

Radical Reduction

International Edition: DOI: 10.1002/anie.201601930
German Edition: DOI: 10.1002/ange.201601930

Radical Hydrodeiodination of Aryl, Alkenyl, Alkynyl, and Alkyl Iodides with an Alcoholate as Organic Chain Reductant through Electron Catalysis

Abhishek Dewanji, Christian Mück-Lichtenfeld, and Armido Studer*

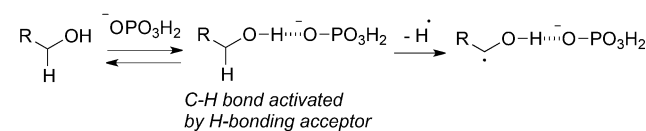
Abstract: A simple and efficient method for radical hydrodeiodination is reported. The novel approach uses electron catalysis. In situ generated Na-alcoholates are introduced as radical chain reducing reagents and reactions work with O_2 as cheap initiator. Hydrodeiodination works on aryl, alkenyl, alkynyl iodides and a tert-alkyl iodide also gets reduced applying the method. Albeit less general, the method is also applicable to the reduction of aryl bromides. The novel reagent is successfully used to conduct typical reductive radical cyclization reactions and mechanistic studies are reported.

Hydrodehalogenation is an essential transformation in organic synthesis and chemical industry.^[1] As halides are hazardous to the environment this process has also been used for industrial detoxification.^[2] Various methods for dehalogenation of organic halides have been developed for example, via metal-halogen exchange,^[3] reduction with hydride reagents,^[4] metal-mediated reductions^[5] and reductive radical dehalogenations. The first three methods suffer from low functional-group tolerance and formation of hazardous metal waste. Radical chain dehalogenation is a valuable option. However, some initiators and stoichiometric reductants used in established radical dehalogenation are explosive (AIBN),^[6] toxic (Bu_3SnH),^[7] and air sensitive (SmI_2 and trialkylboranes).^[8,9] These shortcomings paved the way to the development of “greener” methods for radical dehalogenation.

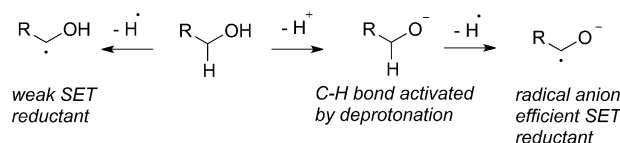
Various Si,^[10] and B-based^[11] reagents have been introduced. Murphy^[12] successfully used organic super electron donors, and organometallic complexes^[13] in combination with hydride donors were also developed. Important contributions by Stephenson^[14] and König^[15] show that *fac*-Ir(ppy)₃ and a perylene diimide are efficient catalysts for radical dehalogenation of alkyl and aryl halides using photoredox catalysis. Herein we show that readily generated Na-alcoholates efficiently dehalogenate various iodides under electron catalysis.^[16–18]

H-bonding of alcohols with a phosphate anion leads to activation of the α -C–H bond thereby facilitating H-abstraction by radicals, as elegantly used by MacMillan (Scheme 1).^[19] α -C–H-activation should be even stronger in fully deprotonated alcohols. Indeed, it was reported that alcoholates are far better H-donors than the corresponding

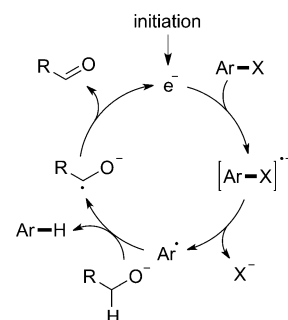
MacMillan 2015



Our idea



Planned application in electron-catalyzed dehalogenation



Scheme 1. Working model.

alcohols.^[20b] H-abstraction from an alcoholate leads to a radical anion that should be an efficient single-electron transfer (SET) reagent for reduction of aryl halides, as shown for the $NaOCH_2$ radical anion.^[20]

Considering these facts, we decided to develop a mild method for hydrodehalogenation of aryl halides via electron catalysis using alcoholates as chain-reducing reagents. SET reduction of the starting $Ar-X$ leads to an aryl radical anion, which reacts via halide fragmentation to an aryl radical. Reduction of the aryl radical by the alcoholate should then provide the targeted reduction product $Ar-H$ along with the radical anion that formally liberates an electron closing the catalytic cycle.^[16,21] An aldehyde is formed as a byproduct.

The hydrodeiodination of iodobiphenyl **1a** to give **2a** was chosen as a test reaction (Table 1). Initial experiments were conducted with the hypodinitrite **3** as an initiator^[22] in 1,4-dioxane. Alcoholates were generated in situ from the corresponding alcohols upon deprotonation. Pleasingly, reaction of **1a** with **3** (50 mol %) and LiO^iPr (10 equiv) as a reductant at 45 °C gave **2a** in 60 % along with 40 % of unreacted **1a** (entry 1). Lowering the reaction temperature did not improve the conversion (entry 2). Reduction did not work with $LiOBn$

[*] A. Dewanji, Dr. C. Mück-Lichtenfeld, Prof. Dr. A. Studer
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstraße 40, 48149 Münster (Germany)
E-mail: studer@uni-muenster.de

Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201601930>.

Table 1: Reaction optimization.^[a]

Entry	ROH	Base	Initiator (mol %)	Conc. [M]	Yield [%] ^[b]
1	<i>i</i> -PrOH	<i>n</i> -BuLi	3 (50)	0.06	60 (40)
2 ^[c]	<i>i</i> -PrOH	<i>n</i> -BuLi	3 (50)	0.06	55 (45)
3	BnOH	<i>n</i> -BuLi	3 (50)	0.06	—
4	MeOH	<i>n</i> -BuLi	3 (30)	0.06	—
5	4	<i>n</i> -BuLi	3 (50)	0.06	> 99
6	4	<i>n</i> -BuLi	3 (40)	0.06	81 (19)
7	4	<i>n</i> -BuLi	3 (30)	0.06	37 (63)
8	4	<i>n</i> -BuLi	3 (30)	0.1	28 (72)
9 ^[d]	4	<i>n</i> -BuLi	DTBP (30)	0.06	—
10 ^[e]	4	<i>n</i> -BuLi	3 (30)	0.06	55 (45)
11 ^[f]	4	<i>n</i> -BuLi	3 (30)	0.06	—
12	4	NaH	3 (30)	0.06	> 99
13	4	NaH	3 (20)	0.06	70 (30)
14	4	NaH	3 (20)	0.2	> 99
15	4	NaH	3 (10)	0.2	48 (52)
16	5	NaH	3 (10)	0.2	76 (24)
17	6	NaH	3 (5)	0.2	> 99
18	7	NaH	3 (5)	0.2	> 99
19	8	NaH	3 (5)	0.2	> 99
20 ^[g]	8	NaH	3 (5)	0.2	72 (28)
21 ^[g]	8	NaH	—	0.2	37 (63)
22 ^[g,h]	8	NaH	O ₂	0.2	59 (41)
23 ^[h,i]	8	NaH	O ₂	0.2	> 99

[a] The reactions were carried out under argon with 0.4 mmol of **1a**, 4.0 mmol (10 equiv) of ROH, 4.0 mmol (10 equiv) of base at 45 °C for 24 h. [b] Yield determined by GC analysis and % unreacted starting material in parenthesis. [c] Reaction performed at 30 °C. [d] Reaction performed at 80 °C. [e] Reaction performed in THF. [f] Reaction performed in PhCF₃. [g] 5 Equivalents of **8** and 5 equivalents of NaH were used. [h] Reaction performed under oxygen atmosphere at room temperature. [i] 7 Equivalents of **8** and 7 equivalents of NaH were used.

or LiOMe as reductants (entries 3 and 4). Full conversion was achieved with the Li-alcoholate derived from 2-phenylethanol (**4**) to give **2a** in a quantitative yield (entry 5). Lowering the loading of initiator **3** led to significantly lower conversions indicating short chains (entries 5–7) and conversion did not increase upon increasing concentration (entry 8). Di-*tert*-butylperoxide (DTBP) as an initiator at 80 °C did not lead to any conversion (entry 9). Reaction in THF gave a similar result as in dioxane but hydrodeiodination did not work in trifluorotoluene (entries 10 and 11).

We then switched to NaH as a base and to our delight at higher concentration full conversion was achieved with 20 mol % of initiator **3**, showing that the counter cation influences the reaction (entries 12–15). A further lowering of the initiator loading to 5 mol % was possible using the Na-alcoholates derived from alcohols **6**, **7** and **8** (entries 16–19).

Further optimization was performed on **8** due to the high solubility of its sodium salt in ethers. Reducing the amount of Na-**8** from 10 to 5 equivalents resulted in a lower conversion (entry 20). Interestingly, a control experiment without any initiator at room temperature showed a 37 % conversion, indicating that the reaction can be initiated with a trace amount of dioxygen (entry 21). Indeed, under O₂ atmosphere the yield increased to 59 % using 5 equivalents of Na-**8** (entry 22) and quantitative conversion was achieved with 7 equivalents of the alcoholate at room temperature (entry 23).

Under optimized condition (Table 1, entry 23) the scope and limitations of the radical dehalogenation were explored (Figure 1). Di- and trimethoxy-substituted iodobenzenes were efficiently reduced and the corresponding arenes **2b–d** were isolated in very good yields (81–95 %). *Ortho*-methyl-

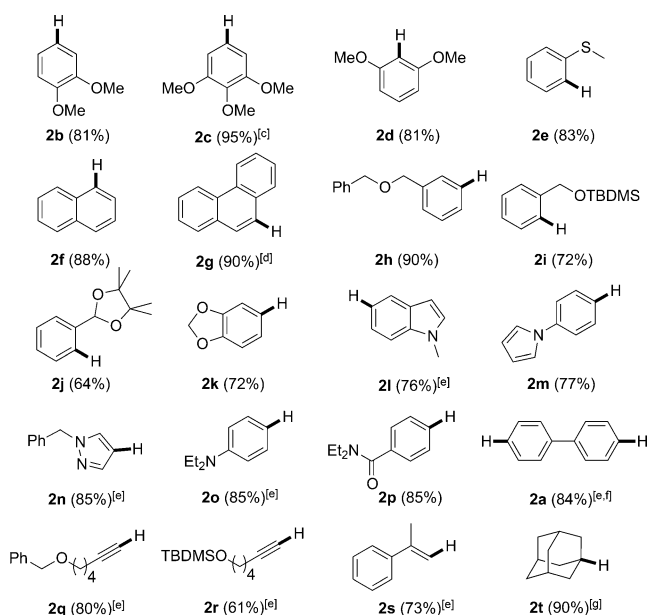
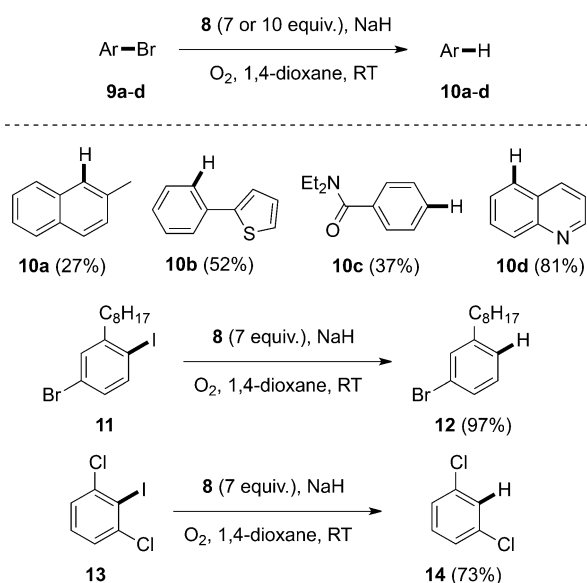


Figure 1. Substrate scope of the hydrodeiodination.^[a,b] [a] The reactions were carried out under oxygen atmosphere with 0.4 mmol of **1**, 2.8 mmol (7 equiv) of **8**, 2.8 mmol (7 equiv) of NaH in 2.0 mL of 1,4-dioxane as solvent at room temperature for 24 h. [b] Yield of isolated product. [c] 8 Equivalents of **8** and 8 equivalents of NaH were used. [d] Reaction was performed done at 45 °C. [e] 10 Equivalents of **8** and 10 equivalents of NaH were used. [f] 4,4'-Diiodobiphenyl was used as substrate and reaction run for 65 h. [g] **3** (20 mol %) was used as an initiator instead of O₂.

thiyl-iodobenzene was transformed to **2e** (83 %). Naphthalene (**2f**) and phenanthrene (**2g**) were obtained in high yields from the corresponding iodides (88–90 %). Benzyl ethers and silyl ethers are compatible with the applied conditions and **2h** and **2i** were isolated in good yields (72–90 %). The acetal functionality is stable under the reducing conditions (see **2j** and **2k**). Iodinated heteroarenes such as iodinated indoles, pyrroles and pyrazoles are efficiently hydrodeiodinated (see **2l–n**, 76–85 %). The electron-rich *N,N*-diethyl-*para*-iodoaniline and also the electron-poorer iodobenzamide are good substrates providing **2o** and **2p** (85 % each). Double reduction was achieved on 4,4'-diiodobiphenyl to give biphenyl **2a**

(84 %). Pleasingly, reaction is not restricted to the dehalogenation of iodoarenes. Reduction also worked for iodoacetylenes as shown by the successful preparation of **2q** and **2r**. An iodinated styrene derivative was successfully dehalogenated (see **2s**) and iodoadamantane was also reduced (see **2t**). In the latter transformation, the O₂-initiation process delivered **2t** in 42 % yield. 1-Adamantyl radical derived from trapping of the adamantyl radical by dioxygen was formed as a side product. Therefore, we switched to **3** as an initiator and found the yield to improve to 90 %.^[23]

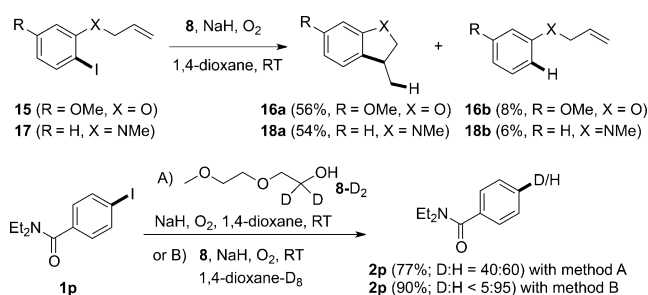
We next tested whether aryl bromides are also suitable substrates. As expected, reactivity was lower as compared to the iodides (Scheme 2). 2-Methyl-1-bromonaphthalene was reduced to **10a** in 27 % yield.^[24] Slightly better results were achieved for hydrodebromination of **9b** and **9c** to give the corresponding arenes **10b** and **10c** (37–52 %).^[24] A high yield



Scheme 2. Hydrodebromination and chemoselective dehalogenation.

was obtained for reduction of 5-bromoquinoline (**9d**) to quinoline (**10d**, 81 % isolated yield). Knowing reactivity differences between bromides and iodides we attempted chemoselective reduction of the bromo-iodo-arene **11**. Pleasingly, selective hydrodeiodination occurred in excellent yield (**12**, 97 %) and octylbenzene derived from a double reduction was not identified by GC analysis. Along these lines, the aryl-Cl bond is inert under the standard condition and iodide **13** reacted chemoselectively in good yield to dichlorobenzene **14**.

We found that **8** can also be applied to typical reductive radical cyclization reactions (Scheme 3): iodide **15** was successfully converted to **16a** (56 %). As a side product, **16b** derived from direct reduction was formed in 8 %. A similar result was observed for the transformation of **17** to give the targeted **18a** along with **18b**. From these results, it is obvious that **Na-8** is likely a highly efficient H-donor. However, since 1,4-dioxane is used as a solvent it might also act as H-donor in these chain reactions. To address this point we prepared α,α -dideuterated alcohol **8** and used it for the reduction of iodide



Scheme 3. Cyclization and reduction with deuterated **8**.

1p. Deuterium incorporation occurred only to 40 % showing that the intermediately generated aryl radical is reduced to a large extent by the solvent. Considering that the reaction is initiated with little O₂, reduction by 1,4-dioxane is likely not a chain-terminating step and the generated dioxanyl radical gets reduced by **Na-8** thereby sustaining the chain. If reaction is conducted with tetrahydropyran, a solvent known to be a poor H-atom donor,^[25] the hydrodeiodination of **1p** occurred in 86 % yield, revealing that 1,4-dioxane is not mandatory for efficient reduction. This is further supported by running reduction of **1p** with perdeuterated 1,4-dioxane-D₈ and **Na-8** delivering **2p** (90 %) with very little deuterium incorporation (D:H < 5:95).

Finally, DFT calculations on the reaction of the phenyl radical with **8**, the free alkoxide (**8⁻**) and **Na-8** were performed to study the effect of deprotonation on the bond dissociation energy (BDE) of the α -C–H bond. For comparison, we also calculated the relative BDE of the C–H bond in 1,4-dioxane. Figure 2 presents the calculated free energies of

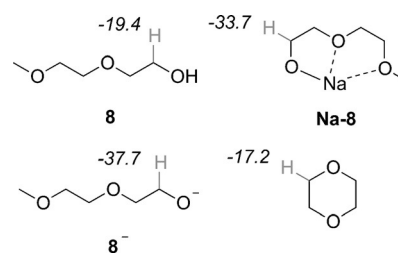


Figure 2. DFT-calculated ΔG_{298} [kcal mol⁻¹] for hydrogen transfer to Ph[•] (solvent: 1,4-dioxane).

hydrogen transfer to the phenyl radical (PW6B95-D3//B3LYP-D3/def2-TZVP).^[26] As expected, the C–H BDEs in 1,4-dioxane and the α -H in **8** are similar. It is obvious that 1,4-dioxane considering its high concentration as a solvent is a good H-donor for a phenyl radical, as experimentally observed. Upon deprotonation of **8**, the α -C–H bond in **8⁻** is strongly weakened by around 18 kcal mol⁻¹. If we include the Na-counteraction by switching to **8-Na** the α -C–H bond relative to alcohol **8** is weakened by around 14 kcal mol⁻¹. Hence, in agreement with the experiments, **8-Na** is a very good H-donor for the reduction of the phenyl and also of the dioxanyl radical.

In summary, we have introduced alcohol **8** as a commercially available cheap reagent to conduct radical chain

dehalogenation reactions. Hydrodeiodination works well for aryl, alkenyl and alkynyl iodides and reactive aryl bromides are also reduced. Importantly, in contrast to most radical reducing reagents, alcohol **8** is not sensitive towards air. The active reagent is the corresponding Na-alcoholate, which is readily generated in situ by deprotonation with cheap NaH. Chains are initiated with O₂ and reactions proceed via electron catalysis under mild conditions at room temperature. Reductions are experimentally easy to conduct and the excess of alcohol is removed by simple aqueous extraction.

Acknowledgements

We thank the WWU Münster for financial support.

Keywords: chemoselectivity · green chemistry · hydrodeiodination · radicals · transition-metal free synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6749–6752
Angew. Chem. **2016**, *128*, 6861–6864

- [1] a) R. A. Hites, *Acc. Chem. Res.* **1990**, *23*, 194–201; b) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047–1062; c) A. R. Pinder, *Synthesis* **1980**, 425–452.
- [2] a) Y. Mitoma, S. Nagashima, C. Simion, A. M. Simion, T. Yamada, K. Mimura, K. Ishimoto, M. Tashiro, *Environ. Sci. Technol.* **2001**, *35*, 4145–4148; b) T. Vincent, S. Spinelli, E. Guibal, *Ind. Eng. Chem. Res.* **2003**, *42*, 5968–5976; c) H. Sajiki, A. Kume, K. Hattori, H. Nagase, K. Hirota, *Tetrahedron Lett.* **2002**, *43*, 7251–7254.
- [3] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, A. V. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302–4320; *Angew. Chem.* **2003**, *115*, 4438–4456; b) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009–4091; c) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1–46.
- [4] N. M. Yoon, *Pure Appl. Chem.* **1996**, *68*, 843–848.
- [5] a) J. Chen, Y. Zhang, L. Yang, X. Zhang, J. Liu, L. Li, H. Zhang, *Tetrahedron* **2007**, *63*, 4266–4270; b) C. Desmarets, S. Kuhl, R. Schneider, Y. Fort, *Organometallics* **2002**, *21*, 1554–1559; c) K.-i. Fujita, M. Owaki, R. Yamaguchi, *Chem. Commun.* **2002**, 2964–2965; d) H. Guo, K.-i. Kanno, T. Takahashi, *Chem. Lett.* **2004**, *33*, 1356–1357.
- [6] J. Sanchez, T. N. Myers, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., Wiley, Hoboken, **2000**, p. 431.
- [7] a) W. P. Neumann, *Synthesis* **1987**, 665–683; b) P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.* **1998**, *37*, 3072–3082; *Angew. Chem.* **1998**, *110*, 3272–3283; c) A. Studer, S. Amrein, *Synthesis* **2002**, 835–849.
- [8] a) A. Krief, A.-M. Laval, *Chem. Rev.* **1999**, *99*, 745–777; b) M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.
- [9] K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143–147.
- [10] a) C. Chatgililoglu, *Acc. Chem. Res.* **1992**, *25*, 188–194; b) A. Studer, S. Amrein, *Angew. Chem. Int. Ed.* **2000**, *39*, 3080–3082; *Angew. Chem.* **2000**, *112*, 3196–3198.
- [11] a) D. P. Curran, A. Solov'yev, M. M. Brahmi, L. Fensterbank, M. Malacria, E. Lacote, *Angew. Chem. Int. Ed.* **2011**, *50*, 10294–10317; *Angew. Chem.* **2011**, *123*, 10476–10500; b) X. Pan, E. Lacote, J. Lalevée, D. P. Curran, *J. Am. Chem. Soc.* **2012**, *134*, 5669–5674; c) G. Povie, P. Renaud, *Chimia* **2013**, *67*, 250–252.
- [12] a) J. A. Murphy, T. A. Khan, S. Z. Zhou, D. W. Thomson, M. Mahesh, *Angew. Chem. Int. Ed.* **2005**, *44*, 1356–1360; *Angew. Chem.* **2005**, *117*, 1380–1384; b) E. Cahard, F. Schoenebeck, J. Garnier, S. P. Y. Cutulic, S. Zhou, J. A. Murphy, *Angew. Chem. Int. Ed.* **2012**, *51*, 3673–3676; *Angew. Chem.* **2012**, *124*, 3733–3736.
- [13] a) K. Fujita, T. Nakamura, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 3137–3138; b) M. E. Weiss, M. K. Kreis, A. Lauber, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 11125–11128; *Angew. Chem.* **2011**, *123*, 11321–11324; c) A. Ekomié, G. Lefèvre, L. Fensterbank, E. Lacote, M. Malacria, C. Ollivier, A. Jutand, *Angew. Chem. Int. Ed.* **2012**, *51*, 6942–6946; *Angew. Chem.* **2012**, *124*, 7048–7052.
- [14] J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanan, C. R. J. Stephenson, *Nat. Chem.* **2012**, *4*, 854–859.
- [15] I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, *Science* **2014**, *346*, 725–728.
- [16] A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765–773.
- [17] a) A. Dewanjji, S. Murarka, D. P. Curran, A. Studer, *Org. Lett.* **2013**, *15*, 6102–6105; b) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2013**, *52*, 10792–10795; *Angew. Chem.* **2013**, *125*, 10992–10995; c) D. Leifert, A. Studer, *Org. Lett.* **2015**, *17*, 386–389; d) M. Hartmann, C. G. Daniliuc, A. Studer, *Chem. Commun.* **2015**, *51*, 3121–3123.
- [18] A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58–102; *Angew. Chem.* **2016**, *128*, 58–106.
- [19] J. L. Jeffrey, J. A. Terrett, D. W. C. MacMillan, *Science* **2015**, *349*, 1532–1536.
- [20] a) J. F. Bunnett, C. C. Wamser, *J. Am. Chem. Soc.* **1967**, *89*, 6712–6718; b) J. W. Boyle, Jr., J. F. Bunnett, *J. Am. Chem. Soc.* **1974**, *96*, 1418–1422; c) C. Amatore, J. Badoz-Lambling, C. Bonnel-Huyghe, J. Pinson, J. M. Savéant, A. Thiébaud, *J. Am. Chem. Soc.* **1982**, *104*, 1979–1986; d) Very recently, it was shown that CsO_iPr can be used in chain hydrodehalogenations, see: R. Ueno, T. Shimizu, E. Shirakawa, *Synlett* **2016**, DOI: 10.1055/s-0035-1561342.
- [21] Savéant suggested that 2-chloroquinoline in liquid NH₃ can be electrochemically reduced with alcoholates in a chain process (see Ref. [20b]), see also Ref. [20a] and [20d].
- [22] a) G. D. Mendenhall, *Tetrahedron Lett.* **1983**, *24*, 451–452; b) A. Kapat, A. König, F. Montermini, P. Renaud, *J. Am. Chem. Soc.* **2011**, *133*, 13890–13893.
- [23] In the reduction of 1-iodo-hexadecane we found HI-elimination under the applied conditions to compete with the radical deiodination.
- [24] Since the dehalogenation product could not be separated from the starting bromide, yield was calculated based on GC analysis.
- [25] H. Yasuda, Y. Uenoyama, O. Nobuta, S. Kobayashi, I. Ryu, *Tetrahedron Lett.* **2008**, *49*, 367–370.
- [26] For details of the DFT calculations, see supporting information.

Received: February 24, 2016

Revised: March 31, 2016

Published online: April 21, 2016