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# A Facile Parallel Synthesis of Trifluoroethyl-Substituted Alkynes**

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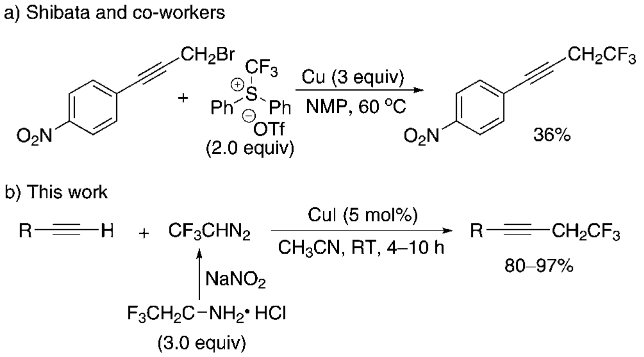
The physicochemical and biological properties of an organic compound are profoundly modified by the presence of fluorine functional groups, which alter the steric, electronic, lipophilic, and metabolic characteristics of the compound. The incorporation of fluorinated moieties into organic molecules has captured the attention of synthetic chemists over the past decades.[1] As a reactive intermediate, 2,2,2-trifluorodiazoethane is an attractive C2 synthon for the construction of fluorine-containing building blocks. The earlier studies involving this reagent primarily focused on noncatalytic reactions.[2] These methods usually suffer from relatively harsh reaction conditions and limited substrate scope. To overcome these problems, recent research has paid more attention to metal-catalyzed transformations of 2,2,2-trifluorodiazoethane. For instance, the Simonneaux and Komarov groups reported metal-catalyzed cyclopropanation reactions of gaseous $F_3CCHN_2$ with various olefins.[3] Carreira and co-workers demonstrated the catalytic generation of 2,2,2-trifluorodiazoethane in situ from $CF_3CH_2NH_2{\cdot}HCl$.[4] Several metal catalysts have been found to be compatible with the diazotization reaction, allowing a tandem transformation to take place in aqueous media. However, the generation of $C_{sp^3}$–$CH_2CF_3$ or $C_{sp^2}$–$CH_2CF_3$ bonds has been the focus of nearly all such studies.[5] In sharp contrast, the formation of $C_{sp}$–$CH_2CF_3$ bonds through simple trifluoroethylation of terminal alkynes has not been reported to date, and still remains an interesting challenge.

A survey of the literature reveals that the use and preparation of trifluoroethyl-substituted alkynes is extremely rare, which likely correlates with the absence of practical general methods for their synthesis. Only one recent report by Shibata and co-workers has addressed the trifluoromethylation of 3-(4′-nitrophenyl)propargyl bromide with [$CuCF_3$] species, which were generated in situ from an electrophilic trifluoromethylating reagent and a stoichiometric amount of copper, but the desired product was obtained in only 36 % yield (Scheme 1 a).[6] Herein, we report our efforts in developing a direct catalytic trifluoroethylation of terminal alkynes by using 2,2,2-trifluorodiazoethane (Scheme 1 b). This cross-coupling reaction can be conducted under mild conditions without the need for additional base or ligands. Furthermore, the ease of preparation and workup allows for the quick and efficient parallel synthesis of a broad variety of trifluoroethylated alkynes. These products, which bear a $CH_2CF_3$ group in the propargyl position, are versatile precursors for the synthesis of other types of fluorinated molecules. Additionally, both experimental and theoretical analyses indicate that this trifluoroethylation could proceed by a concerted $C_{sp}$–H insertion process.



**Scheme 1.** Synthesis of trifluoroethyl-substituted alkynes. NMP = *N*-methyl-2-pyrrolidone, OTf = trifluoromethanesulfonate.

In general, reactions of terminal alkynes with diazo compounds lead to cyclopropenation or $C_{sp}$–H insertion.[7] The reaction course strongly depends on the nature of the metal and the catalyst structure. For example, the groups of Pérez[8a] and Doyle[8c] described cyclopropenation reactions of alkynes with diazoesters catalyzed by $Cu^I$ or $Rh^{II}$ complexes, whereas the groups of Fu,[8b] Fox,[8d] and Wang[8e–i] reported the cross-coupling of alkynes with diazo compounds catalyzed by $Cu^I$ or $Pd^{II}$ to afford the corresponding products. Very recently, Morandi and Carreira disclosed a rhodium-catalyzed cyclopropenation of alkynes by $CF_3CHN_2$ generated in situ from $CF_3CH_2NH_2{\cdot}HCl$ in aqueous media.[4b] Based on these important precedents, we examined the ability of various $Cu^I$ and $Cu^{II}$ salts to catalyze the trifluoroethylation of phenylacetylene **1a** using gaseous $CF_3CHN_2$. A preliminary result was obtained using CuI as a catalyst under mild conditions to provide the corresponding trifluoroethylated product **2a** in 63 % yield without the use of extra base or ligands. However, a disadvantage of this method is that it requires the use of a large excess of $CF_3CH_2NH_2{\cdot}HCl$ (5–8 equiv). In order to use gaseous $CF_3CHN_2$ more efficiently, we needed to set up a recycling system. After the reactor, a storage balloon was placed to trap and reuse the escaping gaseous $CF_3CHN_2$. Gratifyingly, examination of the same test reaction with the recycling system in place revealed that the yield can be significantly improved to 85 % and that the amount of $CF_3CH_2NH_2{\cdot}HCl$ can be lowered to three equivalents. Furthermore, a multireactor setup has been designed to provide an integrated system for simultaneously running

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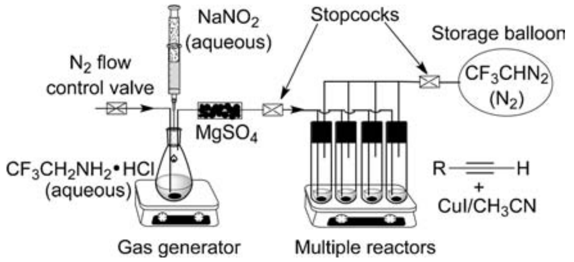
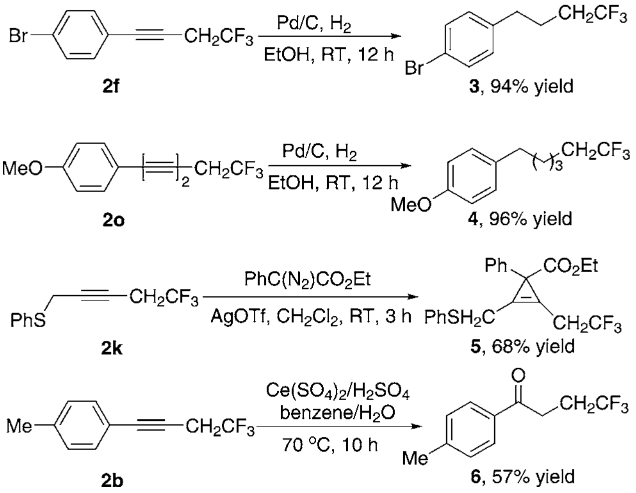


**Figure 1.** Setup for the catalytic cross-coupling trifluoroethylation of terminal alkynes.

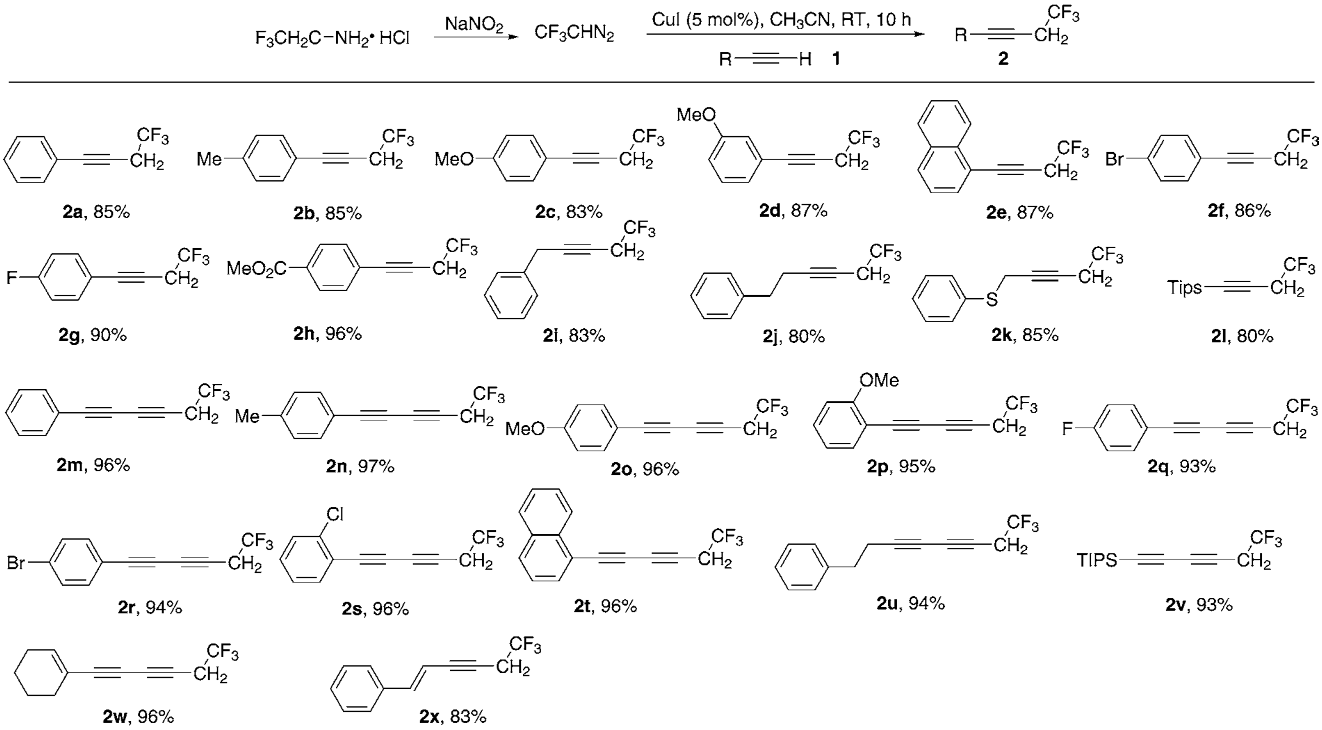
multiple reactions. Using such a system, trifluoroethylated alkyne **2a** was obtained in 83–92 % yield (Figure 1).

Based on the studies described above, we explored the scope of the cross-coupling reaction of gaseous $CF_3CHN_2$ with terminal alkynes **1a–x**. Thus, constructing a flow setup (as shown in Figure 1, four reactors in parallel) for the continuous gaseous $CF_3CHN_2$ generation/trifluoroethylation sequence, we could prepare a series of trifluoroethylated alkynes **2a–x** (Scheme 2). Although a standard reaction time of 10 h was chosen, most of the reactions were complete within 4 h. Alkynes with aryl, alkyl, phenylthio, or silyl substituents are all suitable substrates, providing the isolated trifluoroethylated products **2a–l** in 80–96 % yield. Furthermore, we found that various terminal 1,3-diynes react smoothly with gaseous $CF_3CHN_2$ under the same reaction conditions to furnish the corresponding products **2m–v** in excellent yields. Two enynes also worked well in the cross-coupling reactions to afford the desired adducts **2w** and **2x**. It is noteworthy that the reactions are very clean; in all cases, side products, such as cyclopropenes from alkynes and $CF_3CHN_2$, self-coupling products of alkynes, and allene isomers of the trifluoroethylated adducts, were not observed.

Trifluoroethylated alkynes are also versatile synthetic intermediates and can be readily transformed into highly functionalized organofluorine compounds that are otherwise difficult to access (Scheme 3). For example, direct hydrogenation of **2f** and **2o** using a Pd/C catalyst and $H_2$ at atmospheric pressure gave rise to the corresponding fluorinated alkanes **3** and **4** in high yields. Reaction of **2k** with ethyl phenyldiazoacetate in the presence of AgOTf delivered the



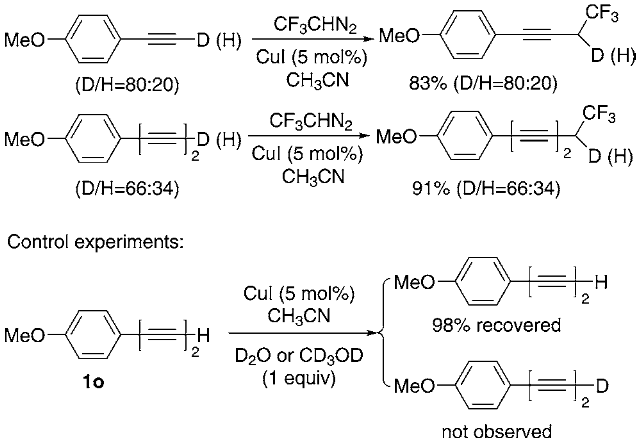
**Scheme 3.** Further synthetic transformation of products.



**Scheme 2.** Scope of the Cu-catalyzed trifluoroethylation of terminal alkynes with $CF_3CHN_2$. Reactions conducted in four parallel stirred reactors. Yields shown are of isolated products from an average of two runs. TIPS = triisopropylsilyl.

highly substituted cyclopropene **5** in 68% yield. Also, treatment of trifluoroethylated alkyne **2b** with $Ce(SO_4)_2$ and concentrated $H_2SO_4$ at 70°C afforded the corresponding ketone **6** in moderate yield. These promising results indicate that the present protocol provides a reliable and rapid approach for the synthesis of diverse $CH_2CF_3$-containing compounds.

The reaction mechanism of the trifluoroethylation could involve the insertion of a carbene into a $C_{sp}$–H bond, a key process in this type of cross-coupling that has been reasonably implicated, but remains largely unproven.[7] To obtain more information about our reaction, we conducted the CuI-catalyzed cross-coupling of deuterium-labeled terminal alkynes with gaseous $CF_3CHN_2$ under the standard reaction conditions (Scheme 4, top). It was found that the ratio of deuterium to hydrogen at the propargyl positions in the corresponding products is identical to that in the alkyne substrates. Subsequently, we performed several control experiments. While a mixture of substrate **1o** and CuI was shown to be homogeneous by $^1H$ NMR analysis in $CD_3CN$, copper acetylide was not detected on the timescale of the NMR experiment. Moreover, we did not observe any incorporation of deuterium at the propargyl position when $D_2O$ or $CD_3OD$ were used as additives (Scheme 4, bottom). These experimental results provide supportive evidence that the trifluoroethylation could proceed by a $C_{sp}$–H insertion process.



*Scheme 4.* Isotopic labeling and control experiments.

To shed some light on the mechanism, we carried out a frontier molecular orbital analysis[9] for the model reactants of propyne (pp) and copper carbenoid (cc; Figure 2a). The energy gap of $HOMO_{pp}$–$LUMO_{cc}$ is much smaller than that of $HOMO_{cc}$–$LUMO_{pp}$ (11.9 vs. 17.2 eV), which indicates that the most favored orbital interaction is between the ethyne moiety of the propyne and the p* orbital of the Cu=C coordinate bond in the copper carbenoid. DFT calculations using the B3LYP/6-31G(d) method[10] were also performed with a view to delineating the details of the putative insertion of carbenes into the $C_{sp}$–H bond. The computed path of the model reaction is shown in Figure 2b. The barrierless [2+2] cycloaddition between copper carbenoid and propyne was found to be strongly exothermic, indicating that the generation of metallacyclobutene intermediate (**IN-1**) is more favorable than that of **TS** in the cyclopropenation. This prediction is consistent with our experimental results. From **IN-1**, the critical four-membered-ring transition state (**TS-1**) is identified with an energy barrier of 26.8 kcal mol$^{-1}$. Although significant, this energy requirement is more than compensated for by the energy released in the preceding steps. Through **TS-1**, the intermediate **IN-2** is generated. Finally, the formation of the cross-coupling product from the intermediate **IN-2** proceeds through a concerted 1,2-hydride shift (**TS-2**) with an energy barrier of 15.0 kcal mol$^{-1}$. Therefore, the overall process for the cross-coupling is exothermic and thermodynamically favorable.

In summary, we have disclosed a direct and efficient copper(I)-catalyzed trifluoroethylation of terminal alkynes employing gaseous $CF_3CHN_2$ under mild conditions without

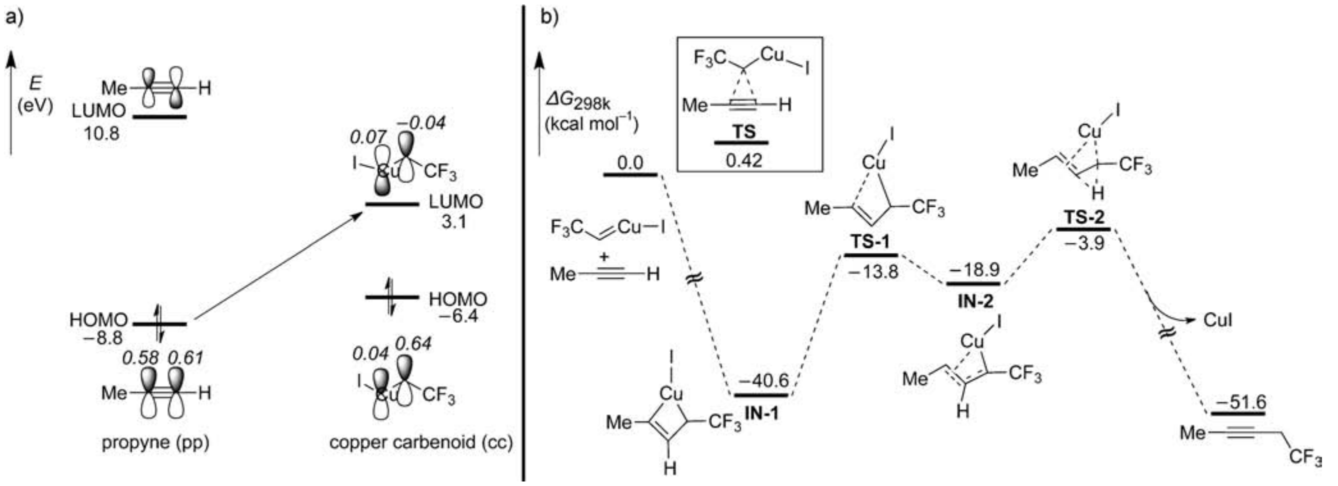


*Figure 2.* Calculations for the model reaction of a copper carbenoid with propyne. a) Frontier molecular orbital diagram. Orbital coefficients are given in italics. b) DFT-computed energy surfaces. Reaction coordinate calculated using the B3P86/CPCM basis set: SDD for Cu, Lanl2DZ for I, and 6-311+G(2d,p) for other atoms.

the need for additional base or ligands. Most significant of all is the ease of execution, which enables the rapid synthesis of a wide number of trifluoroethylated alkynes in parallel. The presence of an ethyne moiety in the products also allows for subsequent conversion to more functionalized trifluoroethylated compounds. Moreover, we present the first piece of evidence for the mechanism of the insertion of a carbene into a $C_{sp}$–H bond in a copper-catalyzed cross-coupling of terminal alkynes with diazo compounds.

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