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The “Aqueous” Prins Reaction

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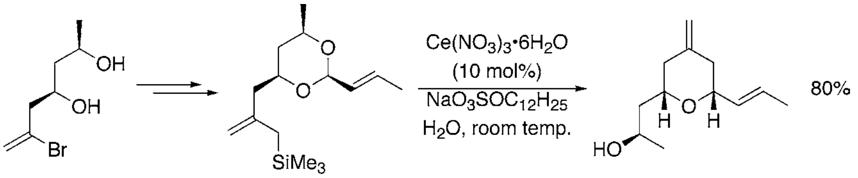
ABSTRACT



In this communication we demonstrate that Prins cyclization reactions occur under very mild conditions when cyclic α,β-unsaturated acetals are employed as oxocarbenium ion progenitors and allylsilanes are used as nucleophiles. Cyclizations proceed efficiently inside Lewis acidic micelles in water, demonstrating that colloidal suspensions can protect highly electrophilic intermediates from hydrolysis. Reactions are experimentally facile and useful in the preparation of a variety of vinyl- and aryl-substituted tetrahydropyrans with excellent stereocontrol.

Although water is inexpensive, nontoxic, and nonflammable, it is not routinely[1] used as a solvent for organic reactions. In addition to the limited aqueous solubilities of most organic compounds, a significant drawback to using water as a solvent is its ability to act as both a nucleophile and as an acid, making it incompatible with highly electrophilic and basic species. Solubility and reactivity problems can, in principle, be circumvented by encapsulating reactions in the hydrophobic interiors of micelles, whereby the practical benefits of aqueous chemistry can be realized while the familiar reactivity patterns conferred by organic microsolvation are maintained.[2] A stringent test of the extent to which micelles protect sensitive species from water would be provided by their use in reactions that proceed through hydrolytically labile intermediates. In this communication we report that acetals ionize in Lewis acidic micelles under very mild conditions and that the intermediate oxocarbenium ions undergo efficient and stereoselective Prins reactions in preference to hydrolysis.

Initiating Prins cyclization reactions by activating cyclic acetals under strongly acidic conditions[3] has proved to be a powerful method for accessing the 2,4,6-trisubstituted tetrahydropyran nucleus found in numerous natural products. Relative to Prins reactions that proceed through direct dehydrative conditions,[4] sequestering two hydroxyl groups into an acetal allows a convergent condensation of functionalized segments without recourse to selective protecting group manipulations. In accord with our objective of conducting these reactions at advanced stages in complex molecule synthesis, cyclization substrates should be designed to react at ambient temperature with mild Lewis acids that tolerate other acid-sensitive functional groups. We postulated that this could be accomplished by employing α,β-unsaturated acetals to facilitate the initial ionization step and using electron-rich olefins to expedite the cyclization step (Figure 1). Proceeding through relatively stable conjugated oxocarbenium ions is also expected to hinder oxonia-Cope rearrangements, which have been shown to cause partial racemization and other side reactions in this process.[5]

As an initial test of our design, we exposed allylsilane[6] **1** to anhydrous $CeCl_3$ in CH_3CN at room temperature and observed the formation of **2** as a single diastereomer in 57%

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(1) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blake Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley and Sons: New York, 1997.

(2) (a) *Reactions and Synthesis in Surfactant Systems*; Texter, J., Ed.; Marcel Dekker: New York, 2001. (b) *Structure and Reactivity in Aqueous Solution*; Cramer, C. J., Truhlar, D. G., Eds.; American Chemical Society: Washington, DC, 1994. (c) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (d) Tascioglu, S. *Tetrahedron* **1996**, *52*, 11113.

(3) (a) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035. (b) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. (c) Rychnovsky, S. D.; Yang, G.; Hu, Y. Q.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (d) Wilson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F. *Tetrahedron* **1990**, *46*, 1767. (e) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650.

(4) For recent examples, see: (a) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. D. *Org. Lett.* **2002**, *4*, 3407. (c) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669. (d) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092.

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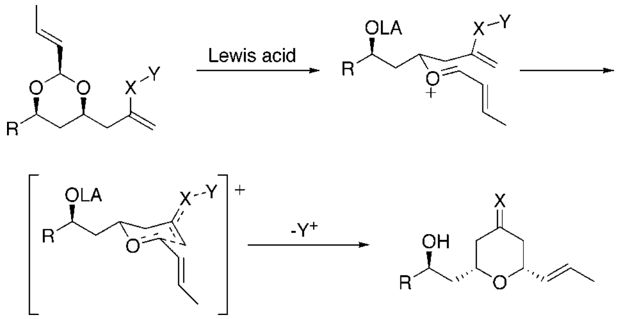
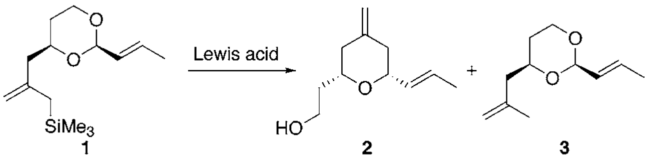


Figure 1. Reactivity enhancement in intramolecular Prins cyclizations.

yield along with **3**, the product of substrate desilylation, in 22% yield. In consideration of the correlation between the rate of silyl group loss and the nucleophilicity of the counterion on the Lewis acid, we examined scandium dodecyl sulfate in water,[7] Kobayashi's micellar Lewis acid catalyst, as a potential solution to this problem. While these conditions have been employed to activate carbonyl groups toward reactions with various nucleophiles,[8] they had not been shown to effect reactions in which the intermediate electrophilic species would be irreversibly consumed when exposed to water.[9] Therefore, we were pleased to observe that a colloidal mixture of **1** and scandium dodecyl sulfate (10 mol %, prepared in situ by adding $ScCl_3$ to a suspension of **1** and sodium dodecyl sulfate (SDS) in water) at ambient temperature provided a 71% yield of **2** as a single diastereomer with no formation of **3**. To make the process more cost-effective, we examined other Lewis acids that have been predicted to be compatible with water on the basis of their rate constants for hydrolysis and exchange of inner-sphere water ligands.[10] We found that micelles formed from inexpensive $Ce(NO_3)_3{\cdot}6H_2O$[11] and SDS, although somewhat less reactive than $ScCl_3$-based micelles, effected the cyclization in 76% yield, providing an attractive alternative to our original conditions.[12] A range of substrates were prepared and subjected to cyclization conditions in order to examine



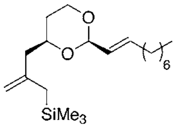
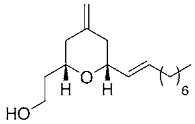
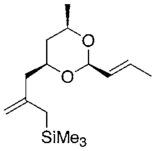
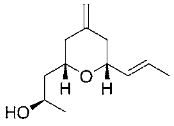
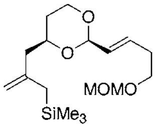
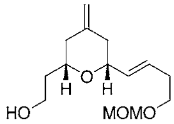
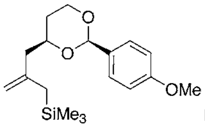
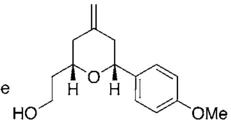
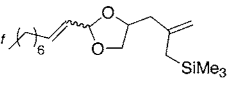
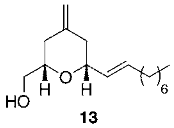
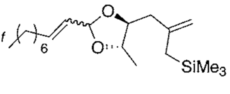
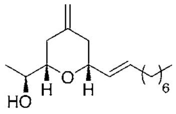
1 **2** **3**

Lewis acid	solvent	yield **2**	yield **3**
$CeCl_3$	CH_3CN	57%	22%
$ScCl_3$/SDS	H_2O	71%	-
$Ce(NO_3)_3$/SDS	H_2O	76%	-

Figure 2. Prins cyclizations with mild Lewis acids.

the scope of the reaction (Table 1).[13] Increasing the length of the hydrocarbon chain of the acetal and, therefore, the hydrophobicity of the substrate, has a negligible effect on reaction efficiency (entry 1). Initiating the reaction through coordination to a secondary ether group does not inhibit the process or lead to competitive oxecane formation (entry 2).

Table 1. Reaction Scope

entry	substrate[a]	product[b]	conditions[c,d]	yield (%)[e]
1	 **4**	 **5**	A	73
2	 **6**	 **7**	B	80
3	 **8**	 **9**	A	53
4	 **10**	 **11**	A	75
5[f]	 **12**	 **13**	A	77
6[f]	 **14**	 **15**	A	51

[a] See Supporting Information for substrate syntheses. [b] Product stereochemistry was determined by observing NOE enhancements between the hydrogens on C2 and C6. [c] A: 10 mol % $ScCl_3{\cdot}nH_2O$, 30−60 mol % SDS, 0.5 M substrate in water. [d] B: 10 mol % $Ce(NO_3)_3{\cdot}6H_2O$, 30−60 mol % SDS, 0.5 M substrate in water. [e] Isolated yields of purified products. [f] Performed with 100 mol% SDS.

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(5) (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. D. *Org. Lett.* **2002**, *4*, 577. (b) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. The advantage of employing conjugated oxocarbenium ions for Prins cyclizations has recently been reported. See: Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429.

(6) For recent examples of allylsilanes in Prins cyclizations, see: (a) Leroy, B.; Marko, I. E. *J. Org. Chem.* **2002**, *67*, 8744. (b) Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189. (c) Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252. (d) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955. (e) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

(7) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202.

(8) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.

(9) For dehydrative Prins reactions conducted in mixtures of water and ionic liquids, see: Keh, C. C. K.; Namboodiri, V. V.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 4993.

(10) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.

(11) While 1 mmol of $ScCl_3$ costs $12.41 (Sigma-Aldrich), 1 mmol of $Ce(NO_3)_3{\cdot}6H_2O$ costs $0.09.

Compatibility of these conditions with other acid-sensitive functional groups has been demonstrated through the cyclization of methoxymethyl ether **8** (entry 3). The alkenyl group of the acetal can be replaced by electron-rich arenes, but the reactivity is diminished. For example, the cyclization of *p*-methoxybenzylidine acetal **10** (entry 4) requires the more reactive $ScCl_3$-based micelles, and the corresponding benzylidine acetal is unreactive. Control reactions established that the allylsilane is necessary for cyclization, that acetal hydrolysis does not occur to a significant extent in the absence of a good nucleophile, that unsaturation is required for oxocarbenium ion stabilization, and that SDS is necessary for reactivity. Interestingly, enolsilane analogues of **1** were inert toward $Ce(NO_3)_3$-based micelles and provided only a poor yield with $ScCl_3$-based micelles (data not shown), indicating mechanistic subtleties that transcend simple π-nucleophilicity analyses.[14]

Cyclizations can also be initiated by ionizing 1,3-dioxolanes, with reactions being significantly faster than those of 1,3-dioxanes. While both $Ce(NO_3)_3$- and $ScCl_3$-based micelles effect this transformation, the scandium system provided superior yields of the desired products. The major byproduct in these reactions contains a tertiary alcohol rather than an exocyclic olefin in the tetrahydropyran. On the basis of our isolation of desilylated starting material in the cyclization of **14** and our inability to hydrate the exocyclic olefin of **15** by resubjecting it to the reaction conditions, we propose that this process occurs through substrate desilylation followed by cyclization of the nonactivated olefin and trapping the intermediate cation with either water or dodecyl sulfate. This demonstrates that enhancing acetal reactivity allows less nucleophilic olefins to participate in these reactions. Of further note is that cyclizing an enantioenriched sample of **14** (80% ee) provides **15** with no detectable racemization.

We have demonstrated that Prins cyclization reactions can be conducted under very mild conditions when initiated by ionizing α,β-unsaturated acetals in the presence of electron-rich olefins. These reactions proceed efficiently and without racemization with Lewis acidic surfactant catalysts *at room temperature in water* to provide a variety of 2,4,6-trisubstituted tetrahydropyrans, demonstrating that the interiors of micelles are sufficiently anhydrous to protect oxocarbenium ions from hydrolysis. The stability of acetals toward these conditions demonstrates that acid-sensitive functional groups are tolerated in cyclization substrates. These operationally simple and environmentally benign conditions should be applicable to other systems in which facile Lewis acid-initiated ionizations are followed by rapid and thermodynamically favorable steps. Further studies of metal/surfactant combinations are expected to result in an expanded role for these conditions in organic synthesis.

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Supporting Information Available: Synthetic schemes for all cyclization substrates and experimental procedures and characterization for all cyclization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For another example of the use of Sc(III) to initiate dehydrative Prins reactions, see: Zhang, W.-C.; Visiwanathan, G. S.; Li, C.-J. *Chem. Commun.* **1999**, 291

(13) All new compounds have been characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS.

(14) (a) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.