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# Regioselective Approach to Multisubstituted Benzenes

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Various multisubstituted benzenes were synthesized in highly chemo- and regioselective manners via nucleophilic aromatic substitution and *ortho*-metalation from 1,3,5-trifluorobenzene.

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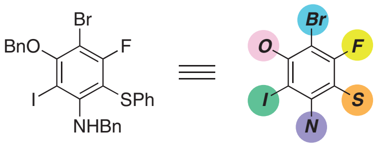
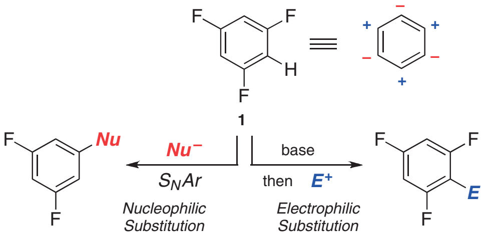
Highly substituted benzene is an attractive structural motif in organic chemistry.[1] Despite the numerous synthetic methods for aromatic compounds developed so far, it remains difficult for site-specific installation of multiple functionalities to a benzene nucleus.[2] We became interested in this topic, as a literature search[3] showed that *no precedent for six or even five different substituents on a benzene ring other than C and H has been recorded* (Scheme 1).

We report herein facile regioselective synthesis of such benzene derivatives by exploiting 1,3,5-trifluorobenzene (**1**) as the platform to achieve this goal. Alternate potential polarity pattern results from two key reactivities provided by fluorine atom(s) on a benzene ring; (1) nucleophilic aromatic substitution ($S_NAr$) facilitated by the strong electronegativity of fluorine[4] and (2) electrophilic substitution via lithiation, where a fluorine atom acts as a strong *ortho*-metalation director (Scheme 2).[5]

1,3,5-Trifluorobenzene (**1**) was treated with benzyl alkoxide[6] (1.1 equiv, 0 °C, NMP, 3 h), where one of fluorine atoms was smoothly replaced to give ether **2** in 87% yield (Scheme 3). Ether **2** was lithiated with LDA (−78 °C, THF, 1 h), to which was added phenyl benzenethiosulfonate[7] affording sulfide **3**. The lithiation predominantly occurred at the most acidic proton between two fluorine atoms. Although a small amount of regioisomer and disulfide were also produced, these were separable by silica gel column chromatography or recrystallization (AcOEt/hexane), allowing clean isolation of sulfide **3**.[8,9]

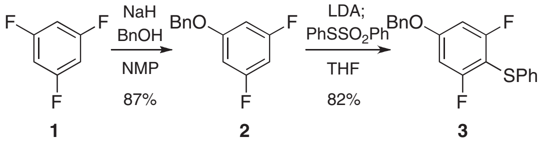


**Scheme 1.** Highly functionalized benzene with six-different hetero substituents.



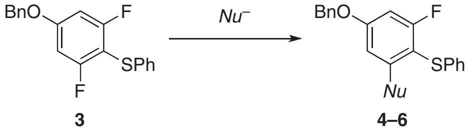
**Scheme 2.** Characteristic reactivity of 1,3,5-trifluorobenzene.

For the third substitution, the $S_NAr$ reaction of difluoride **3** was carried out with several nucleophiles (Table 1).[9] Phenol **4** was obtained in excellent yield by treatment of **3** with 2-(methylsulfonyl)ethanol in the presence of NaH (Run 1).[10] Nitrogen nucleophiles were also introduced by using the amide anions derived from aniline or benzylamine to give aniline derivatives **5** and **6** in high yields (Runs 2 and 3). Compounds **4**–**6** were used as the platforms for accessing penta- and hexa-substituted benzenes.



**Scheme 3.** $S_NAr$ reaction and *ortho*-metalation.

**Table 1.** $S_NAr$ reaction of oxygen and nitrogen nucleophiles[a]

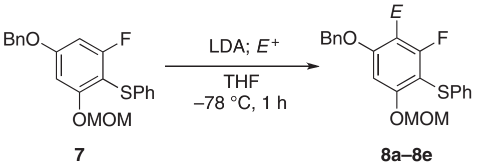


| Run | Reagent | Base | *Nu* | Product | Yield/% |
|---|---|---|---|---|---|
| 1 | $MeSO_2(CH)_2OH$ | NaH | OH | **4** | 92 |
| 2 | $PhNH_2$ | KH | NHPh | **5** | 98 |
| 3 | $BnNH_2$ | *n*-BuLi | NHBn | **6** | 88 |

[a] For detailed reaction conditions, see Supporting Information.[9]

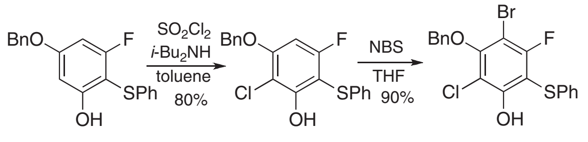
For the regioselective functionalization of tetra-substituted benzene **7**, derived from phenol **4**, we could exploit the directing ability of a fluorine atom superior to a MOMO group (Table 2).[5b] MOM ether **7** underwent the *ortho*-metalation (LDA, 1.1 equiv, THF, −78 °C, 1 h), and trapping with

**Table 2.** Regioselective substitution via direct *ortho*-metalation[a]



| Run | Reagent | *E* | Product | Yield/% |
|---|---|---|---|---|
| 1 | $CH_3I$ | $CH_3$ | **8a** | 83 |
| 2 | $CF_3SO_2Cl$[b] | Cl | **8b** | 96 |
| 3 | $I_2$ | I | **8c** | 82 |
| 4 | $Me_3SiCl$ | $SiMe_3$ | **8d** | 77 |
| 5 | $Ph_2PCl$ | $PPh_2$ | **8e** | 49 |

[a] Reaction conditions: LDA (1.1 equiv), reagent (1.5 equiv).
[b] 2.0 eqiuv.



**4** **9** **10**

**Scheme 4.** Regioselective synthesis of hexa-substituted benzene **10**.

iodomethane (1.5 equiv) afforded **8a** as a single product (Run 1). By similar protocols, various substituents were installed by trapping with $CF_3SO_2Cl$,[11] $I_2$, TMSCl, and $Ph_2PCl$ gave the respective products in good yields (Runs 2–5).

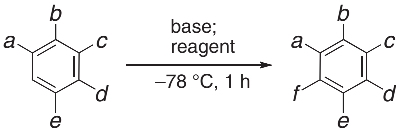
Scheme 4 illustrates the synthesis of a hexa-substituted benzene derivative with six different hetero substituents. Starting with phenol **4**, regioselective introduction of the fifth substituent was achieved by taking advantage of the reactivity difference of the two remaining positions. Treatment of phenol **4** with sulfuryl chloride in the presence of diisobutylamine gave **9**, where a chlorine atom was selectively introduced at the *ortho*-position to the phenol.[12] Bromination of **9** by using *N*-bromosuccinimide (NBS) gave benzene **10** possessing six different hetero substituents.[9]

Table 3 shows examples of the synthesis of various hexa-substituted benzenes via the *ortho*-metalation.[9] The reaction of **8a** with *n*-butyllithium (1.1 equiv) followed by the addition of iodine (1.5 equiv) gave the corresponding hexa-substituted benzene **12a** in 58% yield as a single product (Run 1). In this case, *n*-butyllithium is essential for the deprotonation. The same protocol was applied to other penta-substituted benzenes to give the respective hexa-substituted product (Runs 2–5). LDA was used for lithiating the position next to a fluorine atom. The reaction of benzyl ether **11**, derived from phenol **9**, using LDA and iodine gave iodide **12f** in excellent yield (Run 6). Methylation proved possible (Run 7) and, especially, stannane **12h** was also obtained in 73% yield (Run 8), which would be a useful compound for further transformation.

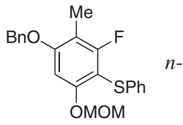
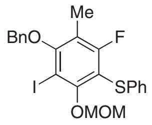
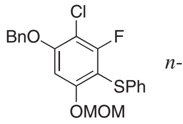
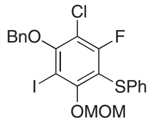
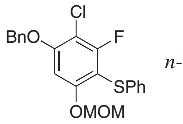
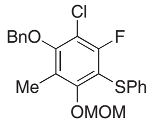
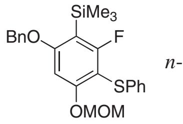
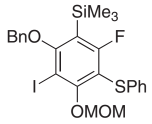
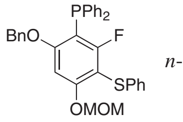
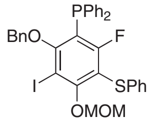
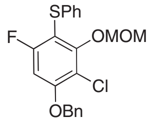
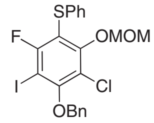
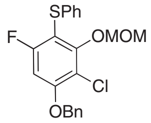
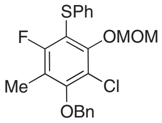
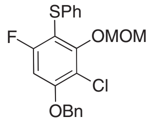
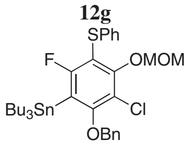
As an optional way for the regioselective hexa-substitution, electrophilic halogenation was effective (Scheme 5). Starting with **6** derived from benzylamine, the reaction with NBS gave the regioselectively brominated compound **13a** in excellent yield. Iodination by using *N*-iodosuccinimide (NIS) gave **14a**.[13] On the other hand, the reversed order of the halogenations was also possible, i.e., the chlorination (NCS) followed by the bromination (NBS) afforded hexa-substituted benzene **14b**. These compounds are the first examples of hexa-substituted benzene, which has all different hetero-substituents.[9]

All products could be readily characterized by $^1H$ NMR spectroscopy, where the fluorine atoms served as a clue for the assignments by the aid of H–F couplings. The *ortho* H–F coupling constants in fluorobenzenes are in a range of 6–10 Hz, while 0–1 Hz of the *para* H–F coupling constant.[14] The structures of **13a** and **14a** were also determined by single-crystal X-ray analyses (Figure 1).[15] The benzene ring in **13a** was planar, but apparently suffering distortion; the interior angle of the fluorine-substituted carbon was slightly wider (124°), and the C–C bond length of C1–C2 (1.37 Å) was relatively shorter than benzene.[4a,16] However, these tendencies decreased in hexa-substituted benzene **14a**.

**Table 3.** Synthesis of hexa-substituted derivatives via *ortho*-metalation[a]

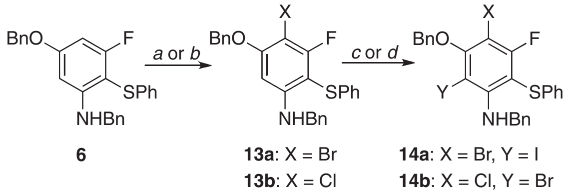


**8a–8e 11** **12a–12h**

| Run | Substrate | Base | Reagent | Product | Yield/% |
|---|---|---|---|---|---|
| 1 |  **8a** | *n*-BuLi | $I_2$ |  **12a** | 58 |
| 2 |  **8b** | *n*-BuLi | $I_2$ |  **12b** | 56 |
| 3 |  **8b** | *n*-BuLi | MeI |  **12c** | 32 |
| 4 |  **8d** | *n*-BuLi | $I_2$ |  **12d** | 14 |
| 5 |  **8e** | *n*-BuLi | $I_2$ |  **12e** | 66 |
| 6 |  **11** | LDA | $I_2$ |  **12f** | 97 |
| 7 |  **11** | LDA | MeI |  **12g** | 98 |
| 8 |  **11** | LDA | $Bu_3SnCl$ |  **12h** | 73 |

[a]Reaction conditions: *n*-BuLi or LDA (1.1 equiv), reagent (1.5 equiv).

Moreover, after transformation to sulfoxide **15** from sulfide **12f**, the remaining fluoro group could also be replaced by a hydroxy group via the $S_NAr$ reaction (Scheme 6). The compound **16** would serve as a promising building block for total synthesis of natural phluoroglucinol derivatives, because three hydroxy groups are fully distinguished.[9]



**Scheme 5.** Hexa-substituted benzenes via electrophilic halogenation. Conditions: a) NBS (1.1 equiv), $CH_2Cl_2$, 0 °C, 2.5 h (quant.). b) NCS (1.8 equiv), $CH_2Cl_2$, 0 °C → room temp., 3 d (69%). c) NIS (1.1 equiv), $TsOH\cdot H_2O$ (1.5 equiv), $CH_2Cl_2$, 0 °C, 24 h (14%). d) NBS (1.1 equiv), $CH_2Cl_2$, 0 °C → room temp., 24 h (32%).

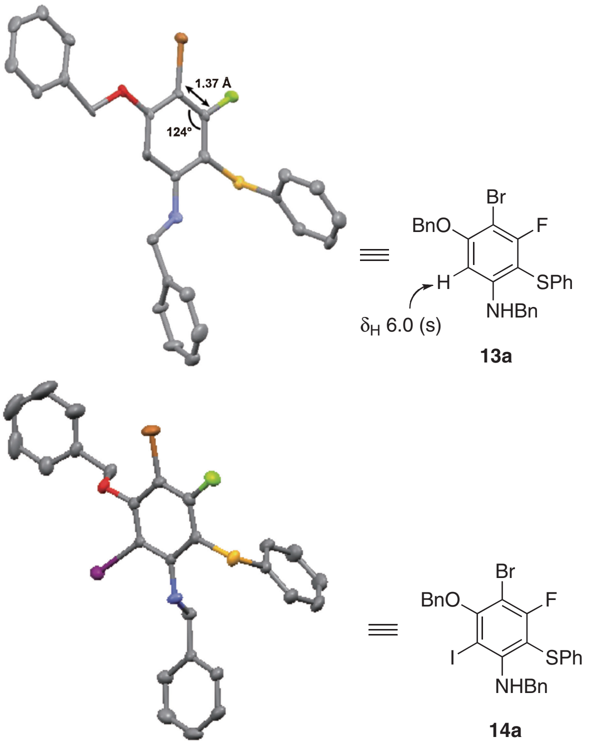
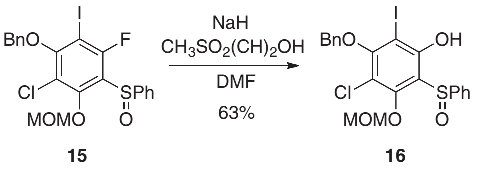


**Figure 1.** X-ray structures of **13a** and **14a** (Hydrogens are omitted for clarity).



**Scheme 6.** Synthesis of phluoroglucinol derivative.

In conclusion, we have illustrated a facile regioselective synthesis of multisubstituted benzenes via combined use of nucleophilic aromatic substitution and *ortho*-metalation of fluoroarenes, which have various implications for designing functional molecules.

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## References and Notes

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