Trifluoromethylation

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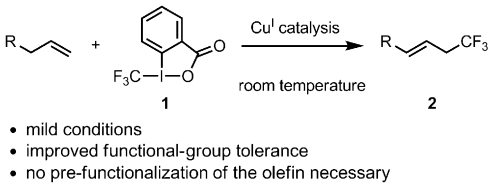
Copper-Catalyzed Trifluoromethylation of Unactivated Olefins**

*Andrew T. Parsons and Stephen L. Buchwald**

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 and lipophilicity, and is electron-withdrawing in nature.[3] A 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, thus demonstrating the continuing need for the development of efficient methods to incorporate these groups.

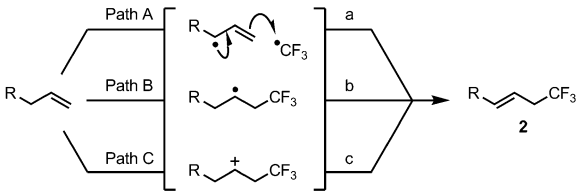
Early research into C–CF_3 bond formation primarily focused on the exploration of nucleophilic and radical sources of the CF_3 group.[5] These efforts resulted in the development of many trifluoromethylation reactions, including nucleophilic addition to carbonyl electrophiles,[6,7] halotrifluoromethylation of olefins,[8] enolate addition to the CF_3 radical,[9] and formation of aryl–CF_3 bonds.[10,11] While less extensively explored, the use of electrophilic trifluoromethylating reagents enabled the trifluoromethylation of a range of nucleophiles.[12,13] In particular, the development of hypervalent iodine based trifluoromethylating reagents by Togni and co-workers 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** (Scheme 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, superstoichiometric quantities of transition metal promoters, and toxic or 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.



Scheme 1. Cu^I-catalyzed oxidative trifluoromethylation of olefins.

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 copper-based strategy involving the generation of an allylic radical and a subsequent CF_3· transfer (Scheme 2, Path A).[18] Alternatively, if reagent **1** could be used as an electrophilic CF_3· equivalent, **2** may be generated through an atom transfer radical addition type pathway (Scheme 2, Path B).[19] Finally, an electrophilic trifluoromethylation proceeding via a cationic intermediate may also be viable (Scheme 2, Path C).



Scheme 2. Plausible allylic trifluoromethylation mechanisms: allylic oxidation (Path A) and radical trifluoromethylation (a), atom transfer radical addition (Path B) and oxidation/elimination (b), electrophilic trifluoromethylation (Path C) and elimination (c).

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 to provide the corresponding linear allylic trifluoromethylation product **2a** in good yield and high *E*/*Z* selectivity (Scheme 3). We found the use of **1** to be convenient as it is easily prepared from inexpensive and recyclable starting materials in three steps that do not require chromatography.[14d] Mass spectral analysis indicated that the desired product **2a** was accompanied by chlorinated and other mono- and bis(trifluorome-

[*] Dr. A. T. Parsons, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: sbuchwal@mit.edu

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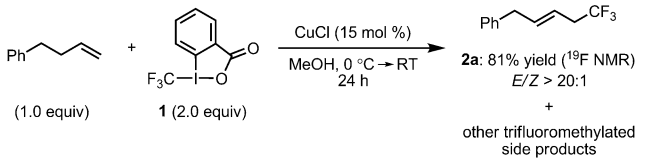
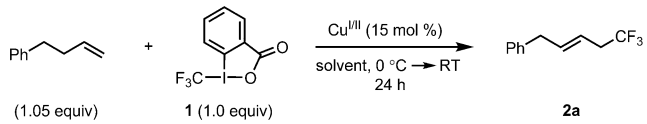


Scheme 3. CuCl-catalyzed trifluoromethylation of 4-phenyl-1-butene.

thylated) side products, which complicated purification. Unfortunately, conducting the reaction at 0°C only suppressed the formation of side products 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 the 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 approximately 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 because of the Lewis acid catalyzed decomposition of **1**.[20] The modestly superior results obtained with $[(MeCN)_4Cu]PF_6$ prompted us to continue optimization using this copper source. We found that reactions carried out in a range of solvents yielded a significant amount of desired product **2a**.

Table 1: Selected optimization studies for the Cu^{I}-catalyzed trifluoromethylation of 4-phenyl-1-butene with **1**.[a]



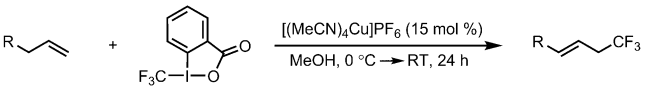
Entry	Cu^{I} Source	Solvent	Conv. [%][b]	Yield [%][b]	*E*/*Z*[c]
1	CuCl	MeOH	100	63	96:4
2	CuTC	MeOH	100	68	97:3
3	$[Cu(OTf)]_2PhH$	MeOH	93	61	86:14
4[d]	$Cu(OTf)_2$	CH_2Cl_2	81	0	–
5	$[(MeCN)_4Cu]PF_6$	MeOH	100	68	98:2
6[d,e]	**$[(MeCN)_4Cu]PF_6$**	**MeOH**	**100**	**71**	**98:2**
7	$[(MeCN)_4Cu]PF_6$	EtOH	100	63	96:4
8	$[(MeCN)_4Cu]PF_6$	*i*PrOH	100	43	95:5
9	$[(MeCN)_4Cu]PF_6$	*t*BuOH	100	50	83:17
10	$[(MeCN)_4Cu]PF_6$	Me_2CO	100	52	90:10
11	$[(MeCN)_4Cu]PF_6$	MeCN	24	0	–
12	$[(MeCN)_4Cu]PF_6$	C_6H_6	100	27	89:11
13	$[(MeCN)_4Cu]PF_6$	CH_2Cl_2	100	57	90:10

[a] Reaction conditions: alkene (0.205 mmol, 1.05 equiv), **1** (0.20 mmol, 1.0 equiv), Cu^{I} (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 ^{19}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 yield of isolated product of two independent runs on a 1.0 mmol scale (relative to **1**). CuTC = copper(I) thiophene-2-carboxylate. Entry in bold represents the optimized reaction conditions.

Interestingly, the *E*/*Z* ratio varied substantially depending on the identity of the alcoholic solvent examined (Table 1, entries 5–9). Methanol provided the best yield and *E*/*Z* ratio of the conditions studied (Table 1, entry 5). An additional increase in the alkene/**1** ratio to 1.25:1.0 provided more consistent results and marginally higher yields (Table 1, entry 6).

We next examined 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) thio-

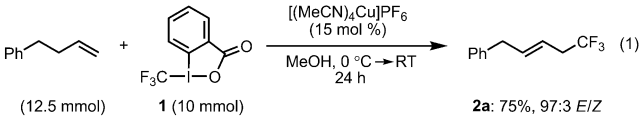
Table 2: Scope of the Cu^{I}-catalyzed trifluoromethylation of terminal olefins with **1**.[a]



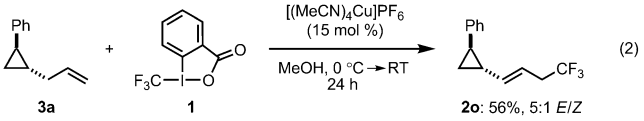
Entry	Product	Yield [%][b]	*E*/*Z*[c]
1	**2b**[d]	54	97:3
2	**2c**[e]	67	97:3
3	**2d**[e]	69	95:5
4	**2e**	72	94:6
5	**2f**	67	97:3
6	**2g**[f]	70	93:7
7	**2h**	78	96:4
8	**2i**	79	95:5
9	**2j**	75	94:6
10	**2k**	73	94:6
11	**2l**[e]	72	97:3
12	**2m**	75	89:11
13	**2n**[e]	80	95:5

[a] Reaction 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 carried out on a 0.50–1.00 mmol scale of **1**. [b] Average yield of isolated product of two independent runs. ^{19}F NMR spectroscopy showed that products contained approximately $\leq$5% other mono- and bis(trifluoromethylated) side products. [c] Determined by ^{19}F NMR spectroscopy. [d] 1.0 equiv of the alkene was used. [e] $[(MeCN)_4Cu]PF_6$ (0.25 equiv) was used. [f] CuTC (0.15 equiv) was used.

phene-2-carboxylate (CuTC) was used for 2-(hex-5-en-1-yl)oxirane (Table 2, 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 because of the formation of complex regioisomeric product mixtures. Furthermore, cyclic substrates furnished only trace amounts of product.[21]

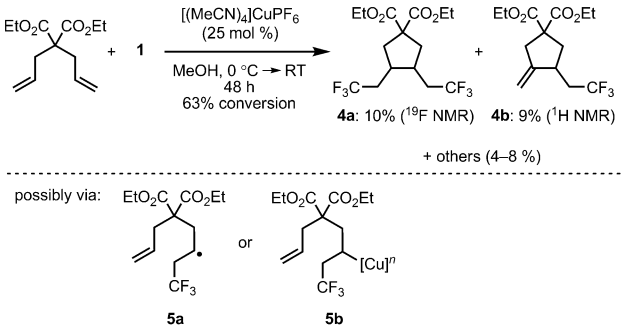


In order to demonstrate the robustness of this transformation, we conducted the trifluoromethylation of 4-phenyl-1-butene on a 10 mmol scale [Eq. (1)]. All reagents were weighed on the benchtop, open to the air, and the setup was conducted using standard Schlenk techniques. The results from this experiment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



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 via an allylic radical intermediate. We were intrigued, however, by the high selectivity for the linear trifluoromethylated products obtained by using the method described herein. This result is in contrast to most reports of Kharasch–Sosnovsky-type oxidative alkene functionalizations, and therefore suggests a possible divergence from this mechanistic pathway. In order to determine whether this transformation did indeed proceed via 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; this result suggests that a mechanism involving the formation of an allylic radical is unlikely. However, we note that other trifluoromethylated side products were present but unidentifiable ($\leq 3\%$ yield each), thus precluding us from conclusively stating that no ring-opened product was formed.

The results with cyclopropane **3a** prompted us to consider an alternative mechanistic possibility, wherein the trifluoromethylation event occurs through an atom transfer radical addition type pathway by 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 4). 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



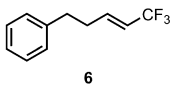
Scheme 4. Examination of a diallylmalonate cyclization radical clock.

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 our understanding of the reaction mechanism.[22] Further analysis will be necessary to elucidate the nature of this transformation more accurately.

In conclusion, we have developed an allylic trifluoromethylation of unactivated terminal olefins. This method allows for the preparation of allyl–CF_3 products that were previously difficult to access in a straightforward and efficient manner. The mild conditions for this transformation enable the trifluoromethylation of a range of substrates that bear 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 on the way to expanding the generality and increasing the efficiency of this transformation.

Experimental Section

(*E*)-(5,5,5-trifluoropent-2-en-1-yl)benzene (**2a**) on a 10.0 mmol scale: A 100 mL Schlenk flask was flame-dried under high vacuum and backfilled with argon. On the benchtop, open to air, $[(MeCN)_4Cu]PF_6$ (0.559 g, 1.50 mmol, 0.15 equiv) and **1** (3.16 g, 10.0 mmol, 1.0 equiv) were weighed and added to the Schlenk flask. The flask was then sealed with a rubber septum, evacuated, and backfilled with argon (this process was repeated a total of three times) and cooled to 0 °C in an ice–water bath. The flask was charged successively with anhydrous methanol (50 mL) and 4-phenyl-1-butene (1.65 g, 1.88 mL, 12.50 mmol, 1.25 equiv) by syringe (a bright green-blue color was 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 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 saturated aqueous $NaHCO_3$ (75 mL), dried over Na_2SO_4, and concentrated in vacuo. The resultant oil was purified by column chromatography (pentane) on silica gel to afford **2a** (1.503 g, 75 %) as a clear colorless oil (*E*/*Z* = 97:3) contaminated with 2.5 mol % of a



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bis(trifluoromethylated) side product. 3.5 mol% of a mono(trifluoromethylated) side product with a ^{19}F NMR chemical shift value consistent with the vinyl trifluoromethylation product (**6**) was also identified.

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

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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-substituted 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 butylated hydroxytoluene (1.0 equiv). The conversion of **1** and the yield of **2a** varied considerably depending on the identity of the scavenger that was employed.
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