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A Straightforward Entry to γ-Trifluoromethylated Allenamides and Their Synthetic Applications

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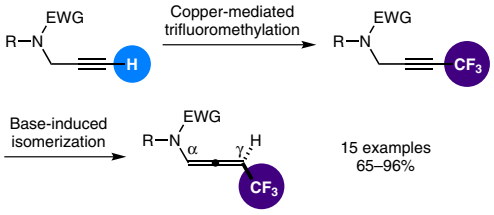

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Abstract γ-Trifluoromethylated allenamides were obtained in good to excellent yields through a base-induced isomerization from the corresponding protected trifluoromethylated propargylic amines. This method, which simply required the treatment of the starting propargylic amines with sodium hydroxide in THF, was found to be fairly general and tolerates various alkyl and aryl substituents and a range of protecting groups on the nitrogen atom. The reactivity of the γ-trifluoromethylated allenamides was explored and they were found to be excellent substrates for radical- and gold(I)-catalyzed cyclizations yielding fluoroalkylated nitrogen heterocycles.

Key words allenamides, trifluoromethyl, copper-mediated reaction, isomerization, radical reaction, gold(I) catalysis

Allenes are central building blocks in organic synthesis, and many research groups have reported a broad range of efficient transformations based on the remarkable reactivity of these cummulenes.[1] Among all types of allenes reported to date, allenamides, stable surrogates of the more labile and highly sensitive allenamines, have attracted much attention recently.[2] They have indeed been shown to possess a unique balance between stability and reactivity, mostly due to the delocalization of the nitrogen lone pair into both the allene and the electron-withdrawing group, and they were recently demonstrated to be ideal substrates for a broad range of transformations including,[2] just to mention a few, addition reactions,[3] cycloadditions,[4] metal-catalyzed cyclizations,[5] or, more recently, gold-catalyzed transformations.[6] If the development of new methods for the synthesis of allenamides is still an active field of research,[7] less attention has been paid to the development of new classes of allenamides, despite an important synthetic potential. These new classes of allenamides could indeed be designed to modulate their reactivity or to introduce additional functional groups when using them as starting materials in allenamide-based transformations. Trifluoromethylated allenamides clearly fall into this category since the additional trifluoromethyl group in these push–pull allenes should enhance their reactivity compared to more traditional allenamides and could also be incorporated in products resulting from their transformations (Figure 1). While their non-nitrogenated analogues, namely trifluoromethylated allenes, have elicited a great deal of interest and were shown to be conveniently prepared by elimination reactions,[8] sigmatropic rearrangements,[9] S_N2' reactions,[10] silver-[11] or palladium-catalyzed processes,[12] and $CuCF_3$-mediated reactions.[13] Trifluoromethylated allenamides have not been reported so far, to the best of our knowledge.

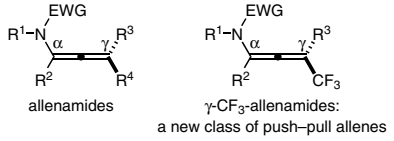
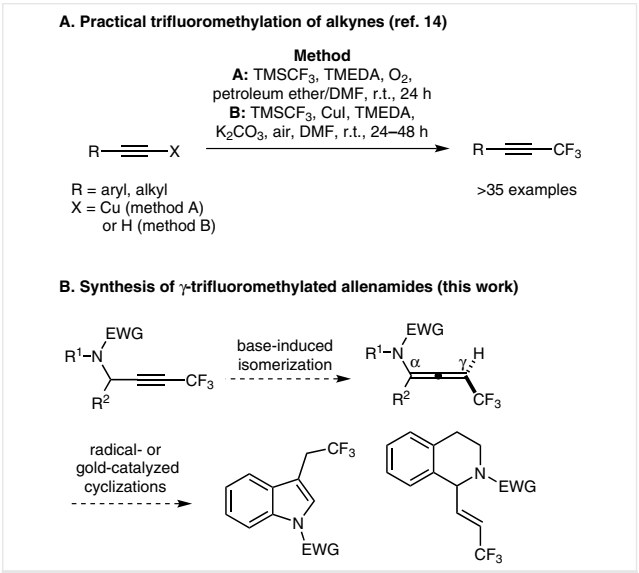


Figure 1 Allenamides and γ-trifluoromethylated allenamides, a new class of push–pull allenes

Surmising that γ-trifluoromethylated allenamides could be valuable building blocks for the rapid incorporation, in a single operation, of both a nitrogen atom and a fluoroalkyl chain to a range of derivatives, we became interested in their chemistry. We report herein that γ-trifluoromethylated allenamides could be easily obtained by a base-induced isomerization of the corresponding, readily available, trifluoromethylated propargylic carbamates or phosphoramidates

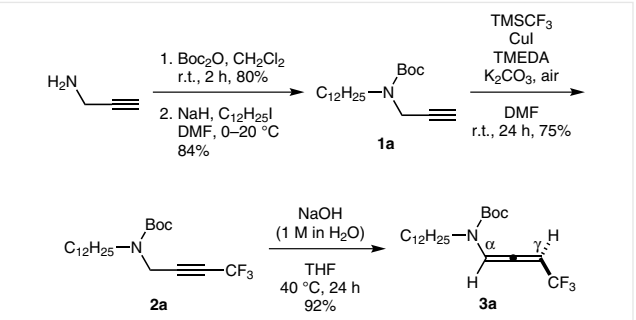
and that the resulting electron-deficient allenamides could be cyclized to diverse nitrogen heterocycles under radical conditions or gold(I) catalysis.

We indeed recently reported that terminal alkynes could be efficiently trifluoromethylated under mild conditions and with a broad substrate scope under two distinct sets of oxidative copper-mediated conditions (Scheme 1,A).[14] This trifluoromethylation being amenable to the preparation of a range of trifluoromethylated protected propargylic amines, we next wondered if their base-induced isomerization could afford an easy entry to trifluoromethylated allenamides (Scheme 1,B).



Scheme 1 Previously reported trifluoromethylation of alkynes (A) and working hypothesis: base-induced isomerization of protected trifluoromethylated propargylic amines to γ-trifluoromethylated allenamides (B)

Anticipating that this isomerization, which has stimulated ab initio and DFT investigations recently,[15] should be a rather facile process, we initiated model studies on a terminal alkyne bearing a *tert*-butylcarbamate motif (**1a**) in the propargylic position (Scheme 2). The latter was easily prepared in two steps from propargylamine by protection with Boc_2O (80%) followed by N-alkylation with iododododecane (84%). Using our previously reported conditions,[14] **1a** was smoothly converted into the corresponding trifluomethylated propargylic carbamate **2a** in 75% yield.[16] Different mineral and organic bases potentially able to promote the desired isomerization were then screened. Whereas sodium hydride, cesium carbonate, potassium *tert*-butoxide,[17] and *N*,*N*,*N*′,*N*′-tetramethylguanidine[18] were moderately effective, a simple aqueous solution of sodium hydroxide[19] in THF at 40 °C proved ideal and cleanly afforded the desired γ-trifluoromethylated allenamide **3a** in 92% as the sole product.[20]

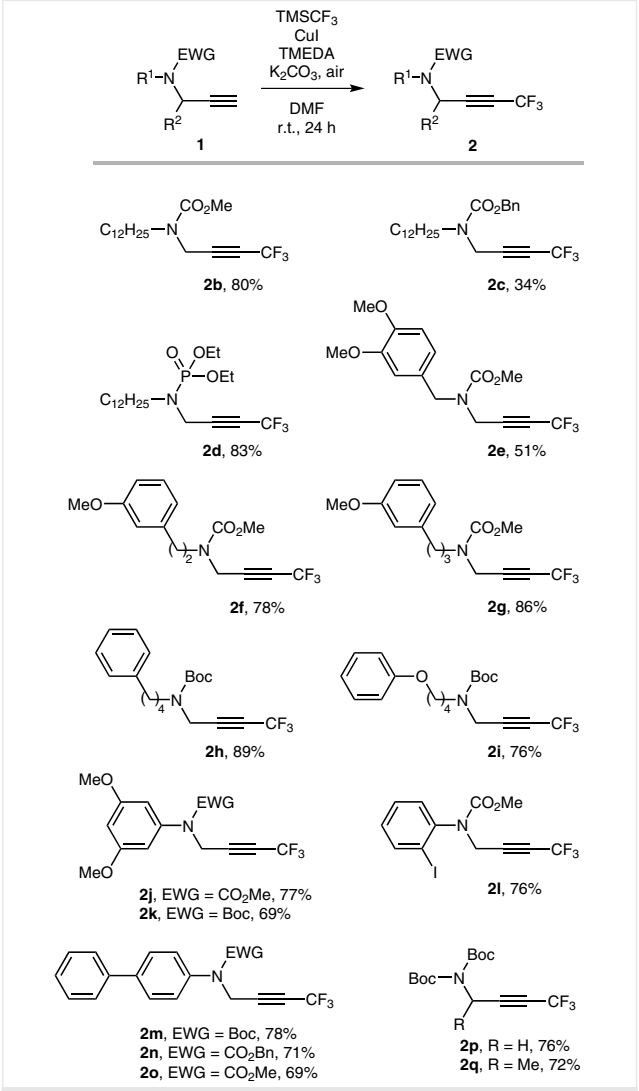


Scheme 2 Preliminary studies on the feasibility of the base-induced isomerization to γ-trifluoromethylated allenamides

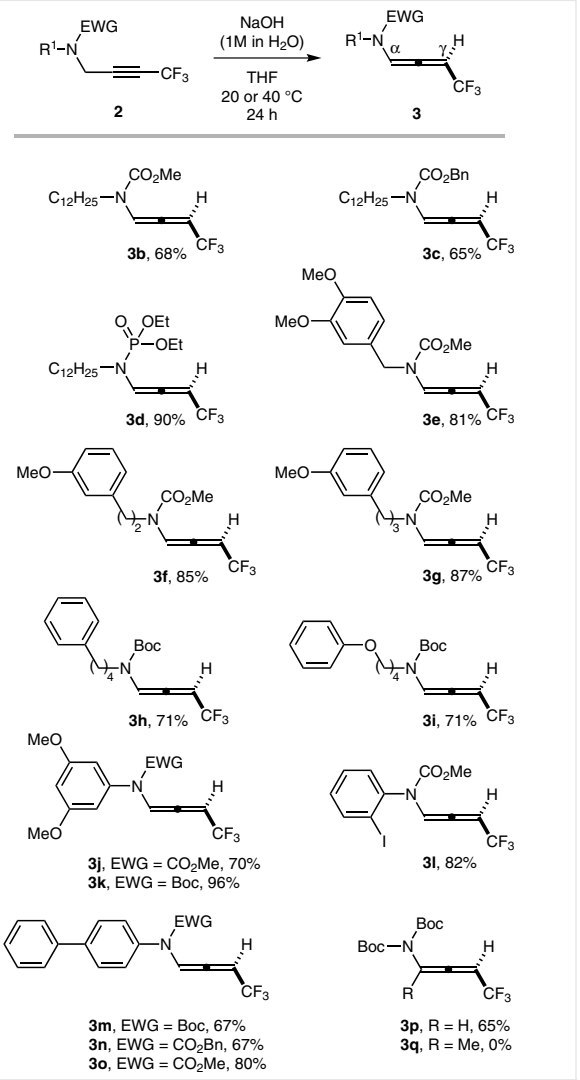
After demonstrating the feasibility of our strategy, the scope of the isomerization was then studied, starting with the preparation of a range of propargylic amines possessing different representative substituents on the nitrogen atom. We first kept the dodecyl chain constant (as in **1a**, Scheme 2) and focused on the influence of the nature of the electron-withdrawing group. Accordingly, a series of propargylic methylcarbamate (**1b**), benzylcarbamate (**1c**) and phosphoramidate (**1d**) was prepared in two steps from dodecylamine by N-protection followed by propargylation with propargyl bromide.

Trifluoromethylation of the corresponding terminal propargylic amines **1b–d** proceeded in good yields (except for **1c**), affording the precursors of the γ-trifluoromethylated allenamides **2b–d** (Scheme 3).[21] Keeping constant a methyl or *tert*-butylcarbamate as the protecting group, the nature of the second substituent of the nitrogen atom was studied. Terminal alkynes **1e–i** possessing an alkyl side chain and **1j–o** possessing an aryl substituent were therefore subjected to the oxidative copper-mediated trifluoromethylation conditions: the corresponding trifluoromethylated propargylic amines **2e–o** were isolated in 51–89% yield as the sole products. In a last example of oxidative copper-mediated trifluoromethylation reaction, the reactivity of terminal alkynes **1p** and **1q** possessing two *tert*-butylcarbamates on the nitrogen atom was explored. As in the previous examples, the trifluoromethylation of the Csp C–H bond proceeded smoothly, delivering the desired trifluoromethylated alkynes **2p** and **2q** in 76% and 72% yield, respectively.

The reactivity of the above-prepared trifluoromethylated alkynes in base-induced isomerization was then studied (Scheme 4). Upon treatment of **2b–p** with aqueous sodium hydroxide in THF, a complete conversion to the desired γ-trifluoromethylated allenamides **3b–p** was observed in all cases, and the products were isolated in good to excellent yields (65–96%), thus demonstrating that various carbamates (methyl, benzyl, and *tert*-butyl) as well as diethylphosphoramidate were tolerated as the protecting groups of the nitrogen atom of allenamides. In addition, these re-



Scheme 3 Copper-mediated synthesis of protected trifluoromethylated propargylic amines



Scheme 4 Sodium hydroxide induced isomerization of protected trifluoromethylated propargylic amines to γ-trifluoromethylated allenamides

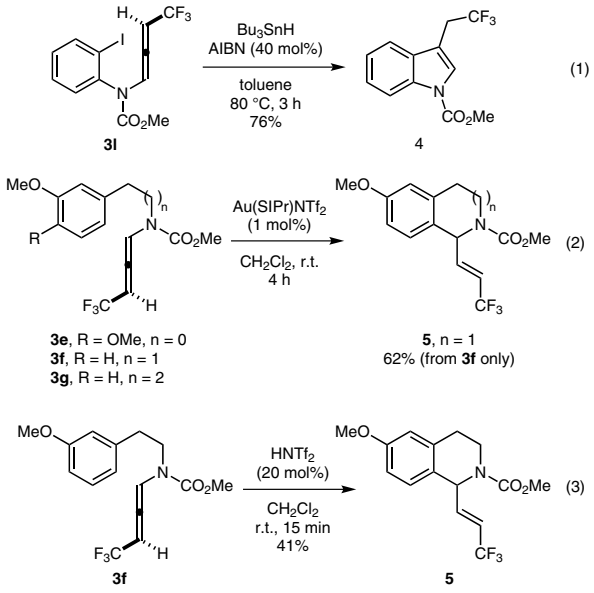
sults indicate that this sequence is well matched with the presence of electron-rich aromatics (as in **2e–k**) and iodoaromatics (as in **2l**) on the nitrogen atom.

A limitation to the present isomerization was, however, found when the reactivity of substrates **2p** and **2q** was compared (Scheme 4). Indeed, upon treatment of these propargylic carbamates with aqueous sodium hydroxide, it was noticed that only **2p** underwent isomerization to the desired γ-trifluoromethylated allenamide **3p** in 65% yield, demonstrating that substitution of the propargylic position of the trifluoromethylated alkynes **2** with a methyl group impeded the desired isomerization.[22]

Having in hand a straightforward entry to previously unreported γ-trifluoromethylated allenamides **3**, their use for the synthesis of fluoroalkylated nitrogen-containing heterocycles was then briefly studied (Scheme 5). In line with results previously reported by the Hsung group,[23] radical cyclization of **3l**, with tributyltin hydride and AIBN as a radical initiator, to the central carbon of the trifluoromethylallene motif, delivered 3-(2,2,2-trifluoroethyl)-1*H*-indole **4** in 76% isolated yield (Scheme 5, eq. 1).

Gold-catalyzed reactions of allenes[24] and, more specifically, allenamides[6,25] have also attracted much attention recently and when transposed to γ-trifluoromethylated allenamides **3**, these coinage-metal transformations would have the potential to deliver interesting nitrogenated scaffolds substituted by fluoroalkyl groups.

The reactivity of three allenamides **3e–g**, differing by the length of the tether between the electron-rich aromatic and the nitrogen atom was thus investigated since these



Scheme 5 Radical gold- and acid-mediated cyclization of γ-trifluoromethylated allenamides: useful entries to trifluoroalkylated nitrogen heterocycles

substrates have the potential to generate, in a single step, 1-(2,2,2-trifluoroethyl)isoindoline (from **3e**), 1-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (from **3f**), and 1-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (from **3g**). Upon treatment of **3e–g** with Au(SIPr)NTf_2 (1 mol%) in dichloromethane, it was observed that only **3f** led to a productive cyclization, delivering tetrahydroisoquinoline **5** in 62% isolated yield (Scheme 5, eq. 2).[26]

Lewis or Brønsted acid catalyzed cyclizations of allenamides also constitute a remarkably useful entry to a wide range of nitrogen heterocycles, as demonstrated during the course of previous studies in which the transient α,β-unsaturated *N*-acyliminiums[27] were intercepted with aromatics, tethered to the nitrogen atom.[28] Investigations of $HNTf_2$-catalyzed cyclization of γ-trifluoromethylated allenamide **3f** indeed demonstrated that tetrahydroisoquinoline **5** could be formed under these conditions (20 mol% $HNTf_2$, CH_2Cl_2, r.t. 15 min), although in moderate yield (Scheme 5, eq. 3).

In conclusion, we have reported an efficient entry to previously unknown γ-trifluoromethylated allenamides, a new class of push–pull allenes. Upon simple reaction with sodium hydroxide, a range of protected trifluoromethylated propargylic amines – easily prepared by copper-mediated trifluoromethylation of the corresponding terminal alkynes – were shown to be readily isomerized to γ-trifluoromethylated allenamides in good to excellent yields. In addition to its operational simplicity, this procedure was found to be fairly general and should contribute to expand the ever-growing chemistry of allenamides. The γ-trifluoromethylated allenamides prepared were found to be excellent substrates for radical and gold-catalyzed cyclizations, enabling an easy synthesis of fluoroalkylated nitrogen heterocycles incorporating both the nitrogen atom and the trifluoromethyl group of the starting allenamide.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562518.

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(16) **Typical Procedure for the Synthesis of Trifluoromethylated Alkyne 2 from Terminal Alkyne 1**
The reaction of **1a** is representative. A 50 mL round-bottom flask was charged with CuI (143 mg, 0.75 mmol, 1.5 equiv), K_2CO_3 (207 mg, 1.5 mmol, 3.0 equiv), TMEDA (112 µL, 0.75 mmol, 1.5 equiv), and DMF (2.3 mL). The resulting deep blue mixture was vigorously stirred at room temperature under air atmosphere for 20 min. $TMSCF_3$ (148 µL, 1.00 mmol, 2.0 equiv) was added, and the resulting deep green mixture was stirred for an additional 15 min under air atmosphere, then cooled to 0 °C. A solution of terminal alkyne **1** (0.50 mmol, 1 equiv) and $TMSCF_3$ (148 µL, 1.00 mmol, 2.0 equiv) 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, H_2O was added and the aqueous layer was extracted with Et_2O (three times). The combined organic layers were washed with H_2O (three times), brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was then purified by flash column chromatography on silica gel to afford the desired trifluoromethylated alkyne **2**.
***t*-Butyl Dodecyl(4,4,4-trifluorobut-2-yn-1-yl)carbamate (2a)**
This product was obtained following the general procedure from *tert*-butyl dodecyl(prop-2-yn-1-yl)carbamate (**1a**, 250 mg, 0.77 mmol) to afford the desired product (226 mg, 0.58 mmol, 75%) as a yellow oil. Solvent system for flash chromatography: pentane–Et_2O (9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.28–3.95 (m, 2 H), 3.28 (t, *J* = 7.3 Hz, 2 H), 1.58–1.50 (m, 2 H), 1.47 (s, 9 H), 1.34–1.21 (m, 18 H), 0.88 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (br s), 114.0 (q, *J* = 257.1 Hz), 84.5 (br s), 80.8, 70.4 (q, *J* = 50.9 Hz), 47.3 (br s), 36.5 and 35.7 (br s, rot.), 32.0, 29.77, 29.75, 29.70 (2 C), 29.5, 29.4, 28.4 (3 C), 28.2, 26.8, 22.8, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –51.3 (br s, 3 F). IR (ATR): ν_{max} = 2924, 2859, 2283, 1696, 1457, 1402, 1283, 1152, 870, 750 cm^{-1}. HRMS (APCI): *m/z* calcd for $C_{21}H_{36}F_3NaNO_2$ $[M + Na]^+$: 414.2590; found: 414.2583.
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(20) **Typical Procedure for the Synthesis of γ-Trifluoromethylated Allenamide 3 from Trifluoromethylated Alkyne 2**
The reaction of **2a** is representative. To a stirred solution of the trifluoromethylated propargyl amide **2** (0.15 mmol) in THF (2.40 mL) was added NaOH (1.20 mL, 1.20 mmol, 1 M in H_2O, 8 equiv), and the reaction was stirred at 40 °C for 24 h. After completion of the reaction, the crude mixture was quenched with a sat. aq NH_4Cl solution, and the aqueous layer was extracted with Et_2O (three times). The combined organic layers were washed with water (twice), brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel to afford the desired γ-trifluoromethylated allenamide **3**.
***tert*-Butyl Dodecyl(4,4,4-trifluorobuta-1,2-dien-1-yl)carbamate (3a)**
This product was obtained from *tert*-butyl dodecyl(4,4,4-trifluorobut-2-yn-1-yl)carbamate (**2a**, 50 mg, 0.13 mmol) to afford the desired product **3a** (46 mg, 0.12 mmol, 92%) as a colorless oil. Solvent system for flash chromatography: cyclohexane–EtOAc–Et_3N (100:1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 and 7.47 (br s, 1 H, rot.), 5.95 (app. quint, *J* = 5.5 Hz, 1 H), 3.28 (t, *J* = 6.5 Hz, 2 H), 1.55–1.45 (m, 11 H), 1.25 (s, 18 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9 and 198.4 (br s, rot.), 152.7 and 152.0 (br s, rot.), 121.7 (q, *J* = 271.3 Hz), 107.1 (br s), 95.4 (q, *J* = 39.6 Hz), 82.0 (br s), 46.2 and 45.7 (rot.), 32.1, 29.8 (2 C), 29.69, 29.66, 29.5, 29.4, 28.3 (3 C), 27.4 (br s), 26.8, 22.8, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.1 (dd, *J* = 5.3, 3.3 Hz, 3 F). IR (ATR): ν_{max} = 2935, 2856, 1707, 1467, 1370, 1283, 1141, 870 cm^{-1}. HRMS (APCI): *m/z* calcd for $C_{21}H_{36}F_3NaNO_4$ $[M + Na]^+$: 414.2590; found: 414.2588.
(21) Sulfonamides were not tolerated in this process, the highly electrophilic tosyl iminium intermediate being hydrolyzed over time. This is a clear indication that a one-pot trifluoromethylation–isomerization sequence is feasible, although such a process was not systematically explored in this work.
(22) We currently do not have a sound explanation for this lack of reactivity. Along the same lines, it was noticed that the oxidative copper-mediated trifluoromethylation reaction of terminal alkynes was inhibited with certain classes of substrates such as *N*-propargyl phthalimide or substrates possessing a phenyl group in the propargylic position.
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