

demonstrate the reproducibility of these highly efficient processes, TriP₁₆₀ was successfully subjected to two cycles of mechanically induced cycloreversion and subsequent Cu catalyzed cycloaddition with similar results (21).

Collectively, these results demonstrate that directed mechanical forces can effect the previously elusive retroclick reaction, transforming triazoles into their azide and alkyne precursors. The ability to selectively deconstruct triazoles with high fidelity presents the opportunity to employ these readily accessible moieties in mechanoresponsive materials or as mechanically labile protecting groups. The former could include dye-sensitized force sensors (24) or force responsive fluorescent tags for biological assays. The latter would be of particular appeal for preventing undesired side reactivity in the presence of strong nucleophiles, especially considering that a broad range of substituents covalently bonded to the azide and alkyne coupling partners should tolerate ultrasonication. In a broader perspective, the methodology for triazole cycloreversion established here could be used to coax other kinetically stable molecules to exhibit uncommon

reactivity under the influence of exogenous mechanical forces.

References and Notes

- V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **41**, 2596 (2002).
- C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **67**, 3057 (2002).
- J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **48**, 8018 (2009).
- R. K. Iha *et al.*, *Chem. Rev.* **109**, 5620 (2009).
- P. Antoni *et al.*, *Macromolecules* **43**, 6625 (2010).
- H. D. Agnew *et al.*, *Angew. Chem. Int. Ed.* **48**, 4944 (2009).
- T. Yamada *et al.*, *J. Org. Chem.* **76**, 1198 (2011).
- J. Lietard, A. Meyer, J. J. Vasseur, F. Morvan, *J. Org. Chem.* **73**, 191 (2008).
- G. Pourceau, A. Meyer, J. J. Vasseur, F. Morvan, *J. Org. Chem.* **74**, 6837 (2009).
- T. S. Seo, Z. Li, H. Ruparel, J. Ju, *J. Org. Chem.* **68**, 609 (2003).
- F. Seela, S. A. Ingale, *J. Org. Chem.* **75**, 284 (2010).
- M. M. Caruso *et al.*, *Chem. Rev.* **109**, 5755 (2009).
- C. R. Hickenboth *et al.*, *Nature* **446**, 423 (2007).
- J. M. Lenhardt *et al.*, *Science* **329**, 1057 (2010).
- S. L. Potisek, D. A. Davis, N. R. Sottos, S. R. White, J. S. Moore, *J. Am. Chem. Soc.* **129**, 13808 (2007).
- M. J. Kryger *et al.*, *J. Am. Chem. Soc.* **132**, 4558 (2010).

- J. M. Lenhardt, A. L. Black, S. L. Craig, *J. Am. Chem. Soc.* **131**, 10818 (2009).
 - K. M. Wiggins *et al.*, *J. Am. Chem. Soc.* **132**, 3256 (2010).
 - J. Ribas-Arino, M. Shiga, D. Marx, *Angew. Chem. Int. Ed.* **48**, 4190 (2009).
 - G. S. Kochhar, A. Bailey, N. J. Mosey, *Angew. Chem. Int. Ed.* **49**, 7452 (2010).
 - Materials and methods are available as supporting material on *Science* Online.
 - K. S. Suslick, J. W. Goodale, P. F. Schubert, H. H. Wang, *J. Am. Chem. Soc.* **105**, 5781 (1983).
 - D. M. Khramov, C. W. Bielawski, *Chem. Commun. (Camb.)* (39): 4958 (2005).
 - D. A. Davis *et al.*, *Nature* **459**, 68 (2009).
- Acknowledgments:** We are grateful to the Army Research Office (grant W911NF-07-1-0409) and the Robert A. Welch Foundation (grant F-1621) for their generous financial support.

Supporting Online Material

www.sciencemag.org/cgi/content/full/333/6049/1606/DC1
Materials and Methods
SOM Text
Figs. S1 to S18
Tables S1 and S2
References (25–32)

4 May 2011; accepted 26 July 2011
10.1126/science.1207934

Primary Alcohols from Terminal Olefins: Formal Anti-Markovnikov Hydration via Triple Relay Catalysis

Guangbin Dong,¹ Peili Teo,^{1,3} Zachary K. Wickens,¹ Robert H. Grubbs^{1,2*}

Alcohol synthesis is critical to the chemical and pharmaceutical industries. The addition of water across olefins to form primary alcohols (anti-Markovnikov olefin hydration) would be a broadly useful reaction but has largely proven elusive; an indirect hydroboration/oxidation sequence requiring stoichiometric borane and oxidant is currently the most practical methodology. Here, we report a more direct approach with the use of a triple relay catalysis system that couples palladium-catalyzed oxidation, acid-catalyzed hydrolysis, and ruthenium-catalyzed reduction cycles. Aryl-substituted terminal olefins are converted to primary alcohols by net reaction with water in good yield and excellent regioselectivity.

Olefin hydration, the addition of water across a carbon-carbon double bond, is an important industrial process for the synthesis of alcohols (1) and can be readily catalyzed by acids, metal oxides, zeolites, and clays (2). However, in accord with Markovnikov's rule, the proton bonds to the less substituted carbon in these processes (3), and thus, primary alcohols (except ethanol) are difficult to obtain (Fig. 1, equation 1). Given the broad usefulness of pri-

mary alcohols in bulk/fine chemical and pharmaceutical industries (1), there is a compelling need to develop selective catalysts for direct anti-Markovnikov hydration of alkenes (4, 5). Currently, a popular indirect protocol involving hydroboration/oxidation (3) affords hydration products with anti-Markovnikov regioselectivity (Fig. 1, equation 2). This two-step process requires a stoichiometric amount of borane reagents and generates boron waste that is difficult to recycle. Moreover, the peroxides used in the oxidation step raise safety concerns for large-scale production. A hydroformylation/reduction sequence can also produce primary alcohols albeit through a homologation process (Fig. 1, equation 3) (6, 7). Campbell *et al.* recently developed an interesting strategy using a Pd-catalyzed allylic oxidation/ester hydrolysis/olefin reduction sequence to achieve the transformation of termi-

nal olefins to primary alcohols (8). Although effective, this approach requires a three-step operation.

In contrast to anti-Markovnikov olefin hydroamination (9) and alkyne hydration (10), two closely related reactions, very limited success has been achieved toward anti-Markovnikov olefin hydration (Fig. 1, equation 4) (5, 9). In 1986, it was reported that *trans*-PtHCl(PMe₃)₂ (Me, methyl) was able to catalyze hydration of 1-hexene to 1-hexanol (11); unfortunately, this work was difficult to reproduce (5, 12), as was the method in a later report (13). Reliable one-step catalytic protocols are currently limited to certain activated classes of olefin (14, 15). Here, we describe an effective method for the direct synthesis of primary alcohols from nonactivated terminal olefins (defined as non-Michael reaction acceptors) using a triple relay catalysis (16) system, as progress toward an ideal system for catalytic anti-Markovnikov olefin hydration.

Our strategy for anti-Markovnikov olefin hydration is based on a two-catalyst cooperative system involving an oxidation cycle followed by a reduction cycle (Fig. 2). Studies of the Wacker oxidation (17) have established that Pd^{II} salts such as PdCl₂ (X = Cl) can oxidize olefins in the presence of water to produce a carbonyl compound, an acid (HCl), and a palladium hydride (H-Pd-Cl). Precedents also exist for certain metal hydrides (M-H; M = Ru, Ir, Fe, Ni, Pt, etc.) to readily reduce carbonyl compounds, while in the process forming metal alkoxides that can be subsequently protonated by an acid (HX) to give an alcohol and metal salts (M-X) (18). In principle, these two known processes could be combined through a hydride transfer from Pd to M, in which the carbonyl compound and the acid generated from the oxidation cycle constitute the reactants

¹Arnold and Mabel Beckman Laboratories for Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA.

²Visiting Chair Professor at King Fahd University of Petroleum and Minerals, Dhahran, Saudi Arabia 31261. ³Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833.

*To whom correspondence should be addressed. E-mail: rhg@caltech.edu

Fig. 1. Synthesis of alcohols from olefins. R, alkyl or aryl groups; R', hydrogen or alkyl groups.

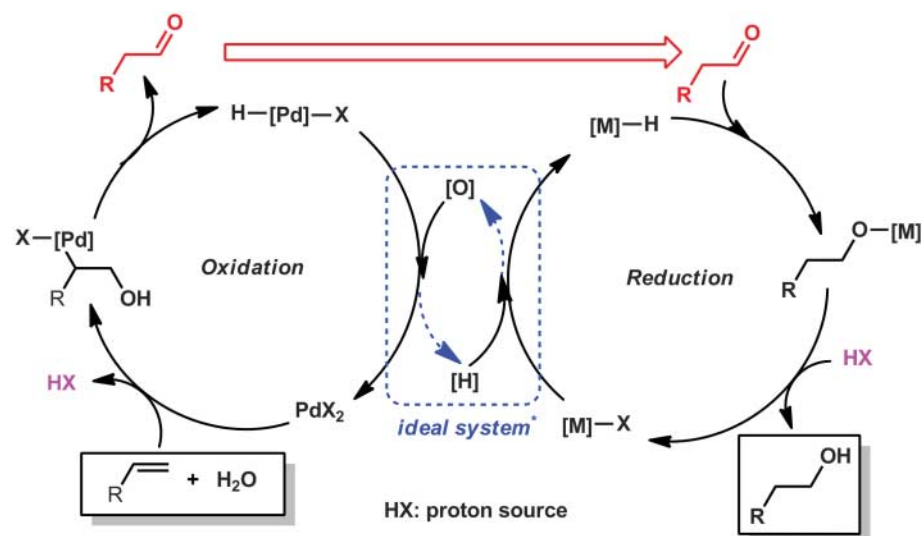
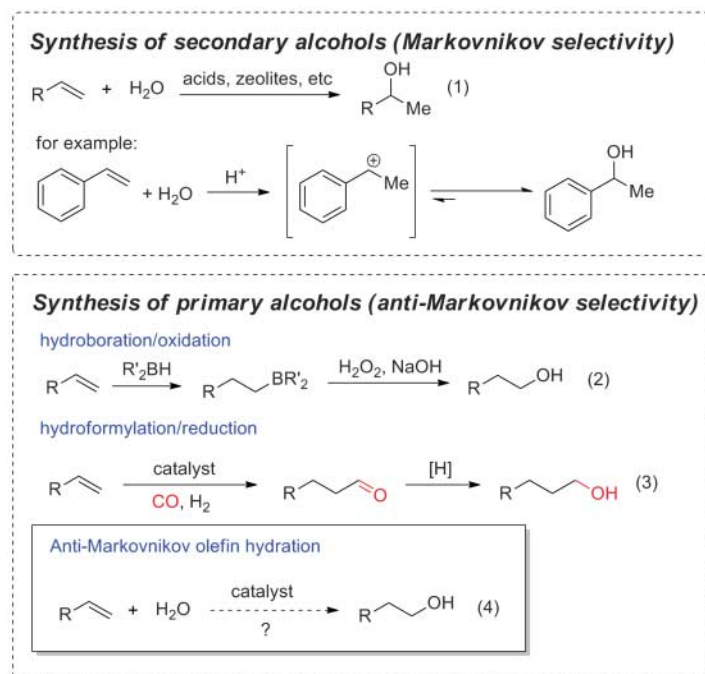
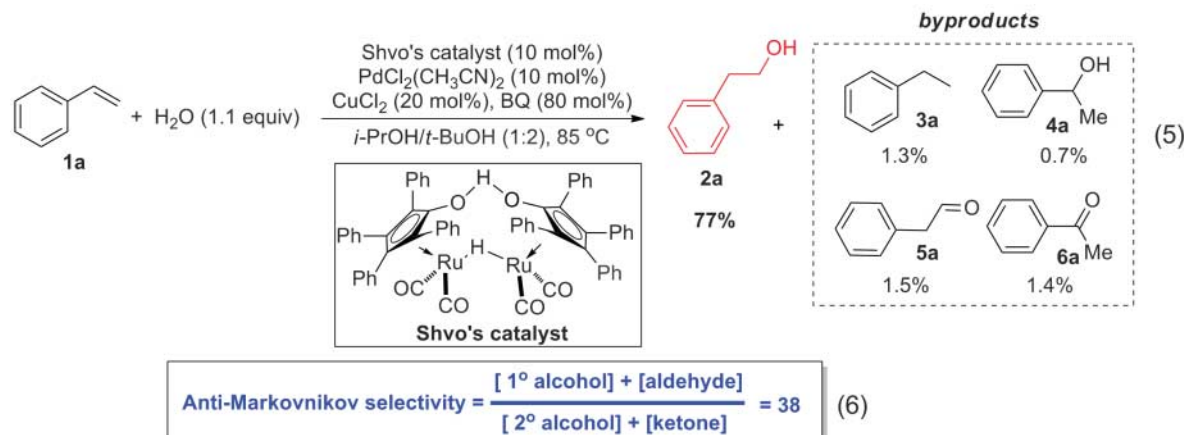


Fig. 2. Proposed cooperative catalytic system for alcohol synthesis from olefins and water. Asterisk: In the ideal system, either the hydride would be directly transferred from Pd to M or the oxidant [O] and the reductant [H] would be coupled with each other. X, anionic ligands, such as chlorides and acetates.



in the reduction cycle, to provide a facile catalytic methodology for the hydration of olefins. The success of this strategy relies on three criteria: First, the oxidation of olefins must be selective for aldehyde products, as normal Wacker oxidation favors methyl ketones (Markovnikov addition) (17). Second, the oxidation cycle must be compatible with the reduction cycle. Third, migration of the hydride from Pd to M should be facile. In this work, we focus on addressing the challenges of anti-Markovnikov selectivity and compatibility of the two cycles; thus, we developed a modified catalytic system by adding both oxidant and reductant to turn over the two catalysts individually (Fig. 2). Success in this modified system provides critical information about the feasibility of the ideal system.

We chose styrene as the initial substrate because under the acid-catalyzed hydration conditions, the secondary alcohol, 1-phenylethanol, is essentially the only product formed due to the generation of a stable benzyl cation (Fig. 1, equation 1) (19). Furthermore, under Brown's classic hydroboration conditions, styrene is a challenging substrate to functionalize with high anti-Markovnikov selectivity (the selectivity with diborane is only 4.2:1, whereas catechol borane gives 11.5:1 selectivity) (20). In addition, the product, 2-phenylethanol, is an important ingredient in artificial flavors, perfumery, and soaps (21). Few successful aldehyde-selective Wacker reactions with styrene derivatives have been reported [for a review, see (22)]. When *t*-BuOH is used as a solvent, high aldehyde selectivities in Wacker oxidations have been well established, albeit in low yields. In the case of styrene, only a 9% yield of phenylacetaldehyde was obtained (22–25). Recently, Wright *et al.* reported better aldehyde selectivity (6.4:1) with styrene, using PdCl₂ as the catalyst and DMF/H₂O (DMF, dimethylformamide) as the mixed-solvent under an inert atmosphere; the chloride ligands were proposed to play an integral role in the regioselectivity (26). We envisioned that by combining both the *t*-BuOH solvent effect and the chloride-ligand factor, we would further enhance the anti-Markovnikov selectivity. For the reduction cycle, we selected a combination of *i*-PrOH and Shvo's catalyst (27), because *i*-PrOH can serve as an inexpensive, clean,

Fig. 3. General reaction scheme for styrene hydration to produce 2-phenylethanol (2a), ethylbenzene (3a), 1-phenylethanol (4a), phenylacetaldehyde (5a), and acetophenone (6a). Pr, propyl; Bu, butyl; Ph, phenyl.

and safe reductant via metal-catalyzed transfer hydrogenation [for a review series, see (28)], and Shvo's complex is commonly used as a catalyst for transfer hydrogenation of carbonyl compounds and is also known to tolerate aqueous conditions (29).

To our delight, after initial optimization of the reaction conditions, we obtained 2-phenylethanol (**2a**) in 77% yield (Fig. 3, equation 5) with ex-

ceptionally high anti-Markovnikov selectivity (38:1) (Fig. 3, equation 6). Subsequently, we investigated the role of each reactant through a series of control experiments (see table S1). Under the standard conditions, the reaction proceeded with an excellent product selectivity, and by-products (**3a** to **6a**) were all formed in less than 2% yield. The absence of the Pd catalyst shut down the production of oxygenated products

completely, although the over-reduction product (ethylbenzene) still formed in 26% yield. Without Shvo's catalyst, we observed no alcohol products, and aldehyde **5a** was the major product. CuCl_2 was originally intended as a co-oxidant and later appeared to play a critical role in slowing down the over-reduction, as the absence of CuCl_2 led to substantially increased yields of ethylbenzene. 1,4-Benzoquinone (BQ) is widely used as a hydrogen acceptor and two-electron oxidant in Pd^{II} -catalyzed reactions (30) and was found to be the best co-oxidant for this transformation; omission of this component resulted in no alcohol formation. The role of *i*-PrOH as the reductant was highlighted by formation of aldehyde **5a** (57% yield) almost exclusively in its absence. *t*-BuOH proved to be responsible for enhanced reactivity and selectivity, whereas without *t*-BuOH, we obtained lower yields and regioselectivity of the primary alcohol. As expected, removal of water from the reaction mixture (using 4 Å molecular sieves) is detrimental: No oxygenated product was observed under anhydrous conditions.

We next examined the substrate scope on a preparative scale (0.4 mmol, Table 1). The primary alcohol products were isolated, purified with silica-gel flash column chromatography, and characterized via nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry or identified by comparison of the NMR and gas chromatography–mass spectrometry (GC-MS) data with the authentic samples. In general, aryl-substituted terminal olefins provide good yields of primary alcohols with excellent anti-Markovnikov selectivity ($\geq 20:1$). A number of functional groups are tolerated under these reaction conditions, such as alkyl, naphthyl, trifluoromethyl, and nitro groups, as well as various halides. Aliphatic olefins also provided hydration products, despite the challenging nature of these substrates [entries 11 and 12 (31)]. Although obtaining high regioselectivity for aliphatic substrates is more difficult, these results are promising because under previous conditions, only a Markovnikov product was observed for aliphatic substrates (26). One key merit of this method is that the major stoichiometric by-product, 1,4-hydroquinone (HBQ), can be easily recovered (see supporting online material) and converted to BQ in an excellent yield via a facile aerobic oxidation (32).

A triple relay catalysis system is proposed for this formal anti-Markovnikov olefin hydration process (Fig. 4A). We postulate that in the presence of *t*-BuOH, the olefin (**a**) would first undergo Pd-catalyzed oxidation to generate a *t*-butyl vinyl ether (**b**). Due to the bulkiness of *t*-BuOH, the linear vinyl ether is preferred, which constitutes a key factor underlying the high anti-Markovnikov selectivity (22, 24). During such a Wacker-like process, we expect the generation of acids (HCl and hydroquinone). Subsequently, in the presence of water, ether **b** would be converted to aldehyde **c** through acid-catalyzed hydrolysis. Finally, aldehyde **c** would be reduced to primary alcohol **d** via Ru-catalyzed transfer-hydrogenation reaction.

Table 1. [Pd]/[Ru]-catalyzed hydration of functionalized styrenes, 1-octene, and allylbenzene.

Entry	Substrate	Product	Yield	Selectivity (1°OH : 2°OH) [#]
1			61% (GC yield 65%)* 84% (GC yield 83%) [‡]	$\geq 20:1$
2			42% [†]	$\geq 20:1$
3			61% [†]	$\geq 20:1$
4			60% [‡]	$\geq 20:1$
5			72% [†]	$\geq 20:1$
6			75% [‡]	$\geq 20:1$
7			72% [†]	$\geq 20:1$
8			63% [†] 84% [‡]	$\geq 20:1$
9			83% [‡]	$\geq 20:1$
10			74% [†]	$\geq 20:1$

11		 	56% [§] (2k:4k = 1:1.4) 54% [§] (2k:4k = 1:1.9)	
12		 	12% [‡] (2m) (2m:4m = 1:2.1) [#]	

*Isolated yield and [C] (initial substrate concentration) = 0.25 M.

†Isolated yield and [C] = 0.125 M.

‡Isolated yield, [C] = 0.067 M, and 1 equiv of BQ was employed.

§Attempted purification through column chromatography; yield was determined via ¹H-NMR using mesitylene as the internal standard.

||*i*-PrOH:*t*-BuOH = 1:1, [C] = 0.067 M, and 1 equiv of BQ.

#The ratio was determined via ¹H-NMR analysis of the crude reaction mixture.

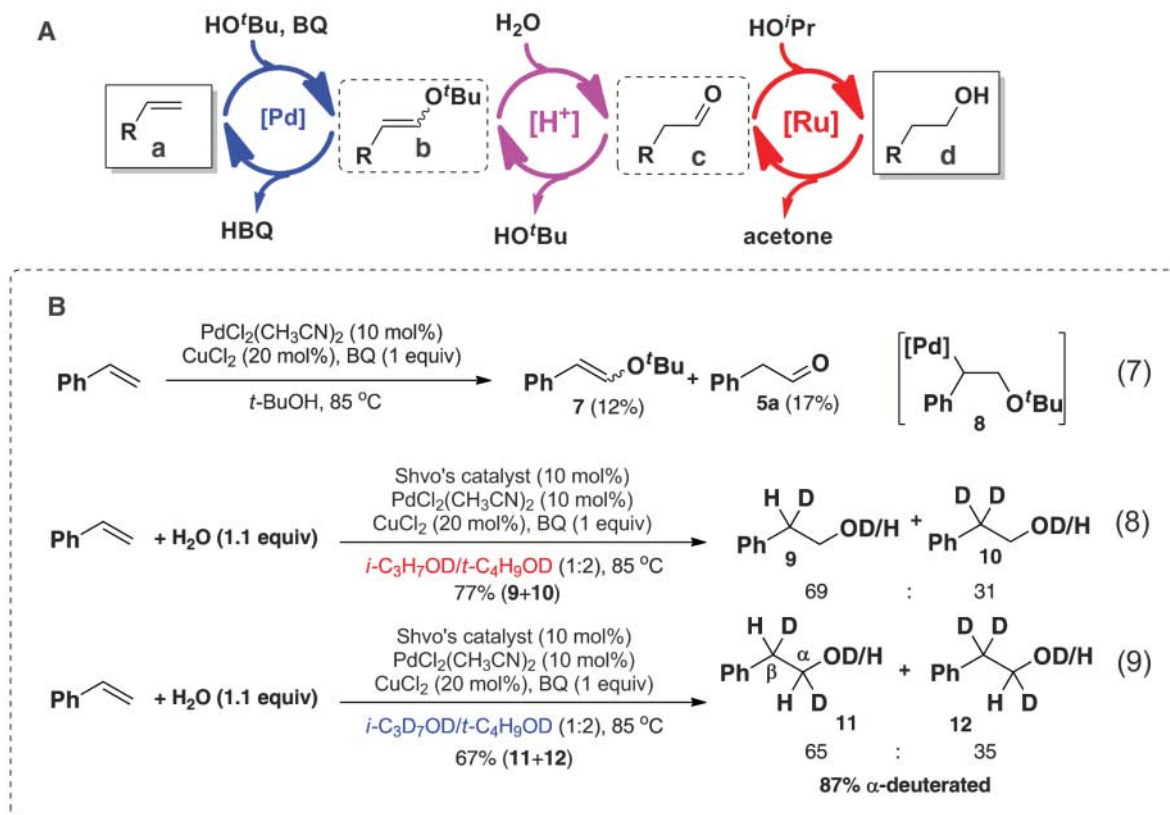


Fig. 4. (A and B) Proposed mechanism and initial mechanistic studies.

We then conducted a number of experiments to examine this hypothesis. In the absence of water, *i*-PrOH, and Shvo's catalyst, we observed a mixture of vinyl *t*-butyl ether geometric isomer **7** and aldehyde **5a** by ¹H-NMR spectroscopy and GC-MS, providing evidence for the proposed *t*-butyloxypalladation pathway (Fig. 4B, equation 7). When *i*-C₃H₇OD and *t*-C₄H₉OD were used, we observed mono- and di-deuterium incorporation at the β position, supporting a proton-mediated enol ether hydrolysis pathway, although deuteration via an aldehyde-enol tautomerization after the aldehyde formation cannot be ruled out (Fig. 4, equation 8) (33). We used regular H₂O because it only constitutes 0.14% by volume and undergoes rapid H/D exchange with deuterated alcohols. When *i*-C₃D₇OD and *t*-C₄H₉OD were used instead, we witnessed 87% deuterium incorporation at the α position as well, strongly supporting an *i*-PrOH-mediated transfer hydrogenation mechanism (Fig. 4, equation 9).

Compared to the classic hydroboration/oxidation sequence, our approach is still far from perfect, with its relatively high catalyst loadings and use of stoichiometric BQ. However, we are strongly encouraged by the excellent selectivity with aryl-substituted olefins, initial promising results with aliphatic alkenes, and the facile recovery of BQ to reduce the overall expense. Despite being in its infancy, this methodology has demonstrated great potential and will stimulate ongoing research in the field of olefin hydration.

References and Notes

- K. Weissmerl, H.-J. Arpe, *Industrial Organic Chemistry*, translated by C. R. Lindley, S. Hawkins (Wiley-VCH, New York, ed. 4, 2003).
- P. Wiseman, *An Introduction to Industrial Organic Chemistry* (Applied Science, London, 1979).
- M. B. Smith, J. March, *March's Advanced Organic Chemistry* (Wiley, New York, ed. 5, 2001).
- J. Haggin, *Chem. Eng. News* **71**, 23 (1993).
- L. Hintermann, *Top. Organomet. Chem.* **31**, 123 (2010).
- P. Eilbracht *et al.*, *Chem. Rev.* **99**, 3329 (1999).
- K. Takahashi, M. Yamashita, T. Ichihara, K. Nakano, K. Nozaki, *Angew. Chem. Int. Ed.* **49**, 4488 (2010) and references therein.
- A. N. Campbell, P. B. White, I. A. Guzei, S. S. Stahl, *J. Am. Chem. Soc.* **132**, 15116 (2010).
- T. E. Müller, K. C. Hultzsich, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **108**, 3795 (2008).
- M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **43**, 3368 (2004).
- C. M. Jensen, W. C. Trogler, *Science* **233**, 1069 (1986).
- D. Ramprasad, H. J. Yue, J. A. Marsella, *Inorg. Chem.* **27**, 3151 (1988).
- H. F. Koch, L. A. Girard, D. M. Roundhill, *Polyhedron* **18**, 2275 (1999).
- I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **125**, 8696 (2003).
- A. J. Boersma *et al.*, *Nat. Chem.* **2**, 991 (2010).
- H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **129**, 13796 (2007).
- J. M. Takacs, X.-T. Jiang, *Curr. Org. Chem.* **7**, 369 (2003).
- J.-E. Bäckvall, *J. Organomet. Chem.* **652**, 105 (2002).
- W. M. Schubert, J. R. Keefe, *J. Am. Chem. Soc.* **94**, 559 (1972) and references therein.
- H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **97**, 5249 (1975).
- Susan Budavari, Ed., in *Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals* (Merck, Rahway, NJ), ed. 11, 1989, p. 7185.
- J. Muzart, *Tetrahedron* **63**, 7505 (2007).
- T. T. Wenzel, *J. Chem. Soc. Chem. Commun.* **1993**, 862 (1993).
- B. L. Feringa, *J. Chem. Soc. Chem. Commun.* **1986**, 909 (1986).
- T. Ogura, R. Kamimura, A. Shiga, T. Hosokawa, *Bull. Chem. Soc. Jpn.* **78**, 1555 (2005).
- J. A. Wright, M. J. Gaunt, J. B. Spencer, *Chemistry* **12**, 949 (2006).
- Y. Shvo, D. Czarkie, *J. Organomet. Chem.* **315**, C25 (1986).
- M. J. Krische, Y. Sun, Eds. *Acc. Chem. Res.* **40**, 1237 (2007).
- K. Itami, A. Palmgren, A. Thorarensen, J.-E. Backvall, *J. Org. Chem.* **63**, 6466 (1998) and references therein.
- T.-K. Yang, C.-Y. Shen, in *Encyclopedia of Reagents for Organic Synthesis*, L. Paquette, Ed. (Wiley, New York, ed. 2, 2009), pp. 544–547.
- When allylbenzene was used as the substrate, the major by-product was β-methylstyrene arising from olefin isomerization.
- S. Kim, D. Kim, J. Park, *Adv. Synth. Catal.* **351**, 2573 (2009) and references therein.
- A. J. Kresge, *Acc. Chem. Res.* **20**, 364 (1987) and references therein.

Acknowledgments: We gratefully acknowledge financial support from the King Abdullah University of Science and Technology Center in Development, King Fahd University of Petroleum and Minerals, and the NSF. G.D. thanks the Camille and Henry Dreyfus Foundation for a postdoctoral fellowship. P.T. thanks A*STAR (Agency for Science, Technology and Research) for a postdoctoral fellowship (2009 to 2011). P.T. and Z.K.W. contributed equally to this paper. We also thank V. Lavallo and B. K. Keitz for proofreading the manuscript. A provisional patent was filed for work described in this Report.

Supporting Online Material

www.sciencemag.org/cgi/content/full/333/6049/1609/DC1
Materials and Methods
SOM Text
Table S1
NMR Spectra
References (34–42)

20 May 2011; accepted 27 July 2011
10.1126/science.1208685