ORGANIC
LETTERS

2003
Vol. 5, No. 23
4297−4300

Mg-Promoted Double Silylation of Trifluoroacetimidoyl Chlorides. A New Entry to the Fluorinated Dianion Equivalents

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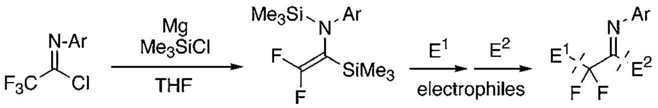
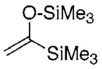
Received August 13, 2003

ABSTRACT

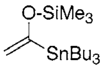


A Mg(0)/Me$_3$SiCl system was found to be effective for the preparation of a novel fluorinated dianion equivalent. A one-pot reaction sequence involving reductive C–F and C–Cl bond cleavage reactions of trifluoroacetimidoyl chlorides afforded bis-silylated difluoroenamines. Subsequent carbon–carbon bond-forming reactions of the bis(silyl)enamines with two kinds of electrophiles gave a variety of difluorinated imines.

An acyl anion equivalent is of great interest as an intermediate for nucleophilic introduction of the acyl group into organic molecules.[1] A highly functionalized acyl anion is especially attractive because it provides direct access to the multifunctionalized ketones. (1-Siloxyvinyl)silane **1a**[2] and (1-siloxyvinyl)stannane **1b**[3] are synthetically useful dianion equivalents which function not only as acyl anions but also as enolate anions. However, in general, multistep procedures have been used for the introduction of silicon and tin atoms into the dianion equivalents **1a** and **1b**.



1a



1b

In synthetic organofluorine chemistry, the fluorinated acyl anions and their equivalents[5−10] have been regarded as highly useful synthons in accessing the fluorinated ketones and their derivatives. And in recent years, *gem*-difluorinated organic compounds have received considerable attention because many of these compounds exhibit interesting biological activities and high performance in medicinal chemistry such as anticancer agent gemcitabine,[11] HIV-1 protease inhibitors,[12] phosphotyrosine (pTyr) mimetics,[13] and fluorinated sugars.[14] Accordingly, there has been a growing interest in developing new difluorinated building blocks for the synthesis of the *gem*-difluorinated compounds. Percy demonstrated the preparations of **2a** and **2b** and their utilization for a variety of difluorinated compounds.[8]

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(1) Ager, D. J. In *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*; Hase, T. A., Ed.; Wiley: New York, 1987; p 19.

(2) (a) Bassindale, A. R.; Brook, A. G.; Harris, J. *J. Organomet. Chem.* **1975**, *90*, C6. (b) Murai, S.; Ryu, I.; Iriguchi, J.; Sonoda, N. *J. Am. Chem. Soc.* **1984**, *106*, 2440. (c) Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1985**, *50*, 5410. (d) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1994**, *50*, 7783.

(3) (a) Verlhac, J. B.; Pereyre, M.; Shin, H. A. *Organometallics* **1991**, *10*, 3007. (b) Verlhac, J. B.; Kwon, H.; Pereyre, M. *J. Organomet. Chem.* **1992**, *437*, C13. (c) Barbero, A.; Pulido, F. J. *Synlett* **2001**, 827.

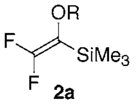
(4) (a) Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds. *Biochemical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996. (b) Filler, R.; Kobayashi, Y., Eds. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha Ltd. and Elsevier Biomedical Press: Tokyo and Amsterdam, 1982. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (d) Walsh, C. *Tetrahedron* **1982**, *38*, 871. (e) Stremler, K. E.; Poulter, C. D. *J. Am. Chem. Soc.* **1987**, *109*, 5542. (f) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (g) Iseki, K.; Kobayashi, Y. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 40. (h) Iseki, K.; Kobayashi, Y. *Rev. Heteroat. Chem.* **1995**, *15*, 211.

(5) (a) Jin, F.; Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 1221. (b) Jin, F.; Xu, Y. *J. Fluorine Chem.* **1993**, *62*, 207. (c) Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc., Chem. Commun.* **1993**, 814. (d) Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 795.

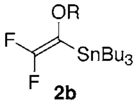
(6) Bordeau, M.; Clavel, P.; Barba, A.; Berlande, M.; Biran, C.; Roques, N. *Tetrahedron Lett.* **2003**, *44*, 3741.

(7) Dubuffet, T.; Sauvetre, R.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1989**, 677.

10.1021/ol035528y CCC: $25.00



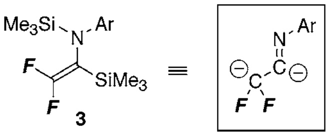
2a



2b

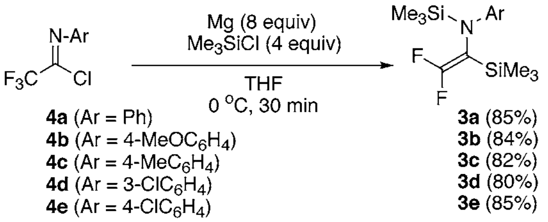
(R = MEM, CONEt$_2$)

Herein, we report a one-pot preparation of new *gem*-difluorinated dianion equivalents **3** involving reductive C−F and C−Cl bond cleavage reactions of trifluoroacetimidoyl chlorides **4**.[15] Mg(0)-promoted double silylation of **4** in a one-pot procedure provided bis-silylated difluoroenamines **3** serving as both an acyl anion synthon and an enolate synthon.



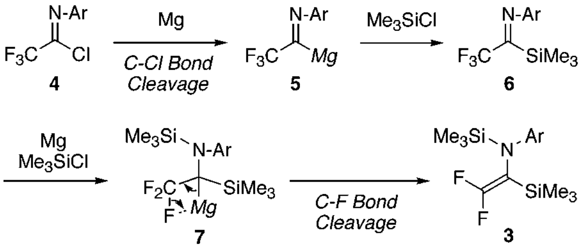
The preparation of the requisite dianion equivalents **3** is very simple. When imidoyl chlorides **4** were treated with Mg metal (8 moleequiv to **4**) and chlorotrimethylsilane (4 equiv) in distilled THF at 0 °C for 30 min, the dehalogenative double silylation reactions proceeded smoothly to afford bis-silylated difluoroenamines **3** in high yields (Scheme 1). Both C−F and imidoyl C−Cl bonds in **4** were cleaved subsequently under mild conditions; each reaction was completed within 30 min. As shown in Scheme 1, the presence of electron-withdrawing and electron-donating substituents on the *N*-aryl groups in **4** had little effect on the yields of **3**. Notably, Cl-arene functionalities in **3d** and **3e** were compatible under the present reaction conditions.

Scheme 1



The formation of **3** can be explained by assuming the pathway pictured in Scheme 2. Initially, the reductive cleavage of C−Cl bonds of the imidoyl chlorides **4** took place to generate imidoylmagnesium species **5**, which reacted with chlorotrimethylsilane to provide the imidoylsilanes **6**.[16,17] Subsequent two-electron reduction of the imidoylsilanes **6** afforded the β-fluorinated organomagnesium species **7**, which readily underwent β-elimination to form **3**.

Scheme 2



An interesting feature of the present "one-pot" reactions is the double functionalization of imidoyl C−Cl bonds and C−F bonds of **4** which possess their different nature.

Generally, C−Cl bonds of acyl chlorides and imidoyl chlorides are highly reactive toward nucleophiles. Due to the aggressive nature of their C−Cl bonds, these compounds have been widely used for the electrophilic introduction of acyl and imidoyl groups into organic molecules. On the contrary, a C−F bond is known to be strong; the cleavage of a C−F bond is not easy due to the large bond energy (ca. 552 kJ mol^{-1}).[18] However, the bond breaking does rather easily occur when a CF$_3$ group is attached to the π-electron system because electron acceptance into the π-system and subsequent extrusion of a fluoride ion may make large

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(8) (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201. (b) Howarth, J. A.; Owton, W. M.; Percy, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 757. (c) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron* **1995**, *51*, 10289. (d) Crowley, P. J.; Howarth, J. A.; Owton, W. M.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 5975. (e) Crowley, P. J.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 8233. (f) Crowley, P. J.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 8237. (g) Balnaves, A. S.; Gelbrich, T.; Hursthouse, M. B.; Light, M. E.; Palmer, M. J.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2525. (h) DeBoos, G. A.; Fullbrook, J. J.; Owton, W. M.; Percy, J. M.; Thomas, A. C. *Synlett* **2000**, 963. (i) DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M. *Org. Lett.* **2001**, *3*, 2859. (j) Garayt, M. R.; Percy, J. M. *Tetrahedron Lett.* **2001**, *42*, 6377.

(9) (a) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 1641. (b) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 5437. (c) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 6379. (d) Ichikawa, J.; Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961. (e) Ichikawa, J.; Hamada, S.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 337. (f) Okada, Y.; Minami, T.; Yamamoto, T.; Ichikawa, J. *Chem. Lett.* **1992**, 547. (g) Ichikawa, J.; Minami, T.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 3779. (h) Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739. (i) Ichikawa, J.; Yonemaru, S.; Minami, T. *Synlett* **1992**, 833.

(10) (a) Watanabe, H.; Yamashita, F.; Uneyama, K. *Tetrahedron Lett.* **1993**, *34*, 1941. (b) Tamura, K.; Yan, F.-Y.; Sakai, T.; Uneyama, K. *Bull. Chem. Soc., Jpn.* **1994**, *67*, 300. (c) Watanabe, H.; Yan, F.-Y.; Sakai, T.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 758. (d) Uneyama, K.; Noritake, C.; Sadamune, K. *J. Org. Chem.* **1996**, *61*, 6055.

(11) Chou, T. S.; Heath, P. C.; Patterson, L. E.; Poteet, L. M.; Laikin, R. E.; Hunt, A. H. *Synthesis* **1992**, 565.

(12) (a) Schirlin, D.; Van Dorsselar, V.; Weber, F.; Weill, C.; Altenburger, J. M.; Neises, B.; Flynn, G.; Remy, J. M.; Tarnus, C. *Bioorg. Med. Chem.* **1993**, *3*, 3. (b) Sham, H. L.; Eideburg, N. E.; Spanton, S. G.; Kohlbrenner, D. W.; Betebenner, D. A.; Kempf, D. J.; Norbeck, D. W.; Platter, J. J.; Erickson, J. W. *J. Chem. Soc., Chem. Commun.* **1991**, 110.

(13) Berkowitz, D. B.; Sloss, D. G. *J. Org. Chem.* **1995**, *60*, 7047 and references therein.

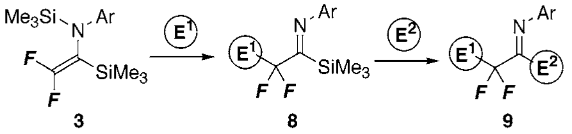
(14) (a) Barnett, J. E. D. *Carbon−Fluorine Compounds*; Elsevier: Amsterdam, The Netherlands, 1972. (b) Taylor, N. F., Ed. *Fluorinated Carbohydrates*; American Chemical Society: Washington, DC, 1996.

(15) (a) Uneyama, K. *J. Fluorine Chem.* **1999**, *97*, 11. (b) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32.

(16) Bourgeois, P.; Dunogues, J.; Duffaut, N.; Lapouyade, P. *J. Organomet. Chem.* **1974**, *80*, C25.

(17) The formation of the imidoylsilane **6b** (Ar = PMP) was observed by conducting the reaction with a reduced amount of Mg (3 equiv) at much lower temperature (−75 °C).

contributions to the driving force of the reaction.[19] Both electrochemical reduction[20] and chemical reduction by the use of Mg metal[21] were found to be effective for the selective defluorination of trifluoromethyl ketones, imines, and trifluoroacetates. These reductive C−F bond cleavage reactions were applied successfully to the preparation of difluoromethylene building blocks.

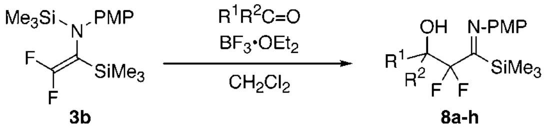


(1)

By means of the successive double dehalogenation reactions as shown above, the resultant bis-silylated difluoroenamines **3** are very promising bifunctional synthetic blocks, which have not only *N*-silylenamine skeletons but also α-aminovinylsilane skeletons. An interesting application of **3** is represented by chemoselective sequential transformations with different electrophiles (**3** → **8** → **9** in eq 1). First, the reactions of **3** with electrophiles (E^1) by utilizing the properties of difluoroenamine would provide the difluorinated imidoyl silanes **8**. Second, the resulting imidoyl silanes **8** would undergo in turn the reactions with other electrophiles (E^2) by utilizing the properties of imidoylsilane, giving a wide variety of difluorinated iminoacyl compounds **9**.

The first stage of the reaction sequence involved the Lewis acid-catalyzed aldol-type reaction of bis(silyl)enamines **3**. In each case, C−C bond formation with high chemoselectivity at the *β*-carbon atom of **3b** has been accomplished (Table 1). Treatment of enamine **3b** with various aldehydes in the presence of BF_3 etherate in CH_2Cl_2 at 0 °C provided *β*-hydroxy-α,α-difluoro imidoylsilanes **8a**−**g** in moderate to high yields (entries 1−7). With α,*β*-unsaturated aldehyde, enamine **3b** selectively underwent 1,2-addition (entry 6). In contrast, the reaction of **3b** with acetone gave the corresponding adduct **8h** in 40% yield (entry 8).

Table 1. Lewis Acid-Catalyzed C−C Bond Formation of **3b** with Carbonyl Compounds[a]

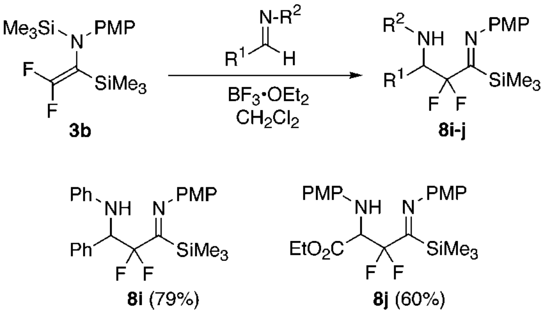


entry	$R^1R^2C{=}O$		**8**	yield (%)[b]
	R^1	R^2		
1	Ph	H	**8a**	88
2	4-MeOC_6H_4	H	**8b**	84
3	4-ClC_6H_4	H	**8c**	86
4	2-furyl	H	**8d**	87
5	2-thienyl	H	**8e**	85
6	(*E*)-PhCH=CH	H	**8f**	59
7	*i*-Pr	H	**8g**	87
8[c]	Me	Me	**8h**	40

[a] Unless noted, each reaction was carried out at 0 °C for 1.5 h by the use of aldehyde (1.2 equiv) and $BF_3{\cdot}OEt_2$ (1.2 equiv). [b] Isolated yields. [c] The reaction was carried out at 0 °C for 30 min by the use of acetone (4 equiv) and $BF_3{\cdot}OEt_2$ (4 equiv).

The aldol-type reactions of **3b** with aldehydes and ketones afforded *β*-hydroxy imidoylsilanes **8a**−**h**, new fluorinated acyl anion equivalents possessing both difluoromethylene and hydroxy groups. Instead of aldehydes, aldimines were used as an electrophile in these reactions providing the amino group-containing acyl anion equivalents. In the presence of $BF_3{\cdot}OEt_2$, the aldol reaction of **3b** worked well with *N*-benzylideneaniline to give the corresponding *β*-amino-α,α-difluoro imidoylsilane **8i** in 79% yield (Scheme 3). Furthermore, the reaction of **3b** with the Schiff base of ethyl glyoxylate[22] gave a fascinating acyl anion equivalent **8j** endowed with an α-amino acid moiety.

Scheme 3



These successful results of selective functionalizations of bis(silyl)enamines **3** at the *β*-carbon atoms with various electrophiles encouraged us in our own pursuit of further synthetic applications. In general, an imidoylsilane per se is a stable compound, but it is amenable to a reaction as an acyl anion equivalent in the presence of fluoride ion.[10d]

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(18) (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373. (b) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber. Recl.* **1997**, *130*, 145. (c) Richmond, T. G. In *Activation of Unreactive Bonds and Organic Synthesis*; Topics in Organometallic Chemistry, Vol. 3); Murai, S., Ed.; Springer-Verlag: Berlin, Germany, 1999; p 243.

(19) (a) Chaussard, J.; Folest, J.-C.; Nedelec, J.-Y.; Périchon, J.; Sibille, S.; Troupel, M. *Synthesis* **1990**, 369. (b) Saboureau, C.; Troupel, M.; Sibille, S.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 1138. (c) Andrieux, C. P.; Combellas, C.; Kanoufi, F.; Savéant, J.-M.; Thiébault, A. *J. Am. Chem. Soc.* **1997**, *119*, 9527. (d) Cavel, P.; Léger-Lambert, M.-P.; Biran, C.; Serein-Spirau, C. F.; Bordeau, M.; Roques, N.; Marzouk, H. *Synthesis* **1999**, 829. (e) Stepanov, A. A.; Minyaeva, T. V.; Martynov, B. I. *Tetrahedron Lett.* **1999**, *40*, 2203. (f) Clavel, P.; Biran, C.; Bordeau, M.; Roques, N.; Trévin, S. *Tetrahedron Lett.* **2000**, *41*, 8763. (g) Clavel, P.; Lessene, G.; Biran, C.; Bordeau, M.; Roques N.; Trévin, S.; de Montauzon, D. *J. Fluorine Chem.* **2001**, *107*, 301.

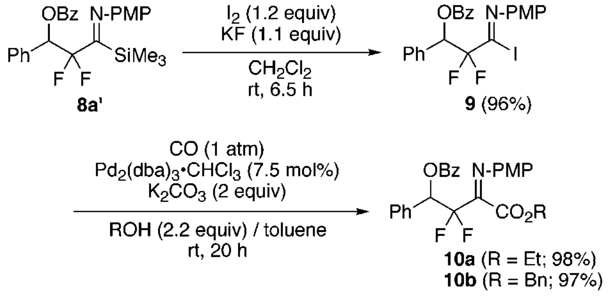
(20) (a) Uneyama, K.; Maeda, K.; Kato, T.; Katagiri, T. *Tetrahedron Lett.* **1998**, *39*, 3741. (b) Uneyama, K.; Kato, T. *Tetrahedron Lett.* **1998**, *39*, 587. (c) Uneyama, K.; Mizutani, G. *Chem. Commun.* **1999**, 613. (d) Uneyama, K.; Mizutani, G.; Maeda, K.; Kato, T. *J. Org. Chem.* **1999**, *64*, 6717.

(21) (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323. (b) Amii, H.; Kobayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001. (c) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893. (d) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103. (e) Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. *J. Org. Chem.* **2001**, *66*, 7216. (f) Mae, M.; Matsuura, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2002**, *43*, 2069. (g) Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, *43*, 6099.

(22) Tietze, L. F.; Bratz, M. *Synthesis* **1989**, 439.

We have explored iodination of *O*-protected imidoylsilane **8a′** as a synthetically useful transformation. Upon treatment with 1.1 equiv of KF, the reaction of **8a′** with I_2 (1.2 equiv) proceeded cleanly at 0 °C to afford the corresponding imidoyl iodide **9** in 96% yield (Scheme 4). A particularly good use of the iodination product **9** is made for transition metal catalyzed C−C bond formation.[23] Pd-catalyzed carboalkoxylation reactions of imidoyl iodide **9** would provide the iminoesters **10**, promising precursors of the highly functionalized α-amino acids.[24] Under a CO atmosphere, the imidoyl iodide **9** smoothly underwent the carboalkoxylation reactions at room temperature for 20 h in the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ to provide imino esters **10a** (R = Et) and **10b** (R = Bn) in almost quantitative yields.

Scheme 4



In conclusion, the novel fluorinated synthetic blocks **3** were obtained from trifluoroacetimidoyl chlorides **4**, which were readily prepared by refluxing a mixture of commercially available trifluoroacetic acid, arylamines, PPh_3, and Et_3N in CCl_4.[15b] The double silylation of **4** with use of only a Mg/Me_3SiCl system allowed selective formation of the dianion equivalents **3**. The chemoselective homologation sequences of **3** acting as enolate and acyl anion equivalents were accomplished. Thus, the protocols involving one-pot cleavage of both C−F and C−Cl bonds, introduction of two silyl groups, and their individual transformations greatly expanded the scope of the fluorinated building blocks in synthetic organic chemistry.

Acknowledgment. This work has been supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Scientific Research (B), No. 13555254, Grant-in-Aid for Young Scientists (B), No. 14750684, and Grant-in-Aid for Scientific Research on Priority Areas (“Reaction Control of Dynamic Complexes”), No. 15036249). We also thank the SC-NMR laboratory of Okayama University for ^{19}F NMR analysis.

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

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[23] (a) Uneyama, K.; Watanabe, H. *Tetrahedron Lett.* **1991**, *32*, 1459. (b) Watanabe, H.; Hashizume, Y.; Uneyama, K. *Tetrahedron Lett.* **1992**, *33*, 4333. (c) Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, *65*, 3404. (d) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109.

[24] Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313.