

Titanium(II)-Mediated Asymmetric Intramolecular Cyclization of 2,7- and 2,8-Enynyl Chiral Acetals. Synthetic Equivalent of Stoichiometric Intramolecular Asymmetric Metallo-Ene Reaction

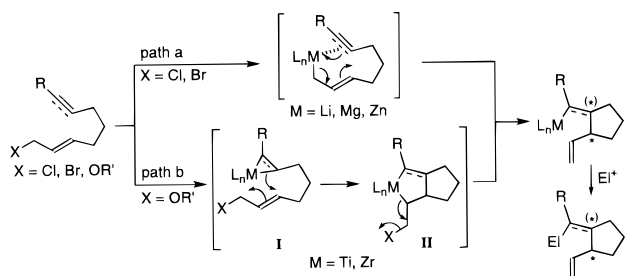
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Stoichiometric intramolecular lithium-, magnesium-, and zinc-ene reactions and the trapping of the resulting cyclized metallic intermediates with electrophiles have been widely utilized for the synthesis of polysubstituted cycloalkanes and the corresponding natural products.¹ As can be seen in Scheme 1 (path a), the

Scheme 1. Metallo-ene and Its Synthetically Equivalent Reactions



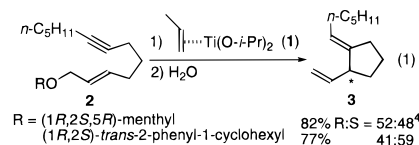
reaction generates a stereogenic center(s) on the ring; however, it seems difficult to carry out these metallo-ene reactions in an asymmetric manner, and thus far, no successful results have been reported.² Recently, we have reported (η^2 -propene)Ti(O-*i*-Pr)₂ (**1**)-mediated intramolecular cyclization of 2,7- or 2,8-dienyl and -enynyl ethers affording cyclized titanium compounds. The resulting titanium compounds readily react with electrophiles including aldehydes; thus, the reaction can be used as a synthetic equivalent, at least in part, to stoichiometric metallo-ene reactions³ (path b in Scheme 1). Since this cyclization reaction probably proceeds through, successively, the intermediates **I** and **II** and subsequent elimination of the OR' group, we were interested in carrying out the reaction in an asymmetric way by starting with substrates having an optically active OR' group. We selected the enynyl ethers, since the chiral induction might be induced only at the step of the transformation from the intermediate **I** to **II**.

(1) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 29–61. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38–52. Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *J. Org. Chem.* **1995**, *60*, 863–871 and references therein.

(2) (a) The preparation of optically active compounds containing an intrinsic stereogenic center of the optically active starting substrates through highly diastereoselective metallo-ene reaction has been reported; see ref 1. (b) Catalytic asymmetric intramolecular metallo-ene reactions induced by chiral ligands on the metal showing low to moderate enantioselectivity have been reported recently, see: Oppolzer, W.; Kuo D. L.; Hutzinger M. W.; Léger, R.; Durand J.-O.; Leslie C. *Tetrahedron Lett.* **1997**, *38*, 6213–6216.

(3) Takayama, Y.; Gao, Y.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 851–853. Takayama, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8351–8354. Yamazaki, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7333–7336. For Cp₂Zr-mediated reaction; see, Knight, K. S.; Waymouth, R. M. *Organometallics* **1994**, *13*, 2575–2577. Takahashi, T.; Kondakov, D. Y.; Suzuki, N. *Organometallics* **1994**, *13*, 3411–3412. Bird, A. J.; Taylor, R. J. K.; Wei, X. *Synlett* **1995**, 1237–1238.

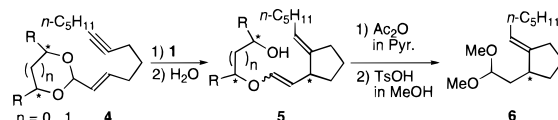
Initially, we carried out the reaction of **1** with 2,7-enynyl ethers **2** having a (1*R*,2*S*,5*R*)-menthyl or (1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexyl moiety, which, however, resulted in low chiral induction as shown in eq 1. It was apparent from these results



that a simple ether functionality combined with modest steric biases far removed from the reacting center, would have minimal influence on the stereochemistry of the reaction.

The experiments were then focused on the substrates of those having, as a leaving group, a chiral acetal moiety with C₂-symmetry, since this kind of chiral acetal has been successful in directing asymmetric transformations with a variety of organometallics.⁵ A representative series of chiral acetals **4** was prepared from tridec-7-yn-2-enal and the corresponding optically active diol and subjected to the reaction with **1**. The reaction proceeded smoothly to afford the cyclized products **5** as a mixture of *E*- and *Z*-enol ethers in excellent combined yield, where the former was predominant irrespective of the acetal moiety (Scheme 2).

Scheme 2



The resulting enol ether mixture was converted into the dimethylacetal **6** (Scheme 2) without separation and/or after separation (in some cases, partly), and its enantiomeric excess (ee) was determined by GC analysis using a chiral column (Chirasil-DEX CB); meanwhile, its absolute stereochemistry was established by correlation to the known compound **9**⁶ (see Scheme 3). The results are summarized in Table 1.

As can be seen from Table 1, the *E/Z* ratio of **5** and the *R/S* ratio of **6** are apparently related to each other, which is most outstanding in the case of the five-membered acetals, where they are almost coincident with each other regardless of the substituent of the acetal (entries 1, 2, and 4). This result strongly suggests that the absolute configurations of **6** derived from *E*- or *Z*-**5** are opposite from each other and the degree of the ee of both *E*- and *Z*-**5** is good to excellent. We confirmed this in several cases where pure *E* and/or *Z*-**5** could be isolated as shown in entries 3, 5, and 8 in Table 1.

From a practical viewpoint, the 1,2-diphenylethylene acetal derivative appears to be most attractive because it affords the highest *E/Z*-ratio as well as the highest ee value, and moreover, *E*- and *Z*-**5c** can be readily separated by column chromatography (entry 4 in Table 1). Thus, as shown in entry 5, *E*-**5c** with 96% ee was isolated in 83% yield.

(4) Enantiomeric excess (ee) was determined as follows: for **3**, GC analysis after converting to **6**; for **9**, ¹H NMR analysis using a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-comphorato]europium(III); for **12**, GC analysis after changing to **6** by dehalogenation with *t*-BuLi; for **15** and **17**, GC analysis after converting to the corresponding dimethylacetal.

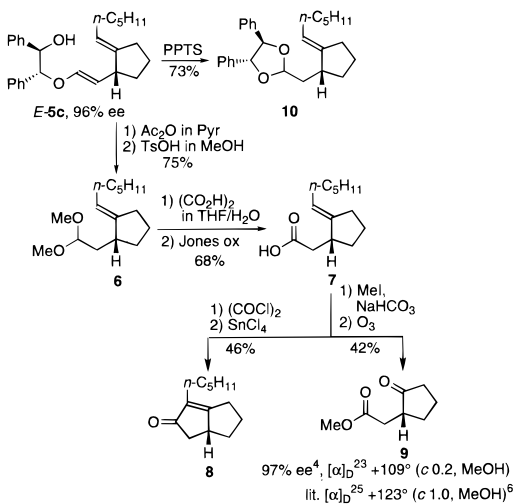
(5) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590. Alexakis, A.; Mangeney P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511. Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265–1276 and references therein.

(6) Hashimoto, S.; Miyazaki, Y.; Ikegami, S. *Synth. Commun.* **1992**, *22*, 2717–2722. Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171–7172.

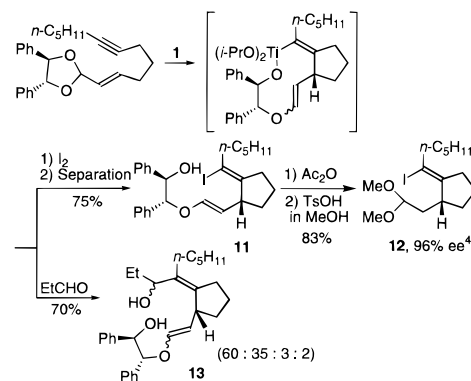
Table 1. Ti(II)-Mediated Intramolecular Cyclization Reaction of **4**

Entry	Acetal moiety in 4	5		6 ^c	
		% Yield ^a	<i>E/Z</i> ^b	R : S ^d	
1 ^e		(4a)	(quant)	66/34	66 : 34
2		(4b)	(93)	88/12	87 : 13
3		(4b)	{ 77 12	pure <i>E</i> pure <i>Z</i>	97.5 : 2.5 20 : 80
4		(4c)	91	95/5	94 : 6
5 ^e		(4c)	{ 83 4	pure <i>E</i> pure <i>Z</i>	98 : 2 5 : 95
6		(4d)	(quant)	78/22	27 : 73
7		(4e)	(98)	55/45	49 : 51
8		(4e)	{ 31 24	pure <i>E</i> 4/96	4.3 : 95.7 96.3 : 3.7
9		(4f)	(63)	52/48	51 : 49

^a Isolated yield. NMR yield in parentheses. ^b Determined by ¹H NMR spectroscopy. ^c Yield from **5** to **6** was >70%. ^d Decided by GC analysis. ^e Use of ClTi(O-*i*-Pr)₃ instead of Ti(O-*i*-Pr)₄ gave very similar results with respect to the yield and *E/Z* ratio of **5**, and *R/S* ratio of **6**. For entry 1, the *E/Z* ratio of **5a** was 60/40 and the *R/S* ratio of **6** was 60/40. For entry 5, the 76% yield of *E*-**5c** with 96% ee and 12% yield of *Z*-**5c** with 98% ee were obtained.

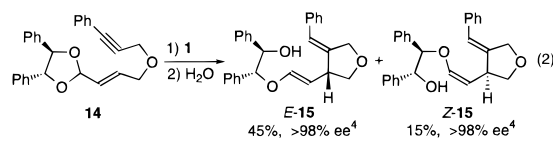
Scheme 3. Several Synthetic Transformations of *E*-**5c**

(7) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1037–1064. Recently, asymmetric Pauson–Khand reaction providing bicyclo[3,3,0]oct-1-en-3-ones has met with great success, see: Castro, J.; Sørensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericás, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388–9389. Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A. *Tetrahedron Lett.* **1994**, *35*, 3521–3524. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688–11689.

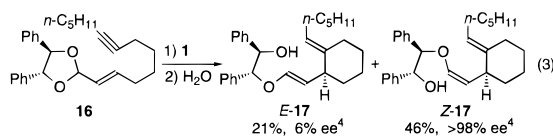
Scheme 4. Trap of the Resulting Vinyltitanium Derived from **1** and **4c** with I₂ or Aldehydes

We have also confirmed that the resulting organotitanium derived from **1** and **4c** can be trapped with iodine and an aldehyde, providing **11** and **13**, respectively, as illustrated in Scheme 4. Noteworthy is the high yield of **11** with a pure *E*-enol ether moiety that was readily obtained after separation from the *Z*-isomer by column chromatography.

This synthetic equivalent of a stoichiometric intramolecular asymmetric metallo-ene reaction appears to be broad in scope. An oxygen atom can be accommodated in the chain (eq 2).⁸ The



reaction is also applicable to the synthesis of optically active cyclohexane compounds as represented by the cyclization of 2,8-enynyl acetal **16** to **17**⁹ (eq 3). The stereochemistry of this reaction,



however, is somewhat different from that of the cyclization of **4**; the major isomer of the resulting enol ether has the *Z*-configuration, and the ee value of *Z*-**17** is excellent whereas that of *E*-**17** is very low. Meanwhile, the major isomers of both *E*- and *Z*-**17** have the same (*S*)-configuration.

In conclusion, the titanium(II)-mediated cyclization of 2,7- and 2,8-enynyl chiral acetals provides an efficient method for synthesizing optically active polysubstituted cyclopentanes or -hexanes. Synthetic applications of the present asymmetric cyclization and investigations to confirm the mechanistic rationale of the reaction are now in progress in our laboratory.

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Supporting Information Available: Typical experimental procedure for the preparation of **5c**, characterization data of starting materials **4c**, **14**, **16**, and products **5c**, **6**, **11**, **13**, **15**, **17**, structural determination of several compounds and the possible transition state to afford **5c** from **4c** and the Ti(II)-reagent (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) Absolute configuration of **15** was speculated on the basis of analogy for the conversion **4** to **5**.

(9) Absolute configuration of *Z*-**17** was established by correlation to known (*S*)-2-ethylcyclohexanone (see Supporting Information). Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druehlinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081–3087.