Synthetic Methods

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Trifluoromethoxylation of Arenes: Synthesis of *ortho*-Trifluoromethoxylated Aniline Derivatives by OCF_3 Migration**

*Katarzyna N. Hojczyk, Pengju Feng, Chengbo Zhan, and Ming-Yu Ngai**

Dedicated to Professor Iwao Ojima on the occasion of his 70th birthday

Abstract: *Aryl trifluoromethoxylation by a two-step sequence of O-trifluoromethylation of N-aryl-N-hydroxylamine derivatives and intramolecular OCF_3 migration is presented. This protocol allows easy access to a wide range of synthetically useful ortho-OCF_3 aniline derivatives. In addition, it utilizes bench-stable reagents, is operationally simple, shows high functional-group tolerance, and is amenable to gram-scale as well as one-pot synthesis. A reaction mechanism of a heterolytic cleavage of the N–OCF_3 bond followed by recombination of the resulting nitrenium ion and trifluoromethoxide is proposed for the OCF_3-migration reaction.*

Fluorine atoms are often introduced into organic molecules to enhance their pharmacological properties such as solubility, metabolic and oxidative stability, lipophilicity, and bioavailability.[1] Among the fluorine-containing functional groups, the trifluoromethoxy group (OCF_3) is of current interest because of its unique structural and electronic properties, which can be useful in materials, agricultural, and pharmaceutical science.[2] For example, one of the distinct structural features of trifluoromethoxylated arenes (Ar-OCF_3) is that the OCF_3 moiety is orthogonal to the aryl plane.[1b,3] As a result, lone-pair electrons on oxygen only weakly delocalize into the ring, which renders OCF_3 an electron-withdrawing group ($\chi = 3.7$).[4] In addition, the OCF_3 group has one of the highest lipophilicity values ($\pi_x = 1.04$) compared to that of the CF_3 ($\pi_x = 0.88$), CH_3 ($\pi_x = 0.52$), F ($\pi_x = 0.14$), and OCH_3 ($\pi_x = -0.02$) groups.[5] Compounds with higher lipophilicity show enhancement in their in vivo uptake and transport in biological systems. Indeed, many OCF_3-containing pharmaceuticals and agrochemicals show enhanced effectiveness often coupled with diminished side effects (Figure 1 a,b).[2a,b,6]

Despite the intriguing properties of the OCF_3 group, facile introduction of this functional group into organic molecules remains a challenge. Only a handful of transformations have been developed over the last few decades.[1l,2a–c,e,6g] These include 1) chlorine–fluorine exchange on trichlorinated precursors;[7] 2) deoxyfluorination of fluoroformates;[8] 3) oxidative fluorodesulfurization;[9] 4) electrophilic trifluoromethylation of alcohols;[10] 5) nucleophilic trifluoromethoxylation;[11] 6) transition metal-mediated trifluoromethoxylation of aryl borates and stannanes;[12] and 7) radical trifluoromethoxylation.[13] However, most of these approaches either suffer from poor substrate scope or require use of highly toxic and/or thermally labile reagents. As a result, many of OCF_3-containing building blocks are prohibitively expensive (Figure 1 c).

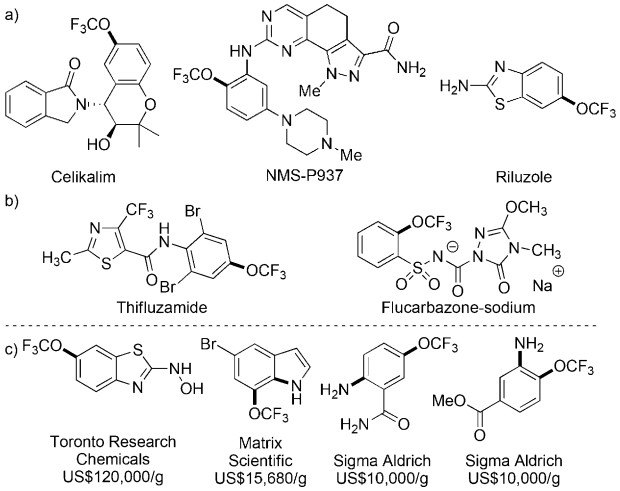

Figure 1. Examples of OCF_3-containing a) pharmaceuticals, b) agrochemicals, and c) building blocks.

Clearly, direct trifluoromethoxylation reactions which avoid the use of highly toxic and thermally labile reagents are greatly desired. Therefore, we initiated a program to develop easily handled and bench-stable trifluoromethoxylation reagents for direct introduction of the OCF_3 group into various organic molecules to facilitate studies of this functional group in the context of materials, agricultural, and pharmaceutical regimes. In the course of the trifluoromethoxylation reagent development, we observed a thermally induced OCF_3 migration to generate synthetically useful *ortho*-trifluoromethoxylated aniline derivatives (Scheme 1).[14] Herein, we report the first synthesis, isolation, and characterization of protected *N*-aryl-*N*-(trifluoromethoxy)amines[15] and their application in the synthesis of *ortho*-trifluoromethoxylated aniline derivatives.

[*] K. N. Hojczyk,[+] Dr. P. Feng,[+] C. Zhan, Prof. M.-Y. Ngai
Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794-3400 (USA)
and
Institute of Chemical Biology and Drug Discovery
State University of New York at Stony Brook
Stony Brook, NY 11794-3400 (USA)
E-mail: ming-yu.ngai@stonybrook.edu

[+] These authors contributed equally to this work.

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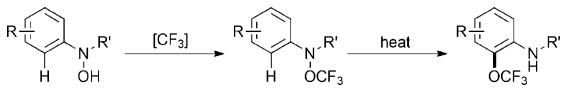
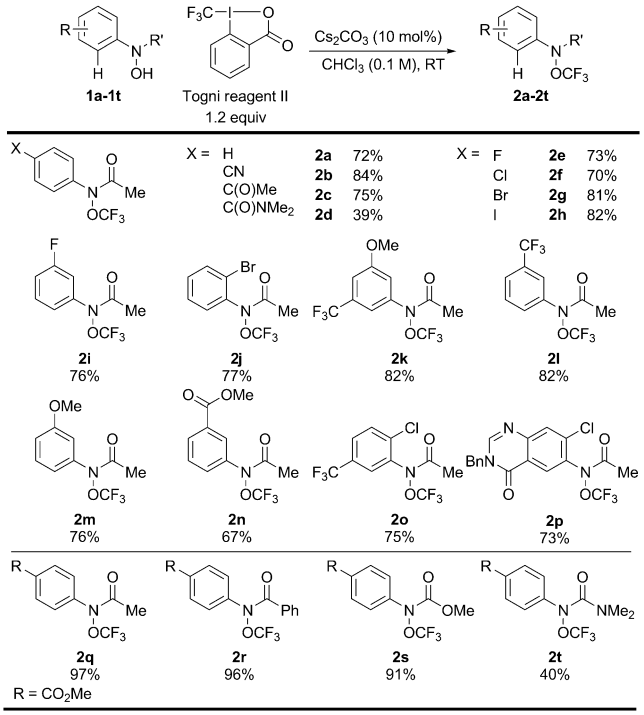


Scheme 1. Aryl trifluoromethoxylation by OCF_3 migration.

Li and Studer reported that sodium 2,2,6,6-tetramethylpiperidin-1-oxide (TEMPONa) reacted with 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni reagent II)[16] to form TEMPO-CF_3.[17] Based on this reactivity, Togni and co-workers developed *O*-trifluoromethylation of *N*,*N*-dialkylhydroxylamines using 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni reagent I).[15b] Therefore, we envisioned that protected *N*-aryl-*N*-hydroxylamines could react with Togni reagents to provide the desired products of *O*-trifluoromethylation. Indeed, treatment of *N*-phenyl-*N*-hydroxamic acid (**1a**) with 1.2 equivalent of Togni reagent II in the presence of 10 mol% Cs_2CO_3 in $CHCl_3$ (0.1 M) at room temperature furnished the desired product **2a** in 72% yield (Scheme 2). Addition of a stoichiometric amount of a radical

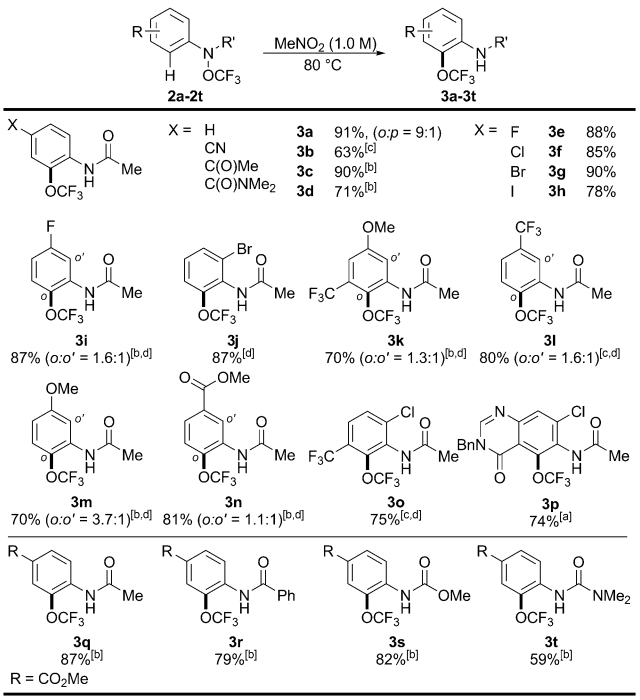


Scheme 2. Selected examples of *O*-trifluoromethylation of protected *N*-aryl-*N*-hydroxylamines. Reaction time: 14–23 h. Cited yields are for isolated material following chromatography. See the Supporting Information for further experimental details.

trap 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) diminished the product yield. Moreover, this reaction is oxygen sensitive, so strictly degassed chloroform is required for high yield. These observations are consistent with a radical mechanism.[15b,17]

Under the optimized reaction conditions, various protected *N*-aryl-*N*-hydroxylamines (**1a**–**t**; Scheme 2) were surveyed to determine the scope and limitations of this reaction. Gratifyingly, the reaction tolerated a wide range of functional groups including nitrile (**2b**), ketone (**2c**), amide (**2d**), halogens (**2e**–**2j, 2o, 2p**), CF_3 group (**2k, 2l, 2o**), ether (**2k, 2m**), ester (**2n, 2q**–**2t**), and a heterocycle substituent (**2p**). Examination of different nitrogen protecting groups revealed that acetyl-, benzoyl-, and methoxycarbonyl-protected *N*-[(4-methoxycarbonyl)phenyl]-hydroxylamines showed excellent and comparable reactivities (**2q**–**s**), while dimethylcarbamoyl-protected *N*-[(4-methoxycarbonyl)phenyl]hydroxylamine was found to react sluggishly (**2t**). Substrates bearing a dimethylcarbamoyl group (**2d, 2t**) afforded the corresponding products in lower yields. This low yield is probably due to decomposition of the dimethylcarbamoyl group resulting from a hydrogen-atom abstraction of N-CH_3 by a *N*-hydroxyl radical.[18] It is noteworthy that this class of the OCF_3 compounds (**2a**–**t**) shows the most shielded chemical shift ($\delta \approx -65$ ppm) in the ^{19}F NMR spectroscopy compared to that of other OCF_3-containing compounds such as TEMPO-CF_3 ($\delta = -55.7$ ppm),[19] Ph-OCF_3 ($\delta = -58$ ppm),[20] and *n*-$C_{10}H_{21}$-OCF_3 ($\delta = -61.3$ ppm).[21]

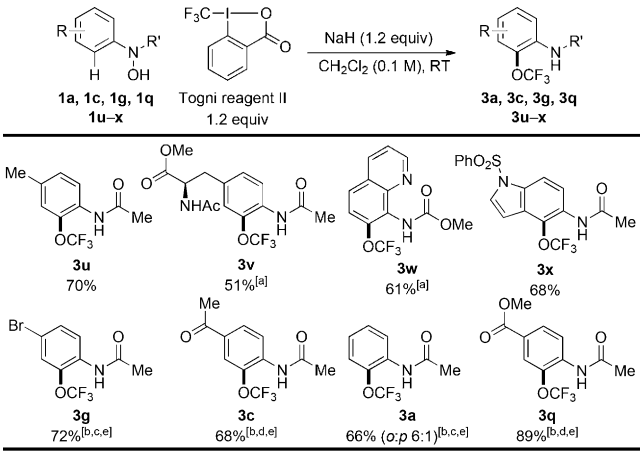
With the protected *N*-aryl-*N*-(trifluoromethoxy)amines (**2a**–**t**) in hand, we next directed our attention to examining the OCF_3-migration reaction. Systematic variation of different reaction parameters, including solvent, concentration, and temperature, identified optimal reaction conditions. A significant degree of structural and electronic variation on the aryl ring was tolerated (Scheme 3). Products derived from electron-rich (**3m**) and electron-poor (**3b**–**l, 3n**–**t**) aniline derivatives were formed in high yields, though electron-poor aniline derivatives, with exception of **3p**, required higher



Scheme 3. Selected examples of the OCF_3-migration reaction. Reaction time: 11–48 h. Cited yields and isomeric ratios are for isolated material following chromatography. [a] 50 °C. [b] 120 °C. [c] 140 °C. [d] Less than 5% *para* product was detected. See the Supporting Information for further experimental details.

reaction temperatures for full conversion. Notably, halogen functionalities, in particular Br and I, remained intact after reaction (**3e–j, 3o, 3p**). These groups provide easy handles for further synthetic elaborations. Other functional groups including ester (**3n, 3q–3t**), nitrile (**3b**), ketone (**3c**), ether (**3k, 3m**), heterocycle (**3p**) and multiple substitutions on arenes (**3k, 3o, 3p**) were well tolerated under the reaction conditions. In general, this reaction showed high levels of *ortho* selectivity (**3a, 3i–o**), although in the presence of two non-identical *ortho* positions, low levels of regiocontrol were obtained (**3i, 3k–n**).

Next, we explored the possibility of integrating this two-step sequence into a one-pot transformation to simplify the reaction protocol. To our delight, exposure of **1u** to Togni reagent II and NaH in CH_2Cl_2 at room temperature provided the desired product **3u** in 70% isolated yield (Scheme 4). These reaction conditions tolerate an α-amino acid ester (**3v**), quinoline (**3w**), and indole (**3x**). Moreover, products from Scheme 3 such as **3a**, **3c**, **3g**, and **3q** can be directly obtained

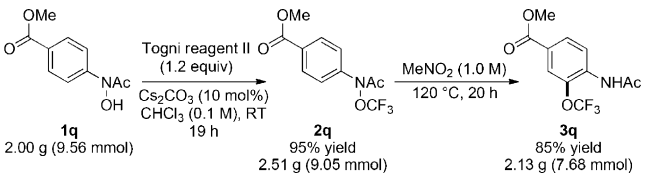


Scheme 4. Selected examples of the one-pot synthesis of *ortho*-trifluoromethoxylated aniline derivatives. Cited yields are for isolated material following chromatography. [a] Following the trifluoromethylation, the reaction mixture was heated to 50 °C. [b] Following the trifluoromethylation, the reaction mixture was concentrated, the residue was dissolved in $MeNO_2$, and the resulting mixture was heated. [c] 80 °C. [d] 120 °C. [e] Yield determined by NMR spectroscopy. See the Supporting Information for further experimental details.

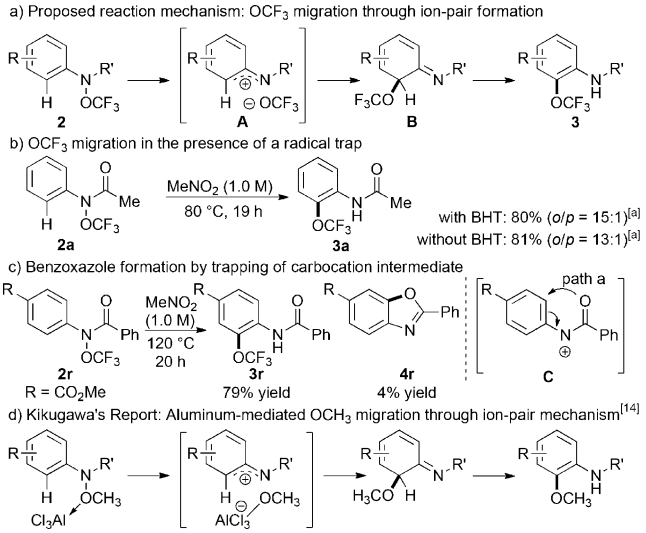
from the corresponding hydroxylamines by a one-pot reaction protocol without the isolation of the intermediates **2**. However, removal of CH_2Cl_2 at the end of the trifluoromethylation reaction followed by re-dissolving the resulting residue in $MeNO_2$ is needed, because the OCF_3 migration for these substrates requires a higher reaction temperature.

To demonstrate both the practicality and effectiveness of our method for large-scale synthesis, **3q** was prepared on a gram scale under the standard trifluoromethylation/OCF_3-migration sequence in high yield (Scheme 5).

A proposed mechanistic pathway for OCF_3 migration is depicted in Scheme 6a. The thermally induced heterolytic cleavage of the N–O bond of **2** liberates an ion pair of a nitrenium ion and trifluoromethoxide (**A**).[22] Recombination of this ion pair affords the intermediate **B**, which then tautomerizes to restore the aromaticity and generate the desired product **3**. The proposed mechanism is supported by the following observations. First of all, comparable yields were obtained regardless of the presence or absence of the radical trap BHT in the reaction mixture (Scheme 6b). This indicates that formation of long-lived radical species under the reaction conditions is unlikely. Secondly, we isolated benzoxazole **4r** from the rearrangement reaction of **2r** (Scheme 6c). Presumably, this side product can result from the competing reaction path a once the nitrenium ion **C** is generated. Finally, Kikugawa and co-workers reported an $AlCl_3$-mediated regioselective OCH_3 migration of *N*-methoxy-*N*-phenylamides to produce *ortho*-methoxylated aniline derivatives.[14] A reaction mechanism involving a heterolytic cleavage of the N–O bond to furnish an ion pair was proposed (Scheme 6d).



Scheme 5. Gram-scale synthesis.



Scheme 6. Evidence for the proposed reaction mechanism. [a] 1 equiv of BHT was used. See the Supporting Information for further experimental details.

In summary, we have developed the first *O*-trifluoromethylation of a wide range of protected *N*-aryl-*N*-hydroxylamines and the first OCF_3-migration reaction to afford various *ortho*-trifluoromethoxylated aniline derivatives, which can be useful synthons for agrochemical and pharmaceutical development.[2a,b,6g,23] The OCF_3-migration reaction proceeds through the heterolytic cleavage of the N–O bond followed by recombination of the resulting ion pair. Our reaction protocol utilizes bench-stable reagents, is amenable to gram-scale and one-pot synthesis, and displays high levels

of *ortho* selectivity as well as functional-group tolerance. Further efforts will be devoted to expansion of the substrate scope and development of intermolecular trifluoromethoxylation reactions.

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