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Visible-Light-Induced, Copper-Catalyzed Three-Component Coupling of Alkyl Halides, Olefins, and Trifluoromethylthiolate to Generate Trifluoromethyl Thioethers

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Visible-Light-Induced, Copper-Catalyzed Three-Component Coupling of Alkyl Halides, Olefins, and Trifluoromethylthiolate to Generate Trifluoromethyl Thioethers

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ABSTRACT: Photoinduced, copper-catalyzed coupling reactions are emerging as a powerful method for generating Csp3–Y (Y = C or heteroatom) bonds from alkyl electrophiles and nucleophiles. Corresponding *three*-component couplings of alkyl electrophiles, *olefins*, and nucleophiles have the potential to generate an additional Csp3–Y bond and to efficiently add functional groups to both carbons of an olefin, which serves as a readily available linchpin. In this report, we establish that a variety of electrophiles and a trifluoromethylthiolate nucleophile can add across an array of olefins (including styrenes and electron-poor olefins) in the presence of CuI/binap and blue-LED irradiation, thereby generating trifluoromethyl thioethers in good yield. The process tolerates a wide range of functional groups, and an initial survey of other nucleophiles (i.e., bromide, cyanide, and azide) suggests that this three-component coupling strategy is versatile. Mechanistic studies are consistent with a photoexcited Cu(I)/binap/SCF3 complex serving as a reductant to generate an alkyl radical from the electrophile, which likely reacts in turn with the olefin and a Cu(II)/SCF3 complex to afford the coupling product.

KEYWORDS: *copper catalysis, C–S bond formation, three-component cross-coupling, photoredox catalysis, photochemistry*

INTRODUCTION

Because of its high lipophilicity and electron-withdrawing nature,[1] the incorporation of an SCF3 group into bioactive molecules (see Figure 1) can significantly alter their pharmacokinetic and physicochemical properties.[2,3] While C–H functionalization,[4] radical addition,[5] and electrophilic substitution[6,7] can be exploited to construct C–SCF3 bonds, the toxicity of gaseous CF3SCl and the multistep routes needed to access certain other electrophilic SCF3 reagents can be an impediment to such approaches.[8] Consequently, the incorporation of an SCF3 group through the use of an SCF3 nucleophile is attractive, e.g., through an SN2 reaction with an alkyl electrophile.[9-11]
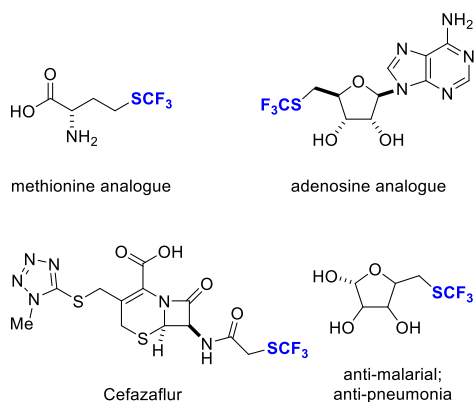

Figure 1. Examples of bioactive compounds that contain an alkyl–SCF3 subunit.

We have recently reported that cross-couplings of a variety of nucleophiles with organic electrophiles can be achieved under mild conditions (–40 to 30 °C) in the presence of light and a copper catalyst.[12-15] In one of the simplest mechanistic scenarios that we have considered, an organic radical (R•), generated through electron transfer from a photoexcited copper(I)–nucleophile adduct (**B**) to the electrophile, reacts with a copper(II)–nucleophile complex to yield the cross-coupling product (top of Figure 2, **C→D**).[16] We have established that, in at least some photoinduced, copper-catalyzed couplings, bond formation occurs after cage escape of the radicals.[17]

We have been interested in further enhancing the scope and the utility of photoinduced, copper-catalyzed coupling reactions, e.g., by creating two new bonds in the process, rather than one. For example, we speculated that it might be possible to intercept the organic radical (R•) with an olefin, prior to C–Nu bond formation (bottom of Figure 2). If the resulting radical (R'•) were subsequently trapped by a Cu(II)–nucleophile complex (**C**), then a three-component coupling would be achieved. Among the potential impediments to the success of such a process are direct substitution of the alkyl electrophile by the nucleophile (either via an SN2 reaction or via the pathway illustrated at the top of Figure 2) and olefin polymerization.[18]

It is important to note that there are several recent reports of copper-catalyzed three-component couplings of

alkyl halides, olefins, and nucleophiles, both thermally (>80 °C)[19] and photochemically induced,[20] although none employ SCF$_3$ as a nucleophile.[21,22] The photoinduced processes are limited to the use of perfluoroalkyl iodides as electrophiles and employ high-energy ultraviolet irradiation (254 nm),[20] conditions under which the C–I bond of the electrophile may undergo direct homolysis.[23] Additionally, prior photoinduced, three-component couplings with alkyl electrophiles have generally employed mono-substituted olefins as substrates; there is a single reported example using a 1,2-disubstituted olefin (the cyanofluoro-alkylation of *trans-β*-methylstyrene).[20a]
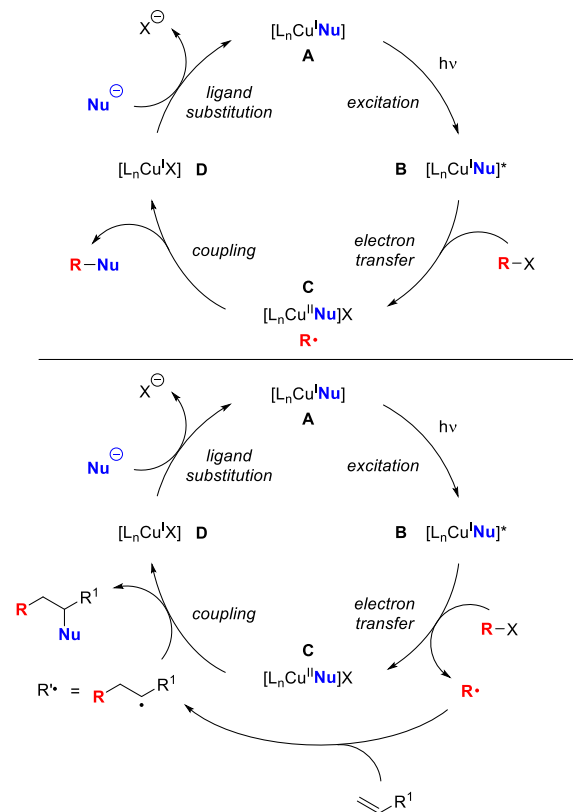

Figure 2. Top: Outline of a possible pathway for photoin-duced, copper-catalyzed cross-coupling; Bottom: Outline of a possible pathway for photoinduced, copper-catalyzed three-component cross-coupling.

In this report, we establish that copper-catalyzed three-component couplings of an array of alkyl halides and olefins with trifluoromethylthiolate can be achieved under mild conditions (r.t. or below; blue-LED irradiation) to generate functionalized trifluoromethyl thioethers in good yield (eq 1). The scope with respect to the alkyl electrophile and the olefin compares favorably with previous studies of copper-catalyzed three-component couplings.[20]
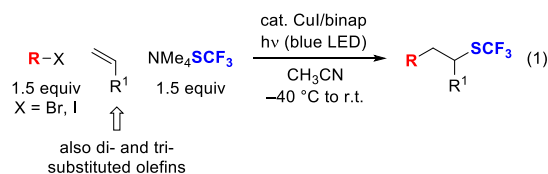
RESULTS AND DISCUSSION

Upon surveying an array of reaction parameters, we identified a procedure that achieves the desired three-component coupling (Table 1, entry 1; 82% yield). Control experiments establish the importance of CuI, binap, and light (entries 2–4); notably, essentially none of the target product is observed in the absence of light even at 80 °C (entry 5). Irradiation at 350 or 300 nm, rather than with blue LED, leads to significantly less-efficient coupling (entries 6 and 7). A variety of Cu(I) and Cu(II) sources provide the desired product in fairly good yield (entries 8–10), whereas copper nanoparticles do not (entry 11). Replacement of binap with several other phosphines, as well as 1,10-phenanthroline, leads to little desired product (entries 12–16), and commonly used iridium and ruthenium photocatalysts[24] are relatively ineffective (entries 17 and 18). The three-component coupling proceeds somewhat less efficiently with less binap (entry 19), less CuI/binap (entry 20; no further reaction after 24 h), and less electrophile/NMe$_4$SCF$_3$ (entry 21). Although the coupling cannot be conducted under an atmosphere of air (entry 22), it is not highly water-sensitive (entry 23).

This photoinduced, copper-catalyzed three-component coupling is effective for a variety of olefins (Table 2). For example, terminal olefins that bear an alkyl, aryl, or carbonyl group engage in the coupling in good yield (entries 1–9); in the case of benzyl acrylate, conjugate addition of thiolate can be avoided by conducting the reaction at –10 °C. Importantly, the method is not limited to couplings of terminal olefins: 1,1- and 1,2-disubstituted olefins, as well as a trisubstituted olefin, are also suitable reaction

Table 1. Photoinduced, Copper-Catalyzed Three-Component Coupling: Effect of Reaction Parameters

entry	change from the "standard conditions"	yield (%)[a]
1	**none**	**82**
2	no CuI	<1
3	no binap	<1
4	no hν	<1
5	no hν, 80 °C	<1
6	hν (350 nm)	52
7	hν (300 nm)	49
8	CuBr, instead of CuI	78
9	CuCl, instead of CuI	77
10	CuCl$_2$, instead of CuI	64
11	copper nanoparticle (60–80 nm), instead of CuI	23
12	xantphos, instead of binap	12
13	dppe, instead of binap	3
14	dppf, instead of binap	<1
15	PPh$_3$, instead of binap	4
16	phen, instead of binap	<1
17	10% Ir(ppy)$_3$, instead of CuI and binap	21
18	10% Ru(bpy)$_3$(PF$_6$)$_2$, instead of CuI and binap	5
19	5% binap	75
20	5% CuI, 5% binap	66
21	1.2 equiv EtO$_2$CCF$_2$Br, 1.2 equiv NMe$_4$SCF$_3$	65
22	under an atmosphere of air, instead of nitrogen	<1
23	0.1 equiv H$_2$O added	72

[a] Yields were determined via ^{1}H NMR analysis versus an internal standard (average of two or three experiments).

Table 2. Scope with Respect to the Olefin

entry	olefin	yield (%)[a]
1	⌁Ph	77
2	⌁*n*-Hex	70
3	⌁OPh	65
4	⌁NHBoc	73
5	(styrene) R = Me	83
6	OMe	90
7	CF$_3$	91
8	Ph	84
9	(acrylate OCH$_2$Ph)	85[b]
10	Ph, R = Me	85
11	Cy	98
12	Ph (Me)	69
13	Me⌁Ph	72[c]
14	Me/Me/Ph (E/Z = 3.3:1)	57[d,e]
15	(estrone-derived)	93[f]

[a] Yield of purified product (average of two experiments). [b] −10 °C, 24 h. [c] d.r. = 11:1. [d] 30% Cu, 30% binap. [e] d.r. > 20:1. [f] d.r. = 1:1.

Table 3. Scope with Respect to the Alkyl Halide

entry	electrophiles	temp. (°C)	yield (%)[a]
1	EtO–C(O)–Br	−40	58
2	Ph–C(O)–Br	−10	78
3	EtO–C(O)–CH(Br)–C(O)–OEt	−40	60
4	MeO–C(O)–CH(Me)–Br	−10	71[b,c]
5	MeO–C(O)–CH(CH$_2$OMe)–Br	−10	72[b,d]
6	(indanone) Br	−10	70[e]
7	Et$_2$N–C(O)–CF$_2$–Br	r.t.	90
8	MeO–C(O)–C(Me)(Me)–Br	r.t.	65[b]
9	F$_3$C–I	r.t.	75
10	*n*-C$_3$F$_7$–I	r.t.	80
11	ClF$_2$C–CF$_2$–I	r.t.	85
12	F$_3$C–CH$_2$–I	r.t.	92
13	Ph–SO$_2$–CH$_2$–Br	r.t.	87

[a] Yield of purified product (average of two experiments). [b] 3.0 equiv of electrophile and NMe$_4$SCF$_3$ were used. [c] d.r. = 1.3:1. [d] d.r. = 1.8:1. [e] d.r. = 1.3:1.

partners (entries 10–14); it is noteworthy that, for the couplings that generate diastereomers, the stereoselectivity is high (> 10:1; entries 13 and 14). The method can be applied to a more complex substrate derived from estrone, giving the desired product in excellent yield (entry 15). On a gram-scale, the three-component coupling illustrated in entry 8 proceeds in 82% yield.

The scope with respect to the alkyl halide is also fairly broad (Table 3). Thus, a variety of α-bromocarbonyl compounds, including primary, secondary, and tertiary electrophiles, participate in the three-component coupling (entries 1–8). Because of the high nucleophilicity of trifluoromethylthiolate and the high electrophilicity of primary and secondary α-bromocarbonyl compounds, three-component reactions of the latter were conducted at low temperature (−40 to −10 °C) in order to disfavor direct S$_N$2 reactions (entries 1–6);[9b] of course, this solution would not be available in the case of thermal (vs. photochemical) copper-catalyzed three-component couplings.

This method is not limited to the use of α-bromocarbonyl compounds as electrophilic coupling partners: perhalogenated electrophiles (Table 3, entries 9–11), 2-iodo-1,1,1-trifluoroethane (entry 12), and an α-bromosulfone (entry 13) also participate in the three-component coupling, providing very good yields of the desired trifluoromethyl thioethers (entries 9–13). On the other hand, our standard conditions are not effective for the coupling of an unfunctionalized alkyl halide.
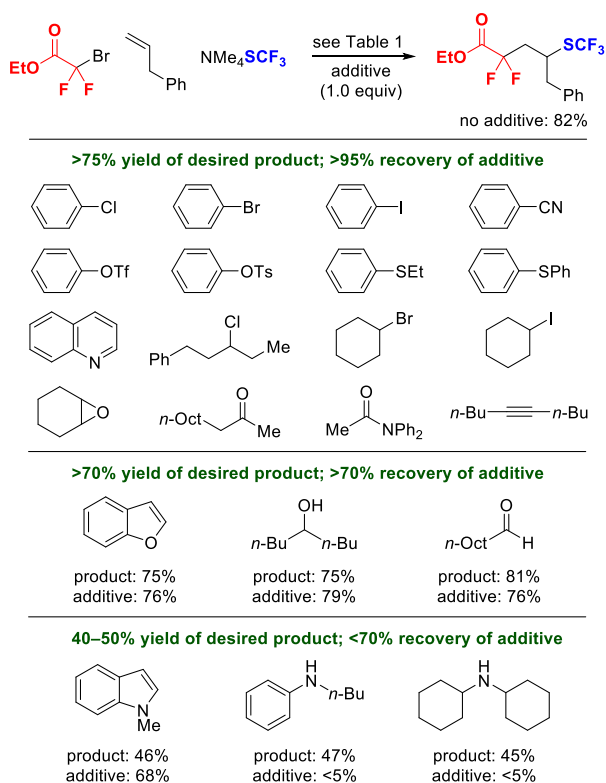
With regard to the functional-group tolerance of this photoinduced, copper-catalyzed three-component coupling, the examples provided in Tables 2 and 3 demonstrate compatibility with esters, ethers, carbamates, amides, ketones, and sulfones. We have further examined the functional-group compatibility of this method by carrying out the model reaction in the presence of various additives (Table 4).[25] Thus, with a wide range of additives, the three-component coupling proceeds with little or no impact on the yield of the desired product or on the additive (top of Table 4). In the case of a benzofuran, a secondary alcohol, and an aldehyde, the yield of the desired product is also largely unaffected, and most, but not all, of the additive is recovered (middle of Table 4). In contrast, the three-component coupling is inhibited somewhat by the presence of an indole, an *N*-alkyl aniline, and a. secondary amine, and the additive is partly or entirely consumed (bottom of Table 4)

Table 4. Functional-Group Tolerance: Effect of Additives

no additive: 82%

>75% yield of desired product; >95% recovery of additive

(Ph–Cl, Ph–Br, Ph–I, Ph–CN, Ph–OTf, Ph–OTs, Ph–SEt, Ph–SPh, quinoline, Ph(CH₂)₂CH(Cl)CH₂Me, cyclohexyl–Br, cyclohexyl–I, cyclohexene oxide, n-Oct-C(O)-Me, Me-C(O)-NPh₂, n-Bu–C≡C–n-Bu)

>70% yield of desired product; >70% recovery of additive

benzofuran	n-Bu-CH(OH)-n-Bu	n-Oct-CHO
product: 75%	product: 75%	product: 81%
additive: 76%	additive: 79%	additive: 76%

40–50% yield of desired product; <70% recovery of additive

N-Me indole	Ph-NH-n-Bu	dicyclohexylamine
product: 46%	product: 47%	product: 45%
additive: 68%	additive: <5%	additive: <5%

From the outset, as schematically outlined at the bottom of Figure 2, our longer-term objective has been to develop photoinduced, copper-catalyzed three-component couplings of electrophiles, olefins, and nucleophiles into a general strategy for the convergent synthesis of functionalized organic compounds under mild conditions. We therefore regard it as significant that the method that we have developed for trifluoromethylthiolation can be applied directly to three-component couplings that utilize other nucleophiles (Table 5). Thus, under the same conditions, bromide, cyanide, and azide serve as suitable nucleophiles, furnishing the target compounds in promising yield (Table 5).[26] These initial observations provide a strong impetus for further reaction-development efforts in this area.

With regard to the mechanism of the photoinduced, copper-catalyzed three-component coupling to form trifluoromethyl thioethers, Figure 2 (bottom) provides an outline of one of the pathways that we have considered.[27] In this mechanistic scenario, $[L_n(binap)Cu^I(SCF_3)]$ may serve as compound **A**, undergoing photoexcitation to generate $[L_n(binap)Cu^I(SCF_3)]^*$ (**B**). This intermediate engages in electron transfer with the alkyl halide, providing $[L_n(binap)Cu^{II}(SCF_3)]$ (**C**) and an organic radical (R•). The organic radical adds to the olefin to produce a new organic radical, which reacts with a persistent copper(II) radical (**C**)[16b,28,29] to afford the three-component coupling product and a copper(I)–halide (**D**). Ligand exchange between complex **D** and trifluoromethylthiolate completes the catalytic cycle and regenerates complex **A**.

Table 5. Use of Other Nucleophiles

entry	coupling product	yield (%)[a]
1[b]	EtO-C(O)-CF₂-CH₂-CH(Br)-CH₂-Ph	80
2[b]	EtO-C(O)-CF₂-CH₂-CH(CN)-C₆H₄-Ph	54
3[c]	F₃C-CH₂-CH₂-CH(N₃)-C₆H₄-Ph	65
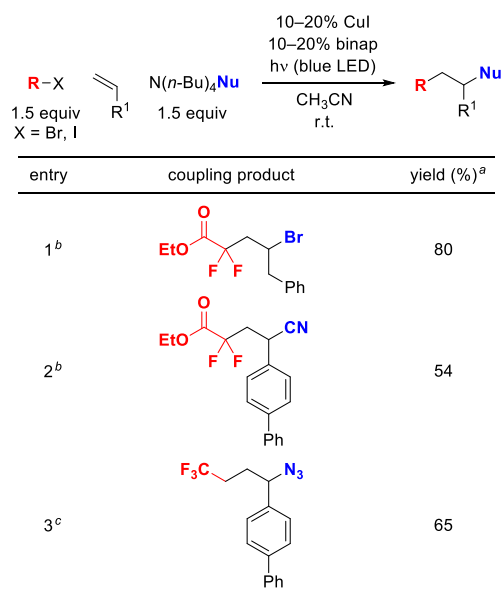
[a] Yield of purified product (average of two experiments).
[b] X = Br. [c] X = I

Through treatment of CuI first with AgSCF₃ (1.0 equiv) and then with binap (1.0 equiv) in CH₃CN at room temperature, followed by crystallization, we have been able to obtain pale-yellow crystals that we have crystallographically characterized as $[(binap)Cu(SCF_3)]_2$ (**1**, Figure 3a).[22a] In the solid-state, two Cu centers are bridged by trifluoromethylthiolates, with the $Cu_2(SCF_3)_2$ subunit forming a planar four-membered ring with a C_2 axis along the Cu⋯Cu vector. The absorption spectrum of complex **1** in acetonitrile shows an absorption profile with intensity tailing into the region of blue-LED excitation (380-520 nm) (Figure 3b). The excitation and the emission profiles of copper complex **1** are provided in Figure 3c; we have established that ethyl bromodifluoroacetate quenches the luminescence (see the Supporting Information).

Complex **1** can be used in place of CuI and binap as a catalyst for the three-component coupling, affording the product in virtually the same yield as under the standard conditions using 10% CuI/10% binap (eq 2); essentially no coupling is observed in the dark (<1%). Irradiation of copper complex **1** in acetonitrile with ethyl bromodifluoroacetate and allylbenzene provides the thioether product in moderate yield (48%); again, no reaction occurs in the absence of light (eq 3). These observations indicate that complex **1**, or a compound derived from complex **1**, may be an intermediate in the photoinduced, copper-catalyzed three-component coupling.

Irradiation of the model reaction in the absence of CuI does not consume the electrophile, which suggests that the SCF₃ anion itself is not photoreactive under the coupling conditions (see the Supporting Information). Replacing binap with a Ru or Ir photosensitizer affords the three-component coupling product, but in much lower yield (eq 4).[30]

To test whether a carbocation intermediate might be formed when using an aliphatic olefin substrate, we subjected 4-penten-1-ol to the standard conditions shown in

Table 1. The cyclized product expected from a carbocation intermediate was not observed (see SI).
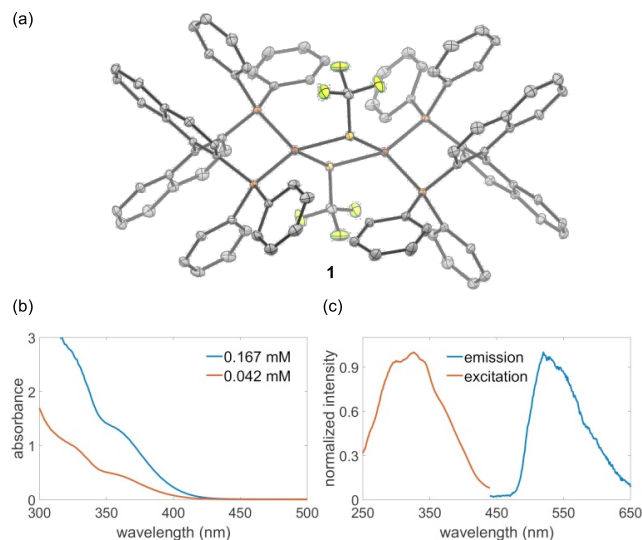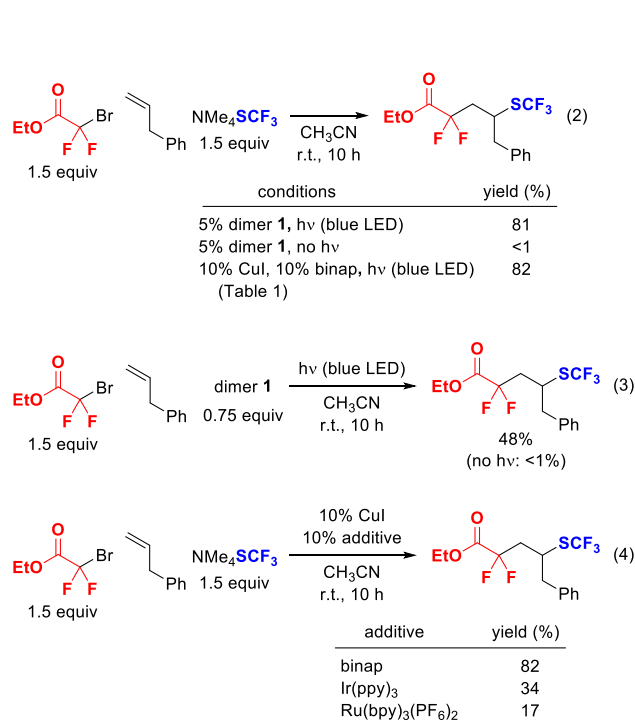
(a)

1

(b)   (c)

Figure 3. (a) Crystal structure of dicopper complex **1** (thermal ellipsoids drawn at 50% probability; hydrogens omitted for clarity). (b) Absorption spectra of complex **1** in CH_3CN at room temperature. (c) Excitation (emission wavelength: 520 nm) and emission (excitation wavelength: 350 nm) spectra in CH_3CN at room temperature.

(2)

conditions	yield (%)
5% dimer **1**, hv (blue LED)	81
5% dimer **1**, no hv	<1
10% CuI, 10% binap, hv (blue LED) (Table 1)	82

(3)

48%
(no hv: <1%)

(4)

| additive	yield (%)
binap	82
Ir(ppy)$_3$	34
Ru(bpy)$_3$(PF$_6$)$_2$	17

To probe for the release of an organic radical R• upon photoreduction of the electrophile (bottom of Figure 2), the model reaction was irradiated under the standard conditions, but in the presence of TEMPO. A moderate yield of the TEMPO–R adduct was observed (eq 5), but essentially none of the three-component coupling product. Furthermore, we have performed a radical-clock

experiment which indicates that R'•, generated from radical addition of the olefin (Figure 2, bottom), undergoes C–S coupling more slowly than the ring-opening reaction (eq 6). These observations are consistent with the involvement of an organic radical intermediate.

(5)

32%

(6)

83% (E/Z = 2.5:1)
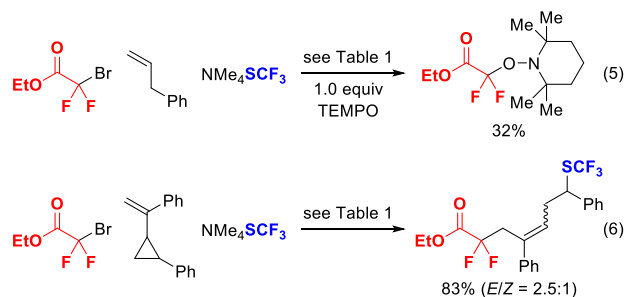
In view of our observation that bromide can serve as a nucleophile in photoinduced, copper-catalyzed three-component couplings (Table 5, entry 1), we sought to exclude the possibility that, in the synthesis of thioethers from aliphatic olefins, an alkyl bromide is generated as an intermediate. We therefore irradiated a mixture of an alkyl bromide and NMe$_4$SCF$_3$ in the presence of CuI/binap (eq 7). No thioether was observed, indicating that the alkyl bromide is not an intermediate in the synthesis of the thioether (eq 7).

(7)

<1%
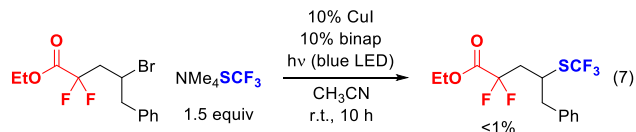
We have also carried out EPR studies to explore whether a copper(II) species accumulates during a catalyzed three-component coupling. Upon irradiation of the model reaction (Table 1) for 10 minutes at room temperature, only a trace of a copper(II) signal was evident, and the signal had disappeared after 60 minutes of irradiation (see the Supporting Information). Given that the reaction is ~20% complete after 60 minutes, this indicates that copper(II) does not accumulate during the reaction. Curiously, irradiation of the model reaction at –40 °C for 10 min, conditions under which little coupling product is formed, followed by freeze-quenching at –198 °C, gives rise to a strong EPR signal (see the Supporting Information). This signal shows an unpaired spin coupled to $^{63/65}$Cu ($I = 3/2$). The same EPR-active species could be detected by the addition of tris(4-bromophenyl)ammoniumyl hexachloroantimonate (Magic Blue) to CuSCF$_3$ at –78 °C in the presence of NMe$_4$SCF$_3$, but in the absence of binap. Hence, this EPR-active species is likely an SCF$_3$-ligated copper(II) species (e.g., Cu^{II}(SCF$_3$)$_3^-$ or Cu^{II}(SCF$_3$)$_4^{2-}$). Its role in the catalytic pathway, if any, remains unclear.

We have previously considered related *tandem* photoredox and bond-forming cycles for photoinduced, copper-catalyzed couplings,[13e,13f] and we note that such a scenario may be operative in the three-component couplings de-

scribed herein. It may also be that more than one pathway is viable.

CONCLUSIONS

As schematically outlined at the bottom of Figure 2, we have been interested in expanding our efforts in photoinduced, copper-catalyzed couplings to include three-component couplings of electrophiles, olefins, and nucleophiles, which could provide a powerful approach to the convergent synthesis of functionalized organic compounds; in the present study, we describe our initial progress, specifically, the development of an efficient method for the coupling of activated alkyl halides, olefins, and trifluoromethylthiolate to generate trifluoromethyl thioethers in good yield using a simple catalyst (CuI/binap). The ability to conduct these photoinduced reactions without heating and with blue-LED (rather than 254 nm) irradiation is advantageous relative to related methods. Beyond providing the first example of Csp^3–SCF$_3$ bond construction using photoinduced copper catalysis, we have observed that nucleophiles other than thiolate can also be used in the methodology described herein, thereby furnishing C–Br, C–CN, and C–N$_3$ bonds. This observation points to rich opportunities to exploit photoinduced, copper-catalyzed three-component couplings to generate functionalized products that contain an array of useful C–C and C–heteroatom bonds. Ongoing efforts are directed at exploring the full scope of such processes.

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Notes
The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI:
Procedures and characterization data (PDF)

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TOC Graphic

R–X + (alkene) + NMe₄**SCF₃** →[cat. CuI/binap, hν (blue LED), CH₃CN, –40 °C to r.t.] R–CH₂–C(R¹)H–**SCF₃**

1.5 equiv
X = Br, I

R¹   1.5 equiv

also di- and tri-substituted olefins