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Regioselective Approach to Multisubstituted Benzenes

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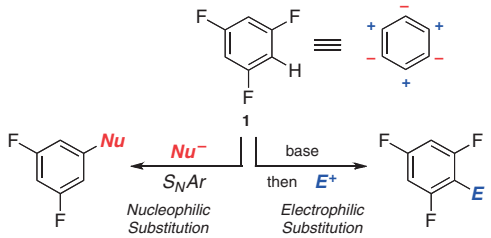
Various multisubstituted benzenes were synthesized in highly chemo- and regioselective manners via nucleophilic aromatic substitution and *ortho*-metalation from 1,3,5-trifluorobenzene.

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]

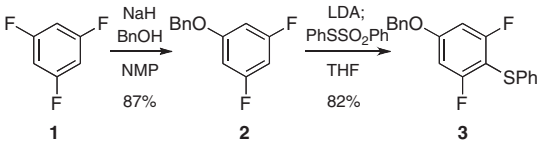
1,3,5-Trifluorobenzene (**1**) was treated with benzyl alkoxide[6] (1.1 equiv, 0 °C, NMP, 3 h), where one of fluorine atoms was smoothly replaced to give ether **2** in 87% yield (Scheme 3). Ether **2** was lithiated with LDA (−78 °C, THF, 1 h), to which was added phenyl benzenethiosulfonate[7] affording 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.



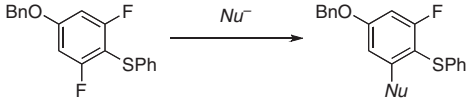
Scheme 2. Characteristic reactivity of 1,3,5-trifluorobenzene.

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]

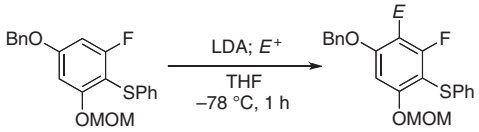


Run	Reagent	Base	*Nu*	Product	Yield/%
1	$MeSO_2(CH_2)_2OH$	NaH	OH	**4**	92
2	$PhNH_2$	KH	NHPh	**5**	98
3	$BnNH_2$	*n*-BuLi	NHBn	**6**	88

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

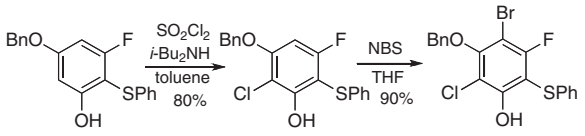
For the regioselective functionalization of tetra-substituted benzene **7**, derived from phenol **4**, we could exploit the directing ability of a fluorine atom superior to a MOMO group (Table 2).[5b] MOM ether **7** underwent the *ortho*-metalation (LDA, 1.1 equiv, THF, −78 °C, 1 h), and trapping with

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.



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).

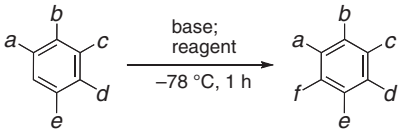
Scheme 4 illustrates the synthesis of a hexa-substituted benzene derivative with six different hetero substituents. Starting with phenol **4**, regioselective introduction of the fifth substituent was achieved by taking advantage of the reactivity difference of the two remaining positions. Treatment 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]

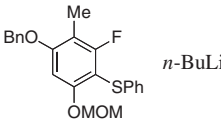
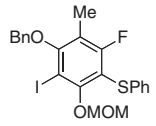
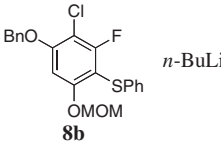
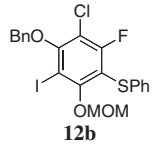
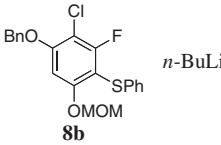
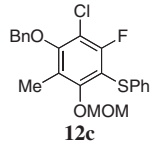
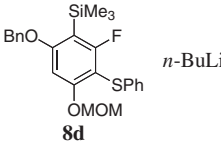
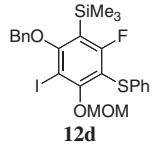
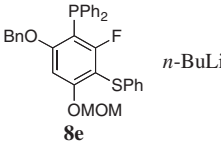
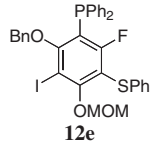
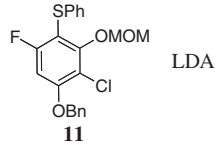
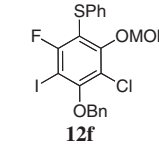
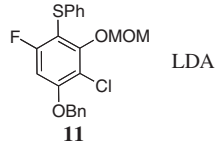
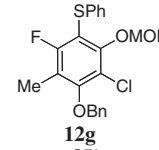
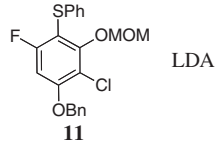
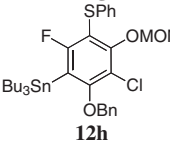
Table 3 shows examples of the synthesis of various hexa-substituted benzenes via the *ortho*-metalation.[9] The reaction of **8a** with *n*-butyllithium (1.1 equiv) followed by the addition of iodine (1.5 equiv) gave the corresponding hexa-substituted benzene **12a** in 58% yield as a single product (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 ^{1}H 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**.

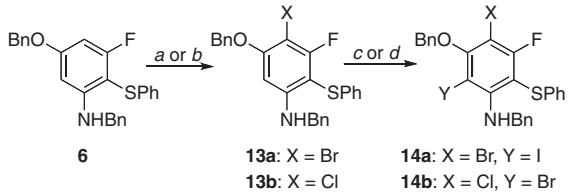
Table 3. Synthesis of hexa-substituted derivatives via *ortho*-metalation[a]



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%).

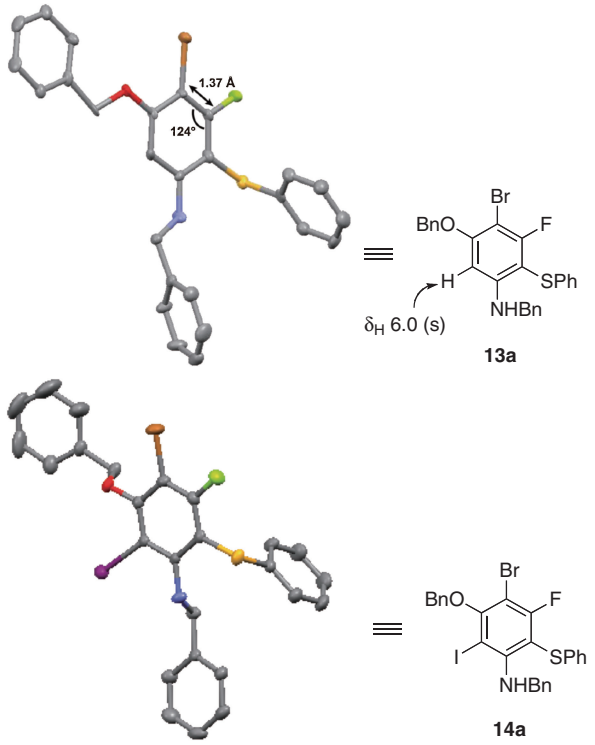
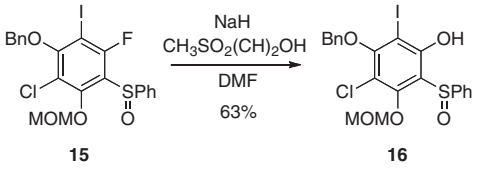


Figure 1. X-ray structures of **13a** and **14a** (Hydrogens are omitted for clarity).



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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8 Pure prisms of **3** were obtained by recrystallization (EtOAc and hexane), when the reaction was carried out in a gram scale. Thus, stating from 6.4 g of **2**, the product **3** was obtained in 67% yield (6.4 g) after recrystallization.
9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
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