ORGANIC LETTERS

2011
Vol. 13, No. 19
5342–5345

Efficient and Direct Nucleophilic Difluoromethylation of Carbonyl Compounds and Imines with Me_3SiCF_2H at Ambient or Low Temperature

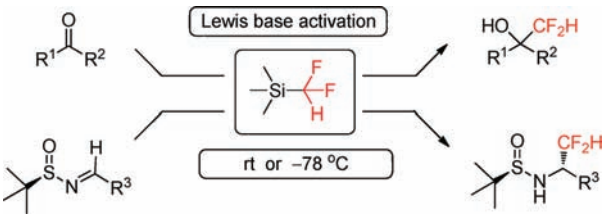
Yanchuan Zhao, Weizhou Huang, Ji Zheng, and Jinbo Hu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

jinbohu@sioc.ac.cn

Received August 15, 2011

ABSTRACT



Since 1995, Me_3SiCF_2H has been widely believed to be an inefficient difluoromethylating agent, which requires harsh reaction conditions to cleave its rather inert Si−CF_2H bond. However, it has now been found that, by using a proper Lewis base activator, Me_3SiCF_2H can efficiently difluoromethylate various aldehydes, ketones, and imines to give the corresponding products in good to excellent yields at room temperature or even at −78 °C.

As the fluoroorganics have found increasing applications in different fields, such as pharmaceuticals, biochemistry, and material science, selectively incorporating a fluorinated moiety into organic molecules has become a subject of intense investigation.[1] Among various fluorinated moieties, the difluoromethyl group (CF_2H) is of particular interest because it is known to be isosteric to a carbinol group (CH_2OH) and behaves as a hydrogen donor through hydrogen bonding.[2] Thus, the difluoromethylated analogues of biologically active compounds are strong candidates for pharmaceuticals due to the unique character of the difluoromethyl group as a lipophilic bioisostere of CH_2OH.[3] Nucleophilic fluoroalkylation has been proven to be a convenient method for the preparation of fluorinated compounds.[1,4] However, although direct nucleophilic trifluoromethylation reactions are widely used with the Ruppert–Prakash reagent (Me_3SiCF_3),[4] methods for direct nucleophilic difluoromethylation (that is, the direct transfer of a CF_2H group) are scarce.[3] Difluoromethyl organometallic reagents, such as $(CF_2H)Cu$, $(CF_2H)_2Cd$, and $(CF_2H)_2Zn$, were unable to efficiently undergo nucleophilic difluoromethylation of carbonyl compounds and imines.[5] In 1995, Fuchikami et al.

(1) (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: New York, 2000. (b) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (f) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley: Chichester, 2009. (g) Bégué, J. P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008. (h) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (i) Uneyama, K. *J. Fluorine Chem.* **2008**, *129*, 550.

(2) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626. (b) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 769 and references therein. (c) Li, Y.; Hu, J. *Angew. Chem.* **2005**, *117*, 6032. (e) *Angew. Chem., Int. Ed.* **2005**, *44*, 5882. (d) Prakash, G. K. S.; Weber, C.; Chacko, S.; Olah, G. A. *Org. Lett.* **2007**, *9*, 1863.

(3) See a recent review on di- and monofluoromethylation reactions: Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.

(4) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (c) Prakash, G. K. S.; Mandal, M. *J. Fluorine. Chem.* **2001**, *112*, 123.

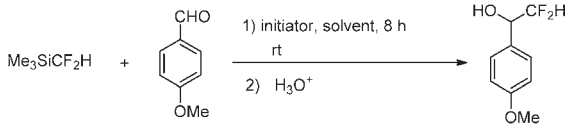
(5) (a) Hartgraves, G. A.; Burton, D. J. *J. Fluorine Chem.* **1988**, *39*, 425. (b) Burton, D. J.; Hartgraves, G. A.; Hsu, J. *Tetrahedron Lett.* **1990**, *31*, 3699. (c) Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007**, *128*, 1198.

10.1021/ol202208b
Published on Web 09/12/2011

reported that, unlike the Ruppert–Prakash reagent, both $PhMe_2SiCF_2H$ and Me_3SiCF_2H reagents were unable to undergo nucleophilic difluoromethylation of carbonyl compounds at room temperature.[6] They found that a harsh reaction condition (100 °C) was required for the KF-initiated difluoromethylation with $PhMe_2SiCF_2H$ and Me_3SiCF_2H reagents, and the reaction only worked for some aldehydes, with the product yields being generally low (20–35%) for ketones.[6] Based on molecular orbital calculation on (difluoromethyl)- and (trifluoromethyl)fluorotrimethylsilicates, they found that the bond order of the Si–CF_2H bond (0.436) is significantly higher than that of the Si–CF_3 bond (0.220), which supports their conclusion that cleavage of the Si–CF_2H bond is more difficult than that of the Si–CF_3 bond and, therefore, "more elevated conditions should be required".[6] Since Fuchikami's report, difluoromethylsilanes (such as Me_3SiCF_2H and $PhMe_2SiCF_2H$) are generally believed to be inefficient difluoromethylating agents, and their synthetic utility was largely ignored over the past 16 years.[1i,3,7a] Currently, difluoromethyl phenyl sulfone ($PhSO_2CF_2H$)[7a] as well as functionalized difluorosilanes $Me_3SiCF_2SiMe_3$[7b] and $PhXCF_2SiMe_3$ (X = SO_2,[7c–e] S,[7f–i] Se[7j,k]) are usually employed as *indirect* nucleophilic difluoromethylation reagents, and an additional step for the removal of the functional or auxiliary group(s) is required after the fluoroalkylation.[3]

In our continuing effort to develop efficient nucleophilic difluoromethylation methods,[7a,c–h] we have been interested in seeking a *general* and *direct* nucleophilic difluoromethylation method for carbonyl compounds and imines under mild reaction conditions. Herein, we wish to disclose our remarkable success in the long-sought-after, efficient, and direct nucleophilic difluoromethylation of aldehydes, ketones, and imines with **1** at ambient or even low temperature (−78 °C).

Table 1. Survey of Reaction Conditions



1 **2a** **3a**

entry	Me_3SiCF_2H (**1**) (equiv)[a]	initiator (mol %)[a]	solvent	**3a** (%)[b]
1	1 (1.3)	KF (130)	DMF	0
2	1 (2.0)	KF/18-crown-6 (100)	DMF	88
3	1 (1.3)	TBAT (20)	DMF	75
4	1 (1.3)	CsF (130)	DMF	87
5	**1 (2.0)**	**CsF (13)**	**DMF**	**91**
6	1 (1.3)	CsF (130)	THF	0[c]
7	1 (1.3)	CsF (130)	toluene	0[c]
8	1 (1.3)	TBAT (20)	THF	**0**[c]
9	1 (2.0)	*t*BuOK (200)	THF	63

[a] The equivalent is relative to that of **2a**. [b] Isolated yield. [c] Determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCF_3$ as an internal standard.

Me_3SiCF_2H (**1**) can be prepared by Mg-mediated difluoromethylation of chlorotrimethylsilane with $PhSO_2CF_2H$.[8a] Recently, Igoumnov et al. elegantly reported that compound **1** can be readily prepared from commercially available Ruppert–Prakash reagent (Me_3SiCF_3) and $NaBH_4$ in 70% isolated yield.[8b] With reagent **1** in hand, we first examined its reaction with aldehydes, by using anisaldehyde (**2a**) as a model substrate in the presence of various Lewis base initiators at room temperature (Table 1). As reported previously,[6] KF alone could not cleave the Si–CF_2H bond in DMF at room temperature (Table 1, entry 1). However, in the presence of KF/18-crown-6, tetrabutylammonium difluorotriphenylsilicate (TBAT), or CsF, the reaction proceeded smoothly at room temperature (entries 2–4). Highly polar solvent DMF was found to be much better than THF and toluene for the reaction, as the reaction between **1** and **2a** could not occur in THF and toluene when TBAT was used as an initiator (entries 6 and 7).

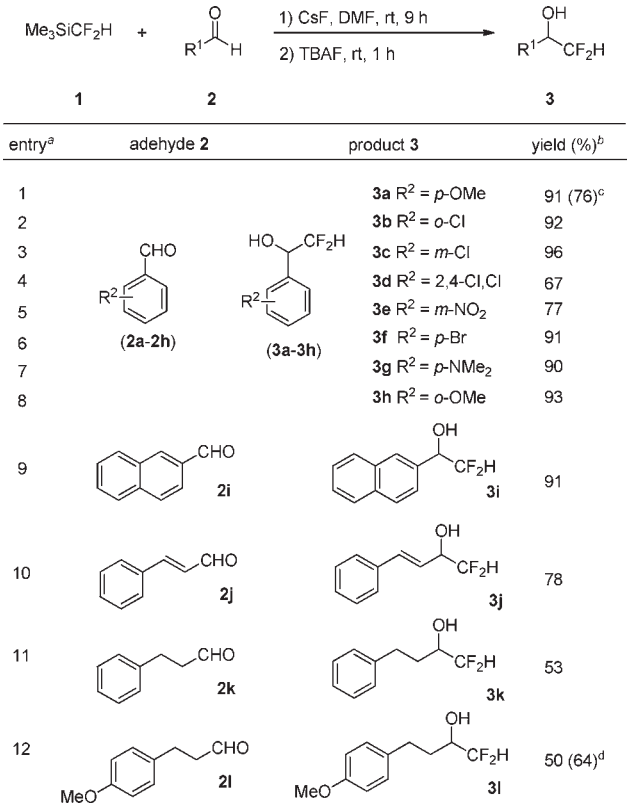
Interestingly, *t*BuOK was found to be able to cleave the Si–CF_2H bond more efficiently in THF than various fluoride salts (entries 6, 8 and 9), and this observation could be attributed to the better solubility of *t*BuOK in THF than those of fluoride salts. However, CsF was found to be the best initiator (entries 4 and 5) when DMF was used as a solvent. After a quick optimization of the reactant ratio, we were able to isolate 2,2-difluoro-1-(4-methoxyphenyl)ethanol (**3a**) in 91% yield when the reactant ratio **1**/**2a**/CsF = 2.0:1.0:0.13 (Table 1, entry 5).

By using the optimized reaction conditions (as those in Table 1, entry 5) as the standard, we next examined the substrate scope of this difluoromethylation reaction between **1** and various aldehydes **2**. As shown in Table 2, various aldehydes **2** were treated with **1**, smoothly giving the corresponding difluoromethyl carbinols **3** in good to excellent yields. This method tolerates various substrates on aryl aldehydes. It was found that aldehydes with electron-donating groups gave slightly higher yields than those with electron-withdrawing groups (entries 1–8), which is consistent with the initiating ability of the generated carbinolate species [$R^1(CF_2H)(H)CO^-$] (please note that the reaction is autocatalytic, which is similar to the reactions with Me_3SiCF_3[4a]). The reaction is also amenable to both aliphatic and conjugated aldehydes (entries 10–12). It is important to mention that a similar reaction with

(6) Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 717.
(7) (a) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. (b) Yudin, A. K.; Prakash, G. K. S.; Deffieux, D.; Bradley, M.; Bau, R.; Olah, G. A. *J. Am. Chem. Soc.* **1997**, *119*, 1572. (c) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273. (d) Liu, J.; Ni, C.; Wang, F.; Hu, J. *Tetrahedron. Lett.* **2008**, *49*, 1605. (e) Zhu, L.; Li, Y.; Zhao, Y.; Hu, J. *Tetrahedron Lett.* **2010**, *51*, 6150. (f) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 527. (g) Pohmakotr, M.; Panichakul, D.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2007**, *63*, 9429. (h) Li, Y.; Hu, J. *J. Fluorine Chem.* **2008**, *129*, 382. (i) Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798. (j) Qin, Y.-Y.; Qiu, X.-L.; Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *J. Org. Chem.* **2005**, *70*, 9040. (k) Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575.
(8) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457. (b) Tyutyunov, A. A.; Boyko, V. E.; Igoumnov, S. M. *Fluorine Notes*, 2011, *74*, 1; http://notes.fluorine1.ru/public/2011/1_2011/letters/letter2.html.

(difluoromethyl)dimethyl(phenyl)silane ($PhMe_2SiCF_2H$)[6] also gave a good yield of the difluoromethylated product under the current reaction conditions (Table 2, entry 1).

Table 2. Direct Nucleophilic Difluoromethylation of Various Aldehydes **2** with (Difluoromethyl)trimethylsilane **1**

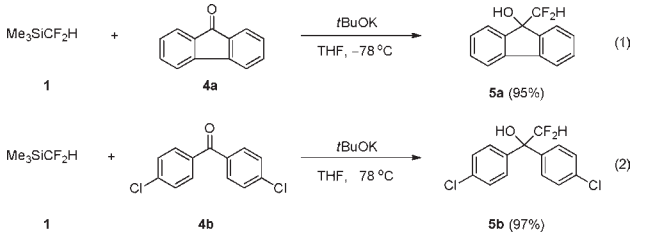


entry[a]	adehyde **2**	product **3**	yield (%)[b]
1	(**2a-2h**)	**3a** R^2 = *p*-OMe	91 (76)[c]
2		**3b** R^2 = *o*-Cl	92
3		**3c** R^2 = *m*-Cl	96
4		**3d** R^2 = 2,4-Cl,Cl	67
5		**3e** R^2 = *m*-NO_2	77
6		**3f** R^2 = *p*-Br	91
7		**3g** R^2 = *p*-NMe_2	90
8		**3h** R^2 = *o*-OMe	93
9	**2i**	**3i**	91
10	**2j**	**3j**	78
11	**2k**	**3k**	53
12	**2l**	**3l**	50 (64)[d]

[a] In all cases, 2.0 equiv of **1** and 13 mol % CsF were used. [b] Isolated yield. [c] 1.5 equiv of $PhMe_2SiCF_2H$ was used as a difluoromethylation reagent. [d] 1.5 equiv of TBAT was used as an initiator.

Encouraged by the above results, we next examined the difluoromethylation of ketones with reagent **1**. Similar to Fuchikami's results,[6] when we treated ketones with reagent **1** under the same reaction conditions as those described in Table 2, only low yields of product (30−40%) were obtained. Careful examination of the reaction products showed that the Me_3SiCF_2H/CsF/DMF system tends to undergo irreversible nucelophilic difluoromethylation of the carbonyl group of DMF, which causes competition especially when electrophilicity of the substrate is low. THF and other non-base-sensitive solvents seemed to be beneficial to suppress the side reactions; however, CsF and TBAT could not induce the reaction in those solvents (Table 1, entries 6−8). As mentioned above (Table 1, entry 9), certain *O*-initiators are more efficient in cleaving the Si−CF_2H bond than *F*-initiators in THF (Table 1, entry 9), and therefore, various *O*-initiators were tried and we were pleased to find that the reaction beween **1** and ketones **4** could proceed smoothly in the presence of *t*BuOK in THF at −78 °C. Under the optimized reaction conditions (**1**/**4**/*t*BuOK = 2.9:1.0:2.9), we examined the scope and limitations of this nucleophilic difluoromethylation reaction between **1** and ketones **4**. It was found that the reactions with nonenolizable ketones (such as biaryl ketones **4a** and **4b**) gave CF_2H-carbinols in excellent yields (Scheme 1, eqs 1 and 2), whereas the reaction with enolizable methyl ketones (such as acetophenone) failed to give the corresponding products due to the labile enolization and subsequent aldol reaction of these substrates under the basic reaction conditions. It should be mentioned that a stoichiometric amount of *t*BuOK must be employed, which suggests that *t*BuOK possesses better activating power for Si−CF_2H bond cleavage than the in situ generated difluoromethyl carbinolate species. This observation is different from the autocatalyzed nucleophilic difluoromethylation of aldehydes (see Table 2) as well as the autocatalyzed trifluoromethylation of aldehydes and ketones with Me_3SiCF_3.[4a]

Scheme 1. Difluoromethylation of Ketones **4**



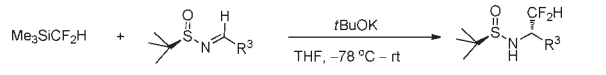
We also found that *t*-BuOK/THF was the best initiating system to facilitate the nucleophilic difluoromethylation of Ellman's *N*-*tert*-butylsulfinyl imines[9] with **1**. With an optimized reaction condition (reactant ratio **1**/**6**/*t*BuOK = 2.9:1.0:2.9), we examined the scope of the current direct diastereoselective nucleophilic difluoromethylation of *N*-*tert*-butylsulfinyl imines **6**. As shown in Table 3, a variety of structurally diverse *N*-*tert*-butylsulfinyl imines **6** could be efficiently difluoromethylated by **1** at −78 °C, giving the corresponding products **7** in good to excellent yields and with good diastereoselectivities (dr = 80:20−93:7). The observed lower diastereoselectivity (compared with corresponding nucleophilic trifluoromethylation using Me_3SiCF_3[10]) may be due to the smaller steric hindrance of the difluoromethyl group (CF_2H) than the trifluoromethyl group (CF_3). The relative configuration of the main isomer of product **7a** was confirmed by comparison with the previous report,[2c] and the configurations of other products **7b**−**7h** were assigned by analogy.

To demonstrate further synthetic application of the present difluoromethylation with reagent **1** under mild conditions, we applied it in the synthesis of tricylic compound **9** (Scheme 2), which is the key structural motif of a useful HIV reverse transcriptase inhibitor. The trifluoromethyl analogue of **9** has been easily prepared by using

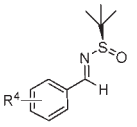
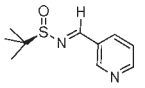
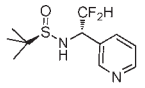
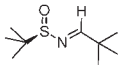
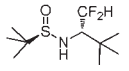
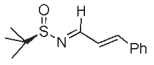
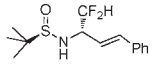
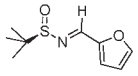
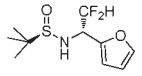
(9) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(10) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589.

Table 3. Direct Nucleophilic Difluoromethylation of *N-tert*-Butylsulfinyl Imines **6** with (Difluoromethyl)trimethylsilane **1**



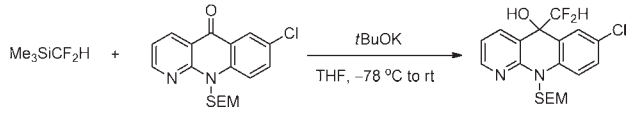
1 6 7

entry[a]	sulfinyl imine **6**	product **7**	yield (%)[b]	dr[c]
1		**7a** R^4 = *p*-OMe	91	92:8
2		**7b** R^4 = *o*-OMe	88	92:8
3		**7c** R^4 = *p*-Me	95	92:8
4	**6a**–**6d**	**7a**–**7d** **7d** R^4 = *p*-Br	87	91:9
5	 **6e**	 **7e**	68	90:10
6	 **6f**	 **7f**	90	92:8
7	 **6g**	 **7g**	88	80:20
8	 **6h**	 **7h**	90	91:9

[a] In all entries, 2.9 equiv of **1** and 2.9 equiv of *t*BuOK were used. [b] Overall isolated yield of two diastereomers. [c] Diastereometric ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.

Me_3SiCF_3 reagent, while **9** was previously obtained through a long synthetic procedure partially due to the lack of an efficient and direct method to introduce a difluoromethyl group (CF_2H).[11] We found that by using the reactant ratio **1**/**8**/*t*BuOK = 2.9:1.0:2.9, compound **9** could be obtained in 79% yield directly from compound **8** (Scheme 2).

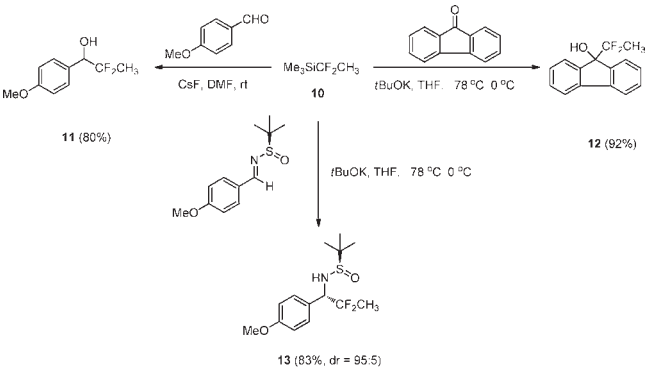
Scheme 2. Synthesis of a Tricyclic Compound **9** [SEM = 2-(Trimethylsilyl)ethoxymethyl]



1 8 **9** (79%)

This Lewis base activation (in a proper solvent) protocol was also applicable to other (difluoroalkyl)silane reagents. For instance, a direct nucleophilic 1,1-difluoroethylation reaction with (1,1-difluoroethyl)trimethylsilane **10** worked equally well under similar reaction conditions to afford the corresponding products (which is otherwise very difficult to obtain by using previously reported methods[6,12]) in good to excellent yields (Scheme 3). These results suggest that, by applying a similar protocol, a wide range of biologically important difluoroorganics can be readily prepared with corresponding (difluoroalkyl)silanes.

Scheme 3. Direct Nucleophilic 1,1-Difluoroethylation of Aldehyde, Ketone, and *N-tert*-Butylsulfinyl Imine with (1,1-Difluoroethyl)trimethylsilane **10**



In conclusion, we have developed an efficient and direct nucleophilic difluoromethylation of aldehydes, ketones, and *N-tert*-butylsulfinimines with Me_3SiCF_2H (**1**). The reactivity of Me_3SiCF_2H as a nucleophile has been disclosed in detail. We found that the use of a proper Lewis base and solvent plays a crucial role in activating the Si–CF_2H bond at ambient or even low temperature. The present synthetic protocol not only paves the way for a general and direct nucleophilic difluoromethylation but also can be extended to other fluoroalkylations with corresponding fluoroalkylsilanes (as demonstrated in Scheme 3). Given the high importance of introducing of the CF_2H group into organic molecules,[3] the easy prepration of reagent **1** from commercially available Me_3SiCF_3,[8b] and the practical simplicity of the reaction procedure, the present difluoromethylation method promises to find many applications in life science and material science related fields.

Acknowledgment. Dedicated to Professor G. K. Surya Prakash (University of Southern California) for his pioneering contribution of using (fluoroalkyl)silanes as nucleophilic fluoroalkylating agents. J.H. thanks Professor Alexander Dilman (Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences) for helpful discussions. Financial support by the National Natural Science Foundation of China (20825209, 20832008) and the Chinese Academy of Sciences is gratefully acknowledged.

Supporting Information Available. Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Johnson, B. L.; Patel, M.; Rodgers, J. D.; Wang, H. S. WO 2001029037.

(12) Mogi, R.; Morisaki, K.; Hu, J.; Prakash, G. K. S.; Olah, G. A. *J. Fluorine Chem.* **2007**, *128*, 1098.