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Digest Paper

Recent progress in copper-catalyzed difunctionalization of unactivated carbon—carbon multiple bonds

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ABSTRACT

Copper-catalyzed difunctionalization of unactivated carbon—carbon multiple bonds involving a carbon—carbon bond formation process is reviewed. Carboamination, carbooxygenation, carboboration, and other difunctionalization reactions of alkenes, alkynes, and allenes are described.

Contents

Introduction

Difunctionalization of unactivated carbon—carbon (C—C) multiple bonds, adding two distinct functional groups on each side of the C—C bond, in a single operation is one of the most attractive transformations in organic chemistry.[1] Typically, insertion of a C—C multiple bond (reactant 1) into a metal—X bond (reactant 2) generates an organometallic species in situ, which reacts with a third reactant (reactant 3) to give a difunctionalized product. Products with wide structural diversity can be synthesized by changing the combination of reactants in this three-component reaction. Combining two different bond-forming processes in one pot contributes to both step-[2] and atom-economy[3], and reduces laborious isolation and purification operations, leading to rapid synthesis of the target molecules. In addition, the difunctionalization reaction can form unstable, reactive organometallic intermediates that are

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otherwise difficult to generate. Such reactions should be designed with compatible consecutive bond-forming steps.

Copper catalysts promote various reaction types due to multiple abilities of the copper atom acting as a Lewis acid, a π-acid, a single-electron mediator, and a two-electron mediator. In addition, Cu—X species generated as reaction intermediates can act as either a nucleophile or an electrophile, depending on the reaction conditions and oxidation state of the copper atom. Such properties of copper species account for the high utility of copper catalysts in the difunctionalization of C—C multiple bonds.

Although it is difficult to clarify the precise mechanism underlying a copper-catalyzed reaction, for convenience, we classified the copper-catalyzed difunctionalization of C—C multiple bonds into three types according to the expected role of the copper catalysts in the first bond-formation step (Scheme 1). Type A involves nucleocupration of C—C multiple bonds with a nucleophilic Cu—X species (X = C, N, O, etc.) to generate organocopper intermediates **A**, which can act as either nucleophiles or radical precursors. Type B involves activation of C—C multiple bonds by organocopper(III) species, generating electrophilic carbocation-like species **B** or organocopper(III) species **C**. Type C involves the formation of radical species through single-electron transfer from a copper catalyst to a precursor (e.g., organohalides) and subsequent addition of the thus-generated radical species to C—C multiple bonds, generating elongated carbon radical **D** or organocopper species **E** after recombination with a copper catalyst.

Historically, the first example of copper-mediated difunctionalization of unactivated C—C multiple bonds was reported by Normant's group (Scheme 2).[4] In their Letter, the stoichiometric addition of organocopper species **1** to unactivated terminal alkynes **2** (carbocupration) was followed by an electrophilic trap of the resulting alkenylcopper species **3**. The difunctionalization occurred in a *syn* Markovnikov fashion. This reaction is classified as type A in Scheme 1.

Difunctionalization of alkenes is generally more difficult than that of alkynes due to the lower polarizability of alkenes. The first report of copper-mediated difunctionalization of alkenes was disclosed by Nakamura's group in 1988, using strained cyclopropene acetals **7** (Scheme 3).[5] Both alkyl and alkenyl organocuprates were applicable to the reaction. The cuprio cyclopropane intermediates **8** reacted with several carbon electrophiles to provide *cis*-cyclopropanes **9**.

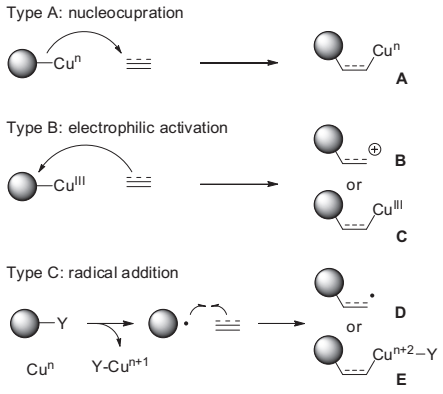
Since these seminal reports, copper-mediated and -catalyzed difunctionalization of C—C multiple bonds have been intensively investigated. In this review, we focus on recent advances in copper-catalyzed 'carbofunctionalization' of unactivated C—C multiple bonds, where a C—C bond and a C—X bond are formed simultaneously. The reaction is highly valuable because functional group introduction and carbon skeleton extension proceed in one pot from C—C multiple bonds, allowing for a rapid increase in molecular complexity. Difunctionalization reactions via sequential reagent addition, such as copper-catalyzed carbometalation followed by an electrophilic trap,[6] are not discussed here. Cycloaddition reactions, such as the Diels-Alder reaction and 1,3-dipolar cycloaddition, are also not included in this review.

Difunctionalization of alkenes

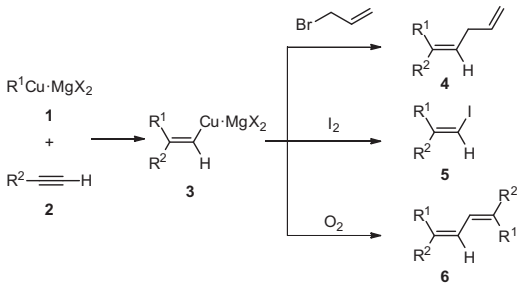
Epoxidation, aziridination, dihydroxylation, aminohydroxylation, and cyclopropanation are commonly-used methods for difunctionalization of alkenes. The incorporation of two distinct functional groups into alkenes through C—C bond-formation in one step is, however, a difficult transformation (Scheme 4).

Nucleocupration of alkenes (type A reactions)

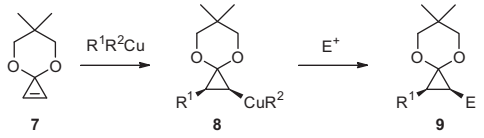
Chemler's group developed $Cu(OAc)_2$-mediated intramolecular oxidative carboamidation of alkenes, constructing a cyclic sultam



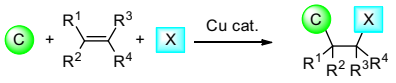
Scheme 1. Classification of copper-catalyzed difunctionalization of C—C multiple bonds.



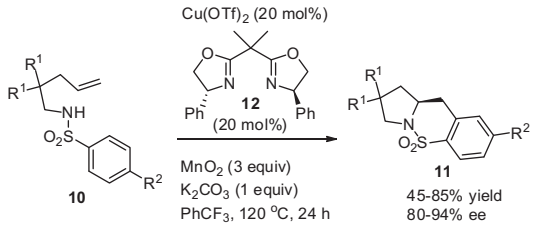
Scheme 2. The first carbocupration of alkynes followed by electrophilic trap reported by Normant.



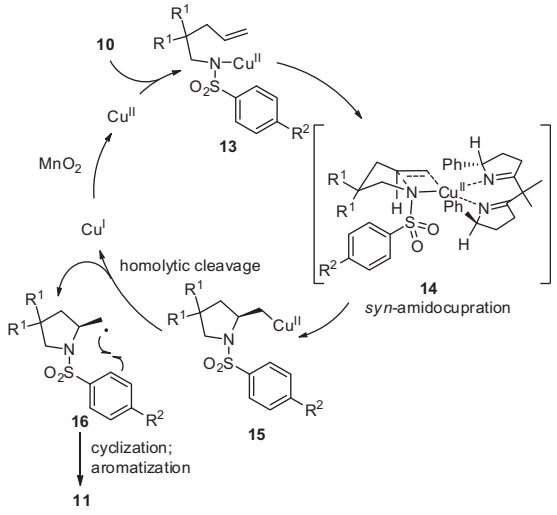
Scheme 3. Carbocupration of cyclopropene acetals followed by electrophilic trap reported by Nakamura.



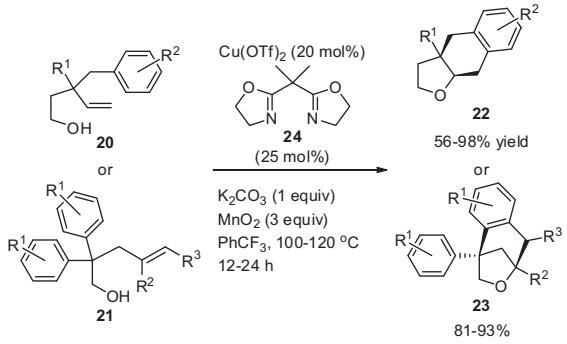
Scheme 4. General scheme of copper-catalyzed difunctionalization of alkenes involving C—C bond-formation.



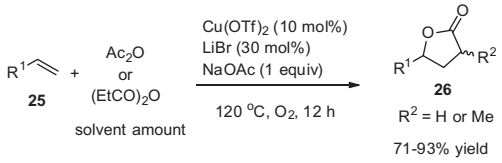
Scheme 5. Catalytic enantioselective intramolecular carboamidation of alkenes developed by Chemler.



Scheme 6. Proposed mechanism of the copper-catalyzed intramolecular carboamidation of alkenes.



Scheme 8. Intramolecular carboetherification developed by Chemler.



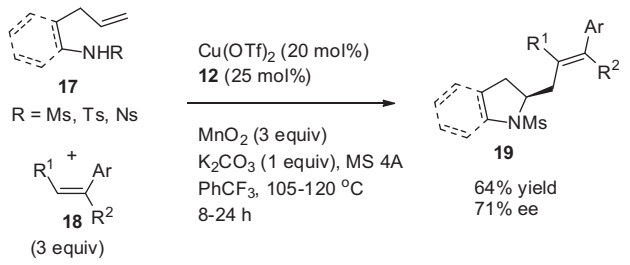
Scheme 9. Carbooxygenation of alkenes developed by Jiang.

skeleton.[7] The same group extended the reaction to provide the first example of a catalytic asymmetric variant (Scheme 5).[8] The use of $Cu(OTf)_2$/(*R,R*)-Ph-Box **12** as a catalyst afforded products **11** in good yield and high enantioselectivity in the presence of MnO_2 and K_2CO_3 as an oxidant and a base, respectively. The proposed reaction mechanism was as follows[9] (Scheme 6): (1) intramolecular enantioselective *syn*-amidocupration of the C—C double bond proceeds from in situ-generated copper amide **13**, and (2) the thus-formed unstable C—Cu(II) bond undergoes homolytic cleavage to generate copper(I) species and carbon radical species **16**, which is trapped by the tethered aromatic group. Oxidation of the copper(I) species by MnO_2 regenerates the active copper(II) catalyst. The copper catalyst has two consecutive distinct roles in this reaction: that as a π-acid to facilitate the intramolecular *syn*-amidocupration step (**14**) and that as a single-electron oxidant to generate a nucleophilic carbon radical (**15**–**16**).

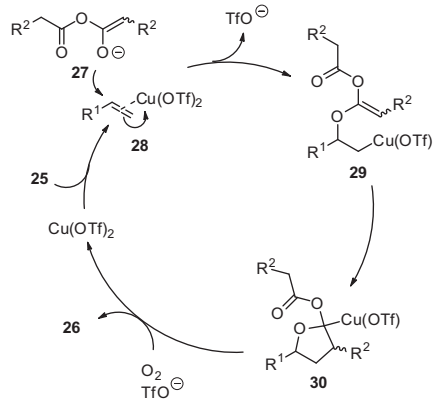
Chemler's group further explored a copper(II)-catalyzed carboamidation reaction of alkenes involving intermolecular radical addition to olefins (vinyl arenes) as the C—C bond-forming step (Scheme 7).[10] The putative radical intermediate **16** preferentially reacted with vinyl arenes rather than with the tethered sulfonyl benzene (in the cases when R = Ts and Ns). The copper catalysis was also applicable to intramolecular carboetherification of alkenes (Scheme 8).[11,12]

Jiang's group developed a copper-catalyzed carbooxygenation of alkenes using acid anhydrides as carbon and oxygen sources (Scheme 9).[13] Lactones **26** were obtained in one step from simple alkenes **25** through formal [3+2]-cycloaddition. Although its precise role was not discussed, the addition of a bromide salt, especially LiBr, was crucial to promote the reaction. Using a solvent amount of acid anhydrides, the reaction proceeded in good yield with various terminal alkenes, including an aliphatic alkene, 1-octene. Because radical trapping agent TEMPO or BHT hardly affected the yield, radical intermediates are not likely involved. The reaction proceeded through *syn*-oxycupration, based on the product's stereochemistry using an (*E*)-monodeuterated styrene as the substrate. A proposed mechanism that can explain these experimental observations is as follows (Scheme 10): (1) an alkene is activated by coordination to the cationic copper(II) catalyst (**28**), and *syn*-oxycupration proceeds with an enolate oxygen atom of anhydride **27** acting as a nucleophile: (2) insertion of the electron-rich C—C double bond proceeds to form a cyclized intermediate **30**: (3) reaction between **30** and molecular oxygen followed by elimination of peroxide ($R^2CH_2CO_3H$) affords product **26**. In contrast to Chemler's carboamidation reaction, a migratory insertion mechanism was proposed rather than carbon radical addition for the C—C bond-forming step. Although the radical trapping experiment partially supports the migratory insertion mechanism, further investigation is required to clarify the exact reaction pathway.

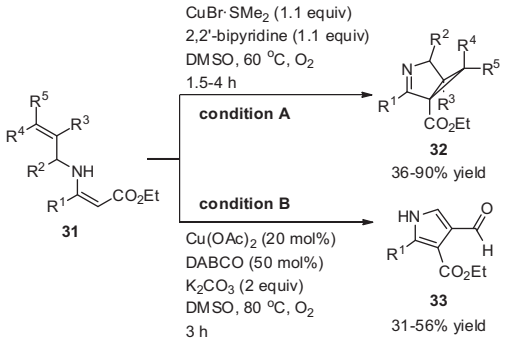
In addition to amido- and oxycupration of alkenes, carbocupration is another possible approach to generate active organocopper species. In 2011, copper-mediated formation of 3-azabicy-



Scheme 7. Intramolecular amidation/intermolecular Heck-type reaction cascade developed by Chemler.



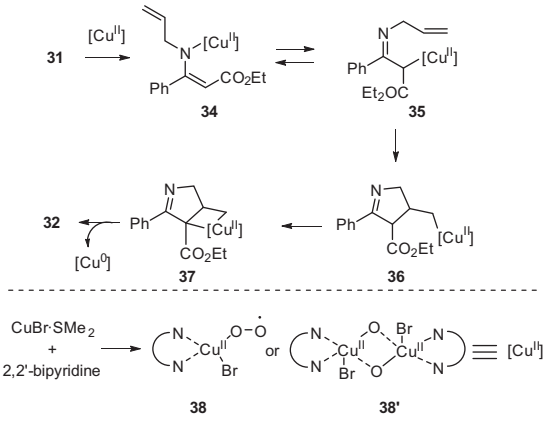
Scheme 10. Proposed mechanism of carbooxygenation.



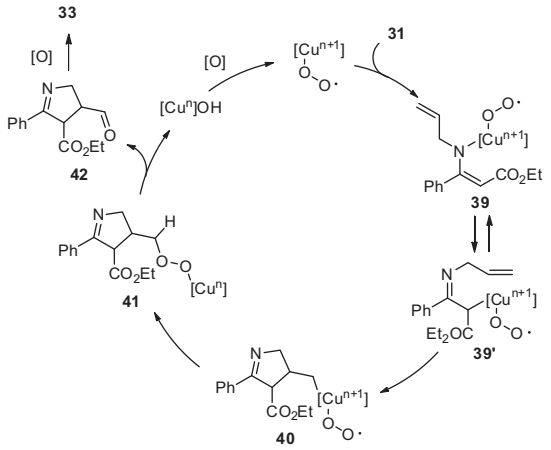
Scheme 11. Two reaction pathways of *N*-allyl enamine substrates through intramolecular carbocupration of alkenes reported by Chiba.

clo[3.1.0]hex-2-enes **32** and copper-catalyzed formation of 4-formylpyrrole **33** from *N*-allyl enamine carboxylates **31** were developed by Chiba's group (Scheme 11).[14,15] Although the detailed role remains unclear, the addition of K_2CO_3 dramatically switched the reaction pathway to form 4-formylpyrrole **33**. Otherwise, 3-azabicyclo[3.1.0]hex-2-ene **32** was formed under similar conditions. Both reaction pathways started with the generation of copper azaenolate species (**34** or **39**), which underwent intramolecular carbocupration of the C—C double bond (Schemes 12 and 13). In condition A, a mononuclear **38** or a dinuclear copper-peroxo complex **38′** was assumed as an active species to promote carbocupration step. Subsequent metallacyclobutane **37** formation followed by reductive elimination produced 3-azabicyclo[3.1.0]hex-2-ene **32**. On the other hand, isomerization proceeded from copper-peroxo species **40** to peroxide intermediate **41**. Subsequent elimination of [Cu^n]-OH and oxidation afforded 4-formylpyrrole **33** under condition B. Results indicated that slight modifications of the reaction conditions can dramatically switch the reaction pathway from in situ-generated transient C—Cu(II) species.

Organoboron compounds are versatile in organic synthesis, and thus many approaches to prepare valuable organoboron compounds have been extensively studied. In 2000, groups of Hosomi and Miyaura independently reported copper-catalyzed conjugate addition of the B(pin) group to enones.[16] Miyaura's group also demonstrated copper-mediated addition of the B(pin) group to α,β-unsaturated esters, nitriles or a terminal alkyne and a coupling with an allyl chloride. The proposed active species was CuB(pin) generated through transmetalation from bis(pinacolato)diborane. More recently Sadighi's group reported insertion of alkenes to IPr-CuB(pin) complex **43** (Scheme 14).[17] The reaction proceeded at



Scheme 12. Postulated mechanism of copper-mediated synthesis of 3-azabicyclo[3.1.0]hex-2-enes **32** from **31**.



Scheme 13. Postulated mechanism of copper-catalyzed synthesis of 4-formylpyrroles **33** from **31**.

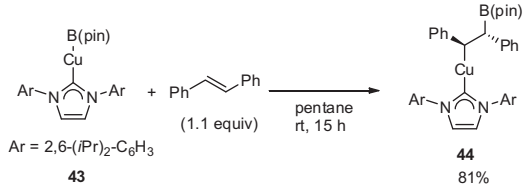
room temperature and high selectivity for *syn*-addition was observed when *trans*- and *cis*-stylbene were used as substrates.

In 2008, Ito and Sawamura's group realized a copper-catalyzed carboboration of γ-silylated allylic carbonates **45** (Scheme 15).[18] The reaction proceeded through borylcupration of alkenylsilanes with borylcopper species generated via transmetalation from diboronate, and subsequent intramolecular substitution (cyclization). The regioselectivity of borylcupration is determined by the α-stabilization effects of the silyl group.[19] Chiral ligands, especially (*R*,*R*)-QuinoxP* (**53**) and (*R*)-Segphos (**54**), induced high enantioselectivity to afford chiral *trans*-cyclopropane derivatives **46**. Like the silyl group in **45**, an aromatic substituent on the C—C double bond also controlled the regioselectivity of borylcupration when allylic phosphates **47** were used as substrates.[20] Moreover, the borylcupration-cyclization strategy was extended to diastereoselective cyclobutane- and cyclopentane-forming reactions using an OMs group as a leaving group (from **49** and **50** to **51** and **52**, respectively).[21]

The same group further established a related reaction using simple terminal alkenes **56**, **57** as substrates (Scheme 16).[22] The use of Xantphos (**60**) as a ligand for copper atoms showed good reactivity, whereas monophosphine and NHC ligands produced far less satisfactory results. Although the diastereoselectivity was low in this reaction (1:1–1.4:1), three-, four-, and five-membered ring formation proceeded smoothly.

Electrophilic activation of alkenes (type B reactions)

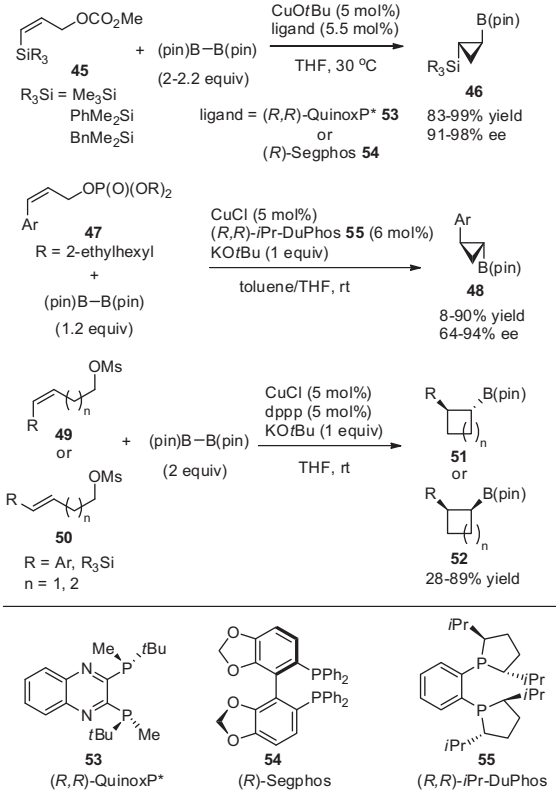
A reaction between alkenes and organocopper(III) species was demonstrated by Gaunt's group (Scheme 17).[23] In contrast to the above-mentioned nucleocupration strategy, high oxidation state organocopper(III) species acted as electrophiles, while alkenes acted as nucleophiles. The combination of a copper catalyst and diaryliodonium salt **62** generated aryl-Cu(III) intermediate **65**, which acted as highly activated aryl cation-like species **65′**. An



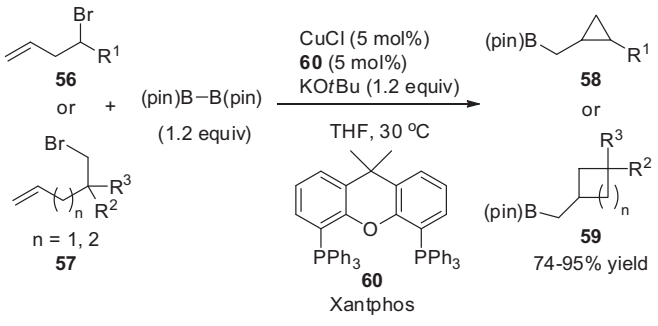
Scheme 14. Stoichiometric borylcupration of alkenes reported by Sadighi.

alkene nucleophile **61** attacked the aromatic electrophile to form a C—C bond. Deprotonation from intermediate **66** regenerated a C—C double bond. Interestingly, the product ratio (**63**:**64**) was significantly different from that of a typical Heck reaction product.

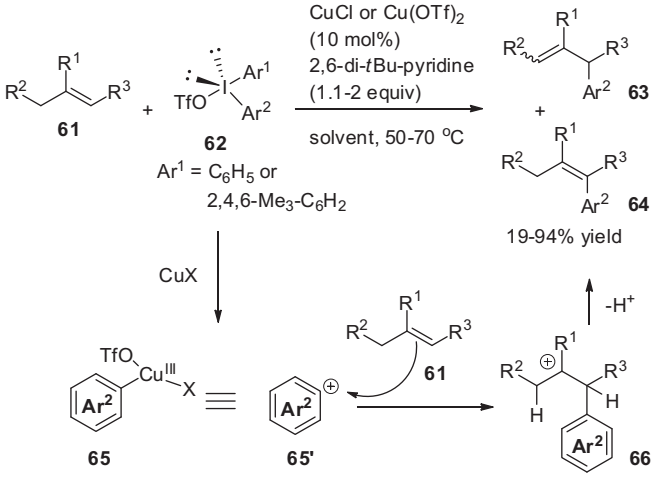
By applying this chemistry to allylic amides **67**, *anti*-oxyarylation and -oxyvinylation proceeded to construct *trans*-oxazine scaffolds **69** (Scheme 18: R^3 = aryl and vinyl).[24] Putative carbocation intermediates, generated through the reaction between aryl-Cu(III) and alkenes, were trapped by the oxygen atom of the amide group. It is noteworthy that *endo*-cyclization proceeded selectively, and a variety of functional groups were tolerated. When allylic amide **70** bearing a phenyl group at the internal position of the C—C double bond was used as a substrate, however, *exo*-cyclization product **71** was obtained exclusively. In this case, the reaction should proceed through a stable tertiary carbocation intermediate.



Scheme 15. Carboboration of alkenes developed by Ito and Sawamura.



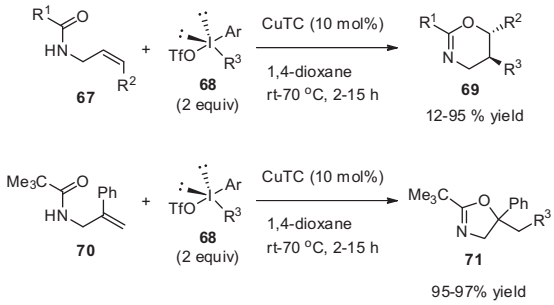
Scheme 16. Carboboration of simple terminal alkenes developed by Ito and Sawamura.



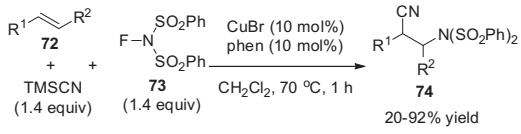
Scheme 17. Electrophilic arylation of alkenes developed by Gaunt.

Radical addition to alkenes (type C reactions)

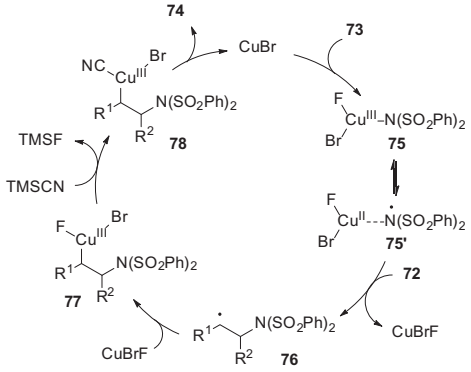
Copper-catalyzed three-component imidocyanation reactions, initiated with an aminyl radical addition to alkenes, were developed by Xiong, Li, and Zhang's group (Scheme 19).[25] The reac-



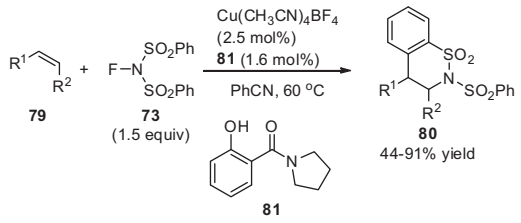
Scheme 18. Electrophilic oxazine formation developed by Gaunt.



Scheme 19. Three-component imidocyanation of alkenes developed by Xiong, Li, and Zhang.



Scheme 20. Proposed mechanism of three-component imidocyanation of alkenes.

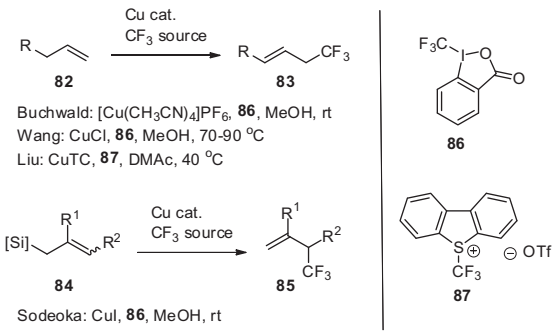


Scheme 21. Catalytic intermolecular carboimidation of alkenes developed by Matsunaga and Kanai.

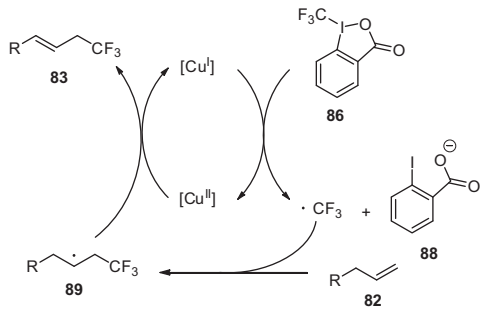
tion utilized NFSI (**73**) and TMSCN as nitrogen and cyanide sources, respectively. A plausible catalytic cycle begins with oxidation of CuBr with NFSI, producing Cu(III) complex **75**, which can generate Cu(II)-stabilized aminyl radical **75′** through an equilibrium (Scheme 20). The addition of the aminyl radical to alkenes generates carbon radical **76**, which is recombined with Cu(II) to afford organocopper(III) intermediate **77**. A radical clock experiment supported the generation of a carbon radical intermediate. Subsequent transmetalation and reductive elimination afford imidocyanation product **74**. The use of other cyanide sources dramatically retards the reaction, indicating that the interaction between the silicon atom and fluoride plays an important role.

Matsunaga and Kanai's group developed copper-catalyzed intermolecular carboimidation of aliphatic alkenes utilizing NFSI (**73**) as an oxidant as well as a nitrogen source (Scheme 21).[26] The catalyst loading was as low as 2.5 mol % and the reaction yield was increased by the addition of a weakly coordinating additive **81**. Various functional groups such as Br, NO_2, OH, and OAc were tolerated, providing rapid access to functionalized sultams. In contrast to the above-mentioned imidocyanation reaction, a carbon radical intermediate, generated through the addition of the aminyl radical to alkene, reacts with an electron-deficient aromatic group intramolecularly.

In 2011, the Buchwald,[27] Liu,[28] and Wang[29] groups independently disclosed a copper-catalyzed trifluoromethylation of unactivated alkenes. Sodeoka's group also reported trifluoromethylation of allyl silanes in 2012 (Scheme 22).[30] All the groups utilized a combination of copper(I) salt and either Togni's reagent **86** or Umemoto's reagent **87**. Buchwald's group later conducted radical clock experiments and a TEMPO trap experiment to reveal that the reaction proceeded via trifluoromethyl radical addition to alkenes **82**, giving **89** (Scheme 23).[31] The mechanism of the subsequent C—C double bond-generation step from **89**, however, remains unclear. Two possible pathways are; (a) single-electron oxidation of **89** by Cu(II) to carbocation species, followed by deprotonation, and (b) recombination of **89** with Cu(II) to afford organocopper(III) species, which undergoes β-hydride elimination to generate a C—C double bond.



Scheme 22. Trifluoromethylation of unactivated alkenes.

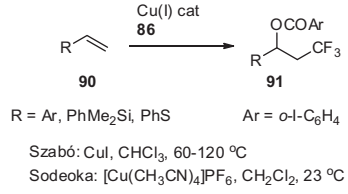


Scheme 23. Plausible mechanism of trifluoromethylation of alkenes.

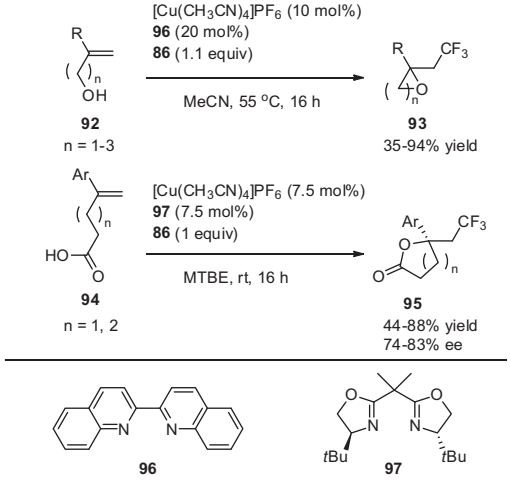
After these seminal works, many groups have actively investigated trapping of the reactive intermediate **89** or its derivatives by various reactants. The Szabó[32] and Sodeoka[33] groups independently realized copper-catalyzed carboxytrifluoromethylation of alkenes, which are conjugated with aromatic, silyl, or sulfur groups (Scheme 24). Togni's reagent **86** was utilized both as a trifluoromethyl and a carboxylate sources. The same conditions were also applicable to arylacetylenes.

A successful example of copper-catalyzed oxytrifluoromethylation utilizing aliphatic alkenes was reported by Buchwald's group (Scheme 25).[34] When terminal alkenes tethered with oxygen-based nucleophiles **92** were subjected to a Cu(I)/2,2′-biquinoline **96** catalyst in the presence of Togni's reagent **86**, oxytrifluoromethylation proceeded efficiently. Carboxylic acids, alcohols, and phenols could be used as oxygen-based nucleophiles to trap the radical intermediate.

Because ligand **96** was essential to promote the oxytrifluoromethylation reaction, Buchwald's group further developed an asym-



Scheme 24. Carboxytrifluoromethylation of styrenes developed by Szabó and Sodeoka.



Scheme 25. Oxytrifluoromethylation of unactivated alkenes and extension to an asymmetric reaction reported by Buchwald.

metric variant using a chiral ligand, (*S*,*S*)-*t*Bu-Box (**97**), in MTBE solvent.[31] Significant enantioselectivity was induced, indicating that the copper catalyst is relevant to the cyclization step.

Based on these pioneering works, carbon- and nitrogen-based trapping agents have also been applied extensively by several groups.[35] Although terminal alkenes were used in most of the examples, difunctionalization of internal alkenes[35b,d,h] and dienes[35a] was also amenable.

Difunctionalization of alkynes

In contrast to difunctionalization of alkenes, difunctionalization of alkynes preserves a C—C unsaturated bond (i.e., double bond) after the reaction (Scheme 26). Therefore, the transformation is effective for the synthesis of poly-substituted alkenes or aromatized products. In addition, the generated C—C double bonds can be utilized for further transformations.

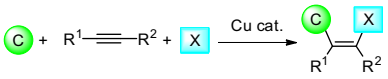
Nucleocupration of alkynes (type A reactions)

In 2002, Hiroya's group reported a successful copper-mediated carboamidation reaction (Scheme 27).[36] They found that $Cu(OTf)_2$ or $Cu(OAc)_2$ was especially effective for the *endo-dig* cyclization of **98** to form indolylcopper species through intramolecular amidocupration. Although the indolylcopper intermediate was protonated in the absence of any additives, deprotonation of the sulfonamide group by KH facilitated the subsequent C—C bond-formation, producing cyclization product **99** in moderate yield. The scope was limited to five- and six-membered ring constructions, and the reaction involving intramolecular addition to a formyl group was not successful under the same reaction conditions.

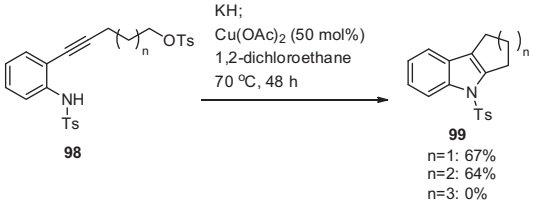
Hirano and Miura's group extended the nucleocupration strategy to dehydrogenative coupling between *o*-alkynylphenols **100** with oxadiazoles **101** (Scheme 28).[37] A postulated mechanism involves C—H cupration of oxadiazoles by CuF_2 to give arylcopper species **103**, intramolecular oxycupration to give benzofurylcopper **104**, and reductive elimination to form coupling product **102**. Although most of the reported examples employed a stoichiometric amount of the CuF_2/1,10-phenanthroline (2/1) complex, two examples of catalytic reactions using MnO_2 as an oxidant were demonstrated. The redox property of copper atoms played a key role in the C—C bond-forming step, in contrast to Hiroya's report.

Difunctionalization of alkynes was triggered by amido- or oxycupration of C—C triple bonds in the above two reports. The reverse sequence, that is, carbocupration-triggered difunctionalization of alkynes, was reported by Li's group in 2011 (Scheme 29).[38] They developed $CuCl_2$-catalyzed oxidative cyclization of 1,6-enyn-3-ones **105**. 1,4-Addition of H_2O to the enone moiety generated copper enolate **108**, which attacked the C—C triple bond in an intramolecular manner (Scheme 30). Finally, the C—Cu bond was oxygenated through copper-peroxo species **110**, giving product 1,4-naphthoquinone **106**. Although additive oxidant $Ce(SO_4)_2$ was not essential, it markedly enhanced the reactivity. ^{18}O-labeling experiments showed that incorporated oxygen atoms were derived from both water and molecular oxygen, consistent with the proposed catalytic cycle.

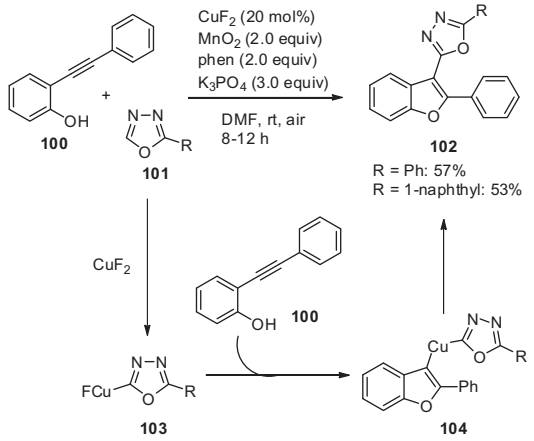
Chiba's group also developed carbocupration-initiated alkyne carbooxygenation to construct aza-heterocycles (Scheme 31).[39] Under CuBr/1,10-phenanthroline catalysis, enamine carboxylates **112** and O_2 were used as carbon nucleophiles and an oxygen



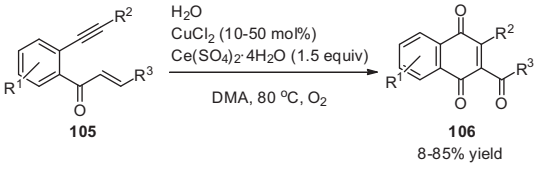
Scheme 26. General scheme of copper-catalyzed difunctionalization of alkynes involving C—C bond-formation.



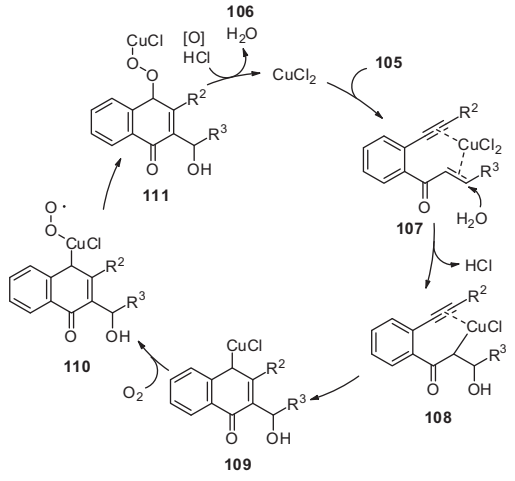
Scheme 27. Indole formation via amidocupration followed by substitution developed by Hiroya.



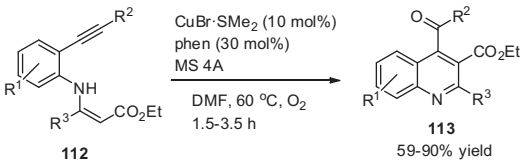
Scheme 28. Intramolecular oxycupration of alkynes followed by biaryl coupling developed by Hirano and Miura.



Scheme 29. Oxidative cyclization of 1,6-enyn-3-ones to produce benzoquinones developed by Li.



Scheme 30. Proposed mechanism of oxidative cyclization of 1,6-enyn-3-ones.

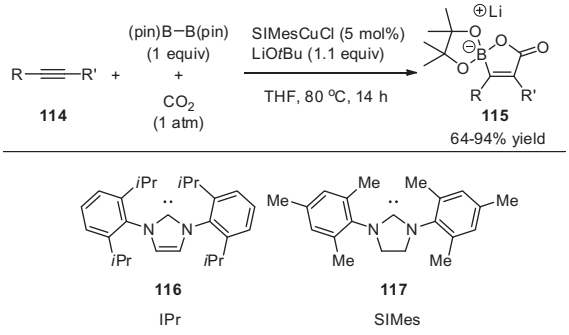


Scheme 31. Carbooxygenation of alkynes to produce quinolines developed by Chiba.

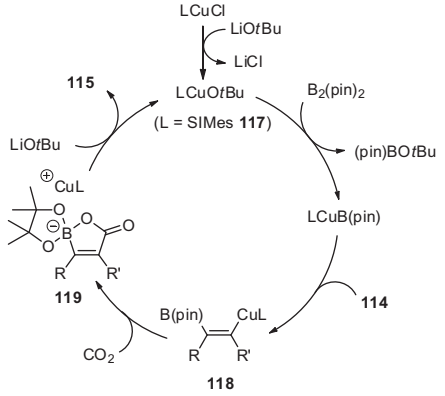
source, respectively. The sequence produced highly substituted quinolines **113**, which are difficult to obtain by other means. Ligand 1,10-phenanthroline improved the yield, and the addition of molecular sieves 4A made the reaction more reproducible. It is noteworthy that other metal sources such as Fe(III), Pd(II), and Co(II) afforded no product or an inferior yield, indicating that both the π-philic nature and the one-electron redox property of the copper catalyst are keys for the successful transformation.

In 2012, Hou's group and Tortosa's group independently reported copper-catalyzed carboboration of alkynes. In both reactions, borylcopper species were first generated through metathesis between diborane and a copper alkoxide catalyst. Then, vinylcopper species, generated through borylcupration of alkynes, reacted in the subsequent C—C bond-forming step.

Hou's group used CO_2 as an electrophile to trap the vinylcopper intermediate (Scheme 32).[40] Use of bulky NHC ligand, IPr **116**, produced product **115** in only a trace amount; however, less sterically-demanding and electron-rich SIMes **117** proved to be a suitable ligand, affording the product in high yield. The proposed catalytic cycle shown in Scheme 33 begins with CuO*t*Bu formation from CuCl and LiO*t*Bu. Reaction of the thus-generated CuO*t*Bu and $B_2(pin)_2$ affords CuB(pin) through metathesis, to which insertion



Scheme 32. Boracarboxylation of alkynes developed by Hou.



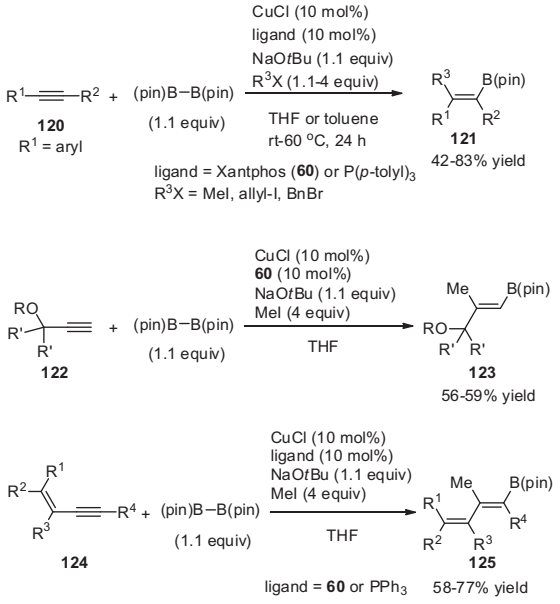
Scheme 33. Proposed catalytic cycle of boracarboxylation of alkynes.

of alkyne **114** proceeds in a *syn* fashion, furnishing vinylcopper intermediate **118**. Nucleophilic addition of the vinylcopper species **118** to CO_2 gives β-boralactone derivatives **119**, which upon reaction with LiO*t*Bu regenerate CuO*t*Bu and release product **115**. They isolated the key intermediates (**118** and **119**) under stoichiometric conditions, and characterized the structure by X-ray analysis, which supports their proposed mechanism.

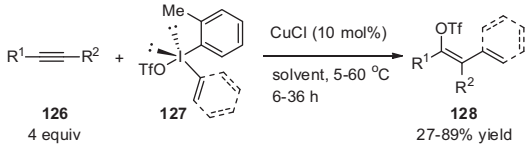
On the other hand, Tortosa's group exploited alkyl halides as electrophiles (Scheme 34).[41,42] Investigation of the phosphine ligand effects in the presence of CuCl and NaO*t*Bu revealed that Xantphos (**60**) was the best ligand for terminal alkynes, whereas P(*p*-tolyl)$_3$ was the best ligand for internal alkynes. In addition to aryl-substituted alkynes, propargylic ethers **122** and 1,3-enynes **124** were applicable for the reaction.

Electrophilic activation of alkynes (type B reactions)

Taking advantage of the highly electrophilic nature of organocopper(III) species, Gaunt's group developed a novel strategy to construct tri- or tetra-substituted alkenes through an electrophilic *syn*-carbotriflation of alkynes (Scheme 35).[43] The combined use of a CuCl catalyst and vinyl- or diaryliodonium triflates **127** generates highly electrophilic carbon species, possibly vinyl- or aryl—Cu(III) species **129**, which react with alkynes to give putative vinyl—Cu(III) intermediates **131** (Scheme 36). Reductive elimination from **131** results in tri- and tetra-substituted vinyltriflates **128**. This electrophilic carbofunctionalization approach can complement nucleometalation of alkynes. The reaction is applicable to both internal and terminal alkynes. Products **128** appear to be versatile precursors for cross coupling reactions.



Scheme 34. Carboboration of alkynes using alkyl halides as electrophiles developed by Tortosa.



Scheme 35. Tri- and tetra-substituted vinyltriflates synthesis developed by Gaunt.

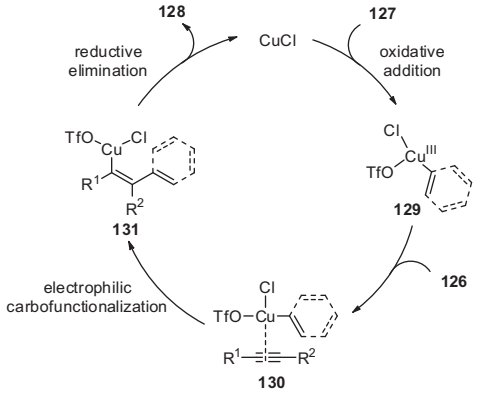
As an extension of this chemistry, Gaunt's group reported copper-catalyzed carboarylation of aryl- or nitrogen-substituted alkynes **132** (Scheme 37).[44] In contrast to aryltriflation of alkyl-substituted alkynes described in Scheme 35, vinyl cation intermediate **136** stabilized by adjacent aryl group (R^1) was assumed to be the key intermediate rather than vinyl—Cu(III) species **131**. The putative vinyl cation **136** was intercepted by the tethered aryl group acting as a nucleophile to form cyclized product **134**. The reaction tolerated various functional groups, and was applied to a streamlined synthesis of the anticancer agent nafoxidine **140** (Scheme 38). An intermolecular 3-component coupling variant also resulted, albeit in lower yield.

Difunctionalization of allenes

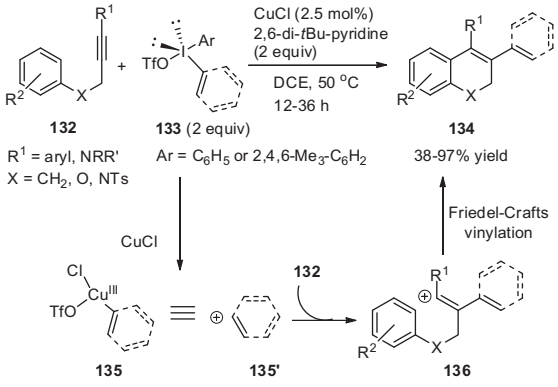
Allenes possess unique structural features compared to alkenes and alkynes. Because allenes comprise three carbons, the formation of regioselective C—C and C—X bonds is more difficult than that of other C—C multiple bonds. Recent successful examples of regioselective difunctionalization of allenes are discussed in this section (Scheme 39).

Nucleocupration of allenes (type A reactions)

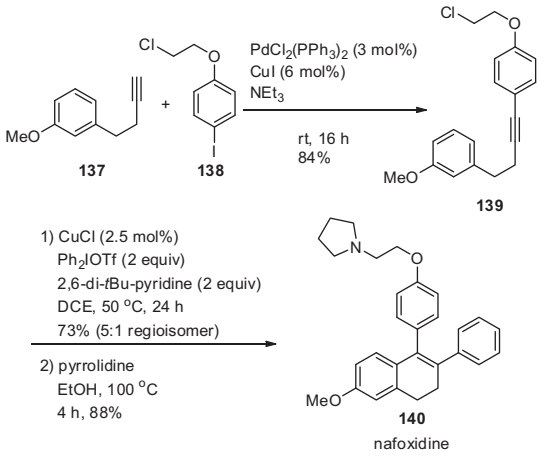
In 2013, two groups reported the use of in situ-generated allylcopper species from allenes for asymmetric nucleophilic addition to carbonyl compounds. Regioselectivity was very high in these reports.



Scheme 36. Plausible mechanism of tri- and tetra-substituted vinyltriflates synthesis.



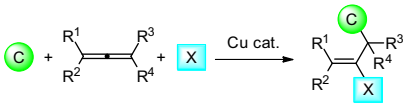
Scheme 37. Carboarylation of alkynes developed by Gaunt.



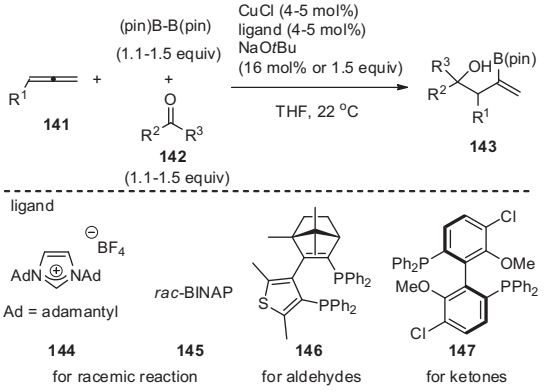
Scheme 38. Streamlined synthesis of nafoxidine by Gaunt.

Hoveyda's group revealed that borylcupration of allenes produced allylcopper species in situ, which could be utilized for enantioselective nucleophilic addition to aldehydes and ketones (Scheme 40).[45] Both NHC **144** and diphosphine **145** ligands were effective for the racemic reaction, while chiral diphosphines (**146** for aldehydes and **147** for ketones) were effective for the asymmetric reaction. The reaction was initiated by the catalytic generation of allylcopper species **148** through the insertion of allenes **141** to the reactive Cu—B bond of an in situ-generated borylcopper species, with the B(pin) group selectively incorporated at the central carbon of the allenes (Scheme 41). The thus-generated allylcopper species **148** reacted with carbonyl compounds **142**. Regio-, diastereo-, and enantioselectivity were quite high (>98% γ-selective, 88:12 to >98:2 dr, 70–94% ee). The applicability of this reaction to ketone electrophiles is noteworthy because ketones are significantly less electrophilic than aldehydes. Products **143** are versatile, and were converted to β-hydroxyketones via oxidation with $NaBO_3$, and vinyl bromides via bromination with $CuBr_2$.

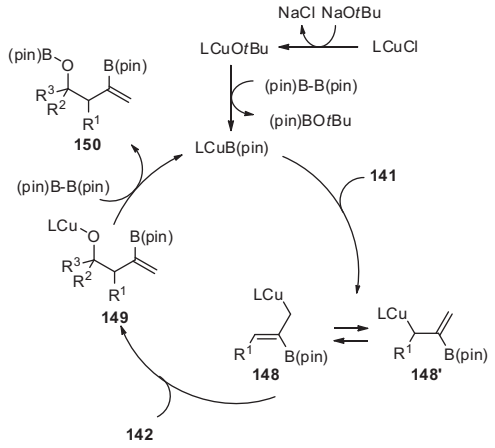
Shimizu and Kanai's group developed an oxycupration approach to generate organocopper species containing an iso-



Scheme 39. General scheme of copper-catalyzed difunctionalization of allenes involving C—C bond-formation.



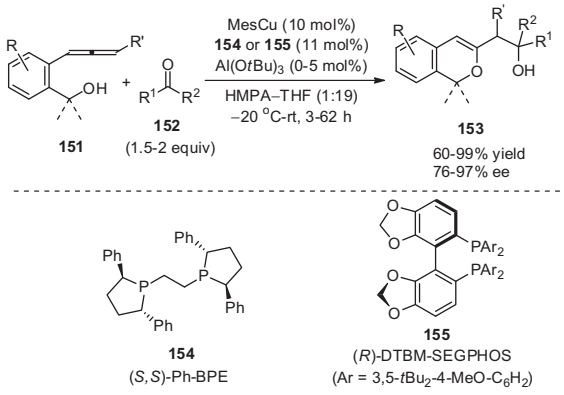
Scheme 40. Regioselective carboboration of allenes developed by Hoveyda.



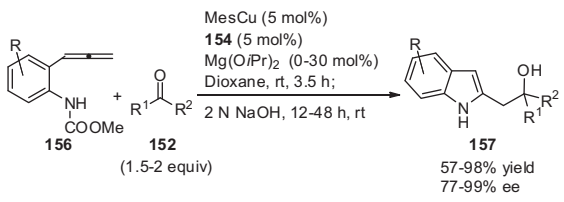
Scheme 41. Plausible catalytic cycle of regioselective carboboration of allenes.

chromene skeleton (such as **160** and **160′**) from allenes (Schemes 42 and 44).[46] Asymmetric addition of the thus-generated organocopper species to carbonyl compounds **152**, including aldehydes and a ketone, produced a unique scaffold **153**. Notably, C—C bond-formation of the reactive organocopper species proceeded preferentially to protonolysis by the OH groups of the substrates. The addition of $Al(OtBu)_3$ co-catalyst improved product yield, especially in the reaction with aliphatic aldehydes.

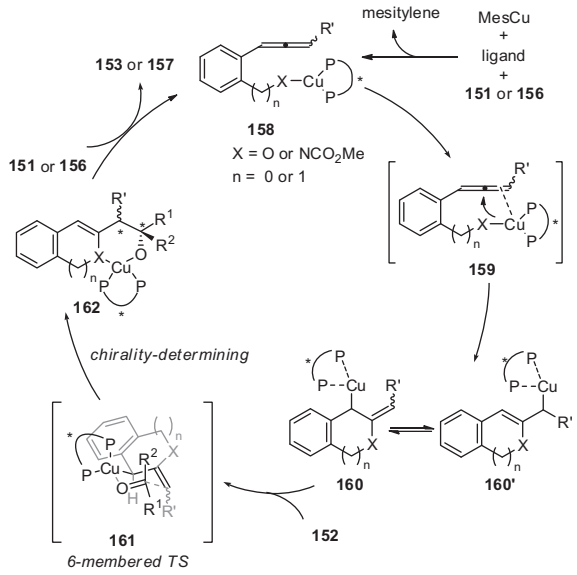
Because the $Al(OtBu)_3$ co-catalyst did not affect enantioselectivity, it likely accelerated the catalyst turnover step (**162**–**158**) by liberating the copper catalyst from the product (Scheme 44). Enantioselectivity was generally high and regioselectivity was virtually perfect. Furthermore, the reaction was stereoconvergent when applied to racemic disubstituted allenes. This result indicates that putative two allylcopper species **160** and **160′** exist in equilibrium through 1,3-metallotropic rearrangement, where chirality of starting **158** disappeared.



Scheme 42. Oxycupration followed by asymmetric addition of carbonyl compounds for construction of isochromene scaffold developed by Shimizu and Kanai.



Scheme 43. Amidocupration followed by asymmetric addition of carbonyl compounds for construction of indole scaffold developed by Shimizu and Kanai.



Scheme 44. Proposed mechanism of carbooxygenation and carboamidation of allenes.

We extended this strategy to the formation of enantio-enriched 2-(2-hydroxyethyl)indole derivatives starting from allenic anilides **156** (Scheme 43).[47] $Mg(OiPr)_2$ co-catalyst effectively increased the yield of reactions with aliphatic aldehydes and ketones.

Conclusion

Although miscellaneous reaction patterns have been reported, there remains much room for improvement in this field. First, the development of a three-component, convergent assembly method is still in its infancy despite its potential utility for constructing complex molecules. Second, beyond methodology development, the method should contribute to the facilitation of molecular synthesis by achieving high reactivity and functional group tolerance under mild reaction conditions. Enantiocontrol is a prerequisite in this sense. Finally, elucidation of the basic reaction mechanism (especially for reactions using unactivated alkenes and alkynes) is extremely important. An understanding of the basic mechanism and concept underlying the catalytic generation of active species would allow for the design of new reaction sequences.

Acknowledgments

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References and notes

1. (a) Zeng, X. *Chem. Rev.* **2013**, *113*, 6864–6900; (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *111*, 2981–3019; (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234–6458; (d) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142–1152; (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocomola, S. *Chem. Rev.* **2007**, *107*, 5318–5365; (f) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083–4088.
2. (a) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511; (b) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.
3. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
4. (a) Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1971**, *27*, 2583–2586; (b) Normant, J. F.; Alexaxis, A. *Synthesis* **1981**, 841–870.
5. Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297–1298.

6. (a) Todo, H.; Terao, J.; Watanabe, H.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2008**, 1332–1334; (b) Liao, L.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322–14323; (c) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671; (d) Terwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382–5383; (e) Simaan, S.; Marek, I. *Org. Lett.* **2007**, *9*, 2569–2571; (f) Tarwade, V.; Selvaraj, R.; Fox, J. M. *J. Org. Chem.* **2012**, *77*, 9900–9904.
7. (a) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573–1575; (b) Fuller, P. H.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 5477–5480; (c) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905.
8. (a) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949; (b) Miao, L.; Haque, I.; Manzoni, M. R.; Tham, W. S.; Chemler, S. R. *Org. Lett.* **2010**, *12*, 4739–4741.
9. Paderes, M. C.; Belding, L.; Fanovic, B.; Dudding, T.; Keister, J. B.; Chemler, S. R. *Chem. Eur. J.* **2012**, *18*, 1711–1726.
10. Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020–2023.
11. Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149–12156.
12. Other types of difunctionalization reactions were also developed by Chemler's group. Amidooxygenation (a) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639; (b) Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009**, *351*, 467–471; (c) Paderes, M. C.; Chemler, S. R. *Eur. J. Org. Chem.* **2011**, 3679–3684; Diamination: (d) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365–6368; (e) Turnpenny, B. W.; Chemler, S. R. *Chem. Sci.* **2014**, *5*, 1786–1793.
13. Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652–17654.
14. Toh, K. K.; Wang, Y.-F.; Jian, E. P.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942–13945.
15. A copper-catalyzed C–H functionalization of *N*-aryl enaminones through similar copper azaenolate species was reported: Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078–8081.
16. (a) Ito, H.; Yamanaka, H.; Tateiwa, J.-I.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825; (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *5*, 982–983.
17. Litar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics* **2006**, *25*, 2405–2408.
18. Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424–7427.
19. Brinkman, E. A.; Berger, S.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 8304–8310.
20. Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440–11442.
21. Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990–5992.
22. Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635–2640.
23. Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, S. R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773–10776.
24. Cahard, E.; Bremeyer, N.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9284–9288.
25. Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 2529–2533.
26. Kaneko, K.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2013**, *15*, 2502–2505.
27. Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120–9123.
28. Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300–15303.
29. Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410–16413.
30. Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577–4580.
31. Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655–12658.
32. Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882–2885.
33. Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503–5506.
34. Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462–12465.
35. Oxytrifluoromethylation: (a) Lu, D.-F.; Zhu, C.-L.; Xu, H. *Chem. Sci.* **2013**, *4*, 2478–2482; (b) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Q.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 5687–5689; Carbotrifluoromethylation: (c) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000–4003; (d) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang; Zhou, Z.-Z.; Hua, H.-L.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2014**, *16*, 270–273; (e) Chen, Z.-M.; Bai, W.; Wang, S.-H.; Yang, B.-M.; Tu, Y.-Q.; Zhang, F.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9781–9785; (f) Liu, X.; Xiong, F.; Huang, X.; Xu, L.; Li, P.; Wu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6962; (g) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841–7844; (h) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1881–1886.
36. a) Hiroya, K.; Itoh, S.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280; b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.
37. Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 3076–3079.
38. Wang, Z.-Q.; Zhang, W.-W.; Tang, R.-Y.; Yang, X.-H.; Liu, Y.; Li, J.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8968–8973.
39. Toh, K. K.; Sanjaya, S.; Chong, S. Y.; Chiba, S. *Org. Lett.* **2012**, *14*, 2290–2292.
40. Zhang, L.; Cheng, J.; Carry, C. B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314–14317.
41. Alfaro, R.; Parra, A.; Alemán, J.; Ruano, J. L. G.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165–15168.
42. (a) Yoshida, H.; Kageyuki, I.; Takaki, K. *Org. Lett.* **2013**, *15*, 952–955; (b) Tai, C.-C.; Yu, M.-S.; Chen, Y.-L.; Chuang, W.-H.; Lin, T.-H.; Yap, G. P. A.; Ong, T.-G. *Chem. Commun.* **2014**, *50*, 4344–4346.
43. Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332–5335.
44. Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532–12535.
45. Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 5046–5051.
46. Kawai, J.; Chikkade, P. K.; Shimizu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7177–7180.
47. Chikkade, P. K.; Shimizu, Y.; Kanai, M. *Chem. Sci.* **2014**, *5*, 1585–1590.