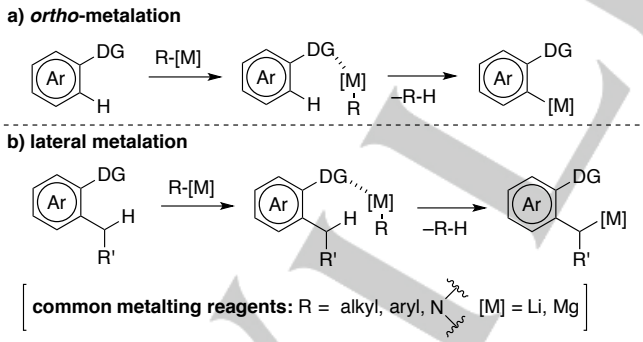
Amide-Directed C-H Sodiation by a Sodium Hydride-Iodide Composite

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

Dedicated to Professor Teruaki Mukaiyama in celebration of his 90th birthday (Sotsuju)

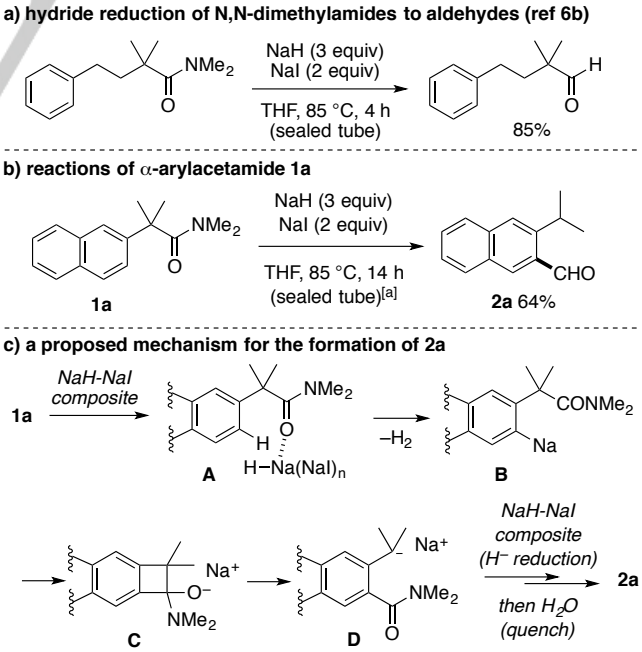
Abstract: A new protocol for amide-directed *ortho*- and lateral C-H sodiation was enabled by sodium hydride (NaH) in the presence of sodium iodide (NaI) or lithium iodide (LiI). The transient organosodium intermediates could be transformed into functionalized aromatic compounds.

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 the aromatic sp^2 C-H bond and lateral metalation for benzylic sp^3 C-H bond), which is one of the most useful and practical methods in production of functionalized aromatic chemicals (Scheme 1).[1,2] Typically, organolithium/magnesium reagents and lithium/magnesium amides are employed as the metalating reagents of choice, whereas organo- and inorganic sodium reagents have rarely been utilized for the metalation due to 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 amide-directed *ortho*-sp^2-C-H or lateral benzylic sp^3-C-H sodiation. Subsequent reactions of the resulting organosodium intermediates with the amide moiety furnished useful aromatic building blocks such as *ortho*-2°-alkyl arylaldehydes, 2-indanones, and polycyclic aromatic hydrocarbons. The discovery and scope/limitation of these processes are described herein.



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

We recently disclosed that unprecedented hydride donor reactivity could be installed onto sodium hydride (NaH) by solvothermal treatment with NaI or LiI in THF and the resulting composites could be used for a series of hydride reduction.[6] For example, the NaH-iodide composite enabled hydride reduction of N,N-dimethylamides into aldehydes (Scheme 2a).[6b] During the course of the substrate scope study in the hydride reduction of aliphatic amides by the NaH-NaI system, we found that the reduction of α-arylacetamide **1a** delivers 3-isopropyl-2-naphthaldehyde (**2a**) in 64% yield (Scheme 2b). In the 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. It should be noted that no reaction was observed with only NaH. We assumed that the NaH-iodide composite bears reasonable Lewis acidity to form complex **A** with the Lewis basic amide moiety (Scheme 2c). With complex induced proximity effect,[7] subsequent *ortho*-deprotonation takes place to form arylsodium **B**, that undergoes nucleophilic addition to the amide carbonyl group to provide 4-membered ring anionic carbinolamine **C**. To release the ring strain of **C**, ring-opening takes place through C-C bond cleavage to generate arylamide **D** (1,3-carbamoyl migration). Further hydride reduction of the amide moiety of **D** results in the formation of aldehyde **2a**.



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 isolated yields of **2a** were noted above. No reaction was observed without NaI.

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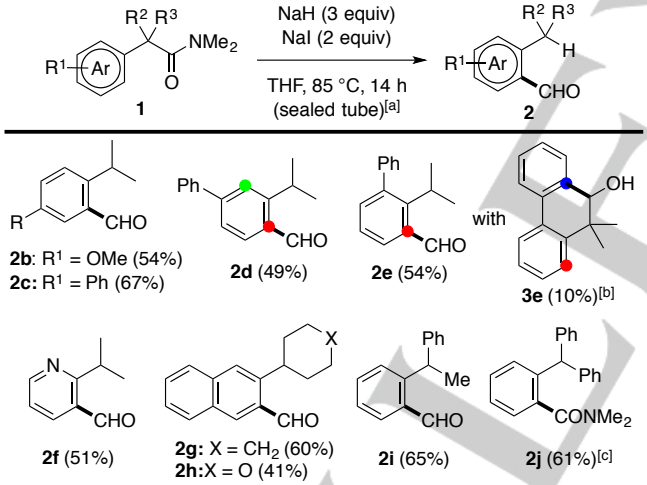
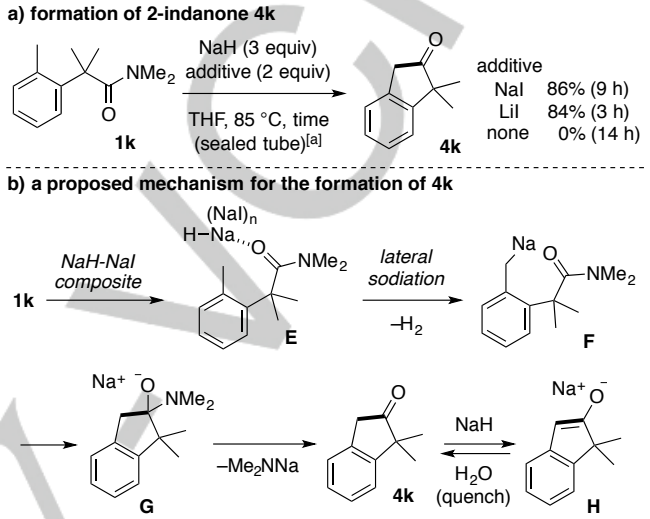
This process is a sequence of unprecedented anionic C-Fries type rearrangement[8,9] and amide reduction enabled by the NaH-iodide composite, offering a concise access to *ortho*-2°-alkyl arylaldehydes **2** from readily available α-quaternary α-arylacetamides **1**. Thus, we next investigated the scope and limitation of this multi-step molecular transformation (Scheme 3).[10] As the substituent R^1 on the aryl group, methoxy and phenyl groups could be installed (for **2b**-**2e**). The reaction of meta-phenyl substrate **1d** resulted in selective installation of the formyl group on the sterically less hindered carbon of **2d** (marked in red). Interestingly, when *ortho*-phenyl substrate **1e** was employed, not only biarylaldehyde **2e** but also 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, that is followed by a sequence of cyclization and reduction.[12] It is worthy to note that pyridyl moiety (for **2f**) is compatible in the present process. The protocol allowed for synthesis of benzaldehydes having cyclohexyl (for **2g**) and tetrahydropyranyl (for **2h**) moieties. The reaction of α-diphenylacetamide **1i** provided the corresponding benzaldehyde **2i** in 65% yield, whereas that of α-triphenylacetamide **1j** afforded N,N-dimethylbenzamide **2j** in 61% yield. The resulting bulky *ortho*-diphenylmethyl moiety of **2j** might impede further hydride reduction of the rearranged amide moiety by the NaH-iodide composite.



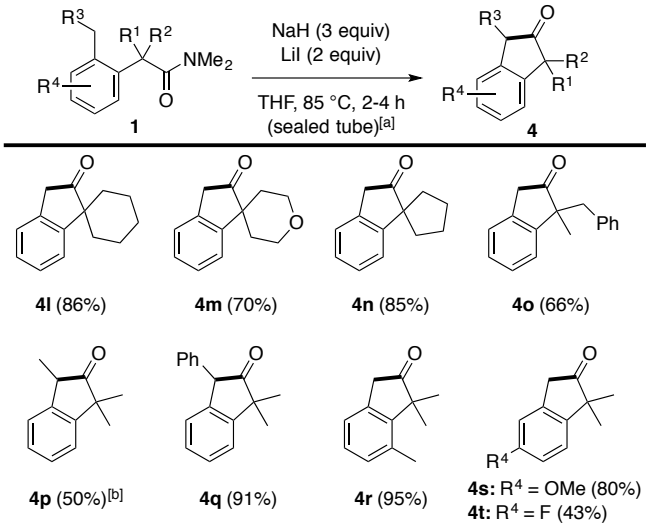
Scheme 3. Substrate scope on synthesis of *ortho*-2°-alkyl arylaldehydes **2**. [a] The reactions were conducted using 0.5 mmol of **1** in THF (2.5 mL: 0.2 M) for 14 h and isolated yields of the products were noted above. [b] 9,10-Dihydrophenanthren-9-ol **3e** was obtained together with aldehyde **2e**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

Interestingly, the treatment of α-(2-tolyl)acetamide **1k** with the NaH-iodide composites provided 2-indanone **4k** as a sole product (Scheme 4a), in which use of the NaH-LiI system rendered the process faster in rate.[13] Again, NaH alone did not perform at all, indicating the unique reactivity from the NaH-iodide composite. In this case, the transient NaH-amide complex **E**, in turn, undergoes lateral benzylic sp^3 C-H sodiation exclusively to generate benzyl sodium **F**, which cyclizes with the amide moiety to give 5-membered ring anionic carbinol amine **G** (Scheme 4b). Elimination of sodium dimethylamide produces 2-indanone **4k**. Further hydride reduction of the carbonyl group could be prevented by formation of enolate **H** through α-deprotonation.



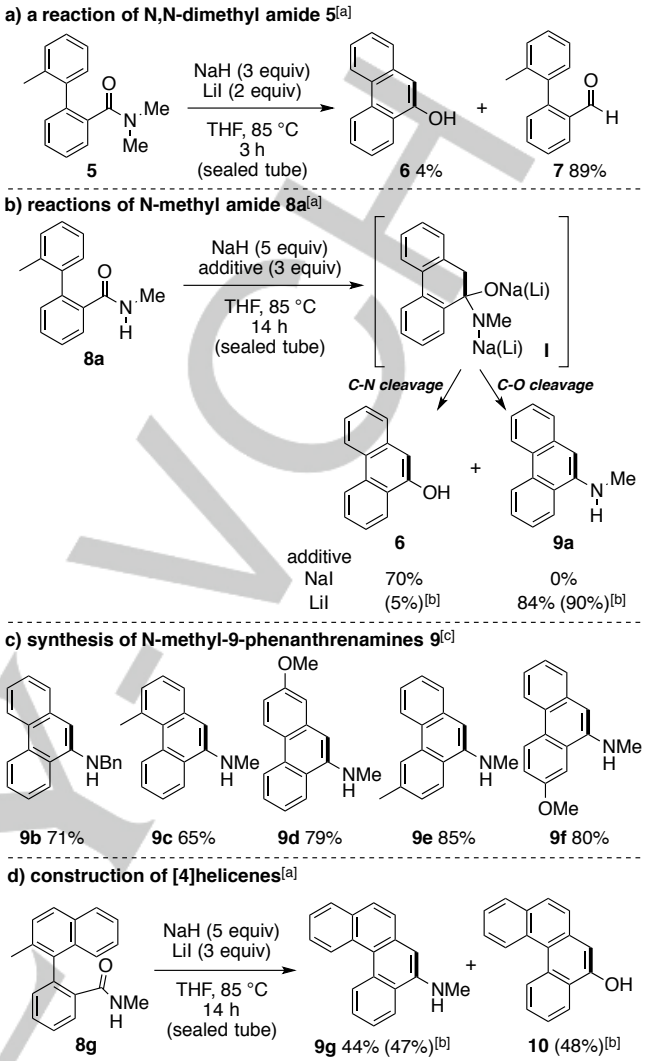
Scheme 4. Lateral sodiation for synthesis of 2-indanone **4k**. [a] The reactions were conducted using 0.5 mmol of **1k** in THF (2.5 mL: 0.2M) and isolated yields of **4k** were noted above.

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 synthesize 2-indanones,[15] the scope and limitation were explored (Scheme 5).[10] The method allowed for construction of spirocyclic 2-indanones **4l**-**4n** efficiently. Installation of two different alkyl groups (benzyl and methyl groups) at the C1 of 2-indanone **4o** was readily accomplished. Lateral sodiation of the methylene moiety also worked with the current protocol, 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 (for **4r**-**4t**), while the yield of 5-fluoro-2-indanone **4t** was moderate.



Scheme 5. Substrate scope on 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 isolated yields of **4** were noted above unless otherwise stated. [b] NaI (2 equiv) was used instead of LiI and the reaction was run for 6 h.

We next attempted construction of a phenanthrene scaffold by a sequence of lateral sodiation-cyclization of biaryl amides.[16] For this purpose, use of N,N-dimethylbenzamide **5** was not optimal with the NaH-iodide composite, affording 9-phenanthrenol (**6**) only in 4% yield (Scheme 6a). In this case, the major product was a hydride reduction product, biarylaldehyde **7** (89% yield). Since we observed in the previous study that secondary amides could tolerate such undesired hydride reduction,[6a] the reactions of 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 NaH-NaI system predominantly provided 9-phenanthrenol (**6**) via the C-N bond cleavage of cyclized anionic carbinolamine intermediate **I**, whereas use of the NaH-LiI system delivered N-methyl-9-phenanthrenamine (**9a**) via the 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 limitation with the NaH-LiI system was examined (Scheme 6c). The method allowed for installation of a cleavable benzyl group on the nitrogen of phenanthrenamine **9b**. Synthesis of N-methyl-9-phenanthrenamines **9c**-**9f** having methyl and methoxy groups were successfully achieved. Moreover, the present protocol was applicable to the reaction of biarylamide **8g**, which was otherwise difficult to undergo lateral metalation-cyclization sequence by the conventional method with LDA due to the hindered rotation on the biaryl axis.[16] The 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]



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 isolated yields of products were noted above unless otherwise stated. [b] Yields in 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 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 isolated yields of **9** were noted above. Bn = benzyl.

This work demonstrates potential use of NaH-iodide composite for directed C-H sodiation under the concise manners. We are currently investigating other possible directing groups to establish versatile protocols for C-H sodiation under user-friendly reaction conditions and procedures.

Acknowledgements

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Keywords: sodium hydride • *ortho*-metalation • lateral metalation • organosodium compounds • amides

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[9] The reactions of **1a** with 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 due to inherent Brønsted basicity of NaH.

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[13] It should be noted that solvothermal treatment of NaH and LiI induces counter-ion 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, which 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*, P. I. Dargan, D. M. Wood, Eds. (Elsevier Inc., 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.

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[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 of the crude material) with 67% recovery of **8a** (see the Supporting Information).

[18] N-Methyl-9-phenanthrenamines are involved in 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 5-hydroxy-[4]helicene **10** as a 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).

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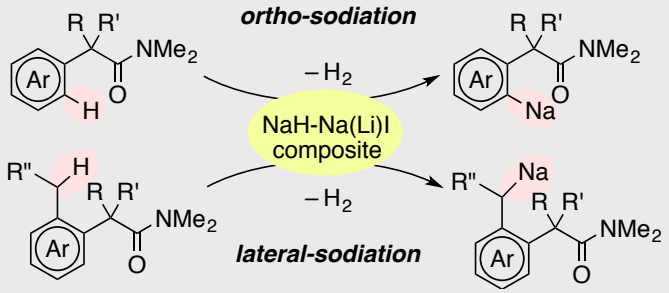

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Page No. – Page No.

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