Journal of Fluorine Chemistry 143 (2012) 226–230

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

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

Replacement of BF_4^- by PF_6^- makes Selectfluor greener

Zhuang Jin [a], Bo Xu [a], Stephen G. DiMagno [b,*], Gerald B. Hammond [a,**]

[a] Department of Chemistry, University of Louisville, Louisville, KY, USA
[b] Department of Chemistry and Center for Materials Research and Analysis, University of Nebraska–Lincoln, Lincoln, NE, USA

ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form 8 May 2012
Accepted 10 May 2012
Available online 18 May 2012

Keywords:
Imides
Amide oxidation
Selectfluor

ABSTRACT

A combination of F-TEDA-PF_6 and CuBr (0.1 equiv.) provides a potent oxidant that readily oxidizes amides to provide imides at room temperature. Replacement of BF_4^-, the anion of Selectfluor (F-TEDA-BF_4), by PF_6^-, dramatically reduces CuBr loading in this oxidative reaction. A possible rationale for this dramatic counterion effect is provided.

1. Introduction

Imides are core structures in many therapeutic agents and agrochemicals [1]. Imides are readily prepared by condensation reactions of carboxylic acid derivatives and ammonia or primary amines [2], however a number of other protocols have been employed for imide synthesis [3], including cross coupling [3d, e], oxidation of oxazoles [3b], N-formylation [3c], and the metal catalyzed nucleophilic ring opening of aziridines with malonates [3a]. We are interested in a direct synthetic pathway to prepare unsymmetrical imides by direct oxidation of the α-methylene group of amides. Several methods to accomplish this transformation have been reported [4], however, efficient methodologies for α-methylene oxidation are relatively rare [4e, i], and most of the proposed oxidative methods suffer from low yields and/or limited substrate scope [4a–d, f–h, j]. For example, although RuO_4 is widely recognized as a capable oxidant for amide oxidation [4a, f, j]; it is such an active reagent that amide oxidation is accompanied by the oxidation of even unactivated tertiary C–H bonds [5]. Of the two most efficient amide oxidative methods, the first employs a heavy metal (chromium VI) reagent [4i]. Later, Nicolau and coworkers demonstrated that such toxic heavy metal oxidants could be supplanted by the more environmentally benign Dess–Martin periodinane (DMP), although effective oxidation did require heating of the hypervalent iodine reagent to elevated temperatures (80–85 °C) [4e].

Previously, we reported that the combination of stoichiometric amounts of CuBr and excess Selectfluor (F-TEDA-BF_4) can oxidize amides to imides at room temperature [6]. Although this method is efficient, the use of a stoichiometric amount of copper makes the methodology unattractive for process chemistry. Thus, we investigated conditions that would permit use of a catalytic amount of cuprous salt. Here we are pleased to disclose an interesting finding: a simple counterion exchange on Selectfluor (F-TEDA-PF_6 instead of F-TEDA-BF_4) permits the amount of copper catalyst to be reduced significantly (to 10 mol%). The oxidizing power of F-TEDA-PF_6, a reagent that can be easily prepared from Selectfluor, is at least as potent as Selectfluor itself; amides are oxidized to imides as rapidly and efficiently as we reported previously, despite the significant reduction in CuBr loading (Scheme 1).

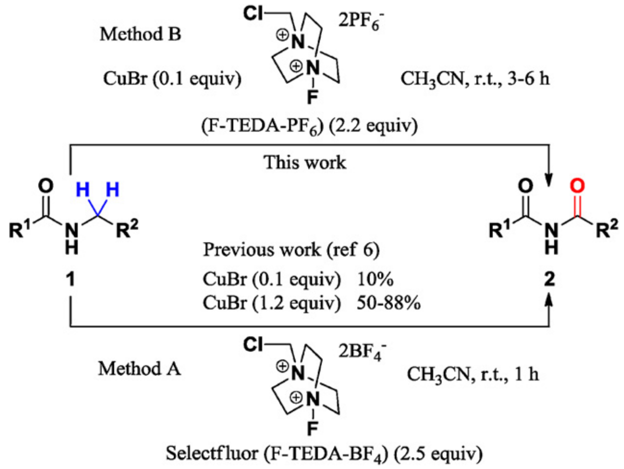
2. Result and discussions

The results of amide oxidation experiments are summarized in Table 1, where a direct comparison is made between the stoichiometric (Condition **A**, 120 mol% (or 1.2 equiv.) CuBr) and catalytic (Condition **B**, 10 mol% CuBr) processes. First, amide **1a**, CuBr (10 mol%) and F-TEDA-PF_6 (2.2 equiv.) were allowed to react in acetonitrile for 5 h. This procedure provided a yield of imide (**2a**) that was nearly identical to our previous results obtained for the stoichiometric reaction, albeit after a slightly longer reaction time. Similarly, amides **1b** (entry 2) and **1c** (entry 3) were also efficiently oxidized into the corresponding imides in good yield under catalytic conditions. For entry 4 (amide **1d**), the new protocol gave an enhanced yield of imide. Table 1 entries 5–8 further demonstrate the comparability of the catalytic and stoichiometric protocols. Ester functionality can be tolerated in the new oxidative system and in the former system (entries 9 and 10), indicating that

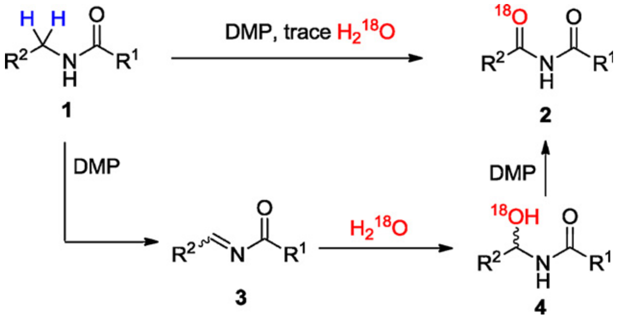
---

* Corresponding author.
** Corresponding author.
E-mail address: gb.hammond@louisville.edu (G.B. Hammond).

0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2012.05.010



Scheme 1. Cu-catalyzed amide oxidation with F-TEDA-PF_6 and F-TEDA-BF_4.



Scheme 2. Nicolaou's proposal of amide oxidation by DMP.

α-methylene radical stability or metal ion coordination might be the factor that controls the initial steps of the oxidation reaction. Unfortunately, both methodologies failed to oxidize a lactam into a cyclic imide (entry 11), suggesting that only acyclic amides are suitable substrates for these two oxidative systems.

Nicolaou has proposed a mechanism [4e], for amide oxidation by DMP, in which an amide was dehydrogenated to form an imine intermediate **3** (Scheme 2). Compound **3** reacts with water to generate a hemiaminal **4**, which can be further oxidized by DMP to give the final product, **2**. Initially, we thought that our oxidation proceeded through a similar reaction mechanism, since the ultimate source of the newly formed oxygen comes from trace water in the reaction mixture [6]. In order to test the above hypothesis, we added an aromatic compound with moderate electron density, N-arylacetamide, to the reaction mixture in an attempt to capture the conjugated imine intermediate **3**; two attempts are outlined in Scheme 3.

Amide **1h**, N-arylacetamide, CuBr, and F-TEDA-PF_6 were mixed under catalytic conditions (Condition **B** in Table 1, Eq. 1 in Scheme 3). Surprisingly, amide **1h** was not oxidized into **2h**; instead, N-arylacetamide was fluorinated by electrophilic aromatic substitution. No evidence for the trapped imine product was observed. In a second attempt to trap the putative imine intermediate, the oxidation of **1h** was performed under normal catalytic conditions, at which

Table 1
Comparison of the effectiveness of F-TEDA-PF_6 and F-TEDA-BF_4 in amide oxidation.

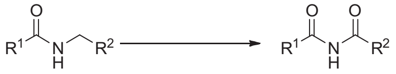
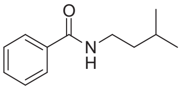
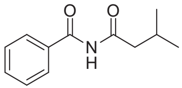
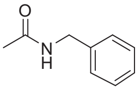
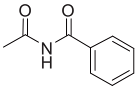
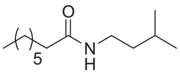
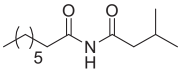
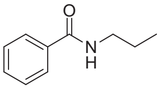
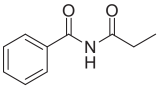
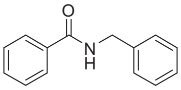
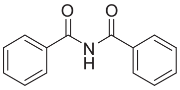
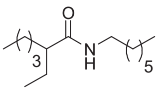
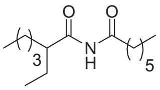
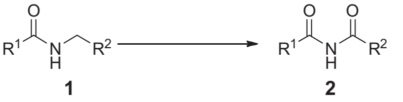
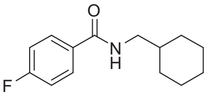
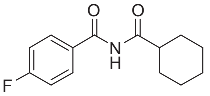
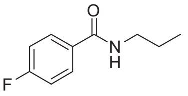
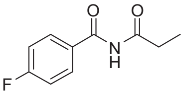
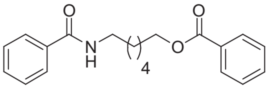
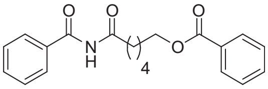
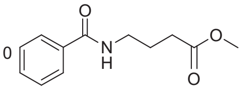
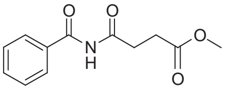
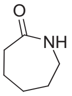
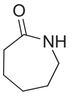
Entry	 **1** **2**		% Yield[a] (SM)[b]	
	Amides	Imides	**A**[c]	**B**[d]
1	 **1a**	 **2a**	88 (7)	90 (2)
2	 **1b**	 **2b**	83	79
3	 **1c**	 **2c**	79 (13)	83 (5)
4	 **1d**	 **2d**	77 (10)	90 (3)
5	 **1e**	 **2e**	84 (11)	85 (6)
6	 **1f**	 **2f**	66 (30)	71 (12)

Table 1 (*Continued*)

Entry	 1 → 2		% Yield[a] (SM)[b]	
	Amides	Imides	**A**[c]	**B**[d]
7	 **1g**	 **2g**	50 (10)	65 (15)
8	 **1h**	 **2h**	80 (5)	91
9	 **1i**	 **2i**	84 (6)	70 (10)
10	 **1j**	 **2j**	82 (6)	78 (8)
11	 **1k**	 **2k**	0 (96)	0 (95)

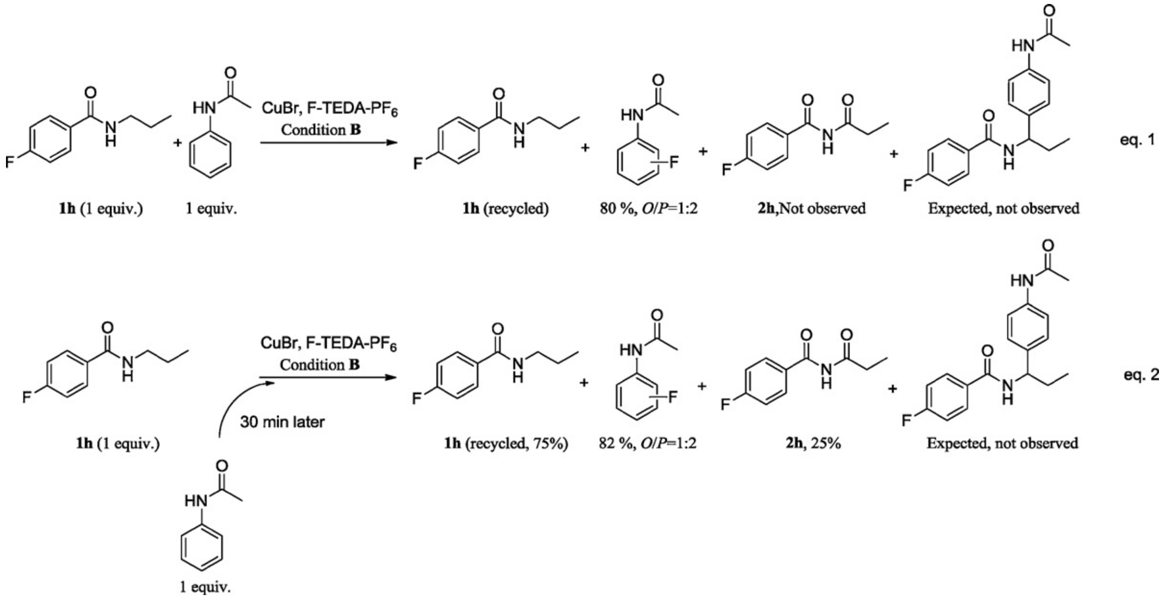
[a] Yield was based on starting amide.

[b] Starting material recovery.

[c] Condition **A**: Amide **1** (0.25 mmol), Selectfluor (F-TEDA-BF_4) (0.625 mmol, 2.5 equiv.) and CuBr (0.3 mmol, 1.2 equiv., added in six portions over 40 min) reacted in acetonitrile (5 mL) at room temperature for 1 h.

[d] Condition **B**: Amide **1** (0.25 mmol), F-TEDA-PF_6 (0.55 mmol, 2.2 equiv.) and CuBr (0.025 mmol, 0.1 equiv.) reacted in acetonitrile (5 mL) at room temperature for 3–6 h.

time we added N-arylacetamide to the reaction mixture (Eq. 2). Under this revised protocol the imide (25%) and fluorinated N-arylacetamide was observed, but again, there was no evidence for the captured imine intermediate. Further investigations of the reaction of N-arylacetamide with of F-TEDA-PF_6 were conducted, since no reaction had been observed previously between N-arylacetamides and Selectfluor (F-TEDA-BF_4) in acetonitrile at room temperature. Control experiments revealed that N-arylacetamide could be

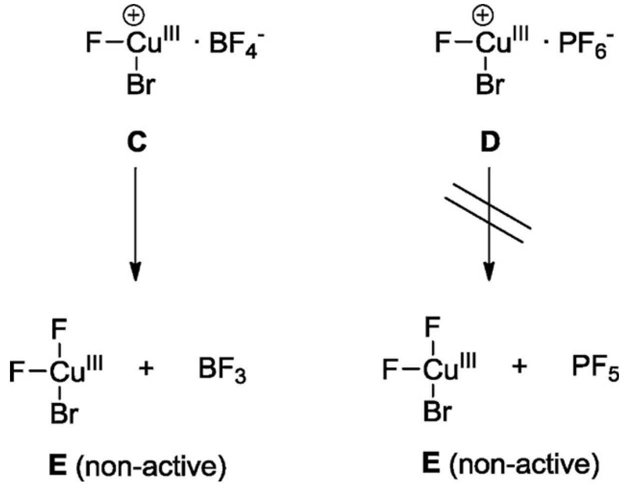


Scheme 3. Attempts to capture possible imine intermediate 3.

fluorinated by F-TEDA-PF_6 under exceptionally mild conditions, indicating that F-TEDA-PF_6 is a significantly more active electrophilic fluorinating agent than Selectfluor (F-TEDA-BF_4). The above two observations indicate that if the oxidation pathway involves an imine or iminium intermediate, it cannot be trapped using such an electron rich arene in the presence of F-TEDA-PF_6. Lactam **1k** could not be oxidized using both systems (Table 1, entry 11), perhaps because its imine intermediate is more difficult to form due to enforced eclipsing interactions in the 7-membered ring imine.

It is puzzling that the mere change of a counterion from Selectfluor (F-TEDA-BF_4) to F-TEDA-PF_6 drastically reduces the amount of CuBr needed to drive the amide oxidation to completion. In previous studies of fluorination [7] and oxidation [8] reactions, the difference between PF_6^- and BF_4^- is reported to be insignificant. Nevertheless, this effect is real and significant in the copper-catalyzed oxidation. It is not yet clear to us what the nature of the catalytically active copper salt is in this oxidation. The ^1H NMR spectrum of the reaction mixture shows significant line broadening as soon as Selectfluor (or F-TEDA-PF_6) is added; this phenomenon suggests the presence of paramagnetic Cu(II) ions. However, we have demonstrated that Cu(II) salts were not effective mediators of this process in our previous work [6]. It might also be possible that a high valent Cu(III) ion generated under the strongly oxidizing conditions used here is the principle oxidant that initiates the reaction with amides. How, then, can one explain the need for a stoichiometric amount of copper salts when Selectfluor is employed, but the need for only a catalytic amount of CuBr when of F-TEDA-PF_6 is used? Cu(III) salts are typically not very stable with simple halogen ligands; in the few cases where Cu(III) salts have been isolated, a relatively small subset of ligands have been reported to support the high oxidation state for copper [9]. These considerations suggest that the initially formed Cu(III) ion might undergo a relatively slow quenching reaction with Selectfluor that is not available with F-TEDA-PF_6. Since Cu(III) is expected to be a relatively hard and fluorophilic Lewis acid, it is reasonable to suspect that it is capable of extracting a fluoride ion from the BF_4 anion, whereas it might not be sufficiently Lewis acidic to abstract a fluoride ion from the PF_6 anion. PF_5 is a much more potent Lewis acid than BF_3 on the F-scale; computational studies reported by Christe and co-workers [10] show that PF_5 has stronger affinity (94.9 kcal/mol) towards fluoride ion than BF_3 (83.1 kcal/mol). Such an explanation could account for the need for a slow addition of CuBr when Selectfluor is used as the oxidant.

The decomposition of the catalytically active, Lewis acidic Cu(III) species, outlined in Scheme 4, is a possible rationale that explains the need for different CuBr loading when using the two different counterions. Although both complexes **C** and **D** in Scheme 4 may be catalytically competent to initiate amide oxidation, fluoride extraction by **C** to form complex **E** may result in a less active complex. Therefore, large amounts of CuBr are needed for oxidation in the case of F-TEDA-BF_4, since the putatively active species is being consumed during the course of the reaction. However, for the high valence copper in **D** it is difficult to extract the fluoride ion from PF_6^- to form complex **E** due to the stronger P–F bond in the PF_6^-, therefore, **D** remains active in the reaction system.



Scheme 4. Proposed rationale for different effects of BF_4^- and PF_6^- counterions.

In conclusion, we have developed a mild and efficient methodology for copper-mediated oxidation of amides to imides by Selectfluor. Simply changing the counterion on Selectfluor (F-TEDA-PF_6 instead of F-TEDA-BF_4) can significantly reduce the amount of copper (10 mol%) that is needed. The oxidative ability of copper bromide (10 mol%) and F-TEDA-PF_6 is as efficient as that of stoichiometric amount of CuBr and Selectfluor, but more environmentally friendly. Both methodologies could be used to synthesize unsymmetrical imides from amides, however, the mechanistic considerations that explain the marked differences in reactivity of the two salts have not been fully elucidated; thorough mechanistic studies are needed to clarify the profound counterion effect.

3. Experimental

3.1. General

All chemicals were commercially obtained from Alfa or Adrich, and were used without further purification. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded on a Varian MR400 NMR spectrometer. Chemical shifts (δ) were reported as part per million (ppm). δ 7.26, δ 77.00 of $CHCl_3$, 0.00 of $CFCl_3$ were used as internal standards for ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra, respectively. High-resolution mass spectra (HRMS) were performed at mass spectrometry facility of Center for Regulatory and Environmental Analytical Metabolomics, University of Louisville. Melting points of imides are measured by a DigiMelt MPA160 melting point apparatus. FTIR spectra were recorded in ATR (attenuated total reflection) solid mode using a Perkin Elmer Spectrum 100.

General procedure for copper-mediated oxidation of amide **1** into imide **2** by Selectfluor (F-TEDA-BF_4) (Condition **A**):

Amide **1** (0.25 mmol, 1 equiv.) and Selectfluor (0.625 mmol, 2.5 equiv.) were dissolved in acetonitrile (5 mL) at room temperature, and CuBr (0.3 mmol, 1.2 equiv.) was added over a 40 min period in 6 portions. After all the CuBr was added, the resulting mixture was stirred for extra 20 min, and then acetonitrile was evaporated under reduced pressure. Saturated ammonium chloride solution (20 mL) was added into reaction mixture and extracted with diethyl ether (25 mL × 4); the ether layers were combined and dried over Na_2SO_4, filtered, evaporated under reduced pressure to give the crude product. Silica gel flash chromatography of the crude product [hexanes–ethyl acetate (10:1) to hexanes–ethyl acetate (4:1)] yielded pure imide **2**.

General procedure for copper-catalyzed oxidation of amide **1** into imide **2** by F-TEDA-PF_6 (Condition **B**):

Amide **1** (0.25 mmol, 1 equiv.), F-TEDA-PF_6 (0.625 mmol, 2.5 equiv.) and CuBr (0.025 mmol, 0.1 equiv.) were dissolved in acetonitrile (5 mL) and stirred at room temperature for 3–6 h, monitored by TLC until the reaction showed no further progress. The work-up was the same as in Condition **A**.

N-(3-Methyl-butyryl)-benzamide, (**2a**) [3b]

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.92 (bs, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 6.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 2.82 (d, J = 6.8 Hz, 2H), 2.18 (m, 1H), 0.96 (d, J = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 175.9, 165.6, 133.1, 132.9, 128.9, 127.7, 46.2, 24.8, 22.52.

Acknowledgments

We are grateful to the National Science Foundation for financial support (CHE-1111316), and acknowledge the support provided by the CREAM Mass Spectrometry Facility (University of Louisville) funded by NSF/EPSCoR (EPS-0447479).

References

[1] (a) K. Krohn, C. Franke, P.G. Jones, H.J. Aust, S. Draeger, B. Schulz, Liebigs Annalen der Chemie (1992) 789–798;
(b) H.B. Maruyama, Y. Suhara, J. Suzuki-Watanabe, Y. Maeshima, N. Shimizu, M. Ogura-Hamada, H. Fujimoto, K. Takano, Journal of Antibiotics 28 (1975) 636–647;
(c) L. Ross, L.A. Guarino, Virology 232 (1997) 105–113;
(d) Y. Suhara, H.B. Maruyama, Y. Kotoh, Y. Miyasaka, K. Yokose, H. Shirai, K. Takano, P. Quitt, P. Lanz, Journal of Antibiotics 28 (1975) 648–655;
(e) J. Thirkettle, E. Alvarez, H. Boyd, M. Brown, E. Diez, J. Hueso, S. Elson, M. Fulston, C. Gershater, M.L. Morata, P. Perez, S. Ready, J.M. Sanchez-Puelles, R. Sheridan, A. Stefanska, S. Warr, Journal of Antibiotics 53 (2000) 664–669.

[2] (a) E.L. Eliel, R.T. McBride, S. Kaufmann, Journal of the American Chemical Society 75 (1953) 4291–4296;
(b) G.E. Ficken, R.P. Linstead, Journal of the Chemical Society (1952) 4846–4854.

[3] (a) H. Alper, C. Mahatantila, F. Einstein, A. Willis, Journal of the American Chemical Society 106 (1984) 2708–2710;
(b) D.A. Evans, P. Nagorny, R. Xu, Organic Letters 8 (2006) 5669–5671;
(c) A.P. Gledhill, C.J. McCall, M.D. Threadgill, Journal of Organic Chemistry 51 (1986) 3196–3201;
(d) A. Schnyder, A.F. Indolese, Journal of Organic Chemistry 67 (2002) 594–597;
(e) F. Wang, H. Liu, H. Fu, Y. Jiang, Y. Zhao, Advanced Synthesis and Catalysis 351 (2009) 246–252.

[4] (a) C. Altomare, A. Carotti, G. Casini, S. Cellamare, M. Ferappi, E. Gavuzzo, F. Mazza, G. Pantaleoni, R. Giorgi, Journal of Medicinal Chemistry 31 (1988) 2153–2158;
(b) A. Gorka, L. Hazai, C. Szantay Jr., V. Hada, L. Szabo, C. Szantay, Heterocycles 65 (2005) 1359–1371;
(c) F. Minisci, C. Punta, F. Recupero, F. Fontana, G.F. Pedulli, Journal of Organic Chemistry 67 (2002) 2671–2676;
(d) H. Nakayama, A. Itoh, SYNLETT (2008) 675–678;
(e) K.C. Nicolaou, C.J.N. Mathison, Angewandte Chemie International Edition 44 (2005) 5992–5997;
(f) J.P.N. Papillon, R.J.K. Taylor, Organic Letters 2 (2000) 1987–1990;
(g) T. Sueda, D. Kajishima, S. Goto, Journal of Organic Chemistry 68 (2003) 3307–3310;
(h) J.-R. Wang, L. Liu, Y.-F. Wang, Y. Zhang, W. Deng, Q.-X. Guo, Tetrahedron Letters 46 (2005) 4647–4651;
(i) L. Xu, S. Zhang, M.L. Trudell, Chemical Communications (2004) 1668–1669;
(j) S. Yoshifuji, Y. Arakawa, Chemical and Pharmaceutical Bulletin 37 (1989) 3380–3381.

[5] E. McNeill, J.D. Bois, Journal of the American Chemical Society 132 (2010) 10202–10204.

[6] Z. Jin, B. Xu, G.B. Hammond, Tetrahedron Letters 52 (2011) 1956–1959.

[7] T. Furuya, A.E. Strom, T. Ritter, Journal of the American Chemical Society 131 (2009) 1662–1663.

[8] Q. Michaudel, D. Thevenet, P.S. Baran, Journal of the American Chemical Society 134 (2012) 2547–2550.

[9] (a) L.M. Huffman, S.S. Stahl, Journal of the American Chemical Society 130 (2008) 9196–9197;
(b) A.E. King, L.M. Huffman, A. Casitas, M. Costas, X. Ribas, S.S. Stahl, Journal of the American Chemical Society 132 (2010) 12068–12073.

[10] K.O. Christe, D.A. Dixon, D. McLemore, W.W. Wilson, J.A. Sheehy, J.A. Boatz, Journal of Fluorine Chemistry 101 (2000) 151–153.