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Full Paper

Brønsted Acid Mediated (sp^3)Carbon-Fluorine Bond Activation: Inter- and Intramolecular Arylation of Trifluoromethylated Arenes†

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Trifluoromethanesulfonic acid (triflic acid) was found to be able to efficiently activate the benzylic sp^3 C—F bond. Thus, under the catalysis of triflic acid at room temperature, trifluoromethylated arenes readily reacted with benzene to give benzophenones in moderate to good yields. Under similar Bønsted acid catalysis, intramolecular arylation also happened in the cases of some CF_3-arene substrates bearing an additional nucleophilic aryl group. Strong CF···H^+ interaction or hydrogen bonding, is believed to play an important role in the current Brønsted acid-mediated C—F bond activation chemistry.

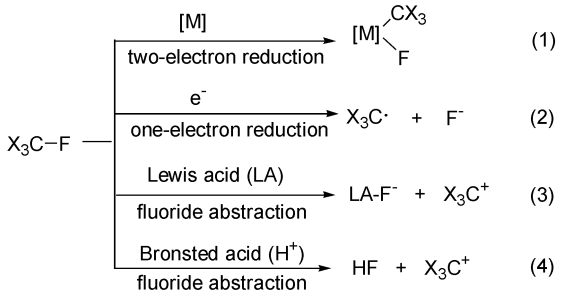
Keywords C—F activation, Brønsted acid, F···H interaction, trifluoromethyl

Introduction

Carbon—fluorine (C—F) bond is widely recognized as the strongest single bond to carbon, and the selective C—F bond activation (or transformation) under mild conditions remains a challenging task in modern organic chemistry.[1-7] In retrospect, C—F bond activation (or transformation) did not attract much attention for a long period of time, especially in the field of fluorine chemistry. Introducing fluorine atom(s) and fluorinated building blocks to organic molecules are two important aspects of organofluorine chemistry. Since the naturally occurring organofluorine compounds are scarce and the C—F bond formation is generally an expensive process, a deliberate C—F bond cleavage is seemingly lack of practical interest. The few exceptional examples that involve C—F bond cleavage as a key step in organic synthesis include: (a) glycosyl fluorides are used as glycosyl donors for glycosidation because of their enhanced stability, ease of handling, and higher stereoselectivity compared with other glycosyl halides; (b) aromatic fluorides with electron-withdrawing groups at *ortho*- or *para*-position are frequently used in the aromatic nucleophilic substitution (S_NAr) reactions; (c) Mg/Me_3SiCl-mediated reductive defluorinations of trifluoromethyl ketones and related compounds are frequently used as a practical way to prepare difluoromethylene-containing compounds.[1,8-12]

Recently, substantial attention has been paid to the transition metal-catalyzed C—F activation chemistry.[1-6] However, most of the work involves the activation of sp^2 C—F bonds, and much less success has been achieved in sp^3 C—F bond activation (or transformation). On the other hand, many sp^3 C—F bond-containing compounds such as perfluorooctanesulfonic acid derivatives (PFOs), chlorofluorocarbons (CFCs or Freons) and hydrofluorocarbons (HFCs) are of significant environmental concern, thus the development of efficient and economic cleavage of sp^3 C—F bonds for disposal of these compounds is highly desired.[13,14] Currently, the transition metal-mediated C—F bond activation typically involves a reduction process on alkyl fluoride (X_3C—F), either through an oxidative addition or a single-electron transfer process (Scheme 1, Eqs. 1 and 2).[15] Other reducing metal-mediated reductive defluorination has also been reported, two well-known examples being the Li^0/NH_3-mediated defluorination of poly(tetrafluoroethylene)[16] and Mg^0/Me_3SiCl-mediated defluorination of trifluoromethyl compounds.[11,12] Lewis

Scheme 1 Different approaches of C—F bond cleavage



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† Dedicated to Professor Qingyun Chen on the occasion of his 80th birthday.

acid-mediated fluoride abstraction is also well-recognized as an efficient method to cleave the sp^3 C—F bonds (Scheme 1, Eq. 3). Olah and co-workers have extensively used the reaction between alkyl fluorides and strong Lewis acids to generate carbocations and/or for other synthetic applications.[17-19] In 2006, Akiyama and co-workers reported a low-valent niobium-mediated activation of C—F bond.[20] Kambe and co-workers also developed several C—C and C—heteroatom bond formation reactions using alkyl fluorides as the starting materials.[21,22] More recently, Douvris and Ozerov elegantly reported the hydrodefluorination of perfluoroalkyl groups using silyl cation as the Lewis acid for fluoride abstraction.[15] However, although the Lewis acid-mediated C—F bond activations (Scheme 1, Eq. 3) are well developed, the Brønsted acid-mediated C—F bond activation chemistry (Scheme 1, Eq. 4) has not drawn much attention.[23] It is known that concentrated sulfuric acid can catalyze the hydrolysis of *α*,*α*,*α*-trifluorotoluene ($PhCF_3$) to give benzoic acid.[24] Under similar sulfuric acid catalysis, 2-(trifluoromethyl)biphenyl can be transformed to 9*H*-fluoren-9-one in 26% yield.[25] The sensitivity of C—F bond to acid-catalyzed hydrolysis was arguably accounted for by the possibility of strong fluorine-hydrogen bonding.[24] In this paper, we wish to report a triflic acid-mediated C—F bond activation, which enabled us to accomplish inter- and intramolecular arylation of trifluorinated arenes. These results not only represent another synthetic approach for the preparation of benzophenone and its deivatives, but also provide some intriguing experimental facts that deserve further mechanistic understanding.

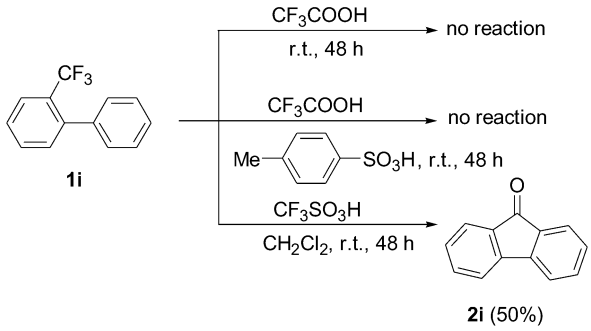
Results and discussion

In order to test some Brønsted acids for C—F activation, we used 2-(trifluoromethyl)biphenyl (**1i**) as a model substrate, and then selected several organic Brønsted acids such as trifluoroacetic acid, *p*-methylbenzenesulfonic acid, and triflic acid to activate the C—F bond of compound **1i** (Scheme 2). It was found that both trifluoroacetic acid and *p*-methylbenzenesulfonic acid could not activate the C—F bond of **1i**, while triflic acid was able to promote the C—F bond cleavage. In the present of CH_2Cl_2 as a solvent at room temperature, 9*H*-fluoren-9-one (**2i**) was obtained in 50% yield from 2-(trifluoromethyl)biphenyl (**1i**) through a C—F cleavage/intramolecular arylation process (Scheme 2).

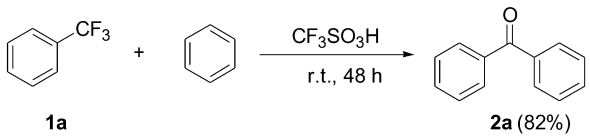
Under the similar reaction conditions, the intermoleculer arylation reactions were also found to be successful. For example, in the presence of triflic acid (10 equiv.), *α*,*α*,*α*-trifluorotoluene (**1a**) readily reacted with benzene (as both substrate and solvent) at room temperature to give benzophenone (**2a**) in high yield (82%) (Scheme 3).

As shown in Table 1, a range of trifluoromethylated arenes **1a**—**1j** were able to undergo triflic acid catalyzed C—F cleavage (followed by arylation reaction) to

Scheme 2 Influence of the acidity on C—F bond activation



Scheme 3 Triflic acid-mediated C—F cleavage



give corresponding products **2a**—**aj** in moderate to good yields. In the cases of substrates **1c** and **1b**, the relatively lower yield of **2c** is possibly due to the steric effect (Entries 2 and 3). In the case of mesitylene (instead of benzene), product **2a'** was obtained in 62% yield (campare Entries 9 and 1), which can also be explained by the steric effect. It is particularly remarkable that, when CH_2Cl_2 was used as solvent, the intramolecular arylation of **1i** occurred, and compound **2i** was obtained as the sole product in moderate yield (Entry 10). However, when benzene (instead of CH_2Cl_2) was used as solvent, intermolecular arylation products **2i'** and **2i"** were obtained as the major products (Entry 11). For a better mechanistic understanding, we used 9*H*-fluoren-9-one (**2i**) as a substrate to react with benzene under the treatment of triflic acid, the expected products **2i'** and **2i"** were not obtained (Scheme 4). This result indicates that in the case of Entry 11, the products **2i'** and **2i"** were not formed through **2i** as an intermediate. It is also interesting that, when **1j** was used as a substrate (in the presence of both benzene and triflic acid), we did not observe any intermolecular phenylation product, and only intramolecular arylation product **2j** was obtained in 93% yield (Entry 12). When the solvent was changed to CH_2Cl_2 (instead of benzene) in the case of Entry 12, product **2j** was formed in a similar

Scheme 4 The reaction between 9*H*-fluoren-9-one (**2i**) and benzene

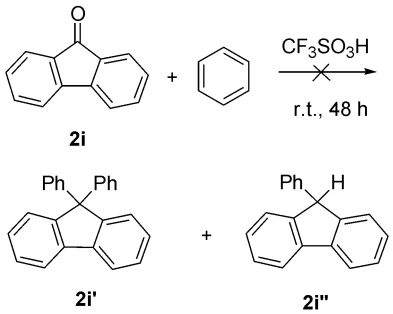
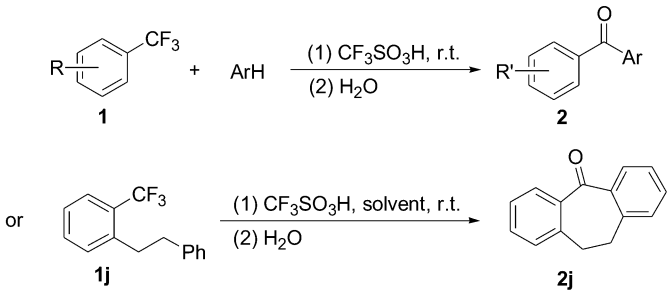
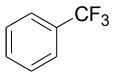
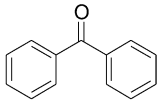
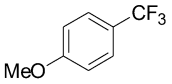
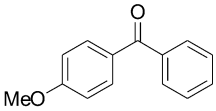
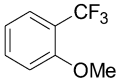
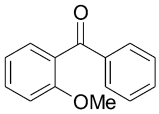
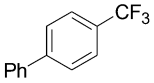
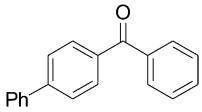
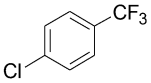
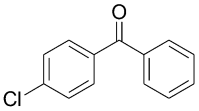
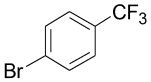
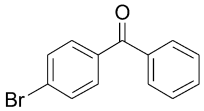
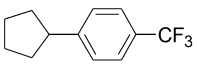
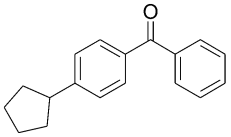
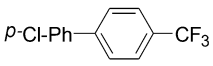
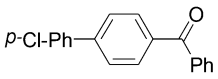
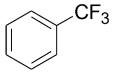
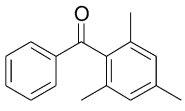
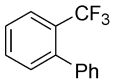
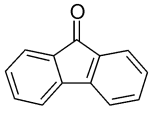
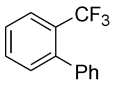
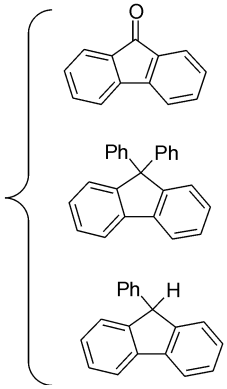
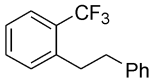
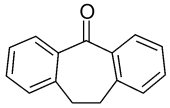


Table 1 Inter- and intramolecular arylation of trifluoromethylated arenes



Entry[a]	$ArCF_3$		Time/h	Product		Yield[b]/%
1		**1a**	48		**2a**	82
2		**1b**	48		**2b**	77
3		**1c**	48		**2c**	52
4		**1d**	48		**2d**	60
5		**1e**	72		**2e**	71
6		**1f**	72		**2f**	62
7		**1g**	48		**2g**	72
8		**1h**	48		**2h**	70
9[c]		**1a**	96		**2a'**	62
10		**1i**	48		**2i**	50

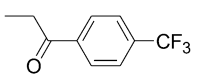
Continued

Entry[a]	$ArCF_3$		Time/h	Product		Yield[b]/%
11		**1i**	48		**2i**	Trace
					2i'	45
					2i"	26
12		**1j**	48		**2j**	93 (91[d])

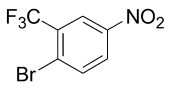
[a] For all cases, the reactant ratio **1** : CF_3SO_3H = 1 : 10. [b] Isolated yields. [c] Mesitylene instead of benzene as the solvent, and the reactant ratio **1** : CF_3SO_3H = 1 : 20. [d] CH_2Cl_2 instead of benzene as the solvent.

yield (91%).

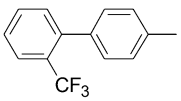
It should be noted that, some trifluomethylated arenes with additional electron-withdrawing groups, such as **1k** and **1l**, could not undergo C—F cleavage and inter- or intramolecular arylation reactions under similar triflic acid catalyzed reaction conditions. A similar reaction with compounds **1m** (or **1n**) resulted in a messy unidentified product mixture.



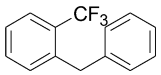
1k



1l



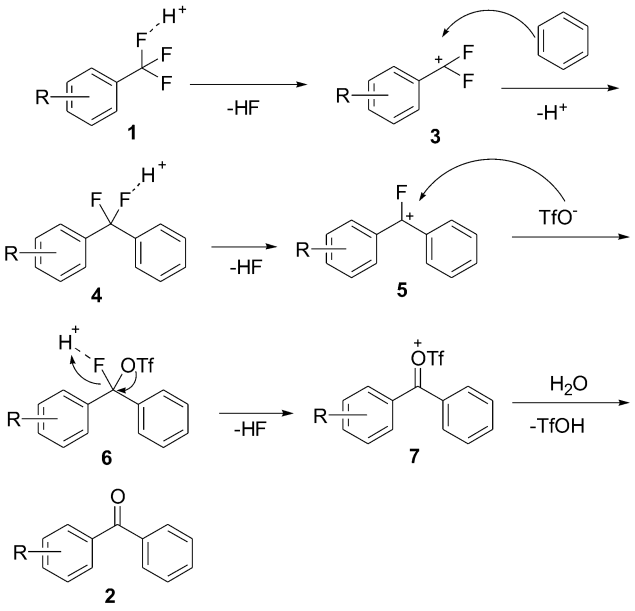
1m



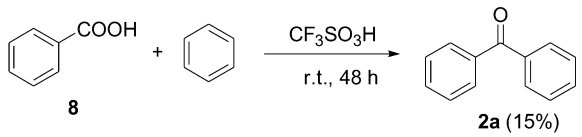
1n

The plausible reaction mechanism is proposed as shown in Scheme 5. In the presence of triflic acid, the C—F bond in trifluoromethylated arenes **1** is cleaved via strong CF···H^+ interaction (or say, hydrogen bonding) to give difluorobenzylic carbocation species **3**. The cation **3** reacts with benzene to give compound **4**, and the latter one further undergoes acid-mediated C—F bond cleavage to give cation **5**. It is possible that the triflate anion captures the cation **5**, which releases a HF molecule to give cation **7**. Intermediate **7** can be quenched by water (small amount of water always exists in triflic acid) to give product **2**. It is also possible that, the water molecule directly captures cation **5** and gives the product **2** (after HF elimination). We also applied the same method using benzoic acid **8** as a substrate to obtain product **2a** in low yield (15%) (Scheme 6), which suggests that in the reactions as mentioned in Table 1, products **2** may not be formed through a carboxylic acid intermediate.

Scheme 5 Proposed reaction mechanism



Scheme 6 The reaction between benzoic acid and benzene



Conclusion

In conclusion, we found that trifluoromethanesulfonic acid was able to efficiently activate the benzylic sp^3

C—F bond. Under the catalysis of triflic acid at room temperature, trifluoromethylated arenes readily reacted with benzene to give benzophenones in moderate to good yields. Under similar Bønsted acid catalysis, intramolecular arylation also happened in the case of some CF_3-arene substrates bearing an additional nucleophilic aryl group. Strong $CF\cdots H^+$ interaction or hydrogen bonding, if not a real protonation of the fluorine atom of a benzylic C—F bond, is believed to play an important role in the current Brønsted acid mediated C—F bond activation chemistry.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ on a BRUKER AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a BRUKER AM-300 spectrometer (300 MHz) using $CFCl_3$ as external standard. IR spectra were obtained with a Nicolet AV-360 spectrometer. Mass spectra were obtained on a mass spectrometer. All the solvents were redistilled before use.

General procedure for the reaction

Under N_2 atmosphere, the compound **1a** (0.146 g, 1.0 mmol) was stirred in dry benzene (3 mL) at ambient temperature. Then added trifluoromethanesulfonic acid (0.88 mL, 10.0 mmol) using a syringe. After 48 h, the reaction was quenched by adding 10 mL of brine, followed by extraction with ether (15 mL) three times. The organic phase was washed successively with $NaHCO_3$ solution and brine, and then dried over with anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1∶40, *V*/*V*) as eluent to give product **2a**.

Benzophenone (**2a**): White solid. ^{1}H NMR δ: 7.81 (m, 4H), 7.60 (t, J=7.1 Hz, 2H), 7.49 (t, J=7.1 Hz, 4H); MS (EI) *m*/*z* (%): 182 (M^+, 48.85), 105 (100.00), 77 (51.84). The characterization data was consistent with reference.[26]

(4-Methoxyphenyl)(phenyl)methanone (**2b**): White solid. ^{1}H NMR δ: 8.00—7.41 (m, 7H), 7.09—6.90 (m, 2H), 3.89 (s, 3H); MS (EI) *m*/*z* (%): 212 (M^+, 34.20), 135 (100.00), 77 (47.68). The characterization data was consistent with reference.[27]

(2-Methoxyphenyl)(phenyl)methanone (**2c**): White solid. ^{1}H NMR δ: 7.82 (d, J=3.9 Hz, 2H), 7.60—7.34 (m, 5H), 7.08—6.97 (m, 2H), 3.73 (s, 3H); MS (EI) *m*/*z* (%): 212 (M^+, 47.52), 135 (100.00), 77 (65.97). The characterization data was consistent with reference.[28]

Biphenyl-4-yl(phenyl)methanone (**2d**): White solid. ^{1}H NMR δ: 7.93—7.81 (m, 4H), 7.74—7.62 (m, 4H), 7.59 (d, J=7.3 Hz, 1H), 7.55—7.45 (m, 4H), 7.42 (d, J=7.3 Hz, 1H); MS (EI) *m*/*z* (%): 258 (M^+, 67.83), 181 (100.00), 77 (26.26). The characterization data was consistent with reference.[29]

(4-Chlorophenyl)(phenyl)methanone (**2e**): White solid. ^{1}H NMR δ: 7.98—7.36 (m, 9H); MS (EI) *m*/*z* (%): 216 (M^+, 42.60), 105 (100.00), 77 (96.47). The characterization data was consistent with reference.[28]

(4-Bromophenyl)(phenyl)methanone (**2f**): White solid. ^{1}H NMR δ: 7.78 (d, J=7.5 Hz, 2H), 7.71—7.57 (m, 5H), 7.49 (t, J=7.8 Hz, 2H); MS (EI) *m*/*z* (%): 260 (M^+, 37.65), 105 (100.00), 77 (46.97). The characterization data was consistent with reference.[30]

(4-Cyclopentylphenyl)(phenyl)methanone (**2g**): White solid. ^{1}H NMR δ: 7.84—7.71 (m, 4H), 7.59 (t, J=7.4 Hz, 1H), 7.48 (t, J=7.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 3.16—3.00 (m, 1H), 2.20—2.04 (m, 2H), 1.92—1.59 (m, 6H); MS (EI) *m*/*z* (%): 250 (M^+, 76.75), 175 (100.00). The characterization data was consistent with reference.[31]

(4'-Chlorobiphenyl-4-yl)(phenyl)methanone (**2h**): White solid. ^{1}H NMR δ: 7.90 (d, J=7.7 Hz, 2H), 7.84 (d, J=7.9 Hz, 2H), 7.70—7.42 (m, 9H); MS (EI) *m*/*z* (%): 292 (M^+, 18.09), 215 (100.00), 77 (91.96). The characterization data was consistent with reference.[32]

9*H*-Fluoren-9-one (**2i**): Yellow solid. ^{1}H NMR δ: 7.66 (d, J=7.3 Hz, 2H), 7.51 (t, J=8.7 Hz, 3H), 7.29 (t, J=7.0 Hz, 3H); MS (EI) *m*/*z* (%): 180 (M^+, 100.00). The characterization data was consistent with reference.[33]

9,9-Diphenyl-9*H*-fluorene (**2i'**): White solid. ^{1}H NMR δ: 7.75 (d, J=7.1 Hz, 2H), 7.40 (d, J=7.8 Hz, 2H), 7.34—7.16 (m, 14H); MS (EI) *m*/*z* (%): 318 (M^+, 100.00). The characterization data was consistent with reference.[34]

9-Phenyl-9*H*-fluorene (**2i"**): White solid. ^{1}H NMR δ: 7.80 (d, J=7.7 Hz, 2H), 7.38 (t, J=7.7 Hz, 2H), 7.34—7.05 (m, 9H), 5.05 (s, 1H); MS (EI) *m*/*z* (%): 242 (M^+, 100). The characterization data was consistent with reference.[35]

10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one (**2j**): White solid. ^{1}H NMR δ: 8.01 (d, J=7.2 Hz, 2H), 7.44 (t, J=7.2 Hz, 2H), 7.33 (t, J=7.2 Hz, 2H), 7.25 (d, J=5.2 Hz, 2H), 3.22 (s, 4H); MS (EI) *m*/*z* (%): 208 (M^+, 90.38), 179 (100.00), 178 (95.23). The characterization data was consistent with reference.[36]

Mesityl(phenyl)methanone (**2a'**): White solid. ^{1}H NMR δ: 7.81 (d, J=7.7 Hz, 2H), 7.64—7.53 (m, 1H), 7.51—7.39 (m, 2H), 6.90 (s, 2H), 2.34 (s, 3H), 2.08 (s, 6H); MS (EI) *m*/*z* (%): 224 (M^+, 100.00), 223 (100.00), 147 (75.88). The characterization data was consistent with reference.[37]

References

1 *Organofluorine Compounds*: *Chemistry and Applications*, Ed.: Hiyama, T., Springer, New York, **2000**.

2 Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev*. **1994**, *94*, 373.

3 Perutz, R. N.; Braun, T. In *Comprehensive Organometallic Chemistry III*, Eds.: Mingos, M. D.; Crabtree, R. H., Elsevier, Amsterdam, **2007**.

4 Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber*. **1997**, *130*, 145.

5 Richmond, T. G. In *Topics in Organometallic Chemistry*, Vol. 3, Ed.: Murai, S., Springer, New York, **1999**.
6 Saunders, G. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2615.
7 Huang, Y.; Zhou, J. *J. Organomet. Chem.* **1988**, *348*, 235.
8 Uneyama, K. *Organofluorine Chemistry*, Blackwell, Oxford, **2006**.
9 Kirsch, P. *Fluoroorganic Chemistry*: *Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.
10 Chambers, R. D. *Fluorine in Organic Chemistry*, Blackwell, Oxford, **2004**.
11 Hideki, A.; Uneyama, K. In *Fluorine-Containing Synthons*, Ed.: Soloshonok, V. A., ACS Symposium Series 911, American Chemical Society, Washington DC, **2005**.
12 Uneyama, K.; Hideki, A. *J. Fluorine Chem.* **2002**, *114*, 127.
13 Ochoa-Herrera, V.; Sierra-Alvarez, R.; Somogyi, A.; Jacobsen, N. E.; Wysocki, V. H.; Field, J. A. *Environ. Sci. Technol.* **2008**, *42*, 3260.
14 Shine, K. P.; Sturges, W. T. *Science* **2007**, *315*, 1804.
15 Douvris, C.; Ozerov, O. V. *Science* **2008**, *321*, 1188 and the references cited therein.
16 Chakrabarti, N.; Jacobus, J. *Macromolecules* **1988**, *21*, 3011.
17 Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393.
18 Olah, G. A.; Prakash, G. K. S.; Krishnamurthy, V. V. *J. Org. Chem.* **1983**, *48*, 5116.
19 Prakash, G. K. S.; Hu, J.; Simon, J.; Bellew, D. R.; Olah, G. A. *J. Fluorine Chem.* **2004**, *125*, 595.
20 Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 1434.
21 Terao, J.; Begum, S. A.; Shinohara, Y.; Tomita, M.; Naitoh, Y.; Kambe, N. *Chem. Commun.* **2007**, 855.
22 Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545.
23 Ichikawa, J.; Yokota, M.; Kudo, T.; Umezaki, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4870.
24 Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, New York, **1976**.
25 Pettit, M. R.; Tatlow, J. C. *J. Chem. Soc.* **1954**, 1071.
26 Ishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K. *Synlett* **2005**, 2309.
27 Aber, D. F.; Sethuraman, M. R. *J. Org. Chem.* **2000**, *65*, 254.
28 Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645.
29 Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
30 Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693.
31 Baddeley, G.; Gordon, M. *J. Chem. Soc.* **1958**, 4379.
32 Bolton, R.; Burley, R. E. *J. Chem. Soc., Perkin Trans. 2* **1977**, 426.
33 Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 952.
34 Hori, M.; Kataoka, T.; Shimizu, H.; Ikemori, M.; Aoyama, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1209.
35 Patsidis, K.; Alt, H. G. *J. Organomet. Chem.* **1995**, *501*, 31.
36 Kamata, K.; Kasai, J.; Yamaguchi, K.; Mizuno, N. *Org. Lett.* **2004**, *6*, 3577.
37 Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219.

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