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Trifluoromethylation of Propargylic Halides and Trifluoroacetates Using $(Ph_3P)_3Cu(CF_3)$ Reagent

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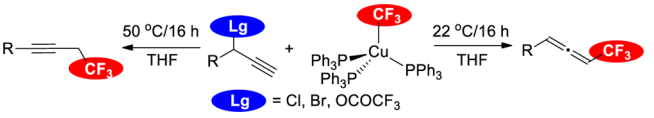
ABSTRACT



A copper-mediated trifluoromethylation of propargylic halides and trifluoroacetates was performed with high allenyl or propargyl selectivity. The reaction proceeds smoothly with aliphatic and aromatic substituents bearing either electron-withdrawing or -supplying groups. Preliminary mechanistic results indicate an ionic mechanism involving nucleophilic transfer of the CF_3 group from the Cu complex to the propargylic substrate.

The development of new methods for the preparation of trifluoromethylated compounds has become an important field in organic synthesis, because of the large demand for structurally diverse species by the pharmaceutical and agrochemical industries.[1] In particular, the late stage introduction of the CF_3 group into aromatic and heteroaromatic substrates has received a lot of recent attention.[2,3] Several excellent methods have also been published for the trifluoromethylation of alkenes, including allylic C–H functionalization based methods.[4] However, despite the importance of functionalized allenes[5] and propargylic compounds, very few methods have been reported for preparation of CF_3-derivatives. Most of the reported methods are based on the transformation of alkynyl-CF_3 compounds.[6] To the best of our knowledge, only two previous reports[7] have been published for the late stage introduction of the CF_3 group into propargylic substrates. One possible reason is that the late stage introduction was

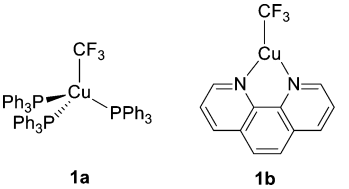


Figure 1. Well-defined, stable nucleophilic CF_3 transfer reagents.

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carried out using Cu-CF_3 reagent generated from CF_3–CdBr species. Apart from the toxicity of the organocadmium reagent, a limitation of this method is that Cu–CF_3 is a poorly defined, elusive, and complex species,[8] which easily undergoes α-fluoroelimination, leading to perfluoroalkyl–Cu complexes. Therefore, the reactions mediated by Cu–CF_3 often lead to the formation of complex mixtures of CF_3 and $(CF_2)_nCF_3$ products[8,3a,4g] (therefore the Cu-mediated direct introduction of the CF_3 group is usually more difficult than the introduction of their difluoro- and perfluoroalkyl counterparts[9]). An excellent solution to this problem is to apply some of the recently reported stable, easily accessible, and well-defined Cu–CF_3 trifluoromethylating agents, such as **1a**[3a] or **1b**[3b] (Figure 1). These types of reagents have successfully been used for the trifluoromethylation of aromatic halides.[3] We have now found that **1a** can be employed for direct introduction of the CF_3 group into propargylic chlorides and trifluoroacetates under mild conditions. Depending on the reaction conditions and substrates, these reactions led to the selective formation of allenylic or propargylic trifluoromethyl derivatives (Figure 2, Table 1).

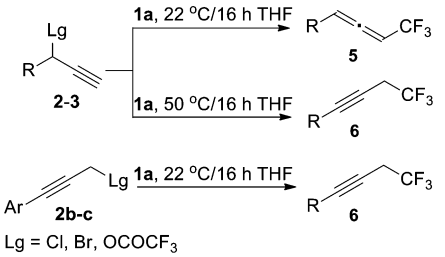
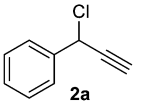
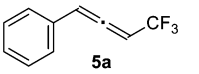
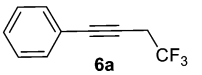
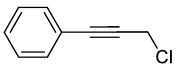
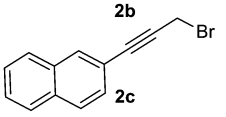
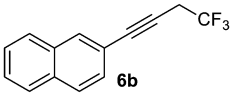
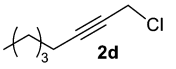
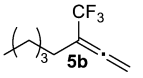
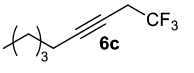
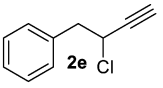
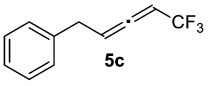
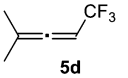
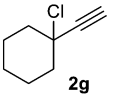
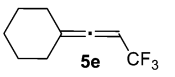
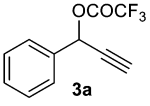
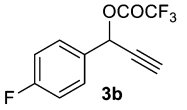
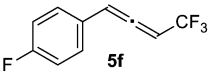
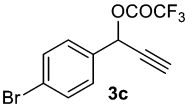
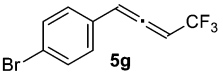
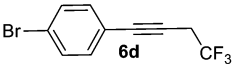
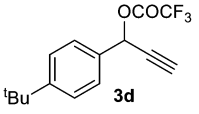
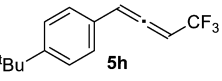
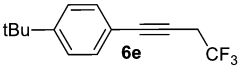
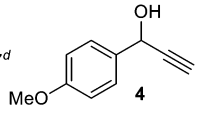
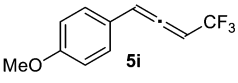


Figure 2. Trifluoromethylation of propargylic substrates by **1a**.

The best solvent for the trifluoromethylation reaction was THF. The reaction in benzene/toluene proceeds slower, and formation of both isomeric products occurred in some cases. The trifluoromethylation proceeds smoothly in DMF as well; however the selectivity is lower than in THF, and the isolation of the volatile CF_3-products is also more difficult. Inspection of the ^{19}F NMR spectrum of the crude reaction mixtures indicates that perfluoroalkyl products did not form under the applied reaction conditions. Formation of HCF_3 arising from protolysis of **1a** was also insignificant. According to Grushin and co-workers[3a] these side reactions sometimes

Table 1. Reaction of Propargylic Substrates with **1a**[a]

entry	substrate	temperature [°C]	product	yield[b]
1	 **2a**	22	 **5a**	68
2	**2a**	50	 **6a**	82
3	 **2b**	22	**6a**	74
4	 **2c**	22	 **6b**	86
5	 **2d**	22	 **5b**	67
6	**2d**	50	 **6c**	63
7	 **2e**	22	 **5c**	92
8	 **2f**	50	 **5d**	(86)[c]
9	 **2g**	22	 **5e**	87
10	 **3a**	22	**5a**	85
11	**3a**	50	**6a**	74
12	 **3b**	22	 **5f**	86
13	 **3c**	22	 **5g**	63
14	**3c**	50	 **6d**	87
15	 **3d**	22	 **5h**	58
16	**3d**	50	 **6e**	73
17[d]	 **4**	22	 **5i**	52

[a] Substrate **2**, **3**, or **4** (0.1 mmol) and **1a** (912 mg, 0.1 mmol) reacted in THF (0.4 mL) for 16 h at the indicated temperatures. [b] Isolated yield (%). [c] Volatile product; NMR yield is given. [d] The trifluoroacetate was generated in situ.

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decrease the yields in trifluoromethylation reactions of aryl iodides by **1a**. The relatively low reaction temperature (22−50 °C) is probably beneficial to avoid these side reactions.

The reactions of the branched propargylic chlorides (**2a**, **2e**−**g**) in THF at room temperature (22 °C) gave linear allenylic trifluoromethyl derivatives (entries 1 and 7−9). Aryl substituted linear propargylic chlorides **2b**−**c** under identical conditions selectively gave linear propargylic products (entries 3 and 4). Interestingly, linear substrate **2d** with an alkyl substituent afforded branched allenylic product **5b** (entry 5). When the branched propargylic substrates were reacted at a higher temperature (50 °C) instead of the linear allenylic products, the linear propargylic products were obtained. For example, **2a** at 50 °C gave propargylic product **6a** instead of the allenylic isomer **5a** (entry 2). Similarly, product **6c** was obtained from linear substrate **2d** at 50 °C. In the case of **2f** and **2g** the products are not able to undergo allenyl to propargyl isomerization, and thus only the allenylic products **5d** and **5e** were formed (entries 8−9).

As shown above, chloro- and bromo-functionalized propargylic substrates (**2**) can be efficiently converted to the corresponding trifluoromethyl derivatives **5** and **6**. However, a usual problem with the halogenation of branched propargylic alcohols is the formation of mixtures of propargyl and allenyl chloride derivatives.[10] Difficulties in obtaining the branched propargyl halides by selective transformation of propargylic alcohols led us to search for other types of leaving groups. Propargylic acetates proved to be inactive in the above trifluoromethylation reaction. However, to our delight, propargylic trifluoroacetates **3a**−**d** reacted under similar conditions as the corresponding halides. In fact, reactions performed with the branched substrates with aromatic substituents afforded the products in a higher yield than the corresponding chlorides (cf., entries 1 and 10). The process works equally well in the presence of electron-withdrawing (entries 12−13) and electron-supplying (entries 15−17) groups on the aromatic ring. We have found that allenylic derivatives **5f**−**h** could easily be obtained from trifluoroacetates **3b**−**d** and **1a** at room temperature.

Similarly to the chlorides, when the reaction was conducted at 50 °C the linear propargylic products formed instead of the corresponding allenylic isomers (cf., entries 13−14 and 15−16). We failed to obtain a chloro-derivative from propargylic alcohol **4**, and even the corresponding trifluoroacetate was too unstable to isolate. However, we found that the trifluoroacetoxylation of **4** can be performed prior to the trifluoromethylation in a one-pot sequence (entry 17). Thus, the robustness of the trifluoromethylation reaction by **1a** allows the solvolysis-sensitive trifluoroacetate precursors to be generated in situ. This feature can be useful for the trifluoromethylation of propargylic substrates with electron-donating groups in the propargylic position (such as **4**). Since isomerically pure branched propargylic trifluoroacetates can easily be obtained from the corresponding alcohols, the possibility of using these substrates considerably widens the synthetic scope of the above trifluoromethylation reactions.

Reagent **1b**, reported recently by Hartwig and co-workers,[3b] was also tested in the above trifluoromethylation reactions. It was found that under identical reaction conditions **1b** reacts more slowly than **1a**. For example, the reaction of **2d** and **1b** proceeds with a low conversion to **5b** at 22 °C in 16 h, while under the same conditions the process is complete with **1a**. Although both **1a** and **1b** are commercially available, their price is prohibitively high. In our experience, the synthesis of **1a** according to the literature procedure published by Grushin and co-workers[3a] is more straightforward than the synthesis of **1b**, which is an additional factor for using **1a** in the above process.

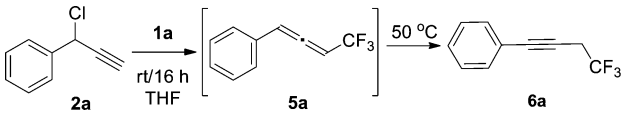

Figure 3. Rearrangement of the allenylic to propargylic product.

Although exploration of the mechanistic details of the introduction of the CF_3 group by halogen/$OCOCF_3$ displacement using **1a** requires further in-depth studies, we have investigated three important aspects of the reaction: the allenyl vs propargyl selectivity, the radical vs ionic character of the transferred CF_3 group, and the stereochemistry of the reaction. As mentioned above the outcome of the displacement reactions of substrates **2a**, **2d**, **3a**, and **3c**−**d** was dependent on the reaction temperature. The reaction at room temperature gave the corresponding allenyl products (such as **5a**, **5g**−**h**) and **5b**, while at 50 °C the propargyl product was obtained. To investigate the propargyl vs allenyl selectivity of the process, **1a** and **2a** were reacted at room temperature (Figure 3), which led to the expected formation of **5a**. After consumption of **2a** the crude reaction mixture was heated to 50 °C, which induced rearrangement of **5a** to **6a**. Interestingly, this rearrangement did not proceed when isolated **5a** was heated to 50 °C in THF, even if **1a**, CuCl/$CuCl_2$, or $CuOCOCF_3$ was added. This indicates that a Cu(I) complex formed in the **2a** → **5a** reaction may mediate the **5a** to **6a** rearrangement.

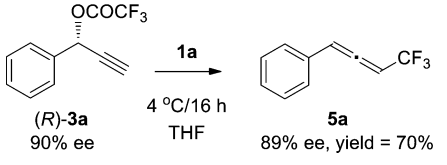

Figure 4. Reaction of enantiomerically enriched substrate (*R*)-**3a** with **1a**.

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Some recent studies on the trifluoromethylation of alkenes (in particular with hypervalent iodine reagents) reported that the reactions may proceed via CF_3 radical intermediates.[4a,b,d,e] To test this possibility we carried out the reaction of **3b** and **1a** in the presence of TEMPO, (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl, which is a well-known radical scavenger. The addition of TEMPO did not have any significant effect on the reaction. For example, **5a** was formed in similar yield both in the absence (85%, entry 10) and in the presence (72%) of the radical scavenger. This finding indicates that the reaction occurs by an ionic mechanism. Considering the electronic structure[11] of complex **1a**, it can be classified as a nucleophilic reagent, which is able to transfer a CF_3^- functional group. To explore the stereochemistry of the nucleophilic CF_3 transfer from **1a** to a propargylic substrate, we prepared enantiomerically enriched (90% ee) **3a** by a standard trifluoroacetoxylation procedure from the corresponding alcohol and reacted it with **1a**. In this reaction **5a** was formed with 89% ee at 4 °C in 16 h (Figure 4), indicating that the nucleophilic displacement of the trifluoroacetate proceeds in one step with an S_N2'-type mechanism. At room temperature the reaction proceeds only with moderate stereoselectivity (56% ee). In the case of terminal propargylic substrates (such as **2b**–**c**) the terminal CF_3 derivative is formed, which may be due to steric reasons analogous to the Pd-catalyzed nucleophilic substitution reactions.[12]

In summary, we have shown that copper complex **1a** is an excellent reagent for trifluoromethylation of propargylic halides and trifluoroacetates. The reaction proceeds smoothly and selectively in the presence of both electron-withdrawing and -supplying substituents. The reaction of branched aryl propargylic derivatives gives the allenylic product. At a slightly elevated temperature the corresponding propargylic-CF_3 derivative is formed. In these reactions probably the primary product is the allenylic isomer, which is rearranged to the propargylic derivative. By using our method, the application of organocadmium precursors and unstable Cu–CF_3 species previously employed[7] for the trifluoromethylation of propargylic chlorides can be avoided. Furthermore, enantiopure trifluoromethyl allenes can be obtained from trifluoroacetates of chiral propargylic alcohols (Figure 4). Thus, the above method opens new selective synthetic routes for the synthesis of allenylic- and propargylic-CF_3 derivatives, which are important species in pharmaceutical and agrochemical applications.[1a,c,e,13]

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Supporting Information Available. Detailed experimental procedures and compound characterization data are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.