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ASYMMETRIC CYCLIZATION OF DIENE HAVING AN ALKOXY MOIETY IN A TETHER

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Abstract - Asymmetric cyclization of diene having a hydroxymethyl or hydroxyethyl group in a tether gave a *trans*-product with a high ee derived from *trans*-zirconacycle, while the ee of a *cis*-product derived from *cis*-zirconacycle was low. Coordination of the hydroxy group to zirconium as an intermediary zirconacycle would affect the ee of the cyclized product.

Zirconium-promoted cyclization is very useful in synthetic organic chemistry because the new carbon-carbon bonds are formed between the multiple bonds.[1] The reaction was further extended to the zirconium-catalyzed cyclization using a catalytic amount of Cp_2ZrCl_2 and Grignard reagent.[2] As a result, the reaction could be extended to the asymmetric synthesis[3] using a catalytic amount of (EBTHI)ZrBINOL.[4] We have succeeded in the asymmetric cyclization of diene, and many heterocyclic and carbocyclic compounds could be synthesized.[5] In this reaction two new asymmetric carbons are formed. During the course of our study on this cyclization, we found that a hydroxymethyl group in a tether affects the ee of the *trans*-product[6] (*trans*-**3b**) derived from *trans*-zirconacycle. In this reaction, the ee of the *cis*-product (*cis*-**3b**) derived from

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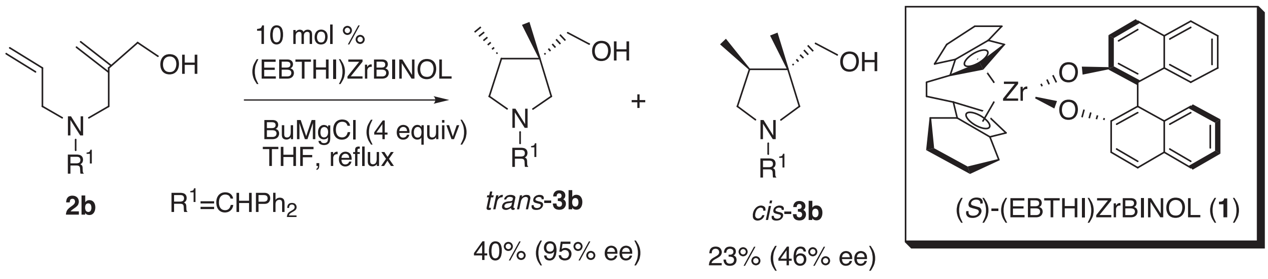
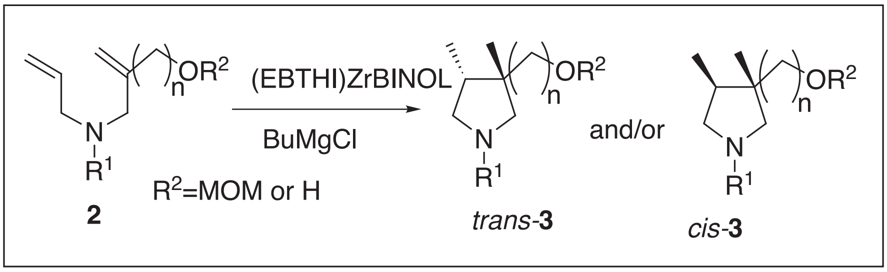
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd Birthday.

cis- zirconacycle is moderate.[5a] Here we report an asymmetric cyclization of diene having a hydroxyalkyl group on alkene using (EBTHI)ZrBINOL in the presence of BuMgCl, and the effect of the hydroxy group on the asymmetric cyclization.

Scheme 1



Scheme 2. Plan for asymmetric cyclization of diene having alkoxy group in a tether



When a THF solution of diene (**2a**) and **1** (10 mol %) was refluxed in the presence of BuMgCl (4 equiv) for 5.5 h, we are very surprised to find that spiro-compound (**4**) was obtained in 92% yield along with a small amount of *trans*-**3a** and *cis*-**3a** (Table 1, run 1). However, the ee of **4** was only 36%. The result was very different from that of the reaction of **2b** with **1**. The strong coordination of the oxygen of the methoxymethyl group to the zirconium metal of the zirconacycle (**7**) probably plays an important role in the formation of **4** in this reaction (Scheme 3). Thus, we prepared compounds (**2c**) and (**2d**), which have the alkoxyethyl moiety on the alkene. When the reaction of **2c** with **1** was carried out in a similar manner, *cis*-**3c** was obtained as a main product. However, the ee of *cis*-**3c** was low (run 3, 11% ee,). On the other hand, compound (**2d**) having the hydroxyethyl group on the alkene gave *trans*-**3d** with 96% ee in 33% yield and *cis*-**3d** with 40% ee in 47% yield (run 4). In this case, *trans*-**3d** derived from *trans*-zirconacycle (**3d**) gave the high ee although the yield was moderate. Moreover, compounds (**2e**) and (**2f**) having hydroxypropyl group on the alkene were examined. In these cases, only *cis*-**3e** and *cis*-**3f** were obtained in good yields, but the ees of these compounds were low (runs 5 and 6).

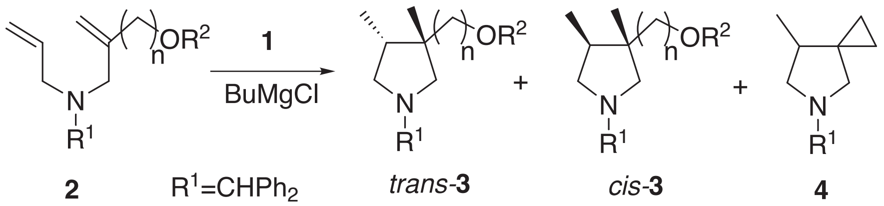


Table 1. Reaction of **2** with **1**

run	R	n	Substrate	time (h)	*trans*-**3** %	*trans*-**3** % ee	*cis*-**3** %	*cis*-**3** % ee	**4**[c] %	**4**[c] % ee
1	MOM	1	**2a**	5.5	5	—	2	—	92	36
2[g]	H	1	**2b**	9.5	40	95[a]	23	46[b]	0	—
3	MOM	2	**2c**	16	0	—	87	11[d]		
4	H	2	**2d**	2.5	33	96[e]	47	40[d]		
5	MOM	3	**2e**	13.5	0	—	68	16[f]		
6	H	3	**2f**	23.0	0	—	75	3[f]		

The ee was determined by HPLC analysis (DAICEL CHIRALPAC AD; hexane:iPrOH=9:1) after conversion into [a]*trans*-**3** (n=1, R^1=Bz, R^2=H), [b]*cis*-**3** (n=1, R^1=Bz, R^2=H), [c]**4** (R^1=Bz), [d]*cis*-**3** (n=2, R^1=Bz, R^2=MOM), [e]*trans*-**3** (n=2, R^1=Bz, R^2=MOM), and [f] *cis*-**3** (n=3, R^1=Bz, R^2=MOM). [g]Published data.[5a]

The reaction course is shown in Scheme 3. Reaction of **2** with **1** gives *trans*- and *cis*-zirconacycles **7**, which react with BuMgCl to give ate-complexes (**8**). Then carbon-zirconium bond fission occurs to afford magnesium complex (**9**) and then (**10**). Hydrolysis of **10** affords **3**. In this reaction, dienes (**2b** and **2d**) having a hydroxymethyl or a hydroxyethyl group in the tether, respectively, gave *trans*-products (*trans*-**3b** and *trans*-**3d**) with the high ees derived from *trans*-zirconacycles (*trans*-**7b** and *trans*-**7d**). However, the ees of *cis*-products (*cis*-**3b** and *cis*-**3d**) derived from *cis*-zirconacycles (*cis*-**7b** and *cis*-**7d**) were low. Moreover, dienes (**2e**) and (**2f**) gave only *cis*-**3e** and *cis*-**3f**, respectively. In all cases, *cis*-products were formed, but the ees were moderate, and only dienes having a hydroxy group in the tether gave *trans*-products.

Further studies on asymmetric cyclization using zirconium complex are now in progress.

ACKNOWLEDGEMENT

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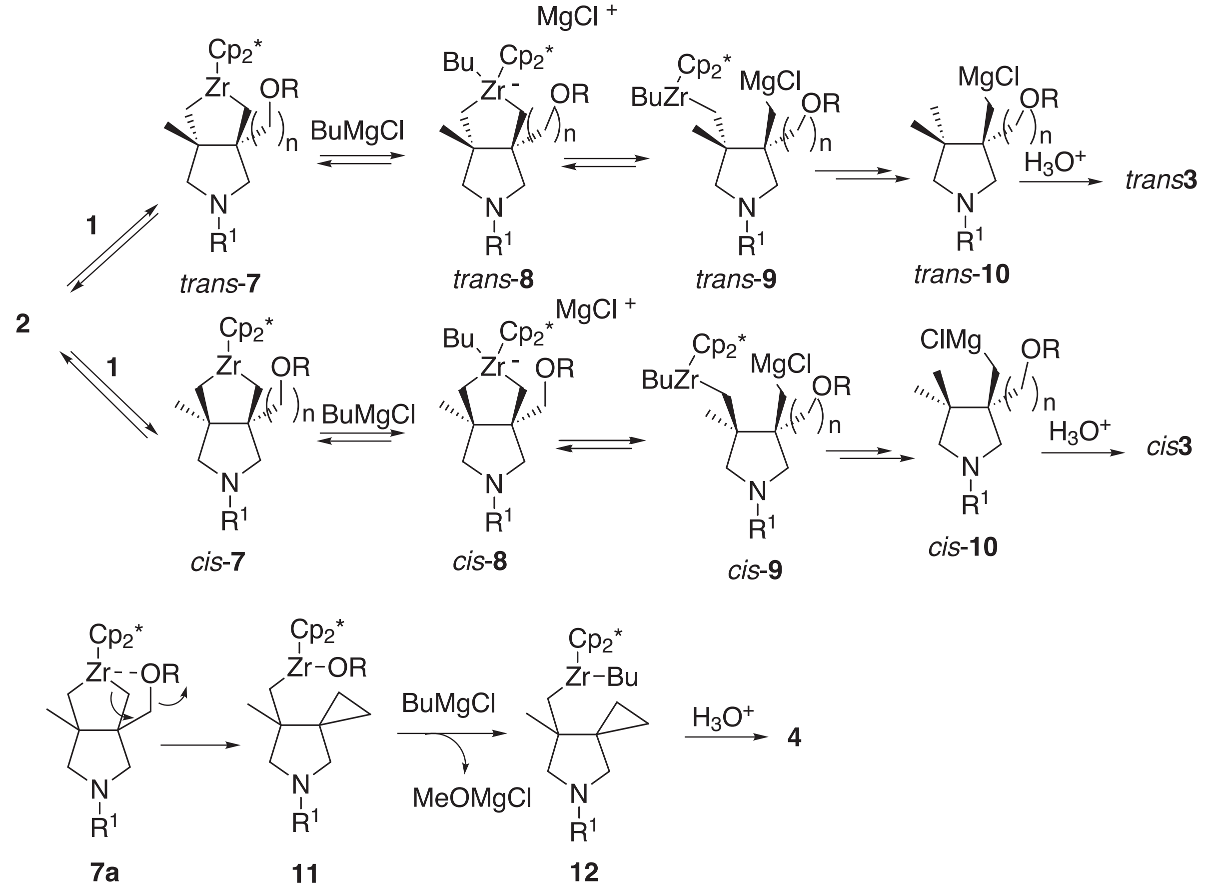
Scheme 3. Reaction Course



REFERENCES AND NOTES

1. (a) E. Negishi, S. J. Holmes, J. M. Tour, and J. A.; Miller, *J. Am. Chem. Soc.*, **107**, 2568 (1985). (b) E. Negishi and T. Takahashi, *Acc. Chem. Res.,* **27**, 124 (1994). (b) W. A. Nugent, and J. C. Calabrese, *J. Am. Chem. Soc.,* **106**, 6422 (1984).
2. (a) U. M. Dzhemilev, O. S. Vostrikova, and R. M. Sultanov, *Izv. Akad. Nauk. SSSR, Ser. Khim.,* 219 (1983). (b) A. H. Hoveyda and Z. Xu, *J. Am. Chem. Soc.,* **113**, 5079, (1991). (c) T. Takahashi, T. Seki, Y. Nitto, M. Saburi, C. J. Rousset, and E. Negishi, *J. Am. Chem. Soc.,* **113**, 6266 (1991).. (d) K. S. Knight and R. M. Waymouth, *J. Am. Chem. Soc.,* **113**, 6268 (1991). (e) D. P. Lewis, P. M. Muller, R. J. Whitby, and R. V. H. Jones, *Tetrahedron Lett.* **32**, 6797 (1991).
3. For a review, see: A. H. Hoveyda and J. P. Morken, J. P. *Angew. Chem. Int. Ed. Engl.,* **35**, 1262 (1996).
4. (a) F. R. W. P. Wild, M. Wasiucionek, G. Huttner, and H. H. Brintzinger, *J. Organomet. Chem.,* **288**, 63 (1985). (b) S. Collins, B. A. Kuntz, N. J. Taylor, and D. G. Ward, *J. Organomet. Chem.,* **342**, 21 (1988). (c) R. B. Grossman, W. M. Davis, and S. L. Buchwald, *J. Am. Chem. Soc.*, **113**, 2321 (1991).
5. (a) Y. Yamaura, M. Hyakutake, and M. Mori, *J. Am. Chem. Soc.,* **119**, 7615 (1997). (b) Y. Yamaura, and M. Mori, *Tetrahedron Lett.* **40**, 3221 (1999).
6. In this report, *cis*- and *trans*- refer to the relative positions of the corresponding substituents connected with the stereochemistry of the 5-5 membered ring junction of the zirconacycle.
7. The stereochemistry of *cis*- and *trans*-isomers was confirmed by NMR experiments (COSY and NOESY).