11

COPPER-CATALYZED ALKYNYLATION, ALKENYLATION, AND ALLYLATION REACTIONS OF ARYL DERIVATIVES

Ren-Jie Song and Jin-Heng Li

11.1 INTRODUCTION

As with other copper-mediated transformations, the copper-mediated alkynylation and alkenylation reactions of aromatic derivatives have seen tremendous progress in recent years, notably due to the introduction of a variety of simple organic ligands that allowed a significant softening of the reaction conditions. Reliable and robust procedures for the synthesis of alkynyl-, alkenyl-, and allyl-substituted aromatics have recently emerged and constitute remarkably efficient synthetic tools. This chapter will cover the most general copper-catalyzed syntheses of arylalkynes and arylalkenes by Stille-, Sonogashira-, and Suzuki–Miyaura-type cross-coupling reactions, as well as key recent developments in the copper-mediated allylation of aryl derivatives. In addition, recent advances in copper-mediated C–H bond activation and decarboxylation reactions for the synthesis of arylalkynes and arylalkenes will be presented.

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11.2 COPPER-CATALYZED ALKYNYLATION OF ARYL DERIVATIVES

Alkynes are most useful building blocks in organic synthesis as well as basic functional groups that are found in many natural products and bioactive compounds.[1] The Stille reaction, the Sonogashira reaction, and the direct functionalization of C–H bonds represent most powerful and straightforward methods for the construction of arylalkynes, and they have been extensively studied. In addition, these methods have been also widely used for the synthesis of natural products, biologically active molecules, and materials. They have been recently found to be conveniently catalyzed by copper salts. Key and representative advances in this area will be overviewed in this subchapter, in which examples have been classified according to the nature of the coupling partners, starting with organotin reagents.

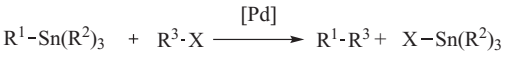
11.2.1 Synthesis of Aryl–Ynes by Stille-Type Cross-Coupling Reaction

The transition-metal-catalyzed cross coupling of organotin compounds with electrophiles, namely, the Stille cross-coupling reaction first reported by John Kenneth Stille and David Milstein in 1977, has emerged as an extremely powerful tool for carbon–carbon bond formation (Scheme 11.1). This palladium-catalyzed cross-coupling reaction is usually performed under an inert gas atmosphere, using dried and degassed solvent, because oxygen can cause the oxidation of the palladium catalyst and promote homocoupling of stannylated derivatives. These side reactions often lead to a decrease in the yield of the desired cross-coupling product.[2]

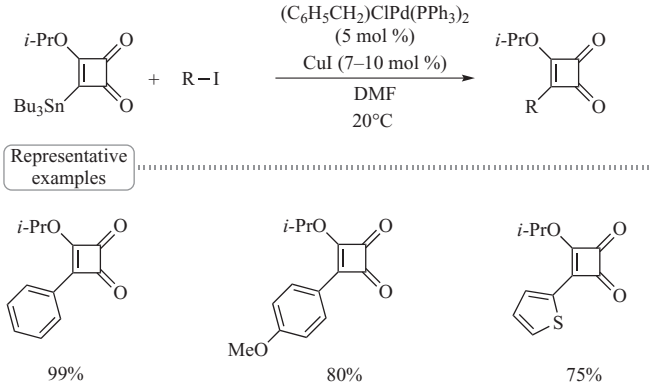
In 1990, Liebeskind and coworkers found that the use of a copper(I) cocatalyst could dramatically enhance the reaction rate of a palladium-catalyzed Stille cross coupling (Scheme 11.2).[3] The practical utility of the "copper effect" was immediately recognized, and the underlying mechanisms have triggered intense research efforts (see Chapter 18, Section 18.4.4 for a more detailed discussion).[2b]

In a remarkable report published in 1997, Kang and coworkers demonstrated that the Stille coupling could be catalyzed by a catalytic amount of copper(I) iodide (10 mol %) in the presence of stoichiometric sodium chloride without palladium catalysts at all (Scheme 11.3).[4]

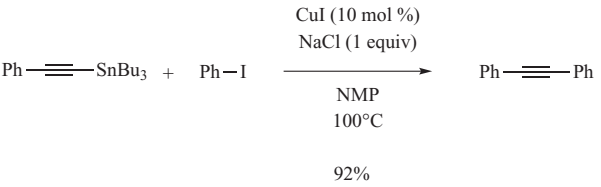
These conditions were later on extended to the Stille-type alkynylation of a polymer-bound aryl iodide with stannylated alkyne, affording the



Scheme 11.1 Palladium-catalyzed Stille reaction.



Scheme 11.2 Copper cocatalyzed Stille cross coupling of stannylcyclobutenedione with aryl iodides.

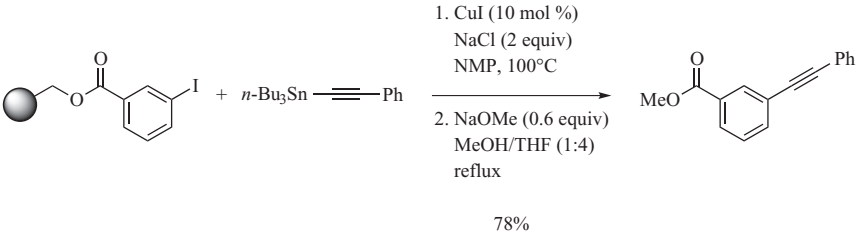


Scheme 11.3 Early example of copper-catalyzed cross coupling of alkynyltin derivatives with aryl iodides.

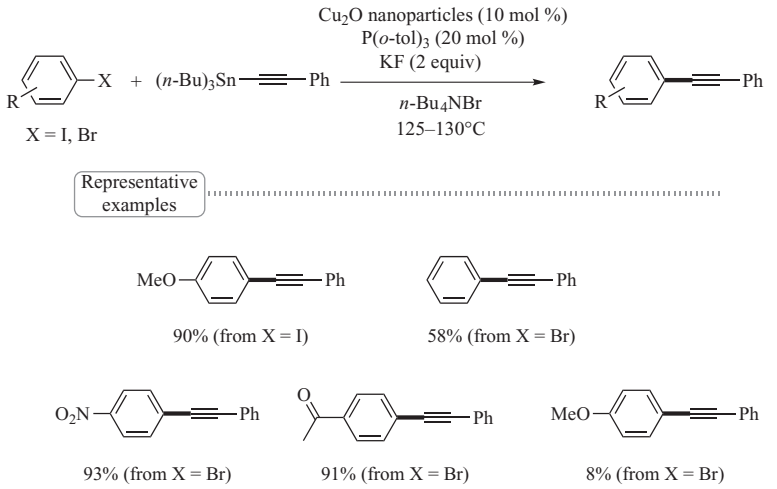
corresponding arylalkyne in 78% yield after cleavage from the resin by transesterification (Scheme 11.4).[5]

The scope of aryl halides that can be used in this copper-catalyzed Stille cross coupling was extended in 2006 by Li and coworkers (Scheme 11.5):[6] aryl bromides could undergo the Stille reaction using a catalytic amount of copper(I) oxide nanoparticles combined with tri-*o*-tolylphosphine as the ligand (20 mol %), although good yields were obtained only from activated aryl bromides. It is noteworthy that the $Cu_2O/P(o\text{-tol})_3/n\text{-}Bu_4NBr$ catalytic system can be recovered and reused at least three times without any loss of catalytic activity (see Chapter 20 for an overview of reusable catalytic systems).

The polarity of the reagents can be reversed and 1-iodoalkynes were shown to undergo the cross-coupling reactions with arylorganotin reagents in the presence of copper(I) iodide (10 mol %) in dimethylformamide (DMF) at room temperature for 6 hours. The desired conjugated arylated alkynes were obtained in good yields provided that the 1-iodoalkynes were slowly added to the reaction mixture containing the aryl- and heteroaryl tin derivatives. (Scheme 11.6).[7] Although the scope with respect to the alkynyl halides is quite limited, this report provided a novel and alternative route to internal aromatic alkynes.



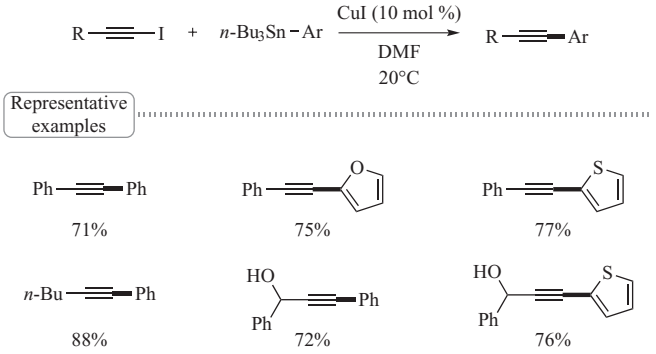
Scheme 11.4 Copper(I) iodide-catalyzed cross coupling of polymer-bounded aryl iodide with an ethynylstannane.



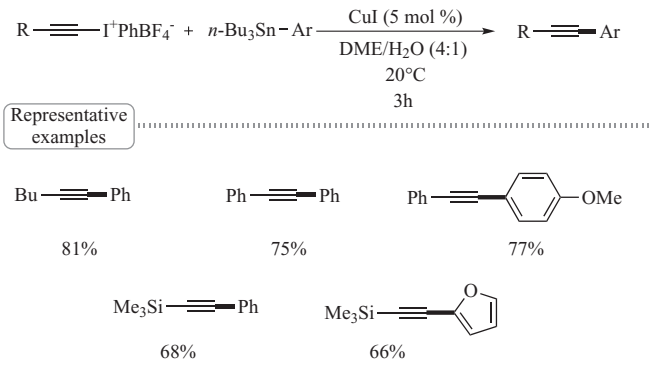
Scheme 11.5 Cu_2O nanoparticle-catalyzed Stille cross couplings of aryl halides with alkynyltin derivatives in *n*-Bu_4NBr.

In addition, highly active electrophiles such as alkynyliodonium tetrafluoroborates, which, however, have to be synthesized, were also found to be excellent reaction partners for the copper-catalyzed Stille cross coupling with aryl- and heteroaryltin derivatives in aqueous 1,2-dimethoxyethane (DME) under mild conditions (room temperature, 3 hours) (Scheme 11.7).[8] As a note, arylboronic acids were also found to be efficient reaction partners in this cross coupling under similar reaction conditions.

The major inherent drawback associated with the use of the Stille cross coupling and related reactions such as the ones described in this section are the use of organotin reagents and the generation of highly toxic waste. The development of other copper-mediated processes involving other reagents has been also recently developed and represents a useful alternative. Recent developments in the copper-catalyzed Sonogashira-type cross coupling involving aryl halides will be described in the following paragraphs.



Scheme 11.6 Copper-catalyzed cross coupling between 1-iodoalkynes and aryltin reagents.

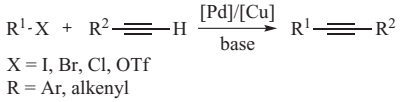


Scheme 11.7 Copper-catalyzed Stille cross coupling of alkynyliodonium tetrafluoroborates with aryltin reagents.

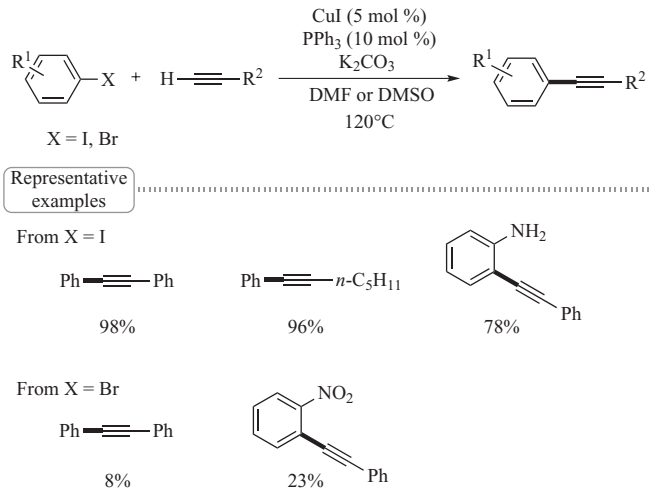
11.2.2 Synthesis of Aryl–Ynes by Sonogashira-Type Cross-Coupling Reaction

The Sonogashira coupling is the reaction of terminal alkynes with organohalides leading to new substituted alkynes. This reaction was first reported by Kenkichi Sonogashira and coworkers in 1975 (Scheme 11.8).[9] Since then, the Sonogashira coupling has been a central tool for the straightforward synthesis of biologically and/or synthetically important alkynes. Generally, this reaction utilizes a palladium complex (at the 0 or +2 oxidation state) and a copper(I) halide (often copper(I) iodide) as the catalytic system, which is problematic for industrial use due to the evolution of the price of palladium (see Chapter 19, Fig. 19.2). These limitations have elicited intense research efforts, including the use of copper(I) alone as the catalyst for the cross-coupling reactions of aryl halides and terminal alkynes.

In comparison with the common palladium-catalyzed coupling reactions, which are sensitive toward oxygen or moisture, the copper-mediated



Scheme 11.8 The Sonogashira-type cross-coupling reaction.

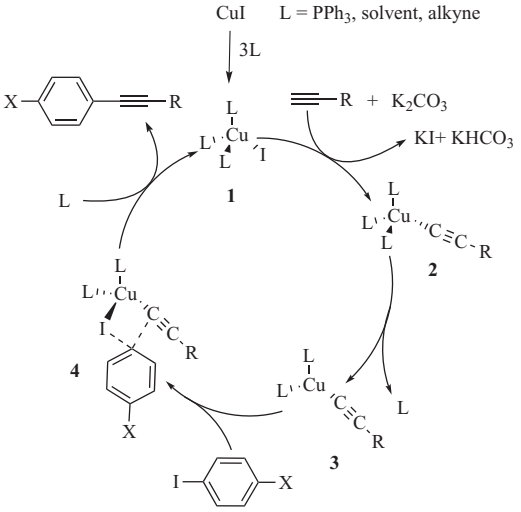


Scheme 11.9 Copper-catalyzed Sonogashira-type reaction of aryl halides with terminal alkynes.

Sonogashira-type alkynylation reaction can be conducted with satisfactory yields under aerobic conditions to produce the desired alkynes, provided that the nature and/or the stoichiometry of the ligand is appropriate.

In 1992, Miura and coworkers found that aryl iodides smoothly reacted with terminal alkynes and a catalytic amount of copper(I) iodide using potassium carbonate as the base and triphenylphosphine, giving the corresponding coupled products in good yields without the need of an additional palladium catalyst (Scheme 11.9).[10] This protocol represents the first truly copper-catalyzed Sonogashira alkynylation reaction. The scope and limitations of the copper-catalyzed Sonogashira-type reactions including the stereochemistry of the reaction were thoroughly investigated, and it was notably found that vinyl halides were also suitable substrates, while aryl bromides gave poor yields. Other copper catalysts, such as copper(I) bromide, copper(I) chloride, or copper(II) acetate were also effective, but copper(I) oxide was ineffective.[11]

The 1992 reaction mechanism of the copper-catalyzed Sonogashira alkynylation reaction proposed by Miura is shown in Scheme 11.10, where ligand **L** may be a neutral ligand (e.g., triphenylphosphine), the solvent, and/or the alkyne.[11a] In the first step, the terminal alkyne is deprotonated by potassium carbonate in the presence of copper(I) iodide, thereby generating the liganded copper acetylide **2** and then the coordinatively unsaturated copper acetylide **3**.



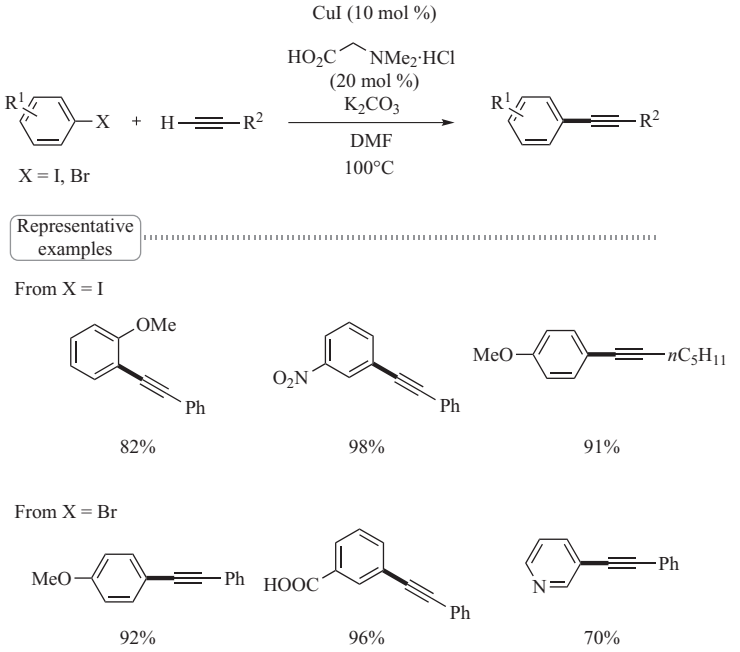
Scheme 11.10 The 1992 reaction mechanism of the copper-catalyzed Sonogashira alkynylation reaction or aryl iodides (see also Scheme 11.22).

Upon reaction of the latter with the aryl iodide partner, a four-centered transition state **4** might be operative by analogy with the Castro–Stephens reaction.[11b] A final ligand exchange would then regenerate the active copper(I) catalyst. However, recent mechanistic investigations by Bolm demonstrated that a different transition state should be considered, as discussed in Scheme 11.22.

While Miura used phosphine ligands to promote the reaction, Ma and Liu developed a palladium- and phosphine-free reaction condition for the Sonogashira-type alkynylation, in which copper(I) iodide (10 mol %) and *N*,*N*-dimethylglycine hydrochloride (30 mol %) was used as the catalytic system.[12] The 3/1 ratio between ligand and copper(I) was necessary to limit the homocoupling of alkyne. The functional group tolerance of this transformation is particularly noteworthy, and as the ligand is water-soluble, workup of this copper-catalyzed cross coupling is very simple and straightforward (Scheme 11.11). Overall, it is one of the most useful copper-catalyzed Sonogashira-type cross coupling for the synthesis of aromatic alkynes.

Pyrimidines could also be used as ligands for the copper-catalyzed Sonogashira-type alkynylation reaction. Indeed, Li and coworkers have reported that a catalytic system comprising 2-amino-4,6-dimethoxypyrimidine (20 mol %) and copper(II) acetate (10 mol %) was particularly effective in promoting the cross coupling between aryl iodides and terminal alkynes under solvent-free and aerobic conditions (Scheme 11.12).[13] Aryl bromides were less-reactive partners in the reaction, although the yields could be improved when 1 equiv of tetrabutylammonium bromide (TBAB) was added to the catalytic system.

Subsequently, Li and coworkers found that 1,4-diazabicyclo[2.2.2]octane (DABCO) was also an efficient ligand for the Sonogashira-type alkynylation

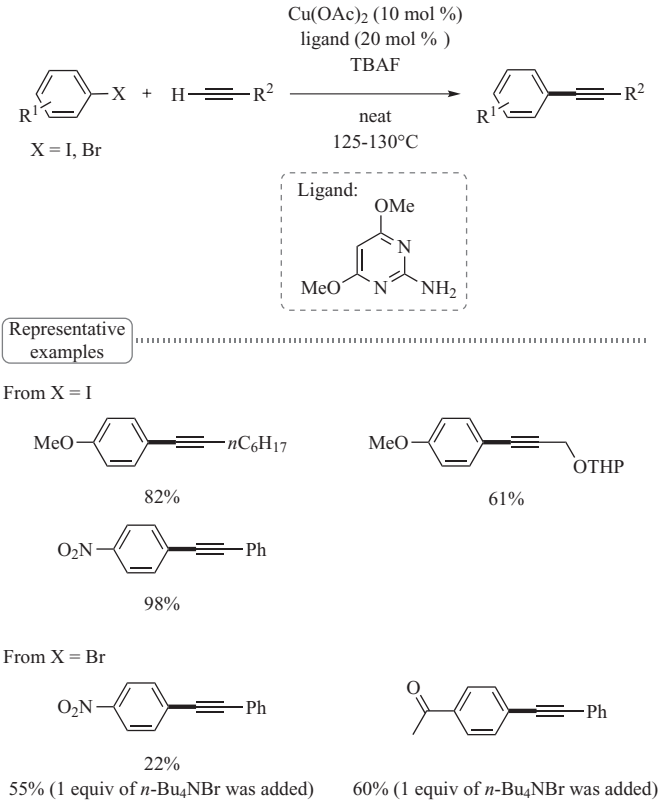


Scheme 11.11 Sonogashira-type alkynylation in the presence of copper(I) iodide and *N*,*N*-dimethylglycine hydrochloride.

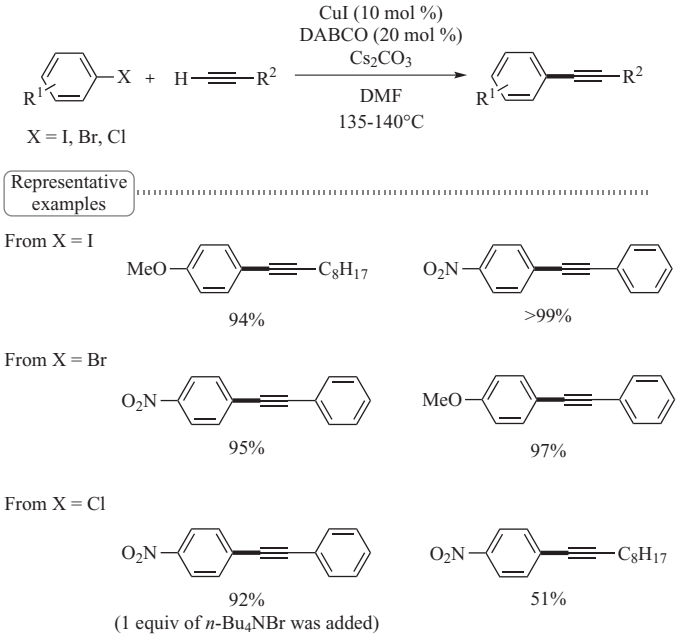
reaction using copper catalysts (Scheme 11.13).[14] Interestingly, the scope was extended to less activated aryl chlorides.

Capitalizing on the well-known *ortho*-effect in copper-mediated transformations, Zhao and coworkers have developed an efficient copper-catalyzed Sonogashira alkynylation method using *o*-iodoacetanilide derivatives and alkynes at room temperature, affording the corresponding arylated alkynes in good-to-excellent yields (Scheme 11.14).[15] The high catalyst and ligand loadings (30 and 100 mol %, respectively) were required to prevent cyclization to the corresponding indole. Overall, it should be noted that this inexpensive CuI/*N*-methylpyrrolidine-2-carboxamide catalyst system shows excellent functional group compatibility.

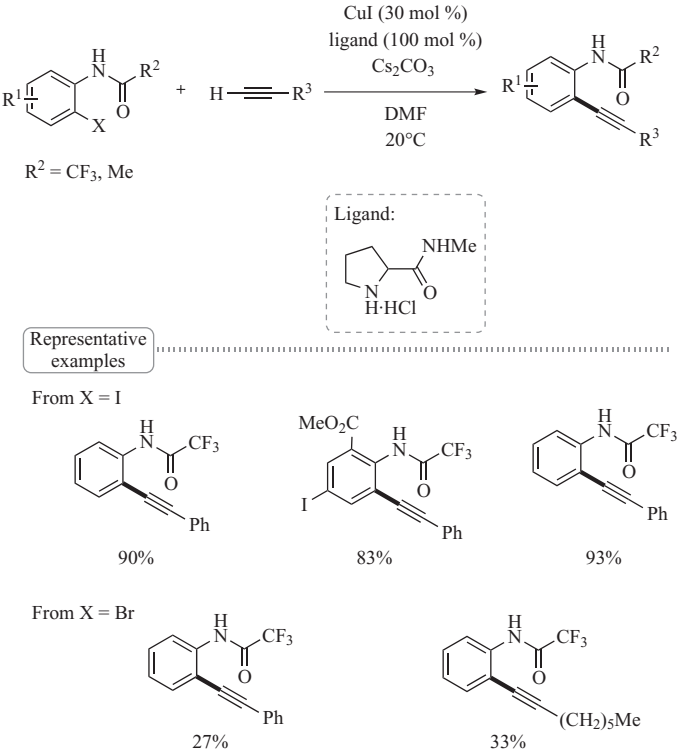
Recently, a number of ligands were discovered to promote the copper-catalyzed Sonogashira alkynylation reaction. For example, Mao and coworkers reported a copper-catalyzed cross coupling of aryl halides and heteroaryl halides with phenylacetylene in DMF at 110–130°C that afforded the corresponding alkyne products in satisfactory-to-good yields when 8-hydroxyquinoline was used a ligand (Scheme 11.15).[16] Copper(I) iodide (10 mol %) and 8-hydroxyquinoline (20 mol %) generated *in situ* a bifunctional catalyst that is very efficient at promoting this carbon–carbon bond formation. It is worth noting that tetrabutylammomium bromide could greatly improve the yields of the reaction when using aryl chlorides. Mao and



Scheme 11.12 Copper(II)-catalyzed Sonogashira cross-coupling reaction using pyrimidine as a ligand.



Scheme 11.13 DABCO as an efficient ligand for the copper-catalyzed Sonogashira-type alkynylation reaction.



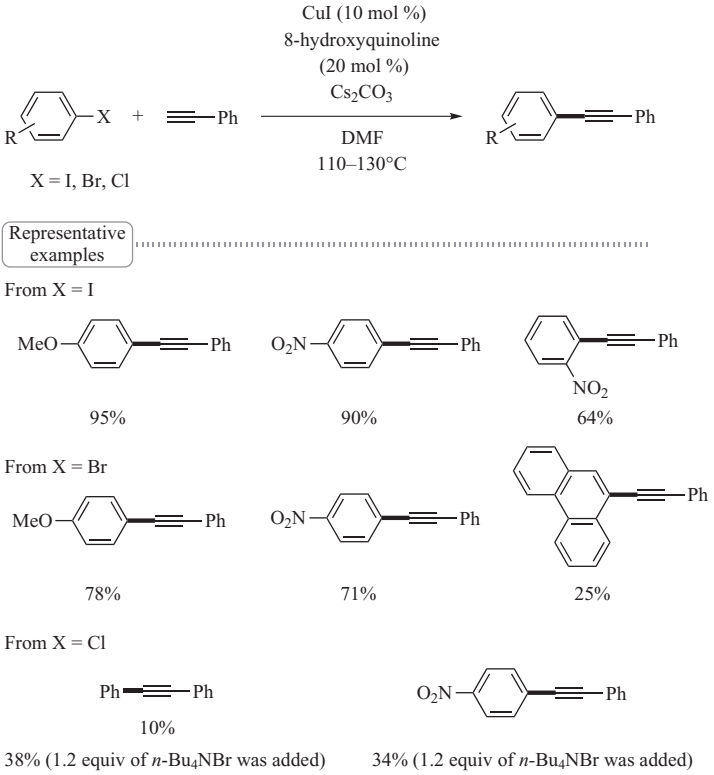
Scheme 11.14 Copper(I)-catalyzed Sonogashira alkynylation using an amino carboxamide as the ligand.

coworkers also employed racemic 1,1′-bi(2-naphthol) (BINOL) as a ligand to improve the copper(I) bromide-catalyzed Sonogashira-type alkynylation reaction.[17] However, the yields were generally lower.

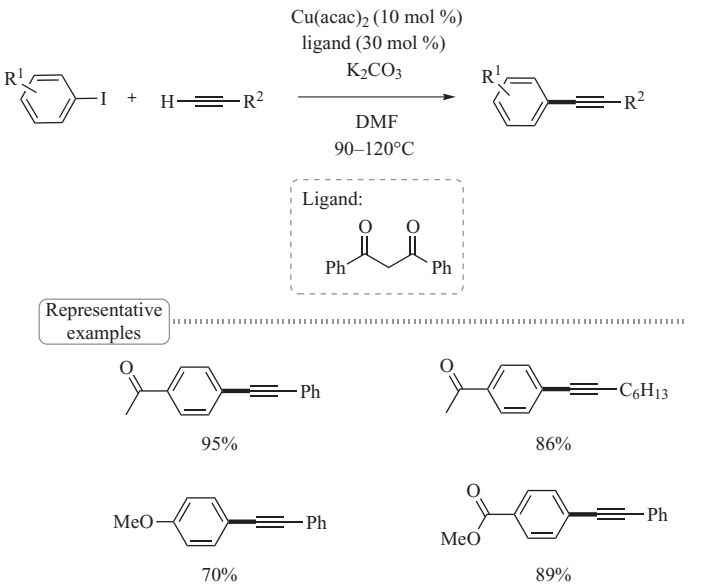
Taillefer and coworkers also reported a mild and efficient catalysis of the Sonogashira-type alkynylation reactions using copper(II) acetylacetonate (10 mol %) and 1,3-diphenyl-1,3-propanedione (30 mol %) as the catalyst (Scheme 11.16).[18] This method, which is among the most general ones, was applicable to the coupling of a wide range of substituted aryl iodides with either alkyl- or aryl-substituted terminal alkynes.

Sekar and coworkers demonstrated that 1,1′-binaphtyl-2,2′-diamine (BINAM) ligands were quite effective at promoting the copper(I) catalyzed Sonogashira alkynylation reactions between aryl halides and terminal alkynes under rather harsh reaction conditions (Scheme 11.17).[19] Notably, aryl bromides could also react with terminal alkynes leading to the corresponding arylated alkynes.

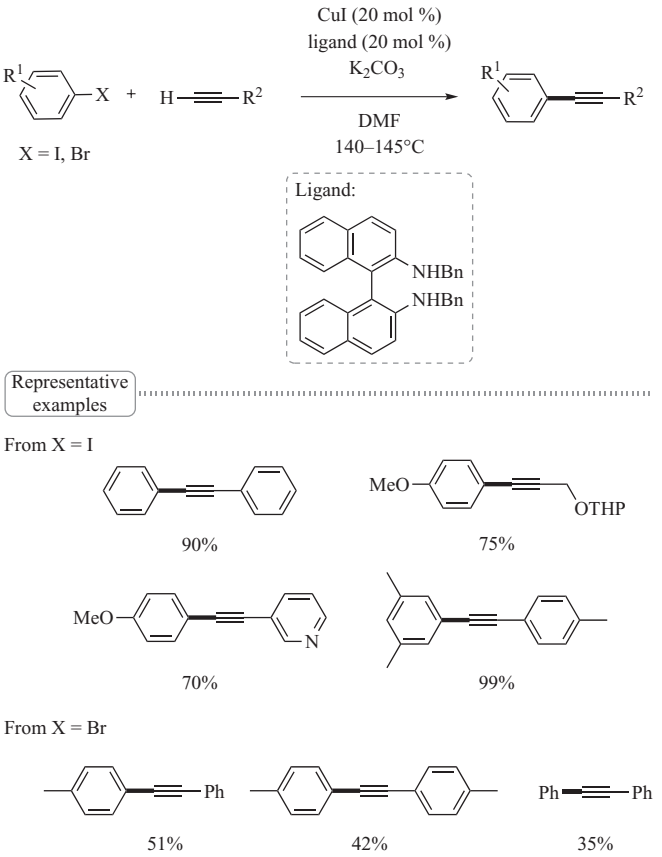
The same group disclosed a second efficient catalytic system consisting of copper(I) bromide (20 mol %) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 20 mol %) as a ligand, under quite harsh conditions, since the reaction was performed in DMF at 140°C (Scheme 11.18).[20]



Scheme 11.15 Copper(I)-catalyzed Sonogashira alkynylation using 8-hydroxyquinoline as the ligand.



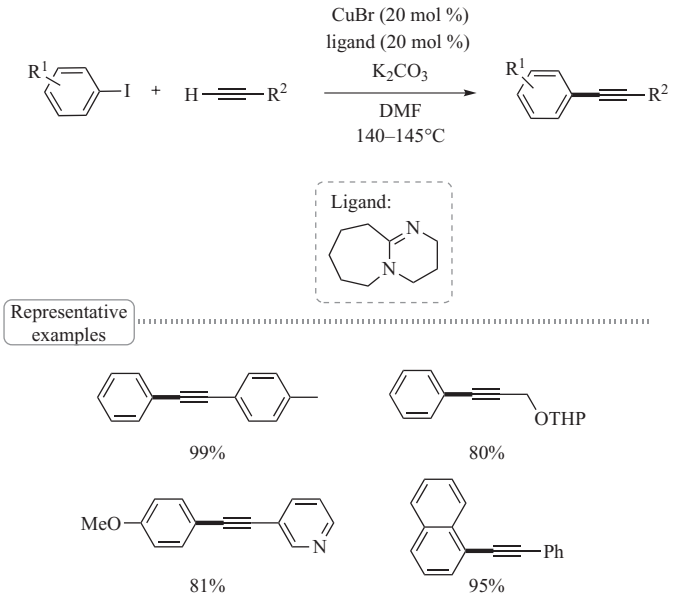
Scheme 11.16 Copper(II)-catalyzed Sonogashira alkynylation using 1,3-diphenyl-1,3-propanedione as the ligand.



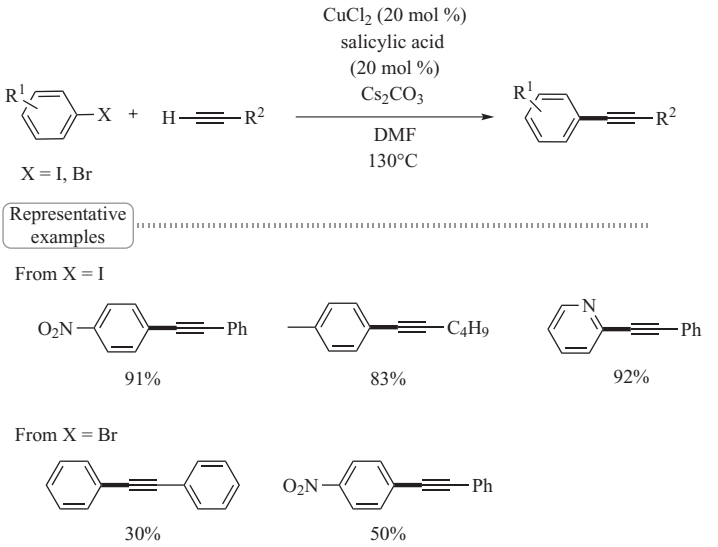
Scheme 11.17 Copper(I)-catalyzed Sonogashira alkynylation using BINAM as a ligand.

Chen and coworkers showed that salicylic acid is a powerful ligand in the copper(II) chloride Sonogashira-type alkynylation reaction of haloarenes with terminal alkynes in DMF at 130°C (Scheme 11.19).[21] The authors postulated that this bidentate *O*,*O*-donor ligand might activate copper(II) chloride during the alkynylation reaction.

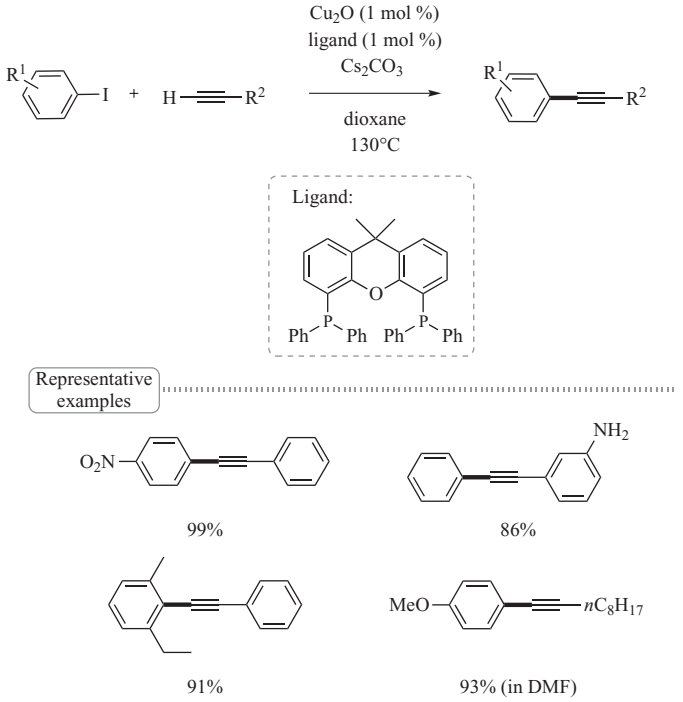
To the best of our knowledge, di-*ortho*-substituted aryl halides were only rarely employed as coupling partners in the Sonogashira reaction.[16] Recently, Lee and coworkers described that the combination of copper(I) oxide (1–2.5 mol %) with the diphosphine ligand xantphos (1–2.5 mol %) served as a powerful catalytic system for the alkynylation reactions of aryl iodides with terminal alkynes (Scheme 11.20).[22] The catalytic system tolerates a broad range of functional groups, such as enolizable ketones, esters, nitro group, unprotected amines, chloride, bromide, and heterocycles. Moreover, a highly sterically demanding substrate, 2-ethyl-6-methyliodobenzene, was also suitable for this Sonogashira reaction, which renders this method highly valuable.



Scheme 11.18 Copper(I)-catalyzed Sonogashira alkynylation using DBU as the ligand.



Scheme 11.19 Copper(II)-catalyzed Sonogashira alkynylation using salicylic acid as the ligand.

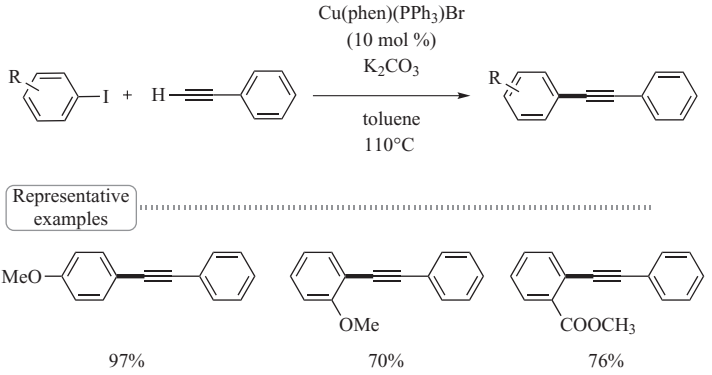


Scheme 11.20 Copper(I)-catalyzed Sonogashira alkynylation using xantphos as the ligand.

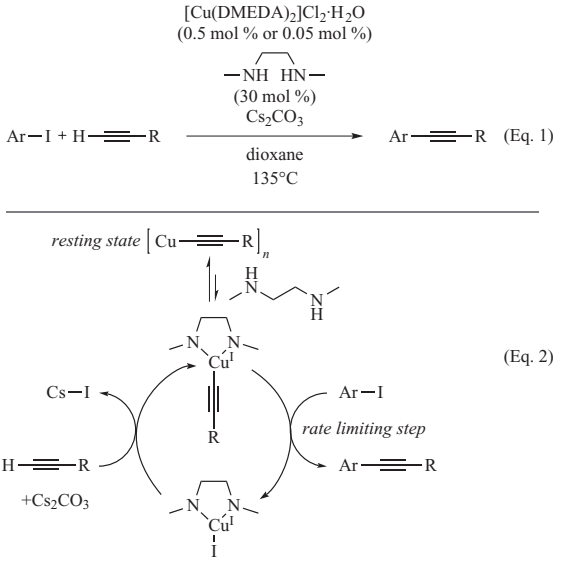
Traditionally, copper-mediated coupling reactions have some drawbacks: most copper(I) salts are insoluble in organic solvents, and hence, the coupling reactions are often heterogeneous. In 2001, Venkataraman and coworkers reported that a stable and soluble copper(I) complex could catalyze the Sonogashira reaction with the aid of a base (Scheme 11.21).[23] Both electron-rich and electron-poor aryl iodides were smoothly coupled with phenylacetylene, leading to the corresponding diaryl-substituted alkynes in good yields.

Another frequent drawback of copper-catalyzed reaction is the high catalyst loading typically used (often above 5 mol %). Trying to overcome this limitation, Bolm and coworkers have demonstrated that the Sonogashira reaction could in fact be performed using a submole percent copper loading in the presence of 30 mol % of *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand (Scheme 11.22, Eq. 1).[24a] The very low catalyst loading of $[Cu(DMEDA)_2]Cl_2{\cdot}H_2O$ (0.5–0.05 mol %) is especially noteworthy. Kinetic measurements and density functional theory (DFT) calculations showed later on that a concerted breaking of the aryl halide and elaboration of the carbon-carbon bond was operating in a rate-limiting step. No stable copper(III) intermediate was found after the transition state (Scheme 11.22, Eq. 2).[24b]

The third drawback often met with copper catalysis is the usually low reactivity of aryl chlorides. As already shown earlier, additives such as



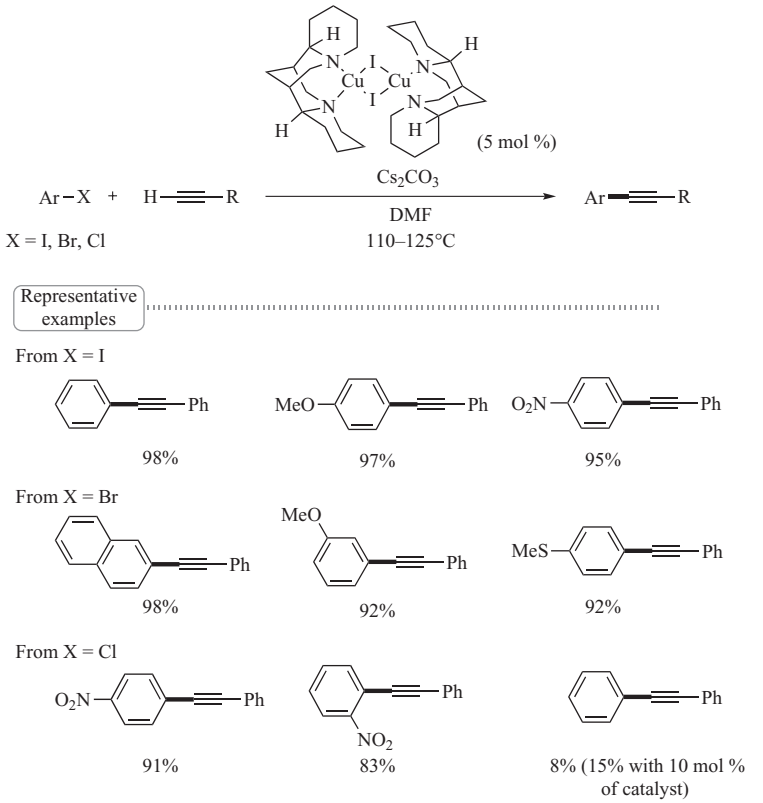
Scheme 11.21 Venkataraman's copper(I)-catalyzed Sonogashira alkynylation using a soluble, preformed copper complex.



Scheme 11.22 Very low catalyst loading in the copper(II)-catalyzed Sonogashira cross coupling.

tetrabutylammonium bromide can improve their cross coupling, but more reactive catalytic systems would be attractive options. In this context, Kantam and coworkers found that a variety of haloarenes could be reactive partners, including activated aryl chlorides, in the Sonogashira reaction using the bis(μ-iodo)bis[(–)-sparteine]dicopper(I) catalyst (5 mol %) under mild conditions (Scheme 11.23).[25]

Recently, Mao and coworkers developed an efficient alternative process for the Sonogashira-type cross-coupling reaction using $[Cu(acac)_2]\cdot H_2O$

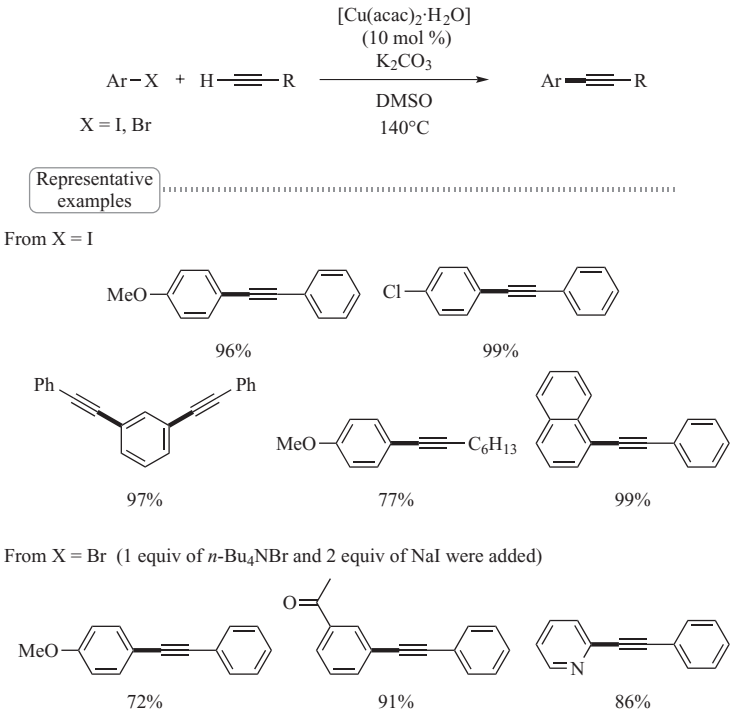


Scheme 11.23 Bis(μ-iodo)bis[(–)-sparteine]dicopper(I)-catalyzed Sonogashira alkynylation.

(10 mol %) as the catalyst, affording the corresponding alkynes in high yields (Scheme 11.24).[26] The reaction was carried out under an inert gas atmosphere and no homocoupling (Glaser type) product was detected, but the coupling had to be performed at 140°C in DMSO.

The number of ligands able to catalyze this reaction being obviously ever expanding, Shao and coworkers also reported that 2,2′-diamino-6,6′-dimethylbiphenyl was a good ligand for the copper(I) iodide-catalyzed Sonogashira coupling reaction. Both aryl iodides and bromides were reacted with terminal alkynes to furnish the corresponding products in moderate-to-excellent yields, even if high reaction temperatures in a polar solvent were required with this system (Scheme 11.25).[27]

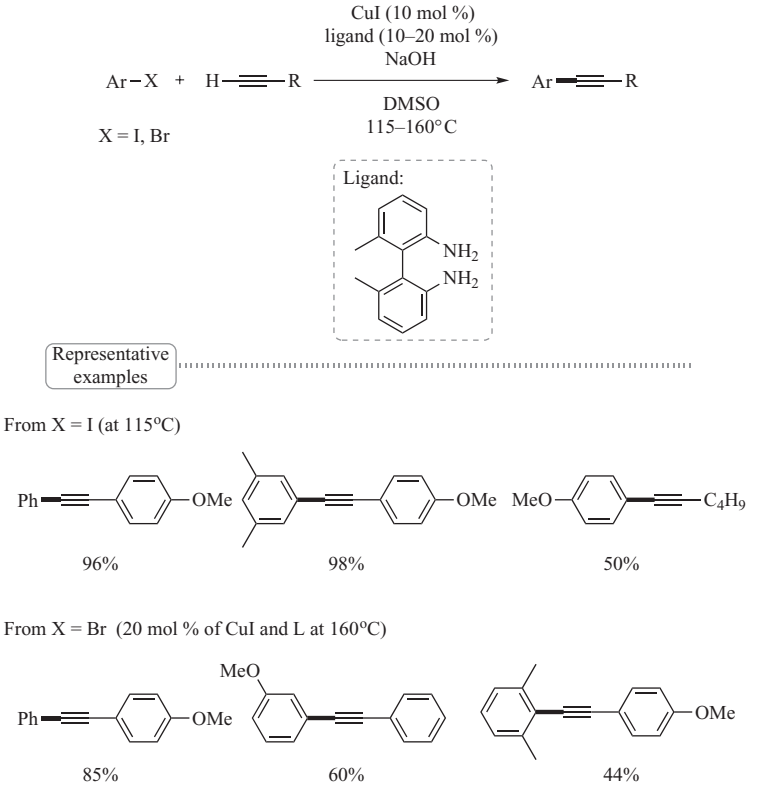
As seen with all examples collected, there are many ligands available to date to promote the copper-catalyzed cross coupling between aryl halides and terminal alkynes, which renders the choice of the catalytic system rather tricky. For activated aryl iodides (and bromides), the simplest and commercially available ligands are usually sufficient, and there is clearly no need to spend



Scheme 11.24 $Cu(acac)_2$-catalyzed Sonogashira alkynylation reaction.

time preparing a ligand that would not be readily available. For more challenging systems such as aryl chlorides or sterically hindered aryl halides, more complex systems whose advantages have been outlined might be needed. They are, however, usually readily synthesized.

The early reported copper-based catalytic systems were not recovered and reused because of their solubilities in harmful organic solvents (often DMF) and their instability after a few catalytic cycles. Moreover, alkynols were found to be unsuitable substrates, and cross coupling involving heteroaryl halides remained largely unexplored. Li and coworkers developed an efficient and reusable catalytic system based on copper(I) nanoparticles with triphenylphosphine as a ligand in tetrabutylammonium bromide for the alkynylation reaction of aryl and heteroaryl halides with terminal alkynes (Scheme 11.26).[28] The results demonstrated that the octahedral Cu_2O nanoparticles were the most effective catalyst for the reaction: A variety of aryl and heteroaryl halides could be reacted with alkynes in the presence of these octahedral Cu_2O nanoparticles (10 mol %), triphenylphosphine (20 mol %), potassium carbonate (2 equiv), and tetrabutylammonium bromide (TBAB). It is noteworthy that the Cu_2O/PPh_3/TBAB system can be recovered and reused several times without loss of activity. Furthermore, the scope of the substrates was nicely

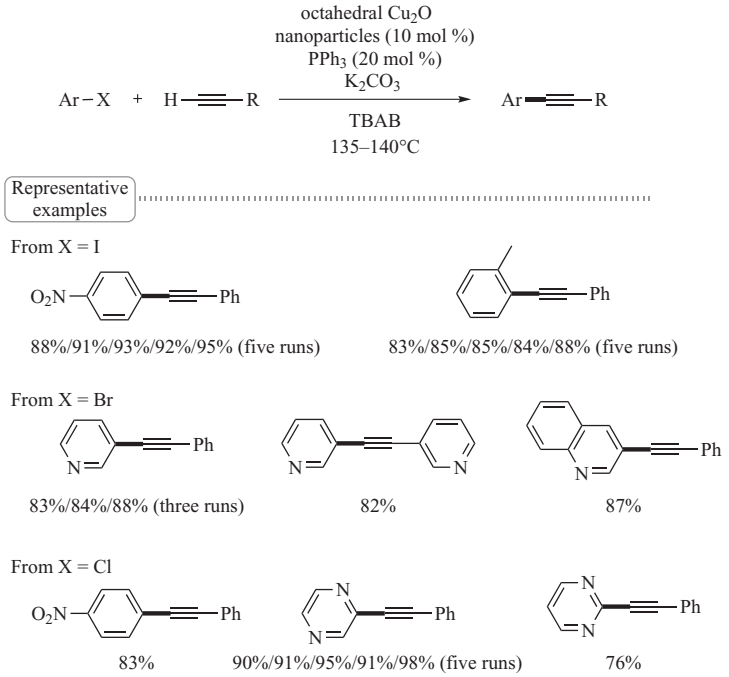


Scheme 11.25 Copper(I)-catalyzed Sonogashira reaction using 2,2′-diamino-6,6′-dimethylbiphenyl as a ligand.

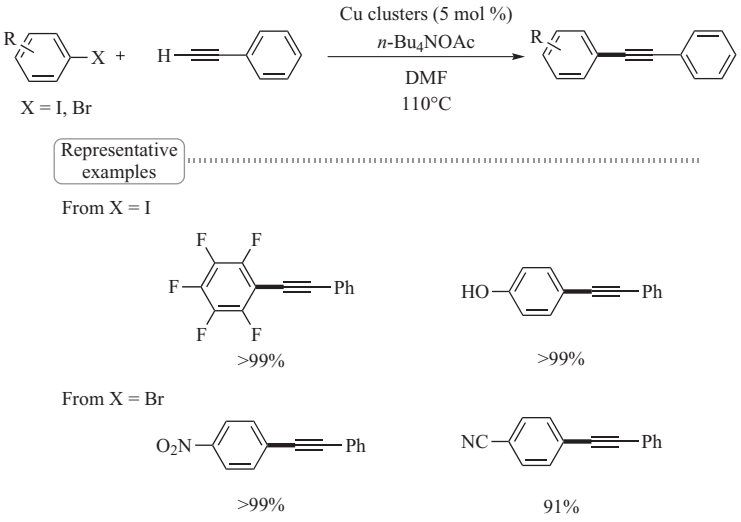
expanded to alkynols (a comprehensive coverage on reusable copper catalysts in copper-mediated reactions can be found in Chapter 20).

Another recoverable system was developed by Rothenberg and coworkers, who used copper nanoclusters to catalyze the Sonogashira alkynylation reaction of aryl iodides or bromides with alkynes (Scheme 11.27).[29] The clusters were simple to prepare, stable, and displayed different catalytic properties from their homogeneous analogues. The recycling of the active catalyst was also studied and it was shown that the cross coupling of phenylacetylene and *p*-iodotrifluorotoluene could be catalyzed by the same copper cluster three times in a row without any deactivation (final turnover number [TON] of 73).

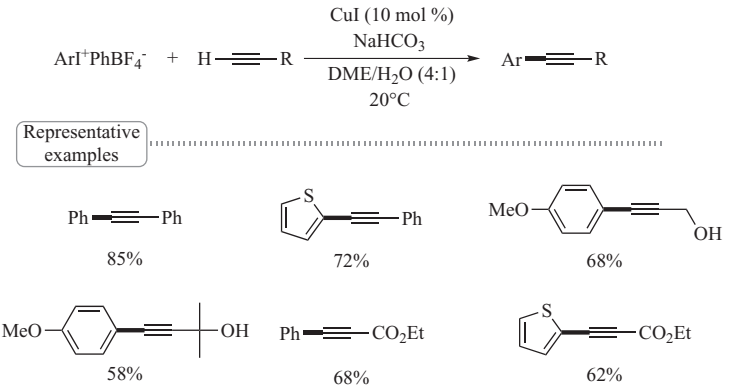
In most of these copper-mediated cross-coupling reactions, organic solvents are employed as the media, often creating safety, health, and environmental issues owing to their flammability, toxicity, and volatility. The use of water or aqueous solvents represents one of the most environmentally benign alternatives to organic solvents for the copper-catalyzed reactions.



Scheme 11.26 Reusable octahedral copper(I) nanoparticle-catalyzed Sonogashira reaction.



Scheme 11.27 Reusable copper nanocluster-catalyzed Sonogashira reaction.



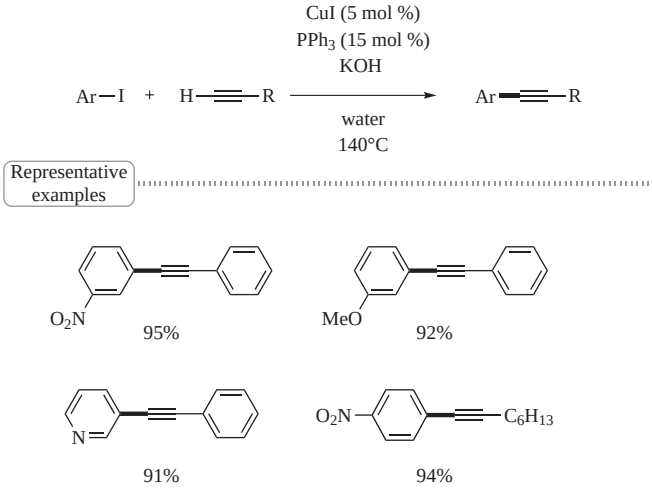
Scheme 11.28 Copper(I)-catalyzed Sonogashira reaction with hypervalent iodonium salts.

Kang and coworkers have developed a new and mild Sonogashira alkynylation protocol for the synthesis of disubstituted arylated alkynes in DME/H_2O (4:1) utilizing copper(I) iodide (10 mol %) as the catalyst and hypervalent iodonium salts as the electrophilic coupling partner (Scheme 11.28).[30] The scope of the reaction is quite interesting since aryl-, alkyl-, and ester-substituted alkynes could be employed for this purpose. In addition, 2-methyl-3-butyn-2-ol could nicely be used as surrogates for terminal alkynes under basic conditions (sodium hydroxide) with remarkable efficiencies. Hypervalent alkenyl iodonium salts could also be employed (not shown). A limitation of this procedure is that it requires the synthesis of the hypervalent iodonium salt, which is clearly less practical than starting from more available aryl- or alkenyl halides. The reaction can, however, be performed at room temperature in 30 minutes with these reagents, which is clearly a marked advantage over other methods.

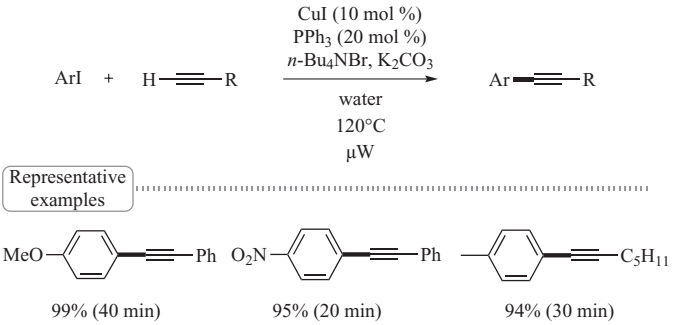
While water was only used as a minor cosolvent in the previous system, Liu and coworkers subsequently described another system in which only water was used as the solvent for the alkynylation reaction in the presence of copper(I) iodide (5 mol %), triphenylphosphine (15 mol %) and potassium hydroxide as the base (Scheme 11.29).[31] Both electron-rich and electron-deficient aromatic iodides could successfully undergo the reaction with aryl- and alkyl-substituted alkynes.

Wan and coworkers reported an alternative procedure for the copper-catalyzed Sonogashira alkynylation reaction in water, under microwave irradiation, or at reflux (Scheme 11.30).[32] A stoichiometric amount of tetrabutylammonium bromide was necessary to enhance the yields.

Lamaty and coworkers found that the copper-catalyzed Sonogashira reaction could be performed in poly(ethylene)glycol (PEG) with various molecular weights in the 300–3400 range under microwave activation (Scheme



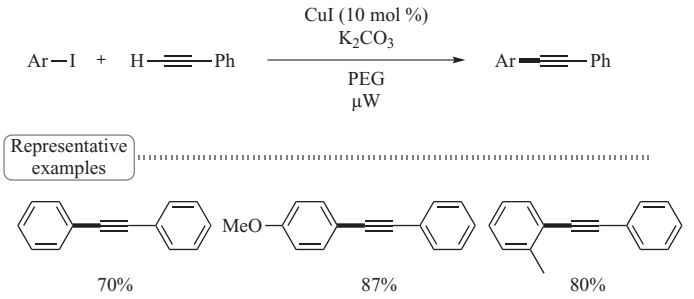
Scheme 11.29 Copper(I)-catalyzed Sonogashira reaction in water.



Scheme 11.30 Microwave assisted copper(I)-catalyzed Sonogashira reaction in water.

11.31).[33] A variety of substituted diarylacetylenes were synthesized in the presence of copper(I) iodide (10 mol %) and potassium carbonate, PEG most certainly acting as a chelating ligand for copper. This environmentally more friendly procedure might prove useful in the near future, especially since the recovery of the PEG-based catalytic system is based on a precipitation step.

As seen with all results described in this section, tremendous efforts have been devoted to the development of copper-based systems for the Sonogashira reaction that can be performed without the need for a palladium catalyst. In most cases, heating at elevated temperatures in a polar solvent is, however, needed, which might be problematic for sensitive or fragile substrates. Efforts will clearly have to be devoted to the design of more efficient copper-based catalysts to answer this challenging problem. Another option is to use other



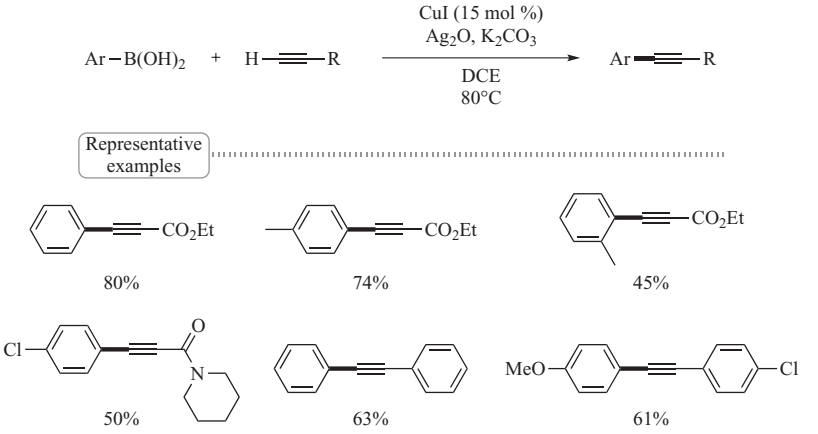
Scheme 11.31 Copper(I)-catalyzed Sonogashira reaction in poly(ethylene glycol).

coupling partners than aryl halides. Indeed, arylboronic acids have been recently shown to be readily coupled with terminal alkynes under mild oxidative conditions. This strategy will be overviewed in the next section.

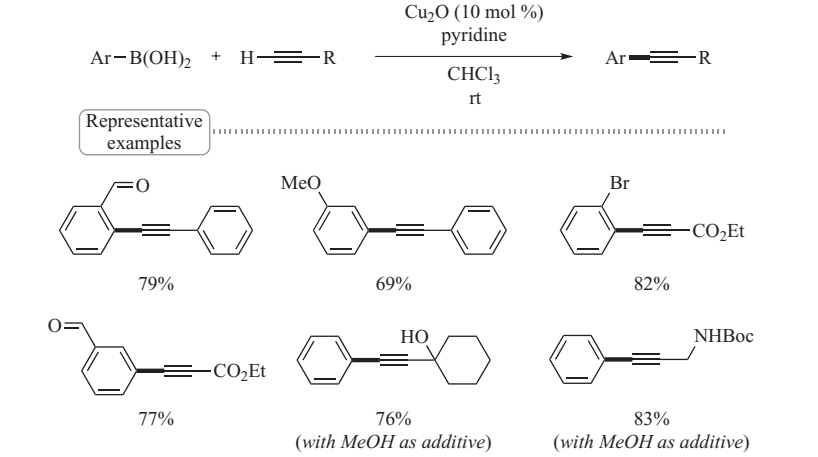
11.2.3 Synthesis of Aryl–Ynes by Oxidative Cross Coupling of Alkynes and Arylboronic Acids

The synthesis of alkynyl-substituted aromatics by oxidative cross coupling between arylboronic acids and terminal alkynes is especially attractive from a conceptual point of view since it does not involve any oxidative addition step and could therefore be performed under mild conditions using copper catalysis, provided that the easy homodimerization of both starting materials can be minimized. After early developments of this reaction based on the use of palladium catalysts, this concept was actually validated in 2006 by Cheng and coworkers, who reported a remarkable copper(I)-catalyzed, ligand-free, oxidative cross coupling of arylboronic acids and terminal alkynes.[34] Using a catalytic amount of copper(I) iodide (15 mol %) and cesium carbonate in 1,2-dichloroethane at 80°C in combination with silver(I) oxide as the oxidant, a range of activated alkynes (arylacetylenes, propiolates, and conjugated acetylenic amides) was readily coupled to a series of arylboronic acids in moderate-to-good yields (Scheme 11.32). This simple alternative to the traditional Sonogashira reaction performed well regardless of the electronic properties of the starting arylboronic acid. However, steric hindrance of the arylboronic acid had a detrimental effect on the reaction and the reactivity of alkyl-substituted alkynes was not reported.

Milder conditions were reported a year later by the Fu group, who demonstrated the crucial effect of additives for this oxidative cross coupling. The protocol used inexpensive copper(I) oxide as the catalyst, air as the stoichiometric oxidant, and pyridine (and methanol with some substrates) as the additive.[35] Under these conditions, the cross coupling could be performed with a wide range of substrates at room temperature in chloroform (Scheme 11.33). The electronic effect of substituents on the aromatic boronic acids had little



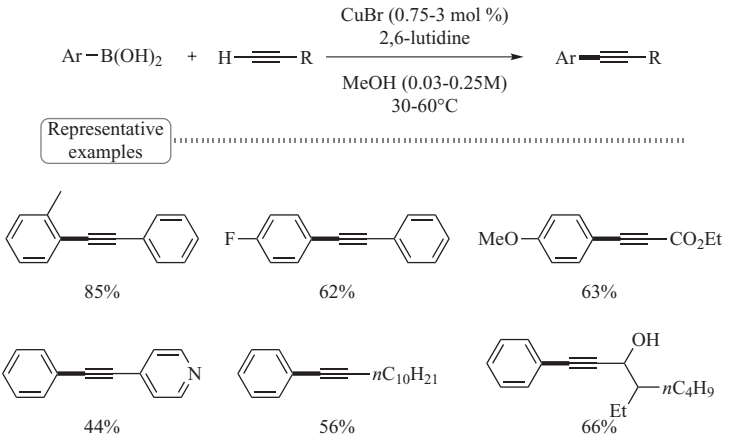
Scheme 11.32 Copper(I)-catalyzed oxidative cross coupling of arylboronic acids with terminal alkynes.



Scheme 11.33 Crucial role of additives in the room-temperature copper(I)-catalyzed oxidative cross coupling of arylboronic acids with terminal alkynes.

influence on the outcome of the reaction, and the reaction rates were more influenced by the nature of the terminal alkynes, the one containing unprotected alcohols or carbamates requiring small amount of methanol as extra additive.

Another advance in this area was reported in 2011 by Kobayashi and coworkers, who demonstrated the dramatic rate enhancement of the oxidative cross coupling with 2,6-lutidine.[36] Using this reagent as an additive or a cosolvent in methanol allowed for a smooth copper(I)-bromide-catalyzed alkynylation of a series of arylboronic acids with an impressive range of terminal alkynes with remarkable selectivities and yields (Scheme 11.34). The low



Scheme 11.34 Remarkable selectivity of the copper(I)-catalyzed oxidative cross coupling of arylboronic acids with terminal alkynes using 2,6-lutidine as an additive.

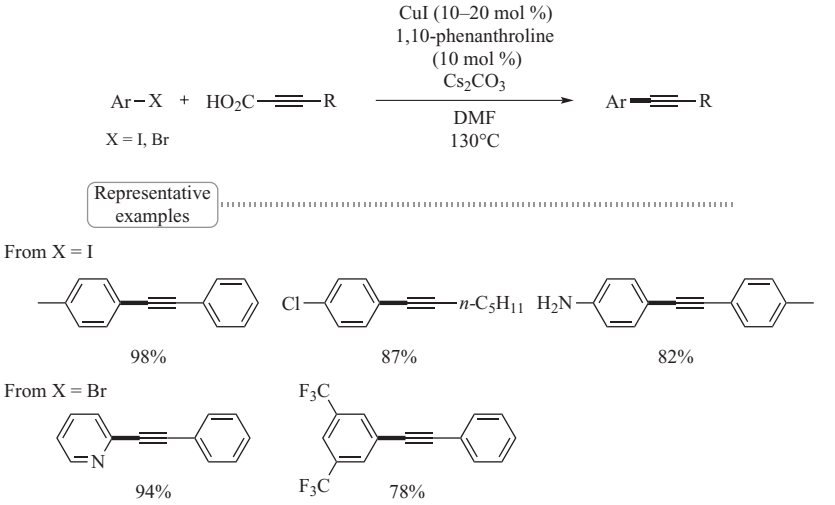
catalyst loading (0.75–3 mol %) is another astonishing feature of this system, which, in combination with the concentration of the reaction mixture, was key to suppress the homocoupling side reactions.

As evidenced with these three recent developments, the copper-catalyzed oxidative cross coupling of alkynes and arylboronic acids has clearly evolved recently into a powerful method for the synthesis of aryl-substituted alkynes with remarkable efficiency and under mild conditions. Compared with the more classical approach involving oxidative addition from alkynyl bromides (which have been recently shown to be catalyzed by catalytic amounts of copper(I) iodide in ethanol at 80°C[37a]) or 1,1-dibromoalkene in the presence of copper(I) iodide (10 mol %), 8-hydroxyquinoline (10 mol %) and potassium phosphate as a base,[37b] or metallation/oxidation from the corresponding terminal alkynes, the reaction conditions are milder, which renders this approach particularly attractive for the preparation of sensitive substrates.

Besides the use of this strategy, other methods have also been reported, such as the decarboxylative cross coupling involving propiolic acids or the direct functionalization of C–H bonds in activated arenes. The former strategy will be briefly described in the following section.

11.2.4 Synthesis of Aryl–Ynes by Decarboxylative Cross Coupling from Propiolic Acids

Decarboxylative cross-coupling reactions have been extremely studied recently, and various classes of carboxylic acids have been shown to be excellent reaction partners for various transformations, mostly associated with palladium catalysis, copper salts being often used for the decarboxylation step. Among all carboxylic acids that have been shown to participate in such



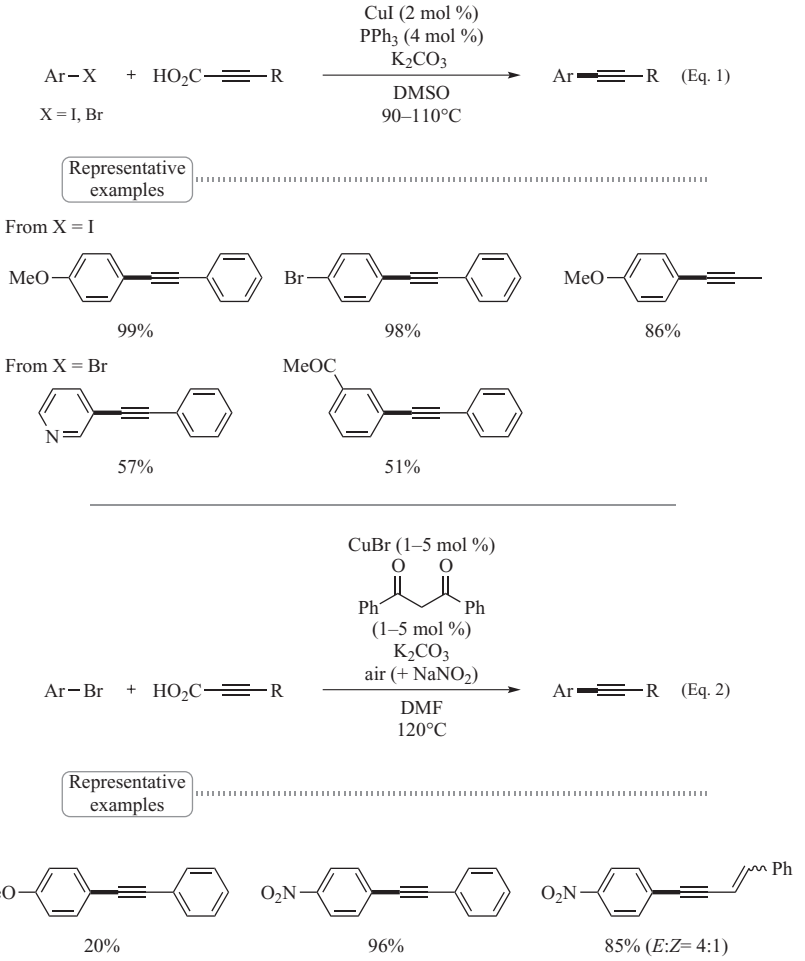
Scheme 11.35 Copper(I)-catalyzed decarboxylative cross coupling of propiolic acids with aryl halides.

coupling reactions, propiolic acids (or alkynoic acids) have been demonstrated to be rather efficient reagents for the introduction of a triple bond and therefore act as efficient alkynes surrogates.

Indeed, they have recently been shown to participate in copper-catalyzed cross coupling with aryl halides without the assistance of palladium complexes.

Initial efforts in this area were reported by You, Xue, and coworkers in 2010. In a seminal publication, they demonstrated that a wide range of aryl iodides and activated aryl bromides could be efficiently alkynylated by various propiolic acids in the presence of copper(I) iodide, 1,10-phenanthroline and cesium carbonate in DMF at 130°C (Scheme 11.35).[38] This reaction is quite attractive in terms of scope and functional group tolerance, although an elevated reaction temperature is required, which is inherent to the decarboxylation step. Worthy of note is that aliphatic propiolic acids could be effectively coupled in good-to-excellent yields and that treatment of 2-iodophenol with alkynyl carboxylic acids under these conditions yields to the corresponding benzofurans after *in situ* cyclization.

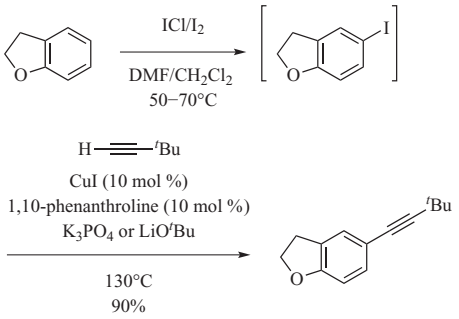
A year later, the Mao and Jiao groups independently reported alternative conditions for this decarboxylative cross coupling based on the use of copper(I) iodide (2 mol %)/triphenylphosphine (4 mol %) in DMSO at 90–110°C[39a] (Scheme 11.36, Eq. 1) or copper(I) bromide (1–5 mol %)/dibenzoylmethane (1–5 mol %) in the presence of potassium carbonate, air, and sodium nitrite in DMF at 120°C (Scheme 11.36, Eq. 2),[39b] respectively. These systems are also fairly efficient, although in the second case, aryl bromides require palladium cocatalysis. In addition, the reactivity of alkyl-substituted propiolic acids



Scheme 11.36 Copper(I)-catalyzed decarboxylative cross coupling of propiolic acids and aryl halides.

has not been addressed and the role of air and sodium nitrite is rather unclear. As a note, this decarboxylative cross coupling has also been recently shown to be efficiently performed in water using a quite low catalyst loading[40a] and could also use aryl boronic acids as coupling partners.[40b]

The copper-catalyzed decarboxylative cross coupling therefore represents an interesting strategy for the synthesis of aryl–ynes provided that the propiolic acids needed are readily available and that the substrates are compatible with the high temperatures required for these cross-coupling reactions. An advantage of these methods is the higher boiling points of propiolic acids compared to the ones of the corresponding alkynes, which can be quite interesting when the latter are too volatile.



Scheme 11.37 Daugulis copper(I)-catalyzed formal C–H bond functionalization of benzofurans.

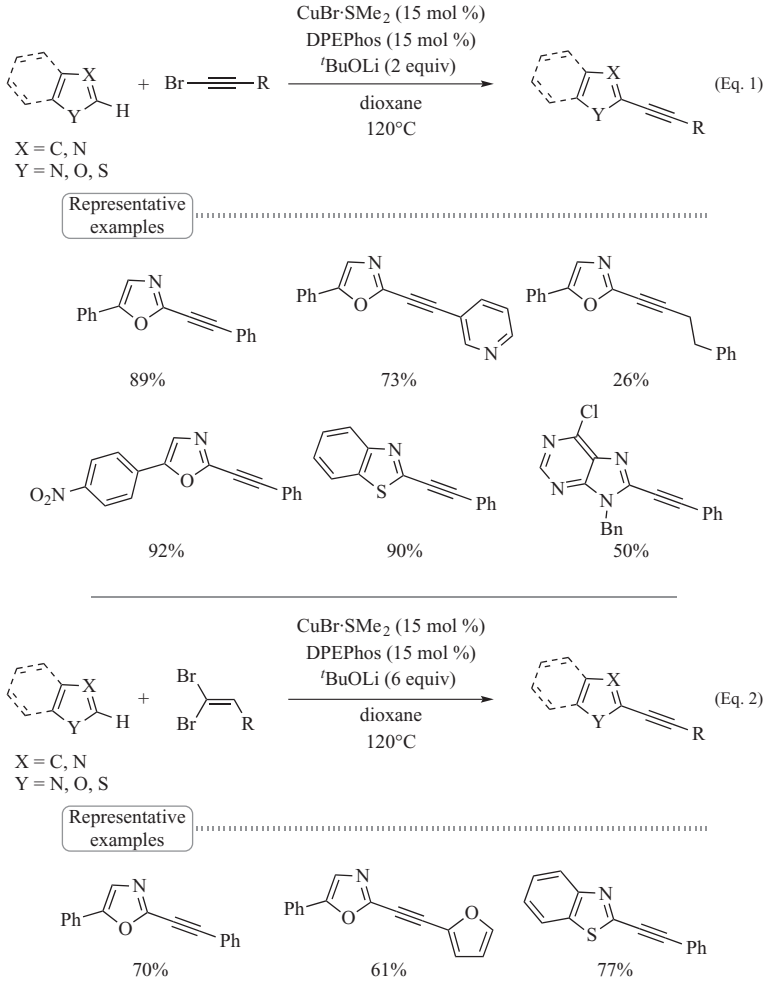
Before closing this subchapter on the synthesis of aryl–ynes, a last strategy that has also been developed over the last couple of years and that clearly holds promises will be described: the direct alkynylation of C–H bonds in activated arenes.

11.2.5 Synthesis of Aryl–Ynes by Direct C–H Functionalization of Arenes

Transition-metal-catalyzed direct C–H functionalization has gained enormous attention over the past decade because it presents many advantages over traditional cross-coupling reactions.[41] Logically, copper-mediated oxidative direct carbon–carbon bond formation has spurred a lot of interest and the most relevant examples are presented in the following paragraphs.[41d]

In 2009, Do and Daugulis reported a single example of the synthesis of an arylated alkyne by a formal copper-catalyzed C–H alkynylation reaction (Scheme 11.37).[42] The reaction was conducted by an initial electrophilic iodination of benzofuran, followed by arylation of the newly formed carbon–iodide bond with copper(I) iodide (10 mol %) and phenanthroline (10 mol %).

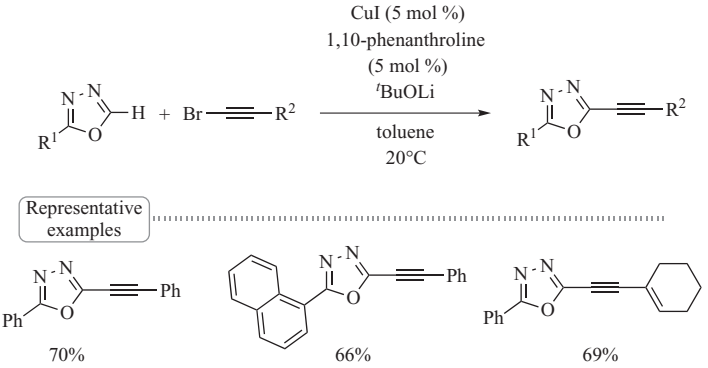
A key report in the synthesis of aromatic alkynes by direct copper-mediated alkynylation of acidic C–H bonds was described by Besselièvre and Piguel in 2009 when they developed an efficient system for the direct alkynylation reaction of various heterocycles (Scheme 11.38, Eq. 1).[43a] This straightforward protocol relies on $CuBr{\cdot}SMe_2$ (15 mol %), DPEPhos (15 mol %), and lithium *tert*-butoxide in dioxane at 120°C. It is worth noting that these reaction conditions were also successfully applied to both electron-rich and electron-deficient oxazoles. Furthermore, this work illustrated once again that inexpensive copper salts are able to replace palladium catalysis in the field of C–H bond activation. A year later, the same group reported that *gem*-dibromoalkenes could also be used for the direct alkynylation of azoles under the exact same reaction conditions but using a larger amount of lithium *tert*-butoxide to promote the elimination involved in the process (Scheme 11.38, Eq. 2).[43b]



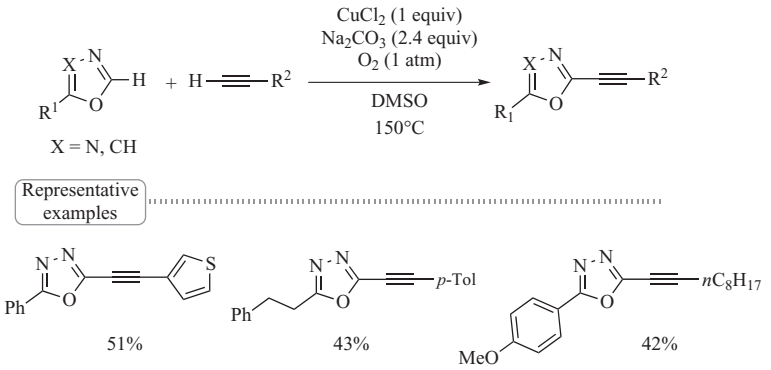
Scheme 11.38 Piguel's direct alkynylation reaction of azoles.

In a subsequent study, Miura and coworkers described a milder system for the copper-catalyzed direct alkynylation of 1,3,4-oxadiazoles with alkynyl bromides, allowing the creation of the corresponding heteroaryl-alkynyl linkage in good yields (Scheme 11.39).[44] It is important to note that the reaction can proceed at room temperature.

In continuation of their studies, the Miura group next reported a copper-mediated direct oxidative alkynylation of 1,3,4-oxadiazoles and oxazoles with terminal alkynes through the formal union of sp^2 C–H and sp C–H bonds, furnishing the corresponding alkynylazoles in good yields, under much harsher conditions than in the previous procedure, however (Scheme 11.40).[45]



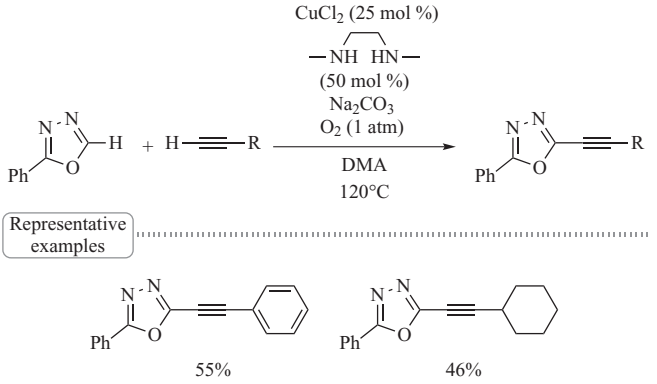
Scheme 11.39 Miura's copper(I)-catalyzed room-temperature direct alkynylation of 1,3,4-oxadiazoles with alkynyl bromides.



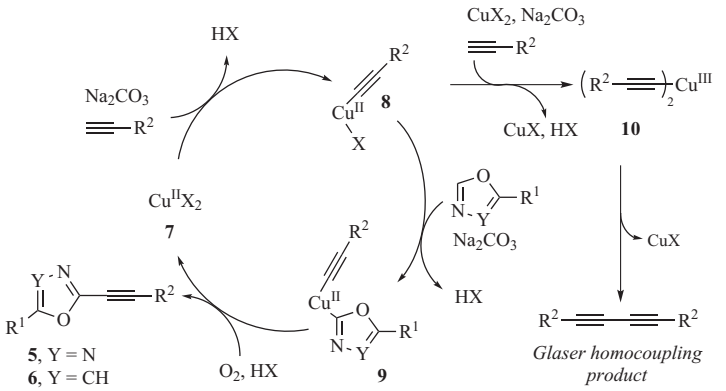
Scheme 11.40 Miura's copper(II)-mediated direct alkynylation of 1,3,4-oxadiazoles with terminal alkynes.

Control experiments suggested that the reaction could, quite logically, proceed in the presence of only a substoichiometric amount of copper(II) chloride under an oxygen atmosphere: The copper(II) chloride/*N*,*N*′-dimethylethylenediamine catalytic system was indeed found to efficiently mediate this transformation, at the expense of a rather high catalyst loading (Scheme 11.41).

A plausible reaction mechanism for this transformation is shown in Scheme 11.42. Formation of copper acetylide **8** in a first step is followed by the cupration of an oxazole or oxadiazole using sodium carbonate, thereby generating the [Cu^{II}-(alkynyl)(heteroaryl)] intermediate **9**. Oxidation of the latter by oxygen or by copper(II) should lead to a copper(III) intermediate which upon reductive elimination should give the desired products **5** and **6** together with copper(I), which is subsequently reoxidized to the catalytically active



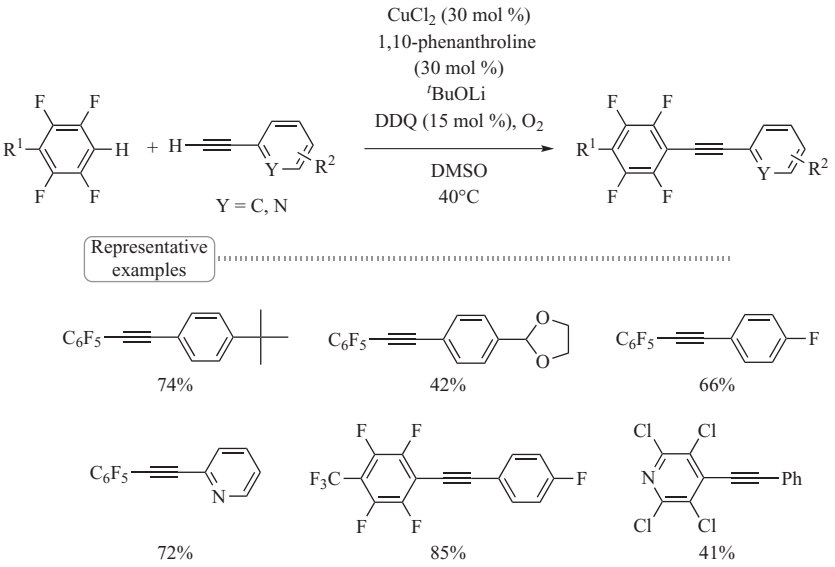
Scheme 11.41 Miura's preliminary results for the copper(II)-catalyzed direct alkynylation of 1,3,4-oxadiazoles with terminal alkynes.



Scheme 11.42 A plausible reaction mechanism for the copper(II)-mediated direct cross coupling of 1,3,4-oxadiazoles with terminal alkynes.

copper(II) salt **7**. In order to minimize the classical Glaser homocoupling reaction of terminal alkynes, a slow addition technique of the alkyne partner is mandatory (for mechanistic insights of the Glaser reaction and of its variants, see Chapter 12, Section 12.2). The exact role of the oxygen atmosphere was not clearly understood, but the authors hypothesized that it might facilitate the reductive elimination step (by generation a copper(III) intermediate; see Chapter 7 for a detailed discussion of the mechanism of the related Chan–Lam–Evans reaction).

Su and coworkers have also described a copper(II)-catalyzed method for the construction of $C(sp^2)$–C(sp) bond via a direct alkynylation of highly activated aromatic C–H bond of perfluoroarenes with a broad range of terminal alkynes as the coupling partners (Scheme 11.43).[46] This protocol used molecular oxygen as the terminal oxidizing reagent and enables the direct



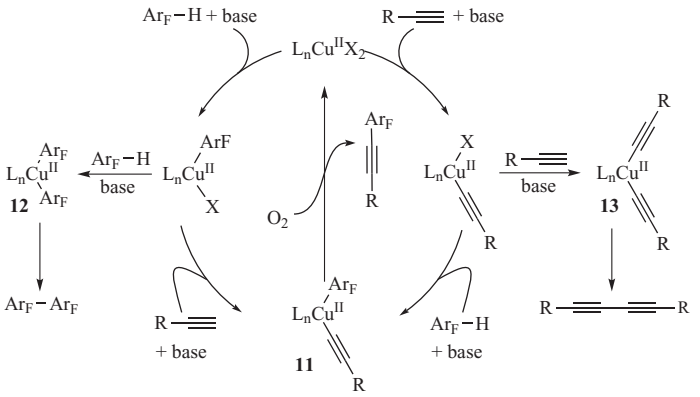
Scheme 11.43 Copper(II)-catalyzed direct alkynylation of polyfluoroaryl C–H bond.

alkynylation of electron-deficient polyfluoroarenes (and tetrachloropyridine) under mild conditions. The products, fluorinated arylalkynes, are valuable intermediates in organic synthesis and material science.

A possible mechanism for this copper-catalyzed direct alkynylation of polyfluoroarenes with terminal alkynes has been proposed by the authors and is shown in Scheme 11.44. The formation of the key Cu(alkynyl)(fluoroaryl) complex **11**, which gives the desired cross-coupling products via reductive elimination, is expected to compete with the formation of the symmetrically substituted Cu(fluoroaryl)$_2$ complex **12** and Cu(alkynyl)$_2$ complex **13**. Reductive eliminations from the latter two give rise to homocoupling products (bipolyfluoroaryls and 1,3-diynes).

As described in this subchapter, tremendous advances have been reported in a short period of time in the development of efficient and general processes for the synthesis or aryl–ynes by the means of copper catalysis. A variety of aromatic partners including aryl halides, stannanes, hypervalent iodonium salts, boronic acids, or activated C–H arenes can now be readily alkynylated by simple alkynes as well as alkynyl halides, stannanes, or hypervalent iodonium salts. Depending on the availability of the starting materials, the required reaction conditions and on the substitution pattern of the aryl–yne one wishes to prepare, at least one of the methods should definitely be most useful.

Copper catalysis also had a deep impact on the synthesis of styrene derivatives, compounds for which there are also now various copper-mediated processes available for their synthesis. The most significant strategies in this area will be the subject of the next section.



Scheme 11.44 A possible mechanism for the copper(II)-catalyzed direct alkynylation of polyfluoroarenes with terminal alkynes.

11.3 COPPER-CATALYZED ALKENYLATION OF ARYL DERIVATIVES

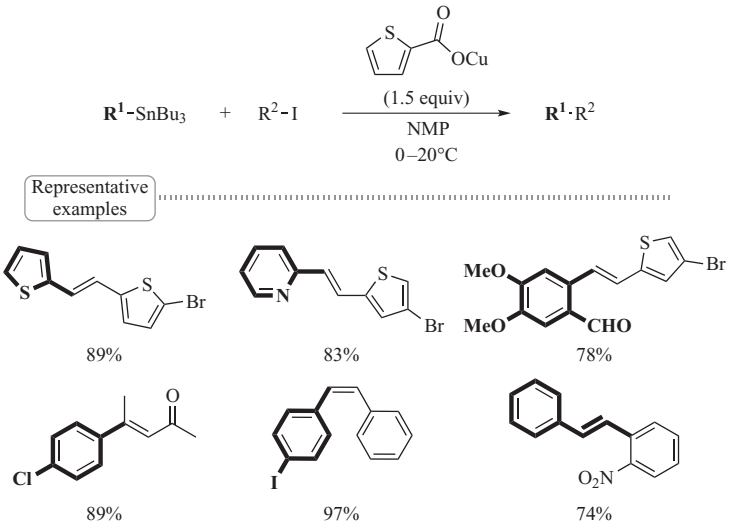
Copper-mediated Stille-, Heck-, and Suzuki–Miyaura-type alkenylation reactions have emerged as the most efficient tools for the introduction of an aryl substituent to an alkene via carbon–carbon bond formation, and most of these reactions can now be performed with copper as the only catalyst, without the need of additional palladium complexes.

11.3.1 Synthesis of Aryl–Enes by Stille-Type Cross Coupling

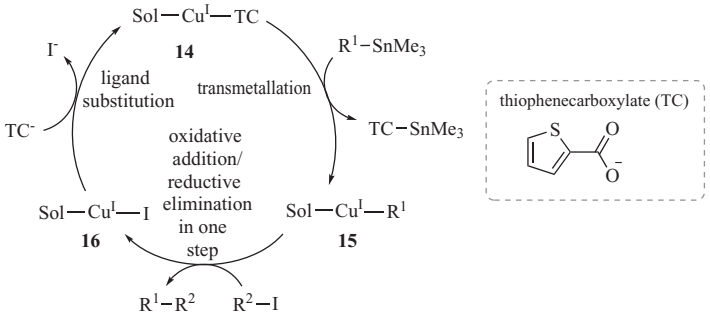
As shown in Scheme 11.45, Allred and Liebeskind demonstrated that 1.5 equiv of copper(I) thiophene-2-carboxylate (CuTC) was an efficient mediator for the alkenylation reactions of aryl-, heteroaryl-, and alkenylstannanes with alkenyl or activated aryl iodides in *N*-methyl pyrrolidinone (NMP) at 0°C or room temperature.[47a] The reaction is stereospecific and could tolerate many functional groups.

Lin and coworkers proposed a mechanism for the CuTC-mediated Stille alkenylation reaction of vinylstannane (R^1-$SnMe_3$) with vinyl iodide (R^2-I) using density functional theory calculations (Scheme 11.46).[47b] The first step is the transmetallation between the solvent-CuTC complex **14** and R^1-$SnMe_3$, giving the copper intermediate Sol–Cu-R^1 (**15**). The second step is a one-step process: oxidative addition of R^2-I to Sol–Cu-R^1 and reductive elimination providing the desired coupled product and Sol–Cu–I (**16**). Further ligand exchange with thiophenecarboxylate regenerates the catalytically active copper(I) species **14**.

Aryl–alkene bond formation could also be catalyzed by copper(I) iodide (10 mol %) without any added ligand, starting from organotin derivatives and aryl or vinyl iodides, in the presence of sodium chloride (Scheme 11.47).[4]



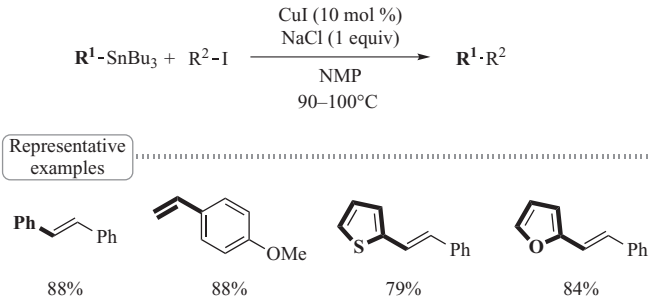
Scheme 11.45 Copper(I) 2-thiophenecarboxylate (CuTC)-mediated synthesis of styrene derivatives by Stille-type cross coupling (group originating from the organotin reagent shown in bold).



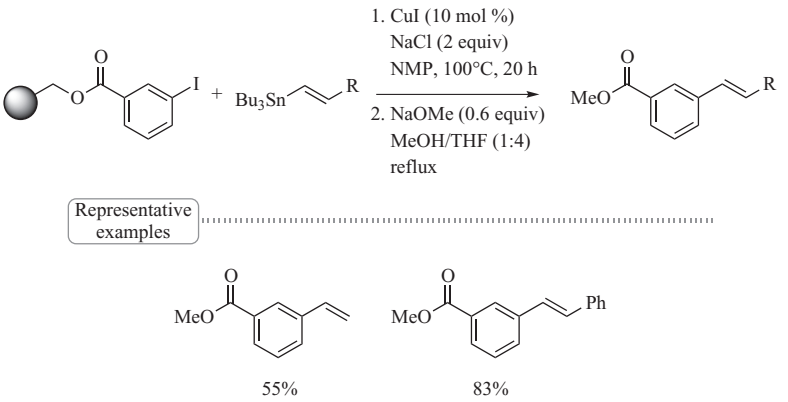
Scheme 11.46 Lin's mechanism for the CuTC-mediated the Stille alkenylation reaction.

This catalytic system was later extended to the alkenylation reaction of vinylstannanes with polymer-bounded aryl iodides (Scheme 11.48).[5] It is worth noting that organostannanes must be added slowly by a syringe pump to improve the yields, which limits the practical use of this cross coupling.

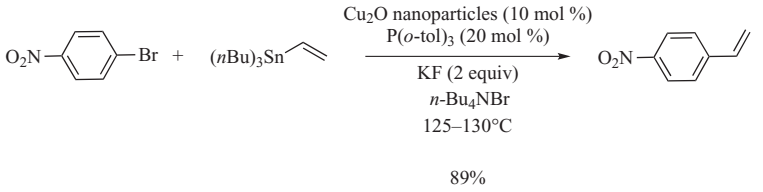
Copper nanoparticle-catalyzed Stille-type alkenylation reaction between aryl halides and vinyltin derivatives for the synthesis of alkenes could also be performed in inexpensive ionic liquids such as tetrabutylammonium bromide (Scheme 11.49).[6] In the presence of copper(I) oxide nanoparticles (10 mol %) and tri-*o*-tolylphosphine (20 mol %), 1-bromo-4-nitrobenzene underwent the Stille reaction with tributyl(vinyl)stannane smoothly in 89% yield.



Scheme 11.47 Copper(I) iodide-catalyzed synthesis of styrene derivatives by Stille-type cross coupling (group originating from the organotin reagent shown in bold).



Scheme 11.48 Copper(I)-catalyzed alkenylation reaction of vinylstannanes with polymer-bounded aryl iodide.



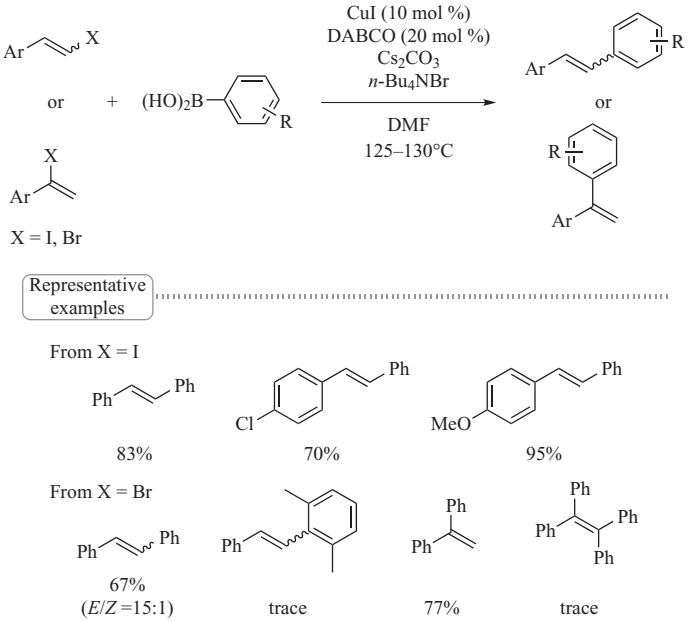
Scheme 11.49 Cu_2O nanoparticle-catalyzed Stille reaction for the synthesis of 1-nitro-4-vinylbenzene in ionic liquid.

11.3.2 Synthesis of Aryl–Enes by Suzuki–Miyaura-Type Cross Coupling

The Suzuki–Miyaura cross coupling is the reaction between an organoboronic acid and an organohalide. The Suzuki–Miyaura reaction was first published in 1979 by Akira Suzuki and Norio Miyaura,[48] the former being awarded the Nobel Prize in Chemistry (in 2010) for the discovery and development of this reaction.

The most common catalytic system used for this transformation is based on palladium combined with a ligand (often a phosphine). However, both the palladium catalysts and the ligands could be quite expensive. From the economic and environmental points of view, the development of cheaper metals in place of palladium-based catalysts is extremely attractive. Although copper has been widely used as the catalyst in many cross-coupling transformations, little attention was paid to the use of copper as the catalyst for the Suzuki–Miyaura cross-coupling reaction (see Chapter 10 for a detailed account on the synthesis of biaryls using this approach), which has been only scarcely explored for the synthesis of styrene derivatives.

Li and coworkers have reported the Suzuki–Miyaura alkenylation reaction of vinyl halides with arylboronic acids in the presence of copper(I) iodide (10 mol %), DABCO as a ligand (20 mol %), and tetrabutylammonium bromide to afford the corresponding 1,1- or 1,2-diarylethenes in moderate-to-good yields (Scheme 11.50).[14] One exception is the cross coupling of

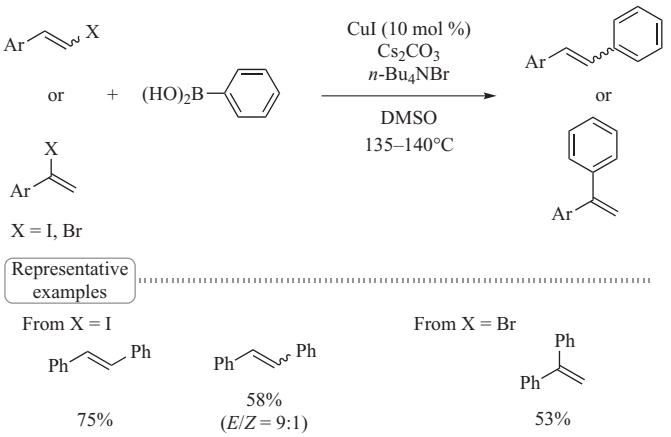


Scheme 11.50 Copper(I)-catalyzed Suzuki–Miyaura cross coupling for the synthesis of diarylethenes using DABCO as a ligand.

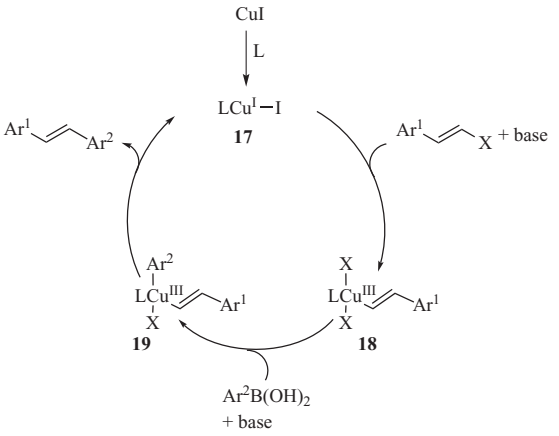
1-(2-bromovinyl)benzene with the highly sterically demanding 2,6-dimethylphenylboronic acid that leads only to traces of the targeted compound. It is noteworthy that 1-(1-bromovinyl)benzene can be coupled with phenylboronic acid in 77% yield under the standard conditions.

The same authors found that the reaction also proceeds without DABCO, in DMSO at 135°C. Tetrabutylammonium bromide (20 mol %) was mandatory in this copper(I)-catalyzed cross-coupling reaction (Scheme 11.51).[49]

Li and coworkers proposed a possible catalytic cycle outlined in Scheme 11.52. The reaction of the active catalyst **17** with vinyl halides would afford



Scheme 11.51 Copper(I)-catalyzed Suzuki–Miyaura cross coupling for the synthesis of diarylethenes in the presence of TBAB.



Scheme 11.52 Possible mechanism for the copper(I)-catalyzed Suzuki–Miyaura reaction.

intermediate copper(III) **18**. Transmetallation of this intermediate **18** with the arylboronic acid would then follow, yielding copper(III) complex **19**. Subsequent reductive elimination would then give the coupled product and the active copper(I) complex **17**. This mechanism is just a proposal and is not based on any experimentation. A more detailed presentation of related mechanisms can be found in Chapter 7.

While copper-catalyzed Stille or Suzuki–Miyaura cross-coupling reactions represent efficient entries to styrene derivatives, they require prefunctionalization of the starting alkene coupling partner, either as an alkenyl metal or as an alkenyl iodide. An interesting alternative, which is devoid of this constraint, is the use of the Heck cross coupling, which can also now be performed under copper catalysis. Recent and significant examples in this area will be overviewed in the next section.

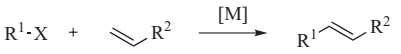
11.3.3 Synthesis of Aryl–Enes by Heck-Type Cross Coupling

The Heck cross coupling is the reaction of an organohalide (or pseudohalide) with an alkene to form a newly substituted alkene (Scheme 11.53) and was named after Tsutomu Mizoroki and Richard F. Heck, the latter being awarded the 2010 Nobel Prize in Chemistry for the discovery and development of this reaction.

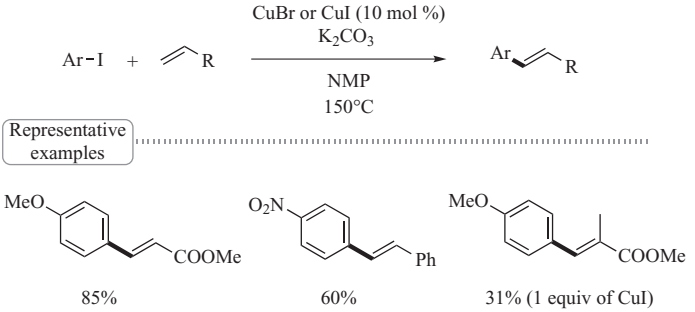
Many transition-metal complexes, such as palladium, nickel, cobalt, rhodium, or iridium complex can catalyze the reaction of aryl halides with alkenes to give the coupled products in high yields, and copper-based catalysts are also part of this list since the late 1990s.

Indeed, Iyer and coworkers reported the first copper-catalyzed Heck reaction of aryl and vinyl iodides with olefins via both inter- and intramolecular processes in 1997. The catalytic system is very simple: copper(I) iodide (10 mol %) or copper(I) bromide (10 mol %) and potassium carbonate in NMP at 150°C (Scheme 11.54).[50] Interestingly, phosphine and other ligands were not required for the reaction. Under the optimal conditions, aryl iodides could react with activated alkenes (styrene derivatives and acrylates) to form the corresponding aromatic alkenes in good yield. However, less-activated aryl bromides and chlorides could not undergo the reaction under the same conditions.

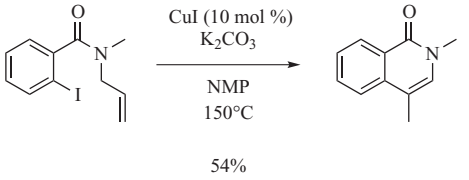
As a minor note, the cyclization of *N*-methyl-*N*-allyl-2-iodobenzamide afforded *N*-methyl-4-methylisoquinolone in 54% yield in the presence of copper(I) iodide (10 mol %) (Scheme 11.55).



Scheme 11.53 The Heck-type cross-coupling reaction.



Scheme 11.54 Copper(I)-catalyzed Heck-type vinylation of aryl iodides.



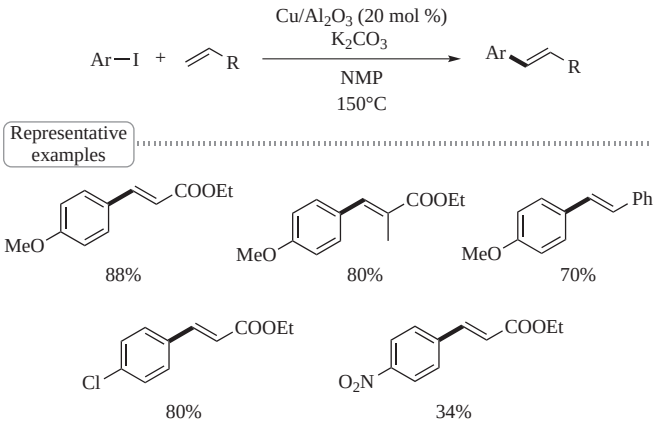
Scheme 11.55 Copper(I)-catalyzed cyclization of *N*-methyl-*N*-allyl-2-iodobenzamide.

Iyer and Thakur also demonstrated that a heterogeneous catalyst, Cu/Al_2O_3, could catalyze the reaction of aryl and vinyl halides with olefins to yield the corresponding substituted alkenes in high yields (Scheme 11.56).[51] Interestingly, the catalytic system can be recycled: Three to four cycles could be carried out, but with a rapid decrease in yield. In addition, considerable leaching from the supported catalyst was demonstrated.

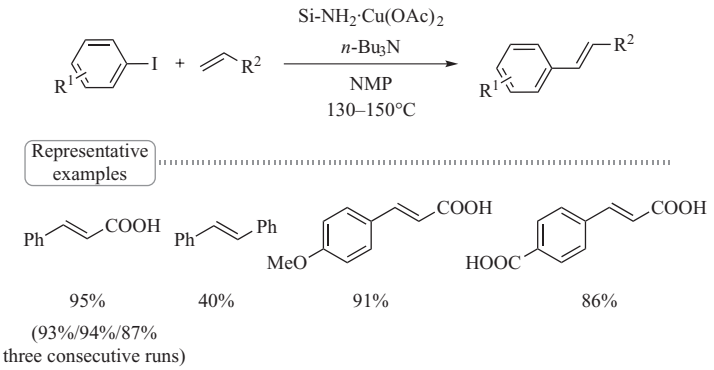
Zheng and coworkers have also reported that the silica-supported poly-γ-aminopropylsilane copper(II) complex (abbreviated as "Si"-NH_2·$Cu(OAc)_2$) could catalyze the alkenylation of substituted aryl iodides with olefins in NMP at 130–150°C, yielding the corresponding *trans*-alkene in high yields (Scheme 11.57).[52] This complex exhibited a high reactivity and stereoselectivity and could be reused after washing without loss of activity. It is interesting to note that an induction period of more than 2 hours was observed in the first run for this catalyst.

Li and coworkers have developed a mild route for the alkenylation reaction using copper(I) iodide (10 mol %), DABCO (20 mol %), and potassium carbonate in ethanol (Scheme 11.58).[53] Thanks to the DABCO ligand, the Heck-type alkenylation reaction was carried out at 80°C for aryl iodides and 100°C for activated aryl bromides, affording the desired products in moderate-to-excellent yields. However, deactivated aryl bromides were not reactive enough.

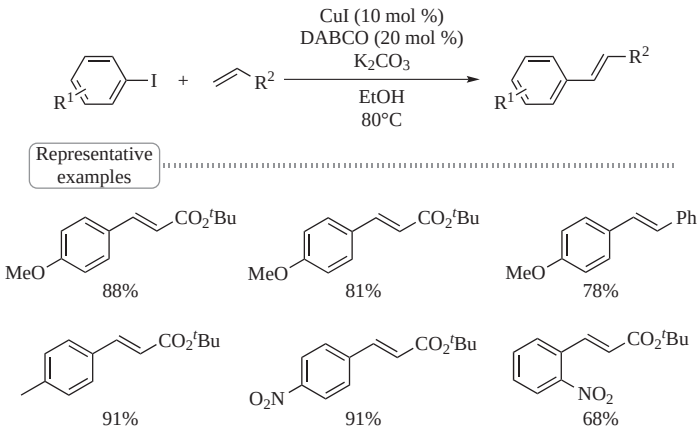
As with most systems, green variants have rapidly appeared using recyclable systems or aqueous systems. In this context, Calò and coworkers found



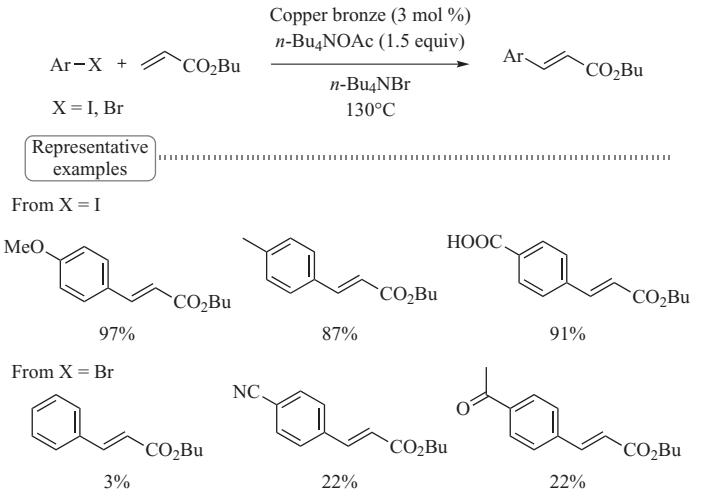
Scheme 11.56 Cu/Al_2O_3-catalyzed Heck reaction with aryl iodides and activated alkenes.



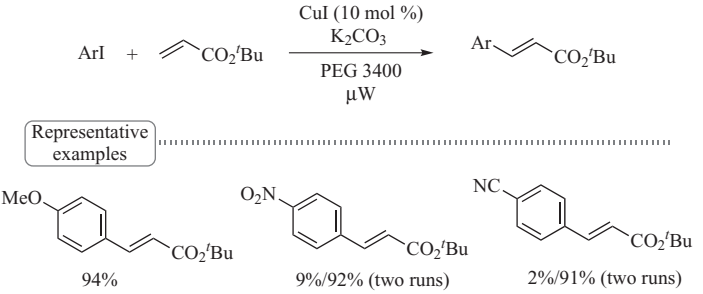
Scheme 11.57 Silica-supported copper(II) catalyst in the Heck reaction of aryl iodides with activated alkenes.



Scheme 11.58 Copper(I)-catalyzed Heck reaction for the synthesis of aryl–enes with DABCO as the ligand.



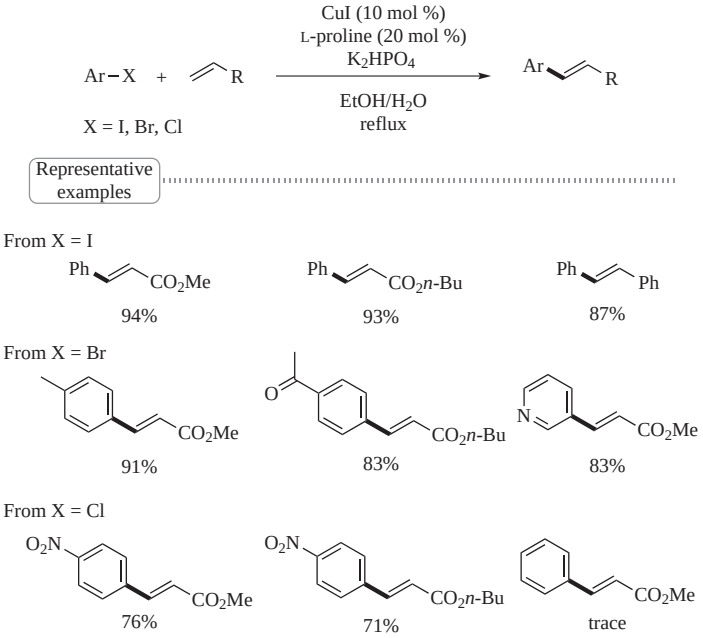
Scheme 11.59 Copper bronze-catalyzed Heck reaction in ionic liquid.



Scheme 11.60 Copper(I)-catalyzed Heck reaction of different aryl halides in PEG.

that copper nanocolloids, derived from the reaction of iodobenzene with copper bronze, could catalyze the reactions of aryl iodides or activated bromides with acrylates in the ionic liquid tetrabutylammonium bromide using tetrabutylammonium acetate as a base (Scheme 11.59).[54] These copper nanoparticles displayed an excellent catalytic activity over 20 reuse (turnover numbers of ca. 490), a stability that was attributed by the authors to the surrounding of the nanoparticles by these salts, which would impose a coulombic barrier for collision and would therefore impede the formation of clusters and aggregation.

The copper-catalyzed Heck-type alkenylation reaction usually requires high boiling point organic solvents, such as DMF or NMP. Recently, Lamaty and coworkers reported a copper(I) iodide-catalyzed Heck reaction in the presence of potassium carbonate and PEG 3400 under microwave condition. It was noted that the catalysts/solvent system could be recycled and that better results were usually obtained after recycling (Scheme 11.60).[55]



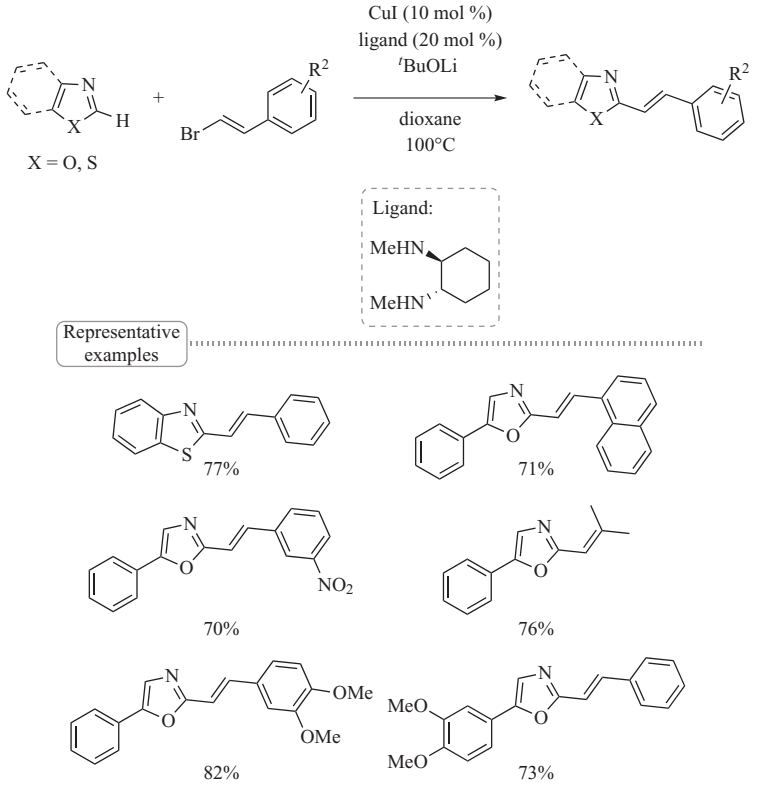
Scheme 11.61 Efficient copper(I)-catalyzed alkenylation reactions of aryl halides using L-proline as the ligand.

Guo and coworkers reported a real improvement for the copper-catalyzed Heck reaction of acrylic esters or styrene with aryl halides, which allowed the obtention of the coupling products in good-to-excellent yields in an aqueous two-phase system at only 75–85°C using L-proline as the ligand (Scheme 11.61).[56] This method provides a new, simple, and inexpensive access to the Heck-type alkenylation: A variety of aryl halides, including activated aryl chlorides, smoothly underwent the reaction with acrylic esters or styrene thanks to copper(I) iodide (10 mol %), L-proline (20 mol %), and dipotassium hydrogenphosphate in moderate-to-excellent yields.

Not surprisingly, the evolution of strategies based on copper-mediated transformations for the synthesis of alkenyl aromatics closely follows the one observed with their alkynyl counterparts. The copper-catalyzed direct alkenylation of acidic C–H bonds in arenes has been therefore also investigated recently and will be briefly discussed, with focus on the most significant results, in the coming paragraphs.

11.3.4 Synthesis of Aryl–Enes by Direct C–H Functionalization of Arenes

In 2008, the copper-catalyzed direct C–H alkenylation of 5-aryl-oxazoles and related heterocycles (oxazole, benzoxazole, and benzothiazole) with various

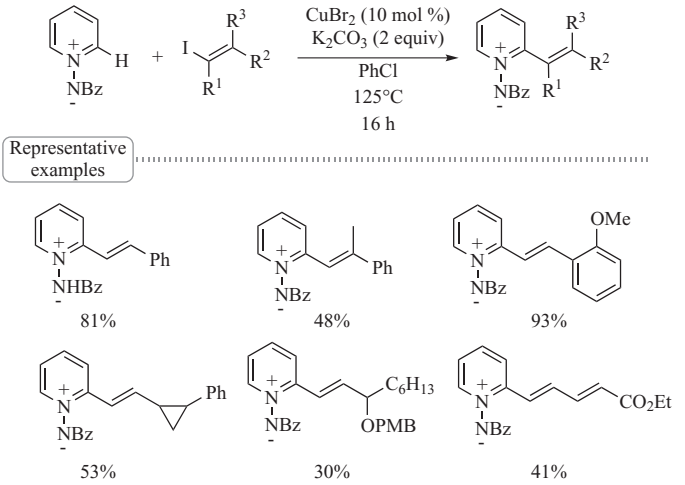


Scheme 11.62 Copper(I)-catalyzed direct alkenylation of oxazoles and related heterocycles with bromoalkenes.

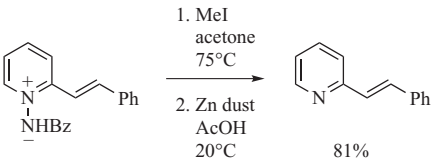
styryl bromides or iodides was reported by Piguel and coworkers (Scheme 11.62).[57] The method was found to be both regio- and stereoselective and tolerated a variety of functional groups. A wide range of 2-*E*-vinyl-substituted oxazoles including the highly fluorescent alkaloid annuloline were obtained in high yields using a combination of copper(I) iodide, racemic *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine, and lithium *tert*-butoxide in dioxane at 100°C.

Recent works demonstrated that the C–H alkenylation reactions could be applicable to activated pyridinium species. Indeed, Charette and coworkers reported the first copper(II)-catalyzed direct alkenylation of *N*-iminopyridinium ylides with inexpensive copper salts and using potassium phosphate as the base (Scheme 11.63).[58] This remarkable reaction allowed for the direct alkenylation of a wide range of substrates with high efficiency and in a most straightforward manner.

It was noted that the *N*–*N* bond could be cleaved in two elementary steps (methylation with methyl iodide followed by reductive cleavage of the N–N



Scheme 11.63 Copper(II)-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



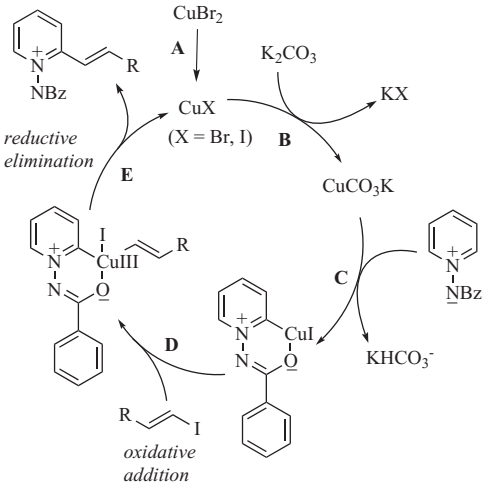
Scheme 11.64 Reductive cleavage of the N–N bond to 2-alkenyl-pyridines.

bond with zinc dust) to provide the corresponding 2-alkenylated pyridines (Scheme 11.64).

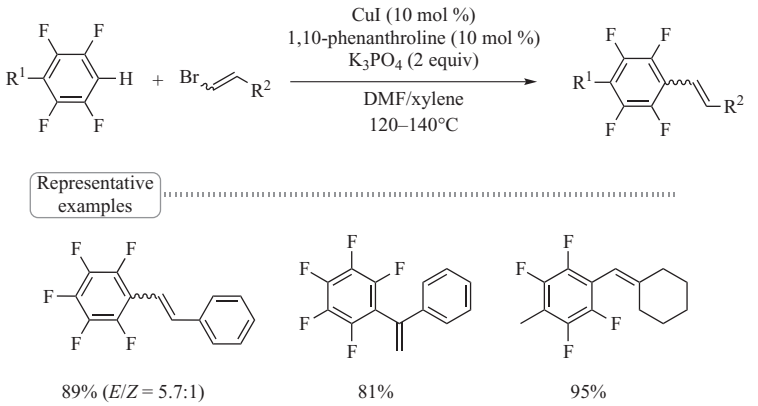
A possible mechanism suggested by Charette is illustrated in Scheme 11.65. Initially, Cu(II) would be reduced to Cu(I) with the aid of the pyridinium ylide (step **A**). Next, a carbonate–halide exchange would generate $CuCO_3K$ (step **B**), which can promote a deprotonation/metallation of the pyridinium to generate an organocupracycle stabilized by the Lewis basic iminobenzoyl moiety (step **C**). Finally, oxidative addition (step **D**) into the alkenyl iodide and subsequent reductive elimination (step **E**) would afford the corresponding 2-alkenylated derivative.

The Daugulis group has also recently described a direct copper-catalyzed alkenylation of activated aromatics. Using a combination of copper(I) iodide (10 mol %), 1,10-phenanthroline (10 mol %), and potassium phosphate in DMF/xylene at 120–140°C, C–H bonds in polyfluoroarenes could be readily activated to introduce a double bond at this position (Scheme 11.66).[59]

Before closing this subchapter, a last strategy that has been only little explored ought to be mentioned: the decarboxylative cross coupling, which is described in the next subsection.



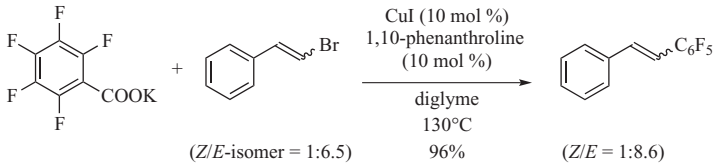
Scheme 11.65 Proposed mechanism for the copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides.



Scheme 11.66 Copper(I)-catalyzed direct alkenylation of polyfluoroarenes.

11.3.5 Synthesis of Aryl–Enes by Decarboxylative Cross Coupling

The first example of copper-catalyzed decarboxylation was reported by Shepard and coworkers in 1930.[60] Halogenated furancarboxylic acids were decarboxylated in the presence of copper or copper salt at high temperatures (about 250°C). The importance of transition-metal-catalyzed decarboxylative cross-coupling chemistry has grown rapidly in recent years. Carboxylic acids are available at low cost in great structural diversity both from natural and synthetic sources, and are easy to store and handle. Most of the decarboxylative alkenylation reactions were performed using a palladium catalyst in the presence of a phosphane ligand and alternative systems are therefore needed.



Scheme 11.67 Copper(I)-catalyzed the decarboxylative alkenylation of potassium perfluorobenzoate.

In 2009, Gooβen and coworkers reported the copper-catalyzed decarboxylation of aromatic carboxylic acids. Nonetheless, there has not been any example for the synthesis of alkenes by copper-catalyzed decarboxylative alkenylation reaction.[61] Liu and coworkers have achieved the copper-catalyzed decarboxylative alkenylation of potassium perfluorobenzoate with styryl bromide in the presence of phenanthroline (10 mol %) in diglyme at 130°C. An excellent yield was obtained, although the scope of this transformation is somehow quite restricted (Scheme 11.67).[62]

As evidenced with representative examples overviewed in this subchapter, the renaissance of copper catalysis also had a deep impact on the construction of Csp^2(aryl)-Csp^2(alkenyl) bonds. A variety of strategies, reagents, and conditions based on readily available, inexpensive copper-based systems are now available and should expedite the synthesis of styrene derivatives.

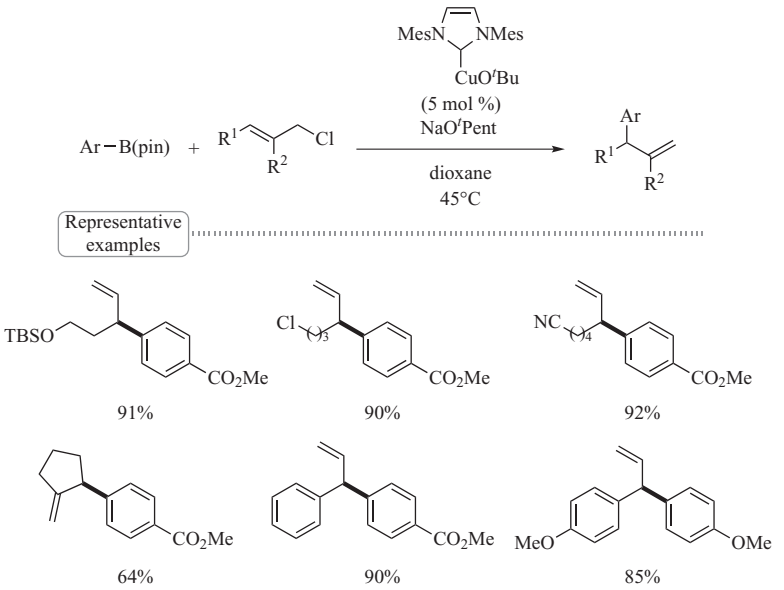
The last bond construction that will be considered in this chapter is the Csp^2(aryl)–Csp^3(allyl) one. Efficient procedures have been described for the formation of this kind of bonds using copper-based catalytic systems, and representative recent examples have been collected in the next section.

11.4 COPPER-CATALYZED STRATEGIES FOR THE FORMATION OF ALLYL–ARYL BONDS

The allylation reaction is one of the most fundamental and important transformations in organic synthesis because allyl moieties are easily manipulated to a diversity of functional groups. To date, various transition-metal catalysts such as palladium, rhodium, iridium, and copper have been employed to enable the introduction of allyl groups to several aryl metal compounds, including magnesium, aluminum, zinc, and boron reagents.

The use of preformed, nonisolable metal reagents is outside the scope of this book and will therefore not be covered. Instead, recent significant advances in the copper-mediated allylation of arylboron reagents will be highlighted in this section, which does not intend to be exhaustive, together with the direct allylation of C–H bonds of activated arenes.

The Lalic group has reported in 2010 an efficient copper-catalyzed SN_2'-selective arylation of allylic chlorides using arylboronic esters as nucleophiles



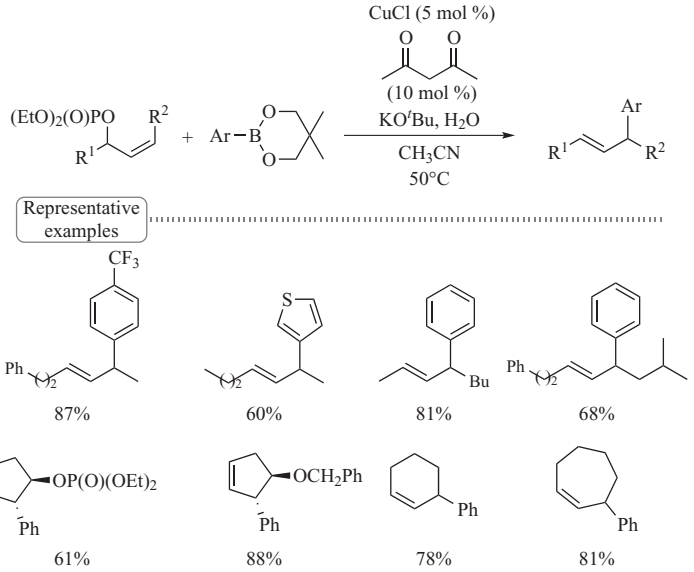
Scheme 11.68 Copper-catalyzed SN_2'-selective aryl allylation using arylboronic esters as nucleophiles.

(Scheme 11.68).[63] This approach is particularly appealing considering the availability, stability, and excellent functional group compatibility of the starting arylboronic esters. In addition, the results are the first examples of the use of arylboronic esters in copper-catalyzed allylation reactions.

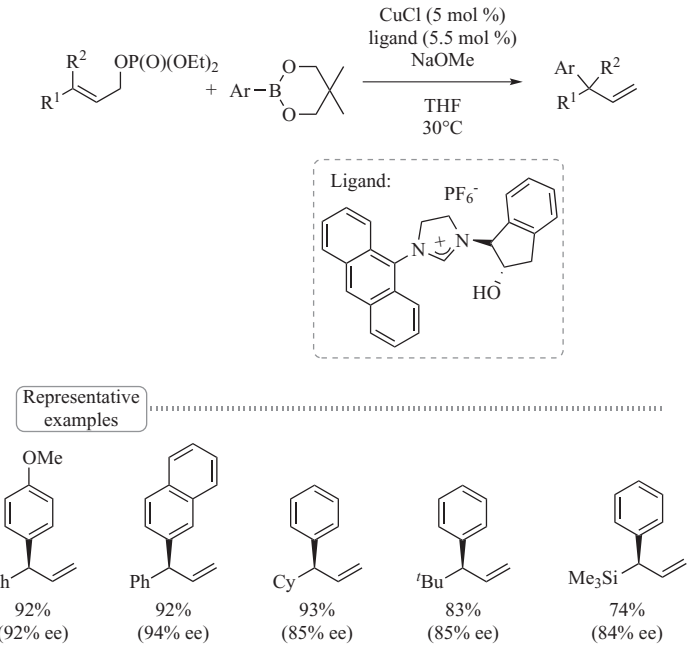
Ohmiya and Sawamura have developed a copper(II)-catalyzed γ-selective and stereospecific allyl–aryl cross-coupling reaction between (*Z*)-acyclic or cyclic allylic phosphates and arylboronates to give the corresponding cross-coupled products possessing benzylic and allylic stereogenic centers (Scheme 11.69).[64] This copper-based catalytic system is complementary to the reported palladium-based one in that it tolerates (*Z*)-acyclic and cyclic allylic systems. Notably, the use of arylmetal reagents as nucleophilic coupling partners has not been well exploited previously in copper chemistry due to the poor nucleophilicity of the arylcopper species relative to that of the alkylcopper species.

Finally, Shintani and Hayashi have described a copper(I)/*N*-heterocyclic carbene complex-catalyzed asymmetric allylic substitution of allyl phosphates with arylboronic acid esters to construct both tertiary and quaternary carbon stereocenters with high regio- and enantioselectivities (Scheme 11.70).[65]

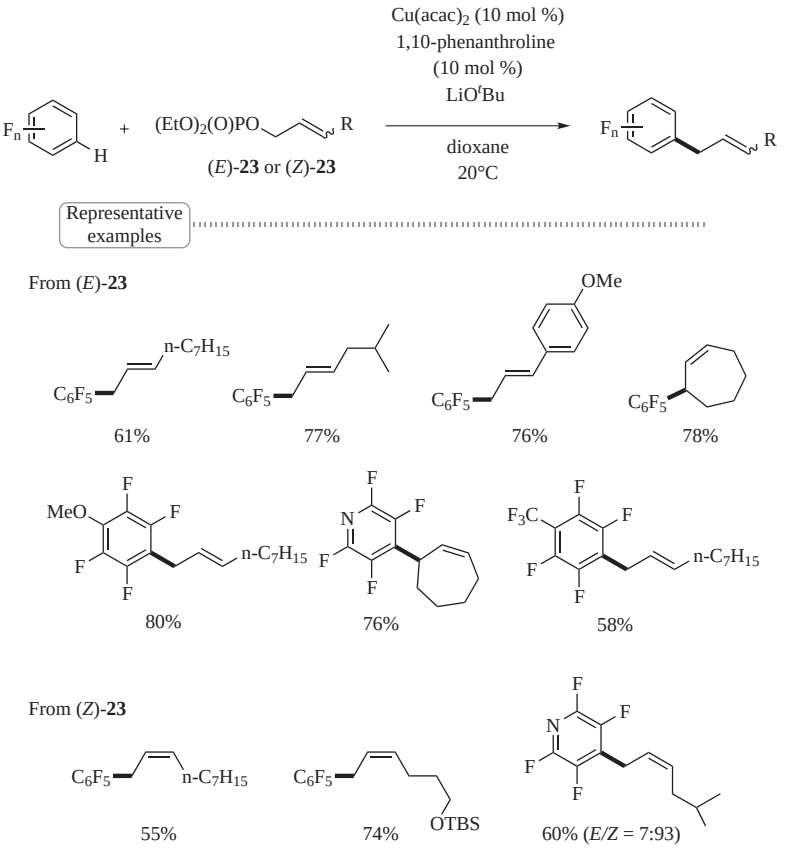
Recently, the copper-mediated C–C bond formation by C–H functionalization has grown rapidly and could be considered as a complementary process to the conventional cross-coupling methodologies. Elegant direct C–H arylations, alkenylations, alkynylations, and alkylations were achieved with great efficiency. On the other hand, the corresponding allylation reaction is still rare



Scheme 11.69 Copper(I)-catalyzed aryl allylation with cyclic allylic phosphates.



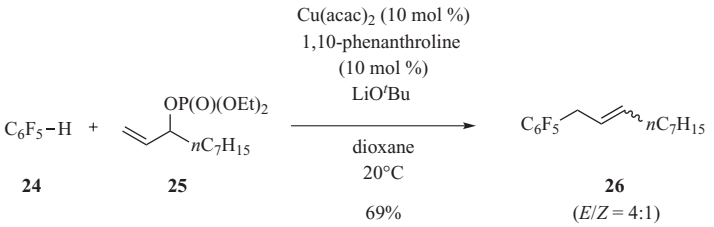
Scheme 11.70 Copper(I)-catalyzed asymmetric allylic substitution of allyl phosphates with arylboronates.



Scheme 11.71 Copper(II)-catalyzed direct C–H allylation of fluoroarenes with allylic phosphates.

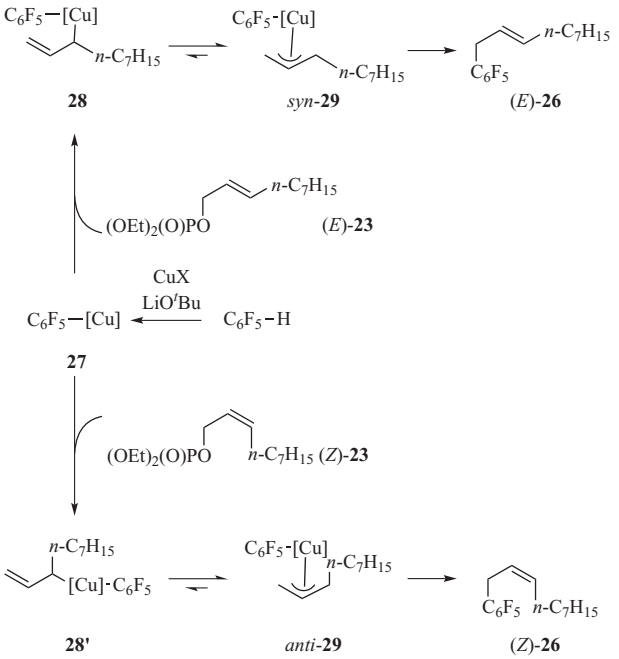
despite its potential. Hirano and coworkers reported a rare example of direct C–H allylation of polyfluoroarenes with (*E*)- and (*Z*)-allyl phosphates in the presence of $Cu(acac)_2$ (10 mol %), 1,10-phenanthroline (10 mol %), and lithium *tert*-butoxide (2 equiv) (Scheme 11.71).[66] The proposed catalytic system provided a straightforward access to stereodefined substituted allyl arenes that contain fluorinated aromatic cores, central building blocks in materials and life sciences, and demonstrated the feasibility of the direct allylation of acidic aromatic C–H bonds.

The authors also investigated the regiospecificity of the reaction under the standard reaction conditions from branched allylic phosphate **25** (Scheme 11.72). The reaction proceeded smoothly to furnish the linear allylated product **26** exclusively with moderate *E*/*Z* selectivity, indicating that a π-allyl copper intermediate was probably involved in the catalytic cycle.



24 **25** **26** (*E*/*Z* = 4:1)

Scheme 11.72 Regiospecificity of the copper(II)-catalyzed direct C–H allylation of fluoroarenes with allylic phosphates.



Scheme 11.73 Proposed mechanism for the direct C–H allylation of polyfluoroarenes with allylic phosphates.

A possible reaction mechanism was proposed on the basis of these results and literature precedents (Scheme 11.73). The mechanism would first involve a lithium *tert*-butoxide-assisted direct cupration of pentafluorobenzene to give the pentafluorophenylcopper intermediate **27**, in which copper is liganded to phenanthroline, acetylacetonate, or phosphate. Subsequently, oxidative addition of (*E*)- or (*Z*)-**23** would proceed in a SN_2' manner followed by rapid σ–π conversion to give the π-allyl copper species *syn*-**29** or *anti*-**29**, respectively. Finally, the corresponding allylated products (*E*)- or (*Z*)-**26** would be

generated by reductive elimination. The σ–π interconversion between σ-allyl isomers **28** and **28′** needs to be much faster than bond rotation for the stereochemical information of the starting allyl phosphate **23** to be transferred into the product.

11.5 CONCLUSION AND OUTLOOK

Copper-catalyzed alkynylation, alkenylation, and allylation reactions of aryl derivatives are now essential methodologies in organic synthesis from both practical and economical points of view. Importantly, these copper-catalyzed C–C bond formation reactions have emerged as key steps in the total syntheses of various natural products, bioactive molecules, and functional materials (see Chapter 18 for a detailed discussion). Up to now, numerous alkynylation, alkenylation, and allylation reactions of aryl derivatives have been reported and copper is clearly an interesting alternative to palladium catalysis in a number of transformations. However, these processes still often require reaction conditions that are still harsh and call for high catalyst loadings, which will clearly have to be improved in the near future.

More recently, a shift in paradigm was noted with the spectacular development of copper-catalyzed direct cross-coupling reactions of aromatic C–H bonds. The generalization of ever more efficient and sustainable copper-catalyzed alkynylation, alkenylation, and allylation (including asymmetric allylation) reactions of aryl C–H bond is one of the most exciting challenges in the near future.

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