Digest Paper

Recent advances in copper-catalyzed propargylic substitution

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The copper-catalyzed propargylic substitution reaction has become a powerful synthetic method to prepare the compounds containing the propargylic subunit. Compared with the other transition-metals applied in the propargylic substitution, copper has many obvious advantages, such as much more inexpensive, easier to handle, milder reaction condition, and higher selectivity. This digest summarizes the recent development in the copper-catalyzed propargylic substitutions with various nitrogen, carbon, oxygen, and sulfur nucleophiles. In addition, the cycloadditions involving the copper-catalyzed propargylic substitution as the key step are included.

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Introduction

Propargyl compounds are common motifs in many natural products, fine chemicals, and synthetic pharmaceuticals, as well as useful synthetic intermediates in organic synthesis. The presence
of the nucleophilic triple bond, accompanied by a fairly acidic terminal acetylenic hydrogen in many cases, make these propargylic compounds highly potential for a wide variety of transformations.\(^1\)

The Nicholas reaction,\(^2\) a well-known substitution reaction of propargylic alcohol derivatives with various nucleophiles, represents one of the most effective methods for the synthesis of a wide range of propargylic compounds. However, this reaction requires a stoichiometric amount of toxic Co\(_2\)(CO)\(_8\), which significantly limited its application. Therefore, the development of a catalytic propargylic substitution becomes a pre-requisite task for organic chemists. In comparison with the transition-metal-catalyzed allylic substitution reaction which is one of the most reliable methods in organic synthesis,\(^3\) the catalytic propargylic substitution reaction has been lagging far behind. To date, the catalytic propargylic substitution reaction was mostly limited to work using Pd, Cu, Ti, and Ru catalysts,\(^4\) and the first catalytic asymmetric version\(^5\) occurred until 2003. Among various catalysts used in the propargylic substitution reaction, copper salts display some distinct advantages: (1) low cost, (2) low toxicity, (3) mild reaction condition, (4) operational simplicity, (5) broad substrate scope, (6) excellent selectivity. In particular, recent progress in the Cu-catalyzed asymmetric propargylic substitution further demonstrated its superiority. Although some recent reviews about propargylic substitution have been reported,\(^6\) there are no specific reviews focused on the copper-catalyzed propargylic substitution reaction. Herein, we describe recent developments in the emerging field of copper-catalyzed propargylic substitution reactions, classified by the nucleophiles.

**Propargylic substitution using nitrogen nucleophiles**

Propargylic amines are versatile building blocks and intermediates for organic synthesis.\(^7\) Transition-metal catalyzed propargylic substitution using nitrogen nucleophile is one of the most attractive strategies to synthesize these compounds. In recent years, the copper-catalyzed propargylic substitutions using nitrogen nucleophiles have made great progress. Different kinds of copper-catalyzed propargylic aminations, as well as the cycloadditions with propargylic amination as the key step, have been developed.

**Propargylic amination of propargylic esters**

In 1960, Hanzel and co-workers developed a propargylic amination of tertiary propargylic chlorides with various amines.\(^7\) It was found that the copper catalyst (CuCl–Cu) was necessary to achieve good yields when the aromatic amines were used as the nucleophiles. The formation of a more reactive copper acetylide species was proposed to be responsible for the improved reactivity. In 1994, Murahashi and co-workers developed a highly effective CuCl-catalyzed propargylic amination of propargylic acetates and phosphates\(^1\) with various amines\(^2\) under mild conditions (Scheme 1).\(^3\) The reaction was highly regioselective and no allenylamine byproducts were observed. Additionally, a terminal acetylenic proton was essential for this copper-catalyzed amination, and an internal alkene did not undergo the amination even under severe conditions. This result suggested a copper–acytelylide complex should be formed as the key intermediate. Although still in the racemic series at this stage, this work sets the stage for an enantioselective version.

However, it is until 2008, van Maarseveen and Nishibayashi independently reported the first copper-catalyzed asymmetric propargylic amination.\(^9\)\(^10\) These methods provided an efficient
route to prepare optically active propargylic amines 3 in high yields and with good enantioselectivities. The major difference between van Maarseveen’s and Nishibayashi’s methods is the structure of the chiral ligand. In van Maarseveen’s method, a chiral 2,6-bis(oxazolinyl)pyridine-type ligand (diPh-pybox L1) in combination with Cúl was used as the catalyst, and primary amines proved to be more suitable nucleophiles (up to 88% ee, Scheme 2). In comparison, Nishibayashi employed the complex of CuOTf·1/2C6H5 with an atropisomeric diphosphine ligand (Cl-MeO-BIPHEP L2) as the catalyst and only secondary amines worked as suitable nucleophiles (up to 98% ee, Scheme 2).

Scheme 4. Model of the transition state of the copper–allenylidene complex bearing (R)-BIPHEP.

Scheme 5. Cu-catalyzed asymmetric propargylic amination of propargylic pentafluorobenzoates with secondary amines.

Nishibayashi and co-workers made an exhaustive research on the reaction mechanism and proposed a reaction pathway similar to van Maarseveen’s (Scheme 3). The experimental results revealed that the copper–allenylidene complex should be the key intermediate. This conclusion is also supported by density functional theory calculations for the model reaction. Here the attack of the amines to the Cα atom of the copper allenylidene complex is the key step in determining both the regio- and stereoselectivities. This mechanism explains why the reaction requires the use of propargyl substrates with terminal acetylene.

A transition state of the copper–allenylidene complex with the chiral ligand (R)-BIPHEP L2 is proposed to account for high enantioselectivity of the reaction (Scheme 4). The re-face of the γ-carbon of the copper–allenylidene complex is open to attack by the N-methylaniline. The edge-to-face interaction between the carbon–hydrogen bond of the substrate and the phenyl group at the pseudo-equatorial position of (R)-BIPHEP L2 is considered as an essential factor in achieving high enantioselectivity.

In 2011, Nishibayashi and co-workers realized the copper-catalyzed enantioselective propargylic amination of aliphatic propargylic esters 1, a challenging substrate class, with secondary

Scheme 7. Cu-catalyzed asymmetric propargylic amination with chiral P,N,N-ligands.

Scheme 8. Cu-catalyzed asymmetric propargylic amination with (R)-BICMAP.
amines 2, in which moderate yields with high enantioselectivities were achieved in the presence of 5 mol % CuOTf $\cdot$ 2C$_6$H$_6$ (5 mol%) (L$_3$)-L$_4$ or L$_8$ complex, both primary and secondary amines could be used as efficient nucleophiles for the highly enantioselective catalytic amination of both aliphatic and aromatic propargylic acetates.

In 2013, Sakamoto and co-workers reported the copper-catalyzed asymmetric propargylic amination of aromatic propargylic acetates. In 2012, Hu and co-workers demonstrated that chiral tridentate P,N,N-ligands, (S,R$_2$)-L$_5$ and (R)-L$_6$, were highly efficient for the Cu-catalyzed asymmetric propargylic amination of propargylic acetates 1. In the presence of CuCl[(S,R$_2$)]-L$_5$ complex, both primary aromatic amines and secondary amines 2 were found to be suitable nucleophiles, providing the corresponding propargylic amines 3 in high yields and with excellent enantioselectivities (up to 97% ee for secondary amines, and up to 96% ee for primary amines, Scheme 7). Moreover, in the catalysis of Cu(OAc)$_2$·H$_2$O/(R)-L$_6$ complex, aliphatic propargylic acetates also served well, providing the products with good enantioselectivities (Scheme 7). It was noteworthy that this Cu/P,N,N-ligand catalytic system represents the first successful example in which both primary and secondary amines could be used as efficient nucleophiles for the highly enantioselective catalytic propargylic amination of both aliphatic and aromatic propargylic acetates.
Very recently, Nishibayashi and co-workers disclosed a copper-catalyzed asymmetric intramolecular propargyl amination of propargylic acetates \( 4 \) bearing a secondary amine moiety at a suitable position.\(^{16}\) In the catalysis of CuOTf \( \cdot \) 1/2C\(_4\)H\(_8\)NO/pybox \((\text{L}4 \text{ or L}8)\) complex, a variety of optically active 1-ethynylisodoindolines \( 5 \) were obtained in good yields and with high enantioselectivities (up to 98\% ee, Scheme 9). They also made a preliminary investigation on the sequential inter- and intramolecular double propargyl amination, however, the result was still far from satisfactory (Scheme 10).

Ring-opening reaction of ethynyl epoxides with amines

In 2009, Nishibayashi and co-workers reported the copper-catalyzed asymmetric ring-opening reaction of ethynyl epoxides \( 9 \) with amines \( 2 \) catalyzed by Cu(OTf)\(_2\)/DTBM-MeO-BIPHEP \( \text{L9} \) complex. Optically active \( \beta \)-amino alcohols \( 10 \) bearing a tertiary carbon at the \( \alpha \)-position of the amine were obtained in high yields with high enantioselectivities (up to 94\% ee, Scheme 11).\(^{17}\) The catalytic reaction was considered to proceed via copper–allenylidene complexes as the key intermediates. Furthermore, good yields and excellent enantioselectivities were also observed even in the presence of only 0.1 mol \% of copper catalyst (84\% yield, 94\% ee, TON = 840).

Decarboxylative propargyl amination of propargyl carbamates

Although great advances have been made in propargyl substitution using nitrogen nucleophiles, the development of new strategy for the catalytic synthesis of propargyl amines remains a highly desirable and challenging task. In 2014, Hu and co-workers reported a Cu-catalyzed asymmetric decarboxylative propargyl amination of propargyl carbamates \( 11 \) with a tridentate ketimine \( \text{P,N,N-ligand L10 (Scheme 12)}.\(^{18}\) The reaction could be performed under very mild condition for a broad range of substrates, providing the corresponding propargyl amines \( 3 \) in good yields and with high enantioselectivities (up to 97\% ee). In this method, both the nucleophile and the electrophile were formed in situ by the loss of CO\(_2\) in catalytic concentration (Scheme 12). This reaction represents a new and complementary strategy for access to optically active propargyl amines.

Propargyl amination/cyclization tandem reactions

The catalytic sequential reaction using transition metal complexes have attracted much attention due to the advantage of simplicity and facility in the preparation of complex and useful compounds. Recently, some cycloaddition reactions based on the copper-catalyzed propargyl amination have also been developed.

In 2010, Nishibayashi and co-workers reported the copper-catalyzed asymmetric propargyl amination/[4+2]-cycladdition tandem reaction of propargyl acetates \( 1 \) with \( \text{N-(E)-penta-2,4-dienylaniline L12} \) to give chiral 1,2-disubstituted tetrahydropyrididine derivatives \( 13 \) in high yields and with high diastereo-/enantioselectivities (up to >30/1 dr, up to 90\% ee, Scheme 13).\(^{15}\) This work is the first example of the copper-catalyzed diastereo- and enantioselective sequential reaction, in which only a single copper complex worked as a catalyst to promote both the propargyl amination and the intramolecular [4+2] cycladdition reaction.

A proposed reaction pathway is shown in Scheme 14. At first, \( \text{N-(E)-2,4-pentadienylaniline L12} \) might attack the copper acetylide complex \( A \) bearing a cationic \( \gamma \)-carbon atom from the re face to give \( C \) with high enantioselectivity. Then, the intramolecular [4+2] cycladdition reaction occurs via the copper acetylide complex \( D \), which is formed from \( C \) and the chiral copper complex. The direct transformation from \( B \) to \( D \) without the formation of \( C \) as a reactive intermediate may also be conceivable in the sequential reactions.

In 2011, Zhan and co-workers described a Cu(OTf)\(_2\)-catalyzed tandem reaction of propargyl alcohols \( 14 \) with amine \( 15 \) to provide 2,4-disubstituted or 2,4,6-trisubstituted pyrimidines \( 16 \) in moderate to good yields (up to 91\% yield, Scheme 15), which are important heterocyclic units in pharmaceuticals, agrochemicals, biologically active molecules, and novel materials.\(^{20}\) The reaction is proposed to undergo a propargylation/cyclization/oxidation tandem mechanism (Scheme 16). In the initial step, Cu(OTf)\(_2\)-induced propargyl amination of propargyl alcohol \( 14 \) with benzimidamide leads to \( C \). The intramolecular nucleophilic attack of amide nitrogen at the Cu-activated triple bond of alkyne produces cyclic dihydropyrimidine intermediate \( D \) (6-end-dig). Then, the dihydropyrimidine \( D \) is aromatized to the pyrimidine ring via the oxidation with air. In this reaction, the Cu(OTf)\(_2\) acts as a bifunctional catalyst, not only does it assist in the leaving of the hydroxyl group from the propargyl alcohol, furnishing the propargyl cation \( B \), but also activate the triple bond, rendering the cyclization process more facile.

Propargyl substitution using carbon nucleophiles

The development of new, efficient, and valuable synthetic methodologies for the direct construction of the carbon–carbon bond is a highly important task in organic chemistry. The propargyl substitution using carbon nucleophile offers a straightforward and efficient route to form the new carbon–carbon single bond, whereas synthesizes the compound bearing the carbon–carbon triple bond. In recent years, the copper-catalyzed propargyl substitutions using carbon nucleophiles have attracted much attention, and some related cycloadditions have also been developed.

Ketone enolates or their equivalents as nucleophiles

Propargyl alkylation of enoxysilanes

In 2007, Zhan and co-workers reported a very efficient method for the synthesis of \( \beta \)-alkynyl ketones \( 18 \) by the substitution reaction of propargyl acetates \( 1 \) with enoxysilanes \( 17 \) in the catalysis of 1 mol \% Cu(OTf)\(_2\) (Scheme 17).\(^{21}\) The reaction was completed rapidly within 5 min under the mild condition. It was noticed that the steric bulkiness of side chains \( \text{R}^3 \) in propargyl acetates \( 1 \) had a significant effect on the regioselectivity of the reaction (18 vs 19). Propargyl acetates \( 1 \) bearing the terminal or internal alkyne group were also tolerated. Furthermore, the substitution reaction could be followed by a TsOH-catalyzed cyclization without purification of the \( \beta \)-alkynyl ketone intermediates, offering a straightforward synthetic route to polysubstituted furans \( 20 \).
Propargylic alkylation of enamines

In 2009, Hou and co-workers developed the first copper-catalyzed asymmetric propargylic substitution of propargylic acetates 1 with enamines 21 catalyzed by 5 mol % of Cu(CH$_3$CN)$_4$ClO$_4$/(R)-Cl-MeO-BIPHEP complex (Scheme 18). A series of β-ethynyl ketones 22 were prepared in good yields and with good enantioselectivities (up to 91% ee). The aliphatic enamine derived from cyclohexanone was also examined, providing the product in 33% yield with 10:1 dr and 72% ee when a propargylic benzoate instead of the acetate was used.

Very recently, Hu and co-workers reported a highly diastereo- and enantioselective copper-catalyzed propargylic alkylation of morpholine-derived acyclic ketone enamines 23 with propargylic acetate (Scheme 19). The reaction was catalyzed by a Cu(OTf)$_2$-based complex and could be carried out under aerobic conditions. The product was obtained in high yield and with excellent diastereo- and enantioselectivity.

**Scheme 14.** Proposed catalytic cycle for copper-catalyzed sequential reactions.

**Scheme 15.** Cu-catalyzed tandem reactions of propargylic alcohols with amidines.

**Propargylic alkylation of enamines**

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**Scheme 16.** Proposed reaction pathway for copper-catalyzed tandem synthesis of pyrimidines.

**Scheme 17.** Cu-catalyzed propargylic alkylation of enoxysilanes.
esters 1 in the presence of a bulky and structurally rigid tridentate ketamine P,N,N-ligand (S)-L10 to forge two vicinal tertiary stereocenters, in which excellent diastereoselectivities (up to >95:5 dr) and perfect enantioselectivities (up to >99% ee) were obtained for a wide range of substrates (Scheme 19).23

Decarboxylative propargylic alkylation of propargyl b-ketoesters

Although some ketone enolate equivalents proved to be suitable reagents for catalytic asymmetric propargylic substitutions, the use of simple ketone enolates as nucleophiles is still very limited. In 2014, a breakthrough was made by Hu and co-workers. They developed an intramolecular asymmetric decarboxylative propargylic alkylation of propargyl b-ketoesters 25 by use of Cu(CH3CN)2BF4/(S)-L10 (5 mol %) as the catalyst, in which a variety of b-ethyl ketones 22 were obtained in good yields and with high enantioselectivities (up to 98% ee) (Scheme 20).24

In this reaction, both the nucleophile and the electrophile were formed in situ in catalytic concentration by the loss of CO2, instead

Scheme 18. Cu-catalyzed asymmetric propargylic alkylation of enamines with propargyl acetates.

Scheme 19. Cu-catalyzed diastereo-/enantioselective propargylic alkylation of acyclic ketone enamines with propargyl acetates.

Scheme 20. Cu-catalyzed asymmetric decarboxylative propargylic alkylation of propargyl b-ketoesters.


Scheme 22. Cu-catalyzed asymmetric intermolecular decarboxylative propargylic alkylation of b-keto acids with propargyl esters.
of the need to prepare preformed enolate equivalents. The nucleophilic attack of the enolate to the \( \gamma \)-carbon atom of the copper allenylidene complex should be the key step in determining stereoselectivity (Scheme 21). This work also represents the first successful example of the catalytic asymmetric decarboxylative propargylic alkylation. In addition, the reaction showed to be less sensitive to the nature of the solvent, and the best reaction solvent was toluene in terms of enantioselectivity. This result is different with those observed in the copper-catalyzed enantioselective propargylic substitution, in which only a polar protic solvent such as MeOH proved to be suitable.

A copper-catalyzed intermolecular enantioselective decarboxylative propargylic alkylation of propargylic esters 1 with \( \beta \)-keto acids 26 was subsequently developed by the same group. A variety of \( \beta \)-keto acids 26 with propargylic esters 1 underwent the decarboxylative propargylic alkylation to give the corresponding products as a mixture of two diastereoisomers in good yields with excellent enantioselectivities (up to 98% ee, Scheme 22). In comparison to the corresponding intramolecular decarboxylative propargylic alkylation of propargyl \( \beta \)-ketoesters 25, this method displays some significant advantages: (1) more readily available substrates; (2) generally better enantioselectivities; (3) broader substrate scope, especially for aliphatic propargylic esters.

### Propargylic alkylation of aldehydes

Recently, the combination of distinct catalysts for dual activation of distinct reacting partners has emerged as a new strategy for developing novel and valuable reactions that are difficult or impossible by the use of single catalyst. In 2011, Nishibayashi and co-workers reported the asymmetric propargylic alkylation of propargylic pentafluorobenzoate 1 with aldehydes 27 using a CuOTf-1/2CH\(_2\)CO\(_2\)H/racemic BINAP 3 complex and a chiral secondary amine L\(_{11}\) as the co-catalyst. The reaction gave propargylic alkylation products 29 as a mixture of two diastereoisomers in good yields and with high enantioselectivities (Scheme 23). Interestingly, the stereochemistry of BINAP did not affect the enantioselectivity of the alkylation product 29.

In this reaction, copper complex (transition metal catalyst) and secondary amine L\(_{11}\) (organocatalyst) activated propargylic esters 1 and aldehydes 27, respectively, and both catalysts worked cooperatively and simultaneously to promote the propargylic alkylation enantioselectively (Scheme 24). This work is an extension of the study of asymmetric propargylic substitution of propargylic alcohols with aldehydes using a thiolate-bridged diruthenium complex and a chiral secondary amine as cocatalysts. However, higher diastereoselectivity but lower catalytic activity was observed in the copper-catalyzed propargylic alkylation.

### Propargylic alkylation of \( \beta \)-dicarbonyl compounds

In 2011, van Maarseveen and co-workers attempted the first copper-catalyzed asymmetric propargylic substitution of 1-phenyl-2-propynyl acetate with 2,2,5-trimethyl-1,3-dioxane-4,6-dione, a cyclic derivative of malonate. However, only low enantioselectivity (6% ee) was obtained. The development of a catalytic
ketimine P,N,N-ligand (R)-L10. A series of propargylic alkylation products 29 were obtained in high yields and with excellent enantioselectivities (up to >99% ee, Scheme 25).²⁹ The catalytic system was also efficient for cyclic β-ketoesters and cyclic malonate derivatives as nucleophiles. In this reaction, the use of the bulky and structurally rigid chiral ketimine-type P,N,N-ligand (R)-L10 was critical to achieve good performance.

Very recently, Wu and co-workers developed a diastereo- and enantioselective propargylic alkylation of 2-substituted benzofuran-3(2H)-ones 32 with propargylic esters in the catalysis of a copper–pybox complex (Scheme 26).³⁰ A series of 2,2-disubstituted benzofuran-3(2H)-ones 33 bearing two vicinal chiral centers and one terminal alkyne functional group were obtained in good to excellent diastereoselectivities (up to 98:2 dr) and enantioselectivities (up to 98% ee).

**Propargylic substitution of indoles**

In 2011, van Maarseveen and co-workers reported a copper-catalyzed asymmetric propargylation of propargylic acetates 1 with indoles 34 in the presence of diPh-pybox ligand L1 (Scheme 27).³¹ Indole and N-methylindole were suitable nucleophiles, giving the 3-propargylinoldes 35 in high yields (up to 91% yield) and with excellent enantioselectivities (up to 98% ee). This is different with the Ru-catalyzed asymmetric propargylation of indoles, in which the presence of a bulky group such as triisopropylsilylethoxycarbonyl at the nitrogen atom of indoles was essential for achieving high enantioselectivity.³² However, the limited scope of the reaction was examined.

**Propargylic substitution of terminal alkynes**

1,4-Diynes are traditionally obtained by the nucleophilic substitution of propargyl halides or sulfonates with metal acetylides, in which large amounts of salt waste are generated simultaneously.³³ In 2011, Zhan and co-workers reported a copper-catalyzed propargylic substitution of propargylic alcohols 14 with terminal alkynes 36 using 10 mol% Cu(OTf)₂ as the catalyst.³⁴ The reaction could be finished in 5 min with water as the only byproduct. A range of propargyl alcohols 14 and terminal alkynes 36 were well tolerated, and a variety of 1,4-diynes products 37 were obtained in good yields (up to 87% yield, Scheme 28).

**Propargylic trifluoromethylation**

The introduction of a trifluoromethyl (CF₃) group into organic molecules has attracted considerable attention since the resulting system that could catalyze the asymmetric propargylic substitution in broad substrate spectrum with regard to β-dicarbonyl compounds is therefore highly desirable.

Recently, Hu and co-workers reported the first highly enantioselective copper-catalyzed propargylic alkylation of propargylic acetates 1 with β-diketones 30 by employing the chiral tridentate

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**Scheme 26.** Cu-catalyzed diastereo- and enantioselective propargylic alkylation of 2-substituted benzofuran-3(2H)-ones.

**Scheme 27.** Cu-catalyzed asymmetric propargylic alkylation of indoles.

**Scheme 28.** Cu-catalyzed propargylic alkylation of terminal alkynes.

**Scheme 29.** Cu-catalyzed trifluoromethylation of propargylic chlorides with trifluoromethyltrimethylsilane.
trifluoromethylated compounds are highly promising skeletons in the field of pharmaceuticals, agrochemicals, and materials. Recently, Nishibayashi and co-workers reported the reaction of primary and secondary propargyl halides with trifluoromethyltrityl methylsilane (CF$_3$SiMe$_3$) in the presence of 5 mol % copper(I) thiophene-2-carboxylate (CuTC) to give the corresponding trifluoromethylated products in good to high yields. This represents the first example on the catalytic trifluoromethylation of propargylic halides by directly using CF$_3$SiMe$_3$ as a trifluoromethylating reagent.

The study indicated that the regioselectivity of the reaction was dictated by the substrate, with primary propargyl chlorides providing propargyl trifluoromethanes and secondary propargyl chlorides affording trifluoromethylallenes. The authors proposed that the catalytic reaction should proceed via a pathway involving cat-ionic propargyl/allyl-copper complexes as reactive intermediates, not via an anti-SN$_2$ pathway.

Very recently, Altman and co-workers developed a two-step copper-catalyzed decarboxylative trifluoromethylation of propargyl bromodifluoroacetates into a mixture of propargyl trifluoromethanes and secondary propargyl chlorides affording trifluoromethylallenes. The activation procedure presumably served to convert the pre-catalytic combination of CuI/DMEDA/sodium bromo(difluoro)acetate (NaO$_2$CCF$_2$Br)/KF into the active catalyst, (DMEDA)Cu–CF$_3$ (Scheme 31).

Moreover, the activation procedure might circumvent an induction period, during which the substrate could be destroyed via nonproductive pathways. Since NaO$_2$CCF$_2$Br participated only in the activation procedure, it was required just at a substoichiometric amount (25 mol%) in this reaction.

![Scheme 30](image)

**Scheme 30.** Cu-catalyzed decarboxylative trifluoromethylation of propargyl bromodifluoroacetates.

![Scheme 31](image)

**Scheme 31.** Proposed catalytic cycle via an activation procedure.

![Scheme 32](image)

**Scheme 32.** Cu-catalyzed tandem reactions of propargylic alcohols or acetates with 1,3-dicarbonyl compounds.

![Scheme 33](image)

**Scheme 33.** Mechanism for propargylic alkylation/cycloisomerization tandem reaction.

![Scheme 34](image)

**Scheme 34.** Cu-catalyzed asymmetric cycloaddition of β-ketoesters with propargyl acetates.
Propargylic alkylation/cycloaddition tandem reaction

In 2009, Zhan and co-workers reported a convenient one-pot propargylic alkylation/cycloisomerization tandem process to construct substituted furans derivatives 43 from 1,3-dicarbonyl compounds 30 and propargylic alcohols 14 or acetates 1 catalyzed by copper(II) triflate as a bifunctional catalyst in good yields (up to 93% yield, Scheme 32). Increased yields were obtained in all cases when propargylic acetates were used as substrates instead of propargylic alcohols.

The authors proposed the mechanism as outlined in Scheme 33. Initially, the ionization of propargylic alcohols 14 would lead to propargylic cation B and the subsequent propargylic substitution of the enol A gives γ-alkynyl ketone D. Coordination of cationic copper(II) to the alkyne forms the π-alkyne copper complex E and enhances the electrophilicity of alkyne. Subsequent 5-exo-dig nucleophilic attack of the hydroxy group on β-carbon of Cu(II)-alkyne complex E would generate the alkynyl-copper derivative F. Protonolysis of F affords dihydrofuran G, which then undergoes isomerization to furan 43.

Since dihydrofurans are widely found in many natural products and pharmaceutical molecules, and also serve as attractive precursors for an array of organic transformations. If the last isomerization step of alkylene-2,3-dihydrofurans G in Scheme 33 can be efficiently interrupted, it would provide a concise access to synthesize 2-alkylene-2,3-dihydrofurans. Based on this consideration, very recently, Hu and co-workers reported the first copper-catalyzed asymmetric [3+2] cycloaddition of β-ketoesters 30 with propargylic esters 1 to generate optically active 2,3-hydrofuranos 44 bearing the exocyclic C=C bond in high yields and enantioselectivities (up to 97% ee, Scheme 34). Bulky and structurally rigid chiral ketimine-type P,N,N-ligand was critical to achieve good performance. A range of substitution patterns at the β-ketoesters 30 and propargylic acetates 1 were well tolerated. It was noted that the reaction worked well for the aliphatic propargylic substrates when an aliphatic pentafluorobenzoates were used instead of the corresponding acetates. In addition, the exocyclic double bond can be hydrogenated in a highly diastereoselective fashion to give unusual cis-2,3-dihydrofuran derivatives, which further enhances the scope of this transformation.

In 2012, Hu and co-workers developed a new Cu-catalyzed asymmetric [3+3] cycloaddition of propargyl esters 1 with cyclic enamine.


Scheme 37. Cu-catalyzed propargylic etherification of propargyl chlorides or esters with phenols.

Scheme 38. Cu-catalyzed propargylic etherification of propargyl chlorides with phenols.

the present of 2 mol% CuI to give 1,1-dialkylpropargyl ethers \textit{48} in 21–100% yields (Scheme 38).\textsuperscript{42} The study indicated that phenols bearing the electron-withdrawing group tended to give higher yields. Moreover, the resulting propargyl ethers could be readily converted into 2H-1-benzopyrans \textit{49}.

Nicolaou and coworkers applied the copper-catalyzed propargyl etherification in the total synthesis of biologically active compounds \textit{50}, tovophyllin B, which possesses a significant inhibitory activity against \textit{Mycobacterium tuberculosis} (Scheme 39).\textsuperscript{21} The O-propargylation of the readily available phenol \textit{47} with methyl 2-methyl-3-yn-2-yl carbonate in the presence of DBU and the catalytic amount of CuCl proceeded smoothly to afford 1,1-dimethylpropargyl ether \textit{48}, a key intermediate in the total synthesis of tovophyllin B \textit{50}.

In 2008, Huang and co-workers developed a novel copper-catalyzed propargyl etherification reaction of propargyl alcohols \textit{14} with alcohols in the presence of copper(II) bromide with excellent regioselectivity and high yields under very mild conditions (up to 98% yield, Scheme 40).\textsuperscript{44} Importantly, thiols were also tolerated in the reaction.

Conclusions and future outlook

In summary, significant advances have been achieved in the copper-catalyzed propargyl substitutions over the last two decades. Diverse nucleophiles such as nitrogen, carbon, oxygen, sulfur nucleophiles have been successfully applied in the reaction. Many kinds of propargyl compounds have been prepared in satisfactory yields, regioselectivities, and enantioselectivities under very mild conditions. Especially, some carbocyclic and cyclohexyl substrates, that are hard to prepare with conventional methods, could be readily synthesized via propargyl-catalyzed propargyl substitution/cyclization tandem reactions. Although great progress has been achieved, the Cu-catalyzed propargyl substitution, in particular its asymmetric version, is still in underdeveloped and full of challenges. For instances, only a limited number of chiral ligands are found to be efficient. The scope of the propargyl substrates is narrow, and no successful asymmetric example has been reported for either propargyl esters with an internal alkene moiety or tertiary propargyl esters. The range of suitable nucleophiles is quite limited, and O- or S-nucleophiles has never been employed in an asymmetric reaction. Moreover, the diastereo- and enantioselective construction of multistereogenic centers via the copper-catalyzed asymmetric propargyl substitution scheme is rarely explored. It is expected, however, that with a deeper understanding of these reactions, new chiral ligands as well as new strategies will be developed, and the scope of both the nucleophiles and the substrates will be expanded in the future.

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References and notes

