Organic LETTERS

Letter

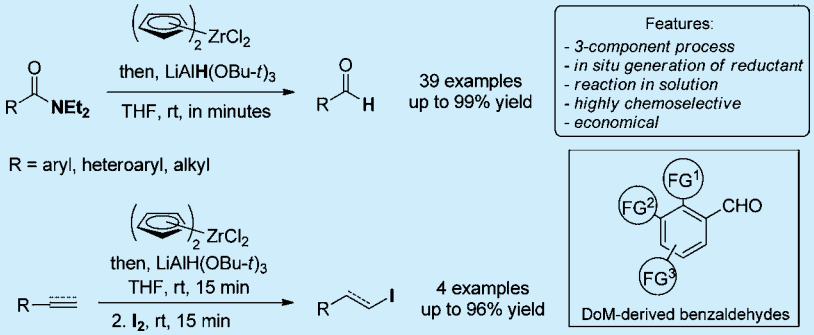
pubs.acs.org/OrgLett

A Practical in situ Generation of the Schwartz Reagent. Reduction of Tertiary Amides to Aldehydes and Hydrozirconation

Yigang Zhao and Victor Snieckus*

Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

Supporting Information



ABSTRACT: A new, highly efficient in situ protocol (Cp_2ZrCl_2/LiAlH(OBu-t)$_3$) is described for the generation of the Schwartz reagent which provides a convenient method for the amide to aldehyde reduction and the regioselective hydrozirconation–iodination of alkynes and alkenes. Highlighted are chemoselective reductions of benzamides derived by directed *ortho* metalation (DoM) chemistry, allowing the synthesis of valuable 1,2,3-substituted benzaldehydes. The single-step, three-component process proceeds in a very short reaction time, shows excellent functional group compatibility, and uses inexpensive and long-storage stable reducing reagents.

First prepared in 1969,[1] the Schwartz reagent, $Cp_2Zr(H)Cl$, has developed into a stalwart reagent for hydrozirconation, reduction, and other functional group transformations.[2] In 2000, Georg reported that the Schwartz reagent is very effective for the mild and general reduction of tertiary amides to aldehydes.[3] However, although the Schwartz reagent is commercially available, it is expensive and problematic for long-term storage due to its sensitivity to air, light, and moisture.[2c,d] Moreover, this reagent is feebly soluble in common inert solvents. These drawbacks lower the effective use of the Schwartz reagent and limit its application. Previously reported in situ procedures for independent generation of the Schwartz reagent for hydrozirconation[4] and amide reduction[4d] by using different hydride sources such as $LiAlH_4$,[4a] $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Red-Al),[4a] t-BuMgCl,[4a,b] $LiEt_3BH$,[4c] and DIBAL-H[4d] led to the formation of a heterogeneous reagent (Figure 1, process A) that is typically contaminated with unreacted reductant (which may react with substrate and intermediates), over-reduced Cp_2ZrH_2, and other salts.[2c,d] To overcome these deficits,[2c,d,5] we envisaged that an ideal, three-component, one-pot procedure for the in situ generation and use of the Schwartz reagent would embody the following features (Figure 1, process B): provides a freshly prepared reagent ready for immediate use, effects chemoselective reduction of Cp_2ZrCl_2 without reaction with substrates and organozirconium intermediates, and does not lead to over-reduction.

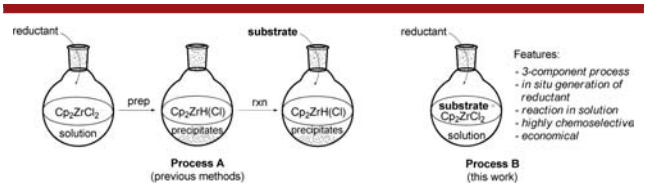


Figure 1. Comparison of (A) two-step and (B) three-component, one-pot in situ Schwartz reagent reduction processes.

Herein we report on the formulation and development of an in situ generated Schwartz reagent process for the reduction of amides to aldehydes and hydrozirconation–iodination of alkenes and alkynes by using LiAlH(OBu-t)$_3$ as reductant which meets all the ideal requisites of Figure 1, process B.[6] We further demonstrate its connection to the powerful regioselective directed *ortho* metalation (DoM) and cross-coupling methodologies, separate[7] and combined,[8] for aromatic amides allowing the regioselective construction of polysubstituted aromatic and heteroaromatic aldehydes with contiguous and uncommon patterns that are difficult to obtain by classical routes.

Following our successful use of the Georg procedure in the course of our Ergot alkaloid synthetic studies,[6a] we were confronted by the deficiencies of the commercial Schwartz

Received: November 12, 2013
Published: December 20, 2013

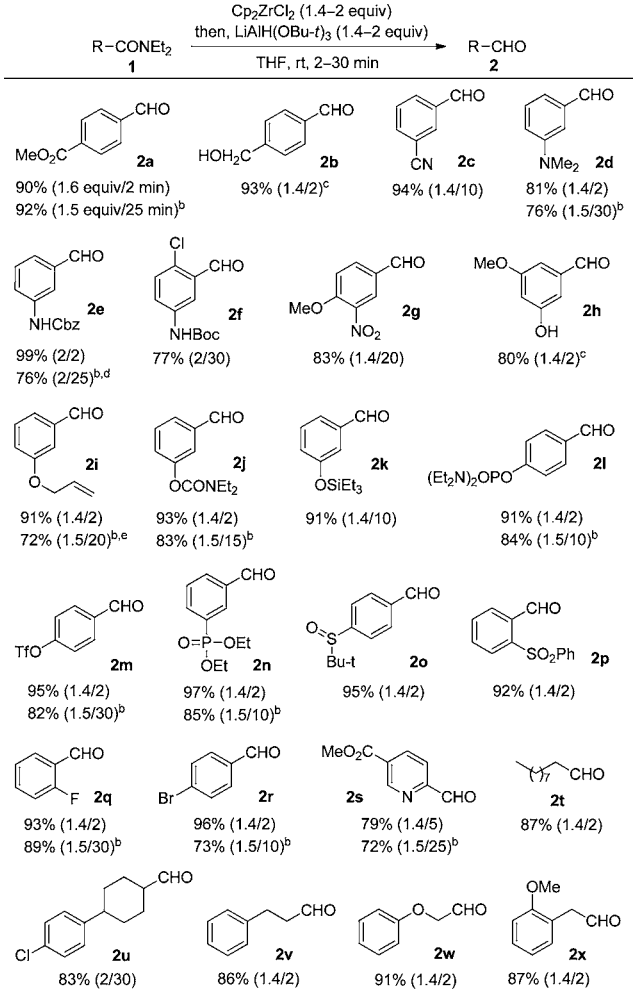
ACS Publications © 2013 American Chemical Society

dx.doi.org/10.1021/ol403183a | *Org. Lett.* 2014, 16, 390–393

reagent mentioned above which stimulated the discovery and development of the synthetic chemistry reported herein.

In initial studies, we were motivated to assess the new in situ method with the well-defined Georg procedure for the reduction of *N,N*-diethylbenzamides to benzaldehydes.[3a,c] We aimed to establish new methodology which tolerates the presence of other powerful directed *ortho* metalation groups (DMGs), functional groups (FGs) which act as cross coupling partners, as well as other FGs which had not been examined previously[3a,c] (Scheme 1). Thus, in a comparative set of

Scheme 1. Comparative Schwartz Reagent Reduction of *N,N*-Diethylamides via the Georg and in situ Methods[a]

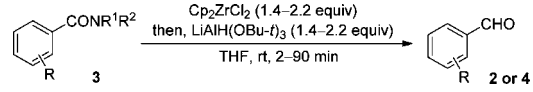


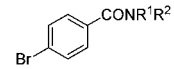
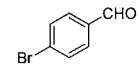
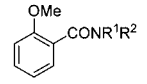
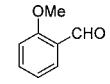
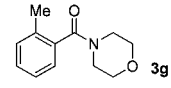
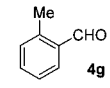
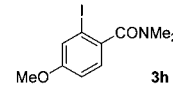
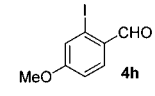
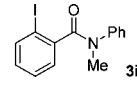
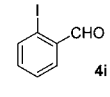
[a]Yields are of isolated products. Equivalents of Cp_2ZrCl_2:LiAlH(OBu-*t*)$_3$ (1:1) /times of reduction (in minutes) are shown in parentheses. [b]Data for Schwartz reagent ($Cp_2Zr(H)Cl$) reduction employing the Georg procedure. [c]Reduction via inverse addition: a solution of Cp_2ZrCl_2 (1.4 equiv) was added to a solution of substrate and LiAlH(OBu-*t*)$_3$ (2.4 equiv). [d]Accompanied by the corresponding 3-(NHCbz)benzyl alcohol (24%). [e]Accompanied by the corresponding 3-*n*-PrO-benzaldehyde (7%).

experiments, when subjected to the Georg conditions (1.5 equiv of Schwartz reagent/THF/rt), a *p*-carbomethoxybenzamide underwent chemoselective reduction to give the benzaldehyde **2a** in 92% yield within 25 min while the in situ procedure (1.6 equiv of Schwartz reagent) afforded **2a** in the same yield within 2 min. In other comparative studies, the in situ method was shown to have an advantage in yield and time of reaction, e.g., **2d**, **2e**, **2i**, **2j**, **2l**–**n**, and **2q**–**s**. A variety of FGs (CO_2Me, CN, NMe_2, NHBoc, NHCbz, NO_2, $OCH_2CH{=}CH_2$, $OCONEt_2$, $OSiEt_3$, $OP(O)(NEt_2)_2$, OTf, $P(O)(OEt)_2$, S(O)*t*-Bu, SO_2Ph, F, Cl, Br)[2n,9] are tolerant to these Schwartz reduction conditions, including the powerful DMGs $OCONEt_2$[7c,10a] and $OP(O)(NEt_2)_2$[10b] which offer useful data for further synthetic design based on DoM chemistry. The partial over-reduction for an NHCbz benzamide using the Georg method (aldehyde product **2e**, 76% yield accompanied by the corresponding alcohol, 24% yield) was not observed under the in situ conditions (quant yield of **2e**). Interestingly, the valiant *N*-Boc was found to be stable to the Schwartz reduction conditions (**2f**), and the coexistence of an amide–alkene FG, which was complicated by hydrozirconation under the Georg conditions (**2i**), was not compromised under the in situ 2 min protocol to give product **2i** in 91% yield. As an example of the chemoselective reduction of a heterocycle, a picolinamide afforded the corresponding aldehyde **2s** in a useful yield.[11] Furthermore, a reverse addition procedure was developed for high-yield reduction of amide substrates bearing acidic hydrogens: a solution of Cp_2ZrCl_2 (1.4 equiv) was added to a solution of substrate and LiAlH(OBu-*t*)$_3$ (2.4 equiv) of which 1 equiv of reductant presumably served to deprotonate the substrate (**2b** and **2h**). Reduction of aliphatic amides also proceeded smoothly in high yields (**2t**–**x**) under the in situ conditions, including a branched aliphatic amide which furnished **2u** under prolonged reaction times.

Having established the optimum conditions for the in situ method, a series of differentially *N,N*-disubstituted benzamides were investigated (Table 1). Thus, while a *N,N*-diethylamide **3a** underwent reduction in high yield in 2 min under the standard

Table 1. in situ Schwartz Reagent Reduction of Differentially Substituted Tertiary Amides 3a–i



entry	amide	Schwartz reagent, time (yield) [equiv, min (%)[a]] Georg method	*in situ* method	aldehyde
				
1	R^1,R^2 = Et, Et (**3a**)	1.5, 10 (73)	1.4, 2 (96)	**2r**
2	= *i*-Pr, *i*-Pr (**3b**)		2.2, 25 (88)	**2r**
				
3	R^1,R^2 = Me, Me (**3c**)		1.4, 2 (94)	**4c**
4	= Et, Et (**3d**)	1.5, 10 (94)	1.4, 2 (93)	**4c**
5	= Et, cumyl (**3e**)	2.0, 90 (55)	2.2, 90 (trace)	**4c**
6	= *i*-Pr, *i*-Pr (**3f**)	2.0, 90 (59)	2.2, 90 (trace)	**4c**
7	 **3g**		1.4, 2 (95)	 **4g**
8	 **3h**		1.4, 8 (89)	 **4h**
9	 **3i**		1.4, 7 (90)	 **4i**

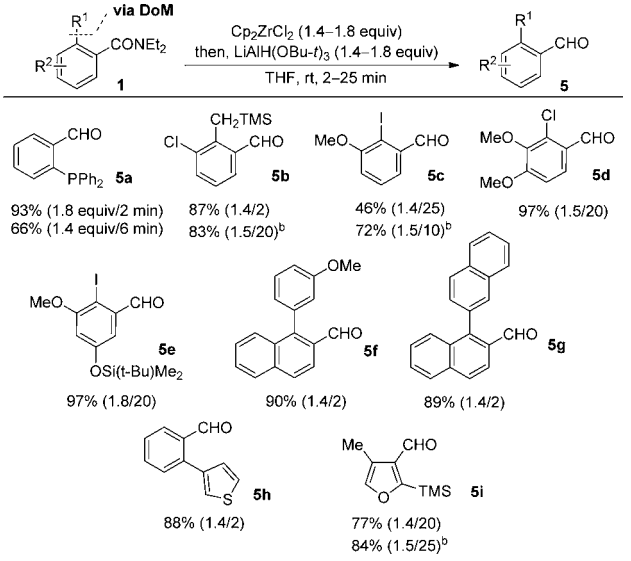
[a]Yields are of isolated products. [b]Cumyl = 2-phenylpropan-2-yl.

dx.doi.org/10.1021/ol403183a | *Org. Lett.* 2014, 16, 390–393

conditions (entry 1), the corresponding *N,N*-diisopropylamide **3b** required a prolonged reaction time and excess reductant to obtain a good yield of the aldehyde product **2r** (entry 2). Less-hindered, mono *ortho*-substituted benzamides **3c**, **3d**, and **3g−i** were reduced in high yields (entries 3, 4, and 7−9). Notable are the cases **4h** and **4i** (entries 8 and 9), which demonstrate for the first time the stability of aryl iodides under the reduction conditions. However, the corresponding bulky substituted amides such as *N,N*-diisopropyl- and *N*-ethyl-*N*-cumylamides **3e** and **3f** were resistant to reduction while, in comparison, these cases underwent reduction in moderate yields under the Georg conditions (entries 5 and 6).[12]

In order to demonstrate the utility of a linked D*o*M−Schwartz reduction tactic for the synthesis of valuable and difficult to access benzaldehydes, a variety of D*o*M-derived and -related amide substrates were investigated (Scheme 2).

Scheme 2. Reduction of D*o*M-Derived and -Related Aromatic *N,N*-Diethylamides to Aldehydes via the in situ Method[a]

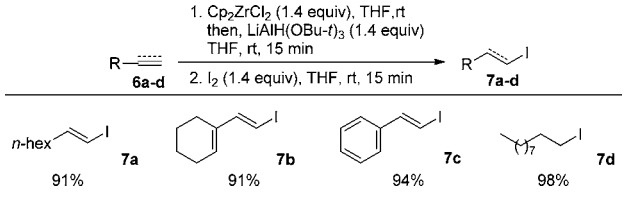


[a]Yields are of isolated products. [b]Data for Schwartz reagent ($Cp_2Zr(H)Cl$) reduction employing the Georg procedure.

Inherently, all *ortho*-substituted *N,N*-diethylbenzamides performed well under the reduction conditions to give the corresponding benzaldehydes **5a−i** in good yields. P- and Si-substituents were found to be tolerated as seen from products **5a** and **5b,e**, respectively. Although the hindered *o*-PPh_2 benzamide was reduced in moderate yield under the standard conditions, the use of excess reductant (1.8 equiv) furnished aldehyde **5a** in 93% yield. Similarly, use of an excess amount of reductant (1.8 equiv) drove the reduction of a hindered 2,3-disubstituted benzamide to completion to furnish aldehyde product **5e** in 97% isolated yield. 1-Aryl-2-naphthamides were smoothly reduced (**5f,g**). While a thiophenene-ylbenzamide (**5h**) behaved unexceptionally, surprisingly, a di-*ortho*-substituted furanamide was reduced to the corresponding aldehyde **5i** in good yield under the standard conditions.[13] A possible rationalization is the less encumbered environment of an amide between two furan ring substituents compared to the corresponding aryl amide due to bond angle differences of the respective substituents.[14] Besides the *N,N*-diethyl aromatic amides, the D*o*M-derived *N,N*-dimethyl and *N*-methyl-*N*-phenylbenzamides **3h** and **3i** (Table 1) behaved very well in the in situ Schwartz reduction process. These results establish a useful benzamide D*o*M−in situ Schwartz reduction connection for the preparation of unusual contiguously substituted benzaldehydes of potential further synthetic value.[15]

After the amide to aldehyde reduction study, we expanded the new in situ method to hydrozirconation chemistry. For a brief targeted investigation, we chose the conversion of alkynes to (*E*)-iodoalkenes which was previously reported in a three-step (preparation of Schwartz reagent and hydrozirconation at 0 °C; iodination at −78 °C) one-pot process using Cp_2ZrCl_2/DIBAL-H.[4d] The results, summarized in Scheme 3, demonstrate that aliphatic and aromatic alkynes **6a−c** are regio- and stereoselectively converted to the expected (*E*)-iodoalkenes **7a−c** in high yields under simpler reaction conditions. Notably, in contrast to the low reaction temperatures (0 and −78 °C) required for the comparative method,[4d] the in situ method is conducted at room temperature with high efficiency, e.g., **7a** is obtained in 91% yield by both methods. Further, hydrozirconation−iodination of an alkene **6d** under the same conditions furnished iodoalkane **7d** in excellent yield and high regioselectivity. Thus, the in situ protocol appears to be an advantageous procedure for the provision of (*E*)-iodoalkenes and iodoalkanes which are useful for the important Negishi cross-coupling regimen.[16]

Scheme 3. One-Pot Regio-and Stereoselective Conversion of Alkynes to (*E*)-Iodoalkenes and Alkenes to Iodoalkanes via the in situ Hydrozirconation Method[a]



[a]Yields are of isolated products.

In summary, stimulated by the Georg report,[3a] we have discovered and developed an advantageous in situ protocol (Cp_2ZrCl_2/LiAlH(OBu-*t*)$_3$ for the generation of the Schwartz reagent which provides a general, convenient, and economic method for the reduction of aliphatic, aromatic, and heteroaromatic tertiary amides to the corresponding aldehydes and the regioselective hydrozirconation−iodination of alkynes and alkenes. The reaction demonstrates advantages of a very short reaction time, excellent functional group compatibility, and use of inexpensive and long-storage stable reducing reagents. Of considerable significance is the D*o*M−Schwartz protocol. The large number of benzamide precursors of benzaldehyde products **2d**, **2f**, **2j−n**, **2p**, and **2q** (Scheme 1) represent prototypes bearing additional DMGs, on which D*o*M chemistry[7] prior to reduction can lead to unusually substituted aromatics. More recommendable are the contiguously substituted products **5b−e** and **5i** (Scheme 2), which have seen abundant use in modern synthetic practice.[17] From these considerations, substantially greater synthetic utility and application of these results is anticipated. Considerable generalization and mechanistic studies will be reported in due course.

dx.doi.org/10.1021/ol403183a | *Org. Lett.* 2014, 16, 390−393

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds and products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: snieckus@chem.queensu.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Francoise Sauriol (Queen's University) for assistance in NMR spectroscopy, Dr. Jiaxi Wang (Queen's Univ.) for discussion of MS spectra, and NSERC Canada (Discovery Grant) for continuing support of our synthetic programs.

■ REFERENCES

(1) (a) Kautzner, B.; Wailes, P. C.; Weigold, H. *J. Chem. Soc., Chem. Commun.* **1969**, 1105. (b) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405.

(2) Selected reviews: (a) Marek, I., Ed. *Titanium and Zirconium in Organic Synthesis*; Wiley-VCH: Weinheim, 2002; pp1−318. (b) Marek, I.; Chinkov, N.; Levin, A. *Synlett* **2006**, 501. (c) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2005**, *8*, 1. (d) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. Selected recent applications: (e) Machara, A.; Werner, L.; Endoma-Arias, M. A.; Cox, D. P.; Hudlicky, T. *Adv. Synth. Catal.* **2012**, *354*, 613. (f) Wu, F.; Green, M. E.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 1131. (g) Joosten, A.; Lambert, E.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2010**, *12*, 5128. (h) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 904. New expansions: allylation of amides: (i) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950. Reduction of amides to azahemiacetals: (j) Romeo, R.; Giofre, S. V.; Macchi, B.; Balestrieri, E.; Mastino, A.; Merino, P.; Carnovale, C.; Romeo, G.; Chiacchio, U. *ChemMedChem* **2012**, *7*, 565. (k) Metallinos, C.; John, J.; Zaifman, J.; Emberson, K. *Adv. Synth. Catal.* **2012**, *354*, 602. (l) Piperno, A.; Carnovale, C.; Giofre, S. V.; Iannazzo, D. *Tetrahedron Lett.* **2011**, *52*, 6880. Asymmetric C−C bond formation from alkenes: (m) Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nature Chem.* **2012**, *4*, 649. Reduction of aryl *O*-carbamates to phenols: (n) Morin, J.; Zhao, Y.; Snieckus, V. *Org. Lett.* **2013**, *15*, 4102. Moreover, a unique transformation of secondary amides to imines by the Schwartz reagent was dramatically demonstrated in the large-scale synthesis of the anticancer drug paclitaxel: (o) Ganem, B.; Franke, R. R. *J. Org. Chem.* **2007**, *72*, 3981.

(3) (a) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995. (b) Leighty, M. W.; Spletstoser, J. T.; Georg, G. I.; Umihara, H.; Fukuyama, T. *Org. Synth.* **2011**, *88*, 427. (c) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408. (d) Spletstoser, J. T.; White, J. M.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 2787.

(4) (a) Negishi, E.; Miller, J. A.; Yoshida, T. *Tetrahedron Lett.* **1984**, *25*, 3407. (b) Makabe, H.; Negishi, E. *Eur. J. Org. Chem.* **1999**, 969. (c) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257. (d) Huang, Z.; Negishi, E.-I. *Org. Lett.* **2006**, *8*, 3675.

(5) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

(6) (a) Zhao, Y., Ph.D. Thesis, Queen's University, Kingston, Ontario, Canada, 2010. (b) Zhao, Y.; Snieckus, V. A. US 8,168,833, 2012.

(7) (a) Snieckus, V.; Macklin, T. *Handbook of C−H Transformations*; Wiley-VCH: Weinheim, 2005; Vol. *1*, p 106. (b) Hartung, C. G.; Snieckus, V. *Modern Arene Chem.* **2002**, 330. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(8) (a) Anctil, E. J. G.; Snieckus, V. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. *2*, p 761. (b) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150.

(9) (a) Wang, J.; Qi, W.; Zhang, Y.; Xu, Y. *Youji Huaxue* **1985**, 317. CAN 104: 186091. (b) Zablocka, M.; Delest, B.; Igau, A.; Skowronska, A.; Majoral, J. P. *Tetrahedron Lett.* **1997**, *38*, 5997.

(10) (a) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. (b) Alessi, M., Ph.D. Thesis, Queen's Univesity, Kingston, Ontario, Canada, 2008.

(11) Wagner, F. F.; Comins, D. L. *Tetrahedron* **2007**, *63*, 8065.

(12) An intriguing rationale for this observation is the formation of a coordinated $Al(OBu\text{-}t)_3$-Schwartz reagent species, thus providing additional steric hindrance in the reduction process.

(13) By standard desilyation, this yields a 3,4-disubstituted furan derivative, a not readily accessible class of molecules; see: Bures, E.; Nieman, J. A.; Yu, S. Y.; Spinazze, P. G.; Bontront, J. L. J.; Hunt, I. R.; Rauk, A.; Keay, B. A. *J. Org. Chem.* **1997**, *62*, 8750.

(14) O'Sullivan, P. S.; De La Vega, J.; Hameka, H. F. *Chem. Phys. Lett.* **1970**, *5*, 576.

(15) Besides THF, other solvents such as DME, dioxane, CH_2Cl_2, chloroform, and even toluene were found to be suitable solvents for the in situ reduction process. The above solvent effects are dramatically different from those observed by Georg;[3c] see the Supporting Information.

(16) Negishi, E.; Hu, Q.; Huang, Z. H.; Qian, M. X.; Wang, G. W. *Aldrichimica Acta* **2005**, *38*, 71.

(17) (a) Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187. (b) Silveira, C. C.; Larghi, E. L.; Mendes, S. R.; Bracca, A. B. J.; Rinaldi, F.; Kaufman, T. S. *Eur. J. Org. Chem.* **2009**, 4637. (c) Mautino, M.; Kumar, S.; Waldo, J.; Jaipuri, F.; Kesharwani, T. WO2012/142237, 2012.