

## Synthetic Methods

International Edition: DOI: 10.1002/anie.201600305  
German Edition: DOI: 10.1002/ange.201600305

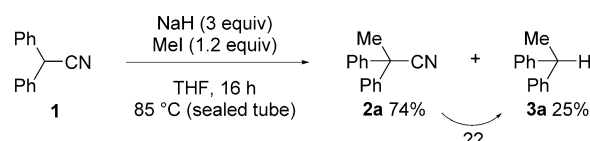
## Hydride Reduction by a Sodium Hydride–Iodide Composite

Pei Chui Too, Guo Hao Chan, Ya Lin Tnay, Hajime Hirao,\* and Shunsuke Chiba\*

**Abstract:** Sodium hydride (NaH) is widely used as a Brønsted base in chemical synthesis and reacts with various Brønsted acids, whereas it rarely behaves as a reducing reagent through delivery of the hydride to polar  $\pi$  electrophiles. This study presents a series of reduction reactions of nitriles, amides, and imines as enabled by NaH in the presence of LiI or NaI. This remarkably simple protocol endows NaH with unprecedented and unique hydride-donor chemical reactivity.

Hydride reduction of polar  $\pi$  electrophiles, such as carbonyl compounds, carbonitriles, and imines, is one of the most fundamental and important molecular transformations in chemical synthesis.<sup>[1]</sup> In this context, a variety of covalent hydrides, such as borane, alane, metal borohydrides, metal aluminum hydrides, and silanes, have often been employed as the reagents of choice for stereo-, regio-, and chemoselective hydride-transfer processes. By contrast, alkali-metal hydrides have rarely been employed as hydride sources; instead, they are used almost exclusively as strong Brønsted bases for deprotonation reactions in chemical synthesis.<sup>[2,3]</sup> Herein, we report that NaH can act as a hydride donor in reactions with nitriles, amides, and imines when it has been subjected to simple solvothermal treatment with LiI or NaI in THF. Of particular interest is the outcome of hydride reduction reactions of nitriles and amides, which deliver the corresponding alkanes (through decyanation) and aldehydes, respectively.

During the course of our experiments on the  $\alpha$ -methylation of diphenylacetonitrile (**1**) to prepare tertiary carbonitrile **2a**, we investigated its reaction with NaH (3 equiv) and MeI (1.2 equiv) in THF (85 °C in a sealed tube; Scheme 1). Although the desired tertiary nitrile **2a** was isolated in 74% yield, we were surprised to observe the formation of 1,1-diphenylethane (**3a**) in 25% yield as a side product. Assuming that **3a** was formed by the decyanation of nitrile **2a**, we expected that this decyanation reaction could be generalized to a more versatile synthetic strategy. Therefore, we optimized the reaction conditions for the decyanation of nitrile **2a** by NaH (Table 1). We found that NaH alone was not



**Scheme 1.** Serendipitous reductive decyanation during the methylation of **1**.

**Table 1:** Optimization of reaction conditions for the decyanation of **2a**.<sup>[a]</sup>

Entry	NaH (equiv)	Additive (equiv)	<i>t</i> [h]	Yield of <b>3a</b> [%] <sup>[b]</sup>
1	3	–	24	trace <sup>[c]</sup>
2	3	NaI (2)	14	96
3	3	KI (2)	40	9 <sup>[c]</sup>
4	3	LiI (1)	3.5	98
5	3	MgI <sub>2</sub> (1)	20	96
6	3	LiBr (2)	24	8 <sup>[c]</sup>
7	3	LiCl (2)	24	3 <sup>[c]</sup>
8	3	LiI (1)	6	98
9	3	LiI (0.2)	48	98
10	2	LiI (1)	7	98
11	1.5	LiI (1)	24	79 (17) <sup>[d]</sup>

[a] The reactions were conducted with 0.3–0.5 mmol of nitrile **2a** in THF (2.5 mL). [b] Yield of the isolated product. [c] Recovery of **2a** in >90% yield was confirmed by <sup>1</sup>H NMR spectroscopy of the crude material. [d] Recovery yield of **2a**.

sufficient to drive the decyanation (Table 1, entry 1). Upon the methylation of **1** with NaH and MeI (Scheme 1), a stoichiometric amount of sodium iodide (NaI) is necessarily generated, and thus we speculated that the cooperation of NaH and NaI could be the key to the decyanation. Indeed, the treatment of **2a** with NaH (3 equiv) and NaI (2 equiv) in THF delivered **3a** in 96% yield (Table 1, entry 2). Although KI was not optimally effective as an additive (Table 1, entry 3), LiI rendered the process very rapid to afford **3a** in 98% yield within 3.5 h (entry 4). Similarly, a reaction with MgI<sub>2</sub> produced **3a** in 96% yield, albeit at a slower reaction rate (Table 1, entry 5). Interestingly, LiBr or LiCl did not promote the decyanation effectively (Table 1, entries 6 and 7), thus indicating the important role of dissolved iodide ions in enabling this unprecedented decyanation by NaH. When the amount of LiI was decreased (Table 1, entries 8 and 9), we found that the use of even a catalytic amount of LiI (20 mol%) enabled full conversion of **2a** with a longer reaction time (48 h; entry 9). When 1 equivalent of LiI was used as the promoter, the amount of NaH could be decreased

[\*] Dr. P. C. Too, G. H. Chan, Dr. Y. L. Tnay, Prof. H. Hirao, Prof. S. Chiba  
Division of Chemistry and Biological Chemistry  
School of Physical and Mathematical Sciences  
Nanyang Technological University, Singapore 637371 (Singapore)  
E-mail: hirao@ntu.edu.sg  
shunsuke@ntu.edu.sg

Supporting information for this article can be found under <http://dx.doi.org/10.1002/anie.201600305>.

© 2016 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

to 1.5–2 equivalents (Table 1, entries 10 and 11). However, the reduction of **2a** with LiH in the presence of LiI did not proceed at all, thus indicating the specific reactivity of NaH for the present decyanation.

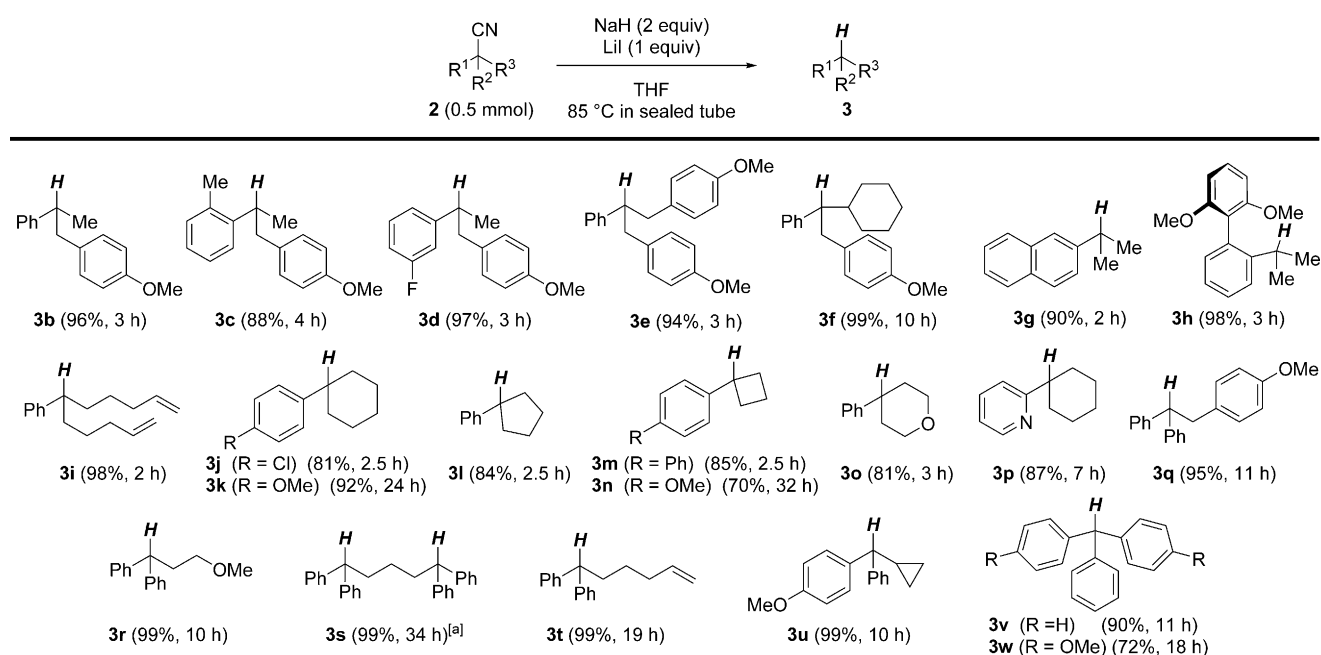
The present protocol with NaH–LiI (Table 1, entry 10) is complementary to existing methods for the reductive decyanation of carbonitriles<sup>[4–7]</sup> and could be useful as a new protocol with a distinct reaction mechanism. Therefore, we next examined the scope of the decyanation of carbonitriles under these reaction conditions (Scheme 2). The present protocol is suitable for the facile construction of tertiary carbon centers of monoaryl (products **3b–p**), diaryl (products **3q–u**), and even triaryl methanes (products **3v** and **3w**) from the corresponding carbonitriles, thus offering a new retrosynthetic strategy to access this class of compounds.<sup>[8]</sup> Notably, this method allows the preparation of cycloalkyl arenes (products **3j–p**) possessing strained cyclobutyl (products **3m** and **3n**) and tetrahydropyranyl moieties (product **3o**) as well as 2-cyclohexylpyridine (**3p**) with high efficiency. It was observed that an electron-rich 4-methoxyphenyl group rendered the reaction rate of the decyanation slower (**3j** vs. **3k** and **3m** vs. **3n**). We initially speculated that the decyanation might be mediated by single-electron reduction of the carbonitrile by NaH,<sup>[9]</sup> followed by C–CN bond homolysis to give the corresponding C radical and a cyanide anion. However, all of the results of experiments with radical-clock substrates (for **3i**, **3t**, and **3u**),<sup>[10]</sup> as well as deuterium-labeling experiments with [D<sub>8</sub>]THF and D<sub>2</sub>O (see Scheme S1 in the Supporting Information), exclude this possibility. The decyanation of carbonitriles **2** with the NaH–NaI system (Table 1, entry 2) gave comparable yields of products **3**, although much longer reaction times were generally required (see Scheme S2). In contrast, the reduction of carbonitriles with LiAlH<sub>4</sub> and *i*Bu<sub>2</sub>AlH (DIBAL) generally provides the corresponding primary amines and aldehydes, respectively,

thus indicating unprecedented and unique reactivity of the NaH–Li(Na)I composites in the present decyanation.

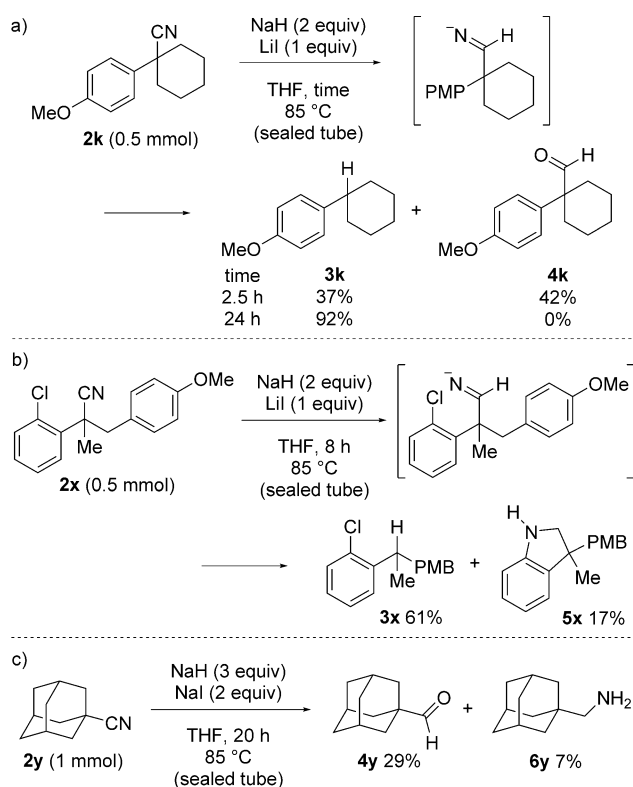
The reactions of certain substrates provided critical clues about the reaction mechanism. When the reaction of nitrile **2k** was quenched after 2.5 h, before full conversion, aldehyde **4k** was isolated in 42% yield along with the decyanated alkane **3k** in 37% yield (Scheme 3a). The formation of aldehyde **4k** indicated that the decyanation might involve an iminyl anion intermediate, which could be formed by hydride attack on the CN triple bond. Moreover, the reaction of nitrile **2x**, which contains a 2-chlorophenyl moiety (Scheme 3b), afforded not only decyanated **3x** (61% yield) but also dihydroindole **5x** (17% yield); the latter product should be formed by cyclization of the iminyl anion species through either *ipso* aromatic substitution or nucleophilic addition to the benzyne, followed by further hydride addition to the resulting cyclic imine (see also Scheme 5c). The assumption of hydride transfer is further supported by the reduction of adamantane-1-carbonitrile (**2y**; Scheme 3c), which gave the corresponding aldehyde **4y** and primary amine **6y** in 29 and 7% yield, respectively.

The stereochemical outcomes of the present decyanation were also investigated. Decyanation of *exo*-2-(4-methoxyphenyl)-*endo*-2-norbornylcarbonitrile (**2z**) afforded only decyanated **3z** with retention of the original stereoconfiguration (Scheme 4a). Significantly, decyanation of optically active (+)- and (–)-**2b** (Scheme 4b) gave the corresponding product containing a tertiary carbon center with the original enantiomeric purity.

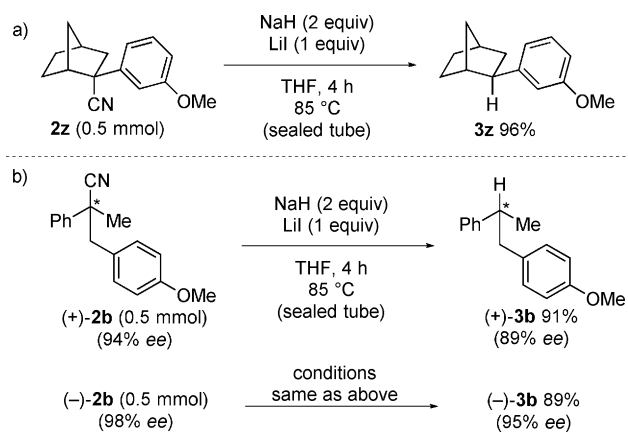
We conducted DFT calculations to investigate the origin of the hydride-donor reactivity of these NaH inorganic composites and the reaction mechanisms of the decyanation by using 2-phenylisobutyronitrile as a model substrate. NaH has ionic character with the cubic halite crystal structure composed of sodium cations and hydride anions, which make



**Scheme 2.** Scope of the decyanation. [a] The reaction was conducted with 3 equivalents of NaH and 1 equivalent of LiI.

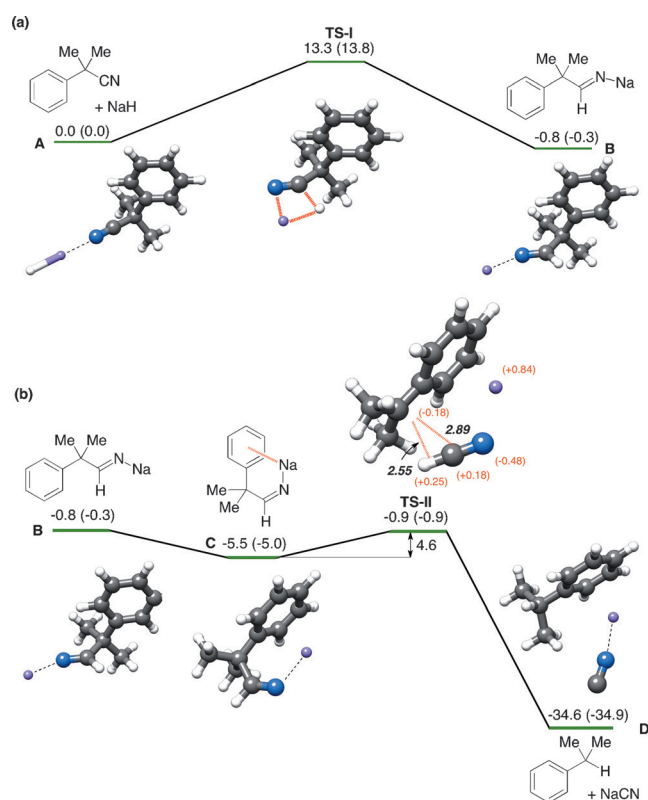


**Scheme 3.** Implications of hydride transfer from NaH.



**Scheme 4.** Stereochemical outcomes of the reductive decyanation.

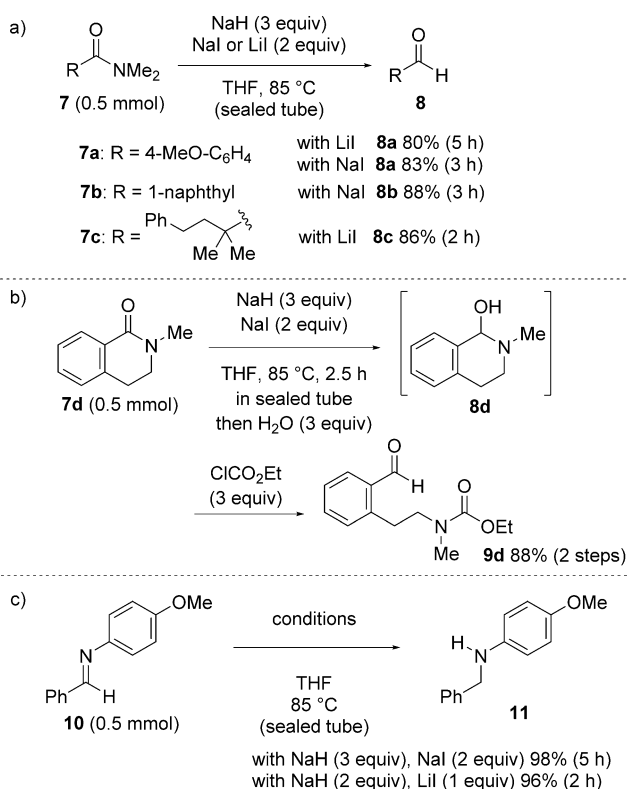
these compounds insoluble in inert organic solvents.<sup>[2]</sup> To evaluate the intrinsic hydride-donor ability of NaH, we performed DFT calculations by using a single molecule of NaH (Figure 1a).<sup>[11,12]</sup> Interestingly, the barrier for hydride transfer to the nitrile moiety to form iminyl anion intermediate **B** is very low (**TS-I**, 13.3 kcal mol<sup>-1</sup>). This result indicates that NaH is intrinsically reactive as a hydride donor to polar  $\pi$  electrophiles, and a reactive state of NaH close to its single molecule state might be generated in the composite with Lil or NaI.<sup>[13]</sup> Next, we investigated the mechanism of the decyanation process in which the original stereoconfiguration was retained (Scheme 4). DFT calculations successfully



**Figure 1.** Free-energy profiles for decyanation by NaH (in kcal mol<sup>-1</sup>, determined at the B3LYP/def2-TZVP//B3LYP/6-31G level of theory). The values obtained at the B3LYP/def2-TZVP level of theory are also shown in parentheses for comparison. a) Reaction of 2-phenylisobutyronitrile with NaH. b) Decyanation.

located the transition state **TS-II** (Figure 1b) for concerted C–C bond cleavage and H-atom transfer with elimination of NaCN<sup>[14]</sup> from putative *E* iminyl anion intermediate **C**, in which a sodium cation– $\pi$  interaction occurs.<sup>[15]</sup> Intermediate **C** is formed by facile isomerization of the initially formed *Z* isomer **B**. The energy barrier for the C–C bond cleavage was very low (4.6 kcal mol<sup>-1</sup>) when Na<sup>+</sup> acted as the counterion. In the transition state **TS-II**, the hydrogen atom originating from NaH bears partial positive charge ( $\delta+$ ) and thus has some protic character. This hydrogen atom is likely to be rearranged to the adjacent carbon atom ( $\delta-$ ) through proton transfer with retention of the stereoconfiguration. This result demonstrates the unique umpolung nature<sup>[16]</sup> of the decyanation, in which the nucleophilic hydride derived from NaH acquires electrophilic protic properties in the later stages. Li<sup>+</sup> as the counterion also provided a low C–C cleavage barrier (5.0 kcal mol<sup>-1</sup>; see Figure S2 in the Supporting Information). However, the transition state with AlMe<sub>2</sub><sup>+</sup> as the counterion (for the model of DIBAL reduction) could not be determined (see Figure S2). This result is consistent with the actual outcome of the DIBAL reduction of carbonitriles, that is, formation of the corresponding aldehydes.

Having identified the unprecedented hydride-donor reactivity of the NaH–Li(Na)I composites, we next turned our attention to the use of this protocol to reduce other polar



**Scheme 5.** Reduction of *N,N*-dimethylamides, an *N*-methyl lactam, and an *N*-aryl aldimine.

$\pi$  electrophiles (Scheme 5). It was found that the reduction of *N,N*-dimethylamides **7a–c** and *N*-methyl lactam **7d** proceeded smoothly to give the corresponding aldehydes **8a–c** (Scheme 5a) and hemiaminal **8d** (Scheme 5b), respectively, in good yields. Because of its instability, the resulting hemiaminal **8d** was further converted into acyclic carbamate **9d**. *N*-Methoxy-*N*-methylamides (Weinreb amides)<sup>[17]</sup> are commonly utilized for synthesis of the corresponding aldehydes by their hydride reduction with LiAlH<sub>4</sub> or DIBAL, which proceeds via tetrahedral five-membered-chelate intermediates. The present protocol uniquely produces aldehydes from simple *N,N*-dimethylamides. Moreover, the reduction of *N*-aryl aldimine **10** proceeded smoothly to give the corresponding amine **11** in good yields (Scheme 5c). However, the reduction of esters and aldehydes was found to give complex results because of the inherent basicity of NaH (see Scheme S3).

Further materials characterization to gain an in-depth understanding of the origin of the hydride-donor reactivity of NaH in the present inorganic composites is currently under way. We are also continuously working to explore further applications of the present protocol for the development of other types of hydride-reduction processes.

## Acknowledgements

Funding of S.C. for this research was provided by the Singapore Ministry of Education (Academic Research Fund

Tier 2: MOE2012-T2-1-014). H.H. gratefully acknowledges a Nanyang Assistant Professorship and the computer resources at the High-Performance Computing Centre of NTU.

**Keywords:** amides · decyanation · density functional calculations · reduction · sodium hydride

**How to cite:** *Angew. Chem. Int. Ed.* **2016**, *55*, 3719–3723  
*Angew. Chem.* **2016**, *128*, 3783–3787

- [1] a) *Modern Reduction Methods* (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**; b) H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567.
- [2] a) “Sodium Hydride”, R. E. Gawley, D. D. Hennings in *e-EROS Encyclopedia of Reagents for Organic Synthesis* (Ed.: D. Crich), Wiley, Chichester, **2006**; b) “Hydrides”, P. Rittmeyer, U. Wietelmann in *Ullmann’s Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2012**; c) S. Aldridge, A. J. Downs, *Chem. Rev.* **2001**, *101*, 3305.
- [3] Several exceptional examples of the reduction of carbonyl compounds and their derivatives by alkali-metal hydrides have been reported; see: a) D. Heseck, M. Lee, B. C. Noll, J. F. Fisher, S. Mobashery, *J. Org. Chem.* **2009**, *74*, 2567; b) T. Ohkuma, S. Hashiguchi, R. Noyori, *J. Org. Chem.* **1994**, *59*, 217; c) R. Pi, T. Friedl, P. von R. Schleyer, P. Klusener, L. Brandsma, *J. Org. Chem.* **1987**, *52*, 4299; d) P. A. A. Klusener, L. Brandsma, H. D. Verkruijsse, P. von R. Schleyer, T. Friedl, R. Pi, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 465; *Angew. Chem.* **1986**, *98*, 458.
- [4] For reviews on reductive decyanation, see: a) J. M. Mattalia, C. Marchi-Delapierre, H. Hazimeh, M. Chanon, *Arkivoc* **2006**, *iv*, 90; b) F. F. Fleming, Z. Zhang, *Tetrahedron* **2005**, *61*, 747; c) C. J. Sinz, S. D. Rychnovsky, *Top. Curr. Chem.* **2001**, *216*, 51.
- [5] For free-radical-mediated decyanation, see: a) T. Kawamoto, S. J. Geib, D. P. Curran, *J. Am. Chem. Soc.* **2015**, *137*, 8617; b) D. P. Curran, C. M. Seong, *Synlett* **1991**, 107.
- [6] For the decyanation of (half-)malononitriles by organic super electron donors, see: E. Doni, J. A. Murphy, *Org. Chem. Front.* **2014**, *1*, 1072.
- [7] For reviews on the transition-metal-catalyzed cleavage of C–CN bonds, see: a) R. Wang, J. R. Falck, *RSC Adv.* **2014**, *4*, 1062; b) Y. Nakao, *Bull. Chem. Soc. Jpn.* **2012**, *85*, 731; c) M. Tobisu, N. Chatani, *Chem. Soc. Rev.* **2008**, *37*, 300.
- [8] For selected reports on the construction of diaryl and triaryl methanes, see: a) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383; b) M. Nambo, C. M. Cruden, *Angew. Chem. Int. Ed.* **2014**, *53*, 742; *Angew. Chem.* **2014**, *126*, 761; c) Q. Zhou, H. D. Srinivas, S. Dasgupta, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 3307; d) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 3303; e) A. Bellomo, J. Zhang, N. Trongsiwat, P. J. Walsh, *Chem. Sci.* **2013**, *4*, 849; f) Y. Xia, F. Hu, Z. Liu, P. Qu, R. Ge, C. Ma, Y. Zhang, J. Wang, *Org. Lett.* **2013**, *15*, 1784; g) J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2012**, *134*, 13765; h) B. L. H. Taylor, M. R. Harris, E. R. Jarvo, *Angew. Chem. Int. Ed.* **2012**, *51*, 7790; *Angew. Chem.* **2012**, *124*, 7910; i) G. I. McGrew, J. Temaismithi, P. J. Carroll, P. J. Walsh, *Angew. Chem. Int. Ed.* **2010**, *49*, 5541; *Angew. Chem.* **2010**, *122*, 5673.
- [9] For reports on the use of NaH in single-electron reduction, see: a) P. Caubère, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 599; *Angew. Chem.* **1983**, *95*, 597; b) R. B. Nelson, G. W. Gribble, *J. Org. Chem.* **1974**, *39*, 1425.
- [10] M. Newcomb in *Encyclopedia of Radicals in Chemistry, Biology and Materials, Vol. 1* (Eds.: C. Chatgililoglu, A. Studer), Wiley, Chichester, **2012**, p. 107.

- [11] For a DFT study on the bonding nature of several alkal-metal hydrides, see: F. M. Bickelhaupt, M. Solá, C. F. Guerra, *Faraday Discuss.* **2007**, *135*, 451.
- [12] For a DFT study on the transition states for the reaction of NaH or LiH with carbonyl compounds, see: a) Y.-D. Wu, J. A. Tucker, K. N. Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5018; b) Y.-D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **1987**, *109*, 908.
- [13] The kinetic profiles of the decyanation suggested that the reaction of NaH with LiI (or NaI) resulted in the formation of new inorganic composite materials that probably display hydride-donor reactivity. See the Supporting Information for more details.
- [14] After decyanation by the NaH–NaI system, the ATR-FTIR spectrum of the bulk material revealed the presence of  $\text{CN}^-$  ( $2086\text{ cm}^{-1}$ ; see the Supporting Information).
- [15] A. S. Mahadevi, G. N. Sastry, *Chem. Rev.* **2013**, *113*, 2100.
- [16] D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239; *Angew. Chem.* **1979**, *91*, 259.
- [17] S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, 3707.

Received: January 11, 2016

Published online: February 17, 2016