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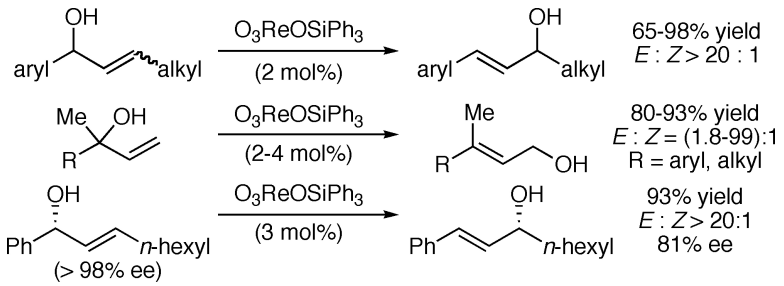

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Highly Selective 1,3-Isomerization of Allylic Alcohols via Rhenium Oxo Catalysis

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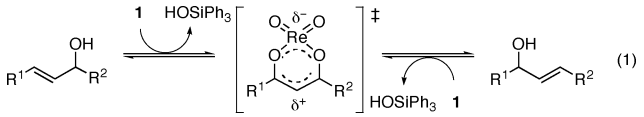
Allylic alcohols and their derivatives serve as useful precursors for numerous synthetic transformations, including Claisen[1] and Cope[2] rearrangements, directed epoxidations[3] and cyclopropanations,[4] carbonyl formation,[5] and palladium-catalyzed electrophilic substitutions.[6] The 1,3-isomerization of allylic alcohols (eq 1) is a useful reaction because one regioisomer is often more difficult to prepare than the other. Various transition metal oxo complexes catalyze this transformation: early catalysts required temperatures above 120 °C,[7] but later catalytic isomerizations proceeded at ambient temperatures.[8,9] $O_3ReOSiPh_3$ (**1**),[10] reported by Osborn and co-workers, is currently the most efficient catalyst for this isomerization process, allowing these reactions to attain equilibrium within 5 min at 0 °C.[11] Calculations[12] on the mechanism indicate a [3,3] sigmatropic rearrangement, which proceeds through a chairlike transition state containing an anionic perrhenate moiety and a cationic allyl moiety (eq 1), suggesting that the high catalytic activity of **1** arises from the stabilizing effect of its spectator oxo ligands.

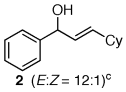
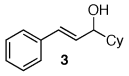
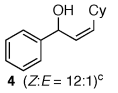
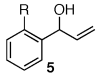
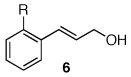
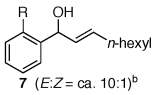
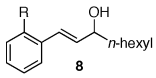
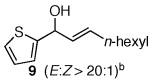
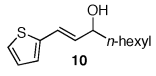
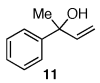
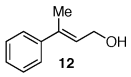
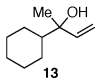
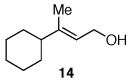


(1)

Rhenium catalyst **1** has the potential to provide ready access to allylic alcohols, but this isomerization typically results in a thermodynamic mixture of regioisomers, limiting its utility. We report herein reaction strategies that realize the highly selective 1,3-isomerization of a variety of allylic alcohols, both racemic and enantioenriched, while maintaining short reactions times, low catalyst loadings, and mild conditions.

Our first approach to promoting a selective reaction utilized allylic alcohols whose regioisomers contained conjugated alkenes. Previous work with other catalysts[8b,d,e] has shown that the more conjugated isomer predominates at equilibrium, thus capitalizing on thermodynamics to obtain high yields. Our initial experiments with catalyst **1** resulted in extensive dehydration and condensation reactions.[13] For example, the reaction of **1** with alcohol **7a** (CH_2Cl_2, rt) leads to a product distribution of **7a**/**8a**/side products = 0:15:85 (^{1}H NMR) within 2 min. However, with the proper solvent and sufficiently low reaction temperatures, the side reactions are completely suppressed, leading to the selective 1,3-isomerization of various allylic alcohols within about 30 min (Table 1). The side products presumably result from a competing reaction pathway involving the formation of an allylic cation,[8b,d] which should be more easily suppressed with lower temperatures. These reactions are highly *E*-selective, regardless of the initial alkene geometry (entries 1 and 2). This selectivity may be due to a destabilizing steric interaction between the axial aryl group and a rhenium oxo ligand that is present in the proposed chairlike transition state leading to *Z*-isomer formation.[12]

Table 1. 1,3-Isomerization of Allylic Alcohols Catalyzed by **1**[a]

entry	R	substrate	temp. (°C)	time (h)	product	isolated yield (%)	*E* : *Z*[b]
1		 **2** (*E*:*Z* = 12:1)[c]	–50	0.5	 **3**	95	> 20 : 1
2		 **4** (*Z*:*E* = 12:1)[c]	–50	0.5	**3**	93	> 20 : 1
3	H (a)	 **5**	0	0.5	 **6**	98	> 20 : 1
4[d]	NO_2 (b)		rt	0.5		98	> 20 : 1
5	OMe (c)		–50	0.5		65	> 20 : 1
6	H (a)	 **7** (*E*:*Z* = ca. 10:1)[b]	–50	0.5	 **8**	98	> 20 : 1
7	NO_2 (b)		rt	0.5		98	> 20 : 1
8	OMe (c)		–50	0.5		68	> 20 : 1
9		 **9** (*E*:*Z* > 20:1)[b]	–50	0.25	 **10**	92	> 20 : 1
10[e]		 **11**	–40	16	 **12**	84	18 : 1[c]
11		 **13**	0	0.5	 **14**	30[f]	4.7 : 1[c]

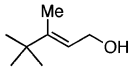
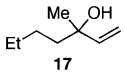
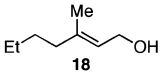
[a] 0.4 mmol scale, 2 mol % **1**, 0.2 M in diethyl ether. [b] Determined by 300 Mz NMR. [c] Determined by GC. [d] CH_2Cl_2 used as solvent. [e] 4 mol % **1**. [f] 70% of **13** recovered.

The reactivity of an allylic alcohol depends strongly upon its electronic properties. For example, substrates containing electron-poor allyl moieties (**5a**, **5b**, **7b**) undergo 1,3-isomerization efficiently only at or above 0 °C. However, substrates with electron-rich allyl moieties (**2**, **4**, **5c**, **7a**, **7c**, **9**) readily isomerize at −50 °C and exhibit extensive side product formation at higher temperatures. These observations are consistent with the formation of a partially cationic allyl moiety in the proposed transition state (eq 1).

While this procedure enables the selective formation of conjugated allylic alcohols, it still affords product mixtures with substrates that lack conjugation (e.g., Table 1, entry 11). To broaden the reaction scope, we developed a more general isomerization procedure that employs *N*,*O*-bis(trimethylsilyl)acetamide (BSA). The addition of BSA (1.2 equiv) promotes the nearly quantitative isomerization of tertiary allylic alcohols to form primary alcohols (Table 2). Because silylation by BSA is faster for primary alcohols than for tertiary alcohols, the product is selectively and irreversibly silylated, removing it from the reaction equilibrium.[14] The products can be deprotected and isolated in high yields, demonstrating the efficiency of this procedure for the synthesis of allylic alcohols containing either conjugated or nonconjugated trisubstituted alkenes.

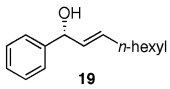
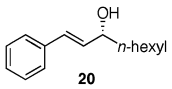
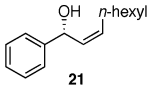
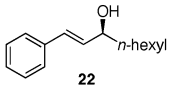
10.1021/ja044054a CCC: $30.25

Table 2. BSA-Assisted 1,3-Isomerization of Tertiary Allylic Alcohols[a]

entry	substrate	temp. (°C)	time (min)	product	isolated[b] yield (%)	$E:Z$[c]
1[d]	 **15**	0	60	 **16**	80	> 99 : 1
2	**13**	0	30	**14**	89	4.7 : 1
3[e]	 **17**	0	30	 **18**	93	1.8 : 1
4	**11**	−10	30	**12**	92	23 : 1

[a] 0.4 mmol scale, 2 mol % **1**, 1.2 equiv of BSA, 0.2 M in diethyl ether. [b] Determined after deprotection via K_2CO_3/MeOH. [c] Determined by GC. [d] 4 mol % **1**. [e] 4.0 mmol scale.

Table 3. 1,3-Isomerization of Enantioenriched Allylic Alcohols[a]

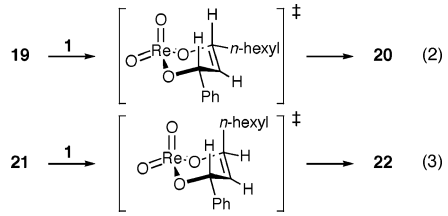
entry	substrate	product[b]	isolated yield (%)	ee (%)[c]	$[\alpha]_D$[d]
1	 **19** $E:Z > 50:1$[e] > 98% ee[c]	 **20**	93	81	−18.6
2	 **21** $Z:E = 11:1$[e] > 98% ee[c]	 **22**	92	72	+16.7

[a] 0.4 mmol scale, 3 mol % **1**, 0.2 M in diethyl ether, −78 °C, 2 h. [b] Only the *E*-isomers were visible by 300 MHz NMR. [c] Determined by chiral HPLC. [d] EtOH, 29−30 °C, $c = 2.5$. [e] Determined by GC.

In general, these reactions proceed with high *E*-selectivity, which increases with increasing steric bulk around the tertiary alcohol (e.g., entries 1−3: *t*-Bu ≫ Cy > *n*-Bu). It is also noteworthy that the favored regioisomer (i.e., the primary alcohol) in these BSA-assisted isomerizations is actually the thermodynamically disfavored regioisomer (Table 1, entry 11).[8a,d,15]

Substrate **11** isomerizes in high yield in the absence of BSA to afford conjugated alkene **12** only at or below −40 °C, which necessitates long reaction times and a higher catalyst loading (Table 1, entry 10). Both **11** and **12** readily undergo dehydration, condensation, and *E*/*Z*-isomerization at higher temperatures. However, BSA addition dramatically improves the 1,3-isomerization of **11** (Table 2, entry 4), resulting in higher yields and *E*-selectivity, since the product is trapped by silylation before side reactions can occur. Consequently, lower catalyst loadings, higher temperatures, and significantly shorter reaction times can now be employed.

Since all of the allylic alcohols employed during our studies possessed a stereogenic center, we wondered if chirality could be transferred during the 1,3-isomerization of nonracemic allylic alcohols.[16] As shown in Table 3, the isomerization of enantioenriched substrates **19** and **21** is highly stereoselective, proceeding at −78 °C with only a small loss of enantiopurity.[17] The absolute configuration of products **20** and **22** is controlled by the alkene geometry of the respective starting materials and can be rationalized by consideration of a chairlike transition state (eqs 2 and 3), therefore providing experimental evidence to support the proposed reaction mechanism. The observed minor loss of enantiopurity is likely the result of competing reaction pathways, such as that invoking an allylic cation.[8b,d]



In summary, we have developed two different reaction strategies to efficiently promote the 1,3-isomerization of allylic alcohols with catalyst **1**. The procedures feature low catalyst loadings and short reaction times, delivering products in high yields and *E*-selectivities for substrates with either aryl or alkyl substitution. The fundamental reaction properties that we have observed, namely the lower reactivity of electron-poor substrates, the dependence of *E*-selectivity on the steric bulk surrounding tertiary alcohols, and the correlation between the alkene geometry and the absolute configuration of enantioenriched allylic alcohols, are all consistent with the proposed chairlike transition state that contains a partially cationic allyl moiety.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844−849. (b) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059−2068. (c) Belgacem, J.; Kress, J.; Osborn, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 1501−1502. (d) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, *17*, 1835−1840. (e) Fronczek, F. R.; Luck, R. L.; Wang, G. *Inorg. Chem. Commun.* **2002**, *5*, 384−387. (f) Wang, G.; Jimtaisong, A.; Luck, R. L. *Organometallics* **2004**, *23*, 4522−4525.
(9) For a review of 1,3-isomerizations of allylic alcohols, see: Bellemin-Laponnaz, S.; Le Ny, J.-P. *C. R. Chim.* **2002**, *5*, 217−224.
(10) Schoop, T.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H.-G. *Organometallics* **1993**, *12*, 571−574.
(11) Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J.-P.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 976−978.
(12) Bellemin-Laponnaz, S.; Le Ny, J.-P.; Dedieu, A. *Chem.−Eur. J.* **1999**, *5*, 57−64.
(13) See page S8 of the Supporting Information for details.
(14) Trimethylsilyl allylic ethers undergo 1,3-isomerization at room temperature with **1**, though at a slower rate than allylic alcohols. (Bellemin-Laponnaz, S.; Le Ny, J.-P.; Osborn, J. *Tetrahedron Lett.* **2000**, *41*, 1549−1552.) We did not, however, observe significant isomerization of the trimethylsilyl allylic ethers formed during our reactions.
(15) Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976−8978.
(16) Chirality transfer has been observed in the 1,3-isomerization of cyclic nonracemic allylic alcohols with catalyst **1** (Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262−11263) and with $VO(acac)_2$ (ref 8a).
(17) Reaction temperatures above −78 °C lead to a greater loss of enantiopurity.

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