



Directed *ortho* Metalation - mediated F⁺ Introduction. Regiospecific Synthesis of Fluorinated Aromatics

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Abstract: Regiospecific fluorination using *N*-fluorobenzenesulfonimide (NFSi) and *N*-fluoro-*O*-benzenedisulfonimide (NFOBS) reagents via directed *ortho* metalation (Scheme 1) is reported and exceptions of PhSO₂ transfer from NFSi are described.

The increasing and sustained interest in organofluorine compounds¹ related to biochemical/biological,² pharmacological,³ and material science⁴ research has had an explosive impact on the development of new synthetic methods for electrophilic and nucleophilic fluorine introduction.⁵ Of special value for the preparation of fluorinated aromatics and heteroaromatics, substances of paramount interest in pharmaceutical and agrochemical fields,⁶ is the evolution of new F⁺ sources⁷ which supercede the earlier, at times dangerous⁸ and not readily available,⁹ reagents for preparative scale fluorination. In this Letter, we report the reactions of *N*-fluorobenzenesulfonimide (NFSi)¹⁰ and *N*-fluoro-*O*-benzenedisulfonimide (NFOBS)¹¹ with *ortho* metalated aromatic and heteroaromatic substrates (1 → 2, Scheme 1) which allow regiospecific access to a variety of fluorinated products (Table). In view of the connection of this new methodology to the diversely evolving DoM strategy,¹² its broad utility in synthetic aromatic chemistry may be anticipated.

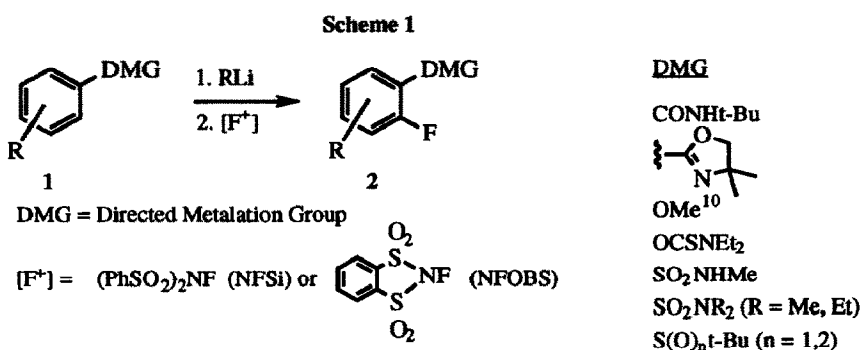
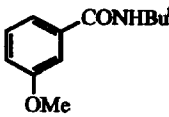
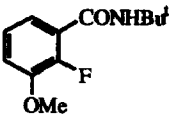
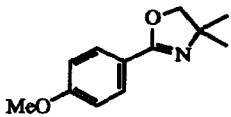
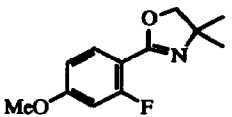
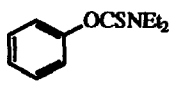
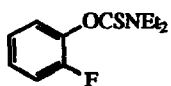
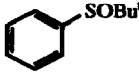
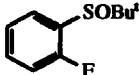
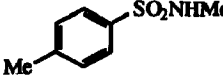
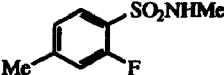
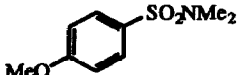
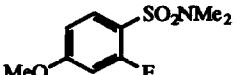
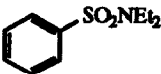
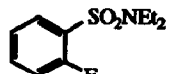
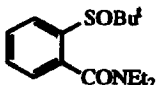
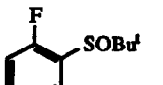
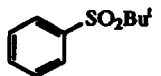
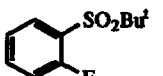
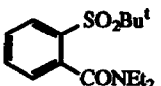
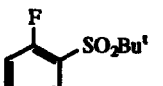


Table. Synthesis of *ortho*-Fluorinated Aromatics using NFSi and NFOBS Reagents

| Entry | Substrate | Conditions | F ⁺ reagent | Product | Yield, % ^a | ¹⁹ F NMR δ ppm ^b |
|-------|---|----------------------------|------------------------|--|-----------------------|---|
| 1 |  | 2 eq n-BuLi THF / 0°C | NFSi |  | 56 | -137.2 |
| 2 |  | 1 eq s-BuLi THF / -78°C | NFSi |  | 78 | -106.6 |
| 3 | | NFOBS | 48 | | | |
| 4 |  | 2 eq s-BuLi / TMEDA | NFSi |  | 62 | -127.9 |
| 5 | | THF / -78°C | NFOBS | | 0 | |
| 6 |  | 1 eq n-BuLi | NFSi |  | 74 | -120.0 |
| 7 | | THF / -78°C | NFOBS | | 70 | |
| 8 |  | 2 eq n-BuLi THF / -40°C | NFOBS |  | 71 | -112.6 |
| 9 |  | 1 eq n-BuLi | NFSi |  | 55 | -128.8 |
| 10 | | THF / -40°C | NFOBS | | 47 | |
| 11 |  | 1 eq n-BuLi THF / 0°C | NFSi |  | 52 | -117.9 |
| 12 |  | 1 eq n-BuLi | NFSi |  | 26 ^c | — |
| 13 | | THF / -78°C | NFOBS | | 31 ^c | |
| 14 |  | 1 eq n-BuLi | NFSi |  | 74 | -113.7 |
| 15 | | THF / -78°C | NFOBS | | 30 | |
| 16 |  | 1 eq n-BuLi | NFSi |  | 58 ^c | -108.4 |
| 17 | | THF / -78°C | NFOBS | | 31 ^c | |

^a Reported yields are of isolated, chromatographically purified materials. All new compounds show spectral (¹H, ¹³C NMR, IR, HRMS) and analytical data in accord with the depicted structure. ^b CFC13 reference. ^c Yield based on recovered starting material.

Selected results of reactions of NFOBS and NFSi with *ortho*-metalated DMG aromatics are summarized in the Table.¹³ Using metalation conditions appropriate for the specific DMGs, fluorination was achieved in modest to good yields with carbon-based (entries 1-3), oxygen-based (entries 4,5), and sulfur-based (entries 6-17) groups.¹⁴ Comparable yields of fluorinated products were obtained in parallel use of NFOBS and NFSi reagents, e.g. entries 6,7 and 9,10 with the exception of the *ortho*-lithiated O-thiocarbamate which was successful only with NFSi (compare entries 4 and 5).¹⁵ Preliminary experiments using NFOBS with several other *ortho*-lithiated DMG systems (OMOM, NHT-Boc, CONEt₂, OCONEt₂) failed to give fluorinated products while using NFSi for the corresponding CONEt₂ and OCONEt₂ systems led to PhSO₂ rather than F⁺ transfer.^{16,17,18} 2-Sulfone (entries 16,17) and sulfoxide (entries 12,13) benzamides give lower yields of products but demonstrate the previously established more powerful DMG character of sulfone and sulfoxide over tertiary amide.¹⁴

In summary, we have described a DoM-based method for the regiospecific introduction of fluoro substituents into aromatic substrates. With two exceptions (CONEt₂ and OCONEt₂),¹⁶ a range of *ortho*-lithiated carbon-, oxygen-, and sulfur-based DMG systems have been shown to undergo reaction with NFSi, a commercially available reagent, to provide regiospecifically fluorinated aromatic products. The application of this method to other DMG systems¹² and the connectivities with further DoM chemistry based on the fluoro DMG¹⁹ and with nucleophilic fluorine displacement,²⁰ are aspects of potential synthetic value some of which are under investigation in our laboratories.²¹

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