C-C and C-X Coupling Reactions of Unactivated Alkyl Electrophiles Using Copper Catalysis

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REVIEW ARTICLE

C-C and C-X Coupling Reactions of Unactivated Alkyl Electrophiles Using Copper Catalysis

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Transition metal-catalysed cross-coupling reactions are widely used for construction of carbon-carbon and carbon-heteroatom bonds. However, compared to aryl or alkenyl electrophiles, the cross-coupling of unactivated alkyl electrophiles containing β hydrogens remains a challenge. Over the past few years, the use of suitable ligands such as bulky phosphines or N-heterocyclic carbenes (NHCs) has enabled reactions of unactivated alkyl electrophiles not only limited to the traditional cross-coupling with Grignard reagents, but also including a diverse range of organic transformations via either S_N2 or radical pathways. This review provides a comprehensive overview of the recent development in copper-catalysed C-C, C-N, C-B, C-Si and C-F bond-forming reactions using unactivated alkyl electrophiles.

I. Introduction

In the past decades, transition metal-catalysed cross-coupling reactions have become powerful methods for the construction of carbon-carbon and carbon-heteroatom bonds and have shown wide applicability in the synthesis of pharmaceutically active compounds, agricultural chemicals, natural products and functional materials.[1] Among them, cross-coupling reactions of alkyl electrophiles have received renewed attention recently as they would offer significant advantages over traditional S_N1 or S_N2 substitution reactions if fully developed, such as allowing milder reaction conditions or preventing elimination side reactions especially for sterically hindered secondary or tertiary alkyl substrates containing β hydrogens.[2] However, compared to the widely established methodologies for coupling reactions of aryl or vinyl electrophiles, the cross-coupling reactions of unactivated alkyl electrophiles containing β hydrogens remain challenging.[3] This is mainly due to the following two factors. First, $C(sp^3)$-X bonds are more electron rich than $C(sp^2)$-X bonds, making oxidative addition of $C(sp^3)$-X bonds to a metal centre considerably more difficult. Second, even if the oxidative addition of a $C(sp^3)$-X bonds occurs, the resulting alkyl metal species likely suffers from β-hydride elimination as a side reaction competing with productive cross coupling. If β-hydride elimination occurs, the resulting metal hydride species can also cause undesired reduction side reactions of the $C(sp^3)$-X partner.

Nevertheless, following the pioneering studies on cross-coupling reactions of unactivated alkyl halides by Kochi and Tamura in the 1970s[4] and Suzuki[5] and Knochel[6] in the 1990s, significant progress has been achieved in this field by design of new catalyst systems.[7] For example, although noble metal catalyst like Pd have been well explored in many transformations, recently base metals such as Ni, Fe, Co, and Cu have become much more attractive due to their high earth abundance, low price, low toxicity, and unique catalytic characteristics that are well suited to cross-coupling with $C(sp^3)$-X electrophiles.

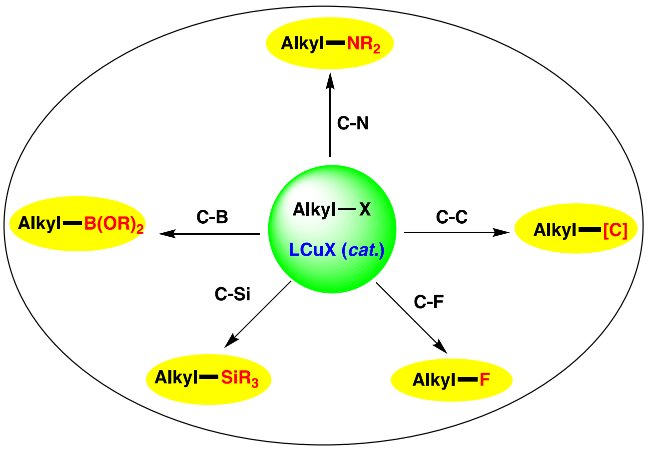

Figure 1. Pathways for C-C and C-X coupling with alkyl electrophiles enabled by copper catalysis.

Copper complex was employed stoichiometrically in the Ullman reaction over a century ago.[8] However, the catalytic use of copper salts in the reaction of unactivated alkyl electrophiles did not emerge until in the 1970s with Grignard reagents as coupling partners.[4] Recent implementation of bulky ligands such as phosphines and *N*-heterocyclic carbenes (NHCs) with copper have greatly expanded the reaction scope, enabling copper complexes be used as highly active catalysts in diverse organic transformations, including C-C, C-N, C-B, C-Si and C-F bond-forming reactions (Figure 1) that operate by either S_N2 or radical pathways that often avoid alkylcopper intermediates altogether and thus circumvent problematic side reactions. Notably, some of these reactions are difficult to achieve with other transition metals.

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In this review, we outline recent advances in copper-catalysed cross-coupling of unactivated alkyl electrophiles. It is noteworthy that although the cross-coupling of unactivated alkyl electrophiles via copper catalysis has been previously reviewed in the literature, it has always been as part of a discussion with other electrophiles,[9] specified to C-C bond formation,[10] or focused narrowly on copper-boryl catalysis.[11] The Cu-catalysed C-C and C-X cross-coupling of unactivated alkyl electrophiles has not been reviewed collectively or in a comprehensive fashion in its own right. This review has been organized first by the bond formation achieved and then further by the type of transformation employed. Activated alkyl substrates such as benzyl, allylic, fluorinated, or α-carbonyl compounds will be not included except in specialized cases where the contributions are particularly unique. Also, this review will focus on use of copper as the sole catalyst; thus bimetallic catalysis involving copper as co-catalyst with Ru or Ir photocatalysts or with Ni or Pd cross-coupling catalysis, which have been recently reviewed elsewhere,[12] will not be covered in this review.

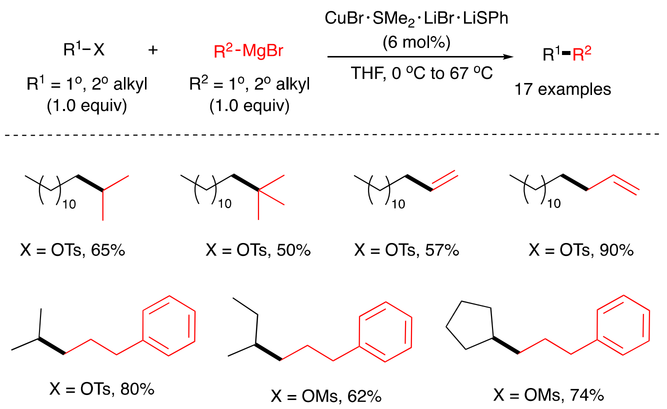
II. C-C bond formation

2.1 Cross-coupling of alkyl electrophiles with organometallic reagents

The transition metal-catalysed cross-coupling reactions of organometallic reagents with organic halides and pseudo-halides are among the most important C-C bond-forming reactions in organic synthesis. During past decades, remarkable progress has been made in the cross-coupling of alkyl electrophiles using various metals, such as Pd, Ni and Cu. In the Cu catalysis, it is normally proposed that the reaction of the copper catalyst and the organometallic reagent generates an organocopper intermediate that is reactive towards S_N2-type substitution with alkyl halides and pseudohalides with complete inversion of configuration.

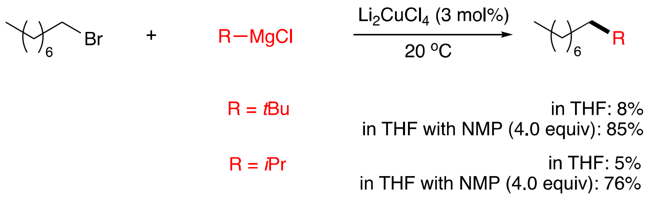
2.1.1 Coupling with Grignard reagents

The cross-coupling reactions of alkyl halides with Grignard reagent mediated by copper complex was pioneeringly reported by Kochi and Tamura.[4] Thereafter, several early examples have been described by other groups.[9] However, these reactions generally suffer either from use of stoichiometric copper to obtain the products in high yields or from proceeding with narrow substrate scope with catalytic amounts of copper. Additionally, high yields were typically only observed with primary alkyl Grignards and electrophiles. In 1997, the Burns group discovered that a new copper complex was formed by mixing equal amounts of CuBr-SMe$_2$, LiBr, and LiSPh in THF (Scheme 1).[13] This copper complex showed much higher efficiency than other copper catalysts such as CuBr and Li$_2$CuCl$_4$ in coupling of secondary tosylates and mesylates with primary Grignard reagents. In addition, the coupling of primary, secondary, tertiary, aryl, vinyl, and allylic Grignard reagents with primary tosylates also worked well using the same copper complex. Notably, only 1 equiv of the Grignard reagent was used in their work to give the product in good yield. According to ^{1}H NMR analysis, they proposed that the active catalyst was ligated by thiophenol, THF, and LiBr in aggregated forms.



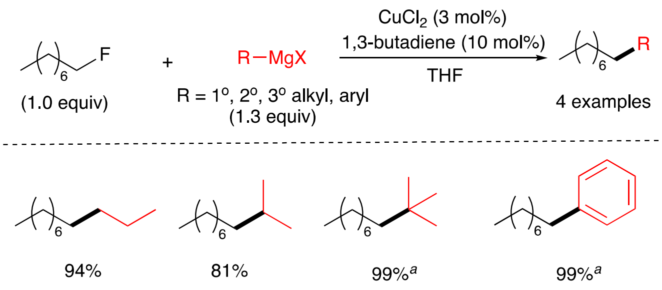
Scheme 1 Cross-coupling of secondary alkyl Grignard reagents or secondary alkyl tosylates and mesylates.

In 2000, Cahiez and co-workers demonstrated the addition of *N*-methyl pyrrolidinone (NMP) in THF with Li$_2$CuCl$_4$ or CuCl as a catalyst could dramatically improve the yield and chemoselectivity of Cu-catalysed coupling of primary alkyl halides with secondary and tertiary alkyl Grignard reagents (Scheme 2).[14] Functional groups including ester, amide, nitrile and ketone were all tolerated. Unfortunately, such enhanced effect was not observed with secondary or tertiary alkyl halides. Also, with aromatic Grignards, it was found to be better to perform the reaction without NMP. In 2010, the same group found that a slow and regular addition of the primary alkyl Grignard reagent to the primary alkyl halides could also provide the coupling products in excellent yield without adding the previous additive.[15] For secondary and tertiary alkyl Grignard reagents, benzonitrile (10 mol%) was identified to be a very effective additive.



Scheme 2 Cross-coupling of secondary and tertiary Grignard reagents with primary alkyl bromides using NMP as additive.

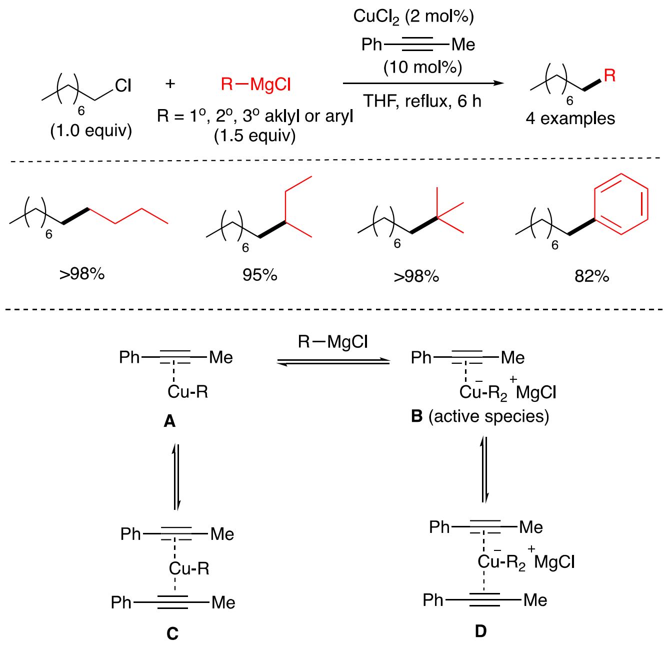
In 2003, Kambe and co-workers first reported cross-coupling of primary alkyl fluorides with various Grignard reagents using either nickel or copper catalyst (Scheme 3).[16] The additive, 1,3-butadiene, was observed to play an important role in the Cu-catalysed cross-coupling reaction, and low yields were found with primary and secondary alkyl Grignard reagents in the absence of 1,3-butadiene. However, 1,3-butadiene showed little effect in the reaction using tertiary alkyl and phenyl Grignard reagents, where the corresponding coupling products were obtained in good to high yields without additives. Although the mechanism was unclear, a radical pathway was ruled out based on appropriate control experiments.



[a]without 1,3-butadiene

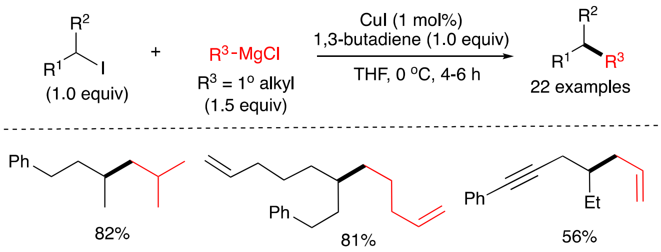
Scheme 3 Cross-coupling of Grignard reagents with primary alkyl fluorides.

Compared to alkyl bromides and iodides, alkyl chlorides are much less reactive in transition metal-catalysed coupling reactions due to the inert C-Cl bond. In 2007, Kambe and co-workers discovered that use of 1-phenylpropyne as an additive could promote the Cu-catalyzed coupling of primary alkyl chlorides with Grignard reagents (Scheme 4).[17] This reaction proceeds efficiently with *n*-butyl, *sec*-butyl, *tert*-butyl, and phenyl Grignard reagents. It is worthy to note that under the same reaction conditions, alkyl fluorides, tosylates, and mesylates were also suitable electrophiles to afford the corresponding products in high yields. A S_N2 mechanism was supported by the observation of the inversion of configuration of a diastereomerically pure alkyl halide. Although the exact role of 1-phenylpropyne was not clear, the authors suspected that the coordination of alkynes to the copper(I) ion to form complexes **A** and **B** (Scheme 4) could prevent the decomposition of thermally unstable alkylcopper intermediates. Depending on the concentration of the alkyne additive, the bis(alkyne)copper(I) complexes **C** and **D** were also possibly generated as catalytic resting states in equilibrium with **A** and **B**, respectively.



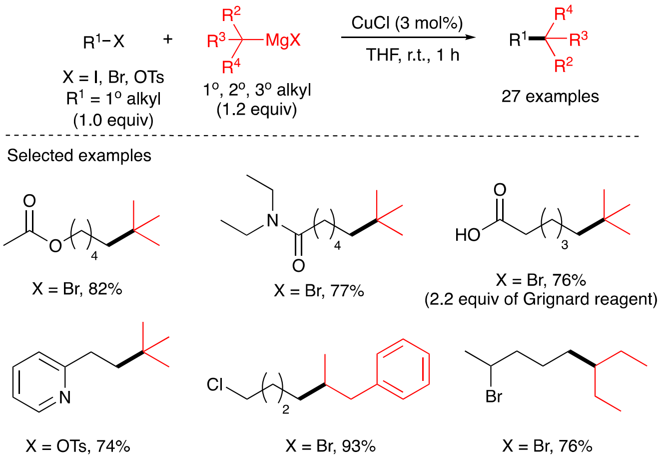
Scheme 4 Cross-coupling of Grignard reagents with primary alkyl chlorides.

By applying 1,3-butadiene as an additive in the presence of CuI catalyst, in 2012 Kambe and co-workers also realized the cross-coupling of challenging unactivated secondary alkyl iodides with primary alkyl Grignard reagents (Scheme 5).[18] Here, again, the use of 1,3-butadiene enabled a remarkable improvement in both of efficiency and selectivity of the coupling reaction to give the alkyl-alkyl coupled products in good yield under mild reaction conditions. Later, in 2014, they found the alkyl-alkyl cross-coupling reactions could proceed with very high turnover numbers (TONs) of over 1 x 10^6 using a Cu/1,3-butadiene or phenylpropyne catalytic system.[19] Based on mechanistic studies, they concluded that the additive played important roles in achieving highly efficient cross-coupling by suppressing side reactions as well as the preventing degradation of the Cu catalyst.



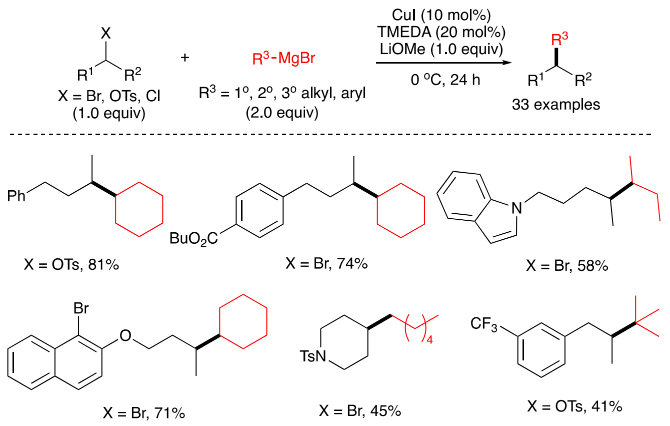
Scheme 5 Cross-coupling of alkyl Grignard reagents with secondary alkyl iodides.

As can been seen from the above reactions with secondary and tertiary alkyl Grignard reagents, only simple alkyl halides, such as octyl and decyl halides, were used as the substrates, probably due to the poor functional group tolerance of Grignard reagents. In 2012, the Hu group described an efficient copper-catalysed C-C coupling of secondary and tertiary Grignard reagents with functionalized primary alkyl iodides, bromides, and tosylates (Scheme 6).[20] The reactions proceeded at room temperature using CuCl as the catalyst without any additives. Many alkyl electrophiles bearing a variety of sensitive groups could be efficiently coupled to secondary and tertiary alkyl Grignard reagents to give the products in high yields within one hour. It is noteworthy that although this work focused on the coupling of secondary and tertiary alkyl Grignard regents, the coupling of primary alkyl Grignard regents also worked well under the same reaction conditions. Mechanistic studies revealed that activation of the alkyl electrophile likely went through a S_N2 pathway instead of a radical mechanism, which is consistent with Kambe 's observations.[17]



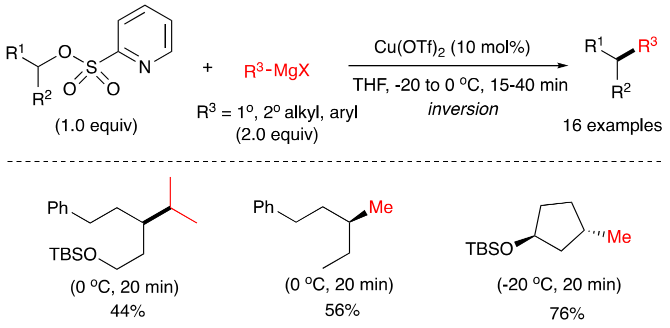
Scheme 6 Cross-coupling of functionalized alkyl electrophiles with secondary and tertiary alkyl Grignard reagents.

Although Burns and Kambe had achieved cross-coupling of secondary alkyl electrophiles previously,[13, 18] the nucleophiles were limited to primary Grignard reagents. Inspired by the Burns system, in 2012 Liu and co-workers reinvestigated other Li additives and found a new catalytic system consisting of CuI/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)/LiOMe, which enabled the cross-coupling reactions of secondary alkyl bromides and tosylates with various secondary alkyl Grignard reagents (Scheme 7).[21] Notably, under the same reaction conditions, aromatic and tertiary alkyl Grignard reagents as well as the less reactive primary alkyl halides were also applicable. Inversion of configuration of a chiral tosylate substrates revealed that the reaction proceeded via an S_N2 mechanism. Based on this observation, the authors also demonstrated the stereocontrolled formation of C–C bonds between two tertiary carbons using easily available chiral tosylates.



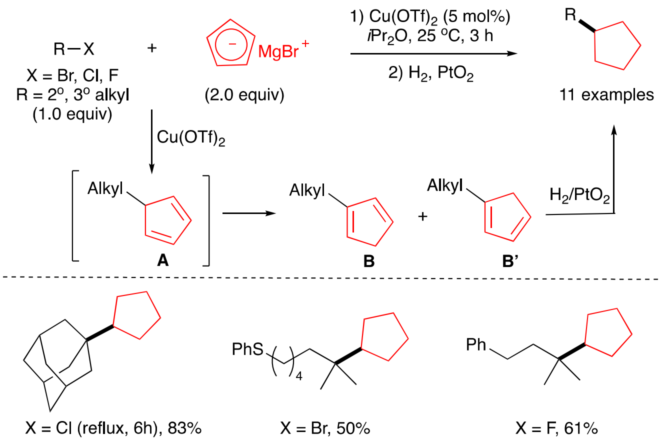
Scheme 7 Cross-coupling of secondary alkyl electrophiles with Grignard reagents.

In Liu's work, it usually took 12-24 h for the reaction to complete. To improve the reactivity of the secondary alkyl electrophiles, recently, the Kobayashi group introduced a more reactive 2-pyridinesulfonyloxy leaving group and found it could effectively shorten the reaction time to less than 40 min at 0 °C using $Cu(OTf)_2$ as catalyst (Scheme 8).[22] The additives (LiOMe, TMEDA) typically previously used in Liu's work for couplings of tosylates were not necessary, and the less reactive MeMgCl worked as well as other Grignard reagents. Complete inversion of the stereocenter from chiral substrates was also observed under their reaction conditions.



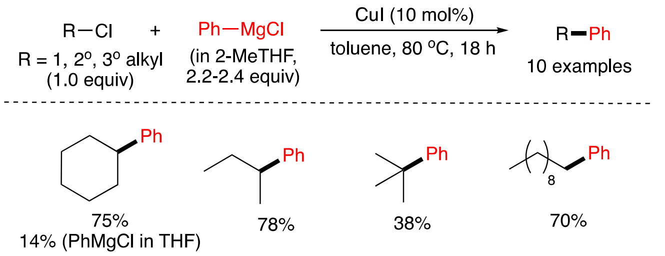
Scheme 8 Cross-coupling of secondary 2-pyridinesulfonates with Grignard reagents.

A rare example of coupling of tertiary alkyl halides was reported in 2008 by Yorimitsu and Oshima, who employed the cyclopentadienyl Grignard reagent as the nucleophile with catalytic $Cu(OTf)_2$ in diisopropyl ether solvent (Scheme 9).[23] This coupling reaction gave the products in two isomers (**B** and **B'**) which were assumed be generated from compound **A** via isomerization because of the high acidity of the hydrogen on the cyclopentadiene ring. In order to simplify the analysis of the products, they subjected the mixture of two isomers to hydrogenation and obtained the fully reduced cyclopentyl-substituted products. Tertiary alkyl bromide, chloride and even fluoride electrolphiles were all found to be suitable reactants. Later, in 2009, they also found that allylic Grignard reagents were suitable nucleophiles in coupling reactions with secondary and tertiary alkyl halides under the similar catalytic reaction conditions.[24]



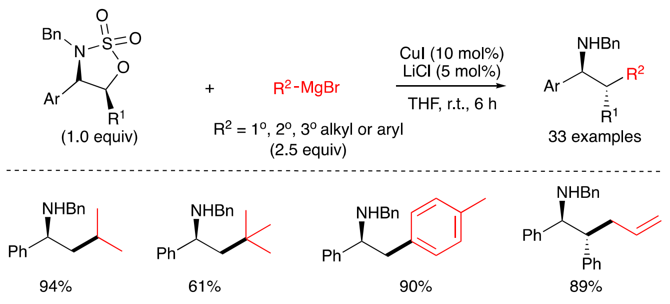
Scheme 9 Cross-coupling of tertiary alkyl halides with cyclopentadienylmagnesium reagent.

The previous examples of using the secondary alkyl electrophiles were usually limited to alkyl iodides, bromides, or tosylates. Unactivated secondary or tertiary alkyl chlorides still remained difficult in copper-catalysed cross-coupling reactions. In 2017, Tao and co-workers reported a copper-catalysed coupling reaction of unactivated secondary, tertiary and primary alkyl chlorides with phenylmagnesium bromide in the absence of additives and ligands (Scheme 10).[25] The preparation of phenylmagnesium bromide in 2-methyltetrahydrofuran was critical for the success of the reaction. Similar to the role of alkyne or alkene additives in Kambe's work, they proposed that the coordination of 2-methyltetrahydrofuran to the copper(I) ion prevented decomposition of thermally unstable copper(I) intermediates via competing *β*-hydride elimination. Unfortunately, extending the Grignard reagent to other aryl magnesium halides led to unsuccessful results.



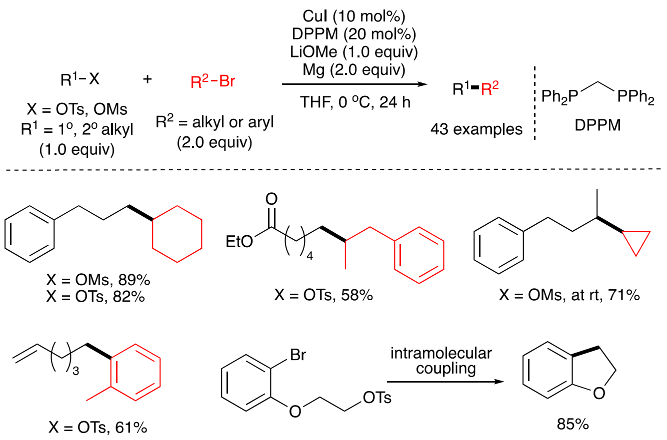
Scheme 10 Cross-coupling of alkyl chlorides with phenylmagnesium bromide.

Addition of LiCl as an additive has also been demonstrated to have remarkable effect in Cu-catalysed cross-coupling reactions. For example, in 2014 the Kobayashi group found that Cu-catalysed coupling reactions of primary alkyl halides with Grignard reagents could be accelerated by using 2.0 equivalent of LiCl.[26] Then in 2015, a catalytic amount of lithium chloride proved to be an efficient additive in Lee's Cu-catalysed regio- and stereoselective ring-opening of chiral cyclic 1,2-sulfamidates with Grignard reagents (Scheme 11).[27] The latter reaction allowed use of primary, secondary, and tertiary alkyl as well as aryl Grignards as nucleophiles, providing an attractive approach to synthesize enantioenriched *α*-branched benzylamine derivatives in good yield. The authors reasoned that coordination of the lithium ion to the bridging oxygen in the sulfamidates contributed to the regio- and stereoselective ring-opening process during the coupling reaction.



Scheme 11 Ring-opening of cyclic sulfamidates with Grignard reagents.

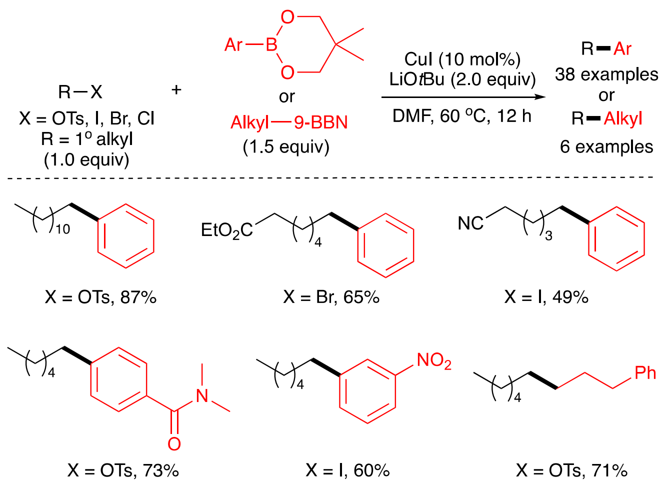
Instead of directly using Grignard reagent, in 2014 Fu and Liu developed a copper-catalysed reductive cross-coupling reaction of unactivated alkyl tosylates and mesylates with alkyl and aryl bromides, in which the Grignard reagents were generated in situ.[28] This method exhibits practical advantages as it avoids the prior preparation and handling of sensitive or expensive organometallic reagents. The reaction was carried out under mild conditions using CuI as the catalyst, bis(diphenylphosphino)methane (DPPM) as the ligand, LiOMe as an additive, and Mg powder as the reductant (Scheme 12). Both intermolecular and intramolecular variants proceeded well to create aryl-alkyl and alkyl-alkyl C-C bonds. Based on control experiments, the authors proposed that the alkyl bromide first reacted with Mg to generate a Grignard reagent, which then coupled with alkyl sulfonates via S$_N$2 substitution in the presence of a copper catalyst.



Scheme 12 Reductive cross-coupling of nonactivated alkyl tosylates and mesylates with alkyl and aryl bromides.

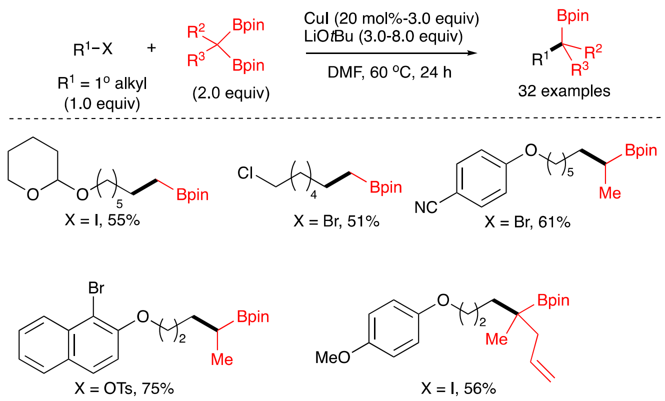
2.1.2 Coupling with organoboron reagents

Compared to Grignard reagents, the use of organoboron reagents has many obvious advantages including availability and stability of the reagents and high tolerance towards a wider range of functional groups. In 2011, Liu and co-workers developed the copper-catalysed C-C coupling of organoboron reagents with primary alkyl electrophiles (Scheme 13).[29] They found that arylboronate esters could react with a variety of alkyl electrophiles including alkyl iodides, bromides, tosylates, mesylates, and even chlorides using the CuI as catalyst and LiOBu as base. Under the same reaction conditions, a C(sp^3)-C(sp^3) bond could also be formed when alkyl 9-BBN reagents (9-BBN = 9-borabicyclo[3.3.1]nonane) were used as nucleophiles. This reaction tolerated many functional groups such as ester, cyano, amide and even nitro groups which were previously not compatible with Grignard reagents. Based on the observation that the reactivity increases in the order: chloride < mesylate < tosylate < bromide < iodide, a sequential coupling of 4-chlorobutyl tosylate at -OTs and -Cl sites was realized. Mechanistic studies ruled out a radical pathway. The author proposed that an arylcopper was first generated from copper and the boronate ester nucleophile, and then a S$_N$2-type substitution with the alkyl electrophile afforded the final product.



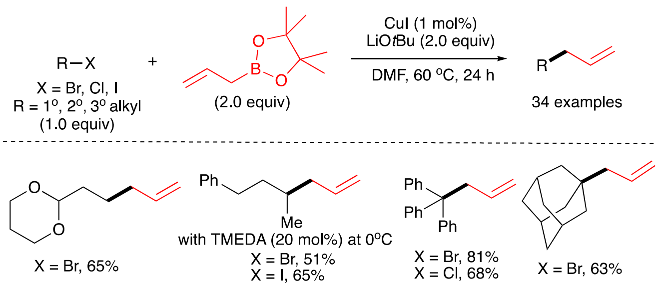
Scheme 13 Cross-coupling of organoboron reagents with primary alkyl electrophiles.

Following Liu's work, in 2014 Fu and co-workers reported a copper catalysed/promoted Suzuki–Miyaura cross-coupling of *gem*-diborylalkanes with unactivated primary alkyl electrophiles, providing a new method for the synthesis of alkylboronic esters (Scheme 14).[30] The reaction proceeded smoothly in the presence of CuI, LiO^{t}Bu, and DMF. Depending on steric hindrance of the diborylalkanes, different amount of CuI and LiO^{t}Bu were applied. For example, 10–20 mol % CuI and 3.0 equiv of LiO^{t}Bu were used in the reaction of the less bulky diborylmethane, while 3.0 equiv of CuI and 8 equiv of LiO^{t}Bu were required for the coupling with bulkier tertiary alkylboronic esters. Consistent with Liu's previous observation, a radical mechanism was excluded based on control experiments.



Scheme 14 Cross-coupling of gem-diborylalkanes with primary alkyl halides.

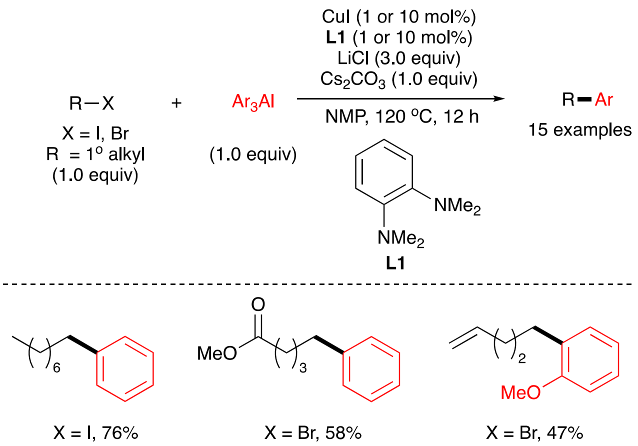
In 2015, a similar catalytic system was used by Fu and Xu to develop the cross-coupling reaction of allyl boronate esters with alkyl halides (Scheme 15).[31] This reaction showed excellent compatibility with unactivated primary, secondary, and even tertiary alkyl halides under mild conditions. For secondary alkyl halides bearing a hydrogen at β-position, addition of a catalytic amount of TMEDA and lowering the temperature were necessary to prevent elimination as a side reaction.



Scheme 15 Cross-coupling of allyl boron ester with alkyl halides.

2.1.3 Coupling with organoaluminum reagents

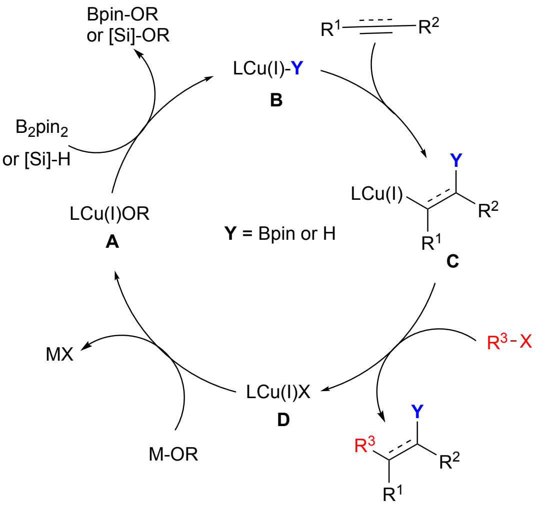
In 2015, the Giri group developed a Cu-catalyzed coupling of electron-neutral or electron-rich triarylaluminum reagents with primary alkyl iodides and bromides (Scheme 16) [32]. *N*,*N*,*N*′,*N*′-tetramethyl-*o*-phenylenediamine (**L1**) was found to be an efficient ligand with CuI as a catalyst in the presence of LiCl and Cs_2CO_3. Like Grignard reagents, a similar arylcopper species was proposed be generated via transmetalation of the triarylaluminum reagent.



Scheme 16 Cross-coupling of triarylaluminum reagents with primary alkyl halides.

2.2 Addition to C–C π-bonds

Recently, tremendous efforts have been put in the Cu-catalysed hydroalkylation and alkylboration of unsaturated bonds with alkyl halides.[11,33] Compared to traditional cross-coupling reactions with organometallic reagents, these transformations allow organocopper intermediates to be catalytically generated *in situ* from addition of Cu-H or Cu-B(OR)$_2$ species to alkynes, alkenes or allenes rather than stoichiometric use of reactive organometallic reagents. A general reaction mechanism is shown in Scheme 17. Firstly, the coper hydride or the borylcopper species **B** is generated from the reaction of copper alkoxide **A** and a hydrosilane or a diboron reagent. Then, the *syn* addition of **B** across the C-C unsaturated bond gives a corresponding organocopper intermediate **C**, which subsequently reacts with an alkyl halide to deliver the hydroalkylation or alkylboration product and a copper halide **D**. Finally, the copper halide **D** is transformed to copper alkoxide **A** in the presence of an alkoxide base to complete the catalytic cycle.

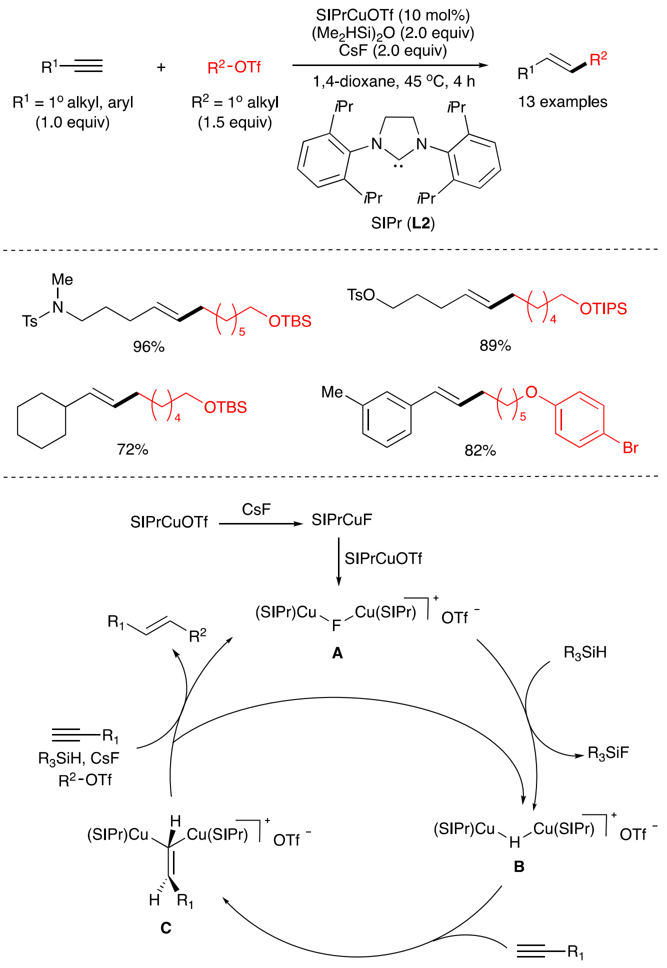


Scheme 17 General catalytic cycle for Cu-catalysed hydroalkylation and alkylboration of unsaturated C-C bond with alkyl electrophiles.

2.2.1 Hydroalkylation

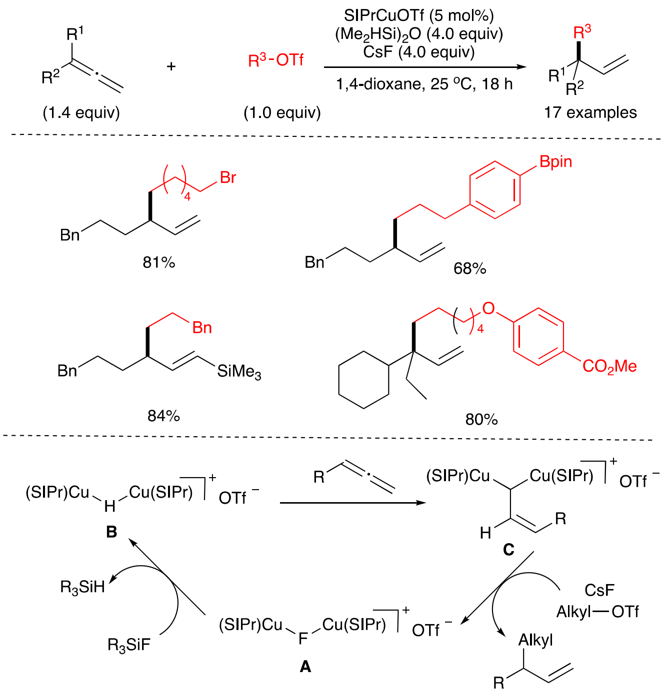
In 2015, Lalic and co-workers reported the first Cu-catalysed hydroalkylation of terminal alkynes with primary alkyl triflates using

SIPrCuOTf (**L2**) as the catalyst, $(Me_2HSi)_2O$ as the hydride source, and CsF as the turnover reagent (Scheme 18).[34] The hydroalkylation proceeded with excellent *anti*-Markovnikov regioselectivity to provide exclusively (*E*)-alkenes in high yield. It is noteworthy that both the reduction[35] and fluorination (see section VI)[36] of alkyl triflates, which occurred under similar Cu-catalysed reaction conditions, were inhibited in the presence of alkynes. The authors initially proposed that the hydroalkylation mechanism involved formation of mononuclear (NHC)CuX (X = F, H, alkenyl) as the active catalytic species. However, after a thorough mechanistic investigation, [37] they finally identified the dinuclear $[(NHC)Cu]_2(\mu\text{-}X)(OTf)$ (X = F, H, alkenyl) complexes instead of (NHC)CuX as the active catalytic intermediates in the hydroalkylation reaction. These dinuclear complexes were demonstrated to suppress the reduction or fluorination of alkyl triflates during the course of the hydroalkylation reaction, although exact mechanism of the transformation of $[(NHC)Cu]_2(\mu\text{-alkenyl})(OTf)$ (**C**) into the final product remains unclear.



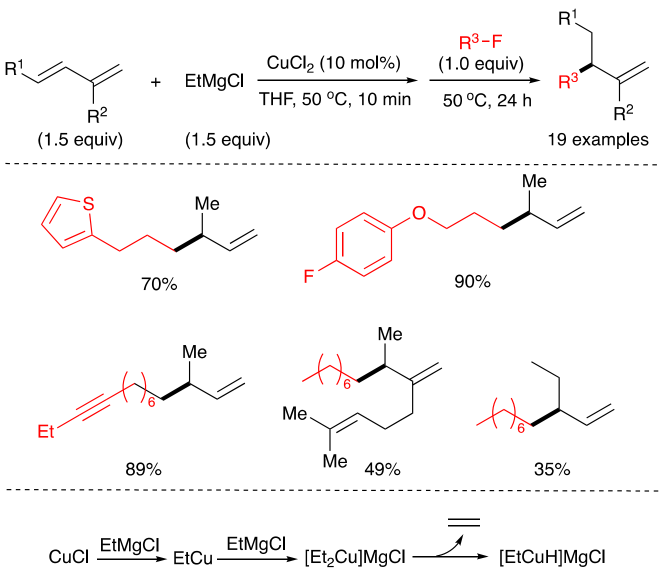
Scheme 18 Hydroalkylation of terminal alkynes with alkyl triflates.

The above reaction conditions were further successfully applied to develop the hydroalkylation of allenes with primary alkyl triflates by Lalic and co-workers in 2017 (Scheme 19).[38] This method provides access to a wide range of substituted terminal alkenes or vinyl silanes bearing a variety of functional groups. Besides mono-substituted allenes, 1,1-disubstituted allenes were also suitable substrates, affording products containing quaternary carbon centers. Like the mechanism in the hydroalkylation of alkynes, similar dinuclear $[(NHC)Cu]_2(\mu\text{-}X)(OTf)$ (X = F, H, allyl) complexes were proposed as the key catalytic intermediates by the authors.



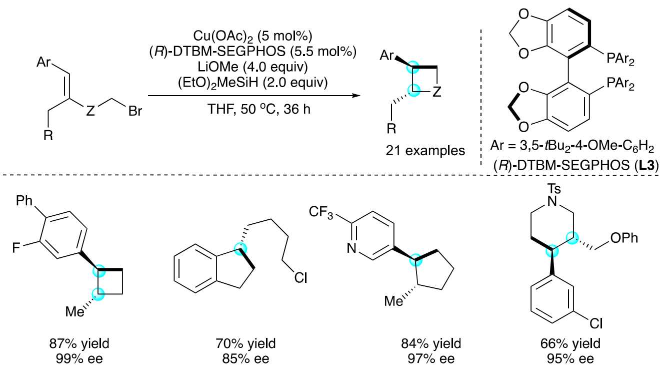
Scheme 19 Hydroalkylation of allenes with alkyl triflates.

During their studies on the cross-coupling of unactivated alkyl fluorides with alkyl Grignard reagents, in 2015 Iwasaki and Kambe found addition of primary alkyl fluorides to a mixture of $CuCl_2$ (5 mol%), EtMgCl and 1,3-dienes resulted in 1,2-hydroalkylation of 1,3-dienes instead of cross-coupling of alkyl fluorides with the Grignard reagent (Scheme 20).[39] The internal carbon atom of the 1,3-diene was selectively alkylated to afford branched terminal alkenes in good to excellent yields. Besides alkyl fluorides, alkyl tosylates were also suitable electrophiles, whereas alkyl chlorides, bromides, and iodides gave complex mixtures. Mechanistic studies revealed that a catalytically active hydrocuprate was probably generated by β-hydrogen elimination of the diethylcuprate before its addition to 1,3-dienes to form the allylcuprates. In addition, kinetic studies and the observed kinetic isotope effect (KIE) indicated that either the formation of diethylcuprate from ethylcopper and EtMgCl or the subsequent β-H elimination was involved in the rate-limiting step.



Scheme 20 Hydroalkylation of 1,3-dienes with alkyl fluorides.

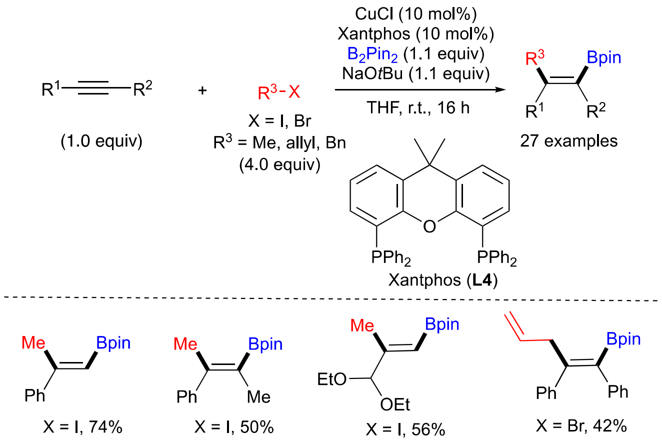
An intramolecular, enantioselective hydroalkylation of bromide-tethered styrenes was developed by Buchwald and co-workers in 2015 (Scheme 21).[40] The bisphosphine, (*R*)-DTBM-SEGPHOS (**L3**), was identified to be the optimal ligand, and use of lithium methoxide as a base was crucial for the success of this reaction. Several scaffolds, including cyclobutanes, cyclopentanes, indanes, and saturated 6-membered heterocycles could be efficiently approached with complete diastereoselectivity and good to excellent enantioselectivity.



Scheme 21 Enantioselective, intramolecular hydroalkylation of halide-tethered styrenes.

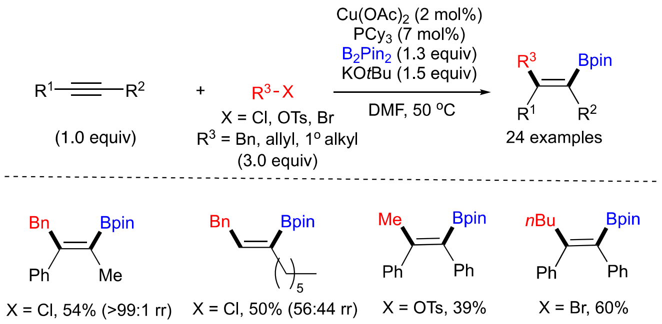
2.2.2 Intermolecular Alkylboration

The Cu-catalysed alkylboration reaction allows simultaneous installation of C-B and C-C bonds across an unsaturated C-C bond in a single transformation, representing one of the most direct ways to access highly substituted organoboron compounds. In 2012, Tortosa and co-workers developed the first copper-catalysed alkylboration of alkynes using Xantphos (**L4**) as ligand (Scheme 22).[41] The reaction proceeded with high regioselectivity and *syn*-stereoselectivity to form tri- and tetrasubstituted vinylboronic esters as single isomers. Various aryl-substituted terminal alkynes were suitable substrates. However, for unsymmetrical internal alkynes, the substrate scope was limited to methyl and aryl-substituted alkynes. In addition, only methyl iodide, benzyl bromide and allyl iodide were used as electrophilic coupling partners.



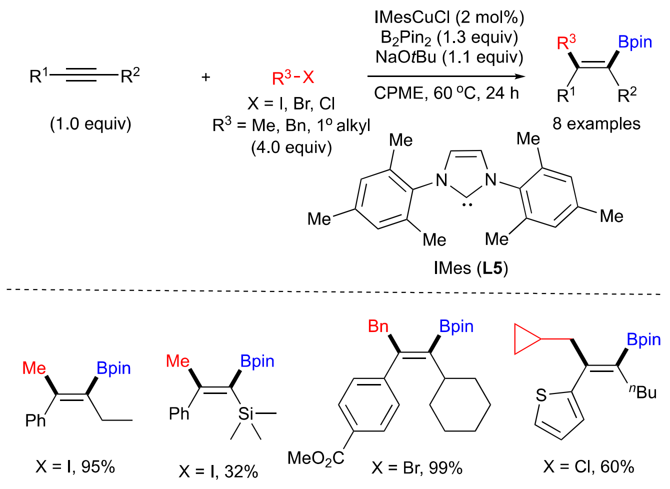
Scheme 22 Alkylboration of alkynes using Xantphos as ligand.

Shortly afterwards, in 2013 Yoshida's group also independently reported the alkylboration reaction of alkynes using a Cu(OAc)$_2$/PCy$_3$ catalyst system (Scheme 23).[42] In contrast to the results reported by Tortosa, in this work terminal aliphatic alkynes such as 1-octyne and cyclopentylacetylene were also suitable substrates to afford the alkylboration products in moderate yield, albeit with poor regioselectivity. Besides benzyl chloride and methyl tosylate, unactivated alkyl bromides were also applicable. A non-radical pathway was hypothesized based on the results that no ring-opening product was observed with cyclopropylmethyl bromide.



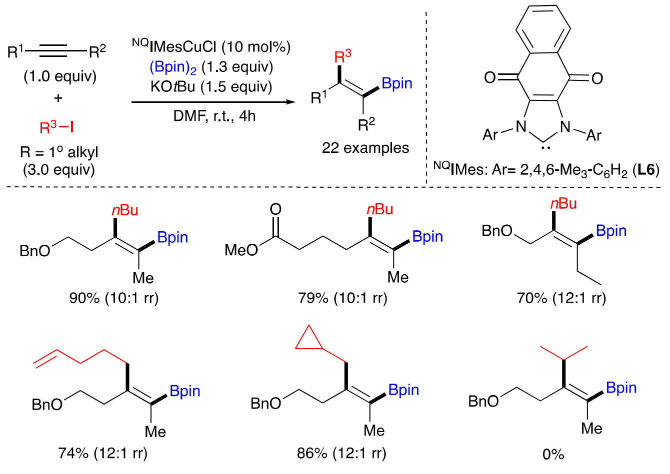
Scheme 23 Alkylboration of alkynes using PCy$_3$ as ligand.

Later, in 2014, Cazin and co-workers reported borylation of internal alkynes using IMesCuCl as the catalyst, allowing tetrasubstituted vinylboronates to be synthesized as single isomers from the aryl- and alkyl-substituted internal alkynes when alkyl halides were used as electrophiles in the presence of B$_2$pin$_2$ (Scheme 24).[43] The formation of a robust catalytic system using the *N*-heterocyclic carbene ligand enabled the reaction to be conducted in air with a relatively low catalyst loading (2 mol%). Although methyl iodide was used as the electrophile in most reported examples, a less reactive alkyl chloride was also included in one example.



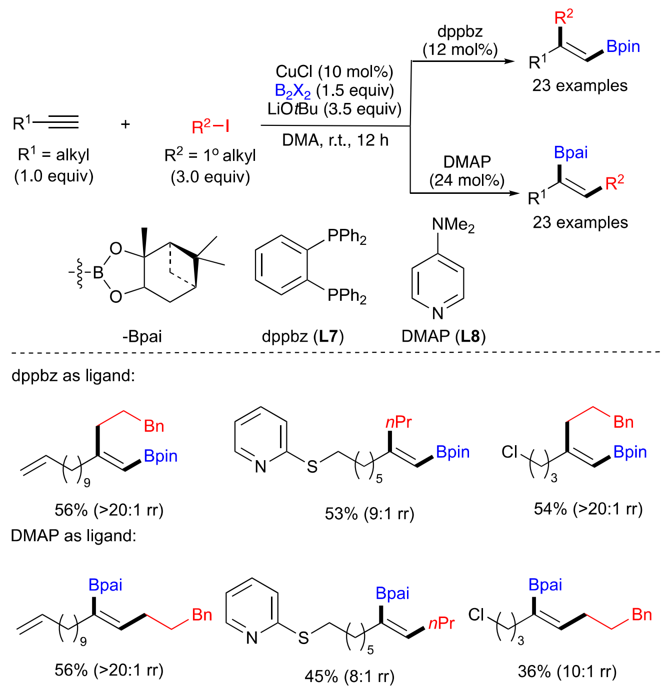
Scheme 24 Alkylboration of alkynes using IMes as ligand.

In the previous reports, the alkyne scope was predominantly limited to aryl-substituted alkynes. In 2016, Kanai and co-workers developed the first copper-catalysed regio- and stereoselective borylalkylation of dialkylsubstituted internal alkynes with B_2pin_2 and alkyl halides (Scheme 25).[44] This method provides a straightforward method to synthesize trialkyl-substituted alkenylboronates, which are good precursors for synthesis of all-carbon tetra-substituted alkenes. The π-accepting naphthoquinone-conjugated NHC ligand ^{NQ}IMes (**L6**) was found to be essential for controlling the high regio- and chemoselectivity. Broader substrate scope was found with primary alkyl halides in this work, whereas secondary alkyl iodides were still not applicable. Consistent with Yoshida's work, a non-radical process was proposed based on the result that (iodomethyl)cyclopropane solely produced the desired borylalkylation product without ring-opening.



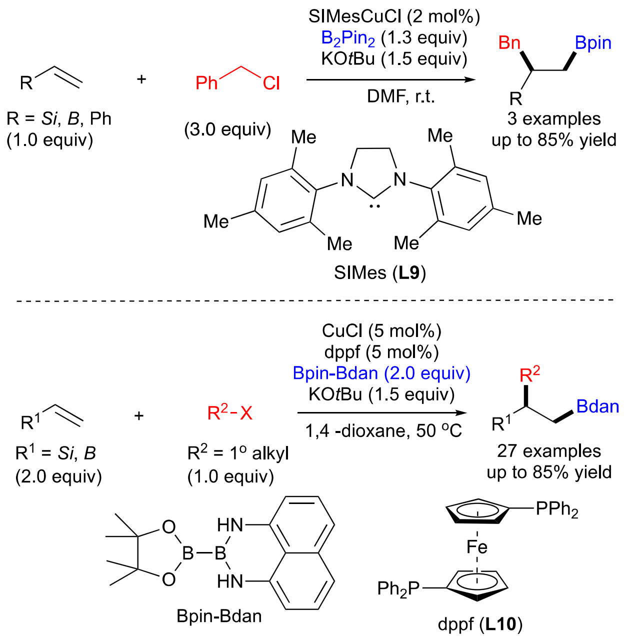
Scheme 25 Alkylboration of dialkylsubstituted internal alkynes using ^{NQ}IMes as ligand.

A ligand-controlled regiodivergent and stereospecific copper-catalysed alkylboration of unactivated terminal alkynes was developed by Xiao and Fu in 2016 (Scheme 26).[45] Both internal and terminal vinylboronic esters could be efficiently synthesized from a single unactivated terminal alkyne. When the reaction was performed using a bisphosphile ligand, dppbz (**L7**), anti-Markovnikov alkylboration products were selectively formed in the presence of B_2Pin_2, whereas with a pyridine-type ligand DMAP (**L8**), Markovnikov alkylboration products were obtained and B_2pai_2 showed better performance than B_2Pin_2. A preliminary mechanistic study excluded radical participation in the coupling step.



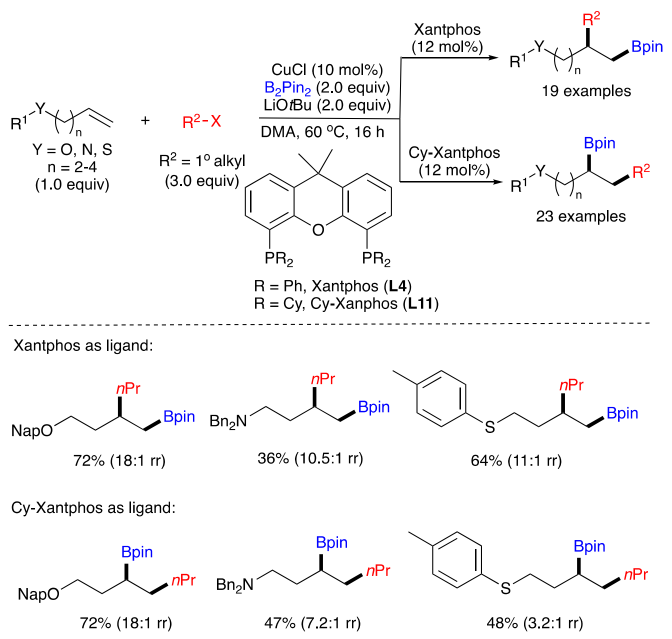
Scheme 26 Ligand-controlled regiodivergent copper-catalysed alkylboration of unactivated terminal alkynes.

During their studies in the alkylboration of alkynes,[42] Yoshida's group also briefly investigated copper-catalysed intermolecular alkylboration of alkenes and found vinylsilanes, vinylboranes, and styrene could react with benzyl chloride in the presence of B_2Pin_2 to give the alkylated boronate product in good yield using SIMesCuCl as catalyst (Scheme 27). Later, they employed the unsymmetrical diboron [(pin)B–B(dan)] reagent in the Cu-catalysed alkyboration of vinylsilanes or vinylboranes to produce protected alkylboron compounds in presence of dppf ligand (**L9**).[46] In this work, not only benzyl chloride, but also primary alkyl halides were suitable electrophiles to provide diverse alkylboron compounds in good yield with high regioselectivity.



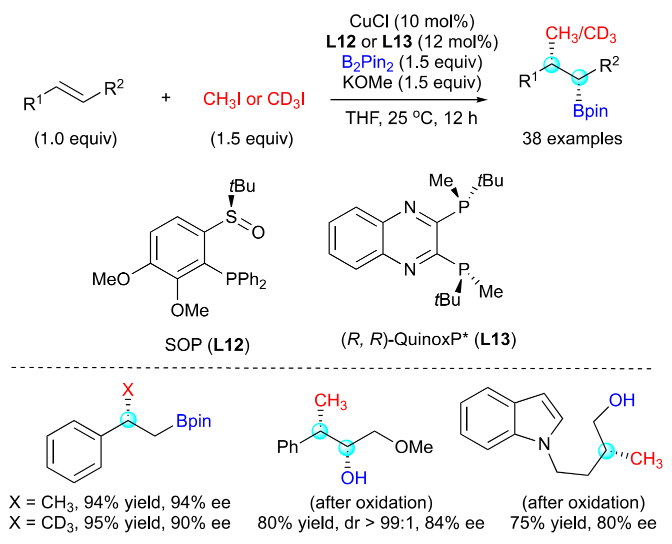
Scheme 27 Alkylboration of activated alkenes.

Only activated alkenes were used in Yoshida's work. The alkylboration of unactivated alkenes is more challenging. In 2015, Xiao and Fu found that introduction of a heteroatom into the unactivated alkene could facilitate the addition of a [CuBpin] intermediate to the C-C double bond by a weak coordination effect (Scheme 28).[47] Moreover, by judicious choice of phosphine ligands Xantphos (**L4**) or Cy-Xantphos (**L11**), they successfully developed a regiodivergent, copper-catalysed alkylboration of unactivated alkenes with bis(pinacolato)diboron and alkyl halides. In addition, under similar reaction conditions, regiodivergent deuteroboration and aminoboration reactions were also realized. Preliminary mechanistic studies ruled out the involvement of a radical mechanism. Later, Yu and Fu performed DFT calculations and found that migratory insertion of alkenes was the regioselectivity-determining step.[48] The Cy-Xantphos ligand with bulky cyclohexyl groups facilitates the approach of the substituents on the alkene towards the Bpin group in the migratory insertion step and thus leads to the internally borylated products. On the other hand, the less bulky phenyl-substituted Xantphos ligand favors approach with the alkene substituents away from the Bpin group in the migratory insertion step and thus results in terminally borylated products.



Scheme 28 Ligand-controlled regiodivergent alkylboration of unactivated alkenes. Nap = 2-naphthylmethyl.

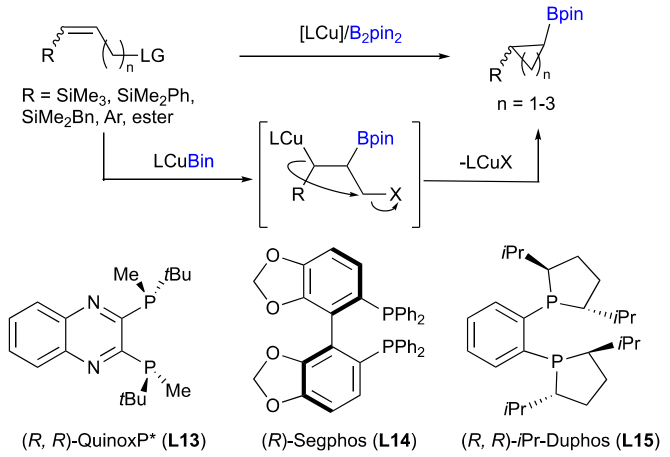
Recently, Liao and co-workers developed the first intermolecular enantioselective copper-catalysed alkylboration of alkenes using SOP (**L12**) or (*R, R*)-QuinoxP*(**L13**) as ligands (Scheme 29).[49] Although the alkyl electrophile scope is limited to methyl iodide, this work provides an efficient method for synthesis of chiral methyl containing bioactive molecules. Styrenes, β-substituted styrenes, and challenging aliphatic olefins all worked well to give the desired methylboration products in high yields with excellent diastereoselectivities and enantioselectivities. Notably, the use of deuterated methyl iodide CD_3I as electrophiles was also introduced in their work.



Scheme 29 Enantioselective methylboration of alkenes.

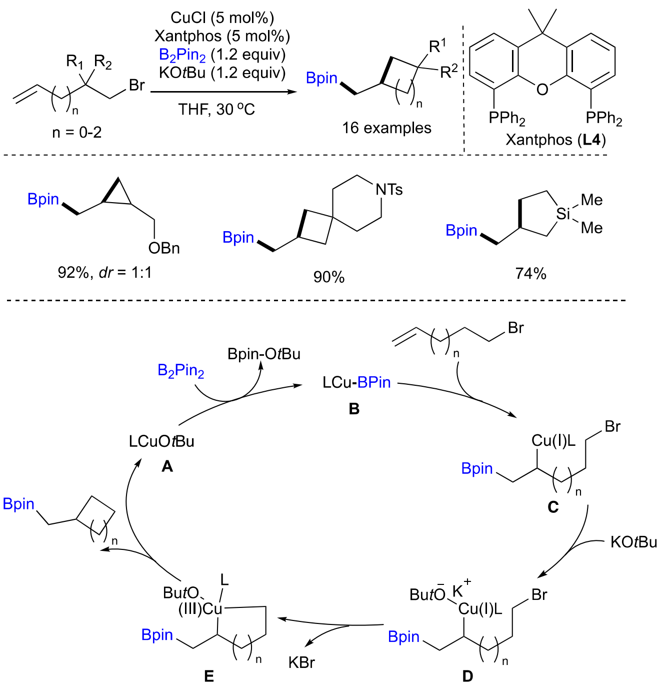
2.2.3 Intramolecular alkylboration

The Cu-catalysed intramolecular alkylboration (also called borylative cyclization) of unsaturated C-C bonds offers a direct way to synthesize a verity of cyclic organoboron compounds (Scheme 30).[50] In 2008, Sawamura and Ito reported the first Cu-catalysed asymmetric borylative cyclization of *γ*-silylated allylic carbonates using (*R*, *R*)-QuinoxP* (**L13**) or (*R*)-Segphos (**L14**) as the chiral ligands, providing *trans*-cyclopropane derivatives containing B and Si functional groups in good yield with high enantioselectivity.[51] In 2010, they described a similar Cu-catalysed process for synthesis of racemic silyl- or aryl-substituted cyclobutylboronates from homoallylic sulfonates in the presence of a 1,3-bis(diphenylphosphino)propane (dppp) ligand, with (*Z*)- and (*E*)-homoallylic sulfonates being converted to the *trans* and *cis* products, respectively.[52] Later, the same group reported a highly enantioselective synthesis of *trans*-aryl and -heteroaryl-substituted cyclopropylboronates through the Cu-catalysed borylative cyclization of (*Z*)-allylic phosphates using the (*R*, *R*)-*i*Pr-Duphos (**L15**) as a chiral ligand.[53] Recently, Zhong group reported the stereoconvergent synthesis of *cis*-*β*-boron-substituted five- and six-membered carbocycle and heterocycle esters via borylative cyclization of ω-mesylate-α,β-unsaturated compounds using a simple Cu-bisphosphine catalyst.[54] Mechanistically, these above reactions go through an *endo*-cyclization process, consisting of a stepwise transformation that involves addition of a borylcopper(I) intermediate to the alkene, followed by intramolecular nucleophilic attack towards the leaving group to afford the corresponding cyclic organoboronates. The electronic effect of the activating groups such as silyl, aryl, or ester adjacent to the alkene was assumed to be responsible for the resulting high reactivity and regioselectivity.



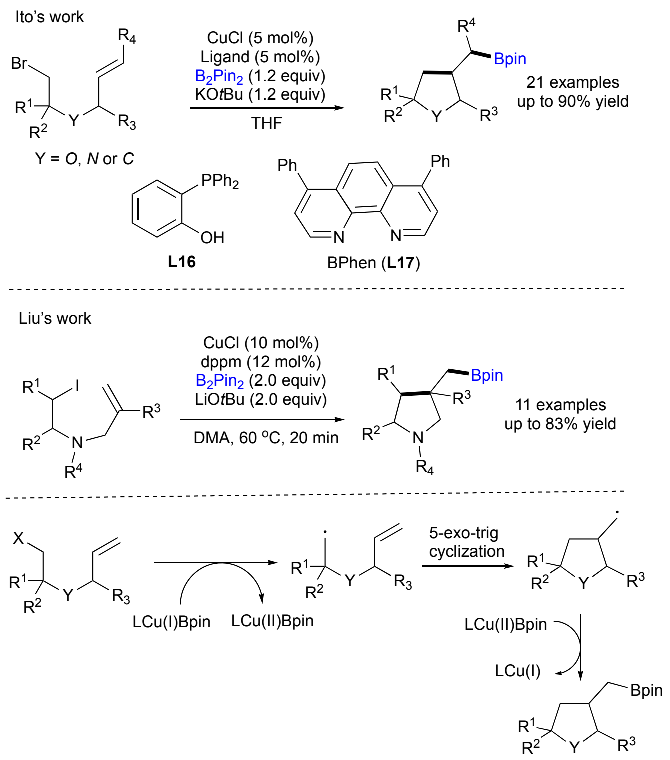
Scheme 30 Borylative endo-cyclization of activated alkenes.

In 2013, Ito and co-workers developed a copper-catalysed borylative *exo*-cyclization of unactivated terminal alkenes to afford products containing three- to five-membered ring with a borylmethyl moiety (Scheme 31).[55] They found that use of Xantphos (**L4**) as ligand was crucial to enhance the reactivity of the borylcopper(I) intermediate toward addition to the unactivated C-C double bond while preventing competing borylation of the alkyl bromide moiety. Interestingly, a lower energy barrier was observed in the DFT calculation when the bulky Cu-(Xantphos) complex was added to the internal carbon of the double bond to form alkylcopper(I) **C**. Control experiments excluded a radical pathway in the cyclization process, and they instead proposed that a cyclic copper(III) intermediate **E** was formed with inversion of stereochemistry after the intramolecular oxidative addition of alkylcopper(I) (**C**) with alkyl halide in the presence of KO*t*Bu. Subsequent reductive elimination of **E** produces the cyclization product and regenerates catalyst **A**. This reaction was further developed by Fernández and co-workers to prepare [m. n]-spiroheterocyclic structures (m, n = 3–5) and also a dispirocycle scaffold with a methylene boronate substituent.[56]



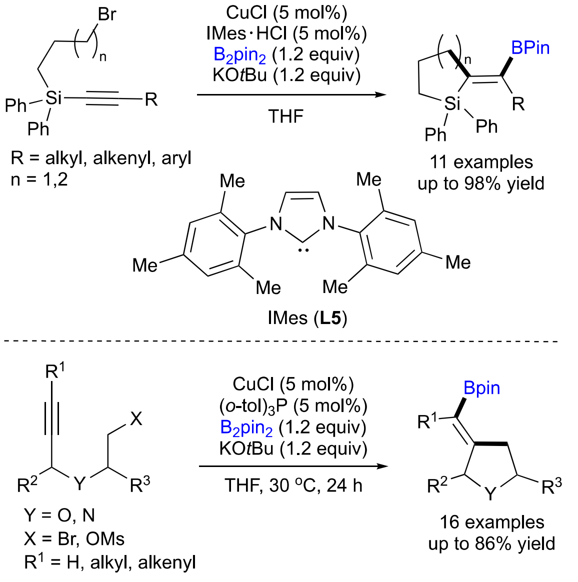
Scheme 31 Borylative exo-cyclization of unactivated terminal alkenes.

In 2017, Ito and co-workers reported a stereoselective copper(I)-catalysed borylative radical cyclization reaction of alkyl halides containing an alkene moiety (Scheme 32).[57] This reaction enables the chemoselective synthesis of a wide variety of five-membered cyclic organic compounds bearing a boron functional group. Depending on the type of substrates, three different ligands, PCy_3, **L16**, and BPhen (**L17**) were used in the presence of CuCl catalyst. At the same time, a similar transformation was also reported by the Liu group using bis(diphenylphosphino)methane (dppm) as the ligand. Notably, the latter method could be used to construct borylated pyrrolidine derivatives bearing a quaternary carbon center.[58] Both of the groups proposed that the borylation proceeded through a radical mechanism, in which the alkyl halide was activated by a [Cu(I)Bpin] intermediate to give an alkyl radical, followed by a 5-*exo*-trig radical cyclization to form the C-C bond.



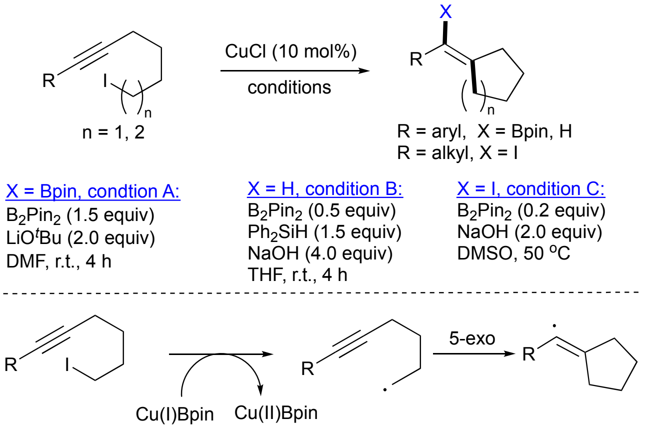
Scheme 32 Borylative radical cylization of alkyl halides containing an alkene moiety.

To enhance the reactivity and regioselectivity of the alkylboration of alkynes, the Ito group introduced heteroatoms into the alkyne substrates. For example, in 2015 they developed an intramolecular copper-catalysed borylative cyclization of silicon-tethered alkynes containing alkyl bromide moieties using a CuCl/IMes catalyst system (Scheme 33).[59] The reaction proceeded with high regioselectivity and complete *syn*-selectivity to give five- or six-membered ring products. The presence of a silyl group had a significant effect on the reactivity, as no reaction was detected when the silyl group was absent in the substrate. In 2017, they reported the copper(I)-catalysed intramolecular alkylboration of propargyl ethers and amines to provide alkenylboronates with a tetrahydrofuran or pyrrolidine structure using a monophosphine ligand.[60] In these reactions, an alkenylcopper intermediate was proposed to be formed from the addition of the borylcopper to alkyne, followed by its S_N2 displacement of a pendant leaving group. Density functional theory (DFT) calculations suggested that electronic effects of the heteroatoms contributed to controlling the regioselectivity step. In addition, in 2019, one example of intramolecular alkylboration of propargyl ether was reported by Sollogoub and co-workers using cyclodextrin-encapsulated *N*-heterocyclic carbene copper complex previously developed by their group.[61]



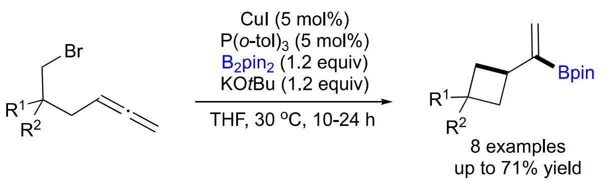
Scheme 33 Intramolecular alkylboration of alkynes containing heteroatoms.

In 2018, Wang and Zhao achieved intramolecular alkylboration, hydroalkylation, and iodoalkylation of alkynes lacking heteroatom activation using CuCl as catalyst by controlling the reaction conditions, affording various five- or six-membered cyclic exocyclic alkene derivatives as products (Scheme 34).[62] It is worthy to note that no ligand is required in this reaction. Based on control experiments, a radical mechanism was proposed in which the alkyl radical was generated from reaction of [Cu(I)Bpin] with alkyl iodide via a single electron transfer process, followed by radical ring cyclization.



Scheme 34 Intramolecular alkylboration, hydroalkylation and iodoalkylation of alkynes.

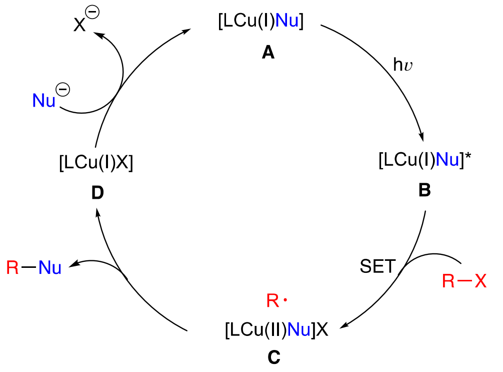
Recently, Ito and co-workers also developed a copper(I)-catalyzed intramolecular 2,3-alkylboration of terminal allenes bearing an alkyl halide moiety (Scheme 35).[63] A control experiment excluded radical initiation between borylcopper(I) and alkyl halide, and the authors proposed that facile isomerization of the allylcopper(I) intermediates allowed the alkenylboronates bearing a four-membered ring structure be kinetically generated with high regio- and diastereoselectivities.



Scheme 35 2,3-alkylboration of terminal allenes.

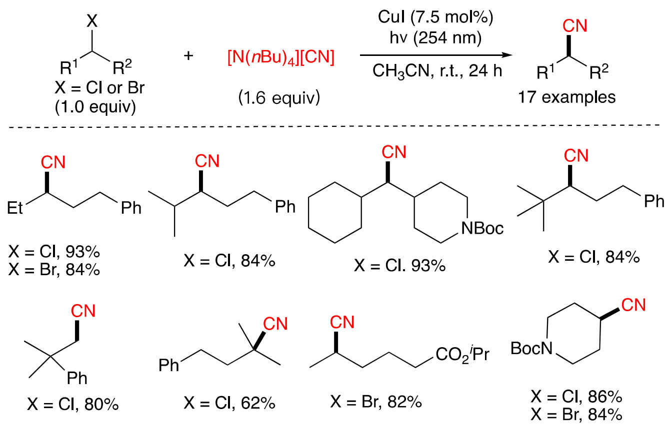
2.3 Photoinduced C-C couplings

In the past decades, photoredox catalysis has enabled many novel approaches to C-C and C-X bond formation with unactivated alkyl halides under mild conditions, using visible light as an energy source.[64] However, although significant advances have been achieved with Ru or Ir-catalysed photoredox reactions, the use of Cu complexes as abundant and inexpensive photoredox catalysts is still underdeveloped and highly desired.[65] A general mechanism for a photoinduced Cu-catalysed coupling reaction of alkyl halides with nucleophiles is shown in Scheme 36. A Cu(I)–nucleophile complex (**A**) first undergoes photoexcitation to generate an excited-state species (**B**). Then, the single electron transfer between **B** and the alkyl electrophile (R–X) gives a Cu(II)–nucleophile complex (**C**) and an alkyl radical (R·). Finally, these two intermediates couple to form the desired product (R–Nu) and a Cu(I)–halide complex (**D**) which regenerates the Cu(I)–nucleophile complex (**A**) after ligand substitution.



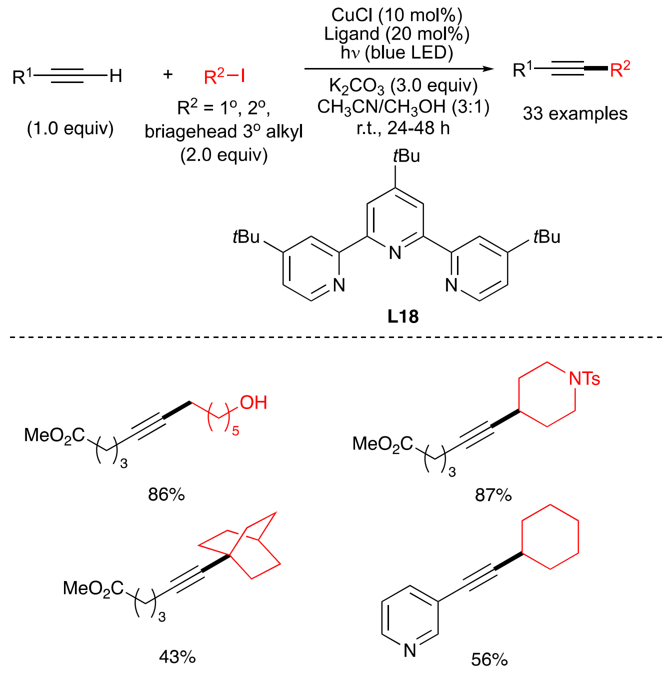
Scheme 36 General mechanism for photoinduced, copper-catalysed coupling of alkyl halides with nucleophiles.

Recently, Peters and Fu used this concept to develop a series of photoinduced, copper-catalysed C-N coupling reactions of alkyl halides using amines or amides as nucleophiles (see section III for more details). In 2015, they successfully extended the nucleophile scope from nitrogen to carbon for C-C bond formation (Scheme 37).[66] In presence of UV light (254 nm), the cyanation of unactivated secondary alkyl halides proceeded well to give the corresponding nitriles in good yields at room temperature with $[N(nBu)_4][CN]$ (TBACN) as the cyanide source and CuI as the catalyst. It is worthy to note that no added ligand is required in this reaction. A variety of unactivated secondary alkyl chlorides or bromides, including very sterically demanding cases, were suitable substrates. According to a series of control experiments, the *in-situ* formed $Cu(CN)_2^-$ was proposed to be the key intermediate in the photoinduced, copper-catalysed process, serving the role of **A** in Scheme 36.



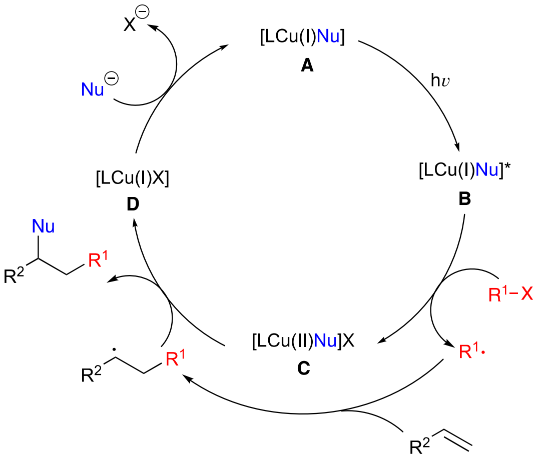
Scheme 37 Cyanation of alkyl halides.

In 2018, Lalic and co-workers developed a photoinduced, copper-catalysed alkylation of terminal alkynes with unactivated primary, secondary, or tertiary alkyl iodides (Scheme 38).[67] The reaction was conducted at room temperature under blue light (450 nm) irradiation, and a terpyridine ligand (L18) was found to be crucial for the success of the reaction by suppressing the polymerization of alkynes. The reaction was found to have a broad substrate scope and tolerated ester, nitrile, alcohol, amide, epoxide, aryl halide, and ether functional groups. A plausible catalytic cycle that involves photoexcitation of a copper acetylide intermediate was proposed by the authors. Further mechanistic studies indicated that the alkylation process between the photoexcited copper acetylide and an unactivated alkyl iodide likely proceeded through a radical pathway.



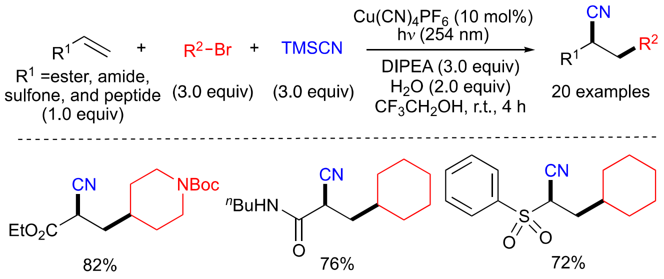
Scheme 38 Alkylation of terminal alkynes with alkyl halides.

Compared to metal-catalysed two-component coupling of alkyl electrophile with nucleophiles to form the C-C or C-X bonds, the metal-catalysed three-component coupling of alkyl electrophiles, olefins and nucleophiles enables the construction of the C-X bond and C-C bond across an olefin in a single catalytic cycle. In this transformation, the generated alkyl radical adds to an alkene to form a new alkyl radical, which then couples with Cu(II)-nucleophile **C** to give the corresponding three-component coupling products and Cu(I)–halide complex (**D**) (Scheme 39).



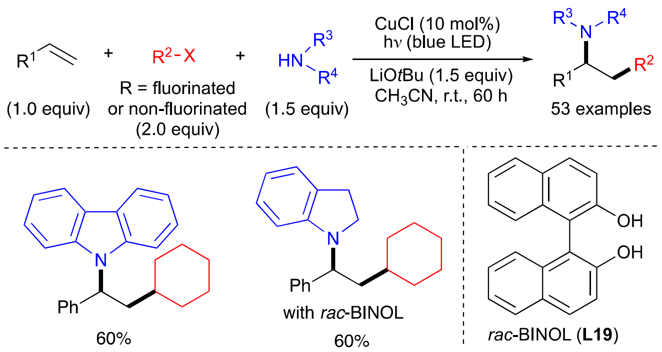
Scheme 39 General mechanism for three-component coupling reaction of alkyl electrophiles, olefins and nucleophiles.

In 2017, Xu and co-workers reported the first example of Cu-catalysed cyanofluoroalkylation of alkenes using fluoroalkyl iodides as fluoroalkylation reagents under UV irradiation.[68] Later, by employing activated alkenes bearing electron withdrawing groups, they extended the electrophile scope to non-fluorinated alkyl electrophiles (Scheme 40).[69] Unactivated primary, secondary and tertiary alkyl bromides were all suitable substrates to provide the products in good yields.



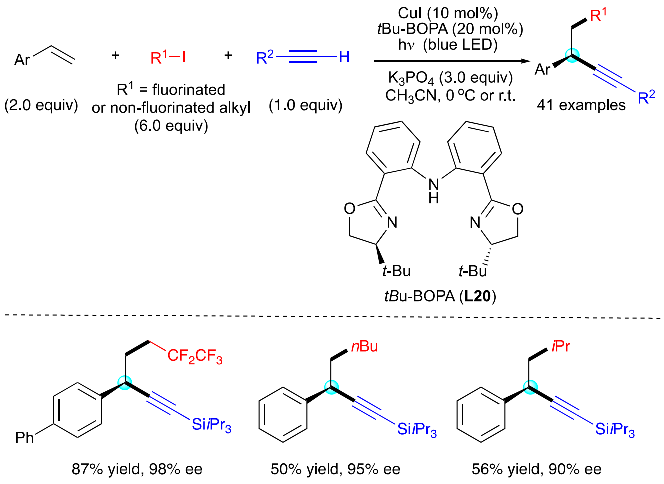
Scheme 40 Cyanoalkylation of alkenes

In 2019, Zhang and co-workers developed a copper-catalysed carboamination of alkenes using amines as nucleophiles under blue LED irradiation (Scheme 41).[70] Both fluorinated and non-fluorinated alkyl halides were suitable electrophiles to give the products in good yields. It is worthy to note that for amines bearing a π system, such as carbazole, indole, or imidazole, the reaction proceeds well without any added ligand. However, for simple amines lacking such conjugation, use of BINOL as a ligand was necessary to facilitate the photoexcitation process.



Scheme 41 Carboamination of alkenes with alkyl halides and amines.

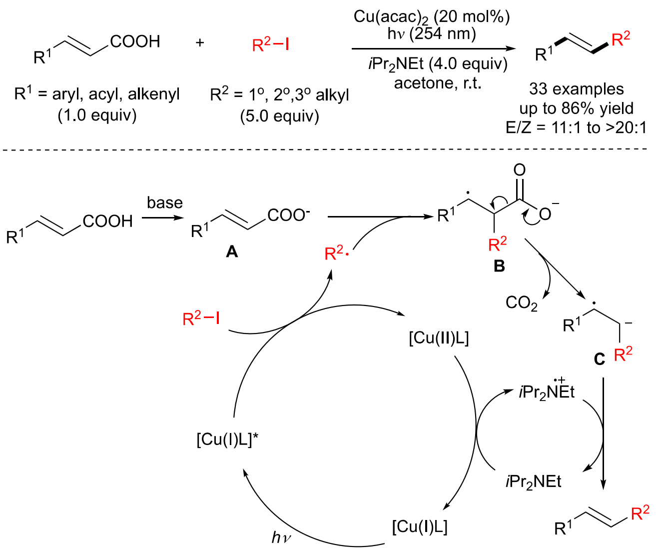
Very recently, by using alkynes as the nucleophilic partners, the Zhang group also developed a copper-catalysed enantioselective carboalkynylation of styrenes using a chiral BOPA–Cu(I) complex (**L20**) under blue LED irradiation, providing an efficient way to approach enantioenriched propargylic compounds (Scheme 42).[71] Various alkynes, alkenes, and both fluorinated and non-fluorinated alkyl iodides worked well in this three-component coupling reaction.



Scheme 42 Enantioselective carboalkynlation of styrenes.

In 2017, Wang and Xu group developed a UV light-induced, copper-catalysed decarboxylative coupling of α,β-unsaturated acids with alkyl iodides (Scheme 43).[72] Primary, secondary, and tertiary alkyl iodides all proceeded well to form the alkylated *E*-alkenes in usually good yields and high stereoselectivities (up to *E*/*Z* > 20:1). In the catalytic cycle they proposed the amine acted as both a base and an electron transfer reagent. On one hand, the amine deprotonates the α, β-unsaturated acid to generate the carboxylate anion **A**, which is trapped by alkyl radical to form complex **B**. On the other hand, the amine is also thought to reduce Cu(II) to Cu(I) with amine radical cation formation. After decarboxylation of **B**, an amine radical cation was proposed to oxidize intermediate **C** to afford the final alkene product.

In addition to these examples, visible light-mediated alkylation of C-H bonds is described below in section 2.5.

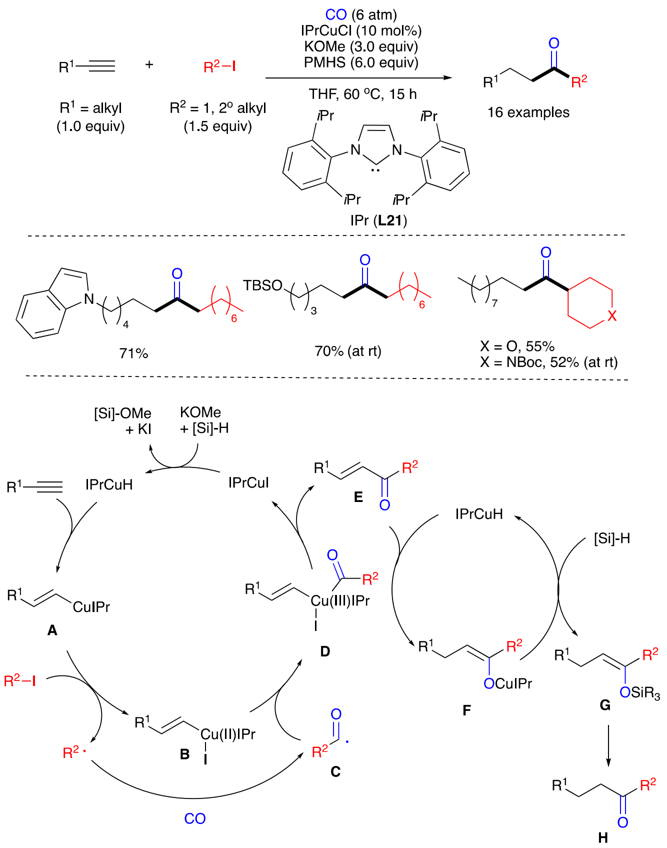


Scheme 43 Decarboxylative alkylation of unsaturated acids with alkyl iodides.

2.4 Carbonylative coupling

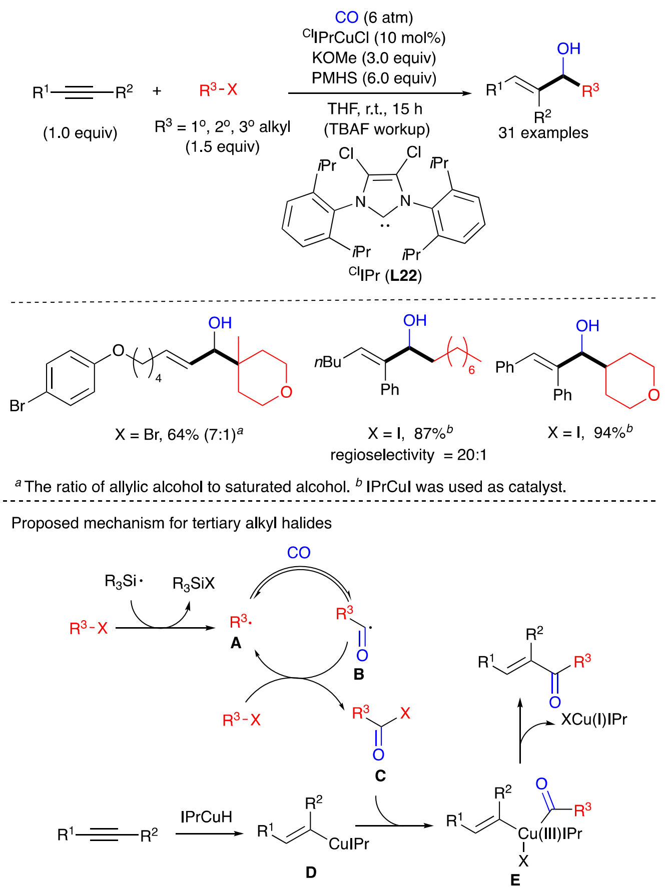
Rather than trapping alkyl radicals with alkenes as in the previous examples, alkyl radicals can also be efficiently trapped by CO,[73] opening the possibility for radical carbonylation reactions of alkyl halides. It is worthy to note that despite transition metal-catalyzed carbonylation reactions being long-established for synthesis of carbonyl compounds,[74] some challenges still exist in this research area. For example, in most cases, precious metals such as palladium are used as catalysts. In addition, while aryl, vinyl, allyl, and benzyl halides or pseudohalides have been well explored as the electrophiles, the use of unactivated alkyl electrophiles is much less developed, possibly due to their slow rate of oxidative addition as well as competitive β-hydride elimination under carbonylative conditions. Thus, developing new strategies in carbonylation of unactivated alkyl electrophiles using earth-abundant catalysts is highly desirable.[73c,74d]

In 2017, inspired by the recent work on Cu-catalysed hydrofunctionalization of alkynes,[33] our group developed a Cu-catalysed hydrocarbonylative coupling of alkyl iodides with terminal alkynes, providing an unprecedented procedure to synthesize unsymmetrical dialkyl ketones from easily available starting materials (Scheme 44).[75] Under 6 atm CO, both of primary and secondary alkyl halides worked well to give ketones in good yield in the presence of IPrCuCl as the catalyst, KOMe as the base and polymethylhydrosiloxane (PMHS) as the reducing reagent. Based on mechanistic studies, we proposed an auto-tandem sequence of two Cu-catalysed processes, one for carbonylative coupling to generate an α, β-unsaturated ketone intermediate and another for subsequent 1,4-reduction to the ketone product. Crucially, unlike the radical coupling reactions of alkyl halides under photoirradiation cited previously, here an alkyl radical R· is directly generated from alkyl iodide with alkenyl copper **A** without requiring irradiation.



Scheme 44 Synthesis of ketones via hydrocarbonylative coupling of terminal alkynes with alkyl halides.

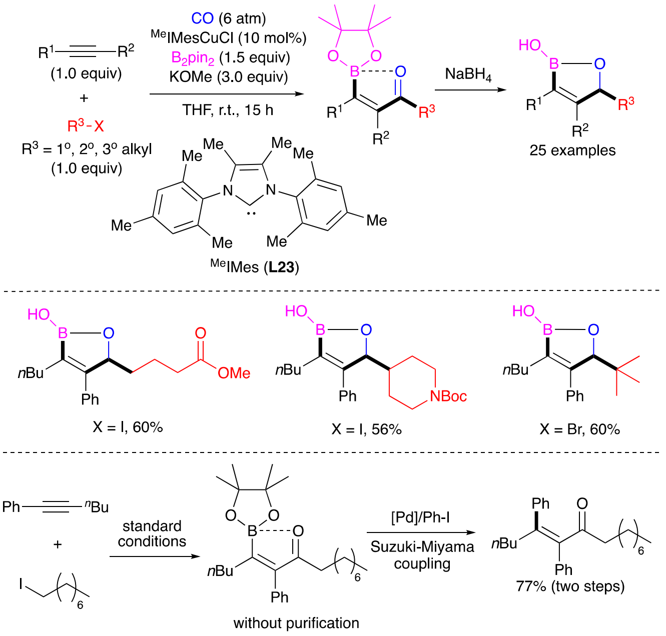
By controlling the reaction conditions, we also developed a related transformation that provided allylic alcohols with high selectivity from tertiary, secondary, primary alkyl halides and alkynes via a Cu-catalysed hydrocarbonylative coupling and 1,2-reduction (rather than 1,4-reduction) tandem sequence (Scheme 45).[76] When *tert*-alkyl bromides were used as electrophiles, both terminal and internal alkynes gave allylic alcohols bearing α-quaternary carbon centers, rather than dialkyl ketones observed for less bulky electrophiles, in good yield at room temperature; ^{Cl}IPrCuCl showed better performance than IPrCuCl as the catalyst. Futher mechanistic studies revealed that tertiary alkyl halides undergo a different reaction pathway than primary and secondary alkyl halides for generating the key copper(III) oxidative adduct. We proposed, for the tertiary alkyl halides, the copper(III) oxidative adduct **E** was generated from the reaction of alkenylcopper **D** and an acyl halide **C**, the latter of which was formed from the alkyl halide reactant via an atom transfer carbonylation (ATC) process.[73a] Further investigatation revealed that by employing internal alkynes with one aryl substituent, even primary and secondary alkyl electrophiles were able to provide tri-substituted allylic alcohols rather than dialkyl ketones in high yield with good regioselectivity in the presence of IPrCuCl. The origin of regioselectivities in the hydrocarbonylative coupling of alkynes with primary, secondary and tertiary alkyl halides was recently detailed by Chen and co-workers using the DFT analysis, in which they found that steric effects play an important role in controlling the 1,2-reduction over 1,4-reduction of the enone intermediate.[77]



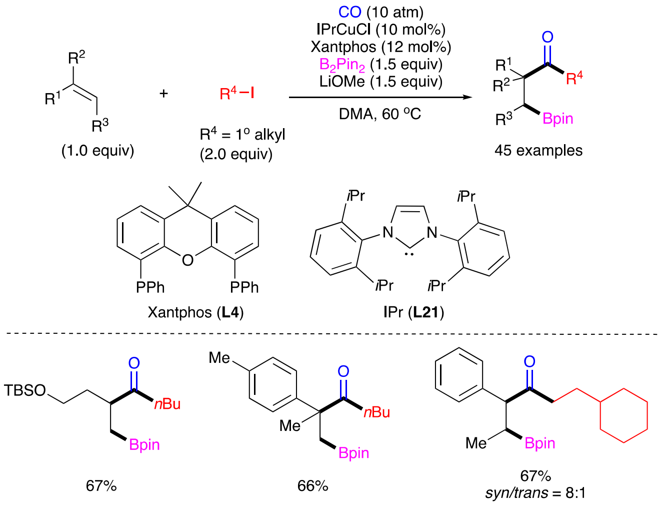
Scheme 45 Synthesis of allylic alcohols via hydrocarbonylative coupling of alkyl alkyne with alkyl halides.

α,β-Unsaturated ketones (enones) are highly important compounds in organic synthesis due to their versatile downstream transformations. In our previous hydrocarbonylative coupling reactions, despite enones being formed as intermediates, they were further reduced to afford ketones or allylic alcohols. In 2018, we developed a copper-catalysed borylcarbonylative coupling reaction to synthesize β-borylated tetrasubstituted enones from internal alkynes and alkyl halides by using a borylating reagent, B_2pin_2 to replace the hydrosilane reagent (Scheme 46).[78] The resulting borylated enones showed moderate stability on silica gel columns, and so they were typically reduced to the corresponding oxaborole by $NaBH_4$ reduction for purification. Primary, secondary and even tertiary alkyl halides all worked well to afford the products in moderate to good yields. For diaryl alkynes, SIMes was identified as the best NHC ligand, whereas for aryl, alkyl-disubstitued alkynes, ^{Me}IMes showed better performance. Notably, without purification, a *in-situ* formed β-boryl-tetrasubstituted enone could undergo Suzuki-Miyaura coupling reaction with an aryl halide to provide an all-carbon tetrasubstituted enone. Consistent with our previous hydrocarbonylative processes, a radical pathway for activation of alkyl halides was evidenced by the fact that the ring-opening product was exclusively produced when (iodomethyl)cyclopropane was used as the electrophile.

Recently, a Cu-catalyzed borocarbonylative coupling of unactivated alkenes with primary alkyl halides was reported by Wu and co-workers (Scheme 47).[79] This work provides an efficient way to synthesize β-boryl ketones. Interestingly, the use of Xantphos as an addition ligand with IPrCuCl catalyst was found to be crucial to obtain the products in good yield. According to mechanistic studies, the authors proposed that the Xantphos ligand promoted the formation of a copper(III) intermediate via a radical process.

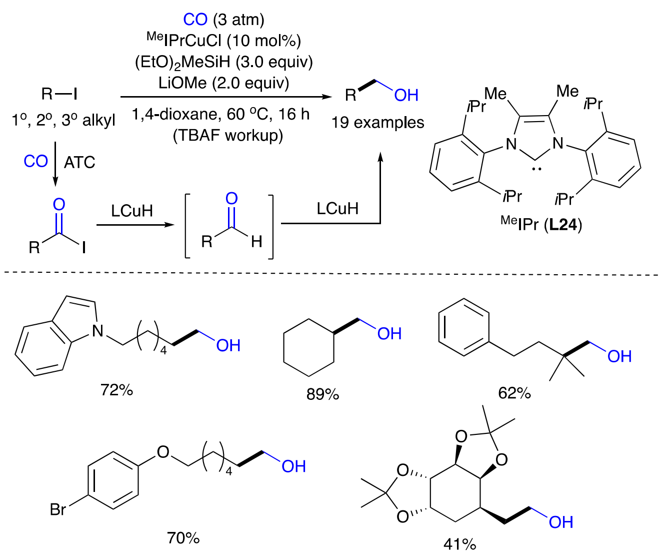


Scheme 46 Borylcarbonylative coupling of internal alkynes with alkyl halides.



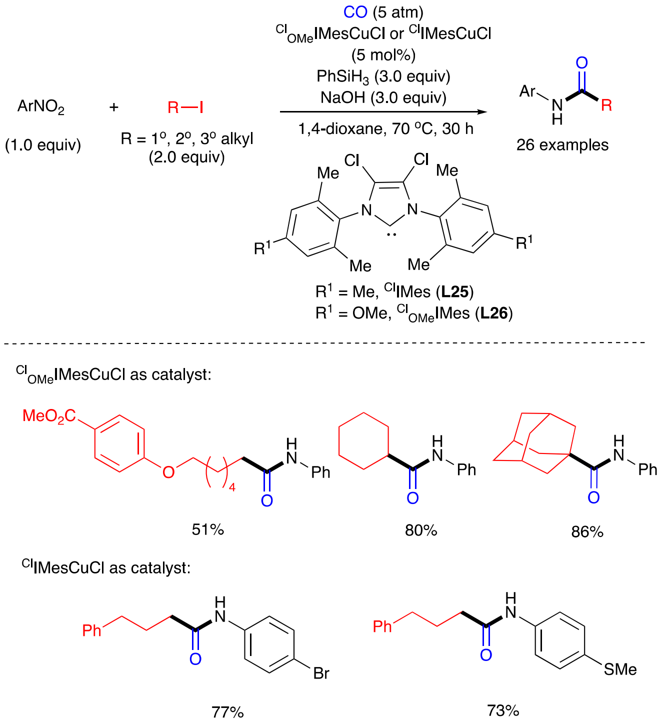
Scheme 47 Borylcarbonylative coupling of unactivated alkenes with alkyl halides.

Next, by omitting the alkyne partner, we found the alkyl halides underwent reductive carbonylation to provide one-carbon-extended alcohol products under similar Cu-catalysed conditions (Scheme 48).[80] Here the reaction was catalysed by ^{Me}IPrCuCl under 3 atm CO in the presence diethoxymethylsilane as reducing reagent and LiOMe as base. The mild reaction conditions tolerated a variety of functional groups. Primary, secondary, and tertiary alkyl iodides were all suitable substrates to afford the hydroxymethylated products in good yields. Mechanistic experiments indicated that the transformation started with atom transfer carbonylation (ATC) of the alkyl iodide to generate an acyl iodide as the key intermediate, which is similar to the mechanism we previously proposed for the tertiary alkyl halides in the hydrocarbonylative coupling reaction. Then the acyl iodide intermediate was reduced first to an aldehyde and then to an alcohol by tandem CuH-catalysed processes.



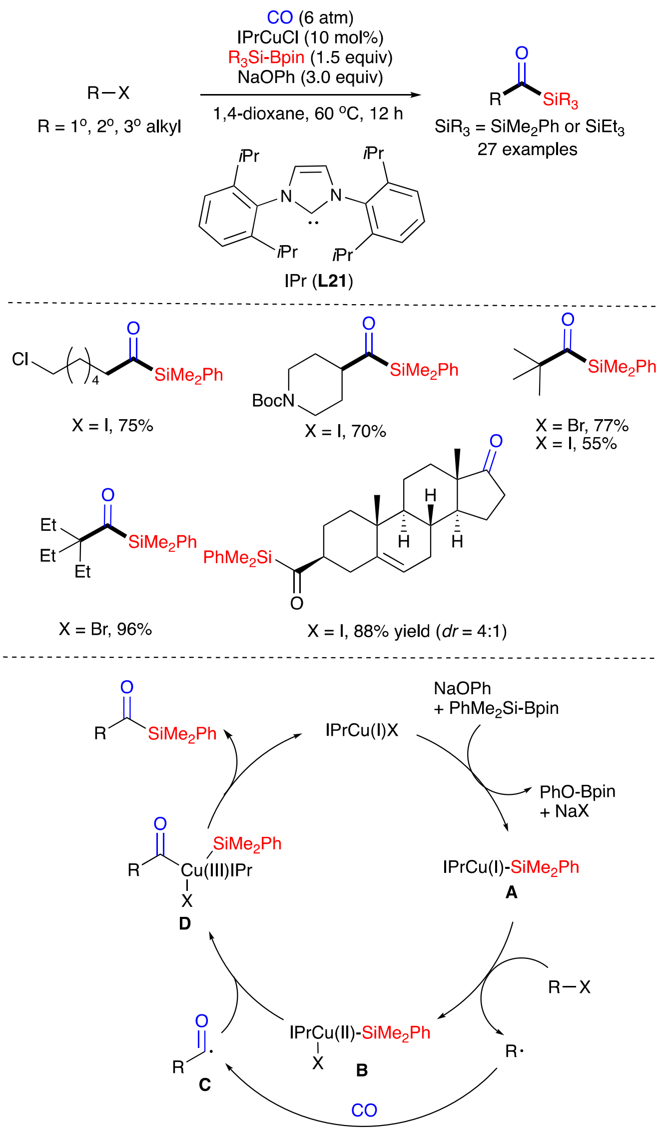
Scheme 48 Hydroxymethylation of unactivated alkyl iodides.

Under these reductive conditions, nitroarenes were found to serve as surrogates for anilines, thus acting as a nitrogen nucleophile in carbonylative C-N coupling reactions. This enabled our group to develop a Cu-catalysed reductive aminocarbonylation of alkyl iodides to produce amides using nitroarenes as the nitrogen source (Scheme 49).[81] The reaction was performed under 5 atm CO in the presence of $PhSiH_3$ as reductant and NaOH as base in 1,4-dioxane. The novel $^{Cl}{}_{OMe}$IMes (**L26**) was identified as the optimal ligand when nitrobenzene was used as substrate, whereas, for the reaction with substituted nitroarenes, ^{Cl}IMes (**L25**) performed better than $^{Cl}{}_{OMe}$IMes. This reaction has broad scope and high functional group compatibility, allowing the rapid synthesis amides in good yields. While the detailed mechanism is not clear, control experiments suggested that the copper catalyst played dual roles in this reaction: acting as catalyst in generation of acyl iodide from alkyl iodide, and reduction of the nitroarene to aniline. These above two intermediates then underwent a rapid, uncatalysed step to engage in the C-N bond coupling, leading to amide as final product.



Scheme 49 Reductive aminocarbonylation of alkyl iodides with nitroarenes.

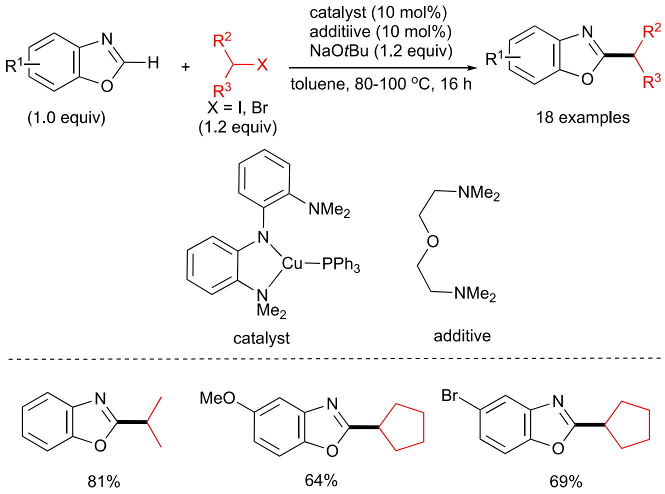
By employing a commercially available silylborane as silyl nucleophile source, our group recently developed a Cu-catalyzed carbonylative silylation of unactivated alkyl halides, providing a direct way to synthesize alkyl-substituted acylsilanes which are versatile synthetic building blocks but still challenging to be approached by other reported methods (Scheme 50).[82] Primary, secondary and tertiary alkyl halides were all suitable substrates to give the corresponding acylsilanes in good yields. Based on control experiments, we proposed that for both primary and tertiary electrophiles (which used different reaction pathways in carbonylative C-C coupling reaction) underwent the same radical initiation process with a silylcopper(I) intermediate. In addition, the similar reaction rates observed during competition experiments between primary, secondary, tertiary alkyl iodides indicated the carbon-halogen bond cleavage was not involved in the rate-determining step.



Scheme 50 Carbonylative silylation of alkyl halides.

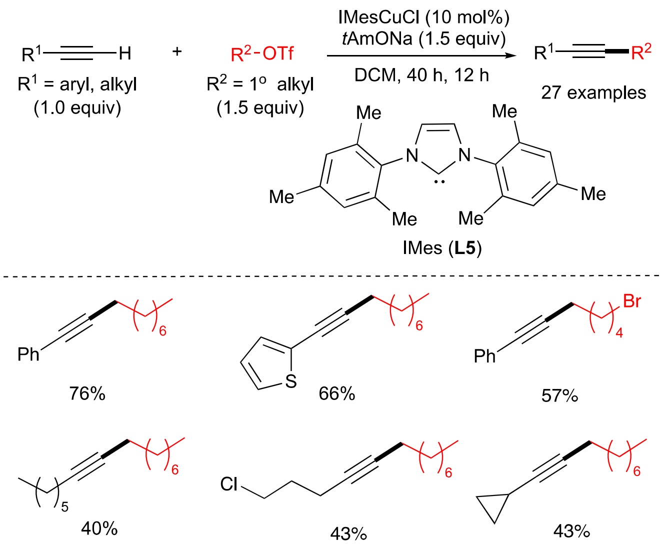
2.5 Alkylation of C-H bonds

As a convenient alternative to C-C coupling reactions, the direct alkylation of a C-H bond with alkyl electrophile represents a straightforward way for C-C bond formation. In 2012, the Hu group developed a copper-catalysed alkylation of benzoxazoles using unactivated secondary alkyl halides (Scheme 51).[83] A copper catalyst containing a pincer ligand and a triphenyl phosphine ligand was designed and found superior to other copper catalysts in the presence of bis[(2-(*N*,*N*-dimethylaminoethyl)]ether as an additive. The authors reasoned that the hemilabile property of the pincer ligand might contribute to the efficiency of the catalyst. Mechanistic studies supported that homogeneous Cu complexes were the active species and the alkylation reaction went through a radical mechanism.



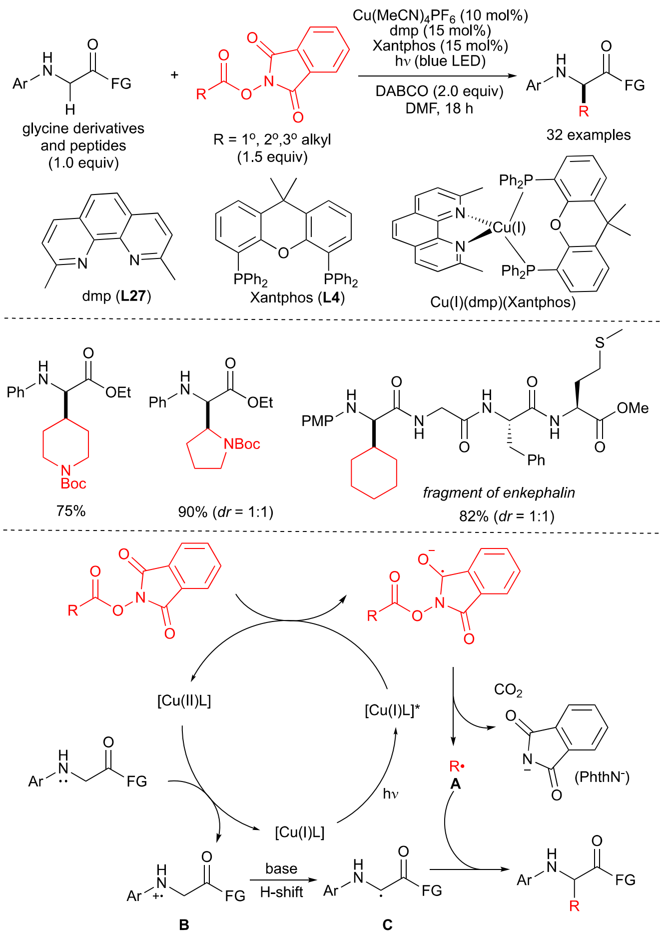
Scheme 51 C-H alkylation of benzoxazoles with secondary alkyl halides.

The copper-catalysed direct coupling of alkynes with alkyl electrophiles provides an attractive way to synthesize internal alkynes by avoiding use of palladium or nickel catalysts as in most Sonogashira conditions.[84] In 2016, Shi and co-workers reported a Cu-catalysed cross-coupling of alkyl halides and pseudohalides with terminal alkynes to provide internal alkynes using amides as directing groups.[85] Without using the directing groups, in 2017 the Bao group described a Cu-catalysed decarboxylative alkylation of terminal alkynes with alkyl diacyl peroxides as the alkyl source.[86] In the same year, Hu and co-workers developed a copper-catalysed alkylation of terminal alkynes with alkyl triflates (Scheme 52).[87] The use of a strong σ−donating NHC ligand (IMes) was crucial for the success of this transformation. They reasoned that the NHC ligand could increase the nucleophilicity of the key copper acetylide intermediate as well as prevent the formation of inactive polymeric copper acetylide species. Both aryl and alkyl terminal alkynes were suitable nucleophiles. However, the electrophiles were limited to primary alkyl substrates. The similar transformation was reported in 2018 by the Lalic group, who developed a photoinduced variant that enabled use of less reactive primary, secondary and tertiary alkyl iodides as electrophiles,[67] as described in section 2.3. The copper acetylide was proposed as the common active species in these catalytic cycles.



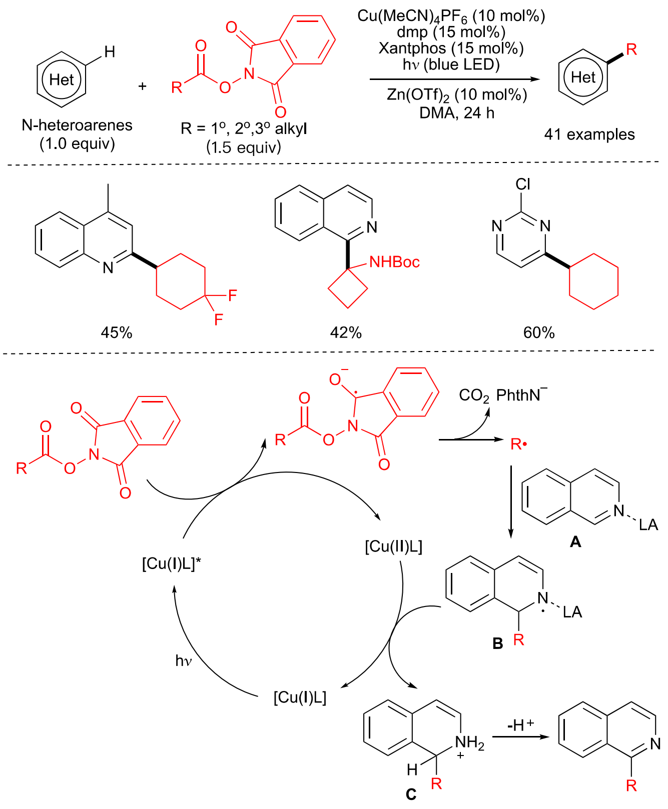
Scheme 52 Alkylation of terminal alkynes with alkyl triflates.

Compared with alkyl halides, alkyl carboxylic acids are less toxic and more abundant in nature. Thus, the alkyl *N*-hydroxyphthalimide (NHP) esters or their analogues derived from carboxylic acids have recently been intensively investigated as alkylation reagents in the radical couplings. The decarboxylative alkylation of C(sp^3)-H bonds with NHP esters provides a convenient alternative for C(sp^3)-C(sp^3) cross-coupling. In 2018, Wang and Xu developed the first example of visible-light-induced Cu-catalysed C(sp^3)-H alkylation of glycine and peptides by decarboxylation of alkyl NHP esters (Scheme 53).[88] This reaction provides an efficient way to prepare α-alkylated unnatural *α*-amino acids and alkylated peptides under mild reaction conditions. The reaction was catalysed by a Cu(dmp)(xantphos)BF_6 complex which was formed *in situ* from $Cu(MeCN)_4PF_6$ with dmp (**L27**) and xantphos (**L4**) ligands. Based on control experiments and literature precedents, the authors proposed a radical-radical cross-coupling mechanism. A single electron transfer between the excited state [Cu(I)L]* and the NHP esters was proposed to give alkyl radical **A** and a [Cu(II)L] complex. The [Cu(II)L] complex then oxidized the glycine derivatives to form radical cation intermediate **B**, which next was deprotonated and underwent a 1,2-H shift process to provide a stable α-carbon radical **C**. Finally, the radical–radical cross-coupling between **A** and **C** is thought to produce the alkyl-alkyl cross-coupling product.



Scheme 53 Decarboxylative C(sp^3)-H alkylation of glycine.

Using the same catalyst, Wang and co-workers developed a copper-catalysed C(sp^2)-H alkylation of *N*-heteroarenes by decarboxylation of alkyl *N*-hydroxyphthalimide esters in the presence of a Lewis acid under the blue LED irradiation (Scheme 54).[89] Various NHP esters bearing the primary, secondary and tertiary alkyl substituents reacted with isoquinoline, quinoline, pyridine, pyrimidine, quinazoline, phthalazine, phenanthridine, and pyridazine to give the alkylated heteroarenes in modest to excellent yields. Based on mechanistic studies, the authors proposed that the heteroarene was activated by a Lewis acid to form an electron-deficient complex **A**, which could be attacked by an alkyl radical generated from single electron transfer between the NHP ester and [Cu(I)L]*. Subsequently, the resulting complex **B** was oxidized by [Cu(II)L] to give the cationic intermediate **C** and regenerate [Cu(I)L]. Finally, dehydroaromatization of **C** would deliver the desired product.



Scheme 54 Decarboxylative C(sp^2)-H alkylation of N-heteroarenes.

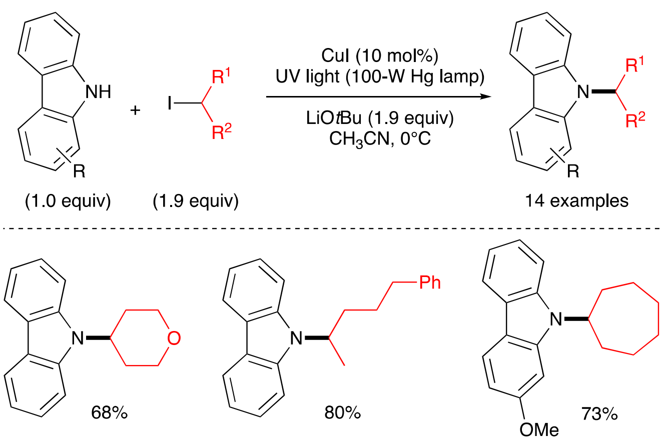
III. C-N bond formation

Formation of C(sp^3)-N bonds is readily achieved by the reaction of amines with alkyl halides, and this transformation has been a staple of organic synthesis for decades. However, due to the S$_N$2 mechanism of this transformation, high temperatures are required for hindered primary alkyl halides as well as secondary and tertiary derivatives. Transition metal catalysis could enable *N*-alkylation of amines under milder conditions. Most established catalytic methods for C-N bond formation, such as the Buchwald-Hartwig reaction and the Ullmann coupling, are compatible only with C(sp^2)-hybridized electrophiles. Thus, an opportunity exists for further catalyst development. In recent years, both thermal and photochemical Cu catalysis motifs have emerged as useful solutions for *N*-alkylation under mild conditions.

3.1 Photocatalytic *N*-alkylation reactions

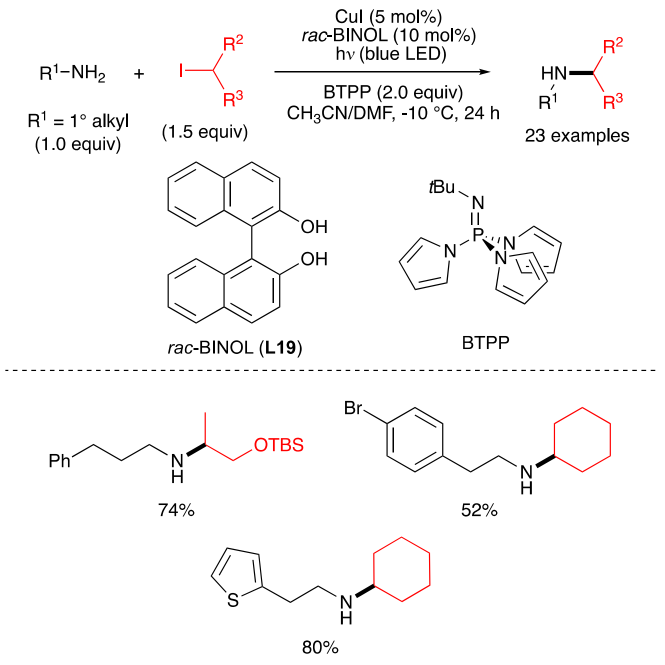
3.1.1 *N*-alkylation of amines

In 2012, Peters and Fu discovered evidence of carbazole *N*-alkylation during mechanistic studies of photocatalytic Ullmann coupling mediated by copper(I).[90] Full development of that transformation was subsequently reported in 2013,[91] representing the first general metal-catalysed method for amine *N*-alkylation (Scheme 55). A moderate number of carbazole derivatives were successfully *N*-alkylated using both cyclic and acyclic secondary alkyl iodides at 0°C under UV irradiation, using just CuI as the catalyst. Two examples with secondary alkyl bromides were also included, both requiring slightly higher temperatures (30°C). The cuprate species, Li[Cu(carbazolide)$_2$], was identified as forming under catalytic conditions and is thought to be the active catalyst in the absence of any ancillary ligands for copper. Further mechanistic studies were reported in 2017 and indicated the possible role of various [Cu(carbazolide)$_n$]$^{m-}$ catalytic intermediates.[92]



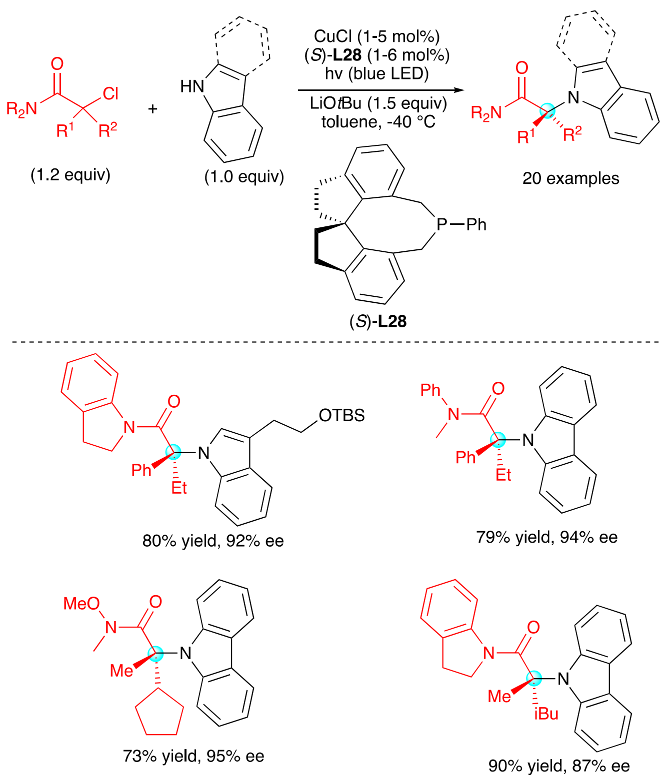
Scheme 55 Carbazole *N*-alkylation with secondary alkyl iodides.

The scope of this transformation was expanded to aliphatic primary amines in 2017 with the introduction of *rac*-BINOL ligand under blue LED irradiation in the presence of a special phosphazene base (Scheme 56).[93] Primary amines bearing various functionalized alkyl groups were successfully *N*-alkylated using cyclic and acyclic secondary alkyl iodides at -10°C. Due to the radical nature of this photocatalytic reaction evidenced by TEMPO inhibition, remote aryl-chloride and -bromide groups were compatible with the reaction conditions and did not undergo activation.

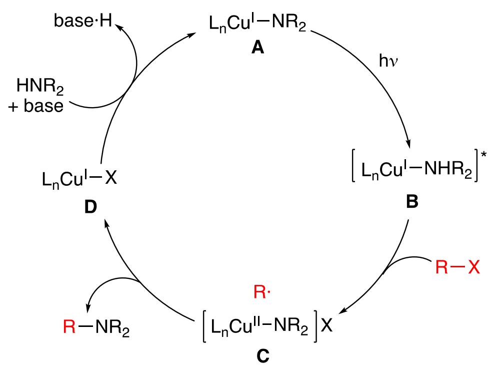


Scheme 56 *N*-alkylation of aliphatic amines with secondary alkyl iodides.

A key advance in photocatalytic *N*-alkylation of amines came in 2016, when Peters and Fu used the copper-catalysed technology described above to mediate enantioconvergent *N*-alkylation of amines with tertiary alkyl chlorides at -40°C using a chiral monodentate phosphine ligand ((*S*)-**L28**)(Scheme 57).[94] Racemic α-chloro carbonyl compounds derived from indolines and acyclic amides were used as the electrophilic partners, and a range of substituted carbazoles and indoles were used as the nucleophilic partners, giving rise to single enantiomers of the *N*-alkylated products with high yield and good enantioselectivity. A catalytically competent (phosphine)$_2$Cu(carbazolide) intermediate was identified during mechanistic studies.



Scheme 57 Enantioconvergent amine alkylation.

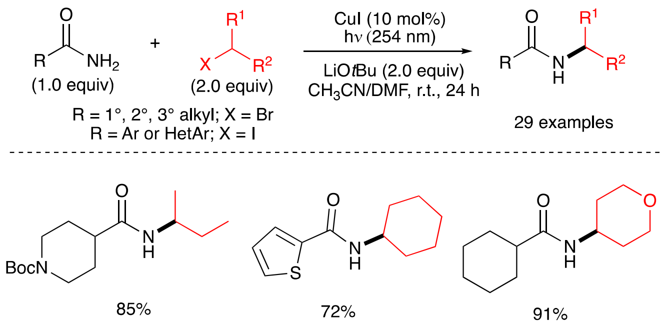


Scheme 58 General mechanism for photocatalytic *N*-alkylation of amines mediated by copper.

The general mechanism for the preceding transformations developed by Peters and Fu is shown in Scheme 58. Under basic conditions, the conjugate base of the amine nucleophile coordinates to copper(I) to generate active intermediate **A**, which takes different forms depending on the presence or absence of ancillary ligands. Photoexcitation produces excited-state intermediate **B**, which reacts with the alkyl halide electrophile to generate copper(II) intermediate **C** and an alkyl radical. A C(*sp*^{3})-N radical coupling step releases the final product and generates catalytic intermediate **D**, which undergoes base-mediated ligand substitution to regenerate **A**. The success of this mechanistic scheme is based on the MLCT character of the excitation of **A** and the copper(II)-aminyl radical character of intermediate **C**, both of which had been established by Peters previously.[95] In the case of the enantioconvergent variant described above, the two enantiomers of the alkyl chloride convert to the same alkyl radical intermediate, which then undergoes C(*sp*^{3})-N radical coupling in a stereocontrolled manner dictated by the chiral environment of bis(phosphine) derivative **C** to produce a single product stereoisomer.

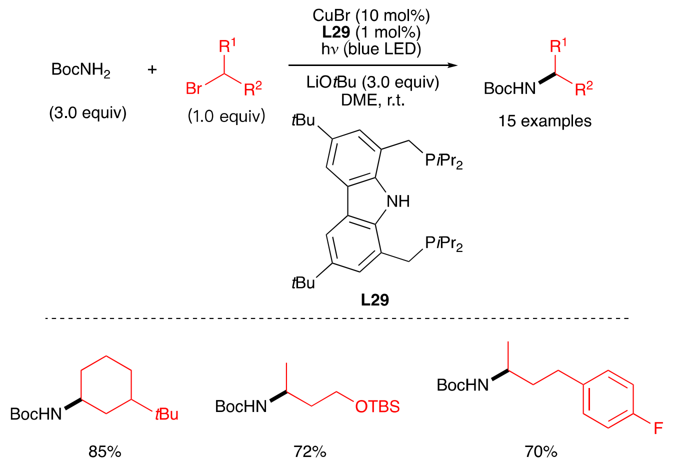
3.1.2 *N*-alkylation of amides, phthalimides, and carbamates

Although most of the reactions described above require highly conjugated nitrogen nucleophiles to facilitate efficient photoexcitation, the successful use of aliphatic amines in one case (Scheme 56) indicates that other nitrogen bases can be viable in the mechanistic manifold shown in Scheme 58. In fact, the first such evidence was reported in 2014, when Peters and Fu demonstrated room-temperature *N*-alkylation of primary amides under UV irradiation (Scheme 59).[96] Primary amides bearing primary, secondary, and tertiary alkyl groups were efficiently *N*-alkylated with cyclic and acyclic secondary alkyl bromides, while alkyl iodides were required to alkylate amides bearing aryl or heteroaryl substituents. A wide range of remote functional groups were tolerated. Furthermore, primary alkyl chlorides and bromides as well as one tertiary alkyl bromide also participated in the reaction. Simple CuI with no ancillary ligand was used as the catalyst in this case, and a tetracopper(I) species with bridging amidate ligands was identified as a catalytically competent intermediate serving the role of **A** in Scheme 58.



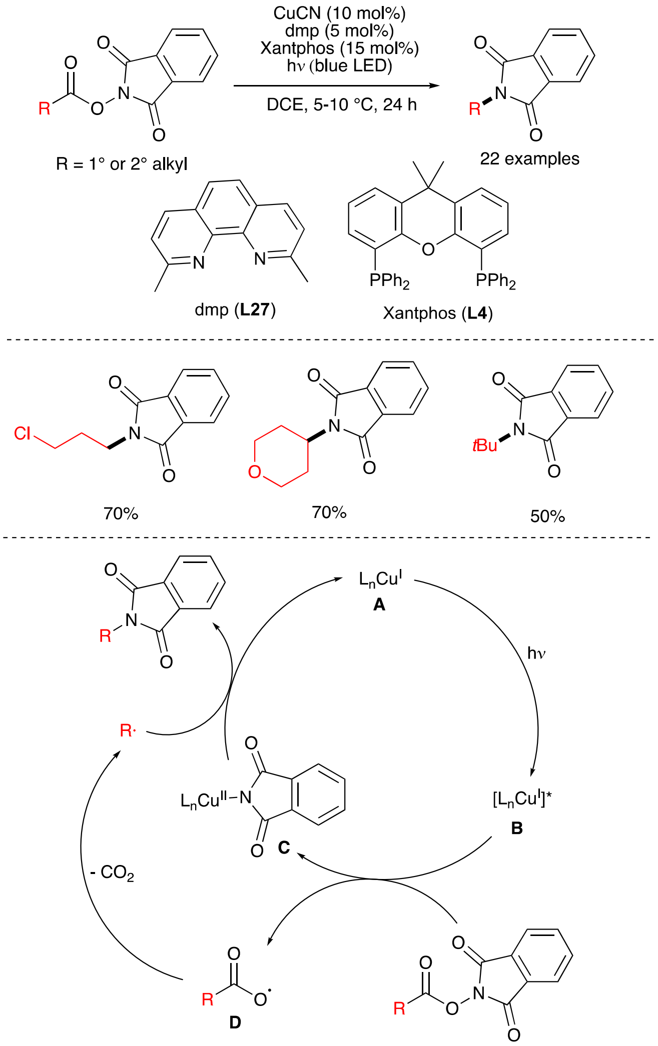
Scheme 59 *N*-alkylation of primary amides.

By using a pincer-type bis(phosphino)carbazolide ligand (**L29**), the scope of this transformation was expanded to primary carbamates (Scheme 60).[97] Various carbamates including BocNH$_2$ were *N*-alkylated with secondary alkyl bromides at room temperature under blue LED irradiation. Because carbamates are cleaved under orthogonal conditions to the copper-mediated photocatalysis, this method can be viewed as a convenient way to access Boc-protected primary amines from the corresponding bromides.



Scheme 60 Synthesis of Boc-protected primary amines by *N*-alkylation of primary carbamates.

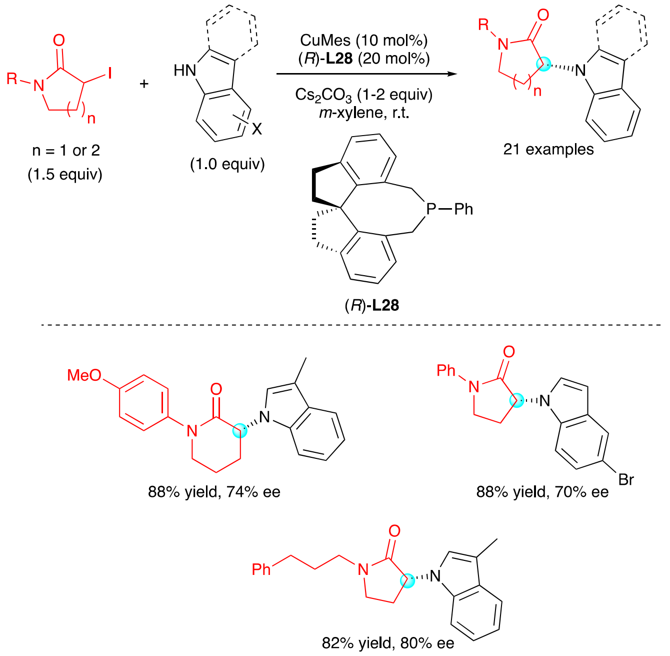
In 2017, analogous phthalimide-protected primary amine products were generated by Peters and Fu by photocatalytic decarboxylation of *N*-hydroxyphthalimide (NHP) esters derived from readily available aliphatic carboxylic acids (Scheme 61).[98] Efficient decarboxylation was observed at 5-10°C under blue LED irradiation in the presence of catalytic CuCN, neocuproine (dmp) (**L27**), and Xantphos (**L4**). Broad functional group tolerance was observed through a combination of substrate scope studies and additive tests. By allowing for direct conversion of a carboxylic acid derivative to a protected primary amine, this transformation can be viewed as an azide-free alternative to the classic Curtius rearrangement. Supported by mechanistic studies, a slightly different mechanistic manifold was proposed for this transformation compared to previous reactions: a photoexcited copper(I) catalyst (**B**) was proposed to oxidize the NHP ester, resulting in N-O cleavage to generate a copper(II) phthalimide intermediate **C** and a carboxyl radical **D**. Intermediate **D** rapidly decarboxylates[99] to generate an alkyl radical, which then undergoes radical C(sp^3)-phthalimide coupling with **C** to release product and regenerate catalyst **A**.



Scheme 61 Decarboxylation of *N*-hydroxyphthalimide esters as an azide-free alternative to the Curtius rearrangement.

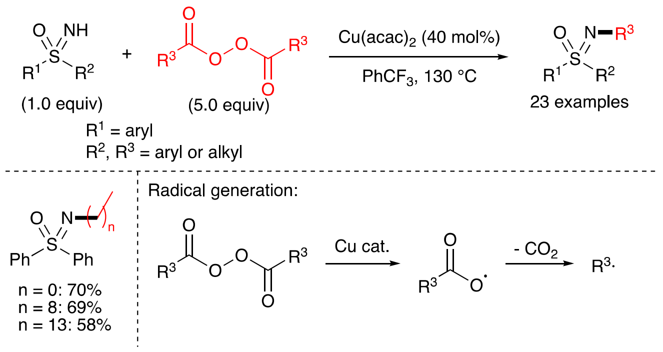
3.2 Thermal C(sp^3)-N coupling

The preceding examples of Cu-catalysed C(sp^3)-N bond formation relied on UV or visible light irradiation to access a reactive catalytic intermediate capable of alkyl halide activation. In 2019, Fu reported a thermal variant[100] of the enantioconvergent amine *N*-alkylation that had previously employed blue light excitation.[94] Use of CuMes as a catalyst in the presence of a chiral phosphine ligand ((*R*)-**L28**) enabled synthesis of enantiopure, *N*-alkylated indoles and carbazoles using racemic α-iodolactams at room temperature in the absence of photoexcitation (Scheme 62). The chiral phosphine employed in this study was the enantiomer of that used in the photocatalytic transformation above (Scheme 57). Excess amount of alkyl iodide was required, consistent with the mechanistic finding that thermal enantioconvergence in this case derives from kinetic resolution, i.e. that the copper catalyst reacts more rapidly with one alkyl iodide stereoisomer than the other. High yields and good enantioselectivities were obtained using a range of substituted indoles and carbazoles. The authors were unable to definitively distinguish between two thermal pathways involving a [(phosphine)$_2$Cu^I-NR$_2$] intermediate kin to **A** in Scheme 58: either stereochemistry-determining oxidative addition of the alkyl iodide (i.e. S$_N$2 by Cu^I) or stereochemistry-determining direct displacement of iodide (i.e. S$_N$2 by nitrogen). It is notable that, unlike the photochemical processes studied previously, this thermal reaction seems to employ a two-electron mechanism for alkyl halide activation rather than radical pathway.



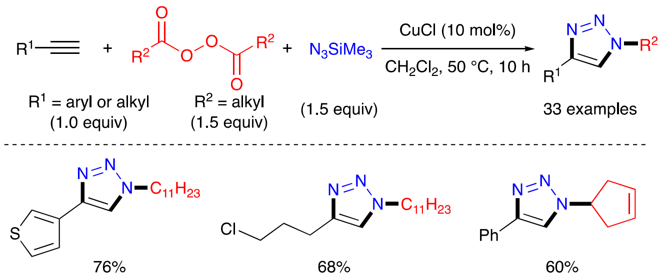
Scheme 62 Enantioconvergent coupling of amines with α-iodolactams under thermal conditions.

In 2016, Yu and coworkers reported *N*-alkylation and *N*-arylation reactions of sulfoximines with acyl peroxides.[101] A variety of reactive functional groups contained within the sulfoximine unit were tolerated, and transfer of simple *n*-alkyl groups as well as functionalized aryl groups was achieved (Scheme 63). The reaction was proposed to involve decarboxylation of acyl radicals to generate alkyl or aryl radicals, in a manner akin to the Cu-catalysed decarboxylative alkylation chemistry developed more broadly by the Bao group.[102]



Scheme 63 Decarboxylative alkylation of sulfoximines.`

Bao and coworkers reported in 2018 a copper-catalysed synthesis of 1,4-substituted 1,2,3-triazoles, also using acyl peroxides as the alkyl source.[103] The acyl peroxides were combined with azidotrimethylsilane and terminal alkynes to generate the triazole products via three-component coupling. A broad tolerance for different (hetero)aryl alkynes was observed, and both primary and secondary alkyl groups as well as aryl groups were transferred from the acyl peroxide reagents (Scheme 64). A tandem mechanism was proposed in which Cu-catalysed decarboxylative alkylation of azidotrimethylsilane provided azidoalkane intermediates, which then engaged in a second Cu-catalysed azide-alkyne cycloaddition reaction (CuAAC).



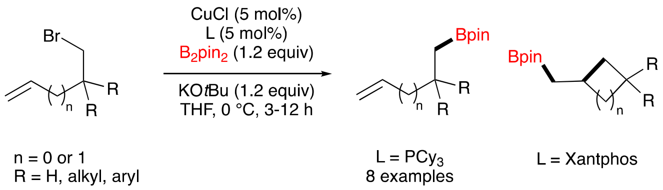
Scheme 64 Three-component coupling reaction to generate 1,4-substituted 1,2,3-triazoles.

IV. C-B bond formation

Alkylboronic acid derivatives are widely sought after as synthetic building blocks because of their participation as nucleophilic partners in versatile Suzuki-Miyaura cross-coupling reactions.[104] Compared to other organometallic nucleophiles such as organomagnesium and organozinc reagents, organoboron derivatives also offer advantages of benchtop purification and storage as well as broader tolerance of protic and electrophilic functional groups in complex molecule settings.[105] Alkylboronic acid derivatives are typically formed either by quenching alkyllithium reagents with boron electrophiles or by alkene hydroboration. Direct C(sp^3)-X borylation of alkyl electrophiles represents an attractive complementary strategy to those methods. Borylation of C(sp^2)-X electrophiles is commonly accomplished by Miyaura's Pd-catalysed conditions.[106] For C(sp^3)-hybridized analogues, copper has emerged among a range of other transition metal catalysts and metal-free conditions.[107]

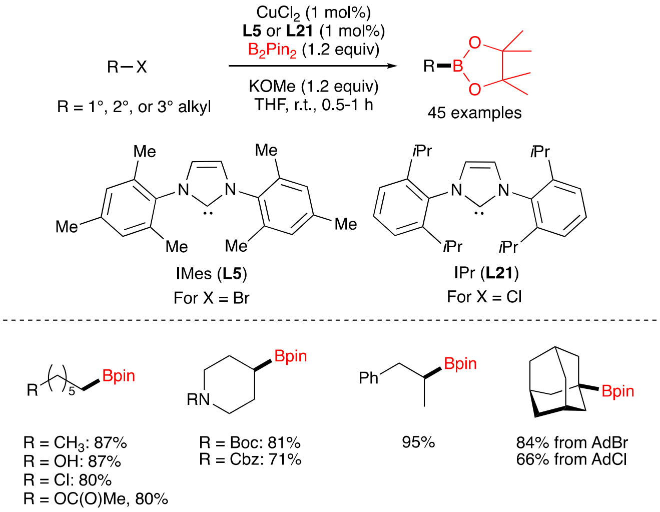
In 2012, Steel, Marder, and Liu reported that alkyl electrophiles could be borylated using B$_2$pin$_2$ in the presence of catalytic CuI (10 mol%) and PPh$_3$ at room temperature.[108] Primary alkyl iodides, bromides, chlorides, and tosylates as well as cyclic and acyclic secondary alkyl iodides and bromides underwent borylation. In the case of 6-chlorohexyl bromide, site-selective C(sp^3)-Br borylation was achieved by limiting the amount of B$_2$pin$_2$ reagent to 1.5 equivalents. A wide range of remote functional groups were tolerated. Even aryl bromide groups withstood the reactions conditions despite Cu-catalysed aryl halide borylation proceeding under similar conditions,[109] presumably due to the kinetically more rapid C(sp^3)-X activation by the copper(I) catalyst. Several mechanistic observations in this initial report pointed to a radical pathway for alkyl halide borylation: stereoretentive borylation of a bromonorbornane substrate, cyclization of a radical clock substrate, and formation of bibenzyl side products from benzyl halides. However, other observations contradicted the possibility of radical intermediates: addition of radical scavengers to the reaction medium did not impact the reaction rate, and primary alkyl tosylates were effective substrates. Lou and coworkers later employed very similar conditions to borylate alkyl halides with B_2npg_2 (npg = neopentyl glycolate).[110]

A contemporaneous study from Ito using xantphos in place of PPh_3 produced slightly higher catalytic activity with CuCl (3 mol%) under analogous conditions.[111] Once again, the intermediacy of radical intermediates was suggested by certain mechanistic observations and contradicted by others. In this study, another mechanistic possibility – base-mediated elimination of the alkyl electrophiles followed by copper-catalysed alkene hydroboration – was ruled out based on several experimental results: alkene hydroboration did not proceed under the optimized reaction conditions, base-mediated alkyl halide elimination was inhibited by the addition of B_2pin_2 through formation of a base-B_2pin_2 adduct, and secondary alkyl halides were borylated regiospecifically. Thus, while an elimination/hydroboration sequence has been ruled out definitively by Ito, the true mechanism for copper(I)-catalysed borylation of alkyl halides and sulfonates remains unclear and may involve multiple parallel pathways.



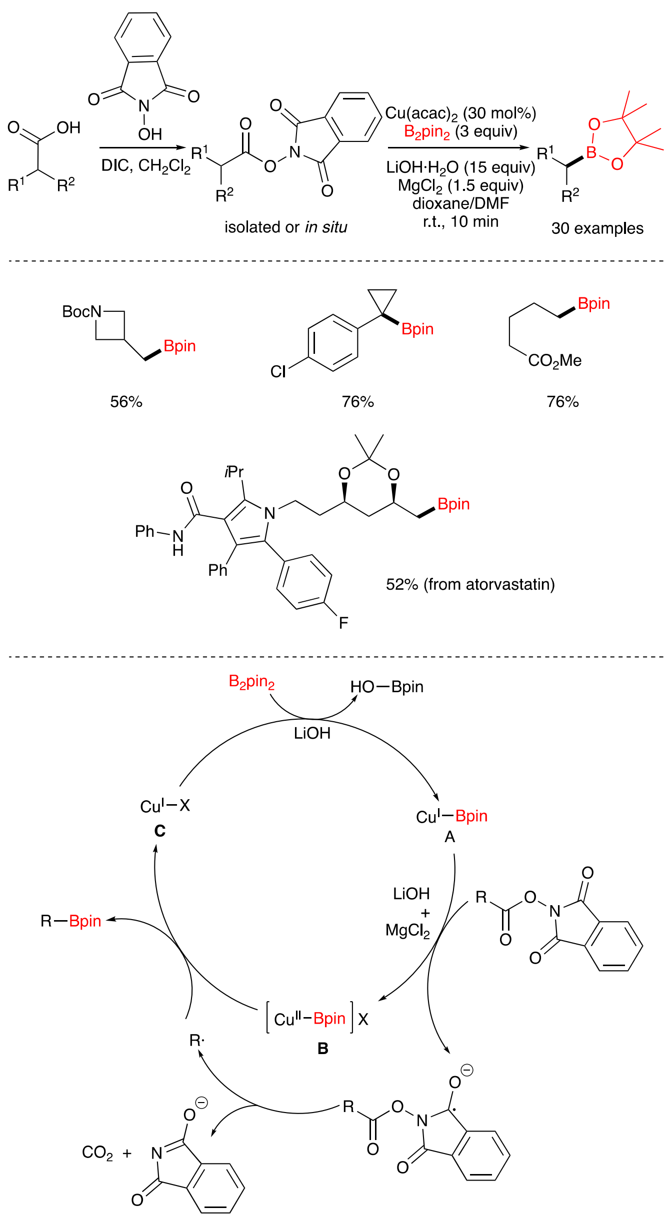
Scheme 65 Borylation vs. borylative cyclization under ligand control.

In 2015, Ito showed that for alkyl bromides bearing pendant α-olefin groups, C(sp^3)-Br borylation could be favoured over competing borylative cyclization using ligand control.[112] Whereas the xantphos ligand the same group used previously was found to initiate borylative cyclization selectively, use of PCy_3 as the ligand instead favoured direct C(sp^3)-Br borylation without reaction at the C-C double bond (Scheme 65). The authors proposed that selectivity was controlled by reactivity of the key LCuBpin intermediate, which could either substitute the bromide directly or could first add across the alkene before nucleophilically displacing the bromide. Optimization of the borylative cyclization reaction was also accomplished by the same group and is described above in section 2.2.3.



Scheme 66 Borylation of alkyl halides.

The best conditions reported to date for alkyl halide borylation were disclosed by Marder and coworkers in 2016, using catalytic $CuCl_2$ (1 mol%) with N-heterocyclic carbene ligands and requiring only ≤1 h reaction times at room temperature.[113] Primary, secondary, and tertiary alkyl chlorides and bromides were effectively borylated (Scheme 66). For secondary alkyl halides, both cyclic and acyclic variants as well as alkyl iodide derivatives underwent the reaction successfully. Mechanistic observations strongly suggested a reaction pathway involving radical intermediates: alkyl tosylates were unreactive, radical clock substrates cyclized, and the radical scavengers 9,10-dihydroanthracene and TEMPO inhibited the reaction. However, it is unclear whether the active catalyst is a borylcopper(II) species, or if *in-situ* reduction instead provides copper(I) akin to the active species in previous reports. Related conditions were used by Yoshida to generate R-B(dan) products (dan = 1,8-diaminonaphthalene) using pinB-Bdan in place of B_2pin_2.[114]

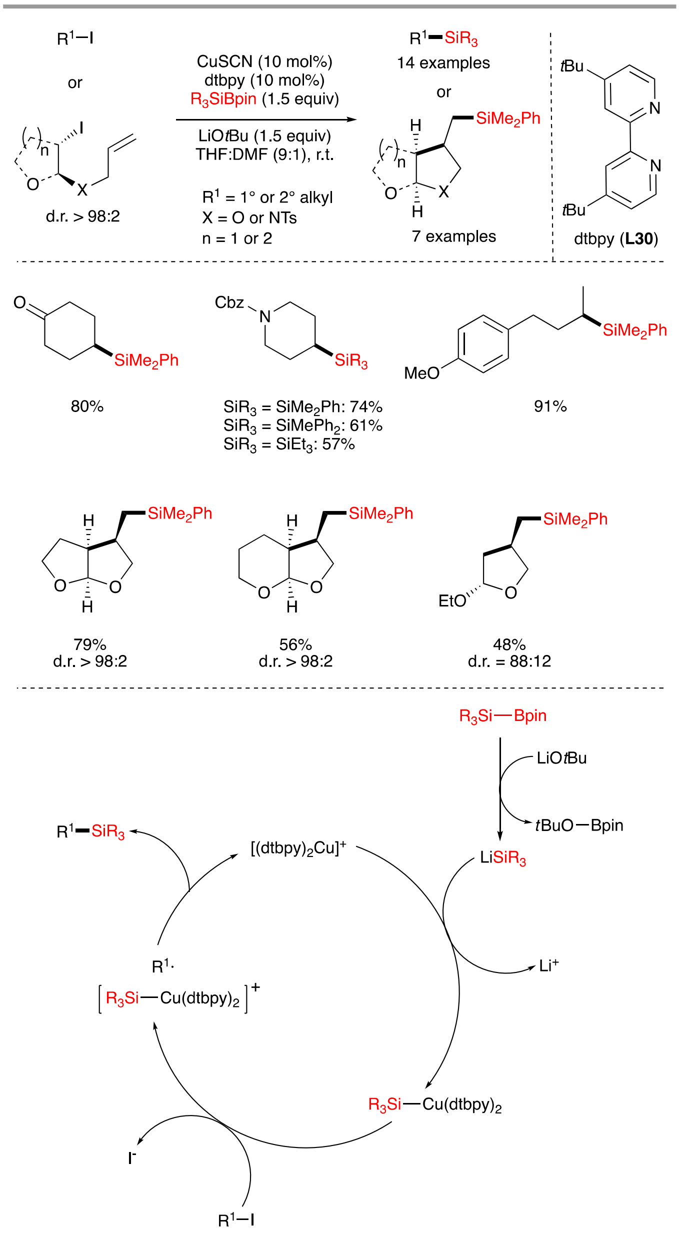


Scheme 67 Decarboxylative boryation of redox-active esters.

In 2018, Blackmond and Baran reported a decarboxylative transformation to form alkylboronic ester derivatives from redox-active NHP esters derived from carboxylic acids feedstocks.[115,116] Borylation proceeded both with isolated samples of the NHP esters as well as using a protocol where carboxylic acids were esterified *in situ* and then borylated in the same pot (Scheme 67). The reaction was remarkably efficient, proceeding to completion in <10 minutes without requiring inert atmosphere conditions. Moreover, a very broad range of substrates was tolerated, including variants with pharmaceutically relevant core structures. A radical mechanism was proposed on the basis of mechanistic probes and kinetics measurements. A borylcopper(I) intermediate **A** was proposed to reduce the redox active ester, producing borylcopper(II) intermediate **B** and an alkyl radical. A radical C(sp^3)-B coupling step was then proposed to form product and generate a copper(I) intermediate **C** capable of reacting with B$_2$pin$_2$ to reform **A**.

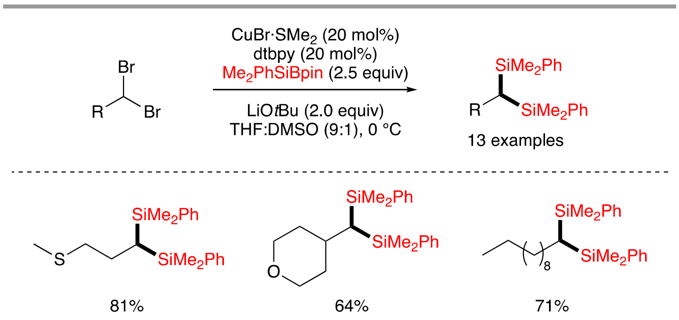
V. C-Si bond formation

Formation of C(sp^3)-Si bonds via copper catalysis can often be achieved under analogous conditions to C-B coupling reactions by substituting B$_2$pin$_2$ for commercially available Me$_2$PhSi-Bpin or related silicon pronucleophiles.[117] In 1984, Oshima and co-workers reported the first example of a copper-catalyzed C(sp^3)-Si bond formation by treatment of dodecyl tosylate or dodecyl bromide with a silylmagnesium reagent during their mechanistic studies on the cyclization of acetylenes.[118] However, the corresponding alkylsilanes products were formed in very low yields. Thereafter, it was not until 2016 when Oestreich and coworkers discovered a synthetically useful Cu-catalysed silylation of primary alkyl triflates with Me$_2$PhSi-Bpin.[119] However, this method still has limitations: secondary alkyl triflates underwent elimination rather than silylation, and alkyl halides performed poorly as substrates. Later in the same year, improved conditions were reported for silylation of alkyl iodides that were compatible with cyclic and acyclic secondary derivatives in addition to primary ones (Scheme 68).[120] 1-Iodoadamantane also underwent efficient silylation, but other tertiary substrates performed poorly. For alkyl iodide substrates bearing pendant α-olefin groups, C(sp^3)-Si coupling occurred in conjunction with 5-exo-trig cyclization, yielding silylated heterocycle products with controlled diastereospecificity. The observation of radical-type cyclization behaviour combined with computational studies led to a proposed radical mechanism for C(sp^3)-Si bond formation. A key point in the proposal is the off-cycle formation of silyl anions from the reaction of R$_3$Si-Bpin reagents with the alkoxide base, providing a reactive LiSiR$_3$ species capable of rapid transmetallation to Cu(I).



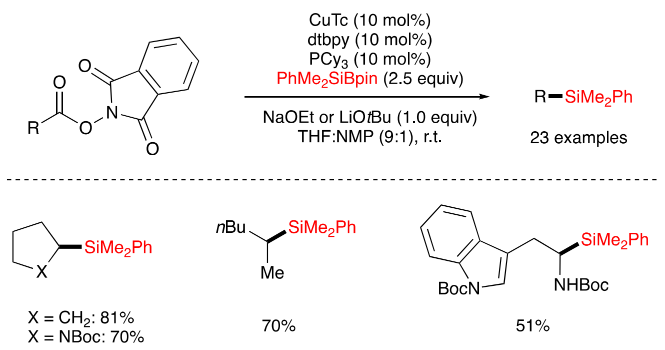
Scheme 68 Silylation of alkyl iodides.

Subsequent studies employed analogous conditions for silylation of activated alkyl electrophiles[121] and for the double silylation of geminal dibromoalkanes (Scheme 69).[122] In the latter transformation, the first C(sp^3)-Si coupling event was proposed to go by an ionic mechanism, followed by a radical pathway mediating the second C(sp^3)-Si bond formation.



Scheme 69 Double silylation of *gem*-dibromoalkanes.

Given the SET pathways invoked for Cu-catalysed C(sp^3)-Si coupling, the methodology is readily translated to decarboxylative reactions of redox-active carboxylic acid derivatives that are prone to reduction by electron-rich copper(I) catalysts. In 2017, the Oestreich group reported decarboxylative silylation of NHP esters in the absence of photoactivation (Scheme 70).[123] Interestingly, both dtbpy and PCy_3 were required for efficient reactivity. Under the optimized conditions, a range of primary, secondary, and tertiary carboxylic acid derivatives underwent silylation to provide alkylsilane products. Radical clock experiments, racemization experiments, and radical trapping experiments all confirmed the presence of alkyl radical intermediates.

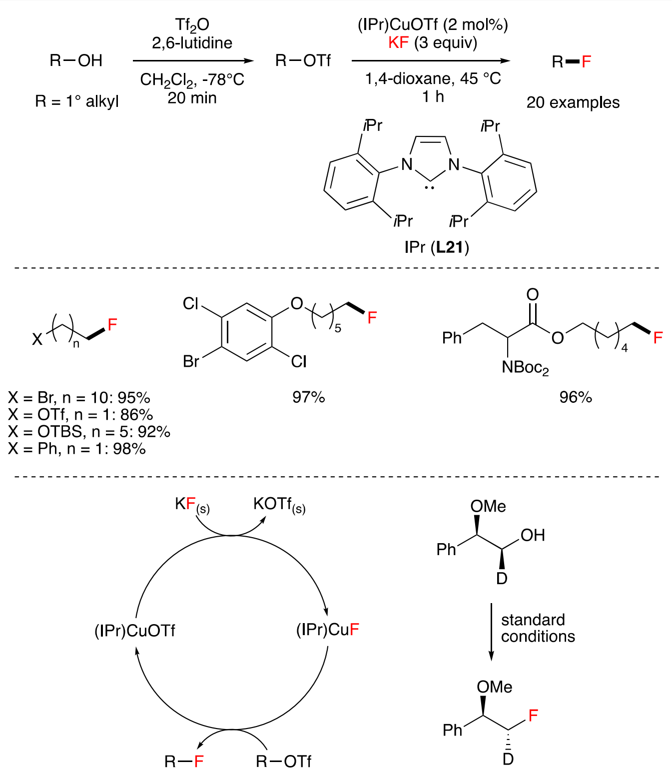


Scheme 70 Decarboxylative silylation of redox-active esters.

VI. C-F and C-CF_3 bond formation

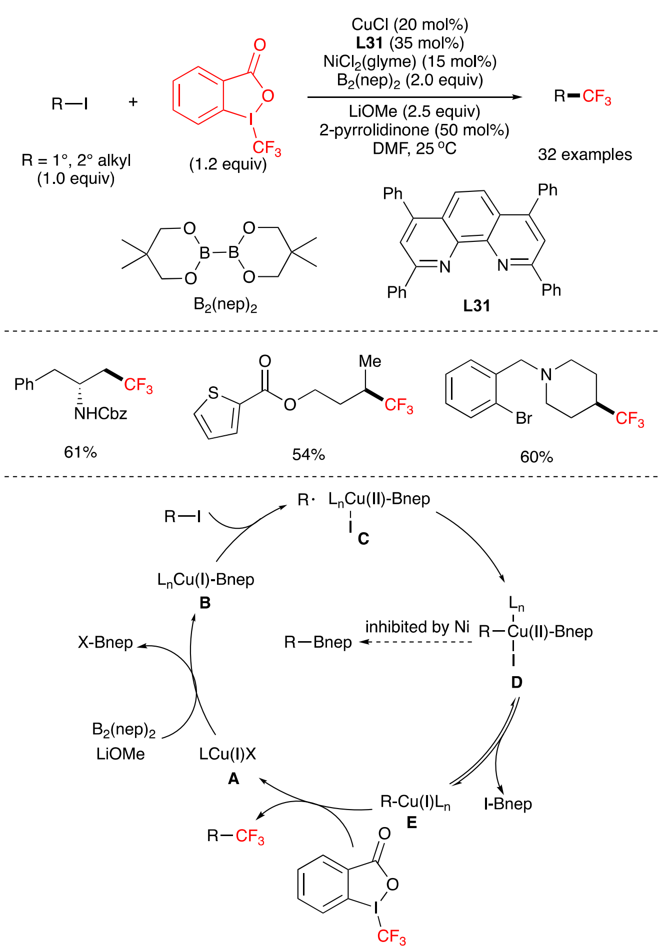
Alkyl fluorides are generally formed by nucleophilic substitution of alkyl electrophiles with fluoride sources. However, harsh conditions are sometimes required due to the poor nucleophilicity of fluoride under benchtop conditions, especially in unreactive cases such as tertiary, secondary, or hindered primary electrophiles. Moreover, the poor solubility of standard fluoride salts such as KF in organic solvents requires use of additives for phase transfer of fluoride from an aqueous phase into organic media. Development of catalytic methods for C(sp^3)-F formation thus provides an opportunity for enabling substitution under mild conditions, especially if the catalyst also plays the role of solubilizing fluoride catalytically. Particularly efficient catalytic methods also have potential applications for synthesis of fluorine-based PET probes.

In 2014, Lalic developed a Cu-catalysed method for the fluorination of alkyl triflates with KF in 1,4-dioxane solution at 45°C (Scheme 71).[124] The alkyl triflate substrates are easily obtained from alcohols using Tf_2O, and as-purchased KF was found to be more effective than dry KF. A variety of primary alkyl triflates were successfully fluorinated, and the mildly basic reaction conditions tolerated sensitive functional groups including aryl halides, nitroarenes, nitriles, alkyl bromides, and alkyl tosylates. One example of a secondary alkyl electrophile was also included, albeit in an activated case. A mechanism in which the copper catalyst serves to mediate both phase transfer and C(sp^3)-F coupling was supported by stoichiometric reactivity experiments. Radical intermediates were ruled out by the fact the reaction proceeded with clean inversion of stereochemistry.



Scheme 71 Fluorination of alkyl triflates.

Copper-catalysed C(sp^3)–CF_3 bond formation[125] also results in the introduction of fluorine into organic molecules and will be discussed here instead of in the C-C bond formation section. In 2017, the Li group described the trifluoromethylation of primary and secondary alkyl halides using (bpy)Cu(CF_3)$_3$ as a stoichiometric reagent.[126] Later, in 2018, the MacMillan group developed a decarboxylative trifluoromethylation of alkyl carboxylic acids with Togni's reagent I by combining photoredox and copper catalysis.[127] Thereafter, Gong and co-workers realised the first Cu-catalyzed/Ni-promoted reductive trifluoromethylation of alkyl iodides with Togni's reagent II (Scheme 72).[128] This reaction was conducted at room temperature in the presence of CuCl/**L31** as the catalyst, $NiCl_2$ · glyme as the promoter, and $B_2(nep)_2$ as the terminal reductant. Primary and secondary alkyl iodides bearing a variety of functional groups proceeded well to give the corresponding trifluoromethylation products in good yields. Control experiments demonstrated that the use of Ni was crucial to inhibit competing alkyl borylation. Based on mechanistic studies, the authors proposed a radical pathway for generation of the $L_nCu^{III}(R)(I)[B(nep)]$ intermediate (**D**) from the $L_nCu(I)$-B(nep) (**B**) and alkyl iodide. The elimination of I-B(nep) from **D** gives L_nCu^IR species (**E**), which react with Togni's reagent to afford the final product and regenerate the copper catalyst **A**.



Scheme 72 Trifluoromethylation of alkyl iodides.

Conclusions

As illustrated in this review, Cu-catalysed cross-coupling reactions of unactivated alkyl electrophiles have enabled diverse transformation in forming C-C, C-N, C-B, C-Si and C-F bonds. The judicious choice of ligands and additives in C-C coupling with organometallic reagents allows using challenging sterically hindered alkyl substrates and less reactive alkyl chlorides, and even alkyl fluorides. With phosphines or *N*-heterocyclic carbenes (NHCs) as ligands, Cu-H and Cu-B(OR)$_2$ species can be generated as intermediates to engage in hydroalkylation and alkylboration of C-C π-bonds as well as direct borylation of alkyl electrophiles. By using CO as a C1 building block, carbonylative C-C coupling of alkyl halides with various nucleophiles provides efficient ways to synthesize valuable carbonyl compounds or alcohols as products via a radical carbonylation paradigm. In addition, photoinduced C-C and C-N bond formations have also been successfully approached under the mild reaction conditions. Furthermore, with or without light irradiation, the development of Cu-catalysed decarboxylation of alkyl N-hydroxyphthalimide esters renders the more abundant and less toxic carboxylic acids as viable alkyl sources.

All of these achievements demonstrate the usefulness of copper catalysts in the coupling of unactivated alkyl electrophiles. However, in spite of the impressive advances in the field, several areas still need further development. (1) Most reactions have been performed to give racemic products, while enantioselective coupling reactions are still rare and challenging. For example, in section 2.2, although enantioselective intramolecular hydroalkylation and alkylboration have been realized, the intermolecular variant is restricted to only methyl iodide. (2) Compared to Cu-B(OR)$_2$ and Cu-H intermediates, the addition of Cu-SiR$_3$ intermediates to C-C π-bonds has not yet been reported in C-C coupling with unactivated alkyl electrophiles. (3) The catalyst loadings are relatively high (5-10 mol%) in most cases; therefore, targeting catalytic system with higher efficiency is worthy of further effort for possible industrial applications. Nevertheless, the work so far has set a solid foundation in this area. We hope this review will stimulate more chemists to exploit new and efficient Cu-catalyzed methodologies in the future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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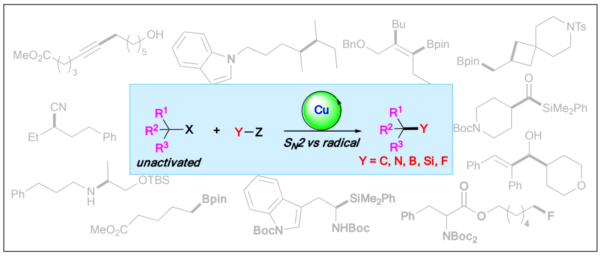

Copper catalysts enable cross-coupling reactions of unactivated alkyl electrophiles to generate C-C and C-X bonds.