Aryltrifluoromethylation

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Metal-Free Aryltrifluoromethylation of Activated Alkenes**

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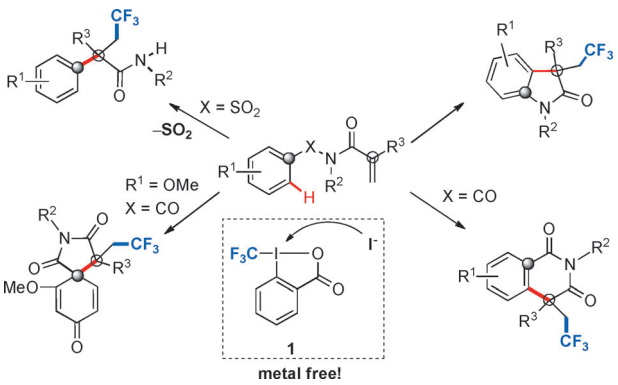
The introduction of trifluoromethyl groups into organic molecules has found widespread use in medicinal chemistry because of the improved properties (including permeability and metabolic stability) that fluorine-containing compounds display compared to their C–H counterparts.[1,2] Transition-metal-catalyzed trifluoromethylation reactions have been developed, as they feature mild reaction conditions and high functional-group compatibility.[3] In this context, reactions that involve the selective difunctionalization of alkenes have received increasing attention, as they enable the formation of C–C/C–heteroatom and C–CF_3 bonds in a single synthetic operation. Thus, efficient methods for oxotrifluoromethylation[4] and aryltrifluoromethylation reactions that are catalyzed by Pd[5] or Cu[6] complexes have been devised. In contrast, metal-free processes have been much less explored.[7] The Togni reagent (**1**) has become the most popular stoichiometric source of the CF_3 moiety in both metal-catalyzed and metal-free alkene trifluoromethylation reactions, owing to its stability, versatility, and commercial accessibility. Activation of the hypervalent iodine–CF_3 reagent **1** can occur by single electron transfer (SET) with copper salts[3f,g] or sodium aminoalkoxide in stoichiometric amounts[7] to generate a CF_3 radical ($CF_3^{\bullet}$), which can further react with unactivated alkenes. On the other hand, activation of **1** in the presence of copper or zinc complexes[8] can generate an electrophilic source of CF_3 (CF_3^+) in situ, which can further interact with both activated and unactivated olefins. We envisioned that alternatively, the reactivity of iodine(III) in **1** could be enhanced by the presence of a soft nucleophile, in analogy to the well-established late-transition-metal-free activation of ArI(X)(Y) species.[9] Because of our ongoing interest in the development of methods for the selective oxidative difunctionalization of alkenes,[10] particularly those using iodonium species,[11] we decided to test this hypothesis for the development of a metal-free aryltrifluoromethylation of alkenes. Herein, we present the realization of this concept, which was achieved through the combination of the Togni reagent (**1**) with substoichiometric amounts of tetrabutylammonium iodide (Scheme 1).

Our study commenced with the reaction of methacryloyl benzamide (**2a**) with **1**.[12] In the presence of tetrabutylammonium iodide (30 mol%) and $NaHCO_3$ (1 equiv), the trifluoromethylated isoquinolinedione **3a** could be obtained in 85% yield. Other additives, such as trimethylsilyliodide (TMSI) or KI, also delivered the desired product, albeit with lower efficiency.[12] Substitution with a *tert*-butyl group at the *meta* position of the amide led to product **3b** in 78% yield. A derivative of gallic acid produced the corresponding isoquinolinedione **3c** in 68% yield.



Scheme 1. Metal-free aryltrifluoromethylation of alkenes.

A substrate with a *para*-chlorobenzoate substituent on the nitrogen atom was converted into **3d**, the structure of which was confirmed by X-Ray diffraction analysis.[13] When a trisubstituted alkene (R^5 = Me) was used, the cyclized aryltrifluoromethylation product **3e** was obtained in 59% yield as a 8:1 mixture of diastereoisomers, thus showing that good levels of stereocontrol could be attained in these transformations (Scheme 2).

We decided to further explore the regioselectivity of this benzannulation.[14] Various substrates bearing nonsymmetric arenes were synthesized. Interestingly, in the presence of electron-withdrawing groups at the R^1 position, the *para* cyclization products **3f–h** were selectively obtained.[15] Furthermore, *para*/*meta* was preferred to *ortho*/*meta* benzannulation, as **3i** was obtained as single product from the reaction of **2i**. Substrate **2j**, in which the alkyl group on the nitrogen atom has been replaced by a *m*-CF_3-C_6H_4 group, offered four different sites for cyclization (Scheme 2): positions a or b to give the corresponding trifluoromethylated oxindoles, and positions c or d to give regioisomeric isoquinolinediones. The reaction proceeded with excellent site control, and the 6-membered-ring product **3j** was formed as a single regioisomer. Interestingly, the more sterically demanding substrate **2k** afforded the expected product **3k**, together with compound **3k″** in a 5:1 ratio and 51% yield (Scheme 3). Product **3k″** is formed by a formal 1,2-migration of the amide group, trifluoromethylation, and cyclization. The 2,4-dimethoxybenzamide **2l** delivered spirobicyclic compound **3l** as a mixture of

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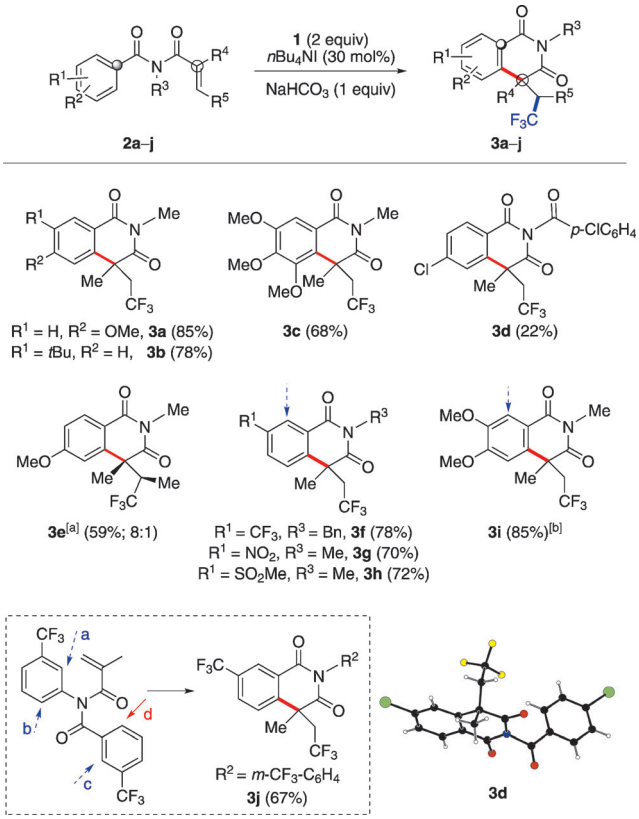
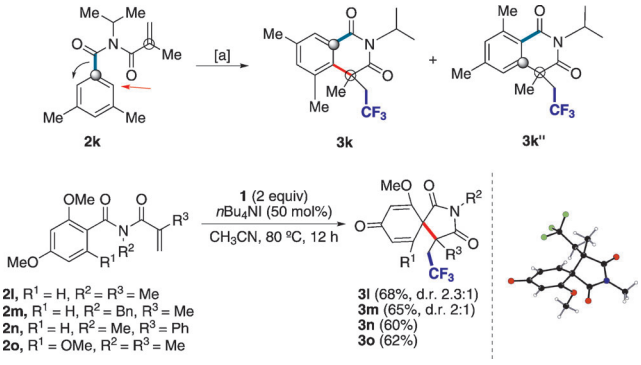


Scheme 2. Scope of the metal-free aryltrifluoromethylation reaction. Reaction conditions: CH_3CN (0.5 M), 80 °C, 12 h. Yields of isolated products after purification by column chromatography on silica gel are given. [a] Major diastereoisomer shown. [b] Reaction in the absence of base, with nBu_4NI (50 mol%).

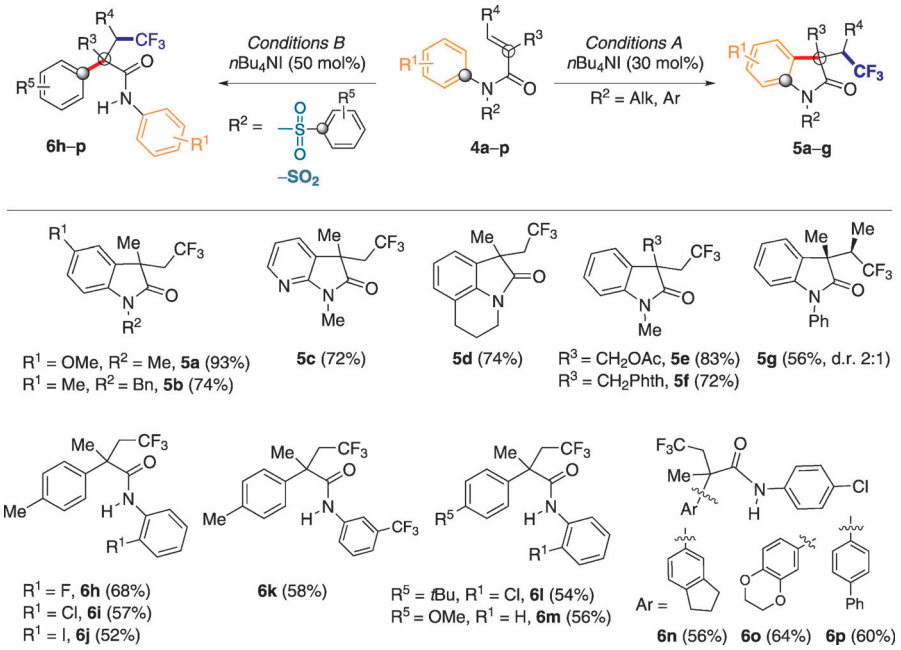


Scheme 3. Formation of other trifluoromethylated products. [a] For reaction conditions, see Scheme 2.

5a–d were isolated in good yields. The double bond was also amenable to structural variations, so that **5e** and **5f** could be also efficiently obtained. Trisubstituted alkenes were also tested (R^4 = Me), and the cyclized aryltrifluoromethylation product **5g** was isolated as a 2:1 mixture of diastereoisomers. The presence of an aromatic substituent on the nitrogen atom of **4g** was compatible with the reaction conditions. In contrast, reactions of *N*-tosylated substrates did not afford the expected oxindoles, but different trifluoromethylated compounds. Upon reduction of the amount of **1** to 1.5 equivalents and the addition of $NaHCO_3$ (1 equiv), we were able to observe the clean formation of α-aryl-β-trifluoromethyl amides **6**.[11b] These compounds result from a remarkable series of transformations, including alkene trifluoromethylation, which is followed by a formal intramolecular 1,4-aryl

diastereoisomers in a ratio of approximately 2.3:1 in 68% yield in the presence of nBu_4NI (50 mol%; Scheme 3). The structure of the major isomer was confirmed by X-ray diffraction analysis.[13] A similar outcome was obtained when the *N*-benzyl-substituted substrate **3m** was employed; a phenyl substituent at the olefin was also well tolerated, as **3n** was obtained in 60% yield as a single isomer. Interestingly, 2,4,6-trimethoxy-substituted **2o** delivered trifluoromethylated spirobicycle **3o** as the sole reaction product in 62% yield.[16,17]

This metal-free aryltrifluoromethylation of alkenes was extended to the synthesis of oxindoles[5,6] by employing α,β-unsaturated amides **4**.[18] Different substitution patterns on the aromatic ring and various alkyl or aryl groups on the nitrogen atom (R^1 and R^2 of compound **4**; Scheme 4) were well-tolerated, and the trifluoromethylated oxindoles



Scheme 4. Synthesis of trifluoromethylated oxindoles and α-aryl-β-trifluoromethylamides. Yields of isolated products after purification by column chromatography on silica gel are given. Products **5a–g** were obtained under conditions A: **1** (2 equiv), CH_3CN (0.5 M), 80 °C, 12 h. Products **6h–p** were obtained under conditions B: **1** (1.5 equiv), $NaHCO_3$ (1 equiv), CH_3CN (0.5 M), 80 °C, 12 h. Bn = benzyl, Phth = phthaloyl.

migration, desulfonylation, and H atom abstraction. First, we studied variations in the substitution pattern of the aryl group that is directly bonded to the nitrogen atom of the tosyl amides (R^1; Scheme 4). Thus, *ortho*-substituted arenes were converted into products **6h–j** in moderate to good yields (52–68%). The introduction of electron-deficient groups such as CF_3 (**6k**) did not seem to interfere with the reaction. The substitution pattern on the aromatic ring of the sulfonamide group (R^2; Scheme 4) was also explored. Substrates with *para-tert-b*utyl or *para*-methoxy sulfonamide substituents were efficiently transformed into the corresponding β-trifluoromethylamides **6l** and **6m**, respectively. The reaction is completely regioselective, as the 1,4-migration of the aryl group takes place exclusively through the carbon atom that was bonded to the SO_2 group in the starting material. Thus, substrates bearing indane, 1,4-dioxolane, or biphenyl sulfonyl moieties (**4n–p**) were transformed into amides **6n–p** in good yields. Control experiments for the identification of the intermediates involved in these transformations were also designed.[12] The ^{1}H NMR spectra recorded for the crude mixtures at the end of the reaction indicated the presence of CF_3I and the tetrabutylammonium salt of 2-iodobenzoic acid (**7**).[19] In a sealed NMR tube, a 1:1 mixture of **1** and nBu$_4$NI in CD_3CN was heated to 80°C for 16 h. ^{1}H and ^{19}F NMR spectroscopy confirmed the sole presence of salt **7** and CF_3I (Figure 1a). A solution of **2a** was then added, and the mixture was heated to 80°C for another 12 h. The starting material was recovered intact, which demonstrates that in situ-generated CF_3I is not a productive trifluoromethylating agent in these transformations. In contrast, when the mixture of **1** and nBu$_4$NI was heated to 80°C for two hours, we could observe the disappearance of **1** and the formation of a new intermediate, along with formation of the salt **7** in a ratio of approximately 2:1 (Figure 1b). When a solution of **2a** was added to this mixture, full conversion into **3a** was observed. We assume that reagent **1** reacts with I^- to form an iodonium complex **I**, which is in line with the species detected by HRMS-ESI. The spectroscopic characterization of **I** showed a quartet ($J = 3.0$ Hz) for the ^{13}C signal of the C–H atom in the α position of the iodine atom that is due to through-space interactions with the CF_3 group, thus supporting a 10-I-3 structure[20] for this reaction intermediate.[8a,12] The reactions of **2a** and **4l** in the presence of di-*tert*-butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) led to the desired products in yields almost comparable to those obtained under the standard conditions. When these reactions were followed by ^{19}F NMR spectroscopy, the corresponding TEMPO–CF_3 adducts could not be detected, which points towards a non-radical mechanism for these transformations; this finding is in contrast to the radical trifluoromethylation of isonitriles that was recently reported by Studer and co-workers, and which proceeded under similar conditions.[21] A mechanistic proposal that is compatible with these experimental observations is summarized in Scheme 5. In the first step of the reaction, tetrabutylammonium iodide seems to activate the Togni reagent, thus generating the highly reactive iodine(III) intermediate **I**. This highly electrophilic species then reacts with the activated double bond to

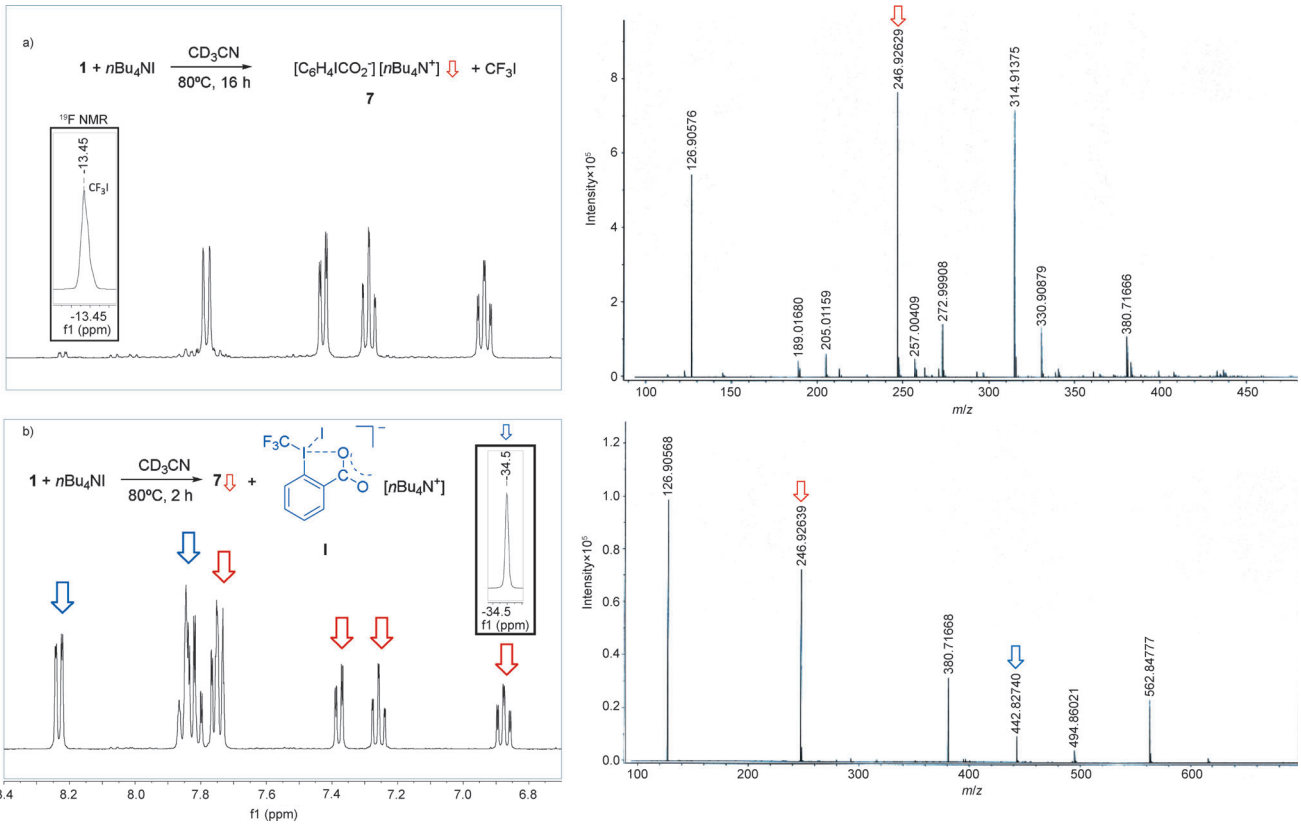
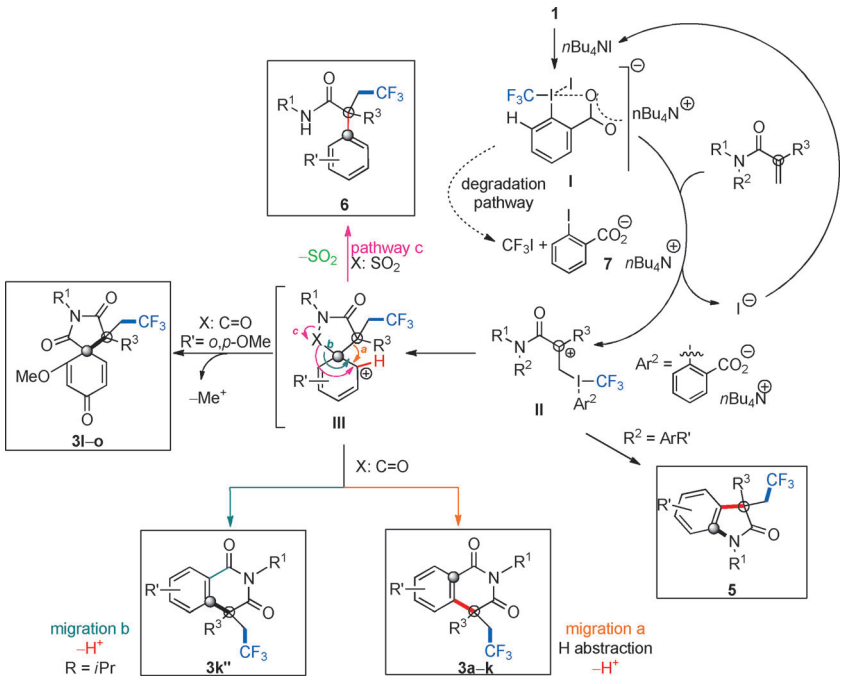


Figure 1. Characterization of the active species.



Scheme 5. Proposed reaction mechanism.

give intermediate **II**. The reaction of **II** with the aromatic ring can proceed in two different ways depending on the substrate. For acryloyl benzamides **2**, a 5-*ipso* cyclization takes place on the aromatic ring, which generates aryl cation **III**, where X = C(O). This intermediate can then undergo 1,2-migration of the $C(sp^3)$–$C(sp^3)$ bond (*a*, orange), which is followed by H atom abstraction to give isoquinolinediones **3a–k**.[16] Alternatively, migration of the $C(sp^3)$–$C(sp^2)$ bond (*b*, blue) will form product **3k″** in a formal 1,2-migration of the carbonyl group. The presence of methoxy groups in the *ortho* and *para* positions of the benzamide moiety seems to favor the termination of the reaction by the loss of a methyl cation of the transient oxonium ion to produce spirobicyclic products **3l–o**.[17] Alternatively, in the case of tosyl amides, a 5-*ipso* cyclization takes place on the sulfonyl aromatic ring **III** (X = SO_2), which will be followed by rapid desulfonylation to give quaternary amides **6** (*c*, pink). In contrast, for shorter tethers, reaction of **II** (R^2 = Ar) with the aromatic ring in a 5-*exo* manner will generate oxindoles **5**.

In summary, the first metal-free aryltrifluoromethylation of alkenes has been developed. Trifluoromethylated isoquinolinediones and oxindoles can be synthesized in excellent yields and in a highly regioselective fashion. Trifluoromethylated spirobicycles and α-aryl-β-trifluoromethylamides that bear an α-quaternary stereocenter were also obtained. Tetrabutylammonium iodide is able to activate the Togni reagent by producing a highly reactive iodine(III) species, which reacts with alkenes to form a new C–CF_3 bond. Further studies on the mechanisms of these transformations are currently underway.

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[12] For optimization of the reaction conditions, detailed experimental procedures, and the characterization of starting materials and products, see the Supporting Information.

[13] CCDC 940668 (**3d**) and CCDC 945177 (**3l**) contain 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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