Trifluoromethylation

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Trifluoromethylation Reactions for the Synthesis of β-Trifluoromethylamines**

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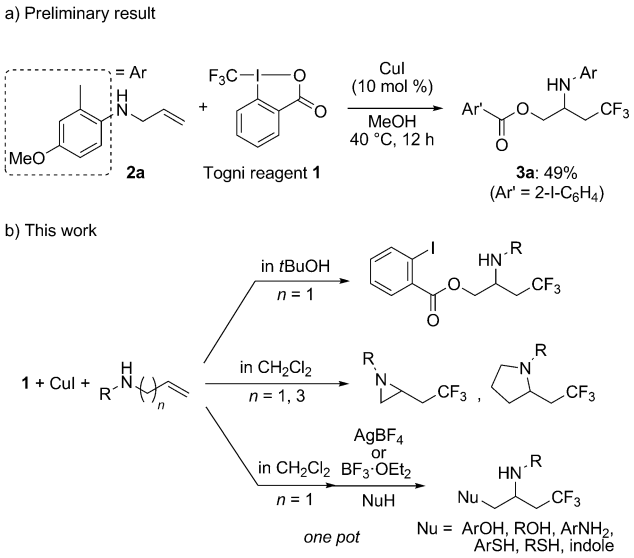
The trifluoromethyl group has gained significance in the pharmaceutical and agrochemical industries owing to its unique properties.[1,2] Many trifluoromethylated compounds are known for their bioactivity, and the β-trifluoromethylamine unit is one of the major components found in this class of bioactive species.[3] However, relatively few synthetic methods provide access to β-trifluoromethylamines, and therefore new methodology is still required.

Currently, the trifluoromethylation of non-prefunctionalized alkenes is attracting considerable attention. Several successful examples have been reported[4] since the deprotonative trifluoromethylation of simple alkenes with electrophilic trifluoromethylating reagents[5,6] was established by the research groups of Buchwald, Liu, and Wang in 2011.[7] Since 2010, we have been independently investigating trifluoromethylation reactions with Togni reagent **1** in the presence of Cu^{I}.[8] Our recent focus has been on the trifluoromethylation of alkenes on the basis of a difunctionalization strategy. This approach has enabled the oxytrifluoromethylation of styrene derivatives[9,10] as well as the carbotrifluoromethylation of simple alkenes[11] with the Cu^{I}/Togni reagent system. These reactions afforded β-trifluoromethylated alcohol derivatives as well as carbocycles and heterocycles bearing a trifluoromethyl group. Furthermore, the research groups of Szabó and Buchwald have independently developed copper-catalyzed oxytrifluoromethylation reactions of alkenes with **1**,[12] and Liu has reported an elegant aryltrifluoromethylation of acryloanilides with a palladium/ytterbium catalyst system under oxidative trifluoromethylation conditions.[13]

In the course of our studies, we encountered a curious reaction outcome when the allylaniline derivative **2a** was exposed to a catalytic amount of CuI and **1** in MeOH (Scheme 1a). Specifically, an *N*-migratory oxytrifluoromethylation product **3a**, which is a potentially useful intermediate for the synthesis of bioactive compounds, was obtained in 49% yield. Inspired by this finding, we investigated the use of allylamine derivatives as precursors for the β-trifluoromethylamine unit. Herein, we report copper-catalyzed *N*-migratory oxytrifluoromethylation reactions of allylamine derivatives, the aminotrifluoromethylation of alkenyl amine derivatives, and a one-pot *N*-migratory three-component coupling reaction for the generation of various β-trifluoromethylamine derivatives (Scheme 1b).



Scheme 1. Preliminary result and summary of the present study.

By screening of the reaction conditions, we found that the use of CuI as a catalyst in *t*BuOH was optimal for the *N*-migratory oxytrifluoromethylation.[14] Under the optimized conditions, we examined the scope of this reaction (Table 1). Compound **2a**, containing a 4-methoxy-2-methylaniline moiety, was a good substrate for this reaction, and **3a** was obtained in 90% yield (Table 1, entry 1). Simple *N*-allylaniline (**2b**) was also smoothly converted into the corresponding product **3b** in 92% yield (Table 1, entry 2). The reaction efficiency was somewhat affected by the substituents on the aniline ring. The reaction of **2c** provided the desired product **3c** in 71% yield (Table 1, entry 3). The reaction conditions were compatible with C_{Ar}–halogen (F, Cl, Br, I) bonds: the yields of **3d**–**3g** ranged from 63 to 70% (Table 1, entries 4–7). An electron-withdrawing group, such as an ethyl ester group, had little effect on the reaction (Table 1, entry 8). The reaction of **2i**, containing a methylenedioxy unit, afforded **3i** in 70% yield (Table 1, entry 9). Alkyl allylamines were also

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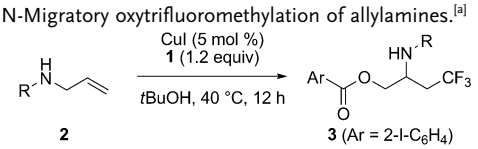
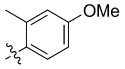
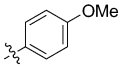
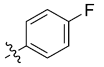
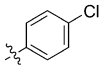
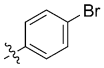
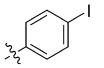
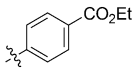
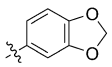
Table 1: N-Migratory oxytrifluoromethylation of allylamines.[a]

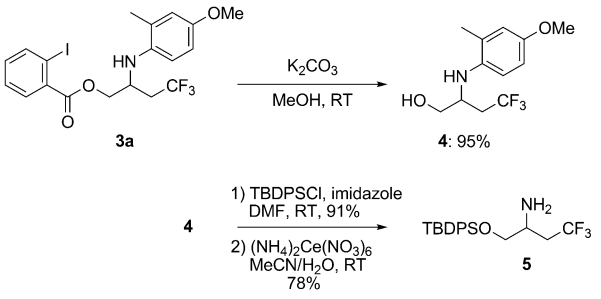


Entry	R	Product	Yield [%][b]
1		**3a**	90
2		**3b**	92
3		**3c**	71
4		**3d**	70
5[c]		**3e**	70
6[c]		**3f**	63
7		**3g**	69
8		**3h**	77
9[c]		**3i**	70
10		**3j**	67

[a] The reactions were carried out on a 0.5 mmol scale. [b] Yield of the isolated product. [c] The reaction was carried out for 24 h.

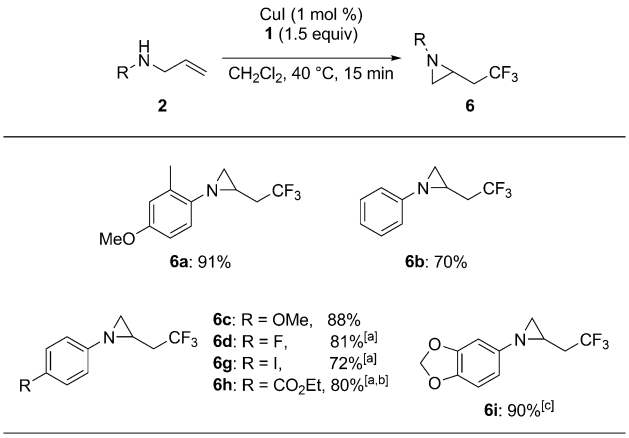
applicable to this reaction, and the benzyl derivative **3j** was obtained in 67% yield (Table 1, entry 10). Next, to demonstrate the synthetic utility of these products, we examined further transformations of **3a** (Scheme 2). The treatment of **3a** with K_2CO_3 in MeOH provided the hydroxy product **4** in 95% yield, and the primary amine **5** was obtained in high yield by oxidative removal of the 4-methoxy-2-methylphenyl group after the protection of **4** with a *tert*-butyldiphenylsilyl (TBDPS) group.

We hypothesized that *N*-migratory oxytrifluoromethylation reactions would proceed via an aziridine intermediate, and indeed, we found that an aziridine product was formed during the reaction. For example, when the reaction was



Scheme 2. Transformation of **3a**. DMF = *N*,*N*-dimethylformamide.

terminated after 1 h, compound **6a** was obtained in 29% yield together with **3a** (40%). From the viewpoint of synthetic utility, the aziridine group is a useful functional group owing to its characteristic reactivity.[15,16] There have been many studies reported on the construction of the aziridine framework and transformations of aziridine derivatives.[17] Therefore, we next investigated suitable conditions for the synthesis of the aziridine (Scheme 3).[14] Aziridine **6a** was formed

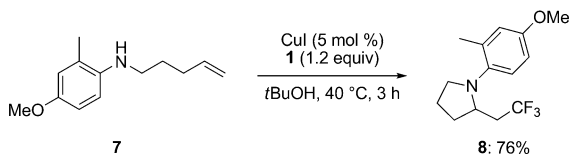


Scheme 3. Aminotrifluoromethylation with the Togni reagent. The reactions were carried out with CuI (1 mol%) and **1** (1.5 equiv) in CH_2Cl_2 on a 0.5 mmol scale, unless otherwise mentioned. [a] The reaction was carried out for 3 h. [b] The reaction was carried out with 5 mol% of CuI. [c] The reaction was carried out for 30 min.

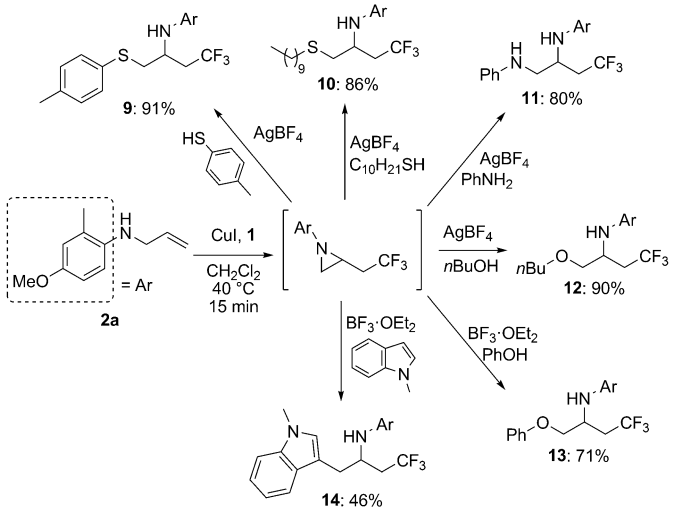
selectively in 91% yield in 15 min in the presence of 1 mol% of the catalyst with CH_2Cl_2 as the solvent. In the aminotrifluoromethylation, reactions of substrates bearing an electron-donating group on the aniline ring were faster than those of substrates bearing an electron-withdrawing group. Compounds **2c** and **2i** were transformed into the corresponding aziridines **6c** and **6i** in 88 and 90% yield, respectively, whereas the yield of **6b**, without a substituent on the aromatic ring, was somewhat lower (70%), although the reaction still proceeded smoothly. The reaction of substrate **2d** with an electron-withdrawing fluorine group was slow; however, product **6d** was obtained in 81% yield when the reaction was carried out for 3 h. Again, the C_{Ar}–I bond was compatible with these reaction conditions, and the expected product **6g** was obtained in 72% yield. Although 5 mol% of CuI was required, the yield of **6h**, which has an electron-withdrawing ester group, was as high as 80%. In contrast, the reaction of *N*-(*tert*-butoxycarbonyl)allylamine did not proceed, probably because of the low nucleophilicity of the nitrogen atom.

Encouraged by these results, we also attempted the aminotrifluoromethylation of the 4-pentenyl aniline derivative **7**, and obtained the pyrrolidine derivative **8** in 76% yield (Scheme 4).

Having established suitable conditions for selective aziridine formation, we next focused on one-pot trifluoromethylation-initiated *N*-migratory functionalization (Scheme 5). Thus, we investigated the direct transformation of aziridines in the reaction mixture.[14] We found that sulfur nucleophiles,



Scheme 4. Formation of a pyrrolidine ring by aminotrifluoromethylation.



Scheme 5. One-pot three-component coupling reactions.

such as 4-methylthiophenol and decanethiol, were successfully introduced into the products when $AgBF_4$ (20 mol%) was added as an additional Lewis acid together with the nucleophile in the second step.[14] Compounds **9** and **10** were obtained in 91 and 86% yield, respectively, without difficulty. Furthermore, aniline functioned as a good nucleophile in this sequential reaction and afforded **11** in 80% yield. Treatment with *n*BuOH provided the corresponding product **12** in 90% yield. Pleasingly, the use of $BF_3{\cdot}Et_2O$ led to success in the reaction with phenol, with the formation of **13** in 71% yield. Notably, an indole derivative could also be used as a nucleophile: the desired tryptamine derivative **14** bearing a trifluoroethyl group was obtained in 46% yield.

In summary, we have developed a copper-catalyzed trifluoromethylation of alkenyl amines, including an *N*-migratory oxytrifluoromethylation of allylaniline derivatives, an aminotrifluoromethylation reaction,[18] and a one-pot three-component coupling reaction. We believe that these reactions, which generate β-trifluoromethylamine derivatives with high efficiency, will open up a new avenue for the synthesis of bioactive compounds containing a β-trifluoromethylamine unit. Further investigations of this reaction system and mechanistic studies are under way.

Experimental Section

Typical procedure for the *N*-migratory oxytrifluoromethylation of allylanilines: CuI (4.8 mg, 5 mol%) and Togni reagent (**1**; 190 mg, 1.2 equiv) were placed in a Schlenk flask, which had been flame dried under vacuum. The flask was evacuated and refilled with nitrogen, and then *t*BuOH (2.5 mL) and **2a** (88.6 mg, 0.5 mmol) were added. The reaction mixture was stirred at 40°C for 12 h and then diluted with dichloromethane (5 mL). The solution was passed through a short pad of Florisil. The organic solvent was evaporated, and the residue was subjected to column chromatography on silica gel (hexane/ethyl acetate 20:1) to give the trifluoromethylated product **3a** (222 mg, 90%).

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