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Copper-Catalyzed Photoinduced Enantioselective Dual Carbofunctionalization of Alkenes

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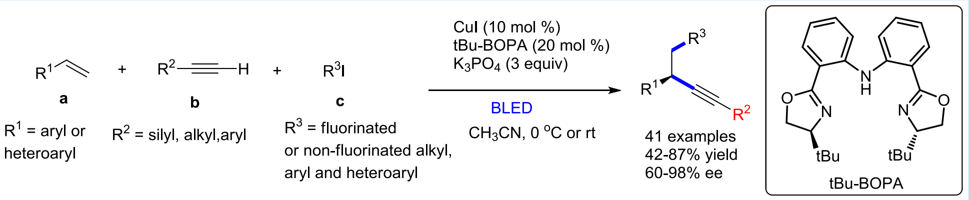
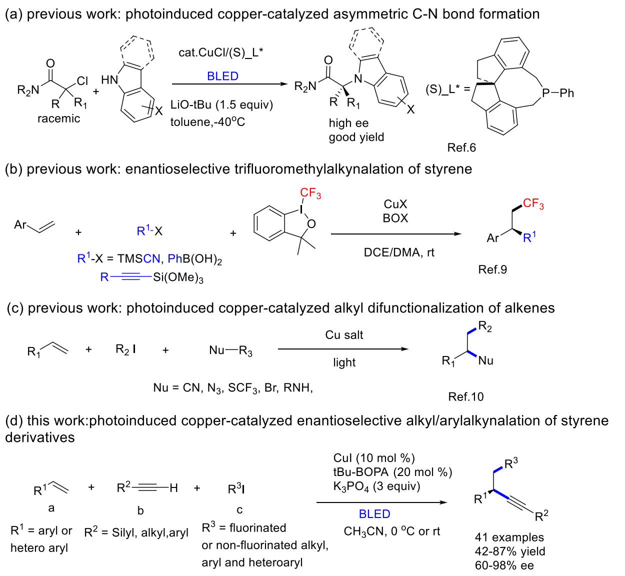


ABSTRACT: A photoinduced, copper-catalyzed, highly enantioselective dual alkylation/arylation and alkynylation of alkene is reported. A single chiral copper(I) complex serves to enable photoredox catalysis and induce enantioselectivity during the reaction. This reaction couples three different components under mild reaction conditions, exhibits a broad substrate scope, and provides facile access to chiral propargylic systems, including those featuring valuable fluorinated substituents.

Visible-light photoredox catalysis has enabled novel approaches for the construction of carbon−carbon and carbon−heteroatom bonds under mild reaction conditions through high-energy intermediates such as carbon- or heteroatom-centered radicals that cannot be easily accessed under thermal conditions.[1] Enantioselective photoredox reactions have emerged as an attractive synthetic strategy for the preparation of valuable chiral molecules.[2] Significant advances have been achieved in this field by employing a ruthenium(II) or an iridium(III) complex as the photocatalyst, and the asymmetric induction is realized by a separate chiral catalyst[3] or a bifunctional catalyst featuring chirality at the metal center.[4] In contrast, the use of complexes derived from the first-row transition metal such as nickel and copper as the photocatalyst in asymmetric synthesis is underdeveloped.

During the past several years, a fast-growing number of copper(I) complexes have been evaluated as visible-light photocatalysts. For example, achiral CuI-(phenanthroline)$_2$ complexes are predominantly employed as the photoredox catalysts.[5] However, the lack of photoactive, chiral copper complexes limits the application in the photoredox asymmetric transformation. The pioneering photoinduced, copper-catalyzed enantioselective cross-coupling reaction was reported by Fu and co-workers. In this reaction, C−N bonds were constructed with a high enantiomeric excess in the presence of catalytic amounts of CuCl and a chiral phosphine ligand (Scheme 1, eq a).[6] Gong and co-workers recently reported two enantioselective nucleophilic additions of carbon radicals generated through photooxidation by chiral Ni and Cu(II) complexes.[7] Despite the progress, a new Cu complex with a dual-function photo and chiral catalyst would offer unique opportunities for visible-light-mediated synthetic transformations. The difunctionalization of olefins is an expedient method for increasing molecular complexity by virtue of the formation of two new bonds concurrently.[8] Recently, Liu and co-workers reported a series of studies of copper-catalyzed enantioselective

Scheme 1. Copper-Catalyzed Coupling Reactions


(a) previous work: photoinduced copper-catalyzed asymmetric C-N bond formation

(b) previous work: enantioselective trifluoromethylalkynalation of styrene

(c) previous work: photoinduced copper-catalyzed alkyl difunctionalization of alkenes

(d) this work:photoinduced copper-catalyzed enantioselective alkyl/arylalkynalation of styrene derivatives

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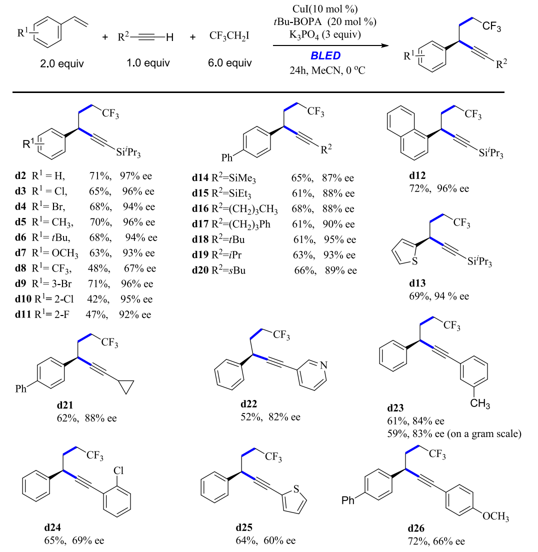
radical relay trifluoromethyl dual functionalization of styrene derivatives featuring CF_3 radical generation under thermal conditions (eq b). The hypervalent iodine fluoroalkylation reagent, e.g., Togni's reagent, was employed both as the stoichiometric external oxidant and as the CF_3 radical precursor.[9] Meanwhile, privileged (Box) served as the chiral ligands.

Photoinduced copper-catalyzed radical difunctionalization of alkenes with haloalkanes is an active subject. Various nucleophiles have been utilized as suitable coupling partners (eq c).[10] However, the asymmetric version remains challenging. Very recently, Xu, Wang, and co-workers reported a photoinduced fluoroalkylcyanation of alkenes using a well-established Box−Cu(I) complex, and only fluoroalkyl iodide served as the radical precursor.[10e] We were interested in the radical difunctionalization of alkenes, including 1,3-butadiene feedstock using alkyl halides as the radical precursor and Cbzbox as the carbazole-based tridentate monoanionic pincer ligand. It provided high enantioselectivities with the Cr catalysis.[11] Inspired by Fu's work on photoinduced copper-catalyzed C−N bond formation using carbazole as the reactant and the photocatalyst,[12] we proposed that the carbazole-based Cbzbox ligand could potentially serve as the chiral ligand in photoredox catalysis.

Hwang and Lalic reported copper could catalyze the coupling of acetylene with aryl[13a] and alkyl halide[13b] under light irradiation, and copper acetylide served as the photoexcitable intermediate. Inspired by those pioneering studies, we hypothesized that the alkyne might be used as a proper nucleophile to test our ideas about a photoinduced enantioselective alkyl/arylalkynylation of alkenes. Herein, we describe the successful implementation of this hypothesis; in the presence of a single chiral Cu complex, various monosubstituted alkynes, alkenes, and alkyl and aryl iodides undergo photoredox couplings leading to valuable enantioenriched propargylic compounds, a privileged building block frequently prevalent in pharmaceutical agents and advanced intermediates leading to functional materials (eq d).[14]

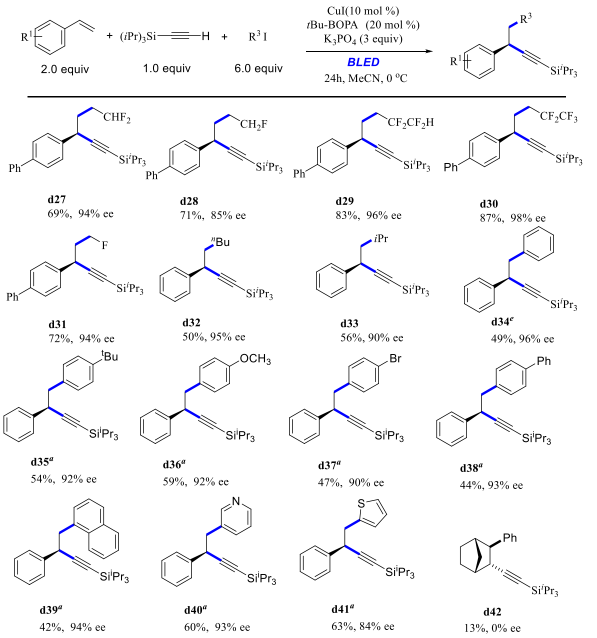
A detailed reaction condition study can be found in the Supporting Information. Notably, although *i*Pr-Cbzbox[15] provides the desired product with moderate ee, *t*Bu-BOPA (bisoxazoline diphenylamine)[16] serves as the best chiral ligand. The optimal reaction conditions are listed in Scheme 2, and the substrate scope was investigated by varying the alkenes, alkynes, and haloalkanes. Styrenes with different substitutions at the *para* position, including Cl, Br, CH_3, *t*-Bu, and OCH_3, were suitable substrates for this reaction, giving products in moderate to good yields with excellent ee's (**d2**−**d7**). The Br, Cl, and F could be allowed at the *ortho* or *meta* position without compromising the ee. However, yields were decreased for the *ortho*-substituted components probably due to the steric hindrance (**d10** and **d11**). 2-Vinylnaphthalene was also a good substrate (**d12**). A heterocycle such as thiophene was also tolerated well (**d13**). Styrene with an electron-withdrawing group such as CF_3 did react but with a decreased ee value and yield (**d8**). We next turned our attention to the alkynes. Compared with triisopropylsilylacetylene, ethynyltrimethylsilane and ethynyltriethylsilane gave the products in moderate yields with a slightly lower ee, indicating that the enantiomeric induction was sensitive to the steric effect (**d14** and **d15**). Other linear aliphatic alkynes such as 1-hexyne and but-3-yn-1-yl benzene underwent the reaction smoothly to provide **d16** and **d17**, respectively, in comparable ee values (88% and 90%, respectively). The ee value was increased with enhanced bulkiness of the substitution (cyclopropyl < isobutyl < isopropyl < *tert*-butyl) (**d18**−**d21**), proving again the critical role of the steric effect in the enantiomeric induction. The ee's from the reactions with aryl and hetero aryl alkynes were 60−84%, even though good yields were obtained (**d22**−**d26**).

Scheme 2. Substrate Scope with Alkyne and Alkenes



The readily available haloalkanes were also evaluated and showed that 1,1-difluoro-2-iodoethane, 1-fluoro-2-iodoethane, 1-fluoro-1-iodomethane, 1,1,1,2,2-tetrafluoro-3-iodopropane, and 1,1,1,2,2-pentafluoro-3-iodopropane were successfully engaged in this three-component coupling reaction, giving enantioenriched propargylic compounds bearing difluoromethylene (CF_2), monofluoromethane (CF), polyfluoroethane (CF_2CF_2H), and 1,1,1,2,2-pentafluoroethane (CF_2CF_3) (**d27**−**d31**) (Scheme 3). All functionalities were found with significant pharmaceutical interest.[17]

Scheme 3. Substrate Scope with Alkyl/Aryl Iodides



Additionally, this method was not limited to fluorinated halides; the simple primary and secondary aliphatic iodides were also good substrates, leading to the desired products with high efficiency (**d32** and **d33**). To our delight, when the reaction of iodobenzene was performed at room temperature, 1,2-diaryl-3-butyne **d34** was provided in 49% yield with 96% ee. When the reaction temperature was simply increased to room temperature, aryl iodides bearing a series of functional groups and heteroaryl iodides such as 2-iodothiophene and 3-iodopyridine also worked well with excellent ee's (**d34**−**d41**). Notably, we also tested the performances of unactivated alkenes under the catalytic system, which were consistent with the literature case,[10e] and the desired product derived from norbornene did form under BLED, albeit in a low yield with zero ee. Disubstituted styrenes such as (*E*)-prop-1-enylbenzene and prop-1-en-2-ylbenzene were not suitable substrates under the reaction conditions.

A control experiment probed the radical nature of this photoinduced three-component coupling reaction. When the reaction mixture was open to air, the product yield dropped significantly, suggesting that the active catalytic species was sensitive to oxygen. The reaction was totally ceased upon addition of the radical-trapping agent TEMPO, and the trifluoroethylated TEMPO was formed in 35% yield by ^{19}F NMR, further proving the generation of the alkyl radical.

The UV−vis spectra of individual reagents or complexes were recorded at the same concentration in CH_3CN. None of the alkyne, CuI, or ligand absorbed at wavelengths of >400 nm. However, copper with a ligand, copper acetylide, and L_nCuNu (which should form in situ in the reaction) absorbed in the range of 400−500 nm, with the last being more significant in terms of intensity and broadness.[18] These results suggest that an aggregation of BOPA, copper, and a nucleophile accounts for the photoactive species under BLED irradiation. The cyclic voltammogram of copper acetylide shows a reversible wave at −1.50 V versus the saturated calomel electrode (SCE) corresponding to the Cu(I)/Cu(II) redox couple. The excited states of copper acetylide have high redox potentials *E* of −1.77 V versus SCE.[18] The reduction potential of the trifluoroethyl iodide measured to be −1.61 V suggests that it can be reduced by electron transfer from excited copper acetylide.[19] In addition, the Stern−Volmer experiment indicated that the excited state of the in situ-formed ligand copper acetylide complex could be quenched by haloalkane (ICH_2CF_3). Moreover, the quantunm yield (Φ = 0.6%) suggested that a radical-chain process might not be involved (see the Supporting Information for details).

On the basis of the literature[12,20,21] and these findings, we proposed the following reaction mechanism (Figure 1). In the presence of a base, the $[L_nCu(I)(C{\equiv}CR)]^- K^+$ (**A**) formed in situ serves as the photoactive species to undergo photoexcitation to generate $[L_nCu(I)(C{\equiv}CR)]^*$ (**B**). This intermediate delivers an electron to the alkyl halide leading to $[L_nCu(II)(C{\equiv}CR)]$ (**C**) and an alkyl radical ($R^\bullet$). The organic radical was trapped by the styrene to generate a benzylic radical. The benzylic radical reacts with copper(II) to deliver a copper(III) complex (**D**) that undergoes reductive elimination to furnish the product. Alternatively, a direct SET process results in the same product. Related examples of this so-called radical relay strategy have been extensively studied by Liu,[9] Xiao,[22a] and Liu.[22b]

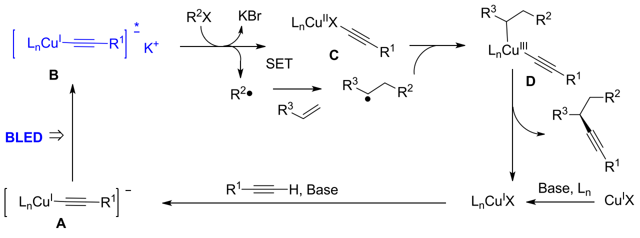
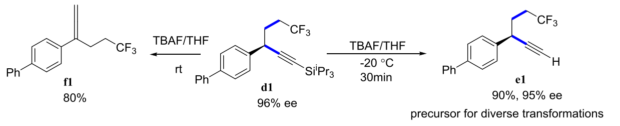


Figure 1. Proposed reaction mechanism.

Fluorinated propargylic compounds can serve as valuable building blocks in organic synthesis and pharmaceutical chemistry.[14] We briefly demonstrated the potential utilities of the products. Scheme 4 shows simple cleavage of the silyl group using TBAF at −20 °C provides the free alkyne as the coupling partners. Instead, the same reaction performed at rt led to allene **f1**. 1,2-Diaryl-3-butynes are the core structure of bioactive molecules for estrogen receptor-*β* potency-selective ligands.[23]

Scheme 4. Transformations of the Fluorinated Propargylic Product and Utility of 1,2-Diaryl-3-butynes



In summary, we report a photoinduced, copper-catalyzed, enantioselective carboalkynlation of styrenes enabled by a single BOPA−Cu(I) complex. An aggregation of the BOPA−Cu(I) complex with alkyne serves as the photoreductant and the source of enantiomeric induction. This novel aggregation-photoinduced asymmetric coupling reaction will open up new possibilities for the application of cheap metals and carbohalides in photoredox chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. Research details, experimental procedures, full characterization of products, and NMR spectra The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00071.

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Notes

The authors declare no competing financial interest.

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