Reductive Cyclization of Enones by a Titanium Catalyst

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While the use of early transition metal catalysts for the reductive cyclization of dienes and enynes has been reported,[1−5] to date there has been no catalytic process developed for the reductive cyclization of an alkene or an alkyne with a heteroatom-containing unsaturated functional group. Herein we show the viability of such a process as exemplified by the conversion of enones to cyclopentanols.

Whitby has demonstrated that stoichiometric quantities of $Cp_2Ti(PMe_3)_2$ can convert 1,6-enones to titanacycles in good yields.[3a] Cleaving the titanium−oxygen bond in these metallacycles in a controlled manner to regenerate the catalyst is a significant challenge due to the oxophilicity of the titanium.[6] Since it has been shown that silanes react with titanium alkoxides with concomitant formation of Ti−H and Si−O bonds[7] via a σ-bond metathesis process, a reasonable means for the catalytic conversion of enones to cyclopentanols can be proposed (Scheme 1). After initial formation of titanacycle **1**, the silane can cleave the Ti−O bond to form (alkyl)titanocene hydride **2**, which then would undergo ligand-induced reductive elimination[8] to afford the silyl-protected cyclopentanol **3**, with regeneration of the catalyst. Hydrolysis of the silyl ether during workup produces the product cyclopentanol.

In initial experiments we found that the combination of an enone, diphenylsilane, and 10 mol % $Cp_2Ti(PMe_3)_2$ produces the silyl ether of cyclopentanol **4** along with a small amount of the silyl ether of cyclic isomer **5** and a significant amount of the silyl ether of acyclic alcohol **6**, formed by the reduction of the carbonyl (see Table 1). We believe that this carbonyl reduction product is generated by partial decomposition of the original catalyst, $Cp_2Ti(PMe_3)_2$, into a Ti(III) complex,[9] some of which are known to reduce carbonyls.[8,10] It was found that running the reaction at a lower temperature in the presence of excess trimethylphosphine virtually eliminates formation of the acyclic product **6**. Table 1 shows the results of the reaction under these conditions.

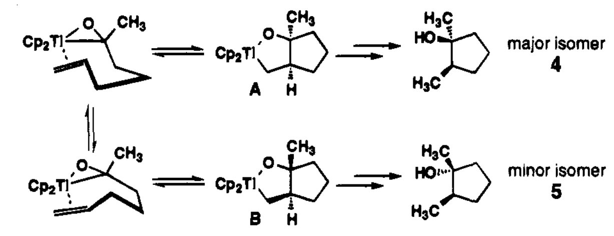
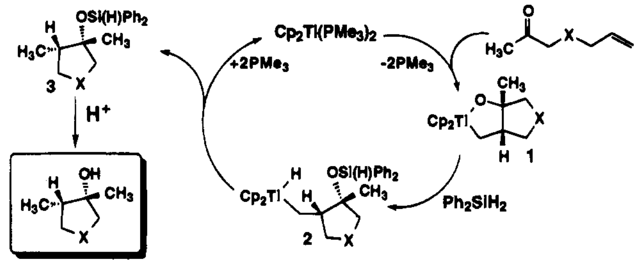


Figure 1.

Scheme 1



While the diastereoselectivity of this reaction is generally very good,[11] a small amount of diastereomer **5** is usually observed. The major isomer **4** comes from the more stable *cis* metallacycle, **A**, which may arise from a chair-like intermediate as shown in Figure 1. In the presence of a stoichiometric amount of the titanium complex, the *cis* isomer of the titanacycle is formed exclusively,[3] since the steps leading to metallacycle formation are reversible. In the catalytic process, the organic fragments are cleaved from the metallacycles before they can completely equilibrate, so a mixture of isomers is produced.[12] This includes a small amount of isomer **5**, which comes from the *trans* metallacycle **B** shown in Figure 1. The major isomer can be separated, and the isolated yields are given in Table 1. In a related system, Nugent and co-workers[13] have examined the relative stabilities of *cis* versus *trans* metallacycles in the zirconium-mediated cyclization of dienes. They have found both experimentally and theoretically that, in the zirconocene system, the *trans* metallacycle is more stable. This is the opposite of what we observe for titanocene-catalyzed enone cyclizations.[14] Substrates containing a heteroatom in the backbone (entries 8 and 9) are transformed with little or no diastereoselectivity. When these substrates are treated with a stoichiometric amount of the titanium complex, mixtures of *cis* and *trans* metallacycles initially form, which only slowly equilibrate to the *cis* isomer over several days.[15,16]

Enones which are disubstituted in the β-position (entries 5 and 6) produce a greater amount of the minor isomer **5** than in the unsubstituted case. However, in the case of the disubstituted aldehyde (entry 4), none of the *trans* isomer is observed. The reasons for these anomalous results are unclear at the present

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[1] For stoichiometric diene, enyne, and diyne cyclizations using early transition metals, see: (a) Negishi, E.-I.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem.* **1989**, *111*, 3336. (b) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. (c) Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. (d) For a review, see: Negishi, E.-I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 9.5, p 1163.

[2] For stoichiometric alkene/hydrazone cyclizations, see: Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495.

[3] For stoichiometric enone cyclizations using an early transition metal, see: (a) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684. For stoichiometric enone cyclizations using a late transition metal, see: (b) Bryan, J. C.; Arterburn, J. B.; Cook, G. K.; Mayer, J. M. *Organometallics* **1992**, *11*, 3965.

[4] For catalytic diene cyclizations, see: (a) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. (b) Knight, K. S.; Wang, D.; Waymouth, R. M.; Ziller, J. *J. Am. Chem. Soc.* **1994**, *116*, 1845. (c) Knight, K. S.; Waymouth, R. M. *Organometallics* **1994**, *13*, 2575.

[5] For catalytic enyne cyclizations, see: Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912; **1994**, *116*, 8593.

[6] Titanium−oxygen bonds have a bond strength of ~100 kcal/mol compared with ~45 kcal/mol for a carbon−titanium bond. Connor, J. A. *Top. Curr. Chem.* **1977**, *71*, 71.

[7] Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093.

[8] Gell, K. I.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2687.

[9] Aitken, C. T.; Harrod, J. F.; Samuel, E. *J. Am. Chem. Soc.* **1986**, *108*, 4059.

[10] Nakamo, T.; Nagai, Y. *Chem. Lett.* **1988**, 481.

[11] For a discussion of diastereoselectivity in enyne cyclizations, see: Lund, E. C.; Livinghouse, T. *J. Org. Chem.* **1989**, *54*, 4487.

[12] Poor diastereoselectivity in catalytic transformations compared to the corresponding stoichiometric processes has previously been observed: Uesaka, N.; Mori, M.; Okamure, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4542.

[13] Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 9457.

[14] At present we have no explanation for the stereochemical discrepancies between the zirconocene-mediated diene cyclization and the titanocene-catalyzed enone cyclization.

[15] A similar effect upon heteroatom substitution has been seen: (a) Davis, J. A.; Whitby, R. J.; Jaxa-Chamiee, A. *Tetrahedron Lett.* **1992**, *33*, 5655. (b) Reference 13.

[16] The equilibration of these substrates to the *cis* isomer was monitored using ^1H NMR versus an internal standard, and the stereochemistry was determined by NOE analysis of the resulting silyl ether.

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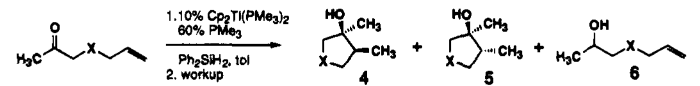
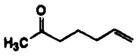
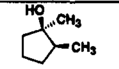
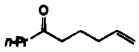
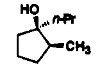
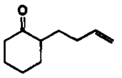
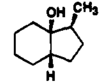
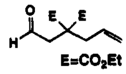
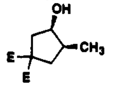
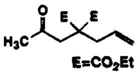
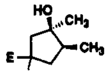
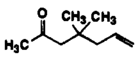
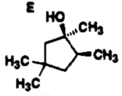
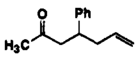
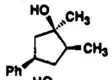
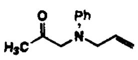
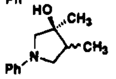
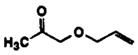
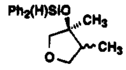
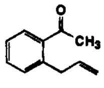
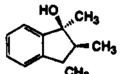
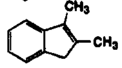
Table 1



Entry	Enone	Product[a]	Workup[b]	Temp(°C)	(4+5)/6[c]	4/5[c]	Yield (%)[d]
1			A	-20	17/1	43/1	64
2			A	-20	23/1	22/1	64
3[e]			A	-20	6/1	70/1	72[f]
4[g]			B	21	99/1	99/1	65
5			B	-20	99/1	10/1	68
6			A	-20	16/1	13/1	56
7			A	-20	99/1	2.5/1	63[h]
8			A	-20	99/1	1/1	75[i]
9			D	-20	80/1	3/2	72[j]
10			C	-20	99/1	99/1	86
			A	-20	99/1	99/1	71

[a] Major isomer. [b] Workup A: HCl/acetone, 3 h. B: TFA/H_2O/THF/CH_2Cl_2, 0 °C, 12 h. C: TBAF/THF, 15 min. D: silyl ether purified by distillation. [c] As determined by GC. [d] Isolated yield of major isomer analytically pure except for entries 1, 2, and 6, which are of >95% purity as judged by GC and ^1H NMR analyses. [e] $PhMeSiH_2$ was used instead of Ph_2SiH_2 in this entry. [f] Isolated as a 9/1 mixture of **4** and **6**. [g] No excess PMe_3 used with this substrate. [h] Yield of single isomer. [i] Total yield is 75%, but isomers were separated chromatographically in 37% and 38% yields. [j] Isolated as mixture of **4** and **5**.

time. In the case of entry 7, which has only one substituent on the backbone, poor diastereoselectivity is also observed.[17]

The net transformation described here resembles the conversion of enones to cyclopentanols by radical mechanisms reported by several groups,[18] but several differences should be noted. The titanium-catalyzed method affords a different isomer than the radical cyclizations. Furthermore, the intermediacy of titanacycle **1** provides a handle for potential improvements on the general reaction, such as the use of a chiral titanocene catalyst or further functionalization of the Ti−C bond.[5]

Table 1 shows that a variety of enones can be cyclized with this method. Aldehydes and alkyl ketones are suitable substrates, although smaller silanes are required for the more congested compounds (entry 3). Presumably, this is a reflection of the sensitivity to steric factors of the key Ti−O bond cleavage step. Smaller silanes also increase the formation of the Ti(III) catalyst,[9] resulting in an increase in the proportion of acyclic reduction product. Substitution on the alkene inhibits metallacycle formation in both the stoichiometric and catalytic cases. As also observed by Whitby in the stoichiometric case,[3a] substrates that would form cyclohexanols do not cyclize under these conditions. Early transition metal catalysts are often incompatible with polar functional groups,[19] but in the transformation reported here, enones containing allylic ethers (entry 9) or esters (entries 4 and 5) are tolerated. A substrate such as that in entry 10 can provide either a bicyclic cyclopentanol or the substituted indene in good yield depending on the method of workup employed.

In summary, we have reported the first example of an early transition metal catalyzed reductive cyclization of an alkene with a heteroatom-containing functional group. Efforts toward the development of more synthetically useful methods including those that afford more functionalized and/or enantiomerically enriched products are in progress. Additionally, methods to simplify this process experimentally are currently under study.

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Supplementary Material Available: Complete experimental procedures as well as analytical and spectroscopic data for all new compounds and spectroscopic data for known organic products (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(17) For entry 7, the diastereomeric ratio was observed to be temperature dependent. Further elaboration as well as a possible explanation of these results will be presented in a full paper.

(18) For leading references, see: (a) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545. (b) Lee, G. H.; Choi, E. B.; Lee, E.; Pak, C. S. *J. Org. Chem.* **1994**, *59*, 1428. (c) Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura R. *J. Org. Chem.* **1994**, *59*, 1730.

(19) Negishi, E.-I.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568.