

ASYMMETRIC CYCLIZATION OF DIENE HAVING AN ALKOXY MOIETY IN A TETHER

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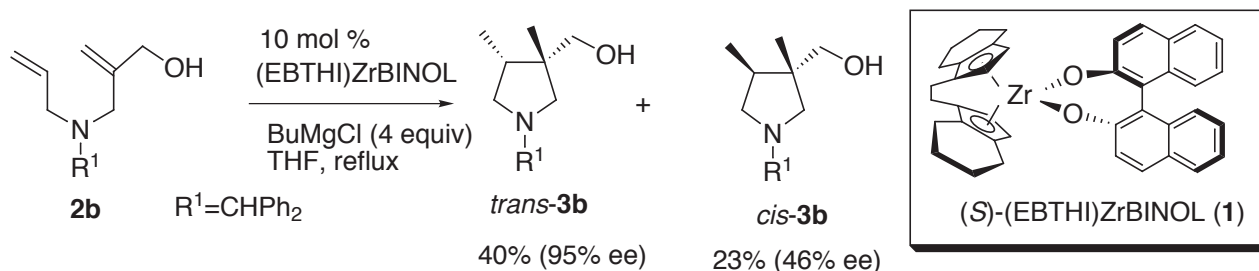
Abstract - Asymmetric cyclization of diene having a hydroxymethyl or hydroxyethyl group in a tether gave a *trans*-product with a high ee derived from *trans*-zirconacycle, while the ee of a *cis*-product derived from *cis*-zirconacycle was low. Coordination of the hydroxy group to zirconium as an intermediary 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 Cp₂ZrCl₂ and Grignard reagent.² As a result, the reaction could be extended to the asymmetric synthesis³ 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*-product⁶ (*trans*-**3b**) derived from *trans*-zirconacycle. In this reaction, the ee of the *cis*-product (*cis*-**3b**) derived from

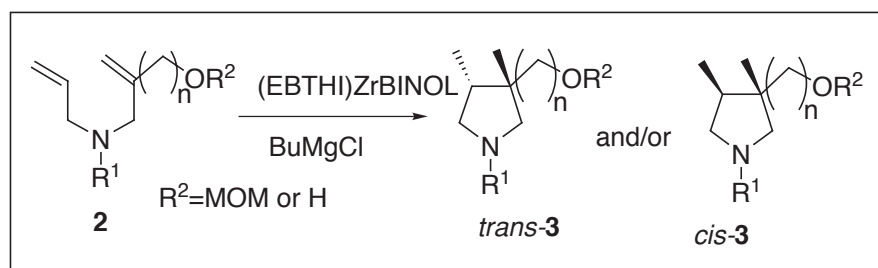
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd Birthday.

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).

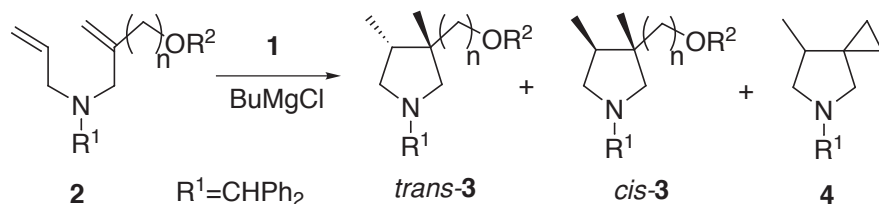


Table 1. Reaction of **2** with **1**

run	R	n	Substrate	time (h)	<i>trans</i> - 3		<i>cis</i> - 3		4 ^c	
					%	% ee	%	% ee	%	% 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, R¹=Bz, R²=H), ^b*cis*-**3** (n=1, R¹=Bz, R²=H), ^c**4** (R¹=Bz), ^d*cis*-**3** (n=2, R¹=Bz, R²=MOM), ^e*trans*-**3** (n=2, R¹=Bz, R²=MOM), and ^f*cis*-**3** (n=3, R¹=Bz, R²=MOM). ^gPublished data.^{5a}

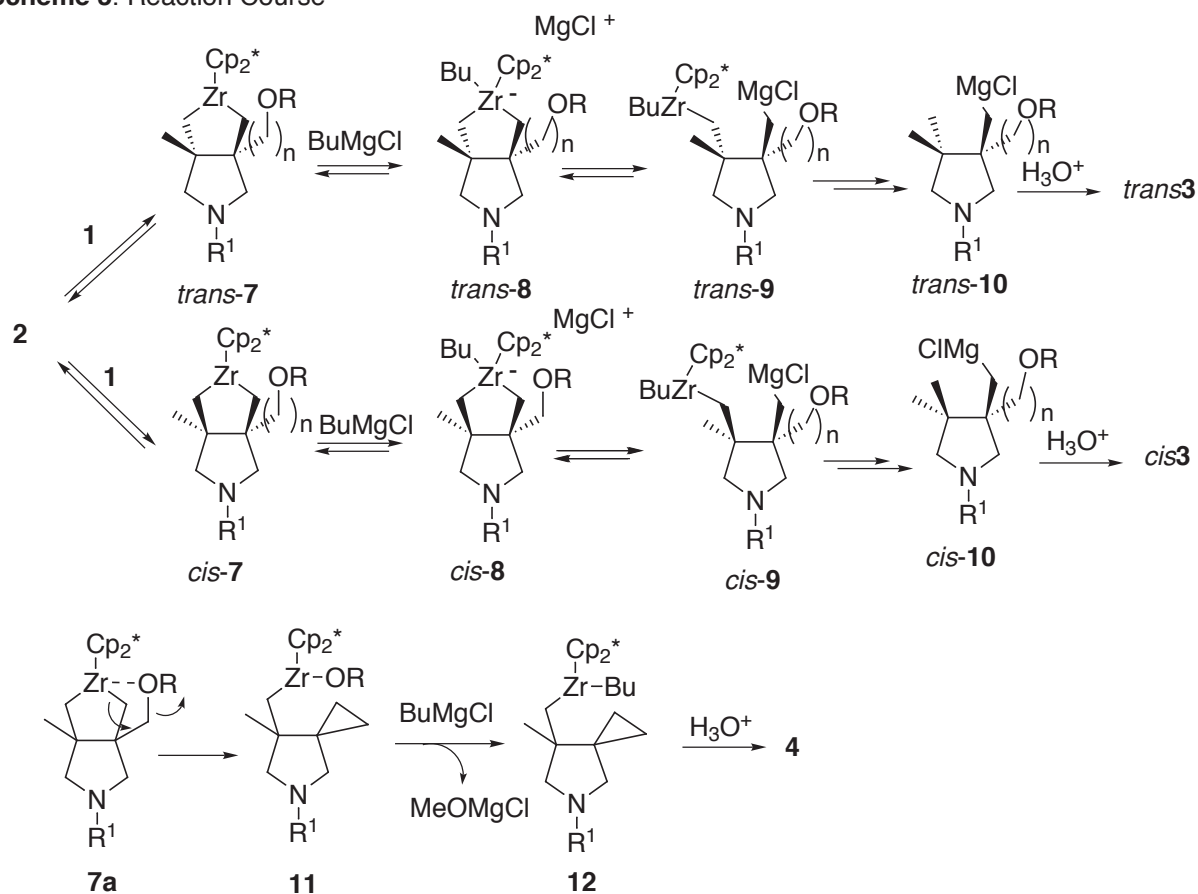
The reaction course is shown in Scheme 3. Reaction of **2** with **1** gives *trans*- and *cis*-zirconacycles **7**, which react with BuMgCl to give ate-complexes (**8**). Then carbon-zirconium bond fission occurs to afford magnesium complex (**9**) and then (**10**). Hydrolysis of **10** affords **3**. 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



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- 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.
- The stereochemistry of *cis*- and *trans*-isomers was confirmed by NMR experiments (COSY and NOESY).