Fluorination of Ketones Using Iodotoluene Difluoride

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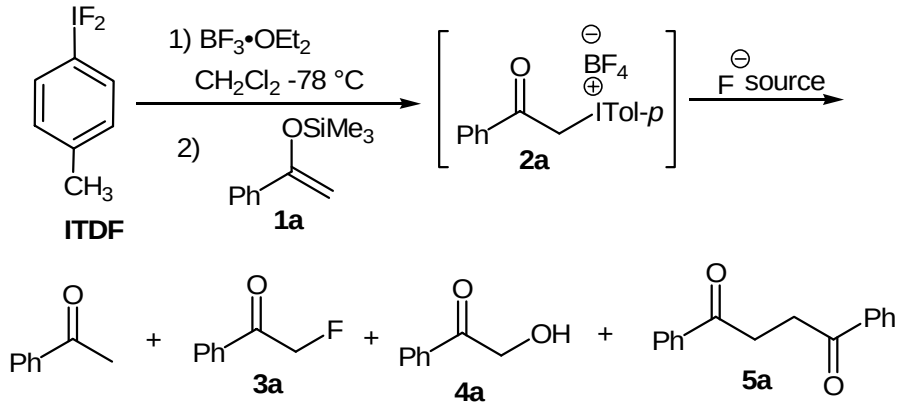
Abstract: Fluorination of ketones was achieved by the reaction of silyl enol ethers with iodotoluene difluoride in the presence of BF_3·OEt_2 and a Et_3N·HF complex.

Key words: fluorination, iodotoluene difluoride, silyl enol ether, ketone, hypervalent iodine

Introduction of a fluorine atom into the α-position of carbonyl compounds is the most effective method for the synthesis of α-fluorinated carbonyl compounds which have been used as important synthons in the preparation of more complex fluorine compounds.[1,2] Though electrophilic fluorination reagents such as *N*-fluoro reagents have been used for their synthesis,[3] dangerous F_2 is necessary for their preparation, and such reagents are expensive even if they are commercially available. Recently we reported that the direct fluorination reaction of β-dicarbonyl compounds can be achieved using iodotoluene difluoride (ITDF)[4,5] which can be prepared in large quantity without F_2.[6,7] However, application of ITDF is restricted to β-dicarbonyl compounds[4,5] or α-sulfanylated carbonyl compounds,[8-11] and ITDF is inert to monocarbonyl compounds. Previously, Tsushima et al. applied ITDF for the reaction with silyl enol ethers of steroidal ketones for the synthesis of steroidal fluoroketones.[12] However, olefinic by-products were competitively formed and yields of the desired α-fluoro ketones were low. During our continuous study of fluorination of carbonyl compounds using ITDF, we succeeded in improving the yield of fluorinated carbonyl compounds in the reaction of ITDF with silyl enol ethers.

When a silyl enol ether of acetophenone (**1a**) was allowed to react with ITDF at room temperature, it took 3 hours until the complete consumption of **1a**, and acetophenone and its dimmer (**5a**) were obtained as main products. Under the conditions, the formation of an iodonium salt (**2a**), which must be a key intermediate for the fluorinated product (**3a**),[12] seems to be slow and the generated iodonium salt **2a** decomposed to acetophenone or reacted with the remaining **1a** to give **5a** (Scheme 1). Zhadnkin et al. reported that the iodonium salts can be stably prepared at lower temperature by the reaction of **1** with an iodoarene difluoride-BF_3•OEt_2 complex.[13] In order to make **2a** at low temperature, BF_3•OEt_2 was used with ITDF, and various fluoride

sources were applied to accelerate the fluorination of **2a** (Table 1). Though **1a** was consumed at -78 °C in the presence of BF_3•OEt_2, the addition of metal fluorides such as KF and CsF, which are only slightly soluble in an organic solvent, failed to improve the yields of **3a**. On the other hand, the addition of Et_3N•HF complexes (Et_3N•nHF) could improve the results. When a commercially available Et_3N•3HF[14,15] was used as the fluoride source, **3a** could be obtained in 71% yield with a little amount of **4a** (9%) and **5a** (4%). Et_3N•2HF could slightly improve the result but Et_3N•HF, TBAF, and Et_4NF were less effective than Et_3N•2HF or Et_3N•3HF.



Scheme 1

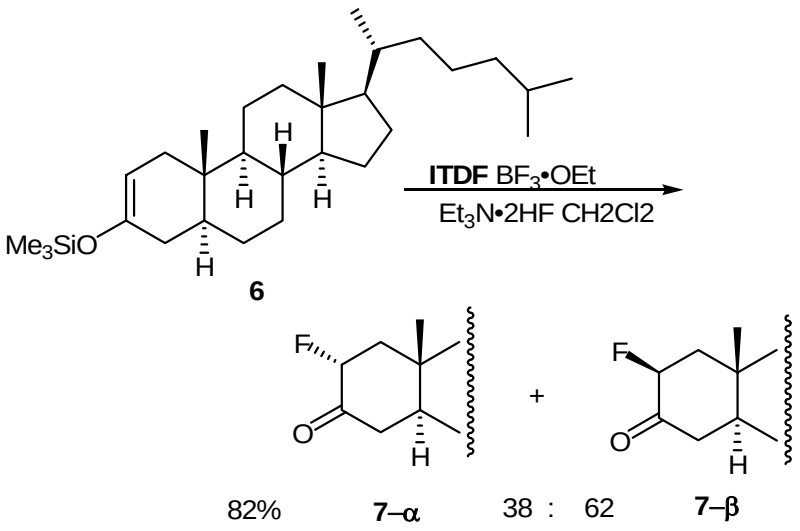
Table 1 Effect of Fluoride source on the Fluorination of **1a**[a]

Fluoride source	Yield (%)[b]		
	3a	**4a**	**5a**
Et_3N•3HF	71	9	4
Et_3N•2HF	73	7	4
Et_3N•HF	40	—	10
TBAF	25	9	3
Et_4NF	1	49	8
CsF[c]	—	80	4
KF[c]	10	75	5

[a] If otherwise not mentioned, CH_2Cl_2 was used as solvent.
[b] NMR yield based on **1a**. [c] CH_3CN was used as solvent.

Under the conditions, silyl enol ethers of various acyclic and cyclic ketones could be converted to the corresponding α-fluoroketones (**3**) (Table 2).

Introduction of a fluorine atom to methyl (entry 4), methylene (entries 1,2,5-9), and even methyne carbon (entry 3) was also possible. When cyclic ketone silyl enol ethers were used (entries 6-9), the formation of an olefinic by-product was observed to an extent of <5 %. Fluorinated analogs of steroids have been of great interest for the study of their metabolic mechanism, and 2-fluorocolesterols were synthesized from their enol esters by the reaction with electrophilic fluorinating regents. However, the products obtained by these methods are always α-isomers which are more favorable both kinetically and thermodynamically, and it was difficult to synthesize the β-isomers.[16-18] On the other hand, when silyl enol ether of cholestan-3-one (**6**) was treated with ITDF, the β-isomer of 2-fluorocholestan-3-one (**7-β**) was obtained as a main product (Scheme 2). This unusual stereoselectivity can be explained by the formation of the iodonium intermediate.[12] ITDF attacks **6** from the less hindered α-face to give the α-isomer of the iodonium intermediate which reacts with a fluoride ion with inversion of stereochemistry to give the **7-β**.[19]



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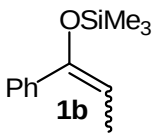
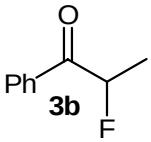
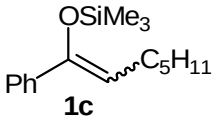
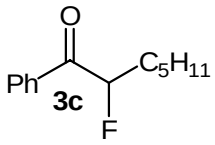
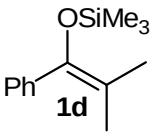
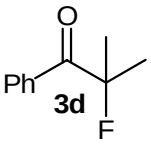
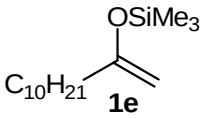
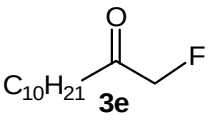
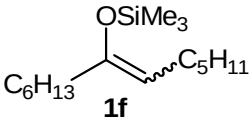
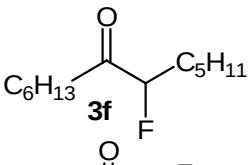
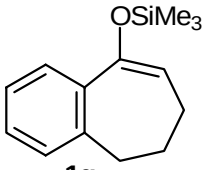
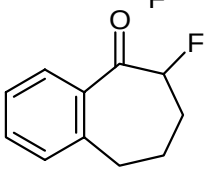
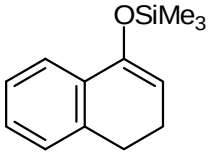
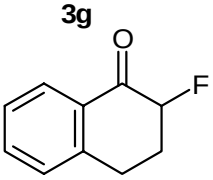
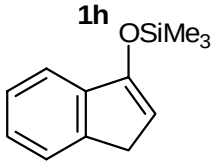
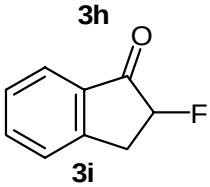
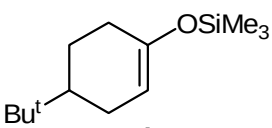
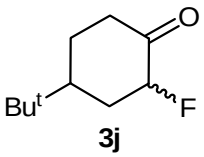
Scheme 2

Table 2 Reaction of Sily Enol Ethers **1** with ITDF[a]

Entry	Silyl Enol Ether **1**	Product **3**	Yield (%)[b]
1	 **1b**	 **3b**	60
2	 **1c**	 **3c**	82
3	 **1d**	 **3d**	66
4	 **1e**	 **3e**	70
5	 **1f**	 **3f**	85
6	 **1g**	 **3g**	62
7	 **1h**	 **3h**	60
8	 **1i**	 **3i**	50
9	 **1j**	 **3j**	61[c]

[a] The reactions were carried out in CH_2Cl_2 using ITDF, BF_3•OEt_2, and Et_3N•2HF to **1**. b Isolated yields based on **1** and yields of olefinic by-products were less than 5 %. c Ratio of *cis : trans* = 1 : 1

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400MHz), ^{19}F NMR (376MHz), and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Melting points are measured by Yanagimoto micro melting point apparatus and are uncorrected.

ITDF was prepared from iodotoluene as reported previously.[7] BF_3•OEt_2 and Et_3N•3HF were purchased from Tokyo Kasei Co., Ltd., and distilled under N_2 before use. Et_3N•2HF and Et_3N•HF were prepared by the addition of freshly distilled Et_3N to Et_3N•3HF. The silyl enol esters **1** were prepared from the corresponding ketones according to a literature.[20] Ketones were obtained from Tokyo Kasei Co., Ltd., and used without purification.

Fluorination of Ketones 1 with Iodotoluene Difluoride; General Procedure

To a CH_2Cl_2 solution (10 mL) of ITDF (256 mg, 1.0 mmol) in Teflon FEP vessel[21] were added at -78 °C, BF_3•OEt_2 (142 mg, 1.0 mmol), and after 10 min, silyl enol ether **1** (1.0 mmol). The reaction mixture was stirred at -78 °C for 2 h and a CH_2Cl_2 solution (5 mL) of Et_3N•2HF (706 mg, 5.0 mmol) was added. After 1 h, the mixture was poured into water and the separated aqueous layer was extracted with CH_2Cl_2 (2X10mL). The combined organic layers were dried over $MgSO_4$ and product **3** was obtained by column chromatography (silica gel/hexane-Et_2O).

2-Fluoroacetophenone (3a)

IR (neat): 2992, 1700, 1598, 1450, 1233, 1132 cm^{-1}.

^{1}H NMR δ = 5.55 (d, $J_{H\text{-}F}$ = 46.8 Hz, 2H), 7.26-7.53 (m, 2H), 7.62-7.66 (m, 1H), 7.89-7.94 (m, 2H).

^{19}F NMR δ = -231.4 (t, $J_{H\text{-}F}$ = 46.8 Hz, 1F) [(lit.[22] -230.3 (t, J = 47 Hz)].

2-Fluoro-1-phenyl-1-propanone (3b)

IR (neat): 2955, 2932, 2860, 1699, 1597, 1449 cm^{-1}.

^{1}H NMR: δ = 1.64 (dm, $J_{H\text{-}F}$ = 38.6 Hz, 3H), 5.70 (dq, $J_{H\text{-}F}$ = 48.8, $J_{H\text{-}H}$ = 5.6 Hz, 1H), 7.48-7.52 (m, 2H), 7.60-7.64 (m, 1H), 7.96-7.99 (m, 2H).

^{19}F NMR: δ = -181.95 to -182.27 (m, 1F) (lit.[22] -180.5).

2-Fluoro-1-phenyl-1-heptanone (3c)

IR (neat): 2955, 2932, 2860, 1699, 1597, 1449 cm^{-1}.

^{1}H NMR: δ = 0.89 (t, $J_{H.H}$ = 7.3 Hz, 3H), 1.30-1.38 (m, 4H), 1.50-1.57 (m, 2H), 1.90-2.02 (m, 2H), 5.57 (dm, $J_{H.F}$ = 49.5 Hz, 1H), 7.47-7.97 (m, 5H).

^{19}F NMR: δ = -190.54 - -190.27 (m, 1F).

^{13}C NMR: δ = 14.01, 22.47, 24.54 (d, $J_{C.F}$ = 3.3 Hz), 31.41, 32.83 (d, $J_{C.F}$ = 20.7 Hz), 93.97 (d, $J_{C.F}$ = 182.8 Hz), 128.80 (2C), 128.91 (d, $J_{C.F}$ = 3.3 Hz), 133.78 (2C), 134.42, 197.03 (d, $J_{C.F}$ = 19.8 Hz).

HRMS (EI): m/z calcd for $C_{13}H_{17}OF$: 208.1250; found: 208.1257.

2-Fluoro-2-methyl-1-phenyl-1-propanone (3d)

IR (neat): 2988, 1685, 1179 cm^{-1}.

^{1}H NMR: δ = 1.70 (d, $J_{H.F}$ = 21.5 Hz, 6H), 7.44-7.48 (m, 2H), 7.55-7.58 (m, 1H), 8.06-8.08 (m, 2H).

^{19}F NMR: δ = -144.32 to -143.98 (m, 1F) (lit.[22] -142.1).

1-Fluoro-2-dodecanone (3e)

IR (neat): 2925, 2855, 1728, 1465, 1047.

^{1}H NMR: δ = 0.88 (t, $J_{H.F}$ = 7.0 Hz, 3H), 1.26-1.30 (m, 14H), 1.56-1.65 (m, 2H), 2.54 (td, $J_{H.H}$ = 7.4, $J_{H.F}$ = 2.9 Hz, 2H), 4.80 (d, $J_{H.F}$ = 47.8 Hz, 2H).

^{19}F NMR: δ = -228.01 (t, $J_{H.F}$ = 47.8 Hz, 1F).

^{13}C NMR: δ = 14.12, 22.69, 22.76, 29.15, 29.31, 29.35, 29.45, 29.55, 31.90, 38.31, 84.97 (d, $J_{C.F}$ = 184.4 Hz), 207.29 (d, $J_{C.F}$ = 19.0 Hz).

HRMS (EI): m/z calcd for $C_{12}H_{23}FO$: 202.1741; found: 202.1737.

6-Fluoro-7-tridecanone (3f)

IR (neat): 2956, 2932, 1699, 1597, 1449 cm^{-1}.

^{1}H NMR: δ = 0.87-0.91 (m, 6H), 1.28-1.37 (m, 10H), 1.40-1.48 (m, 2H), 1.54-1.61(m, 2H), 1.70-1.86 (m, 2H), 2.53-2.64 (m, 2H), 4.71 (dm, $J_{H.F}$ = 50.4 Hz, 1H).

^{19}F NMR: δ = -192.64 to -192.35 (m, 1F).

^{13}C NMR: δ = 13.97, 14.03, 22.44 (d, $J_{C.F}$ = 10.8 Hz), 22.64, 24.21 (d, $J_{C.F}$ = 2.5 Hz), 28.84, 31.34, 31.58, 31.93, 32.14, 38.04, 96.09 (d, $J_{C.F}$ = 183.6 Hz), 210.54 (d, $J_{C.F}$ = 24.8 Hz).

HRMS (EI): m/z calcd for $C_{13}H_{25}OF$: 216.1890; found: 216.1890.

6-Fluoro-6,7,8,9-tetrahydrobenzocyclohepten-5-one (3g)

IR (neat): 2943, 1696, 1599, 1449 cm^{-1}.

^{1}H NMR: δ = 1.89-2.19 (m, 3H), 2.29-2.43 (m, 1H), 2.92-3.08 (m, 2H), 5.24 (dm, $J_{H.F}$ = 48.8 Hz, 1H), 7.22-7.26 (m, 1H), 7.31-7.35 (m, 1H), 7.42-7.46 (m, 1H), 7.77 (d, $J_{H,F}$ = 7.8 Hz, 1H).

^{19}F NMR: δ = -183.3 to -183.15 (m, 1F) (lit.[23] -183).

2-Fluoro-1-tetralone (3h)

White solid; Mp 34 °C (lit.[23] 38-40 °C).

IR (KBr): 2938, 2898, 1707, 1602, 1271, 1227 cm^{-1}.

^{1}H NMR: δ = 2.31-2.43 (m, 1H), 2.55-2.63 (m, 1H), 3.13-3.16 (m, 2H), 5.14 (dm, $J_{H.F}$ = 48.1 Hz, 1H), 7.26-7.55 (m, 3H), 8.08 (d, $J_{H.F}$ = 7.8 Hz, 1H).

^{19}F NMR: δ = -190.99 (dm, $J_{H.F}$ = 48.2, 1F) [(lit.[23] -192 (dm, $J_{H.F}$ = 47.5 Hz)].

2-Fluoroindan-1-one (3i)

White solid; Mp 56-58 °C (lit.[23] 54-56 °C).

IR (KBr): 2924, 1719, 1607, 1465, 1087 cm^{-1}.

^{1}H NMR: δ = 3.19-3.30 (m, 1H), 3.60-3.68 (m, 1H), 5.27 (dm, $J_{H.F}$ = 51.0 Hz, 1H), 7.43-7.48 (m, 2H), 7.66-7.70 (m, 1H), 7.81 (d, J = 7.6 Hz, 1H).

^{19}F NMR: δ = -194.17 (ddd, $J_{H.F}$ = 51.0, 23.2, 7.4 Hz, 1F) [(lit.[23] -192.5 (ddd, $J_{H.F}$ = 50, 22.5, 9 Hz)].

***cis*-2-Fluoro-4-*tert*-butylcyclohexanone (*cis*-3j)**

White solid; Mp 37 °C (lit.[16] 40 °C).

IR (KBr): 2962, 1737, 1368cm^{-1}.

^{1}H NMR: δ = 0.95 (s, 9H), 1.39-1.50 (m, 1H), 1.54-1.69 (m, 2H), 2.07-2.18 (m, 1H), 2.28-2.37 (m, 1H), 2.49-2.56 (m, 2H), 4.93 (dm, $J_{H.F}$ = 48.5 Hz, 1H).

^{19}F NMR: δ = -188.62 (dm, $J_{H.F}$ = 48.2 Hz, 1F).

trans-2-Fluoro-4-_tert_-butylcyclohexanone (_trans_-3j)

White solid; Mp 69-71 °C (lit.[16] 74 °C).

IR (KBr): 2956, 2871, 1722, 1365 cm^{-1}.

^1H NMR: δ = 0.92 (s, 9H), 1.42-1.70 (m, 2H), 1.84-1.92 (m, 1H), 2.10-2.19 (m, 1H), 2.35-2.45 (m, 2H), 2.76-2.86 (m, 1H), 4.67 (dm, $J_{H.F}$ = 46.8 Hz, 1H).

^{19}F NMR: δ = -186.28 to -185.98 (m, 1F).

2α-Fluorocholestan-3-one (7-α)

White solid. Mp 161-163 °C (lit.[17] 168-169 °C)

IR (KBr): 2939, 2865, 1735, 1467, 1382 cm^{-1}.

^1H NMR: δ = 0.85-2.03 (m, 41H), 2.21-2.53 (m, 3H), 4.98 (dm, $J_{H.F}$ = 48.1 Hz, 1H).

^{19}F NMR: δ = -194.67 (dm, $J_{H.F}$ = 48.1 Hz, 1F) (lit.[17] -194.48).

2β-Fluorocholestan-3-one (7-β)

White solid; Mp 85-87 °C.

IR (KBr): 2932, 2861, 1735, 1467, 1382 cm^{-1}.

^1H NMR: δ = 0.85-1.87 (m, 40H), 1.97-2.02 (m, 1H), 2.16-2.26 (m, 2H), 2.59-2.68 (m, 1H), 4.79 (dt, $J_{H.F}$ = 49.8, $J_{H.H}$ = 4.6 Hz, 1H).

^{19}F NMR: δ = -183.72 to -184.00 (m, 1F).

^{13}C NMR: δ = 12.03, 13.82, 13.86, 18.64, 21.51, 22.55, 22.80, 23.80, 24.14, 27.99, 28.19, 28.64, 31.47, 34.91, 35.74, 35.99, 36.11, 39.48, 39.81, 41.69, 44.90 (d, $J_{C.F}$ = 19.0 Hz), 45.84, 54.68, 56.10, 56.21, 92.33 (d, $J_{C.F}$ = 180.3 Hz), 206.90 (d, $J_{C.F}$ = 18.2 Hz).

HRMS (EI): m/z calcd for $C_{27}H_{45}FO$: 404.3454; found: 404.3453.

References

(1) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111.
(2) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, **1991**.
(3) For a review article of electrophilic fluorination, see: Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431.
(4) Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *Chem. Commun*. **1996**, 1899.
(5) Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *Arkivoc* **2003**, 36.
(6) Carpenter, W. *J. Org. Chem*. **1966**, *31*, 2688.
(7) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, 1802.
(8) Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett*. **2000**, *41*, 4463.
(9) Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett*. **2000**, *41*, 4467.
(10) Greaney, M. F.; Motherwell, W. B. Tocher, D. A. *Tetrahedron Lett*. **2001**, *42*, 8523.
(11) Motherwell, W. B.; Greaney, M. F.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2809.
(12) Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett*. **1982**, *23*, 1165.
(13) They obtained dimmer **5** in good yields by this method, see: Zefirov, N. S.; Samoniya, N. S. Kutateladze, T. G.; Zhdankin, V. V. *Zh. Org. Khim*. **1991**, *27*, 220; *Chem. Abstr.* **1991**, *115*, 9164.
(14) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 75.
(15) Haufe, G. *J. Prakt. Chem*. **1996**, *338*, 99.
(16) Rozen, S.; Menahem, Y. *J. Fluorine Chem*. **1980**, *16*, 19.
(17) Thomas, M. G.; Suckling, C. J.; Pitt, A. R.; Suckling, K. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3191.
(18) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, 2609.
(19) An equilibrium between two isomers of **7** was not observed under the reaction conditions.
(20) Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasooriya, N. *Eur. J. Org. Chem*. **2003**, 634.
(21) A centrifuge tube with a screw cup made of Teflon FEP, a copolymer of TFE and hexafluoropropylene, was used.
(22) Cousseau, J.; Albert, P. *J. Org. Chem*. **1989**, *54*, 5380.
(23) Stavber, S.; Sket, B.; Zajc, B.; Zupan, M. *Tetrahedron* **1989**, *45*, 6003.