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# Synthesis of trifluoromethylated acetylenes via copper-catalyzed trifluoromethylation of alkynyltrifluoroborates

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## ABSTRACT

A new method for the synthesis of trifluoromethylated acetylenes is developed which involves the copper-catalyzed trifluoromethylation of alkynyltrifluoroborates with an electrophilic trifluoromethylating reagent. This method offers significant advantages such as efficiency and mild and base-free reaction conditions. A plausible mechanism is proposed.

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Trifluoromethylated acetylenes (RC=CCF<sub>3</sub>) have found applications as building blocks in pharmaceuticals and as functional materials.<sup>1</sup> As a result, the development of efficient methods for preparing trifluoromethylated acetylenes has been a topic of increasing importance in organic synthesis. Such molecules have typically been synthesized through Pd-catalyzed cross-coupling reactions of trifluoropropynyl metal reagents with aryl iodides,<sup>2</sup> dehalogenation of trifluoromethylethenes,<sup>3</sup> and trifluoromethylation of alkynyl lithium reagents<sup>4</sup> or stannylacetylenes.<sup>5</sup> However, these methods present several disadvantages. For instance, tedious reaction procedures are generally required and many alkynyl metal reagents or substrates employed in the reactions are hazardous or highly toxic.

Direct C–H bond trifluoromethylation of terminal alkynes has been the subject of extensive research as it provides a straightforward method to synthesize trifluoromethylated acetylenes.<sup>6–8</sup> Qing and co-workers reported the first example of Cu-mediated, and later Cu-catalyzed oxidative trifluoromethylation of terminal alkynes using (trifluoromethyl)trimethylsilane.<sup>6</sup> Our group,<sup>7</sup> and Fu and Guo,<sup>8</sup> have independently developed copper-catalyzed trifluoromethylations of terminal alkynes using electrophilic trifluoromethylating reagents (Togni's and Umemoto's reagents, respectively). However, these methods suffered from individual limitations, such as the requirement of using excess amounts of base or oxidant and high reaction temperatures. As such, there remains a need for further development of methods for the efficient construction of such molecules.

Potassium organotrifluoroborates have advantages in crosscoupling reactions compared to their boronic acid and boronic ester counterparts in terms of easier preparation procedures and greater nucleophilicity.<sup>9</sup> Accordingly, organotrifluoroborates offer a broader reaction scope to synthesize target molecules. Buchwald and co-workers have developed an efficient iron(II)-catalyzed trifluoromethylation of potassium vinyltrifluoroborates to produce vinyl–CF<sub>3</sub> containing products.<sup>10</sup> In connection with our research interest in metal-catalyzed trifluoromethylation chemistry,<sup>7,11</sup> we herein report an alternative method for the synthesis of trifluoromethylated acetylenes via copper-catalyzed trifluoromethylation of alkynyltrifluoroborates with an electrophilic trifluoromethylating reagent.

Trifluoromethylation of *p*-tolylacetylenetrifluoroborate (**1a**) with Togni's reagent (**2**) to give the corresponding trifluoromethylated product **3a** was first attempted as a model reaction under various conditions (Table 1). We were pleased to find that treatment of **1a** with 1.2 equiv of **2** in the presence of 30 mol % of CuSCN, 30 mol % of 2,2'-bipyridine (**L1**), and 4 Å molecular sieves in acetonitrile (MeCN) at room temperature for 16 hours afforded the desired product **3a** in 90% yield (entry 1). The presence of molecular sieves was found to be important for efficient trifluoromethylation to occur; in their absence a decreased yield was obtained (71%, entry 2). Under similar conditions, other nitrogen based ligands, such as 1,10-phenanthroline (**L2**), *N,N/N'*-tetramethylethylenediamine





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## Table 1





<sup>a</sup> Reaction conditions: 1a (0.10 mmol), 2 (0.12 mmol), solvent (1.0 mL), 4 Å MS (200 mg/mmol), r.t., 16 h, Ar atmosphere.

<sup>b</sup> Yields were determined by GC analysis of the crude reaction mixture with nonane as the internal standard.

<sup>c</sup> Without addition of molecular sieves.

(**L3**), and 2,4,6-trimethylpyridine (**L4**) showed much poorer performances (entries 3–5), as was also the case under ligand-free conditions (entry 6). A subsequent screen of copper sources, using 2,2'-bipyridine as the ligand, indicated that CuI and CuCl led to lower yields (entries 7 and 8), whereas Cu(OTf)<sub>2</sub> and Cu(TFA)<sub>2</sub> gave only modest yields (entries 9 and 10). The results indicated that CuSCN, which also served as an effective pre-catalyst in a recent example of oxidative trifluoromethylthiolation of an arylboronic acid,<sup>12</sup> gave the best result. Evaluation of various solvents showed that the trifluoromethylation proceeded with comparable efficiency in diglyme (entry 11). When the reaction was performed in dimethylacetamide (DMAC) or CH<sub>2</sub>Cl<sub>2</sub>, inferior results were obtained (entries 12 and 13).

Having optimized the conditions, we next explored the substrate scope of the copper-catalyzed trifluoromethylation of alkynyltrifluoroborates (Table 2). A broad range of alkynyltrifluoroborates was successfully employed for the trifluoromethylation reaction. Variation of the 4-alkyl-substituted phenyl alkynyltrifluoroborates afforded a useful range of products (3a, 3c-g) in good isolated yields (75-88%; entries 1 and 3-7). Phenyl alkynyltrifluoroborate also reacted efficiently to produce 3b in 75% yield as determined by <sup>19</sup>F NMR spectroscopy with an internal standard (entry 2). Biphenyl alkynyltrifluoroborate underwent the trifluoromethylation very smoothly to afford **3h** in a good yield (83%, entry 8). Notably, halogen-substituted phenyl alkynyltrifluoroborates proved to be suitable substrates as the 4-fluoro- and 3,4-dichloro-phenyl alkynyltrifluoroborates produced the corresponding trifluoromethylated acetylenes 3i and 3j in yields of 47% and 68%, respectively (entries 9 and 10). An electron-donating group such as *p*-methoxy was well-tolerated, affording product **3k** in 70% yield (entry 11). To investigate the compatibility of nonaromatic alkynyltrifluoroborates, hept-1-ynyltrifluoroborate was used as the substrate. Gratifyingly, under these reaction conditions, product **31** was formed in a good yield of 75% (entry 12).

A plausible mechanism for the copper-catalyzed trifluoromethylation of alkynyltrifluoroborates with the electrophilic trifluoromethylating reagent **2** is shown in Scheme 1. Initial complexation of

#### Table 2

Copper-catalyzed trifluoromethylation of alkynyltrifluoroborates<sup>a</sup>



(continued on next page)

#### Table 2 (continued)



<sup>a</sup> Reaction conditions: alkynyltrifluoroborate (0.1 mmol), **2** (0.12 mmol), CuSCN (0.03 mmol), 2,2'-bipyridine (0.03 mmol), 4 Å MS (200 mg/mmol), MeCN (1.0 mL), r.t., 16 h, Ar atmosphere.

<sup>b</sup> Isolated yield.

<sup>c</sup> <sup>19</sup>F NMR spectroscopic yield.

CuSCN with 2,2'-bipyridine forms the copper thiocyanate **A**. Subsequent transmetallation of **A** with the alkynyltrifluoroborate generates copper(I)-acetylide species **B** as the key intermediate. Nucleophilic attack of the alkynyl group of **B** at the CF<sub>3</sub> moiety is assumed to occur next to generate the desired trifluoromethylated acetylene product, along with Cu-alkoxide complex **C**. This undergoes further reaction with the alkynyltrifluoroborate to regenerate **B** to complete the catalytic cycle.

In conclusion, we have developed an effective copper catalyst system for the trifluoromethylation of alkynyltrifluoroborates with Togni's reagent. The results show that the catalytic reactions proceed smoothly at room temperature without addition of a base or oxidant. A variety of functional groups, such as alkyl, alkoxy, and halides were tolerated. Further studies to develop related trifluoromethylation processes under copper catalysis and to elucidate the roles of the ligands are currently underway in our laboratories.

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# Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 09.083.

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Scheme 1. A possible mechanism for the copper-catalyzed trifluoromethylation of alkynyltrifluoroborates.

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