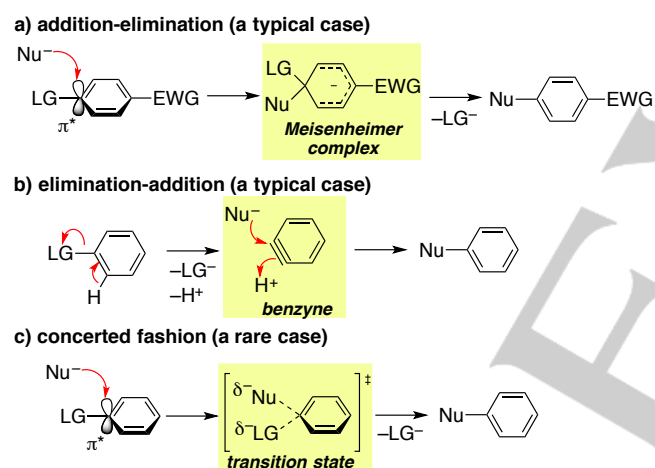


# Nucleophilic Amination of Methoxy Arenes by a Sodium Hydride-Iodide Composite

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**Abstract:** A new protocol for nucleophilic amination of methoxy arenes was established using sodium hydride (NaH) in the presence of lithium iodide (LiI), offering an efficient route to supply benzannulated nitrogen-heterocycles. Mechanistic studies showed that unusual concerted nucleophilic aromatic substitution operates in the present process.

Nucleophilic substitution reactions are one of the most fundamental and practical processes to forge a covalent bond linkage in organic synthesis.<sup>[1]</sup> Nucleophilic substitution at an aromatic sp<sup>2</sup> hybridized carbon<sup>[2]</sup> is generally considered as the



**Scheme 1.** Nucleophilic aromatic substitution reactions. Nu = nucleophile; EWG = electron withdrawing group; LG = leaving group

step-wise event, namely, either addition-elimination via a negatively charged dearomatized intermediate (a Meisenheimer complex) (Scheme 1a) or elimination-addition via a benzyne species (Scheme 1b). These stepwise processes required special settings onto the substrates and reaction conditions (e.g. installation of electron-withdrawing groups (EWG) to stabilize the Meisenheimer complex) with several drawbacks (e.g. regioselective issues in addition to the benzyne intermediate). On the other hand, a concerted nucleophilic aromatic substitution analogous to the S<sub>N</sub>2 reaction at the sp<sup>3</sup> hybridized carbon, where a Nu approaches to a π\* orbital of the sp<sup>2</sup> hybridized carbon having a leaving group to give the transition state, is hardly accepted due to the spatial requirement of high energy barrier (Scheme 1c).<sup>[3,4]</sup>

Amination of arenes enables facile construction of benzannulated saturated nitrogen-heterocycles, which are an omnipresent component of numerous natural alkaloids and potent pharmaceutical.<sup>[5]</sup> At present, the most common approach of arene amination for the construction of such scaffolds involves transition-metal catalyzed amination of (pseudo)haloarenes,<sup>[6]</sup> that have advanced the state of the art (Scheme 2a). On the other hand, the demand of transition-metal-free procedures rises from the standpoints of the rigid guideline that limits the level of residual transition-metal contamination in the pharmaceutical ingredients. In this context, Meyers developed a method for intramolecular amination of methoxy arenes, that are electrophilically activated by an ortho-oxazoline moiety (Scheme 2b).<sup>[7-9]</sup> This amination thus proceeds through the addition-elimination manner with lithium amide species. Annulation of benzynes with nitrogen nucleophiles has been used for construction of several specific nitrogen-heterocycles (Scheme 2c).<sup>[10]</sup> Electrophilic amination of hydroxylamine derivatives was reported for synthesis of benzannulated saturated nitrogen-heterocycles under basic or acidic reaction conditions (Scheme 2d).<sup>[11,12]</sup> However, these strategies have been of use for construction of limited types of nitrogen-heterocycles. Herein, we report an unprecedented example of nucleophilic amination of methoxy arenes by a tethered amine moiety in the presence of sodium hydride (NaH) and lithium iodide (LiI) (Scheme 2e). We found that the resulting sodium amides undergo facile intramolecular substitution of a rather unusual leaving group, a methoxy group on the arenes, to afford benzannulated nitrogen-heterocycles having up-to ten membered rings. Mechanistic studies based on both experimental and theoretical approaches gave a critical insight that the amination process proceeds via concerted fashion rather than the conventional step-wise manner.

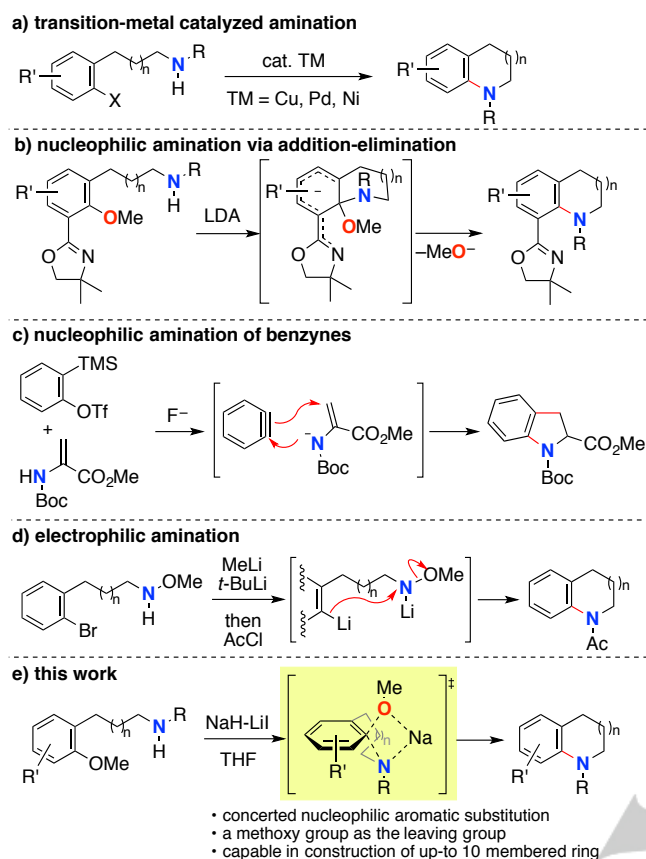
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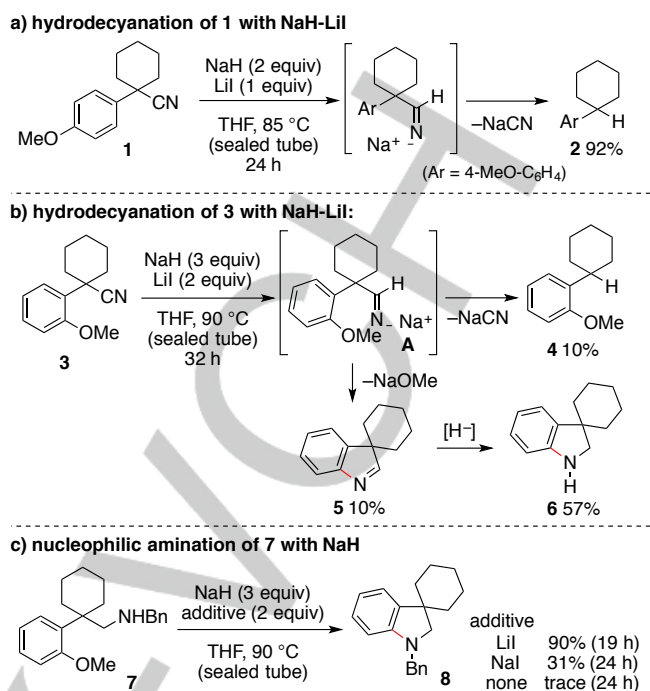
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**Scheme 2.** Synthesis of benzannulated saturated nitrogen-heterocycles

In a recent report, we described use of NaH-iodide composite<sup>[13]</sup> for hydrodeacylation of benzyl cyanides.<sup>[13c]</sup> For example, hydrodeacylation of para-methoxybenzyl cyanide **1** proceeded smoothly with the NaH-LiI composite to give **2** (Scheme 3a). During the course of studying the substrate scope, we were surprised to observe that the reaction of ortho-methoxy substrate **3** with the NaH-LiI composite provided not only an expected decyanated product **4** (in only 10% yield), but also 3*H*-indole **5** and indoline **6** in 10% and 57% yields, respectively (Scheme 3b). Assuming that this unanticipated nitrogen-heterocycles **5** and **6** are formed via nucleophilic substitution with a transient anionic imine nucleophile **A** (subsequent hydride reduction of **5** affords **6**), we wondered if this arene amination via substitution of a methoxy group could be generalized to a more versatile method for the synthesis of benzannulated N-heterocycles. Therefore, as the model experiments, we tested the reactions of readily available N-benzylamine **7** for synthesis of indoline **8** (Scheme 3c). We found that with NaH (3 equiv) as a base, addition of LiI or NaI (2 equiv) is crucial to facilitate the substitution. The reaction with the NaH-LiI composite resulted in a full conversion to afford **8** in 90% yield at 90 °C (sealed conditions) for 19 h, whereas NaH only did not work at all, indicating unique reactivity installed onto the composite.<sup>[14]</sup>



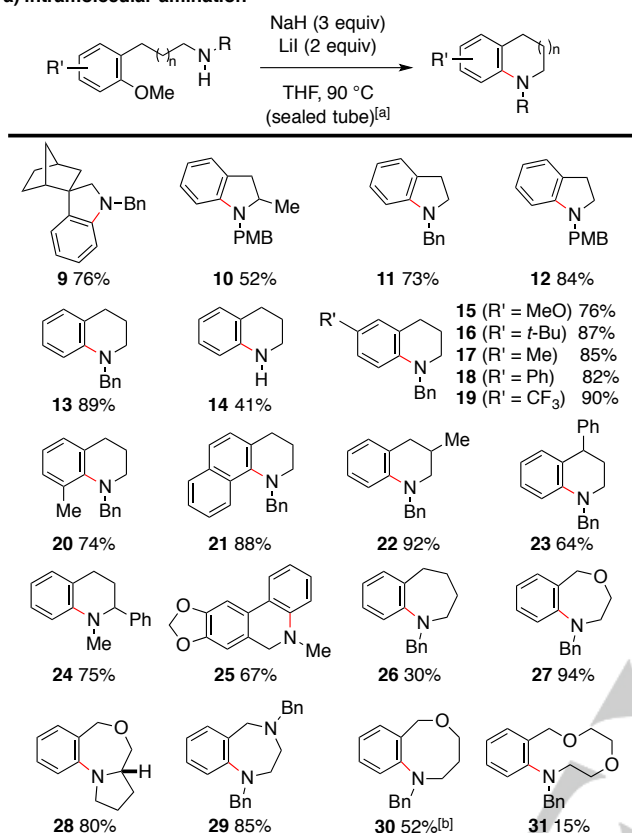
**Scheme 3.** Reactions with the NaH-iodide composite. [a] The reactions were conducted using 0.3–0.5 mmol of substrates in THF (0.1 M) and isolated yields of products were noted above. Bn = benzyl.

We next evaluated the scope of this unprecedented nucleophilic amination of methoxy arenes using the NaH-LiI composite and found it to be broad and versatile for synthesis of benzannulated saturated nitrogen-heterocycles (Scheme 4a). The method allowed for construction of not only C3-spirocyclic indoline **9** but also C2-methyl indoline **10** as well as non-substituted indolines **11** and **12** having cleavable benzyl and *p*-methoxybenzyl protection on the nitrogen. A range of tetrahydroquinolines could also be constructed with this method (for **13–24**). Of worthy to note is that electron-rich and sterically hindered methoxy arenes were viable substrates (**15–17, 20, 21**). Moreover, cyclization with the primary amine and N-methylamine was found to be optimal under the present conditions (for **14, 24**). Installation of the substituents on C2–C4 positions of tetrahydroquinolines (**22–24**) was also tolerated. The present method enabled facile construction of a dihydrophenanthridine core, that was demonstrated by a concise three-step synthesis of 5,6-dihydrobicolorine (**25**).<sup>[15]</sup> This method was also capable in constructing larger membered nitrogen-heterocycles. As for the 7-membered ring, tetrahydro-1*H*-benzo[*b*]azepine **26** as well as tetrahydrobenzo[*e*][1,4]oxazepine and -[1,4]diazepine (**27–29**) were afforded despite the moderate yield of **26**. We observed that during the construction of tricyclic **28**, the preinstalled chirality derived from (*L*)-prolinol is not lost. Tetrahydro-2*H*-benzo[*c*][1,5]oxazocine **30** (8-membered ring) could be constructed in 51% yield, whereas construction of the 10-membered ring **31** became sluggish (only 15% yield).

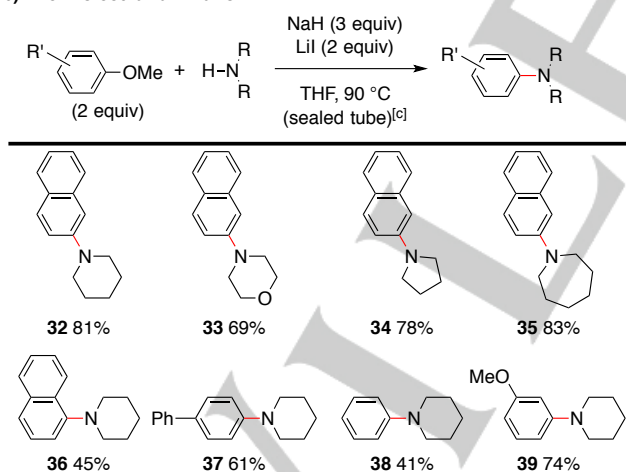
We found that the NaH-iodide composite is also capable of performing intermolecular amination of methoxy arenes with

cyclic secondary amines (Scheme 4b), affording the corresponding aromatic amines **32-39** in good to moderate yields.

#### a) intramolecular amination

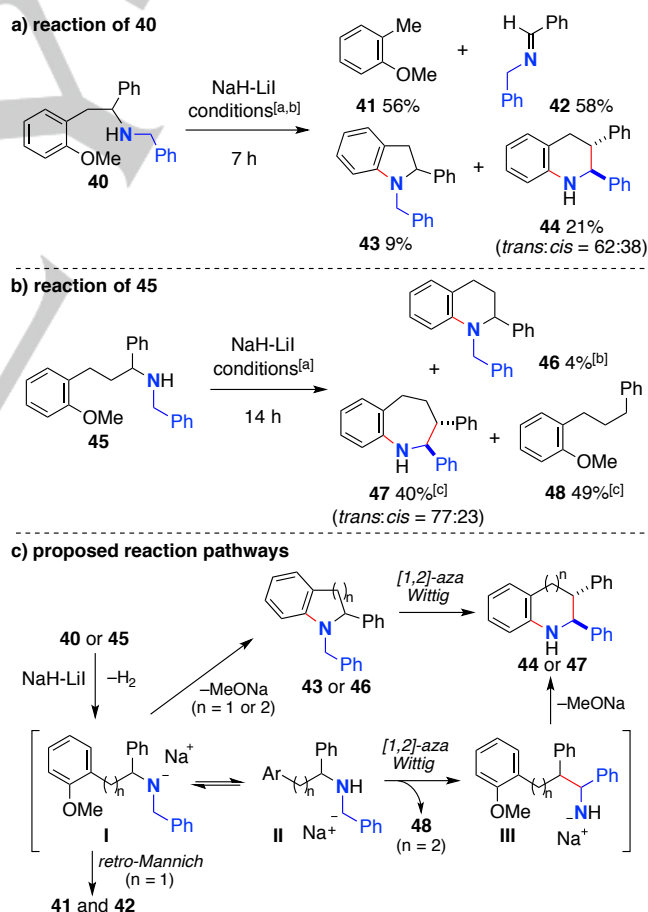


#### b) intermolecular amination



**Scheme 4.** Substrate scope. [a] The intramolecular reactions were conducted using 0.3–0.5 mmol of amines in THF (0.1 M) for 4–47 h and isolated yields of heterocycles were noted above unless otherwise stated. [b] NaH (6 equiv) and Lil (4 equiv) were used. PMB = *para*-methoxybenzyl. [c] The intermolecular reactions were conducted using amines (0.5 mmol) and methoxy arenes (1 mmol) in THF (1 M) for 40 h and isolated yields of aminated arenes were noted above.

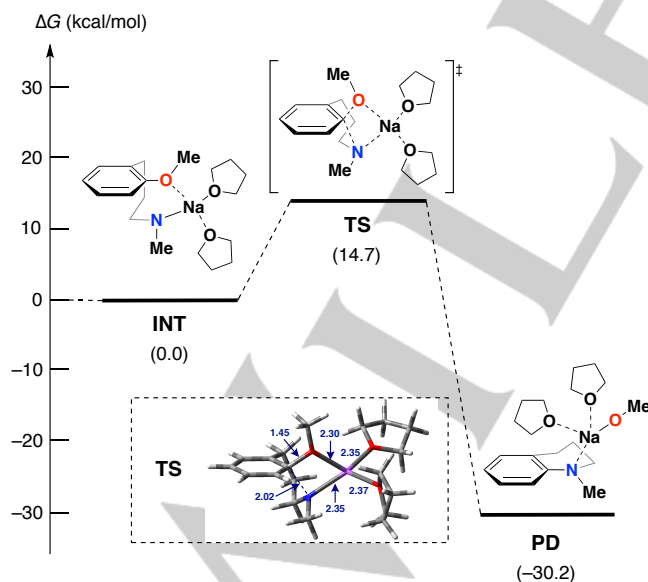
With respect to the limitations, the method has thus far not proven successful with the secondary amines having aryl and acyl groups on the nitrogen probably due to delocalization the resulting anionic charge. In the sharp contrast to the formation of indolines **9-12** (Scheme 4a), the reaction of substrate **40** gave 2-methylanisole (**41**) and aldimine **42** as the major products through the retro-Mannich reaction, whereas indoline **43** was obtained in only 9% yield and formation of tetrahydroquinoline **44** was observed in 21% yield (Scheme 5a). On the other hand, the reaction of **45**, having one-carbon longer tether than **40**, prevented the retro-Mannich reaction (Scheme 5b). In this case, the process provided expected tetrahydroquinoline **46** in only 4% yield, but affording tetrahydro-1*H*-benzo[*b*]azepine **47** in 40% yield along with formation of alkane **48** in 49% yield through C–N bond cleavage. This outcome is totally distinct from the formation of *N*-methyl **24** (Scheme 4a). The proposed reaction pathways for these unexpected reactions were illustrated in Scheme 5c. The retro-Mannich process of **40** is likely facilitated by formation of relatively stabilized benzyl anion (as a precursor of 2-methylanisole **41**) and conjugated benzaldimine **42** from sodium amide **I** ( $n = 1$ ). Nucleophilic aromatic substitution of sodium amide **I** affords **43** or **46**, which might further undergo



**Scheme 5.** Retro-Mannich reaction and skeletal rearrangement. [a] The reactions were conducted using 0.5 mmol of amines with NaH (3 equiv) and Lil (2 equiv) in THF (0.1 M) at 90 °C. [b] <sup>1</sup>H NMR yields. [c] Isolated yields.

aza-[1,2]-Wittig rearrangement<sup>[16]</sup> via deprotonation of the benzylic methylene moiety to form ring-expanded **44** or **47**, respectively. Alternatively, another aza-[1,2]-Wittig rearrangement could be proposed from benzyl sodium **II** to forge a new C-C bond to generate sodium amide **III**, which cyclizes to give **44** or **47**. Meanwhile, alkane **48** might be formed through fragmentation of benzyl sodium **II** ( $n = 2$ ).<sup>[17,18]</sup>

Several experimental observations provided clues about the reaction mechanism of the present nucleophilic amination of methoxy arenes, that is unlikely through addition-elimination via the Meisenheimer complex (from electron-rich substrates **15-17**) nor through elimination-addition via the benzyne species (from 2,6-disubstituted substrates **20** and **21**). We conducted the DFT calculations<sup>[19]</sup> to investigate the mechanism of the formation of N-methyl tetrahydroquinoline as the model reaction (Figure 1). The bulk solvent effect of THF was described with an implicit model, and two molecules of THF were included explicitly. An exothermic pathway with a single transition state (**TS**) having a partial negative charge ( $\delta^-$ ) for concerted nucleophilic aromatic substitution was obtained with the transient Na amides, and the reaction was found to proceed with the reasonable activation barrier (14.7 kcal/mol).<sup>[20]</sup> The concerted nucleophilic aromatic substitution mechanism could also be supported by the Hammett plot of  $\log(k_{\text{X}}/k_{\text{H}})$  versus  $\sigma$  with the substrates **13**, **15-17** and **19**, which provided a linear correlation with a positive  $\rho$  value of 1.99 (See the SI).<sup>[21]</sup> The calculated energy changes to see the substituent effects were consistent with the experimental results (See the SI). One of the keys to enable this unprecedented nucleophilic amination of methoxy arenes could probably be an enhanced Lewis acidity<sup>[13a,22]</sup> installed onto NaH in the composite. Nonetheless, further elucidation of the detailed mechanism is the subject of our ongoing investigations.



**Figure 1.** Reaction pathways of the nucleophilic amination with methoxy arenes. Energy changes and bond lengths at the B3LYP/6-31+G\* level of theory (SCRF (pcm, solvent = THF)) are shown in kcal/mol and Å, respectively.

This work demonstrated a new reactivity of sodium hydride in nucleophilic amination of methoxy arenes that proceeds via a concerted nucleophilic aromatic substitution pathway. Given the prevalence of saturated nitrogen-heterocycles in pharmaceuticals and biologically active natural products, we anticipate that this method will simplify the route to access to these classes of targets. We are currently working to explore other types of molecular transformations with the NaH-iodide composite.

## Acknowledgements

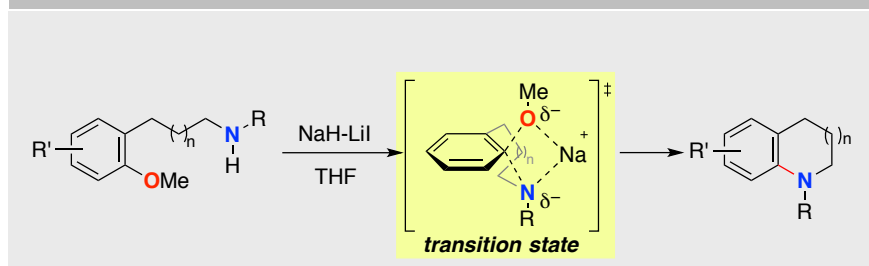
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**Keywords:** sodium hydride • amination • nucleophilic aromatic substitution • nitrogen-heterocycles • DFT calculations

- [1] R. Brückner, in: *Organic Mechanisms: Reactions, Stereochemistry and Synthesis*, (Ed.: M. Harmata), Springer, Berlin, Heidelberg, **2010**, chapter 2 and chapter 5.
- [2] F. Terrier, *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, **2013**, chapter 1.
- [3] For reports on intermolecular concerted nucleophilic aromatic substitution, see: a) L. I. Goryunov, J. Grobe, D. L. Van, V. D. Shteingarts, R. Mews, E. Lork, E.-U. Würthwein, *Eur. J. Org. Chem.* **2010**, 1111; b) A. Hunter, M. Renfrew, D. Rettura, J. A. Taylor, J. M. J. Whitmore, A. Williams, *J. Am. Chem. Soc.* **1995**, *117*, 5484; c) A. H. M. Renfrew, J. A. Taylor, J. M. J. Whitmore, A. Williams, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1703; d) S. E. Fry, N. J. Pienta, *J. Am. Chem. Soc.* **1985**, *107*, 6399.
- [4] For reports on intramolecular concerted nucleophilic aromatic substitution, see: a) C. N. Neumann, J. M. Hooker, T. Ritter, *Nature* **2016**, *534*, 369; b) F. Nawaz, K. Mohanan, L. Charles, M. Rajzmann, D. Bonne, O. Chuzel, J. Rodriguez, Y. Coquerel, *Chem. Eur. J.* **2013**, *19*, 17578; c) G. C. Lloyd-Jones, J. D. Moseley, J. S. Renny, *Synthesis* **2008**, 661.
- [5] a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845; b) C. M. Marson, *Chem. Soc. Rev.* **2011**, *40*, 5514.
- [6] For reviews, see: a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564; b) K. Okano, H. Tokuyama, T. Fukuyama, *Chem. Commun.* **2014**, *50*, 13650; c) J. Bariwal, E. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283; d) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27; e) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177; f) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; *Angew. Chem.* **2008**, *120*, 6438; g) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534.
- [7] A. I. Meyers, M. Reuman, R. A. Gabel, *J. Org. Chem.* **1981**, *46*, 783.
- [8] There are reports on intermolecular nucleophilic amination of aryl ethers with lithium amides, see: a) W. ten Hoeve, C. G. Kruse, J. M. Luteyn, J. R. G. Thiecke, H. Wynberg, *J. Org. Chem.* **1993**, *58*, 5101; b) T. Matsumoto, H. Kakigi, K. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 4337.
- [9] For a recent report on carbazole synthesis via nucleophilic amination of arylsulfones with potassium amides, see: M. Bhanuchandra, K. Murakami, D. Vasu, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* **2015**, *54*, 10234; *Angew. Chem.* **2015**, *127*, 10372.
- [10] For selected recent reports, see: a) T. K. Shah, J. M. Medina, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 4948; b) A. E. Goetz, T. K. Shah,

- N. K. Garg, *Chem. Commun.* **2015**, 51, 34; c) A. E. Goetz, N. K. Garg, *Nat. Chem.* **2013**, 5, 54; d) T. Noji, H. Fujiwara, K. Okano, H. Tokuyama, *Org. Lett.* **2013**, 15, 1946; e) K. Okano, H. Fujiwara, T. Noji, T. Fukuyama, H. Tokuyama, *Angew. Chem. Int. Ed.* **2010**, 49, 5925; *Angew. Chem.* **2010**, 122, 6061; f) C. D. Gilmore, K. M. Allan, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, 130, 1558; g) H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem. Int. Ed.* **2002**, 41, 3247; *Angew. Chem.* **2002**, 114, 3381.
- [11] a) Y. Kikugawa, A. Nagashima, T. Sakamoto, E. Miyazawa, M. Shiya, *J. Org. Chem.* **2003**, 68, 6739; b) P. Beak, G. W. Selling, *J. Org. Chem.* **1989**, 54, 5574; c) Y. Kikugawa, M. Kawase, *J. Am. Chem. Soc.* **1984**, 106, 5728.
- [12] For a recent report Rh-catalyzed aromatic C-H amination with hydroxylamine derivatives for synthesis of benzannulated nitrogen-heterocycles, see: M. P. Paudyal, A. M. Adebesein, S. R. Burt, D. H. Ess, Z. Ma, L. Kürti, J. R. Falck, *Science* **2016**, 353, 1144.
- [13] a) Y. Huang, G. H. Chan, S. Chiba, *Angew. Chem. Int. Ed.* **2017**, 56, 6544; *Angew. Chem.* **2017**, 129, 6644; b) D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2017**, 56, 1840; *Angew. Chem.* **2017**, 129, 1866; c) 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; d) 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.
- [14] Our materials characterization (ref. 13d) revealed that solvothermal treatment of NaH and Lil induces counter ion methathesis to form the activated NaH with NaI and LiH. No reaction was observed with LiH and LiH-Lil composite.
- [15] See the SI for the detailed synthetic scheme starting from commercially available 6-bromopiperonal. For reports on synthesis and isolation, see: a) T.-T. Fan-Chiang, H.-K. Wang, J.-C. Hsieh, *Tetrahedron* **2016**, 72, 5640; b) W.-L. Chen, C.-Y. Chen, Y.-F. Chen, J.-C. Hsieh, *Org. Lett.* **2015**, 17, 1613; c) S. De, S. Ghosh, S. Bhunia, J. A. Sheikh, A. Bisai, *Org. Lett.* **2012**, 14, 4466. d) R. Sanz, Y. Fernández, M. P. Castroviejo, A. Pérez, F. J. Fañanás, *Eur. J. Org. Chem.* **2007**, 62; e) C. J. Cowden, M. G. Banwell, I. C. S. Ho, *J. Nat. Prod.* **1994**, 57, 1746.
- [16] C. Vogel, *Synthesis* **1997**, 497.
- [17] A similar fragmentation was observed in [1,2]-Wittig rearrangement, see: C. R. Hauser, S. W. Kantor, *J. Am. Chem. Soc.* **1951**, 73, 1437.
- [18] We conducted several control experiments to elucidate the mechanisms shown in Scheme 5c. See the SI for the details.
- [19] Gaussian 09 (Revision E.01), M. J. Frisch, et al., Gaussian Inc., Wallingford CT, **2009**.
- [20] Reactions promoted by conceivable interaction with NaI require high energies (about 33 kcal/mol; for details, see the SI), indicating that these pathways seem to be unlikely.
- [21] Nucleophilic aromatic substitution reactions via addition-elimination mechanism normally show larger  $\rho$  values between 3 and 8. For examples, see: a) V. M. Vlasov, *New J. Chem.* **2010**, 34, 2962. b) R. Y. Sung, H. Choi, J. P. Lee, J. K. Park, K. Yang, I. S. Koo, *Bull. Korean Chem. Soc.* **2009**, 30, 1579.
- [22] It was observed that the present aromatic substitution was disturbed by the addition of TMEDA (see the SI).

## COMMUNICATION



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A new protocol for nucleophilic amination of methoxy arenes was established using sodium hydride (NaH) in the presence of lithium iodide (LiI), offering an efficient route to supply benzannulated nitrogen-heterocycles. Mechanistic studies showed that unusual concerted nucleophilic aromatic substitution operates in the present process.