  to achieve olefination (Scheme 4.6.1) [115]. The scope encompasses a large variety of substrates with successful functionalization of aliphatic alkenes, dienes, styrenes and heteroarenes. The copper-NHC systems presented high tolerance even with base sensitive substrates, whereas Wilkinson's catalyst underwent decomposition with nitro-substituted substrates. While 5 mol% of  $[\text{Cu}(\text{Cl})(\text{NHC})]$  was used, the catalyst concentration can be lowered to 0.5 mol% providing that the amount of isopropanol is increased.





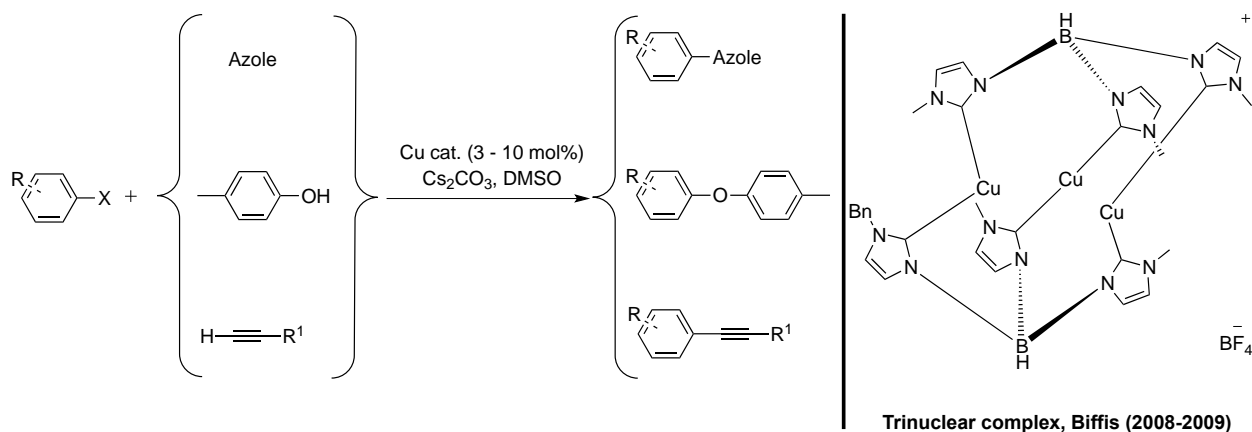
**Scheme 4.6.1: Olefination of carbonyl compounds using  $[\text{Cu}(\text{Cl})(\text{NHC})]$  [115]**

The best results were obtained when THF or 1,4-dioxane were used as solvent. Nevertheless, no important effect was observed when different NHCs were compared. Indeed IMes, ICy and IPr derivatives reached 95% conversion of the cinnamaldehyde under similar conditions. However, the methodology was substrate dependent. In the case of styrene derivatives,  $[\text{Cu}(\text{Cl})(\text{IMes})]$  was more efficient compared to the IPr complex. Copper salts were also examined and in some cases, such as 4-bromostyrene, Cu(I) salts surpassed or equaled the NHC system. However, for most of the styrene derivatives or ketones, the copper-NHC complexes were more efficient.

## 4.7. Cross-coupling

During the last century with Ullmann's and Goldberg's discoveries, copper has been one of the most successful catalyst for cross-coupling reactions [116]. However, the spotlight for cross-coupling catalysis has long rested on palladium, as milder reaction conditions could be used with the latter [117]. The emergence of NHC ligands and their extraordinary efficiency in catalysis brought back interest in copper as an alternative to expensive metals for cross-coupling reactions. In this field, Biffis has developed a trinuclear copper complex and studied its catalytic activity as well that of  $[\text{Cu}(\text{Cl})(\text{IPr})]$  (Scheme 4.7.1) [118]. The neutral linear complex was inactive in the Sonogashira cross-coupling, but some reactivity was observed in the arylation reaction. Nonetheless, the trinuclear copper species surpassed the mononuclear analogue, with 10 times less catalyst to obtain comparable reactivity. Aryl iodides, bromides and chlorides were efficiently converted. Interestingly, a decisive role in the catalytic activity was played by the substituents on the aryl. No trend was directly correlated to the electron-withdrawing properties. However, a decrease in the activity was observed for amide andazole substrates, which might be due to partial catalyst deactivation.

In the case of the Sonogashira reaction, a significant solvent effect was observed. Indeed, a slightly better conversion was obtained in DMSO, but a side-reaction was promoted: the homocoupling of the arene. However, combining the trinuclear species and DMF led to a quantitative conversion to the desired product.



**Scheme 4.7.1: Cross-coupling reactions [118]**

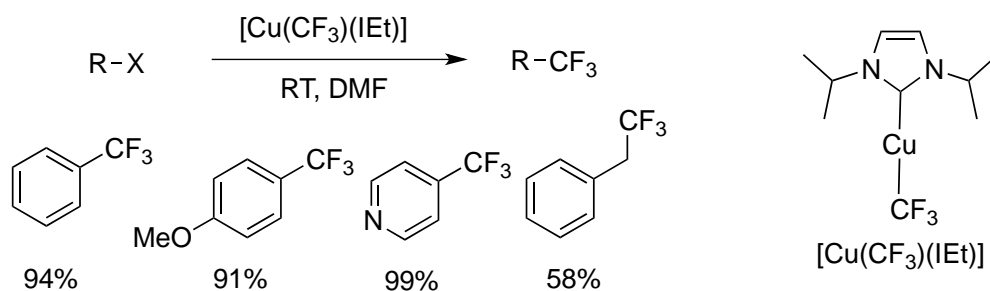
More recently, Whittlesey has also reported on tri-nuclear copper complexes bearing a single oxygen atom [119]. These were prepared using a tripodal class of ligand with a larger spacer. Ullman and Sonogashira couplings were carried out [120, 121]. Recently, Navarro and co-workers reported a collaborative copper/palladium methodology [122]. In combination to Pd(SIPr)(Cl)<sub>2</sub>(TEA) complex, the activity of Cu(Cl)(NHC) complexes was evaluated for the coupling of 3-bromotoluene and phenylacetylene. In the case of saturated carbenes, such as SIPr and SIMes, higher yields (94% and 67%, respectively) were observed compared to the unsaturated analogues (IPr and IMes, 16% and 34% respectively). Regarding the base effect, the most efficient system was K<sub>2</sub>CO<sub>3</sub> in combination with DMSO as solvent. Other bases were evaluated, however, low or no activity was observed. A variety of aryl bromides were coupled with aryl alkynes. Electron-rich, electron-poor but also heterocyclic halides were converted with good to excellent yields (49% to 95%). In the case of substituted alkynes, excellent yields were observed for electron-donating group, whereas poor results were obtained for electron-withdrawing group. Interestingly, the presence of the Glaser homocoupling product was not recorded.

## 4.8. Fluorine chemistry

The introduction of fluorine into molecules can modify their physicochemical properties and the number of articles on such subject is increasing exponentially. Thirty percent of the pharmaceutical molecules contain fluorine. Various methodologies have been developed principally based on readily commercially available fluorinated reagents. Until now, the Baltz-Schiemann or the Halex reactions are

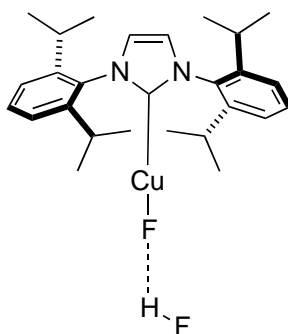
the usual processes for preparation of aromatic compounds [123]. For aliphatic systems, the presence of electrophilic or nucleophilic fluorination reagents is necessary. Despite the low price of such reagents, harsh conditions as well as the limited functional group tolerance remain an important hurdle.

In 2008, the Vicic group made the first breakthrough with the isolation of  $[\text{Cu}(\text{CF}_3)(\text{NHC})]$ , obtained by reacting the *tert*-butoxide species in the presence of the Rupert-Prakash reagent ( $\text{Me}_3\text{SiCF}_3$ ) [124]. Saturated and unsaturated copper-NHC complexes were efficiently obtained. These new species were used as a trifluoromethylation reagents for aryl iodides. However, a stoichiometric amount of the copper species was required (Scheme 4.8.1). Indeed the catalytic version showed no product formation. Nonetheless, another role of such complexes was disclosed as decarboxylative trifluoromethylation reagents [124b]. Indeed, these species are an alternative to expensive fluorinated compounds and Vicic reported a series of systems based on  $\text{OCOCF}_3$  compounds.



**Scheme 4.8.1: NHC-copper catalyzed trifluoromethylation [124]**

In 2012, Riant and co-workers described a copper bi-fluoride complex, prepared from the alkoxide species. The cationic derivatives with the formula  $[\text{Cu}(\text{NHC})_2][\text{HF}_2]$  were also developed (Figure 4.8.1) [111c-e]. Both neutral and cationic complexes present good air-stability in the solid state, but moderate in solution compared to mono-fluoride [125] congener  $[\text{Cu}(\text{F})(\text{IPr})]$ . Remarkably, catalytic activity was tested in several transformations such as in the reduction of ketones, the 1,4-conjugated borylation or silylation and the diastereoselective allylation. This complex family holds great promise.



### Figure 4.8.1: Bi-fluoride complex [111c-e]

Recently, Lalic and co-workers reported a highly efficient copper-catalyzed fluorination of alkyl triflates, using KF as a fluoride source. The reaction was performed at 45 °C using 2 mol% of [Cu(OTf)(IPr)]. The fluorination reaction was compatible with a wide range of functional groups including alkyl tosylates and alkyl bromides [126].

## CONCLUSION

Over the last decade, copper-NHC chemistry has evolved considerably, opening novel spheres of reactivity to this relatively inexpensive metal. Numerous reactions have been developed or rediscovered with important improvements due to the properties of the copper-NHC complexes. The neutral or cationic species were highly efficient in several reactions. Asymmetric reactions were efficiently conducted based on chiral NHC ligands. Exceptional results were observed in the realm of regio-, chemo- and enantioselectivity. Organocopper chemistry is still evolving and the ability of the Cu-NHC family to activate and functionalize C-H and C-C bonds bodes well for a very bright future of the area.

## ACKNOWLEDGEMENTS

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