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Synthesis of *gem*-Difluoromethylenated Bicyclo[*m.n.*0]alkan-1-ols and Their Ring-Expansion to *gem*-Difluoromethylenated Macrocyclic Lactones

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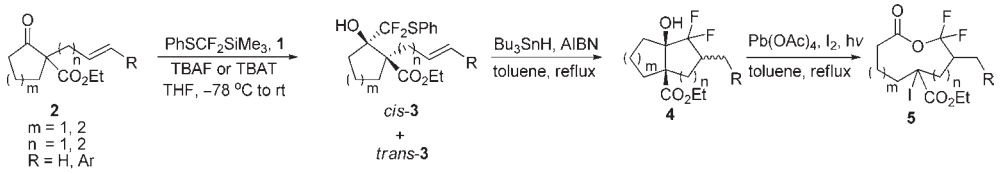
ABSTRACT



Fluoride-catalyzed stereoselective nucleophilic addition of $PhSCF_2SiMe_3$ (1) to α-carboethoxycycloalkanones 2 followed by intramolecular radical cyclization of the resulting *cis*-3 adduct afforded the corresponding *gem*-difluoromethylenated bicyclic compounds 4, which underwent ring-expansion followed by the Baeyer–Villiger-type oxidation of the resulting macrocyclic ketone intermediates to give *gem*-difluoromethylenated macrocyclic lactones 5.

Remarkable efforts have been devoted to the development of general and efficient synthetic strategies to organofluorine compounds,[1] including analogues of natural products.[2] Compounds containing a monofluoroalkyl- or difluoromethylene moiety often enhance the chemical, physical, and biological activities in a large number of biologically active pharmaceuticals and agrochemicals.[3] Recently, $PhSCF_2SiMe_3$ (**1**) has been demonstrated as a difluoromethylating[4] and *gem*-difluoromethylenating agent.[5]

As a part of our continuing efforts in developing an efficient *gem*-difluoromethylenation[6] employing **1** as a difluoromethylene radical anion equivalent ($^{\bullet}CF_2^-$),[7,8] we report herein a general synthetic route leading to *gem*-difluoromethylenated bicyclic compounds **4**, which undergo ring-expansion followed by the Baeyer–Villiger oxidation to *gem*-difluoromethylenated macrocyclic lactones **5** upon treatment with $Pb(OAc)_4/I_2$ in toluene under

(1) See for examples: (a) Soloshonok, V. *Fluorine-Containing Synthons*; Oxford University Press: New York, 2005. (b) Welch, J. T., Ed. *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington, DC, 1991. (c) Shen, X.; Zhang, L.; Zhao, Y.; Zhu, L.; Li, G.; Hu, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2588. (d) Lundgren, R. L.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2. (e) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (f) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 7247. (g) Han, S. Y.; Jeong, I. H. *Org. Lett.* **2010**, *12*, 5518. (h) Qing, F.-L.; Chu, L. *Org. Lett.* **2010**, *12*, 5060. (i) Lui, J.; Hu, J. *Chem.—Eur. J.* **2010**, *16*, 11443. (j) Ni, C.; Hu, J. *Synlett* **2011**, 770 and references cited therein. (k) Van Hende, E.; Verniest, G.; Deroose, F.; Thunring, J.-W.; Macdonald, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 2250. (l) Zhang, W.; Huang, W.; Hu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9858. (m) Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zagatti, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252.

(2) See for examples: (a) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261and references cited therein. (b) Qing, F.-L.; Zheng, F. *Synlett* **2011**, 1052. (c) Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinay, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 6680. (d) Fourrière, G.; Lalot, J.; Van Hijfte, N.; Quirion, J.-C.; Leclerc, E. *Tetrahedron Lett.* **2009**, *50*, 7048. (e) Audouard, C.; Fawcett, J.; Griffith, G. A.; Kérourédan, E.; Miah, A.; Percy, J. M.; Yang, H. *Org. Lett.* **2004**, *6*, 4269. (f) Chang, C. -S.; Negishi, M.; Nakano, T.; Morizawa, Y.; Matsumura, Y.; Ichikawa, A. *Prostaglandins* **1997**, *53*, 83. (g) Fourrière, G.; Van Hijfte, N.; Lalot, J.; Dutech, G.; Fragnet, B.; Coadou, G.; Quirion, J.-C.; Leclerc, E. *Tetrahedron* **2010**, *66*, 3963. (h) Itoh, T.; Kudo, K.; Yokota, K.; Tanaka, N.; Hayase, S.; Renou, M. *Eur. J. Org. Chem.* **2004**, 406. (i) Hayase, S.; Renou, M.; Itoh, T. *Eur. J. Org. Chem.* **2005**, 2777.

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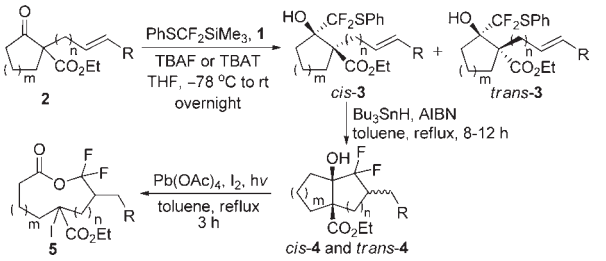
Scheme 1. Synthesis of Compounds **4** and Their Ring Expansions



photolysis (Scheme 1). It should be noted that the observed tandem oxidative fragmentation followed by the Baeyer–Villiger type oxidation has not been previously reported in the literature.

Our investigation began with fluoride-catalyzed stereoselective nucleophilic addition of **1** to α-carboethoxycyclopentanone **2a**[9] using 10 mol % of anhydrous tetrabutylammonium fluoride (TBAF) in dry THF at −78 °C to room temperature overnight (15 h) to afford an adduct **3a**, after acidic workup, as a mixture of *trans*- and *cis*-isomers. After separation by means of preparative thin-layer chromatography (PLC), *cis*- and *trans*-**3a** were obtained in 62% and 15% yields, respectively (Scheme 1, Table 1, entry 1). Similar stereoselectivity and yield of **3a** (*cis*: 63%, *trans*: 15%) were obtained when tetrabutylammoniumtriphenyl difluorosilicate (TBAT) was employed in place of TBAF. Under standard reaction conditions employing either TBAF or TBAT as a catalyst, compound **1** reacted with α-carboethoxycyclopentanones **2b**–**e** providing the corresponding adducts **3b**–**e** in moderate to good yields with moderate stereoselectivities (entries 2–5). Interestingly, highly stereoselective nucleophilic addition of **1** toward α-carboethoxycyclohexanones was observed when **1** was reacted with α-carboethoxycyclohexanone **2f** by using TBAT as a catalyst, giving *cis*- and *trans*-**3f** in 76% and 3% yields, respectively (entry 6). The stereochemistry of the *cis*-**3f** was confirmed by X-ray crystallography (see the Supporting Information). Similarly, the reaction of **1** with α-carboethoxycyclohexanones **2g**–**i** using either TBAF or TBAT as a catalyst proceeded with high stereoselectivity and exclusively provided the *cis*-isomers of the adducts **3g**–**i** in moderate to good yields (entries 7–9).

On the basis of our previous work,[7] a two-step strategy, involving fluoride-catalyzed (phenylsulfanyl)difluoromethylation and reductive cleavage of the phenylsulfanyl group followed by radical-mediated intramolecular cyclization, took the route to the *gem*-difluoromethylenated bicyclic compounds **4**. Overall, reductive cyclization of the *cis*-adducts **3** smoothly took place affording *cis*- and *trans*-**4**,[10] separable by chromatography, in good yields but only modest selectivities. Thus, the reaction of *cis*-**3b** with Bu_3SnH and a catalytic amount of AIBN in refluxing toluene for 8 h afforded, after column chromatography, *cis*- and *trans*-**4b** in 63% and 28% yields, respectively (Scheme 1, Table 1, entry 2). As expected, reductive cleavage of the phenylsulfanyl group of *trans*-**3b** led completely to the corresponding *gem*-difluoromethyl derivative, and no cyclized product was observed. Under similar radical cyclization conditions, *cis*-**3a** and *cis*-**3c**–**i** yielded bicyclic compounds **4a** and **4c**–**i**, respectively (Table 1, entries 1 and 3–9). The *trans*- and *cis*-isomers of **4a**–**d**, **4f**, **g**, and **4i**, of which yields are shown in Table 1 (entries 1–4, 6, 7, and 9), could be chromatographically separated. We proposed that the major isomers of compounds **4a**–**c** and **4f**,**g** are the *cis*-isomers, whereas the *trans*-isomers are the major isomers of **4d**,**e** and **4h**,**i**. These stereochemical outcomes can be rationalized by considering the intramolecular radical cyclization that should proceed via 5-*exo* or 6-*exo* cyclization mode through the more favorable transition state **6A** or **6B**, resulting in the formation of the *cis*-isomers of bicyclic compounds **4a**–**c** and **4f**,**g**, and the *trans*-isomers of **4d**,**e** and **4h**,**i**, respectively (Scheme 2).

Having established a general strategy to *gem*-difluoromethylenated bicyclic compounds **4a**–**i**, we turned our attention to the synthetic utilities of these compounds for the preparation of *gem*-difluoromethylenated macrocyclic lactones **5**. Initially, attempted ring-expansion of **4f** as

(3) (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell Publishing, Ltd.: Cambridge, 2009. (b) Hiyama, T.; Ed. *Organofluorine Compounds Chemistry and Application*; Springer: New York, 2000. (c) Hiyama, T.; Shimizu, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 214 and references cited. (d) Uneyama, K. *Organofluorine Chemistry*, Blackwell: Cambridge, 2006. (e) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis Reactivities, Applications*; Wiley-VCH: Weinheim, 2004.

(4) (a) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921 and references cited. (b) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457. (c) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 529. (d) Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575. (e) Pohmakotr, M.; Panichakul, D.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2007**, *63*, 9429. (f) Boonkitpattarakul, K.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2011**, *132*, 987.

(5) (a) Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2006**, *62*, 5973. (b) Peewasan, K.; Kuhakarn, C.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2012**, *135*, 367.

(6) See for examples: (a) Arimitsu, S.; Fernández, B.; Del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656. (b) Guo, Y.; Fujiwara, K.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2007**, *72*, 8523. (c) Arimisu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559. (d) You, Z.-W.; Jiang, Z.-X.; Wang, B.-L.; Qing, F.-L. *J. Org. Chem.* **2006**, *71*, 7261. (e) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 8665. (f) Zheng, F.; Zhang, X.-H.; Qiu, X.-L.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2006**, *8*, 6083. (g) Wang, R.-W.; Qing, F.-L. *Org. Lett.* **2005**, *7*, 2189. (h) De Kimpe, N.; Van Brabandt, W. *Synlett* **2006**, 2039. (i) Qin, Y.-Y.; Yang, Y.-Y.; Qiu, X.-L.; Qing., F.-L. *Synthesis* **2006**, 1475. (j) Yue, X.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 73. (k) Diab, S. A.; Sene, A.; Pfund, E.; Lequeux, T. *Org. Lett.* **2008**, *10*, 3895. (l) Xu, W.; Dolbier, W. R., Jr.; Salazar, J. *J. Org. Chem.* **2008**, *73*, 3535. (m) Ramachandran, V. P.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195. (n) Uneyama, K. *J. Fluorine Chem.* **2008**, *129*, 550.

(7) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489.

(8) Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798.

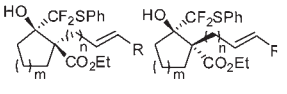
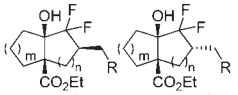
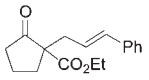
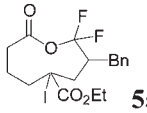
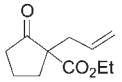
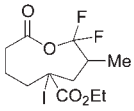
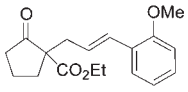
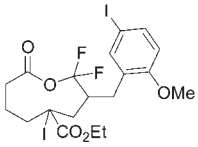
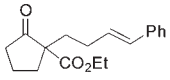
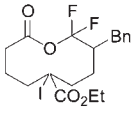
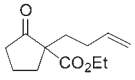
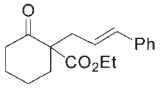
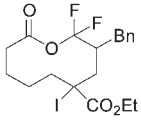
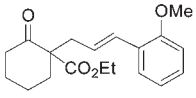
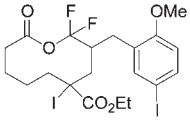
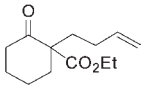
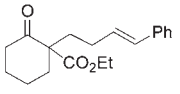
(9) α-Carboethoxycyclopentanones **2** were readily prepared by treatment of the corresponding cyclic β-ketoesters with alkenyl bromide in the presence of potassium *tert*-butylate in DMSO or NaH in THF.

(10) *Cis*- and *trans*-isomers were assigned on the basis of the relative stereochemistry of hydroxyl and alkyl groups.

(11) Matovic, R.; Ivkovic, A.; Manojlovic, M.; Tokic-Vujosevic, Z.; Saicic, R. N. *J. Org. Chem.* **2006**, *71*, 9411.

(12) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963.

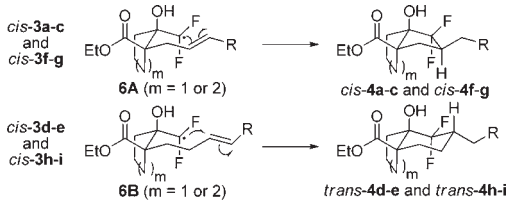
Table 1. Preparation of Compounds **3**–**5**

entry	**2**	**3** (yield%)[a]	**4** (yield%)[a]	**5** (yield%)[a,b]
		 *cis*-**3** *trans*-**3**	 *cis*-**4** *trans*-**4**	
1	 **2a**	*cis*-**3a** (62%); *trans*-**3a** (15%)[c] *cis*-**3a** (63%); *trans*-**3a** (15%)[d]	*cis*-**4a** (46%); *trans*-**4a** (37%)	 **5a** (78%)[e]
2	 **2b**	*cis*-**3b** (55%); *trans*-**3b** (29%)[c]	*cis*-**4b** (63%); *trans*-**4b** (28%)	 **5b** (71%)[g]
3	 **2c**	*cis*-**3c** (66%); *trans*-**3c** (13%)[c] *cis*-**3c** (43%); *trans*-**3c** (17%)[d]	*cis*-**4c** (60%); *trans*-**4c** (38%)	 **5c** (50%)[g]
4	 **2d**	*cis*-**3d** (46%); *trans*-**3d** (30%)[c]	*trans*-**4d** (65%); *cis*-**4d** (33%)	 **5d** (67%)[g]
5	 **2e**	*cis*-**3e** (53%); *trans*-**3e** (10%)[d]	*trans*-and *cis*-**4e** (78%, 2:1)[f]	—[h]
6	 **2f**	*cis*-**3f** (76%); *trans*-**3f** (3%)[d]	*cis*-**4f** (73%); *trans*-**4f** (22%)	 **5f** (67%)[g]
7	 **2g**	*cis*-**3g** (61%)[c] *cis*-**3g** (69%)[d]	*cis*-**4g** (70%); *trans*-**4g** (25%)	 **5g** (68%)[g]
8	 **2h**	*cis*-**3h** (87%)[d]	*trans*-and *cis*-**4h** (94%, 3.6:1)[f]	—[h]
9	 **2i**	*cis*-**3i** (86%)[c] *cis*-**3i** (31%)[d]	*trans*-**4i** (65%); *cis*-**4i** (24%)	—[i]

[a] Isolated yields. [b] Obtained as a mixture of diastereomers. [c] Using TBAF. [d] Using TBAT. [e] Prepared from a mixture of isomers of **4**. [f] Determined by ^{1}H NMR. [g] Prepared from the major isomer of **4**. [h] The reactions were not performed. [i] The reaction led to the recovery of **4i**.

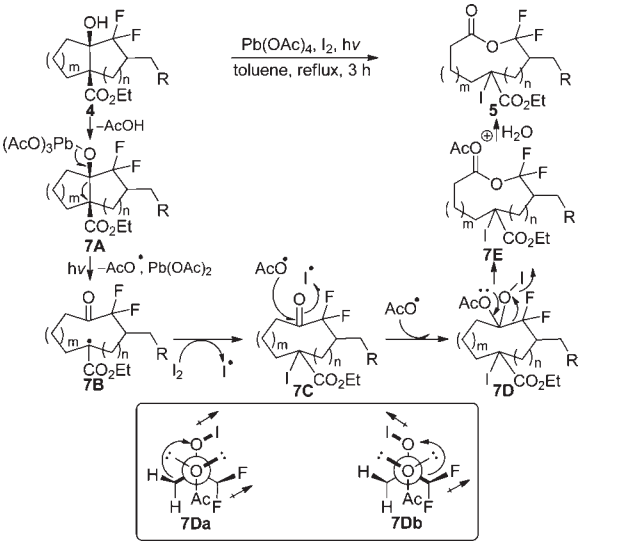
a mixture of isomers (*trans*/*cis* = 1:3) by employing either KHMDS/18-crown-6/THF[11] or NaH/THF, *t*-BuOK/THF at 0 °C to room temperature led completely to the recovery of the starting material. Similar results were obtained when **4f** (*trans*/*cis* = 1:3) was treated with DIB/Et_4NBr/CH_2Cl_2/H_2O/rt, IBX/I_2/DMSO/rt, or HgO/I_2/CCl_4/reflux.[12] Gratifyingly, when a mixture of **4f** (*trans*/*cis* = 1:3) was treated with DIB (3 equiv), I_2 (3 equiv) in CH_2Cl_2 under photolysis (tungsten filament lamp (100W)) for 3 h, compound **5f**, resulting from ring-expansion

Scheme 2. Proposed Transition States for the Intramolecular Radical Cyclization of *cis*-**3**



followed by the Baeyer–Villiger-type oxidation, was isolated in 35% yield. High-resolution mass data, ^{1}H and ^{13}C NMR, as well as C–H correlation in 2D NMR confirm the structure of **5f** (see the Supporting Information). Improved results were obtained when *cis*-**4f** was treated with Pb(OAc)$_4$ (2 equiv) and I$_2$ (2 equiv) in dry toluene under photolysis[13] for 3 h, providing **5f** in 67% yield (Table 1, entry 6). Under similar reaction conditions, *cis*-**4a**–**c**, *trans*-**4d**, and *cis*-**4g** provided the corresponding ring-expanded products **5a**–**d** and **5g** in 50–78% yields as summarized in Table 1. Compounds **5c** and **5g** were obtained as the 4-iodinated methoxybenzene derivatives which resulted from the electrophilic iodination of the corresponding initially formed *gem*-difluoromethylenated macrocyclic lactones. Attempts to perform ring-expansion of a mixture of *cis*- and *trans*-**4i**, under the standard conditions, were not successful, and **4i** was recovered (80–90%). The explanation for the failure of the oxidative ring expansion of **4i** is still unclear. The mechanism for the formation of *gem*-difluoromethylenated macrocyclic lactones **5** was proposed as shown in Scheme 3. Under photolytic conditions, an intermediate **7A**, initially formed from the reaction of **4** with Pb(OAc)$_4$, underwent homolytic cleavage of the Pb–O followed by C–C bond breaking leading to a radical intermediate **7B**, which was then trapped by an iodine atom to give **7C**, which further reacted with acetoxy radical (AcO$^\bullet$) and an iodine atom to give an intermediate **7D**. The Baeyer–Villiger-type oxidation of **7D** afforded **7E**, which was finally converted to *gem*-difluoromethylenated macrocyclic lactones **5** after hydrolysis. The observed regiospecific migration of the *gem*-difluoro-bearing carbon can be explained by primary and secondary stereoelectronic effects as well as a dipole/dipole interaction.[14] Conformations **7Da** and **7Db** fulfill both primary and secondary stereoelectronic effects. However, the conformation **7Da** suffered with dipole/dipole interaction between the iodine and the fluorine atoms. Therefore, the most favorable conformation for the Criegee intermediate would be conformation **7Db** in which the $-CF_2$ group is stereoelectronically favorable for rearrangement.

Scheme 3. Proposed Mechanism for the Formation of **5**



In conclusion, we have demonstrated a general strategy for the preparation of *gem*-difluoromethylenated bicyclic compounds **4** by employing a fluoride-catalyzed nucleophilic addition of PhSCF$_2$SiMe$_3$ to α-carboethoxycycloalkanones followed by radical cyclization of the resulting adducts *cis*-**3**. Compounds **4** underwent ring-expansion to provide *gem*-difluoromethylenated macrocyclic lactones **5** by reacting with Pb(OAc)$_4$/I$_2$/toluene/*hν*.

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Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds and single crystal X-ray analysis of *cis*-**3f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) (a) Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008. (b) Posner, G. H.; Webb, K. S.; Asirvathan, E.; Jew, S.-S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* **1988**, *110*, 4754.

(14) (a) Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2851. (b) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803. (c) Grein, F.; Chen, A. C.; Edwards, D.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 861. (d) Kitazume, T.; Kataoka, J. *J. Fluorine Chem.* **1996**, *80*, 157.