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Copper(I)-Catalyzed Intramolecular Trifluoromethylation of Methylenecyclopropanes

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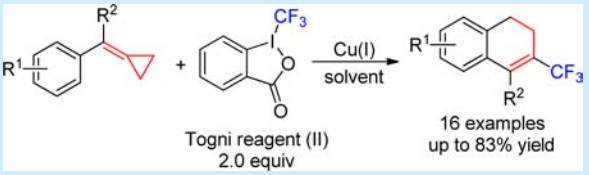
Supporting Information

ABSTRACT: Copper(I)-catalyzed intramolecular trifluoromethylation of methylenecyclopropanes has been developed to produce a variety of CF_3-substituted dihydronaphthalenes in moderate to good yields, relying on the construction of $C(sp^2)-CF_3$ bonds under mild conditions. The reactions proceed through a radical process under copper(I) catalysis with a good compatibility for the functional group.



The trifluoromethyl group is a very important structural motif in many agrochemicals and pharmaceuticals because CF_3-containing molecules usually have remarkable biological activity, high hydrophobicity, and metabolic stability (Figure 1).[1] Over the past decades, research to efficiently introduce a trifluoromethyl group into organic molecules has been a very important part of organic chemistry.[2] Trifluoromethylations, especially transition-metal-mediated or -catalyzed trifluoromethylation reactions, efficiently offer a large number of CF_3-containing compounds. Thus far, the construction of $C(sp^3)-CF_3$ bonds has been reported widely through a transition-metal catalyzed process.[3] Moreover, trifluoromethylation of aromatic compounds has also been achieved through a transition-metal-catalyzed cross-coupling process, resulting in the construction of $C(sp^2)-CF_3$ bonds.[4] More recently, difunctionalization of alkynes has become a useful method to access CF_3-containing molecules, also having a $C(sp^2)-CF_3$ bond. For example, the groups of Szabó,[5] Sodeoka,[6] and Cho[7] have developed the difunctionalization of terminal alkynes to construct $C(sp^2)-CF_3$ bonds, respectively. In addition, the groups of Liu,[8] Liang,[9] Hou,[10] Ding,[11] and Fu[12] achieved trifluoromethylation of internal alkynes (Scheme 1).

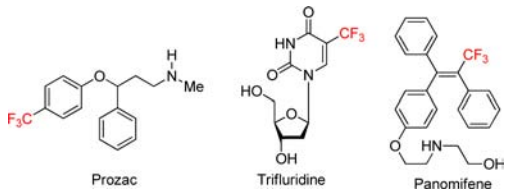
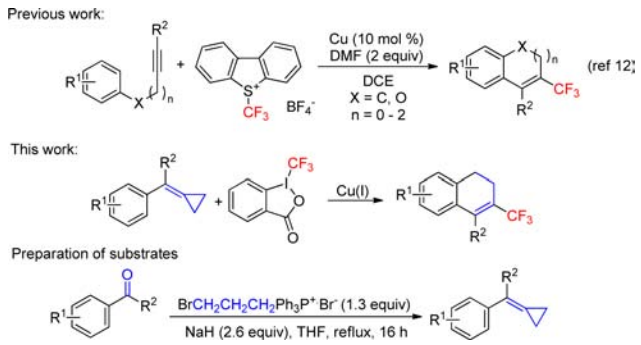


Figure 1. CF_3-containing drugs.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules and have been used very often as important building blocks in organic synthesis.[13] In the past several years, much attention has been paid to the transition metal or Lewis acid catalyzed transformations of MCPs to rapidly construct complex and interesting organic compounds.[14] At the same time, the radical initiated ring-opening processes of MCPs have been also explored extensively.[15]

Scheme 1. Synthesis of CF_3-Substituted Dihydronaphthalenes



On the basis of the above successful examples of trifluoromethylation and our ongoing interest in the exploration of new reactivity of MCPs, we hypothesized that the direct trifluoromethylation of MCPs to obtain a variety of CF_3-substituted dihydronaphthalenes would be possible through a Cu(I)-catalyzed free radical process (Scheme 1).[16] Herein, we report the successful construction of $C(sp^2)-CF_3$ bonds relying on the radical initiated ring opening of MCPs and the subsequent cyclization to afford CF_3-substituted dihydronaphthalenes.

We first investigated the reaction between methylenecyclopropane (**1a**) and the Togni reagent (II) to identify the optimal

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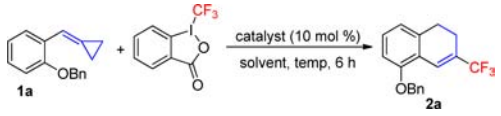
reaction conditions, and the results are summarized in Table 1. Using CuI (10 mol %) as the catalyst in DCE (1,2-dichloroethane) at 80 °C, CF_3-substituted dihydronaphthalene **2a** was obtained in 48% yield (Table 1, entry 1). We also utilized other catalysts instead of CuI, and found that CuTc was the best one, affording the desire product **2a** in 52% yield (Table 1, entry 2). Next, we utilized different solvents in this reaction to examine the solvent effects and found that MeCN was the solvent of choice, giving **2a** in 70% yield (Table 1, entry 3). The examination of reaction temperature revealed that this reaction should be carried out at 80 °C (for more details about the optimization of this reaction, see Table S1 in the Supporting Information). To our delight, the yield of **2a** could be improved to 72% when 2.0 equiv of the Togni reagent (II) was used in the presence of CuTc (10 mol %) in MeCN (1.5 mL) at 80 °C (Table 1, entry 4).

Table 1. Optimization of the Reaction Conditions[a]

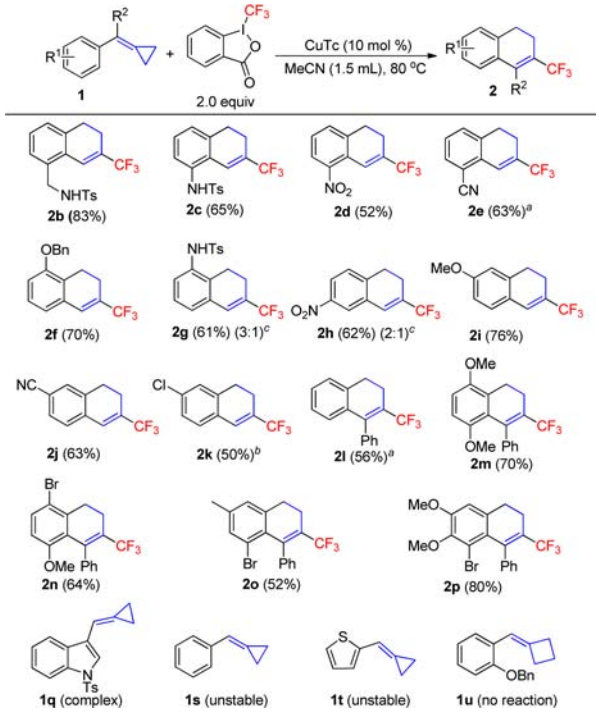


entry	catalyst	solvent	temp/°C	yield [%][b]
1	CuI	DCE	80	48
2	CuTc	DCE	80	52
3	CuTc	MeCN	80	70
4[c]	CuTc	MeCN	80	72

[a]Reaction conditions: **1a** (0.2 mmol), Togni reagent (II) (0.3 mmol), catalyst (10 mol %), and solvent (1.5 mL) were used. [b]Determined by ^{1}H NMR spectroscopy. [c]Togni reagent (II) (0.4 mmol) was used.

Having the optimized conditions in hand, we turned our attention to evaluating the generality of the reaction using a variety of MCPs **1b**−**1k**, bearing either electron-donating or -withdrawing groups on the aromatic ring. The results are shown in Scheme 2. When a substituent at the *ortho*-position of the aromatic ring was an electron-donating substituent such as an alkyl or Ts-protected amino group, the reaction proceeded smoothly to give the desired product **2b** or **2c** in 83% or 65% yield, respectively. The ORTEP drawing of **2b** is shown in Figure 2, and its CIF data have been indicated in the Supporting Information. While the substituent was a strongly electron-withdrawing group such as NO_2, the product **2d** was obtained in a slightly lower yield. By replacing NO_2 by CN, the reaction proceeded efficiently in DCE to afford the desired product **2e** in 63% yield. Subsequently, we examined the influence of the substituents at the *meta*-position of the aromatic ring. For substrate **1f**, the desired product **2f** could be obtained as the sole product in 70% yield. While, in the case of **1g**, the reaction proceeded smoothly to give the desired product **2g** along with its regioisomer **2g′** in 61% total yield as the ratio of 3:1. As for substrate **1h**, in which the *meta*-position of the aromatic ring was substituted by NO_2, the corresponding product **2h** and its regioisomer **2h′** could be also obtained in 62% total yield along with the ratio of 2:1. When substituents at the *para*-position of the aromatic ring were OMe and CN, the desired products **2i** and **2j** were afforded in 76% and 63% yields, respectively. However, as for MCP **1k**, in which the aromatic ring was *p*-ClC_6H_4, the product **2k** could be obtained in 50% yield when a second portion of CuTc and the Togni reagent (II) was added after 6 h. In the case of substrate **1l**, in which R^2 = H was replaced by a phenyl group, the reaction should be carried out in DCE to give the desired product **2l** in 56% yield. As for substrates **1m**−**1o**, in which the aromatic ring had two substituents, the corresponding products **2m**−**2o** were formed in 70−52% yields. The trisubstituted substrate **1p** produced the corresponding product **2p** in 80% yield. A substrate containing an indole group (**1q**) instead of a phenyl counterpart has been also utilized for this reaction. However, we found that the reaction system became complex and no desired product was formed under the standard conditions. As for substrates **1s** and **1t**, both of them are unstable because they could easily decompose even at low temperature under an argon atmosphere. As for methylenecyclobutane **1u**, the reaction did not take place under the standard conditions.

Scheme 2. Substrate Scope of 1



[a]Using DCE as the solvent. [b]A second portion of CuTc (10 mol %) and the Togni reagent (II) (2.0 equiv) was added after 6 h. [c]The ratio of regioisomers. Isolated yields are provided.

To demonstrate the synthetic utility of this method, further transformations of **2b** were performed (Scheme 3). Product **2b** could be readily oxidized by 3.0 equiv of NBS (*N*-bromosuccinimide) to give the corresponding CF_3-substituted naphthalene **3b** in 69% yield (Scheme 3a). In the presence of

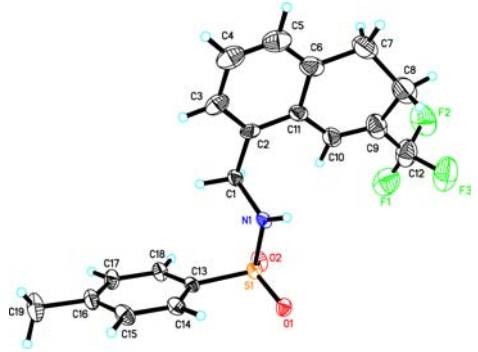


Figure 2. X-ray crystal structure of product **2b**.

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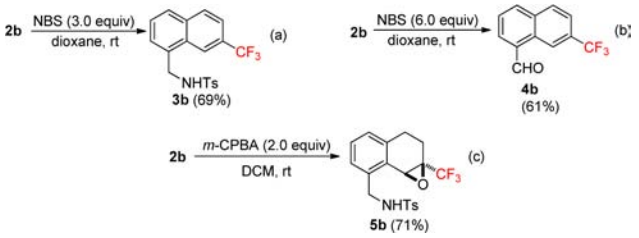
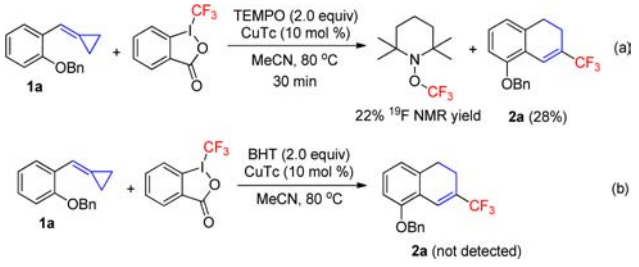
Scheme 3. Transformation of the Product 2b



NBS (6.0 equiv), **2b** could be further oxidized to the CF_3-substituted naphthaldehyde **4b** in 61% yield under identical conditions (Scheme 3b). Furthermore, product **2b** could also be transformed to the CF_3-substituted epoxide **5b** in the presence of *m*-CPBA (2.0 equiv) (Scheme 3c). On the basis of the above-mentioned results, it is obvious that more functionalized CF_3-containing compounds can be easily obtained from product **2**.

To gain mechanistic insight into this reaction, control experiments were conducted. As shown in Scheme 4, when the

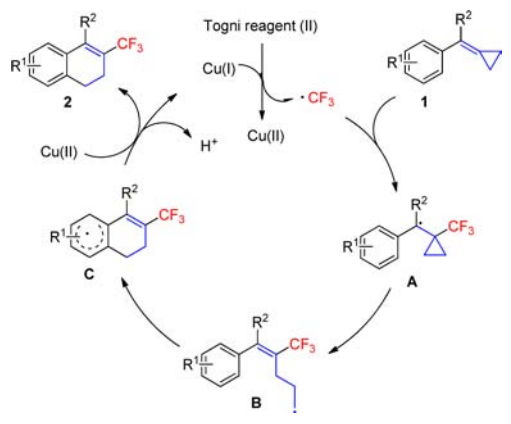
Scheme 4. Mechanistic Investigations



reaction mixture was stirred at 80 °C for 30 min in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (2.0 equiv), the CF_3 radical was captured by TEMPO to give the corresponding TEMPO adduct in 22% ^{19}F NMR yield along with **2a** in only 28% ^{19}F NMR yield (Scheme 4a). If the reaction was performed with the addition of BHT (butylated hydroxytoluene) (2.0 equiv) under the standard conditions, **2a** could not be detected (Scheme 4b), suggesting that the reaction may undergo a radical process.

A plausible mechanism is depicted in Scheme 5 on the basis of the aforementioned control experiments and previously reported literature.[3c,k,11,12] The CF_3 radical can be generated

Scheme 5. Proposed Reaction Mechanism



from the Togni reagent (II) in the presence of copper(I). The CF_3 radical adds to the C=C bond of MCP to give intermediate **A**, which undergoes a ring-opening process to give the alkyl radical intermediate **B**. The key intermediate **B** undergoes direct radical cyclization with an aromatic ring to afford intermediate **C**, which is oxidized by Cu(II) to give the desired product **2** and release a proton.

In summary, we have disclosed a novel synthetic protocol for the construction of CF_3-substituted dihydronaphthalenes through an efficient copper(I)-catalyzed trifluoromethylation of methylenecyclopropanes. The mechanistic studies indicate that the reaction proceeded through a CF_3 radical addition to the C=C bond of MCP, followed by sequential ring opening and oxidative cyclization to afford the desired product. The product **2b** can be easily transformed to other useful trifluoromethylated compounds under mild conditions. Efforts are in progress in the application of this new methodology to synthesize interesting biologically active compounds in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02940.

X-ray structural data (CIF) of compound **2b** (CCDC 1407656) (CIF)

General experimental procedure and characterization data of the products; copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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