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Letter

Directed *Ortho* and *Remote* Metalation of Naphthalene 1,8-Diamide: Complementing S_EAr Reactivity for the Synthesis of Substituted Naphthalenes

Christopher C. V. Jones, Jignesh J. Patel, Ross D. Jansen-van Vuuren, Gregory M. Ross, Bernd O. Keller, Francoise Sauriol, Gabriele Schatte, Erin R. Johnson,* and Victor Snieckus

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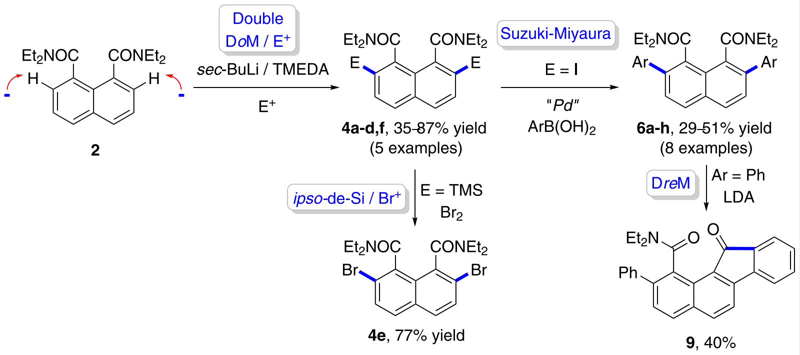

ABSTRACT: Mono- and dianion species of 1,8-naphthalene diamide **2** were generated under *sec*-BuLi/TMEDA conditions and trapped with a variety of electrophiles to give 2- and 2,7- substituted products **3** and **4**. Using Suzuki–Miyaura cross-coupling, mono- and di-iodinated products were converted into the corresponding 2-aryl (**5**) and 2,7-diaryl (**6**) products, respectively. The amide–amide rotation barrier of **2** was established by VT NMR, and the structure of fluorenone structure **9**, obtained by *remote* metalation, was secured.

To organic chemists, the naphthalene ring, initially part of isolates obtained from coal tar distillates,[1,2] has attained considerable representation as a substructure in natural products,[3,4] bioactive molecules and drugs,[5] nanomaterials,[6] transition metal coordinated ligands,[7] and other materials with useful properties.[8,9] The 1,8-disubstituted naphthalenes are of special and long-standing interest due to their properties of atropisomerism,[10] as structural components in natural products,[11] use as proton sponges,[12] nerve growth factor (NGF) inhibitors,[13] models of biological receptors,[14] light-energized compounds,[15] and ligands for catalysis. The synthesis of substituted naphthalenes encompasses a vast number of methods.[16,17] However, as a cursory perusal of the literature will indicate, a need exists for systematic, wide-ranging methodologies for the regioselective construction of naphthalenes with three or more substituents.[18]

In the context of contributions toward providing new, unusually substituted 1,8-naphthal-imides and -diamides, we envisaged the advantage of Directed *ortho* Metalation (DoM) derived routes[19] based on *N*,*N*-diethyl naphthalene 1,8-dicarboxamide **2**, for establishing convenient syntheses of 1,2,8- and 1,2,7,8-substituted derivatives **3** and **4**.

Although the DoM reaction of simple 1- and 2-Directed Metalating Group (DMG)-substituted naphthalenes has been investigated,[18a] disubstituted mono- and di-DMGs systems have received scant attention. Further, dimetalated aromatics are relatively unrecognized and synthetically underdeveloped species and intermediates, based on previous reports from our and other laboratories (**1a**–**g**, Figure 1).[20] In the context of the 1,8-substituted naphthalene containing the powerful *N*,*N*-diethyl carboxamide DMG, and by extension the *N*,*N* diethyl *O*-carbamate, Wuest et al. synthesized 2,7-derivatives of 1,8-naphthalenediol (using the carbamate as the precursor) as novel ligands for titanium catalysts,[20e] Snieckus et al. synthesized 3,6-derivatives of *N*,*N*-diethylnaphthalene-1,8-dicarboxamide,[21] and Clayden et al. prepared a 2-formyl 8-substituted-1-naphthamide.[22] Thus, this work represents the first study involving the preparation of 2- and 2,7-derivatives of

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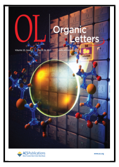

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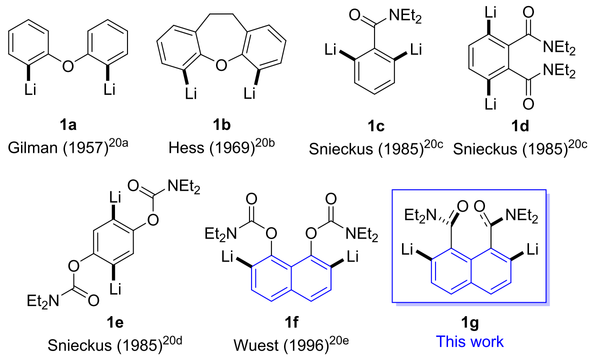
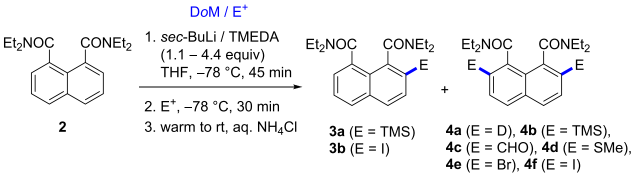


Figure 1. Aromatic dilithiated species.[20]

N,*N*-diethylnaphthalene-1,8-dicarboxamide, which is an attractive pursuit considering the utility of naphthalene derivatives in the design of chiral catalysts,[23] medicinal compounds,[24] and functional materials such as photoswitches[25] and liquid crystals.[26] Furthermore, the novel *ortho*-substituted bis-amides can be transformed to other functional groups, e.g., esters,[27] or cross-coupled with other moieties,[28] opening up a new family of compounds for exploration.

Herein we report studies on the mono- and dianion (**1g**)[29] DoM chemistry of *N*,*N*-diethylnaphthalene-1,8-dicarboxamide (**2**). The Suzuki−Miyaura cross-coupling reactions of the derived halo derivatives **3b** and **4f** (Table 1, Scheme 1), a subsequent Directed *remote* Metalation (D*re*M) reaction[30] to give the fluorenone **9** (Scheme 2), and the assessment of amide rotational barriers of two derivatives **2** and **4f** are also described.[31] This work establishes new and convenient routes toward highly substituted naphthalenes and, categorically, to 2-monosubstituted (**3**) and 2,7-disubstituted (**4**) naphthalene 1,8-dicarboxamides (Table 1), whose utility in various currently active areas of material science has not been adequately tested due to the lack of their availability by synthesis using classical chemistry.[32]

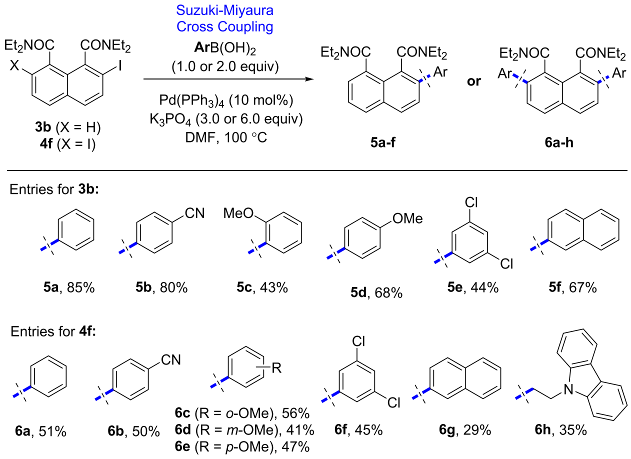
Table 1. DoM and Electrophilic Quench of Naphthalene Bis-amide 2



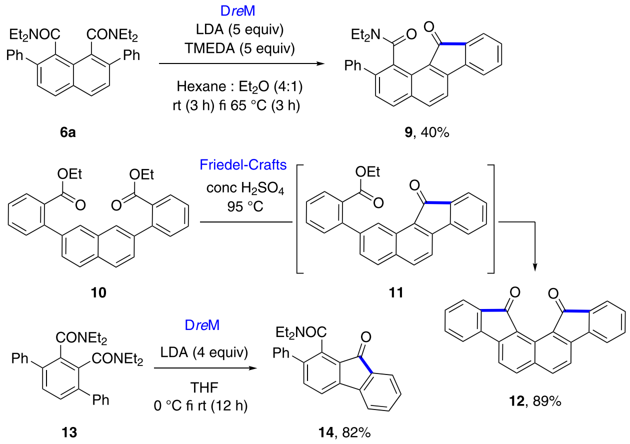
		electrophile quench		% yield of products
entry	*sec*-BuLi/TMEDA (equiv)	E$^+$	E	**3a–b** and/or **4a–f**
1	2.2/2.2	CD_3OD	D	**4a**, 90 (d_1 82%)
2	1.1/1.1	TMSCl	TMS	**3a**, 15 + **4b**, 25[a]
3	4.4/4.4	TMSCl	TMS	**4b**, 50[b]
4	2.2/2.2	DMF	CHO	**4c**, 40
5	2.2/2.2	$(SMe)_2$	SMe	**4d**, 75
6	*ipso*	Br_2	Br	**4e**, 77[c]
7	1.1/1.1	CF_3CH_2I	I	**3b**, 24 + **4f**, 35[d]
8	2.2/2.2	CF_3CH_2I	I	**4f**, 87[b]

[a] 38% of **2** was recovered. [b] 5.0 equiv of E$^+$ were used. [c] Achieved by an *ipso*-desilylation−bromination of **4b** (TMS) in 77% yield with Br_2 (see Supporting Information). [d] 18% of **2** was recovered.

Scheme 1. Suzuki−Miyaura Cross-Coupling of Mono- and Di-iodo Naphthalene Diamides 3b and 4f



Scheme 2. Directed *Remote* Metalation of *N*,*N*-Diethyl-2,7-diphenylnaphthalene-1,8-dicarboxamide 6a



To initiate our study, previous experience with phthalamide metalation,[20c] awareness of accumulated evidence to the nature of lithiated aromatic amide structures,[33] and some appreciation of the profound effects of complexation[30,34] and, hence, reactivity of intermediates as a function of stoichiometry,[35] guided our initial deuteration-quench study (Table 1). In order to determine the relative amounts of deuterated species formed as a function of base concentration, metalation (1.1 equiv of *sec*-BuLi/TMEDA/−78 °C/30 min) of *N*,*N*-diethyl naphthalene-1,8-dicarboxamide (**2**), prepared from the commercially available 1,8-naphthalic anhydride,[36] followed by quenching with excess CD_3OD and warming to rt provided product **4a** in >90% yield. HRMS analysis[37] showed a d_1/d_2 = 33:67 ratio (d_1 = mono incorporation, d_2 = bis incorporation). Maximization of d_2 species (d_1/d_2 = 18:82) was achieved using 2.2 equiv of the *sec*-BuLi/TMEDA complex (entry 1, Table 1), and there was no further substantial change of this ratio when 3 equiv and 4 equiv of base were used (see Supporting Information (SI)). The requirement for an excess of 2 equiv of alkyllithium reagent for a double DoM reaction was previously established for bis-*N*,*N*-diethyl phthalimide.[20c] These results indicate that, whatever the nature of the aggregated species produced, excess equivalents of base result in a higher concentration of the 2,7-dianion **1g** under the equilibrating metalation reaction conditions.

With optimization conditions in hand, compound **2** was subjected to 4.4 equiv of the *sec*-BuLi/TMEDA complex, followed by 4.4 equiv of TMSCl,[38] to afford the 2,7-disilylated derivative **4b** in 50% optimized yield (entry 3, Table 1). As previously argued,[39] successful generation of a dimetalated or higher-order metalated aromatic species promoted by one or more DMGs is dependent upon electrostatic repulsion, additional complexity in aggregation, and solubility, among other factors. The lower yields of the bis-silylated product **4b** compared to those of the deuteration product using the same amounts of base are undoubtedly due to the greater steric effects presented by the TMSCl electrophile. Using these conditions, several other electrophiles were tested. Thus, in addition to silylation (entry 2), thiomethylation (entry 5) and formylation (entry 4) were achieved to give products in moderate yields. Iodination was unsuccessful using elemental I_2, but was achieved using CF_3CH_2I[40] to afford product **4f** in very good yield (entry 8). Attempts to obtain the corresponding dibromo compound **4e** by use of Br_2 and $BrCH_2CH_2Br$ reagents were unsuccessful. However, the application of the *ipso*-desilylation protocol[41] to the readily available bis-TMS **4b** using excess bromine led to the formation of the dibrominated product **4e** in good yield (entry 6). A number of other electrophiles led to formation of mixtures of intractable products and/or decomposition (see Supporting Information).

The X-ray crystal structure of **4b** was obtained (Figure 2; for data, see Supporting Information) and showed that the amides are perpendicular to the naphthalene ring and the carbonyls are pointing in diametrically opposite directions. The *peri* relationship of the amides pushes them outward,[42,43] thus creating a smaller bond angle (116.9°) from the norm (120°), with the resulting orientation of the TMS groups at a large (125.2°) angle.

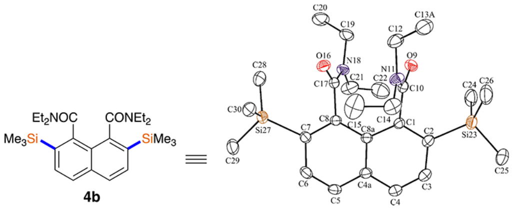


Figure 2. ORTEP X-ray crystal structure of **4b**. Hydrogens are omitted for clarity. Thermal ellipsoids in the molecular plot are shown at the 30% probability level.

The availability of the 2,7-dibromo and 2,7-diiodo naphthalene dicarboxamides **4e** and **4f**, and the knowledge of arylated naphthalene diamides as significant materials in solar-cell research,[15] compelled us to attempt bis Suzuki−Miyaura cross-coupling chemistry.[44] To start, the 2-iodo-*N*,*N*-diethyl-naphthalene-1,8-dicarboxyamide **3b** was subjected to coupling with selected aryl boronic acids under optimized conditions (10 mol % $Pd(PPh_3)_4/K_3PO_4$/anhyd DMF)[45] to afford products **5a−f** in consistently higher yields (Scheme 1). A broad set of catalysts and conditions were screened (see Supporting Information) for the more reactive diiodo **4f** derivative, which afforded the products **6a−h** in similar yields. A number of available aryl/heteroaryl and aliphatic boronic acids (see Supporting Information) did not furnish the expected products when reacted with **3b** and/or **4f**. Of the aliphatic boronate esters/boronic acids explored, only the 2-(9-carbazolyl) ethylboronic acid pinacol ester was able to couple successfully with the 2,7-diiodo-*N*,*N*-diethyl-naphthalene-1,8-dicarboxyamide **4f**. The incorporation of the carbazole moiety presents utility in the ever expanding field of organic electronics.[46]

The extensive studies of rotational barriers of congested *peri*-substituted naphthalene derivatives,[22,47] by Clayden, Fuchter, and Okamoto, and the intriguing X-ray structure of **4b** prompted a VT NMR study[48] of the prototype 1,8-disubstituted naphthalene **2** (Figure 3). Although rotational barriers of *peri*-substituted naphthalenes have been comprehensively studied over the years,[49,50] the results from the Clayden and Staab laboratories for energy barriers of 1,8-disubstituted naphthalenes are most pertinent. Studies of **7** and **8** are of greatest relevance to our case **2**. As gleaned from Figure 3, compound **2** shows the highest $\Delta G^{\ddagger}$ of all listed compounds, indicative of the great electronic-dipole effect hampering free rotation about the aryl−CO bond that, as Clayden suggested,[47a] is more significant than the steric influence of the two substituents. Thus, the additional amide in **2** (*anti* conformation) raises the barrier by ca. 3.5 kcal/mol compared to the mono amide **7**[51] and by 4.5 kcal/mol over the electronically less demanding diketone system **8**.[52] The additional electronic, and most likely steric, requirements of 2,7-diiodo-*N*,*N*-diethyl-naphthalene-1,8-dicarboxyamide **4f** prevent observation of its high rotational barrier.

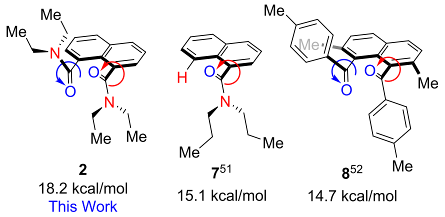


Figure 3. Comparison of rotational barriers of selected 1,8-disubstituted naphthalenes **7**,[51] **8**,[52] and **2**.

The availability of the 2,7-diphenyl derivative **6a** prompted a test of the Directed *remote* Metalation (Dr*e*M) reaction,[30] a process that has been broadly demonstrated for the synthesis of fluorenones from biaryl monoamides.[53] After a brief investigation (see Supporting Information), conditions recently utilized for remote metalation on biaryl systems[54] using equal proportions of LDA and TMEDA in hexane/Et_2O (4:1) afforded the monocyclized product **9** in 40% yield as a bright orange crystalline material (Scheme 2). The structure of **9**, obtained by single-crystal X-ray crystallography (Figure 4), shows significant steric repulsion, resulting in the amide group being nearly orthogonal to the plane of the naphthyl ring.

We then sought to understand the observation of a mono-Dr*e*M reaction to fluorenone **9** and not a double-Dr*e*M process to fluoreno[1,2-*a*]fluorenedione **12** under the excess LDA conditions. DFT calculations using the B3LYP functional,[55,56] the XDM dispersion correction,[57,58] and the PCM continuum solvent[59] model as implemented in Gaussian 09[60] were performed (see Supporting Information for details) to predict the thermochemistry of the putative sequential Dr*e*M reactions of species **6a**, **9**, and **12**. The computed free-energy changes for each reaction, **6a** → **9** (ΔG = 2.9 kcal/mol) and **9** → **12** (ΔG = 6.7 kcal/mol), indicate a lower ΔG for the first reaction, consistent with the observed formation of compound **9**, but not **12**.

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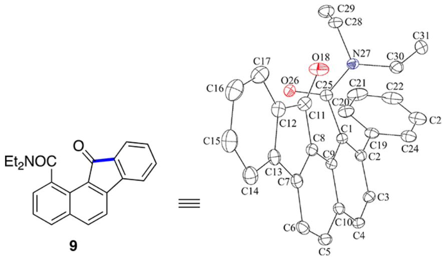

9

Figure 4. ORTEP X-ray crystal structure of **9**. Hydrogens are omitted for clarity. Thermal ellipsoids in the molecular plot are shown at the 30% probability level.

Recently, Frantz reported the synthesis of fluoreno[1,2-α]fluorenedione (**12**), as well as the linear isomeric fluoreno-[2,1-α]fluorenedione, using double intramolecular Friedel−Crafts cyclization reactions.[62] The fluorene-dione **12** (Scheme 2) was obtained in 89% yield using hot sulfuric acid. In THF solvent, the reaction **11** → **12** has a corresponding B3LYP-XDM free energy penalty of 7.7 kcal/mol, similar to that seen for **9** → **12**. Frantz argued that strong acid was needed to stabilize compound **12** and the corresponding protonated transition state interspersed in the sequence **10** → **12**. Calculations at the B3LYP/6-31G* level[62] indicate that the sterically hindered difluorenone **12** has a ground-state energy that is 13.4 kcal/mol higher than the unhindered [2,3-*b*] isomer.[62] For comparison, our B3LYP-XDM calculations predict this relative energy difference to be 12.0 kcal/mol, which is in fairly close agreement with the previous theoretical value. Franz proposed that compound **12** adopts a "twisted, helical C_2-symmetric structure to accommodate steric clashing, and likely electrostatic repulsion, of the two oxygen atoms" and suggested, also based on calculations, that a protonated form (proton squeezed between the two carbonyls) is the thermodynamically controlled product. Given the difference in functional groups (**6a** and **10**) and nature of transition states for the formation of diketone **12** from diamide and diester, further comment is unwarranted.

To further investigate the differences between our two sequential D*re*M reactions of **6a** and **9**, computational studies were performed for both reaction pathways. Here, the LDA catalyst was modeled as lithium dimethyl amide for simplicity. One molecule of THF solvent, coordinated to the lithium, was included in the calculations, following our previous similar mechanistic study.[63] The results for the pathway are shown in Figure 5. Here, both **6a** and **9** form prereaction complexes **15** and **18**, respectively, in which the LDA coordinates to the amide oxygen (Complex-Induced Proximity Effect).[30] Deprotonation leads to the coordinated aryl carbanions **16** and **19**, which undergo cyclization to the tetrahedral carbinolamine alkoxides **17** and **20**, respectively, and thence by loss of LDA to the final products **9** and **12**. The cyclization step is found to have a significantly higher free-energy barrier for **9** than for **6a**, consistent with the experimental finding that the second deprotonation−cyclization reaction fails. The higher free-energy barrier can be attributed to geometry differences in the cyclization transition state. Specifically, the Bűrgi−Dunitz angles (the highlighted C−C−O angles in the ball-and-stick figure) are 107.9° and 110.3° for the transition states to form **17** and **20**, respectively. The latter value is considerably larger than the ideal value of ∼107°, which destabilizes the transition state. Analogous DFT calculations on different biaryl amide systems have led to similar conclusions regarding the inability to achieve the required Bűrgi−Dunitz angle.[64,65]

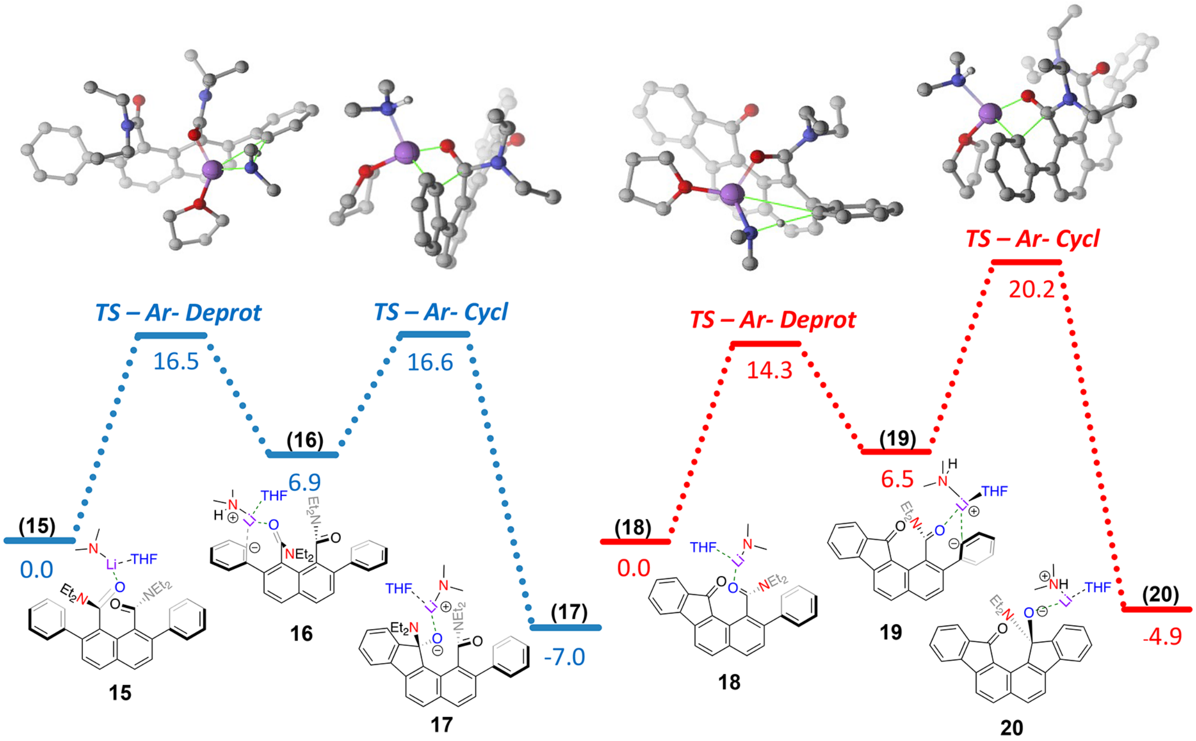

Figure 5. Comparative reaction profiles (relative free energies, in kcal/mol) for the D*re*M reactions of **6a** and **9**, obtained using B3LYP-XDM and a continuum model of THF solvent. Transition-state geometries are shown in ball-and-stick format with the Bűrgi−Dunitz angles highlighted in green.[61]

In conclusion, we have demonstrated a new route for the synthesis of 2- and 2,7-substituted naphthalene 1,8-dicarboxamides **3** and **4** by the Directed *ortho* Metalation (D*o*M) strategy. A useful and high-yielding route to the 2,7-dibromo derivative **4e** was established by the *ipso* bromodesilylation reaction of the bis-TMS derivative **4b**. The D*o*M-Suzuki reaction nexus was demonstrated on both mono- and di-iodo derivatives **3b** and **4f** by coupling with selected aryl boronic acids to obtain **5** and **6**. Additionally, we have uncovered a Directed *remote* Metalation (D*re*M) reaction on **6a** to afford the fluorenone **9** in moderate yield. These preliminary results establish the potential of the D*o*M reaction for the preparation of unusually substituted 1,8-naphthamides and, by implication, the corresponding naphthimides[66] and other functionalizations that may be obtained by transformation of the diethyl amides.[27,28] Such compounds are not available by classical methods and are of considerable current interest for use in solar energy devices,[15] molecular motors,[67] chemo sensors,[68] DNA binders,[69] transition-metal based catalysts,[70] and novel cross-coupling partners.[71] Thus, this novel chemistry opens the door to an untapped class of compounds with a plethora of potential applications in the materials science sphere and beyond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00521.

Full experimental details, ^{1}H and ^{13}C NMR spectra, X-ray data (PDF)

Accession Codes

CCDC 2050790−2050791 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Erin R. Johnson − *Department of Chemistry, Dalhousie University, Halifax, NS B3H 4R2, Canada;* orcid.org/0000-0002-5651-468X; Email: erin.johnson@dal.ca

Authors

Christopher C. V. Jones − *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada;* orcid.org/0000-0002-6975-6805
Jignesh J. Patel − *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada*
Ross D. Jansen-van Vuuren − *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada;* orcid.org/0000-0002-2919-6962
Gregory M. Ross − *Northern Ontario School of Medicine, Laurentian University, Sudbury, ON P3E 2C6, Canada*
Bernd O. Keller − *Numinus Bioscience, Nanaimo, BC V9R 6Z8, Canada*
Francoise Sauriol − *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada*
Gabriele Schatte − *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada*
Victor Snieckus − *Department of Chemistry, Queen's University, Kingston, ON K7L 3N6, Canada;* orcid.org/0000-0002-6448-9832

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00521

Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Prof. Victor A. Snieckus (August 1, 1937 to December 18, 2020). May his legacy live on. This manuscript is Prof. Victor A. Snieckus' last submission to an academic journal before his passing.

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