

## Directed ortho Metalation Strategies. Effective Regioselective Routes to 1,2-, 2,3-, and 1,2,3-Substituted Naphthalenes

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Supporting Information

**ABSTRACT:** The regioselective synthesis of 2,3-di- and 1,2,3trisubstituted naphthalenes via Directed ortho Metalation (DoM) strategies of N,N-diethyl-O-naphthyl-2-carbamate (1) is presented. Sequential LiTMP metalation-electrophile quench and s-BuLi/TMEDA (or t-BuLi)-electrophile quench of naphthyl-2-carbamate 1 provides a general route to contiguously substituted naphthalenes (6) with full regioselectivity. Further derivatization via ipso-halodesilylation and



he significance of the naphthalene nucleus is manifested in important classes of pharmaceutical core structures,<sup>1</sup> natural products,<sup>2</sup> agrochemicals,<sup>3</sup> materials,<sup>4</sup> and powerful ligands for asymmetric catalysis<sup>5</sup> (Figure 1). In part as a



Figure 1. Selected examples of natural products, biologically active molecules, and chiral ligands exhibiting polysubstituted naphthalene scaffolds.

consequence, the 1,2-di-, 2,3-di-, and 1,2,3-trisubstitution patterns have received considerable attention in medicinal chemistry. Although a number of substituted naphthalenes are commercially available, there continues to be a lack of general and flexible methods for the preparation of contiguously substituted, e.g. 2,3-di- and 1,2,3-trisubstituted, naphthalenes.

As part of improving the positional strength of the Directed ortho Metalation (DoM) strategy in aromatic and heteroaromatic synthesis,<sup>7</sup> efforts in our laboratories have aimed to enhance available methodologies for the construction of substituted naphthalenes.<sup>8</sup> In continuation of these goals, herein we report results on the regioselective metalation chemistry of the N,Ndiethyl-O-naphthyl-2-carbamate (1), featuring one of the most powerful directed metalation groups (DMGs),9 and provide general methods for the construction of 2,3-di- and 1,2,3trisubstituted naphthalenes. Furthermore, we demonstrate

regioselective *ipso*-halodesilylation reactions,<sup>10</sup> leading to the synthesis of rare prototype halonaphthols. In addition, we report on Suzuki-Miyaura cross-couplings and directed remote metalation (DreM)-induced anionic Fries rearrangementcyclizations which provides a route to aromatic polycyclic lactones. The recently disclosed mild, Schwartz reagentmediated O-carbamate to naphthol deprotection<sup>11</sup> and Nicatalyzed cross-couplings of aryl O-carbamates with aryl and heteroaryl boronic acids<sup>12</sup> are additional features through which the utility of the reported chemistry may be anticipated.

Some 2-DMG bearing naphthalenes have been shown to undergo C-3 metalation mostly utilizing t-BuLi in Et<sub>2</sub>O.<sup>13</sup> Previous work in our laboratories has shown that DoM reactions of O-naphthyl 2-carbamates using s-BuLi/TMEDA combinations lead to low yields of products and poor  $C_1/C_3$  regioselectivity.<sup>8d</sup> Therefore, to surmount this difficulty we tested the regioselective discrimination behavior of the sterically demanding lithium 2,2,6,6-tetramethylpiperidide (LiTMP) base. As a trial experiment, the naphthyl-2-carbamate 1 (Scheme 1) was subjected to treatment with LiTMP (1.2 equiv/THF/-78  $^{\circ}C/1$  h–warm to rt) in the expectation of observing one or both possible anionic ortho Fries rearrangement products.<sup>14</sup> Encouragingly, N,N-diethyl-3-carboxamido 2-naphthol 2 was obtained





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in 80% yield with no evidence for the formation of the analogous 1-carboxamido product. Replacement of LiTMP with LDA under identical conditions afforded **2** in comparable (69%) yield.

With these results in hand, we carried out systematic LDA and LiTMP metalation/TMSCl or TESCl quench experiments (Table 1). Adding the LDA (1.2 equiv)/TMSCl (2.4 equiv)

# Table 1. Optimization of the DoM Reaction on N,N-Diethyl O-naphthyl-2-carbamate (1)

|                    |              | 1. Base, –78 °C,<br>THF                          |                 | OCONEt <sub>2</sub> |
|--------------------|--------------|--|-----------------|---------------------|
|                    |              | 2. E <sub>1</sub> <sup>+</sup> , -78 °C<br>to rt | 3a              | E1                  |
| entry <sup>a</sup> | base (equiv) | $E_1^+$ (equiv)                                  | product $(E_1)$ | yield (%)           |
| 1                  | LDA (1.2)    | TMSCl (2.4)                                      | 3a (TMS)        | 39 <sup>c</sup>     |
| 2                  | LDA (1.2)    | TMSCl (2.4)                                      | 3a (TMS)        | 44                  |
| 3                  | LDA (2.0)    | TMSCl (2.2)                                      | 3a (TMS)        | $N/A^{c,d}$         |
| 4                  | LiTMP (1.2)  | TMSCl (2.4)                                      | 3a (TMS)        | 51 <sup>c</sup>     |
| 5                  | LiTMP (1.2)  | TMSCl (2.4)                                      | 3a (TMS)        | 47                  |
| 6                  | LiTMP (3.0)  | TMSCl (3.0)                                      | 3a (TMS)        | 85                  |
| 7                  | LiTMP (3.0)  | TESCl (3.0)                                      | 3b (TES)        | 87                  |
| $8^b$              | LiTMP (3.0)  | TMSCl (3.0)                                      | 3a (TMS)        | 85                  |

"A mixture of base and electrophile were added to starting material at either 0 or -78 °C. <sup>b</sup>Base was added to starting material, the mixture was metalated for 1.5 h, and the electrophile was added. <sup>c</sup>Reactions were performed at 0 °C instead of -78 °C. <sup>d</sup>Mixture of products: 1-TMS/3-TMS (3a)/bis-TMS (6a) = 1.8:0.2:2.2 as determined by GC-MS analysis.

combination to starting material (Martin conditions)<sup>15</sup> at 0 °C led to low yields of the desired product (**3a**) (Table 1, entry 1). Decreasing the temperature was not helpful (entry 2), and when the amount of base was increased, mixtures of mono and bissilylated products were observed (entry 3). Similar results were obtained with LiTMP (entries 4 and 5). However, under excess LiTMP/TMSCl and LiTMP/TESCl conditions, monosilylated products **3a** and **3b** were obtained in excellent yields (entries 6 and 7). Because not all electrophiles are compatible with the base under Martin conditions, the metalation was also established with the addition order of base to starting material, followed by quenching with an electrophile (entry 8).

In an observation of promising synthetic interest, when, instead of 3.0 equiv of TESCl, only 1.2 equiv were used under identical conditions, product **4b** was obtained in 64% yield, resulting from what appears to be sequential  $C_3$ -deprotonation—silylation,  $C_1$ -deprotonation—anionic *ortho* Fries rearrangement (Scheme 2). For comparison purposes, the same reaction was carried out with TMSCl and gave, in addition to the analogous product **4a** (28%), the desired product **3a** (31%) and compound

#### Scheme 2. Anionic ortho-Fries Rearrangement Results



**5** (26%), the result of CIPE-induced<sup>7c</sup>  $\alpha$ -silyl methyl deprotonation—carbamoyl migration. Assignment of the structure of **5** was further secured by CsF-mediated desilylation to 2-naphthol. The greater acidity of the  $\alpha$ -methyl hydrogens of TMS vs TES groups possibly combined with a steric effect may be the rationale for the observed difference in reactivity.<sup>16</sup>

With the optimum conditions established, the reaction was generalized for a series of electrophiles to give diverse 2,3-disubstituted naphthalenes in good to excellent yields (Table 2).

| Ta  | ble 2 | . Scope of  | the DoM  | Reaction | on <i>N,N</i> -Diet | hyl-O- |
|-----|-------|-------------|----------|----------|---------------------|--------|
| naj | phth  | yl-2-carbar | nate (1) |          |                     |        |

|                    | 1. LiTM<br>OCONEt <sub>2</sub> –78 | //P, THF,<br>℃, 1.5 h    |                    |
|--------------------|------------------------------------|--------------------------|--------------------|
| 1                  | 2. E <sub>1</sub> <sup>+</sup>     |                          | -3k                |
| entry <sup>a</sup> | $E_1^+$ (3 equiv)                  | product $(E_1)$          | yield (%)          |
| 1                  | MeI                                | <b>3c/3d</b> (Me/Et)     | 60/21 <sup>b</sup> |
| 2                  | Br <sub>2</sub>                    | <b>3e</b> (Br)           | 65                 |
| 3                  | $I_2$                              | <b>3f</b> (I)            | 94                 |
| 4                  | $C_2Cl_6$                          | 3g (Cl)                  | 91                 |
| 5                  | PhCHO                              | 3h (PhC(OH))             | 63                 |
| 6                  | ClCONEt <sub>2</sub>               | 3i (CONEt <sub>2</sub> ) | 79                 |
| 7                  | MeOBpin                            | 3j (Bpin)                | 65                 |
| 8                  | BzCl                               | <b>3k</b> (PhCO)         | 72                 |

<sup>*a*</sup>LiTMP (3.0 equiv) was added dropwise to a solution of starting material (1.0 equiv) in THF at -78 °C, metalated for 1.5 h, and quenched with the electrophile (3.0 equiv). <sup>*b*</sup>The 3-ethyl derivative (3d) is a result of the slow addition of electrophile. Adding MeI all at once may eradicate it completely. See SI for details.

It is interesting to note that treatment of naphthyl-2-carbamate **1** with 2.4 equiv of *sec*-BuLi/TMEDA at -78 °C followed by the addition of 2.4 equiv of TMSCl provided direct access to 1,3-bis-trimethylsilyl substituted naphthyl-2-carbamate (**6a**; see Supporting Information (SI) for details) in 72% yield.

Justifiably, the availability of the regiochemically pure  $C_3$ substituted naphthalenes 3a-k prompted exploration of second C<sub>1</sub>-DoM reactions. Of special interest were syntheses of silvlated and halogenated C1-derivatives for the purpose of further ipsohalodesilvlation and cross-coupling reactions, respectively. Using O-carbamates 3a, 3b, 3e, and 3g metalation followed by quenching with a variety of electrophiles gave a series of 1,3functionalized O-naphthyl 2-carbamates 6b-j in synthetically useful yields (Table 3). In all cases, temperature control was essential to avoid lower yields due to the ease of competing anionic ortho-Fries rearrangement. This control was achieved via a syringe pump or by changing the metalation system to *t*-BuLi/ Et<sub>2</sub>O (see SI for details). Furthermore, in order to avoid complications of potential alkyllithium-mediated metal-halogen exchange, the C3-bromo derivative 3e was subjected to LDA metalation conditions. Following iodine and TESCl quench, products 6i and 6j, respectively, were obtained in good yields. Noteworthy is the undoubtedly facile conversion of compounds 6b-g into 1-substituted 2-naphthols by acid- or fluoridemediated desilylation and Schwartz reduction.<sup>11</sup>

The availability of bis-silylated carbamate **6a** and monosilylated derivatives **3a**, **6b**, and **6g** encouraged the pursuit of electrophile-induced *ipso*-desilylation studies for the construction of differentially functionalized naphthalenes (Table 4). Thus, treatment of **3a** with pyridinium tribromide cleanly afforded the corresponding 3-bromo derivative **3e** in high yield Table 3. Synthesis of 1,3-Disubstituted O-Naphthyl-2carbamates 6b-j

| 3a-b, 3 | OCONEt <sub>2</sub><br>E <sub>1</sub> | 1. base (1.2 ec<br>THF, –78 °C<br>2. E <sub>2</sub> * | quiv),<br>Σ, 1 h<br>➤ | E <sub>2</sub><br>C | CONEt <sub>2</sub> |
|---------|---------------------------------------|---|-----------------------|---------------------|--------------------|
| a       |                                       | compd   | <b>-</b> +            | product             | yield              |
| entry   | base                                  | $(E_1)$   | E <sub>2</sub> '      | $(E_2)$             | (%)                |
| 1       | s-BuLi/TMEDA                          | 3a (TMS)  | $I_2$                 | <b>6b</b> (I)       | 69                 |
| 2       | t-BuLi <sup>b</sup>                   | 3a (TMS)  | $I_2$                 | <b>6b</b> (I)       | 61                 |
| 3       | s-BuLi/TMEDA                          | 3b (TES)  | $I_2$                 | 6c (I)              | 57                 |
| 4       | t-BuLi <sup>b</sup>                   | 3b (TES)  | $I_2$                 | 6c (I)              | 73                 |
| 5       | s-BuLi/TMEDA                          | 3a (TMS)  | DMF                   | 6d (CHO)            | 51 <sup>c</sup>    |
| 6       | s-BuLi/TMEDA                          | 3a (TMS)  | $C_2Cl_6$             | <b>6e</b> (Cl)      | 81                 |
| 7       | s-BuLi/TMEDA                          | 3a (TMS)  | MeI                   | <b>6f</b> (Me)      | 77                 |
| 8       | t-BuLi <sup>b</sup>                   | 3a (TMS)  | Br <sub>2</sub>       | <b>6g</b> (Br)      | 64                 |
| 9       | s-BuLi/TMEDA                          | 3g (Cl)   | TMSCl                 | <b>6h</b> (TMS)     | 83                 |
| 10      | LDA                                   | <b>3e</b> (Br)  | I <sub>2</sub>        | <b>6i</b> (I)       | 68                 |
| 11      | LDA                                   | <b>3e</b> (Br)  | TESCI                 | <b>6j</b> (TES)     | 63                 |

"Base (1.2 equiv) is added to a solution of starting material at -78 °C; after metalating for 1 h, the electrophile was added slowly. <sup>b</sup>Et<sub>2</sub>O is used, and the metalation time was 20 min. <sup>c</sup>Under the reaction conditions, the carbamoyl group is cleaved affording the 2-hydroxy-3-trimethylsilyl-1-naphthaldehyde **6d** as the product.

#### Table 4. Halo-ipso-desilylation Reactions yield $\mathbf{E}^{+}$ temp entry compound product (equiv) (time) (%) PyHBr<sub>3</sub> 40°C (24 h) 87 1 TMS (2.0)3a 3e PyHBr<sub>3</sub> rt (2h) 2 84 (1.0)6g ICI rt (16 h) 81 (1.0)TMS $Br_2$ 80°C 96 (1.1)(0.2 h)ICl -20 °C 5 96 (2.5)(2h)6k 6g

(Table 4, entry 1). At room temperature and with less pyHBr<sub>3</sub>, the 1,3-disilylated carbamate **6a** gave the derivative **6g** in high yield (entry 2). This regioselective 1-bromo *ipso*-desilylation may be rationalized by the extended conjugation and hence greater stabilization of the incipient  $\beta$ -arenium intermediate than that arising from C<sub>3</sub>-bromonium ion attack. The same regioselectivity was observed upon iodination of **6a** with ICl to give the corresponding 1-iodo derivative **6b** in 81% yield (entry 3). The regiochemical outcome was verified by comparison of spectroscopic data with the materials obtained from DoM chemistry. To affect a second bromo-induced *ipso*-desilylation on **6b**, pyHBr<sub>3</sub> was found to be ineffectual. However, when Br<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 80 °C under microwave heating was used, the reaction proceeded smoothly in 10 min to furnish the 3-bromo-1-iodo O-carbamate **6i** in quantitative yield (entry 4). Interestingly and in contrast, **6g** was found to be reactive and excess ICl at -20 °C furnished the inverted 1-bromo-3-iodo isomer **6k** (entry 5).

The availability of regioselectively iodinated naphthyl 2carbamates **6b** and **6c** prompted the rational step to achieve greater structural complexity by effecting Suzuki–Miyaura crosscoupling–directed remote metalation (DreM) chemistry. Thus, biaryls **7a** and **7b** were efficiently prepared using conventional Suzuki–Miyaura Pd-catalyzed conditions on **6b** and **6c** with phenyl boronic acid respectively (Scheme 3).





By treatment of 7a with an excess of LDA in refluxing THF, the anionic remote Fries rearrangement product **8a** was obtained in low yield together with 23% of byproduct **10a** (analogous to **5**, cf. Scheme 2). In an attempt to increase the yields and to eliminate product **10a**, the TES derivative **7b**, with less acidic and more sterically hindered  $\alpha$ -silyl hydrogens, was subjected to the same LDA conditions. The analogous product **10b** was not obtained although the reaction did not proceed to completion. Introduction of a synergistic OMe DMG *ortho* to the desired remote metalation site (Scheme 3, compounds **7c** and **7d**) clearly improved the yield of the migration product (60% and 84%, respectively). When briefly subjected to heating in acetic acid, **8a**–**8d** afforded the benzonaphthopyranones **9a**–**9d** in good yields, compounds known in the context of synthesis of axially chiral natural products.<sup>17</sup>

In summary, we have developed a new convenient methodology for the synthesis of 2,3-disubstituted (3) and 1,2,3trisubstituted naphthalenes (6), the latter class being readily achieved by two routes: (i) via the regioselective metalations of 3, and (ii) via a regioselective halo-*ipso*-desilylation of **6a**, **6b**, and **6g**. This methodology provides routes for the preparation of naphthalenes which are difficult to obtain by conventional chemistry, are commercially inaccessible, and/or are seemingly simple but unavailable or require expensive derivatives. Furthermore, observations of potential general synthetic value of sequential reactivity, which provide trisubstituted naphthalenes from a monosubstituted *O*-carbamate (Scheme 2), have been presented. Finally, the methodology has been applied to the synthesis of benzonaphthopyranones **9a–9d** which represent prototype skeleta of bioactive axially chiral molecules. Taken together with the recently developed deprotection to phenols<sup>11</sup> and cross-coupling reactions,<sup>12</sup> the broader utility of the presented chemistry of *O*-naphthyl 2-carbamates may be anticipated.

### ASSOCIATED CONTENT

#### **Supporting Information**

Experimental procedures and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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