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

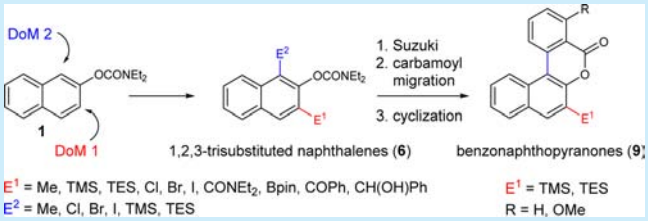
Katherine Groom,[#,†] S. M. Shakil Hussain,[#,‡] Justin Morin,[#] Christian Nilewski,[#,§] Toni Rantanen,[⊥] and Victor Snieckus*[,#]

[⊥]Snieckus Innovations, 945 Princess Street, Kingston, Ontario K7L 3N6, Canada

[#]Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, Ontario K7L 3N6, Canada

Supporting Information

ABSTRACT: The regioselective synthesis of 2,3-di- and 1,2,3-trisubstituted 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 Suzuki−Miyaura cross-coupling leads ultimately to substituted halonaphthalenes and benzonaphthopyranones (**9**).



The significance of the naphthalene nucleus is manifested in important classes of pharmaceutical core structures,[1] natural products,[2] agrochemicals,[3] materials,[4] and powerful ligands for asymmetric catalysis[5] (Figure 1). In part as a 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.[6]

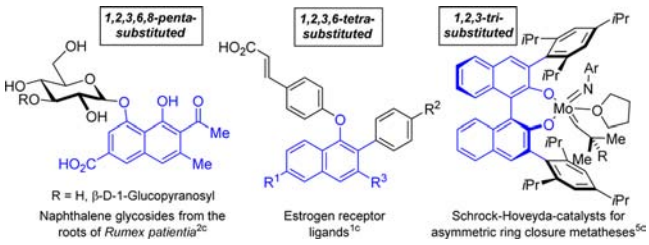
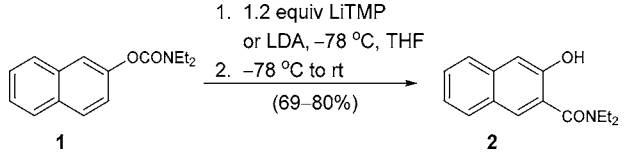


Figure 1. Selected examples of natural products, biologically active molecules, and chiral ligands exhibiting polysubstituted naphthalene scaffolds.

As part of improving the positional strength of the Directed *ortho* Metalation (DoM) strategy in aromatic and heteroaromatic synthesis,[7] efforts in our laboratories have aimed to enhance available methodologies for the construction of substituted naphthalenes.[8] In continuation of these goals, herein we report results on the regioselective metalation chemistry of the *N*,*N*-diethyl-*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 1,2,3-trisubstituted naphthalenes. Furthermore, we demonstrate regioselective *ipso*-halodesilylation reactions,[10] 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 rearrangement−cyclizations which provides a route to aromatic polycyclic lactones. The recently disclosed mild, Schwartz reagent-mediated *O*-carbamate to naphthol deprotection[11] and Ni-catalyzed cross-couplings of aryl *O*-carbamates with aryl and heteroaryl boronic acids[12] 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_2O.[13] 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.[8d] 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 °C/1 h−warm to rt) in the expectation of observing one or both possible anionic *ortho* Fries rearrangement products.[14] Encouragingly, *N*,*N*-diethyl-3-carboxamido 2-naphthol **2** was obtained

Scheme 1. Regioselective Anionic *ortho* Fries Rearrangement



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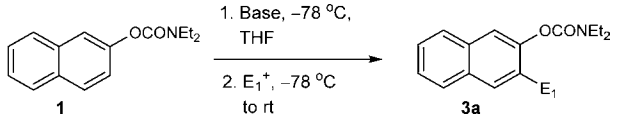
in 80% yield with no evidence for the formation of the analogous 1-carboxamido product. Replacement of LiTMP with LDA under identical conditions afforded **2** in comparable (69%) yield.

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)



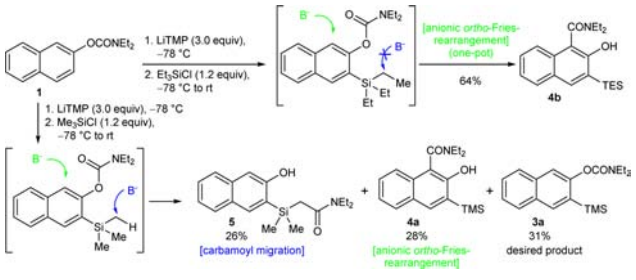
entry[a]	base (equiv)	E_1^+ (equiv)	product (E_1)	yield (%)
1	LDA (1.2)	TMSCl (2.4)	**3a** (TMS)	39[c]
2	LDA (1.2)	TMSCl (2.4)	**3a** (TMS)	44
3	LDA (2.0)	TMSCl (2.2)	**3a** (TMS)	N/A[c,d]
4	LiTMP (1.2)	TMSCl (2.4)	**3a** (TMS)	51[c]
5	LiTMP (1.2)	TMSCl (2.4)	**3a** (TMS)	47
6	LiTMP (3.0)	TMSCl (3.0)	**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]A mixture of base and electrophile were added to starting material at either 0 or −78 °C. [b]Base was added to starting material, the mixture was metalated for 1.5 h, and the electrophile was added. [c]Reactions were performed at 0 °C instead of −78 °C. [d]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)[15] 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 bis-silylated 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

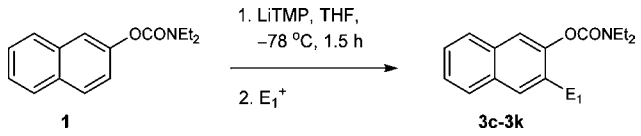
Scheme 2. Anionic *ortho*-Fries Rearrangement Results



5 (26%), the result of CIPE-induced[7c] α-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 α-methyl hydrogens of TMS vs TES groups possibly combined with a steric effect may be the rationale for the observed difference in reactivity.[16]

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).

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



entry[a]	E_1^+ (3 equiv)	product (E_1)	yield (%)
1	MeI	**3c**/**3d** (Me/Et)	60/21[b]
2	Br_2	**3e** (Br)	65
3	I_2	**3f** (I)	94
4	C_2Cl_6	**3g** (Cl)	91
5	PhCHO	**3h** (PhC(OH))	63
6	$ClCONEt_2$	**3i** ($CONEt_2$)	79
7	MeOBpin	**3j** (Bpin)	65
8	BzCl	**3k** (PhCO)	72

[a]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). [b]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_1-DoM reactions. Of special interest were syntheses of silylated and halogenated C_1-derivatives for the purpose of further *ipso*-halodesilylation 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 1,3-functionalized *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_2O (see SI for details). Furthermore, in order to avoid complications of potential alkyllithium-mediated metal−halogen exchange, the C_3-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 fluoride-mediated desilylation and Schwartz reduction.[11]

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

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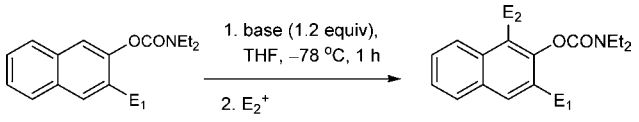
Table 3. Synthesis of 1,3-Disubstituted *O*-Naphthyl-2-carbamates 6b–j

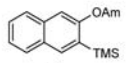
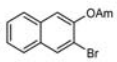
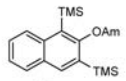
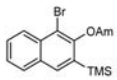
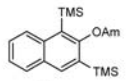
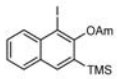
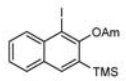
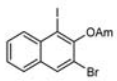
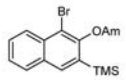
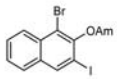


3a-b, 3e, 3g — 6b-j

entry[a]	base	compd (E_1)	E_2^+	product (E_2)	yield (%)
1	*s*-BuLi/TMEDA	**3a** (TMS)	I_2	**6b** (I)	69
2	*t*-BuLi[b]	**3a** (TMS)	I_2	**6b** (I)	61
3	*s*-BuLi/TMEDA	**3b** (TES)	I_2	**6c** (I)	57
4	*t*-BuLi[b]	**3b** (TES)	I_2	**6c** (I)	73
5	*s*-BuLi/TMEDA	**3a** (TMS)	DMF	**6d** (CHO)	51[c]
6	*s*-BuLi/TMEDA	**3a** (TMS)	C_2Cl_6	**6e** (Cl)	81
7	*s*-BuLi/TMEDA	**3a** (TMS)	MeI	**6f** (Me)	77
8	*t*-BuLi[b]	**3a** (TMS)	Br_2	**6g** (Br)	64
9	*s*-BuLi/TMEDA	**3g** (Cl)	TMSCl	**6h** (TMS)	83
10	LDA	**3e** (Br)	I_2	**6i** (I)	68
11	LDA	**3e** (Br)	TESCl	**6j** (TES)	63

[a]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. [b]Et_2O is used, and the metalation time was 20 min. [c]Under the reaction conditions, the carbamoyl group is cleaved affording the 2-hydroxy-3-trimethylsilyl-1-naphthaldehyde **6d** as the product.

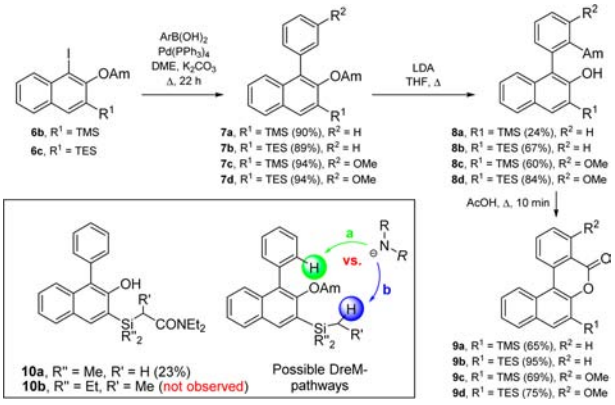
Table 4. Halo-*ipso*-desilylation Reactions

entry	compound	E^+ (equiv)	temp (time)	product	yield (%)
1	 **3a**	$PyHBr_3$ (2.0)	40°C (24 h)	 **3e**	87
2	 **6a**	$PyHBr_3$ (1.0)	rt (2 h)	 **6g**	84
3	 **6a**	ICl (1.0)	rt (16 h)	 **6b**	81
4	 **6b**	Br_2 (1.1)	80°C (0.2 h)	 **6i**	96
5	 **6g**	ICl (2.5)	−20 °C (2 h)	 **6k**	96

(Table 4, entry 1). At room temperature and with less $pyHBr_3$, 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 *β*-arenium intermediate than that arising from C_3-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 D*o*M chemistry. To affect a second bromo-induced *ipso*-desilylation on **6b**, $pyHBr_3$ was found to be ineffectual. However, when Br_2 in CH_2Cl_2 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 2-carbamates **6b** and **6c** prompted the rational step to achieve greater structural complexity by effecting Suzuki–Miyaura cross-coupling–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).

Scheme 3. Suzuki–Miyaura Cross-Coupling and Synthesis of Benzonaphthopyranones



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 *α*-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.[17]

In summary, we have developed a new convenient methodology for the synthesis of 2,3-disubstituted (**3**) and 1,2,3-trisubstituted 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

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prototype skeleta of bioactive axially chiral molecules. Taken together with the recently developed deprotection to phenols[11] and cross-coupling reactions,[12] 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: snieckus@chem.queensu.ca.

Present Addresses

[†]GL Chemtec, 1456 Wallace Road, L6L 2Y2, Oakville, Canada.
[‡]Center for Petroleum and Minerals, King Fahd University of Petroleum and Minerals (KFUPM), Dhahran 31261, Saudi Arabia.
[§]Department of Chemistry, BioScience Research Collaborative (BRC), Rice University, 6100 Main Street, Houston, TX 77005, USA.

Notes

The authors declare no competing financial interest.

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