



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, carboxygenation, carboboration, and other difunctionalization reactions of alkenes, alkynes, and allenes are described.

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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-economy³, 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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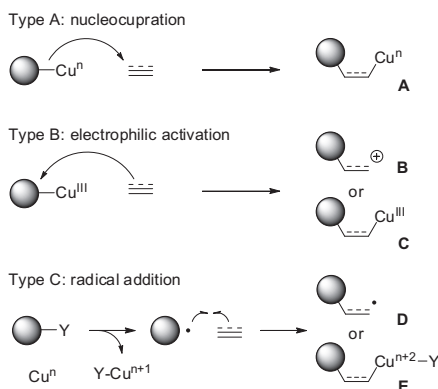
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otherwise difficult to generate. Such reactions should be designed with compatible consecutive bond-forming steps.

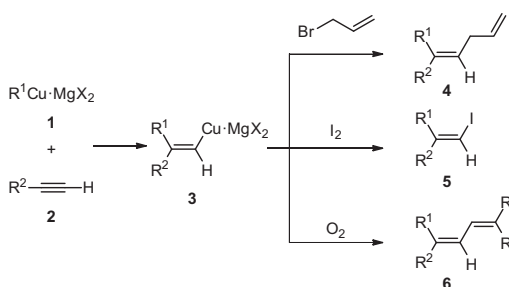
Copper catalysts promote various reaction types due to multiple abilities of the copper atom acting as a Lewis acid, a π -acid, a single-electron mediator, and a two-electron mediator. In addition, Cu–X species generated as reaction intermediates can act as either a nucleophile or an electrophile, depending 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



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.

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**.

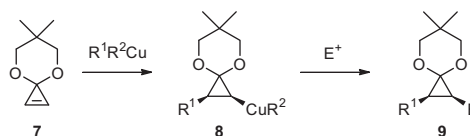
Since these seminal reports, copper-mediated and -catalyzed difunctionalization of C–C multiple bonds have been intensively investigated. In this review, we focus on recent advances in copper-catalyzed 'carbofunctionalization' of unactivated C–C multiple bonds, where a C–C bond and a C–X bond are formed 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

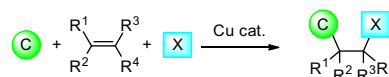
Epoxidation, aziridination, dihydroxylation, aminohydroxylation, and cyclopropanation are commonly-used methods for difunctionalization of alkenes. The incorporation of two distinct functional groups into alkenes through C–C bond-formation in one step is, however, a difficult transformation (Scheme 4).

Nucleocupration of alkenes (type A reactions)

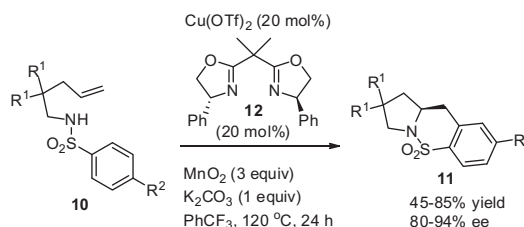
Chemler's group developed Cu(OAc)₂-mediated intramolecular oxidative carboamidation of alkenes, constructing a cyclic sultam



Scheme 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.

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