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Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes Enabled by an Electron-Donor–Acceptor Complex of Togni's Reagent with a Tertiary Amine

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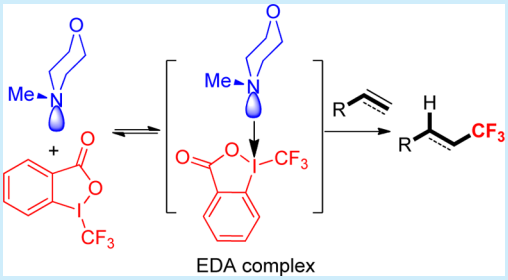
Supporting Information

ABSTRACT: An electron-donor–acceptor (EDA) complex between Togni's reagent and a tertiary amine has been introduced. The existence of this EDA complex was supported by NMR titration experiments. The hydrotrifluoromethylation of unactivated aliphatic alkenes and alkynes enabled by this EDA complex has also been developed. This hydrotrifluoromethylation protocol is operationally simple and promoted by a tertiary amine.



Electron-donor–acceptor (EDA) complexes introduced by Mulliken define a new type of noncovalent interaction.[1] An EDA complex is an association of two molecules, named an electron donor and an electron acceptor.[2] Although the photophysical properties of EDA complexes have been extensively studied,[3] EDA complex-enabled chemical synthesis remains largely unexplored because the electron transfer from the donor to the acceptor is fast and reversible.[4−6] Recently, useful photochemical transformations, such as cycloaddition, alkylation, and arylation of aromatic compounds, have been achieved mediated by EDA complexes.[5] Despite these promising advances, EDA complex-enabled synthetic chemistry is still in its infancy and in need of further investigated.

Very recently, our group reported a new type of EDA complex using a tertiary amine as the electron donor and Umemoto's reagent as the electron acceptor.[7] By taking advantage of this EDA complex, a direct aromatic C–H trifluoromethylation has been developed (Figure 1a).[7] Inspired by this work, we sought to apply the EDA complex to more challenging reactions. Despite the fact that tremendous achievements have been made in the trifluoromethylation of different functional groups, the hydrotrifluoromethylation of unactivated alkenes and alkynes is still synthetically challenging and remains largely unexplored.[8,9] Recently, Liu's research group reported the organic base-promoted radical trifluoromethylation of alkenes and related cascade reactions with Togni's reagent.[9a,c] Despite these advances, the exploration of alternative and mechanistically distinct systems is still imperative. Herein, a strategy for hydrotrifluoromethylation of unactivated aliphatic olefins and alkynes was proposed by taking advantage of the EDA complex between an electrophilic trifluoromethylating reagent and a tertiary amine (Figure 1b).

This rationale was then tested using alkene **2a** as the model substrate (Table 1). To our delight, the desired hydrotrifluoromethylation product **3a** was obtained in 64% yield based on ^{19}F NMR analysis when a solution of Umemoto's reagent **1a**[10a,b] and **2a** in DMF was treated with NMM at room temperature for 24 h (entry 1). When we use Togni's reagent **1b**,[10c−e] another typical electrophilic trifluoromethylating reagent, as an electron acceptor, the yield slightly improved to 66% (entry 2). However, no desired product was furnished when Togni's reagent **1c** was used instead of **1b** (entry 3). Other electron donors, such as 1-methylpiperidine, Et_3N, piperidine, and *i*-

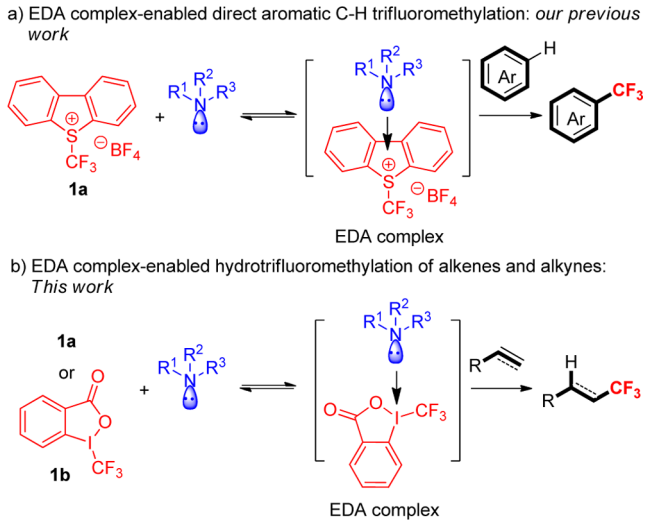


Figure 1. Trifluoromethylation and hydrotrifluoromethylation enabled by an EDA complex.

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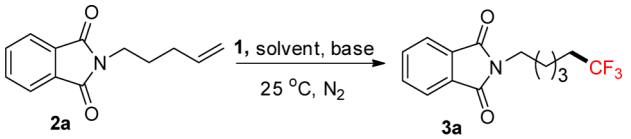
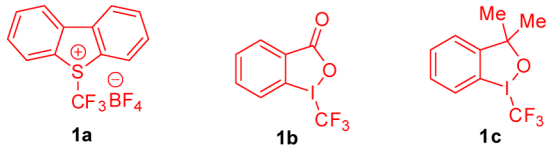
Table 1. Optimized Reaction Conditions[a]





1a 1b 1c

entry	solvent	amine	1	yield (%)[b]
1	DMF	NMM	**1a**	64
2	DMF	NMM	**1b**	66
3	DMF	NMM	**1c**	0
4	DMF	*N*-Me-piperidine	**1b**	63
5	DMF	Et_3N	**1b**	51
6	DMF	piperidine	**1b**	58
7	DMF	*i*-Pr_2NH	**1b**	28
8	NMP	NMM	**1b**	57
9	DMAc	NMM	**1b**	62
10	NMF	NMM	**1b**	64
11	THF	NMM	**1b**	36
12	**pyrrolidin-2-one**	**NMM**	**1b**	**80** (78[c])
13[d]	pyrrolidin-2-one	NMM	**1b**	64
14[e]	pyrrolidin-2-one	NMM	**1b**	80
15	pyrrolidin-2-one	–	**1b**	0
16[f]	pyrrolidin-2-one	NMM	**1b**	70

[a]Reaction conditions: a solution of **2a** (0.2 mmol), **1** (0.4 mmol) and amine (0.4 mmol) in the indicated solvent (2.0 mL) was stirred at 25 °C for 24 h. [b]Determined by ^{19}F NMR with $PhCF_3$ as the internal standard. [c]Isolated yield. [d]Open to air. [e]Degassed solvent was used. [f]In dark. NMM = 4-Methylmorpholine, NMP = 1-Methyl-2-pyrrolidinone, DMAc = *N*,*N*-Dimethylacetamide, NMF = *N*-Methylformamide.

Pr_2NH, could not give improved results (entries 4–7). The solvent effect was then examined (entries 4–12). Pyrrolidin-2-one proved to be the optimal solvent with an 80% NMR yield (78% isolated yield) (entry 12). Oxygen could affect this reaction slightly. The reaction carried out open to air resulted in a 64% yield, while an 80% yield was obtained in the degassed solvent under nitrogen (entries 13 and 14). The electron donor was crucial to this transformation and no product was observed in the absence of the tertiary amine (entry 15). When the reaction was carried out in the dark, a slightly lower yield (70%) was obtained (entry 16). This phenomenon suggests that the EDA complex is activated thermally.

Given that an EDA complex can be formed between an amine and Umemoto's reagent **1a**,[7] we believe that the formation of an EDA complex between Togni's reagent **1b** and an amine is also possible. To our delight, the encounter complex **I** could be generated when NMM was selected as the electron donor. The ^1H NMR signals for the mixture of Togni's reagent **1b** with NMM shifted downfield when the ratio of Togni's reagent **1b** to NMM increased (Figure 2a). Concomitantly, the equilibrium constant K_{EDA} (K_{EDA} = 3.83) for the formation of the EDA complex was determined by NMR analysis (using Foster's method) (Figure 2b).[11] The 1:1 molar ratio for the donor and acceptor was readily established using Job's method of continuous variations (Figure 2c).[12]

In order to gain further insight into the mechanism of this reaction, a series of control experiments were performed. The

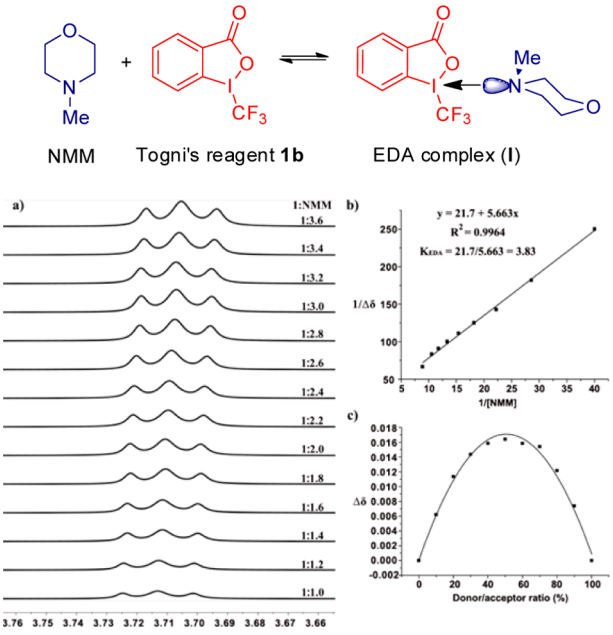
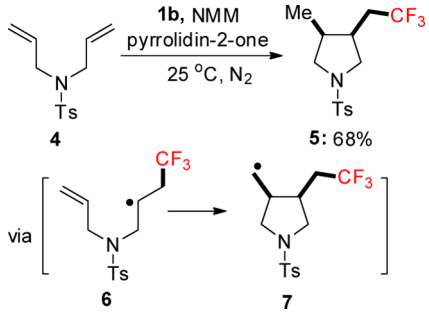


Figure 2. Mechanistic investigations. (a) NMR titration. (b) K_{EDA} for formation of the EDA complex determined by NMR analysis. (c) Job's plot.

model reaction could be totally inhibited when TEMPO was introduced into the reaction mixture. The radical nature of this reaction was further confirmed by a radical clock experiment.[13] When a solution of Togni's reagent (**1b**) and bisallyl sulfonamide **4** was treated with NMM, cyclic sulfonamide **5** was generated through 5-exo-trig radical cyclization of radical **6** (Scheme 1). The CF_3· radical could be also observed using

Scheme 1. A Radical Clock Experiment



electron paramagnetic resonance (EPR) in the presence of a spin trap, *tert*-butyl-α-phenylnitrone (PBN)[14] (for details, see the Supporting Information).

We next tried to determine the source of hydrogen with the assistance of deuteration experiments (Scheme 2). Hydrotrifluoromethylation of alkene **2a** with Togni's reagent **1b** proceeded smoothly (58% yield) in DMF using *n*-Bu_3N as the electron donor. When the reaction mixture was treated with deuterated amine (*n*-Bu_3N-d_{27}), no deuterated product was observed. When the reaction was run in deuterated solvent (DMF-d_7), 20% of the product was deuterated. When we used deuterated amine (*n*-Bu_3N-d_{27}) and solvent (DMF-d_7), the yield of the desired product decreased to 15%, and 37% of the product was deuterated. These results implied that the solvent served as the major hydrogen source.

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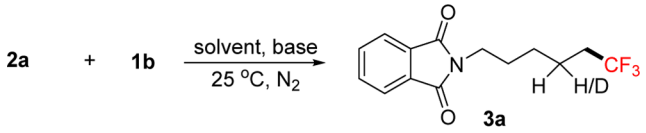
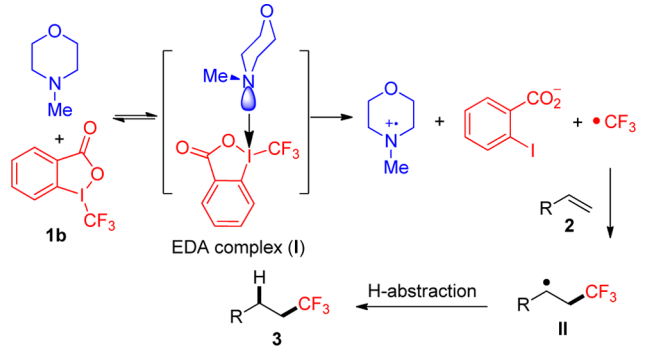
Scheme 2. Deuteration Experiments



conditions 1: (n-Bu)$_3$N, DMF	58%
conditions 2: (n-Bu)$_3$N-d_{27}, DMF	63% (D/H = 0/100)
conditions 3: (n-Bu)$_3$N, DMF-d_7	35% (D/H = 20/80)
conditions 4: (n-Bu)$_3$N-d_{27}, DMF-d_7	15% (D/H = 37/63)

Based on these observations, a rationale for this hydrotrifluoromethylation is posited, as depicted in Scheme 3. An

Scheme 3. Rationale for EDA Complex-Mediated Hydrotrifluoromethylation of Alkenes



encounter complex **I** can be generated when NMM is mixed with Togni's reagent **1b**. The EDA complex **I** can be thermally activated to the excited state, which dissociates into the CF_3· radical, acyl anion, and radical cation $NMM^{+\bullet}$. The CF_3· radical is then captured by an unactivated alkene (**2**) to give an alkyl radical intermediate **II**, which finally gives the desired hydrotrifluoromethylation product after abstracting a hydrogen atom from the solvent.

With the establishment of this simple and efficient hydrotrifluoromethylation protocol, we proceeded to explore the scope and limitations of this transformation. It was found that a variety of terminal alkenes can be transformed into the corresponding hydrotrifluoromethylation products in moderate to good yields (Figure 3a). The mild reaction conditions allowed for high functional group compatibility. A wide array of functional groups, including amide, ester, heterocycle, ether, sulfonamide, silicon ether, and alcohol, were well tolerated (**3a**–**l**). It was remarkable that biologically important natural products or their derivatives could also go through this transformation. For example, quinine was readily hydrotrifluoromethylated to give **3n** in 84% yield. Phenylalanine and estrone derivatives proceeded smoothly to give the corresponding hydrotrifluoromethylated products **3m** (67% yield) and **3o** (61% yield) respectively. In order to demonstrate the practicability of this transformation, 5 mmol of alkene **2a** were subjected to the standard conditions to furnish **3a** in 73% isolated yield (1.04 g).

The success in the hydrotrifluoromethylation of alkenes inspired us to explore the possibility of hydrotrifluoromethylation of alkynes using this EDA complex-based strategy. It was pleasing to find that alkynes could be also hydrotrifluoromethylated under our established standard conditions (Figure 3b). Functionalized terminal alkynes **8a**–**8f** went

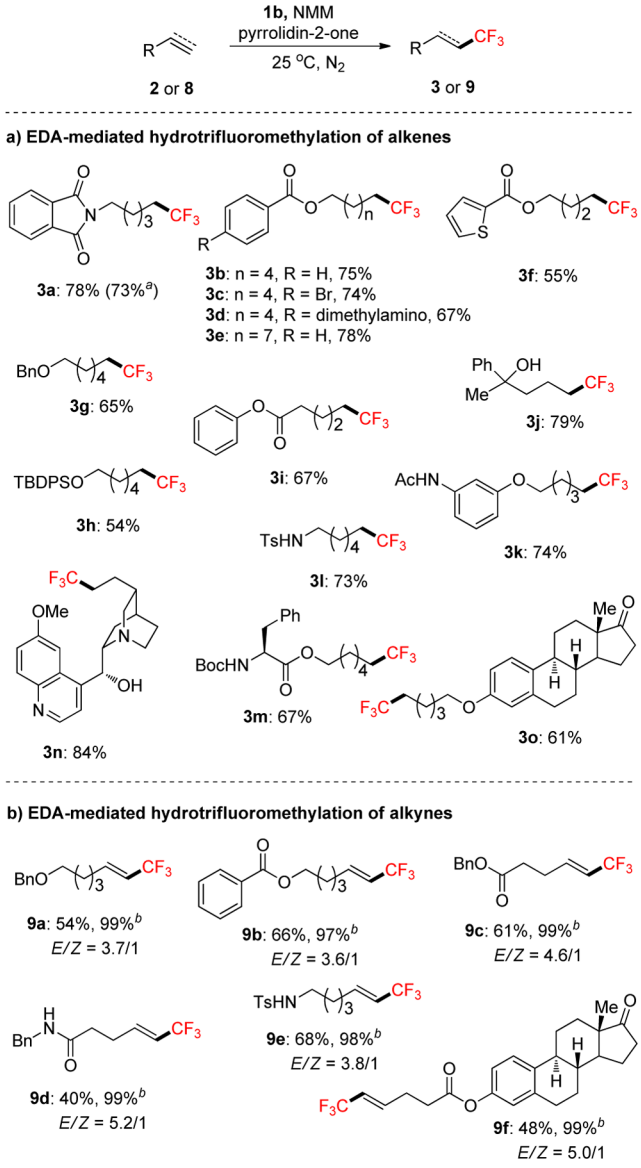


Figure 3. Substrate Scope. Reaction conditions: a solution of **2** or **8** (0.2 mmol), **1b** (0.4 mmol), and NMM (0.4 mmol) in pyrrolidin-2-one (2.0 mL) was stirred at 25 °C for 24–72 h. Isolated yield. The E/Z ratios were determined by NMR analysis. [a] The reaction was run in 5 mmol scale. [b] The yield was based on the recovered starting material.

through this transformation fluently to produce trifluoromethylated alkenes **9a**–**9f** in moderate to good yields (40–68%) as mixtures of E/Z isomers. In all cases, the E-isomers were isolated as the major stereoisomers. These reactions were sluggish and could not go to completion in reasonable time. The yields were quantitative based on the recovered starting materials. The aromatic alkenes and alkynes were not suitable substrates in this transformation and fully recovered under standard conditions.

In summary, an operationally simple and efficient method for hydrotrifluoromethylation of aliphatic alkenes and alkynes enabled by an EDA complex has been developed. The existence of this EDA complex between Togni's reagent **1b** and an amine was supported by NMR titration experiments. The radical clock experiment and electron paramagnetic resonance (EPR) revealed the radical nature of this reaction. The only promoter for this protocol is a tertiary amine. A series of trifluoromethy-

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lated aliphatic alkanes and alkenes with various functionalities can be prepared using this method. Further studies on synthetic application and to gain a better understanding of EDA complexes are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01301.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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