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N-Heterocyclic Carbene-Catalyzed Synthesis of α-Trifluoromethyl Esters

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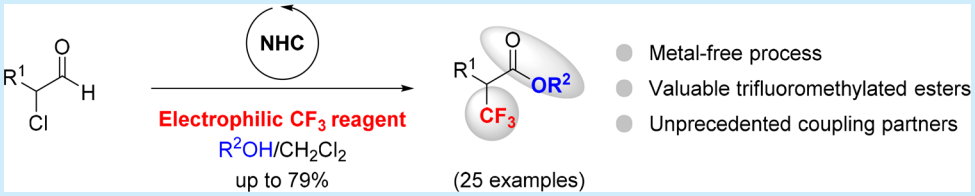
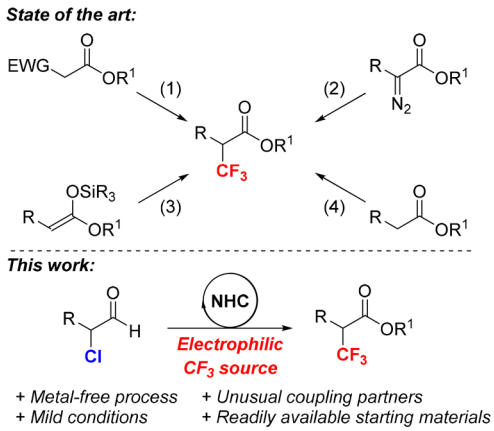
Supporting Information



ABSTRACT: The N-heterocyclic carbene (NHC)-catalyzed trifluoromethylation of α-chloro aldehydes was developed, allowing straightforward access to valuable α-trifluoromethyl ester derivatives. The unique combination of an electrophilic trifluoromethylation reagent with NHC catalysis was the key for the functionalization of a broad range of α-chloro aldehydes, and the products are formed in moderate to good yields. Investigations of the enantioselective version of this reaction afforded the enantioenriched products in moderate yields with good ee values.

Organofluorine chemistry is a research field of constant evolution offering a large variety of fluorinated molecules.[1] As they are key compounds in the agrochemical and pharmaceutical industries,[2] the quest for straightforward and innovative methodologies to incorporate a fluorine atom or a fluorinated group is highly demanding, especially related to the unique features[3] brought by fluorinated groups to molecules. In particular, we turned our attention to the CF_3 group,[4] a moiety widely present in various relevant compounds. Nowadays, a broad panel of transformations enables efficient trifluoromethylation of several classes of compounds of interest. Although efforts have been dedicated to the introduction of the CF_3 motif onto $C(sp^2)$ centers, less attention has been paid to the functionalization of aliphatic compounds. The creation of a $C(sp^3)-CF_3$ bond, otherwise made from a 1,2-addition on a carbonyl group derivative,[5] is scarce, and the α-trifluoromethylation of carbonyl derivatives remains a synthetic challenge. Indeed, to date most of the reports have dealt with the α-trifluoromethylation of ketones,[6] while the α-functionalization of aldehydes[7] and imides[8] with a CF_3 group is restricted to a handful of reports. With regard to the α-trifluoromethylation of esters, most of the reports have focused on highly activated ester derivatives (Scheme 1, eq 1) such as β-keto esters or α-nitro esters.[9] Another strategy relies on the use of prefunctionalized esters like α-diazo ester derivatives (Scheme 1, eq 2)[10] or sensitive ketene silyl acetals (Scheme 1, eq 3).[11] Finally, a couple of examples depicted the direct α-functionalization of esters using either strong base or oxidant

Scheme 1. State of the Art and the Present Work



(Scheme 1, eq 4).[12] With the aim to develop a straightforward access to α-trifluoromethylated esters under mild conditions starting from readily available and bench-stable starting materials, we envisaged that the judicious combination of NHC catalysis and organofluorine chemistry will open new perspectives. Although NHC catalysis appears nowadays as a powerful synthetic tool to offer efficient and selective

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transformations,[13] the use of an electrophilic trifluoromethylation reagent in such transformations remains unexplored.[14]

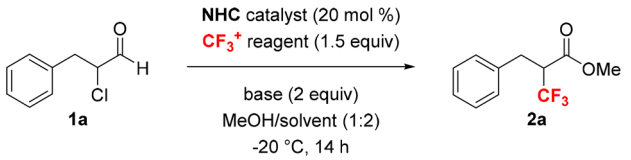
Herein we report the NHC-catalyzed trifluoromethylation reaction of α-chloro aldehyde derivatives to access α-trifluoromethyl ester derivatives. At the outset of this study, the trifluoromethylation of 2-chloro-3-phenylpropanal (**1a**) as a model substrate was investigated. At first, Togni's reagent (**A**) was selected as the electrophilic CF_3 source, methanol as the nucleophile, and DIPEA as the base (Table 1). When **1a** was reacted with **A** using the carbene generated from **NHC I** in a 1:2 MeOH/toluene mixture, the corresponding ester **2a** was observed in 21% yield (Table 1, entry 1). With this encouraging result in hand, a screening of various cosolvents (Table 1, entries 2–4) revealed that CH_2Cl_2 was the best one, furnishing the expected compound in 50% yield (Table 1, entry 4). It is noteworthy that this catalytic system selectively afforded the monotrifluoromethylated product, as no α,α-difunctionalized product was detected. Various bases were then investigated to showcase their importance in the outcome of the transformation (Table 1, entries 4–9). It turned out that DBN was the most efficient one, giving **2a** in 62% yield (Table 1, entry 9), while other organic or inorganic bases led to lower yields (Table 1, entries 4–8). Then other NHC precatalysts (Table 1, entries 10 and 11) and electrophilic reagents (Table 1, entries 12 and 13) were evaluated. In the case of **B**, low conversion was obtained, while **C** gave **2a** with a slight increase in the reaction yield to 67%.

Finally, an increase in the reaction temperature to 0 °C along with a shorter reaction time and the use of **A** as a reagent gave the best reaction conditions, leading to **2a** in 70% isolated yield (Table 1, entry 15). Importantly, in the absence of the NHC catalyst, no product was detected, demonstrating its key role in the process (Table 1, entry 16). This result precludes an enolate formation/nucleophilic attack of Togni's reagent sequence.

With these optimized conditions in hand, the scope of the transformation was investigated, and a panel of esters **2a–y** was synthesized (Scheme 2). We first studied the nature of the nucleophile. Ethanol, isopropanol, and cyclohexanol turned out to be compatible, leading to the corresponding esters **2b–d**, albeit in lower yields in the case of *i*PrOH and CyOH. Therefore, methanol was selected to pursue the study. It should be noted that alternatively 2-bromo-3-phenylpropanal might be used instead of **1a**, affording **2a** in 45% yield. Then, α-chloro hydrocinnamaldehyde derivatives bearing aromatic rings substituted with an electron-donating (OMe, **2e**) or electron-withdrawing group (CF_3, **2f**) as well as a halogen (Br, **2g**) were functionalized in good yields. The developed reaction was not restricted to this class of aldehydes. Indeed, homobenzylic-substituted aldehydes with a phenyl ring (**2i**) and even a heterocyclic compound (**2j**) were trifluoromethylated in good yields. Moreover, aliphatic α-chloro aldehydes were also suitable substrates, as compounds **2k–x** were obtained in moderate to high yields. Simple alkyl-substituted aldehyde **1k** was efficiently functionalized in good yield, and the reaction was successfully scaled up, offering access to **2k** in 73% yield on a 5 mmol scale. Protected alcohols derived from the 2-chloro-3-hydroxypropanal, **1l** and **1m**, were suitable substrates. Furthermore, aliphatic α-chloro aldehydes functionalized at the γ-position using allyl and benzyl ethers (**1n** and **1o**), ester (**1p**), and silyl (**1q**) groups are well-tolerated under the present reaction conditions, affording the corresponding α-trifluoromethylated esters **2n–q** in good yields, thus demonstrating the versatility of the present reaction. The synthetic utility of this transformation was further demonstrated through the functionalization of aliphatic aldehydes **1r–w** bearing various functional groups such as a protected amine, a chlorine atom, cyano and azide groups, and alkyne and alkene moieties. This excellent functional group tolerance offered perspectives for postfunctionalization reactions by using these highly valuable trifluoromethylated building blocks to build up more complex molecules. Moreover, the trifluoromethylation of compounds of interest such as the oleic and stearic acids **2w** and **2x** was efficiently achieved. Finally, with this approach, chlorambucil, an anticancer drug used in the treatment of leukemia, was trifluoromethylated in an efficient way, since the α-chloro aldehyde bearing a substituted 4-aminoaryl group at the γ-position furnished the desired product **2y** in 68% yield.

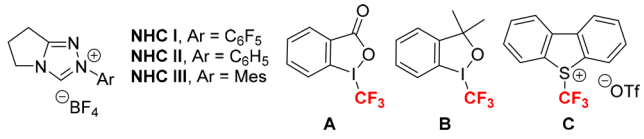
On the basis of the literature data,[15] the mechanism shown in Scheme 3 has been proposed to explain the reaction outcome. The reaction proceeds via the generation of the nucleophilic Breslow intermediate **I**[16] resulting from the reaction of the NHC catalyst with the α-chloro aldehyde **1** in the presence of DBN. Then, under basic conditions, the dehydrohalogenation of **I** leads to the corresponding NHC-bound enolate

Table 1. Optimization of the Reaction Conditions[a]



entry	NHC catalyst	CF_3^+ reagent	base	solvent	yield (%)[b]
1	**NHC I**	**A**	DIPEA	toluene	21
2	**NHC I**	**A**	DIPEA	THF	23
3	**NHC I**	**A**	DIPEA	DCE	47
4	**NHC I**	**A**	DIPEA	CH_2Cl_2	50
5	**NHC I**	**A**	K_2CO_3	CH_2Cl_2	32
6	**NHC I**	**A**	KHMDS	CH_2Cl_2	24
7	**NHC I**	**A**	DMAP	CH_2Cl_2	6
8	**NHC I**	**A**	DBU	CH_2Cl_2	54
9	**NHC I**	**A**	DBN	CH_2Cl_2	62
10	**NHC II**	**A**	DBN	CH_2Cl_2	6
11	**NHC III**	**A**	DBN	CH_2Cl_2	5
12	**NHC I**	**B**	DBN	CH_2Cl_2	2
13	**NHC I**	**C**	DBN	CH_2Cl_2	67
14[c]	**NHC I**	**A**	DBN	CH_2Cl_2	69
15[d]	**NHC I**	**A**	DBN	CH_2Cl_2	72 (70[e])
16	none	**A**	DBN	CH_2Cl_2	–

[a]Reaction conditions: **1a** (0.2 mmol), CF_3^+ reagent (1.5 equiv), NHC catalyst (20 mol %), base (2 equiv), MeOH/solvent (1:2, 0.2 M), −20 °C, 14 h, argon. Abbreviations: DIPEA, *N*,*N*-diisopropylethylamine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DMAP, 4-(dimethylamino)pyridine. NHC catalysts and CF_3^+ reagents:



[b]Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as an internal standard. [c]The reaction was carried out at 0 °C. [d]The reaction was carried out at 0 °C for 2 h. [e]Isolated yield.

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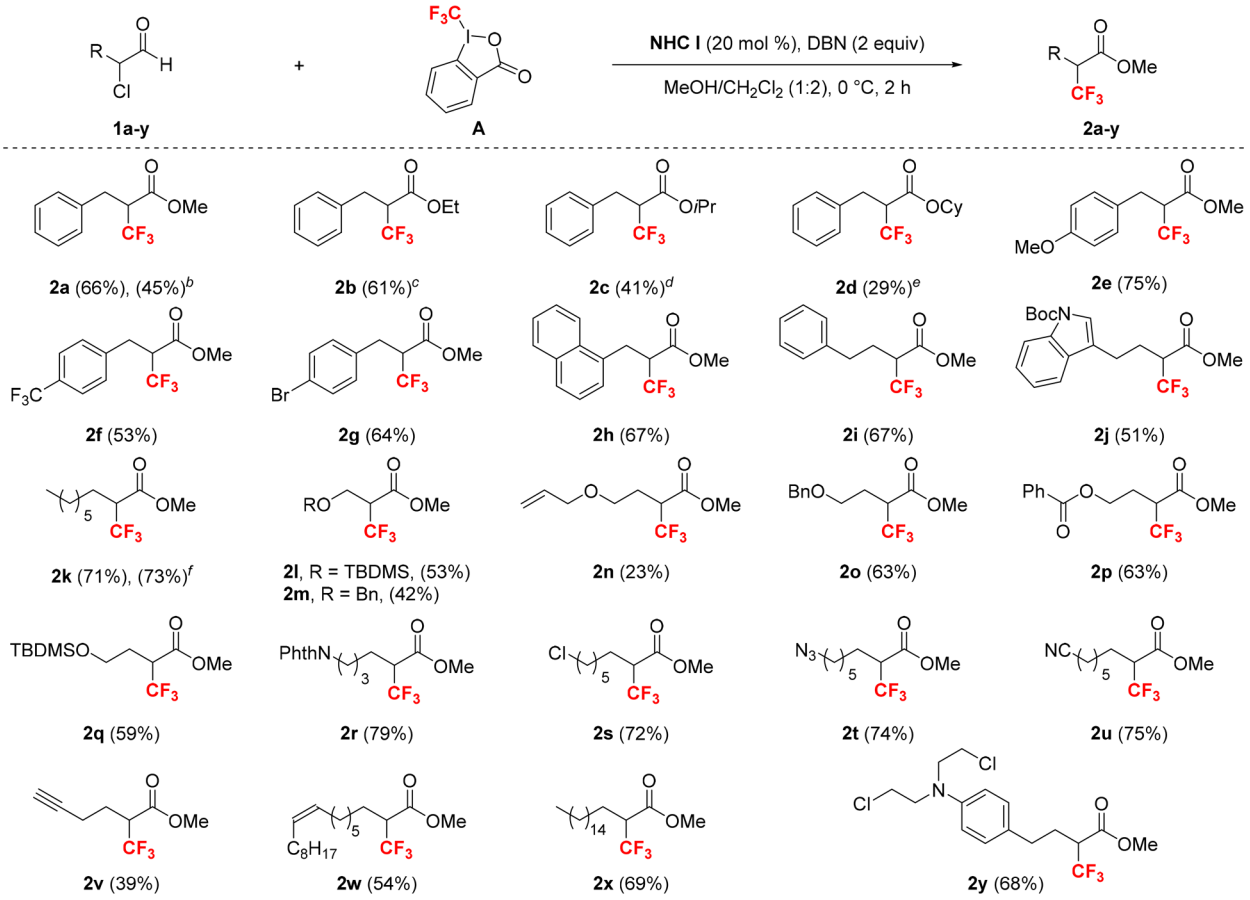
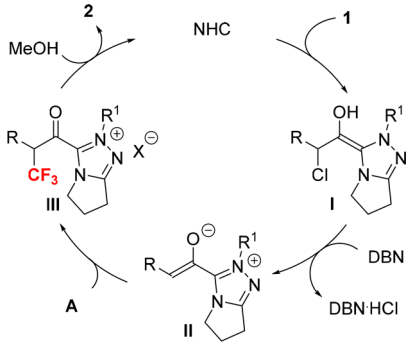
Scheme 2. Substrate Scope[a]

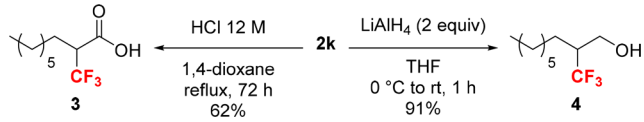


[a]Reaction conditions: **1** (0.5 mmol), Togni reagent **A** (1.5 equiv), **NHC I** (20 mol %), DBN (2 equiv), MeOH/CH_2Cl_2 (1:2; 0.2 M), 0 °C, 2 h, argon. Isolated yields are given. [b]The reaction was performed using 2-bromo-3-phenylpropanal instead of **1a**. [c]EtOH was used instead of MeOH. [d]*i*PrOH was used instead of MeOH. [e]CyOH was used instead of MeOH. [f]The reaction was performed on a 5 mmol scale.

Scheme 3. Proposed Catalytic Cycle



Scheme 4. Postfunctionalization Reactions



intermediate **II**, which reacts with Togni's reagent **A** as the electrophilic CF_3 source to provide species **III**. Finally, nucleophilic attack at the acylazolium by methanol affords the desired α-trifluoromethylated product **2** along with regeneration of the carbene catalyst.

To demonstrate the synthetic utility of the present transformation, ester **2k** was readily converted into other functional groups. Under acidic conditions, the ester was smoothly converted into the corresponding carboxylic acid **3** in 62% yield. Moreover, alcohol **4** was also obtained in 91% yield after reduction using $LiAlH_4$ (Scheme 4).

Finally, we were interested in the development of a catalytic enantioselective trifluoromethylation reaction to access enantioenriched α-trifluoromethyl esters (Scheme 5). After extensive investigations, we found that the chiral catalyst **NHC IV** gave the best results in terms of enantioselectivity.

In addition, during the reaction optimization, the base was carefully chosen to avoid any racemization within the course of the reaction, and DIPEA was the optimum one. Under the optimized conditions, α-chloro aldehydes **1a**, **1h**, and **1r** were readily converted into the corresponding enantioenriched esters in moderate yields (34−57%) with good ee values (up to 81%). This method represents a unique NHC-catalyzed asymmetric reaction to access enantioenriched tertiary α-trifluoromethylated esters.

In conclusion, we have developed a straightforward NHC-catalyzed trifluoromethylation of α-chloro aldehydes to access α-trifluoromethylated esters. The use of an electrophilic trifluoromethylation reagent as a reaction partner in a NHC-catalyzed transformation enabled the functionalization of a panel of α-chloro aldehydes, including complex molecules, in

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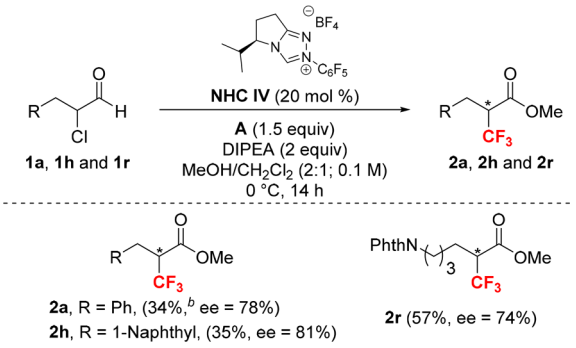
Scheme 5. Studies of an Asymmetric Version[a]



[a]Reaction conditions: **1** (0.2 mmol), Togni reagent **A** (1.5 equiv), **NHC IV** (20 mol %), DIPEA (2 equiv), $MeOH/CH_2Cl_2$ (2:1; 0.1 M), 0 °C, 14 h, argon. Isolated yields are given. The enantiomeric excess was determined by HPLC on a chiral stationary phase. [b]The reaction was performed on a 0.1 mmol scale.

moderate to good yields. A catalytic asymmetric version of this reaction giving the enantioenriched α-CF_3 esters in moderate yields with good ee values has been described. This catalytic asymmetric protocol represents a unique access to enantioenriched tertiary α-trifluoromethylated esters. This method is likely to offer a new synthetic pathway to α-trifluoromethylated esters under mild conditions from readily available starting materials and therefore will extend the current toolbox toward the formation of trifluoromethylated aliphatic carbonyl derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01482.

Procedures, characterization data, and ^1H, ^{13}C, and ^{19}F NMR spectra of trifluoromethylated esters (PDF)

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Notes

The authors declare no competing financial interest.

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