

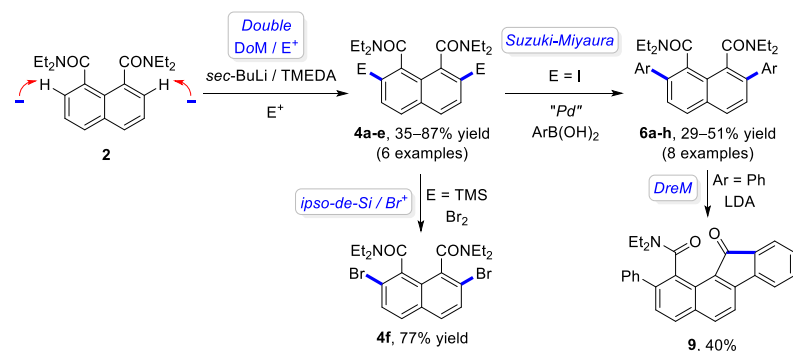
Directed *ortho* and *Remote* Metalation of Naphthalene 1,8-diamide: Complementing S_{EAr} Reactivity for the Synthesis of Substituted Naphthalenes

Keywords: Directed *ortho* metalation / Naphthalene 1,8-diamide / Dilithiated species / Suzuki-Miyaura Cross coupling / Fluorenone

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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 **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 towards 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

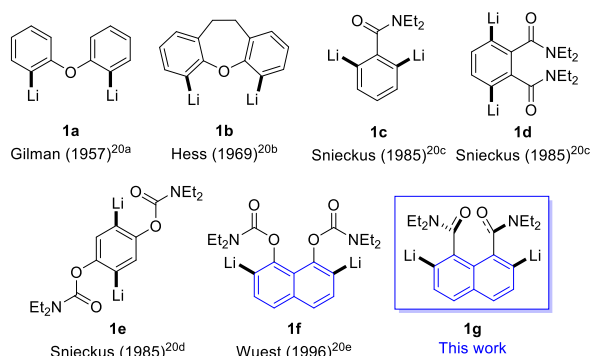
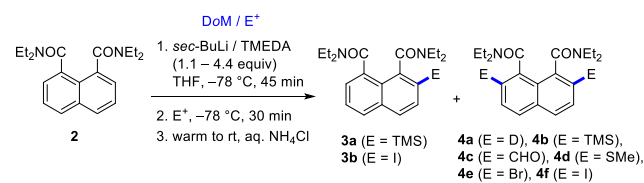


Figure 1. Aromatic Dilithiated Species.²⁰

1,2,8- and 1,2,7,8-substituted derivatives **3** and **4** (Table 1).

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

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

Entry	<i>sec</i> -BuLi / TMEDA (equiv)	Electrophile Quench		% yield of Products 3a-b and/or 4a-f
		E ⁺	E	
1	2.2 / 2.2	CD ₃ OD	D	4a, 90 (<i>d</i> ₁ : <i>d</i> ₂ 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	<i>ipso</i>	Br ₂	Br	4e, 77 ^c
7	1.1 / 1.1	CF ₃ CH ₂ I	I	3b, 24 + 4f, 35 ^d
8	2.2 / 2.2	CF ₃ CH ₂ I	I	4f, 87 ^b

^a38% of **2** was recovered; ^b5.0 equiv of E⁺ were used; ^cachieved by an *ipso*-desilylation-bromination of **4b** (TMS) in 77% yield with Br₂ (See *Supporting Information*); ^d18% of **2** was recovered.

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,^{20c} 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 *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 photoswitches²⁵ 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.

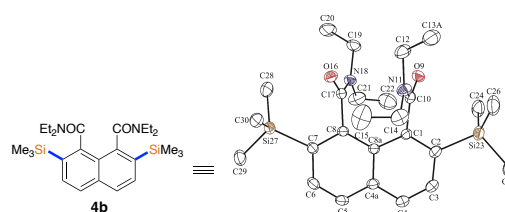
Herein we report studies on the mono- and dianion (**1g**)²⁹ DoM chemistry of *N,N*-diethylnaphthalene-1,8-dicarboxamide (**2**). The Suzuki-Miyaura cross coupling reactions of the derived halo derivatives **3b** and **4f**, a subsequent *DreM* reaction³⁰ to give the fluorenone **9**, and the assessment of amide rotational barriers of two derivatives **2** and **4f** are also described.³¹ This work establishes new and convenient routes towards 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

To initiate our study, previous experience with phthalamide metalation,^{20c} awareness of accumulated evidence on 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

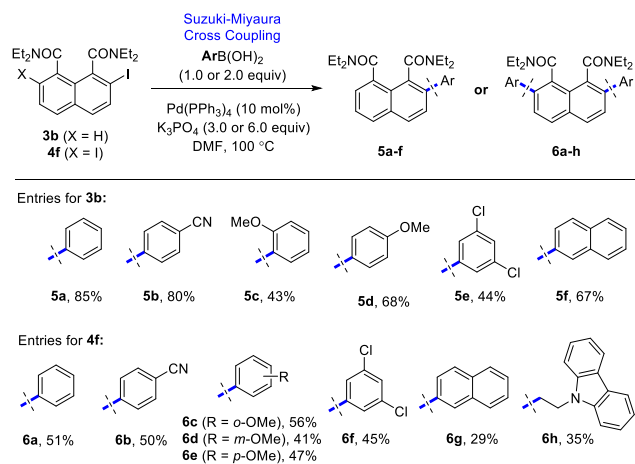
as a function of base concentration, metalation (1.1 equiv of *sec*-BuLi/TMEDA/-78 °C/30 min) of *N,N*-diethyl naphthalene-1,8-dicarboxamide (**2**), prepared from the commercially available 1,8-naphthalic anhydride,³⁶ followed by quenching with excess of CD₃OD and warming to rt provided product **4a** in >90% yield. HRMS analysis³⁷ 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*). 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 is 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 modest yields. Iodination was unsuccessful using elemental I₂, but was achieved using CF₃CH₂I⁴⁰ to afford product **4f** in very good yield (entry 8). Attempts to obtain the corresponding di-bromo compound **4e** by use of Br₂ and BrCH₂CH₂Br reagents were unsuccessful. However, the application of the *ipso*-desilylation protocol⁴¹ on 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 (Fig. 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 outwards,^{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**. Hydrogen and methyl groups on Si are omitted for clarity. Thermal ellipsoids in the molecular plot are shown at the 30% probability level.

Scheme 1. Suzuki Miyaura Cross coupling of Mono- and Di-Iodo Naphthalene Diamide **3b** and **4f**



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*-diethylnaphthalene-1,8-dicarboxamide **3b** was subjected to coupling with selected aryl boronic acids under optimized conditions (10 mol% Pd(PPh₃)₄ / K₃PO₄ / 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 for **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*-diethylnaphthalene-1,8-dicarboxamide **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 study⁴⁸ 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 ΔG^\ddagger of all listed compounds, indicative of the great electronic-dipole effects hampering free rotation about the aryl-CO bond that, as Clayden suggested,^{47a} is more significant than the steric influence of the two

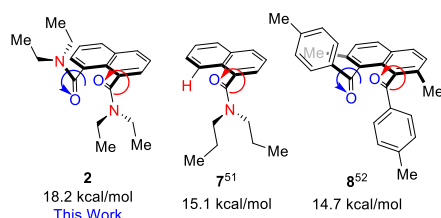
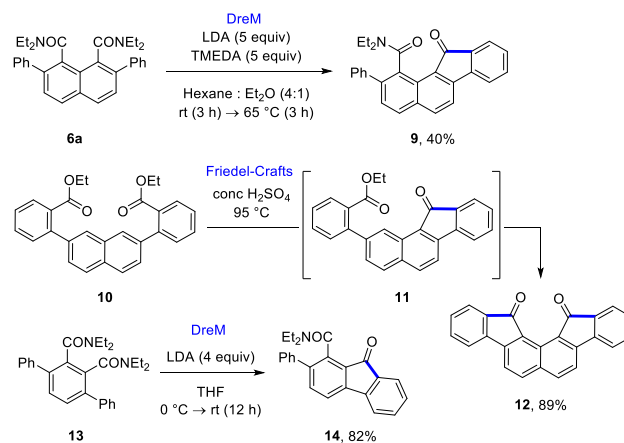


Figure 3. Comparison of Rotational Barriers of Selected 1,8-disubstituted Naphthalenes **7**,⁵¹ **8**⁵² and **2**.

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



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*-diethylnaphthalene-1,8-dicarboxamide **4f** prevent observation of its high rotational barrier.

The availability of the 2,7-diphenyl derivative **6a** prompted a test of the Directed *remote* Metalation (*DreM*) 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 systems⁵⁴ using equal proportions of LDA and TMEDA in hexane:Et₂O (4:1) afforded the mono-cyclized 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.

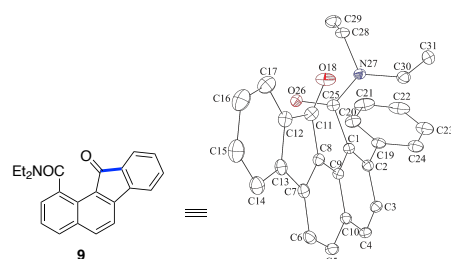


Figure 4. ORTEP X-ray Crystal Structure of **9**. Hydrogen and methyl groups on Si are omitted for clarity. Thermal ellipsoids in the molecular plot are shown at the 30% probability level.

We then sought to understand the observation of a mono-*DreM* reaction to fluorenone **9** and not a double-*DreM* process to fluoreno[1,2- α]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 solvent⁵⁹ model as implemented in Gaussian 09⁶⁰ were performed (See *Supporting Information* for details) to predict the thermochemistry of the putative sequential *DreM* reactions of species **6a**, **9**, and **12**. The computed free-energy changes for each reaction, **6a** \rightarrow **9** ($\Delta G = 2.9$ kcal/mol) and **9** \rightarrow **12** ($\Delta G = 6.7$ kcal/mol), indicate a lower ΔG for the first reaction, consistent with the observed formation of compound **9**, but not **12**.

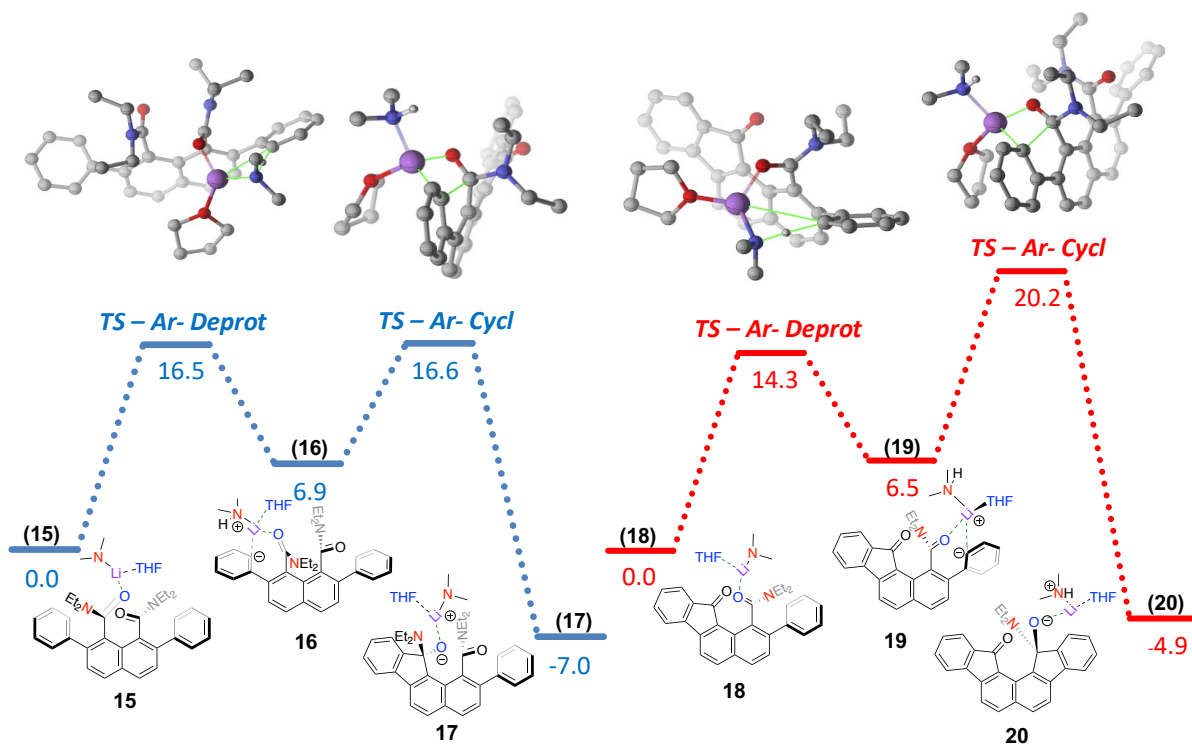


Figure 5. Comparative reaction profiles (relative free energies, in kcal/mol) for the *DreM* reactions of **6a** and **9**, obtained using B3LYP-XDM and a continuum model of THF solvent. Transition-state geometries are shown in ball-and-stick format with the Bürgi-Dunitz angles highlighted in green.⁶¹

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** \rightarrow **12** has a corresponding B3LYP-XDM free energy penalty of 7.7 kcal/mol, similar to that seen for **9** \rightarrow **12**. Frantz argued that strong acid was needed to stabilize compound **12** and the corresponding protonated transition state interspersed in the sequence **10** \rightarrow **12**. Calculations at the B3LYP/6-31G* level⁶² 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 C₂-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 *DreM* 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 pre-reaction complexes **15** and **18**, respectively, in which the LDA coordinates to the amide oxygen (CIPE).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 Bürgi-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 Bürgi-Dunitz angle.^{64,65}

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 (DoM) 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 DoM-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 (*DreM*) reaction on **6a** to afford the fluorenone **9** in modest yield. These preliminary results establish the potential of the DoM reaction for the preparation of unusually substituted 1,8-naphthamides and, by implication, the corresponding naphthimides⁶⁶ 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 of 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.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXX/acs.orglett.XXXXX. Full experimental details, ¹H and ¹³C NMR spectra, X-ray files, (PDF) and Cartesian Coordinates for all DFT-optimized structures.

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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 Victor's last submission to an academic journal before his passing. Once a Cardinal! Always a Cardinal!

REFERENCES

(1) Campbell, N., Aromatic Compounds with Condensed Nuclei: Naphthalene and Related Compounds. In *Rodd's Chemistry of Carbon Compounds: A Modern Comprehensive Treatise*, 2nd ed.;

Coffey, S., Ed. Elsevier: Amsterdam, Netherlands, 1978; Vol. 3(G), pp 99-301.

(2) Collin, G.; Hoke, H.; Greim, H., Naphthalene and Hydronaphthalenes. In *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 23, pp 661-670.

(3) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products, *Chem. Rev. (Washington, DC, U.S.)* **2011**, *111*, 563-639.

(4) Ji, N.; Rosen, B. M.; Myers, A. G. Method for the Rapid Synthesis of Highly Functionalized 2-Hydroxy-1-naphthoates. Syntheses of the Naphthoic Acid Components of Neocarzinostatin Chromophore and N1999A2, *Org. Lett.* **2004**, *6*, 4551-4553.

(5) Makar, S.; Saha, T.; Singh, S. K. Naphthalene, a versatile platform in medicinal chemistry: Sky-high perspective, *Eur. J. Med. Chem.* **2019**, *161*, 252-276.

(6) Chen, S.; Slattum, P.; Wang, C.; Zang, L. Self-Assembly of Perylene Imide Molecules into 1D Nanostructures: Methods, Morphologies, and Applications, *Chem. Rev. (Washington, DC, U.S.)* **2015**, *115*, 11967-11998.

(7) Wang, J.; Soo, H. S.; Garcia, F. Synthesis, properties, and catalysis of p-block complexes supported by bis(arylimino)acenaphthene ligands, *Commun. Chem.* **2020**, *3*, 1-13.

(8) Kobaisi, M. A.; Bhosale, S. V.; Latham, K.; Raynor, A. M.; Bhosale, S. V. Functional Naphthalene Diimides: Synthesis, Properties, and Applications, *Chem. Rev. (Washington, DC, U.S.)* **2016**, *116*, 11685-11796.

(9) Suraru, S.-L.; Würthner, F. Strategies for the Synthesis of Functional Naphthalene Diimides, *Angew. Chem., Int. Ed.* **2014**, *53*, 7428-7448.

(10) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atroposelective Chemical Transformations, *Chem. Rev. (Washington, DC, U.S.)* **2015**, *115*, 11239-11300.

(11) Fernandes, R. A.; Kumari, A.; Pathare, R. S. A Decade with Dötz Benzannulation in the Synthesis of Natural Products, *Synlett* **2020**, *31*, 403-420.

(12) Filatova, E. A.; Gulevskaya, A. V.; Pozharskii, A. F.; Ermolenko, E. A.; Ozeryanskii, V. A.; Misharev, A. D. Synthesis of 2-Aryl- and 2,7-Diaryl-1,8-bis(dimethylamino)naphthalenes. Overview of the "Buttressing effect" in 2,7-Disubstituted Proton Sponges, *ChemistrySelect* **2020**, *5*, 9932-9945.

(13) Shamovsky, I. L.; Ross, G. M.; Riopelle, R. J.; Weaver, D. F. Theoretical and Biochemical Studies on the Selectivity of Nerve Growth Factor for Transition Metal Cations, *J. Am. Chem. Soc.* **1999**, *121*, 9797-9806.

(14) Pozharskii, A. F.; Dyablo, O. V.; Pogosova, O. G.; Ozeryanskii, V. A.; Filarowski, A.; Vasilikhina, K. M.; Dzhangiryan, N. A. Modeling Biologically Important NH... π Interactions Using *peri*-Disubstituted Naphthalenes, *J. Org. Chem.* **2020**, *85*, 12468-12481.

(15) Zhang, G.; Zhao, J.; Chow, P. C. Y.; Jiang, K.; Zhang, J.; Zhu, Z.; Zhang, J.; Huang, F.; Yan, H. Nonfullerene Acceptor Molecules for Bulk Heterojunction Organic Solar Cells, *Chem. Rev. (Washington, DC, U.S.)* **2018**, *118*, 3447-3507.

(16) For an excellent review on the synthesis of naphthalenes, see (a) De Koning, C. B.; Rousseau, A. L.; Van Otterlo, W. A. L. Modern methods for the synthesis of substituted naphthalenes, *Tetrahedron* **2003**, *59*, 7-36.; for a review on naphthaldehydes, see (b) Pozharskii, A. F. Naphthaldehydes, *Russ. Chem. Rev.* **2003**, *72*, 447-470.

(17) For recent work, see inter alia (a) electrophilic (SEAr) Cai, G.; Chatterjee, S.; Hisaki, I.; Tobe, Y. [2.2.2](2,7)-1-Bromonaphthalenophane from a Desymmetrized Building Block Bearing Electrophilic and Masked Nucleophilic Functionalities, *Helv. Chim. Acta.* **2019**, *102*, e1800242.; (b) cycloaddition Szlapa-Kula, A.; Kula, S.; Filapek, M.; Fabianczyk, A.; Bujak, K.; Siwy, M.; Kotowicz, S.; Janeczek, H.; Smolarek, K.; Maćkowski, S.;

- Krompiec, S.; Schab-Balcerzak, E. Synthesis, electrochemistry and optical properties with electroluminescence ability of new multisubstituted naphthalene derivatives with thiophene and carbazole motifs, *J. Lumin.* **2018**, *196*, 244-255.; (c) benzyne Sato, S.; Kawada, T.; Takikawa, H.; Suzuki, K. Preparation of 2-Substituted 3-Methoxycarbonyl-4-methoxyfurans that Allow Access to Highly Functionalized Naphthalenes via Regioselective Cycloaddition with Alkoxybenzyne, *Synlett* **2017**, *28*, 1719-1723.
- (18) For recent work from our laboratories, see (a) Groom, K.; Hussain, S. M. S.; Morin, J.; Nilewski, C.; Rantanen, T.; Snieckus, V. Directed *ortho* Metalation Strategies. Effective Regioselective Routes to 1,2-, 2,3-, and 1,2,3-Substituted Naphthalenes, *Org. Lett.* **2014**, *16*, 2378-2381.; (b) Patel, J. J.; Laars, M.; Gan, W.; Board, J.; Kitching, M. O.; Snieckus, V. Directed Remote Lateral Metalation: Highly Substituted 2-Naphthols and BINOLs by In Situ Generation of a Directing Group, *Angew. Chem., Int. Ed.* **2018**, *57*, 9425-9429. and refs therein.
- (19) (a) Clayden, J., Directed Metallation of Aromatic Compounds. In *The Chemistry of Organolithium Compounds*, Rappoport, Z.; Marek, I., Eds. John Wiley & Sons, Ltd: Hoboken, N.J., U.S.A., 2004; pp 495-646; (b) Snieckus, V. Directed *ortho* metalation. Tertiary amide and *O*-carbamate directors in synthetic strategies for polysubstituted aromatics, *Chem. Rev. (Washington, DC, U.S.)* **1990**, *90*, 879-933.; (c) Hartung, C. G.; Snieckus, V., The Directed *ortho* Metalation Reaction – A Point of Departure for New Synthetic Aromatic Chemistry. In *Modern Arene Chemistry*, Astruc, D., Ed. Wiley-VCH: Weinheim, Germany, 2002; pp 330-367; (d) Snieckus, V.; Macklin, T., Metalation of arenes. Directed *ortho* and *remote* Metalation (DoM and DreM). In *Handbook of C-H Transformations*, Dyker, G., Ed. Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, pp 106-118, 262-264.
- (20) (a) Oita, K.; Gilman, H. The Preparation of Some Derivatives of Phenoxasilin, a Silicon Analog of Xanthene, *J. Am. Chem. Soc.* **1957**, *79*, 339-342.; (b) Hess, B. A.; Bailey, A. S.; Bartusek, B.; Boekelheide, V. 8,16-Oxido[2,2]metacyclophane-1,9-diene. Valence tautomer of pyrene cis-15,16-epoxide, *J. Am. Chem. Soc.* **1969**, *91*, 1665-1672.; (c) Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. Dilithiated synthons of tertiary benzamides, phthalamides, and 0,0'-aryl dicarbamates, *Tetrahedron Lett.* **1985**, *26*, 1145-1148.; (d) Doadt, E. G.; Snieckus, V. 3,5-Dilithiated tertiary thiophene 2-carboxamide. Regioselective entries into diversely substituted thiophenes, *Tetrahedron Lett.* **1985**, *26*, 1149-1152.; (e) Poirier, M.; Simard, M.; Wuest, J. D. Synthesis of 2,7-Disubstituted Derivatives of 1,8-Naphthalenediol. Unusual Structure of a Chlorotitanium 1,8-Naphthalenediolate, *Organometallics* **1996**, *15*, 1296-1300.
- (21) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. Iridium-Catalyzed C-H Activation versus Directed *ortho* Metalation: Complementary Borylation of Aromatics and Heteroaromatics, *Chem. - Eur. J.* **2010**, *16*, 8155-8161.
- (22) Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. Perilithiation and the synthesis of 8-substituted-1-naphthamides, *Tetrahedron* **1999**, *55*, 14161-14184.
- (23) Shibusaki, M.; Matsunaga, S., BINOL. In *Privileged Chiral Ligands and Catalysts*, Zhou, Q.-L., Ed. Wiley-VCH: Weinheim, Germany, 2011; pp 295-332.
- (24) (a) Upadhayaya, R. S.; Vandavasi, J. K.; Kardile, R. A.; Lahore, S. V.; Dixit, S. S.; Deokar, H. S.; Shinde, P. D.; Sarmah, M. P.; Chattopadhyaya, J. Novel quinoline and naphthalene derivatives as potent antimycobacterial agents, *Eur. J. Med. Chem.* **2010**, *45*, 1854-1867.; (b) Feixas, J.; Jiménez, J.-M.; Godessart, N.; Puig, C.; Soca, L. d.; Crespo, M. a. I. Naphthalene derivatives: A new series of selective cyclooxygenase-2 inhibitors, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2687-2690.
- (25) Rahman, M. L.; Yusoff, M. M.; Hegde, G.; Malek, M. N. F. A.; Samah, N. A.; Srinivasa, H. T.; Kumar, S. Synthesis and Characterization of Naphthalene-Based Banana-Shaped Liquid Crystals for Photoswitching Properties, *J. Chin. Chem. Soc. (Weinheim, Ger.)* **2014**, *61*, 571-577.
- (26) (a) Svoboda, J.; Novotná, V.; Kozmík, V.; Glogarová, M.; Weissflog, W.; Diele, S.; Pelzl, G. A novel type of banana liquid crystals based on 1-substituted naphthalene-2,7-diol cores, *J. Mater. Chem.* **2003**, *13*, 2104-2110.; (b) Reddy, R. A.; Baumeister, U.; Keith, C.; Tschierske, C. Influence of the core structure on the development of polar order and superstructural chirality in liquid crystalline phases formed by silylated bent-core molecules: naphthalene derivatives, *J. Mater. Chem.* **2007**, *17*, 62-75.
- (27) Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. Conversion of amides to esters by the nickel-catalysed activation of amide C–N bonds, *Nature* **2015**, *524*, 79-83.
- (28) (a) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide activation: an emerging tool for chemoselective synthesis, *Chem. Soc. Rev.* **2018**, *47*, 7899-7925.; (b) Takise, R.; Muto, K.; Yamaguchi, J. Cross-coupling of aromatic esters and amides, *Chem. Soc. Rev.* **2017**, *46*, 5864-5888.
- (29) Chen, G. J.; Tamborski, C. Regiospecific synthesis of aromatic compounds via organometallic intermediates: II. 1,3,5-(Trimethylmetal(IV))benzene compounds, *J. Organomet. Chem.* **1983**, *251*, 149-158.
- (30) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions, *Angew. Chem., Int. Ed.* **2004**, *43*, 2206-2225.
- (31) Jones, C. C. V. Synthesis of 2,7-Disubstituted *N,N*-Diethyl Naphthalene-1,8-Dicarboxamide Derivatives by Directed *ortho* Metalation - Cross Coupling Methodology. M.Sc. Thesis, Queen's University, Kingston, ON, Canada, May 2005.
- (32) (a) Jung, K. Y.; Koreeda, M. Synthesis of 1,4-, 2,4-, and 3,4-dimethylphenanthrenes: a novel deoxygenation of arene 1,4-endoxides with trimethylsilyl iodide, *J. Org. Chem.* **1989**, *54*, 5667-5675.; (b) Takahashi, M.; Asaba, K.; Lua, T. T.; Inuzuka, T.; Uemura, N.; Sakamoto, M.; Sengoku, T.; Yoda, H. Controllable Monobromination of Perylene Ring System: Synthesis of Bay-Functionalized Perylene Dyes, *J. Org. Chem.* **2018**, *83*, 624-631.; (c) George, L.; Ahmed, Z.; Lemmetyinen, H.; Efimov, A. Controlled Regioselective Amination of Peryleneimides, *Eur. J. Org. Chem.* **2015**, *2015*, 584-590.
- (33) Wheatley, A. E. H. The Directed Lithiation of Benzenoid Aromatic Systems, *Eur. J. Inorg. Chem.* **2003**, *2003*, 3291-3303.
- (34) (a) Reich, H. J. Role of Organolithium Aggregates and Mixed Aggregates in Organolithium Mechanisms, *Chem. Rev. (Washington, DC, U.S.)* **2013**, *113*, 7130-7178.; (b) Anderson, D. R.; Faibish, N. C.; Beak, P. Complex-Induced Proximity Effects in Directed Lithiations: Analysis of Intra- and Intermolecular Kinetic Isotope Effects in Directed Aryl and Benzylic Lithiations, *J. Am. Chem. Soc.* **1999**, *121*, 7553-7558.
- (35) Jorgenson, M. J., Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. In *Organic Reactions*, John Wiley & Sons, Inc.: Hoboken, N.J., U.S.A., 1970; Vol. 18, pp 1-98.
- (36) Mason, F. A. Derivatives of 1 : 8-naphthalic acid. Part I. The preparation and properties of 1 : 8-naphthalyl chloride, *J. Chem. Soc., Trans.* **1924**, *125*, 2116-2119.
- (37) Since the Naphthalene 1,8-diamide is a symmetrical molecule, ¹H NMR does not allow determination of % d-incorporation since the signals for the 2- and 2,7-deuterated derivatives show identical chemical shifts (See SI).
- (38) Krizan, T. D.; Martin, J. C. In situ trapping of *ortho* lithiated benzenes containing electrophilic directing groups, *J. Am. Chem. Soc.* **1983**, *105*, 6155-6157.
- (39) Mills, R. J.; Snieckus, V. Directed metalation of tertiary benzamides. Silicon protection of *ortho* sites and *ortho* methyl groups, *J. Org. Chem.* **1983**, *48*, 1565-1568.
- (40) Blackmore, I. J.; Boa, A. N.; Murray, E. J.; Dennis, M.; Woodward, S. A simple preparation of iodoarenes, iodoalkenes and

- iodoalkynes by reaction of organolithiums with 2,2,2-trifluoro-1-iodoethane, *Tetrahedron Lett.* **1999**, *40*, 6671-6672.
- (41) Zhao, Z.; Snieckus, V. Directed *ortho* Metalation-Based Methodology. Halo-, Nitroso-, and Boro-Induced *ipso*-Desilylation. Link to an *in situ* Suzuki Reaction, *Org. Lett.* **2005**, *7*, 2523-2526.
- (42) Balasubramanian, V. *peri* Interaction in Naphthalene Derivatives, *Chem. Rev. (Washington, DC, U.S.)* **1966**, *66*, 567-641.
- (43) Cohen, S.; Thirumalaikumar, M.; Pogodin, S.; Agranat, I. *Peri* Interactions in Naphthalene Diketones: A Preference for (*Z,Z*) Conformations, *Struct. Chem.* **2004**, *15*, 339-346.
- (44) Snieckus, V.; Anctil, E. J. G., The Directed *ortho* Metallation (DoM)-Cross-Coupling Nexus. Synthetic Methodology for the Formation of Aryl-Aryl and Aryl-Heteroatom-Aryl Bonds. In *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH: Weinheim, Germany, 2013; pp 1067-1133.
- (45) (a) Fu, J. M.; Zhao, B. P.; Sharp, M. J.; Snieckus, V. *ortho* and remote metalation – cross coupling strategies. Total synthesis of the naturally occurring fluorenone dengibsinin and the azafuoranthene alkaloid imeluteine, *Can. J. Chem.* **1994**, *72*, 227-236.; (b) Fu, J.; Snieckus, V. The directed *ortho* metalation - palladium catalyzed cross coupling connection. A general regioselective route to 9-phenanthrols and phenanthrenes. Exploratory further metalation, *Can. J. Chem.* **2000**, *78*, 905-919. ; (c) Wang, X.; Fu, J.-M.; Snieckus, V. Directed Metalation Cross-Coupling Strategies. Total Syntheses of the Alleged and the Revised Phenanthrene Natural Product Gymnopusin, *Helv. Chim. Acta* **2012**, *95*, 2680-2694.
- (46) Ledwon, P. Recent advances of donor-acceptor type carbazole-based molecules for light emitting applications, *Org. Electron.* **2019**, *75*, 105422.
- (47) (a) Clayden, J.; McCarthy, C.; Helliwell, M. Bonded *peri*-interactions govern the rate of racemisation of atropisomeric 8-substituted 1-naphthamides, *Chem. Commun. (Cambridge, U. K.)* **1999**, 2059-2060.; (b) Okamoto, A.; Ohisa, S.; Yoshiwaka, S.; Yonezawa, N. Conformational Exchange of 1,8-Dibenzoyl-2,7-Dimethoxynaphthalene Analogues in Solution, *Eur. Chem. Bull.* **2015**, *4*, 67-73.; (c) Judge, D. K.; Haycock, P.; Richardson, R. D.; Fuchter, M. J. *ortho*-substituted 1,8-diarylnaphthalenes: conformational thermodynamics and kinetics, *Synlett* **2013**, *24*, 2365-2369.
- (48) Lorentzen, M.; Kalvet, I.; Sauriol, F.; Rantanen, T.; Jørgensen, K. B.; Snieckus, V. Atropisomerism in Tertiary Biaryl 2-Amides: A Study of Ar-CO and Ar-Ar' Rotational Barriers, *J. Org. Chem.* **2017**, *82*, 7300-7308.
- (49) Wolf, C., Chapter 3 Racemization, Enantiomerization and Diastereomerization. In *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, 1st ed.; The Royal Society of Chemistry: Cambridge, United Kingdom, 2008; pp 29-135.
- (50) Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Warren, J. E.; Whiting, A. The structure, modelling and dynamics of 2,7-diisopropoxy-1,8-diarylnaphthalenes, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510-1519.
- (51) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. Barriers to rotation about the chiral axis of tertiary aromatic amides, *Tetrahedron* **1998**, *54*, 13277-13294.
- (52) Staab, H. A.; Chi, C.-S.; Dabrowski, J. Steric and electronic contributions to barriers of internal rotation in 1,8-dibenzoylnaphthalenes, *Tetrahedron* **1982**, *38*, 3499-3505.
- (53) Fu, J. M.; Zhao, B. P.; Sharp, M. J.; Snieckus, V. Remote aromatic metalation. An anionic Friedel-Crafts equivalent for the regioselective synthesis of condensed fluorenones from biaryl and *m*-teraryl 2-amides, *J. Org. Chem.* **1991**, *56*, 1683-1685.
- (54) Patel, J. J.; Blackburn, T.; Alessi, M.; Sawinski, H.; Snieckus, V. Tetraethylphosphorodiamidate-Directed Metalation Group: Directed *ortho* and *Remote* Metalation, Cross Coupling, and Remote Phospha Anionic Fries Rearrangement Reactions, *Org. Lett.* **2020**, *22*, 3860-3864.
- (55) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.* **1993**, *98*, 5648-5652.
- (56) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B Condens. Matter Mater. Phys.* **1988**, *37*, 785-789.
- (57) Otero-de-la-Roza, A.; Johnson, E. R. Non-covalent interactions and thermochemistry using XDM-corrected hybrid and range-separated hybrid density functionals, *J. Chem. Phys.* **2013**, *138*, 204109.
- (58) Johnson, E. R., The Exchange-Hole Dipole Moment Dispersion Model. In *Non-Covalent Interactions in Quantum Chemistry and Physics*, Otero de la Roza, A.; DiLabio, G. A., Eds. Elsevier: Amsterdam, Netherlands, 2017; pp 169-194.
- (59) Scalmani, G.; Frisch, M. J. Continuous surface charge polarizable continuum models of solvation. I. General formalism, *J. Chem. Phys.* **2010**, *132*, 114110.
- (60) Frisch, M. J., et. al. *Gaussian 09 Revision B.01 Gaussian Inc.*: Wallingford, CT, 2009.
- (61) Legault, C. Y., *CYLVIEW, 1.0b* <http://www.cylview.org>: Université de Sherbrooke. Sherbrooke, QC, Canada, 2009.
- (62) Hacker, A. S.; Pavano, M.; Wood, J. E.; Immoos, C. E.; Hashimoto, H.; Genis, S. P.; Frantz, D. K. Synthesis and Electronic Properties of Fluoreno[2,1-a]fluorenedione and Fluoreno[1,2-a]fluorenedione, *J. Org. Chem.* **2018**, *83*, 510-515.
- (63) Jørgensen, K. B.; Rantanen, T.; Dörfler, T.; Snieckus, V. Directed Metalation-Suzuki-Miyaura Cross-Coupling Strategies: Regioselective Synthesis of Hydroxylated 1-Methylphenanthrenes, *J. Org. Chem.* **2015**, *80*, 9410-9424.
- (64) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. Stereochemistry of reaction paths at carbonyl centres, *Tetrahedron* **1974**, *30*, 1563-1572.
- (65) Cieplak, A. S., Organic Addition and Elimination Reactions; Transformation Paths of Carbonyl Derivatives. In *Structure Correlation*, Bürgi, H.-B., Dunitz, J. D., Ed. Wiley-VCH: Weinheim, Germany, 1994; Vol. 1, pp 205-302 (pp210-218).
- (66) Wang, G.; Liu, L.; Wang, H.; Ding, Y.-S.; Zhou, J.; Mao, S.; Li, P. N,B-Bidentate Boryl Ligand-Supported Iridium Catalyst for Efficient Functional-Group-Directed C-H Borylation, *J. Am. Chem. Soc.* **2017**, *139*, 91-94.
- (67) Pfeifer, L.; Hoang, N. V.; Scherübl, M.; Pshenichnikov, M. S.; Feringa, B. L. Powering rotary molecular motors with low-intensity near-infrared light, *Sci. Adv.* **2020**, *6*, eabb6165.
- (68) Dong, H.-Q.; Wei, T.-B.; Ma, X.-Q.; Yang, Q.-Y.; Zhang, Y.-F.; Sun, Y.-J.; Shi, B.-B.; Yao, H.; Zhang, Y.-M.; Lin, Q. 1,8-Naphthalimide-based fluorescent chemosensors: recent advances and perspectives, *J. Mater. Chem. C* **2020**, *8*, 13501-13529.
- (69) Simon, J.; Stammer, A.; Oldengott, J.; Bögge, H.; Glaser, T. Proof of Phosphate Diester Binding Ability of Cytotoxic DNA-Binding Complexes, *Inorg. Chem.* **2020**, *59*, 14615-14619.
- (70) Akporji, N.; Thakore, R. R.; Cortes-Clerget, M.; Andersen, J.; Landstrom, E.; Aue, D. H.; Gallou, F.; Lipshutz, B. H. N2Phos – an easily made, highly effective ligand designed for ppm level Pd-catalyzed Suzuki-Miyaura cross couplings in water, *Chem. Sci.* **2020**, *11*, 5205-5212.
- (71) Yoshida, H.; Seki, M.; Kamio, S.; Tanaka, H.; Izumi, Y.; Li, J.; Osaka, I.; Abe, M.; Andoh, H.; Yajima, T.; Tani, T.; Tsuchimoto, T. Direct Suzuki-Miyaura Coupling with Naphthalene-1,8-diaminato (dan)-Substituted Organoborons, *ACS Catal.* **2020**, *10*, 346-351.