



Copper(I)–Acetylides: Access, Structure, and Relevance in Catalysis

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ABBREVIATIONS

Bz benzoyl

CAAC cyclic (alkyl)(amino) carbene

CuAAC copper-catalyzed azide–alkyne cycloaddition

DCE 1,2-dichloroethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMAc dimethylacetamide

DMEDA *N,N'*-dimethylethylenediamine

dppe 1,2-bis(diphenylphosphino)ethane

ee enantiomeric excess

IPr 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene

NHC N-heterocyclic carbene

phen phenanthroline

TBHP *tert*-butyl hydroperoxide

TBTA tris(benzyltriazolylmethyl)amine

TMEDA *N,N,N',N'*-tetramethylethylenediamide

TMS trimethylsilyl



1. INTRODUCTION

Ethyne-1,2-diylcopper(I) [Cu₂C₂] was the first organocopper(I) compound ever reported.¹ Prepared by bubbling acetylene through a solution of CuCl in aqueous ammonia, this energetic reagent is stable while wet, but explosive when dry. The explosive decomposition of [Cu₂C₂] can be initiated by either heating above 120°C, impact, or electric spark. On the other hand, alkynide copper(I) derivatives were only reported a century later,² but they have become increasingly popular due to their straightforward synthesis,³ commercial availability, and remarkable thermal and shock stability. Actually, in spite of the Cu–C bond, some of these yellow–orange compounds are among the most stable copper(I) derivatives and might be stored for prolonged periods of time,⁴ which is directly linked to their polymeric structures. Homoleptic [CuC≡CR] complexes remain rare in the literature and only recently have the solid structures for R = *t*-Bu, *n*-Pr, and Ph been elucidated.⁵ *tert*-Butylethynylcopper(I) displayed a C₂₀ cluster structure with an interlocking of a distorted Cu₈ ring with two hexagonal C₆ rings. Each of the rings was supported by μ,η^{1,1}-C≡C–Cu₂ and μ,η^{1,2}-C≡C–Cu₂ bonding, while μ³,η^{1,1,2}-C≡C–Cu₃ and μ⁴,η^{1,1,1,1,2}-C≡C–Cu₄ bridging modes were found to bring the Cu atoms of different rings together (Fig. 1). On the other hand, phenylethynylcopper(I) has a polymeric ladderane structure with short copper(I)–copper(I) distances, ranging from 2.49 to 2.83 Å and μ,η^{1,2}-C≡C bridging ligands. Hence, both steric and electronic properties of the alkynyl ligands have a strong influence on the actual structures. The use of additional ligands does improve the solubility of the obtained complexes, but still lead to highly aggregated species with a range of σ- and π-interactions solid structures.⁶

This review will focus on catalytic/synthetic applications of copper alkynyl derivatives. Nevertheless, this family of compounds has found other interesting applications, including luminescent complexes,⁷

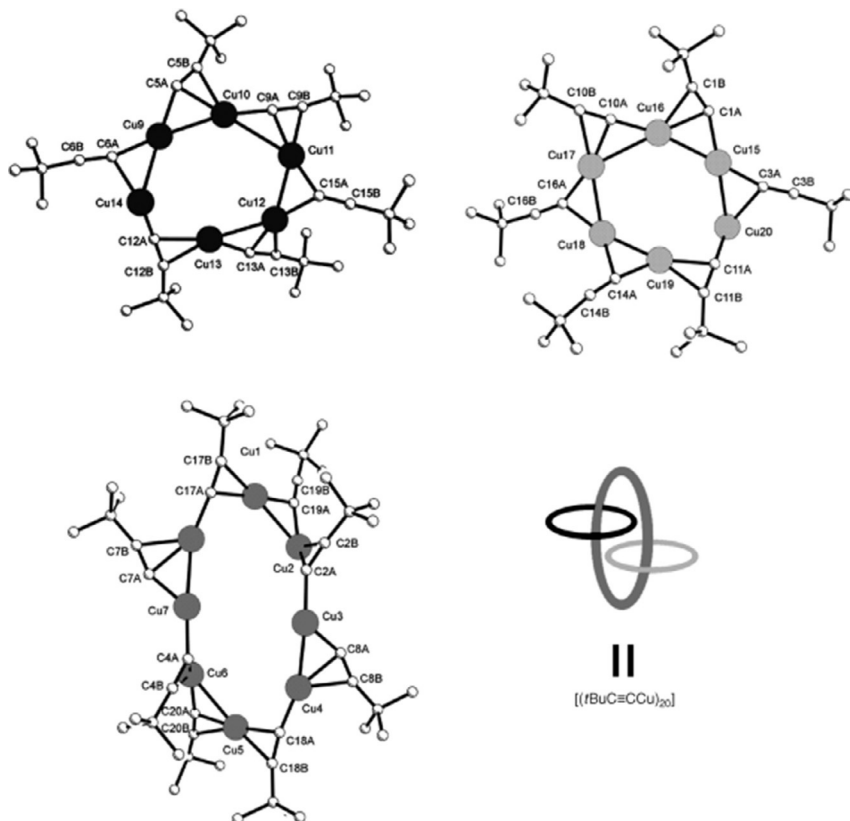


Fig. 1 Schematic drawing of the cluster assembly of three interlocking $[\text{CuC}\equiv\text{C}(t\text{-Bu})]$ ring: central Cu_8 unit (medium gray) and two peripheral C_6 units (dark gray and light gray). Reproduced from Chui, SSY, Ng, MFY, Che, C-M. Structure determination of homo-leptic Au^I , Ag^I , and Cu^I aryl/alkylethyne coordination polymers by X-ray powder diffraction. *Chem Eur J.* 2005;11:1739–1749 with permission.

fluorescence quenchers for copper detection in living cells,⁸ or preparation of semiconducting nanowires and thin metallic nanowires by self-assembling.⁹ We do not intend to provide a comprehensive view of the uses of copper(I)-acetylide in organic chemistry, and in consequence, “classical” organocopper reactivity (i.e., 1,2- or 1,4-addition to (conjugated) carbonyl compounds) will not be covered.¹⁰ Instead, the central role of copper acetylides in the catalytic transformations of alkynes and how the reaction conditions might affect the actual structure of the acetylide intermediates (and the mechanistic rationale) will be discussed while providing a historical perspective for the development of each transformation.



2. OXIDATIVE COUPLING REACTIONS

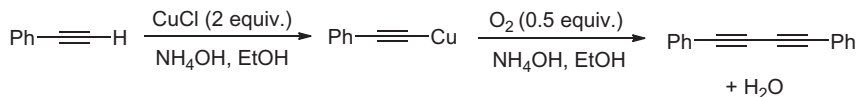
Copper can easily access 0, +I, +II, and +III oxidation states, and in consequence, its redox chemistry is extremely rich with both one-electron (radical reactions) and two-electron processes (organometallic processes) possible. Even if other reagents can be used in the laboratory, oxygen is a particularly desirable oxidant as it is directly related to the biological role of copper and it can act as a sink for electrons (oxidase activity), or a source of oxygen atoms for incorporation in the organic product (oxygenase activity). Copper enzymatic oxidizing systems are highly performant and have inspired generations of chemists for the development of a wide variety of oxidative processes under typically mild reaction conditions.¹¹

2.1 Glaser and Hay Coupling Reactions

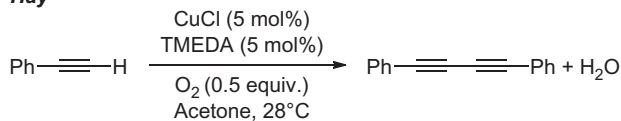
The oxidation of copper(I) phenylacetylide into diphenyldiacetylene in air was discovered by Glaser in the XIXth century (Scheme 1).¹² This transformation has become a standard procedure for the homocoupling of terminal alkynes thanks to its many variations that nowadays do not involve the isolation of any organometallic species.¹³ Among these, the Hay coupling,¹⁴ reported almost 100 years after the Glaser's ground-breaking work, deserves particular mention. Indeed, the use of TMEDA as bidentate ligand in these reactions significantly improved the solubility of the copper species, allowing for substoichiometric metal loadings, and milder reaction conditions while also improving the overall outcome of the reactions (Scheme 1).

Early proposals on the involvement of free radicals in the Glaser coupling were gradually abandoned as evidence against such intermediates gathered in

Glaser^{12a}



Hay^{14b}



Scheme 1 Original Glaser and Hay coupling reactions.

the literature. Notably, Bohlmann and coworkers showed that when two electronically different alkynes were used in these reactions, the homocoupled products remained predominant, which would not be expected with free radicals.¹⁵ Furthermore, they also showed that in acidic media more acidic alkynes dimerized more slowly and only in the presence of a copper(I) salt. In consequence, the activation of alkynes toward deprotonation via the formation of a π -complex was postulated for the first time and dimeric copper(II) acetylides complexes were proposed as intermediates in order to account for the observed second-order dependence of the reaction rate on the concentration of alkyne (Fig. 2). Extensive work by Fedenok supported this proposal by showing that under buffered conditions (NEt_3 , AcOH , pyridine), all copper in the reaction was in +II oxidation state, with dioxygen oxidizing Cu^{I} species and regenerating the active Cu^{II} centers.¹⁶ Nevertheless, when nonbuffered pyridine was used in these coupling reactions, the regeneration of copper(II) by oxygen was significantly slower, with copper(I) species actively involved in the couplings.¹⁷ Unfortunately, the role of copper(I) could not be further clarified due to the complex dependence of the rate and order of the reaction on the concentration of the alkyne and CuCl . These early studies clearly showed that the actual mechanism was highly dependent on the conditions employed, and even if some recent advances have been made, the mechanistic complexity of this reaction remains to be entangled. Still, species shown in Fig. 2 represents a widely accepted mechanistic rationale.

The first DFT study on this reaction, on the Glaser–Hay variant in particular, unveiled a complex mechanistic picture in which a copper(I)/(III)/(II)/(I) would take place with two molecules of homocoupled product formed in each catalyst turnover and oxygen acting as an oxidant for copper(I) intermediates (Scheme 2).¹⁸ The copper center was found to form first a π -complex with acetylene that would then evolved to a copper acetylide intermediate via a proton transfer reaction assisted by the TMEDA

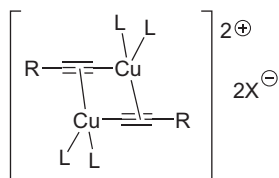
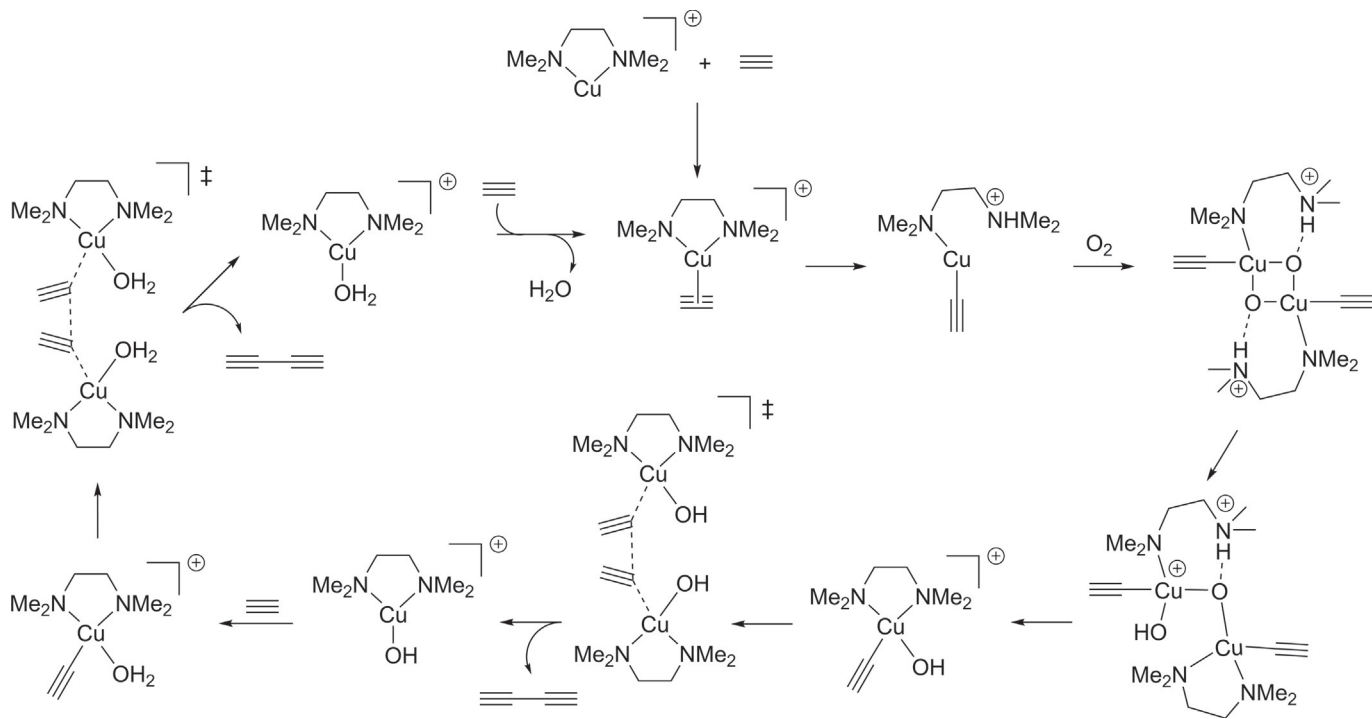


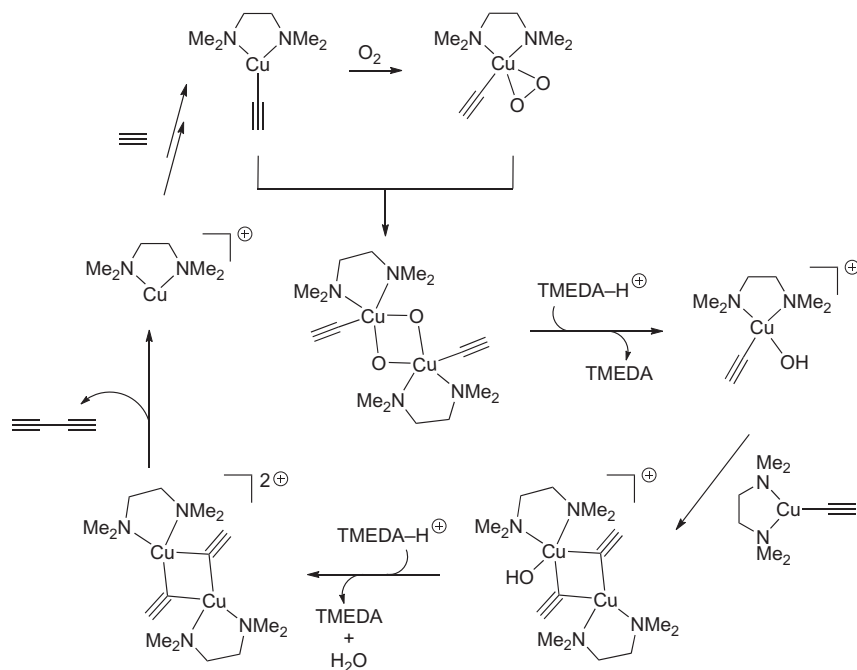
Fig. 2 Intermediate dimeric copper(II) acetylides in Glaser couplings.



Scheme 2 First computed mechanism for the Glaser-Hay coupling reaction.

ligand. This intramolecular process was found to be favored both kinetically and thermodynamically with respect to a second TMEDA molecule abstracting the acetylenic proton. In the next step, oxygen would react with the metal center to form a bis(μ -oxo)dicopper(III) intermediate. The reactivity of copper(I) complexes with dioxygen has been consistently studied for decades due to its important implications in catalysis as well as in biochemistry, and indeed, this proposal was supported by the experimental preparation of similar complexes with amine ligands.¹⁹ Two consecutive proton transfers from the protonated amine to the $[\text{Cu}_2(\mu\text{-O}_2)]$ core would then break the dimer and form a monomeric copper(III) acetylide that would generate an equivalent of diacetylene and a copper(II) hydroxide via a dicopper transition state. This hydroxide would then react with another molecule of alkyne and through a similar sequence form a second molecule of diacetylene and a copper(I) aqua complex, closing the catalytic cycle. It is important to note that the reduction of a (TMEDA)copper(II) complex to copper(I) by terminal alkynes has been directly observed by X-ray absorption spectroscopy and in situ electron paramagnetic resonance, with the formation of the corresponding diynes.²⁰ These observations also explain why copper(II) salts might also be used as catalyst precursors in these coupling reactions, as well as in many other copper(I)-mediated reactions involving alkynes (*vide infra*).

These results shed some new light on the role of the ligand in this reaction, which was found to actively participate in the reaction and not only avoid the formation of polymeric, insoluble forms of copper acetylide derivatives. On the other hand, concerns about the suitability of the chosen level of theory to study copper-oxo complexes²¹ and the high free energy values (instead of the reported potential energy barriers) justified a second theoretical study of the Hay coupling.²² In this case, only intermolecular deprotonations by TMDEA were considered, and the oxygen activation step was studied in much more detail (Scheme 3). It was found that the cleavage of the $\text{O}=\text{O}$ bond takes place in two steps, first forming a copper(III)- η^2 -peroxo complex upon the transfer of two electrons from the copper to the ligand. This spin-crossing from triplet to singlet would most likely take place through a low barrier minimum energy crossing point.²³ A second two-electron transfer would then occur upon reaction with another copper(I)-acetylide to form a similar Cu_2O_2 core to the originally proposed (see Scheme 2). Then, two consecutive protonations involving protonated TMEDA would lead to a monomeric copper(III) hydroxide. From this point, a much different reaction pathway was found



Scheme 3 Revised computational proposal for the Glaser–Hay coupling reaction.

with this hydroxide reacting with the original copper(I)–acetylide to form a copper(II) dimer with bridging acetylide ligands by a concomitant electron transfer from one copper center to the other. Protonation of the hydroxide ligand by TMEDA-H^+ would eventually lead to the elimination of water and form another copper(II) dimer which would easily undergo reductive elimination to generate the coupling product and close the catalytic cycle.

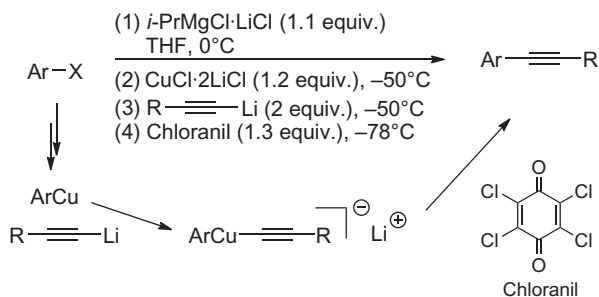
The computed energy barrier for this reaction was of only $17.5 \text{ kcal mol}^{-1}$ (free energy) and was linked to the alkyne deprotonation step. Hence, it explained the experimental observations of reactions proceeding smoothly at room temperature. Whereas such mild reaction conditions and the fact that reactions might be carried out in the presence of water are beneficial for these (and other related) coupling reactions, this high reactivity implies that the Glaser–Hay homocoupling typically competes with any other transformation if inert conditions are not employed. Even if an excess alkyne might be used, such a side reaction generally decreases the yields and complicates the purification of the desired products.

2.2 Oxidative Cross-Coupling Reactions

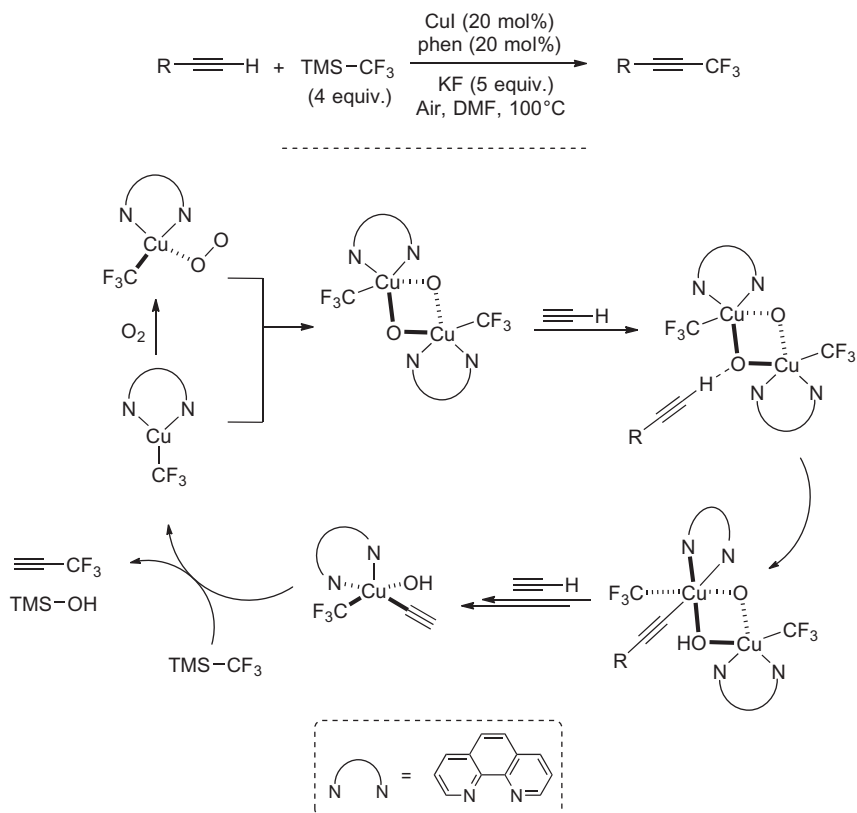
The first example of asymmetrical diyne preparation through a cross-coupling reaction was reported by Cadiot and Chodkiewicz via the coupling of a terminal alkyne and a bromoalkyne (see Section 3 for more non-oxidative cross-coupling reactions).²⁴ However, oxidative Glaser–Hay conditions have proven more powerful in this context, with either two different terminal alkynes (one of them in large excess)²⁵ or one terminal alkyne and one propionic acid via a decarboxylative cross-coupling reaction.²⁶

Over the years, an increasing number of nucleophiles have found application in these oxidative couplings, many of them stoichiometric in copper. Seminal work by Knochel and coworkers involved the cross-coupling of aryl magnesium halides and alkynyl lithium reagents (Scheme 4).²⁷ It was proposed that an arylcopper(I) complex reacted with the organolithium reagent to form a mixed lithium aryl(alkynyl)cuprate that upon reaction with chloranil would generate the cross-coupled product. In spite of being efficient and proof of concept for the real potential of copper-mediated oxidative cross-couplings, this methodology suffers from the generation of superstoichiometric amounts of metal waste and the use of chloranil as oxidant.²⁸

The oxidative cross-coupling of a nucleophilic trifluoromethylating reagent has had a much bigger impact as it represents the first efficient and tolerant methodology for the formation of C(sp)–CF₃ bonds. The original report employed again a stoichiometric amount of copper and phenanthroline ligand; a slow addition of the reactants was also necessary to ensure good yields and avoid the formation of undesired homocoupled products.²⁹ Moreover, it was soon found that 20 mol% of the CuI/phen system was enough to ensure good yields in cross-coupled products (Scheme 5).³⁰



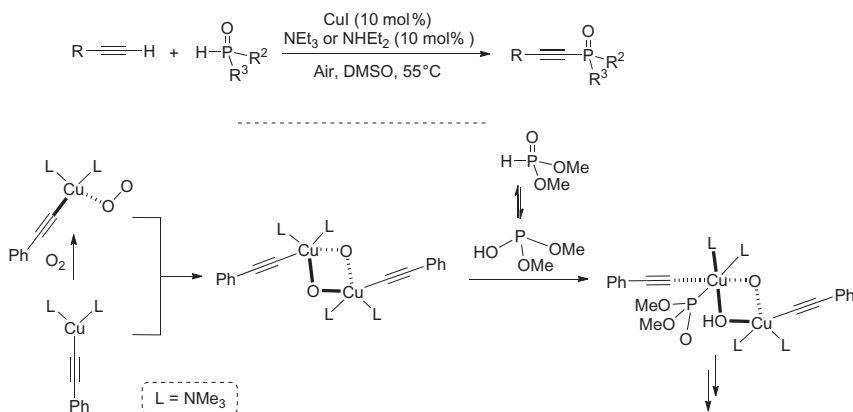
Scheme 4 Oxidative cross-coupling of organolithium and magnesium reagents.



Scheme 5 Copper-mediated oxidative trifluoromethylation of alkynes and proposed mechanism.

A DFT study on this reaction found that an in situ generated $[(\text{phen})\text{Cu}-\text{CF}_3]$ species would react with oxygen to form a η^1 -superoxocopper(II) intermediate.³¹ Reaction with another molecule of the CuCF_3 species would eventually form a bis(μ -oxo)dicopper(III) intermediate, the lowest energetic point in the proposed catalytic cycle. Sequential reaction of two molecules of alkyne via hydrogen bond interaction with this copper(III) intermediate would lead to two-proton transfer processes to give a copper(III) hydroxide that would undergo reductive elimination, and form the final product and complete the catalytic cycle.

These cross-coupling reactions are by no means limited to C-nucleophiles.^{32,33} For instance, phosphorylation reactions have been reported with 10 mol% of CuI and 20 mol% of an N-additive to form

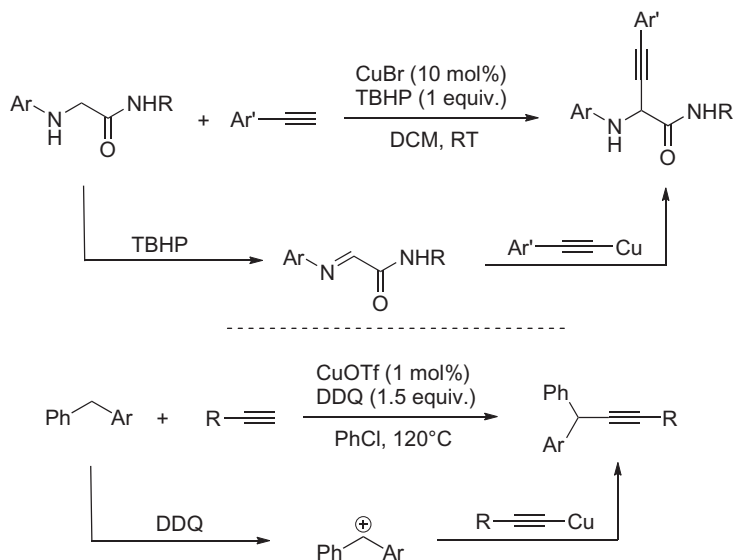


Scheme 6 Copper-assisted phosphorylation of alkynes and proposed mechanism.

the corresponding alkynylphosphonates in very high yields (Scheme 6).³⁴ A theoretical study of this reaction disclosed a similar mechanistic picture than for the trifluoromethylation reactions with a significant difference: the alkyne would interact with the copper center first, leading to an electrophilic copper(III) acetylide upon oxidation by O₂ to then react with the dialkyl phosphonite (Scheme 6).³⁵ This proposal is in accordance with the experimental observation of formation of polymeric (insoluble) copper acetylide derivatives during the reaction.

These transformations are sometimes referred to as “umpolung” oxidative couplings since the copper acetylide might act as the electrophile upon oxidation to copper(III).^{4b} However, it seems apparent that a better mechanistic understanding is necessary in order to establish unarguably which reagent is acting as nucleophile or electrophile in each coupling reaction.

Several oxidative cross-coupling reactions involving the activation of C–H bonds have also been reported. However, examples involving the dehydrogenative cross-coupling of activated arenes and azoles are considered to take place via copper(II)/copper(0) catalytic cycles and therefore will not be discussed here.³⁶ On the other hand, the activation of C–H bonds adjacent to a nitrogen center followed by coupling with a copper(I)–acetylide has been reported to proceed smoothly at room temperature in the presence of CuBr with *tert*-butyl hydroperoxide as the oxidant of the starting compound, either a methylamine or a glycine derivative (Scheme 7).³⁷ Similarly, benzylic C–H bonds can be oxidized by DDQ, leading to the coupling with alkynes in the presence of a copper catalyst (Scheme 7).³⁸



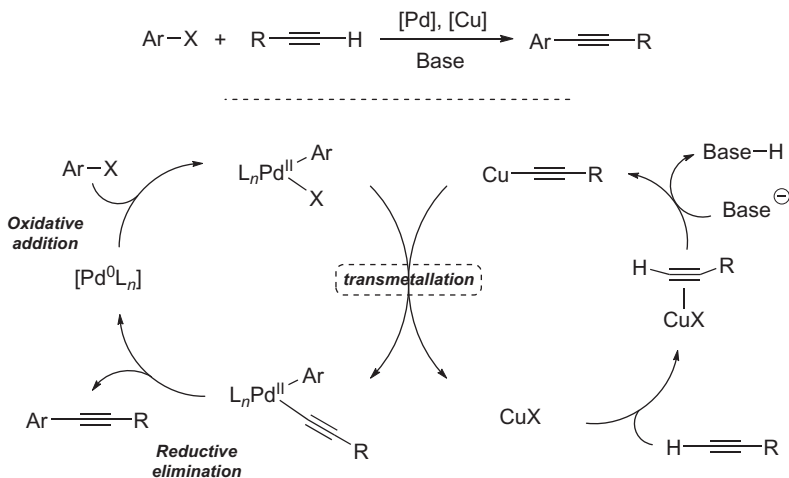
Scheme 7 Cross-dehydrogenative coupling of alkynes and amines or benzylic derivatives.



3. CROSS-COUPLING REACTIONS

3.1 Group 10-Mediated Reactions: Sonogashira Cross-Coupling

It is fair to say that palladium-catalyzed cross-coupling reactions have changed forever how chemists envision retrosynthetic analysis, particularly for bisarylic molecules. Even though these reactions had been known in the presence of copper for over a century, the use of palladium, together with very intense research by both academic and industrial laboratories, has allowed for extremely competent catalytic systems, with a very broad substrate scope and current application in large-scale production.³⁹ Original work on the coupling of haloarenes and terminal alkynes by Heck⁴⁰ and Cassar⁴¹ employed palladium as the only metal source and required harsh conditions, whereas Sonogashira and Hagihara showed soon after that a substoichiometric amount of CuI enabled the alkynylation reaction at room temperature.⁴² It has since been proposed that copper-acetylides act as the transmetalating agents in these couplings. However, even if the individual mechanistic steps in cross-coupling reactions are well established (oxidative addition, transmetalation, and reductive elimination), the actual nature of these elementary reactions

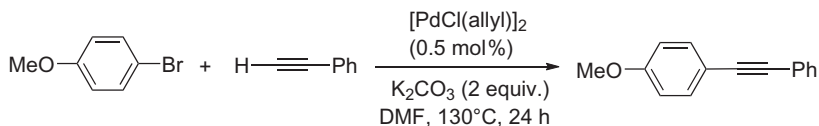


Scheme 8 Sonogashira reaction and proposed mechanism in the presence of a copper(I) cocatalyst.

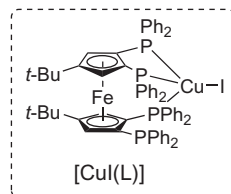
is far from being understood, and the use of copper in the case of Sonogashira reactions brings an additional layer of complexity to this understanding.

It is generally agreed on that the base present in the Sonogashira reactions facilitates the formation of the copper–acetylide intermediates that would then transmetallate the alkynyl moiety onto a palladium(II) center (Scheme 8).⁴³ This simple picture is blurred not only by the complex behavior of copper acetylides in solution but also by the possibility of ligand transfer processes between the palladium and the copper species. Recent kinetic studies have shown that this cross-coupling reaction is first order dependent on the concentration of copper, indicating that the transmetallation is the rate-determining step and that copper acetylides and $[\text{Pd}(\text{Ar})(\text{X})\text{L}_n]$ are the resting states of the catalyst.⁴⁴

On the other hand, studies with ferrocenyl polyphosphine ligands showed that preisolated copper complexes performed better than simple CuI in a model Sonogashira reaction (Scheme 9) and avoided the undesired formation of diynes or enynes, commonly observed by-products in these reaction.⁴⁵ In this case, no coupling was observed in the absence of a palladium source. Catalytic tests, together with NMR studies, showed that a tridentate ligand could be transferred between the copper and the palladium centers. These results are therefore relevant for systems using more labile monodentate phosphines, as well as those with other good additives for copper, such as N-ligands. Also, the reported observations imply that



[Cu]	L	GC conversion
CuI (5 mol%)	—	<5%
—	1 mol%	22%
[Cu(L)] (1 mol%)	—	91%



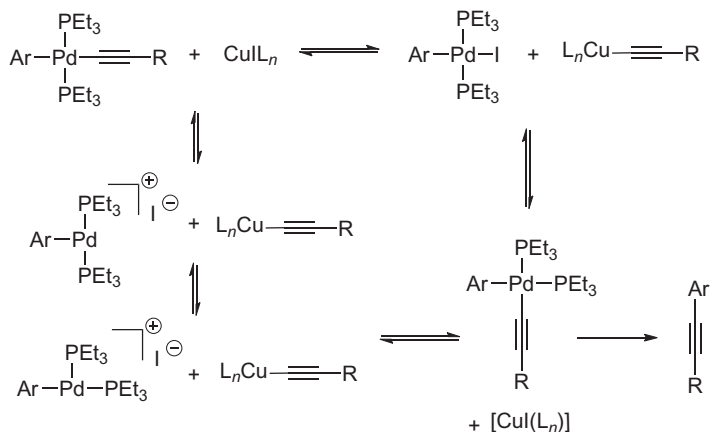
Scheme 9 Comparison of catalytic activity in a model Sonogashira reaction.

the use of well-defined copper complexes might lead to the development of better performing catalytic systems.

Of note, palladium complexes are known to undergo intermolecular transfer of aryl ligands, but such processes are kinetically disfavored with respect to alkynyl transfer reactions avoiding the formation of undesired biaryl products.⁴⁶ On the other hand, the transfer of the alkynyl group from copper to palladium can be reversible depending on the reaction conditions.⁴⁷ This would lead to the formation of a mixture of *cis* and *trans* isomers of the palladium–alkynyl intermediates via cationic tricoordinated palladium species (Scheme 10). The *cis* isomer would undergo rapid reductive elimination to form the cross-coupled product, whereas the *trans* would transfer the alkynyl group back to a copper center.

An alternative possible role for CuI in Sonogashira reactions when phosphine ligands are used for the palladium system is for CuI to act as a phosphine scavenger,⁴⁸ facilitating the formation of tricoordinated (alkynyl) (aryl)palladium(II) species, which are particularly prone to reductive elimination. Copper–acetylides might still be formed in this case, but not imperatively, since there is a large number of catalytic systems that do not use CuI as cocatalyst.

Finally, nickel catalysts have also been studied in these alkynylation reactions as they could provide a significantly cheaper alternative to palladium-based systems.⁴⁹ Pincer ligands are particularly interesting in these reactions with good to excellent yields reported even with highly challenging alkyl chlorides as coupling partners.⁵⁰ Recent mechanistic studies pointed toward (dialkynyl)nickel complexes as the active species in these coupling reactions.⁵¹ These would be formed after a transmetalation step from an in situ generated copper–acetylide, and interestingly the copper center was proposed to remain π -coordinated to one of the C–C triple bonds, maybe supported by one of the



Scheme 10 Plausible equilibria in Sonogashira couplings.

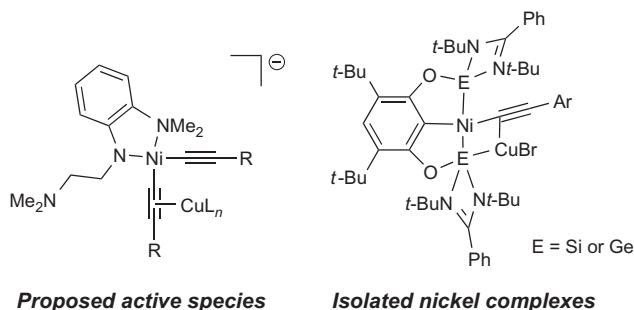


Fig. 3 Ni–Cu bimetallic species relevant in Sonogashira reactions.

amine donors in the pincer ligand (Fig. 3). These proposals were firmly backed up by the isolation and characterization of Ni–Cu bimetallic complexes bearing bis(silylene) or bis(germylene) pincer ligands during the study of Sonogashira reactions with vinyl iodides.⁵²

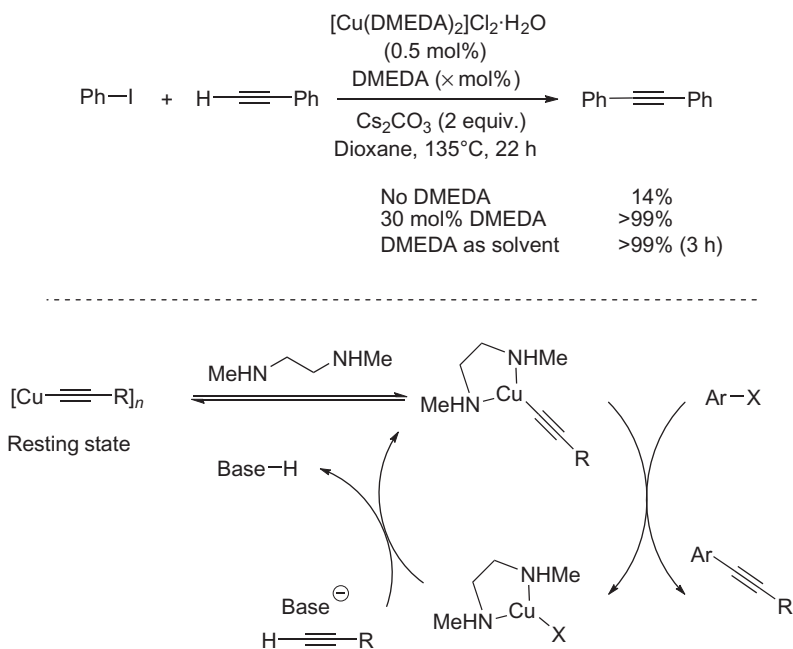
Interestingly, careful study of the copper binding in these complexes indicates that these are not examples of classical “side-on” coordination modes and the existence of a $C\equiv C \rightarrow Cu$ bond with only minor (if at all) modification of the triple bond. This work also supports the occurrence of the transmetalation step before the oxidative addition of the halogenated substrate.

3.2 Copper-Mediated Cross-Couplings: Catalytic Castro–Stephens Reactions

Cross-coupling reactions in the presence of (super)stoichiometric copper have been known since the beginning of the XXth century and they are

often gathered under the term of Ullman chemistry. Even if Castro and Stephens reported in 1963 the reaction of aryl iodides with copper(I)-acetylides in dry pyridine,⁵³ the first copper-catalyzed formation of an aryl-alkyne bond was only disclosed 30 years later.⁵⁴ Despite significant efforts on this area,⁵⁵ the copper loadings remain typically around 5–10 mol% with high reaction temperatures (and therefore high-boiling polar solvents) required. As for other Ullman-related couplings, the use of bidentate ligands has been crucial in order to improve the copper efficiency, with ethylenediamine and phenanthroline as privileged ligands.

It is often hypothesized that the use of ligands prevents the formation of inactive polymeric forms of the relevant copper–acetylide derivatives, even if this aspect of the reaction is rarely investigated. A notable exception was reported by Bolm and coworkers, who studied the catalytic Castro–Stephens reaction mediated by $[\text{Cu}(\text{DMEDA})_2]\text{Cl}_2 \cdot \text{H}_2\text{O}$ (DMEDA = *N,N'*-dimethylethylenediamine).⁵⁶ This reaction was found to be an example of ligand-accelerated catalysis and high reaction rates were observed with only 0.5 mol% of copper as long as a large excess of the ligand with respect to copper was employed (Scheme 11). Kinetic studies on this system



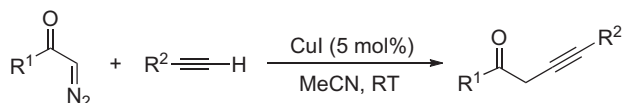
Scheme 11 Model reaction and proposed mechanism with $[\text{Cu}(\text{DMEDA})_2]\text{Cl}_2 \cdot \text{H}_2\text{O}$ /DMEDA.

showed that the resting state of the catalyst was a ligand-free polymeric form of alkynylcopper. The role of the secondary amine here would be dual: to solubilize such polymer as well as to form a monomeric acetylide, the actual active species in this reaction,⁵⁷ via complexation.⁵⁸ Furthermore, the strong donor properties of the ligand would also facilitate the next proposed step in the cycle, an oxidative addition of the haloarene. This mechanistic sequence is supported by DFT calculations⁵⁹ as well as experimental work showing that copper(III) species bearing an aryl and an acetylide ligand are intermediates in these reactions.⁶⁰

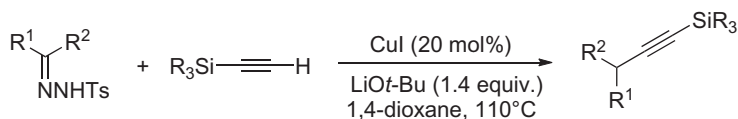
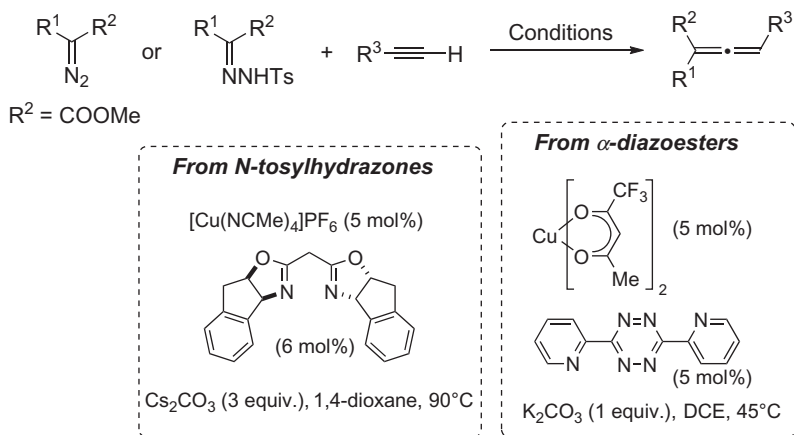
Arguably at present copper catalysis does not necessarily represent a cheaper or more sustainable alternative to palladium-based systems for these cross-coupling reactions. Nevertheless, and as it was already observed by Castro and Stephens,⁵³ in the presence of copper catalysts *ortho*-substituted aryl halides (or trisubstituted vinyl halides) are suitable coupling partners, whereas such substrates are typically inactive with palladium catalysis conditions. This has notably led to a straightforward access to diverse heterocycles via cross-coupling/cyclization cascade reactions. This reactivity has an obvious synthetic interest since indoles, isoquinolines, isocumarins, dihydro-benzofuranes, or furanones, just to name a few, might be prepared using this methodology.⁵⁵ More importantly for this review, it confirms that copper species can mediate these cross-couplings since no such products are obtained with palladium catalysts. Indeed, much controversy around not only reported copper but also iron or gold catalysts for cross-coupling has recently raised in the literature.⁶¹ Even if it undeniable that palladium contamination might be relevant in some reported systems,⁶² overall it cannot explain all copper-based reports in this context.

3.3 Copper-Mediated Cross-Coupling of Diazo Compounds

It is well established that the reaction of metal carbenes and alkynes leads to the formation of the corresponding cyclopropene derivatives. However, as early as in 1965, it was reported that copper sulfate could mediate the cross-coupling of ethyl diazoacetate and 1-octyne with no traces of the expected cyclopropene.⁶³ Despite the interest of this transformation, it remained unexplored for almost 20 years due to the low yields and the formation of several by-products, including polymers. In 2004, Fu reported an extremely simple and performing catalytic system for these cross-coupling reactions (Scheme 12).⁶⁴ In acetonitrile at room temperature, no cyclopropenation or



Scheme 12 Copper-catalyzed synthesis of alkynoates.

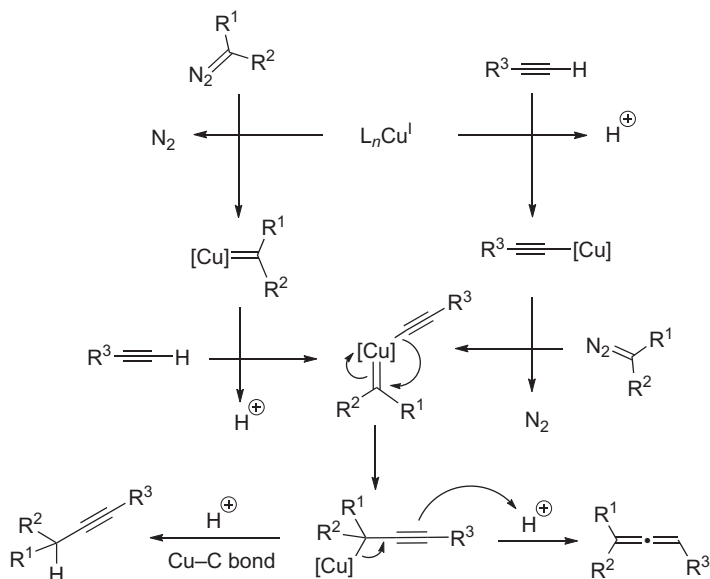


Scheme 13 Cross-coupling reactions of secondary carbenes and terminal alkynes.

oligomerization was observed, and only trace amounts of the corresponding allenes, fumarate, and maleate by-products were obtained.

Interestingly, when secondary carbene precursors were used instead, the reactions afforded trisubstituted allenes exclusively, provided that basic conditions and a suitable ligand were employed (Scheme 13).⁶⁵ The origin of these two possible reaction products relies on the regioselective protonation of the copper–propiolate intermediate (vide infra). This is most likely to be determined by both steric and electronic factors, since when silyl-substituted alkynes were coupled with secondary carbenes, alkynoates became again the principal reaction product (Scheme 13).⁶⁶

Two different mechanistic proposals can be found in the literature for these cross-coupling reactions with the copper center interacting first either with the alkyne or with the carbene (Scheme 14).⁶⁷ In the first case, based on the well-established palladium-catalyzed coupling of diazo compounds,⁶⁸ a copper–acetylide would be first formed to then react with

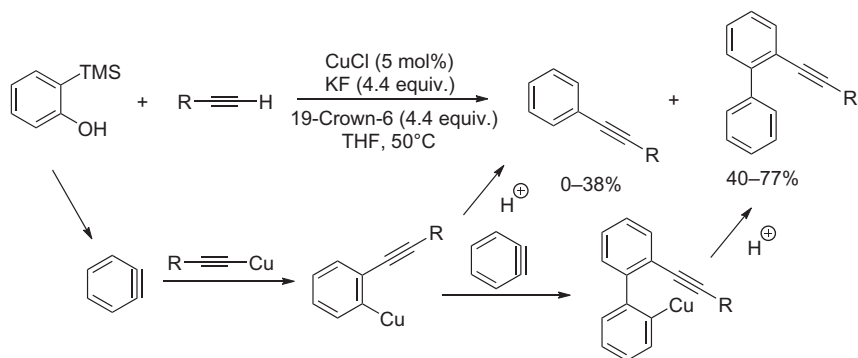


Scheme 14 Mechanistic proposal for the cross-coupling of diazo and alkynes.

the diazo compound (either preisolated or formed in situ from the corresponding tosylhydrazone). A migratory insertion of the alkynyl ligand to the copper carbenoid would afford a propargylic derivative. Hydrolysis of the copper–carbon bond would generate a propargylic product, whereas protonation at the $C\equiv C$ would deliver an allene. Alternatively, a copper carbenoid could be formed first, to then evolve to the same intermediate upon reaction with the alkyne.⁶⁹

To date, very little mechanistic insights on these reactions can be found in the literature. Whereas it is noteworthy that the reaction of a preformed copper–acetylide and α -diazoester did not lead to the formation of any cross-coupled product,^{65a} such acetylides have been supported by recent DFT calculations.⁷⁰ Nevertheless, the influence of ligands on the mechanistic sequence or factors affecting the selectivity of the protonation step remains unexplored since the reported calculations focused on rationalizing the formation of propargylic compounds from silyl-substituted alkynes.

A related reaction, the 2:1 coupling of in situ generated arynes and alkynes has also been reported in the presence of $CuCl$ (Scheme 15).⁷¹ In this case, a formal insertion of two equivalents of arynes into the acetylenic $C-H$ bond takes place. The selectivity of insertion of highly reactive arynes is noteworthy since only the product issue of a 1:1 coupling was formed as the minor product in some of the reported entries.



Scheme 15 Aryne–alkyne coupling reactions.



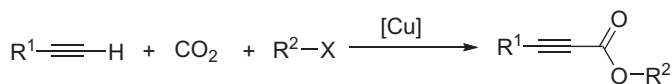
4. OTHER COUPLING REACTIONS

The stoichiometric reactions of alkynyl organolithium or organomagnesium compounds with electrophiles are well established in the literature. Nevertheless, catalytic versions of these reactions were soon sought after in order to avoid the generation of stoichiometric amounts of metal waste as well as to broaden the functional group tolerance of this methodology. Indeed, copper-mediated coupling reactions now offer a straightforward access to propiolates or propionic acids (carboxylation reactions), or propargylic amines (A^3 coupling). Both families of compounds are extremely useful synthons in organic chemistry toward heterocycles, biorelevant compounds, and materials.⁷²

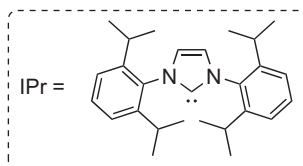
4.1 Carboxylation and Carboxylative Coupling Reactions

CO_2 has gained an increasing popularity as reagent in organic synthesis in the last few years.⁷³ This has been partially motivated by the societal concern over the increasing levels of this greenhouse gas in the atmosphere and its consequences on our global climate. It is unclear whether the use of CO_2 as reactant can be part of the solution to such a complex issue, but in any case CO_2 remains an abundant, inexpensive, and nontoxic C1 carbon source to access carboxylic acids, esters, lactones, or polymers.

In 1994 the copper-catalyzed synthesis of propargylic esters from terminal alkynes, CO_2 , and bromoalkenes was reported by Inoue.⁷⁴



[Cu]	Conditions	Results
CuI (4 mol%)	K ₂ CO ₃ (6 equiv.), DMAc, 100°C	5 entries, 50–89%
[CuCl(IPr)] (10 mol%)	K ₂ CO ₃ (2 equiv.), DMF, 60°C	28 entries, 42–93%
CuI (8 mol%), PEt ₃ (8 mol%)	Cs ₂ CO ₃ (3 equiv.), DMAc, RT	20 entries, 20–99%

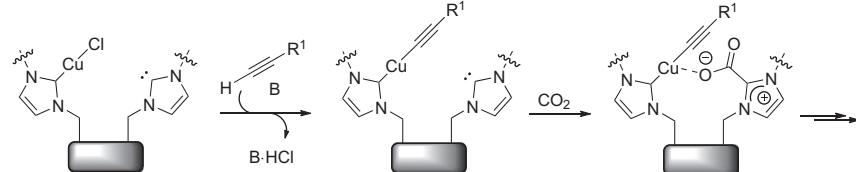
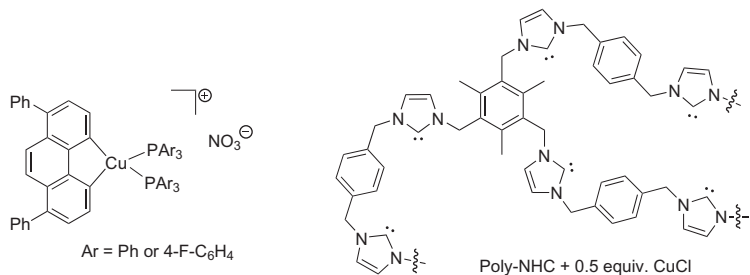


Scheme 16 Copper-catalyzed formation of propiolates.

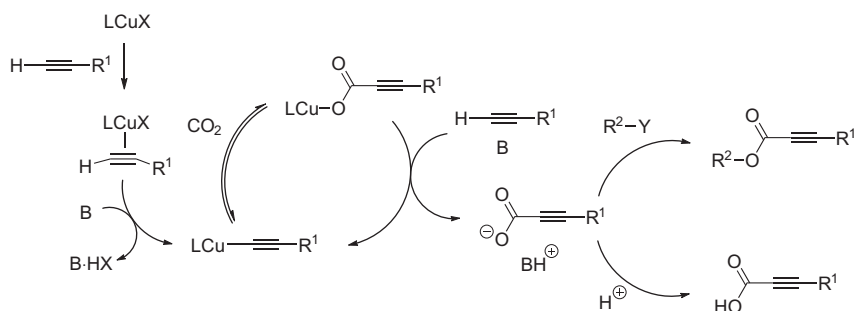
An alkylating reagent was used in order to displace the reaction equilibrium toward the carboxylated products as decarboxylation occurred at temperatures as low as 35°C (Scheme 16). This observation was not surprising since the insertion of CO₂ in organocopper complexes was known to be reversible,⁷⁵ and indeed, copper catalysts have been used in a number of decarboxylative reactions.⁷⁶ Furthermore, early stoichiometric studies had shown that the use of a strong σ -donor ligand was critical for the outcome of the reaction,⁷⁷ and milder conditions and a broader substrate scope were later achieved by using N-heterocyclic carbenes⁷⁸ or alkyl phosphines⁷⁹ as ancillary ligands.⁸⁰

In order to access propiolic acids directly more elaborated catalytic systems were required. In this case it is crucial to keep the reaction conditions mild in order to avoid the decarboxylation of the copper propynoate intermediate. The first reported examples for this reaction were unsurprisingly based on very strong σ -donor ligands such as phenanthroline⁸¹ and poly-NHC ligands⁸² (Scheme 17). The latter example is particularly interesting since it evidenced a notable synergic effect of transition metal catalysis and organocatalysis. Indeed, in this poly-NHC system, half of the imidazol-2-ylidene moieties would support the formation of a copper acetylide, whereas the other half would activate CO₂,⁸³ which would turn the formation of the copper propionate an intramolecular process.

This proposal is slightly different from the generally accepted mechanism for these reactions, where no preactivation of CO₂ is available



Scheme 17 Catalysts for the synthesis of propionic acids from terminal alkynes.



Scheme 18 Proposed mechanism for carboxylation reactions.

(Scheme 18). Assisted deprotonation of the starting alkyne by the carbonate base would form a copper–acetylide intermediate. No detailed studies on these have been reported for this reaction and hence their actual structure remains unknown. The following step, insertion of CO_2 into the copper–carbon bond is believed to be accelerated by the presence of strong σ -donor ligands on the copper center.^{75,77,84} The formed copper–propionate might then be hydrolyzed into the corresponding carboxylic acid or reacted with an alkyl halide to form an ester derivative instead.

Interestingly, the insertion step might better be described as a nucleophilic attack since DFT calculations showed no interaction between copper and

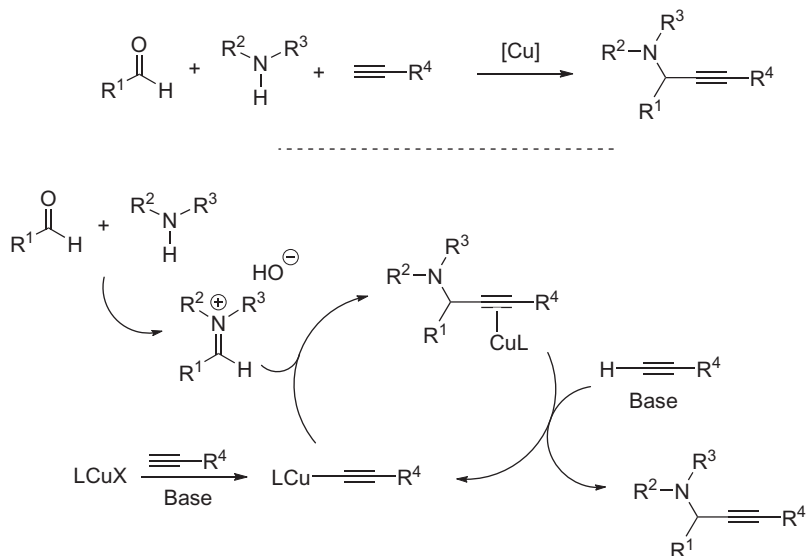
CO₂ in the located transition state.⁸⁵ On the other hand, the steric profile of the ligands and their donor properties could be of importance in this reaction. Indeed, a computational article in early 2010, only months before the effect of ligands in these reactions was reported, found the insertion of CO₂ into an (NHC)Cu–C(ethynyl) bond to be endothermic by 30 kcal mol⁻¹.⁸⁶ However, the model NHC used, 1,3-dimethylimidazol-2-ylidene, is significantly less sterically hindering than IPr,⁷⁸ which could explain the lack of correlation between the theoretical and experimental reports. On the other hand, these calculations were carried out in the context of the related carboxylation of boronic esters, and to date a single example has been reported for the carboxylation of an alkynyl boronic ester, under quite forcing conditions.⁸⁷

4.2 A³-Coupling Reactions

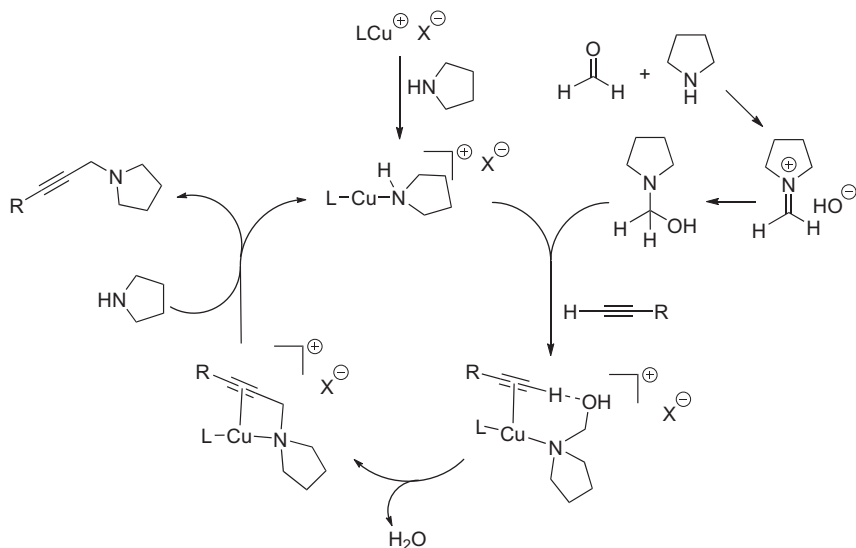
The reaction of an Aldehyde, an Amine, and a terminal Alkyne (AAA = A³) in the presence of a transition metal catalyst is generally known as A³ coupling. The catalytic addition of an alkyne to an in situ generated imine (or enamine) in the presence of copper species has been steadily developed since the first general methodology was reported in the 1990s.⁸⁸ A variety of catalytic systems have allowed for the use of challenging primary amines, the replacement of the aldehyde by acetals or 1,1-dihaloalkanes, and the enantioselective preparation of propargylic amines.⁸⁹

The mechanism of this subtype of Mannich coupling remains again poorly understood, but it is commonly proposed that a copper–acetylide would be formed under catalytic conditions (most probably assisted by π -coordination of the copper and the starting amine) and attack the iminium ion (or imine, depending on the substrates) in order to form the observed propargylic amines (Scheme 19). In fact, the isolation of polymeric alkynylcopper(I) species from these reactions has been reported, as well as the use of such polymers as the copper catalyst in a solvent mixture of water and DMSO.⁹⁰

However, when cationic copper complexes bearing biphenylphosphine ligands were employed as catalysts in this reaction,⁹¹ no alkynylcopper derivatives could be isolated from the reaction mixtures, even if the original compounds were shown to be highly effective in the A³ coupling.⁹² Further stoichiometric experiments pointed toward the formation of a copper–amine intermediate instead, which would support the formation of a propargyl amine via π -coordination, without the involvement of



Scheme 19 A^3 coupling and proposed mechanism.



Scheme 20 Alternative mechanism for the copper-mediated A^3 coupling.

a copper(I)–acetylide (Scheme 20). Even if only pyrrolidine and formaldehyde were considered in this study, it is obvious that further studies are required in order to clarify the role of the copper catalyst in this coupling reaction.



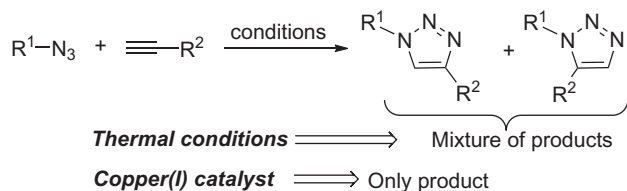
5. 1,3-DIPOLAR CYCLOADDITIONS

5.1 Azide–Alkyne Cycloadditions and Click Chemistry

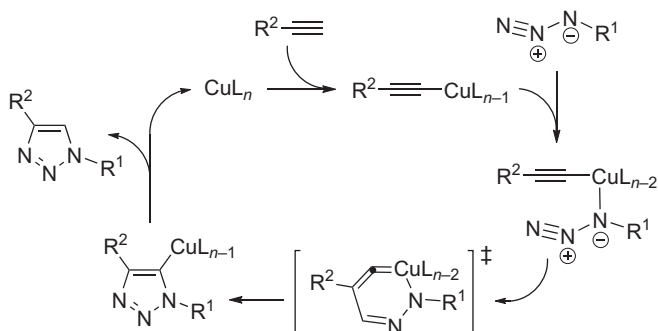
1,3-Dipolar cycloadditions, commonly referred to as Huisgen cycloadditions,⁹³ represent one of the most powerful methodologies for the preparation of a wide range of five-membered heterocycles. Classically carried out under thermal conditions, these [3 + 2] cycloaddition reactions remain very popular reactions particularly due to the development of metal-catalyzed versions.⁹⁴ Indeed, the copper-catalyzed azide–alkyne cycloaddition (CuAAC; *Scheme 21*) has become the first fashionable reaction of the XXI century and it has served as proof of concept of the relevance of Click chemistry, a term coined by Sharpless in 2001.⁹⁵

Even if L'abbé had already reported a copper(I)-catalyzed [3 + 2] cycloaddition reaction in 1984,⁹⁶ the full potential of this reactivity was overlooked until 2002, when Sharpless⁹⁷ and Meldal⁹⁸ reported independently that copper(I) species mediated the cycloaddition of azides and alkynes to yield 1,4-disubstituted-1,2,3-triazoles as single products.⁹⁹ One of the biggest achievements of this transformation is how quickly it has found a myriad of applications in a variety of fields such as polymer and material science,¹⁰⁰ biology,¹⁰¹ or carbohydrate chemistry.¹⁰²

Early efforts in understanding the mechanism of the CuAAC reaction focused on rationalizing the observed regioselectivity as well as the outstanding accelerating effect of the copper catalysts.¹⁰³ DFT calculations showed that π -coordination of the copper center onto a model alkyne (propyne) lowered its pK_a by 10 units.¹⁰⁴ However, a cycloaddition reaction involving such an intermediate, without the deprotonation of the terminal alkyne, actually had a higher energy barrier than the uncatalyzed, thermal reaction. Indeed, only the intermediacy of a copper(I)-acetylide could account for the dramatic increase in the rate of the reaction. Using mononuclear copper-acetylides, the calculations showed that the copper-catalyzed reaction is a



Scheme 21 Cycloaddition reaction of azides and terminal alkynes.



Scheme 22 Early mechanistic proposal for the CuAAC.

stepwise process in which the N3 nitrogen of the azide would attack the C2 carbon of the acetylide forming a then unusual six-membered copper(III) metallacycle transition state (Scheme 22). A reductive elimination would then lead to a triazolide–copper(I) intermediate, which might be easily hydrolyzed to form the final triazole and close the catalytic cycle. Such proposal represents a decrease in the calculated energetic barriers of around 10 kcal mol^{-1} and rationalizes the complete regioselectivity obtained experimentally.

The fact that these reactions are typically run in the presence of air and/or water is by no means incompatible with the intermediacy of copper–acetylides since it is well established that these species can be stable even in acidic aqueous solutions.¹⁰⁵ The fact that homocoupled product issue of a Glaser reaction is rarely encountered in this reactions is a clear indication of the very strong driving force of these cycloadditions, a must in Click chemistry. Similarly, the use of an external base is not required for highly active cycloaddition catalysts.

On the other hand, questions around the actual nuclearity of this reaction mechanism quickly raised since copper–acetylides tend to form polymeric species and exist in solution in dynamic equilibrium of different species (vide supra). Indeed, it was soon established that at low copper concentrations and in the presence N-additives such as phenanthroline, the reaction is second order in copper.^{104,106} Furthermore, di- and tetranuclear copper–acetylides were computed to display an enhanced reactivity toward azides, when compared to mononuclear ones.¹⁰⁷

Notably, the computed copper⋯copper distances and geometries were very similar to the known ladder structures of polymeric alkynylcopper(I) complexes (vide supra, Fig. 4), which were consequently

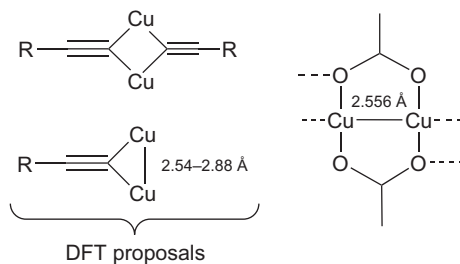


Fig. 4 Dinuclear copper(I) species.

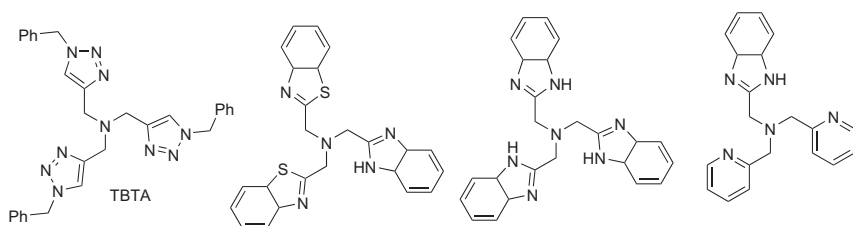


Fig. 5 TBTA and related ligands in CuAAC.

shown to be able to catalyze the reaction, even if the reactivity was not outstanding.¹⁰⁸ Similarly, the dimeric structure of $\text{Cu}(\text{OAc})_2$ also inspired its application in CuAAC.¹⁰⁹ In this case, the copper(II) salt has to be reduced under the reaction conditions, which has been shown to be possible.²⁰

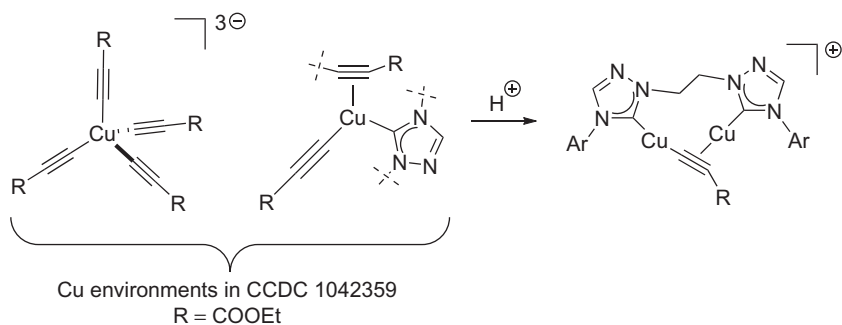
Nevertheless, it is important to note that the order of the CuAAC reaction in copper does not delimit the actual composition of the catalytically active species and the mechanistic picture for this reaction remains far from clear as exemplified by the reports on tris-triazole (and related) ligand-based catalytic systems. Polytriazoles, and TBTA in particular, represent one of the first family of ligands developed specifically for this cycloaddition reaction (Fig. 5).¹¹⁰ Extensive kinetic studies revealed that the choice of the best-performing ligand among these tertiary amines depends on the actual reaction conditions, such as concentration, pH value, and coordinating ability of the solvent. These factors were shown to modify the kinetic profiles as well as the optimal metal/ligand ratios.¹¹¹

Considering the relatively low configurational stability of these ligands and the rich coordination chemistry of copper, it is conceivable that the actual active species and the rate-determining step in this reaction could differ depending on the conditions and the employed copper source/ligand combination.¹¹² Hence, it is not overly surprising that strongly coordinating ligands, and N-heterocyclic carbenes in particular, have played a major role

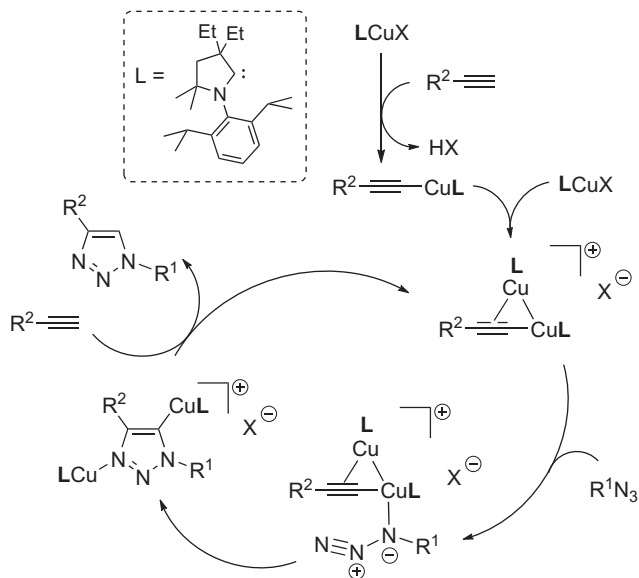
not only in the development of highly performing catalytic systems^{99b} but also in the mechanistic understanding of this transformation.¹¹³ For starting with, a well-defined copper–acetylide cluster bearing bidentate NHCs as ancillary ligands displayed a much higher activity than the previously reported polymeric species.^{108,114} The X-ray analysis of this compound (CCDC 1042359) showed that two of the copper atoms were σ -coordinated by four acetylide ligands, whereas the other six copper centers were connected to one NHC and two acetylides, one in a σ - and another in a π -coordination mode (Scheme 23). Considering its stability, this cluster was proposed to be the catalyst resting state and it could indeed be activated upon addition of acid to release the active dinuclear acetylide complexes supported by the NHC framework.¹¹⁵

Significantly, such dinuclear copper acetylides (with a different NHC ligand) were first evidenced by means of mass spectrometry,¹¹⁶ and even more remarkably, isolated and fully characterized when using a cyclic (alkyl)(amino) carbene (CAAC).¹¹⁷ In this work, a bis(copper)triazolide was also identified and the kinetic studies showed that both mono- and dimeric pathways are active under catalytic conditions, but that the latter is strongly favored (Scheme 24).

The great interest that the CuAAC reaction has gathered has definitely inspired a number of recent mechanistic proposals in other copper-mediated transformations. Without diminishing their relevance, dinuclear copper acetylides cannot necessarily be easily extrapolated to other reactions and if something has become obvious thanks to the CuAAC reaction is that factors such as the ligand or solvent can modify the actual active species and therefore should be taken into account.



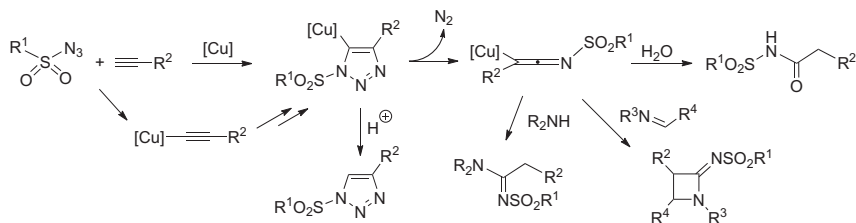
Scheme 23 Isolated copper(I)–acetylide species with NHCs.



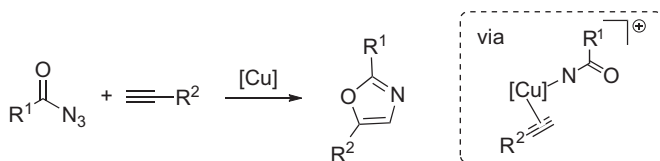
Scheme 24 Mechanistic proposal with L = CAAC.

It is important to note that not all copper-mediated reactions of azides and alkynes lead to the formation of the corresponding triazoles. Noteworthy are the formation of 2,5-disubstituted-1,2,3-triazoles with a palladium(0)/copper(I) bimetallic catalytic system,¹¹⁸ as well as the reactions of electron-poor azides. For the latter, a number of catalytic systems (all of them ligand-based) have been reported for the formation of 4-substituted-1-sulfonyl-1,2,3-triazoles from the corresponding sulfonyl azides.¹¹⁹ However, in this case the corresponding copper-triazolide intermediate has a N–N bond whose cleavage is particularly straightforward, leading to the formation of the corresponding ketimines species that can be then trapped with different nucleophiles such as amines, imines, or water (Scheme 25).¹²⁰

More strikingly, the reaction of ketoazides and alkynes was reported to form 2,5-disubstituted oxazole instead of triazoles (Scheme 26).¹²¹ DFT calculations, together with crossover experiments, precluded the involvement of alkynylcopper species in this case. Instead, they supported a mechanism involving the formation of a copper-nitrene from the starting azide and formation of the oxazole motif after π -coordination of the alkyne to this intermediate in order to form the observed oxazole.¹²²



Scheme 25 Reactivity of *N*-sulfonyl copper–triazolide intermediates.



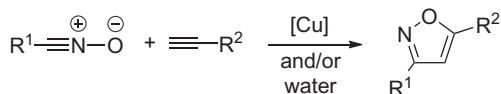
Scheme 26 Reaction of carbonylazides and alkynes.

5.2 Other Cycloaddition Reactions

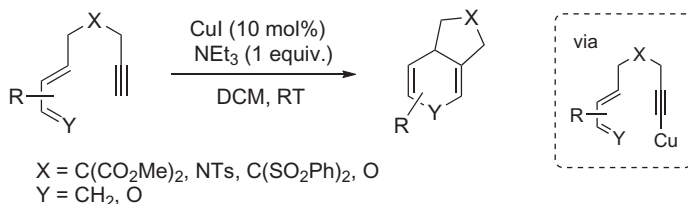
The formation of copper–acetylide derivatives has the general effect of rising the HOMO of the dipolarophile and hence it is not surprising that azides are not the only reactive dipoles for such species.¹²³ Indeed, in the early work published by Sharpless and Fokin, *in situ* generated nitrile oxides were also studied for the synthesis of 3,5-disubstituted isoxazoles and their calculations with monomeric copper–acetylides presented a very similar mechanistic picture with this dipole (Scheme 27).¹⁰⁴ However, comparatively little attention has been paid to this transformation since, which is probably related to the fact that many of these reactions are known to run smoothly in aqueous media without the need of adding a copper source.¹²⁴

The same mechanistic rationale has also been proposed for the intramolecular Diels–Alder cycloaddition of inactivated alkynes.¹²⁵ These reactions proceeded smoothly in the presence of one equivalent of base, suggesting the formation of a copper–acetylide under catalytic conditions (Scheme 28). Labeling experiments together with the fact that only terminal alkynes reacted in the presence of copper species, unlike with gold(I) catalysts, further support this proposal. Nevertheless, no additional mechanistic studies have been reported to date for this transformation.

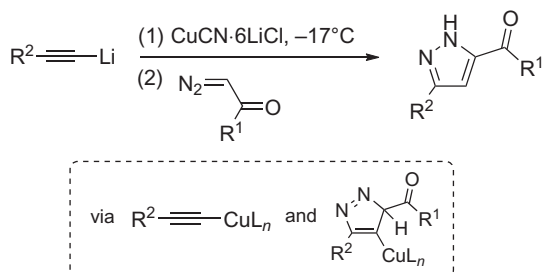
In the case of diazocarbonyl compounds, a third type of propargyl/allenyl anion dipole type, electron-deficient alkynes might be used in cycloaddition reactions in the presence of a Lewis acid, but no simple alkyl or aryl alkynes.¹²⁶ Instead, such inverse electron demand cycloaddition reactions can be mediated by copper(I) catalysts, provided that alkynyl anions are used



Scheme 27 Synthesis of isoxazoles.



Scheme 28 Copper(I)-mediated Diels–Alder reaction.



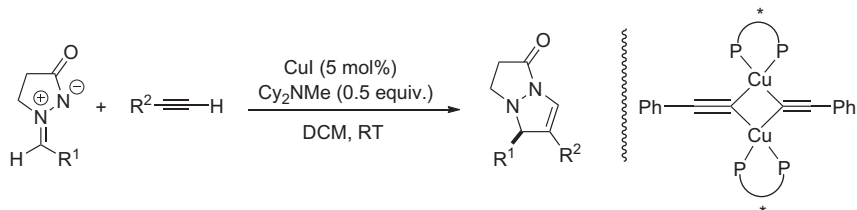
Scheme 29 Lithium acetylides-diazocarbonyl compounds' cycloadditions.

as cycloaddition partners (Scheme 29).¹²⁷ Otherwise, the alkylation product was obtained instead (see Section 3.3).

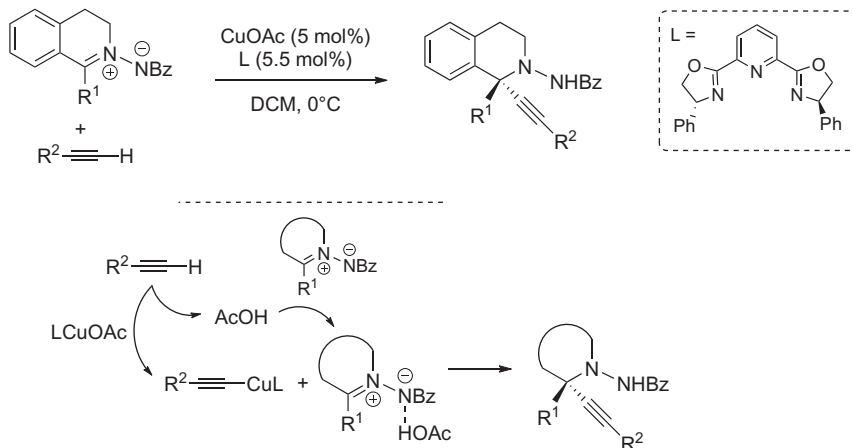
With the support of some preliminary mechanistic studies, the authors proposed that this reaction has a similar catalytic cycle than the CuAAC reaction, with copper–acetylides and pyrazolyl–copper species as intermediates. It is important to note that even if the scope of the reaction was explored with one equivalent of the copper salt, the authors state that the substoichiometric amounts of copper(I) can promote these transformations.

Considering a different family of dipoles, aza-allyl type dipoles, the copper-catalyzed azomethine imine–alkyne cycloaddition reaction was first reported in 2003. A combination of CuI/amine led to the corresponding bicyclic oxopyrazolidines in good yields, and with high enantioselectivities when a phosphoferrocene–oxazoline ligand was used (Scheme 30).¹²⁸

Unsurprisingly, copper–acetylide derivatives were assumed to be intermediates in this reactions, but some experimental evidence only appeared in the literature in 2012, when structurally stable dimeric copper phenylacetylide–(S)-BINAP was shown to be active in this reaction when using only 2.5 mol%



Scheme 30 Azomethine imine–alkyne cycloaddition reactions.



Scheme 31 Alkynylation of azomethine imines.

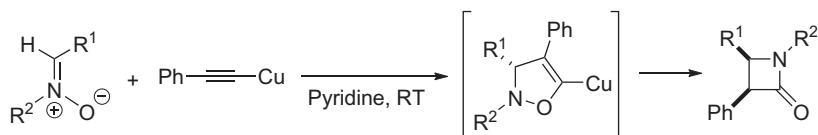
(Scheme 30).¹²⁹ Furthermore, these mechanistic studies strongly supported a stepwise reaction (1,2-addition of copper–acetylide onto the dipole followed by intramolecular cyclization).

It is important to note that in the case of C,N-cyclic azomethine imines only the product issue of a C1-alkynylation was obtained under similar catalytic conditions, with no trace of the related cycloadduct (Scheme 31).¹³⁰ These reactions must be carried out in the absence of a basic additive since the acid formed in the reactions upon the formation of a copper–acetylide intermediate was postulated to play an essential role. Protonation of the azomethine imine would lead to its electrophilic activation toward a nucleophilic attack by the copper acetylide, leading to the observed reaction product. Indeed, the use of a chiral Brønsted as the cocatalyst in these reactions led to improved enantioselectivities and a broader substrate scope.

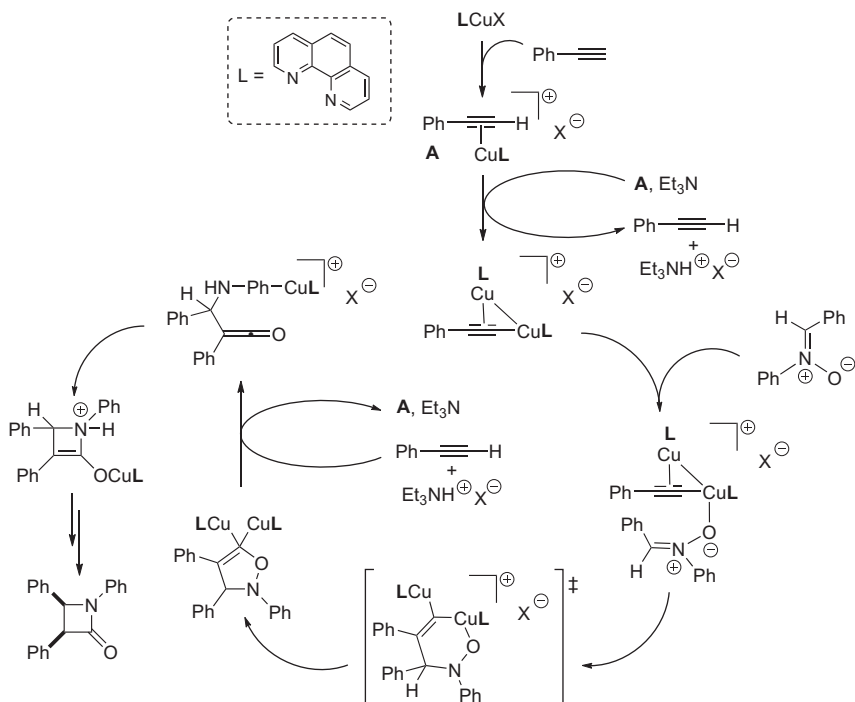
Nitrones, another aza–allyl type dipole, are probably the most popular dipoles for copper-mediated cycloadditions with alkynes, together with azides. Commonly known as the Kinugasa reaction, the original reports were published in the 1970s, with preisolated copper acetylides and nitrones

in anhydrous pyridine to produce β -lactams (Scheme 32).¹³¹ In this reaction, the initial cycloadduct rearranges into its corresponding enolate and a final protonation step delivers the observed 2-azetidinone. The use of ligands such as dppe or phenanthroline allows for the reaction to be catalytic in copper, avoiding the use of preisolated acetylides.¹³² Indeed, nowadays there are a number of user-friendly systems reported for this reaction in protic media including in water and “on water” conditions.¹³³ Ligand design has also led to the synthesis of β -lactams with high enantioselectivities.¹³⁴

A recent theoretical study supported important similarities between the Kinugasa and the CuAAC reactions, with a dicopper-acetylide formed as intermediate under catalytic reactions (Scheme 33).¹³⁵ Nucleophilic attack of the oxygen in the nitron would eventually lead to a six-membered



Scheme 32 Original Kinugasa reaction.



Scheme 33 Proposed mechanism for the Kinugasa reaction.

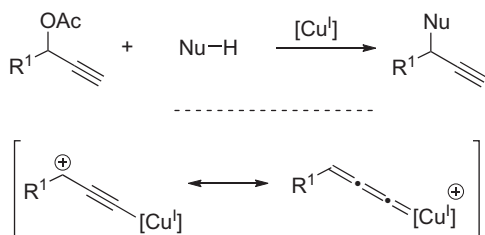
copper(III) transition state and the formation of a C–C bond. The C–O bond would form in the next step, upon a formal reductive elimination. After decoordination of one of the copper centers and protonation of the nitrogen atom, a ring-opening step would generate a ketene intermediate. Cyclization via a nucleophilic attack would again be assisted by the copper center and would lead to the corresponding enolate with the final product being released after hydrolysis and tautomerization.



6. MISCELLANEOUS REACTIONS

The transition metal-catalyzed nucleophilic substitution reaction of propargylic substrates represents a straightforward access to synthetically useful organic compounds such as propargylic amines. Even if they remain far less developed than allylic substitutions, different metals have been reported for these reactions, with ruthenium occupying a prominent place in the literature.¹³⁶ Nevertheless, several high-performing copper catalysts have also been developed in the last few years, including chiral ones.¹³⁷ Compared to Lewis and Brønsted acids, transition metal catalysis has the limitation of only being applicable to monosubstituted alkynes.¹³⁸ This is due to the accepted intermediacy of metal–allenylidene species (Scheme 34). Such complexes are well established with other metals such as ruthenium, which readily reacts with propargylic alcohols to form stable complexes.¹³⁹ However, allenylidene have proved far more elusive with Group 11 metals, and to date a single example with silver has been disclosed.¹⁴⁰

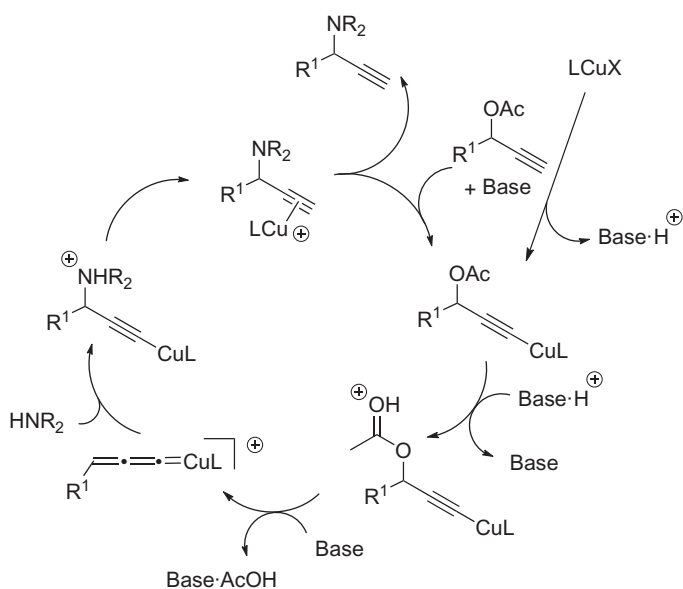
C-, N-, O-, and S-nucleophiles have been used under copper catalysis, but recent advances have mainly focused on N-nucleophiles since this methodology represents a straightforward path to propargylic amines, which are versatile synthons (see also Section 4.2). The copper-catalyzed amination of propargylic acetates was first reported in the 1990s,¹⁴¹ and it took almost



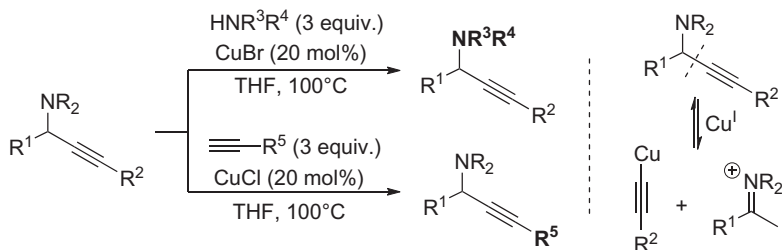
Scheme 34 Nucleophilic substitution reactions and proposed key intermediates.

15 years for the asymmetric version to be developed with either pybox¹⁴² or biphep¹⁴³ ligands. Stoichiometric experiments in the latter case did not allow for the isolation of a copper allenylidene; however, a catalytically active dimeric copper acetylide could be fully characterized.¹⁴⁴ Based on an almost first-order dependence of the reaction to the copper salt and the linear relationship between the *ee* of the ligand and the final product, a monomeric copper acetylide bearing one phosphine ligand was proposed as the active species in this reaction. The full catalytic cycle, supported by DFT calculations, is shown in Scheme 35. After formation of a copper acetylide, the acetate group on the substrate would be protonated and then eliminated to form a carbocation. This electrophilic intermediate would be stabilized by resonance as a copper–allenylidene, which was found to have a relatively weak Cu–C bond. Nucleophilic attack by the amine would form a first propargylic amine that would undergo a proton atom shift to the acetylenic position before being liberated.

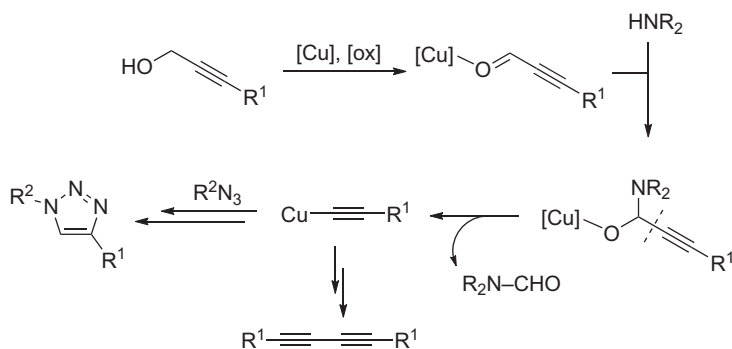
It is important to note that even if a similar cycle is expected to be operative in related substitution reactions, the actual active species might be different depending on the catalytic system. Indeed, dimeric species have recently been privileged in copper-catalyzed propargylic etherification reactions.¹⁴⁵



Scheme 35 Proposed mechanism for the copper-mediated propargylic amination reaction.



Scheme 36 Substitution reactions of propargyl amines.



Scheme 37 Cleavage of a C–C bond in propargylic alcohols.

These propargylic amines can also undergo substitution reactions with secondary amines or monosubstituted alkynes via a copper(I)-mediated C(sp)–C(sp³) bond cleavage (Scheme 36).¹⁴⁶ Amines are poor leaving groups, but such C–C activation would be assisted by the lone pair of the nitrogen to form an iminium intermediate that readily undergoes fragment exchange,¹⁴⁷ preventing the formation of Glaser-type by-products.

Primary propargylic alcohols undergo similar reactions under oxidative conditions (Scheme 37).¹⁴⁸ In this case, it has been proposed that the alcohol group is first oxidized to aldehyde to then react with an amine additive forming a hemiaminal. A copper acetylide would then form upon the cleavage of a C–C bond, to form a diyne, or a 1,4-disubstituted triazole if an organic azide is present (see Sections 2.1 and 5.1 for further details).



7. CONCLUSIONS

Even if major advances have been made, the mechanism and the structure of the actual species involved in these alkyne transformations remain mostly speculative. The well-established tendency of copper to form

polynuclear complexes and the ease of ligand exchange at the metal center make every single mechanistic study a challenging quest. Albeit caution should be applied when extrapolating to other reactions, the intense research around CuAAC has definitely revived the area and shed new light in the understanding of copper acetylide chemistry. This is of great importance not only to improve the efficiency and sustainability credentials of the discussed copper-mediated transformations but also for the discovery of novel ones.

REFERENCES

1. Böttger R. Ueber die Einwirkung des Leuchtgases auf verschiedene Salzsolutionen, insbesondere auf eine ammoniakalische Kupferchlorürlösung. *Annalen*. 1859;109:351–362.
2. (a) Nast R, Pfab W. Alkinyloverbindungen von Übergangsmetallen, V. Mitteil.: Alkinylokomplexe von Kupfer. *Chem Ber*. 1956;89:415–421. (b) Blake D, Calvin G, Coates GE. Copper and silver ethynyl coordination complexes. *Proc Chem Soc*. 1959;396–397.
3. See, for example: (a) Sazonova VA, Kronrod NY. Reaction of potassium fluoborate with styrylmagnesium bromide and phenylethynylmagnesium bromide. *Zh Obshch Khim*. 1956;26:1876–1881; (b) Atkinson RE, Curtis RF, Taylor JA. Naturally-occurring thiophens. Part III. Synthesis of thienyl- and furyl-acetylene derivatives from cuprous acetylides. *J Chem Soc C*. 1967;578–582; (c) Ito H, Arimoto K, Sensui H-O, Hosomi A. Direct alkynyl group transfer from silicon to copper: new preparation method of alkynylcopper(I) reagents. *Tetrahedron Lett*. 1997;38:3977–3980.
4. (a) Owsley DC, Castro CE. Substitution of aryl halides with copper(I) acetylides: 2-phenyl[3,2-*b*]pyridine. *Org Synth*. 1972;52:128–130. (b) Evano G, Jouvin K, Theunissen C, et al. Turning unreactive copper acetylides into remarkably powerful and mild alkyne transfer reagents by oxidative umpolung. *Chem Commun*. 2014;50:10008–10018.
5. Chui SSY, Ng MFY, Che C-M. Structure determination of homoleptic Au^I, Ag^I, and Cu^I aryl/alkylethynyl coordination polymers by X-ray powder diffraction. *Chem Eur J*. 2005;11:1739–1749.
6. For a review, see: Lang H, Jakob A, Milde B. Copper(I) alkyne and alkynide complexes. *Organometallics*. 2012;31:7661–7693.
7. Yam VW-W, Lo KK-W, Fung WK-M, Wang C-R. Design of luminescent polynuclear copper(I) and silver(I) complexes with chalcogenides and acetylides as the bridging ligands. *Coord Chem Rev*. 1998;171:17–41.
8. Qi J, Han MS, Tung C-H. A benzothiazole alkyne fluorescent sensor for Cu detection in living cell. *Bioorg Med Chem Lett*. 2012;22:1747–1749.
9. Judai K, Nishijo J, Nishi N. Self-assembly of copper acetylide molecules into extremely thin nanowires. *Adv Mater*. 2006;18:2842–2846.
10. Krause N, ed. *Modern Organocopper Chemistry*. Weinheim: Wiley-VCH GmbH; 2002.
11. For relevant reviews, see: (a) Allen SE, Walvoord RR, Padilla-Salinas R, Kozlowski MC. Aerobic copper-catalyzed organic reactions. *Chem Rev*. 2013;113:6234–6458; (b) Wendlandt AE, Suess AM, Stahl SS. Copper-catalyzed aerobic oxidative C–H functionalizations: trends and mechanistic insights, copper-catalyzed aerobic oxidative C–H functionalizations: trends and mechanistic insights. *Angew Chem Int Ed*. 2011;50:11062–11087; (c) Shao Z, Peng F. Metal-mediated oxidative cross-coupling of terminal alkynes: a promising strategy for alkyne synthesis. *Angew Chem Int Ed*. 2010;49:9566–9568; (d) Gamez P, Aubel PG, Driessen WL, Reedijk J.

- Homogeneous bio-inspired copper-catalyzed oxidation reactions. *Chem Soc Rev.* 2001;30:376–385.
- (a) Glaser C. Beiträge zur Kenntniss des acetylnylbenzols. *Ber Dtsch Chem Ges.* 1869;2:422–424. (b) Glaser C. Untersuchungen über einige Derivate der Zimmtsäure. *Justus Liebigs Ann Chem.* 1970;154:137–171.
 - For relevant and more comprehensive reviews on this topic, see: (a) Siemsen P, Livingston RC, Diederich F. Acetylenic coupling: a powerful tool in molecular construction. *Angew Chem Int Ed.* 2000;39:2632–2657; (b) Sindhu KS, Anilkumar G. Recent advances and applications of Glaser coupling employing greener protocols. *RSC Adv.* 2014;4:27867–27887.
 - (a) Hay AS. Electrophilic substitution of 1,3-dichloroazulene. *J Org Chem.* 1960;25:1275–1276. (b) Hay AS. Oxidative coupling of acetylenes II. *J Org Chem.* 1962;27:3320–3321.
 - Bohlmann F, Schönowsky H, Inhoffen E, Grau G. Polyacetylenverbindungen, LII. Über den Mechanismus der oxydativen Dimerisierung von Acetylenverbindungen. *Chem Ber.* 1964;97:794–800.
 - (a) Fedenok LG, Berdikov VM, Shvartsberg MS. Kinetics and mechanism of the oxidative condensation of acetylene compounds. I. Dehydrodimerization of phenylacetylene. *Zh Org Khim.* 1973;9:1781–1785. (b) Fedenok LG, Berdikov VM, Shvartsberg MS. Kinetics of the oxidative condensation of acetylenic compounds. IV. Catalytic oxidation of phenylacetylene by oxygen. *Zh Org Khim.* 1976;12:1385–1387.
 - (a) Fedenok LG, Berdikov VM, Shvartsberg MS. Kinetics and mechanism of the oxidative condensation of acetylenic compounds. V. Role of copper(I) acetylenides during the catalytic oxidation of phenylacetylene by oxygen in pyridine. *Zh Org Khim.* 1978;14:1423–1429. (b) Fedenok LG, Berdikov VM, Shvartsberg MS. Kinetics and mechanism of the oxidative condensation of acetylenic compounds. VI. Mechanism of the initial stage of propargyl alcohol oxidation by copper(II) in a buffer solution. *Zh Org Khim.* 1978;14:1429–1432.
 - Fomina L, Vazquez B, Tkatchouk E, Fomine S. The Glaser reaction mechanism. A DFT study. *Tetrahedron.* 2002;58:6741–6747.
 - For a recent example, see: (a) Kang P, Bobyr E, Dustman J, *et al.* Bis (μ -oxo) dicopper(III) species of the simplest peralkylated diamine: enhanced reactivity toward exogenous substrates. *Inorg Chem.* 2010;49:11030–11038. For reviews, see: (b) Mirica LM, Ottenwaelder X, Stack TDP. Structure and spectroscopy of copper–dioxygen complexes. *Chem Rev.* 2004;104:1013–1045; (c) Lewis EA, Tolman WB. Reactivity of dioxygen–copper systems. *Chem Rev.* 2004;104:1047–1076.
 - Zhang G, Yi H, Zhang G, *et al.* Direct observation of reduction of Cu(II) to Cu(I) by terminal alkynes. *J Am Chem Soc.* 2014;136:924–926.
 - Gherman BF, Cramer CJ. Quantum chemical studies of molecules incorporating a $\text{Cu}_2\text{O}_2^{2+}$ core. *Coord Chem Rev.* 2009;253:723–753.
 - Jover J, Spuhler P, Zhao L, McArdle C, Maseras F. Towards a mechanistic understanding of oxidative homocoupling: the Glaser–Hay reaction. *Catal Sci Technol.* 2014;4:4200–4209.
 - Qi X, Bai R, Zhu L, Jin R, Lei A, Lan Y. Mechanism of synergetic Cu(II)/Cu(I)-mediated alkyne coupling: dinuclear 1,2-reductive elimination after minimum energy crossing point. *J Org Chem.* 2016;81:1654–1660.
 - (a) Chodkiewicz W, Cadiot P. New synthesis of symmetrical and asymmetrical conjugated polyacetylenes. *C R Hebd Seances Acad Sci.* 1955;241:1055–1057. (b) Chodkiewicz W. Synthesis of acetylenic compounds. *Ann Chim (Paris).* 1957;2:819–869.

25. For relevant examples, see: (a) Zheng Q, Hua R, Wan Y. An alternative CuCl-piperidine-catalyzed oxidative homocoupling of terminal alkynes affording 1,3-diynes in air. *Appl Organomet Chem.* 2010;24:314–316; (b) Wang D, Li J, Li N, Gao T, Hou S, Chen B. An efficient approach to homocoupling of terminal alkynes: solvent-free synthesis of 1,3-diynes using catalytic Cu(II) and base. *Green Chem.* 2010;12:45–48; (c) Maue M, Bernitzki K, Ellermann M, Schrader T. Bifunctional bisamphiphilic transmembrane building blocks for artificial signal transduction. *Synthesis.* 2008;2247–2256.
26. Yu M, Pan D, Jia W, Chen W, Jiao N. Copper-catalyzed decarboxylative cross-coupling of propionic acids and terminal alkynes. *Tetrahedron Lett.* 2010;51:1287–1290.
27. Dubbaka SR, Kienle M, Mayr H, Knochel P. Copper(I)-mediated oxidative cross-coupling between functionalized alkynyl lithium and aryl magnesium reagents. *Angew Chem Int Ed.* 2007;46:9093–9096.
28. For the formation of similar compounds *via* the oxidative coupling of boronic acids and alkynes, see: (a) Pan C, Luo F, Wang W, Ye Z, Cheng J. Ligand-free copper(I)-catalyzed Sonogashira coupling of arylboronic acids with terminal alkynes. *Tetrahedron Lett.* 2009;50:5044–5046; (b) Rao H, Fu H, Jiang Y, Zhao Y. Highly efficient copper-catalyzed synthesis of internal alkynes *via* aerobic oxidative arylation of terminal alkynes. *Adv Synth Catal.* 2010;352:458–462; (c) Yasukawa T, Miyamura H, Kobayashi S. Copper-catalyzed, aerobic oxidative cross-coupling of alkynes with arylboronic acids: remarkable selectivity in 2,6-lutidine media. *Org Biomol Chem.* 2011;9:6208–6210.
29. (a) Chu L, Qing F-L. Copper-mediated aerobic oxidative trifluoromethylation of terminal alkynes with Me_3SiCF_3 . *J Am Chem Soc.* 2010;132:7262–7263. See also, (b) Tresse C, Guissart C, Schweizer S, *et al.* Practical methods for the synthesis of trifluoromethylated alkynes: oxidative trifluoromethylation of copper acetylides and alkynes. *Adv Synth Catal.* 2014;356:2051–2060 (CF_3^-); (c) Jiang X, Chu L, Qing F-L. Copper-mediated oxidative cross-coupling reaction of terminal alkynes with α -silyldifluoromethylphosphonates: an efficient method for α,α -difluoropropargylphosphonates. *Org Lett.* 2012;14:2870–2873 ($\text{CF}_2\text{P}(\text{O})(\text{OR})_2$); (d) Besset T, Poisson T, Pannecoucke X. Access to difluoromethylated alkynes through the Castro-Stephens reaction. *Eur J Org Chem.* 2014;7220–7225 ($\text{CF}_2\text{COOEt}^-$).
30. Jiang X, Chu L, Qing F-L. Copper-catalyzed oxidative trifluoromethylation of terminal alkynes and aryl boronic acids using (trifluoromethyl)trimethylsilane. *J Org Chem.* 2012;77:1251–1257.
31. Jover J, Maseras F. Computational characterization of a mechanism for the copper-catalyzed aerobic oxidative trifluoromethylation of terminal alkynes. *Chem Commun.* 2013;49:10486–10488.
32. For SCF_3^- , see: Pluta R, Nikolaienko P, Rueping M. Direct catalytic trifluoromethylthiolation of boronic acids and alkynes employing electrophilic shelf-stable *N*-(trifluoromethylthio)phthalimide. *Angew Chem Int Ed.* 2014;53:1650–1653. For SeCF_3^- , see: Lefebvre Q, Pluta R, Rueping M. Copper catalyzed oxidative coupling reactions for trifluoromethylselenolations—synthesis of R-Se CH_3 compounds using air stable tetramethylammonium trifluoromethylselenate. *Chem Commun.* 2015;51:4394–4397.
33. Even if no mechanistic studies have been reported to date, reactions with N-nucleophiles are assumed to go through the formation of copper(II)-acetylides and hence will not be further discussed here. For selected references, see: (a) Peterson LI. A novel synthesis of ynamines. Copper catalyzed oxidation of phenylacetylene in the presence of secondary amines. *Tetrahedron Lett.* 1968;51:5357–5360; (b) Hamada T, Ye X, Stahl SS. Copper-catalyzed aerobic oxidative amidation of terminal alkynes: efficient synthesis of ynamides. *J Am Chem Soc.* 2008;130:833–835; (c) Jia W, Jiao N.

- Cu-catalyzed oxidative amidation of propiolic acids under air via decarboxylative coupling. *Org Lett.* 2010;12:2000–2003; (d) Jouvin K, Heimbürger J, Evano G. Click-alkynylation of N- and P-nucleophiles by oxidative cross-coupling with alkynylcopper reagents: a general synthesis of ynamides and alkynylphosphonates. *Chem Sci.* 2012;3:756–760; (e) Laouiti A, Jouvin K, Bourdreux F, Rammah MM, Rammah MB, Evano G. Oxidative alkynylation of imines with alkynylcopper reagents: a straightforward and practical entry to ynimines. *Synthesis.* 2012;44:1491–1500.
34. (a) Gao Y, Wang G, Chen L, et al. Copper-catalyzed aerobic oxidative coupling of terminal alkynes with H-phosphonates leading to alkynylphosphonates. *J Am Chem Soc.* 2009;131:7956–7957. See also: (b) Jouvin K, Veillard R, Theunissen C, Alayrac C, Gaumont A-C, Evano G. Unprecedented synthesis of alkynylphosphine-boranes through room-temperature oxidative alkynylation. *Org Lett.* 2013;15:4592–4595; (c) Gérard P, Veillard R, Alayrac C, Gaumont A-C, Evano G. Room-temperature alkynylation of phosphine oxides with copper acetylides: practical synthesis of alkynylphosphine oxides. *Eur J Org Chem.* 2016;633–638.
 35. Liu L, Wu Y, Wang Z, Zhu J, Zhao Y. Mechanistic insight into the copper-catalyzed phosphorylation of terminal alkynes: a combined theoretical and experimental study. *J Org Chem.* 2014;79:6816–6822.
 36. For selected references, see: (a) Wei Y, Zhao H, Kan J, Su W, Hong M. Copper-catalyzed direct alkynylation of electron-deficient polyfluoroarenes with terminal alkynes using O₂ as an oxidant. *J Am Chem Soc.* 2010;132:2522–2523; (b) Matsuyama N, Kitahara M, Hirano K, Satoh T, Miura M. Nickel- and copper-catalyzed direct alkynylation of azoles and polyfluoroarenes with terminal alkynes under O₂ or atmospheric conditions. *Org Lett.* 2010;12:2358–2361; (c) Kitahara M, Hirano K, Tsurugi H, Satoh T, Miura M. Copper-mediated direct cross-coupling of 1,3,4-oxadiazoles and oxazoles with terminal alkynes. *Chem Eur J.* 2010;16:1772–1775; (d) Liu Y-J, Liu Y-H, Yin X-S, Gu W-J, Shi B-F. Copper/silver-mediated direct *ortho*-ethynylation of unactivated (hetero)aryl C–H bonds with terminal alkynes. *Chem Eur J.* 2015;21:205–209. For a notable exception, see: Sagadevan A, Ragupathi A, Hwan KC. Photoinduced copper-catalyzed regioselective synthesis of indoles: three-component coupling of arylamines, terminal alkynes, and quinones. *Angew Chem Int Ed.* 2015;54:13896–13901.
 37. (a) Li Z, Li C-J. CuBr-catalyzed efficient alkynylation of sp³ C–H bonds adjacent to a nitrogen atom. *J Am Chem Soc.* 2004;126:11810–11811. (b) Anaya de Parrodi C, Walsh PJ. All kinds of reactivity: recent breakthroughs in metal-catalyzed alkynes chemistry. *Angew Chem Int Ed.* 2009;48:4679–4682.
 38. Correia CA, Li C-J. Copper-catalyzed cross-dehydrogenative coupling (CDC) of alkynes and benzylic C–H bonds. *Adv Synth Catal.* 2010;352:1446–1450.
 39. de Meijere A, Bräse S, Oestreich M, eds. In: *Metal-Catalyzed Cross-Coupling Reactions and More.* vol 1 & 2. Weinheim: Wiley-VCH; 2014.
 40. Diek HA, Heck FR. Palladium catalyzed synthesis of aryl, heterocyclic and vinylic acetylene derivatives. *J Organomet Chem.* 1975;93:259–263.
 41. Cassar L. Synthesis of aryl- and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes. *J Organomet Chem.* 1975;93:253–257.
 42. Sonogashira K, Tohda Y, Hagihara N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* 1975;16:4467–4470. For a review, see: Negishi E-I, Anastasia L. Palladium-catalyzed alkynylation. *Chem Rev.* 2003;103:1979–2017.
 43. Chinchilla R, Nájera C. Recent advances in Sonogashira reactions. *Chem Soc Rev.* 2011;40:5084–5121. Negishi also proposed an alternative mechanism involving a carbopalladation/reductive β-dehydropalladation tandem, see: (a) Negishi E-I. Palladium- or nickel-catalyzed cross-coupling. A new selective method for carbon-carbon bond

- formation. *Acc Chem Res.* 1982;15:340–348; (b) Zhou M-B, Huang X-C, Liu Y-Y, Song R-J, Li J-H. Alkylation of terminal alkynes with transient σ -alkylpalladium(II) complexes: a carboalkynylation route to alkyl-substituted alkynes. *Chem Eur J.* 2014;20:1843–1846.
44. He C, Ke J, Xu H, Lei A. Synergistic catalysis in the Sonogashira coupling reaction: quantitative kinetic investigation of transmetalation. *Angew Chem Int Ed.* 2013;52:1527–1530.
45. (a) Beupérin M, Fayad E, Amardeil R, et al. First copper(I) ferrocenyltetraphosphine complexes: possible involvement in Sonogashira cross-coupling reaction? *Organometallics.* 2008;27:1506–1513. (b) Beupérin M, Job A, Cattey H, Royer S, Meunier P, Hierro J-C. Copper(I) iodide polyphosphine adducts at low loading for Sonogashira alkylation of demanding halide substrates: ligand exchange study between copper and palladium. *Organometallics.* 2010;29:2815–2822.
46. (a) Ozawa F, Fujimori M, Yamamoto T, Yamamoto A. Mechanism of the reaction of *trans*-bis(diethylphenylphosphine)di-*m*-tolylpalladium(II) with methyl iodide affording *m*-xylene. Evidence for a reductive elimination process involving the intermolecular exchange of organic compounds. *Organometallics.* 1986;5:2144–2149. (b) Yagyu T, Hamada M, Osakada K, Yamamoto T. Cationic arylpalladium complexes with chelating diamine ligands, [PdAr(N–N)(solv)]BF₄ (N–N = *N,N,N',N'*-tetramethylethylenediamine, 2,2'-bipyridine, 4,4'-dimethyl-2,2'-bipyridine). Preparation, intermolecular coupling of the aryl ligands, and insertion of alkyne and allene into the Pd–C bond. *Organometallics.* 2001;20:1087–1101. (c) Wang D, Izawa Y, Stahl SS. Pd-catalyzed aerobic oxidative coupling of arenes: evidence for transmetalation between two Pd(II)-aryl intermediates. *J Am Chem Soc.* 2014;136:9914–9917.
47. (a) Osakada K, Sakata R, Yamamoto T. Preparation and properties of *trans*-Pd(Ar)(C≡CPh)(PET₃)₂. Intermolecular alkynyl ligand transfer between copper(I) and palladium(II) complexes relevant to palladium complex catalyzed cross-coupling of terminal alkyne with haloarene in the presence of CuI cocatalyst. *Organometallics.* 1997;16:5354–5364. See also: (b) Espinet P, Formiés J, Martínez F, Sotes M. Synthesis of mono- and polynuclear perhalophenyl palladium–platinum acetylide complexes. Molecular structure of (NBu₄)₂[Pt₂Ag₂(C₆F₅)₄(C≡CPh)₄]·4CH₂Cl₂. *J Organomet Chem.* 1991;403:253–267.
48. Lipshutz BH, Frieman B, Birkedal H. Scavenging and reclaiming phosphines associated with group 10 metal-mediated couplings. *Org Lett.* 2004;6:2305–2308.
49. For selected examples, see: (a) Beleskaya IP, Latyshev GV, Tsvetkov AV, Lukashev NV. The nickel-catalyzed Sonogashira–Hagihara reaction. *Tetrahedron Lett.* 2003;44:5011–5013; (b) Wang L, Li P, Zhang Y. The Sonogashira coupling reaction catalyzed by ultrafine nickel(0) powder. *Chem Commun.* 2004;514–515; (c) Yi J, Lu X, Sun Y-Y, Xiao B, Liu L. Nickel-catalyzed Sonogashira reactions of non-activated secondary alkyl bromides and iodides. *Angew Chem Int Ed.* 2013;52:12409–12413.
50. Vechorkin O, Barmaz D, Proust V, Hu X. Ni-catalyzed Sonogashira coupling of nonactivated alkyl halides: orthogonal functionalization of alkyl iodides, bromides, and chlorides. *J Am Chem Soc.* 2009;131:12078–12079.
51. Pérez García PM, Ren P, Scopelliti R, Hu X. Nickel-catalyzed direct alkylation of terminal alkynes at room temperature: a hemilabile pincer ligand enhances catalytic activity. *ACS Catal.* 2015;5:1164–1171.
52. Gallego D, Brück A, Irran E, et al. From bis(silylene) and bis(germylene) pincer-type nickel(II) complexes to isolable intermediates of the nickel-catalyzed Sonogashira cross-coupling reaction. *J Am Chem Soc.* 2013;135:15617–15626.
53. Stephens RD, Castro CE. The substitution of aryl iodides with cuprous acetylides. A synthesis of tolanes and heterocyclics. *J Org Chem.* 1963;28:3313–3315. See also Ref. 4a.

54. Okuro K, Furuune M, Enna M, Miura M, Nomura M. Synthesis of aryl- and vinylacetylene derivatives by copper-catalyzed reaction of aryl and vinyl iodides with terminal alkynes. *J Org Chem.* 1993;58:4716–4721.
55. (a) Thomas AM, Sujatha A, Anilkumar G. Recent advances and perspectives in copper-catalyzed Sonogashira coupling reactions. *RSC Adv.* 2014;4:21688–21698. (b) Monnier F, Taillefer M. Catalytic C–C, C–N, and C–O Ullmann-type coupling reactions. *Angew Chem Int Ed.* 2009;48:6954–6971. (c) Evano G, Blanchard N, Toumi M. Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis. *Chem Rev.* 2008;108:3054–3131.
56. Zuidema E, Bolm C. Sub-mol % catalyst loading and ligand-acceleration in the copper-catalyzed coupling of aryl iodides and terminal alkynes. *Chem Eur J.* 2010; 16:4181–4185.
57. The secondary amine ligand would also reduce the copper(I) center into active copper(I), see: McGregor WR, Swinbourne FJ. The reaction of iron chlorides with some aliphatic primary amines. *J Inorg Nucl Chem.* 1966;28:1027–1030.
58. For a similar proposition for the stoichiometric reaction, see: Castro CE, Havlin R, Honwad VK, Malte A, Moje S. Copper(I) substitutions. Scope and mechanism of cuprous acetylide substitutions. *J Am Chem Soc.* 1969;91:6464–6470.
59. Zou L-H, Johansson AJ, Zuidema E, Bolm C. Mechanistic insights into copper-catalyzed Sonogashira-Hagihara-type cross-coupling reactions: sub-mol% catalyst loadings and ligand effects. *Chem Eur J.* 2013;19:8144–8152.
60. (a) Wang Z-L, Zhao L, Wang M-X. Construction of C_{aryl}–C_{alkynyl} bond from copper-mediated arene–alkyne and aryl iodide–alkyne cross-coupling reactions: A common aryl–Cu^{III} intermediate in arene C–H activation and Castro–Stephens reaction. *Org Lett* 2012;14:1472–1475. (b) Rovira M, Font M, Acuña-Parés F, et al. Aryl-copper(III)-acetylides as key intermediates in C_{sp2}–C_{sp} model couplings under mild conditions. *Chem Eur J.* 2014;20:10005–10010.
61. Thomé I, Nijs A, Bolm C. Trace metal impurities in catalysis. *Chem Soc Rev.* 2012;41:979–987.
62. Gonda Z, Tolnai GL, Novák Z. Dramatic impact of ppb levels of palladium on the “copper-catalyzed” Sonogashira coupling. *Chem Eur J.* 2010;16:11822–11826.
63. Jones VK, Deutschman Jr AJ. The copper sulfate catalyzed reaction of ethyl diazoacetate and 1-octyne. *J Org Chem.* 1965;30:3978–3979.
64. Suárez A, Fu G. A straightforward and mild synthesis of functionalized 3-alkynoates. *Angew Chem Int Ed.* 2004;43:3580–3582.
65. (a) Hassink M, Liu X, Fox JM. Copper-catalyzed synthesis of 2,4-disubstituted allenates from α -diazoesters. *Org Lett.* 2011;13:2388–2391. (b) Xiao Q, Xia Y, Li H, Zhang Y, Wang J. Coupling of N-tosylhydrazones with terminal alkynes catalyzed by copper(I): synthesis of trisubstituted allenes. *Angew Chem Int Ed.* 2011;50:1114–1117. Di- and trisubstituted allenes have recently been reported from flow-generated diazo compounds with CuI at room temperature, but no rationalization for the divergent selectivity was provided, see: (c) Poh J-S, Tran DN, Battilocchio C, Hawkins JM, Ley SV. A versatile room-temperature route to di- and trisubstituted allenes using flow-generated diazo compounds. *Angew Chem Int Ed.* 2015; 54:7920–7923.
66. (a) Ye F, Ma X, Xiao Q, Li H, Zhang Y, Wang J. C(sp)–C(sp³) bond formation through Cu-catalyzed cross-coupling of N-tosylhydrazones and trialkylsilylalkynes. *J Am Chem Soc.* 2012;134:5742–5745. (b) Wu C, Ye F, Wu G, et al. Synthesis of allenylphosphonates through Cu(I)-catalyzed coupling of terminal alkynes with diazophosphonates. *Synthesis.* 2016;48:751–760.
67. For a similar mechanistic discussion in the related transannulation of pyridotriazoles, see: Helan V, Gulevich AV, Gevorgyan V. Cu-catalyzed transannulation reaction of pyridotriazoles with terminal alkynes under aerobic conditions: efficient synthesis of indolizines. *Chem Sci.* 2015;6:1928–1931.

68. Xia Y, Zhang Y, Wang J. Catalytic cascade reactions involving metal carbene migratory insertion. *ACS Catal.* 2013;3:2586–2598.
69. The insertion of a copper carbenoid into the acetylenic C–H bond has also been proposed and it would not involve the intermediacy of an acetylide derivative. However, this would generate a copper hydride, which seems quite unlikely in this context. See Ref. 65a.
70. Wang T, Wang M, Fang S, Liu J-y. DFT studies on Cu-catalyzed cross-coupling of diazo compounds with trimethylsilylethyne and *tert*-butylethyne: formation of alkynes for trimethylsilylethyne while allenes for *tert*-butylethyne. *Organometallics.* 2014;33:3941–3949.
71. Yoshida H, Morishita T, Nakata H, Ohshita J. Copper-catalyzed 2:1 coupling reaction of arynes with alkynes. *Org Lett.* 2009;11:373–376.
72. (a) Abbiati G, Arcadi A, Marinelli F, Rossi E. Sequential addition and cyclization processes of α,β -ynones and α,β -ynoates containing proximate nucleophiles. *Synthesis.* 2014;46:687–721. (b) Müller TJJ. Synthesis of carbo- and heterocycles via coupling-isomerization reactions. *Synthesis.* 2012;44:159–174. (c) Y. Liu Recent advances on diversity oriented heterocycle synthesis via multicomponent tandem reactions based on A^3 coupling, *ARKIVOC* 2014, 1–20.
73. (a) Cokoja M, Bruckmeier C, Rieger B, Herrmann WA, Kühn FE. Transformation of carbon dioxide with homogeneous transition-metal catalysts: a molecular solution to a global challenge? *Angew Chem Int Ed.* 2011;50:8510–8537. (b) Sakakura T, Choi J-C, Yasuda H. Transformation of carbon dioxide. *Chem Rev.* 2007;107:2365–2387.
74. (a) Fukue Y, Oi S, Inoue Y. Direct synthesis of alkyl 2-alkynoates from alk-1-ynes, CO_2 , and bromoalkanes catalysed by copper(I) or silver(I) salt. *J Chem Soc Chem Commun.* 1994;2091. (b) Oi S, Kufue Y, Nemoto K, Inoue Y. Synthesis of poly(alkyl alkyynoates) from diynes, CO_2 , and alkyl dihalides by a copper(I) salt catalyst. *Macromolecules.* 1996;29:2694–2695.
75. Tsuda T, Chujo Y, Saegusa T. Reversible carbon dioxide fixation by organocopper complexes. *J Chem Soc Chem Commun.* 1975;963–964.
76. For selective recent references, see: (a) Feng Q, Yang K, Song Q. Highly selective copper-catalyzed trifunctionalization of alkynyl carboxylic acids: an efficient route to bis-deuterated β -borylated α,β -styrene. *Chem Commun.* 2015;51:15394–15397; (b) Zhang P, Zhang L, Gao Y, *et al.* Copper-catalyzed tandem phosphination–decarboxylation–oxidation of alkynyl acids with H-phosphine oxides: a facile synthesis of β -ketophosphine oxides. *Chem Commun.* 2015;51:7839–7842; (c) Hu G, Gao Y, Zhao Y. Copper-catalyzed decarboxylative C–P cross-coupling of alkynyl acids with H-phosphine oxides: a facile and selective synthesis of (*E*)-1-alkenylphosphine oxides. *Org Lett.* 2014;16:4464–4467; (d) Priebbenow DL, Becker P, Bolm C. Copper-catalyzed oxidative decarboxylative couplings of sulfoximines and aryl propiolic acids. *Org Lett.* 2013;15:6155–6157; (e) Hu J, Zhao N, Yang B, *et al.* Copper-catalyzed C–P coupling through decarboxylation. *Chem Eur J.* 2011;17:5516–5521; (f) Zhao D, Gao G, Su X, He Y, You J, Xue Y. Copper-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with aryl halides. *Chem Commun.* 2010;46:9049–9051.
77. Tsuda T, Ueda K, Saegusa T. Carbon dioxide insertion into organocopper and organosilver compounds. *J Chem Soc Chem Commun.* 1974;380–381.
78. Zhang W-Z, Li W-J, Zhang X, Zhou H, Lu X-B. Cu(I)-catalyzed carboxylative coupling of terminal alkynes, allylic chlorides, and CO_2 . *Org Lett.* 2010;12:4748–4751.
79. Inamoto K, Asano N, Kobayashi K, Yonemoto M, Kondo Y. A copper-based catalytic system for carboxylation of terminal alkynes: synthesis of alkyl 2-alkynoates. *Org Biomol Chem.* 2012;10:1514–1516.

80. For related examples involving the insertion of CO, see Ref. 54, as well as: Tambade PJ, Patil YP, Nandurkar NS, Bhanage BM. Copper-catalyzed, palladium-free carbonylative Sonogashira coupling of aliphatic and aromatic alkynes with iodoaryls. *Synlett*. 2008;886–888.
81. Gooßen LJ, Rodríguez N, Manjolinho F, Lange PP. Synthesis of propiolic acids *via* copper-catalyzed insertion of carbon dioxide into the C–H bond of terminal alkynes. *Adv Synth Catal*. 2010;352:2913–2917.
82. Yu D, Zhang Y. Copper- and copper-*N*-heterocyclic carbene-catalyzed C–H activating carboxylation of terminal alkynes with CO₂ at ambient conditions. *Proc Natl Acad Sci USA*. 2010;107:20184–20189.
83. (a) Duong HA, Tekavec TN, Arif AM, Louie J. Reversible carboxylation of *N*-heterocyclic carbenes. *Chem Commun*. 2004;112–113. (b) Kayaki Y, Yamamoto M, Ikariya T. *N*-Heterocyclic carbenes as efficient organocatalysts for CO₂ fixation reactions. *Angew Chem Int Ed*. 2009;48:4194–4197.
84. Ohishi T, Nishiura M, Hou Z. Carboxylation of organoboronic esters catalyzed by *N*-heterocyclic carbene copper(I) complexes. *Angew Chem Int Ed*. 2008;47: 5792–5795.
85. Jover J, Maseras F. Computational characterization of the mechanism for coinage-metal-catalyzed carboxylation of terminal alkynes. *J Org Chem*. 2014;79:11981–11987.
86. Dang L, Lin Z, Marder TB. DFT studies on the carboxylation of arylboronate esters with CO₂ catalyzed by copper(I) complexes. *Organometallics*. 2010;29:917–927.
87. Riss PJ, Lu S, Telu S, Aigbirhio FI, Pike VW. Cu^I-catalyzed ¹¹C carboxylation of boronic acid esters: a rapid and convenient entry to ¹¹C-labeled carboxylic acids, esters, and amides. *Angew Chem Int Ed*. 2012;51:2698–2702.
88. Dyatkin AB, Rivero RA. The solid phase synthesis of complex propargylamines using the combination of Sonogashira and Mannich reactions. *Tetrahedron Lett*. 1998;39: 3647–3650.
89. Peshkov VA, Pereshivko OP, Van der Eycken EV. A walk around the A³-coupling. *Chem Soc Rev*. 2012;41:3790–3807.
90. Buckley BR, Khan AN, Heaney H. Mannich reactions of alkynes: mechanistic insights and the role of sub-stoichiometric amounts of alkynylcopper(I) compounds in the catalytic cycle. *Chem Eur J*. 2012;18:3855–3858.
91. (a) Grirrane A, Álvarez E, García H, Corma A. Deactivation of cationic Cu^I and Au^I catalysts for A³ coupling by CH₂Cl₂: mechanistic implications of the formation of neutral Cu^I and Au^I chlorides. *Angew Chem Int Ed*. 2014;53:7253–7258. (b) Grirrane A, Álvarez E, García H, Corma A. Cationic copper(I) complexes as highly efficient catalysts for single and double A³-coupling Mannich reactions of terminal alkynes: mechanistic insights and comparative studies with analogous gold(I) complexes. *Chem Eur J*. 2014;20:14317–14328.
92. Analogue gold derivatives did form digold complexes with phenylacetylene, see: Grirrane A, Álvarez E, García H, Corma A. Intermolecular [2+2] cycloaddition of alkyne-alkene catalyzed by Au(I) complexes. What are the catalytic sites involved? *ACS Catal*. 2011;1:1647–1653.
93. Huisgen R. Kinetics and reaction mechanisms: selected examples from the experience of forty years. *Pure Appl Chem*. 1989;61:613–628.
94. (a) Singh MS, Chowdhury S, Koley S. Progress in 1,3-dipolar cycloadditions in the recent decade: an update to strategic development towards the arsenal of organic synthesis. *Tetrahedron*. 2016;72:1603–1644. (b) Hashimoto T, Maruoka K. Recent advances of catalytic asymmetric 1,3-dipolar cycloadditions. *Chem Rev*. 2015;115: 5366–5412. (c) Wang L-J, Tang Y. Intermolecular 1,3-dipolar cycloadditions of alkenes, alkynes, and allenes. In: Knochel P, Molander GA, eds. 2nd ed. *Comprehensive Organic Synthesis*. vol 4: Amsterdam: Elsevier. 2014:1342–1383. (d) Monon R, Nair V. Intramolecular 1,3-dipolar cycloadditions of alkenes, alkynes, and allenes. 2nd ed. *Comprehensive Organic Synthesis*. vol 4:2014:1281–1341.

95. Kolb HC, Finn MG, Sharpless KB. Click chemistry: diverse chemical function from a few good reactions. *Angew Chem Int Ed.* 2001;40:2004–2021.
96. L'abbé G. Are azidocumules accessible? *Bull Soc Chim Belg.* 2010;93:579–592.
97. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective “ligation” of azides and terminal alkynes. *Angew Chem Int Ed.* 2002;41:2596–2599.
98. Tornøe CW, Christensen C, Meldal M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regioselective copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J Org Chem.* 2002;67:3057–3064.
99. (a) Haldón E, Nicasio MC, Pérez PJ. Copper-catalyzed azide–alkyne cycloadditions (CuAAC): an update. *Org Biomol Chem.* 2015;13:9528–9550. (b) Díez-González S. Well-defined copper(I) complexes for Click azide–alkyne cycloaddition reactions: one Click beyond. *Catal Sci Technol.* 2011;1:166–178. (c) Special issue on Click chemistry. *Chem Soc Rev.* 2010;39:1221–1408. (d) Meldal M, Tornøe CW. Cu-catalyzed azide–alkyne cycloaddition. *Chem Rev.* 2008;108:2952–3015.
100. (a) Delaittre G, Guimard NK, Barner-Kowollik C. Cycloadditions in modern polymer chemistry. *Acc Chem Res.* 2015;48:1296–1307. (b) Espeel P, Prez FEDu. “Click”-inspired chemistry in macromolecular science: matching recent progress and user expectations. *Macromolecules.* 2015;48:2–14. (c) Lutz JF. 1,3-Dipolar cycloadditions of azides and alkynes: a universal ligation tool in polymer and materials science. *Angew Chem Int Ed.* 2007;46:1018–1025.
101. (a) Castro V, Rodríguez H, Albericio F. CuAAC: an efficient click chemistry reaction on solid phase. *ACS Comb Sci.* 2016;18:1–14. (b) Tang W, Becker ML. “Click” reactions: a versatile toolbox for the synthesis of peptide conjugates. *Chem Soc Rev.* 2014;43:7013–7039. (c) El-Sagheer AH, Brown T. Click nucleic acid ligation: applications in biology and nanotechnology. *Acc Chem Res.* 2012;45:1258–1267. (d) Agalave SG, Maujan SR, Pore VS. Click chemistry: 1,2,3-triazoles as pharmacophores. *Chem Asian J.* 2011;6:2696–2718.
102. Tiwari TVK, Mishra BB, Mishra KB, Mishra N, Singh AS, Chi X. Cu-catalyzed click reaction in carbohydrate chemistry. *Chem Rev.* 2016;116:3086–3240.
103. For an early review on the mechanism of this reaction, see: Bock VD, Hiemstra H, van Maarseveen JH. Cu^I-catalyzed alkyne–azide “click” cycloadditions from a mechanistic and synthetic perspective. *Eur J Org Chem.* 2005;51–68.
104. Himo F, Lovell T, Hilgraf R, et al. Copper(I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates. *J Am Chem Soc.* 2005;127: 210–216.
105. Mykhalichko BM, Temkin ON, Mys'kiv MG. Polynuclear complexes of copper(I) halides: coordination chemistry and catalytic transformations of alkynes. *Russ Chem Rev.* 2000;69:957–984.
106. Rodionov VO, Fokin VV, Finn MG. Mechanism of the ligand-free Cu^I-catalyzed azide–alkyne cycloaddition reaction. *Angew Chem Int Ed.* 2005;44:2210–2215.
107. (a) Straub BF. μ -Acetylide and μ -alkenylidene ligands in “click” triazoles syntheses. *Chem Commun.* 2007;3868–3870. (b) Ahlquist M, Fokin VV. Enhanced reactivity of dinuclear copper(I) acetylides in dipolar cycloadditions. *Organometallics.* 2007;26: 4389–4391.
108. (a) Buckley BR, Dann SE, Harris DP, Heaney H, Stubbs EC. Alkynylcopper (I) polymers and their use in a mechanistic study of alkyne–azide click reactions. *Chem Commun.* 2010;46:2274–2276. (b) Buckley BR, Dann SE, Heaney H. Experimental evidence for the involvement of dinuclear alkynylcopper(I) complexes in alkyne–azide chemistry. *Chem Eur J.* 2010;16:6278–6284. (c) Buckley BR, Dann SE, Heaney H, Stubbs EC. Heterogeneous catalytic reactions “on water” by using stable polymeric alkynylcopper(I) pre-catalysts: alkyne/azide cycloaddition reactions. *Eur J Org Chem.* 2011;770–776.

109. (a) Shai C, Cheng G, Su D, Xu J, Wang X, Hu Y. Copper(I): a structurally simple but highly efficient dinuclear catalyst for copper-catalyzed azide-alkyne cycloaddition. *Adv Synth Catal.* 2010;352:1587–1592. (b) Gonda Z, Novák Z. Highly active copper-catalysts for azide-alkyne cycloadditions. *Dalton Trans.* 2010;39:726–729.
110. Chan TR, Hilgraf R, Sharpless KB, Fokin VV. Polytriazoles as copper(I)-stabilizing ligands in catalysis. *Org Lett.* 2004;6:2853–2855.
111. (a) Rodionov VO, Presolski SI, Gardinier S, Lim YH, Finn MG. Benzimidazole and related ligands for Cu-catalyzed alkyne-alkyne cycloaddition. *J Am Chem Soc.* 2007;129:12696–12704. (b) Rodionov VO, Presolski SI, Diaz DD, Fokin VV, Finn MG. Ligand-accelerated Cu-catalyzed azide-alkyne cycloaddition: a mechanistic report. *J Am Chem Soc.* 2007;129:12705–12712. (c) Bevilacqua V, King M, Chaumonot M, et al. Copper-chelating azides for efficient click conjugation reactions in complex media. *Angew Chem Int Ed.* 2014;53:5872–5876.
112. Kalvet I, Tammiku-Taul J, Mäeorg U, Tämm K, Burk P, Sikk L. NMR and DFT study of the copper(I)-catalyzed cycloaddition reaction: H/D scrambling of alkynes and variable reaction order of the catalyst. *ChemCatChem.* 2016;8:1804–1808.
113. (a) Nolte C, Mayer P, Straub BF. Isolation of a copper(I) triazolide: a “click” intermediate. *Angew Chem Int Ed.* 2007;46:2101–2103. (b) Díez-González S, Nolan SP. [(NHC)₂Cu]X complexes as efficient catalyst for azide-alkyne Click chemistry at low catalyst loadings. *Angew Chem Int Ed.* 2008;47:8881–8884.
114. Makarem A, Berg R, Rominger F, Straub BF. A fluxional copper acetylide cluster in CuAAC catalysis. *Angew Chem Int Ed.* 2015;54:7431–7435.
115. Berg R, Straub J, Schreiner E, Marder S, Rominger F, Straub BF. Highly active dinuclear copper catalysts for homogeneous azide-alkyne cycloadditions. *Adv Synth Catal.* 2012;354:3445–3450.
116. Worrel BT, Malik JA, Fokin VV. Direct evidence of a dinuclear copper intermediate in Cu(I)-catalyzed azide-alkyne cycloadditions. *Science.* 2013;340:457–460. For a related example with a phosphine ligand, see: Iacobucci C, Reale S, Gal J-F, De Angelis F. Dinuclear copper intermediates in copper(I)-catalyzed azide-alkyne cycloaddition directly observed by electrospray ionization mass spectrometry. *Angew Chem Int Ed.* 2015;54:3065–3068.
117. (a) Jin L, Tolentino DR, Melaimi M, Bertrand G. Isolation of bis(copper) key intermediates in Cu-catalyzed azide-alkyne “click reaction” *Sci Adv.* 2015;1: e1500304. (b) Jin L, Romero EA, Melaimi M, Bertrand G. The Janus face of the X ligand in the copper-catalyzed azide-alkyne cycloaddition. *J Am Chem Soc.* 2015;137:15696–15698.
118. (a) Kamijo S, Jin T, Huo Z, Yamamoto Y. Synthesis of triazoles from nonactivated terminal alkynes via the three-component coupling reaction using a Pd(0)-Cu(I) bimetallic catalyst. *J Am Chem Soc.* 2003;125:7786–7787. (b) Kamijo S, Jin T, Huo Z, Yamamoto Y. A one-pot procedure for the regiocontrolled synthesis of allyltriazoles via de Pd-Cu bimetallic catalyzed three-component coupling reaction of nonactivated terminal alkynes, allyl carbonate, and trimethylsilyl azide. *J Org Chem* 2004;69:2386–2393.
119. For early examples, see: (a) Yoo EJ, Ahlquist M, Kim SH, et al. Copper-catalyzed synthesis of N-sulfonyl-1,2,3-triazoles: controlling selectivity. *Angew Chem Int Ed.* 2007;46:1730–1733; (b) Wang F, Fu H, Jiang YY, Zhao YF. Copper-catalyzed cycloaddition of sulfonyl azides with alkynes to synthesize N-sulfonyltriazoles ‘on water’ at room temperature. *Adv Synth Catal.* 2008;350:1830–1834; (c) Raushel J, Fokin VV. Efficient synthesis of 1-sulfonyl-1,2,3-triazoles. *Org Lett.* 2010;12:4952–4955; (d) Cano I, Nicasio MC, Perez PJ. Copper(I) complexes as catalysts for the synthesis of N-sulfonyl-1,2,3-triazoles from N-sulfonylazides and alkynes. *Org Biomol Chem.* 2010;8:536–538.

120. For early examples with different nucleophiles, see: (a) Bae I, Han H, Chang S. Highly efficient one-pot synthesis of *N*-sulfonylamidines by Cu-catalyzed three component coupling of sulfonyl azide, alkyne, and amine. *J Am Chem Soc.* 2005;127:2038–2039; (b) Cho SH, Yoo EJ, Bae L, Chang S. Copper-catalyzed hydrative amide synthesis with terminal alkyne, sulfonyl azide, and water. *J Am Chem Soc.* 2005;127:16046–16047; (c) Cassidy MP, Raushel J, Fokin VV. Practical synthesis of amides from in situ generated copper(I) acetylides and sulfonyl azides. *Angew Chem Int Ed.* 2006;45:3154–3157; (d) Whiting M, Fokin VV. Copper-catalyzed reaction cascade: direct conversion of alkynes into *N*-sulfonylazetidino-2-imines. *Angew Chem Int Ed.* 2006;45:3157–3161; (e) Cho SH, Chang S. Rate-accelerated nonconventional amide synthesis in water: a practical catalytic aldol-surrogate reaction. *Angew Chem Int Ed.* 2007;46:1897–1900.
121. Cano I, Álvarez E, Nicasio MC, Pérez PJ. Regioselective formation of 2,5-disubstituted oxazoles via copper(I)-catalyzed cycloaddition of acyl azides and 1-alkynes. *J Am Chem Soc.* 2011;133:191–193.
122. Haldón E, Besora M, Cano I, et al. Reaction of alkynes and azides: not triazoles through copper-acetylides but oxazoles through copper-nitrene intermediates. *Chem Eur J.* 2014;20:3463–3474.
123. Stanley LM, Sibi MP. Enantioselective copper-catalyzed 1,3-dipolar cycloadditions. *Chem Rev.* 2008;108:2887–2902.
124. For selected examples, see: (a) Scobie M, Threadgill MD. Tumor-targeted boranes. 4. Synthesis of nitroimidazole-carboranes with polyether-isoxazole links. *J Org Chem.* 1994;59:7008–7013; (b) Raihan MJ, Kavala V, Kuo C-W, Raju BR, Yao C-F. 'On water' synthesis of chromeno-isoxazoles mediated by [hydroxyl(tosyloxy)iodo]benzene (HTIB). *Green Chem.* 2010;12:1090–1096; (c) Trogu E, Vinattieri C, De Sarlo F, Machetti F. Acid-base-catalysed condensation reaction in water: isoxazolines and isoxazoles from nitroacetates and dipolarophiles. *Chem Eur J.* 2012;18:2081–2093.
125. (a) Fürstner A, Stimson CC. Two manifolds for metal-catalyzed intramolecular Diels–Alder reactions of unactivated alkynes. *Angew Chem Int Ed.* 2007;46:8845–8849. For a related reaction, see: (b) Khoshkholgh MJ, Balalaie S, Bijanzadeh HR, Gross JH. Copper(I) iodide catalyzed domino Knoevenagel hetero-Diels–Alder reaction of terminal acetylenes: synthesis of pyrano[2,3-*c*]pyrazoles. *Synlett.* 2009;55–58
126. Maas G, Diazoalkanes. In: Padwa A, Pearson WH, eds. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*. Hoboken: Wiley; 2003:623–680.
127. Qi X, Ready JM. Copper-promoted cycloaddition of diazocarbonyl compounds and acetylides. *Angew Chem Int Ed.* 2007;46:3242–3244.
128. Shintani R, Fu GC. A new copper-catalyzed [3+2] cycloaddition: enantioselective coupling of terminal alkynes with azomethine imines to generate five-membered nitrogen heterocycles. *J Am Chem Soc.* 2003;125:10778–10779.
129. Imaizumi T, Yamashita Y, Kobayashi S. Group 11 metal amide-catalyzed asymmetric cycloaddition reactions of azomethine imines with terminal alkynes. *J Am Chem Soc.* 2012;134:20049–20052.
130. (a) Hashimoto T, Omote M, Maruoka K. Catalytic asymmetric alkynylation of C1-substituted C,N-cyclic azomethine imines by Cu^I/chiral Bronsted acid co-catalyst. *Angew Chem Int Ed.* 2011;50:8952–8955. See also: (b) Hashimoto T, Takiguchi Y, Maruoka K. Catalytic asymmetric three-component 1,3-dipolar cycloaddition of aldehydes, hydrazides, and alkynes. *J Am Chem Soc.* 2013;135:11473–11476; (c) Das D, Sun AX, Seidel D. Redox-neutral copper(II) carboxylate catalyzed α -alkynylation of amines. *Angew Chem Int Ed.* 2013;52:3765–3769.
131. Kinugasa M, Hashimoto S. The reactions of copper(I) phenylacetylide with nitrones. *J Chem Soc Chem Commun.* 1972;466–467.

132. (a) Okuro K, Enna M, Miura M, Nomura M. Copper-catalyzed reaction of arylacetylenes with C,N-diarylnitrones. *J Chem Soc Chem Commun.* 1993; 1107–1108. (b) Ye M-C, Zhou J, Tang Y. Trisoxazoline/Cu(II)-promoted Kinugasa reaction. Enantioselective synthesis of β -lactams. *J Org Chem.* 2006;71:3576–3582. (c) Mames A, Stecko S, Mikołajczyk P, Soluch M, Furman B, Chmielewski M. Direct, catalytic synthesis of carbapenams via cycloaddition/rearrangement cascade reaction: unexpected acetylenes' structure effect. *J Org Chem.* 2010;75:7580–7587.
133. Chigrinova M, MacKenzie DA, Sherratt AR, Cheung LLW, Pezacki JP. Kinugasa reactions in water: from green chemistry to bioorthogonal labelling. *Molecules.* 2015;20:6959–6969.
134. For leading references, see: (a) Miura M, Enna M, Okuro K, Nomura M. Copper-catalyzed reaction of terminal alkynes with nitrones. Selective synthesis of 1-aza-1-buten-3-yne and 2-azetidinone derivatives. *J Org Chem.* 1995;60:4999–5004; (b) Shintani S, Fu GC. Catalytic enantioselective synthesis of β -lactams: intramolecular Kinugasa reactions and interception of an intermediate in the reaction cascade. *Angew Chem Int Ed.* 2003;42:4082–4085.
135. Santoro S, Liao R-Z, Marcelli T, Hammar P, Himo F. Theoretical study of mechanism and stereoselectivity of catalytic Kinugasa reaction. *J Org Chem.* 2015;80:2649–2660.
136. (a) Nishibayashi Y. Transition-metal-catalyzed enantioselective propargylic substitution reactions of propargylic alcohol derivatives with nucleophiles. *Synthesis.* 2012;44:489–503. (b) Bauer EB. Transition-metal-catalyzed functionalization of propargylic alcohols and their derivatives. *Synthesis.* 2012;44:1131–1151. (c) Ljungdahl N, Kann N. Transition-metal-catalyzed propargylic substitution. *Angew Chem Int Ed.* 2009;48:642–644.
137. (a) Zhang L, Fang G, Kumar RK, Bi X. Coinage-metal-catalyzed reactions of propargylic alcohols. *Synthesis.* 2015;47:2317–2346. (b) Zhang D-Y, Hu X-P. Recent advances in copper-catalyzed propargylic substitution. *Tetrahedron Lett.* 2015;56:283–295.
138. (a) Detz RJ, Hiemstra H, van Maarseveen JH. Catalyzed propargylic substitution. *Eur J Org Chem.* 2009;6263–6279. (b) Miyake Y, Uemura S, Hishibayashi Y. Catalytic propargylic substitution reactions. *ChemCatChem.* 2009;1:342–356.
139. Cadierno V, Gimeno J. Allenylidene and higher cumulenyliidene complexes. *Chem Rev.* 2009;109:3512–3560.
140. Asay M, Donnadiou B, Schoeller WW, Bertrand G. Synthesis of allenylidene lithium and silver complexes, and subsequent transmetalation reactions. *Angew Chem Int Ed.* 2009;48:4796–4799.
141. Imada Y, Yuasa M, Nakamura I, Murahashi S-I. Direct azole amination: C–H functionalization as a new approach to biologically important heterocycles. *J Org Chem.* 1994;59:2282–2284. For the reaction of propargylic chlorides, see: Hennion GF, Hanzel RS. The alkylation of amines with t-acetylenic chlorides. Preparation of sterically hindered amines. *J Am Chem Soc.* 1960;82:4908–4912.
142. Detz RJ, Delville MME, Hiemstra H, van Maarseveen JH. Enantioselective copper-catalyzed propargylic amination. *Angew Chem Int Ed.* 2008;47:3777–3780.
143. Hattori G, Matsuzawa H, Miyake Y, Nishibayashi Y. Copper-catalyzed asymmetric propargylic substitution reactions of propargylic acetates with amines. *Angew Chem Int Ed.* 2008;47:3781–3783.
144. Hattori G, Sakata K, Matsuzawa H, Tanabe Y, Miyake Y, Nishibayashi Y. Copper-catalyzed enantioselective propargylic amination of propargylic esters with amines: copper-allenylidene complexes as key intermediates. *J Am Chem Soc.* 2010; 132:10592–10608.
145. Nakajima K, Shibata M, Nishibayashi Y. Copper-catalyzed enantioselective propargylic etherification of propargylic esters with alcohols. *J Am Chem Soc.* 2015;137:2472–2475.

146. (a) Sugiishi T, Kimura A, Nakamura H. Copper(I)-catalyzed substitution reactions of propargylic amines: importance of C(sp)–C(sp³) bond cleavage in generation of iminium intermediates. *J Am Chem Soc.* 2010;132:5332–5333. (b) Kim Y, Nakamura H. Copper(I)-catalyzed deacetylenative coupling of propargylic amines: an efficient synthesis of symmetric 1,4-diamino-2-butyne. *Chem Eur J.* 2011;17:12561–12563.
147. See Section 4.2 for more details on addition reactions to enamines and imines.
148. Kang Y-W, Cho YJ, Ko K-Y, Jang H-Y. Copper-catalyzed carbon–carbon bond cleavage of primary propargyl alcohols: β -carbon elimination of hemiaminal intermediates. *Catal Sci Technol.* 2015;5:3931–3934.