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Copper-mediated trifluoromethylation of propargyl acetates leading to trifluoromethyl-allenes†

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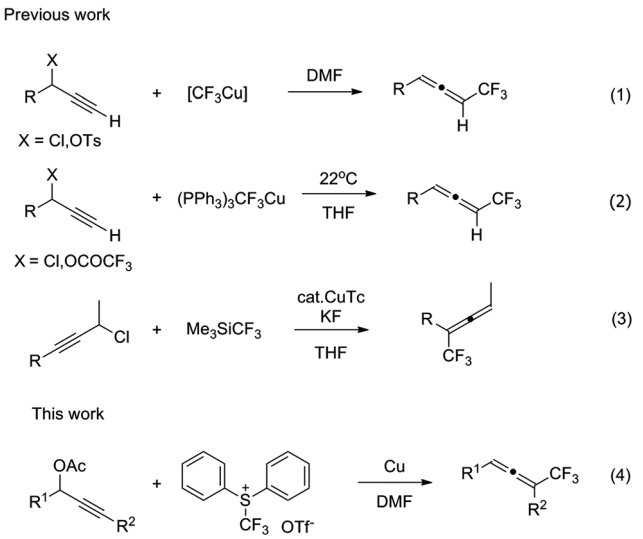
A copper-mediated trifluoromethylation of propargyl acetates with *S*-(trifluoromethyl)diphenylsulfonium triflate leading to trifluoromethylated allenes in moderate to excellent yields is described.

The introduction of a trifluoromethyl group into an organic molecule usually results in a profound effect on its physical, chemical and biological properties.[1] Due to the versatility of this moiety, determined searches have been undertaken to find efficient and general methods for transition metal-promoted trifluoromethylation of a wide range of substrates.[2] However, despite the significance of functionalized allenes,[3] transition metal-mediated trifluoromethylation leading to allene derivatives has been largely ignored.[4] We firstly reported the copper-mediated trifluoromethylation of aromatic and hetero-aromatic iodides by using electrophilic trifluoromethylating reagents.[5] Shortly afterwards, we extended our studies to the trifluoromethylation of arylboronic acids,[6] alkenes[7] and alkynes.[8] As part of our continuing research interest in this area of chemistry, we have now investigated the copper-mediated trifluoromethylation of propargyl acetates with *S*-(trifluoromethyl)diphenylsulfonium triflate leading to trifluoromethyl-allenes, compounds which couldn't previously be easily obtained *via* late stage trifluoromethylation.[9]

Propargyl alcohol derivatives and halides have proved to be valuable building blocks in the synthesis of allenes.[10] Trifluoromethylation of these compounds resulting in trifluoromethyl-allenes has been reported by employing a [$CuCF_3$] reagent prepared in advance or generated *in situ* from nucleophilic trifluoromethyl sources. An early approach described by Burton *et al.* requires the use of a toxic [$CdCF_3$] reagent to get [$CuCF_3$] (eqn (1), Scheme 1).[4a] Recently, Szabó and coworkers found that the stable and easily accessible [$(Ph_3P)_3CuCF_3$] reagent is also applicable for this transformation, but the process usually works only with terminal alkynes as substrates or only results in disubstituted allenes (eqn (2)).[4c] Another approach developed by the group of Nishibayashi can yield trisubstituted allenes, but the substrates are limited to 1-methyl-substituted alkynes (eqn (3)).[4d] In this communication, we report that the electrophilic trifluoromethylating reagent *S*-(trifluoromethyl)-diphenylsulfonium triflate converts a variety of propargyl acetates into trisubstituted trifluoromethyl-allenes (eqn (4)).



Scheme 1 Trifluoromethylation of propargyl esters and chlorides leading to allenes.

Previously, we reported that *S*-(trifluoromethyl)diphenylsulfonium triflate, $[Ph_2SCF_3]^+[OTf]^-$ (**1**), can be reduced by copper powder in DMF to give a [$CuCF_3$] intermediate. Under the same conditions, trifluoromethylation of propargyl acetates **2a** proceeded, but the yield was very low (22%). ^{19}F NMR analysis of the reaction mixture showed that $CuCF_3$ was not completely consumed over a period of 2 h (δ = −33.9 ppm relative to

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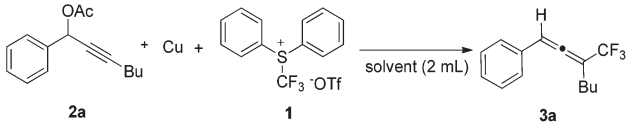
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all compounds. See DOI: 10.1039/c3ob42575d

Table 1 Trifluoromethylation of **2a** by $[Ph_2SCF_3]^+[OTf]^-$[a]



2a 1 3a

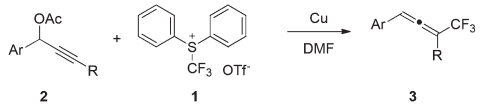
Entry	Solvent	Temp (°C)	Time (h)	Ligand[b]	Yield[c] (%)
1	DMF	60	2	—	22
2	DMF	60	9	—	35
3	DMF	70	2	—	53
4	DMF	80	2	—	50
5[d]	DMF	80	9	—	N.D.
6[e]	DMF	80	9	—	N.D.
7	DMSO	70	2	—	10
8	NMP	70	2	—	24
9	CH_3CN	70	2	—	N.D.
10	1,4-Dioxane	70	2	—	N.D.
11	DMF	70	2	1,10-Phen	50
12	DMF	70	2	PPh_3	49
13[f]	DMF	70	2	—	80
14[f,g]	DMF	70	2	—	99 (94)[h]

[a] Reaction conditions: **2a** (0.1 mmol, 1.0 equiv.), **1** (2 equiv.), Cu (3 equiv.) in a solvent (2 mL). [b] 1 equiv. of ligand was used. [c] Determined by ^{19}F NMR. [d] CuI (1 equiv.) was used instead of Cu. N.D. = not detected. [e] $Cu(OAc)_2$ (1 equiv.) was used instead of Cu. [f] 0.5 mL DMF was used. [g] 4 equiv. of **1** and 6 equiv. of Cu were used. [h] Isolated yield.

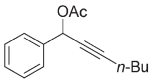
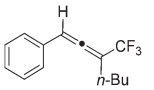
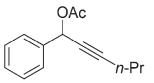
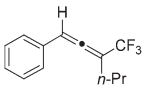
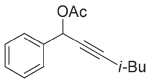
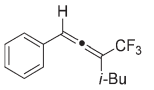
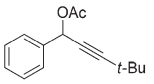
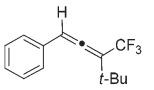
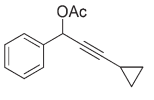
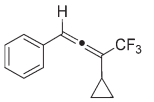
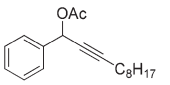
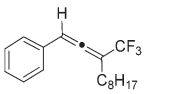
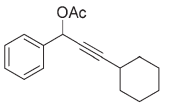
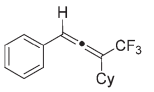
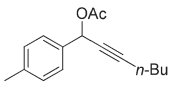
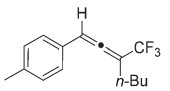
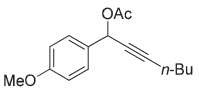
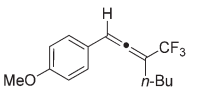
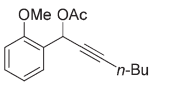
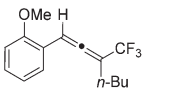
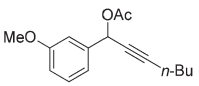
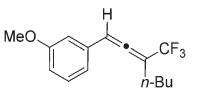
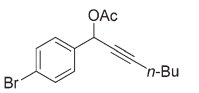
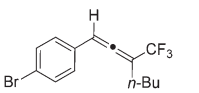
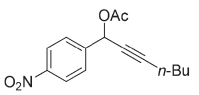
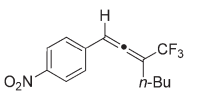
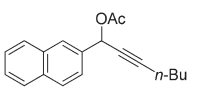
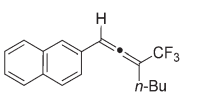
$CFCl_3$) (entry 1, Table 1). On increasing the reaction time to 9 hours, the intermediate $[CuCF_3]$ disappeared, and the yield was increased slightly to 35% (entry 2). On elevating the reaction temperature to 70 °C, the reaction was completed in 2 h and gave the desired product in 53% yield (entry 3). Further increasing the temperature led to the formation of a pentafluoroethylated by-product due to decomposition of $[CuCF_3]$ (entry 4). Cu(I) and Cu(II) were also investigated, but neither of them could promote the desired conversion (entries 5 and 6). An examination of the effect of the solvent suggested that DMF is suitable for this transformation (entry 3 *vs.* entries 7–10). It has been reported that the addition of a ligand improves trifluoromethylation,[11] but in our case, no positive effect was found (entries 11 and 12). Interestingly, the concentration of the reactants had a significant effect on the reaction. When the concentration was increased from 0.05 M to 0.2 M, the desired product was obtained in good yield (entry 13). With the use of 4 equiv. of the triflate **1**, the conversion proceeded very well to give the expected product in quantitative yield, and almost none of the pentafluoroethylated by-product was detected by ^{19}F NMR (entry 14).

With the optimized reaction conditions in hand (entry 14, Table 1), we explored the scope of this trifluoromethylation. As shown in Table 2, the reaction conditions could tolerate various functional groups and gave corresponding trifluoromethylation products with moderate to excellent yields in most cases. The desired transformation proceeded very well even for the substrates substituted by bulky alkyl groups, such as i-Bu and *t*-Bu (entries 3 and 4). In the case of the cyclohexyl-substituted substrate, the reaction afforded the desired product in lower yield, as well as 5% of the pentafluoroethy-

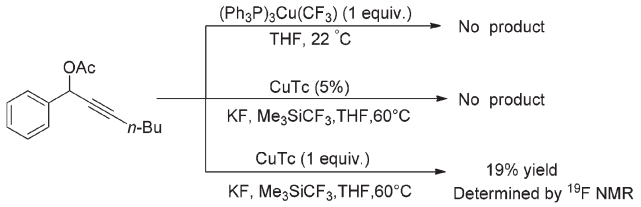
Table 2 Cu(0)-mediated trifluoromethylation of propargyl acetates[a]



2 1 3

Entry	Substrate	Product	3, Yield[b] (%)
1			**3a**, 94
2			**3b**, 90
3			**3c**, 92
4			**3d**, 90
5			**3e**, 86
6			**3f**, 85
7			**3g**, 76
8			**3h**, 96
9			**3i**, 96
10			**3j**, 97
11			**3k**, 80
12			**3l**, 79
13			**3m**, 16[c]
14			**3n**, 76

[a] Propargyl acetate (0.1 mmol, 1.0 equiv.) and **1** (4 equiv.), Cu (6 equiv.) in DMF (0.5 ml) at 70 °C. [b] Isolated yields. [c] The yield was determined by ^{19}F NMR.

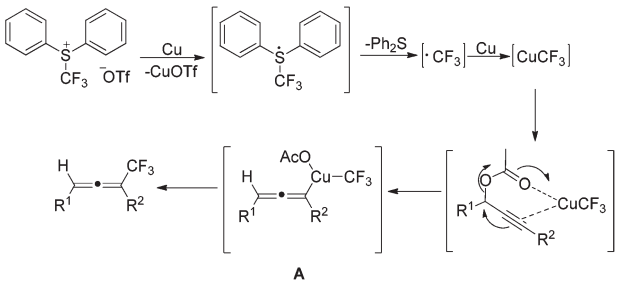


Scheme 2 Attempts for the trifluoromethylation of propargyl acetate by previously described methods.

lated by-product (entry 7). An examination of the effect of phenyl substituents suggested that those that are electron-rich are favorable for the reaction (entries 8–11). The substrate substituted with a weak electron-withdrawing group still could be converted to the expected product in good yield (entry 12). But a strong electron-withdrawing group greatly suppressed the desired conversion (entry 13). The transformation is also applicable for a 2-naphthyl substrate, even though the yield was lower (entry 14).

The groups of Szabó and Nishibayashi have independently reported the trifluoromethylation of propargyl trifluoroacetates and chlorides. In Szabó's case, $[(Ph_3P)_3CuCF_3]$ was used to obtain the desired trifluoromethylated allenes in reactions performed at 22 °C. They found that heating the reaction system to 50 °C resulted in the rearrangement of the allenes to form trifluoromethylated alkynes. In sharp contrast, no trifluoromethylated alkynes were detected under our reaction conditions, even when the reactions were performed at a higher temperature (70 °C). Furthermore, we found that Szabó's reaction system doesn't work for the trifluoromethylation of propargyl acetates (Scheme 2). Nishibayashi's reaction conditions (CuTc, KF and Me_3SiCF_3) were not effective with propargyl acetates either. Even with a stoichiometric amount of CuTc, only 19% yield of the desired product could be detected using ^{19}F NMR, with trifluoromethylbenzene as an internal standard (Scheme 2). These results indicated that different reaction conditions should be applied to different kinds of substrates. The three simple protocols are complementary for the trifluoromethylation of propargyl (trifluoro)acetates and chlorides leading to trifluoromethylated allenes.

Combined with the previous reports,[5,6,12] we propose that the reaction proceeds *via* the oxidative addition of propargyl acetate to the important intermediate $[CuCF_3]$, which is generated from the reaction of *S*-(trifluoromethyl)diphenylsulfonium triflate with copper powder (Scheme 3). Propargyl acetate acts as a bidentate ligand and the coordination to $[CuCF_3]$ favors oxidative addition to give intermediate **A**. The reductive elimination of intermediate **A** gives the final product.



Scheme 3 Proposed mechanism for the trifluoromethylation of propargyl acetates.

Conclusions

In conclusion, we have described the copper-mediated trifluoromethylation of propargyl acetates with *S*-(trifluoromethyl)-diphenylsulfonium triflate under mild conditions leading to trifluoromethyl-allenes in moderate to excellent yields. Trisubstituted allenes are potential intermediates in the synthesis of important drug candidates. The application of our trifluoromethylation system composed of copper powder and *S*-(trifluoromethyl)diphenylsulfonium triflate for tandem reactions is currently under investigation.

Acknowledgements

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