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Ortho Lithiation of *N*-Pivaloylfluoroanilines as a Useful Tool for Either Selective Methylation or Benzoxazole Synthesis

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Abstract:

Lithiation of *N*-pivaloyl-3,4-difluoroaniline (1a) with a slight excess of 2 mole equiv of *n*-butyllithium followed by methylation was studied. The reaction was found to be useful for either the selective methylation of 3,4-difluoroaniline or the synthesis of benzoxazole derivatives, depending on the reaction temperature. In the reaction of *N*-pivaloyl-3-chloro-4-fluoroaniline (1b) and *N*-pivaloyl-3-fluoroaniline (1c), the reaction proceeded rather sluggishly but benzoxazole formation predominated.

Introduction

During the course of our study on the synthesis of recently developed fluoroquinoline antimicrobial agents, 2-methyl-3,4-difluoroaniline was found to be an important starting material.[1−3,5] But preparation of this compound was difficult because of the unavailability of the aromatic raw material having a methyl group at the desired position, and methodology for the selective introduction of the methyl group is limited. If there was a suitable method for the selective introduction of the methyl group at the ortho position of 3,4-difluoroaniline, the desired compound could be obtained via fewer reaction steps at a lower cost. In the literature, lithiation is reported to be a useful tool for the regioselective introduction of alkyl groups or other electrophiles onto aromatic rings.[4] Thus, 2-methyl-3,4-difluoroaniline recently was reported to be obtained via lithiation and methylation of 3,4-difluoroaniline protected by the *tert*-butoxycarbonyl group.[5] However, di-*tert*-butyldicarbonate as the N-protecting agent and *tert*-butyllithium as the lithiation agent were necessary, but both of them were not suitable for industrial synthesis because of their cost, availability, and difficulty in handling. Thus we studied an alternative method for protecting 3,4-difluoroaniline followed by ortho lithiation and alkylation. One of the choices considered was to utilize pivaloyl chloride as the protecting agent and *n*-butyllithium as the base instead of di-*tert*-butyldicarbonate and *tert*-butyllithium.

Results and Discussion

While ortho lithiation of N-protected anilines has been studied widely, reactions of *N*-pivaloyl-3-halogeno (such as 3-chloro or 3-fluoro) anilines were known to form benzoxazole derivatives as the main products via benzyne intermediates formed by the elimination of the halide ion.[6−9] For example, lithiation of *N*-pivaloyl-3,5-dichloroaniline by *sec*-butyllithium at −95 °C followed by reaction with CO_2 and acidification gave a mixture of 75% of 5-chloro-2-*tert*-butyl-7-benzoxazolecarboxylic acid and 25% of *N*-pivaloyl-4,6-dichloroanthranilic acid. The reaction employing *tert*-butyllithium instead of *sec*-butyllithium gave 56% of the benzoxazolecarboxylic acid and 42% the anthranilic acid. On the other hand, lithiation of *N*-(*tert*-butoxycarbonyl)-3,5-dichloroaniline with *tert*-butyllithium at the same temperature gave an improved result with formation of the anthranilic acid (65% yield).[6] In these reactions, dehalogenation of the intermediate carbanion and annulation to benzoxazoles mainly took place even at a very low temperature (−95 °C). Other examples also showed benzoxazole formation as the main reaction in similar systems.[7−9] On the basis of these results, selective ortho lithiation and alkylation of *N*-pivaloyl-3-halogenoanilines seemed to be overly difficult in contrast to the reaction employing *N*-*tert*-butoxycarbonyl derivatives.[10] However, we conducted a feasibility study. At first *N*-pivaloyl-3,4-difluoroaniline (**1a**) was subjected to lithiation with 2.3 equiv of *n*-butyllithium at −50 to −60 °C in THF and subsequent methylation with 1.1 mol equiv of methyl iodide at −40 to −55 °C. Then the mixture was warmed and stirred at room temperature for 2 h and finally worked up. To our pleasant surprise, recrystallization of the crude product gave 77% of pure *N*-pivaloyl-2-methyl-3,4-difluoroaniline (**3a**). None of its regioisomer or *N*-methylation product was observed, but 14.4% of 2-*tert*-butyl-6-fluoro-7-methylbenzoxazole (**8a**) was formed as the main byproduct (Scheme 1). We further studied the effects of reaction temperature and differing halogen substituents at the 3- and 4-position. These results are summarized in Table 1.

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(1) A novel synthesis of the intermediate which can be useful for antimicrobacterial agent such as HSR-903 is described; see: Hamada, Y.; Umezu, K. Patent Application No. JP11-035531.

(2) Hamada, Y.; Umezu, K. Patent Application No. JP11-158150.

(3) The conventional method for obtaining the desired fluoroquinoline was reported as a multistep synthesis; see: (a) Ito, Y.; Kato, H.; Yasui, S.; Kado, N.; Yoshida, T. Patent Application No. JP 07-309864. (b) Masuzawa, K.; Suzue, S.; Hirai, K.; Ishizaki, T. Patent Application No. JP62-215572.

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(9) Fisher, L. E.; Caroon, J. M. *Synth. Commun.* **1989**, *19*, 233−237.

(10) The ortho lithiation of *N*-pivaloylfluoroanilines followed by reaction with ethyl trifluoroacetate was also reported but performed in relatively low yield, probably caused by side reactions of the resulting carbonyl compounds under the basic condition; see: Patel, M.; Ko, S. S.; McHugh, R. J., Jr.; Marwalder, J. A.; Srivastava, A. S.; Cordova, B. C.; Klabe, R. M.; Erickson-Vitanen, S.; Trainor, G. L.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2805−2810.

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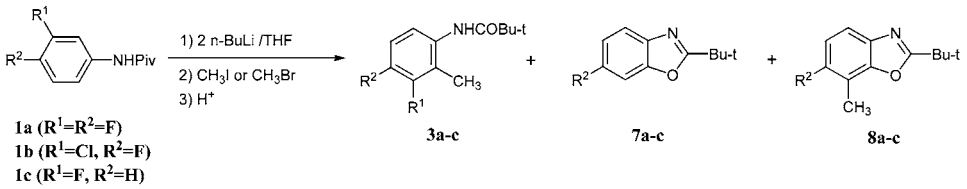
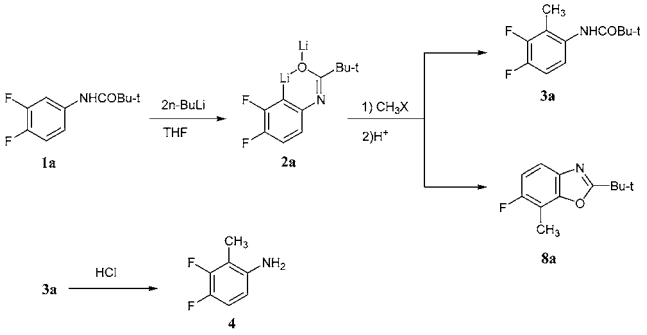
Table 1.



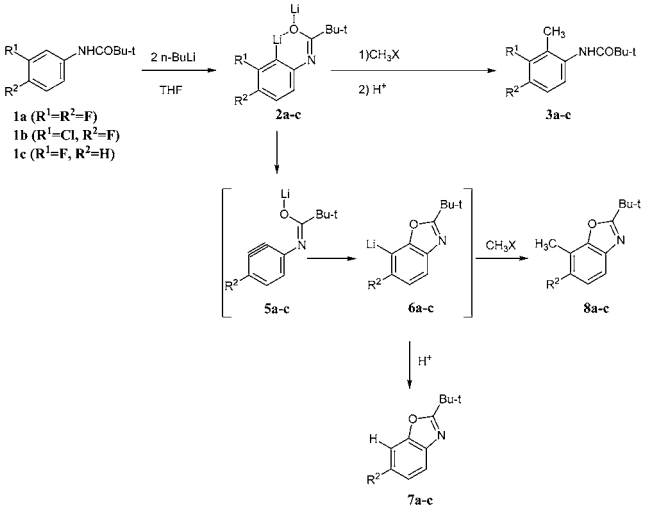
entry	1 R1	1 R2	*n*-BuLi (equiv)	CH_3I (equiv)	temp /time[a]	products[b] (%) 1	3	7	8	others
1	F	F	2.3	1.1	(1) −50 to −60 °C/1 h (2)−40 to−55 °C/1 h, rt/2 h	2.3	80.2 (77)[c]		14.4	3.1
2	F	F	2.2	1.1	(1) −65 to −70 °C/1 h (2) rt/1 h	6.4	90.8	1.2	0.4	1.2
3	F	F	2.2	2.3[d]	−65 to −70 °C/5.5 h	12.3	84.2	0.1	1.4	2.0
4	F	F	2.1	1.1	(1) −15 to −20 °C/2 h (2) 0 to 5 °C/2 h	5.3			81.0 (67)[c]	13.7
5	Cl	F	2.2	1.1	(1) −65 to −70 °C/1 h (2) rt/1 h	25.1	1.0	3.0	64.9	6.0
6[e]	Cl	F	2.2		−15 to −20 °C/1 h			98.4 (89)[c]		1.6
7	Cl	F	2.2	1.3[d]	(1) −15 to −20 °C/1 h (2) rt/1 h			0.8	95.9 (94)[c]	3.3
8	F	H	2.2	1.1	(1) −65 to −70 °C/1 h (2) rt/1 h	85.1	5.1	0.5	7.3	4.2

[a] (1) After lithiation under the described conditions, methyl iodide was added at the same temp. (2) After methylation, the reaction mixture was warmed and stirred under the described conditions. [b] The value shows area ratio determined by gas chromatography. [c] The parentheses show isolated yields. [d] Methyl bromide was used instead of methyl iodide. [e] The reaction was quenched with water after lithiation under the described condition.

Scheme 1



Scheme 2



Lithiation and methylation of **1a** took place in a similar manner at −65 to −70 °C, but formation of **8a** was suppressed to give a higher yield of **3a** (the crude compound contained 90.8% of **3a**). The crude **3a** was then hydrolyzed to give 3,4-difluoro-2-methylaniline (**4**) in 87% yield (two steps). However, at −15 to −20 °C, 2-*tert*-butyl-6-fluoro-7-methylbenzoxazole (**8a**) was formed as the main product in 81.0% (67% isolated) yield (entry 4) with no **3a**. Then *N*-pivaloyl-3-chloro-4-fluoroaniline (**1b**) and *N*-pivaloyl-3-fluoroaniline (**1c**) were subjected to this reaction. Lithiation and methylation of **1b** at −65 to −70 °C gave 2-*tert*-butyl-6-fluoro-7-methylbenzoxazole **8b** (=**8a**) as the main product and only a trace of *N*-pivaloyl-3-chloro-4-fluoro-2-methylaniline (**3b**). No **3b** but 98.4% (determined by GC) of 2-*tert*-butyl-6-fluorobenzoxazole (**7b**) was formed when the reaction was performed at −15 to −20 °C and quenched with water (entry 6). In the case of *N*-pivaloyl-3-fluoroaniline (**1c**), the reaction was considerably slower at −65 to −70 °C, and the formation of **3c** and **8c** was 5.1% and 7.3%, respectively (entry 8).[11] Other components in this reaction mixture were 85.1% of **1c** and 0.5% of 2-*tert*-butylbenzoxazole (**7c**). From these results this reaction is considered to be highly affected by the reaction temperature and the electronic effect of substituents at the 3- and 4-position. In the case of *N*-pivaloyl-3-chloro-4-fluoroaniline (**1b**), the 2-position proton is less acidic than that of **1a**, so deprotonation by *n*-butyllithium is rather slow at the same temperature (−65 to −70 °C). Thus the conversion of entry 5 is ∼74.9% in contrast to that of entry 2 (93.6%). In addition, the intermediate carbanion resulting from **1b** presumably is less stable than **1a**, causing rapid elimination of the chloride ion. In the case of *N*-pivaloyl-3-fluoroaniline (**1c**), the 2-position proton is less acidic than those of **1a** and **1b**, retarding the reaction

at low temperature, but defluorination tends to occur to produce **7c** and **8c**.[11] On the contrary, ortho lithiation and methylation of *N*-pivaloyl-3,4-difluoroaniline (**1a**) occurred selectively in high yield, due to sufficient acidity and carbanion stabilization effected by both 3- and 4-fluorine substituents. The assumed reaction path is shown in Scheme 2.

Conclusion

In conclusion, selective ortho lithiation and methylation of *N*-pivaloyl-3,4-difluoroaniline (**1a**) at −50 to −70 °C were performed. The product was readily hydrolyzed to 3,4-difluoro-2-methylaniline, an important starting material for a fluoroquinoline antimicrobial agent, in high yield. But at elevated temperature annulation to 2-*tert*-butyl-6-fluoro-7-methylbebzoxazole took place via defluorination. In the case of *N*-pivaloyl-3-chloro-4-fluoroaniline (**1b**) and *N*-pivaloyl-3-fluoroaniline (**1c**), the reaction proceeded rather sluggishly, and mainly benzoxazoles were obtained. The reaction gave a useful tool for either selective methylation of a fluoroaniline or benzoxazole derivatives depending on the reaction conditions and substituents.

Experimental Section

General. All reagents and solvents were obtained from commercial suppliers and used without purification. THF was dried over molecular sieves 4Å 1/16 before use. All reactions were carried out under nitrogen atmosphere. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Mercury VX-300 spectrometer in deuteriochloroform as the solvent. Infrared spectra were recorded on a JASCO FT/IR-420 spectrometer. GC−MS (EI) spectra were obtained using a Hewlett-Packard HP6890/MSD spectrometer using a DB-5MS column (J&W Scientific), 25 m × 0.2 mm i.d., film thickness 0.33 μm. GC analysis was performed by Shimadzu GC-9A apparatus using a G-100 column (Chemical Evaluation and Research Institute, Japan), 20 m × 1.2 mm i.d., film thickness 1 μm. The GC analysis data is reported in area %, not adjusted to weight %.

Starting Materials. *N*-Pivaloylfluoroanilines (**1a**−**1c**) were prepared by the reaction of corresponding fluoroanilines and pivaloyl chloride in the presence of triethylamine (molar ratio = 1:1:1) in toluene at ambient temperature.

***N*-Pivaloyl-3,4-difluoroaniline (1a):** mp = 123−124 °C; IR (KBr, cm^{-1}) 3300, 2850−3000, 1660, 1550, 1520, 1430, 1210, 1190; Mass (*m*/*z*) 213 (M^+), 129 ($M^+ - C_4H_8 - CO$); ^{1}H NMR (δ, $CDCl_3$) 1.32 (s, 9H, −C(C*H*$_3$)$_3$), 6.9−7.8 (m, 4H, aromatic protons and N*H*); ^{13}C NMR (δ, $CDCl_3$) 27.59 (s), 39.76 (s), 110.48 (d, J_{FC} = 21.8 MHz), 116.35 (dd, J_{FC} = 5.7 Hz, 3.4 Hz), 117.07 (d, J_{FC} = 16.6 Hz), 134.88 (dd, J_{FC} = 5.2 Hz, 3.4 Hz), 146.94 (dd, J_{FC} = 228.0 Hz, 12.7 Hz), 150.19 (dd, J_{FC} = 231.8 Hz, 15.5 Hz), 177.36 (s).

***N*-Pivaloyl-3-chloro-4-fluoroaniline (1b):** mp = 136−137 °C; IR (KBr, cm^{-1}) 3290, 2850−3000, 1650, 1520, 1500, 1390, 1210, 1170; Mass (*m*/*z*) 231, 229 (M^+) 147, 145 ($M^+ - C_4H_8 - CO$); ^{1}H NMR (δ, $CDCl_3$) 1.30 (s, 9H, −C(C*H*$_3$)$_3$), 7.04 (dd, 1H, J = 8.7 Hz, 8.7 Hz, an aromatic proton), 7.31 (ddd, 1H, J = 8.7 Hz, 3.9 Hz, 2.7 Hz, an aromatic proton), 7.50 (bs, 1H, N*H*), 7.71 (dd, 1H, J = 6.6 Hz, 2.7 Hz, an aromatic proton); ^{13}C NMR (δ, $CDCl_3$) 27.69 (s), 39.80 (s), 116.60 (d, J_{FC} = 21.8 Hz), 120.23 (d, J_{FC} = 6.8 Hz), 121.12 (d, J_{FC} = 14.5 Hz), 122.84 (s), 134.88 (s), 154.90 (J_{FC} = 244.3 Hz), 177.16 (s).

***N*-Pivaloyl-3-fluoroaniline (1c):** mp = 115−116 °C; IR (KBr, cm^{-1}) 3320, 2850−3000, 1650, 1610, 1540, 1190; Mass (*m*/*z*) 195 (M^+), 111 ($M^+ - C_4H_8 - CO$); ^{1}H NMR (δ, $CDCl_3$) 1.29 (s, 9H, −C(C*H*$_3$)$_3$), 6.7−7.6 (m, 5H, aromatic protons and N*H*); ^{13}C NMR (δ, $CDCl_3$) 27.71 (s), 39.88 (s), 107.84 (d, J_{FC} = 25.8 Hz), 111.01 (J_{FC} = 21.8 Hz), 113.55 (J_{FC} = 2.9 Hz), 130.09 (J_{FC} = 9.2 Hz), 139.87 (J_{FC} = 10.9 Hz), 163.16 (J_{FC} = 242.6 Hz), 177.11 (s).

Entry 1. To a 100-mL four-necked reaction flask equipped with a reflux condenser, thermometer, and magnetic stirrer were added 2.13 g (10.0 mmol) of **1a** and 30 mL of anhydrous tetrahydrofuran (THF). The mixture was cooled with dry ice/acetone to −60 °C. After 7.2 g (22.5 mmol) of *n*-butyllithium (20 wt % solution in cyclohexane) were added at −60 to −50 °C, the solution was stirred at −55 °C for 1 h. Then 1.56 g (11.0 mmol) of methyl iodide in 3 mL of THF were added at −40 to −55 °C. The reaction mixture was then stirred at the same temperature for 1 h and then warmed to room temperature and stirred for 2 h. Then the reaction mixture was quenched with 100 mL of water and extracted with 100 mL of ether. The ether extract was washed with 100 mL of water and dried over anhydrous sodium sulfate. After removal of ether, 2.46 g of crude product, which contains 88.2% (determined by GC) of *N*-pivaloyl-2-methyl-3,4-difluoroaniline (**3a**), were obtained. Recrystallization of the crude product from *n*-hexane gave 1.76 g (Y = 77%, P = 99.2% by GC) of pure **3a** as white crystals. Mp 112−114 °C; IR (KBr, cm^{-1}) 3310, 2860−3000, 1650, 1500; Mass (*m*/*z*) 227 (M^+), 143 ($M^+ - CO - C_4H_8$); ^{1}H NMR (δ, $CDCl_3$) 1.33 (s, 9H, −C(C*H*$_3$)$_3$), 2.19 (d, 3H, J = 2 Hz, C*H*$_3$), 6.8−7.8 (m, 3H, aromatic protons and N*H*); ^{13}C NMR (δ, $CDCl_3$) 9.78 (s), 27.59 (d, J_{FC} = 4.6 Hz), 121.14 (dd, J_{FC} = 6.5 Hz, 3.8 Hz), 132.55 (s), 148.58 (dd, J_{FC} = 243.8 Hz, 13.1 Hz), 148.87 (dd, J_{FC} = 242.6 Hz, 12.6 Hz), 177.76 (s).

Entry 2 (and Hydrolysis of Crude 3a). The reaction was repeated at −65 to −70 °C using 7.0 g (21.9 mmol) of *n*-butyllithium and 1.50 g (10.6 mmol) of methyl iodide in a manner similar to that for entry 1 to obtain 2.41 g of crude **3a**. Analytical results by GC are shown in Table 1. The product was then refluxed in a mixture of 30 mL of ethanol and 30 mL of 35% hydrochloric acid for 24 h. Then the resulting mixture was added to 100 mL of 10% NaOH solution and extracted with 100 mL of ether. The ether extract was washed twice with 100 mL of water and dried over anhydrous sodium sulfate. After removal of the ether, 1.69 g of crude product was obtained, which was distilled under reduced pressure to give 1.25 g (Y = 87%, P = 94.2% by GC) of 3,4-difluoro-2-methylaniline (**4**) with spectral data identical with those of the sample obtained according to the literature.[5] Bp 40−45 °C/0.133 kPa; Mass (*m*/*z*) 143 (M^+), 124 ($M^+ - F$); ^{1}H NMR (δ, $CDCl_3$) 2.08 (d, 3H, J_{HF} = 2.0 Hz, −C*H*$_3$), 3.1−

(11) In the similar reaction condition, the formation of 2-*tert*-butyl-7-ethylbenzoxazole was reported in ref 8.

4.2 (bs, 2H, $-NH_2$), 6.34 (ddd, 1H, J = 8.7 Hz, 4.2 Hz, 1.7 Hz, aromatic CF═CH═C*H*), 6.81 (ddd, 1H, J = 8.7 Hz, 8.7 Hz, 8.7 Hz, CF═C*H*═CH).

Entry 3. The lithiation was performed at −65 to −70 °C for 1 h using 2.13 g (10.0mol) of **1a** and 13.8 mL (21.9 mmol) of *n*-butyllithium (1.59 mol/L solution in *n*-hexane) in 30 mL of anhydrous tetrahydrofuran (THF). Then 1.25 g (13.2 mmol) of methyl bromide in 2 mL of THF was added. After the mixture stirred for 3.5 h at the same temperature, 0.90 g (9.5 mmol) of methyl bromide in 2 mL of THF was added, and stirring was continued for 2 h at the same temperature. The reaction was then quenched with 40 mL of water and worked up as usual to obtain 2.20 g of crude material. Analytical results by GC are shown in Table 1. The crude product was recrystallized twice with *n*-hexane to give 1.30 g (Y = 57%, P = 97.6% GC) of **3a**.

Entry 4. To a 100-mL four-necked reaction flask equipped with a reflux condenser, thermometer, and magnetic stirrer were added 2.13 g (10.0 mmol) of **1a** and 30 mL of anhydrous THF; the mixture was cooled to −20 °C with dry ice/acetone. After 7.0 g (21.9 mmol) of *n*-butyllithium (20 wt % solution in cyclohexane) was added at −10 to −15 °C, the solution was stirred at −15 to −20 °C for 1 h. Then 1.50 g (10.6 mmol) of methyl iodide in 3 mL of THF was added at −15 to −5 °C. The reaction mixture was stirred at −15 to −20 °C for 1 h and then warmed to 0 to 5 °C and stirred for 2 h. The reaction mixture was quenched with 100 mL of water and extracted with 100 mL of ether. The ether extract was washed with 100 mL of water and dried over anhydrous sodium sulfate. After removal of the ether, 2.27 g of crude product was obtained. Vacuum distillation of the crude oil gave 1.38 g of 2-*tert*-butyl-6-fluoro-7-methylbenzoxazole (**8a**) (Y = 67%, P = 97% by GC). Bp (Kugelrohr temp) = 130−135 °C/0.133 kPa; IR (film, cm^{-1}) 2850−3000, 1610, 1570, 1490; Mass (*m*/*z*) 207 (M^+), 192 ($M^+ - CH_3$), 150 ($M^+ - C_4H_9$); ^{1}H NMR (δ, $CDCl_3$) 1.47 (s, 9H, −C(C*H*$_3$)$_3$), 2.42 (dd, 3H, J = 1.6 Hz, 0.4 Hz, C*H*$_3$), 6.98 (dd, 1H, J = 8.8 Hz,10.1 Hz, aromatic CH═C*H*—CF═), 7.44 (ddd, 1H, J = 8.8 Hz, 4.8 Hz, 0.4 Hz, aromatic CH═C*H*—CN═); ^{13}C NMR (δ, $CDCl_3$) 8.52 (J_{FC} = 3.5 Hz), 28.64 (s), 34.45 (s), 108.80 (J_{FC} = 24.1 Hz), 111.63 (J_{FC} = 25.8 Hz), 116.75 (J_{FC} = 9.8 Hz), 136.90 (s), 150.37 (s), 158.75 (J_{FC} = 239.8 Hz), 173.96 (J_{FC} = 3.5 Hz).

Entry 5. The reaction was repeated at −65 to −70 °C using 2.30 g (10.0 mol) of **1b** and 7.1 g (22.2 mmol) of *n*-butyllithium and 1.50 g (10.6 mmol) of methyl iodide in a manner similar to that for entry 1 to obtain 2.60 g of crude **3a**. The analytical result by GC and GC−MS is shown in Table 1. The main components were 25.1% of **1b** and 64.9% of **8b** (identical with the product of entry 4).

Entry 6. The reaction was repeated at −15 to −20 °C using 2.30 g (10.0mol) of **1b** and 14.4 mL (22.5 mmol) of *n*-butyllithium (1.56mol/L solution in *n*-hexane) in a manner similar to that of entry 4. Then the reaction was quenched with 30 mL of water and extracted with 50 mL of toluene. The aqueous layer was further extracted with 30 mL of toluene. The combined toluene layer was washed with 80 mL of water and dried over anhydrous sodium sulfate. Work-up and removal of the solvent gave 1.87 g of crude product. Distillation by Kugelrohr gave 1.71 g of 2-*tert*-butyl-6-fluorobenzoxazole (**7b**) as a colorless oil (Y = 89%, P = 97.5% by GC). Bp (Kugelrohr temp) = 100−105 °C/0.133 kPa; mp = 40−41 °C, IR (KBr, cm^{-1}) 2850−3000, 1620, 1570, 1480, 1120, 1100; Mass (*m*/*z*) 193 (M^+), 178 ($M^+ - CH_3$), 137 ($M^+ - C_4H_8$); ^{1}H NMR (δ, $CDCl_3$) 1.49 (s, 9H, −C(C*H*$_3$)$_3$), 7.0−7.7 (m, 3H, aromatic protons); ^{13}C NMR (δ, $CDCl_3$) 28.76 (s), 34.58 (s), 98.77 (d, J_{FC} = 28.1 Hz), 112.15 (d, J_{FC} = 24.1 Hz), 120.22 (d, J_{FC} = 10.4 Hz), 136.87 (J_{FC} = 1.1 Hz), 151.21 (s), 160.63 (J_{FC} = 241.4 Hz), 174.50 (s).

Entry 7. The reaction was repeated at −15 to −20 °C using 2.30 g (10.0mol) of **1b** and 14.4 mL (22.5 mmol) of *n*-butyllithium (1.56 mol/L solution in *n*-hexane) in a manner similar to that of entry 6. Methylation was performed by adding 1.25 g (13.2 mmol) of methyl bromide in 5 mL of THF. Workup and purification as in the case of entry 6 gave 1.94 g (Y = 94%, P = 98.2%) of **8b** whose spectra were identical with those of **8a** of entry 4.

Entry 8. The reaction was repeated at −65 to −70 °C using 1.95 g (10.0 mmol) of **1c** and 7.2 g (22.5 mmol) of *n*-butyllithium and 1.50 g (10.6 mmol) of methyl iodide in a manner similar to that of entry 1. The structure of the small amount of products (**3c, 7c, 8c**) was estimated on the basis of GC−MS analysis of the crude reaction mixture. **3c**: *m*/*z* = 209 (M^+), 125 ($M^+ - COC_4H_9$). **7c**: *m*/*z* = 175 (M^+), 160 ($M^+ - CH_3$), 133 ($M^+ - CH_3 - HCN$). **8c**: *m*/*z* = 189 (M^+), 174 ($M^+ - CH_3$), 147 ($M^+ - CH_3 - HCN$).

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