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Iridium-Catalyzed Hydrosilylative Reduction of Glucose to Hexane(s)

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S Supporting Information

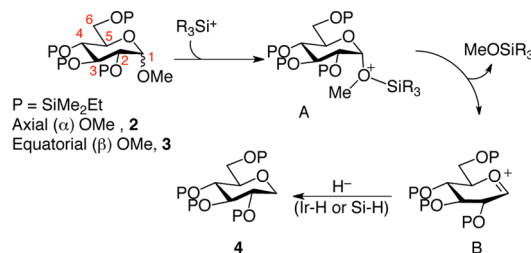
ABSTRACT: In light of diminishing petroleum feedstocks, there is significant interest in developing carbohydrate defunctionalization reactions. In this context we have examined the use of iridium pincer catalysts for the hydrosilylative reduction of sugars, and we report herein complete reduction of silyl-protected glucose to a mixture of hexane isomers.

The dwindling of petroleum resources has made carbohydrates attractive targets for renewable energy and chemical feedstocks.¹ Chemists have sought to defunctionalize sugars to simpler chemical feedstocks, which are compatible with modern chemical processes and infrastructure.² Despite significant effort, most systems relevant to carbohydrate defunctionalization utilize harsh conditions (high temperatures, pressures, and strong acids) and are generally low yielding for defunctionalized products.³ To date, the mildest systems for the reduction of carbon–oxygen bonds are hydrosilylative; however, for sugars these methods have been limited to defunctionalization at the activated C₁ position and take many hours.^{4–6}

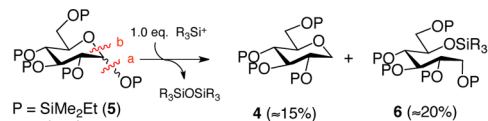
Brookhart has reported a cationic iridium pincer complex, **1**, which acts as a potent catalyst (<1 mol %) for the hydrosilylative reduction of alkyl ethers to alkanes (e.g., Scheme 1).⁷ In combination with triethylsilane, **1** mediates the complete reduction of primary and methyl ethers to the hydrocarbon. In the case of secondary ethers, only a single C–O cleavage occurs, and the secondary silyl ether is obtained. Despite these potential limitations, we surmised that the

enhanced stability of the C₁-carbocation of a sugar might support an alternative, Murai-like⁴ mechanism for the reduction of at least one secondary C–O bond in glucose (Scheme 2). In this scenario we anticipated C₁ reduction to be especially rapid.

Scheme 2

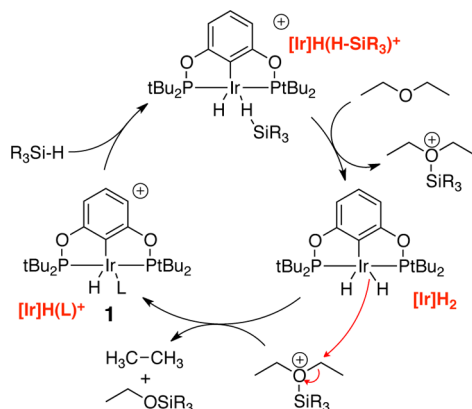


Initial experiments with 1% catalyst, 1.2 equiv of SiMe₂EtH, and the α- and β-anomers of silylated MeO-glucose (**2** and **3**), showed that reduction to **4** was rapid and complete within minutes (over 90% by NMR). Although both the α- and β-anomers reacted too fast to monitor rates, a competition between 1 equiv each of **2** and **3**, with 1 equiv of SiMe₂EtH (1% catalyst), established (by NMR) the near exclusive consumption of the equatorial (β) OMe isomer. The reduction of **5**, on the other hand, was substantially slower, requiring hours of reduction time and many equivalents of either SiMe₂EtH or the more reactive SiEt₂H₂⁸ for complete conversion. In addition to a slower rate, the selectivity for C₁ deoxygenation was compromised (see equation below).



Although reduction of **5** still yielded **4** through cleavage site “a”, a number of other products were also formed, including D-glucitol (**6**), which would require cleavage at site “b.” In situ monitoring by NMR spectroscopy of the reduction of **5** indicated that, like the C₁–OMe case, the β-anomer reacts faster (greater than 10× the rate), leading to the following comparative C–O hydrosilylation rates: C₁ equatorial, OMe > C₁ axial, OMe ≫ C₁ equatorial, OSiR₃ > C₁ axial, OSiR₃ > C_n, OSiR₃ (n = 2,3,4,6). This trend can be rationalized by noting the importance of a basic ether in forming the key silyloxonium

Scheme 1

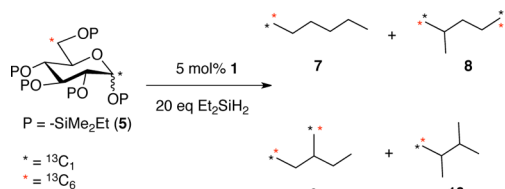


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ion, **A**, and the enhanced stability of the C₁-oxocarbenium ions (**B**, Scheme 2).

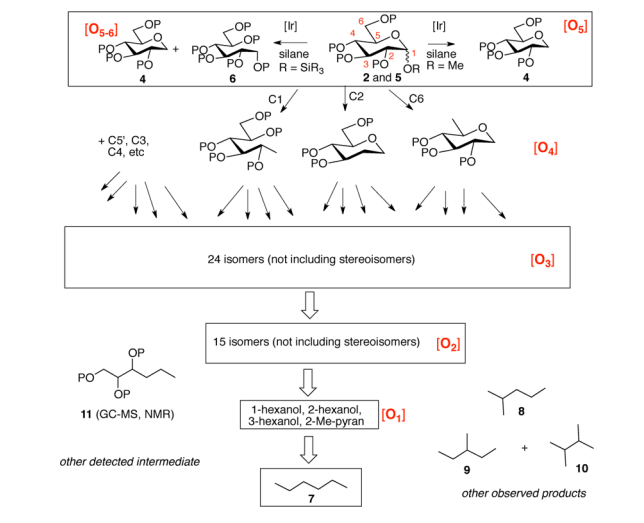
Increasing the catalyst loadings and silane concentration and using the more reactive diethylsilane⁸ revealed that **2** could be completely reduced to hexane isomers (see equation below).⁹



¹³C NMR and the spiking of reaction mixtures with authentic products verified the formation of the indicated hexanes: *n*-hexane (**7**), 2- and 3-methylpentane (**8** and **9**), and trace amounts of 2,3-dimethylbutane (**10**). Using ¹³C₆- and ¹³C₁-labeled **5** to follow the reaction showed that both ¹³C-labeled sugars converged to a similar mixture of hexanes, with one enhanced signal for **7** and **10** and two for **8** and **9**. Over the course of the reduction of ¹³C-**5**, hexanes were observable within 12 h, but the signal continued to develop for weeks. Over the course of 2 weeks, all of the ¹³C NMR peaks associated with C–O bonds (50–100 ppm) diminished below the detection limit, accompanied by continual growth of peaks in the alkyl region (10–50 ppm).

The in situ monitoring of the nonlabeled sugars proved fascinating. As discussed above, **2** and **3** quickly convert to **4**; however, as the signals of this C₁-deoxy product diminish, they are not replaced with new signals until much later when hexane begins appearing. For compound **5**, a dramatic loss of signal intensity occurs immediately upon its consumption. As shown in Scheme 3, we surmised that a nonselective C–O reduction

Scheme 3



would lead to a large increase in the number of components and a concomitant decrease in spectral intensity. This hypothesis was verified by monitoring the reduction of ¹³C-labeled **5** by ¹³C NMR spectroscopy. As shown in Figure 1, numerous intermediates are observed both in the C–O region (50–100 ppm) and in the upfield alkane region. Contributing to this diversity of intermediates are traces of unsaturated compounds (100–150 ppm, not shown), which appear transiently, including a match for 1-hexene. Such an observation

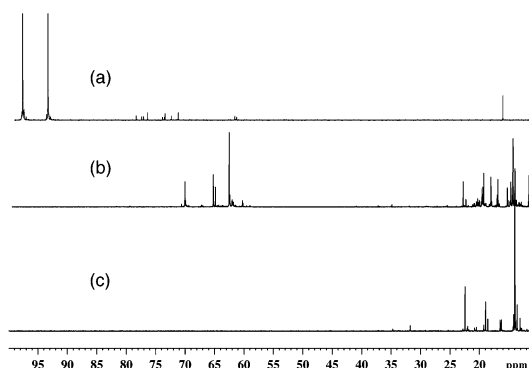


Figure 1. In situ ¹³C NMR spectra of hydrosilylation of ¹³C₁-**5** at various time points: (a) starting material, (b) 14 h, (c) 7 days. Peaks upfield of 10 ppm are silane related.

not unreasonably suggests that elimination is also a competitive process.

To overcome the technical challenges of quantifying the volatile hexane products, the yields were estimated by an in situ ¹³C NMR spectroscopy experiment utilizing internal standard and a calibrated 90° pulse sequence (see SI for details).¹⁰ Both the α - and β -anomers of MeO-glu, **2** and **3**, consistently yielded a higher proportion of the rearranged products than did **5** (Figure 2). A possible source for this surprising divergence in

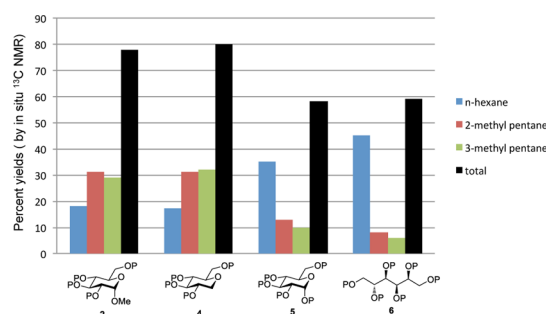


Figure 2. Absolute yields (%) of the hexane isomers **7–9** for the hydrosilylation of **2** and **4–6** as determined by semiquantitative ¹³C NMR spectroscopy. General reaction conditions: 5% catalyst **1** and 20 equiv of SiEt₂H₂ (see SI for details).

hexane isomer production was suggested by the comparative deoxygenation of **4** and **6** (glucitol). Like **2**, the C₁-deoxy **4** gives significant rearrangement, consistent with rapid conversion of **2** to **4** during the reaction. Reduction of **6**, however, gives predominantly *n*-hexane, suggesting that **2** and **5** may bifurcate at the first reaction steps. It thus seems likely that pyranose **4** is the species most likely to initiate branching, presumably through carbocation(s)¹¹ that may or may not involve neighboring group participation.

The nature of the catalytic species responsible for the deoxygenative behavior is not fully understood. As expected, hydride resonances between –8 and –12 ppm were observed. While these resonances are similar to those previously reported by Brookhart,^{7,8} they eventually drop below the detection limit even as catalysis continues.¹² Attempts to utilize simple iridium precursors ([Ir(COE)Cl]₂,¹³ [Ir(COD)Cl]₂,¹⁴ and Vaska's complex (both PPh₃ and PMe₃)¹⁵), both with and without added LiB(C₆F₅)₄·Et₂O, were unsuccessful.

In summary, we have identified a system that catalyzes the full reduction of silyl protected sugars to a mixture of hexane

isomers. MeO- sugars **2** and **3** proceed by selective C₁ reduction to **4**, whereas the persilyl glucose, **5**, is reduced to a mixture that includes **4** and the ring-opened sugar **6**. The hexane isomer distribution is sensitive to the C₁-substituent, with the 1-OMe-protected sugars **2** and **3** yielding mostly 2- and 3-methylpentane, whereas the C₁-OSiR₃, **5**, yielded mostly *n*-hexane. The reaction rate is affected by the silane, with the less hindered Et₂SiH₂ giving the fastest rates. Studies on the role of sugar, catalyst, and silane on the efficiency and hexane selectivity of this reaction are ongoing.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, carbohydrate protections/characterization, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Ragauskas, A. J.; Williams, C. K.; Davison, B. H.; Britovsek, G.; Cairney, J.; Eckert, C. A.; Fredrick, W. J. J.; Hallett, J. P.; Leak, D. J.; Liotta, C. L.; Mielenz, J. R.; Murphy, R.; Templer, R.; Tschaplinski, T. *Science* **2006**, *311*, 484–489. (b) Kerr, R. A.; Service, R. F. *Science* **2005**, *309*, 101.
- (2) Schlaf, M. *Dalton Trans.* **2006**, 4645–4653.
- (3) (a) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411–2502. (b) Ruppert, A. M.; Weinberg, K.; Palkovits, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2564–2601. (c) Barrett, C. J.; Dumesic, J. A.; Liu, Z. Y.; Roman-Leshkov, Y. *Nature* **2007**, *447*, 982–985. (d) Yang, W.; Grochowski, M. R.; Sen, A. *ChemSusChem* **2012**, *5*, 1218–1222. (e) Alonso, D. M.; Wettstein, S. G.; Dumesic, J. A. *Chem. Soc. Rev.* **2012**, *41*, 8075–8098. (f) Gallezot, P. *Chem. Soc. Rev.* **2012**, *41*, 1538–1558. (g) Huber, G. W.; Iborra, S.; Corma, A. *Chem. Rev.* **2006**, *106*, 4044–4098. (h) Schlaf, M.; Thibault, Michellea, E.; DiMondo, D.; Taher, D.; Karimi, E.; Ashok, D. *Int. J. Chem. React. Eng.* **2009**, *7*, 1–13. (i) Mascal, M.; Nikitin, E. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7924–7926. (j) Zhao, H.; Holladay, J. E.; Brown, H.; Zhang, Z. C. *Science* **2007**, *316*, 1597–1600. (k) Schlaf, M.; Ghosh, P.; Fagan, P. J.; Hauptman, E.; Bullock, R. M. *Adv. Synth. Catal.* **2009**, *351*, 789–800. (l) Ahmed Foskey, T. J.; Heinekey, D. M.; Goldberg, K. I. *ACS Catal.* **2012**, *2*, 1285–1289. (m) Ewing, G. J.; Robins, M. J. *Org. Lett.* **1999**, *1*, 635–636. (n) In Hwan, O.; Gray, G. R. *Carbohydr. Res.* **1995**, *278*, 329–338. (o) Taher, D.; Thibault, M. E.; DiMondo, D.; Jennings, M.; Schlaf, M. *Chem.—Eur. J.* **2009**, *15*, 10132–10143. (p) Ghosh, P.; Fagan, P. J.; Marshall, W. J.; Hauptman, E.; Bullock, R. M. *Inorg. Chem.* **2009**, *48*, 6490–6500. (q) Ziegler, J. E.; Zdilla, M. J.; Evans, A. J.; Abu-Omar, M. M. *Inorg. Chem.* **2009**, *48*, 9998–10000. (r) Arceo, E.; Marsden, P.; Bergman, R. G.; Ellman, J. A. *Chem. Commun.* **2009**, *45*, 3357–3359. (s) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416.
- (4) Hydrosilylative reduction of alcohols with metal or borane catalysts: (a) Chatani, N.; Shinohara, M.; Ikeda, S.-i.; Murai, S. *J. Am. Chem. Soc.* **1997**, *119*, 4303–4304. (b) Murai, T.; Furuta, K.; Kato, S.; Murai, S.; Sonoda, N. *J. Organomet. Chem.* **1986**, *302*, 249–254. (c) Mack, D. J.; Guo, B.; Njardarson, J. T. *Chem. Commun.* **2012**, *48*, 7844–7846. (d) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 8919. (e) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090–3098. (f) Nimmagadda, R. D.; McRae, C. *Tetrahedron Lett.* **2006**, *47*, 5755–5758. (g) Gutsulyak, D. V.; Vyboishchikov, S. F.; Nikonov, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 5950–5951. (h) Chatani, N.; Shinohara, M.; Ikeda, S.-i.; Murai, S. *J. Am. Chem. Soc.* **1997**, *119*, 4303–4304.
- (5) Hydrosilylative reduction of sugars: (a) Chatani, N.; Ikeda, T.; Sano, T.; Sonoda, N.; Kurosawa, H.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1988**, *53*, 3387–3389. (b) Rolf, D.; Bennek, J. A.; Gray, G. R. *Carbohydr. Res.* **1985**, *137*, 183–196. (c) In Hwan, O.; Gray, G. R. *Carbohydr. Res.* **1995**, *278*, 329–338. (d) Guo, Z.-W.; Hui, Y.-Z. *Synth. Commun.* **1996**, *26*, 2067–2073. (e) Ewing, G. J.; Robins, M. J. *Org. Lett.* **1999**, *1*, 635–636.
- (6) Several methods for the related activation of aryl C–O bonds and hydrosilylative C–F activation have recently emerged; see for example: (a) Sergeev, A. G.; Hartwig, H. F. *Science* **2011**, *332*, 439–442. (b) Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12554–12555. (c) Scott, V. J.; Çelenligil-Çetin, R.; Ozerov, O. V. *J. Am. Chem. Soc.* **2005**, *127*, 2852–2853. (d) Douvris, C.; Ozerov, O. V. *Science* **2008**, *321*, 1188–1190. (e) Kuehnel, M. F.; Holstein, P.; Kliche, M.; Krüger, J.; Matthies, S.; Nitsch, D.; Schutt, J.; Sparenberg, M.; Lentz, D. *Chem.—Eur. J.* **2012**, *18*, 10701–10714.
- (7) Yang, J.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2008**, *130*, 17509–17518.
- (8) Park, S.; Brookhart, M. *J. Am. Chem. Soc.* **2011**, *134*, 640–653.
- (9) Unprotected glucose also yielded hexanes under the reaction conditions. Preferable were preprotected carbohydrates that avoided excessive H₂ evolution during the reaction.
- (10) Pieters, L. A. C.; Vlietinck, A. J. *J. Pharm. Biomed. Anal.* **1989**, *7*, 1405–1417.
- (11) (a) Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 5801–5810. (b) Olah, G. A. In *Carbonium Ions*; Olah, G. A., Ed.; Wiley: New York, 1970; Vol. 2, pp 655–782.
- (12) The Lewis acid B(C₆F₅)₃, a known deoxygenative hydrosilylation catalyst, was considered as a potential active impurity. In situ ¹⁹F NMR spectroscopy of iridium-catalyzed reaction mixtures revealed only trace [B(C₆F₅)₄][–] decomposition and no observable borane; spiking completed reactions with borane shows it to be readily detectable at 0.1 mol %. Since reactions containing 0.1 mol % borane do not proceed in the absence of iridium catalyst and significantly higher concentrations of borane give a different product distribution, we conclude that Ir predominately catalyzes the reaction. For B(C₆F₅)₃/silane hydrosilylation, see for example references 4c–f.
- (13) Cheng, C.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 11304–11307.
- (14) Apple, D. C.; Brady, K. A.; Chance, J. M.; Heard, N. E.; Nile, T. A. *J. Mol. Catal. A: Chem.* **1985**, *29*, 55–64.
- (15) Pelczar, E. M.; Munro-Leighton, C.; Gagné, M. R. *Organometallics* **2009**, *28*, 663–665.