Journal of Fluorine Chemistry 156 (2013) 367–371

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short communication

# Organocatalysis approach to trifluoromethylation with fluoroform

Yuan Zhang, Motohiro Fujiu, Hiroki Serizawa, Koichi Mikami *

*Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152-8552, Japan*

ARTICLE INFO

*Article history:*
Received 22 May 2013
Received in revised form 16 July 2013
Accepted 26 July 2013
Available online 6 August 2013

*Keywords:*
Fluoroform
Organic base
Organocatalysis
Epoxide
Carbon dioxide

ABSTRACT

The organic base methodology exploits an access to generate the "trifluoromethyl anion" for carbonyl, ester, acid halide, epoxide, deuterium donor, and carbon dioxide substrates to afford the trifluoromethylation products with good overall efficiency even in organocatalysis conditions. The NMR analysis of the mixture of fluoroform and $P_4$-base shows no change thereof. However, on addition of electrophiles, the trifluoromethylation products were obtained efficiently.



## 1. Introduction

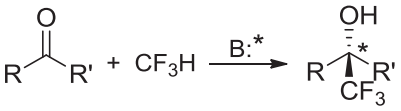
Current attention has greatly been focused on organofluorine compounds from the viewpoint of their fruitful applications in pharmaceutical [1] and material [2] sciences. Especially fluoromethyl compounds are employed as highly potent analogs with lipophilicity, membrane permeability, aqueous solubility, and metabolic stability for hydrocarbon analogs [3]. Therefore, the development of synthetic methods for fluoromethylation with trifluoromethyl ($CF_3$) substituent in particular into the hydrocarbon compounds is an increasingly important issue in modern organofluorine chemistry [4]. Generally, synthetic methods of the fluorine-containing compounds involve: (1) C–C bond forming reactions with fluoromethylating reagents [5], (2) C–C bond forming reactions employing fluorine-containing carbonyl compounds as building blocks [6], and (3) C–F bond forming reactions with fluorinating reagents [7]. The fluoromethylation, which can be exploited in later stage fluorofunctionalization, is further classified into nucleophilic, electrophilic, or radical reactions. However, nucleophilic trifluoromethyl-metal reagents such as the trifluoromethyl-lithium or -magnesium reagent [8] are generally recognized unstable and hard to prepare owing to the facile α-metal fluoride (M-F) elimination [9]. Therefore, trifluoromethylsilane (*Si*-$CF_3$) so called the Ruppert–Prakash reagents has been widely used as the *nucleophilic* trifluoromethyl *carbanion equivalent* via *Si*–C bond *activation* with fluoride [10]. Our direct approach, namely the *activation* of the parent trifluoromethane, fluoroform, HFC-23 (*H*-$CF_3$) as the simple and cheap trifluoromethyl *carbanion* source via deprotonation of a less acidic ($pK_a$ = 25–28 in water) and hence relatively inert carbon–hydrogen (C–H) bond with organic base catalysis to avoid the facile α-M-F elimination is the subject of this communication. Fluoroform is a by-product in manufacturing polymers such as Teflon and PVDF (polyvinylidene difluoride). Furthermore, fluoroform has great global-warming potential and long atmospheric lifetime. Therefore fluoroform is a must-consume compound by trifluoromethylation. This direct trifluoromethylation method with fluoroform is hopefully applicable to the asymmetric trifluoromethylation by a chiral organic base (Scheme 1). Trifluoromethylation with fluoroform to carbonyl compound has been originally reported by Shono using an electrogenerated base or strong inorganic bases such as *t*-BuOK in DMF [11]. Then, Normant [12] and Langlois [13] emphasized the importance of DMF to provide the DMF adduct of fluoroform as a reservoir. Recently, Grushin [14] and Prakash [15] reported the direct cupration in DMF and silylation in THF, ether, or toluene of fluoroform, respectively. Quite recently, Shibata has just reported the carbonyl addition reaction of fluoroform using $P_4$-*t*-Bu base [16].

## 2. Results and discussions

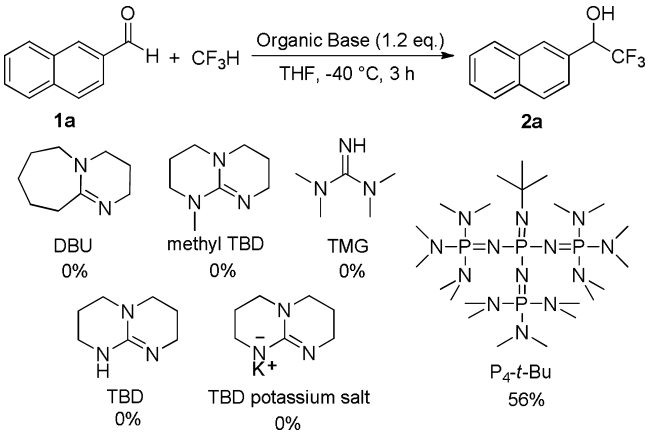
The trifluoromethylation of carbonyl compounds **1** with fluoroform was first scrutinized using an organic base such as DBU ($pK_{BH}$ = 24.34 in acetonitrile), acyclic guanidine TMG ($pK_{BH}$ = 23.3 in acetonitrile) and $P_4$-*t*-Bu base ($pK_{BH}$ = 42.7 in acetonitrile), and cyclic guanidine (methyl TBD ($pK_{BH}$ = 25.49 in

* Corresponding author. Tel.: +81 3 5734 2142; fax: +81 3 5734 2776.
*E-mail address:* mikami.k.ab@m.titech.ac.jp (K. Mikami).

0022-1139/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jfluchem.2013.07.018




**Scheme 1.** Organocatalysis of trifluoromethylation with fluoroform.

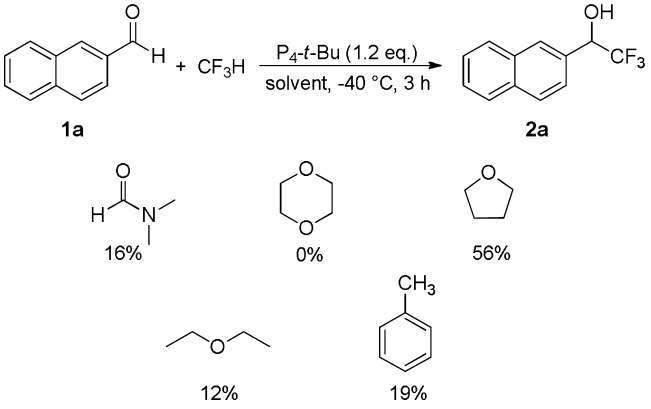



**Scheme 2.** Screening of organic bases.

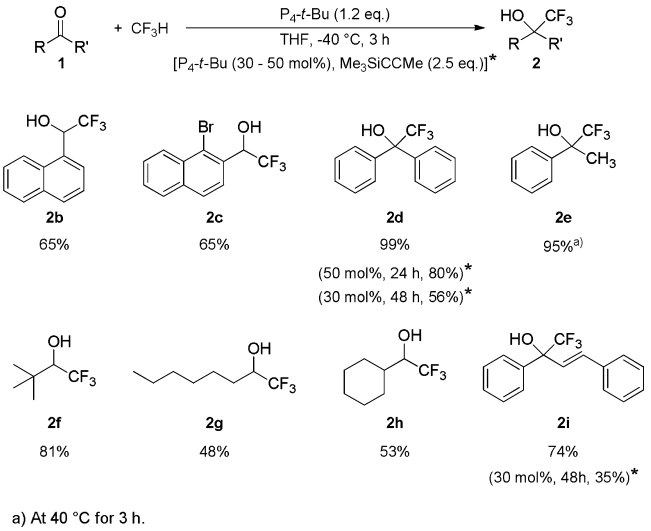
acetonitrile) and TBD ($pK_{BH}$ = 26.03 in acetonitrile) and the potassium salt (Scheme 2) [17]. However, the use of less basic acyclic TMG ($pK_{BH}$ = 23.3) and cyclic methyl TBD ($pK_{BH}$ = 25.49) and TBD ($pK_{BH}$ = 26.03) even as the potassium salt were found to be not effective for the deprotonation of a less acidic ($pK_a$ = 25–28) and hence inert C–H bond of fluoroform. By contrast, $P_4$-*t*-Bu base ($pK_{BH}$ = 42.7) led to the formation of trifluoromethylcarbinol (IR: 3376 $cm^{-1}$) product **2a** [10,16].

Several solvents such as DMSO, DMF, THF, ether, dioxane, and less polar toluene were examined at −40 °C for 3 h (Scheme 3). THF gave good yield of the trifluoromethylation product of carbonyl compound. DMF gave moderate yield of the trifluoromethylation products of carbonyl compounds, along with the formation of the DMF adduct of fluoroform. Less polar solvent such as toluene gave lower yield of the trifluoromethylation products **2**. Amongst the ethereal solvents thus examined, THF gave the best yield of the trifluoromethylation product **2a**.

Various carbonyl compounds were then scrutinized to give good yields of the trifluoromethyl adducts **2** even with quaternary carbon centers [22,23] (Scheme 4). Benzophenone gave virtually quantitative yields of trifluoromethylation product **2d** [13a]; Even in the presence of a catalytic amount of $P_4$-*t*-Bu base (50 and



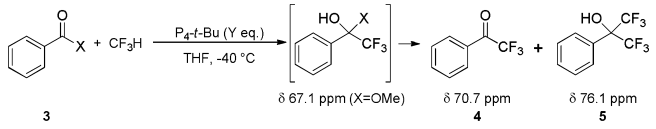

**Scheme 3.** Screening of solvent.




**Scheme 4.** Scope of carbonyl substrates.

30 mol%), the benzophenone adduct **2d** was obtained in 80% and 56% yields at −40 °C for 24 and 48 h, respectively with the aid of trimethylsilyl propyne (2.5 equiv.) [17c]. Even when enolizable acetophenone and aliphatic carbaldehydes with acidic α-protons ($pK_a$ = 19–20 in water) [18] were added to the solution of fluoroform and $P_4$-*t*-Bu base at −40 °C, a similar level of chemical yields (95%, 48%, and 53%) of the trifluoromethylation products (**2e** [13a], **2g** [24] and **2h** [12]) were obtained. A small amount of aldol products accompanied, via deprotonation of enolizable aldehydes with the trifluoromethyl anion as a base.

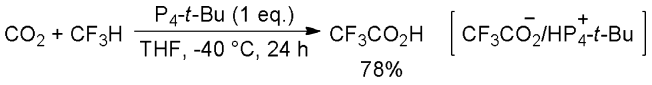
The effect of $P_4$-*t*-Bu base was significant in the success of the present trifluoromethylation (Scheme 5). Furthermore, the molarity of $P_4$-*t*-Bu base affects the ratio of the mono(trifluoromethyl) **4** [25]/the bis(trifluoromethyl) product **5** [26] in the reaction of carboxylic acid esters and halides **3**. Intriguingly, even with two equivalents of base, the acid halides provided the mono(trifluoromethyl) ketonic (IR: 1763 $cm^{-1}$) product **4** in 81% yield at −40 °C for 1 h with negligible amount of formation of the bis(trifluoromethyl)carbinol (IR: 3389 and 3598 $cm^{-1}$) product **5** in 7% yield. After stirring the reaction mixture overnight (24 h), the bis(trifluoromethyl) product **5** was obtained in 90% yield. That is also the case with an aromatic ester to give mono(trifluoromethyl) ketone **4** in 58% yield at −40 °C for 3 h, however, on quench with trimethylsilyl chloride. Otherwise, the intermediary hemiacetal adduct of fluoroform was observed [19]. The selective formation of the mono(trifluoromethyl) product **4** is in sharp contrast to the formation of tertiary alcohols in the reaction of perfluoroalkyllithium reagents with aromatic esters [20].




| | | | | |
|---|---|---|---|---|
| X = Cl | Y= 1.2 | 1.5 h | 72% | trace |
| | | 3 h | 72% | 14% |
| | Y= 2.4 | 1 h | 81% | 7% |
| | | 10 h | 13% | 60% |
| | | 24 h | 0% | 90% |
| X = OMe | Y= 1.2 | 24 h | 58%a) | 0% |

a) On quench with TMSCl.

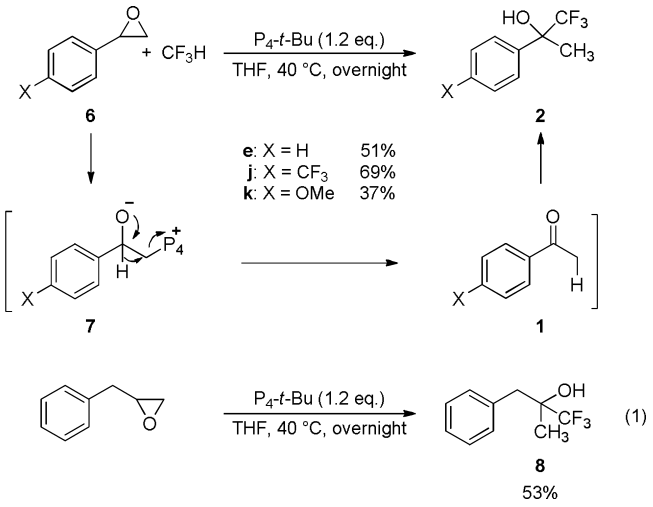
**Scheme 5.** Mono- and bis-trifluoromethylation products from acid halides and esters.




**Scheme 6.** Trifluoromethylation of carbon dioxide.

The reaction of fluoroform with carbon dioxide is noteworthy in view of the fixation, via carbon–carbon bond formation, of carbon dioxide, typical global-warming gas. The reaction of fluoroform with carbon dioxide efficiently proceeds under the standard reaction conditions even at low reaction temperature (Scheme 6). The trifluoromethylation product, namely trifluoroacetic acid [19] was obtained as an onium salt of $P_4$-*t*-Bu base [$CF_3CO_2^-/H^+P_4$-*t*-Bu] [21] in 78% yield based on the amount of $P_4$-*t*-Bu base employed.

The reaction with styrene oxides **6** with not only electron-withdrawing but also electron-donating substituents gave an internal rather than terminal trifluoromethylation products **2** surprisingly with a quaternary carbon center [19] at higher (40 °C) reaction temperature (Scheme 7). The reaction would involve the nucleophilic attack of $P_4$-*t*-Bu base at the terminal carbon of styrene oxides and then hydride shift via a twitter ionic intermediates **7** to give a methyl ketone intermediates **1**. Thus,




**Scheme 7.** Anomalous trifluoromethylation of epoxides.

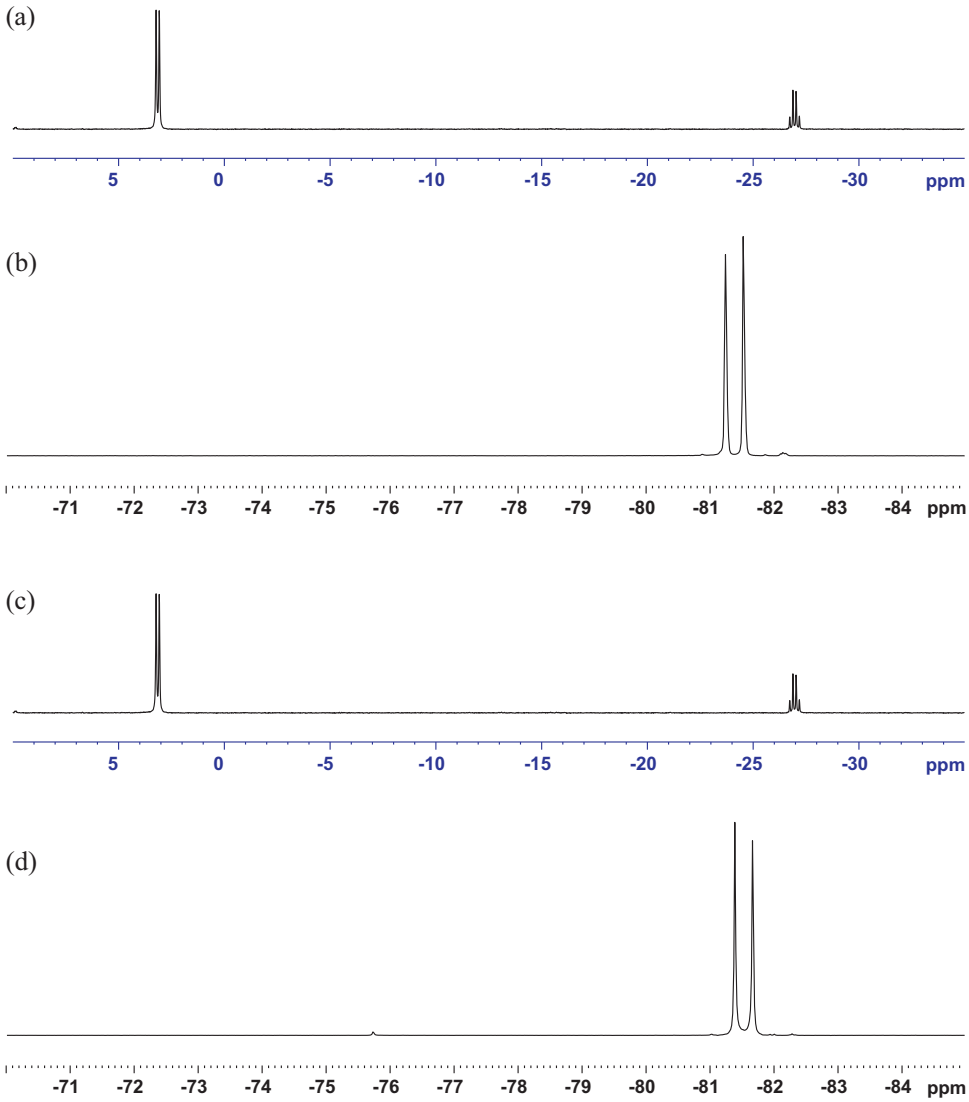
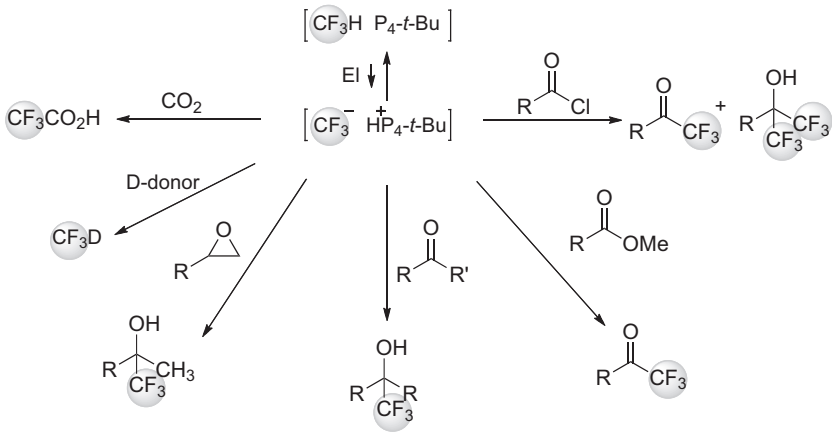



**Chart 1.** $^{31}P$ and $^{19}F$ NMR ($d_8$-THF): (a) $^{31}P$ NMR of $P_4$-*t*-Bu base; (b) $^{19}F$ NMR of fluoroform; (c) $^{31}P$ NMR of the mixture of $P_4$-*t*-Bu base and fluoroform; (d) $^{19}F$ NMR of the mixture of $P_4$-*t*-Bu base and fluoroform.




**Scheme 8.** Wide scope of organocatalytic trifluoromethylation with fluoroform.

styrene oxide **6e** gave the internal trifluoromethylation product **2e** [26] with a quaternary carbon ($^{13}$C NMR: 74.6 (q, $J$ = 30.0 Hz) ppm) center in 51% yield. Furthermore, styrene oxide **6j** with an electron-withdrawing *p*-trifluoromethyl substituent gave higher (69%) yield of the internal trifluoromethylation product **2j** [28]. *p*-Methoxy styrene oxide **6k** also gave the internal trifluoromethylation product **2k** [27]. In addition to styrene oxides **6**, 3-phenylpropyrene oxide gave 53% yield of the internal trifluoromethylation product with a quaternary carbon ($^{13}$C NMR: 73.7 (q, $J$ = 28.0 Hz) ppm) center [29] (Eq. (1)).

Deprotonation of fluoroform with $P_4$-*t*-Bu base may be solvent dependent as shown in $^{19}$F and $^{31}$P NMR analyses. The mixture of fluoroform and $P_4$-*t*-Bu base in $d_8$-THF or $d_6$-DMSO (p$K_a$ = 33 in water) with co-solvent $d_8$-THF surprisingly showed no change in chemical shifts of both fluoroform and $P_4$-*t*-Bu base themselves in $^{31}$P and $^{19}$F NMR analyses (Chart 1a and b vs. 1c and d). The absence of proton–deuterium exchange in $d_6$-DMSO and $d_8$-THF is also due to the lower acidity of these solvents. However, on addition of benzophenone, the α-trifluoromethylation product **2a** was obtained in 92% yield.

Therefore, the following reaction mechanism based on the equilibrium significantly shifted to the parent fluoroform and $P_4$-*t*-Bu base in THF is likely to involve (Scheme 8, Chart 1). A binary complex of $P_4$-*t*-Bu base and fluoroform, "$CF_3^-$/$H^+P_4$-*t*-Bu" was not sufficiently observed but the ternary complex of $P_4$-*t*-Bu base, fluoroform and an electrophile (El) could undergo trifluoromethylation. The present reaction mechanism is thus different from the previous *nucleophilic* trifluoromethylation with the Ruppert–Prakash reagent, trifluoromethyl *carbanion equivalent* via Si–C bond *activation* with fluoride [10] or the trifluoromethyl-metal reagents [8]. Organic base-derived onium salt would be operative to generate in situ the stable "trifluoromethyl anion equivalent" without metal–fluoride interaction.

## 3. Conclusion

This novel methodology provides an access to "trifluoromethyl anion" under the organic base reaction conditions and hence not only quaternary [21] but also tertiary carbon centers could be constructed. Fortunately, the trifluoromethylation is established for enolizable carbonyl compounds, ester, acid halide, epoxide, deuterium donor and carbon dioxide leading eventually to the trifluoromethylation products with good overall efficiency even in organocatalysis conditions. This trifluoromethylation with fluoroform is applicable to the asymmetric catalysis version, which will be reported in due course. This methodology is thus compliment to organometallic trifluoromethylation approach to a variety of electrophiles.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.07.018.

## References

Reviews:

[1] (a) I. Ojima, Fluorine in Medicinal Chemistry and Chemical Biology, Blackwell, Oxford, 2009;
(b) J.-P. Begue, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley, Hoboken, 2008;
(c) V.A. Soloshonok, K. Mikami, T. Yamazaki, J.T. Welch, J.F. Honek, ACS Symp. Ser. 949 (2006);
(d) V. Gouverneur, K. Mueller (Eds.), Fluorine in Pharmaceutical and Medicinal Chemistry, Imperial College Press, London, 2012.

Reviews:

[2] (a) P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, 2004;
(b) T. Hiyama, K. Kanie, T. Kusumoto, Y. Morizawa, M. Shimizu, Organofluorine Compounds: Chemistry and Applications, Springer, Berlin, 2000;
(c) K. Uneyama, Organofluorine Chemistry, Wiley-Blackwell, Oxford, 2006;
(d) R.D. Chambers, Fluorine in Organic Chemistry, Wiley-Blackwell, Oxford, 2004

Reviews:

[3] (a) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330;
(b) K.L. Kirk, Org. Process Res. Dev. 12 (2008) 305–321;
(c) K. Muller, C. Faeh, F. Diederich, Science 317 (2007) 1881–1886.

Reviews:

[4] (a) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, Chem. Rev. 111 (2011) 455–529;
(b) D. Cahard, J.-A. Ma, J. Fluorine Chem. 128 (2007) 975–996.

Reviews:

[5] (a) J. Badoux, D. Cahard, Org. React. 69 (2007) 1–326;
(b) S. Rozen, Chem. Rev. 96 (1996) 1717–1736.

Reviews:

[6] (a) K. Mikami, Y. Itoh, M. Yamanaka, Chem. Rev. 104 (2004) 1–16;
(b) D. O'Hagan, Chem. Soc. Rev. 37 (2008) 308–319.

For examples:

[7] (a) J.-A. Ma, D. Cahard, Chem. Rev. 104 (2004) 6119–6146;
(b) N. Shibata, A. Matsnev, D. Cahard, Beilstein J. Org. Chem. 6 (2010) No65 (and references cited therein).

Review:

[8] D.J. Burton, Z.Y. Yang, Tetrahedron 48 (1992) 189–275.
[9] M. Schlosser, M-F interaction plays an important role in defluorination of α-CF3 carbonyl compounds, in: Organometallics in Synthesis – A Manual, Wiley, Chichester, 1994, pp. 1–166.
[10] (a) G.K.S. Prakash, A.K. Yudin, Chem. Rev. 97 (1997) 757–786;
(b) G.K.S. Prakash, J. Hu, G.A. Olah, Org. Lett. 5 (2003) 3253–3256.
[11] T. Shono, M. Ishifune, T. Okada, S. Kashimura, J. Org. Chem. 56 (1991) 2–4.
[12] B. Folleas, I. Merek, J.-F. Normant, L. Saint-Jalmes, Tetrahedron 56 (2000) 275–283 (and references cited therein).
[13] (a) S. Large, N. Roques, B.R. Langlois, J. Org. Chem. 65 (2000) 8848–8856;
(b) T. Billard, S. Bruns, B.R. Langlois, Org. Lett. 2 (2000) 2101–2103 (and references cited therein).
[14] A. Zanardi, M.A. Novikov, E. Martin, J. Benet-Buchholz, V.V. Grushin, J. Am. Chem. Soc. 133 (2011) 20901–20913.
[15] G.K.S. Prakash, P.V. Jog, P.T.D. Batamack, G.A. Olah, Sci. 338 (2012) 1324–1327.
[16] H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata, Org. Biomol. Chem. 11 (2013) 1446–1450.
[17] (a) T. Ishikawa, Superbases for Organic Synthesis, Wiley, Chichester, 2009;
(b) Y. Kondo, M. Ueno, Y. Tanaka, Chem. Commun. 29 (2006) 3128–3130;
(c) Y. Hirono, K. Kobayashi, M. Yonemoto, Y. Kondo, Chem. Commun. 46 (2010) 7623–7624 (for leading references).
[18] (a) K. Mikami, T. Murase, L. Zhai, S. Kawauchi, Y. Itoh, S. Ito, Tetrahedron Lett. 51 (2010) 1371–1374;
(b) K. Mikami, T. Murase, L. Zhai, Y. Itoh, S. Ito, Tetrahedron: Asymmetry 21 (2010) 1158–1161 (and references cited therein).
[19] R.N. McDonald, A.K. Chowdhury, J. Am. Chem. Soc. 105 (1983) 7267–7271.
[20] P.G. Gassman, N.J. O'Reilly, J. Org. Chem. 52 (1987) 2481–2490.
[21] J. Tang, J. Dopke, J.G. Verkade, J. Am. Chem. Soc. 115 (1993) 5015–5020.

Leading review on the construction of quaternary carbon centers:

[22] (a) M. Shimuzu, Angew. Chem. Int. Ed. 50 (2011) 5998–6000;
(b) For a recent example K. Kikushima, J.C. Holder, M. Gatti, B.M. Stoltz, J. Am. Chem. Soc. 133 (2011) 6902–6905.
[23] M. Fujiu, Y. Nakamura, H. Serizawa, K. Aikawa, S. Ito, K. Mikami, Eur. J. Org. Chem. (2012) 7043–7047.
[24] H. Hamada, M. Shiromoto, M. Funahashi, T. Itoh, K. Nakamura, J. Org. Chem. 61 (1996) 2332–2336.
[25] M. Shi, X.G. Liu, Y.W. Guo, W. Zhang, Tetrahedron 63 (2007) 12731–12734.
[26] X.D. Jiang, S. Matsukawa, K. Kakuda, Y. Fukuzaki, W.L. Zhao, L.S. Li, H.B. Shen, S. Kojima, Y. Yamamoto, Dalton Trans. 39 (2010) 9823–9829.
[27] T.L. Amyes, I.W. Stevens, J.P. Richard, J. Org. Chem. 58 (1993) 6057–6066.
[28] K.T. Liu, M.Y. Kuo, C.F. Shu, J. Am. Chem. Soc. 104 (1982) 211–215.
[29] I. Fleming, R.S. Roberts, S.C. Smith, J. Chem. Soc., Perkin Trans. 1 (1998) 1215–1228.