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A new strategy to construct a C=C–CF_3 subunit *via* CuBr-catalyzed domino reaction of homopropargyl amines: an efficient synthesis of trifluoromethyl containing building blocks 4-trifluoromethyl-2,3-dihydro-pyrroliums†‡

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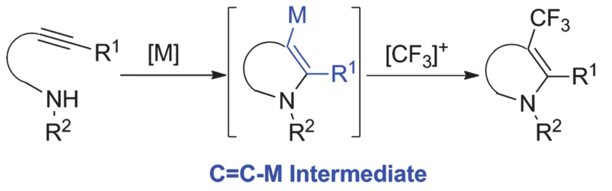
A new strategy for the construction of a C=C–CF_3 subunit has been developed *via* CuBr-catalyzed domino cyclization–trifluoromethylation of homopropargyl amines with Umemoto's reagent. 4-Trifluoromethyl-2,3-dihydro-pyrroliums were produced in high yields. The usefulness of these products has been demonstrated by the transformation of them into various other trifluoromethylated molecules.

Trifluoromethyl-containing compounds are one of the most important classes of selectively fluorinated molecules in pharmaceuticals and agrochemicals because the introduction of trifluoromethyl groups into organic molecules often leads to the significant improvements in their physical, metabolic, and biological properties.[1] For these reasons trifluoromethylation of molecules has attracted great attention of synthetic chemists for more than half century. Tremendous progress has been achieved in recent years in the realm of C–CF_3 bond formation reaction.[2] To date, a wide range of substrates, such as halides,[3] boronic acids,[4] carboxylic acids,[5] alkenes[6] and alkynes,[7] can be converted to trifluoromethyl derivatives efficiently in the presence of transition metal catalysts, and many types of trifluoromethyl-bearing molecules have been synthesized. However, most of them are aromatic and heteroaromatic trifluoromethyl compounds as well as those having sp^3 C–CF_3 bonds. Only a few compounds bearing olefinic trifluoromethyl groups were obtained, most of which used C=C–X as starting material,[4b,5,8] in spite of the fact that carbon–carbon double bonds can easily be converted into many other functional groups. To explore strategies to construct a C=C–CF_3 subunit in a simple and efficient manner is highly demanding.

On the other hand, alkynes are important and easily available compounds in organic synthesis. Transformation of carbon–carbon triple bonds into other functional groups has been well documented.[9] Trifluoromethylation of terminal alkynes has been developed by Qing, affording trifluoromethylalkynes in high yields.[7] However, there is no report on the conversion of triple bonds to trifluoromethylated alkenes with additional functional groups. Metal-catalyzed 5-*endo*-dig cyclization of homopropargyl amines has been well developed to synthesize five-membered N-containing heterocyclic compounds.[10] This cyclization usually involves the formation of a sp^2 C–M bond, however, trapping of a sp^2 C–M bond by a proton is among the most cases.[11] Recently, some examples of exploration of this sp^2 C–M bond to generate a C–C bond have been reported,[12] which would offer a new avenue to fabricate substituted N-containing heterocyclic compounds. As a program aimed at the applications of alkynes in organic synthesis,[13] we found that pyrroles were afforded using amino alkynes.[13d] We envisioned that the cyclization of homopropargyl amines in the presence of triple bond activators will produce an intermediate having a sp^2 C–M bond, which might be trapped by a trifluoromethylation reagent to produce the trifluoromethylated nitrogen-containing cyclic products, an important structural framework found abundantly in both naturally occurring and biologically active compounds (Scheme 1).[14,15] In this communication, we report our preliminary results of the CuBr-catalyzed domino reaction of amino alkynes with Umemoto's reagent, affording trifluoromethyl dihydropyrroliums. The usefulness of the



Scheme 1 Proposed metal-catalyzed cyclization/trifluoro-methylation of amino-alkyne with the CF_3 reagent.

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† This communication is dedicated to Professor Guo-Qiang Lin on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc49059a

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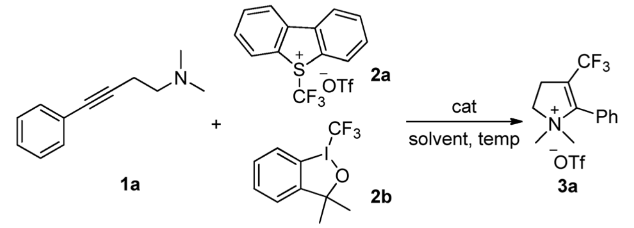
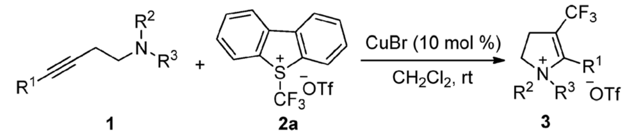
Table 1 Impact of the reaction parameters on the CuBr-catalyzed reaction of homopropargyl amine **1a** with Umemoto's reagent[a]

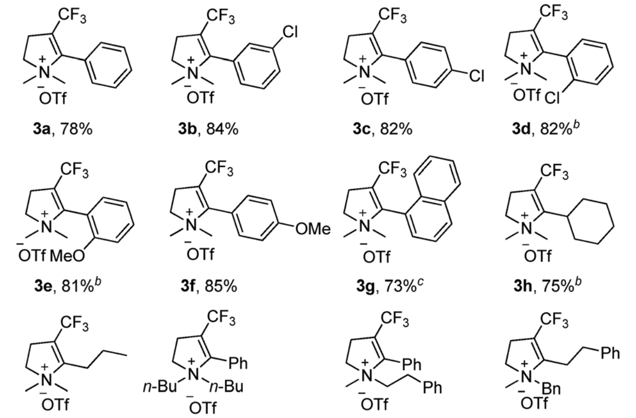


Entry	2	Cat. (mol%)	Temp. (°C)	Solvent	**3a**[b] (%)
1	**2a**	CuBr (100)	80	DMA	79
2	**2b**	CuBr (100)	80	DMA	—
3	**2c**[c]	CuBr (100)	80	DMA	—
4	**2a**	CuBr (100)	80	DMF	75
5	**2a**	CuBr (100)	80	DMSO	50
6	**2a**	CuBr (100)	80	CH_2Cl_2	83
7	**2a**	CuBr (100)	80	DCE	74
8	**2a**	CuBr (100)	80	THF	76
9	**2a**	CuBr (100)	80	EA	76
10	**2a**	CuBr (100)	80	Toluene	Trace
11	**2a**	CuI (100)	80	CH_2Cl_2	78
12	**2a**	CuCl (100)	80	CH_2Cl_2	78
13	**2a**	$CuCl_2$ (100)	80	CH_2Cl_2	62
14	**2a**	AgOAc (100)	80	CH_2Cl_2	12
15	**2a**	$AuCl_3$ (100)	80	CH_2Cl_2	Trace
16	**2a**	CuBr (100)	50	CH_2Cl_2	84
17	**2a**	CuBr (100)	rt	CH_2Cl_2	88
18	**2a**	CuBr (50)	rt	CH_2Cl_2	83
19	**2a**	CuBr (20)	rt	CH_2Cl_2	83 (79)[d]
20	**2a**	CuBr (10)	rt	CH_2Cl_2	80 (78)[d]

[a] Mol ratio: **1a**/**2a** = 1/1.2. [b] Determined by ^{19}F NMR using Umemoto's reagent as internal standard. [c] **2c**: Me_3SiCF_3. [d] Isolated yield shown in parentheses.

Table 2 Substrate scope of CuBr-catalyzed reaction of homopropargyl amines **1** with Umemoto's reagent[a]





[a] Mol ratio: **1**/**2a**/CuBr = 1/1.2/0.1; isolated yield. [b] 20 mol% of CuBr was used. [c] 50 mol% of CuBr was used.

products as versatile trifluoromethyl-containing building blocks has also been revealed.

We initially tested the reaction of N-Ts substituted homopropargyl amines with trifluoromethylation reagents, such as Togni's reagent and Umemoto's reagent, in the presence of CuBr in dimethylacetamide (DMA), respectively, but failed to obtain any desired trifluoromethylated products. The same phenomena were observed when N-Bn substituted homopropargyl amines were used. However, trifluoromethylated product **3a** was produced in 79% yield when *N*,*N*-dimethyl homopropargyl amine **1a** reacted with Umemoto's reagent in the presence of CuBr (Table 1, entry 1). The investigation of the impact of various parameters on the reaction was conducted. It was found that the use of Togni's reagent **2b** made the reaction complicated (entry 2) while no reaction took place when using Me_3SiCF_3 **2c** as the reagent (entry 3). Various solvents were found to be suitable media for the reaction (entries 4–9), except toluene, which suppressed the reaction heavily (entry 10) while dichloromethane (CH_2Cl_2) was identified as the best among those we screened (entry 6), which was selected as the solvent for further investigation. It was found that the anion of copper salts had limited effect on the yield, similar results were obtained when using CuI, CuCl, and CuBr (entries 11 and 12 *vs.* entry 6) while a divalent copper salt such as $CuCl_2$ has lower efficiency (entry 13). Other metals of group 11 such as AgOAc and $AuCl_3$ showed low catalytic activity for the reaction (entries 14 and 15). Some other metal salts such as Fe(acac)$_3$, In(OTf)$_3$ and Zn(OTf)$_2$ failed to promote the reaction (not shown in the table). The yield remained unchanged when the reaction temperature was lowered from 80 °C to 50 °C (entry 16 *vs.* entry 6) but increased slightly to 88% when the reaction was run at room temperature (entry 17 *vs.* entry 6). Importantly, the reaction gave product **3a** in good yield when a substoichiometric amount of CuBr was used (entries 18 and 19). Product **3a** was obtained in 80% yield even when only 10 mol% of CuBr was used (entry 20).

The substrate scope of the reaction was then examined under the optimized reaction conditions (Table 2). A wide range of substrates, not only *N*,*N*-dimethyl homopropargyl amines, but also *N*,*N*-dialkylhomopropargyl amines, are suitable for the reaction, providing the corresponding 4-trifluoromethyl-dihydropyrroliums in high yields (**3a–3i** *vs.* **3j–3l**). The electron withdrawing or electron donating substituents at the *para*, *meta*, or *ortho* position of the phenyl ring on the homopropargyl amines **1** was well tolerated (**3b–3f**). Homopropargyl amines with a 1-naphthalenyl substituent gave product **3g** in low yield due to low conversion of substrates. Pleasingly, the yield of product **3g** increased significantly to 73% by using 50 mol% of CuBr. It is worthwhile to note that the alkyl substituted homopropargyl amines were suitable starting materials in the reaction to produce the desired products in high yields (**3h** and **3i**).

The 4-trifluoromethyl-2,3-dihydro-pyrroliums **3** were demonstrated as the versatile building blocks for the synthesis of other types of important trifluoromethyl-containing organic molecules (Scheme 2). 3-Trifluoromethylbutylamine **4** was obtained in 73% yield when compound **3f** was treated with hydrogen in the presence of Pd/C *via* ring-opening and hydrogenation reactions. 3-Trifluoromethyl pyrrolidine **5** was afforded in 89% yield through debenzylation and hydrogenation reactions of compound **3l**.

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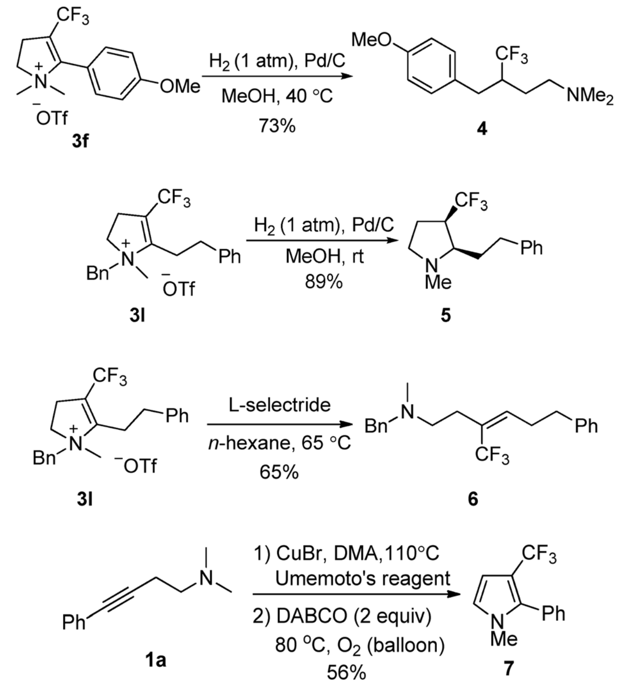
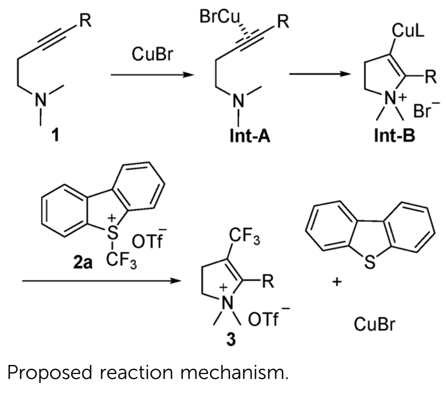


Scheme 2 Transformations of 4-trifluoromethyl-dihydro-pyrroliums **3**.

Furthermore, when compound **3l** was treated with lithium triisobutylborohydride (L-selectride) in *n*-hexane, only a C–N bond cleavage took place, affording a trisubstituted trifluoromethylated alkene **6** in 65% yield with the C═C bond untouched. 3-Trifluoromethylpyrrole **7** was also obtained in 56% yield by a one-pot reaction of homopropargyl amine **1a** and Umemoto's reagent followed by addition of DABCO under oxygen balloon. It should be noted that the formation of compound **7** involved cyclization, trifluoromethylation, demethylation, and aromatization reaction.

A possible reaction mechanism was proposed on the basis of our experimental results and the literature (Scheme 3).[4b,10,17] Coordination of CuBr with a triple bond of homopropargyl amine **1** produces **Int-A**, which undergoes cyclization to give intermediate **Int-B** bearing a C–Cu bond.[16] Final trifluoromethylated product **3** is afforded when the **Int-B** reacts with Umemoto's reagent.[4b]

In conclusion, we developed a new strategy for the construction of a C═C–CF_3 moiety through domino reaction of cyclization–trifluoromethylation of homopropargyl amines under Cu(I)-catalysis, affording 4-trifluoromethyl-2,3-dihydropyrroliums as the diverse trifluoromethyl-containing building blocks in high yields. The versatile utility of these products has been demonstrated by the transformation of products into different types of trifluoromethylated molecules. Further studies on the reaction mechanism, the extension of the reaction scope as well as the utilities of the products in organic synthesis are currently underway in our lab.



Scheme 3 Proposed reaction mechanism.

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17 The reaction of CuBr with Umemoto's reagent in CH_2Cl_2 was performed, but no reaction occurred in 1 hour as monitored by ^{19}F NMR. Then homopropargyl amine **1a** was added and product **3a** was obtained in 69% yield in 10 hour.