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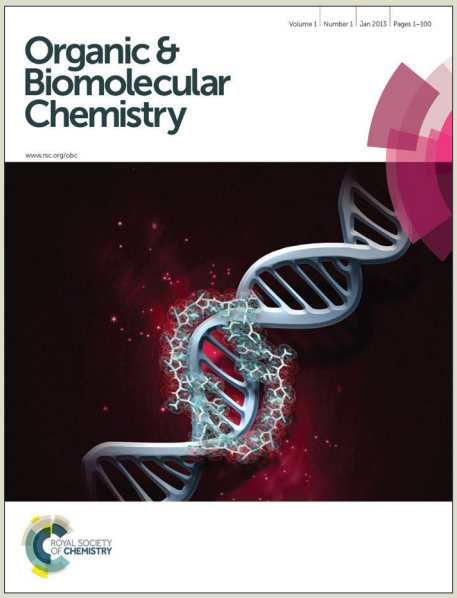

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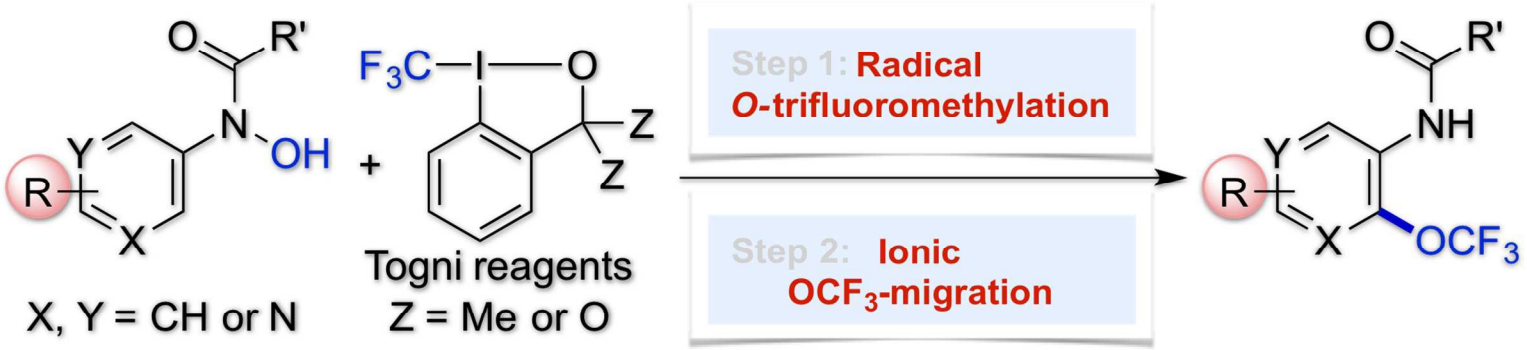
Intramolecular C-H trifluoromethoxylation of arenes and heteroarenes proceeds through a reaction mechanism of radical *O*-trifluoromethoxylation and ionic OCF_3-migration.



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COMMUNICATION

Mechanistic Studies on Intramolecular C-H Trifluoromethoxylation of (Hetero)arenes *via* OCF_3-Migration

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The one-pot two-step intramolecular aryl and heteroaryl C-H trifluoromethoxylation recently reported by our group has provided a general, scable, and operationally simple approach to access a wide range of unprecedented and valuable OCF_3-containing building blocks. Herein we describe our investigations to elucidate its reaction mechanism. Experimental data indicates that the *O*-trifluoromethylation of *N*-(hetero)aryl-*N*-hydroxylamine derivatives is a radical process, whereas the OCF_3-migration step proceeds *via* a heterolytic cleavage of the N–OCF_3 bond followed by rapid recombination of a short-lived ion pair. Computational studies further support the proposed ion pair reaction pathway for the OCF_3-migration process. We hope that the current study would provide useful insights for the development of new transformations using versatile *N*-(hetero)aryl-*N*-hydroxylamine synthons.

Introduction

Addition of fluorine atoms into organic molecules has a profound influence on their chemical, physical and biological properties. As a consequence, fluorine is frequently incorporated into drug molecules to enhance their lipophilicity, bioavailability, and metabolic stability.[1] In recent years, there has been a significant progress towards development of synthetic methodologies that allow introduction of fluorine-containing functional groups into arenes and heteroarenes. Among fluorinated substituents, the trifluoromethoxy group (OCF_3) has attracted increasing attention owing to its unique structural and electronic properties. In contrast to methoxybenzenes, which favor a planar conformation, trifluoromethoxybenzenes prefer to adopt a conformation in which the O–CF_3 bond lies in a plane orthogonal to the aryl ring (Fig. 1a).[2] This unique orientation, which results from the $n_O \rightarrow \sigma^*_{C-F}$ hyperconjugative interaction (Fig. 1b) and the steric bulk of the CF_3 group, provides additional conformational flexibility and renders the OCF_3 group an electron–withdrawing substituent [χ (F) = 4.0, χ (OCF_3) = 3.7].[3] In addition, the OCF_3 group has excellent lipophilicity as indicated by its Hansch-Leo parameter [π_x (SF_5) = +1.23, π_x (OCF_3) = +1.04, π_x (CF_3) = +0.88, π_x (F) = +0.14, π_x (OCH_3) = −0.02].[4] These properties of the OCF_3 group are particularly beneficial in drug discovery and development as introduction of the OCF_3 group into drug candidates may enhance their binding affinity, improve their metabolic stability and efficacy, promote their *in vivo* uptake and transport in biological systems, and minimize their side

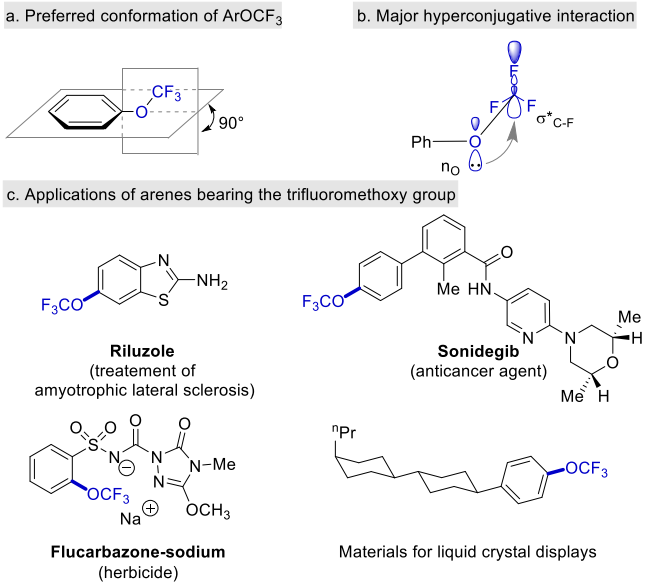

Fig. 1. Properties and applications of OCF_3-containing arenes.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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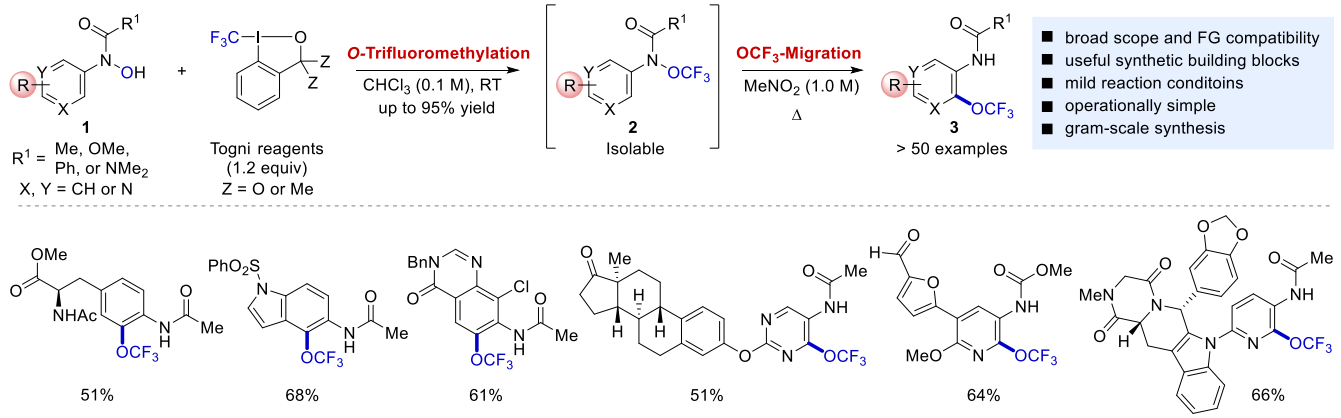


Fig. 2. Synthesis of (hetero)aryl trifluoromethyl ethers *via* *O*-trifluoromethylation of *N*-(hetero)aryl-*N*-hydroxylamine derivatives followed by OCF_3-migration.[19]

effects.[5] Trifluoromethoxylated arenes are thus of great importance in medicinal chemistry and agrochemicals (Fig. 1c).[5c, 5d, 6, 7] Moreover, incorporation of the OCF_3 group into organic molecules increases their melting point and boiling point difference under ambient pressure, and lowers their surface tension, dielectric constant, and pour point.[5e, 8] These properties are particularly useful in designing electronic devices and materials.[9]

Despite the prevalence of the OCF_3 moiety in different areas of science, facile synthesis of (hetero)aryl trifluoromethyl ethers remains an unmet challenge in organic synthesis.[10] Over the past few decades, there have been a number of synthetic routes towards trifluoromethoxylated (hetero)arenes: (i) chlorine-fluorine exchange on (hetero)aryl trichloromethyl ethers;[11] (ii) deoxyfluorination of phenol fluoroformates;[12] (iii) oxidative desulfurization-fluorination of aryl dithiocarbonates (xanthogenates);[13] (iv) electrophilic trifluoromethylation of phenols;[14] (v) nucleophilic trifluoromethoxylation of benzyne;[15] (vi) silver-mediated trifluoromethoxylation of aryl stannanes and aryl boronic acids;[16] (vii) radical trifluoromethoxylation;[17] and (viii) silver-mediated trifluoromethylation of phenols.[18] However, most of these approaches suffer from poor substrate scope and functional group tolerance, require the use of highly toxic, corrosive and/or temperature sensitive reagents, or impractical reaction conditions.

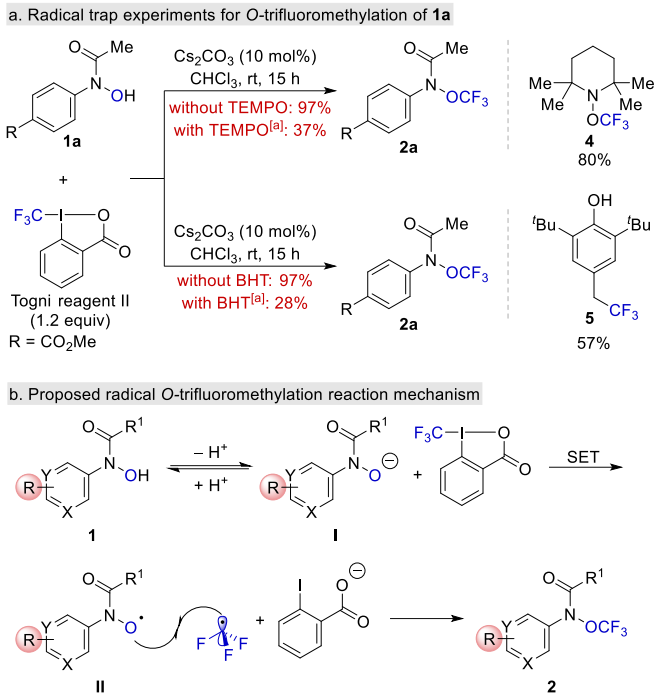
Our group has recently developed a new method for preparation of *ortho*-OCF_3 (hetero)arylamine derivatives *via* a two-step process: *O*-trifluoromethylation of *N*-(hetero)aryl-*N*-hydroxylamine derivatives followed by OCF_3-migration step (Fig. 2).[19] Our approach is operationally simple and amenable to one pot as well as gram-scale synthesis, features a broad substrate scope and high functional group compatibility, and provides a wide range of valuable *ortho*-trifluoromethoxylated (hetero)arylamine scaffolds that would otherwise be difficult to synthesize. In view of its potential synthetic utility, an in-depth understanding of its mechanism is desirable. Herein, we report our mechanistic investigations to provide insights for this two-step transformation. Although the following studies were done using the *N*-aryl-*N*-hydroxylamine derivatives, the proposed mechanism is also applicable to the *N*-(hetero)aryl-*N*-hydroxylamine derivatives.

Results and discussion

***O*-Trifluoromethylation of *N*-aryl-*N*-hydroxylamine derivatives:** Treatment of protected *N*-aryl-*N*-hydroxylamines (**1**) with 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni reagent II, 1.2 equiv) in the presence of a catalytic amount of base (0.1 equiv Cs_2CO_3) in $CHCl_3$ (0.1 M) at room temperature afforded the desired *O*-trifluoromethylation products (**2**) in high yields. These mild reaction conditions tolerate arenes with a wide variety of substitution patterns, electronic properties, and molecular complexities. To probe the nature of this reaction mechanism, we performed the *O*-trifluoromethylation reaction in the presence of radical traps: 2,6-di-*tert*-butyl-*para*-cresol (BHT) and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (Scheme 1a). It is known that Togni reagent II can be used to produce the CF_3 radical in the presence of a one-electron donor through a single electron transfer (SET) process.[20] If such a process takes place in our reaction, BHT and/or TEMPO would trap the CF_3 radical and lower the reaction yields. Indeed, addition of a stoichiometric amount of either BHT or TEMPO to the reaction mixture under standard conditions had a detrimental effect on the formation of *O*-trifluoromethylated *N*-hydroxylamine – the yield of the desired product dropped from 97% to 28%, and 37%, respectively. The CF_3 radical trapping products (BHT-CF_3 and TEMPO-CF_3) were detected by GC-MS and ^{19}F NMR spectroscopy. We have also found that the *O*-trifluoromethylation reaction is oxygen sensitive and requires use of strictly degassed solvent. These results corroborate the intermediacy of trifluoromethyl radical in the reaction pathway, which is in agreement with literature precedents.[20-21]

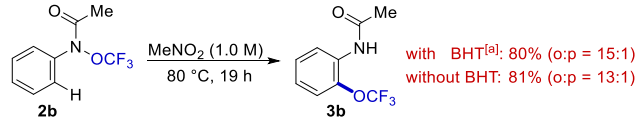
Based on these studies and experimental observations, a plausible mechanism for the *O*-trifluoromethylation is depicted in Scheme 1b. Deprotonation of protected *N*-aryl-*N*-hydroxylamine (**1**) forms *N*-aryl-*N*-hydroxylamine anion **I**. Subsequent SET from **I** to Togni reagent II generates *N*-hydroxyl radical **II** and Togni II radical anion that collapses to liberate the electrophilic CF_3 radical and 2-iodo-benzoate.[22] Recombination

of *N*-hydroxyl radical **II** with trifluoromethyl radical gives the desired *O*-trifluoromethylated hydroxylamine derivative (**2**).



Scheme 1. Radical trap experiments and proposed mechanism for the *O*-trifluoromethylation of *N*-(hetero)aryl-*N*-hydroxylamine derivatives. [a] 1 equiv.

OCF_3-Migration of *N*-(trifluoromethoxy)-*N*-aniline derivatives (2): Compounds **2** with an electron-deficient or -neutral *N*-aryl ring are stable at room temperature and could be purified through column chromatography. However, heating **2** in nitromethane ($MeNO_2$, 1.0 M) cleaved the N–OCF_3 bond and formed a new C–OCF_3 bond to give *ortho*-OCF_3 aniline derivatives (**3**) (Fig. 2). To gain mechanistic insights into the OCF_3-migration step, we first examined whether the N–O bond is broken homo- or heterolytically. Homolytic cleavage of the N–OCF_3 bond would generate *N*-amidyl and trifluoromethoxyl ($\cdot OCF_3$) radicals; we envisioned that if these radicals are indeed being formed, the reaction yield should drop upon addition of a radical trap, which would disable radical recombination process. Thus, we performed the rearrangement reaction of **2b** in the presence of a stoichiometric amount of BHT (Scheme 2). Similar yields were obtained regardless the presence or absence of BHT, which indicates that formation of long-lived radical species under the reaction conditions is unlikely.



Scheme 2. OCF_3-Migration in the presence of radical trap. [a] 1 equiv.

In order to further shed light to the nature of the N–O bond cleavage, we performed linear free energy relationship analysis using Hammett plot. Relative rate constants were determined for the OCF_3-migration with seven *para/meta*-substituted *O*-trifluoromethylated *N*-hydroxylamine derivatives, R-$C_6H_4N(OCF_3)C(O)Me$ (R = H (**2b**), *m*-OMe (**2c**), *p*-I (**2d**), *p*-Br (**2e**), *m*-F (**2f**), *m*-CO_2Me (**2g**), and *m*-CF_3 (**2h**)). The rearrangement reaction was conducted at 80°C and its rate was monitored by ^{19}F NMR spectroscopy. For substrates with fast kinetics (R = H, *m*-OMe, *p*-I, and *p*-Br), the disappearance of the starting material peak was normalized against an internal standard (*α,α,α*-trifluorotoluene) and was measured for at least three half-lives. The k_{obs} of each reaction was determined from a first-order plot of –ln[SM] versus time. For substrates with slow kinetics (R = *m*-F, *m*-CO_2Me, and *m*-CF_3), the rate of the appearance of the first 10-15% of product was measured. The k_{obs} of each reaction was determined from a first-order plot of [P] versus time. The Hammett plot of log (k_R/k_H) versus σ showed a highly negative linear slope (ρ = −11.86; R^2 = 0.99) (Fig. 3), which is commonly observed in organic reactions involving formation of a positive charge.[23] Therefore, these results strongly suggest a heterolytic cleavage of the N–OCF_3 bond, in which a nitrenium ion and trifluoromethoxide are generated.

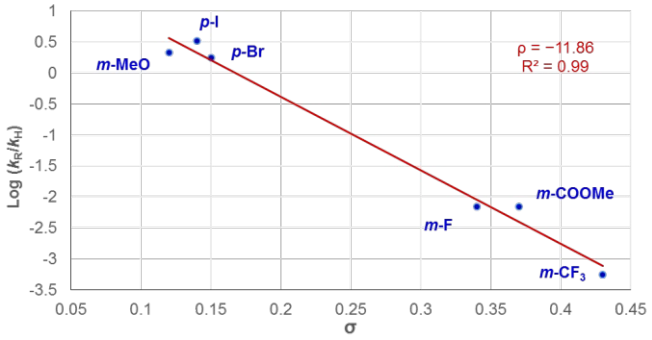
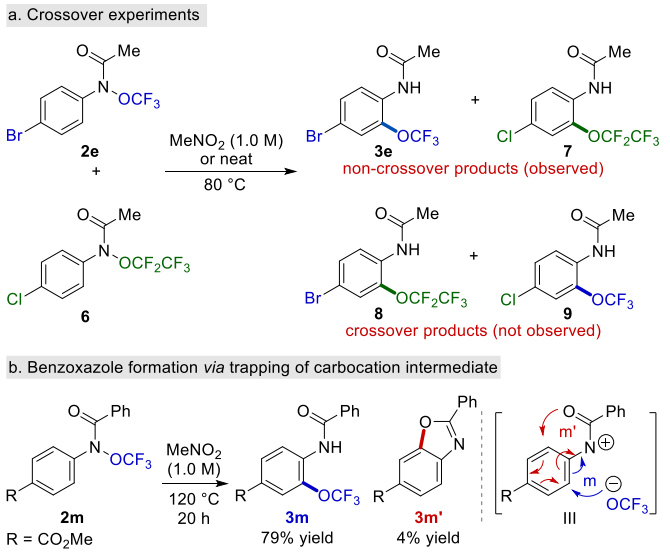


Fig. 3. Hammett plot for OCF_3-migration of R-$C_6H_4N(OCF_3)C(O)Me$ (R = *m*-OMe, *p*-I, *p*-Br, *m*-F, *m*-CO_2Me, and *m*-CF_3.

The formation of an intermediate nitrenium ion, whose stability is dependent on the electronic properties of nitrogen substituents, is further evidenced by the fact that the OCF_3-migration is very slow at 80 °C for substrates bearing a strongly electron withdrawing group at the *para*-position of the *N*-aryl substituent (R = CO_2Me (**2a**), σ_p = 0.45; COMe (**2i**), σ_p = 0.50).[24] These substrates (**2a** and **2i**) require a temperature of 120 °C for the rearrangement reaction to go to completion within a reasonable timeframe (24 h). When R = CN (**2j**, σ_p = 0.56),[24] an even higher reaction temperature (140 °C) is required to thermally cleave the N–O bond. In an extreme case, no desired product is formed upon attempted rearrangement of *N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-(trifluoromethoxy)acetamide (**2k**) due to the presence of two CF_3 groups (σ_m = 0.43)[24] on the aryl ring. In contrast, rearrangement takes place at room temperature when an electron-donating substituent, which can stabilize the positive charge, is present, e.g. R = Me (**2l**, σ_p = −0.17).[24] While the presence of nitrenium ion was evidenced by the Hammett analysis, the intermediacy of trifluoromethoxide was corroborated by detection of fluorophosgene (decomposition product of trifluoromethoxide) and BF_4^- by ^{19}F NMR spectroscopy (see the SI for details).[25]

Having investigated the N–OCF_3 bond cleavage process, we then sought to determine if the final carbon–OCF_3 bond forming step is an intramolecular reaction. We performed a cross-over experiment using *N*-(4-bromophenyl)-*N*-(trifluoromethoxy)acetamide (**2e**) and *N*-(4-chlorophenyl)-*N*-(perfluoroethoxy)acetamide (**6**), which was synthesized by treatment of *N*-(4-chlorophenyl)-hydroxamic acid with pentafluoroethyl analog of Togni reagent II.[26] Heating **2e** and **6** together either in $MeNO_2$ or neat at 80 °C formed only non-crossover products (**3e** and **7**) as monitored by GC-MS and ^{19}F NMR (Scheme 3a). The lack of cross-over products suggests that the OCF_3-migration is likely an intramolecular process and that the rate of recombination of an ion pair is much faster than an intermolecular OCF_3-group transfer (see the SI for possible intermolecular mechanisms of OCF_3-migration), which would require dissociation of two ions of opposite charge. The intramolecular mechanism is further corroborated by formation of benzoxazole **3m'** during the rearrangement reaction of methyl 4-(*N*-(trifluoromethoxy)benzamido)benzoate (**2m**) (Scheme 3b). This side product results from a competing intramolecular trapping of the nitrenium ion by an internal nucleophile, and its isolation further confirms that the nitrenium ion intermediates are very reactive and thus short lived.



Scheme 3. Crossover and trapping of carbocation intermediate experiments.

Computational Studies: Density functional theory (DFT) calculations were performed to investigate the mechanism of the OCF_3 migration of compound **2b**. The calculations were performed at the M06-2X/6-311++G(d,p)//M06-2X/6-31+G(d) level of theory with the SMD solvation model in $MeNO_2$.[27] The computed reaction energy profile of the stepwise OCF_3 migration is shown in Fig. 4a.[28] The heterolytic cleavage of the N–OCF_3 bond of **2b** to form the ion pair intermediate (**10**) requires an activation free energy of 27.6 kcal/mol (**TS1**),[29] which is feasible under the experimental conditions (80 °C). The ion pair (**10**) is an anion-π complex[30] between trifluoromethoxide and the highly electron-deficient phenyl ring. The relatively strong anion-π interaction is evidenced by the short O(OCF_3)–C distances (Fig. 4b). The recombination of the ion pair (**10**) through O–C(*ortho*) bond formation to yield the dearomatized intermediate **11** requires a very low barrier and is highly exothermic. This indicates a very short lifetime of the ion pair intermediate, which is in agreement with the crossover experiments. The low barrier of the ion pair recombination is attributed to the structural similarity of **10** and **TS2**. The O(OCF_3)–C(*ortho*) distance is only slightly shortened to 2.45 Å in the recombination transition state (**TS2**). The subsequent 1,3-hydrogen shift from the dearomatized intermediate **11** to the final product **3b** occurs through a stepwise mechanism involving the autoionization of **11** to form **12a** and **12b** followed by the highly exothermic proton transfer from **12a** to **12b** to form **3b**.[31]

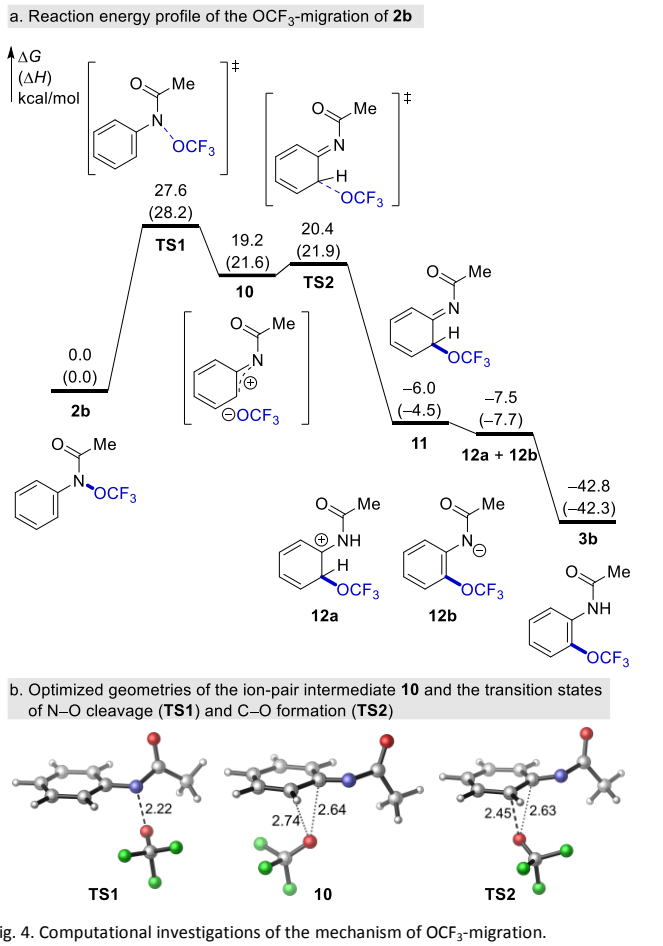
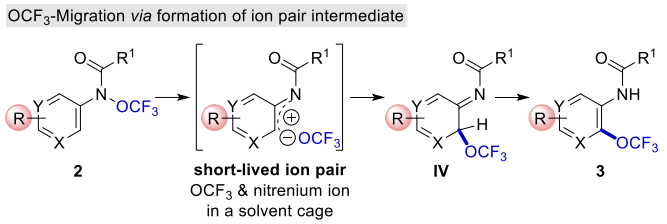


Fig. 4. Computational investigations of the mechanism of OCF_3-migration.

Altogether, these results are consistent with the proposed mechanism shown in Scheme 4. The N–O bond of **2** undergoes the thermally induced heterolytic cleavage to form a short-lived ion pair of a nitrenium ion and trifluoromethoxide. Rapid recombination of this ion pair affords intermediate **IV**, which then tautomerizes to restore aromaticity and generate the desired product **3**. The ionic mechanism for the N–O bond cleavage of *N*-protected *N*-aryl-*N*-hydroxylamines is also well-precedented in the literature.[32]



Scheme 4. Proposed mechanism for the OCF_3-migration process.

Conclusions

In summary, the experimental results obtained in this work delineate the mechanism of the two-step synthesis of *ortho*-OCF_3 (hetero)arylamine derivatives. The radical trapping experiments with TEMPO and BHT indicate that *O*-trifluoromethylated hydroxylamine derivatives are formed *via* radical recombination reaction between *N*-hydroxyl radical and trifluoromethyl radical ($\cdot CF_3$). The highly negative slope ($\rho = -11.86$) of the Hammett plot provides evidence for the generation of a positive charge in the course of the OCF_3-migration reaction and strongly suggests that the N–OCF_3 bond undergoes heterolytic cleavage. The intermediacy of a nitrenium ion and trifluoromethoxide is further verified by isolation of a benzoxazole side product and detection of trifluoromethoxide decomposition products by ^{19}F NMR spectroscopy. The lack of cross-over products in a cross-over experiment supports intramolecular transfer of the OCF_3 group. Computational studies further support the reaction pathway of a heterolytic cleavage of the N–OCF_3 bond followed by rapid recombination of a short-lived ion pair. It is hoped that the deeper mechanistic insights stemming from the current study will be useful for the development of new transformations using versatile *N*-(hetero)aryl-*N*-hydroxylamine synthons.

Acknowledgements

This paper is dedicated to Prof. Stephen L. Buchwald on the occasion of his 60th birthday. K.N.L., Z.L., and M.-Y.N. acknowledge generous start-up funds from Stony Brook University in support of this work. K.N.L. is grateful for the fellowship from the NIH Chemical-Biology training grant (T32GM092714). C.A.M.-R. and P.L. acknowledge generous start-up funds from University of Pittsburgh in support of this work. We thank TOSOH F-Tech, Inc. for their gift of $TMSCF_3$ for the preparation of Togni reagents. Calculations were performed at the Center for Simulation and Modeling at the University of Pittsburgh and the Extreme Science and Engineering Discovery Environment (XSEDE) supported by the NSF (ACI-1053575).

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