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N-Heterocyclic Carbene Catalyzed Trifluoromethylation of Carbonyl Compounds

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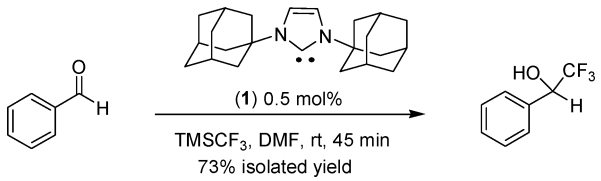
ABSTRACT



A novel N-heterocyclic carbene (NHC) catalyzed trifluoromethylation reaction of carbonyl compounds was discovered. Both enolizable and nonenolizable aldehydes and α-keto esters undergo facile trifluoromethylation with $TMSCF_3$ at room temperature in the presence of only 0.5–1 mol % of the commercially available NHC (1), providing CF_3-substituted alcohols in good yields. Selective trifluoromethylation of aldehydes over ketones can be achieved under NHC catalysis. These conditions are mild and simple and tolerate a variety of functional groups.

Trifluoromethyl-containing molecules are finding increasing applications in drug discovery research as well as synthesis of agrochemicals and polymers.[1] Incorporation of a trifluoromethyl group often leads to desirable changes in physicochemical properties of organic molecules. One of the most straightforward methods to introduce a CF_3 group into a molecule involves the direct trifluoromethylation of carbonyl compounds. In the past 15 years, many useful trifluoromethylation methodologies have been invented.[2] By far the most convenient and widely utilized method is the fluoride-induced (e.g., TBAF or CsF) nucleophilic trifluoromethylation with $TMSCF_3$.[2j−l] This transformation is believed to involve the initial reaction of fluoride with $TMSCF_3$ to form Me_3SiF and a CF_3 anion. The trifluoromethide anion reacts with the carbonyl compound R^1COR^2 to generate the alkoxide intermediate $R^1R^2(CF_3)CO^-$ that propagates the subsequent reactions.[2j] This proposed mechanism was supported by the observation that the reaction can also be initiated by using simple alkoxides such as *t*-BuOK or Me_3SiONa.

Trifluoromethyl transfer from $TMSCF_3$ was also catalyzed by Lewis bases via a different mechanistic pathway. In this case, the Lewis base is the true catalyst that is turned over in catalytic cycles.[2c] This approach avoids the use of strong bases such as fluoride or alkoxides and is more applicable to base-sensitive substrates. Fuchikami et al. have shown that a variety of Lewis bases, such as dibutylamine, triethylamine, pyridine, PPh_3, $AsPh_3$, and $SbPh_3$, can catalyze CF_3 addition reactions to aldehydes and certain activated ketones, although with low efficiencies.[3] More recently, Prakash et al. described

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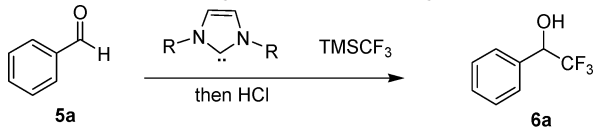
a triethylamine *N*-oxide catalyzed trifluoromethylation reaction with aldehydes.[2c] However, the aforementioned Lewis bases exhibited low catalytic activities in trifluoromethylation reactions and required high catalyst loadings (10−50 mol %) as well as long reaction times. In this paper, we report the discovery of a novel N-heterocyclic carbene (NHC) catalyzed trifluoromethylation reaction of carbonyl compounds using as little as 0.5−1 mol % catalyst loading.

N-Heterocyclic carbenes have received considerable attention in recent years. They have been successfully employed as ligands in a wide range of transition-metal-catalyzed processes.[4] In contrast, there has been limited application of N-heterocyclic carbenes in nucleophilic catalysis.[5] N-Heterocyclic carbenes have been used to catalyze organic transformations such as nucleophilic substitutions,[6] benzoin, and Stetter reactions.[7] Recently, N-heterocyclic carbene catalyzed transesterification reactions were described.[8] Louie also demonstrated that NHCs are effective catalysts for trimerization of isocyanates.[9] In search for a more efficient and milder Lewis base catalyst for trifluoromethylation reactions, we envisioned that we could exploit the strong σ-donating property of NHCs to effect reactions between $TMSCF_3$ and carbonyl compounds.

Our studies commenced with the trifluoromethylation reaction with benzaldehyde (Table 1). Adamantyl-substituted carbene **1** was first chosen for our study because it is commercially available and has good thermal stability.[10] A solution of benzaldehyde and $TMSCF_3$ (3 equiv) in THF at 0 °C was treated with 10 mol % of NHC **1**. After only 1 h at room temperature, the reaction reached completion (entry 1). After cleavage of TMS ether by acid hydrolysis (2 N HCl), the desired alcohol **6a** was obtained. Encouraged by this promising result, a number of solvents were then screened. DMF was found to be another effective solvent[2b,f,3] for this reaction giving complete conversion within 20 min at ambient temperature in the presence of 10 mol % of the catalyst (entry 2). Use of toluene, methylene chloride or MTBE as solvents all resulted in sluggish reactions.

Table 1. Trifluoromethylation of Benzaldehyde



5a **6a**

R = Ad (**1**), *t*Bu (**2**), Mes (**3**), 2,6-di-iso-propylphenyl (**4**)

entry	solvent	cat. (loading)	time	conversion (%)
1	THF	**1** (10 mol %)	1 h	100
2	DMF	**1** (10 mol %)	20 min	100
3	THF	**1** (0.5 mol %)	5 h	79
4	**DMF**	**1 (0.5 mol %)**	**45 min**	**98**
5	DMF	**1** (0.1 mol %)	24 h	62
6	DMF	**2** (0.5 mol %)	30 min	93
7	DMF	**3** (0.5 mol %)	30 min	100
8	DMF	**4** (0.5 mol %)	20 min	100

Further optimization focused on minimizing the catalyst loading. When the reaction was carried out in THF with 0.5 mol % of catalyst, the reaction became slower and a 79% conversion was achieved after 5 h (entry 3). On the other hand, with DMF as the reaction solvent, the catalyst loading can be reduced to 0.5 mol % and the reaction reached 98% conversion within 45 min (entry 4). Further decrease of the catalyst amount to 0.1 mol % significantly slowed the reaction (62% conversion after 24 h at room temperature, entry 5). Three other readily available NHCs (**2** to **4**) were briefly tested at 0.5 mol % catalyst loading level and were found to be equally effective (entries 6−8). The observed high catalytic activity of NHC is remarkable compared to the previously reported Lewis bases for the same or similar transformations. For example, triethylamine-catalyzed trifluoromethylation of benzaldehyde proceeded to only 59−66% conversion after 10 h at room temperature with 10−50 mol % catalyst loadings[3] and the more recent triethylamine *N*-oxide catalyzed reactions also necessitate 50 mol % catalyst loading and ~12 h of reaction time.[2c,11]

The scope of N-heterocyclic carbene catalyzed trifluoromethylation reactions was explored using a variety of carbonyl compounds (Table 2). Aromatic aldehydes with either electron-withdrawing or electron-donating groups (entries 1−4)[12−14] all gave products in good to excellent yields. When *trans*-cinnamaldehyde was subjected to our reaction conditions, 1,2-addition product was obtained in 89% isolated yield (entry 5).[13] Trifluoromethyl addition to sterically demanding aldehyde **5f** was also successful (entry 6).

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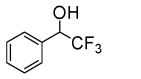
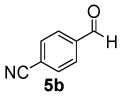
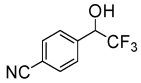
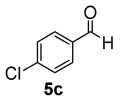
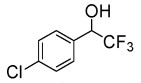
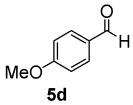
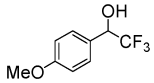
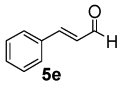
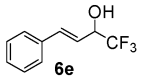
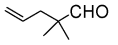
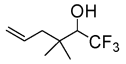
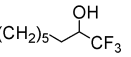
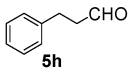
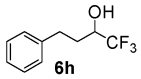
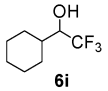
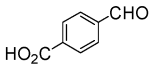
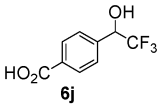
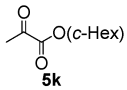
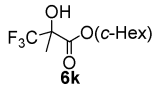
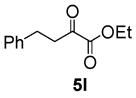
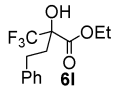
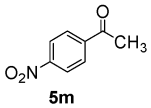
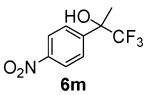
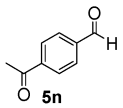
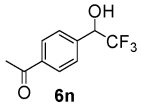
(9) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679.

(10) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(11) As a comparison, we have carried out the fluoride-initiated trifluoromethylation of benzaldehyde using 0.5 mol % TBAF and $TMSCF_3$ (3 equiv). The reaction went to completion in 30 min at room temperature with either THF or DMF as the reaction solvent.

Table 2. Trifluoromethylation Catalyzed by NHCs

entry	substrate	cat. (loading)	product	isolated yield
1	 **5a**	**1** (0.5 mol%)	 **6a**	73%[12]
2	 **5b**	**1** (0.5 mol%)	 **6b**	87%[13]
3	 **5c**	**1** (0.5 mol%)	 **6c**	86%[12]
4	 **5d**	**1** (1 mol%)	 **6d**	81%[14]
5	 **5e**	**1** (0.5 mol%)	 **6e**	89%[13]
6	 **5f**	**1** (1 mol%)	 **6f**	71%
7	$CH_3(CH_2)_6CHO$ **5g**	**1** (0.5 mol%)	$CH_3(CH_2)_5$  **6g**	90%[16]
8	 **5h**	**1** (1 mol%)	 **6h**	80%[17]
9	 **5i**	**1** (0.5 mol%)	 **6i**	81%[17]
10	 **5j**	**1** (1 mol%)	 **6j**	84%[18]
11	 **5k**	**1** (1 mol%)	 **6k**	62%
12	 **5l**	**1** (1 mol%)	 **6l**	54%[20]
13	 **5m**	**3** (10 mol%)	 **6m**	75%
14	 **5n**	**1** (0.5 mol%)	 **6n**	85%

It is noteworthy that enolizable aldehydes, which often present problems in trifluoromethylation reactions,[15] worked very well under our standard conditions to produce the desired CF_3 adducts in high yields (entries 7−9).[16,17] The 4-carboxobenzaldehyde (**5j**) was trifluoromethylated via in situ protection of the acid as its TMS ester by reaction with $TMSCF_3$ followed by the addition of the NHC catalyst (entry 10).[18]

α-Keto esters are an important class of carbonyl compounds that are being widely utilized in organic synthesis.[19] Lewis base catalyzed trifluoromethylation of α-keto esters, however, has not been reported.[2c,3] Using NHC catalysis, we were able to expand the substrate scope to include α-keto esters. Both *c*-hexyl pyruvate (**5k**) and ethyl 2-oxo-4-phenylbutyrate (**5l**) underwent reactions with $TMSCF_3$ in the presence of 1 mol % NHC (**1**) to furnish the CF_3-substituted tertiary alcohols (entries 11 and 12[20]).

Acetophenone gave <1% conversion under the catalysis of carbenes **1**−**3**. However, reactions with a more reactive ketone **5m** did proceed in the presence of 10 mol % of NHC **3** to give trifluoromethyl substituted tertiary alcohol in 75% yield (entry 13). The significant reactivity gap between aldehydes and ketones provides an opportunity to selectively trifluoromethylate an aldehyde in the presence of a ketone functionality. This was illustrated using *p*-acetyl benzaldehyde (**5n**) as a test substrate (entry 14). Even with a large excess of $TMSCF_3$ (5 equiv), clean conversion to the monotrifluoromethylated product **6n** was achieved using 0.5 mol % of adamantyl-substituted carbene **1** as the catalyst. In contrast, the TBAF-initiated trifluoromethylation of **5n** gave a mixture of **6n** and double-addition product even if only 1 equiv of $TMSCF_3$ was used. The ratio between **6n** and double addition product from fluoride initiated reactions was 1.9:1 in DMF, 3.6:1 in THF, and 1:2.1 in toluene as determined by HPLC.

In conclusion, we have discovered a novel N-heterocyclic carbene catalyzed trifluoromethylation reaction of carbonyl compounds. Both enolizable and nonenolizable aldehydes and α-keto esters undergo facile trifluoromethylation at room temperature in the presence of only 0.5−1 mol % of the commercially available NHC (**1**), providing CF_3 substituted alcohols in good yields. Selective trifluoromethylation of aldehydes over ketones can be achieved under NHC catalysis. These conditions are extremely mild and simple and tolerate a variety of functional groups. Importantly, compared to the previously reported Lewis base-catalyzed trifluoromethylation protocols, our new method offers much greater catalytic efficiency as well as broader substrate scope. This methodology exemplifies the ability of NHCs to serve as nucleophilic catalysts for fundamental organic reactions. Efforts to extend NHC catalysis to other organic transformations, including

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(15) Enolizable carbonyl compounds can be trifluoromethylated using fluoride initiated reactions with $TMSCF_3$ (see ref 2j). However, enolizable aldehydes were reported to present problems for some other trifluoromethylation methods (for examples, see ref 2b,c,f).
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carbene-catalyzed asymmetric trifluoromethylation processes are ongoing.

Supporting Information Available: Experimental procedures, ^{1}H NMR data, copies of ^{1}H NMR spectra for isolated compounds **6a**−**n**, as well as ^{13}C NMR and HRMS data for new compounds **6f**,**k**,**m**,**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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