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Metal-Free Direct Intramolecular Carbotrifluoromethylation of Alkenes to Functionalized Trifluoromethyl Azaheterocycles

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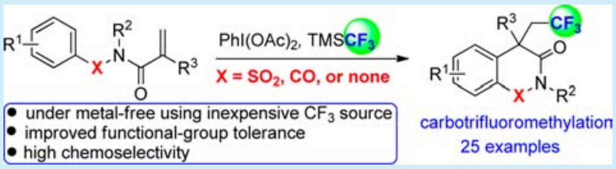
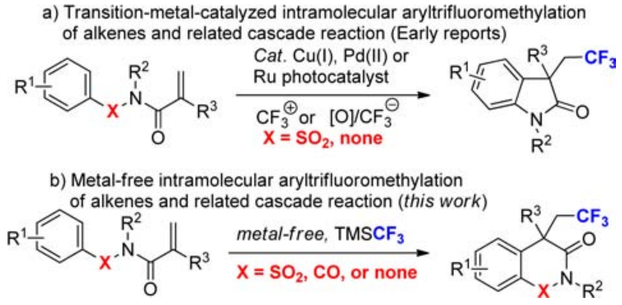
Supporting Information

ABSTRACT: The first example of a metal-free direct carbotrifluoromethylation of alkenes using inexpensive TMSCF$_3$ as the CF$_3$ source is described. The methodology not only exhibits high chemoselectivity for this transformation but also expands the substrate scope that is difficult to access by known transition-metal-catalyzed methods.



The increasing importance of trifluoromethyl aza-heterocycles[1] for the synthesis of anticholinergic, antiemetic, and antispastic drugs as well as enzyme inhibitors has spurred vigorous research for the development of new methods for C−CF$_3$ bond formation with intriguing selectivity and high atom economy.[2,3] More recently, direct difunctionalization of alkenes, such as oxytrifluoromethylation,[4] aminotrifluoromethylation,[5] and carbotrifluoromethylation,[6] has attracted considerable attention, providing the most attractive strategy for the simultaneous formation of two vicinal chemical bonds, with concomitant formation of a C−CF$_3$ bond and rings. For example, transition-metal-catalyzed aryltrifluoromethylation offers a convenient and step-economical synthesis of trifluoromethyl azaheterocycles from the respective acyclic starting materials (Scheme 1a).[6] Although significant progress has been made with high yields and a reasonable substrate scope, some crucial issues have remained fairly unaddressed. First, these reactions generally involve an expensive and highly toxic metal catalyst and the requirement for very expensive electrophilic CF$_3$ reagents,[7] making the process less applicable to large-scale synthesis especially at a late stage. Furthermore, substrates in these transformations[6] are inherently limited to those bearing only alkyl or single carbonyl linkers lacking functionality. However, substrates bearing imide groups next to the alkene remain a formidable challenge for this reaction with metal catalysis, owing to the rapid and strong coordination between the metal center and the bidentate ligand with five-membered ring chelation,[8] to render insufficient activation of the reactive functional group of the substrate. To address some of these limitations, the development of a promising and mechanistically distinct strategy for expanding the carbotrifluoromethylation of alkenes method, especially for the reaction of precursors bearing strong coordinating functional substituents under metal-free conditions with inexpensive CF$_3$ reagents, is still an urgent need.

Scheme 1. Intramolecular Aryltrifluoromethylation



Over the past two decades, hypervalent iodine(III) reagents have been widely used to promote a variety of organic transformations under metal-free conditions.[9] In contrast, the potential of iodine(III) reagents with the combination of an inexpensive CF$_3$ source such as TMSCF$_3$[7] in oxidative carbon−CF$_3$ bond formation under metal-free conditions remains widely unexplored, and examples of trifluoromethylation reactions have only recently emerged.[3f,10] In these reported reactions, the transformation might be realized using iodine(III) reagents for the generation of an electrophilic CF$_3$ radical. These results[10] and the recent advance in radical-involved aryltrifluoromethylation[6] of alkenes have prompted us to envision that the direct aryltrifluoromethylation of alkenes might be performed under metal-free conditions via a single-electron-transfer (SET) process[11] triggered by an electrophilic CF$_3$ radical generated from iodine(III) reagents.[10] Furthermore, we reasoned that the judicious combination of the appropriate hypervalent iodine reagents and TMSCF$_3$ without any metal catalysis could tolerate many different coordinating functional groups, as it would obviate the need for metal catalysis to avoid the strong coordination[8] between the metal center and the functional groups and yet still render the CF$_3$ radical electrophilic.[10] In connection with our continuous efforts devoted to the synthesis of CF$_3$-azaheterocycles,[5d] herein, we describe the first example of the development of a remarkably mild and general PhI(OAc)$_2$-mediated direct

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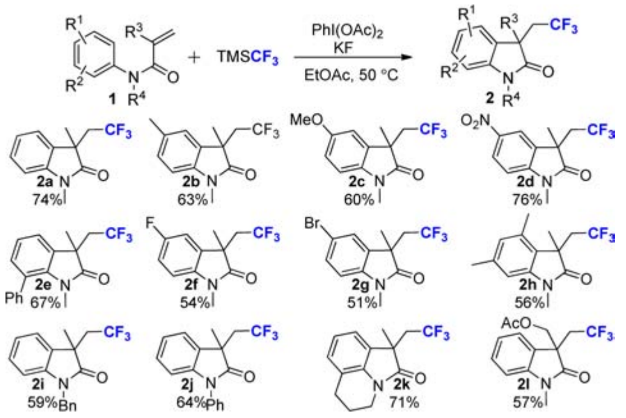
carbotrifluoromethylation of alkenes using inexpensive $TMSCF_3$ under alternative metal-free conditions.[12]

To validate the feasibility of the proposed metal-free processes, we selected *N*-arylacrylamides **1a** as the model substrate for the optimization of reaction conditions, based on recent reports that such a substrate can undergo aryltrifluoromethylation in the presence of transition-metal catalysis.[6] As such, we initially examined the reaction of **1a** by using $TMSCF_3$ as the CF_3 source and $PhI(OAc)_2$ as the oxidant in the presence of KF. We found that such a system could activate this reaction in 1,4-dioxane at 50 °C to form the desired product **2a** in 34% yield (Table S1 in the Supporting Information). Encouraged by this result, we then screened different organic solvents revealing EtOAc as being optimal to give **2a** in 74% yield, suggesting a significant solvent effect for this reaction. Among the reaction temperatures examined, the reaction at 50 °C gave the best results. Subsequently, two more substituted oxidants, such as $PhI(OPiv)_2$ or $PhI(OCOCF_3)_2$, were examined and found to result in sluggish reactions. We then investigated the effect of changing additives and found that the use of inorganic bases[13] such as CsF, Cs_2CO_3, or KF with 4 Å MS can activate the reaction, but gave the desired product in relatively low yields compared with the use of KF.

With optimized reaction conditions for the metal-free carbotrifluoromethylation reaction in hand, we evaluated this methodology with a wide range of substituted *N*-arylacrylamides. Several substituents, such as Me, MeO, Ph, NO_2, F, or Br, on the *para*- or *ortho*-position of the *N*-aryl moiety were consistent with the optimized conditions, and the corresponding oxindoles **2b**−**2g** were obtained in good yields (Scheme 2).

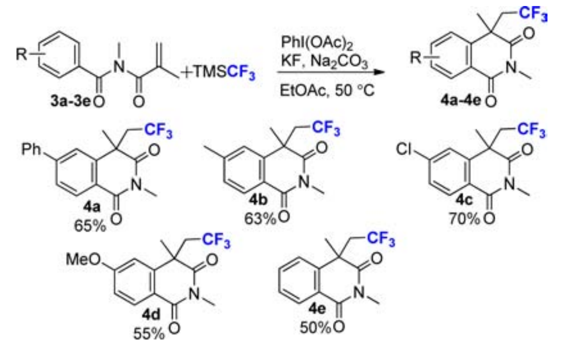
Scheme 2. Trifluoromethylation of Activated *N*-Arylacrylamide Alkenes under Metal-Free Conditions



Substrate **1h** having two substituents on the phenyl ring also provided the product **2h** in 56% yield. This reaction shows excellent compatibility with different *N*-substitution of the amides, including *N*-aryl and *N*-alkyl groups to form different trifluoromethyl heterocyclic compounds **2i**−**2k** in good yields. In addition, a functional group, such as ester (**1l**), at the 2-position of the acrylamide moiety was compatible with this metal-free system to form **2l** in good yield.

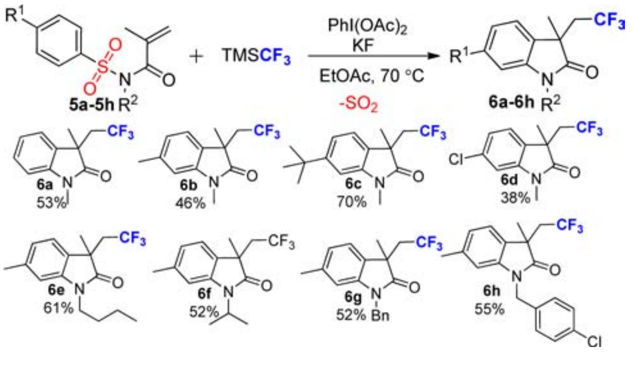
Encouraged by the aforementioned aryltrifluoromethylation reaction of *N*-arylacrylamides, we next turned our attention toward expanding the substrate scope to *α*,*β*-unsaturated imides. Much to our surprise, after optimization of the reaction conditions, the reaction of *α*,*β*-unsaturated imides **3a** gave the desired product **4a** in 65% yield by using $TMSCF_3$, $PhI(OAc)_2$, KF, and Na_2CO_3 in EtOAc at 50 °C (Scheme 3). Additional comparisons were run to evaluate the performance of Togni's reagent with the CuI catalyst in this process, under the conditions identical to those of copper-catalyzed aryltrifluoromethylation.[6] However, no desired product was obtained at different reaction temperatures from 40 to 70 °C for different reaction times in all cases, demonstrating that the catalytic activity of copper may be possibly suppressed by the strong coordination between the metal center and imide groups. It is important to note that this methodology under metal-free conditions allows us to easily realize transformation, which can serve as an attractive complementary approach to the more conventional transition-metal-catalyzed trifluoromethylation reactions.[6] We next investigated the scope of the reaction using different types of substituted *α*,*β*-unsaturated imides. A range of diversely functionalized imides, including those having electron-withdrawing and -donating groups at different positions of the phenyl ring, gave the corresponding products **4a**−**4e** in moderate to good yields.

Scheme 3. Trifluoromethylation of *α*,*β*-Unsaturated Imide Alkenes under Metal-Free Conditions



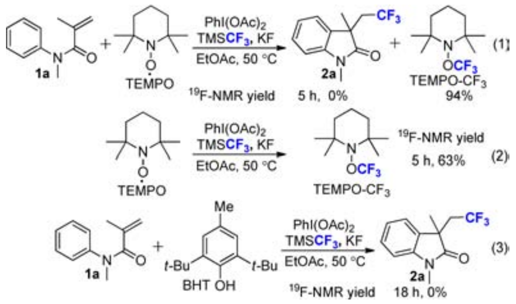
To further expand the application of such a reaction system, we also extended the substrates to conjugated tosyl amides, which underwent a cascade transformation to give trifluoromethylated oxindoles using Togni's reagent with the copper catalyst recently reported by Nevado and co-workers.[6h] To our delight, the results show that, under the standard conditions, *N*-tosyl substrates bearing different substituents at the N-atoms or having electron-withdrawing and -donating groups at the *para*-position of the phenyl ring were good for this transformation, producing desired products **6a**−**6h** in moderate to good yields (Scheme 4). It is worth mentioning that when substrates **5g**

Scheme 4. Trifluoromethylation of *α*,*β*-Unsaturated Imide Alkenes under Metal-Free Conditions



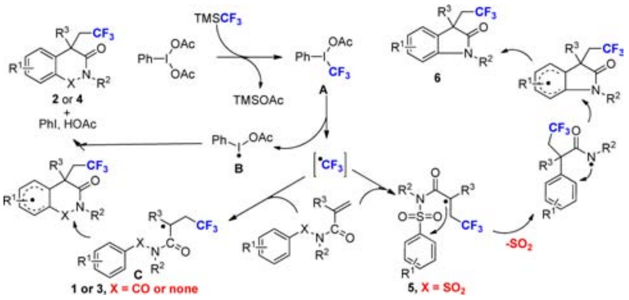
and **5h** with *N*-benzyl groups were employed, the reaction proceeded selectively and afforded the cyclized products **6g** and **6h** in good yields exclusively, which is in sharp contrast to a copper-catalyzed reaction with poor chemoselectivity.[6h]

In order to gain more insight into the reaction mechanism, several control experiments were performed. The reaction of **1a** with TMSCF$_3$, PhI(OAc)$_2$, and KF in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions produced the desired products only in very little yields (eqs 1 and 3), while the TEMPO−CF$_3$ adduct was formed in 94% yield as estimated by ^{19}F NMR analysis. In addition, the TEMPO−CF$_3$ adduct was obtained in 63% yield when TEMPO was reacted with TMSCF$_3$, PhI(OAc)$_2$, and KF under the standard conditions (eq 2). These results reveal that the CF$_3$ radical is likely involved as the reactive species under the current conditions.



Based on the control experimental results and the previous investigation on aryltrifluoromethylation of alkenes,[6] a plausible mechanism for our methodology is depicted in Scheme 5. A ligand exchange between PhI(OAc)$_2$ and TMSCF$_3$ in the presence of KF would give intermediate **A**,[10a,c] which undergoes thermal homolytic cleavage to generate the hypervalent iodine(III)-centered radical **B** and the CF$_3$ radical.[14] The CF$_3$ radical attacks alkene **1** or **3** affording radical intermediate **C**, followed by intramolecular cyclization of the resulting radical **C** with an aryl ring and rearomatization[15] to give rise to the final product **2** or **4**. The trifluoromethylated oxindoles generated from conjugated tosyl amides **5** could undergo a trifluoromethylation/aryl migration/desulfonylation and C-(sp^2)−N bond formation triggered by an electrophilic CF$_3$ radical generated from iodine(III) reagents to give final product **6**, which is consistent with a mechanism of a previously reported copper-catalyzed reaction.[6h]

Scheme 5. Proposed Mechanism for the Aryltrifluoromethylation Reaction of Alkenes



In summary, we have demonstrated the first example of a metal-free direct carbotrifluoromethylation of alkenes using inexpensive TMSCF$_3$ as the CF$_3$ source and PhI(OAc)$_2$ as the oxidant. The methodology furnishes a diverse collection of synthetically valuable trifluoromethylated heterocycles under metal-free and mild conditions. Furthermore, in comparison with reported methods for carbotrifluoromethylation of alkenes, this approach not only exhibits high chemoselectivity for this transformation but also expands the substrate scope that is difficult to access by known transition-metal-catalyzed methods, thus reflecting the synthetic utility of this method. Efforts toward an asymmetric variant of this transformation are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterizations, and Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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