DOI: 10.1002/anie.201307697

Alcohol Deoxygenation

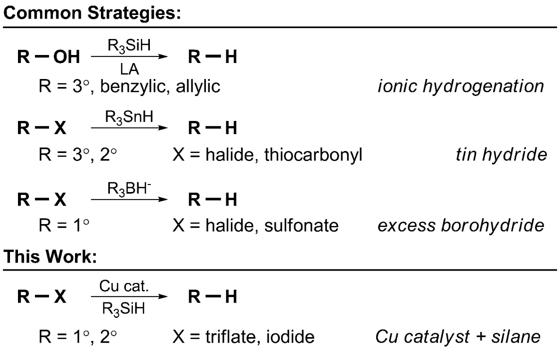
Copper-Catalyzed Reduction of Alkyl Triflates and Iodides: An Efficient Method for the Deoxygenation of Primary and Secondary Alcohols**

*Hester Dang, Nick Cox, and Gojko Lalic**

Abstract: *We describe an effective method for catalytic reduction of 1° alkyl sulfonates, and 1° and 2° iodides in the presence of a wide range of functional groups. This Cu-catalyzed reaction provides a means for the effective deoxygenation of alcohols, as demonstrated by the highly selective reduction of 1° alcohols using a triflation/reduction sequence. A preliminary study of the reaction mechanism suggests that the reduction does not involve free-radical intermediates.*

The catalytic transformation of C–O bonds has garnered much attention owing to the difficulties associated with C–O bond activation,[1] and a growing interest in the ability to convert over-oxygenated biomass into chemical feedstocks.[2] Furthermore, the selective reduction of alcohols to alkanes remains a difficult transformation that is important in organic synthesis.[3] These challenges provide motivation for the development of practical techniques for the deoxygenation of alcohols.

Current strategies for alcohol deoxygenation can be categorized into single-step procedures that reduce the alcohol directly, and two-step procedures that convert the alcohol into a reactive group prior to the reduction step. Although there are several strategies for single-step alcohol deoxygenation,[4] the only widely used technique is ionic hydrogenation.[5] This procedure is best suited for the reduction of alcohols that can generate a stabilized carbenium ion, such as benzylic, allylic, or tertiary alcohols. For the reduction of unactivated primary and secondary alcohols, two-step strategies are predominantly used. The most common strategy involves the formation of halides or thiocarbonyl esters[6] followed by radical reduction with tin hydride reagents.[7] Although other reducing reagents have been successfully used,[8] in practice, alkylstannanes remain the reagent of choice despite their toxicity and problems associated with purification.[9] Furthermore, even with extensive development of the Barton-McCombie reaction, the reduction of primary alcohols using this procedure is still difficult to achieve.[10]



Scheme 1. Cu-catalyzed approach to the deoxygenation of alcohols.

In contrast to the reduction of secondary or tertiary alcohols, there are few practical approaches to primary alcohol deoxygenation (Scheme 1).[11] The most commonly used technique involves the reduction of halides or sulfonates using borohydride reagents.[12] Even the mildest variant of this approach requires prolonged heating with multiple equivalents of $NaBH_4$ in DMSO,[13] making this strategy an impractical option for the reduction of molecules bearing sensitive functional groups.[14] Overall, the deoxygenation of complex primary alcohols remains a particularly challenging task.

We were surprised to find that relatively few attempts have been made to address these challenges through the use of transition-metal catalysis, especially given its role in the selective reduction of alkenes, alkynes, and carbonyls. Thus far, investigations into the reduction of halides and sulfonates using Pd,[15] Ni,[16] and Ir[17] have mostly been focused on unfunctionalized substrates. Recently, we reported the use of copper hydride in a chemoselective catalytic semireduction of alkynes.[18] Considering that copper hydride complexes have been shown to reduce unfunctionalized alkyl halides and sulfonates in moderate yield when used in stoichiometric quantities,[19] we reasoned that the catalytic system developed in our laboratory could provide a new approach to the deoxygenation of alcohols. In this paper, we describe a copper-catalyzed reduction of alkyl triflates and iodides that is practical, efficient, and functional-group tolerant.

As sulfonate esters can be readily accessed from primary alcohols, and their reactivity can be easily tuned,[20] our initial efforts were aimed at the reduction of alkyl sulfonates. We found that primary triflates can be reduced using IPrCuO*t*Bu as the catalyst, tetramethyldisiloxane **2** (TMDSO) as the hydride source, and CsF as an additive that aids catalyst

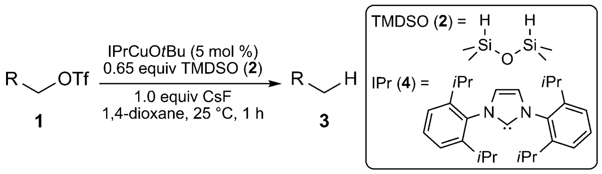
---

[*] H. Dang,[+] N. Cox,[+] G. Lalic
Department of Chemistry, University of Washington
Seattle, WA 98195 (USA)
E-mail: lalic@chem.washington.edu

[+] These authors contributed equally to this work.

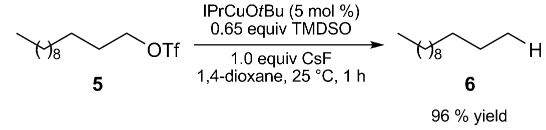
[**] NSF (CAREER Award 1254636) and University of Washington (RRF award A70681) are acknowledged for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307697.



Scheme 2. Conditions for the Cu-catalyzed reduction of 1° triflates.

Table 1: Development of the Cu-catalyzed reduction of 1° triflates.

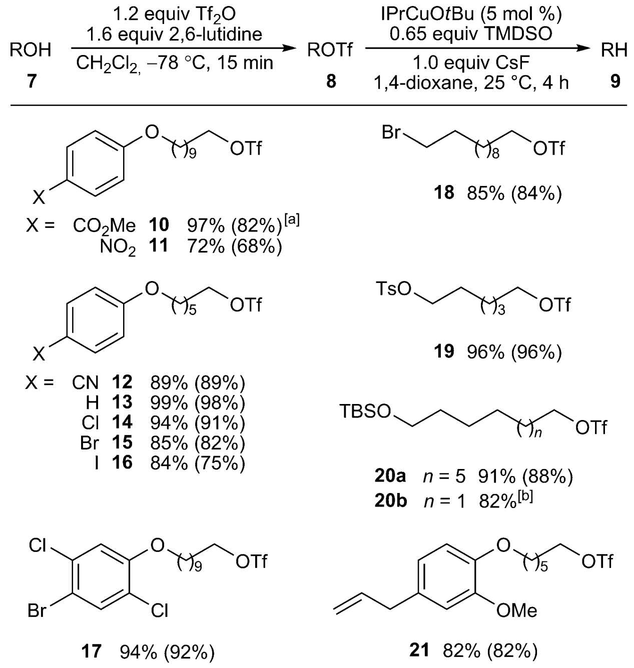


Entry	Change from optimized conditions	Yield [%][a] after 1 h	Yield [%][a] after 48 h
1	None	96	100
2	ROTs instead of ROTf		10
3	RONs instead of ROTf		0
4	No Catalyst		0
5	Cy$_3$PCuI instead of IPrCuO*t*Bu		59
6	XantphosCuI instead of IPrCuO*t*Bu		52
7	IMesCuO*t*Bu instead of IPrCuO*t*Bu		54
8	1.3 equiv Et$_3$SiH instead of TMDSO		71
9	1.3 equiv PMHS instead of TMDSO	10	98
10	Ph$_2$SiH$_2$ instead of TMDSO	89	100
11	NaO*t*Bu instead of CsF		16[b]
12	LiO*t*Bu instead of CsF		13[b]

[a] Yield was determined by GC analysis based on an internal standard. [b] Complete conversion of the starting material was observed. Cy = cyclohexyl, Ns = nosyl, Ts = tosyl, Xantphos = 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene.

turnover (Scheme 2). The reduction occurs in high yield in under 1 hour at ambient temperature, and without competing elimination. Tosylates and nosylates were found to be significantly less reactive, illustrating the mild nature of the reducing agent (Table 1, entries 2–3). No reaction took place in the absence of catalyst (entry 4). Furthermore, IPrCuO*t*Bu performed significantly better than catalysts supported by phosphines or less sterically demanding NHC ligands (entries 5–7). In general, we observed a higher rate of reduction when more reactive silanes such as poly(methylhydrosiloxane) (PMHS) or Ph$_2$SiH$_2$ were used. Surprisingly, the highest rate of reduction was achieved with TMDSO (entries 8–10).[21] Although alkoxide additives are commonly employed in copper-catalyzed reactions of silanes to aid in catalyst turnover,[22] we found that their use resulted in unproductive side-reactions of the triflate starting material (entries 11,12).

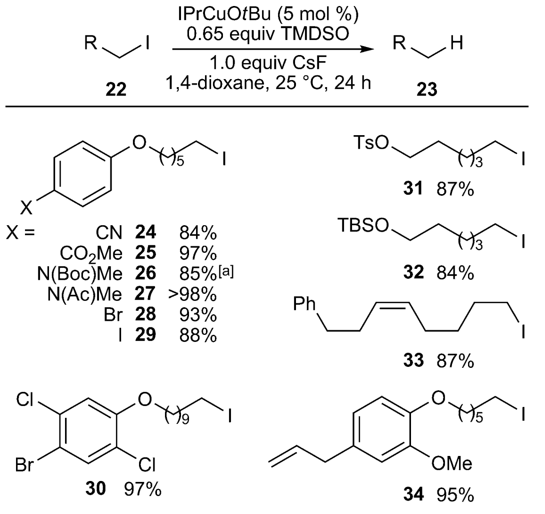
With the copper-catalyzed reduction of alkyl triflates as a starting point, we turned our attention to the development of a two-step procedure for the deoxygenation of primary alcohols. We found that, with slight modifications to existing methods, primary triflates can be efficiently prepared with minimal purification. As shown in Scheme 3, the deoxygenation of alcohols occurs in high yield over two steps and is compatible with many functional groups. High yields were obtained in the presence of substituents that are susceptible to reduction, including cyano, carbomethoxy, nitro, and alkenyl groups (**10**–**12** and **21**).[23] The reaction is compatible with aryl chlorides, bromides, and iodides, all of which are typically reactive in both transition-metal-catalyzed and free-radical reductions (**14**–**17**). The reduction of compounds **18** and **19** shows that the selective reduction of triflates can be accomplished even in the presence of alkyl bromides or tosylates. No deprotection of silyl-protected alcohols was observed, even though a stoichiometric amount of CsF is used in the reaction (**20a** and **20b**). Finally, the reduction of **20b** can successfully be performed on a 20 mmol sale. Overall, the two-step procedure shown in Scheme 3 is a practical approach to primary alcohol deoxygenation that addresses the key limitations of existing methods.



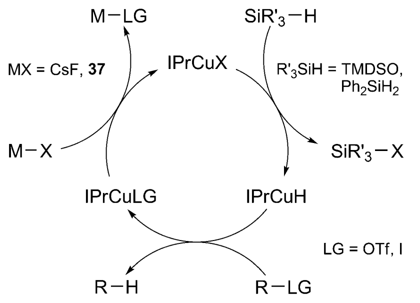
Scheme 3. Two-step deoxygenation of 1° alcohols by the Cu-catalyzed reduction of 1° alkyl triflates. Yields of isolated products are shown; overall yields for the two-step triflation/reduction sequence are given in parentheses. [a] 1 mol% of catalyst was used. [b] Reaction was performed on a 20 mmol scale and yielded 3.6 g of the product.

We also found that the reaction conditions developed for triflate reduction were effective in the reduction of primary alkyl iodides. The results in Scheme 4 show that iodides can be reduced by extending the reaction time to 24 h, while still maintaining the functional-group compatibility observed in the reduction of triflates. Nitriles, esters, carbamates, amides, aryl halides, tosylates, silyl ethers, and alkenes are all well tolerated.

We next turned our attention to the reduction of secondary iodides, which is a common transformation in synthesis.[24] We found that under the standard reaction



Scheme 4. Cu-catalyzed reduction of 1° alkyl iodides. Yields of isolated products are shown. [a] 1.4 equiv Ph_2SiH_2 and 1.1 equiv **37** were used instead of TMDSO and CsF. Ac = acetyl, Boc = *tert*-butoxycarbonyl.



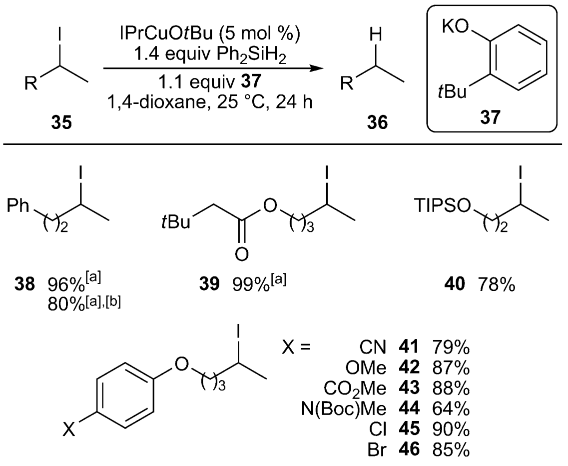
Scheme 6. Proposed catalytic cycle of the Cu-catalyzed reduction of triflates and iodides.

conditions, a competing elimination reaction produced trace amounts of an undesired alkene. To address this problem, we explored the use of alternative hydride sources and additives. Ultimately, we found that switching from TMDSO to Ph_2SiH_2, and from CsF to potassium 2-*tert*-butylphenoxide (**37**) allowed us to achieve high yield in the reduction of secondary iodides without alkene formation.

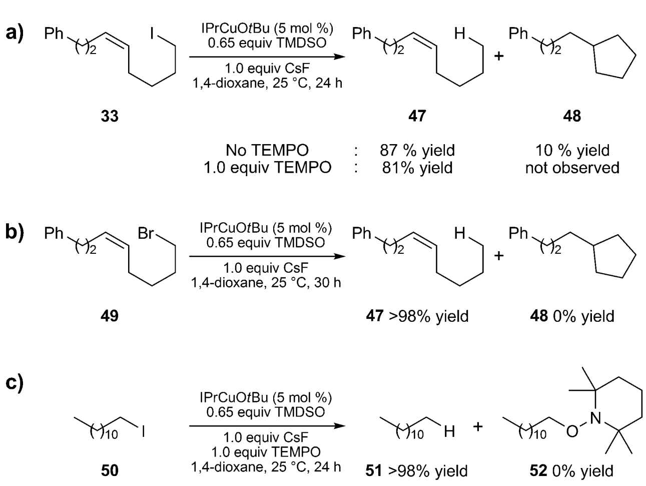
As shown in Scheme 5, these changes to the reaction conditions allowed the successful reduction of secondary iodides bearing a variety of functional groups, including ester, silyl ether, cyano, methoxy, carbamate, and aryl halide groups.[25]

We propose that the copper-catalyzed reduction of triflates and iodides proceeds according to the mechanism depicted in Scheme 6. Given the precedence for the formation of copper(I) hydrides through silicon-to-copper transmetallation,[18,26] we chose to focus our investigation of the mechanism on the proposed copper hydride reduction step. Whereas copper hydride reductions of carbonyls, alkenes, and alkynes have been studied,[22] copper hydride reduction of alkyl halides and sulfonates has not been explored. We reasoned that the reduction step is likely to occur by one of two pathways: 1) the formation of radical intermediates, or 2) an ionic mechanism, which would involve either nucleophilic substitution or oxidative addition followed by reductive elimination.

The reduction of triflates by copper hydride is unlikely to proceed by a radical mechanism, as it would involve homolytic cleavage of the strong C–O bond.[27] However, considering the facile homolytic cleavage of the C–I bond, it is possible that the reduction of iodides involves the formation of free-radical intermediates. To explore this possibility, we conducted the experiments shown in Scheme 7a. We found that, in the copper-catalyzed reduction of iodide **33**, the ratio of reduced product **47** to cyclization product **48** was 9:1. In the presence of the radical trap 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO), formation of the cyclization product **48** was completely suppressed, and reduction product **47** was formed in 81 % yield. This suggests that a free-radical reaction is a minor pathway.



Scheme 5. Cu-catalyzed reduction of 2° alkyl iodides. Unless otherwise specified, yields of isolated products are shown. [a] Yield was determined by GC analysis based on an internal standard. [b] PMHS was used instead of Ph_2SiH_2, and NaO*t*Bu instead of **37**.



Scheme 7. Experiments to test for free-radical formation in the copper-catalyzed reduction of alkyl halides.

In further support of the conclusion that a two-electron pathway is the dominant mechanism, we found that when bromide **49** was submitted to the reaction conditions, reduction product **47** was formed in quantitative yield, and cyclization product **48** was not observed (Scheme 7b). Finally, when we carried out the reduction of iodide **50** in the presence of a stoichiometric amount of TEMPO, the reduction product **51** was observed in quantitative yield and the TEMPO-alkyl adduct **52** was not detected (Scheme 7c). While it is inherently difficult to rule out the possibility of free-radical formation, we believe that, taken collectively, the results presented in Scheme 7 suggest that a radical mechanism is not the major pathway, and that an ionic mechanism is more likely.

In conclusion, we have developed a copper-catalyzed deoxygenation of primary and secondary alcohols that is convenient, versatile, and compatible with many functional groups. We have demonstrated that this transformation can be achieved through a practical two-step procedure in which the alcohol is converted either into a triflate or an iodide prior to a highly efficient copper-catalyzed reduction step. Initial investigation of the mechanism suggests that free-radical formation is a minor pathway, and that the reduction step is more likely to occur by a two-electron process. Overall, this technique is particularly well-suited to the deoxygenation of primary alcohols, which has traditionally been a challenging transformation.

Received: September 2, 2013

Keywords: alcohols · copper · deoxygenation · reduction · silanes

---

[1] a) S. Kundu, J. Choi, D. Y. Wang, Y. Choliy, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *J. Am. Chem. Soc.* **2013**, *135*, 5127–5143; b) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486–1495.

[2] a) M. Schlaf, *Dalton Trans.* **2006**, 4645–4653; b) F. W. Lichtenthaler, S. Mondel, *Pure Appl. Chem.* **1997**, *69*, 1853–1866; c) A. G. Sergeev, J. D. Webb, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 20226–20229.

[3] J. M. a. K. B. Herrmann, *Eur. J. Org. Chem.* **2013**, *31*, 7017–7027.

[4] a) J. B. Hendrickson, M. Singer, M. S. Hussoin, *J. Org. Chem.* **1993**, *58*, 6913–6914; b) M. Yasuda, Y. Onishi, M. Ueba, T. Miyai, A. Baba, *J. Org. Chem.* **2001**, *66*, 7741–7744; c) M. Movassaghi, O. K. Ahmad, *J. Org. Chem.* **2007**, *72*, 1838–1841; d) M. Mirza-Aghayan, R. Boukherroub, M. Rahimifard, *Tetrahedron Lett.* **2009**, *50*, 5930–5932; e) K. Kobiro, K. Sumoto, Y. Okimoto, P. Wang, *J. Supercrit. Fluids* **2013**, *77*, 63–69.

[5] a) M. Schlaf, M. E. Thibault, D. Di Mondo, D. Taher, E. Karimi, D. Ashok, *Int. J. Chem. React. Eng.* **2009**, *7*, A34; b) V. Gevorgyan, J.-X. Liu, M. Rubin, S. Benson, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 8919–8922; c) V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 6179–6186; d) M. Dobmeier, J. M. Herrmann, D. Lenoir, B. Koenig, *Beilstein J. Org. Chem.* **2012**, *8*, 330–336.

[6] a) S. W. McCombie, W. B. Motherwell, M. J. Tozer, *Org. React.* **2012**, *77*, 161–591; b) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585; c) A. G. M. Barrett, P. A. Prokopiou, D. H. R. Barton, *J. Chem. Soc. Chem. Commun.* **1979**, 1175.

[7] a) L. W. Menapace, H. G. Kuivila, *J. Am. Chem. Soc.* **1964**, *86*, 3047–3051; b) H. G. Kuivila, *Acc. Chem. Res.* **1968**, *1*, 299–305; c) N. J. Lawrence, M. D. Drew, S. M. Bushell, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3381–3391.

[8] a) A. R. Pinder, *Synthesis* **1980**, 425–452; b) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009–4091; c) J. K. Kochi, P. E. Mocadlo, *J. Am. Chem. Soc.* **1966**, *88*, 4094–4096; d) J. R. Hanson, *Synthesis* **1974**, 1–8; e) D. P. Curran, T. L. Fevig, C. P. Jasperse, M. J. Totleben, *Synlett* **1992**, 943–961; f) R. Hekmatshoar, S. Sajadi, M. M. Heravi, *J. Chin. Chem. Soc.* **2008**, *55*, 616–618.

[9] B. S. Edelson, B. M. Stoltz, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 6729–6730.

[10] See Ref. [6a] for details. The use of this procedure in the deoxygenation of primary alcohols is complicated by the high energy of the primary radical intermediate.

[11] In a recent publication, an iridium catalyst was used to reduce primary alkyl iodides through a visible-light-mediated process; see: J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2012**, *4*, 854–859.

[12] a) R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, B. E. Maryanoff, *J. Org. Chem.* **1977**, *42*, 82–91; b) F. Rolla, *J. Org. Chem.* **1981**, *46*, 3909–3911; c) E. Santaniello, A. Fiecchi, A. Manzocchi, P. Ferraboschi, *J. Org. Chem.* **1983**, *48*, 3074–3077; d) S. Krishnamurthy, H. C. Brown, *J. Org. Chem.* **1983**, *48*, 3085–3091.

[13] R. O. Hutchins, D. Kandasamy, F. Dux III, C. A. Maryanoff, D. Rotstein, B. Goldsmith, W. Burgoyne, F. Cistone, J. Dalessandro, J. Puglis, *J. Org. Chem.* **1978**, *43*, 2259–2267.

[14] This procedure is known to reduce esters; for an example, see: M. Ono, K. Suzuki, S. Tanikawa, H. Akita, *Tetrahedron: Asymmetry* **2001**, *12*, 2597–2604.

[15] a) R. Boukherroub, C. Chatgilialoglu, G. Manuel, *Organometallics* **1996**, *15*, 1508–1510; b) M. S. Viciu, G. A. Grasa, S. P. Nolan, *Organometallics* **2001**, *20*, 3607–3612; c) R. E. Maleczka, R. J. Rahaim, R. R. Teixeira, *Tetrahedron Lett.* **2002**, *43*, 7087–7090; d) R. J. Rahaim, Jr., R. E. Maleczka, Jr., *Tetrahedron Lett.* **2002**, *43*, 8823–8826; e) A. Arcadi, G. Cerichelli, M. Chiarini, R. Vico, D. Zorzan, *Eur. J. Org. Chem.* **2004**, 3404–3407; f) S. K. Pandey, A. E. Greene, J.-F. Poisson, *J. Org. Chem.* **2007**, *72*, 7769–7770; g) A. Kunai, T. Sakurai, E. Toyoda, M. Ishikawa, Y. Yamamoto, *Organometallics* **1994**, *13*, 3233–3236; h) J. Ohshita, R. Taketsugu, Y. Nakahara, A. Kunai, *J. Organomet. Chem.* **2004**, *689*, 3258–3264; i) P. Srithanakit, W. Chavasiri, *Tetrahedron Lett.* **2011**, *52*, 2505–2507.

[16] a) M. Weidauer, E. Irran, C. I. Someya, M. Haberberger, S. Enthaler, *J. Organomet. Chem.* **2013**, *698-698*, 53–59; b) N. M. Yoon, H. J. Lee, J. H. Ahn, J. Choi, *J. Org. Chem.* **1994**, *59*, 4687–4688.

[17] a) J. Yang, M. Brookhart, *J. Am. Chem. Soc.* **2007**, *129*, 12656–12657; b) J. Yang, M. Brookhart, *Adv. Synth. Catal.* **2009**, *351*, 175–187.

[18] A. M. Whittaker, G. Lalic, *Org. Lett.* **2013**, *15*, 1112–1115.

[19] a) T. Yoshida, E.-i. Negishi, *J. Chem. Soc. Chem. Commun.* **1974**, 762–763; b) E. C. Ashby, A. B. Goel, J. J. Lin, *Tetrahedron Lett.* **1977**, *18*, 3695–3698; c) E. C. Ashby, J.-J. Lin, A. B. Goel, *J. Org. Chem.* **1978**, *43*, 183–188.

[20] a) S. D. Lepore, D. Mondal, *Tetrahedron* **2007**, *63*, 5103–5122; b) P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85–126.

[21] In general, the expected reactivity of the silanes used would be as follows: Et_3SiH < TMDSO < PMHS < Ph_2SiH_2; for details, see: E. Keinan, *Pure Appl. Chem.* **1989**, *61*, 1737–1746.

[22] a) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916–2927; b) S. Rendler, M. Oestreich, *Angew. Chem.* **2007**, *119*, 504–510; *Angew. Chem. Int. Ed.* **2007**, *46*, 498-504.

[23] Although the reaction was found to be tolerant of alkenes, alkynes are known to undergo rapid hydrocupration in the presence of copper hydride. Similarly, aldehydes are not compatible with the reaction conditions, and ketones are partially reduced. See the Supporting Information for details.

[24] a) Secondary iodide reduction has a number of applications in natural product synthesis outside of alcohol deoxygenation; for recent examples, see: b) P. Burch, M. Binaghi, M. Scherer, C. Wentzel, D. Bossert, L. Eberhardt, M. Neuburger, P. Scheiffele, K. Gademann, *Chem. Eur. J.* **2013**, *19*, 2589–2591; c) S. M. Canham, D. J. France, L. E. Overman, *J. Am. Chem. Soc.* **2010**, *132*, 7876–7877; d) F. Fueloep, M. Palko, E. Forro, M. Dervarics, T. A. Martinek, R. Sillanpaeae, *Eur. J. Org. Chem.* **2005**, 3214–3220; e) T. B. Durham, N. Blanchard, B. M. Savall, N. A. Powell, W. R. Roush, *J. Am. Chem. Soc.* **2004**, *126*, 9307–9317; f) T. B. Durham, W. R. Roush, *Org. Lett.* **2003**, *5*, 1875–1878; g) F. Peng, S. J. Danishefsky, *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867; h) D. Zurwerra, J. Gertsch, K.-H. Altmann, *Org. Lett.* **2010**, *12*, 2302–2305; i) E. A. Crane, T. P. Zabawa, R. L. Farmer, K. A. Scheidt, *Angew. Chem.* **2011**, *123*, 9278–9281; *Angew. Chem. Int. Ed.* **2011**, *50*, 9112–9115.

[25] The reaction conditions used in Scheme 5 can also be used in the reduction of primary alkyl iodides (see Scheme 4, compound **26**). However, alkyl triflates are not compatible with the phenoxide **37**.

[26] N. P. Mankad, D. S. Laitar, J. P. Sadighi, *Organometallics* **2004**, *23*, 3369–3371.

[27] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th ed., Wiley, New York, NY, **2001**.