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# *N*-Cumyl Benzamide, Sulfonamide, and Aryl *O*-Carbamate Directed Metalation Groups. Mild Hydrolytic Lability for Facile Manipulation of Directed Ortho Metalation Derived Aromatics

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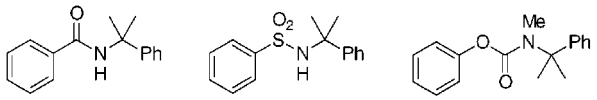
## ABSTRACT

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***N*-Cumyl benzamide (2), sulfonamide (8), and *O*-carbamate (11) compounds undergo directed ortho metalation under standard conditions to give, after quench with a variety of electrophiles, the substituted products 3, 9, and 12, respectively. Regiospecific and convenient approaches to phthalimides (7), 1,2-benzisothiazole 1,1-dioxides (10b), and ortho-substituted phenols (13a) and salicylamides (13b) are thereby established. The mild deprotection protocol for these new cumyl directed metalation groups (DMGs) suggests that they will supersede previous corresponding groups for synthetic anionic aromatic chemistry.**

The directed ortho metalation (DoM) reaction continues a steadfast evolution as an important tool for the regioselective synthesis of polysubstituted aromatics.[1] Tertiary and secondary carboxamides[2,3] and oxazolines[4] constitute powerful and widely used directed metalation groups (DMGs) at the benzoic acid oxidation state which are compromised by difficult, sensitive, functional group incompatible, or less than convenient hydrolysis steps (Scheme 1). Among these, amides **1d**−**g**,[4−9] embodying facilitating hydrolysis mechanisms, appear useful but await broad scrutiny; benzoic acids **1h**, recently uncovered as DoM substrates by Mortier and co-workers,[10] may overcome the hydrolysis requirement.[11]

Herein we describe the following. (a) Amides **2a** and **2b**, inexpensively prepared from benzoyl chlorides and the corresponding secondary amines,[12] serve as powerful DMGs

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(10) (a) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265. (b) Moyroud, J.; Guesnet, J.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881. Substrate **1h** is compromised, to various degrees, by the requirement of low-temperature (−90 °C) metalation conditions, ketone byproduct formation, and less effective DMG power compared to the amides.

(11) A preliminary report by Pfizer chemists concerning the $CO_2CH_2$-*t*-Bu DMG may provide further synthetically useful DoM chemistry: Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054.

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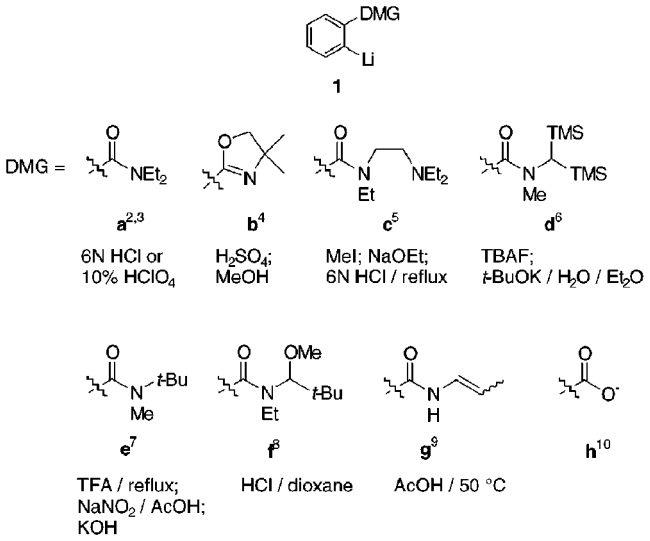
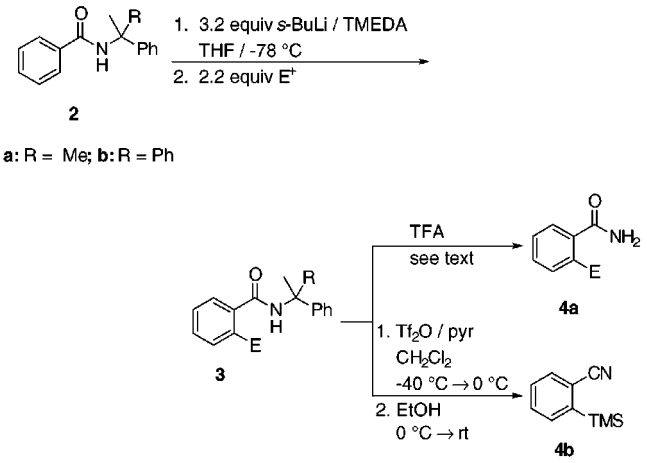
**Scheme 1**




allowing the synthesis of a variety of substituted systems including biaryls via the DoM−Suzuki-Miyaura cross coupling link.[1,13] (b) Products **3a** and **3b** are hydrolyzed under mild conditions (TFA/room temperature, $BF_3{\cdot}OEt_2/CH_2Cl_2$/ room temperature, or $Tf_2O$/pyridine/−40 °C) to the corresponding primary amides or benzonitriles **4**. (c) *N*-Cumyl phthalimidine may be further metalated to provide, after oxidation and decumylation (TFA/50 °C), the first regioselective route to 3-substituted phthalimides **7**.[14] (d) By analogy, the methodology is easily extended for the first time to *N*-cumyl sulfonamide **8**. (e) Most signficantly, *N*-cumyl *N*-methyl benzene-*O*-carbamate **11** behaves well in metalaton and anionic ortho-Fries rearrangement and, by virtue of facile decumylation (TFA/rt or TFE/reflux), will supersede the original *N*,*N*-diethyl carbamate DMG.[15] Our efforts were motivated by the important study of Castro and cowokers concerning the rates of carbocationic solvolysis of *N*-cumyl and *N*-$C(Ph)_2Me$ acetamides.[16]

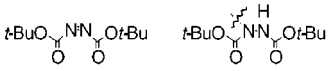
Metalation of **2a** and **2b** under optimized conditions (3.2 equiv of *s*-BuLi-TMEDA/THF/−78 °C/2 h)[17] followed by electrophile quench furnished substituted products **3a** and **3b** in modest to excellent yields (Scheme 2, Table 1). Methyl and aryl carbinols are easily introduced (entries 1 and 2), as

**Scheme 2**



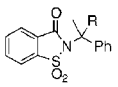

are secondary amides and formyl groups (entries 3 and 4), the latter leading to the phthalimidine product **5**. Using sulfuryl chloride as electrophile also leads to in situ cyclization to afford sultams (entry 5), while di-*tert*-butyl diazodicarboxylate affords the expected hydrazine (entry 6), a proven precursor for $NH_2^+$ equivalent introduction.[18] Silicon, sulfur, tin, and iodo ortho functionalization is also feasible (entries 7−11). The iodo derivative for **3a** (entry 11) serves

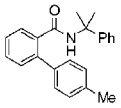
**Table 1.** Synthesis of Ortho-Substituted *N*-Cumyl and *N*-(1,1-Diphenylethyl) Benzamides **3a**,**b**

| | | | yld, %[a] | |
|---|---|---|---|---|
| Entry | $E^+$ | E | **3a** (R=Me) | **3b** (R=Ph) |
| 1 | MeI | Me[b] | 91 | |
| 2 | PhCHO | (HO)CHPh | 86 | |
| 3 | PhNCO | CONHPh | 51 | |
| 4 | DMF | CHO | 93 | 83 |
| 5 | $SO_2Cl_2$ | $SO_2$[c] | 46 | 48 |
| 6 |  | | 55 | |
| 7 | TMSCl | TMS | 94 | 91 |
| 8 | $(MeS)_2$ | SMe | 93 | |
| 9 | $(PhS)_2$ | SPh | | 56 |
| 10 | $Bu_3SnCl$ | $SnBu_3$ | 44 | |
| 11 | $I_2$ | I | 88 | 75 |
| 12 | $B(OMe)_3$ | $C_6H_4$-4-Me[d] | 73 | |

[a] All new compounds show spectral (IR, NMR, MS, HRMS) data in complete accord with the given structures.

[b] 3.2 equiv of MeI used for complete *N*-methylation.

[c] Product 

[d] Overall yield determined after cross-coupling of the crude boronic acid with 4-bromotoluene (5 mol% $Pd(PPh_3)_4$ / $Na_2CO_3$ / DME / reflux) to give 

(12) (a) Brander, M. *Recl. Trav. Chim. Pays-Bas* **1918**, *37*, 67. (b) Cumylamine was prepared from commercially available cumyl alcohol by a modification of the procedure of: Balderman, D.; Kalir, A. *Synthesis* **1978**, 24. The azide was reduced with $LiAlH_4/Et_2O$ from 0 °C to room temperature (18 h, 95% yield) instead of Raney nickel. 1,1-Diphenylethylamine was similarly prepared.

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(14) Previous non-DoM routes involve nucleophilic aromatic substitution of 3-nitrophthalimide, made via nitration of phthalic acid; see: Fischer, W. *Helv. Chim. Acta* **1991**, *74*, 1119 and references therein.

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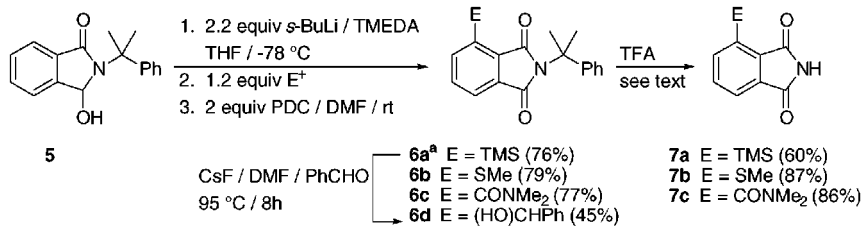
**Scheme 3**




[a]Decumylated with $Br_2$ ($CH_2Cl_2$/reflux) instead of TFA.

as an excellent substrate for Ullmann homocoupling[19] (Cu powder/DMF/110 °C/5 h), furnishing the 2,2′-*N*-cumyl benzamide biphenyl in 77% yield. The intermediate *o*-boronic acid, obtained by quench with $B(OMe)_3$ (entry 12), was subjected to a Pd-catalyzed cross-coupling reaction[13a] to afford the biaryl amide in good yield.

The product benzamides **3a**,**b** are smoothly converted into primary amides **4a**,**b** using very mild conditions. Thus, treatment of *o*-trimethylsilyl and -thiomethyl derivatives (entries 7 and 8) with neat TFA (room temperature/15−30 min) afforded the primary amides **4** (E = TMS (83%), E = SMe (78%),[20] respectively). Alternatively, treatment of *o*-trimethylsilyl derivative **3a** with $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ (room temperature/2 h) also affords the primary amide (86%). Interestingly, application of Charette's methodology[21] ($Tf_2O$/pyridine in $CH_2Cl_2$ (−40 °C to 0 °C/7 h) followed by addition of ethanol) provided *o*-(trimethylsilyl)benzonitrile[22] **4b** (51%) instead of the expected ethyl benzoate. The more sterically encumbered *o*-tolyl system (entry 12) required longer reaction times (4:1 TFA/$Et_2O$/room temperature/4 h).[23]

The availability of the phthalimidine **5** (Scheme 3)[9,24] invited further DoM investigations. Metalation with 2.2 equiv of *s*-BuLi/TMEDA followed by quench with selected electrophiles furnished products which, for ease of isolation, were oxidized (pyridinium dichromate/DMF/room temperature) to give **6a**−**c** in good yields.[25] Compound **6a** may be carbodesilylated in the presence of benzaldehyde (CsF/DMF/95 °C/11 h) to give carbinol **6d**.[26] Thus, given the choice of two DMGs, amide and carbinol amine alkoxide, lithiation is highly favored ortho to the amide group. Decumylation (TFA/50 °C/9 or 16 h) smoothly yielded products **7a**−**c**. In any case, rapid and regioselective access to 3-substituted phthalimides, useful intermediates in the synthesis of dyes,[27] is feasible by this procedure.

In a similar fashion, metalation of sulfonamide **8**[28] or carbamate **11** under optimized conditions (2.2 or 1.2 equiv of *s*-BuLi/TMEDA/THF/−78 °C, respectively) followed by electrophile quench afforded ortho-substituted sulfonamides **9a** and **9b**, substituted carbamate **12a**, and salicylamide **12b**, a prototype anionic Fries rearrangement product[15] (Scheme 4). Treatment of **9a**,**b** and with neat TFA (room temperature/8−10 min) gave primary sulfonamides **10a** (E = TMS (82%)) and 1,2-benzisothiazole 1,1-dioxide **10b** (E = $CPh_2$ (99%)),[29] respectively. Use of the same conditions easily transformed carbamate **12a** (room temperature/6 min) into the intermediate secondary carbamate, which upon mild base treatment (10% NaOH/EtOH/4 h)[30] led to **13a** (E = TMS (79%)),[31] with notable retention of the base- and acid-sensitive TMS moiety. Tertiary amide **12b**, derived from Fries rearrangement, may be decumylated under the mildest conditions of all with 2,2,2-trifluoroethanol (TFE) (reflux/11 h) to give the secondary amide **13b** (87%).[32]

In summary, the four new effective substrates **2a**,**b**, **8**, and **11** have been established for DoM chemistry. Their primary

(17) **Representative Experimental Procedure.** To a solution of **2a** (120 mg, 0.5 mmol) and TMEDA (0.24 mL, 1.6 mmol, 3.2 equiv) in THF (5 mL) at −78 °C under Ar was slowly added *s*-BuLi (1.6 mmol, 3.2 equiv) via syringe. The resulting yellow solution was stirred for 2 h, and TMSCl (0.14 mL, 1.1 mmol, 2.2 equiv) was added. The reaction mixture was stirred for 1 h, saturated $NH_4Cl$ was added, and the reaction mixture was warmed to room temperature. Flash chromatography (hexane/ethyl acetate 9:1) afforded **3a** (Table 1, entry 7). IR (KBr): $\nu_{max}$ 1657 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ 7.64 (dd, $J$ = 6.0, 2.0 Hz, 1H, Ar H), 7.52−7.22 (m, 8H), 6.16 (s, 1H), 1.85 (s, 6H), 0.30 (s, 9H). $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta$ 170.1, 146.8, 143.2, 140.1, 135.5, 129.4, 128.6, 125.5, 126.9, 126.1, 124.9, 56.3, 28.8, 0.3. HRMS: calcd for $C_{19}H_{26}NOSi$ 312.1784, found 312.1780.

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(22) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

(23) The product corresponds to a penultimate intermediate for a high-volume commercial product, OTBN (*o*-tolylbenzonitrile) from Clariant; see: Haber, S.; Koch, M. *Innovations Pharm. Technol.*, submitted for publication.

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(25) Confirmation of C-3 substituted products was secured by parallel HMQC and HMBC 2-D NMR experiments of deuterated products.

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(28) Prepared according to: Takematsu, T.; Konnai, M.; Omokawa, H. German Patent 2 744 137, 1978; *Chem. Abstr.* **1978**, *89*, 42793d.

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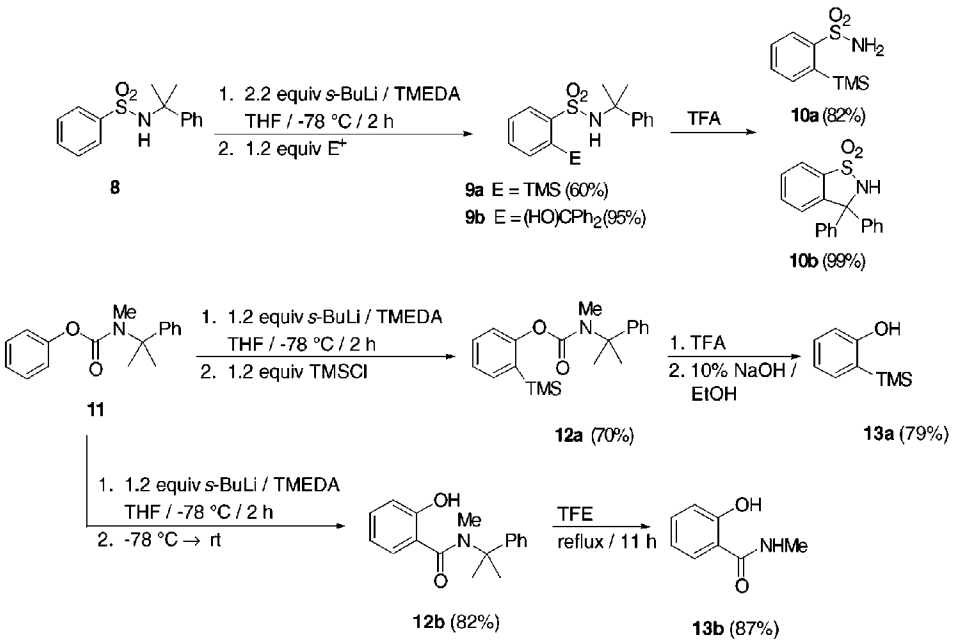
**Scheme 4**




advantages rest in mild hydrolysis to primary amides (**4**) and sulfonamides (**10a**), development of a new route to substituted phthalimides (**7**) and 1,2-benzisothiazole 1,1-dioxides **10b**, and, perhaps most significantly, conversion into ortho-substituted phenols (**13a**). The simplicity of operation, the demonstrated compatibility of a fragile functionality with the hydrolytic conditions (e.g. **10a** and **13a**), and the potential for further metalation in differentiated amide systems (e.g. Table 1, entry 3) bode well for establishing a central position for the cumyl amide DMG in synthetic aromatic chemistry.[33]

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**Supporting Information Available:** Experimental procedures for the metalation of **2a,b** and for the preparation of **4a,b**, **7b**, **10b**, and **13a**,**b** and characterization data for **3a,b**, **6b**, **9b**, and **12a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) We have recently demonstrated that the *N*-cumyl amide DMG is also effective in ferrocene DoM chemistry: Metallinos, C.; Bessler, C.; Green, L.; Snieckus, V. Manuscript in preparation.