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Organocatalytic direct difluoromethylation of aldehydes and ketones with $TMSCF_2H$†

Guang-Fen Du,[ab] Ying Wang,[b] Cheng-Zhi Gu,[b] Bin Dai*[b] and Lin He*[b]

An organic Lewis base promoted direct difluoromethylation reaction of carbonyl compounds with Me_3SiCF_2H has been studied. The Schwesinger's superbase can efficiently activate the Si–CF_2H bond and initiate the difluoromethylation of aldehydes and ketones under very mild conditions, producing difluoromethyl adducts in 42–99% yields.

Organofluorine compounds have found widespread applications in pharmaceuticals, agrochemicals and medicinal chemistry.[1] In particular, the introduction of fluorinated moieties into organic molecules has become a powerful strategy in new drug discovery. As a result, tremendous efforts have been exerted to develop efficient methodologies for the synthesis of fluoroorganics. Among various fluorinated moieties, difluoromethyl group (CF_2H) has attracted considerable attention in recent years.[2] CF_2H is isosteric to hydroxy group (OH) and compared to OH and NH groups, this fluorinated moiety can serve as a lipophilic hydrogen bond donor through hydrogen bonding.[3] These unique properties make the CF_2H group to be particularly interesting with respect to the design of biologically active molecules. However, compared to the extensively studied trifluoromethylation reactions,[4] efficient methods for the introduction of CF_2H group are scarce. Similar with the direct nucleophilic trifluoromethylation reactions, the direct difluoromethylation reaction is the most straightforward method for the introduction of CF_2H group into organic molecules. However, difluoromethylated organometallic reagents are inefficient for difluoromethylation of carbonyl compounds.[5] Difluoromethyl phenylsulfone[6] and several difluoromethylsilanes[7] can undergo indirect difluoromethylation with carbonyl compounds, but additional reactions are needed to remove the auxiliary groups of the difluoromethylated adducts. Silylated reagent $TMSCF_2H$ can be easily prepared from Ruppert–Prakash reagent ($TMSCF_3$).[8] In 1995, Fuchikami and Hagiwara documented[9] that KF can initiate the direct difluoromethylation reaction of $TMSCF_2H$ and carbonyl compounds. However, unlike the analogous Si–CF_3 bond, harsh reaction conditions are required for the cleavage of the relatively inert Si–CF_2H bond, which restricts the applications of this difluoromethylating reagent for long time. Until recently, Hu and co-workers[10] found that CsF or stoichiomeric *t*-BuOK can activate the Si–CF_2H bond efficiently and initiate the difluoromethylation of carbonyl compounds and imines. However, to the best of our knowledge, no other catalysts have been developed for the activation of $TMSCF_2H$ and efficient protocol for the direct difluoromethylation is still highly desirable.

In recent years, several organic Lewis bases such as Bu_4N^+ alkoxides,[11] tris(2,4,6-trimethoxyphenyl)phosphine,[12] sodium phenoxide–phosphine oxides[13] and N-heterocyclic carbenes[14] have been utilized successfully for the activation of different silylated reagents. As an important class of superbases, proazaphosphatranes exhibit high reactivity toward the activation of silylated nucleophiles and a variety of transformations have been developed by Verkade and co-workers[15] in the past decade. As another important type of superbases, phosphazenes[16] have been applied successfully in deprotonative reactions.[17] However, phosphazenes catalysed transformations of organosilanes are farless examined. Until recently, Kondo and co-workers[18] disclosed that phosphazene bases can be utilized to activate several silylated nucleophiles efficiently. We envisioned that phosphazenes and other organic Lewis bases can be utilized to activate $TMSCF_2H$ to initiate the direct difluoromethylation reaction of carbonyl compounds. Herein, we would like to disclose these interesting results.

Our study commenced with the reaction of $TMSCF_2H$ and *p*-chlorobenzaldehyde. To our delight, we found that the reaction proceed smoothly in the presence of 10 mol% *t*-Bu-P_4 (**4a**), producing difluoromethyl carbinol **3a** in 52% yield after 12 h (Table 1, entry 1). Phosphazene bases **4b** and **4c** can also

[a]*School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, P. R. China*

[b]*School of Chemistry and Chemical Engineering, Shihezi University, Xinjiang Uygur Autonomous Region, 832000, P. R. China. E-mail: db_tea@shzu.edu.cn; helin@shzu.edu.cn; Fax: +86-993-2057270*

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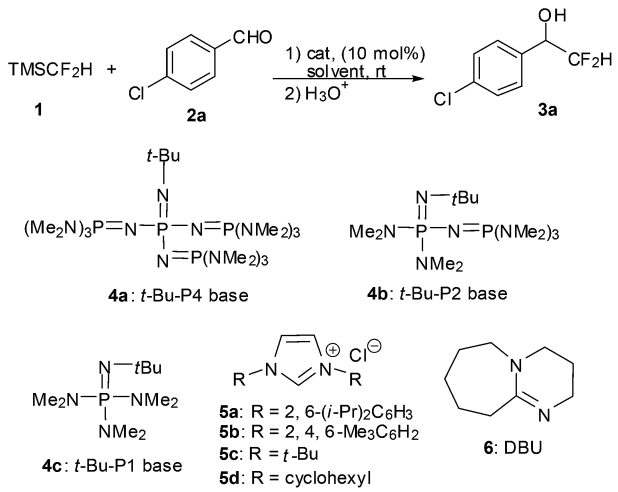
Table 1 Screening of reaction conditions[a]



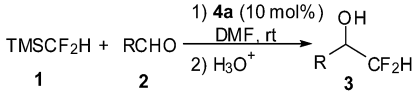
Entry	Conditions	Time (h)	Yield[b] (%)
1	**4a**, THF	12	52
2	**4b**, THF	12	34
3	**4c**, THF	12	18
4	**5a**, ^{t}BuOK, THF	72	11
5	**5b**, ^{t}BuOK, THF	72	12
6	**5c**, ^{t}BuOK, THF	72	<10
7	**5d**, ^{t}BuOK, THF	72	<10
8	**6**, THF	12	0
9	**4a**, DMF	0.5	91
10	**4b**, DMF	2	73
11	**4c**, DMF	2	48
12	**4a**, $PhCH_3$	12	23
13	**4a**, CH_2Cl_2	12	<10
14	**4a**, CH_3CN	12	<10
15[c]	**4a**, DMF	12	63

[a] **1** (1.5 equiv.), **2a** (1.0 equiv.). [b] Isolated yield. [c] Using 5 mol% **4a**.

promote the addition reaction, but in relatively low efficiency (Table 1, entries 2 and 3). To our surprise, N-heterocyclic carbenes **5a–5d**, which were proved to be highly efficient catalysts for trifluoromethylation of aldehydes,[19] only showed very low efficiency for difluoromethylation reaction of aldehydes (Table 1, entries 4–7). Whereas DBU can't catalyse the addition reaction (Table 1, entry 8). The evaluation of other reaction media indicated the high polar solvent of DMF was the best choice with respect to the reaction yield (Table 1, entries 9–14). Reduction of catalyst loading to 5 mol% led to dramatic decrease of reaction rate (Table 1, entry 15).

With the optimized reaction conditions in hand, the substrate scope and the generality of the reaction were subsequently investigated, and the results are summarized in Table 2. Aromatic aldehydes bearing electron-withdrawing, -neutral, and -donating groups can participate in the direct difluoromethylation reaction in excellent yields (Table 2, entries 1–6). Additionally, the substituents on the *ortho*-, *meta*-, and *para*-positions of the aromatic ring showed no obvious effects on the reaction yields (Table 2, entries 7–11). Interestingly,

Table 2 Evaluation of aldehydes[a]



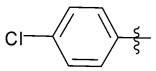
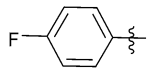
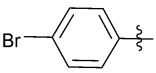
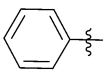
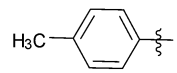
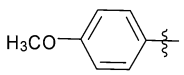
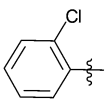
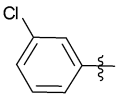
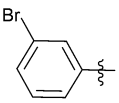
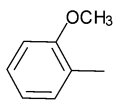
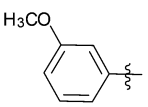
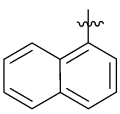
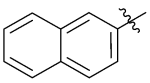
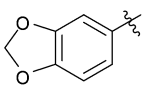
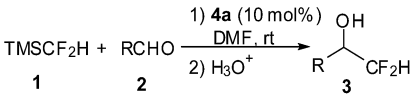
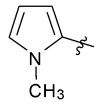
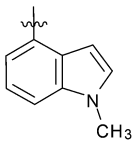
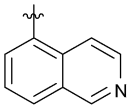
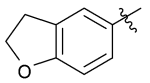
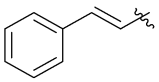
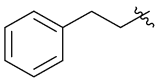
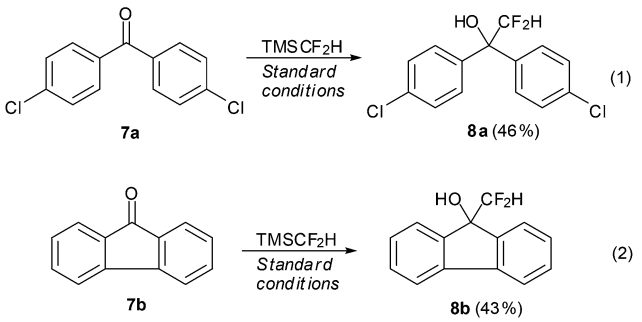
Entry	R	Time (h)	Product	Yield[b] (%)
1		0.5	**3a**	91
2		0.5	**3b**	99
3		0.5	**3c**	99
4		1	**3d**	99
5		1	**3e**	99
6		1	**3f**	99
7		0.5	**3g**	92
8		0.5	**3h**	92
9		0.5	**3i**	99
10		0.5	**3j**	99
11		0.5	**3k**	99
12		3	**3l**	95
13		3	**3m**	88
14		1	**3n**	99
15[c]		0.5	**3o**	87
16[c]		3	**3p**	68

Table 2 (*Contd.*)



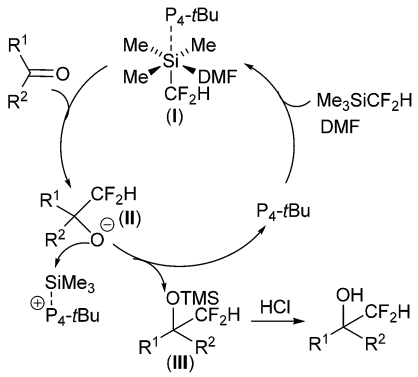
Entry	R	Time (h)	Product	Yield[b] (%)
17[c]		6	**3q**	66
18[c]		6	**3r**	72
19[c]		3	**3s**	95
20		2	**3t**	99
21[c,d]		0.5	**3u**	81
22[c]		1	**3v**	42

[a] Reaction conditions: 10 mol% of **4a**, 1.5 equiv. of **1**, 0.5 mol L^{-1} of **2**, room temperature for 0.5–3 h. [b] Isolated yield. [c] Using 2.0 equiv. TBAF instead of HCl for desilification. [d] Using 20 mol% of **4a**.



Scheme 1 Difluoromethylation of ketones.

naphthaldehyde and heliotropin were proved to be excellent candidates for the reaction, producing the corresponding difluoromethyl carbinols in excellent yields (Table 2, entries 12–14). A variety of heterocyclic aldehydes, such as furfural, 2-thienal, pyrrole-2-carboxaldehyde, indole-4-carboxaldehyde, isoquinoline-5-carboxaldehyde and 5-coumarancarboxaldehyde can participate in the reaction smoothly, producing the corresponding products in good to high yields (Table 2, entries 15–20). Increasing the catalyst loading to 20 mol%,



Scheme 2 Proposed reaction mechanism.

cinnamaldehyde can also undergo the reaction smoothly to produce **3u** in 81% yield (Table 2, entry 21). However, for aliphatic aldehyde **2v**, the strong basicity of *t*-Bu-P4 can cause undesired side reactions, which led to moderate yield of the final fluorinated product (Table 2, entry 22).

We further applied this protocol to the more challenging ketones. Gratifyingly, under the standard reaction conditions, non-enolizable ketones such as biaryl ketone **7a** and fluorenone **7b** react with $TMSCF_2H$ smoothly to afford the corresponding products in 43% and 46% yields, respectively (Scheme 1).

Based on the pioneering work of Kondo[18] and Verkade,[15] a plausible mechanism is proposed and illustrated in Scheme 2. *t*-Bu-P4 attacks the silicon atom of $TMSCF_2H$ to form a hexavalent species **I**, which might trigger the addition to carbonyl compounds and produce oxy anion **II**. The following migration of TMS from *t*-Bu-P4 to **II** led to the formation of **III** with release of the catalyst. And acidic work up produces the difluoromethyl carbinol.

Conclusions

In conclusion, we have demonstrated an organocatalytic difluoromethylation reaction of aldehydes and ketones. The mild conditions, simple procedure and high yields provide an efficient and novel protocol for the introduction of the significantly important difluoromethyl group into organic molecules, which paves the new way for direct difluoromethylation reactions, although the protocol is not suitable for aliphatic aldehydes and enolizable ketones. Further study of the reaction scope and the applications of this methodology in bioactive compounds synthesis are on-going in our group.

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