Copper-Catalyzed Trifluoromethylation of Unactivated Olefins

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Copper-Catalyzed Trifluoromethylation of Unactivated Olefins**

Andrew T. Parsons and **Dr. Stephen L. Buchwald*** **[Prof.]**
Department of Chemistry, Room 18-490, Massachusetts, Institute of Technology, Cambridge, MA 02139 (USA), Fax: (+1) 617-253-329

Keywords

trifluoromethylation; copper; catalysis; fluorine; radical

The inclusion of fluorinated functional groups in small molecules has had a profound impact on the pharmaceutical, material, and agrochemical industries.[1, 2] In particular, the trifluoromethyl (CF_3) substituent has emerged as an important functional group for the modulation of the physical properties in new pharmaceutical candidates as it has excellent metabolic stability, lipophilicity, and is electron-withdrawing in nature.[3] Myriad of fluorinated biologically active pharmaceutical compounds have been identified,[4] with an estimated 20% of drugs on the market containing fluorine.[1] On this basis, there has been a recent surge in the number of reports describing the formation of carbon–trifluoromethyl (C–CF_3) bonds, demonstrating the continuing need for the development of efficient methods to incorporate these groups.

Early research into C–CF_3 bond formation primarily focused on the exploration of nucleophilic and radical sources of the CF_3 group.[5] These efforts resulted in the development of many trifluoromethylation reactions, including nucleophilic addition to carbonyl electrophiles,[6-7] halotrifluoromethylation of olefins,[8] enolate addition to the CF_3 radical,[9] and formation of aryl–CF_3 bonds.[10-11] While less extensively explored, electrophilic trifluoromethylating reagents have allowed for the trifluoromethylation of a range nucleophiles to be achieved.[12-13] In particular development of hypervalent iodine-based trifluoromethylating reagents by Togni has significantly broadened the scope of electrophilic trifluoromethylation methods.[14] Herein, we report our efforts in developing a new catalytic allylic trifluoromethylation of terminal olefins using the Togni electrophilic trifluoromethylating reagent **1** [Figure 1].[15]

Currently, only a limited number of methods are available to construct allylic–CF_3 bonds from olefins. Research in this area has typically focused on perfluoroalkylations using iodonium salts, of which the trifluoromethyl variant is unstable and not synthetically viable.[16] The few methods that describe the preparation of molecules containing allylic–CF_3 functional groups (e.g., **2**) are not only limited in scope, but also require harsh reaction conditions, super-stoichiometric quantities of transition metal promoters, and toxic or

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*sbuchwal@mit.edu.

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Note: Reactions carried out on a 0.50–1.0 mmol scale of **1** [Table 2] were set up in an inert atmosphere glove box under a nitrogen atmosphere.

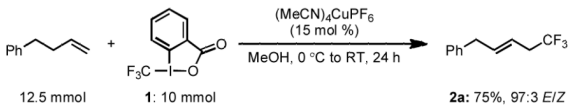
expensive reagents.[17] An additional disadvantage of the reported methods is the required use of pre-functionalized starting materials such as allyl bromides or fluorosulfones.

We sought to develop a direct trifluoromethylation of unactivated olefins as a more convenient method to access **2**. We hypothesized that this transformation might be achieved using a Cu-based strategy involving the generation of an allylic radical and a subsequent CF_3• transfer [Scheme 1, Path A].[18] Alternatively, if reagent **1** could be used as an electrophilic CF_3• equivalent, **2** may be generated via an atom transfer radical addition (ATRA)-type pathway (Path B).[19] Finally, an electrophilic trifluoromethylation proceeding through a cationic intermediate may also be viable (Path C).

Commencing our studies, we examined the ability of various $Cu^{I/II}$ salts to catalyze the trifluoromethylation of 4-phenyl-1-butene using electrophilic trifluoromethylating reagents.[12] Our most promising result was obtained using reagent **1** and CuCl as a catalyst, providing the corresponding linear allylic trifluoromethylation product **2a** in good yield and high *E*/*Z* selectivity [Scheme 2]. We found the use of **1** to be convenient as it is easily prepared in three chromatography-free steps from inexpensive and recyclable starting materials.[14d] Mass spectral analysis indicated the desired product **2a** was accompanied by chlorinated and other mono- and bis(trifluoromethylated) side products, complicating purification. Unfortunately conducting the reaction at 0 °C only suppressed side product formation to a minimal extent.

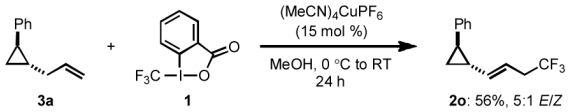
With promising results obtained in our preliminary studies, we continued our efforts toward improving the efficiency of this reaction. Noting that the major side products contained two trifluoromethyl groups, we surmised that suppression of bis(trifluoromethylation) may be accomplished by the use of an excess of olefin. Thus, we evaluated various $Cu^{I/II}$ catalysts in the trifluoromethylation of 4-phenyl-1-butene using an altered reaction stoichiometry of alkene:**1** of 1.05:1 [Table 1]. Gratifyingly, the use of an excess of olefin reduced the amount of bis(trifluoromethylated) side products to ~5% independent of the identity of the Cu^{I} catalyst employed. The yields of these transformations were moderately lower than when **1** was used in excess, presumably due to Lewis acid-catalyzed decomposition of **1**.[20] The modestly superior results obtained with $(MeCN)_4CuPF_6$ prompted us to continue optimization using this copper source. We found that reactions run in a range of solvents yielded a significant amount of desired product **2a**. Interestingly, the *E*/*Z* ratio varied substantially depending on the identity of the alcoholic solvent examined [entries 5-9]. Methanol provided the best yield and *E*/*Z* ratio of the conditions studied [entry 5]. An additional increase in the alkene:**1** ratio to 1.25:1.0 provided more consistent results and marginally higher yields [entry 6].

We next proceeded to examine the scope of this reaction using our optimized protocol [Table 2]. The mild reaction conditions employed allowed for the trifluoromethylation of molecules containing a range of functional groups, including unprotected alcohols, protected amines, esters, amides, and alkyl bromides. Terminal epoxide-containing substrates required the use of a catalyst with lower Lewis acidity in order to avoid nucleophilic ring-opening by methanol; thus copper(I) thiophene-2-carboxylate (CuTC) was used for 2-(hex-5-en-1-yl)oxirane [entry 6]. In most cases, the *E*/*Z* selectivity was excellent, with an average ratio of 94:6 for the substrates examined. We found branched terminal olefins and 1,2-disubstituted olefins to be unsuitable substrates due to the formation of complex regioisomeric product mixtures. Furthermore, cyclic substrates furnished only trace amounts of product.[21]



(1)

In order to demonstrate the robustness of this transformation, we conducted the trifluoromethylation of 4-phenyl-1-butene on a 10 mmol scale [Eq 1]. All reagents were weighed out on the bench top, open to the air, and the setup was conducted using standard Schlenk techniques. The results from this experiment indicate that the method described in this communication can be set up on the bench top without an accompanying sacrifice of the reaction efficiency.



(2)

Similar to the proposed mechanism of the Kharasch-Sosnovsky $Cu^{I/II}$-catalyzed oxidation of olefins to generate allyl esters,[18] we wanted to probe whether this transformation proceeded through an allylic radical intermediate. We were intrigued, however, by the high selectivity for linear trifluoromethylated products obtained using the method described herein. This is in contrast to most reports of Kharasch-Sosnovsky-type oxidative alkene functionalizations, suggesting a possible divergence from this mechanistic pathway. In order to determine whether this transformation did indeed proceed through a free allylic radical, we conducted the trifluoromethylation of cyclopropane radical clock **3a** [Eq 2]. Subjecting this substrate to our standard conditions provided the trifluoromethylated cyclopropane **2o** in moderate yield, suggesting that a mechanism involving formation of an allylic radical is unlikely. However, we note that other trifluoromethylated side products were present (≤ 3 % yield each) that were not identifiable, which precludes us from conclusively stating that no ring-opened product was observed.

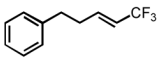
The results with cyclopropane **3a** prompted us to consider an alternative mechanistic possibility, wherein the trifluoromethylation event occurs via an atom transfer radical addition-type pathway via homolytic cleavage of the alkene.[19] Data to support or refute this mechanism was sought by examining diethyl diallylmalonate as a cyclization radical clock [Scheme 3]. The major products obtained under these conditions were cyclopentane derivatives **4a** and **4b**. The presence of these species is explained by the occurrence of a 5-*exo*-trig cyclization that proceeds after the C–CF_3 bond-forming event. It is unclear if the trifluoromethylation results in the generation a free-radical intermediate (**5a**) or an alkylcopper species (**5b**). After cyclization, termination occurs by a second trifluoromethylation or elimination to generate products **4a** or **4b**, respectively. Of note, we found that conducting the trifluoromethylation reaction in the presence of selected radical scavengers provided variable results that did not aid in our understanding of the reaction mechanism.[22] Further analysis will be necessary to more accurately elucidate the nature of this transformation.

In conclusion, we have developed an allylic trifluoromethylation of unactivated terminal olefins. This method allows for the preparation of allyl–CF_3 products previously difficult to

access in a straightforward and efficient manner. The mild conditions for this transformation enable the trifluoromethylation of a range of substrates bearing numerous functional groups. A preliminary analysis suggests that the reaction mechanism is complex and multiple pathways leading to the desired allyl–CF_3 products may be operating.[23] Future efforts will focus on examining the mechanistic details more extensively en route to expanding the generality and increasing the efficiency of this transformation.

Experimental Section

For 10.0 mmol scale reaction [Eq 1]: **(*E*)-(5,5,5-trifluoropent-2-en-1-yl)benzene** (**2a**). A 100 mL Schlenk flask was flame-dried under high vacuum and backfilled with argon. On the bench top, open to air, $(MeCN)_4CuPF_6$ (0.559 g, 1.50 mmol, 0.15 equiv) and **1** (3.16 g, 10.0 mmol, 1.0 equiv) were weighed out and added to the Schlenk flask. The flask was then sealed with a rubber septum, evacuated and backfilled with argon (this process was repeated for a total of three times) and cooled to 0 °C in an ice-water bath. The flask was charged with anhydrous methanol (50 mL) and 4-phenyl-1-butene (1.65 g, 1.88 mL, 12.50 mmol, 1.25 equiv) successively via syringe (a bright green-blue color is observed upon solvent addition). The reaction mixture was stirred for 30 min at 0 °C, after which the ice-water bath was removed and stirring was continued for an additional 23 h the reaction. The reaction mixture was partitioned between CH_2Cl_2 (75 mL) and sat. aq. $NaHCO_3$ (75 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (75 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by silica gel chromatography (pentane) to afford **2a** (1.503 g, 75%) as a clear and colorless oil (*E*/*Z* = 97:3) contaminated with 2.5 mol % of a bis(trifluoromethylated) side product. There was 3.5 mol % of a mono-trifluoromethylated side product with a ^{19}F NMR shift consistent with the vinyl trifluoromethylation product (**6**).



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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[21]. Subjecting cis-cyclodecene to the standard reaction conditions [Table 2] furnished only trace amounts of the expected allylic CF_3 product despite complete consumption of **1**, as determined by ^{19}F NMR spectroscopy. Use of hex-4-en-1-ol produced a complex mixture of mono- and bis(trifluoromethylated) products in approximately 30% combined yield.

[22]. We conducted the trifluoromethylation of 4-phenyl-1-butene under the standard reaction conditions [Table 2] in the presence of varying amounts of several radical scavengers: galvinoxyl (0.30 equiv), 1,4-dinitrobenzene (0.30 equiv), hydroquinone (0.30 equiv), 4-methoxyphenol (1.0 equiv), and butylatedhydroxytoluene (1.0 equiv). The conversion of 1 and yield of 2a varied considerably depending on the identity of the scavenger employed.

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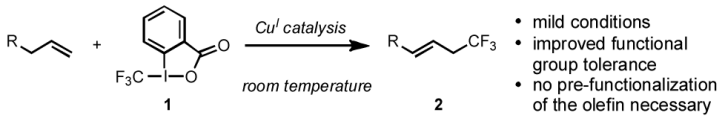
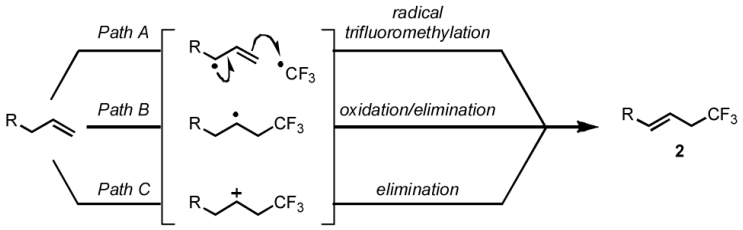
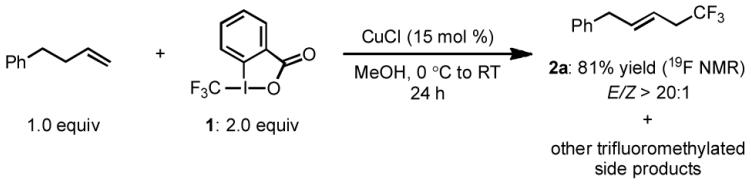


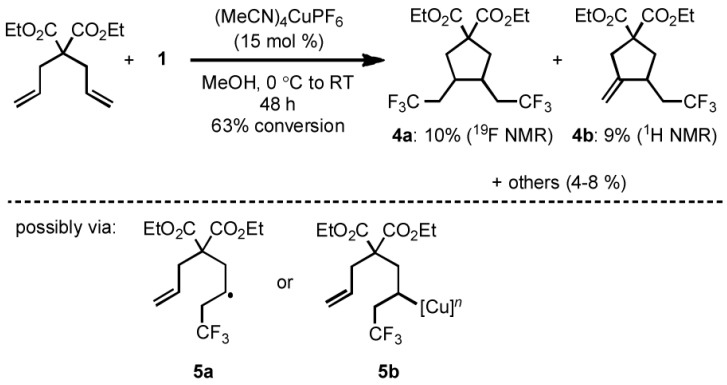
Figure 1.
Cu^{I}-catalyzed oxidative trifluoromethylation of olefins.



Scheme 1.
Plausible allylic trifluoromethylation mechanisms: allylic oxidation (Path A), atom transfer radical addition (Path B), electrophilic trifluoromethylation (Path C).



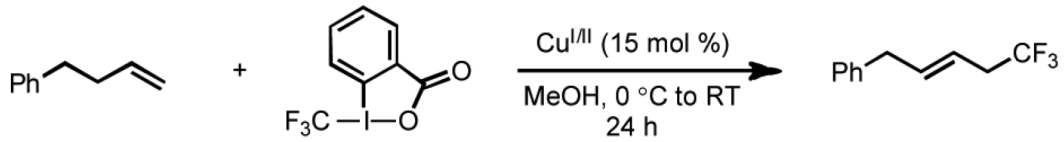
Scheme 2.
CuCl-catalyzed trifluoromethylation of 4-phenyl-1-butene: lead result.



Scheme 3.
Examination of a diallylmalonate cyclization radical clock.

Table 1

Selected optimization studies for the Cu-catalyzed trifluoromethylation of 4-phenyl-1-butene with **1**.[*a*]



1.05 equiv **1**: 1.0 equiv **2a**

Entry	Cu^{I} Source	Solvent	Conversion [%][*b*]	Yield [%][*b*]	*E*/*Z* [*c*]
1	CuCl	MeOH	100	63	96:4
2	CuTC	MeOH	100	68	97:3
3	$[Cu(OTf)]_2PhH$	MeOH	93	61	86:14
4[*d*]	$Cu(OTf)_2$	CH_2Cl_2	81	0	-
5	$(MeCN)_4CuPF_6$	MeOH	100	68	98:2
6 [*d*,*e*]	**$(MeCN)_4CuPF_6$**	**MeOH**	**100**	**71**	**98:2**
7	$(MeCN)_4CuPF_6$	EtOH	100	63	96:4
8	$(MeCN)_4CuPF_6$	*i*-PrOH	100	43	95:5
9	$(MeCN)_4CuPF_6$	*t*-BuOH	100	50	83:17
10	$(MeCN)_4CuPF_6$	Me_2CO	100	52	90:10
11	$(MeCN)_4CuPF_6$	MeCN	24	0	-
12	$(MeCN)_4CuPF_6$	C_6H_6	100	27	89:11
13	$(MeCN)_4CuPF_6$	CH_2Cl_2	100	57	90:10

[*a*]Conditions: alkene (0.205 mmol, 1.05 equiv), **1** (0.20 mmol, 1.0 equiv), Cu (0.030 mmol, 0.15 equiv) in MeOH (1.0 mL) at 0 °C for 15 min, then RT for 23 h.

[*b*]Determined by ^{191}F NMR spectroscopy using (trifluoromethoxy)benzene as an internal standard.

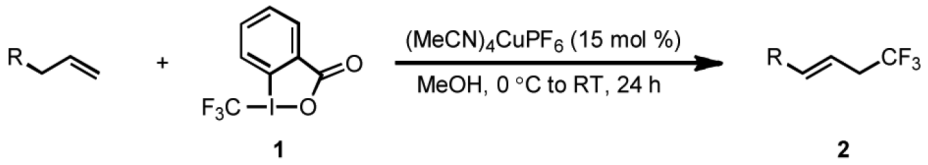
[*c*]Determined by ^{19}F NMR spectroscopy.

[*d*]1.25 equiv of the alkene was used.

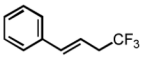
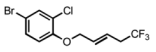
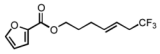
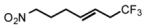
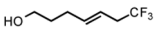
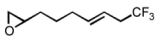
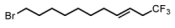
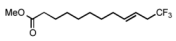
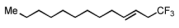
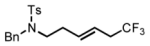
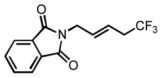
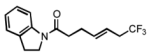
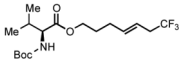
[*e*]Average isolated yield of two independent runs on a 1.0 mmol scale (relative to **1**). CuTC = copper(I) thiophene-2-carboxylate

Table 2

Scope of the CuI-catalyzed trifluoromethylation of terminal olefins with 1.[a]



1 2

Entry	Product		Yield [%][b]	E/Z[c]
1	**2b**[d]		54	97:3
2	**2c**[e]		67	97:3
3	**2d**[e]		69	95:5
4	**2e**		72	94:6
5	**2f**		67	97:3
6	**2g**[f]		70	93:7
7	**2h**		78	96:4
8	**2i**		79	95:5
9	**2j**		75	94:6
10	**2k**		73	94:6
11	**2l**[e]		72	97:3
12	**2m**		75	89:11
13	**2n**[e]		80	95:5

[a] Conditions: alkene (1.25 equiv), **1** (1.0 equiv), Cu^{I} (0.15 equiv) in MeOH (0.5 mL/0.10 mmol **1**) at 0 °C for 15 min, then RT for 23 h. Reactions were run on a 0.50–1.00 mmol scale of **1**.

[b] Average isolated yield of two independent runs. Products contained approximately ≤ 5% other mono- and bis(trifluoromethylated) side products by ^{19}F NMR spectroscopy.

[c] Determined by ^{19}F NMR spectroscopy.

[d] 1.0 equiv of the alkene was used.

[e] $(MeCN)_4CuPF_6$ (0.25 equiv) was used.

[f] CuTC (0.15 equiv) was used.