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# Synthesis of Trifluoromethylated Naphthoquinones via Copper-Catalyzed Cascade Trifluoromethylation/Cyclization of 2-(3-Arylpropioloyl)benzaldehydes

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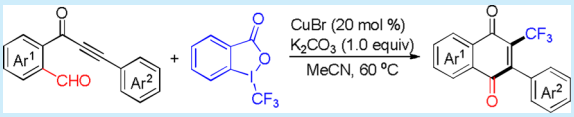
Supporting Information

**ABSTRACT:** A novel copper-catalyzed cascade trifluoromethylation/cyclization of 2-(3-arylpropioloyl)benzaldehydes is described, allowing a direct access to structurally diverse trifluoromethylated naphthoquinones under mild reaction conditions. It represents the first *trans*-acyltrifluoromethylation of internal alkynes.




Naphthoquinones are prevalent in a number of natural products, bioactive molecules, and functionalized materials (Figure 1). Many natural or synthetic naphthoquinones have been found to exhibit versatile pharmacological properties, including antimicrobial,[1] anti-inflammatory,[2] and anticancer activities.[3] Therefore, the development of efficient methods for the construction of naphthoquinones is of significant importance in the fields of both synthetic and medicinal chemistry.

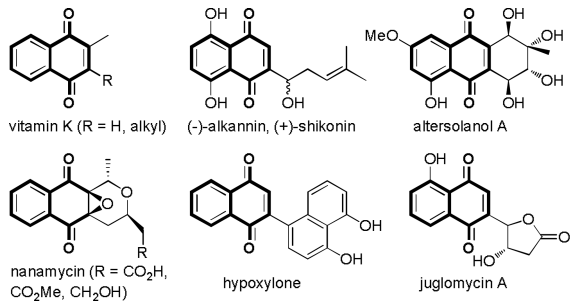
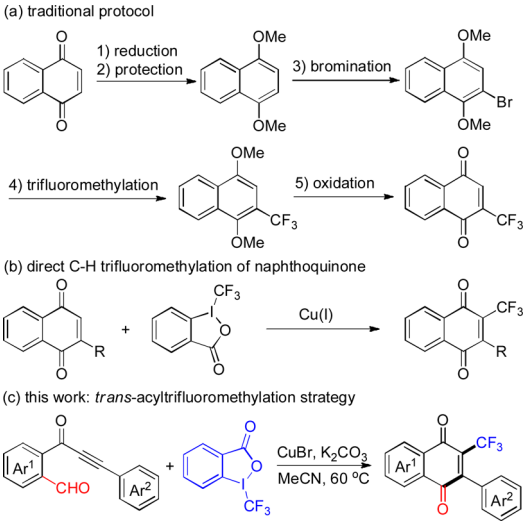



**Figure 1.** Representative bioactive molecules with naphthoquinone motifs.

On the other hand, the incorporation of a trifluoromethyl group ($CF_3$) into organic molecules can significantly improve physical, chemical, and biological properties such as permeability, bioavailability, and metabolic stability.[4] Although a host of methods have been developed for the preparation of trifluoromethylated compounds, there are very limited protocols for introducing $CF_3$ onto naphthoquinones. The traditional protocol involves a five-step procedure consisting of reduction, protection, bromination, trifluoromethylation, and oxidation (Scheme 1a).[5] Undoubtedly, the low step-efficiency limits the synthetic application of this protocol. In 2013, Szabó and Wang independently discovered an elegant method for the concise synthesis of trifluoromethylated naphthoquinones featuring a copper-mediated or catalyzed direct C−H trifluoromethylation (Scheme 1b).[6] Despite this success, the strategy depends on the utilization of naphthoquinones as the starting materials. As such, the exploration of new protocols for the straightforward synthesis of naphthoquinones from readily accessible acyclic precursors, with the concurrent incorporation of a $CF_3$ group, is a highly attractive alternative to the existing methods.

**Scheme 1. Methods for the Synthesis of Trifluoromethylated Naphthoquinones**




We have recently developed a methodology for the ketone synthesis using aldehydes as acceptors for the addition of carbon-centered radicals.[7] Following this concept, we present here a novel, mild, and direct approach to trifluoromethylated naphthoquinones via a Cu-catalyzed cascade trifluoromethylation/cyclization of 2-(3-arylpropioloyl)benzaldehydes using Togni's reagent[8] as the trifluoromethylation reagent (Scheme 1c). It represents the first *trans*-acyltrifluoromethylation of internal alkynes. As compared to the radical trifluoromethylation of alkenes,[9,10] the alkyne trifluoromethylation has been much less

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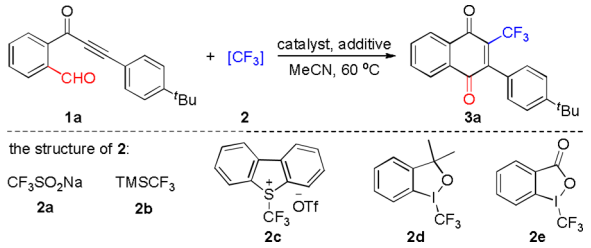
explored,[11] presumably due to the decreased reactivity of C−C triple bonds. Therefore, the method described here constitutes a new advance in the regio- and stereoselective radical trifluoromethylation of disubstituted alkynes, which may be valuable for access to polysubstituted trifluoromethylated alkenes.

At the outset, we utilized **1a** as the model substrate to optimize the reaction conditions (Table 1). The possibility of using

**Table 1. Optimization of the Reaction Conditions**[a]



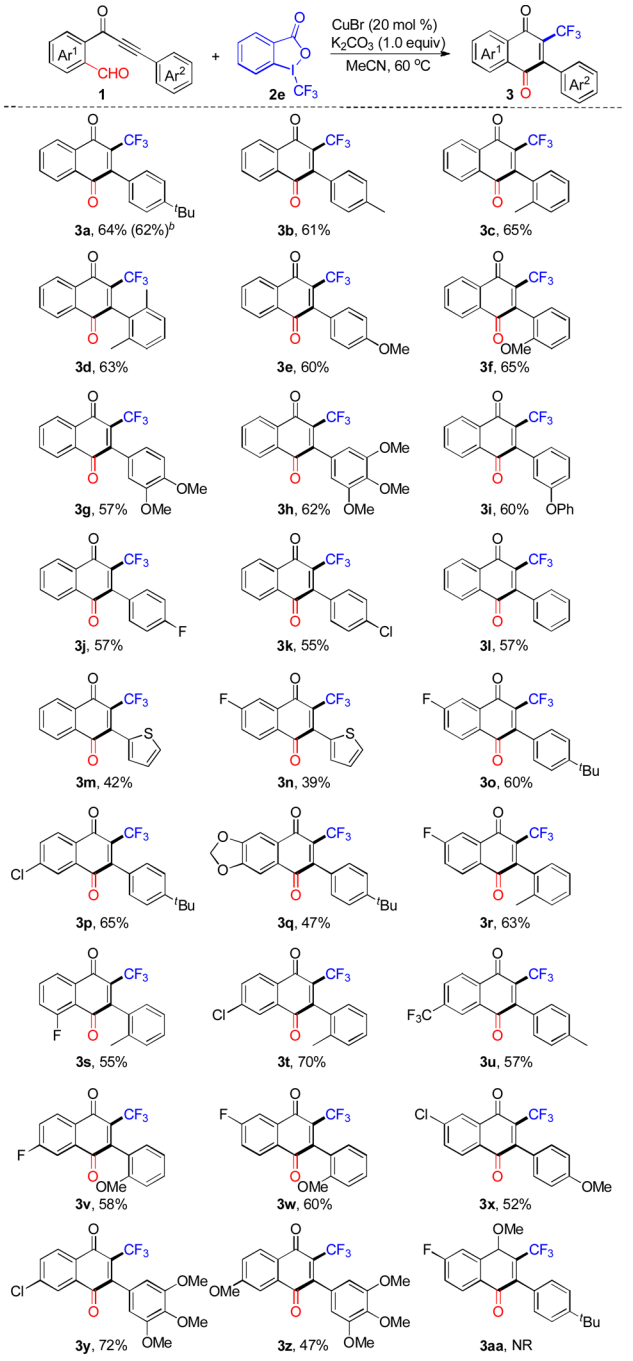

| entry | [$CF_3$] | catalyst | additive | yield[b] (%) |
|---|---|---|---|---|
| 1[c] | **2a** | $AgNO_3$ | $K_2S_2O_8$ | 25 |
| 2[d] | **2b** | $PhI(OAc)_2$ | CsF | 0 |
| 3 | **2c** | $Cu(OAc)_2$ | $K_2CO_3$ | trace |
| 4 | **2d** | $Cu(OAc)_2$ | $K_2CO_3$ | trace |
| 5 | **2e** | $Cu(OAc)_2$ | $K_2CO_3$ | 33 |
| 6 | **2e** | $CuSO_4$ | $K_2CO_3$ | 25 |
| 7 | **2e** | CuOAc | $K_2CO_3$ | 10 |
| 8 | **2e** | $Cu(MeCN)_4PF_6$ | $K_2CO_3$ | 28 |
| 9 | **2e** | CuCl | $K_2CO_3$ | 48 |
| 10 | **2e** | CuBr | $K_2CO_3$ | 64 |
| 11 | **2e** | CuBr | none | 10 |
| 12 | **2e** | CuBr | $Na_2CO_3$ | 56 |
| 13 | **2e** | CuBr | $NaHCO_3$ | 55 |
| 14 | **2e** | CuBr | $K_3PO_4$ | 40 |
| 15[e] | **2e** | CuBr | $K_2CO_3$ | 47 |
| 16[f] | **2e** | CuBr | $K_2CO_3$ | 35 |
| 17[g] | **2e** | CuBr | $K_2CO_3$ | 0 |
| 18 | **2e** | none | $K_2CO_3$ | 0 |

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), catalyst (20 mol %), additive (0.2 mmol), MeCN (2.0 mL), 60 °C, 10 h. [b]Isolated yield. [c]MeCN/DMF (v/v = 2:1) was used instead of MeCN. [d]Run with $PhI(OAc)_2$ (0.4 mmol) and CsF (0.8 mmol). [e]DCE was used instead of MeCN. [f]$PhCF_3$ was used instead of MeCN. [g]THF was used instead of MeCN. DCE = $ClCH_2CH_2Cl$.

$CF_3SO_2Na$ (**2a**) as the trifluoromethylation reagent was first explored. Indeed, the combined use of $AgNO_3$ and $K_2S_2O_8$[12] led to the trifluoromethylated naphthoquinone **3a** in 25% yield, together with the partial decomposition of **1a** (Table 1, entry 1). We then examined the reactivity of $TMSCF_3$ in the presence of $PhI(OAc)_2$ and CsF,[13] but essentially no reaction was observed (entry 2). When the reaction was performed with the combined use of 2 equiv of Togni's reagent **2e**, 20 mol % of $Cu(OAc)_2$, and 1 equiv of $K_2CO_3$, **3a** was obtained in 33% yield (entry 5). The variation of copper salts indicated that CuBr is the best suitable catalyst, delivering **3a** in 64% yield upon isolation (entries 6−10). It should be noted that the addition of $K_2CO_3$ had a significant impact on the reaction efficiency, and a very low conversion was observed in the absence of $K_2CO_3$ (entry 11). Replacement of $K_2CO_3$ with $Na_2CO_3$, $NaHCO_3$ or $K_3PO_4$ led to inferior results (entries 12−14). In addition, the utilization of other solvents including DCE, $PhCF_3$, and THF was not able to increase the yield (entries 15−17). Of note, the reaction yield could not be improved any more even after a number of trials because of the possible decomposition of trifluoromethylated naphthoquinones via the haloform reaction under neutral or mild basic reaction conditions, as reported in the literature.[5b,14]

With the optimized reaction conditions in hand, we investigated the scope of this reaction by using various 2-(3-arylpropioloyl)benzaldehydes, and the results are shown in Scheme 2. The reaction of **1b**, **1c**, and **1d** afforded trifluoromethylated naphthoquinones **3b**, **3c**, and **3d** in 61%, 65%, and 63% yield, respectively, indicating that the steric

**Scheme 2. Substrate Scope**[a]




[a]Reaction conditions: **1** (0.2 mmol), **2e** (0.4 mmol), CuBr (20 mol %), $K_2CO_3$ (0.2 mmol), $CH_3CN$ (2.0 mL), 60 °C, 5−10 h. Isolated yields are given. [b]Isolated yield on a 1 mmol scale.



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hindrance of $Ar^2$ has little impact on the reaction. The chlorinated substrate **1k** was effective for the production of **3k**, which may offer an opportunity for further derivatizations via the transition-metal-catalyzed cross-coupling reaction. Heteroaryl substituents like thiophene were also compatible with the reaction, albeit in moderate yields (**3m** and **3n**). In the meantime, the $Ar^1$ group was varied. Substrates bearing either electron-withdrawing or -donating groups readily underwent this Cu-catalyzed cascade trifluoromethylation/cyclization reaction. The fluorinated substrate **1o** was converted into the corresponding product **3o** in 60% yield, whereas the reaction of **1q** produced **3q** in 47% yield. There results implied that the electronic effect of $Ar^1$ had a correlation with the reaction efficiency, which could also be deduced from the transformation of **1y** and **1z** (**3y** and **3z**). In contrast, no reaction took place when **1aa** was used as the starting material, presumably due to the reduced reactivity of the C−C triple bond (**3aa**). Overall, a wide range of functional groups such as F, $CF_3$, Cl, OMe, OPh, and $OCH_2O$ were tolerated rather well, which is attractive for the synthetic application. The structure of trifluoromethylated naphthoquinone **3w** was unambiguously identified by single-crystal X-ray analysis (Figure 2).[15]

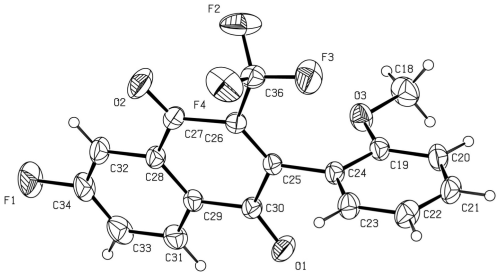
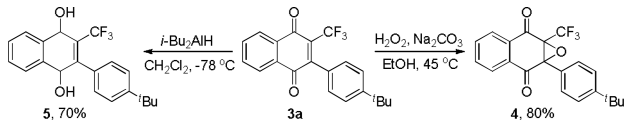



**Figure 2.** ORTEP representation of the X-ray crystal structure of **3w**.

The synthetic utility of this methodology was then explored (Scheme 3). In the presence of 1.5 equiv of $H_2O_2$ and $Na_2CO_3$,

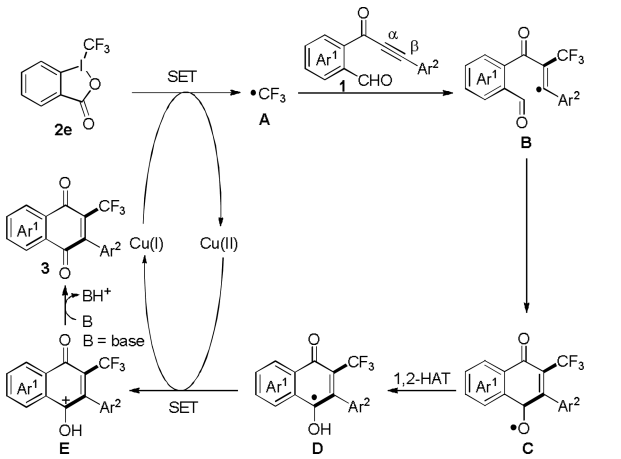
**Scheme 3. Derivatization of Compound 3a**



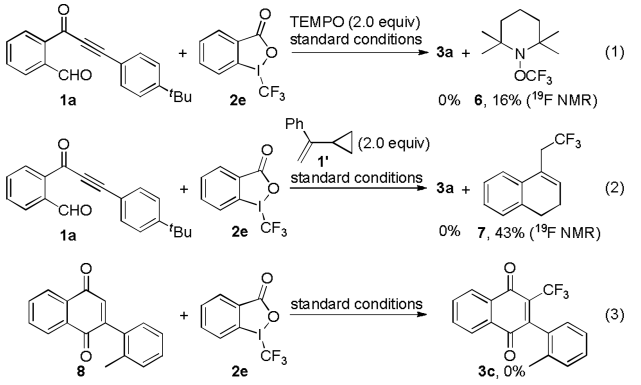

**3a** was smoothly transformed to the naphthoquinone epoxide **4** in 80% yield. This is noteworthy as it has been reported that this type of compound exhibits significant biological activities in the metabolic processes.[16] Moreover, the reduction of **3a** with *i*-$Bu_2AlH$ at a low temperature afforded the diol product **5** in 70% yield.

In order to gain insight into the reaction mechanism, the standard reaction was carried out in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). As a result, **3a** was not formed, and the TEMPO−$CF_3$ adduct **6**[9c] was detected by $^{19}F$ NMR analysis (16% yield) (eq 1). The radical clock reaction using (1-cyclopropylvinyl)benzene (**1′**) as the radical-trapping reagent provided the known product **7**[17] in 43% yield, estimated from the $^{19}F$ NMR spectroscopy (eq 2). Furthermore, compound **8**[18] was subjected to the reaction conditions, and no detectable product **3c** was observed (eq 3), thus ruling out the possibility of forming a naphthoquinone intermediate. Consequently, a radical mechanism is depicted in Scheme 4 for this

**Scheme 4. Proposed Catalytic Cycle**




Cu-catalyzed cascade trifluoromethylation/cyclization reaction. First, the $CF_3$ radical (**A**) is generated by a single-electron transfer (SET) from Cu(I) to **2e**, with the release of Cu(II) species. Since the $\alpha$-position of the carbonyl group has a higher electron density than the $\beta$-position, the $CF_3$ radical (**A**) regioselectively adds to the $\alpha$-carbon of **1** to deliver an alkenyl radical **B**.[6c] Subsequent addition of alkenyl radical to the intramolecular aldehyde provides an alkoxyl radical **C**, which can be converted into the radical **D** via a 1,2-hydrogen atom transfer (1,2-HAT).[7,19] Then, oxidation of **D** by the Cu(II) species results in a cationic intermediate **E**, accompanied by the regeneration of Cu(I) catalyst. Finally, trifluoromethylated naphthoquinones **3** are generated from **E** via the $K_2CO_3$-promoted deprotonation.




In summary, we have developed a novel copper-catalyzed cascade trifluoromethylation/cyclization of 2-(3-arylpropioloyl)-benzaldehydes, providing straightforward access to structurally diverse trifluoromethylated naphthoquinones under mild reaction conditions. The reaction represents the first *trans*-acyltrifluoromethylation of internal alkynes, which offers a novel approach to direct synthesis of polysubstituted trifluoromethylated alkenes.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00095.

Detailed experimental procedures, characterization data for all new products **3**−**5**, and NMR spectra (PDF)
X-ray data for **3w** (ZIP)



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### Notes

The authors declare no competing financial interest.

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(14) As an example, the decomposition of **3s** was observed by GC and HRMS analysis; for details, see Figures S1 and S2 of the Supporting Information.
(15) CCDC 1515077 (**3w**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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