# Contra-Friedel–Crafts *tert*-butylation of substituted aromatic rings *via* directed metallation and sulfinylation†

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*Received (in Cambridge, UK) 6th January 2006, Accepted 2nd February 2006*
*First published as an Advance Article on the web 21st February 2006*
**DOI: 10.1039/b600181e**

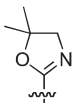
**Directed metallation and sulfinylation yields sulfoxides which undergo *ipso* nucleophilic aromatic substitution with tertiary and secondary alkyllithiums, giving aromatic rings bearing alkyl groups generally incompatible with directed metallation methods and with regioselectivity complementary with classical Friedel–Crafts substitution.**

The combination of electrophilic aromatic substitution,[1] nucleophilic aromatic substitution,[2] and directed metallation[3–5] provides chemists with the tools to elaborate aromatic rings with almost any pattern of substitution. Nonetheless, some limitations remain, and the one we address in this paper is the introduction of *t*-butyl groups. As part of a programme of research into sterically hindered atropisomers,[6] we needed to construct a variety of molecules carrying a *t*-butyl group *ortho* to pre-existing functionality: it is striking that no directed metallation-based method exists for *t*-butylation *ortho* to electron-withdrawing groups. *t*-Butyl electrophiles are of course too hindered to undergo substitution with most organometallics and elimination invariably competes. Commercially unavailable 2-*t*-butylbenzoic acid is currently best made *via* nucleophilic aromatic substitution of methoxide directed by an oxazoline substituent.[7]

In this Communication we describe a generally applicable method for the synthesis of *t*-butylated products *via* directed metallation, allowing the introduction of *t*-butyl groups *ortho* to either electron-withdrawing or -donating metallation directing groups ("DMG's"[4]). The reaction tolerates both electron-deficient and moderately electron-rich aryl ring functionality, and differs markedly from "classical" $S_NAr$ reactions in not requiring the ring to carry an additional anion-stabilising substituent.[8]

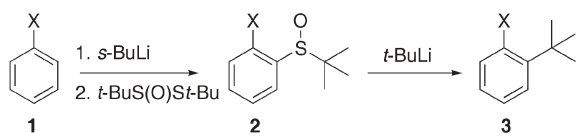
A range of arenes **1** carrying metallation-directing groups X were *t*-butylsulfinylated by ortholithiation followed by trapping with *t*-butyl *t*-butylthiosulfinate.[9] (Table 1). The *t*-butylsulfoxides **2** were treated with an excess of *t*-butyllithium and underwent substitution to yield *t*-butylated anisoles, benzamides and phenyloxazolines **3** (Scheme 1).[10] With electron-withdrawing tertiary amide and oxazoline substituents, excellent yields of *ortho*-*t*-butylated products **3a–3d** are obtained (entries 1–4). Substitution adjacent to the (anionic) secondary amide fails (entry 6), but 2-*t*-butyl secondary amide **3e** can be made by treatment of **3d**, which does undergo successful substitution, with acid (entry 5).[11] Remarkably, even 2-sulfinylanisole **2g** undergoes substitution with *t*-BuLi to yield 2-*t*-butylanisole **3g** in excellent yield (entry 7). 2-Sulfinylaniline **2h** is however apparently too electron-rich to undergo the substitution.

**Table 1** *ortho*-*t*-Butylation *via* sulfinylation

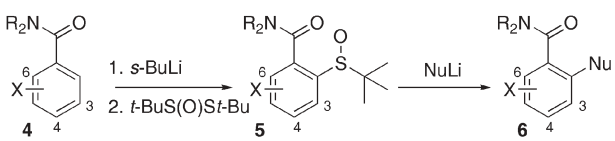
| Entry | X = | **2** yield (%) | **3** yield (%) |
|---|---|---|---|
| 1 |  | **2a** 56 | **3a** 73 |
| 2 | $CONEt_2$ | **2b** 63 | **3b** 100 |
| 3 | $CONi\text{-}Pr_2$ | **2c** 43 | **3c** 73 |
| 4 | CONMe*t*-Bu | **2d** 89 | **3d** 82 |
| 5 | CONHMe | — | **3e** 95[a] |
| 6 | CONH*i*-Pr | **2f** 69 | 0 |
| 7 | OMe | **2g** 40 | **3g** 75 |
| 8 | $NMe_2$ | **2h** 32[b] | 0 |

[a] From **3d** by treatment with acid. [b] Lithiation carried out with n-BuLi/TMEDA at reflux.

Because they combine acidification with powerful complexation-induced proximity effects,[12] electron-withdrawing groups such as amides and oxazolines are more powerful directors of metallation than electron-donating amino and alkoxy groups,[3,13] so our new *t*-butylation method inverts the usual electronic dependence of direct Friedel–Crafts alkylations.[14] Amides **4** substituted in various positions with electron-donating MeO, $Me_2N$ and *t*-$Bu_2P$ substituents were *t*-butylated *via* *t*-butylsulfoxides **5** (Scheme 2). In some hindered cases, yields in either the sulfinylation or *t*-butylation steps were low, but *t*-butylated products **6** were always formed with regioselectivity expected[3] for metallation of arenes carrying a strong ($CONR_2$) and a weak (MeO *etc.*) directing group (Table 2).




**Scheme 1** *t*-Butylation by substitution of a sulfinyl group.




**Scheme 2** Contra-Friedel–Crafts *t*-butylation.

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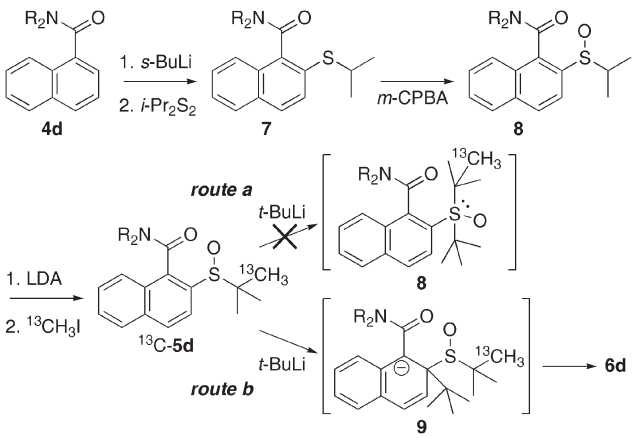
† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all new compounds. See DOI: 10.1039/b600181e

**Table 2** *t*-Butylation of substituted benzamides

| Entry | R = | X = | **5** yield (%) | Nu = | **6** yield (%) |
|---|---|---|---|---|---|
| 1 | *i*-Pr | 6-OMe | **5a** 72 | *t*-Bu | **6a** 46 |
| 2 | *i*-Pr | 3-OMe | **5b** 88 | *t*-Bu | **6b** 15 |
| 3 | *i*-Pr | 4-OMe | **5c** 85 | *t*-Bu | **6c** 79 |
| 4 | | | | *i*-Pr | **6c′** 50 |
| 5 | *i*-Pr | 5,6-benzo[a] | **5d** 64 | *t*-Bu | **6d** 58 |
| 6 | *i*-Pr | 3,6-$(OMe)_2$ | **5e** 15 | *t*-Bu | **6e** 77 |
| 7 | Et | 6-P*t*-$Bu_2$ | **5f** 49 | *t*-Bu | **6f** 9 |
| 8 | Et | 6-$NMe_2$ | **5g** 83 | *t*-Bu | **6g** 59 |
| 9 | | | | *s*-Bu | **6g′** 51 |
| 10 | | | | *n*-Bu | 0 |

[a] 1-Naphthamide.




**Scheme 3** Substitution by attack at C.

Two sulfoxides **5c** and **5g** were treated with other organolithiums (*s*-BuLi, *i*-PrLi, *n*-BuLi). The substitution was successful with the secondary organolithiums, but not the primary, providing complementarity with alkylation *via* direct trapping of ortholithiation, which works only with primary alkylating agents.

Two reasonable mechanisms can be envisaged for this reaction.[15] Substitution reactions of sulfoxides have generally been accounted for by assuming the formation of a σ-sulfurane intermediate which collapses either by "ligand coupling" (see Scheme 3 route *a*) or by loss of an anionic leaving group – "ligand exchange".[16–18] However, with *t*-butyl sulfoxides, attack on the sulfur centre is known to be slow,[17] and direct nucleophilic aromatic substitution of the *t*-butylsulfinyl group by attack of the alkyllithium at C (to yield intermediate **9**) may compete (Scheme 3 route *b*). The result of an isotopic labelling experiment leads us to favour the latter interpretation. Sulfoxide **5d** labelled with C-13 in one of the *t*-butyl's methyl groups was made by lithiation of naphthamide **4d**, quenching with diisopropyl disulfide, oxidizing to the sulfoxide and alkylating with $^{13}CH_3I$. $^{13}$C-**5d** undergoes substitution to yield **6d** devoid of a $^{13}$C label, suggesting the mechanism follows route *b*. Substitution *via* route *a* is consistent with this result only in the unlikely event that both formation and collapse of sulfurane **8** are fully stereospecific. It is remarkable nonetheless that neither sulfoxide–lithium exchange[18] nor ortholithiation[19] competes with the substitution, but presumably the combination of steric hindrance in both the nucleophile and electrophile is at the root of this unusual and valuable chemoselectivity.

We expect that this new *t*-butylation method will find broad applicability in the synthesis of sterically constrained arenes, not least in the synthesis of potential atropisomeric systems, an area we are actively pursuing.

We thank the EPSRC and Eli Lilly for support.

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