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Copper-Catalyzed C(sp^3)−C(sp^3) Bond Formation Using a Hypervalent Iodine Reagent: An Efficient Allylic Trifluoromethylation

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Supporting Information

ABSTRACT: An efficient copper-catalyzed allylic trifluoromethylation reaction has been developed. This reaction provides a general and straightforward way to synthesize allylic trifluoromethylated compounds under mild conditions.

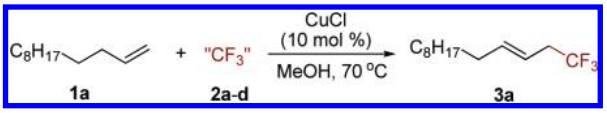
Molecules bearing trifluoromethyl groups have been widely applied in the fields of functional materials, agrochemicals, and pharmaceuticals.[1,2] The unique properties of trifluoromethylated compounds include high electronegativity, hydrophobicity, metabolic stability, and bioavailability, which account for the significance of developing new methods for the introduction of trifluoromethyl groups into organic molecules.[3] Trifluoromethylation of aryl, vinyl, and allyl halides[4] and the corresponding boron reagents[5] employing catalytic or stoichiometric amounts of copper species has provided a number of useful methods to access these trifluoromethyl-containing compounds. In particular, general trifluoromethylation methodology for aryl chlorides has been developed by Buchwald and co-workers.[6] Moreover, recent work on direct replacement of aryl[7] and alkynyl[8] C−H bonds with C−CF_3 bonds has attracted great attention. The remarkable developments in this area have demonstrated the possibility of streamlining the synthetic route for functionalized aromatics while avoiding the use of halides.

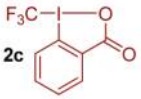
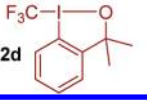
On the other hand, palladium-catalyzed direct functionalization of allylic C−H bonds leading to C−O, C−N, or C−C bond formation is a valuable complement to the well-known Trost−Tsuji reaction.[9] More recently, cheaper catalysts such as copper[10,11] or iron[12] complexes have also been employed to accomplish the direct allylic C−H transformation. Herein we report a copper-catalyzed allylic trifluoromethylation reaction using a hypervalent iodine reagent. This methodology represents a rare example of highly efficient direct trifluoromethylation of terminal olefins.[13]

At the outset of this investigation, we screened the combinations of transition-metal catalysts, oxidants, and trifluoromethyl sources that were essential for allylic trifluoromethylation (Table 1). After some initial experiments, we concluded that CuCl is a suitable catalyst in this transformation. However, no product was observed when we employed $TMSCF_3$ **2a** (Ruppert−Prakash reagent)[14] as the trifluoromethyl source in the presence of CsF and $PhI(OAc)_2$ with CuCl as the catalyst (entry 1). Other oxidants such as *tert*-BuOOH could not achieve this transformation (entry 2). Subsequently, we focused our attention on electrophilic trifluoromethylation reagents. Trifluoromethylation with **2b** (Umemoto reagent)[15] failed (entry 3). To our surprise, the hypervalent iodine(III) reagent **2c** (Togni reagent),[16,17] which is easily accessible from commercially available 2-iodobenzoic acid, provided the desired product in 89% isolated yield (entry 4). Only a trace amount of product was obtained when we used another Togni reagent, 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (**2d**), as CF_3 source (entry 5). For comparison, other transition-metal complexes were also studied under identical reaction conditions. The reaction of **1a** with **2c** in the presence of $FeCl_2$ or $Fe(OAc)_2$ as the catalyst formed the product in only a barely detectable amount (~5%). Other transition-metal catalysts, such as $Pd(OAc)_2$, $CoCl_2$, $Co(OAc)_2$, and $Mn(OAc)_2$, showed no catalytic reactivity.

Upon optimization of the reaction conditions, we proceeded to test a series of olefins to explore the generality of this method (Table 2). The reaction of simple alkenes proceeded efficiently (entries 1 and 2). Notably, the aliphatic aldehyde group, which is

Table 1. Evaluation of Different CF_3 Sources[a]



entry	"CF_3" **2**	yield of **3a**[b]
1	$TMSCF_3$ (**2a**) (2.0 equiv)/CsF (2.0 equiv) $PhI(OAc)_2$ (2.0 equiv)	No Product
2	$TMSCF_3$ (**2a**) (2.0 equiv)/CsF (2.0 equiv) *tert*-BuOOH (2.0 equiv)	No Product
3	 **2b** (1.2 equiv)	No Product
4	 **2c** (1.75 equiv)	89%[c]
5	 **2d** (1.2 equiv)	trace

[a] Reaction conditions: **1a** (0.5 mmol), MeOH (1 mL). [b] Isolated yields. [c] Other CF_3-containing byproducts were detected (≤5%). For details, see the Supporting Information.

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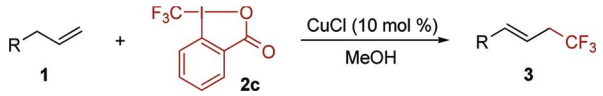
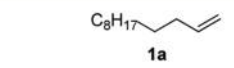
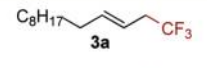
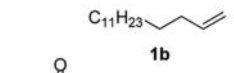
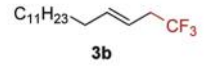
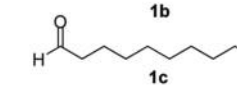
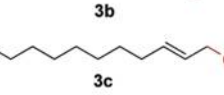
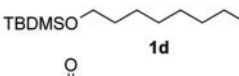
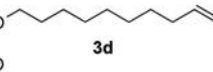
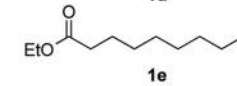
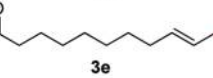
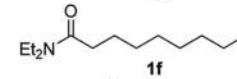
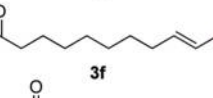
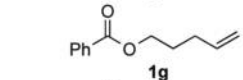
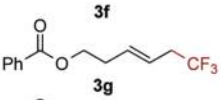
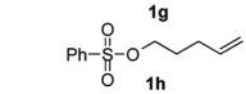
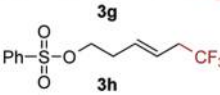
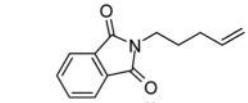
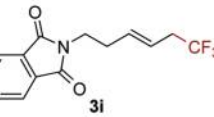
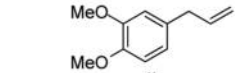
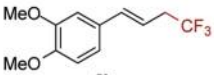
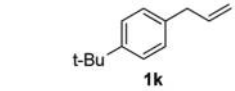
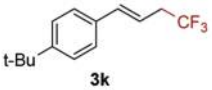
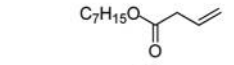
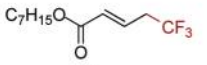
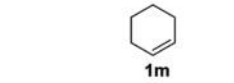
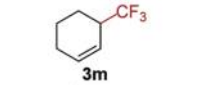
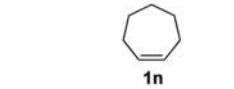
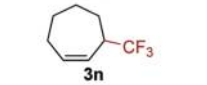
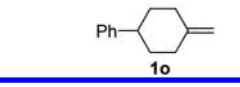
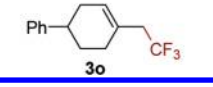
Table 2. Allylic Trifluoromethylation with Hypervalent Iodine(III) Reagent 2c[a]



entry	substrate **1**	CuCl	temp	time	product **3**	yield[b]
1	 **1a**	10 mol %	70 °C	10 min	 **3a**	89%
2	 **1b**	10 mol %	70 °C	10 min	 **3b**	93%
3	 **1c**	10 mol %	70 °C	10 min	 **3c**	75%
4	 **1d**	10 mol %	70 °C	10 min	 **3d**	97%
5	 **1e**	10 mol %	70 °C	10 min	 **3e**	87%
6	 **1f**	10 mol %	70 °C	10 min	 **3f**	93%
7	 **1g**	20 mol %	80 °C	1 h	 **3g**	66%
8	 **1h**	20 mol %	80 °C	1 h	 **3h**	86%
9	 **1i**	20 mol %	80 °C	1 h	 **3i**	68%
10[c]	 **1j**	10 mol %	70 °C	10 min	 **3j**	54%
11[c]	 **1k**	10 mol %	70 °C	10 min	 **3k**	48%
12[d]	 **1l**	10 mol %	70 °C	1 h	 **3l**	63%
13	 **1m**	20 mol %	80 °C	1 h	 **3m**	44%[e]
14	 **1n**	20 mol %	80 °C	1 h	 **3n**	55%[e]
15	 **1o**	20 mol %	90 °C	1 h	 **3o**	53%

[a] The reaction was conducted on a 0.5 mmol scale in 1 mL of MeOH, except for entry 3, where 1 mL of DMF was used. The ratio of **1** to **2c** ranged from 1:1.6 to 2:1. For details, see the Supporting Information. [b] Isolated yields. [c] The branched product was detected as a minor product (in entry 10, linear:branched = 11:1; in entry 11, linear:branched = 7:1). [d] *E*:*Z* = 10:1, as determined by ^{1}H NMR analysis of the crude product. [e] Based on ^{19}F NMR analysis with $C_6H_5CF_3$ as an internal standard.

usually fragile under oxidative conditions, remained intact in this transformation. In this case, *N*,*N*-dimethylformamide (DMF) should be used as the solvent instead of MeOH to avoid acetal formation (entry 3). The *tert*-butyldimethylsilyl (TBDMS) ether protecting group was also tolerated in the reaction, with the desired product being obtained in excellent yield (entry 4). Other linear allylic trifluoromethylated compounds were obtained in preparatively useful yields (66−93%) when terminal olefins featuring ester, amide, benzoate, benzenesulfonate, and phthalimide functional groups were employed as substrates (entries 5−9).

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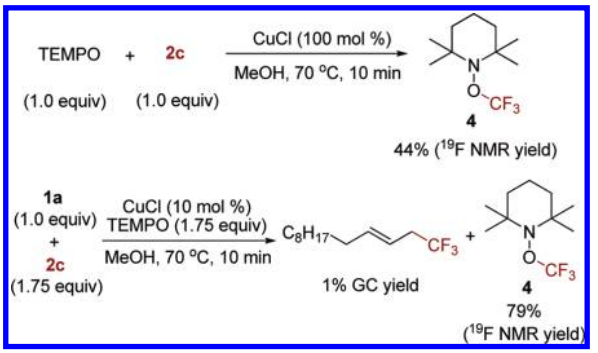
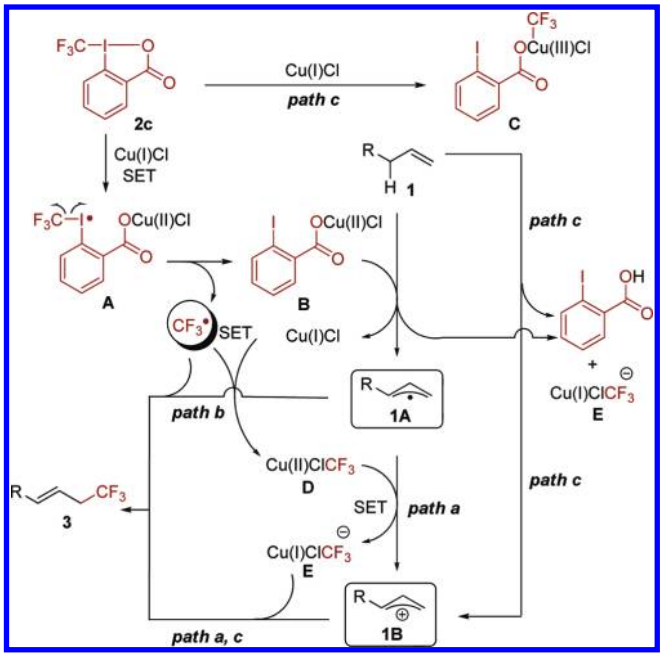
Scheme 1. Capture of CF_3 Radical by TEMPO



Scheme 2. Mechanistic Rationale



Allyl substrates bearing an aromatic moiety yielded a mixture of linear and branched isomers and also showed relatively low efficiency (entries 10 and 11). Terminal olefins bearing an ester group at the allylic position exhibited moderate reactivity in this transformation because the reaction produced α,β-unsaturated ester isomers of the substrate with a shift of the double bond (entry 12). To our delight, cyclohexene and cycloheptene could also react with **2c**, affording the corresponding trifluoromethylated cycloalkenes, albeit in moderate yields (entry 13). Finally, it is noteworthy that a substrate featuring an exocyclic double bond at the cyclohexyl ring could also be trifluoromethylated at slightly elevated temperature, giving the corresponding CF_3-containing cyclohexane derivative **3o** in acceptable yield (entry 15).

For the reaction mechanism of this trifluoromethylation, it is reasonable to conceive a pathway involving radical species according to previous reports.[10−12] To gain insight into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, was reacted with hypervalent iodine(III) reagent **2c** in the presence of stoichiometric CuCl under the standard reaction conditions (Scheme 1), and the TEMPO-trapped complex **4** was detected by GC−MS. The yield of **4** was estimated as 44% on the basis of ^{19}F NMR spectroscopic analysis. Moreover, when TEMPO was added in the standard reaction (Table 1, entry 1), the trifluoromethylation was totally shut down and TEMPO−CF_3 adduct **4** was formed in 79% yield as estimated by ^{19}F NMR analysis. However, the allyl−TEMPO adduct was not detected in our system.[10b]

These experimental results provided supportive evidence that CF_3 radical is likely involved as a reactive species in the reaction mechanism. A mechanistic rationale involving several possible pathways is outlined in Scheme 2. Initially, CuCl catalytically activates **2c**, leading to CF_3-containing radical intermediate **A**. Decomposition of radical intermediate **A** produces (2-iodobenzoyloxy)copper(II) chloride (**B**)[10b] with simultaneous release of a CF_3 radical. It is assumed that olefin substrate **1** undergoes copper-assisted single-electron-transfer (SET) oxidation[18] with the hypervalent iodine(III) reagent to generate the corresponding allyl radical **1A**, which can be further oxidized to allyl cation **1B** (path a). Subsequently, **1B** is attacked by nucleophilic Cu(I)CF_3 species, affording the final product. However, the radical pathway involving the coupling of allyl radical and CF_3 radical (path b) cannot be ruled out. It is also possible that Cu(I)Cl is directly oxidized by hypervalent iodine(III) reagent **2c** to form Cu(III) species **C**,[19] which is highly electrophilic and has strong oxidizing properties. Subsequently, allyl cation **1B** would formed from alkene substrate **1** by oxidation with Cu(III) species **C** (path c). However, we could not trap the allyl radical using TEMPO, and we have no evidence of the involvement of either allylmetal species or trifluoromethylmetal species in the mechanism. Therefore, the details of the C−C bond-forming step are not clear at the present stage.

In summary, an efficient copper-catalyzed allylic trifluoromethylation reaction has been developed. In this transformation, formation of a C(sp^3)−C(sp^3) bond is achieved. This reaction provides a general and straightforward way to construct allylic trifluoromethylated compounds under mild conditions. The reaction employs cheap copper chloride as the catalyst and a hypervalent iodine(III) reagent as both the oxidant and the CF_3 source. More importantly, simple alkenes can be used as substrates, and the reaction tolerates a wide range of functional groups. Further investigations to expand the scope of both the substrate and the hypervalent iodine(III) reagent as well as to clarify the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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