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NHC-Catalyzed Electrophilic Trifluoromethylation: Efficient Synthesis of γ-Trifluoromethyl α,β-Unsaturated Esters**

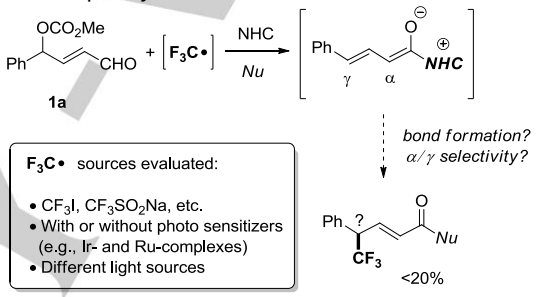
Wen Yang, Dengke Ma, Yu Zhou, Xiuqin Dong, Zhenyang Lin and Jianwei Sun**

Abstract: *Described here is the first NHC-catalyzed γ-trifluoromethylation of vinylogous enolates. The reaction features high regioselectivity and efficiency. Control experiments and DFT calculations provided important insights into the reaction mechanism.*

In the past few decades, organofluorine chemistry has gained tremendous development owing to the unique physiochemical and biological properties of these compounds bestowed by the presence of fluorine.[1] In particular, trifluoromethyl (CF_3) group has been demonstrated to be an important pharmacophore that can lead to improved metabolic stability, bioavailability, efficacy, etc. Consequently, developing new trifluoromethylation methods has evolved into a vibrant research topic in synthetic chemistry.[2] While significant progress has been achieved in the formation of C(sp^2)–CF_3 bonds (especially aryl–CF_3 bonds), formation of aliphatic C(sp^3)–CF_3 bonds still remains underdeveloped.[2] Among the limited examples, significant efforts have been devoted to the synthesis of α-trifluoromethyl carbonyl compounds via electrophilic trifluoromethylation.[2,3a] In contrast, formation of C(sp^3)–CF_3 bonds remote to a carbonyl group has been much less developed.[3b-d] Specifically, to the best of our knowledge, general catalytic introduction of a trifluoromethyl group at the γ position of carbonyl compounds remains unknown.

On the other hand, N-heterocyclic carbenes (NHCs) are well-known versatile organocatalysts that are uniquely capable of polarity reversal processes.[4] Enabled by these species, a range of carbonyl compounds (e.g., aldehydes, ketenes, activated esters, etc.) can be transformed to nucleophilic intermediates, such as NHC-bound acyl anion equivalents, enolates, homoenolates, vinylogous enolates, etc., which then react with a wide range of electrophiles leading to diverse new reaction modes that are otherwise less straightforward to achieve.[4] In continuation of our efforts in NHC-catalysis, here we describe an NHC-catalyzed electrophilic trifluoromethylation process, which also represents the first general C(sp^3)–CF_3 bond formation at the γ position of carbonyl compounds.[5,6]

A brief survey of the known α-trifluoromethylation processes of carbonyl compounds indicated that a radical pathway, i.e. with CF_3· radical as the actual reaction partner, should be a promising choice for the initial evaluation.[2k,3] Therefore, we employed enal **1a** bearing a γ-leaving group as the model substrate, which is known to generate the corresponding vinylogous enolate upon treatment with a suitable NHC catalyst (Scheme 1).[6b-e,7] A range of reaction conditions aiming to generate the trifluoromethyl radical were evaluated, including those well-known radical precursors, such as CF_3I and CF_3SO_2Na, under different conditions, including photo irradiation with or without sensitizers.[2,3] Unfortunately, the expected trifluoromethylation process, either at the α or γ position, was not observed as the major pathway (yield <20%). Compared with our previous success in tribromomethylation and trichloromethylation,[6e] it is obvious that the compatibility of CF_3· radical with this catalytic system is completely different.



Scheme 1. Initial evaluation of radical conditions.

Next, we resorted to the use of non-radical based conditions. Enal **1a** was used as the model substrate, and the well-established electrophilic trifluoromethylation regents **2a**–**2c** were employed as the CF_3-source (Table 1).[8] A range of NHC precatalysts **A**–**H** were evaluated together with KOAc as the base and methanol as the nucleophile. It was encouraging that the reaction in chloroform could be catalyzed by triazolium salts **A** and **B** at room temperature to form the desired trifluoromethylation product **3a** when the Togni reagent **2a** was employed, albeit with moderate efficiency (entries 1-2). Precatalysts **C**–**E** did not lead to any trifluoromethylation products (entries 3-5). However, indane-based racemic triazolium salts **F**–**H** exhibited catalytic activity (entries 6-8). Among them, the one bearing 2,4,6-trichlorophenyl substitution (**G**) proved superior (81% yield, entry 7).[9,10] Next, other trifluoromethylation reagents **2b** and **2c** were evaluated. The Umemoto reagent **2b** showed similar reactivity, furnishing product **3a** in 78% yield (entry 9). However, the other Togni reagent **2c** showed no desired reactivity (entry 10). Next, different bases were compared. Among them, K_2CO_3 provided slightly improved efficiency (entry 11). Other bases, including organic bases DBU and DIPEA, proved inferior (entries 12-15). Subsequent solvent screening indicated that chloroform remained the best (entries 16-20). Finally, decreasing the catalyst loading to 10 mol% did not affect the high efficiency (entry 21). It is worth noting that this process exhibited absolute γ regioselectivity, i.e., the NHC-bound vinylogous enolate

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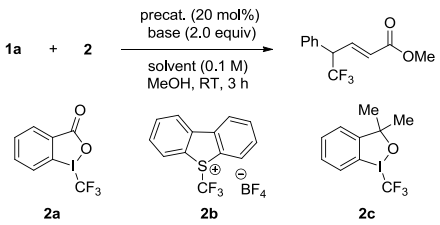
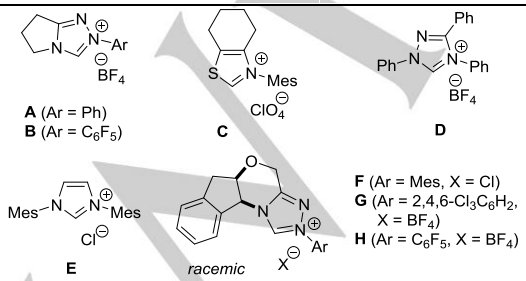
Table 1: Optimization of reaction conditions.[a]



2a 2b 2c

Entry	Precat.	2	Base	Solvent	Yield [%][b]
1	**A**	**2a**	KOAc	$CHCl_3$	39
2	**B**	"	"	"	37
3	**C**	"	"	"	<5
4	**D**	"	"	"	<5
5	**E**	"	"	"	<5
6	**F**	"	"	"	35
7	**G**	"	"	"	81
8	**H**	"	"	"	71
9	**G**	**2b**	"	"	78
10	**G**	**2c**	"	"	<5
11	**G**	**2a**	K_2CO_3	"	85
12	**G**	"	Cs_2CO_3	"	13
13	**G**	"	CsOAc	"	77
14	**G**	"	DIPEA	"	35
15	**G**	"	DBU	"	<5
16	**G**	"	K_2CO_3	CH_2Cl_2	79
17	**G**	"	"	toluene	50
18	**G**	"	"	THF	25
19	**G**	"	"	Et_2O	59
20	**G**	"	"	MeCN	26
21[c]	**G**	"	"	$CHCl_3$	86



[a] The reactions were performed with enal **1a** (0.05 mmol), **2a** (0.06 mmol), base (0.10 mmol), precatalyst (0.01 mmol), MeOH (0.1 mL), and solvent (0.5 mL). [b] Determined by ^1H NMR analysis with CH_2Br_2 as an internal standard. [c] Run with 10 mol% of **G**.

intermediate did not react at the α position although this position is also nucleophilic. This is in sharp contrast to our previous observation of absolute α-regioselective fluorination involving similar vinylogous enolates.[6b] It is also notable that the electrophilic trifluoromethylation reagent showed good compatibility with the nucleophilic NHC catalyst.

With the optimized reaction conditions, we next examined the scope of this NHC-catalyzed γ-trifluoromethylation (Scheme 2). A wide range of enals smoothly participated in the mild intermolecular C(sp^3)–CF_3 bond formation process with generally good efficiency. Electron-withdrawing and electron-donating groups on the γ-aryl ring did not affect the good reactivity. Enals **1n-o** bearing a γ-aliphatic substituent and **1p** with γ-disubstitution were also suitable substrates. It is notable that increasing steric hindrance at the γ position did not affect the good γ-regioselectivity (**3o-p**). Finally, this protocol is also capable of installing a C_2F_5 group (**3q**) using the modified Togni reagent **2d**. The mild conditions could tolerate a diverse set of functional groups, such as aryl halides, ethers, silyl-protected alcohols, free alcohols, ketones, and aldehydes. It is also remarkable that the free aryl aldehyde group in **3l** remained intact under the standard conditions, indicating excellent chemoselectivity of this process.

To demonstrate the utility of our intermolecular trifluoromethylation protocol, we carried out a range of derivatizations (Scheme 3). The representative product **3a** was successfully transformed to a range of trifluoromethylated molecules. For example, Pd/C-catalyzed hydrogenation led to saturated γ-trifluoromethyl ester **4** in 87% yield. Allylic alcohol **5** could be obtained after reduction by DIBAL-H. Acid-catalyzed hydrolysis resulted in formation of the free acid **6**. Moreover, the ester could be easily converted to Weinreb amide **7**, which is poised for further transformations to other γ-trifluoromethyl carbonyl compounds. Finally, the NaH-promoted elimination of HF afforded γ-difluoromethylenated ester **8**. It is worth noting that difluoromethyl-containing molecules are another useful family of organofluorine compounds.[10]

We were curious about whether the NHC-bound vinylogous enolate or the corresponding enolate from the byproduct **3a-H** serves as the real active nucleophile in this reaction. To distinguish these two possibilities, ester **3a-H** was subjected to the standard reaction conditions, but no reaction was observed (Eq. 1). Moreover, strong base LDA was also employed in place of K_2CO_3 to ensure successful formation of the corresponding vinylogous enolate from **3a-H**. However, the reaction led to trace trifluoromethylation product (Eq. 1). These results ruled out the involvement of **3a-H** and its conjugate base (vinylogous enolate) as the intermediate in this process, which is consistent with the involvement of NHC-bound vinylogous enolate as the key nucleophile for trifluoromethylation. The latter control experiment also implies that the previously seemingly straightforward reactivity pattern of vinylogous enolates with electrophiles can not be simply extended to trifluoromethylation, which perhaps explains why γ-trifluoromethylation of carbonyl compounds has remained elusive to date. We attribute the success in our protocol to the well-matched reactivity of the NHC-bound vinylogous enolates with the CF_3-electrophile.

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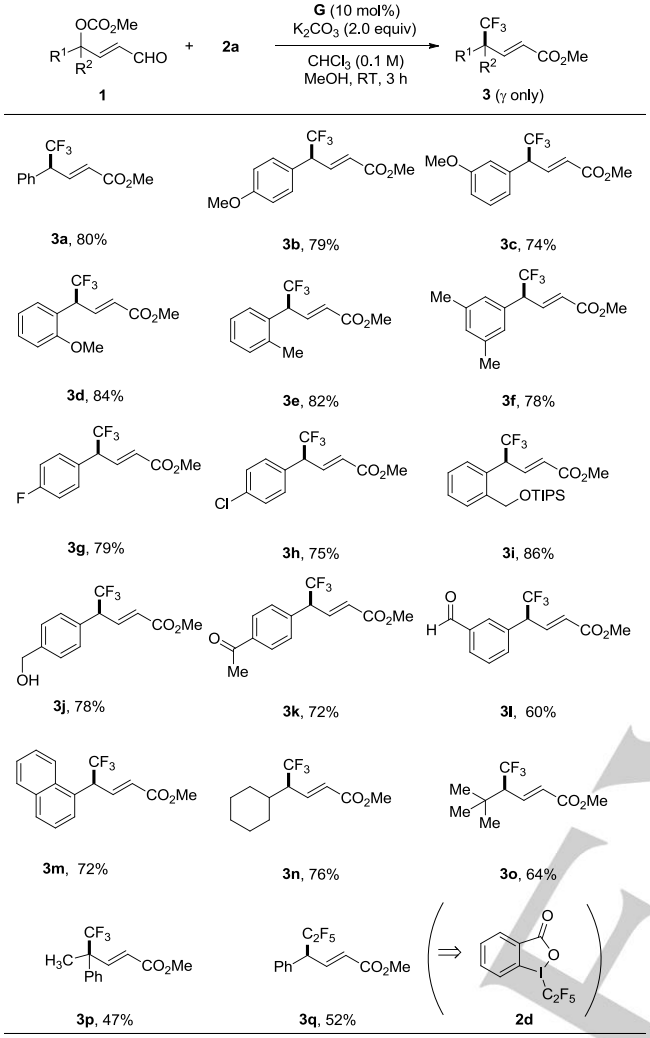
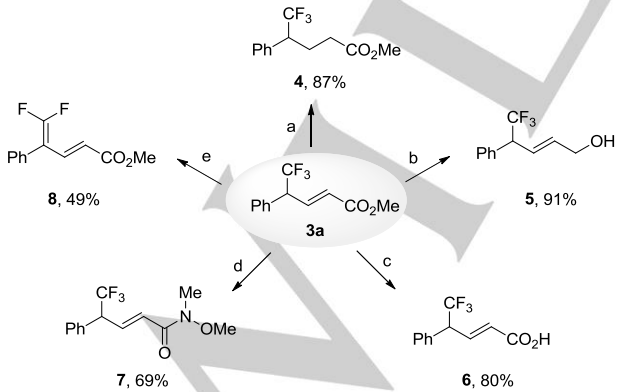
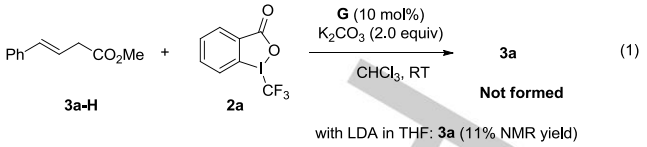
Scheme 2. Scope of γ-trifluoromethylation of enals.[a,b]



[a] All the reactions were carried out with enal **1** (0.50 mmol), **2a** (0.60 mmol), K_2CO_3 (1.0 mmol), **G** (0.05 mmol), MeOH (1.0 mL), and $CHCl_3$ (5.0 mL). [b] Isolated yield.



Scheme 3. Synthetic transformations of **3a**. a) Pd/C, H_2, MeOH, RT; b) DIBAL-H, DCM, –78 °C; c) HCl (*conc.*), 80 °C; d) Me_3Al, Me(MeO)NH•HCl, 0 °C to RT, DCM; e) NaH, DCM, RT.



To further understand the γ-regioselectivity (vs. α), we also carried out DFT calculations. Figure 1 shows the energy profiles of the γ- and α-trifluoromethylation pathways for comparison. Notably, we found that MeOH activates substrate **2a** through hydrogen bonding. Without this activation, the barriers are much higher based on calculation (see SI for the proposed mechanism and more details). This is also consistent with the experimental results. Indeed, in the absence of methanol, trace product was formed under otherwise identical conditions.[11] Furthermore, data in Figure 1(a) indicate that the C−CF_3 bond formation at the γ-position is both kinetically and thermodynamically favored (vs. α-position), which also agrees with experiments. After careful analysis of the calculated transition state structures, here we propose a plausible explanation for the high γ-regioselectivity. Figure 1(b) gives a schematic illustration showing the electrostatic interactions among different moieties in the calculated transition state structures. In the γ-pathway, the hypervalent iodine motif of the trifluoromethylation reagent is located in a perfect position to allow its electrostatic interaction with the NHC motif, thereby leading to a lower barrier. However, in the α-pathway, such a beneficial interaction is disrupted.

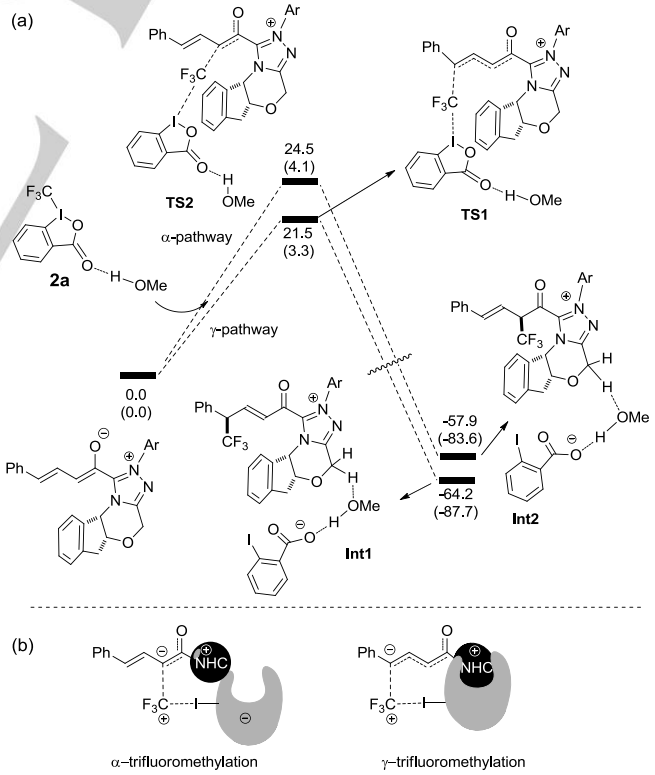


Figure 1. (a) Free energy profiles calculated for the α- and γ-trifluoromethylation of the vinylogous enolate intermediate with **2a**. The relative free energies and electronic energies (in parentheses) are given in kcal/mol. (b) Schematic illustration showing the electrostatic interactions among different moieties in the calculated transition state structures. Ar = 2,4,6-$Cl_3C_6H_2$.

In summary, we have developed the first general trifluoromethylation at the γ position of carbonyl compounds by NHC-catalysis. With suitable choice of the precatalyst as well as the CF_3-electrophile, this intermolecular C(sp^3)–CF_3 bond formation process led to smooth and mild synthesis of a range of γ-trifluoromethyl α,β-unsaturated esters with good efficiency. The reaction exhibits a broad scope and good functional group compatibility. Mechanistically, the key NHC-bound vinylogous enolate intermediate serves as the actual nucleophile for trifluoromethylation, which is crucial to the success of this protocol. Control experiments provided important insights to this aspect. Furthermore, distinct from the previous α-fluorination of the same vinylogous enolates, this process exhibits complete γ-regioselectivity. DFT calculation results also agree with this observation, indicating that trifluoromethylation at the α position has a higher barrier. Finally, the trifluoromethylation products can be transformed to a wide range of useful trifluoromethyl-containing molecules. Further investigations aiming to achieve a catalytic asymmetric variant of this process are underway.

Keywords: *N*-heterocyclic carbene • fluorine • trifluoromethylation • regioselectivity • organocatalysis

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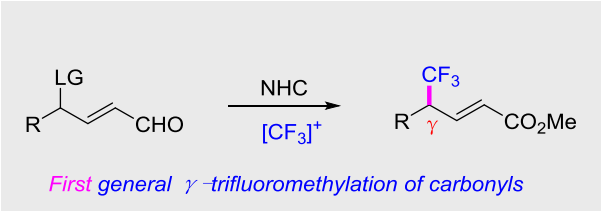

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NHC-Catalyzed Electrophilic Trifluoromethylation: Efficient Synthesis of γ-Trifluoromethyl α,β-Unsaturated Esters

An NHC-catalyzed electrophilic trifluoromethylation process is described. In the presence of a suitable trifluoromethylation reagent, NHC vinylogous enolates participated in smooth intermolecular C(sp^3)–CF_3 bond formation with absolute γ-regioselectivity and good efficiency. Control experiments and DFT calculations provided important insights into the reaction mechanism. This process also represents the first general trifluoromethylation at the γ position of carbonyl compounds.