

Mild and Selective Deuteration and Isomerization of Alkenes by a Bifunctional Catalyst and Deuterium Oxide

Gülin Erdogan and Douglas B. Grotjahn*

Department of Chemistry and Biochemistry, 5500 Campanile Drive, San Diego State University,
San Diego California 92182-1030

Received April 30, 2009; E-mail: grotjahn@chemistry.sdsu.edu

Deuterium- and tritium-labeled compounds are valuable probes in many studies, including reaction mechanisms, kinetics, drug metabolism, and structural elucidation of biological macromolecules.¹ The heavy isotopes of hydrogen are often introduced using multistep syntheses. This strategy involves several synthetic operations with labeled reagents. In contrast, catalyzed exchange of H for D or T is very attractive because it can be done in one step, with unlabeled substrates.^{2,3} The great challenges for catalyzed exchange are regio- and chemoselectivity and functional group tolerance. Most of the methods require high temperature and/or high pressure (in conditions where D₂ is the source of deuterium) or strongly acidic or basic additives.^{2,3} Homogeneous metal catalysis can provide milder conditions with greater functional group tolerance. Methods that use deuterium oxide are especially attractive because of its lower cost and toxicity and ease of handling. Although there are many reports of H/D exchange at aromatic and aliphatic C–H bonds,^{3,4a–f} there are surprisingly few such reports for alkenes and for these^{4g–i} exchange at vinylic positions dominates. A recent catalyst⁴ⁱ stands out for lack of alkene isomerization during deuteration; the others do not control isomerization well when it can occur.

Here we report H/D exchange at *allylic* positions of alkenes catalyzed by recently reported alkene zipper catalyst **1**⁵ using inexpensive deuterium oxide as the isotope source. We describe homogeneous reactions with acetone cosolvent and biphasic reactions which could allow one literally to wash out reactive substrate hydrogens without using organic solvents.

Bifunctional catalyst **1** isomerizes many alkenes to (*E*)-isomer products (upper part of Scheme 1) with low catalyst loading (2–5 mol %) at moderate temperatures (25–70 °C). The heterocyclic ligand is proposed to act as an internal base facilitating the isomerization by deprotonating accessible allylic position(s) of a coordinated alkene.⁵ In accord with the mechanism proposed in Scheme 1, adding deuterium oxide to the isomerization reactions leads to useful H/D exchange. Substrate scope (Scheme 2) was explored using representative hydrocarbon

chains. Substrates were dissolved in acetone-*d*₆, and sufficient deuterium oxide was added so as to provide 20 D per exchangeable H. Assuming equal distribution of D among all exchangeable positions, each such position should be 95% deuterated, judged to be a synthetically useful goal. Deuteration of propene C1 and C3 positions increased over time (Figure 1) reaching 97.5–98.5% of theoretical deuteration within 24 h.⁶ In stark contrast, the single proton at C2 was retained⁶ after reaction times as long as 60 d, in accord with the proposed mechanism. Similar deuteration at only C1 and C3 was seen when 4-allylanisole was heated with **1** and D₂O at 70 °C. Isomerization of diallyl ether gave (*E,E*)-dipropenyl ether without any detectable (*E,Z*)- or (*Z,Z*)-isomer.⁷ In the presence of deuterium oxide, H/D exchange is seen only at positions C1 and C3,⁷ consistent with previous examples.

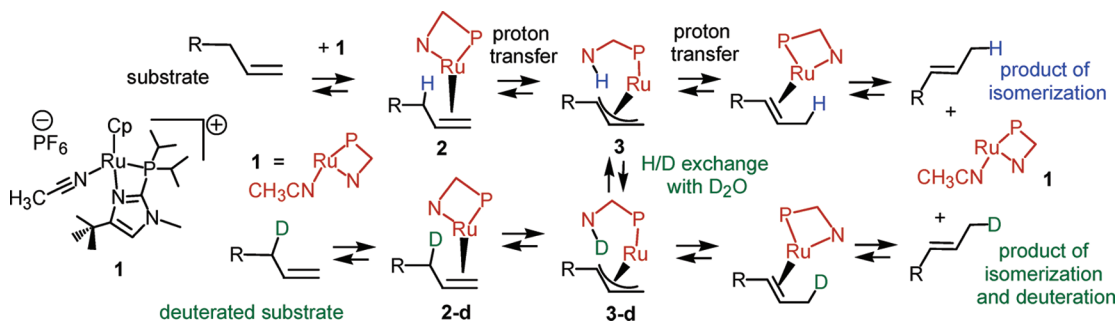
The observed selectivity makes the alternative mechanism (metal hydride formation, alkene insertion, and β -hydride elimination) seen for many other alkene isomerization catalysts⁸ highly unlikely.

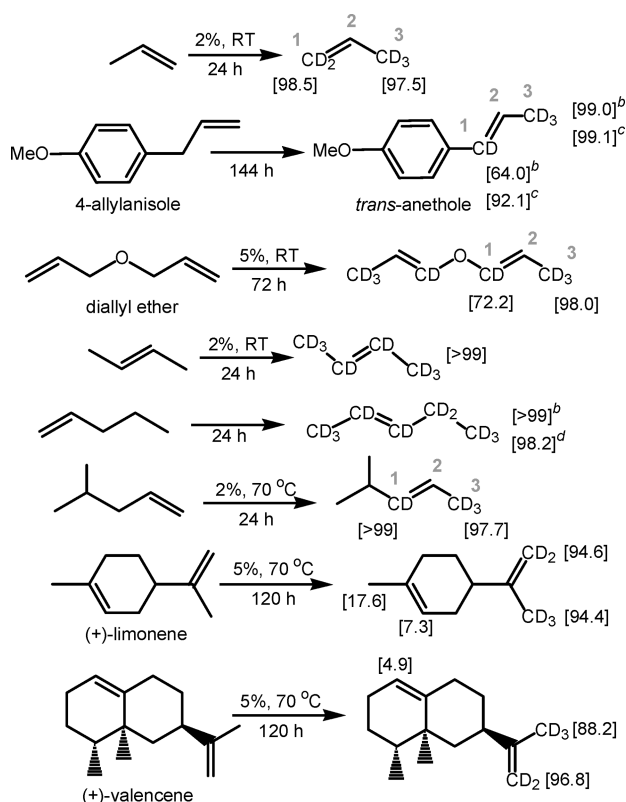
In contrast to the case of substrates with isolated allyl groups, when (*E*)-2-butene and 1-pentene were exposed to D₂O and **1**, H/D exchange occurred at previously unreactive vinylic positions. Presumably η^3 -allyl intermediates formed along the chain, allowing all positions to become allylic through isomerization. Thus, full deuteration of these substrates can be achieved with 2 to 5 mol % catalyst loading and reasonable reaction times.

Catalyst **1** deuterates (*E*)-2-butene quickly ($t_{1/2}$ = ca. 1.2 h) but only slowly ($t_{1/2}$ > ca. 240 h) isomerizes it to the (*Z*)-isomer; hence perdeuteration can occur without *E/Z* isomerization. These features highlight the high kinetic selectivity of **1** in making or acting on terminal or (*E*)-alkenes rather than on (*Z*)-alkenes.

Branched substrates provide additional examples of highly selective deuteration. For example, 4-methyl-1-pentene isomerized to (*E*)-4-methyl-2-pentene and deuteration was observed only at C1 and C3, leaving the C2 proton intact.⁹ Further isomerization was not observed even at elevated temperatures over time. The natural product (+)-limonene underwent H/D

Scheme 1. Proposed Mechanism of Isomerization and Deuteration



Scheme 2. Reactants and Products^a

^a Reactions carried out in acetone- d_6 with enough deuterium oxide so as to provide 20 D per exchangeable H present. The number in brackets indicates the percentage of the theoretical amount (95%) of deuterium. ^b RT with 2% catalyst. ^c 70 °C with 5% catalyst. ^d RT with 5% catalyst.

exchange mainly at the exocyclic isopropenyl group. Deuterium incorporation is observed at the endocyclic double bond but is far from complete, which can be attributed to steric hindrance to **1** forming an η^3 -allyl complex at this position. Deuteration of (+)-valencene was even more selective. Exocyclic isopropenyl groups are found in many terpenoid natural products; hence facile pentadeuteration at such sites is of particular interest.

Biphasic reactions were performed on liquid substrate 4-allylanisole by stirring it with only catalyst and D_2O , avoiding the use of organic solvents. Higher deuterium content was reached in shorter time compared to homogeneous reactions.^{6a} Moreover, using less D_2O , phase separation after equilibration to ~80% deuteration (70 °C, 24 h)^{6c} allowed removal of the aqueous phase and recharging the reaction system with fresh D_2O for further exchange.

In summary, unlike previous catalysts, bifunctional catalyst **1** performs H/D exchange at allylic positions with excellent control of isomerization when it occurs. Inexpensive and safe-to-handle D_2O is the source of label.

The high steric selectivity of **1** for (*E*)-alkenes gives the catalyst a unique reactivity and selectivity profile, which is expected to be especially useful in labeling complex substrates either at a late stage of a synthesis or using material directly from natural sources.

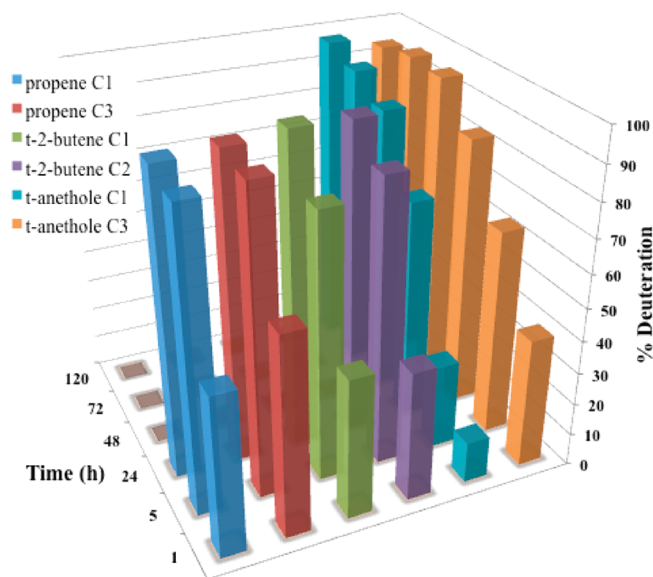


Figure 1

Acknowledgment. We thank Reji Nair for early experiments, Dr. LeRoy Lafferty for his assistance with NMR experiments, and the NSF (CHE 0719575) for supporting this and related work.

Supporting Information Available: Details of reaction conditions and results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Thomas, A. F. *Deuterium Labeling in Organic Chemistry*; Appleton-Century-Crofts: New York, NY, 1971.
- (2) Junk, T.; Catallo, W. J. *Chem. Soc. Rev.* **1997**, 26, 401–406.
- (3) Atzrodt, J.; Deraud, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, 46, 7744–7765.
- (4) (a) Klei, S. R.; Golden, J. T.; Tilley, T. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, 124, 2092–2093. (b) Klei, S. R.; Tilley, T. D.; Bergman, R. G. *Organometallics* **2002**, 21, 4905–4911. (c) Golden, J. T.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, 123, 5837–5838. (d) Hanson, S. K.; Heinekey, D. M.; Goldberg, K. I. *Organometallics* **2008**, 27, 1454–1463. (e) Corberán, R.; Sanaú, M.; Peris, E. *J. Am. Chem. Soc.* **2006**, 128, 3974–3979. (f) Corberán, R.; Sanaú, M.; Peris, E. *Organometallics* **2006**, 25, 4002–4008. (g) Pechtl, M. H. G.; Hölscher, M.; Ben-David, Y.; Theyssen, N.; Loschen, R.; Milstein, D.; Leitner, W. *Angew. Chem., Int. Ed.* **2007**, 46, 2269. (h) Faller, J. W.; Felkin, H. *Organometallics* **1985**, 4, 1488–1490. (i) Faller, J. W.; Smart, C. J. *Organometallics* **1989**, 8, 602–609. (j) Rybtchinski, B.; Cohen, R.; Ben-David, Y.; Martin, J. M. L.; Milstein, D. *J. Am. Chem. Soc.* **2003**, 125, 11041–11050. (k) Yung, C. M.; Skaddan, M. B.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, 126, 13033–13043. (l) Kohl, G.; Rudolph, R.; Pritzkow, H.; Enders, M. *Organometallics* **2005**, 24, 4774–4781. (m) Zhou, J. R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, 47, 5783–5787.
- (5) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. *J. Am. Chem. Soc.* **2007**, 129, 9592–9593.
- (6) See Supporting Information. (a) Determined by integration of 1H -NMR. (b) Determined by 1H and 2D NMR. (c) Table S5.
- (7) Although the integration of the C2 proton signal decreases slowly over time, control experiments with H_2O rather than D_2O showed that this is due to enol ether hydration to aldehyde rather than H/D exchange.
- (8) Examples: (a) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Khalil, A. A.; Wagener, K. B. *Organometallics* **2006**, 25, 6074–6086. (b) McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, 13, 224–235. (c) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, 113, 958–967. (d) Hendrix, W. T.; Von Rosenberg, J. L. *J. Am. Chem. Soc.* **1976**, 98, 4850–4852.
- (9) Determined by 1H and 2D NMR; see Supporting Information.

JA903519A