Metalation Hot Paper

International Edition: DOI: 10.1002/anie.201702512
German Edition: DOI: 10.1002/ange.201702512

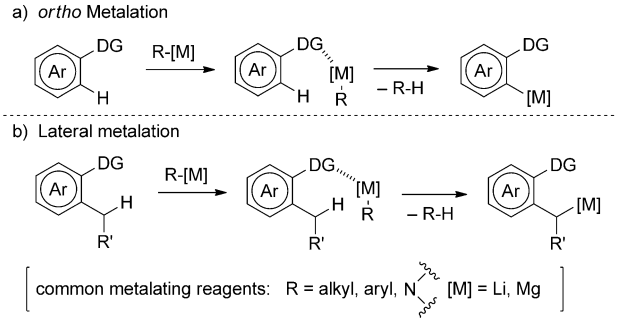
Amide-Directed C–H Sodiation by a Sodium Hydride/Iodide Composite

*Yinhua Huang[+], Guo Hao Chan[+], and Shunsuke Chiba**

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 90th birthday

Abstract: *A new protocol for amide-directed ortho and lateral C–H sodiation is enabled by sodium hydride (NaH) in the presence of either sodium iodide (NaI) or lithium iodide (LiI). The transient organosodium intermediates could be transformed into functionalized aromatic compounds.*

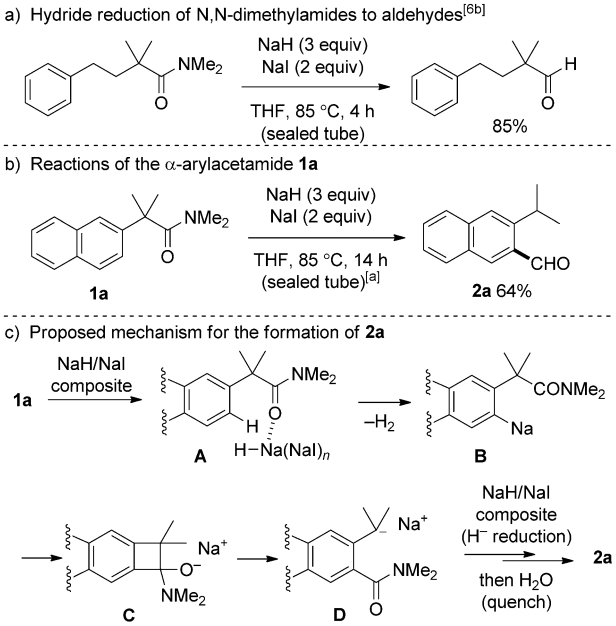
Directed C–H metalation of aromatic compounds with basic metalating reagents is a regioselective way to convert a relatively inert C–H bond into a nucleophilic organometallic species (i.e., *ortho* metalation for aromatic C(sp^2)–H bonds and lateral metalation for benzylic C(sp^3)–H bonds), and is one of the most useful and practical methods in the production of functionalized aromatic chemicals (Scheme 1).[1,2] Typically, organolithium/magnesium reagents



Scheme 1. Directed *ortho*- and lateral metalation. DG = directing group.

and lithium/magnesium amides are employed as the metalating reagents of choice, whereas organo- and inorganic sodium reagents have rarely been utilized for metalation because of their instability, inaccessibility, and limited reactivity despite the lower cost of metallic sodium and its derivatives.[3–5] Herein, we report use of a sodium hydride/iodide composite to perform either amide-directed sodiation of either *ortho* C(sp^2)–H bonds or lateral benzylic C(sp^3)–H bonds. Subsequent reactions of the resulting organosodium intermediates with the amide moiety furnished useful aromatic building blocks such as arylaldehydes bearing secondary alkyl groups at the *ortho*-position, 2-indanones, and polycyclic aromatic hydrocarbons. The discovery and scope/limitations of these processes are described herein.

We recently disclosed that sodium hydride (NaH) could be endowed with unprecedented hydride donor reactivity by solvothermal treatment with either NaI or LiI in THF, and the resulting composites could be used for a series of hydride reductions.[6] For example, the NaH/iodide composite enabled hydride reduction of *N,N*-dimethylamides into aldehydes (Scheme 2a).[6b] During the course of the study of the hydride reduction of aliphatic amides by the NaH/NaI system, we found that the reduction of the α-arylacetamide **1a** delivers 3-isopropyl-2-naphthaldehyde (**2a**) in 64% yield (Scheme 2b). In sharp contrast to the reduction of aliphatic amides shown in Scheme 2a, the reduction of **1a** did not form the corresponding aliphatic aldehyde at all. Notably, no reaction was observed with only NaH. We assumed that the NaH/iodide composite bears reasonable Lewis acidity and

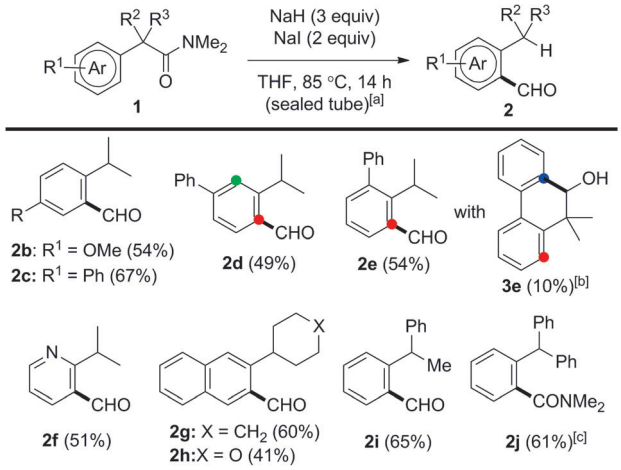


Scheme 2. Reactions of aliphatic amides with a NaH/NaI composite. [a] The reactions were conducted using 0.5 mmol of **1a** in THF (2.5 mL: 0.2 M) and yields of isolated **2a** are noted above. No reaction was observed without NaI. THF = tetrahydrofuran.

[*] Dr. Y. Huang,[+] G. H. Chan,[+] Prof. S. Chiba
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
Singapore 637371 (Singapore)
E-mail: shunsuke@ntu.edu.sg
[+] These authors contributed equally.
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201702512.

forms the complex **A** with the Lewis-basic amide moiety (Scheme 2c). With a complex-induced proximity effect,[7] subsequent *ortho* deprotonation takes place to form the arylsodium **B**, which undergoes nucleophilic addition to the amide carbonyl group to provide the four-membered ring anionic carbinolamine **C**. To release the ring strain of **C**, ring-opening takes place through C–C bond cleavage to generate the arylamide **D** (1,3-carbamoyl migration). Further hydride reduction of the amide moiety of **D** results in the formation of the aldehyde **2a**.

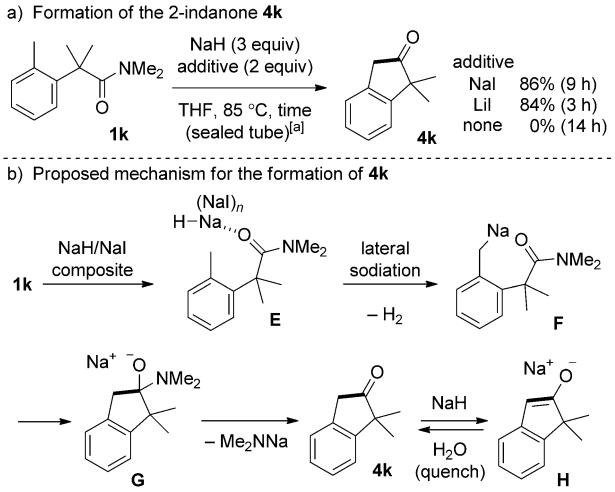
This process is a sequence of unprecedented anionic C-Fries-type rearrangement[8,9] and amide reduction enabled by the NaH/iodide composite, thus offering concise access to arylaldehydes bearing secondary alkyl groups at the *ortho*-position (**2**) from readily available α-quaternary α-arylacetamides (**1**). Thus, we next investigated the scope and limitations of this multistep molecular transformation (Scheme 3).[10] The substituent R^1, either a methoxy or



Scheme 3. Substrate scope for the synthesis of arylaldehydes **2** bearing secondary alkyl groups at the *ortho*-position. [a] The reactions were conducted using 0.5 mmol of **1** in THF (2.5 mL: 0.2 M) for 14 h and yields of the isolated products are noted above. [b] 9,10-Dihydrophenanthren-9-ol (**3e**) was obtained together with the aldehyde **2e** from the reaction of the amide **1e** (see the Supporting Information for more details). [c] The reaction was completed after 18 h to afford the benzamide **2j** in 61% yield instead of the corresponding benzaldehyde.

phenyl group, on the aryl group was tolerated (**2b–e**). The reaction of the *meta*-phenyl substrate **1d** resulted in selective installation of the formyl group at the sterically less hindered carbon center of **2d** (marked in red). Interestingly, when the *ortho*-phenyl substrate **1e** was employed, not only the biarylaldehyde **2e** but also the 9,10-dihydrophenanthren-9-ol **3e** were isolated in 54% and 10% yields, respectively. Formation of **3e** might be triggered by remote sodiation[11] at the biaryl C–H bond (marked in blue) by the NaH/NaI composite, and then followed by a sequence of cyclization and reduction.[12] It is worthy to note that a pyridyl moiety (**2f**) is compatible in the present process. The protocol allowed the synthesis of benzaldehydes having cyclohexyl (**2g**) and tetrahydropyranyl (**2h**) moieties. The reaction of α-diphenylacetamide (**1i**) provided the corresponding benzaldehyde **2i** in 65% yield, whereas that of α-triphenylacetamide (**1j**) afforded the *N*,*N*-dimethylbenzamide **2j** in 61% yield. The resulting bulky *ortho*-diphenylmethyl moiety of **2j** might impede further hydride reduction, by the NaH/iodide composite, of the rearranged amide moiety.

Interestingly, the treatment of the α-(2-tolyl)acetamide **1k** with the NaH/iodide composite provided the 2-indanone **4k** as the sole product (Scheme 4a), in which use of the NaH/

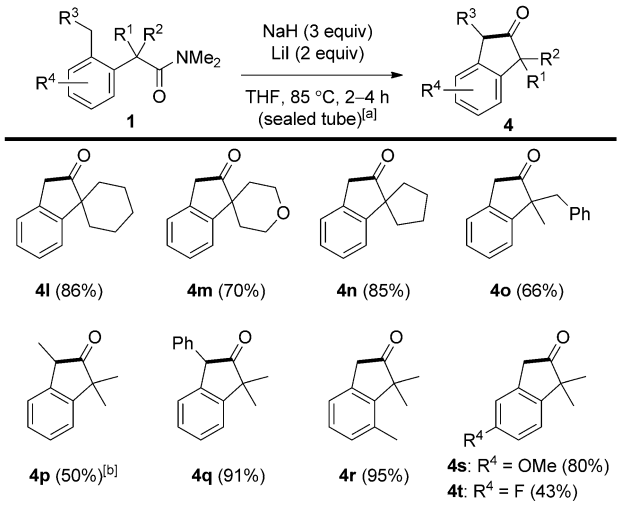


Scheme 4. Lateral sodiation for the synthesis of **4k**. [a] The reactions were conducted using 0.5 mmol of **1k** in THF (2.5 mL: 0.2 M) and yields of isolated **4k** are noted above.

LiI system rendered the process faster.[13] Again, NaH alone was not sufficient for promoting the reaction, thus indicating the unique reactivity from the NaH/iodide composite. In this case, the transient NaH/amide complex **E**, in turn, undergoes lateral benzylic $C(sp^3)$–H sodiation exclusively to generate the benzyl sodium **F**, which cyclizes with the amide moiety to give the five-membered ring anionic carbinol amine **G** (Scheme 4b). Elimination of sodium dimethylamide produces **4k**. Further hydride reduction of the carbonyl group could be prevented by formation of the enolate **H** by α-deprotonation.

2-Indanones are a privileged scaffold for production of pharmaceutical drugs based on the 2-aminoindane core.[14] As the current protocol with the NaH/iodide composite could be an attractive alternative to synthesizing 2-indanones,[15] the scope and limitations were explored (Scheme 5).[10] The method allowed construction of the spirocyclic 2-indanones **4l–n** efficiently. Installation of two different alkyl groups (benzyl and methyl groups) at C1 of **4o** was readily accomplished. Lateral sodiation of the methylene moiety also worked with the current protocol, thus furnishing **4p** and **4q** in moderate to good yields. As for the substituent R^4 on the benzene ring, methyl, methoxy, and fluoro groups were introduced (**4r–t**), while the yield of 5-fluoro-2-indanone (**4t**) was moderate.

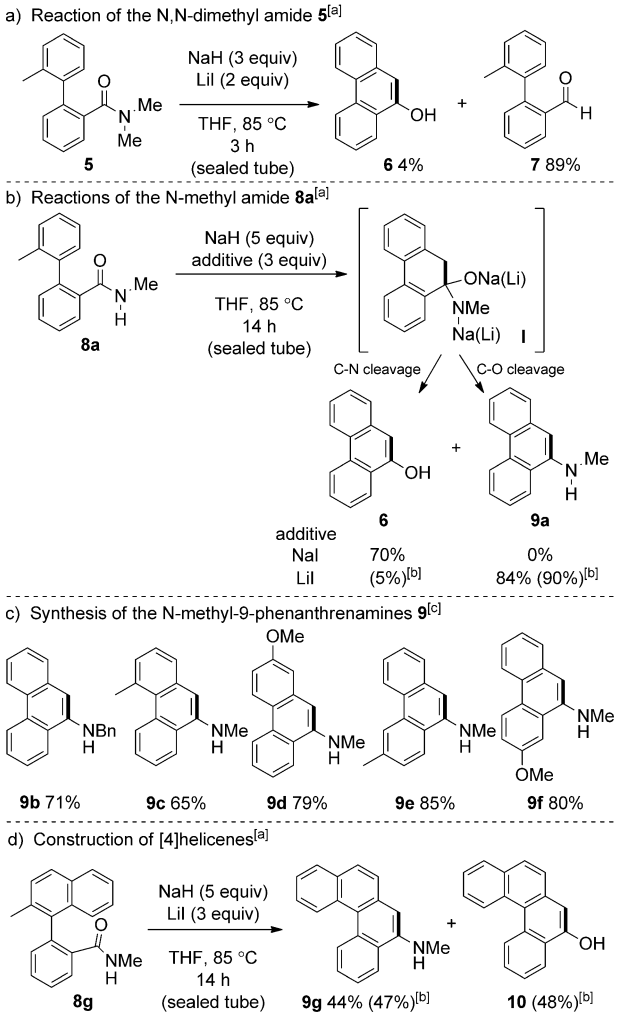
We next attempted construction of a phenanthrene scaffold by a lateral sodiation/cyclization sequence of biaryl



Scheme 5. Substrate scope for the synthesis of 2-indanones **4**. [a] Unless otherwise stated, the reactions were conducted using 0.3–0.5 mmol of **1** in THF (0.2 M) for 2–4 h and yields of isolated **4** were noted above. [b] NaI (2 equiv) was used instead of LiI and the reaction was run for 6 h.

amides.[16] For this purpose, use of the N,N-dimethylbenzamide **5** was not optimal with the NaH/iodide composite, thus affording 9-phenanthrenol (**6**) in only 4% yield (Scheme 6a). In this case, the major product was a hydride reduction product, the biarylaldehyde **7** (89% yield). Since we observed in the previous study that secondary amides could tolerate such undesired hydride reduction,[6a] the reactions of the N-methyl biarylamide **8a** were tested (Scheme 6b). As expected, construction of the phenanthrene skeleton proceeded smoothly, and more fascinatingly, the product distribution could be switched by changing the iodide additive. Namely, the reaction with the NaH/NaI system predominantly provided **6** by C–N bond cleavage of the cyclized anionic carbinolamine intermediate **I**, whereas use of the NaH/LiI system delivered *N*-methyl-9-phenanthrenamine (**9a**) by C–O bond cleavage as the major product. The roles of the iodide additives to differentiate the major product (**6** or **9a**) are the subject of ongoing investigations. As construction of the amino benzene scaffold has rarely been achieved using the lateral metalation/cyclization strategy,[17,18] the scope and limitations of the reaction employing the NaH/LiI system was examined (Scheme 6c). The method allowed installation of a cleavable benzyl group on the nitrogen atom of the phenanthrenamine **9b**. Synthesis of the N-methyl-9-phenanthrenamines **9c–f** having methyl and methoxy groups were successfully achieved. Moreover, the present protocol was applicable to the reaction of the biarylamide **8g**, which did not easily undergo lateral metalation/cyclization sequence by the conventional method with LDA, because of the hindered rotation on the biaryl axis.[16] Cyclization under the NaH/LiI system provided 5-*N*-methylamino-[4]helicene (**9g**) together with 5-hydroxy-[4]helicene (**10**) in good combined yield (Scheme 6d).[19]

This work demonstrates potential use of a NaH/iodide composite for directed C–H sodiation. We are currently



Scheme 6. Lateral sodiation of biaryl amides. [a] The reactions were conducted using 0.5 mmol of amide substrates in THF (2.5 mL: 0.2 M) and yields of isolated products were noted above unless otherwise stated. [b] Yields within the parentheses are determined based on ^{1}H NMR spectroscopy with the aid of an internal standard. [c] The reactions were conducted using 0.5 mmol of the amides **8** with NaH (5 equiv) and LiI (3 equiv) in THF (2.5 mL: 0.2 M) at 85 °C for 14 h and yields of isolated **9** are noted above. Bn = benzyl.

investigating other possible directing groups to establish versatile protocols for C–H sodiation under user-friendly reaction conditions and procedures.

Acknowledgments

Funding of S.C. for this work was provided by Nanyang Technological University, Singapore Economic Development Board (EDB), and Pfizer Asia Pacific Pte. Ltd. G.H.C. thanks to EDB-Industrial Post-graduate Program (IPP) for the scholarship support.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amides · arenes · C–H activation · metalation · sodium hydride

[1] For reviews on directed *ortho*-metalation, see: a) S. Florio, A. Salomone, *Synthesis* **2016**, 1993; b) D. Tilly, J. Magolan, J. Mortier, *Chem. Eur. J.* **2012**, *18*, 3804; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; *Angew. Chem.* **2011**, *123*, 9968; d) V. Snieckus, *Pure Appl. Chem.* **1990**, *62*, 2047; e) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; f) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306.

[2] For a review on directed lateral metalation, see: R. D. Clark, A. Jahangir, *Org. React.* **1995**, *47*, 1.

[3] For reviews on the chemistry of organosodium reagents, see: a) M. Schlosser, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 362; *Angew. Chem.* **1964**, *76*, 258; b) M. Schlosser, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 287; *Angew. Chem.* **1964**, *76*, 124; c) R. A. Benkeser, D. J. Foster, D. M. Sauve, J. F. Nobis, *Chem. Rev.* **1957**, *57*, 867.

[4] For reports on use of in situ generated organosodium reagents for directed *ortho* sodiation, see: a) J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2004**, *45*, 9331; b) A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340; *Angew. Chem.* **2002**, *114*, 350.

[5] For reports on directed magnesiation using Na/Mg bimetallic reagents, see: a) A. J. Martínez-Martínez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834; b) P. C. Andrikopoulos, D. R. Armstrong, D. V. Graham, E. Hevia, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, C. Talmard, *Angew. Chem. Int. Ed.* **2005**, *44*, 3459; *Angew. Chem.* **2005**, *117*, 3525.

[6] a) D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2017**, *56*, 1840; *Angew. Chem.* **2017**, *129*, 1866; b) P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2016**, *55*, 3719; *Angew. Chem.* **2016**, *128*, 3783; c) Z. Hong, D. Y. Ong, S. K. Muduli, P. C. Too, G. H. Chan, Y. L. Tnay, S. Chiba, Y. Nishiyama, H. Hirao, H. S. Soo, *Chem. Eur. J.* **2016**, *22*, 7108.

[7] a) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; *Angew. Chem.* **2004**, *116*, 2256; b) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356.

[8] For selected reports on anionic O- and N-Fries rearrangements, see: a) J. C. Riggs, K. J. Singh, M. Yun, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 13709; b) S. L. MacNeil, B. J. Wilson, V. Snieckus, *Org. Lett.* **2006**, *8*, 1133; c) J. P. H. Charmant, A. M. Dyke, G. C. Lloyd-Jones, *Chem. Commun.* **2003**, 380; d) M. P. Sibi, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1935.

[9] The reactions of **1a** with either *sec*-BuLi or LDA, which are commonly used to induce the anionic Fries rearrangement, did not provide the corresponding amide (a protonated form of intermediate D in Scheme 2) through 1,3-carbamoyl migration (see the Supporting Information).

[10] The methods in Schemes 3 and 5 have thus far not proven successful with α-tertiary and α-secondary amides because of the inherent Brønsted basicity of NaH.

[11] D. Tilly, J.-m. Fu, B.-p. Zhao, M. Alessi, A.-S. Castanet, V. Snieckus, J. Mortier, *Org. Lett.* **2010**, *12*, 68.

[12] X. Tang, A. Studer, *Org. Lett.* **2016**, *18*, 4448.

[13] It should be noted that solvothermal treatment of NaH and LiI induces counterion metathesis to form the NaH/NaI composite, which is responsible for the present hydride-transfer reactions. See Ref. [6c].

[14] There are many examples of small-molecule drugs based on the 2-aminoindane core, and they are commonly prepared from 2-indanones. For reviews, see: a) S. D. Brandt, R. A. Braithwaite, M. Evans-Brown, A. T. Kicman, in *Novel Psychoactive Substances: Classification, Pharmacology and Toxicology* (Eds.: P. I. Dargan, D. M. Wood), Elsevier, Amsterdam, **2013**, pp. 261–283; b) P. D. Sainsbury, A. T. Kicman, R. P. Archer, L. A. King, R. A. Braithwaite, *Drug Test. Analysis* **2011**, *3*, 479.

[15] For reported methods on the synthesis of 2-indanones, see: a) G. Henrion, T. E. J. Chavas, X. L. Goff, F. Gagosz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6277; *Angew. Chem.* **2013**, *125*, 6397; b) J. Zhao, D. A. Clark, *Org. Lett.* **2012**, *14*, 1668; c) D. L. Usanov, H. Yamamoto, *Org. Lett.* **2012**, *14*, 414; d) A. A. Tudjarian, T. G. Minehan, *J. Org. Chem.* **2011**, *76*, 3576; e) A. M. Dalton, Y. Zhang, C. P. Davie, R. L. Danheiser, *Org. Lett.* **2002**, *4*, 2465; f) K. Nakatani, *Tetrahedron Lett.* **1987**, *28*, 165.

[16] Construction of 9-phenanthrenols was accomplished by the reactions of biaryl N,N-diethyl amides with LDA. See: J.-M. Fu, M. J. Sharp, V. Snieckus, *Tetrahedron Lett.* **1988**, *29*, 5459.

[17] The reaction of **8a** with LDA (2.2 equiv), which is commonly used to induce the lateral lithiation, provided only small amounts of the mixture of **6** and **9a** (12 and 15% yield, respectively based on ^{1}H NMR analysis of the crude reaction mixture) with 67% recovery of **8a** (see the Supporting Information).

[18] N-methyl-9-phenanthrenamines are found as the core scaffold of dioxoaporphine alkaloids. See: a) C. Hoarau, A. Couture, E. Deniau, P. Grandclaudon, *Eur. J. Org. Chem.* **2001**, 2559; b) C. Hoarau, A. Couture, E. Deniau, P. Grandclaudon, *Synthesis* **2001**, 1462; c) R. Suau, J. M. López-Romero, R. Rico, F. J. Alonso, C. Lobo, *Tetrahedron* **1996**, *52*, 11307, and references therein.

[19] The reaction of **8g** with the NaH/NaI composite provided **10** as a the sole product, while the reaction rate was found to be very slow. For example, treatment of **8g** with NaH (8.3 equiv) and NaI (5 equiv) for 24 h gave **10** in 32% yield along with 60% recovery of **8g** (see the Supporting Information).

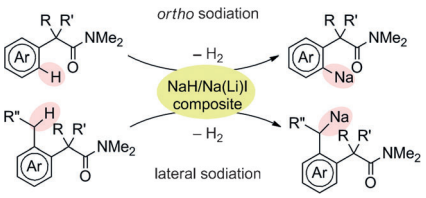
Manuscript received: March 9, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Metalation

Y. Huang, G. H. Chan,
S. Chiba* _____ ■■■■–■■■■

Amide-Directed C–H Sodiation by a Sodium Hydride/Iodide Composite



New direction: An amide-directed *ortho* and lateral C–H sodiation is enabled by sodium hydride (NaH) in the presence of either sodium iodide (NaI) or lithium iodide (LiI). The transient organosodium intermediates could be transformed into functionalized aromatic compounds.