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C–H Functionalization

# Direct Aromatic C–H Trifluoromethylation via an Electron-Donor–Acceptor Complex

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**Abstract:** A novel electron-donor–acceptor (EDA) complex-mediated direct C–H trifluoromethylation of arenes with Umemoto's reagent has been developed. This transformation has been enabled by an unprecedented EDA complex formed by Umemoto's reagent and an amine, which was supported by experiments and theoretical calculations. The radical-based methodology presented here allows to access highly-functionalized trifluoromethyl arenes in up to 81% chemical yield.

Electron-donor–acceptor (EDA) complexes, also called charge-transfer (CT) complexes,[1] were introduced by Mulliken[2] to define a new type of adducts. This new molecular aggregate, generally associated with conspicuous color change and are proved to absorb radiation in the visible region, can be generated by the molecular interactions between electron donors and acceptors. Over the last six decades, the photophysical properties of EDA complexes have been extensively studied.[1,3] Although EDA complexes are considered as key intermediates in some reactions, especially in single-electron transfer (SET) events, their use in chemical synthesis is limited since electron transfers from donors to acceptors in EDA complexes are fast and reversible. Recently, some useful transformations, such as asymmetric alkylation, perfluoroalkylation and arylation of aromatic compounds, have been achieved assisted by EDA complexes.[4] These promising results imply that EDA complexes may find more applications in organic synthesis.

Introducing fluorine-containing functional groups into the molecular scaffold of organic compounds greatly alters their intrinsic properties.[5] It is not surprising that tremendous advances have been achieved in direct C–H trifluoromethylation of arenes.[6] Radical-based trifluoromethylation has received increasing attention because direct C–H trifluoromethylation could be realized relatively under mild conditions using active $CF_3^{\bullet}$ radical species.[7–10] There are three major ways to generate $CF_3^{\bullet}$ radical (Figure 1 a): i) oxidation of nucleophilic trifluoromethylating reagents, such as $TMSCF_3$,[8a–c] Langlois's reagent ($CF_3SO_2Na$)[8d–f] and $(CF_3SO_2)_2Zn$;[8g–h] ii) reduction of electrophilic trifluoromethylating reagents, such as $CF_3SO_2Cl$,[9a–b] Umemoto's reagent,[9c–h] Togni's reagent[9i–l] and $CF_3I$;[9m–o] iii) homolysis or mesolysis of trifluoromethyl halides.[10] Recently, Melchiorre group reported photochemical aromatic perfluoroalkylation driven by the photochemically activated EDA complexes.[4b] Despite these great advances, generation of $CF_3^{\bullet}$ radical through an EDA complex is rare.[11]

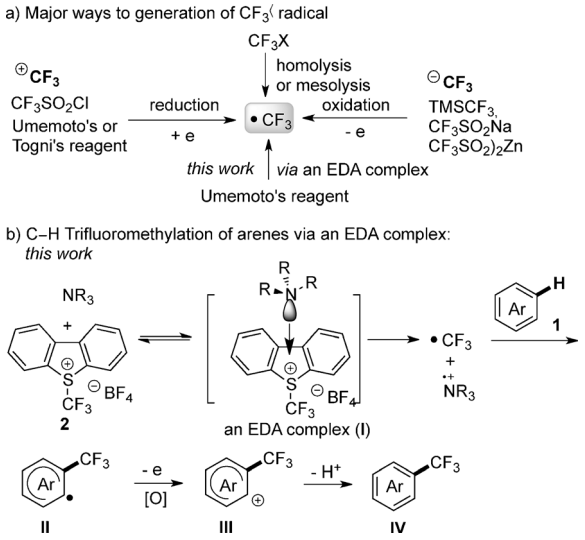


**Figure 1.** Radical trifluoromethylation.

It is known that tertiary amines are able to form EDA complexes with electron-accepting molecules, which can facilitate SET events.[12] We envisage that electron-deficient Umemoto's reagent (**2**) can serve as an electron acceptor to form an EDA complex with a tertiary amine. Thus, we propose a radical C($sp^2$)–H trifluoromethylation by taking advantage of this EDA complex. As shown in Figure 1 b, the lone pair of a tertiary amine can engage in an EDA complex (**I**) with **2**. The reduced Umemoto's reagent generated from electron transfer of the EDA complex can collapse into $CF_3^{\bullet}$ radical irreversibly. The $CF_3^{\bullet}$ radical is then added onto an arene (**1**) to give a radical intermediate **II**. The radical **II** is oxidized to cation **III**. After deprotonation, trifluoromethylated arenes is produced. This EDA complex-mediated process could render direct C–H trifluoromethy-

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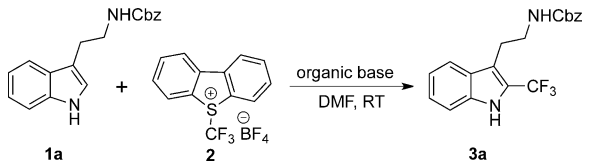
lation of arenes without a directing group and transition-metal catalyst under mild conditions.

Our rationale was evaluated by selecting tryptamine derivative **1a** and Umemoto's reagent **2** as reaction partners. To our delight, the trifluoromethylated product **3a** was obtained in 63% yield based on $^{19}F$ NMR analysis when a solution of **1a** and **2** in DMF was treated with trimethylamine (TEA) at room temperature for 18 h (Table 1, entry 1). This result prompted us to investigate a series of secondary and tertiary amines. All the amines we tested could promote this transformation to give **3a** with 45–73% NMR yield (entries 2–11). *N*-Methylmorpholine (NMM) was superior to other amines with 73% NMR yield (64% isolated yield) (entry 4). Solvents were also examined. However, none of them gave improved results (entries 12–18). Oxygen had no obvious effect on this transformation (entry 19).

**Table 1.** Reaction condition optimization.[a]



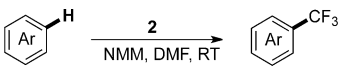

**1a** **2** **3a**

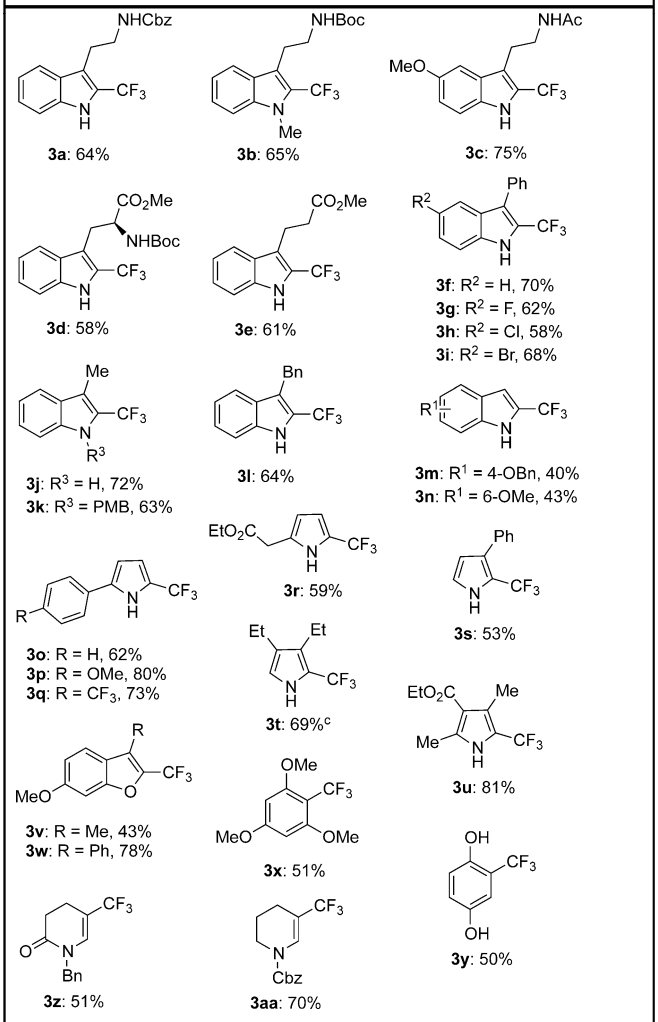
| Entry | Organic base | Solvent | Yield[b] [%] |
|---|---|---|---|
| 1 | $Et_3N$ | DMF | 63 |
| 2 | $iPr_2NEt$ | DMF | 45 |
| 3 | TMEDA | DMF | 63 |
| 4 | NMM | DMF | 73 (64[c]) |
| 5 | morpholine | DMF | 71 |
| 6 | DMEDA | DMF | 72 |
| 7 | $iPr_2NH$ | DMF | 63 |
| 8 | dibenzylamine | DMF | 61 |
| 9 | piperidine | DMF | 53 |
| 10 | pyrrolidine | DMF | 59 |
| 11 | $Et_2NH$ | DMF | 57 |
| 12 | NMM | DMA | 61 |
| 13 | NMM | NMP | 64 |
| 14 | NMM | DMSO | 64 |
| 15 | NMM | MeOH | 31 |
| 16 | NMM | MeCN | 53 |
| 17 | NMM | THF | 46 |
| 18 | NMM | DCM | 50 |
| 19[d] | NMM | DMF | 72 |

[a] Reaction conditions: A solution of **1a** (0.1 mmol), **2** (0.2 mmol) and amine (0.2 mmol) in the indicated solvent (1.0 mL) was stirred at room temperature for 18 h. [b] Determined by $^{19}F$ NMR with $PhCF_3$ as the internal standard. [c] Isolated yield. [d] Under $N_2$ using degassed solvent. TMEDA = *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine, NMM = 4-methylmorpholine, DMEDA = *N*,*N*′-dimethyl-1,2-ethanediamine.

With establishing this simple and efficient trifluoromethylation protocol, we proceeded to explore the scope and limitations of this transformation (Table 2). Firstly, various indole derivatives were examined, including biologically important tryptamine, tryptophan and melatonin derivatives. We were pleased to find that all the indole derivatives could undergo this reaction smoothly to give desired product **3a**–**3n** in 43–75% isolated yield. The N1 position could be free or protected (**3a** vs **3b**, **3j** vs **3k**) without affecting this transformation significantly. C3 Substitution had a positive effect on this reaction and C3-free indoles gave lower yields (40% for **3m** and 43% for **3n**). Pyrrole derivatives could also go through this trifluoromethylation frequently without protecting nitrogen atom. Di-, tri-, tetrasubstituted trifluoromethylated pyrroles **3o**–**3u** were produced in up to 81% yield. 2-Trifluoromethylated benzofurans **3v** (43% yield) and **3w** (78% yield) could also be prepared by means of this method. Electron-rich benzenes, such as 1,3,5-trimethoxybenzene and hydroquinone, were suitable substrates. The desired products were isolated in acceptable yields (51% for **3x** and 50% for **3y**). Cyclic enamides could also be trifluoromethylated to give **3a** and **3aa** with 51 and 70%, yield, respectively. Attempts to trifluoromethylation of electron-neutral and deficient benzenes, as well as pyridine derivatives, failed.

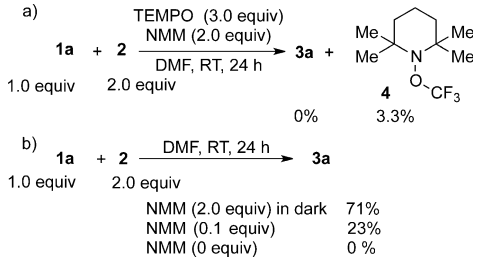
**Table 2.** Substrate Scope and limitation of trifluoromethylation.[a,b]




[a] Reaction conditions: A solution of **1** (0.2 mmol), **2** (0.4 mmol) and NMM (0.4 mmol) in DMF (1.0 mL) was stirred at room temperature. [b] Isolated yield. [c] Determined by $^{19}F$ NMR with $PhCF_3$ as the internal standard.

In order to gain some insights into the mechanism of this reaction, a series of control experiments were carried out (Scheme 1). As shown in Scheme 1a, this transformation could be terminated completely by introducing TEMPO. No desired product **3a** was observed, and $CF_3^{\bullet}$ radical trapping product **3** was obtained instead in 3.3% yield based on $^{19}F$ NMR analysis, which implied the radical nature of this reaction. When the reaction was carried out in dark, the desired product **3a** could be generated in 71% yield, which showed that the light did not affect this transformation. When the loading of NMM was reduced to 0.1 equivalents, **3a** could be obtained in 23% yield, which suggested that NMM was served as an initiator or could be regenerated. In the absence of NMM, the starting material **1a** was fully recovered (Scheme 1b).




**Scheme 1.** Control experiments. The yield and conversions were determined by $^{19}F$ NMR with $PhCF_3$ as the internal standard.

The $CF_3^{\bullet}$ radical could be observed using electron paramagnetic resonance (EPR) in the presence of a spin trap *tert*-butyl-α-phenylnitrone (PBN) (Figure 2). When PBN was added into the reaction mixture under the standard conditions, a spectrum at $g = 2.00646$ (298 K) was recorded that could be clearly traced to the $CF_3$-PBN spin trap.[13]

Given the weak reductive capacity of NMM ($E^{NMM/NMM^{+\bullet}} = 1.2$ V vs SCE)[14] and oxidative capacity of Umemoto's reagent **2** ($E^{2/2^{\bullet-}} = -0.35$ V vs SCE),[15] intermolecular SET from NMM to **2** is thermodynamically disfavored. It is known that tertiary amines are able to form EDA complexes with electron-accepting molecules, so this SET event can be facilitated by an EDA complex of **2** with NMM (Figure 3a).[12] The existence of the EDA complex could be supported by the $^1H$ NMR spectroscopy and UV/VIS spectrum.[1h,16] Using Job's method of continuous variations, a molar donor/acceptor ratio of 1:1 in solution for EDA was readily established.[17] Concomitantly the equilibrium constants $K_{EDA}$ ($K_{EDA} = 18.7$) for formation of the EDA complex were determined spectrophotometrically (using the Benesi–Hildebrand method).[18] Theoretical calculations showed that the formation of the EDA complex was thermodynamically favored (for details, see Supporting information) (Figure 3d). This band is associated with an electron-transfer transition from HOMO (H) to LUMO (L) of this complex. For details, see Supporting Information). The formation of the EDA complex was further supported by NMR titration (Figure 3b). The appearance of a new set of signals in the $^1H$ NMR spectroscopy of the mixture of NMM and **2** provided proof of the EDA complex.

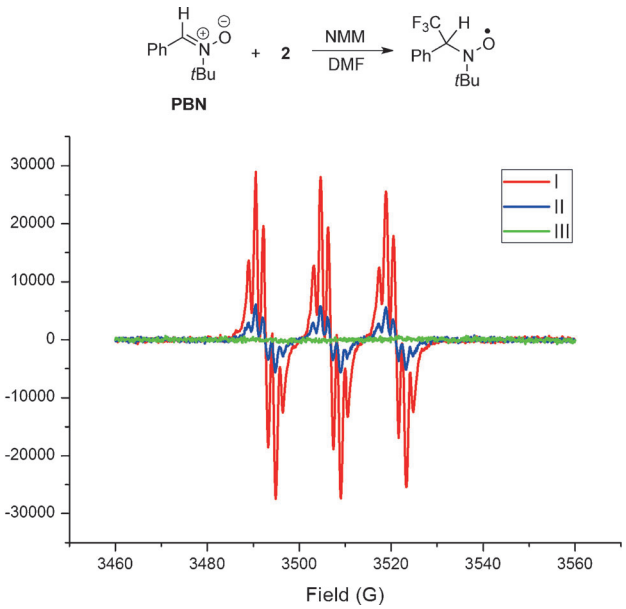



**Figure 2.** X-band EPR spectrum obtained in DMF at 298 K in the presence of PBN. Line **I**: A solution of **1a** (0.1 mmol), **2** (0.2 mmol), NMM (0.2 mmol), PBN (0.2 mmol) in DMF (1 mL). Line **II**: A solution of **1a** (0.1 mmol), **2** (0.2 mmol), PBN (0.2 mmol) in DMF (1 mL). Line **III**: A solution of PBN in DMF (1 mL).

Based on our experimental observations, a possible mechanism is proposed for this transformation (Figure 4). In contrast to recent examples where the photo-activity of EDA complexes is responsible,[4a–d] the reversible electron transfer (ET) in the EDA complex **5** is activated thermally and lead collapse of **5** into $CF_3^{\bullet}$ radical and $NMM^{+\bullet}$ irreversibly.[4f–h,19] The $CF_3^{\bullet}$ radical is then added onto arene **1a** to give radical **7**. Radical **7** is oxidized by radical cation $NMM^{+\bullet}$ to generate cation **8** and regenerate NMM (path A). Ultimately deprotonation of cation **8** assisted by NMM yields the final product **3a**. At this stage, oxidation of **7** to **8** by Umemoto's reagent **2** cannot be ruled out completely (path B).

In summary, we have described originally a simple and efficient method for direct C–H trifluoromethylation of arenes with Umemoto's reagent. The $CF_3$ radical is generated by an EDA complex formed by Umomoto's reagent and an amine, a novel medium which is different from the reported methods. Some experiments and theoretical calculations were furnished to support the EDA complex. Transition-metal catalysts, directing groups and external oxidants can be avoided. The methodology presented here allows to access highly-functionalized $CF_3$-containing indoles, pyrroles, benzofurans and electron-rich benzenes at room temperature in good chemical yields. Further application using this EDA complex, as well as more detailed mechanism investigation, are underway in our laboratory.

## Experimental Section

A 3 mL nap vial was equipped magnetic stir bar and was charged with a solution of arene or heteroarene **1** (0.2 mmol, 1.0 equiv), Umemoto's reagent **2** (0.4 mmol, 2.0 equiv), NMM (0.4 mmol,

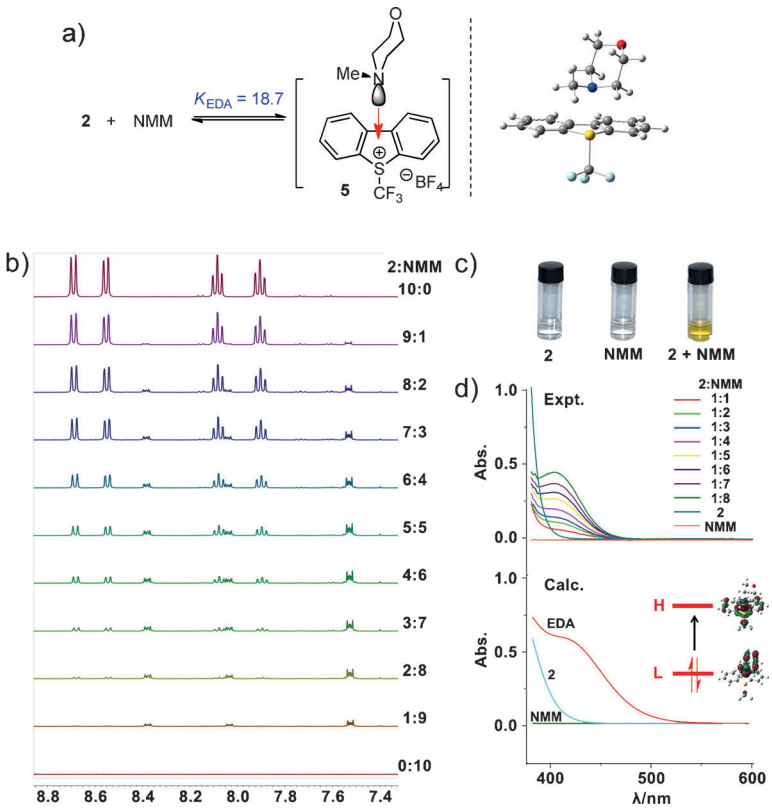



**Figure 3.** Mechanistic investigations. a) EDA complex of NMM and **2** and its theoretical structure (right) using the DFT method with 6-311++G(d,p) basis sets. b) NMR titration. c) Visual appearance of the separate reaction components and the colored EDA complex. d) Experimental (top, recorded in $CH_3CN$) and calculated (bottom) UV/VIS spectrum of NMM, **2** and mixture of NMM and **2**.

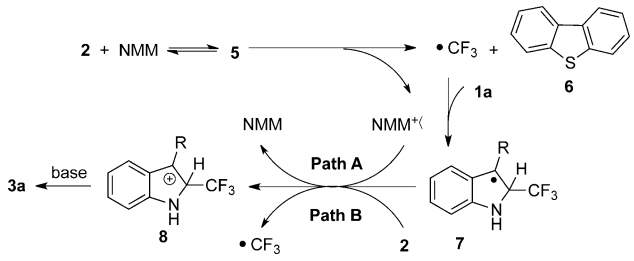



**Figure 4.** Proposed mechanism.

2.0 equiv) in DMF (1 mL). After the reaction was complete (as judged by TLC analysis), the mixture was poured into a separatory funnel containing $H_2O$ (15 mL) and $Et_2O$ (15 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (2× 15 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure after filtration. The crude product was purified by flash chromatography on silica gel to afford the desired product **3**.

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**Keywords:** arenes · C–H functionalization · donor–acceptor systems · electron transfer · trifluoromethylation

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# COMMUNICATION

**C–H Functionalization**

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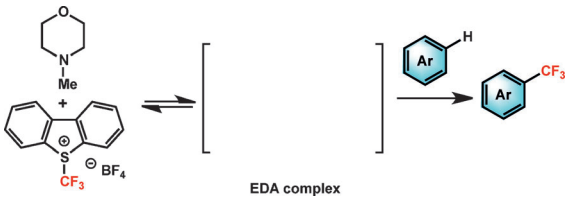
**Direct Aromatic C–H Trifluoromethylation via an Electron-Donor–Acceptor Complex**




**New complex in town**: Direct C–H trifluoromethylation of arenes with Umomoto's reagent is described. This strategy is enabled by a novel electron-donor–acceptor (EDA) complex formed by Umomoto's reagent and an amine.