Rhenium(VII) Catalysis of Prins Cyclization Reactions

Kwanruthai Tadpetch and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025

srychnov@uci.edu

ABSTRACT

The rhenium(VII) complex $O_3ReOSiPh_3$ is a particularly effective catalyst for Prins cyclizations using aromatic and α,β-unsaturated aldehydes. The reaction conditions are mild, and the highly substituted 4-hydroxytetrahydropyran products are formed stereoselectively. Rhenium(VII) complexes appear to spontaneously form esters with alcohols and to directly activate electron-rich alcohols for solvolysis. Re_2O_7 and perrhenic acid are equally effective in catalyzing these cyclizations.

Osborn reported that the Re(VII) complex $O_3ReOSiPh_3$[1] was a highly effective catalyst for allylic alcohol isomerizations.[2] Grubbs studied Osborn's reaction and found that $O_3ReOSiPh_3$ isomerizes allylic alcohols stereospecifically.[3] Both Osborn and Grubbs invoked a concerted [3,3] rearrangement of allylic perrhenate esters to explain this very facile and selective isomerization (Figure 1).[2,3] An alternative mechanism was invoked to explain some of the peculiarities of the reaction. Osborn proposed an ionic mechanism to explain the kinetics for formation of Z-alkenes,[2b] and Grubbs invoked a similar mechanism to explain the loss of optical purity with certain electron-rich allylic alcohol substrates (Figure 1).[3] The proposed ionic mechanism attracted our attention because it suggested that Re(VII) complexes might activate and solvolyze electron-rich alcohols. We report herein a Prins cyclization initiated by Re(VII) catalysts[4] based on this concept that is very mild and shows unusual selectivity.

Prins cyclization reactions between homoallylic alcohols and aldehydes are generally promoted by strong Brønsted or Lewis acids.[5] If halide counterions are present, they are incorporated
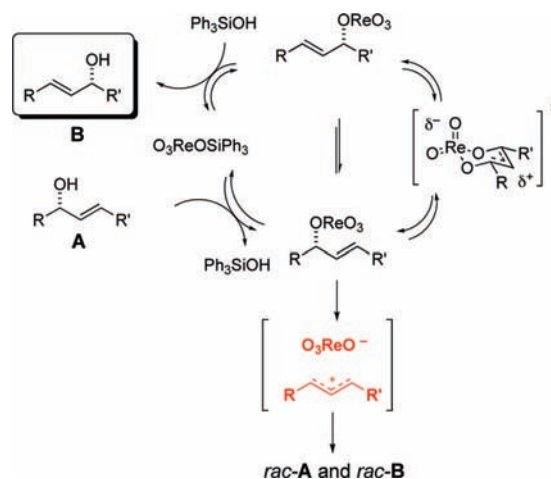

Figure 1. Grubbs−Osborn mechanism for stereoselective isomerization of allylic alcohols and the alternative ionic mechanism that leads to loss of selectivity.

at the 4-position of the newly formed tetrahydropyran (THP) ring.[5] Oxygen atoms can be captured at the 4-position of the THP ring,[6] although most acids lead to esters that must be hydrolyzed to form 4-hydroxy THP products.[7] Most Prins cyclizations use superstoichiometric acid to promote the reaction because the acid counterion is trapped in the product, thus

(1) Schoop, T.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H. G. *Organometallics* **1993**, *12*, 571–574.

(2) (a) Bellemin-Laponnaz, S.; Gisie, H.; Pierre Le Nye, J.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 976–978. (b) Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000**, *41*, 1549–1552.

(3) (a) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842–2843. (b) Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813–7825.

consuming the acid.[5] Re(VII) complex $O_3ReOSiPh_3$ is proposed to catalyze the Prins cyclization as illustrated in Scheme 1.

Scheme 1. Proposed Mechanism for Activation and Prins Cyclization Using $O_3ReOSiPh_3$
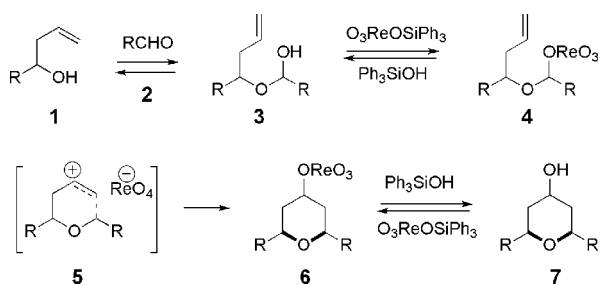
Activation is achieved by forming perrhenate ester **4** from hemiacetal **3**. Solvolysis of ester **4** generates the intermediate **5** as a contact ion pair. Cyclization and trapping leads to perrhenate ester **6**. Ester exchange with Ph_3SiOH would regenerate the catalyst. The proposed Re(VII)-initiated reaction has several potential advantages over traditional Prins cyclization reactions. It avoids the use of strong acid, and the facile transesterification of perrhenate esters with alcohols allows turnover and makes the system catalytic. Additionally, the alcohol product would be produced directly from the reaction rather than requiring a subsequent hydrolysis step. These potentially attractive features led us to explore this reaction.

Table 1 presents an initial exploration of the Re(VII)-catalyzed Prins cyclization. The aldehyde and homoallylic
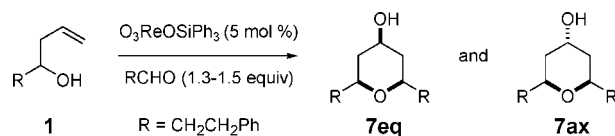
entry	solvent	time (h)	yield (%)	eq/ax
1[a]	CH_2Cl_2	36	54	1.5:1
2	CH_2Cl_2	3	63	1.9:1
3	$CHCl_3$	48	67	2.7:1
4	EtOAc	21	33	4.5:1
5	$MeNO_2$	24	40	6.0:1
6	hexanes	48	62	15:1
7	toluene	48	38	4.4:1
8	MeCN	48	0	NA
9[b]	CH_2Cl_2	72	37	1:2.4
10[c]	CH_2Cl_2	20	43	>10:1

[a] Reaction was carried out with 1 mol % of $O_3ReOSiPh_3$. [b] Reaction was carried out with 30 mol % of $VO(OPr^n)_3$ instead of $O_3ReOSiPh_3$ and with 2 equiv of the aldehyde. [c] Reaction catalyzed with 5 mol % of $H_3[P(Mo_3O_{10})_4]·xH_2O$.

alcohol were selected with the same substituent to avoid complications from oxonia-Cope induced side-chain exchanges.[8] $O_3ReOSiPh_3$ catalyzed the Prins cyclization effectively in most solvents except acetonitrile. Although the reaction was effective using 1 mol % of catalyst (entry 1), 5 mol % of catalyst was selected to screen conditions. Methylene chloride, chloroform, and hexanes all gave yields over 60% on stirring at room temperature (entries 2, 4, and 7). The reaction times varied from several hours to several days. Vanadyl esters were also investigated as catalysts,[9] but they were less efficient. For example, 30 mol % of tri-n-propyl vanadate (entry 9) gave slightly more than 1 mol of product per mol of catalyst after several days. Phosphomolybdic acid catalysis was evaluated for comparison (entry 10) and gave a lower yield but with higher equatorial selectivity.[6g] Two molybdenum oxo complexes were screened as catalysts, but they were ineffective.[10]

One surprising aspect of the oxo-metal-catalyzed reaction is the isolation of axial THP product (**7ax**) as a significant component of the product. Prins reactions normally give predominantly equatorial 4-heteroatom products, and all previously reported 4-oxygen adducts showed high equatorial selectivity.[6,7] We previously reported that the axial selectivity was a function of the lifetime and reactivity of the ion pair, with very reactive nucleophiles, such as bromide anion, leading to high axial selectivity.[11] Typical oxygen nucleophiles, such as $CF_3CO_2^-$ or $AcO·BF_3^-$, have low nucleophilicity and lead to ca. 20:1 selectivity for the equatorial product.[8f] The Re(VII) catalyst, while still favoring the equatorial product, shows a much lower level of selectivity.

(4) For several other related applications of high-oxidation Re catalysts in synthesis, see: (a) Ishihara, K.; Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2983–2986. (b) Maeda, Y.; Nishimura, T.; Uemura, S. *Chem. Lett.* **2005**, *34*, 790–791. (c) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076–6077. (d) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510–4511.

(5) (a) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (c) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661–672. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.

(6) (a) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053–1061. (b) Zhang, W.-C.; Viswanathan, G. S.; Li, C.-J. *Chem. Commun.* **1999**, 291–292. (c) Zhang, W.-C.; Li, C.-J. *Tetrahedron* **2000**, *56*, 2403–2411. (d) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, C. V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89–91. (e) Keh, C. C. K.; Namboodiri, V. V.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 4993–4996. (f) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499–1502. (g) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Aravind, S. *Synthesis* **2008**, 395–400.

(7) (a) Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915–5918. (b) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035–2038. (c) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679–4686. (d) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429–2432. (e) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319–3322.

(8) (a) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129–7140. (b) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815–3818. (c) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961. (d) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577–580. (e) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727–3729. (f) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945. (g) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640–13648.

(9) Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977**, *33*, 1775–1783.

(10) $MoO_2(acac)_2$: (a) Rajan, O. A.; Chakravorty, A. *Inorg. Chem.* **1981**, *20*, 660–664 $MoO_2(OSiPh_3)_2$: (b) Huang, M.; DeKock, C. W. *Inorg. Chem.* **1993**, *32*, 2287–2291.

(11) (a) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904–9905. (b) Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493–1501.

The vanadate ester example (entry 9) actually favors the axial alcohol product. These experiments suggest that perrhenate and other oxo-metal counterions are much more nucleophilic than trifluoroacetate counterion in Prins reactions, and that they may show unusual patterns of reactivity and selectivity. On a practical note, the best selectivity for the equatorial product was found using $O_3ReOSiPh_3$ in hexanes (entry 6).
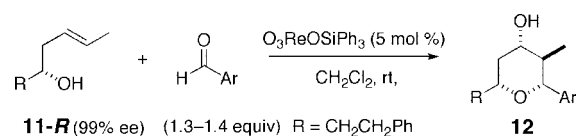
Prins reactions with aromatic and aliphatic aldehydes behave differently when catalyzed by $O_3ReOSiPh_3$. Scheme 2 presents

Scheme 2. Prins Reaction with Aliphatic and Aromatic Aldehydes
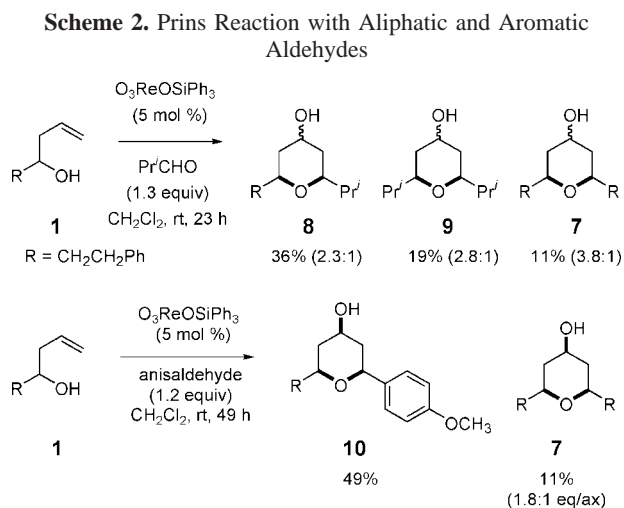
the reaction between isobutyraldehyde and alcohol **1**. The expected product **8** is accompanied by side products **9** and **7** that arise from facile 2-oxonia-Cope rearrangements.[8] The outcome with an electron-rich aromatic aldehyde is very different. Side-chain exchange products are much less prevalent, and the expected Prins product was formed in 49% yield with excellent equatorial alcohol selectivity.[12,13] We believe that the greater nucleophilicity of the perrhenate anion limits oxonia-Cope rearrangement with aromatic aldehydes.[14] The excellent equatorial selectivity is consistent with previous observations, where a more stable oxocarbenium ion leads to a less reactive ion pair and better equatorial selectivity.

The reactivity with aromatic aldehydes was further investigated (Table 2). Substituted alcohol **11-R** and its enantiomer **11-S** were used in this study.[15] Both electron-rich and electron-poor aromatic aldehydes gave good yields and selectivities for the equatorial alcohol Prins product. In entries 2 and 4, the

(12) This result stands in contrast to our Prins reaction approach to kendomycin, where an electron-rich aromatic ring led to side-chain exchange products as the major component in a TFA/DCM promoted reaction (ref 13).

(13) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388–2390.

(14) The aliphatic aldehyde oxonia-Cope rearrangement evident in Scheme 2 should be thermoneutral, whereas the aromatic oxonia-Cope should favor the aromatic oxocarbenium ion. In theory, this effect might suppress oxonia-Cope side reactions with aromatic aldehydes, but in our experience, it does not, perhaps because of a slower Prins cyclization with aromatic aldehydes. See ref 13 for an example.

(15) (a) Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273–1276. (b) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168–9169.

Table 2. Prins Cyclization with Aromatic Aldehyde and $O_3ReOSiPh_3$

entry	aldehyde	time (h)	yield (%)
1	benzaldehyde	24	82
2[a]	4-methoxybenzaldehyde	25	88[b]
3	4-hydroxybenzaldehyde	27	75
4[a]	4-fluorobenzaldehyde	26	89[b]
5[a]	2,4-dimethoxybenzaldehyde	50	58
6	2-methoxybenzaldehyde	18	84
7	aldehyde	168	30[d]
8[c]	aldehyde	23	83
9	4-(trifluoromethyl)benzaldehyde	24	73
10	4-cyanobenzaldehyde	24	55

[a] Enantiomeric series (**11-S** alcohol, 99% ee). [b] 97% ee by HPLC anaylsis. [c] 10 mol % of $O_3ReOSiPh_3$. [d] Starting material was also recovered in 11% yield.

products were demonstrated to have high optical purities. Remarkably, the unprotected phenol in entry 3 worked very well in the reaction. The very electron-rich phenol in entry 7 did give some Prins product, but only very slowly. The corresponding sulfonyl-protected phenol gave an excellent yield of equatorial THP product. The aldehydes in entries 7 and 8 were previously investigated in our approach to kendomycin,[13] but the Re(VII)-catalyzed Prins cyclization conditions appear to be both milder and more general. Electron-withdrawing substituents (entries 9 and 10) lead to slightly lower yields than with electron-rich aldehydes.

A common problem with aliphatic aldehydes is the generation of side-chain exchange products, as shown in Scheme 2. The Re(VII) conditions appear to minimize this exchange with aromatic aldehydes. An indirect solution for selective Prins cyclization of aliphatic aldehydes might be developed using unsaturated aldehydes, followed by reduction or functionalization of the alkene.[16] A few representative unsaturated aldehydes were investigated, and the results are shown in Scheme 3.[17]

Scheme 3. Prins Reaction with Unsaturated Aldehydes

R = CH₂CH₂Ph
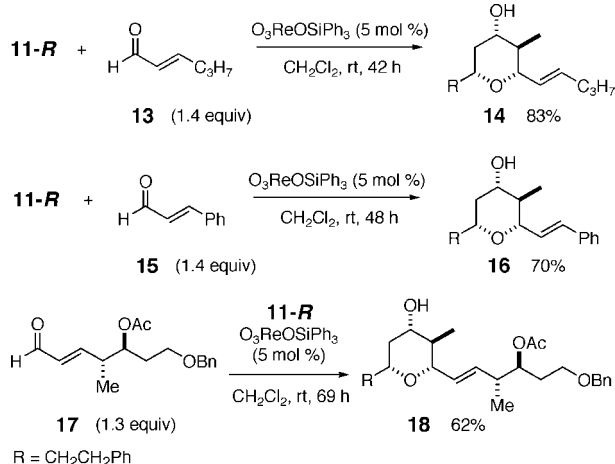
All three aldehydes worked well in the reaction, although the more complex aldehyde **17**, prepared by a metathesis reaction between crotonaldehyde and the corresponding terminal alkene, was noticeably slower than the others. All of the products showed very good selectivity for the equatorial alcohol THP products. Unsaturated aldehydes will be useful for forming complex THP fragments suitable for natural product synthesis.

Several details of the catalytic cycle are not clear at this time, but a few control experiments have placed some limits on possible mechanisms. The Prins reaction in Table 1 in DCM returned only starting material when proton scavenger 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DTBMP) or 4 Å sieves were added. Grubbs reported that hindered tertiary amines also halted the allylic isomerization by O₃ReOSiPh₃.[3] Addition of water stopped the reaction.[18] Added CSA had no effect on the reaction. The basic path of the reaction presumably follows the mechanism outlined in Scheme 1. One significant unanswered question is whether the activation of the hemiacetal **3** is due to perrhenate ester formation or simple acid-promoted solvolysis.

Because of ambiguities in the mechanism, we decided to test other Re(VII) catalysts, and the results are shown in Scheme 4. Solutions of 65−70% aqueous perrhenic acid[18] are equally

Scheme 4. Comparison of Different Re(VII) Catalysts

effective as O₃ReOSiPh₃ in the Prins cyclization of alcohol **11-R** and *p*-anisaldehyde (**19**). Re₂O₇ is also effective for catalyzing Prins reactions. In both cases, these commercially available Re(VII) compounds lead to outcomes essentially indistinguishable from O₃ReOSiPh₃. Perrhenic acid is a strong acid with a $pK_a = -1.25$,[19] so an acid-catalyzed activation of hemiacetal **3** (Scheme 1) is certainly possible. An indirect test for perrhenate ester formation was conducted by exploring the allylic alcohol rearrangement of allylic alcohol **21**.[3] Both O₃ReOSiPh₃ and perrhenic acid lead to efficient rearrangement to conjugated allylic alcohol **22** under similar conditions, suggesting that 65−70% aqueous perrhenic acid is capable of forming perrhenate esters under these conditions.[18] Thus perrhenic acid may be active through the same mechanism (Scheme 1) proposed for O₃ReOSiPh₃.

Re(VII) complexes are uniquely effective catalysts for the Prins cyclization. These catalysts will be useful for Prins cyclizations and will be of interest for the development of other catalytic processes.

Supporting Information Available: Characterization data and experimental procedures for all compounds described are included. This material is available free of charge via the Internet at http://pubs.acs.org.
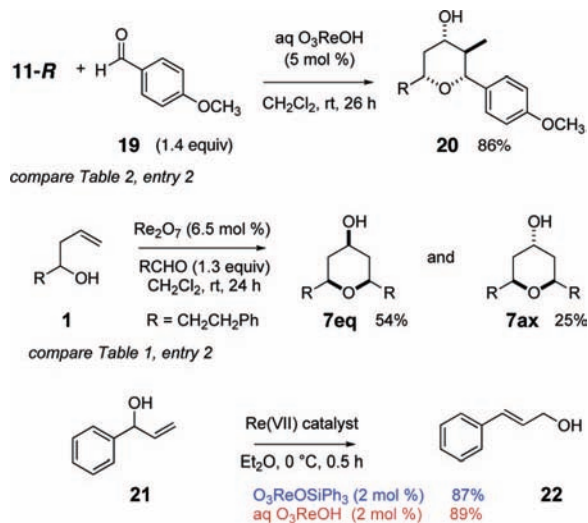
OL8019204

(16) Chan, K.-P.; Ling, Y. H.; Loh, T.-P. *Chem. Commun.* **2007**, 939–941.

(17) A Prins reaction between alcohol **1** and cinnamaldehyde led to the expected product in 40% yield and the side-chain exchanged product **7** in 18% yield. Further work needs to be done to make Prins reactions with terminal alkenes practical.

(18) The "wet" reaction was run in water-saturated DCM. At 27 °C, the concentration of water would be 0.137 M (0.186 wt %): Stephenson, R. M. *J. Chem. Eng. Data* **1992**, *37*, 80–95 With a catalyst concentration of 0.005 M, the molar ratio of water/Re(VII) would be ca. 27:1. For comparison, the molar ratio of commercial 70 wt % perrhenic acid is about 6:1 water/Re(VII). Presumably the difference in the water concentration led to the difference in outcome.

(19) Bailey, N.; Carrington, A.; Lott, K. A. K.; Symons, M. C. R. *J. Chem. Soc.* **1960**, 290–297.