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Practical Methods for the Synthesis of Trifluoromethylated Alkynes: Oxidative Trifluoromethylation of Copper Acetylides and Alkynes

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Dedicated with much respect to Professor Alexandre Alexakis, an inspiring mentor.

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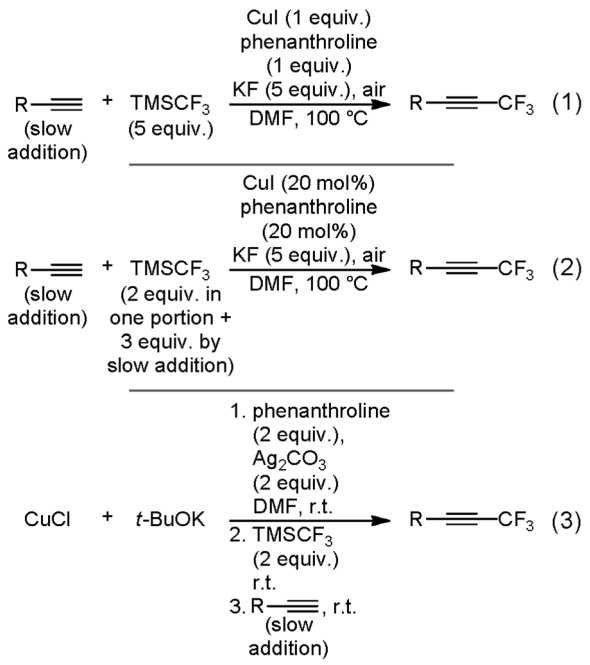
Abstract: Two practical and complementary methods are reported for the synthesis of trifluoromethylated alkynes. The first one, a mix-and-stir process, is based on the oxidative trifluoromethylation of readily available and bench-stable copper acetylides while the second one, which displays a broad substrate scope and has several advantages over existing procedures, is based on the oxidative copper-catalyzed direct trifluoromethylation of terminal alkynes. Both reactions provide user-friendly processes for the synthesis of trifluoromethylated acetylenes which can be easily obtained from readily available starting materials.

Keywords: copper; copper acetylides; oxidative cross-coupling; trifluoromethylated alkynes; trifluoromethylation

Introduction

Trifluoromethylated compounds are of widespread importance in nearly every sector of the chemical industry as well as in pharmaceutical and agrochemical sciences and for the preparation of liquid crystals, dyes or polymers.[1] As with all fluorine-containing derivatives, the incorporation of the trifluoromethyl motif, which is absent in Nature,[2] into an organic molecule results in deep modifications of its chemical and physical properties including, among others, its basicity, hydrophobicity, conformation, binding selectivity or metabolic stability.[3] Because of these unique properties of the trifluoromethyl group, tremendous efforts have been devoted recently to the development of new processes that allow for the introduction of a CF_3 subunit – mostly to an aromatic ring – with surgical precision and remarkable efficiency.[4] Besides the development of these new trifluoromethylation processes, new trifluoromethylated building blocks are also emerging. Trifluoromethylated alkynes clearly fall into this category and have recently found various applications in medicinal chemistry.[1d,5] In addition, they were shown to be excellent precursors for the synthesis of various trifluorinated building blocks such as arenes,[6] alkenes,[7] allenes,[8] enones,[9] enol esters,[10] methyl ketones,[7g,8a] Pauson–Khand adducts[11] or heterocycles.[12]

Despite their apparent simplicity, the preparation of these building blocks is however far from being trivial. In most cases, they are indeed prepared by a palladium-catalyzed cross-coupling reaction starting from trifluoropropynylmetal reagents[13] or by their reaction with electrophiles,[14] by dehydrohalogenation from halogenated trifluoromethylalkenes[15] or by

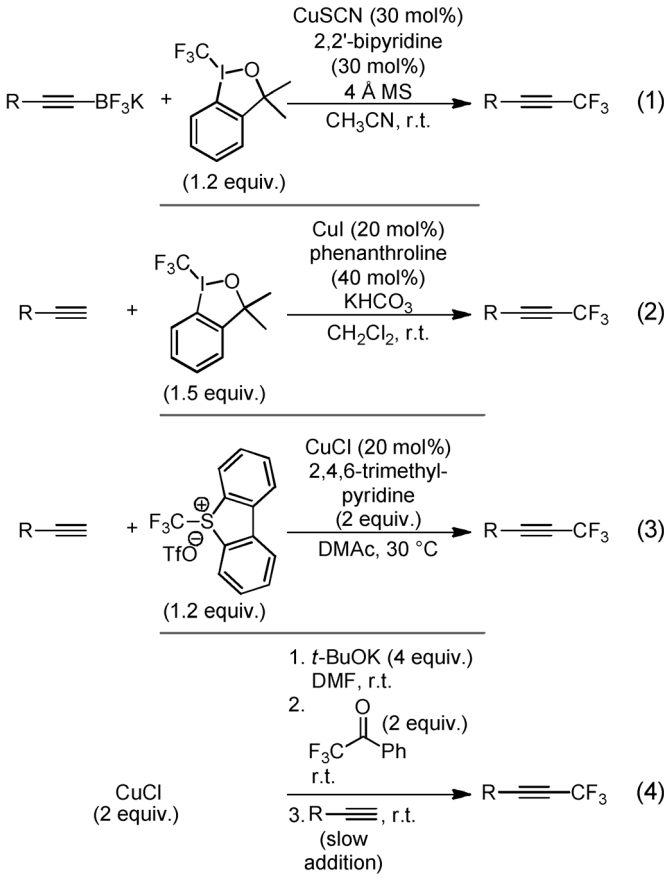


Scheme 1. Direct trifluoromethylation of alkynes with the Ruppert–Prakash reagent.

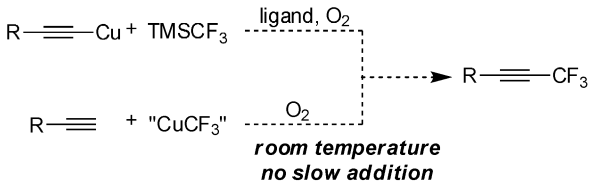
a typically low-yielding electrophilic trifluoromethylation of lithium acetylides.[16]

The low efficiency of these reactions and/or the limited availability of the starting materials required have motivated many research groups to engage in the development of more efficient and straightforward processes. This quest for direct methods for the trifluoromethylation of alkynes recently resulted in the development of innovative and more practical routes to trifluoromethylated acetylenes. In this context, Qing, capitalizing on Stahl's oxidative cross-coupling between terminal alkynes and amides,[17] reported in 2010 the first direct trifluoromethylation of alkynes using a copper-mediated oxidative cross-coupling with Ruppert–Prakash reagent [Scheme 1, Eq. (1)].[18,19] By using stoichiometric amounts of copper iodide and phenanthroline in the presence of potassium fluoride in DMF at 100 °C under air, various trifluoromethylated alkynes could be obtained in good yields provided that the alkyne was slowly added by syringe pump. Although this protocol represented a significant breakthrough, it still suffered from severe limitations including the use of stoichiometric amounts of both the copper salt and the ligand, of an excess of $TMSCF_3$, and the requirement for potassium fluoride, high temperatures – which is quite critical due to the volatility of most trifluoromethylated acetylenes – and, of course, slow addition of the alkyne. These limitations were next, at least partially, addressed by the same group who reported improved procedures based on catalytic [Scheme 1, Eq. (2)][20] or room temperature [Scheme 1, Eq. (3)][21] conditions. While the second and third generation procedures provided an improved access to trifluoromethylated alkynes, they still suffer from important limitations which make them less practical than one could wish, especially on a larger scale.

Following these developments, alternative procedures have been reported later on based either on the use of alkyne surrogates such as potassium alkynyltrifluoroborates [Scheme 2, Eq. (1)],[22] and/or alternative trifluoromethylating agents such as Togni's benziodoxole[20,23] [Scheme 2, Eqs. (1) and (2)] or Umemoto's sulfonium [Scheme 2, Eq. (3)].[24] A remarkable alternative process for the *in situ* generation of trifluoromethylcopper was finally reported recently based on the reaction of $K[Cu(O\text{-}t\text{-}Bu)_2]$ – generated by reaction of copper(I) chloride and two equivalents of potassium *tert*-butoxide – with trifluoroacetophenone [Scheme 2, Eq. (4)].[25] Quite impressively, the reaction which, however, required the generation of trifluoromethylcopper prior to its reaction with the alkyne, provided the desired trifluoromethylated acetylenes at room temperature within one hour, although a slow addition of the alkyne was still required in order to minimize its Glaser–Hay dimerization.



Scheme 2. Other copper-mediated syntheses of trifluoromethylated alkynes.



Scheme 3. Strategies for the development of practical processes for the synthesis of trifluoromethylated alkynes.

While these developments reported in the last four years clearly had a deep impact on the chemistry of trifluoromethylated alkynes, which can now be prepared by direct trifluoromethylation of alkynes or synthetic equivalents,[26] all these procedures still display limitations, the most common one being the slow addition of the alkyne, which renders these processes less practical on a large scale, the use of complex reagents and/or the use of stepwise processes.

In an attempt to address some of the limitations associated with these procedures, we envisioned two strategies as depicted in Scheme 3 for the design of practical and user-friendly methods for the synthesis of trifluoromethylated alkynes that could proceed at room temperature and without the need for slow addition of the alkynyl partner.

The first one is based on the oxidative trifluoromethylation of readily available and bench-stable copper acetylides while the second one relies on $[Cu(CF_3)]$ species for the oxidative trifluoromethylation of terminal alkynes.[27] Results obtained with these two complementary procedures are reported herein.

Results and Discussion

Based on our recent interest in the reactivity of copper acetylides under oxidative conditions,[28] we envisioned that they could represent most useful reagents for the synthesis of trifluoromethylated alkynes. Indeed, we have shown during the last two years that these remarkably stable polymeric reagents, which can be readily prepared on a multigram scale by simply adding a terminal alkyne to a solution of copper(I) iodide in a mixture of ammonia/ethanol/water followed by filtration, can be activated in the presence of oxygen and a ligand and transfer their alkyne subunit to a wide range of nucleophiles. After the success we met with this oxidative umpolung strategy for the preparation of ynamides,[28a] ynimines,[28b] alkynylphosphonates[28a] and alkynylphosphine-boranes,[28d] we envisioned that we could extend this strategy to the formal alkynylation of the trifluoromethyl carbanion that could be generated *in situ* from the Ruppert–Prakash reagent. Among other benefits that we envisioned from the use of these alkynylcopper complexes, the high reactivity of intermediate species resulting from their oxidation should circumvent the need for the *in situ* activation of $TMSCF_3$ with a source of fluoride and the need for high temperatures. In addition, the slow dissolution of these copper acetylides in the course of the reaction should allow for the development of a mix-and-stir process without slow addition of one reagent.

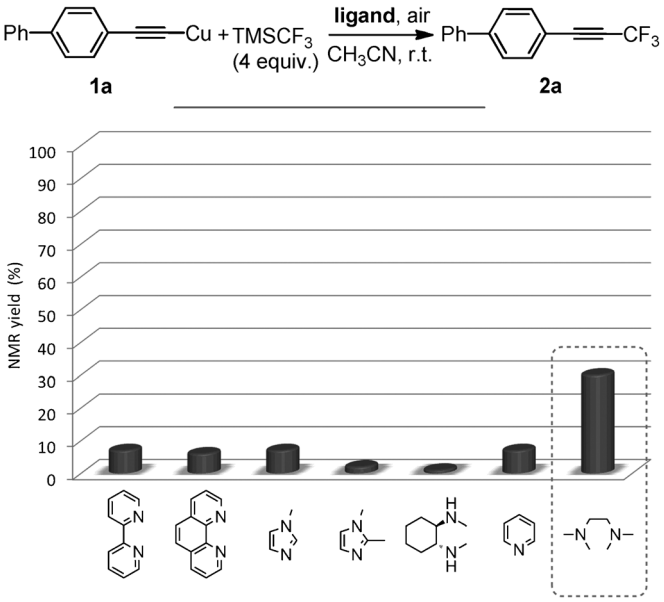


Figure 1. Comparative efficiency of N-ligands for the trifluoromethylation of *para*-biphenylylethynylcopper. *Standard conditions:* 0.5 mmol **1a**, 2.0 mmol $TMSCF_3$, 0.5 mmol ligand (if bidentate) or 1.0 mmol ligand (if monodentate), 2 mL CH_3CN, air, room temperature, 24 h. ^{19}F NMR yields determined using 0.5 mmol of 1*H*,1*H*,8*H*,8*H*-octafluoro-3,6-dioxaoctane-1,8-diol as an internal standard.

With this goal in mind, we first evaluated the efficiency of a set of nitrogen ligands to promote the trifluoromethylation of *para*-biphenylylethynyl-copper **1a** with Ruppert–Prakash reagent (Figure 1). At this first stage of the optimization, acetonitrile was arbitrarily chosen as the solvent, the temperature was set at room temperature, molecular oxygen was chosen as the oxidant for obvious practical reasons (low cost, generation of water as the by-product…) and an excess (four equivalents) of $TMSCF_3$ was used to minimize the oxidative dimerization of **1a**. Various representative mono- and bidentate ligands shown in Figure 1 were then evaluated under these standard conditions and while all of them gave rather low yields of the desired trifluoromethylated alkyne **2a** due to the homodimerization of **1a** being faster than its trifluoromethylation, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was found to be by far superior to all other ligands envisioned.

We then moved to the optimization of the solvent used for this reaction using TMEDA as the ligand. Various solvents with representative polarities (aceto-

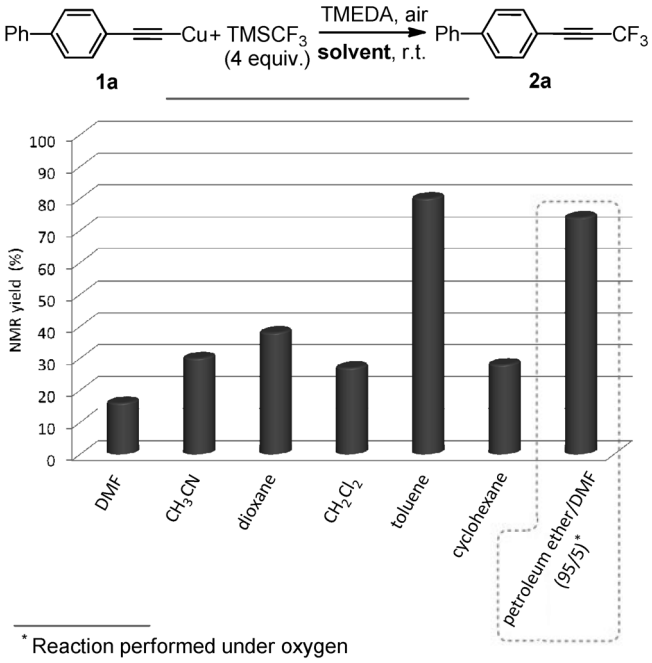


Figure 2. Comparative efficiency of solvents for the trifluoromethylation of *para*-biphenylylethynylcopper. *Standard conditions:* 0.5 mmol **1a**, 2.0 mmol $TMSCF_3$, 0.5 mmol TMEDA, 2 mL solvent, air, room temperature, 24 h. ^{19}F NMR yields determined using 0.5 mmol of 1*H*,1*H*,8*H*,8*H*-octafluoro-3,6-dioxaoctane-1,8-diol as an internal standard.

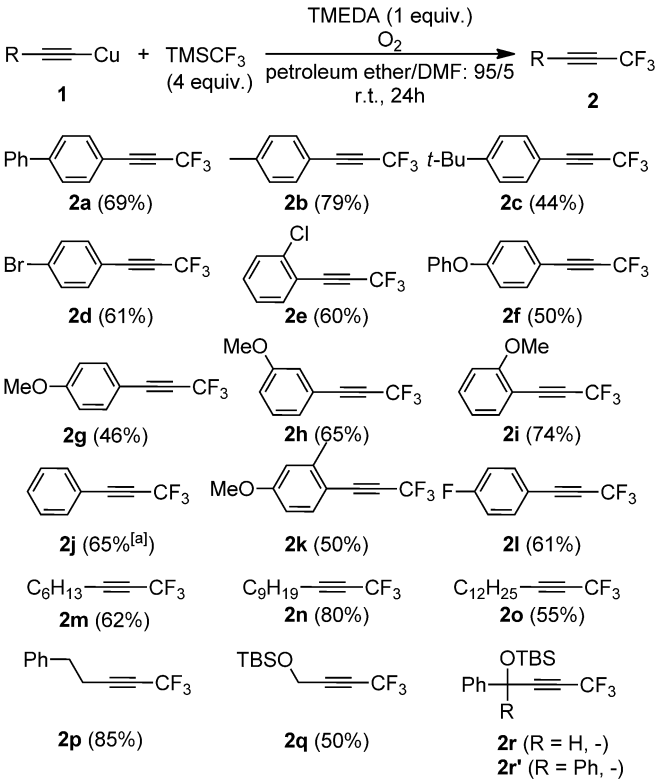


Figure 3. Scope of the oxidative trifluoromethylation of copper acetylides. Yields given correspond to isolated yields of pure products unless otherwise stated.

nitrile, dichloromethane, toluene, dioxane, DMF, cyclohexane) were therefore first screened: as shown by the results collected in Figure 2, toluene proved to be by far the best solvent and allowed for the formation of the desired trifluoromethylated alkyne **2a** in 80% yield (^{19}F NMR yield). While this solvent was shown to be remarkably efficient at this stage of the optimization, we were, however, concerned that its use with other copper acetylides would be problematic due to the low boiling points of most trifluoromethylated alkynes which are, in most cases, below that of toluene. To avoid problems associated with the isolation of the desired trifluoromethylated alkynes, we therefore decided to switch to mixtures of petroleum ether and DMF. Among all mixtures evaluated, a 95/5 ratio of petroleum ether/DMF was found to be optimal and allowed for the formation of **2a** in 74% yield (^{19}F NMR yield, 69% isolated yield), provided that the reaction was run under oxygen rather than air (69% *vs.* 51% yield). While this yield was slightly lower than the one obtained in toluene, we decided to stick with the use of a petroleum ether/DMF solvent mixture due to the easier isolation of trifluoromethylated alkynes with this system.

With the optimized conditions in hand, we next focused on the scope of the reaction by studying the trifluoromethylation of various representative copper acetylides **1**. Results of these studies are collected in Figure 3. As shown by these results, the corresponding trifluoromethylated alkynes **2** could be obtained in moderate to good yields in most cases, even though the homodimerization of the starting alkynylcopper reagents **1** could not be completely suppressed.

The reaction tolerates a wide range of substituents on the starting copper acetylides and was found to be especially convenient for the preparation of aryl-substituted trifluoromethylated alkynes (**2a**–**2l**), which could be easily obtained regardless of the substitution pattern of the starting reagent or the presence of electron-withdrawing/electron-donating substituents. The trifluoromethylation was also amenable to the preparation of alkyl-substituted trifluoromethylated alkynes such as **2m**–**2q**, which could also be obtained in moderate to good yields. In some cases however, some of the corresponding copper acetylides were found to lack the characteristic polymeric organization of these reagents. In these cases, they were found to be highly sensitive to oxygen and to dimerize too rapidly to be used for the trifluoromethylation, which accounts for the impossibility to form trifluoromethylated alkynes such as **2r** and **2r′** using this procedure.

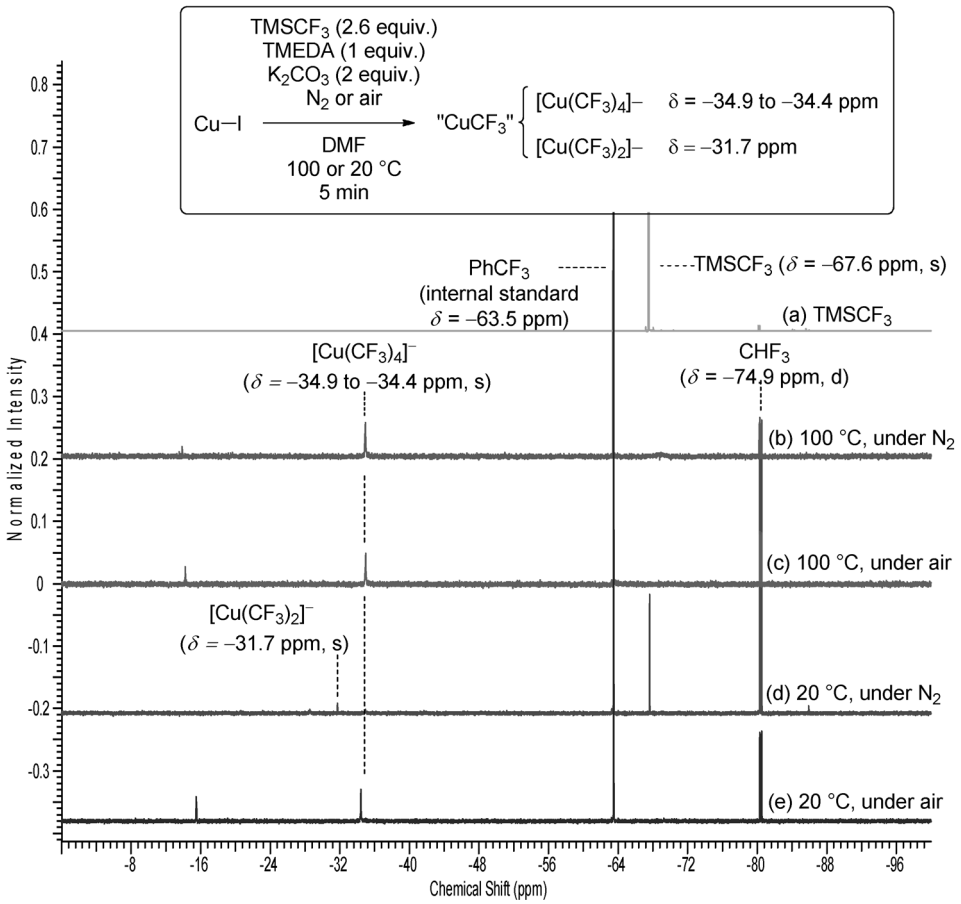


Figure 4. ^{19}F NMR (376 MHz) monitoring of the formation of $[Cu(CF_3)_2]^-$ and $[Cu(CF_3)_4]^-$ at 100 and 20 °C under nitrogen or air, using trifluorotoluene as an internal standard.

Compared to previously reported procedures for the synthesis of trifluoromethylated acetylenes, one of the main advantages of the one reported here lies in its operational simplicity. Indeed, the reaction readily proceeds at room temperature without the need for purified solvents and slow addition of one reagent. From a practical point of view, the completion of the trifluoromethylation is remarkably easy to detect due to the self-indicating nature of the reaction which turns from a yellow heterogeneous suspension to a deep green homogeneous solution upon completion.

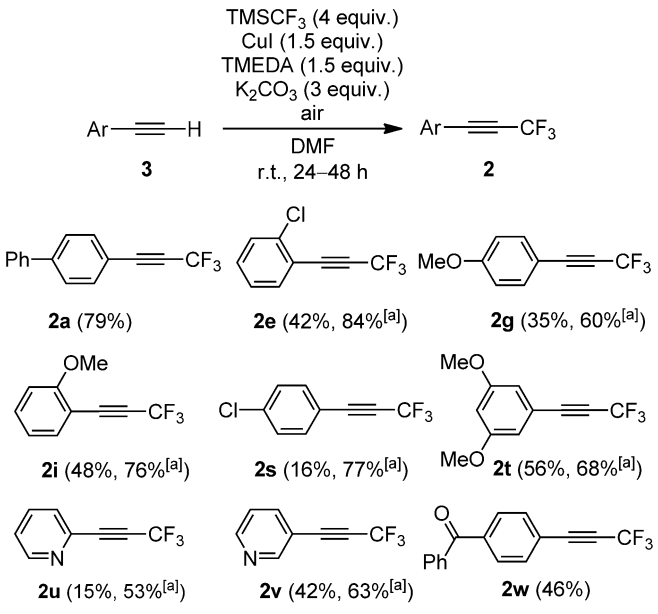
From a mechanistic perspective, it is also interesting to note that while all other copper-mediated trifluoromethylation of alkynes reported to date involve the generation of a trifluoromethylcopper complex prior to its reaction with the alkyne, the order of the elemental steps is reversed in this process, which shows that coordination of the trifluoromethyl anion to copper prior to the alkyne is not strictly required for a clean cross-coupling.

In parallel to these studies, we also investigated the possibility of generating trifluoromethylcopper complexes that could be used for the direct trifluoromethylation of terminal alkynes. In addition to complement our first generation synthesis, the goal of these studies was to expand the scope of the direct trifluoromethylation of alkynes based on trifluoromethylcopper complexes that would be readily prepared and that would show greater reactivity than the previously reported phenanthroline ligated ones. Based on the remarkable efficiency of TMEDA, a much cheaper ligand than 1,10-phenanthroline, to promote the trifluoromethylation of copper acetylides, we envisioned that TMEDA-chelated trifluoromethylcopper complexes could avoid the limitations met with phenanthroline.

Bearing in mind that a practical and functional group-tolerant procedure was highly desirable, as in the first-generation method described above, the use of a non-fluoride base such as K_2CO_3 was preferred. Upon mixing a copper(I) salt, TMEDA, K_2CO_3 and $TMSCF_3$ in DMF, the formation of the active TMEDA-chelated trifluoromethylcopper complex was monitored by ^{19}F NMR (Figure 4). Extensive variations of the nature of the copper(I) salt, of the reactant stoichiometry and of the solvent concentration led to the optimal reaction conditions indicated in Figure 4. For the sake of conciseness, only the optimi-

zation of the reaction temperature is shown in spectra (b) to (e) starting from 100 °C, under a nitrogen atmosphere (spectrum b) or under air (spectrum c), by analogy with the reaction conditions reported by Qing.[18] After 5 min, all the Ruppert–Prakash reagent has disappeared and two new sets of signals could be observed at −34.9 (s) and −80.4 (d, $J = 80.5$ Hz, CHF_3) ppm. The origin of the former could be attributed to the copper(III) complex $[Cu(CF_3)_4]^-$,[29] which is known to be a trifluoromethylation agent stable up to 110 °C.[29c] Running the reaction under a nitrogen atmosphere at 20 °C for 5 min led cleanly to a singlet at −31.7 ppm, ascribed to $[Cu(CF_3)_2]^-$,[29] together with some remaining Ruppert–Prakash reagent ($\delta = -67.6$ ppm, s) (spectrum d). Finally, under an air atmosphere at room temperature, the ^{19}F NMR profile was identical to the one recorded at 100 °C (spectra e and c, respectively), the copper(III) complex $[Cu(CF_3)_4]^-$ resulting from the oxidation of the air-sensitive $[Cu(CF_3)_2]^-$ by oxygen.[29]

These operationally very simple reaction conditions were then used for the direct trifluoromethylation of a variety of terminal aryl- and alkylalkynes **3e–ag** (Figure 5 and Figure 6). It should be noted here that the alkyne was added in one portion a few minutes after the formation of the trifluoromethylcopper complex, in opposition to previous procedures requiring a syringe pump addition of a DMF solution of the alkyne over 4 h.[18]

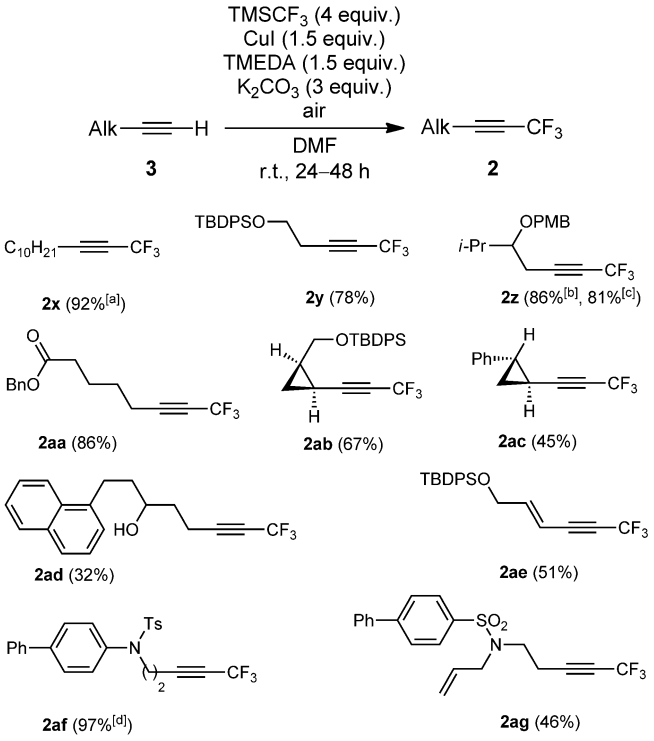


[a] ^{19}F NMR yields determined using trifluorotoluene as an internal standard.

Figure 5. Scope of the oxidative trifluoromethylation of terminal aryl alkynes. Yields given correspond to isolated yields of pure products unless otherwise stated.

Fair to good yields of the desired trifluoromethylated arylalkynes **2a**, **2e**, **2g**, **2i** and **2s–w** were obtained (Figure 5). Electron-poor and electron-rich aromatic and heteroaromatic alkynes led to good yields of the desired trifluoromethylated products, although the isolated yields of **2e**, **2g**, **2i** and **2s–v** were much lower than their corresponding ^{19}F NMR yields, due to their extreme volatility. Interestingly, diaryl ketones were also tolerated, as demonstrated by the synthesis of **2w**, which was however isolated in moderate yield.

Most interestingly, alkynes substituted by alkyl groups led to excellent yields of the desired products even on a gram scale, thereby filling a major gap in current trifluoromethylation processes (Figure 6). Linear alkyl substituents such as in **3x** led to 92% yield of **2x**. Silyl or benzyl ethers are also tolerated (**2y**, 78% and **2z**, 86%) as well as benzyl esters (**2aa**, 86%). 1,2-*cis*- and *trans*-disubstituted cyclopropylalkynes led to moderate yields of the corresponding trifluoromethylated products **2ab** and **2ac**. Homopropargylic alcohol **3ad** led to the desired product **2ad** (32%) demonstrating that free hydroxy groups are compatible with these reaction conditions. 1,3-Enynes



[a] On a 3.0 mmol scale.
[b] On a 1.7 mmol scale.
[c] On a 3.4 mmol scale.
[d] On a 2.8 mmol scale.

Figure 6. Scope of the oxidative trifluoromethylation of terminal alkyl alkynes. All reactions are run on a 0.5 mmol scale unless otherwise stated. Yields given correspond to isolated yields of pure products.

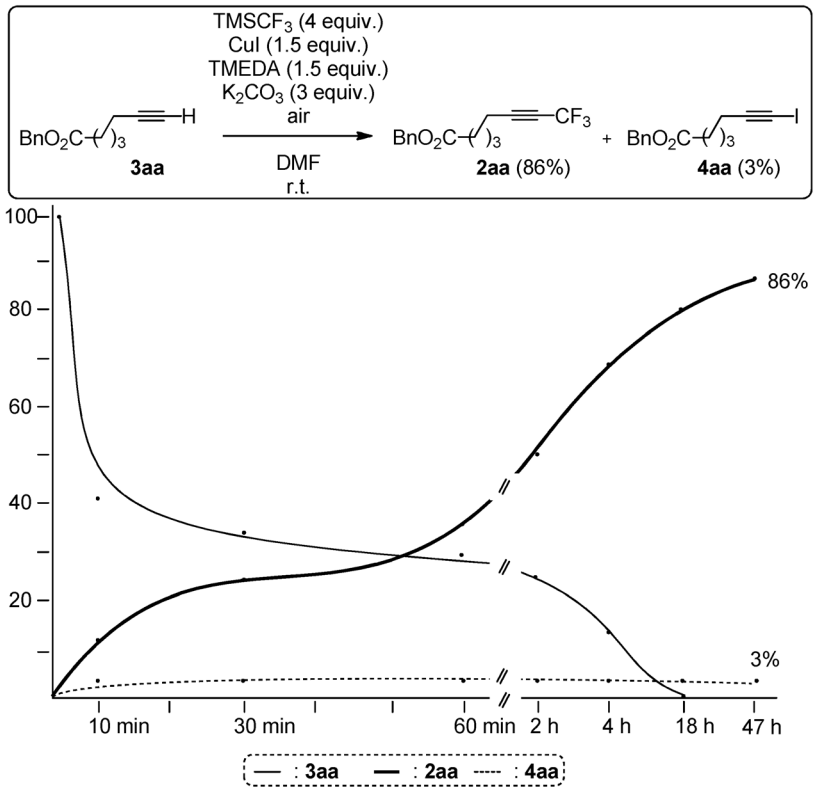


Figure 7. Kinetic profile of the trifluoromethylation reaction of **3aa** leading to **2aa** and **4aa**, determined by HPLC analysis of triplicate experiments, using 1,2-dimethylnaphthalene as an internal standard.

are also suitable substrates, as shown with the synthesis of trifluoromethylated enyne **2ae** (51%). Homopropargylic sulfonamides such as **3af** and **3ag** were also evaluated as substrates and delivered moderate to excellent yields of the corresponding trifluoromethylated alkynes.

From a mechanistic perspective, recent DFT investigations by Maseras shed light on this oxidative copper(I)-mediated trifluoromethylation reaction.[19] To gain insights into the product distribution as a function of time, the kinetic profile of the reaction of alkyne **3aa**, delivering the trifluoromethylated alkyne **2aa** and 1-iodoalkyne **4aa**, was studied by HPLC. As can be seen in Figure 7, a very rapid consumption of terminal alkyne **3aa** is observed since only 40% remains after 10 min. At the same time, less than 15% of the trifluoromethylated alkyne **2aa** is detected. The amount of the latter slowly increases over time, reaching 86% after 47 h. On the other hand, the amount of iodoalkyne **4aa** (3%) remains constant throughout the reaction.

Overall, these data support the fact that a syringe pump addition of the alkyne is not mandatory for the success of the reaction at room temperature since the build-up of the desired trifluoromethylated product **2aa** is relatively slow. In addition, the formation of iodoalkyne **4aa** does not seem to be related to the trifluoromethylation pathway, its yield remaining constant over time.[30] Finally, it should be emphasized that no Glaser-type homocoupling of the terminal alkyne **3aa** could be detected during the reaction course, thus enhancing the efficiency of the trifluoromethylation process.

Conclusions

Two practical methods for the oxidative copper(I)-mediated trifluoromethylation reaction of copper acetylides and terminal alkynes are reported herein. These processes are very simple to set up and proceed at room temperature, under very mild conditions.

Good to excellent yields of trifluoromethylated alkynes were obtained, even on a large scale. The functional group tolerance is especially noteworthy since common protecting groups, such as silyl and benzyl ethers, and sensitive motifs (1,3-enynes, esters, ketones, unprotected alcohols) are not affected. This method should be a useful addition to the current arsenal of the synthetic community and as such, its application to the area of natural product total synthesis is currently under investigations and will be reported in due time.

Experimental Section

General Procedure for the Oxidative Trifluoromethylation of Copper Acetylides

Users should be aware that the use of pure O_2 with organic solvents is potentially explosive.

A 5-mL round-bottom flask was successively charged with the alkynylcopper reagent (0.5 mmol), petroleum ether (1.9 mL), DMF (100 μL) and trifluoromethyltrimethylsilane $TMSCF_3$ (295 μL, 2.0 mmol). The resulting bright yellow slurry was then treated with *N,N,N′,N′*-tetramethylethylenediamine (75 μL, 0.5 mmol) and the reaction mixture was vigorously stirred at room temperature and under an atmosphere of oxygen (balloon). After complete disappearance of the alkynylcopper reagent (complete dissolution to a deep blue/green homogeneous reaction mixture), 20 mL of water were added to the crude reaction mixture. The resulting mixture was extracted with diethyl ether, and the combined organic layers were washed with water (three times) and brine and then dried over magnesium sulfate, filtered and concentrated at 40 °C at atmospheric pressure. The crude product was then purified by flash chromatography (pentane) to afford the desired trifluoromethylated alkyne.

Nonyltrifluoromethylacetylene (2n): This product was obtained from undec-1-yn-1-ylcopper (216 mg, 1.00 mmol) to afford **2n** as a white solid; yield: 176 mg (0.80 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (m, 2H), 1.64–1.54 (m, 2H), 1.45–1.22 (m, 12H), 0.90 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 114.2$ (q, $J = 255.2$ Hz), 89.3 (q, $J = 6.2$ Hz), 68.4 (q, $J = 51.9$ Hz), 31.9, 29.4, 29.3, 29.0, 28.7, 27.3, 22.7, 18.1 (q, $J = 1.6$ Hz), 14.0; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -49.7$ (t, $J = 3.7$ Hz); IR: $\nu = 2927$, 2858, 2266, 1285, 1136, 1024 cm^{-1}.

General Procedure for the Oxidative Trifluoromethylation of Terminal Alkynes

A 50-mL round bottom flask was charged with CuI (143 mg, 0.75 mmol), K_2CO_3 (207 mg, 1.5 mmol), *N,N,N′,N′*-tetramethylethylenediamine (112 μL, 0.75 mmol) and DMF (2.3 mL). The resulting deep blue mixture was vigorously stirred at room temperature under an atmosphere of air (balloon) for 15 min. $TMSCF_3$ (148 μL, 1.0 mmol) was added and the resulting deep green mixture was stirred for an additional 5 min under air atmosphere, then cooled to 0 °C. A solution of terminal alkyne (0.5 mmol) and $TMSCF_3$ (148 μL, 1.0 mmol) in DMF (2.3 mL), previously cooled to 0 °C, was then added in one portion. The reaction mixture was stirred at 0 °C for 30 min, under air atmosphere, and allowed to warm to room temperature and stirred for 24 h. At the end of the reaction, water was added and the aqueous layer was extracted with diethyl ether (three times). The combined organic layers were washed with water (three times), brine, dried over $MgSO_4$, filtered and concentrated at 40 °C and at atmospheric pressure. The crude product was then purified by flash chromatography (pentane/Et_2O) to afford the desired trifluoromethylated alkyne.

2-[2-(4-Methoxybenzyloxy)-3-methyl]butyltrifluoromethylacetylene (2z): This product was obtained from 2-methyl-3-(4-methoxybenzyloxy) hex-5-yne (**3z**) (400 mg, 1.72 mmol) to afford **2z** as a colorless oil; yield: 446 mg (1.49 mmol). ^{1}H NMR (300 MHz, benzene-d_6): $\delta = 7.19$ (d, $J = 8.7$ Hz, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 4.32 (d, $J = 11.3$ Hz, 1H), 4.15 (d, $J = 11.3$ Hz, 1H), 3.29 (s, 3H), 2.95 (m, 1H), 2.01 (ddq, $J = 17.4$, 6.2, 3.8 Hz, 1H), 1.92 (ddq, $J = 17.4$, 5.4, 3.9 Hz, 1H), 1.68 (septet of d, $J = 6.8$, 5.3 Hz, 1H), 0.74 (d, $J = 6.8$ Hz, 3H), 0.69 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, benzene-d_6): $\delta = 160.2$, 131.1, 129.8 (2C), 115.3 (q, $J = 255.7$ Hz, 1C), 114.4 (2C), 88.8 (q, $J = 6.4$ Hz, 1C), 81.2, 72.5, 69.8 (q, $J = 51.6$ Hz, 1C), 55.1, 32.1, 21.3, 18.6, 17.8; ^{19}F NMR (376 MHz, benzene-d_6): $\delta = -44.6$ (t, $J = 3.8$ Hz); HR-MS (APCI): $m/z = 323.1229$, calcd. for $C_{16}H_{19}F_3NaO_2$ $[M+Na]^+$: 323.1229.

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[30] 1-Iodoalkynes were shown to be reluctant partners in this direct trifluoromethylation reaction since only partial conversion (inferior to 40% in the best cases) to the desired trifluoromethylated alkynes was observed even after an extended period of time.

