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A study on the metalation of fluorinated phenyl benzyl ethers

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Lithiation of a series of aryl benzyl ethers containing fluorine atoms or CF_3- group in the phenolic ring has been studied. It was found that the long-distance inductive effect (two fluorine atoms in 2,6- or 2,3-position to the oxygen) and the cooperation of the coordination and inductive effects (fluorine atom or CF_3- group *meta* to oxygen atom) are the main factors directing *ortho*lithiation. Dilithiation of aryl benzyl ethers by butyllithium is generally less effective, but in the presence of PMDTA occurs efficiently and gives compounds containing lithium atoms at the phenyl ring and in the benzylic position. 2,3-Difluoro-benzyloxybenzene was dilithiated using BuLi–PMDTA complex and the intermediate was trapped with Me_3SiCl to give disilylated product in high yield. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: aryl benzyl ether; butyllithium; dilithiation

INTRODUCTION

Lithiation is one of the most powerful methods of the functionalization of organic molecules. Many biologically important compounds have been synthesized by applying organolithium chemistry. Flurbiprofen (anti-inflammatory) was synthesized from 3-fluorotoluene via *ortho* and benzylic lithiation as key steps.[1] Snieckus synthesized ochratoxine (a metabolite of *Aspergillus ochraceus* and *Penicillium viridicatum*) from 4-chlorophenol using a series of directed *ortho* lithiations.[2] The other examples involve the *ortho* lithiation of 1,2-methylenedioxybenzoic acid to obtain corydalic acid methyl ester,[3] *ortho* lithiation of 2-chloropyridine in the synthesis of the antibiotic atpenin B,[4] benzylic metalation of *p*-xylene in the synthesis of ibuprofen[5] and (−)-sparteine assisted enantioselective lithiation of carbamate derivative of *n*-dodecanol.[6] In all mentioned examples the key step relies upon *ortho* or benzylic lithiation (Fig. 1).

In our recent paper we described the lithiation of a series of aryl benzyl ethers (ABE) containing $-OCH_3$ and $-F$ substituents.[7] Lithiated ABEs are valuable starting materials in the synthesis of functionalized arylboronic acids, which are widely used in the preparation of biaryls.[8] In our work we showed that the presence of two types of centres that can be easily metalated (the aromatic ring and the benzylic position) causes some difficulties in prediction of the reaction course. The benzylic lithiation can decrease the amount of desired *ortho* lithiated product, but it gives also the possibility of synthesizing dilithiated ABEs, which can serve as starting materials in the synthesis of more advanced organic molecules. However, the molecule of ABE can be selectively lithiated on the phenyl ring when it contains a fluorine atom *meta* to the oxygen, or two fluorine atoms in a *meta* orientation. In this paper we present the results of our study on the metalation of **4–9** containing $-F$ or $-CF_3$ substituents on the phenyl ring (Fig. 2).

It is interesting to compare the reactivity of ABEs with the reactivity of fluoroanisoles. It is known that both 2- and 4-fluoroanisole can be selectively lithiated by BuLi in the position *ortho* to the —OCH_3 group or by BuLi–PMDTA or BuLi–t-BuOK mixture in the position *ortho* to the fluorine.[9] The lithiation by BuLi is effective but very slow, showing that the $-OCH_3$ group does not activate strongly the *ortho* hydrogen atoms. Since fluorine atom itself shows only weak ability to activate towards ortolithiation,[10] the reaction in the presence of PMDTA is much faster because PMDTA increases the metalation power of BuLi decreasing its aggregation state.[11] The key point in the study on the mechanism of the lithiation of arenes was the work by Bauer,[12] who found that the lithiation can be coordination or acidity driven. The selectivity of the lithiation is also controlled by the

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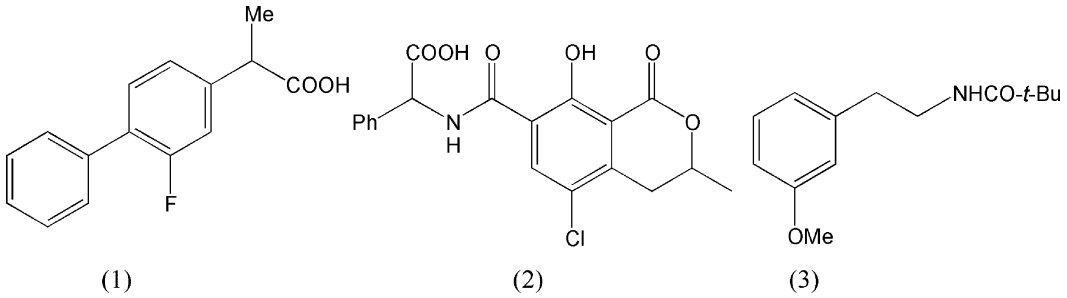

Figure 1. The known compounds obtained using lithiation as a key step.

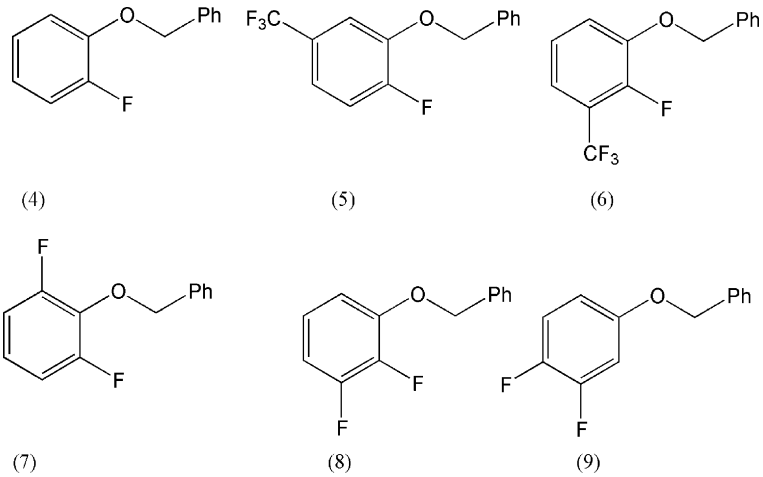

Figure 2. Starting materials.

steric hindrance. Schlosser metalated substituted anisole **3** and he found that BuLi lithiates *ortho* to –OMe at the site where coordination to the amide group is possible; *t*-BuLi at the benzylic site and the bulky *t*-BuLi–t-BuOK prefer to lithiate at the less hindered site *ortho* to –OMe.[13] Treatment with BuLi–t-BuOK is also the most efficient way to metalate trifluoromethylbenzene.[14]

RESULTS AND DISCUSSION

During the lithiation of **4**[15] with BuLi, we discovered that the reaction is not selective and gives a mixture of products after trapping with MeI. The analysis of the ^{1}H-NMR (400 MHz) spectrum of the reaction mixture confirmed that **4** undergoes the lithiation mainly at the benzylic position to give **4a** in the mixture with a few other products which were not analyzed. Integration of the methylene proton signals confirmed that 18.5% of **4** remained unreacted. This result shows that the *ortho* hydrogens in **4** are not adequately activated by the fluorine or oxygen atoms and the formation of thermodynamic stable **4a** is preferred. However, the reactivity of the *ortho* hydrogen in **4** can be increased by the use of the more basic metalating agent. For BuLi–PMDTA complex the reactivity of the hydrogen atom *ortho* to the fluorine is similar to the reactivity of benzylic hydrogen and the mixture of **4a, 4b** and the unreacted **4** is formed. Similar results were obtained after the use of *t*-BuLi as the metalating agent. However, dilithiation of **4** with 2 mol of BuLi–PMDTA occurs only in moderate yield (20%) to give after methylation with MeI the desired **4c** (Fig. 3).

Overall, **4** cannot be lithiated completely and we observed the unreacted substrate even after 24 h of stirring independent of the type of the metalating reagent. However, the introduction of the weak activating CF_3 group into the position *meta* to oxygen atom changes the reactivity drastically and **5** can be lithiated selectively between the oxygen atom and the CF_3 group using BuLi. After methylation with MeI we isolated **5a** quantitatively. The regioselectivity in metalation of **5** is achieved by cooperation of complexation and inductive effects (Fig. 4).

The CF_3 group itself, however, is not a very strong activator towards *ortho* lithiation and **6** is metalated by BuLi to give after methylation with MeI **6a** only a 40% yield. In order to improve the yield, we tried to apply BuLi–tBuOK mixture as a metalating reagent, but after treatment with MeI we isolated a thick, brown oil, which did not contain any amount of **6a**. Probably the lithiated intermediate is unstable and undergoes a side reaction before the addition of MeI.

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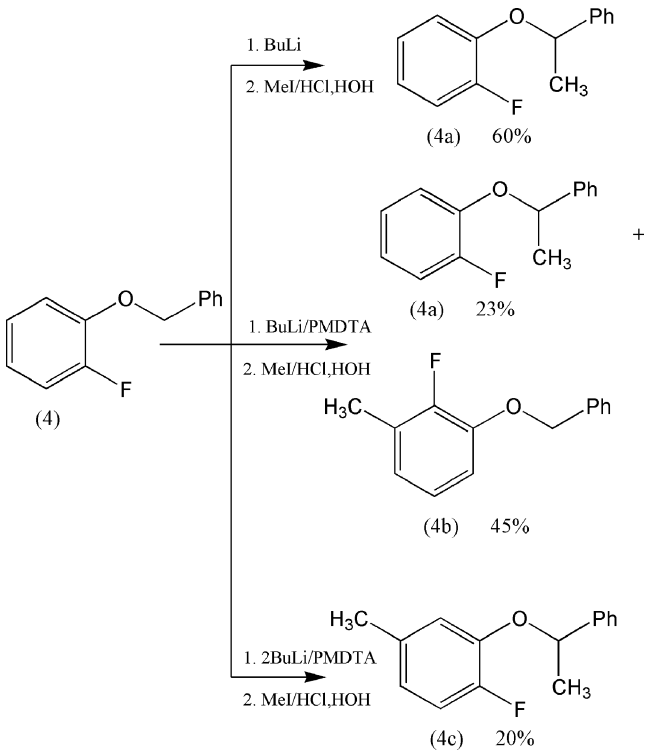

Figure 3. BuLi-mediated metalation of 2-fluorophenyl benzyl ether.

Contrary to the above result, lithiation of **7, 8** and **9** by BuLi occurs efficiently and gives **7a** (78%), **8a** (68.5%) and **9a** (92%) after treatment of the intermediates with DMF (Figs 5 and 6).

The difference between the reactivity of **4** containing one fluorine atom and **7, 8** containing two fluorine atoms is probably achieved by the inductive effect of the remote fluorine atom. This effect does not play any role during lithiation of **6** because the CF_3- group is a weaker activator than fluorine atom. In **9**, however, the coordination effect caused by the oxygen atom directs the selectivity. We found that the regioselectivity depends on the addition order of reagents. When the lithiation of **7** or **8** is carried out in the presence of the excess of BuLi, a complicated mixture of products is formed. The addition order does not play any role during lithiation of **9**. Treatment of **7** with 2 mol of BuLi does not have any synthetic potential. The analysis of the ^{1}H-NMR (400 MHz) spectrum of the reaction mixture after trapping the metalated species with MeI showed that the desired **7c** (^{1}H-NMR benzyl and methyl resonances: q, 5.16; t, 2.13; d, 1.62) was formed in very low yield and the reaction mixture contained mainly **7b**. Prolonged exposure of **7** to the metalation conditions (5 h) did not increase the amount of **7c** but the amount of **7b** increased by 5%. This result indicates that the benzylic lithiation in **7** is much slower than lithiation *ortho* to the fluorine, and dilithiation does not proceed quantitatively. During dilithiation of **7** we did not observe any formation of 3,5-dilithiated intermediates. This reaction should be thermodynamically favored according to semi-empirical calculations.[16] However, **7** can be lithiated twice, introducing two different electrophiles sequentially to give **7d** in high yield. The use of coordinating solvent is an effective way of making dilithiated ABEs. Treatment of **8** with 2 mol of BuLi–PMDTA mixture and the subsequent addition of 2 mol of Me_3SiCl gave **8b** in a satisfactory yield (78%). The ^{1}H-NMR analysis of the product confirmed that the hydrogen atom *ortho* to the fluorine and benzylic hydrogen atom were removed. We did not observe any lithiation *ortho* to the oxygen atom and we conclude that the reaction is under kinetic control (benzylic hydrogen atom in **8** more acidic than the hydrogen atom *ortho* to the oxygen).

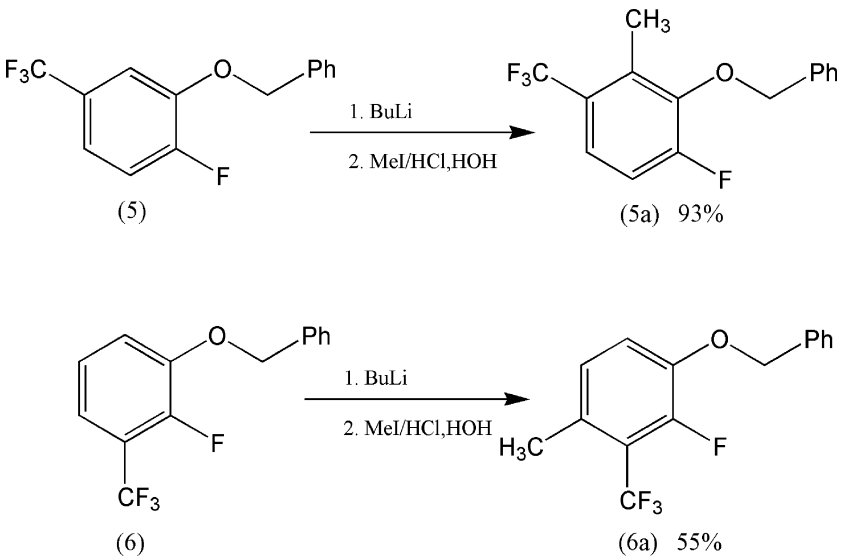

Figure 4. The influence of the position of -CF3 group on the regioselectivity of metalation.

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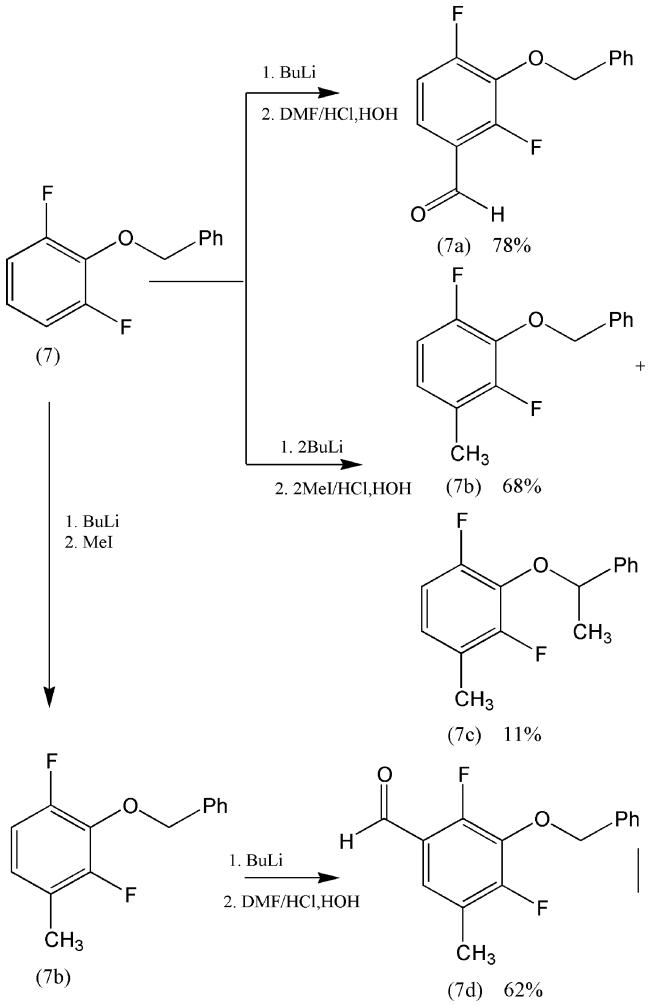

Figure 5. BuLi-mediated two step metalation of 2,6-difluorophenyl benzyl ether.

CONCLUSION

In summary, our experiments revealed that ABEs containing two fluorine atoms in the phenolic ring in 2,3 or 2,6 orientation are activated enough to undergo clean *ortho* lithiation. This activation is probably caused by the inductive effect of the remote fluorine atom. The use of 2 mol of metalating reagent generates dilithiated intermediates containing lithium atoms in the phenyl ring and in the benzylic position, but yield is satisfactory only when PMDTA is used as a coordinating solvent. The remote fluorine atom activation effect does not work when the CF_{3-} group and fluorine atom are in *ortho* orientation, as in **6**. The lithiation *ortho* to CF_{3-} group requires an additional activation which can be achieved, for example, by coordination of the metalating reagent molecule close to the reaction centre by oxygen atom lone pairs like in **5**. For ABEs which do not contain any respective number of fluorine atoms in a proper orientation like in **4**, the activation towards *ortho* lithiation can be also achieved by the use of more basic metalating reagents, but the benzylic lithiation still competes with *ortho* lithiation.

GENERAL PROCEDURE FOR LITHIATION AND REACTION WITH ELECTROPHILES

A 0.05 mol aliquot of the respective ABE was dissolved in 100 ml of THF and the solution was cooled to −68 °C. Into this cooled solution 0.05 mol of BuLi was dropped, maintaining the temperature below −60 °C. The reaction mixture was stirred for 2 h to complete the reaction. Next 0.05 mol of an electrophile (MeI, DMF) was added while maintaining the temperature below −60 °C. The reaction mixture was heated to −40 °C and mixed with water and then acidified to pH = 6. The organic phase was extracted with diethyl ether (2 × 50 ml) and the extract was evaporated to give crude products which were analyzed by NMR. The products were next distilled using vacuum distillation apparatus or purified by recrystallization from hexane and dried in vacuum. Yields are given after purification.

2-Fluoro-(α-methyl-benzyloxy)-benzene (4a)

Analysis: b.p. = 81–82 °C (1 mmHg); ^{1}H-NMR: 7.47 (m, 6H), 7.12 (m, 2H), 6.76 (m, 1H), 5.42 (q, 1H), 1.78 (d, 3H); anal. calcd for $C_{14}H_{13}OF$: C, 77.77; H, 6.02; found: C, 77.91; H, 6.08.

2-Fluoro-3-methyl-benzyloxybenzene (4b)

Analysis: b.p. = 86–89 °C (1 mmHg); ^{1}H-NMR: 7.42 (m, 2H), 7.36 (m, 2H), 6.88 (m, 3H), 6.75 (m, 1H), 5.11 (s, 2H), 2.27 (d, 3H); anal. calcd for $C_{14}H_{13}OF$: C, 77.77; H, 6.02; found: C, 77.89; H, 6.07.

2-Fluoro-3-methyl-(α-methyl-benzyloxy)-benzene (4c)

Analysis: b.p. = 91–93 °C (1 mmHg); ^{1}H-NMR: 7.45 (m, 2H), 7.34 (m, 2H), 6.80 (m, 3H), 6.78 (m, 1H), 5.30 (q, 1H), 2.25 (d, 3H), 1.67 (d, 3H); anal. calcd for $C_{15}H_{15}OF$: C, 78.26; H, 6.52; found: C, 78.48; H, 6.61.

2-Fluoro-6-methyl-5-trifluoromethyl-benzyl-oxybenzene (5a)

Analysis: m.p. = 61–62 °C; ^{1}H-NMR: 7.39 (m, 5H), 7.07 (m, 2H), 5.12 (s, 2H), 2.31 (d, 3H); ^{13}C-NMR: 153.1 (d, J^1_{C-F} = 248.7 Hz), 146.8, 135.8, 128.7, 128.3, 127.5, 126.6, 125.8, 123.8, 120.4, 109.8, 71.4, 14.5; anal. calcd for $C_{15}H_{12}OF_4$: C, 63.38; H, 4.22; found: C, 63.41; H, 4.25.

2-fluoro-4-methyl-3-trifluoromethyl-benzyloxy-benzene (6a)

Analysis: b.p. = 84–87 °C (1 mmHg); ^{1}H-NMR: 7.43 (m, 2H), 7.38 (m, 2H), 7.25 (m., 2H), 6.98 (m, 1H), 5.17 (s, 2H), 2.24 (s, 3H); anal. calcd for $C_{15}H_{12}OF_4$: C, 63.38; H, 4.22; found: C, 63.57; H, 4.35.

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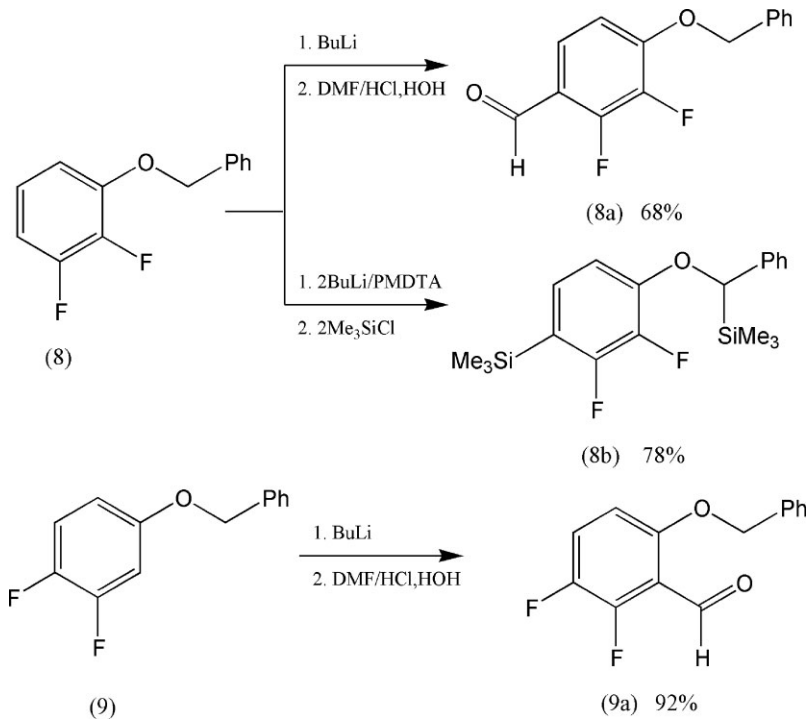

Figure 6. The influence of the position of fluorine atoms on the regioselectivity of metalation.

2,6-difluoro-3-formyl-benzyloxybenzene (7a)

Analysis: m.p. = 61.5–63.0 °C; ^{1}H-NMR: 10.24 (d, 2H), 7.55 (m, 1H), 7.44 (m, 2H), 7.36 (m, 3H), 6.99 (m, 1H), 5.22 (s, 2H); ^{13}C-NMR: 185.7, 160.4 (dd, J^1_{C-F} = 258.6 Hz), 158.8 (dd, J^1_{C-F} = 252.0 Hz), 135.7, 135.3, 128.7, 128.6, 128.3, 122.9, 121.6, 112.9, 76.3; anal. calcd for $C_{14}H_{10}O_2F_2$: C, 67.74; H, 4.03; found: C, 67.31; H, 3.98.

2,6-Difluoro-3-methyl-benzyloxybenzene (7b)

Analysis: b.p. = 71–72 °C (1 mmHg); ^{1}H-NMR: 7.46 (m, 2H), 7.38 (m, 3H), 6.76 (m, 1H), 5.14 (s, 2H), 2.21 (t, 3H); anal. calcd for $C_{14}H_{12}OF_2$: C, 71.79; H, 5.13; found: C, 71.94; H, 5.21.

2,6-Difluoro-3-formyl-5-methyl-benzyl-oxybenzene (7d)

An 11.0 g (0.05 mol) aliquot of **7** was dissolved in 100 ml of THF and the solution was cooled to −68 °C. Into this cooled solution, 5 ml (0.05 mol) of 10 M BuLi solution in hexane were dropped, maintaining the temperature below −60 °C. The reaction mixture was stirred for 2 h to complete the reaction. Next 7.1 g (0.05 mol) of MeI were added while maintaining the temperature below −60 °C. The reaction mixture was stirred for 0.5 h to complete the reaction The next 0.05 mol portion of BuLi was dropped in while maintaining the temperature below −60 °C. After 2 h of stirring, 3.65 g (0.05 mol) of DMF was dropped in, maintaining the temperature below −60 °C. The reaction mixture was heated to −40 °C and mixed with 50 ml of water and then acidified to pH = 6. The organic phase was extracted with diethyl ether (2 × 50 ml) and the extract was evaporated to give 12.1 g of crude product which was recrystallized from hexane and dried in vacuum to give 8.1 g (yield 62%) of **7d**.

Analysis: m.p. = 44.7–46.0 °C; ^{1}H-NMR: 10.22 (s, 1H), 7.38 (m, 6H), 5.19 (s, 2H), 2.26 (t, 3H, J = 1.6 Hz); ^{13}C-NMR: 186.0, 159.0 (dd, J^1_{C-F} = 257.1 Hz), 157.0 (dd, J^1_{C-F} = 258.6 Hz), 136.0, 135.1, 128.6, 128.5, 128.3, 123.6, 122.6, 120.6, 76.3, 14.2; anal. calcd for $C_{15}H_{12}O_2F_2$: C, 68.70; H, 4.58; found: C, 68.47; H, 4.58.

2,3-Difluoro-4-formyl-benzyloxybenzene (8a)

Analysis: m.p. = 69.3–70.7 °C; ^{1}H-NMR: 10.19 (s, 1H), 7.58 (m, 1H), 7.42 (m, 5H), 6.89 (s, 1H), 5.24 (s, 2H); ^{13}C-NMR: 185.2, 153.5 (dd, J^1_{C-F} = 259.4 Hz), 153.5, 140.8 (dd, J^1_{C-F} = 250.2 Hz), 135.0, 128.8, 128.6, 127.4, 123.6, 118.9, 109.8, 71.6; anal. calcd for $C_{14}H_{10}O_2F_2$: C, 67.74; H, 4.03; found: C, 67.84; H, 3.93.

2,3-Difluoro-4-trimethylsilyl-(α-trimethylsilyl-benzyloxy)-benzene (8b)

An 11.0 g (0.05 mol) aliquot of **8** was dissolved in 100 ml THF and the solution was cooled to −68 °C. Into this cooled solution 10 ml (0.1 mol) of 10 M BuLi solution in hexane was dropped, maintaining the temperature below −60 °C. The reaction mixture was stirred for 2 h to complete the reaction. Next 10.9 g (0.1 mol) of Me_3SiCl were added while maintaining the temperature below −60 °C. The reaction mixture was heated to −40 °C, mixed with water and then neutralized to pH = 7. The organic phase was extracted with diethyl ether (2 × 50 ml) and the extract was evaporated to

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give 18.0 g of yellow oil which crystallized after one day. The crude product was recrystallized from hexane and dried in vacuum to give 14.2 g (yield 78%) of **8b**.

Analysis: m.p. = 77.6–79.5 °C; ^{1}H-NMR: 7.30 (m, 2H), 7.18 (m., 3H), 6.80 (m, 1H), 6.57 (m, 1H), 4.94 (s, 2H), 0.25 (s, 9H), 0.11 (s, 9H); ^{29}Si-NMR: 3.73, −4.35; ^{13}C-NMR: 155.2 (dd, $J^1_{C-F} = 240.3$), 150.4, 141.3 (dd, $J^1_{C-F} = 249.4$ Hz), 140,0, 128.4, 127.7, 126.1, 124.8, 118.7, 110.8, 77.6, −1.0, −4.1; anal. calcd for $C_{19}H_{26}OF_2$: C, 62.64; H, 7.14; found: C, 62.19; H, 6.98.

3,4-Difluoro-2-formyl-benzyloxybenzene (9a)

Analysis: m.p. = 74–75 °C; ^{1}H-NMR: 10.46 (t, 1H), 7.41 (m, 4H), 7.36 (m, 1H), 7.31 (m., 1H), 6.76 (m, 1H), 5.17 (s, 2H); ^{13}C-NMR: 186.7, 156.6, 150.2 (dd, $J^1_{C-F} = 263.9$ Hz), 145.0 (dd, $J^1_{C-F} = 242.7$ Hz), 135.3, 128.8, 128.5, 127.2, 122.4, 115.7, 108.2, 71.4; anal. calcd for $C_{14}H_{10}O_2F_2$: C, 67.74; H, 4.03; found: C, 67.77; H, 4.06.

Acknowledgments

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