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N-Trifluoromethylation of Nitrosoarenes with Sodium Triflinate

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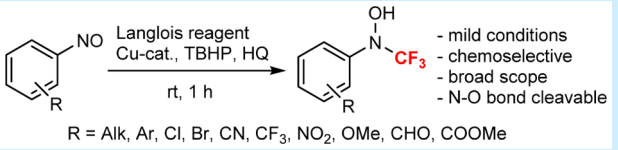
Supporting Information

ABSTRACT: A highly efficient N-trifluoromethylation of nitrosoarenes is reported. The inexpensive and convenient Langlois reagent (sodium triflinate) is employed as a CF_3-radical source in combination with a copper catalyst and an oxidant. N-Trifluoromethylated hydroxylamines are obtained in high yields within 1 h at room temperature. The addition of hydroquinone was found to be instrumental to prevent the formation of side products. The method is high-yielding, is scalable, and displays a high functional group tolerance.



The development of selective methods for the synthesis of C-, O-, and S-trifluoromethylated compounds is a subject of extensive research.[1] In particular, the introduction of a CF_3-group has gained interest due to the possibility of altering important properties of biologically active compounds, such as metabolic stability, lipophilicity, and solubility.[2] Despite the high abundance of nitrogen atoms in pharmaceuticals and other compounds of biological significance, the N-CF_3 moiety remains rather uncommon. An important aspect for achieving efficient and N-selective trifluoromethylation reactions is the choice of reagent. Recently, both electrophilic and nucleophilic CF_3-sources have been employed for the synthesis of various NCF_3-containing products (Figure 1).[3]

Umemoto and co-workers employed a highly reactive *in situ* generated electrophilic CF_3 oxonium salt for the direct trifluoromethylation of anilines, pyridines, and amines.[3g] A more stable hypervalent iodine reagent was later developed by the Togni group and was used in the synthesis of certain N-trifluoromethylated imidoyl compounds and azoles.[3d,e] Zhu and Wang, and their co-workers applied an *in situ* formed hypervalent iodine CF_3-reagent from the Ruppert–Prakash reagent ($TMSCF_3$) in the N-trifluoromethylation of ketimines.[3b] Cheng and Bolm employed $TMSCF_3$ in combination with Ag_2CO_3 in a radical trifluoromethylation of sulfoximines.[3c] Furthermore, the Schoenebeck group recently developed a two-step strategy for the N-trifluoromethylation of secondary amines through the use of the bench-stable reagent $(Me_4N)SCF_3$. The initially formed thiocarbamoyl fluoride intermediates were converted to the trifluoromethylated amines using AgF.[3a]

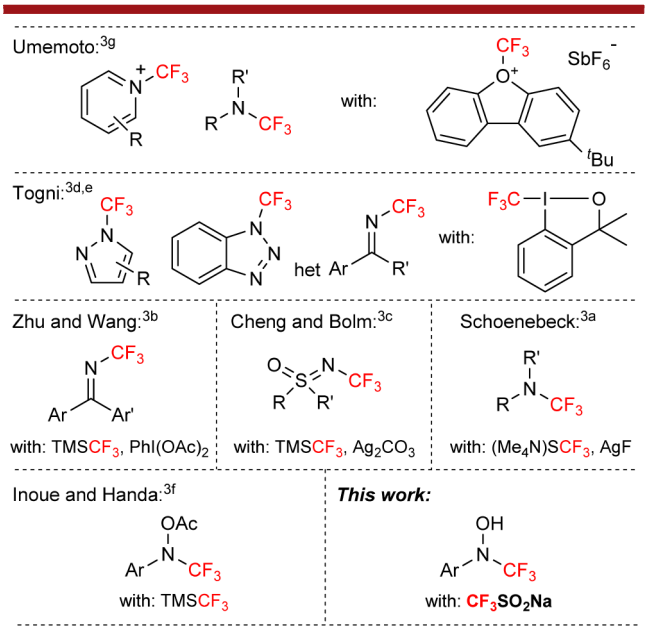


Figure 1. N-Trifluoromethylated products and applied reagents.[3]

Nitrosoarenes are readily synthesized starting materials serving as versatile building blocks for a wide range of nitrogen-containing compounds.[4−6] For example, Inoue and Handa recently disclosed a method for the nucleophilic trifluoromethylation of nitrosoarenes using $TMSCF_3$. In the presence of an acylation reagent, O-acetylated, N-trifluoromethylated hydroxylamines were obtained.[3f]

Herein, we present a rapid, high-yielding, and selective N-trifluoromethylation of nitrosoarenes employing the bench-stable and commercially available Langlois reagent (CF_3SO_2Na). Since the initial reports on radical trifluoromethylation of aromatics,[7] the reagent has received an increased interest as a benign source of CF_3-radicals for C-trifluoromethylation,[1a,j] often in the presence of nitrogen-based functional groups. We envisaged that a radical trifluoromethylation of nitrosoarenes would enable an efficient synthesis of unprotected, trifluoromethylated hydroxylamines, tolerating a wide variety of functional groups. Compared to the previously reported methods for N-trifluoromethylations presented above, our strategy would be complementary and provide access to the hitherto undescribed Ar–N(OH)CF_3 products.

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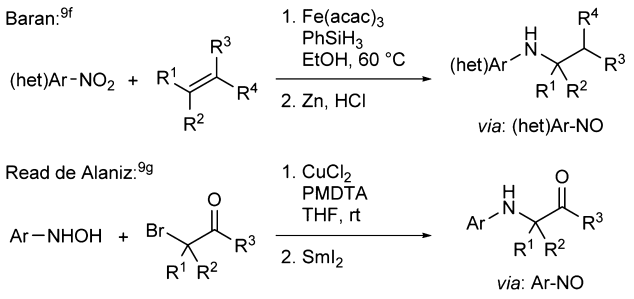
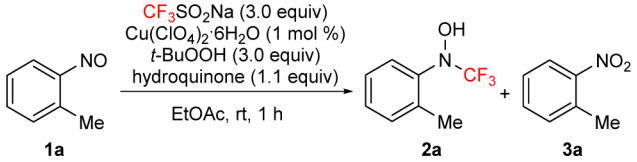
Despite the fact that nitrosocompounds are widely used as spin-trapping reagents, because of their ability to form persistent nitroxide radicals,[8] synthetic applications have so far been limited.[9] Very recently, several groups have developed elegant methods for the *in situ* formation of nitrosoarenes from nitroarenes[9a,b,e,f] or hydroxylamines[9g] followed by a subsequent radical addition. The N−O bond was reduced to obtain sterically hindered secondary amines (Scheme 1). In both cases, N,O-diaddition of the radical species was proposed.[9f,g]

Scheme 1. Synthesis of Secondary Amines by *in Situ* Formation of Nitrosoarenes[9f,g]



After a thorough screening of suitable reaction conditions[10] for the radical trifluoromethylation of nitrosoarene **1a**, we obtained **2a** in 84% yield as a single isomer after just 1 h at room temperature (Table 1, entry 1).

Table 1. Relevant Data from the Screening of Reaction Conditions[a]



entry	change	yield **2a** (%)	yield **3a** (%)	yield **1a** (%)
1	–	84	15	–
2	no Cu(II) source	–	–	>95
3	no hydroquinone	42	27	–
4	no oxidant	–	–	>95
5	no CF_3SO_2Na	–	13	87
6	1 equiv of TEMPO added	27[b]	12	55

[a]Reaction conditions: **1a** (0.10 mmol), CF_3SO_2Na (0.30 mmol), hydroquinone (0.11 mmol), $Cu(ClO_4)_2·6H_2O$ (1 mol %), EtOAc (0.8 mL), and ^{t}BuOOH (70% aq sol, 0.30 mmol, added last) at rt for 1 h. Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard. [b]In addition to product **2a**, 46% of the TEMPO−CF_3 adduct was observed, as determined by ^{19}F NMR in comparison with **2a**. TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.

We found that, in addition to the Langlois reagent, a catalytic amount of a Cu-source [Cu(I) or Cu(II)], *tert*-butyl hydroperoxide, and hydroquinone were all vital components for an efficient reaction of **1a**, also limiting the amount of nitroarene **3a** formed. Furthermore, the reaction could be performed in standard grade solvents without the need to exclude oxygen or moisture.[10]

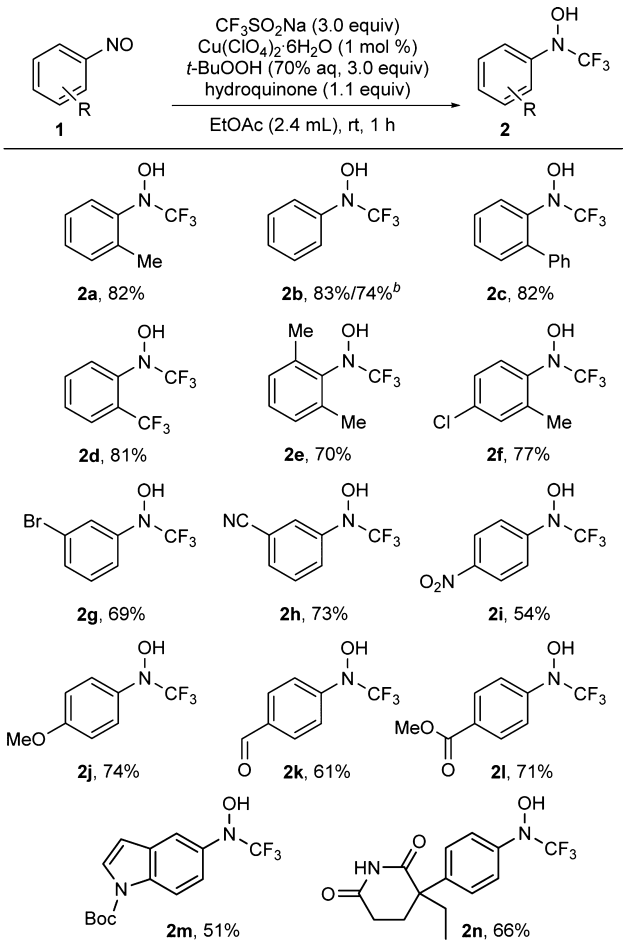
Although several Cu(II) and Cu(I) species were active,[10] $Cu(ClO_4)_2$ was chosen for its high solubility in EtOAc and the slightly higher yields of **2a**. No conversion was observed in the absence of a Cu-salt; other metal salts screened (Fe, Zn, Zr) led to either no conversion or decomposition. Importantly, by omitting the hydroquinone additive, a significantly lower yield (42%) of **2a** was observed along with an increased formation of nitrotoluene **3a**. No reaction was observed without the oxidant unless a stoichiometric amount of Cu(II) was used. In the absence of the Langlois reagent, 13% of nitroarene **3a** was observed; a comparable amount, 15%, was also formed under the optimized reaction conditions, which we attribute to a Cu-catalyzed background oxidation of **1a**.

Upon addition of TEMPO to the reaction mixture, a low conversion of **1a** was observed, and only 27% of product **2a** was formed. In addition, 46% of the TEMPO−CF_3 adduct was formed, indicating the involvement of CF_3-radicals.

We further investigated the scope of the reaction and were pleased to find that a wide variety of functionalized nitrosoarenes could be converted into the corresponding trifluoromethylated hydroxylamines in high yields (Scheme 2).

Both *o*-nitrosotoluene and nitrosobenzene were efficiently converted into products **2a** and **2b** in high yields (82−83%). Moreover, product **2b** was obtained in 74% yield upon performing the reaction on a 10.0 mmol scale. Other *ortho*-substituted nitrosoarenes performed equally well, obtaining **2c**

Scheme 2. N-Trifluoromethylation of Nitrosoarenes[a]



[a]Reaction conditions: **1** (0.30 mmol), CF_3SO_2Na (0.90 mmol), hydroquinone (0.33 mmol), $Cu(ClO_4)_2·6H_2O$ (1 mol %), EtOAc (2.4 mL), and ^{t}BuOOH (70% aq sol, 0.90 mmol, added last) at rt for 1 h (isolated yields). [b]Performed on a 10.0 mmol scale.

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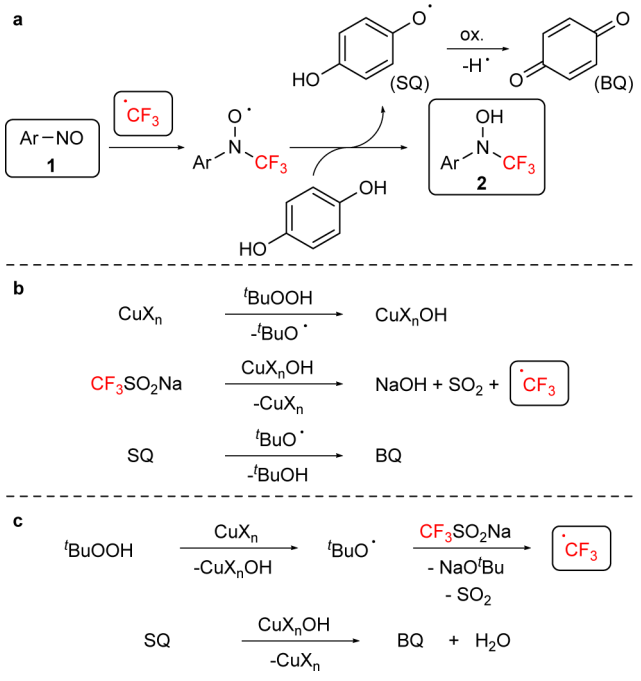
and **2d** in 82% and 81% yield, respectively. The more sterically hindered **2e** was isolated in a slightly lower yield, 70%. Halogen substituents (Br and Cl) on the aromatic ring were tolerated; products **2f** and **2g** were obtained in 77% and 69% yield, respectively. *meta*-Substituted products (**2g** and **2h**) and *para*-substituted products (**2i**–**2l**) were also obtained in good yields (54–74%). Both electron-poor and -rich nitrosoarenes were N-trifluoromethylated as shown by the formation of **2i** and **2j** in 54% and 74% yield, respectively. Furthermore, we were delighted to find that more sensitive functional groups such as aldehyde, ester, and cyano groups were well tolerated (**2h**, **2k**, and **2l**, 61–73% yield). The *N*-Boc indole derivative **2m** was isolated in 51% yield. To demonstrate the applicability of the method to more complex structures, **2n** was synthesized from aminoglutethimide via the corresponding nitrosoarene. Gratifyingly, the product containing the piperidine-2,6-dione moiety could be obtained in 66% yield.

For all substrates mentioned above, the conversion of nitrosoarene **1** was complete after 1 h at room temperature. Competition experiments, using a limited amount of reagents, showed a faster conversion for electron-rich and the less sterically hindered substrates.[10]

From our screening it became evident that the applied Cu-species and hydroquinone as well as ^{t}BuOOH are all crucial for an efficient reaction to take place. Thus, based on our observations and previously suggested mechanisms by the groups of Langlois[7] and Baran,[11] we propose a radical mechanism (Scheme 3).

Scheme 3. Proposed Mechanism for the N-Trifluoromethylation of 1 and the Generation of a CF_3-Radical



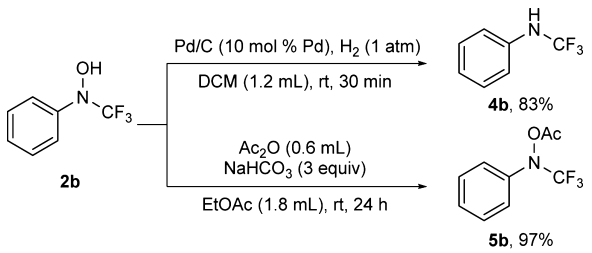
The addition of a CF_3-radical to nitrosoarenes has previously been reported in spin-trapping experiments[8] and most likely does not require a metal catalyst. We propose that the hydroquinone additive acts as a hydrogen donor to deliver product **2** from the nitroxyl radical intermediate. The resulting semiquinone radical (SQ) is then further oxidized to benzoquinone (BQ, Scheme 3a). Notably, in the absence of hydroquinone, an increased amount of nitroarene **3** was observed, possibly formed in a reduction of the nitroxyl radical intermediate by the starting nitrosoarene.

Since no reaction was observed in the absence of copper, the generation of a CF_3-radical from the Langlois reagent is most likely involving copper. We envisage that the oxidation of the Langlois reagent can occur via two pathways (Scheme 3b or c). One possibility is through a single-electron oxidation by an oxidized copper species to produce a CF_3-radical. The reaction can be terminated in an oxidation of the semiquinone radical by ^{t}BuO$^{\bullet}$ as produced in the (re)oxidation of the copper species (Scheme 3b). In the absence of an oxidant, a stoichiometric amount of Cu(II) led to the formation of the product in a low yield, demonstrating the ability of a Cu-species to activate the Langlois reagent to some extent.

In an alternative path (Scheme 3c), copper is involved in the initiation of the reaction by a single-electron reduction of ^{t}BuOOH. The CF_3-radical is subsequently generated through an oxidation of the Langlois reagent by ^{t}BuO$^{\bullet}$. Benzoquinone is formed as the terminating step, in the reduction of the copper species (Scheme 3c). At the current stage, both of the mechanisms outlined in Scheme 3b–c appear to be plausible.

To demonstrate the versatility of the trifluoromethylated hydroxylamine products, we subjected **2b** to a reductive N–O bond cleavage reaction and an O-acylation reaction. The trifluoromethylated aniline **4b** was obtained in 83% yield, and the acetylated hydroxylamine **5b**, in 97% yield (Scheme 4).

Scheme 4. Transformations of Product 2b



In summary, we have developed a highly chemoselective and efficient procedure for the N-trifluoromethylation of nitrosoarenes. The reaction takes place under mild conditions, employing the inexpensive and bench-stable Langlois reagent. We propose a radical mechanism to be operating and found that hydroquinone is an important additive to obtain the trifluoromethylated hydroxylamines in high yields. Furthermore, the method is scalable and provides access to N-trifluoromethylated anilines after reduction of the N–O bond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00908.

Detailed experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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