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Digest Paper

Recent advances in copper-catalyzed propargylic substitution

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ABSTRACT

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

Propargylic compounds are common motifs in many natural products, fine chemicals, and synthetic pharmaceuticals, as well as useful synthetic intermediates in organic synthesis. The presence

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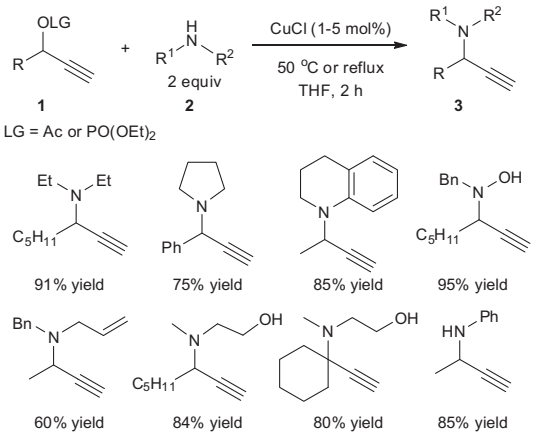
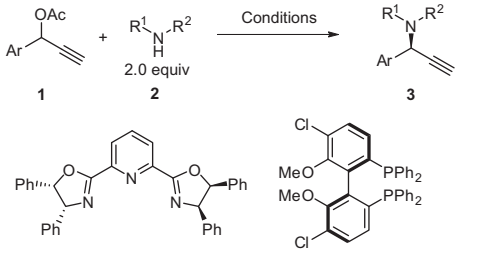


Scheme 1. Cu-catalyzed propargylic amination.

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,[4] 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.



	Conditions[a]	Ar	R^1	R^2	Yield	Ee of **3**
a	**A**	Ph	H	2-$MeOC_6H_4$	97	85
b	**A**	1-naphthyl	H	2-$MeOC_6H_4$	91	85
c	**A**	2-pyridyl	H	2-$MeOC_6H_4$	80	74
d[b]	**A**	^{i}Pr	H	2-$MeOC_6H_4$	27	40
e	**A**	Ph	H	Ph	94	87
f[c]	**A**	Ph	Me	Ph	90	60
g	**B**	Ph	Me	Ph	96	85
h	**B**	4-BrC_6H_4	Me	Ph	91	85
i	**B**	4-MeC_6H_4	Me	Ph	98	81
j	**B**	Ph	Me	4-ClC_6H_4	96	89
k	**B**	Ph	-$(CH_2)_5$-		64	80
l	**B**	Ph	H	Ph	90	53

[a] Condition **A**: CuI (10 mol%)/diPh-pybox **L1** (12 mol%), ^{i}Pr$_2$NEt (4.0 equiv), MeOH, -20 °C. Condition **B**: CuOTf•1/2C_6H_5 (5 mol%)/(*R*)-Cl-MeO-BIPHEP **L2** (10 mol%), ^{i}Pr$_2$NEt (4.0 equiv), MeOH, 0 °C. [b] The reaction was performed at 40 °C. [c] The reaction was performed at rt.

Scheme 2. Cu-catalyzed asymmetric propargylic amination.

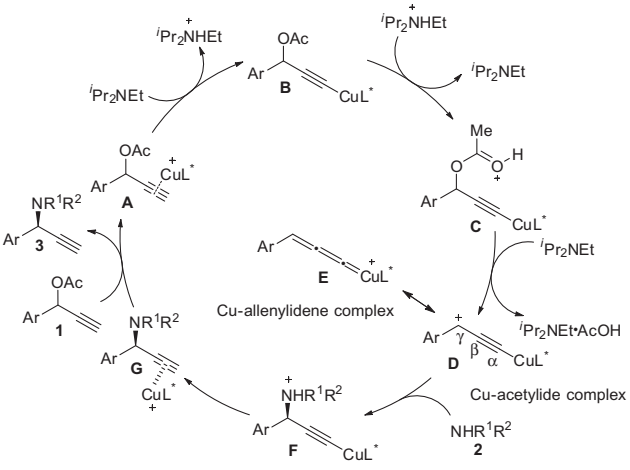
Propargylic substitution using nitrogen nucleophiles

Propargylic amines are versatile building blocks and intermediates for organic synthesis.[6] 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.

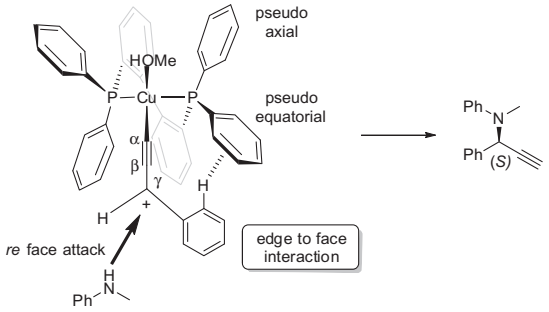
Propargylic amination of propargylic esters

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).[8] 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 alkyne did not undergo the amination even under severe conditions. This result suggested a copper–acetylide 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.

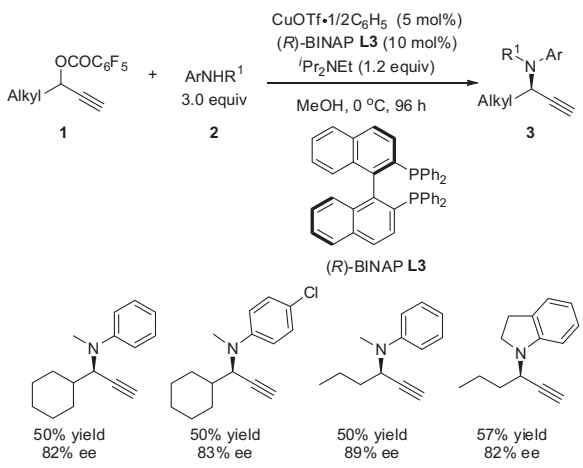
However, it is until 2008, van Maarseveen and Nishibayashi independently reported the first copper-catalyzed asymmetric propargylic amination.[9,10] These methods provided an efficient



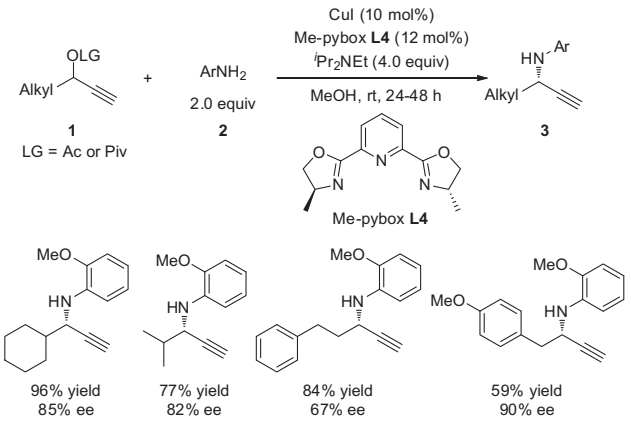
Scheme 3. Proposed reaction pathway for Cu-catalyzed propargylic amination.



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

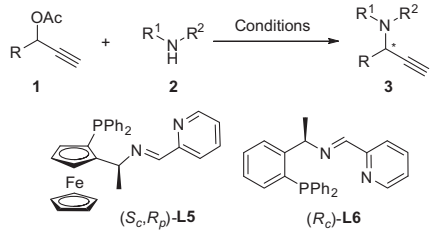


Scheme 5. Cu-catalyzed asymmetric propargylic amination of propargylic pentafluorobenzoates with secondary amines.



Scheme 6. Cu-catalyzed asymmetric propargylic amination of propargylic esters with *o*-anisidines.

route to prepare optically active propargylic amines **3** in high yields and with good enantioselectivities. The major difference between van Maarseveen' 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 CuI 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·1/2C_6H_5 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).



	Conditions[a]	R	R^1	R^2	Yield (%)	ee (%)
a[b]	A	Ph	H	Ph	85	90
b	A	Ph	H	2-$MeOC_6H_4$	89	93
c	A	4-$CF_3C_6H_4$	H	2-$MeOC_6H_4$	85	96
d	A	4-MeC_6H_4	H	2-$MeOC_6H_4$	84	90
e[b]	A	2-furyl	H	2-$MeOC_6H_4$	92	89
f	A	Ph	Me	Ph	86	95
g	A	4-FC_6H_4	Me	Ph	90	97
h	A	4-MeC_6H_4	Me	Ph	84	92
i	A	Ph	Et	Et	87	95
j[c]	A	Ph	-$(CH_2)_5$-		77	91
k	B	Bn	H	2-$MeOC_6H_4$	45	78
l	B	Cy	H	2-$MeOC_6H_4$	52	81
m	B	^{n}Pr	Me	Ph	76	91
n	B	Cy	Me	Ph	69	93

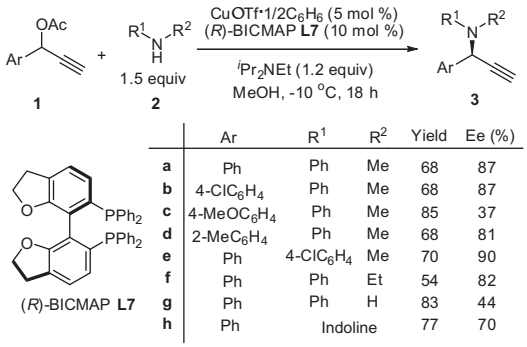
[a] Condition **A**: CuCl (5 mol%)/(S_c,R_p)-**L5** (10 mol%), ^{i}Pr_2NEt (1.2 equiv), MeOH, 0 °C, 12-24 h. Condition **B**: $Cu(OAc)_2$•H_2O (10 mol%)/(R_c)-**L6** (12 mol%), ^{i}Pr_2NEt (4.0 equiv), MeOH, 0 °C, 60 h. [b] The reaction was performed at -20 °C for 48 h. [c] CuOTf•1/2C_6H_6 was used instead of CuCl.

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

Nishibayashi and co-workers made an exhaustive research on the reaction mechanism and proposed a reaction pathway similar to van Maarseveen's (Scheme 3).[11] 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 C_γ atom of the copper allenylidene complex **D** 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.

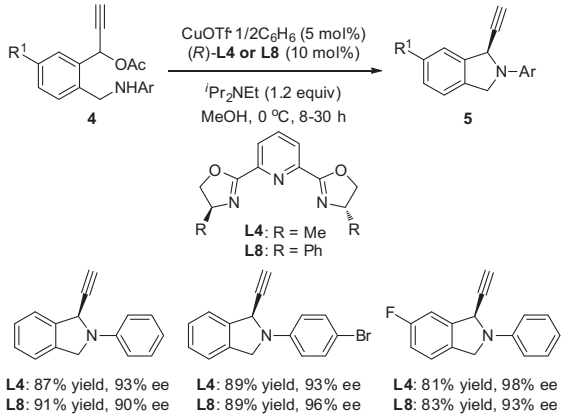
A transition state of the copper–allenylidene complex with the chiral ligand (*R*)-BIPHEP **L2** is proposed to account for high enantioselectivity of the reaction (Scheme 4).[11] The *re*-face of the γ-carbon of the copper–allenylidene complex is open to attack by the *N*-methylaniline. The edge-to-face 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

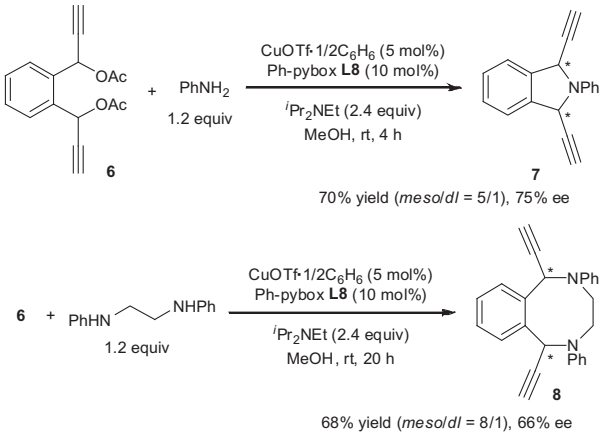


	Ar	R^1	R^2	Yield	Ee (%)
a	Ph	Ph	Me	68	87
b	4-ClC_6H_4	Ph	Me	68	87
c	4-$MeOC_6H_4$	Ph	Me	85	37
d	2-MeC_6H_4	Ph	Me	68	81
e	Ph	4-ClC_6H_4	Me	70	90
f	Ph	Ph	Et	54	82
g	Ph	Ph	H	83	44
h	Ph	Indoline		77	70

Scheme 8. Cu-catalyzed asymmetric propargylic amination with (*R*)-BICMAP.



Scheme 9. Cu-catalyzed asymmetric intramolecular propargylic amination of propargylic acetates bearing a secondary amine moiety.

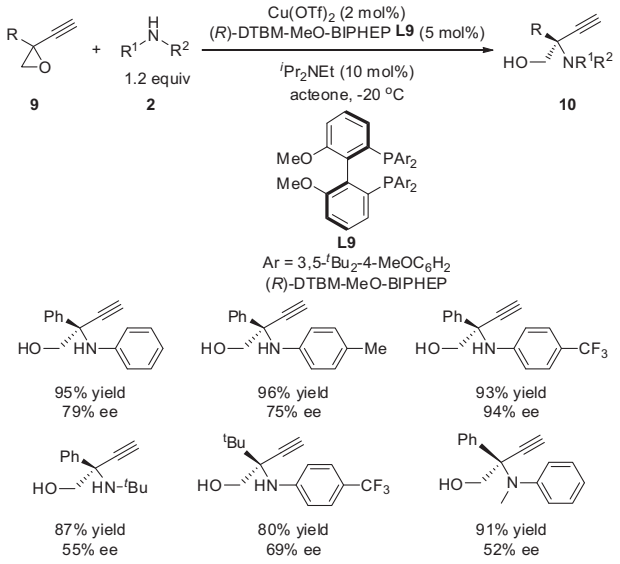


Scheme 10. Cu-catalyzed sequential inter- and intramolecular double propargylic amination.

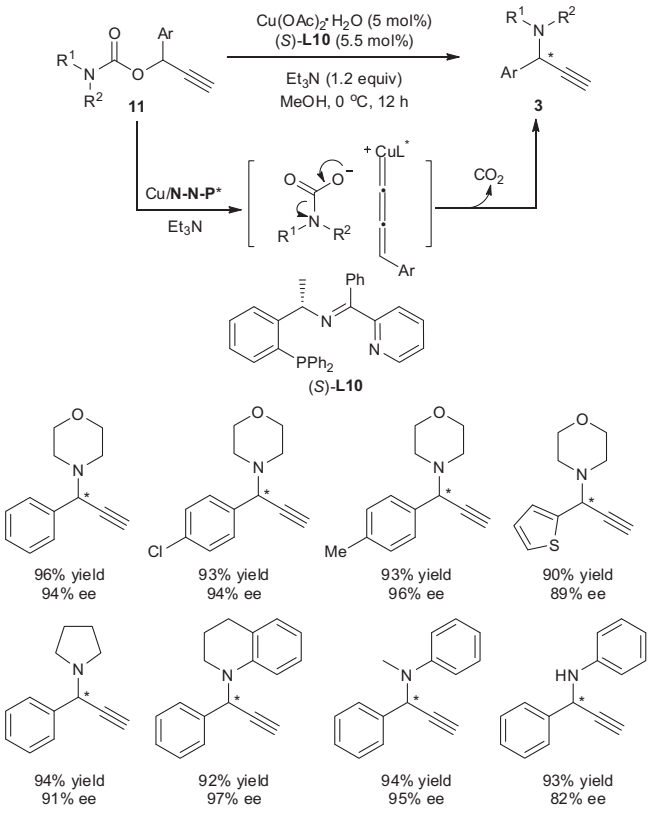
amines **2**, in which moderate yields with high enantioselectivities were achieved in the presence of 5 mol % CuOTf·1/2C_6H_5/(*R*)-BINAP **L3** complex (up to 90% ee, Scheme 5).[12] The introduction of pentafluorobenzoate in place of the acetate group as a leaving group was found to be necessary to promote the amination of aliphatic propargylic esters with secondary amines. However, primary amines were less efficient in this catalytic system.

The copper-catalyzed enantioselective amination of non-aromatic propargylic esters **1** with primary amines **2** could be realized with van Maarseveen's method, in which good yields and high enantioselectivities were achieved by use of 10 mol % CuI with Me-pybox **L4** (up to 90% ee, Scheme 6).[13] Some secondary amines were also tested, however, only moderate enantioselectivities were achieved.

In 2012, Hu and co-workers demonstrated that chiral tridentate P,N,N-ligands, (S_c,R_p)-**L5** and (*R*)-**L6**, were highly efficient for the Cu-catalyzed asymmetric propargylic amination of propargylic acetates **1**.[14] In the presence of CuCl/(S_c,R_p)-**L5** 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_2O/(*R*)-**L6** 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



Scheme 11. Cu-catalyzed asymmetric ring-opening reaction of ethynyl epoxides with amines.



Scheme 12. Cu-catalyzed asymmetric decarboxylative propargylic amination of propargyl carbamates.

amines could be used as efficient nucleophiles for the highly enantioselective catalytic propargylic amination of both aliphatic and aromatic propargylic acetates.

In 2013, Sakamoto and co-workers reported the copper-catalyzed asymmetric propargylic amination of aromatic propargylic esters **1** with amines **2** using (*R*)-BICMAP **L7** as a chiral ligand, giving the desired products **3** in good yields (up to 85% yield) and with moderate to high enantioselectivities (up to 90% ee, Scheme 8).[15]

Very recently, Nishibayashi and co-workers disclosed a copper-catalyzed asymmetric intramolecular propargylic amination of propargylic acetates **4** bearing a secondary amine moiety at a suitable position.[16] In the catalysis of CuOTf·1/2C_6H_6/Pybox (**L4** or **L8**) complex, a variety of optically active 1-ethynylisoindolines **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 propargylic amination, however, the result was still far from satisfactory (Scheme 10).

Ring-opening reaction of ethynyl epoxides with amines

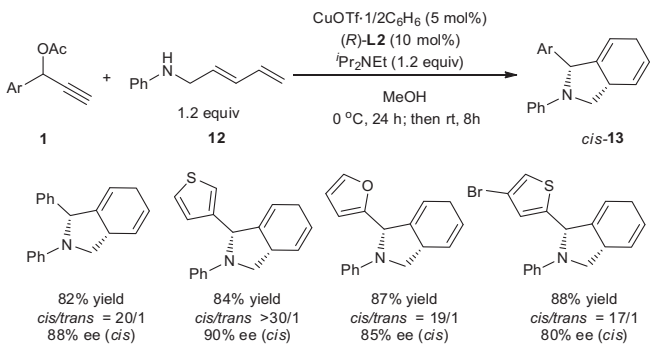
In 2009, Nishibayashi and co-workers reported the copper-catalyzed asymmetric ring-opening reaction of ethynyl epoxides **9** with amines **2** catalyzed by $Cu(OTf)_2$/DTBM-MeO-BIPHEP **L9** complex. Optically active β-amino alcohols **10** bearing a tertiary carbon at the α-position of the amine were 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 propargylic amination of propargyl carbamates

Although great advances have been made in propargylic substitution using nitrogen nucleophiles, the development of new strategy for the catalytic synthesis of propargylic amines remains a highly desirable and challenging task. In 2014, Hu and co-workers reported a Cu-catalyzed asymmetric decarboxylative propargylic amination of propargyl carbamates **11** with a tridentate ketimine 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 propargylic 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 propargylic amines.

Propargylic 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 propargylic amination have also been developed.



Scheme 13. Cu-catalyzed asymmetric propargylic amination/cycloaddition tandem reaction of propargylic acetates with *N*-(*E*)-penta-2,4-dienylaniline.

In 2010, Nishibayashi and co-workers reported the copper-catalyzed asymmetric propargylic amination/[4+2]-cycloaddition tandem reaction of propargylic acetates **1** with *N*-(*E*)-penta-2,4-dienylaniline **12** to give chiral 1,2-disubstituted tetrahydroisoindole derivatives **13** in high yields and with high diastereo-/enantioselectivities (up to >30/1 dr, up to 90% ee, Scheme 13).[19] 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 propargylic amination and the intramolecular [4+2] cycloaddition reaction.

A proposed reaction pathway is shown in Scheme 14. At first, *N*-(*E*)-2,4-pentadienylaniline **12** might attack the copper acetylide complex **A** bearing a cationic γ-carbon atom from the *re* face to give **C** with high enantioselectivity. Then, the intramolecular [4+2] cycloaddition 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 propargylic alcohols **14** with amidine **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 propargylic amination of propargyl alcohol **14** with benzimidamide leads to **C**. The intramolecular nucleophilic attack of amidine nitrogen at the Cu-activated triple bond of alkyne produces cyclic dihydropyrimidine intermediate **D** (6-*endo*-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 propargylic alcohol, furnishing the propargylic cation **B**, but also activate the triple bond, rendering the cyclization process more facile.

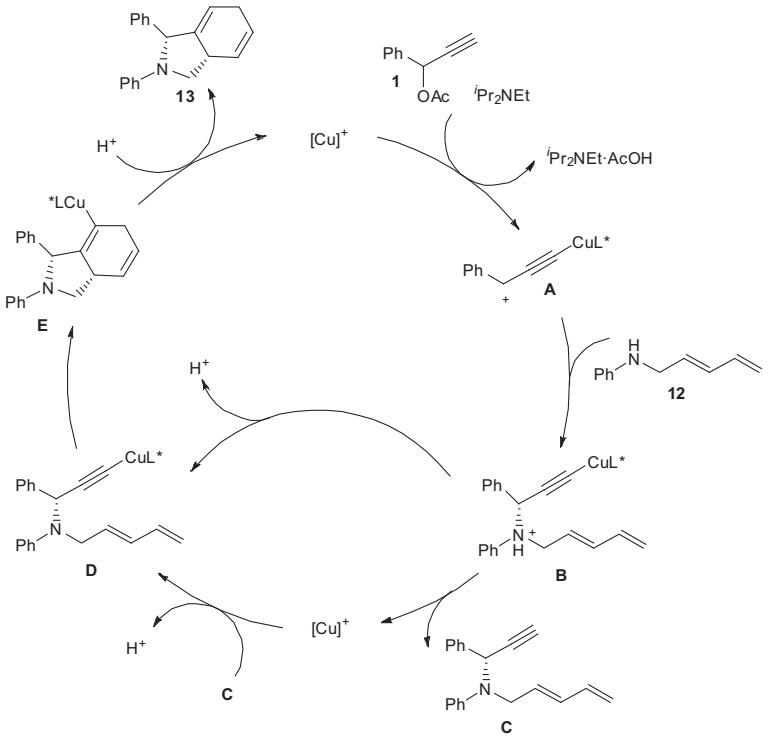
Propargylic substitution using carbon nucleophiles

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 propargylic 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 propargylic substitutions using carbon nucleophiles have attracted much attention, and some related cycloadditions have also been developed.

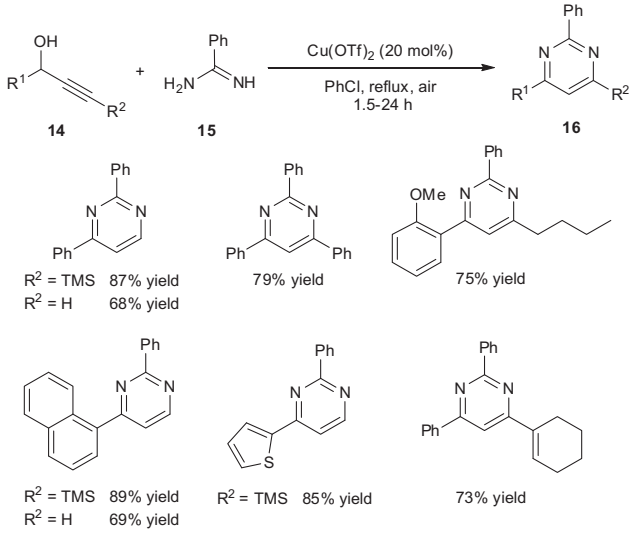
Ketone enolates or their equivalents as nucleophiles

Propargylic alkylation of enoxysilanes

In 2007, Zhan and co-workers reported a very efficient method for the synthesis of β-alkynyl ketones **18** by the substitution reaction of propargylic 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 (R^2) in propargylic acetates **1** had a significant effect on the regioselectivity of the reaction (**18** vs **19**). Propargylic 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 β-alkynyl ketone intermediates, offering a straightforward synthetic route to polysubstituted furans **20**.



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

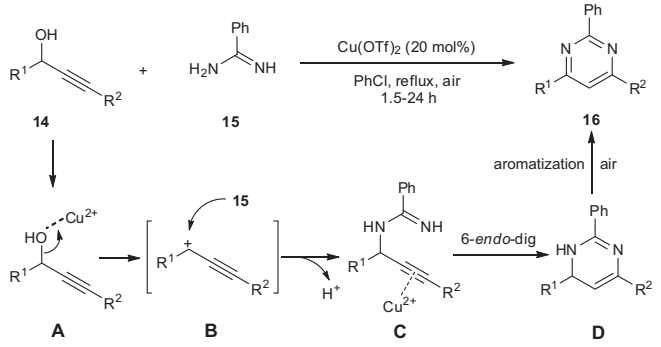


Scheme 15. Cu-catalyzed tandem reactions of propargylic alcohols with amidines.

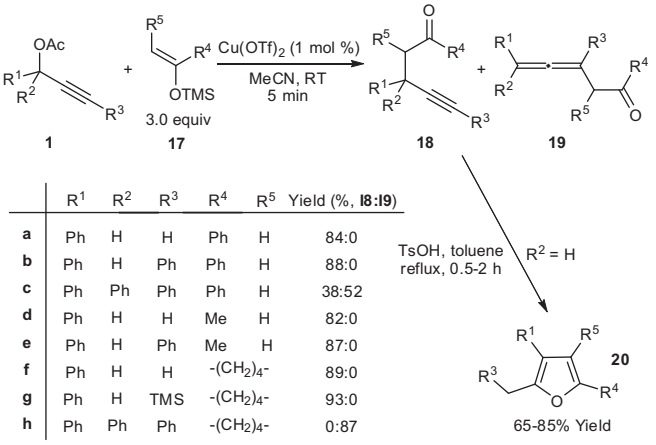
Propargylic alkylation of enamines

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 $Cu(CH_3CN)_4ClO_4$/(*R*)-Cl-MeO-BIPHEP complex (Scheme 18).[22] 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.

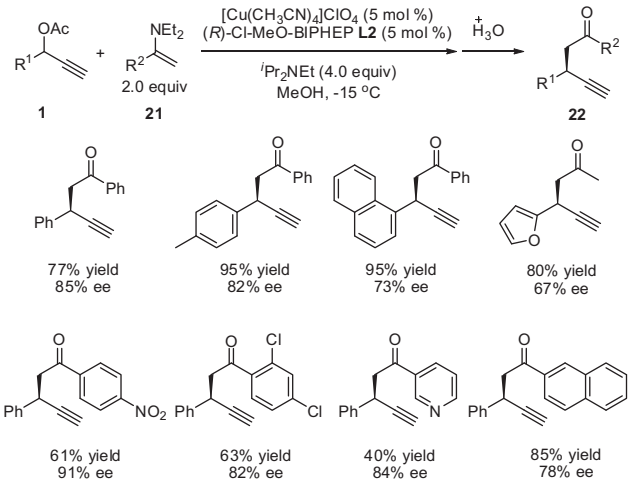
Very recently, Hu and co-workers reported a highly diastereo-/enantioselective copper-catalyzed propargylic alkylation of morpholine-derived acyclic ketone enamines **23** with propargylic



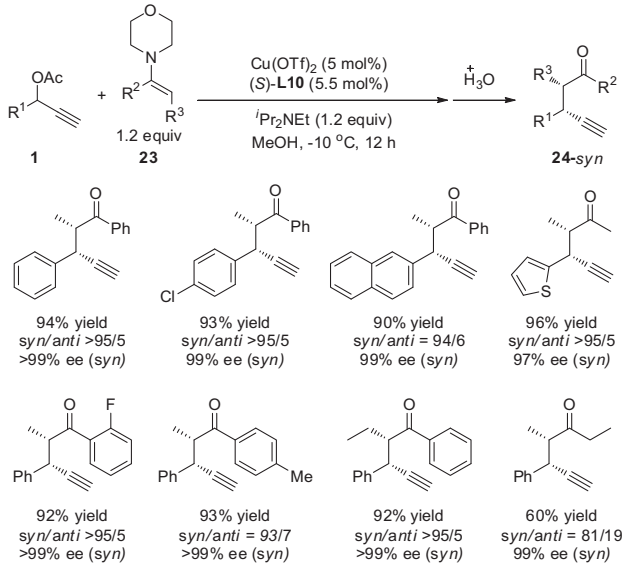
Scheme 16. Proposed reaction pathway for copper-catalyzed tandem synthesis of pyrimidines.



Scheme 17. Cu-catalyzed propargylic alkylation of enoxysilanes.



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



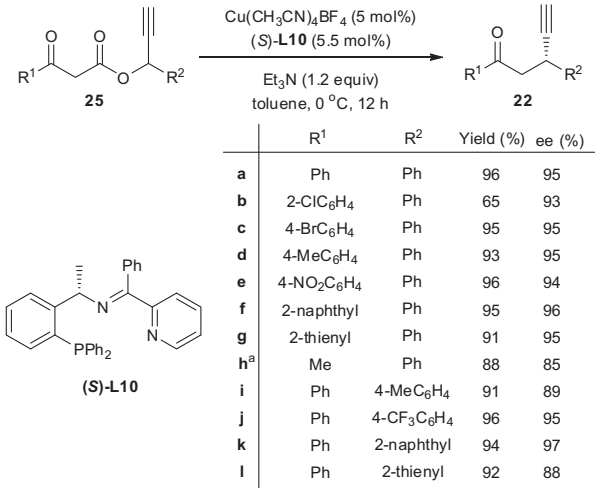
Scheme 19. Cu-catalyzed diastereo-/enantioselective propargylic alkylation of acyclic ketone enamines with propargylic acetates.

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 β-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 β-ketoesters **25** by use of $Cu(CH_3CN)_4BF_4$/(*S*)-**L10** (5 mol %) as the catalyst, in which a variety of β-ethynyl ketones **22** were obtained in good yields and with high enantioselectivities (up to 98% ee) (Scheme 20).[24]

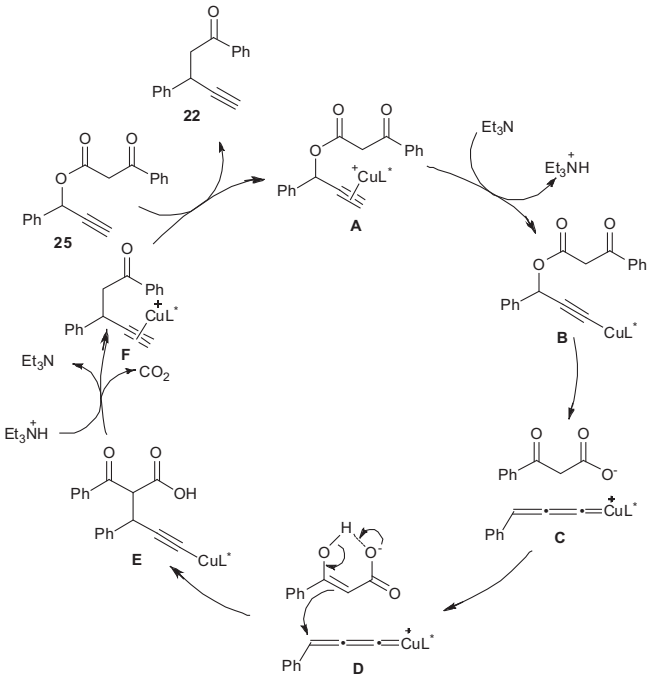
In this reaction, both the nucleophile and the electrophile were formed in situ in catalytic concentration by the loss of CO_2, instead



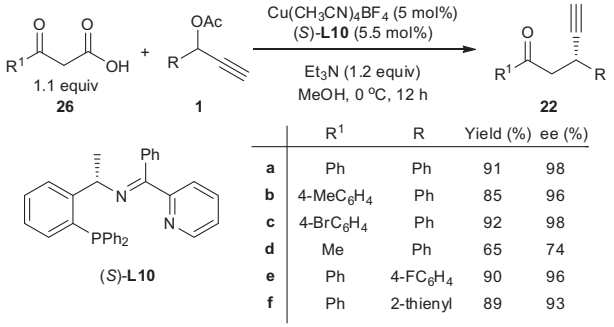
	R^1	R^2	Yield (%)	ee (%)
a	Ph	Ph	96	95
b	2-ClC_6H_4	Ph	65	93
c	4-BrC_6H_4	Ph	95	95
d	4-MeC_6H_4	Ph	93	95
e	4-$NO_2C_6H_4$	Ph	96	94
f	2-naphthyl	Ph	95	96
g	2-thienyl	Ph	91	95
h[a]	Me	Ph	88	85
i	Ph	4-MeC_6H_4	91	89
j	Ph	4-$CF_3C_6H_4$	96	95
k	Ph	2-naphthyl	94	97
l	Ph	2-thienyl	92	88

[a] The reaction was performed in MeOH at a catalyst loading of 10 mol%.

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

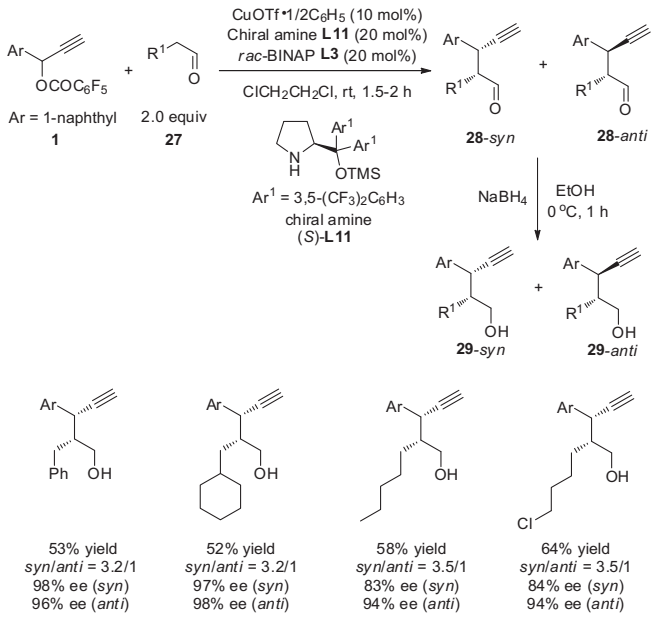


Scheme 21. Proposed reaction pathway for decarboxylative propargylic alkylation.



	R^1	R	Yield (%)	ee (%)
a	Ph	Ph	91	98
b	4-MeC_6H_4	Ph	85	96
c	4-BrC_6H_4	Ph	92	98
d	Me	Ph	65	74
e	Ph	4-FC_6H_4	90	96
f	Ph	2-thienyl	89	93

Scheme 22. Cu-catalyzed asymmetric intermolecular decarboxylative propargylic alkylation of β-keto acids with propargylic esters.



Scheme 23. Cooperative catalytic asymmetric propargylic alkylation of aldehydes.

of the need to prepare preformed enolate equivalents. The nucleophilic attack of the enolate to the γ-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 β-keto acids **26** was subsequently developed by the same group.[25] A variety of β-keto acids **26** with propargylic esters **1** underwent the decarboxylative propargylic alkylation to give the corresponding β-ethynyl ketones **22** in good yields with excellent enantioselectivities (up to 98% ee, Scheme 22). In comparison to the corresponding intramolecular decarboxylative propargylic alkylation of propargyl β-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.

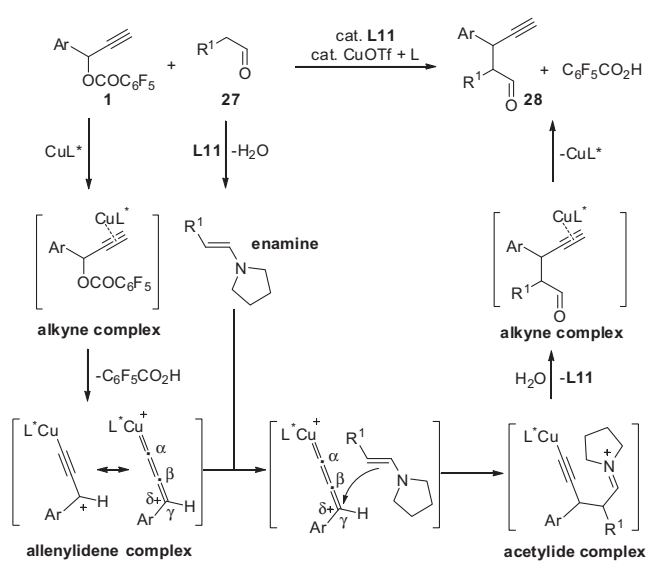
Propargylic alkylation of aldehydes

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.[26] In 2011, Nishibayashi and co-workers reported the asymmetric propargylic alkylation of propargylic pentafluorobenzoate **1** with aldehydes **27** using a CuOTf·1/2C_6H_6/racemic BINAP **L3** complex and a chiral secondary amine **L11** 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).[27] Interestingly, the stereochemistry of BINAP did not affect the enantioselectivity of the alkylation product **29**.

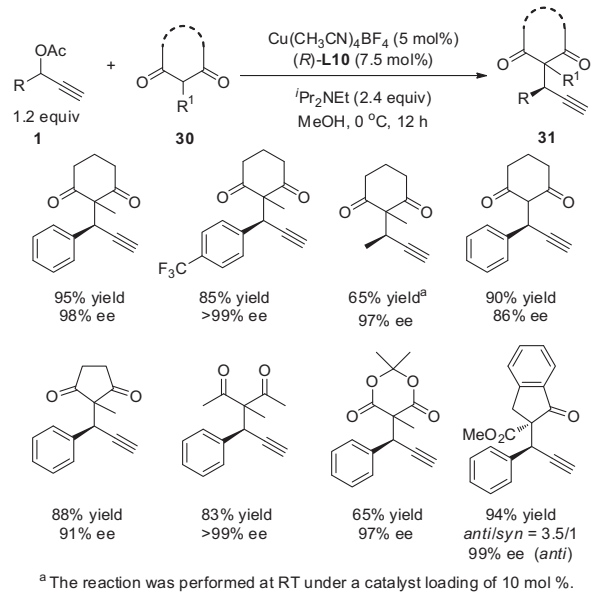
In this reaction, copper complex (transition metal catalyst) and secondary amine **L11** (organocatalyst) activated propargylic esters **1** and aldehydes **27**, respectively, and both catalysts worked cooperatively and simultaneously to promote the propargylic alkylation enantioselectively (Scheme 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.[28] However, higher diastereoselectivity but lower catalytic activity was observed in the copper-catalyzed propargylic alkylation.

Propargylic alkylation of β-dicarbonyl compounds

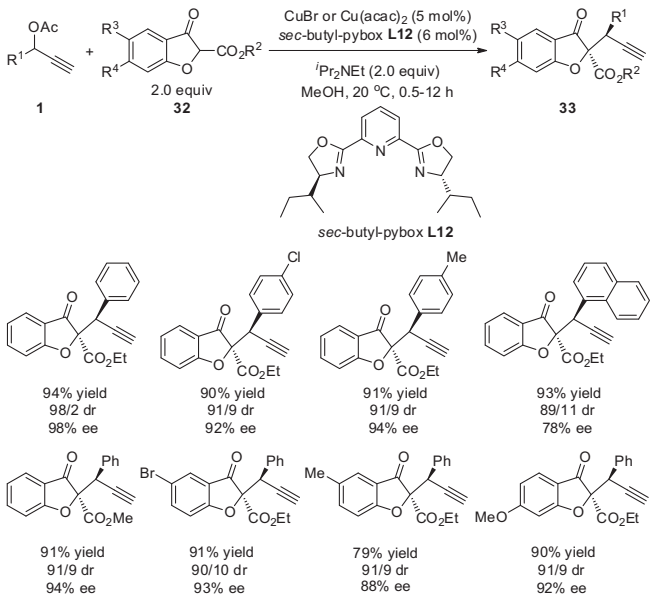
In 2011, van Maarseveen and co-workers attempted the first copper-catalyzed asymmetric propargylic substitution of 1-phenyl-2-propynyl acetate with 2,2,5-trimethyl-1,3-dioxane-4,6-dione, a cyclic derivative of malonate. However, only low enantioselectivity (6% ee) was obtained.[13] The development of a catalytic



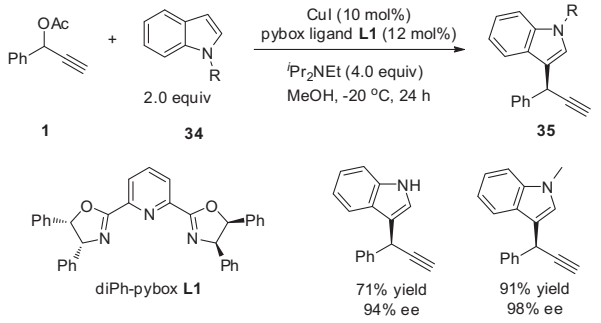
Scheme 24. Proposed reaction pathway for cooperative catalytic propargylic alkylation.



Scheme 25. Cu-catalyzed asymmetric propargylic alkylation of β-dicarbonyl compounds.



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



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

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 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(2*H*)-ones **32** with propargylic esters in the catalysis of a copper–pybox complex (Scheme 26).[30] A series of 2,2-disubstituted benzofuran-3(2*H*)-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

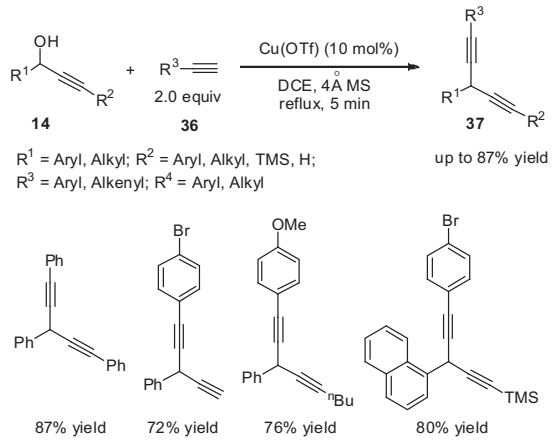
In 2011, van Maarseveen and co-workers reported a copper-catalyzed asymmetric propargylation of propargylic acetates **1** with indoles **34** in the presence of diPh-pybox ligand **L1** (Scheme 27).[13] Indole and *N*-methylindole were suitable nucleophiles, giving the 3-propargylindoles **35** in high 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 triisopropylsilyl at the nitrogen atom of indoles was essential for achieving high enantioselectivity.[31] However, the limited scope of the reaction was examined.

Propargylic substitution of terminal alkynes

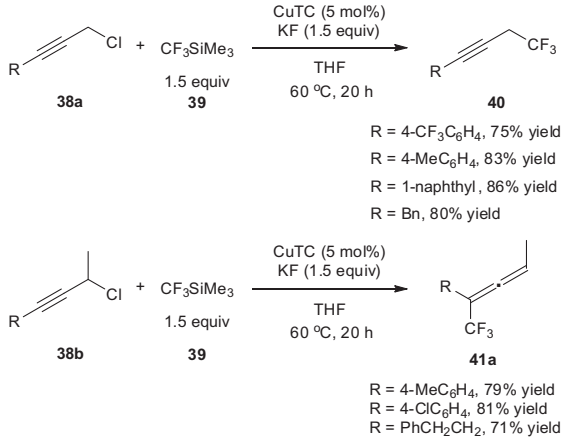
1,4-Diynes are traditionally obtained by the nucleophilic substitution of propargyl halides or sulfonates with metal acetylides, in which large amounts of salt waste are generated simultaneously.[32] In 2011, Zhan and co-workers reported a copper-catalyzed propargylic substitution of propargyl alcohols **14** with terminal alkynes **36** using 10 mol % $Cu(OTf)_2$ as the catalyst.[33] 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

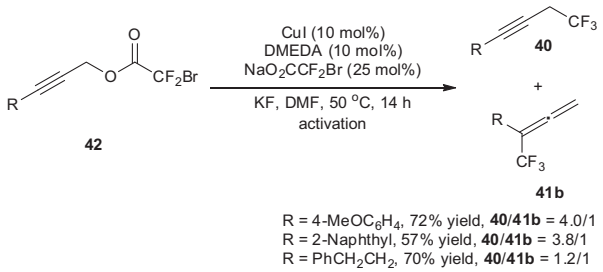
The introduction of a trifluoromethyl (CF_3) group into organic molecules has attracted considerable attention since the resulting



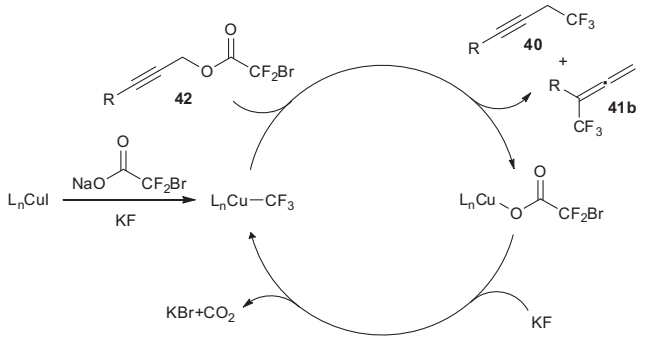
Scheme 28. Cu-catalyzed propargylic alkylation of terminal alkynes.



Scheme 29. Cu-catalyzed trifluoromethylation of propargylic chlorides with trifluoromethyltrimethylsilane.



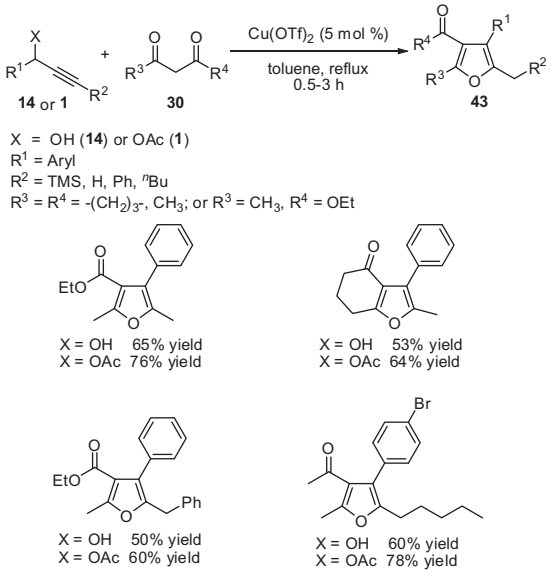
Scheme 30. Cu-catalyzed decarboxylative trifluoromethylation of propargyl bromodifluoroacetates.



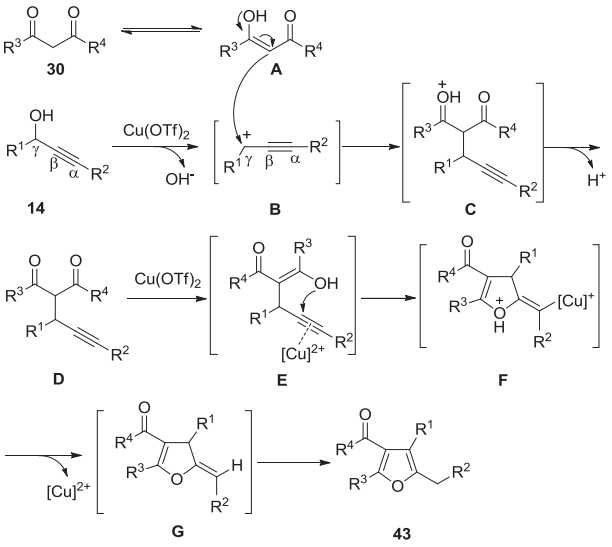
Scheme 31. Proposed catalytic cycle via an activation procedure.

trifluoromethylated compounds are highly promising skeletons in the field of pharmaceuticals, agrochemicals, and materials.[34] Recently, Nishibayashi and co-workers reported the reaction of primary and secondary propargylic halides **38a–b** with trifluoromethyltrimethylsilane (CF_3SiMe_3) **39** in the presence of 5 mol % copper(I) thiophene-2-carboxylate (CuTC) to give the corresponding trifluoromethylated products **40** and **41a** in good to high yields. This represents the first example on the catalytic trifluoromethylation of propargylic halides by directly using CF_3SiMe_3 as a trifluoromethylating reagent (Scheme 29).[35]

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 cationic propargyl/allenyl-copper complexes as reactive intermediates, not via an anti-S_N2' pathway.

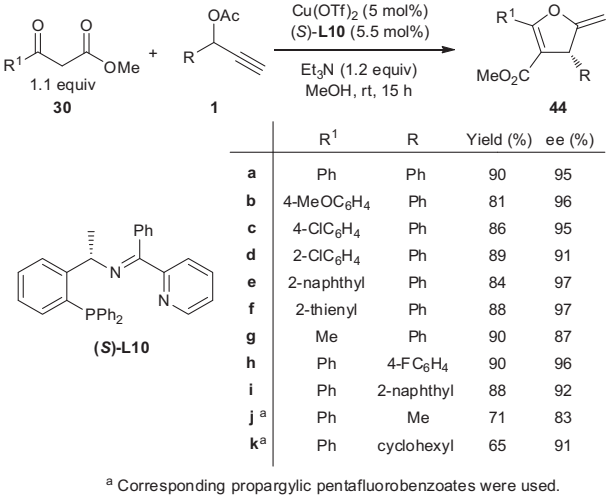


Scheme 32. Cu-catalyzed tandem reactions of propargylic alcohols or acetates with 1,3-dicarbonyl compounds.



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

Very recently, Altman and co-workers developed a two-step copper-catalyzed decarboxylative trifluoromethylation of propargyl bromodifluoroacetates **42** into a mixture of propargyl trifluoromethanes **40** and trifluoromethylallenes **41b** (Scheme 30).[36] In the reaction, an activation procedure and the use of *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand significantly improved the yield of product. The activation procedure presumably served to convert the pre-catalytic combination of CuI/DMEDA/sodium bromo(difluoro)acetate (NaO_2CCF_2Br)/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_2CCF_2Br participated only in the activation procedure, it was required just at a substoichiometric amount (25 mol %) in this reaction.



	R^1	R	Yield (%)	ee (%)
a	Ph	Ph	90	95
b	4-$MeOC_6H_4$	Ph	81	96
c	4-ClC_6H_4	Ph	86	95
d	2-ClC_6H_4	Ph	89	91
e	2-naphthyl	Ph	84	97
f	2-thienyl	Ph	88	97
g	Me	Ph	90	87
h	Ph	4-FC_6H_4	90	96
i	Ph	2-naphthyl	88	92
j [a]	Ph	Me	71	83
k [a]	Ph	cyclohexyl	65	91

[a] Corresponding propargylic pentafluorobenzoates were used.

Scheme 34. Cu-catalyzed asymmetric cycloaddition of β-ketoesters with propargylic acetates.

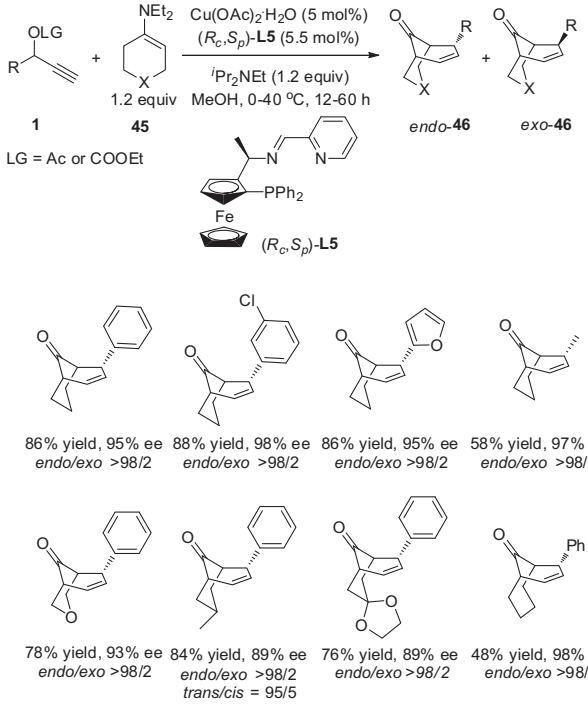
Propargylic alkylation/cycloaddition tandem reaction

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).[37] Increased yields were obtained in all cases when propargylic acetates were used as substrates instead of propargylic alcohols.

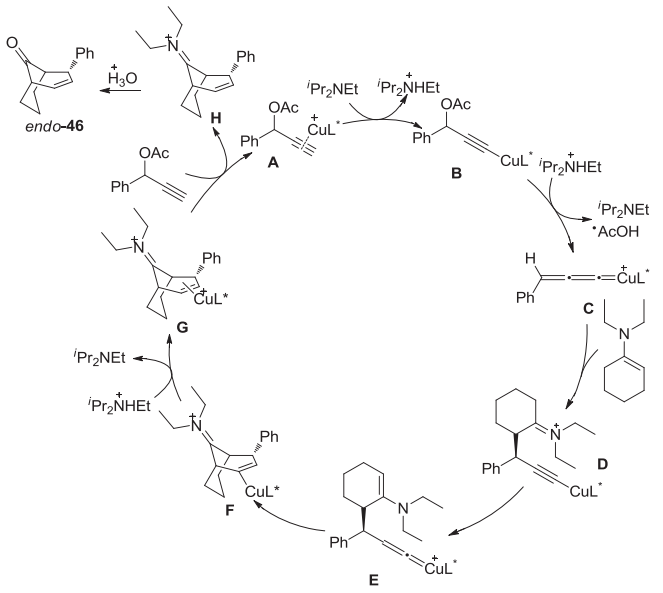
The authors proposed the mechanism as outlined in Scheme 33. Initially, the ionization of propargylic alcohols **14** would lead to propargylic cation **B** and the subsequent propargylic substitution of the enol **A** gives γ-alkynyl ketone **D**. Coordination of cationic copper(II) to the alkyne forms 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 alkenyl-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.[38] 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 formal [3+2] cycloaddition of β-ketoesters **30** with propargylic esters **1** to generate optically active 2,3-hydrofurans **44** bearing the exocyclic C=C bond in high yields and enantioselectivities (up to 97% ee, Scheme 34).[39] 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.

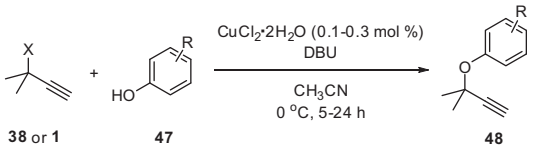
In 2012, Hu and co-workers developed a new Cu-catalyzed asymmetric [3+3] cycloaddition of propargyl esters **1** with cyclic



Scheme 35. Cu-catalyzed asymmetric [3+3] cycloaddition of propargyl esters with cyclic enamines.

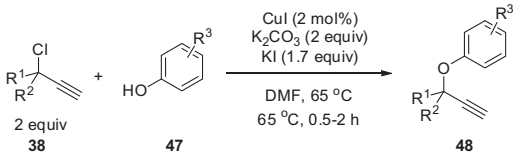


Scheme 36. Proposed mechanism for [3+3] cycloaddition of propargyl ester with cyclic enamine.

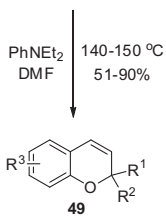


	R	X = Cl Yield	X = OCO_2CH_3 Yield	X = $OCOCF_3$ Yield
a	H	69	70	83
b	4-OMe	67	70	63
c	4-CN	78	86	86
d	4-NO_2	81	78	88
e	4-$COCH_3$	78	86	80

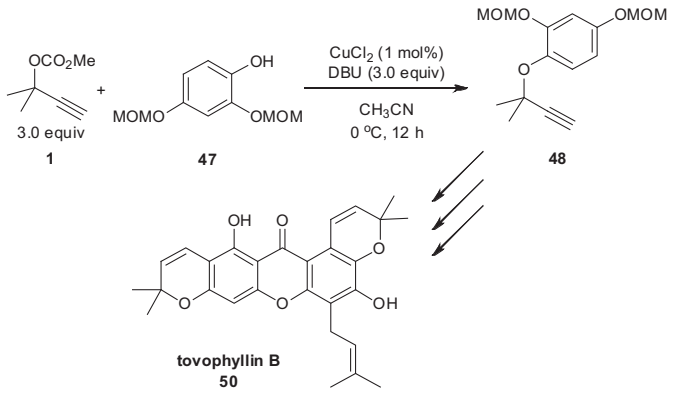
Scheme 37. Cu-catalyzed propargylic etherification of propargylic chlorides or esters with phenols.



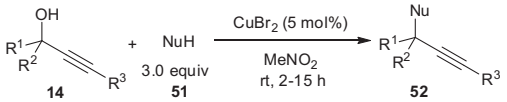
	R^1	R^2	R^3	Yield (%)
a	Me	Me	4-H	40
b	Me	Me	4-CN	96
c	Me	Me	4-C_2F_5	72
d	Me	Me	4-Et	21
e	Me	Me	2-CN	95
f	Me	Et	4-CN	100
g	Et	Et	4-CN	91
h	-$(CH_2)_5$-		4-CN	85



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



Scheme 39. Synthesis of the intermediate for tovophyllin B.



	R^1	R^2	R^3	NuH	Yield (%)
a	Me	Me	Ph	EtOH	84
b	Me	Me	Ph	BnOH	98
c	Me	Me	Ph	H_2C=CHCH_2OH	57
d	Ph	Ph	Ph	Cl$(CH_2)_2$OH	54
e	Ph	Ph	H	EtOH	38
f	H	Ph	H	EtOH	74
g	-$(CH_2)_5$-		Ph	EtOH	57
h	-$(CH_2)_5$-		Ph	Cl$(CH_2)_2$OH	82
i	Me	Me	Ph	EtSH	96
j	Me	Me	Ph	CySH	78
k	-$(CH_2)_5$-		Ph	EtSH	86
l	-$(CH_2)_5$-		Ph	CySH	38

Scheme 40. Cu-catalyzed propargylic etherification of propargylic alcohols with alcohols and thiols.

enamines **45** with a combination of $Cu(OAc)_2{\cdot}H_2O$ and the chiral tridentate ferrocenyl P,N,N-ligand (R_c,S_p)-**L5** as the catalyst.[40] Under mild conditions, perfect *endo* selectivities (*endo*/*exo* >98:2) and excellent enantioselectivities (up to 98% ee) for *endo* cycloadducts **46** were achieved for a wide range of substrates (Scheme 35). The mild conditions, broad substrate scope, good yields, and high diastereo- and enantioselectivities make this process highly useful in the synthesis of optically active bicyclo[n.3.1] frameworks.

The plausible mechanism is proposed as shown in Scheme 36. The cyclic enamine C_β attacks at the C_γ atom of the copper allenylidene complex, which should be the key step for the stereoselection. Then, H atom shifts to C_β of the Cu–acetylide complex to give Cu–vinylidene complex **E** and subsequent intramolecular nucleophilic attack of the cyclic enamine C_β at the C_α atom of **E** affords alkenyl complex **F**.

Propargylic substitution of oxygen and sulfur nucleophiles

In comparison with *N*- and *C*-nucleophiles, less progress has been made with *O*- and *S*-nucleophiles. In 1994, Godfrey and coworkers reported the copper-catalyzed propargylic etherification of propargylic chlorides **38** or esters **1** with phenols **47** to give aryl 1.1-dimethylpropargyl ether **48** in good yields under mild conditions (up to 88% yield, Scheme 37).[41] Importantly, the reaction proceeded regioselectively and no allenic byproducts were observed.

Later, Mann and co-workers also developed the propargylic etherification of dialkylpropargyl chlorides **38** with phenols **47** in the present of 2 mol% CuI to give 1.1-dialkylpropargyl ethers **48** in 21–100% yields (Scheme 38).[42] The study indicated that phenols bearing the electron-withdrawing group tended to give higher yields. Moreover, the resulting propargylic ethers could be readily converted into 2*H*-1-benzopyrans **49**.

Nicolaou and coworkers applied the copper-catalyzed propargylic etherification in the total synthesis of biologically active compounds **50**, tovophyllin B, which possesses a significant inhibitory activity against *Mycobacterium tuberculosis* (Scheme 39).[43] The O-propargylation of the readily available phenol **47** with methyl 2-methyl-3-yn-2-yl carbonate in the presence of DBU and the catalytic amount of $CuCl_2$ proceeded smoothly to afford 1,1-dimethylpropargyl ether **48**, a key intermediate in the total synthesis of tovophyllin B **50**.

In 2008, Huang and co-workers developed a novel copper-catalyzed propargylic etherification reaction of propargylic alcohols **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).[44] Importantly, thiols were also tolerated in the reaction.

Conclusions and future outlook

In summary, significant advances have been achieved in the copper-catalyzed propargylic 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 propargylic compounds have been prepared in satisfactory yields, regioselectivities, and enantioselectivities under very mild conditions. Especially, some carbo- or heterocyclic scaffolds, that are hard to prepare with conventional methods, could be readily synthesized by copper-catalyzed propargylic substitution/cyclization tandem reactions. Although great progress has been achieved, the Cu-catalyzed propargylic 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 propargylic substrates is narrow, and no successful asymmetric example has been reported for either propargylic esters with an internal alkyne moiety or tertiary propargylic 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 multi-stereogenic centers via the copper-catalyzed asymmetric propargylic substitution remains 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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