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Copper-Mediated Radical 1,2-Bis(trifluoromethylation) of Alkenes with Sodium Trifluoromethanesulfinate

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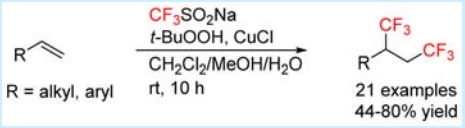
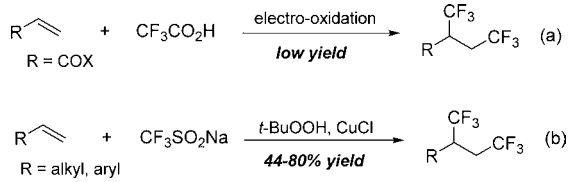
Supporting Information

ABSTRACT: An efficient chemoselective 1,2-bis(trifluoromethylation) of alkenes with CF_3SO_2Na promoted by *t*-BuOOH/CuCl was developed. This protocol provided the first convenient preparation of 1,2-bis(trifluoromethylated) compounds by the vicinal difunctionalization of alkenes. The chemoselectivity of this reaction was accomplished by increasing the concentration of the CF_3 radical.

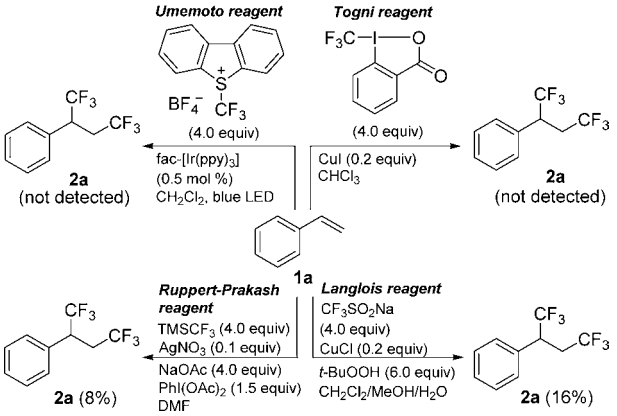


The trifluoromethyl group has received increasing attention in various research fields because of its ability to alter the lipophilicity, metabolic activity, and bioavailability of host compounds.[1] Consequently, numerous methods have been developed for the preparation of trifluoromethylated compounds.[2] However, much less attention has been paid in the synthesis of 1,2-bis(trifluoromethylated) compounds, despite their potential usefulness in many research fields, especially in advanced materials.[3] Fluorination of carboxylic acids with SF_4 is an orthodox route to 1,2-bis(trifluoromethylated) compounds.[4] However, SF_4 is a hazardous reagent and releases HF in a moist atmosphere. Normally, 1,2-bis(trifluoromethylated) compounds are prepared via indirect approaches, such as coupling of trifluoromethylated units[5] and transformation from bis(trifluoromethylated) building blocks.[6] Direct and efficient access to these compounds still remains to be a great challenge, despite Molander's recent breakthrough for the synthesis of vicinally bis(trifluoromethylated) alkylboron compounds through tandem trifluoroethylidene-insertion reactions.[7] The vicinal difunctionalization of alkenes provides a powerful strategy for the construction of compounds with various functional groups.[8] An outstanding example is the Sharpless asymmetric dihydroxylation of alkenes.[9] Other types of difunctionalization of alkenes, such as diamination,[10] diboration,[11] dichlorination,[12] and difluorination reactions,[13] have also been intensively investigated. However, the 1,2-bis(trifluoromethylation) of alkenes has received much less attention, and quite limited precedents were reported. As early as 1974, the electrochemical trifluoromethylation of alkenes with CF_3CO_2H was reported for the preparation of 1,2-bis(trifluoromethylated) compounds.[14a] However, this method was severely restricted to electron-deficient alkenes (acrylamide), and the desired 1,2-bis(trifluoromethylated) compounds were formed in low yields along with several byproducts (Scheme 1a).[14] In continuation of our research interest in trifluoromethylation reactions,[15] herein we report the copper-mediated 1,2-bis(trifluoromethylation) of alkenes with sodium trifluoromethanesulfinate (Langlois reagent, CF_3SO_2Na) (Scheme 1b). This protocol provides the first convenient preparation of 1,2-bis(trifluoromethylated) compounds via the vicinal difunctionalization of alkenes.

Scheme 1. 1,2-Bis(trifluoromethylation) of Alkenes



Scheme 2. 1,2-Bis(trifluoromethylation) of Styrene 1a



Recently, radical trifluoromethylation has experienced a renewal, and most of these works mainly focus on the improvement of old methods and the identification of new CF_3 radical sources.[2f−k] We wondered if it was possible to

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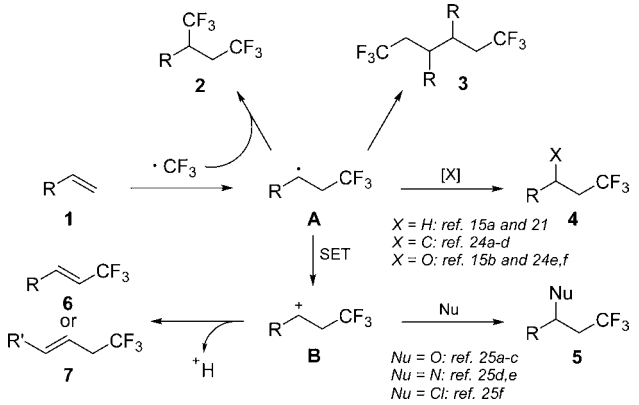
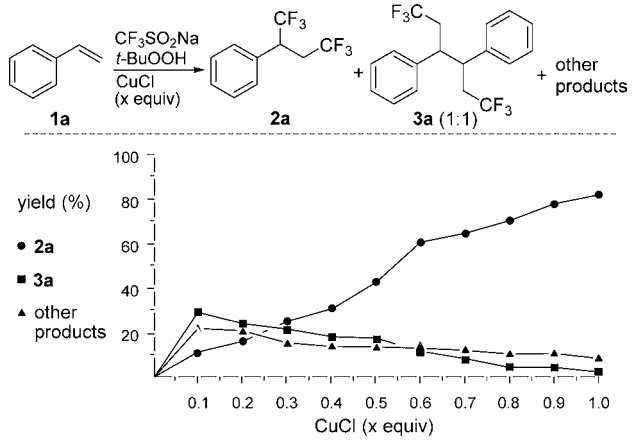
Scheme 3. Competitive Reactions Starting from the Addition of CF_3 Radical to Alkene



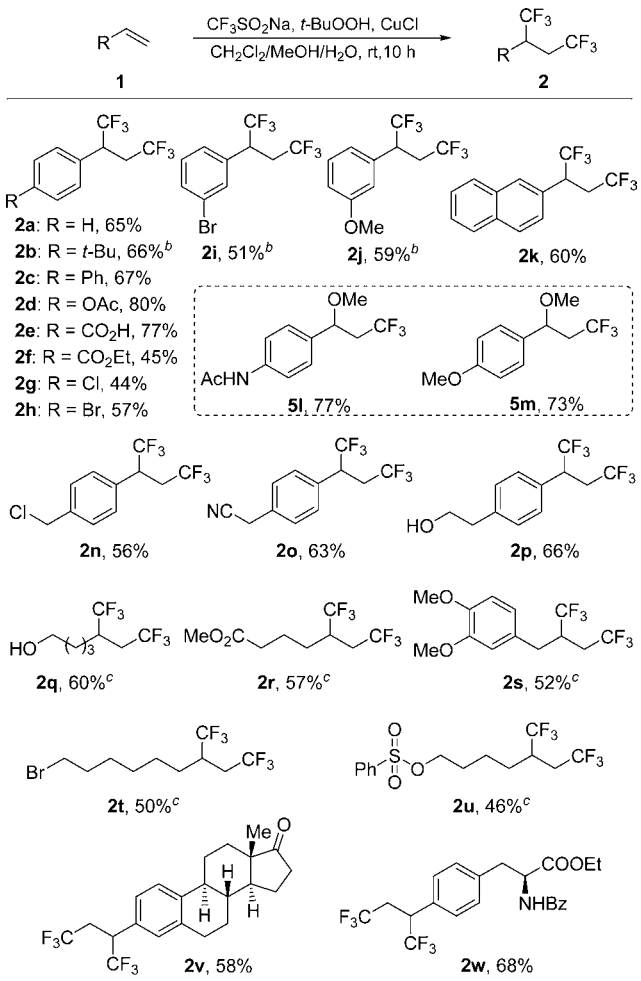
Scheme 4. Effect of the Amount of CuCl on the Yields of Products



achieve 1,2-bis(trifluoromethylation) of alkenes on the basis of the new developments of radical trifluoromethylation. Although CF_3I is the common source for the generation of the CF_3 radical,[16] gaseous CF_3I is not easy to handle. Therefore, solid or liquid trifluoromethylating reagents at room temperature, including (trifluoromethyl)dibenzothiophenium salts (Umemoto reagents),[2a,17] trifluoromethyl benziodoxole derivatives (Togni reagents),[2j,18] (trifluoromehyl)trimethylsilane (Ruppert–Prakash reagent),[2k,19] and sodium trifluoromethanesulfinate (Langlois reagent)[20] were used as the CF_3 radical precursors. As shown in Scheme 2, the 1,2-bis(trifluoromethylation) of styrene **1a** using electrophilic Umemoto reagent[21] or Togni reagent[22] failed to give the desired product. When **1a** reacted with nucleophilic Ruppert–Prakash reagent under silver-catalyzed oxidative conditions,[15a] the 1,2-bis(trifluoromethylated) product **2a** was formed in 8% yield. To our delight, copper-catalyzed 1,2-bis(trifluoromethylation) of **1a** using CF_3SO_2Na[15b] gave compound **2a** in 16% yield.

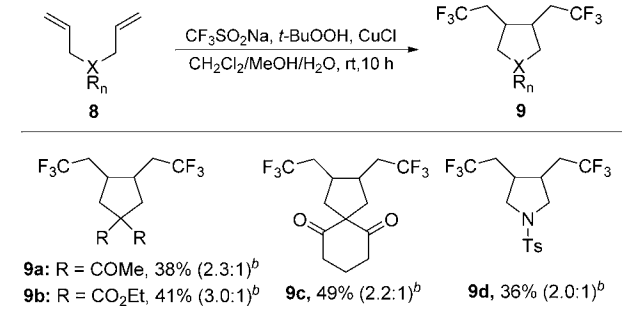
Encouraged by these experimental results, the stable and inexpensive CF_3SO_2Na was chosen as a CF_3 radical source. To improve the yield of the desired 1,2-bis(trifluoromethylated) product, we had to determine all the possible reaction pathways of this process. As shown in Scheme 3, the addition of the CF_3 radical to alkene **1** led to the active radical intermediate **A**, which might be transformed into several products: 1,2-bis(trifluoromethylated) compound **2**, dimerized compound **3**,[23] or difunctionalized compound **4**.[15a,b,21,24] Alternatively, intermedi-

Scheme 5. Scope of Copper-Mediated 1,2-Bis(trifluoromethylation) of Alkenes[a]



[a]Reaction conditions: **1** (1.0 mmol), CF_3SO_2Na (4.0 mmol), CuCl (1.0 mmol), *t*-BuOOH (6.0 mmol), CH_2Cl_2/MeOH/H_2O (2.5 mL/2.5 mL/2.0 mL), 10 h, N_2, rt, isolated yields. [b]A second portion of CF_3SO_2Na (2.0 mmol), CuCl (0.5 mmol), and *t*-BuOOH (3.0 mmol) was added after 8 h, and then the reaction was stirred for another 10 h. [c]CF_3SO_2Na (6.0 mmol), *t*-BuOOH (9.0 mmol).

Scheme 6. Preparation of 1,4-Bis(trifluoromethylated) Products 9[a]



[a]Reaction conditions: **8** (1.0 mmol), CF_3SO_2Na (4.0 mmol), CuCl (1.0 mmol), *t*-BuOOH (6.0 mmol), CH_2Cl_2/MeOH/H_2O (2.5 mL/2.5 mL/2.0 mL), 10 h, N_2, rt, isolated yields of the major isomers. [b]The diastereomer ratios were determined by ^{19}F NMR and GC-MS of the crude products.

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ate **A** might be oxidized into cationic intermediate **B**, which could undergo substitution or elimination to give the difunctionalized product **5**,[25] vinylic product **6**,[26] or allylic product **7**,[27] respectively. Therefore, the selective formation of 1,2-bis(trifluoromethylated) compound **2** remained a significant challenge.

Based on these competitive reactions, starting from the addition of the CF_3 radical to an alkene, we surmised that the high concentration of the CF_3 radical would be beneficial to the chemoselective formation of 1,2-bis(trifluoromethylated) compound **2**. When CF_3SO_2Na was used as the CF_3 radical precursor for radical trifluoromethylation reactions,[15b,24e,28] the concentration of CF_3 radical was strongly affected by the initiator. Copper(I) chloride (CuCl) was commonly used as the initiator for radical trifluoromethylation reactions using CF_3SO_2Na in the presence of *tert*-butylhydroperoxide (*t*-BuOOH).[15b,28b,c] Therefore, the concentration of the CF_3 radical would be improved when the amount of CuCl was increased.[29] With these considerations in mind, we first optimized the reaction conditions by changing the amount of CuCl. As expected, when the amount of CuCl was increased from 0.1 to 1.0 equiv, the yield of 1,2-bis(trifluoromethylated) product **2a** was gradually improved, while the dimerized product **3a** and other products (hydrotrifluoromethylated product, oxytrifluoromethylated product, chlorotrifluoromethylated product, etc.) became fewer and fewer (Scheme 4).

The reaction conditions were further screened including both metal salts and solvents (see Table S-1 in the Supporting Information for details). Accordingly, none of the metal salts gave better results than CuCl. A control experiment showed that no desired product was formed without CuCl. Intensive solvent screening led to a mixed solvent (CH_2Cl_2/MeOH/H_2O = 5:5:4) with the best results. Under the optimal reaction conditions, the substrate scope of copper-mediated 1,2-bis(trifluoromethylation) of alkenes was investigated (Scheme 5). Stryenes **1b**−**j** bearing different electron-donating and -withdrawing groups, as well as halogen atoms, at different positions of the phenyl ring proceeded smoothly to afford the corresponding 1,2-bis(trifluoromethylated) products **2b**−**j** in moderate to good yields (44−80%). For electron-rich styrenes **1l** and **1m**, the oxytrifluoromethylated products **5l** and **5m**, respectively, were produced instead of the desired 1,2-bis(trifluoromethylated) products.[30] In addition, functional groups, including benzyl chloride (**2n**), benzyl cyanide (**2o**), and hydroxyl group (**2p**), were well tolerated in this reaction. The unactivated alkenes **1q**−**u** were also transformed into the 1,2-bis(trifluoromethylated) products **2q**−**u** in moderate yields, although a larger amount of CF_3SO_2Na and TBHP were needed.[31] Remarkably, this facile method could serve as a new synthetic strategy to introduce two trifluoromethyl groups simultaneously to complex molecules, such as vinyl derivatives of estrone and *N*-benzoyl-L-tyrosine ethyl ester (**1v** and **1w**). The corresponding 1,2-bis(trifluoromethylated) products **2v** and **2w** were produced in moderate yields. These results showed that this copper-mediated protocol might be applicable to "late-stage 1,2-bis(trifluoromethylation)" of complex molecules. However, the internal alkene was not a suitable substrate for 1,2-bis(trifluoromethylation).

Besides 1,2-bis(trifluoromethylated) compounds **2**, 1,4-bis(trifluoromethylated) products could also be prepared. Treatment of 1,5-dienes **8a**−**d** with CF_3SO_2Na under the standard conditions gave 1,4-bis(trifluoromethylated) products **9a**−**d** via a tandem trifluoromethylation/cyclization/trifluoromethylation reaction sequence (Scheme 6).[27a] These results indicated that radical processes were involved in these transformations.

In conclusion, we have developed an efficient copper-mediated radical 1,2-bis(trifluoromethylation) of alkenes using the stable and inexpensive CF_3SO_2Na as the CF_3 radical precursor. This reaction provided a practical and convenient route to 1,2-bis(trifluoromethylated) compounds. The chemoselectivities of the radical trifluoromethylation were strongly controlled by the amount of initiator. The mild reaction conditions and wide substrate scope make this protocol attractive in pharmaceutical and material fields.

■ ASSOCIATED CONTENT

Supporting Information

Optimized reaction conditions, experimental procedures, characterization data, and copies of ^1H, ^{19}F, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(31) For these unactivated alkenes, the low yields may be caused by the low stability of the corresponding alkyl radial intermediates. Although trace amounts of other byproducts were detected from 19F NMR of the crude products, no other compounds that had the same mass as the desired product was found by mass.

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