Synthesis of Heterocycles Using Zirconium-Catalyzed Asymmetric Diene Cyclization

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Zirconium-promoted cyclizations of enynes, dienes, and diynes are useful in synthetic organic chemistry,[1] and various natural products have been synthesized using this procedure.[2] Zirconium-catalyzed carbomagnesation and cyclization in the presence of Grignard reagent have recently been reported.[3] On the basis of these results, asymmetric carbomagnesation,[4a,b] carboalumination,[4c] and kinetic resolution[4d] have been reported using a chiral zirconium complex.[5] These studies prompted us to develop a zirconium-catalyzed asymmetric diene cyclization using chiral zirconium complex **1**, as shown in Figure 1. For this purpose, the stereochemistry of the ring junction of the zirconacycle generated from the diene must be controlled. In general, when a stoichiometric amount of zirconium complex is used for cyclization, a thermodynamic zirconacycle is formed, and in a zirconium-catalyzed cyclization using Grignard reagent, a kinetic zirconacycle is formed.[6] Here we report an asymmetric synthesis of heterocycles using zirconium-catalyzed diene cyclization.

When a THF solution of **2** was refluxed with (*R*)-(EBTHI)-ZrBINOL (**1**) (10 mol %) in the presence of Bu_2Mg (8 equiv) for 64 h, we obtained **3a** and **3b** in yields of 13 and 6%, respectively,[7] and the enantiomeric excess (ee) of the trans isomer **3b**[8,9] was only 13% (Scheme 1).[10] Surprisingly, when diallylamine **4**, which has a methyl group on the alkene, was treated in a similar manner, it gave the cyclized product **5**[8] in

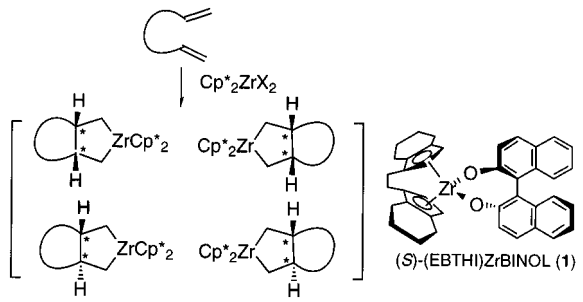
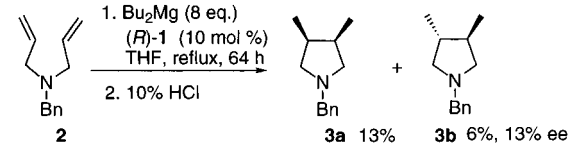
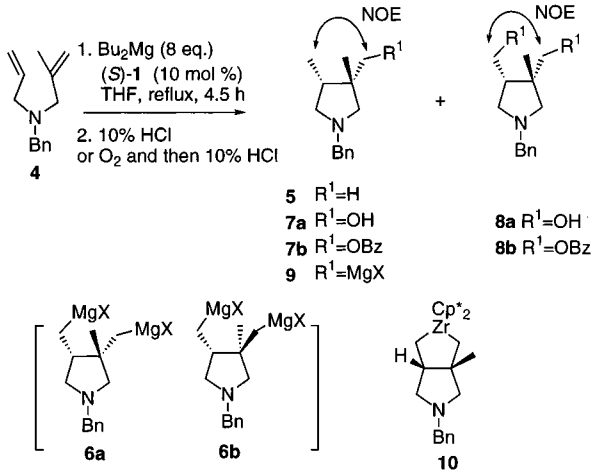


Figure 1.

Scheme 1



Scheme 2



84% yield with 61% ee after only 4.5 h of reflux in THF (Scheme 2). As Grignard reagents, EtMgBr, ^{i}PrMgCl, ^{i}BuMgCl, and ^{t}BuMgCl did not give good results in this case. The hydrolysis product **5** was obtained from both of the cis and trans magnesium complexes, **6a** and **6b**, generated in this reaction. Thus, the reaction mixture was treated with O_2 and then with 10% HCl to give two products, **7a**[8,11] and **8a**,[8] in 36% yield with 62% ee and 12% yield with 70% ee, respectively. Interestingly, NOESY experiments with **7b** and **8b** indicated that only zirconacycle **10** with a cis ring junction was formed in this reaction, which means that the magnesium complexes **6a** and **9** were formed from *cis*-zirconacycle **10** and Bu_2Mg. To establish a catalytic asymmetric cyclization using RMgX in the presence of **1** (10 mol %), the reaction was carried out under various conditions. The results are shown in Table 1. It was quite interesting that only magnesium complex **9** was formed from zirconacycle **10** and BuMgCl (runs 4−8). At higher

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(8) The determinations of ees in the zirconium-catalyzed asymmetric cyclizations were carried out by GC and HPLC analyses, and the detailed procedures are described in the Supporting Information.

(9) The absolute configuration of **3b** was not determined.

(10) *Typical Procedure for the Zirconium-Catalyzed Asymmetric Diene Cyclization:* To a solution of (*S*)-(EBTHI)ZrBINOL (**1**) (127 mg, 0.199 mmol) and **4** (400 mg, 1.99 mmol) in THF (3.9 ml) was added BuMgCl (1.89 M solution in THF, 2.1 ml, 3.97 mmol) at −78 °C. The solution was stirred at the same temperature for 1 h and was refluxed for 14 h. Then, an atmosphere of argon in the reaction vessel was changed to oxygen, and the solution was stirred at room temperature for 2 h. To the solution was added 10% HCl at 0 °C, and the resultant mixture was basified with saturated aqueous $NaHCO_3$. After the usual workup, the residue was purified by column chromatography (AcOEt/MeOH = 1:0, 10:1) to afford 316 mg (72%, 71% ee) of **7a** as a pale yellow oil.

(11) Compound **7a** was converted into methyl (*S*)-[(3*S*,4*R*)-3,4-dimethyl-1-tosylpyrrolidine-3-carboxamide]phenylacetate, and its absolute configuration was determined by a X-ray diffraction method.

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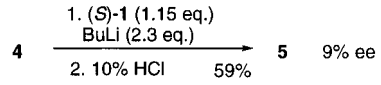
Table 1. Reaction of **4** with RMgX in the Presence of (*S*)-**1** Followed by Treatment with O_2

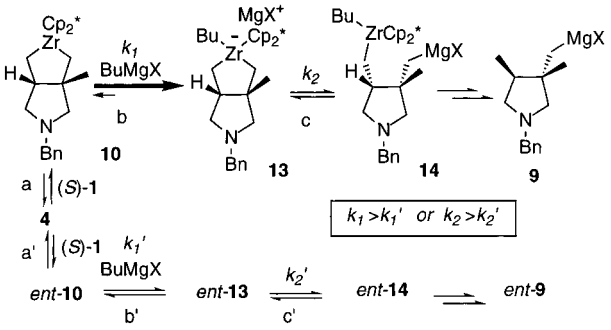
run	RMgX (equiv)	solvent	temp	time (h)	7a yield	7a ee	8a yield	8a ee
1	Bu_2Mg (8)	THF	reflux	4.5	36	62	12	70
2	Bu_2Mg (8)	THF	rt	71.5	24	54	2	46
3	Bu_2Mg (8)	Et_2O	rt	88	18	44	27	46
4	BuMgCl (8)	THF	reflux	9.5	79	61		
5	BuMgCl (4)	THF	reflux	24	54	71		
6	BuMgCl (2)	THF	reflux	24	21	78		
7	BuMgCl (2)[a]	THF	reflux	14	72	71		
8	BuMgCl (4)	THP[b]	80 °C	36	16	86		

[a] In all other cases, a 0.082 M solution of the substrate was used; however, in this case, a 0.33 M solution was used. [b] THP tetrahydropyran.

Scheme 3



Scheme 4. Possible Reaction Course

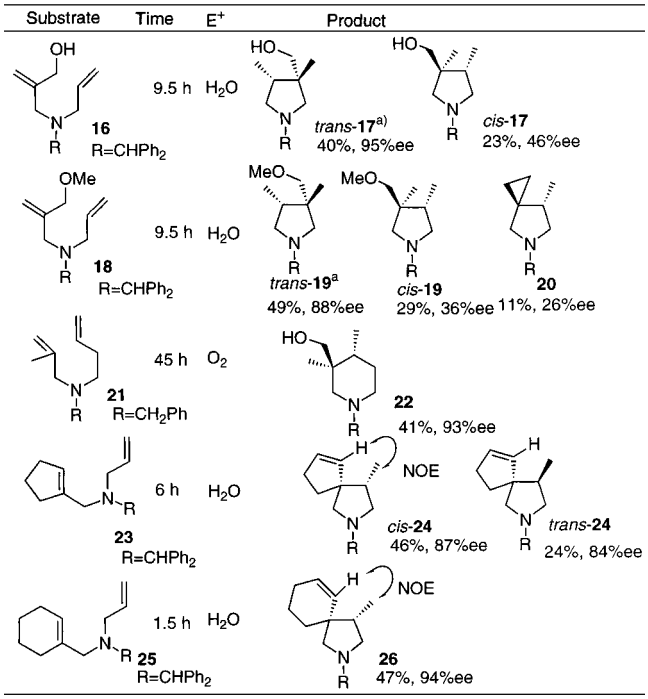


temperature, the reaction gave good yields with higher ees (runs 1, 2, and 8), and with an excess of Grignard reagent, the reaction gave decreased ees of the product (runs 4−6). As a result, when a THF solution of **4** and BuMgCl (2 equiv) was refluxed in the presence of **1** (10 mol %) for 14 h, the cyclized product **7a** with 71% ee was obtained in 72% yield (run 7).

If the enantioselection occurs at the stage of the formation of zirconacycle, the same ee should be obtained when the stoichiometric amount of (*S*)-(EBTHI)$ZrBu_2$ is used for this reaction. Thus, when a THF solution of compound **4** was refluxed in the presence of a stoichiometric amount of (*S*)-(EBTHI)$ZrBu_2$ generated from **1** (1.15 equiv) and BuLi (2.3 equiv)[12] for 4 h, the cyclized product **5** was obtained in 59% yield, but **5** is almost racemic (9% ee) (Scheme 3).[13] This result indicates that enantioselection did not occur when zirconacycle **10** was formed from **4** and chiral zirconium complex **1**.

On the basis of these results, the predicted reaction course of **4** and BuMgCl in the presence of **1** is shown in Scheme 4. The zirconacycles **10** and *ent*-**10** are formed from **4** and (*S*)-(EBTHI)$ZrBu_2$ generated from **1** and BuMgCl, and the ring junctions of zirconacycles **10** and *ent*-**10** show cis stereochemistry.[14] Notably, the ratio of the zirconacycles **10** and *ent*-**10** is almost 1:1 because the ee of the hydrolysis product **5** is only 9%. However, we obtained alcohol **7a** with 86% ee (Table 1, run 8). Thus, enantioselection should occur at the subsequent steps, ate-complexation (step b) or transmetalation (step c). Presumably, the formation of ate-complex **13** from zirconacycle **10** (and/or the formation of **14** from ate-complex **13**) is faster than that of ate-complex from diastereomer *ent*-**10** (and/or that of the magnesium complex of the diastereomer). However, the stage at which enantioselection occurs is not yet clear.[15] Subsequently, we attempted to synthesize various heterocycles using the zirconium-catalyzed asymmetric cyclization. The results are shown in Table 2. Magnesium complexes generated from dienes were treated with H_3O^+ or O_2, and we could obtain the pyrrolidine and piperidine derivatives **17**, **19**,[8] and **22**[8] and spiro-compounds **24**[8,16] and **26**[8] with high ees. The diphenylmethyl group on nitrogen improved the yield of the cyclized product.

Table 2. Zirconium-Catalyzed Asymmetric Cyclization[a]



[a] A THF solution of diene, **1** (10 mol %), and BuMgCl (4 equiv) was refluxed, and then the reaction mixture was treated with electrophiles. The determinations of the relative configurations are described in the Supporting Information. The absolute configurations were assigned by analogy to **7a**.

These results indicate that a catalytic asymmetric diene cyclization using a chiral zirconium complex was realized. In this reaction, the substituent on the alkene carbon affects the reaction course and five- and six-membered cyclized products were obtained with high ees. Further studies are in progress.

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Supporting Information Available: Experimental and X-ray crystallographic details (44 pages). See any current masthead page for ordering and Internet access instructions.

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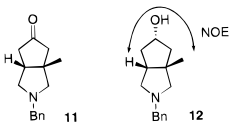
(13) The enantioselection of **5** obtained by a zirconium-promoted asymmetric cyclization (a stoichiometric reaction) is same as that of **5** obtained by a zirconium-catalyzed asymmetric cyclization.

(14) Compound **4** was treated with a stoichiometric amount of Cp_2ZrBu_2 generated from Cp_2ZrCl_2 and BuLi, followed by successive treatment with carbon monoxide and iodine. After acid hydrolysis, bicyclic compound **11** was obtained in 54% yield as a single isomer. To determine the stereochemistry of the ring junction, **11** was reduced with $NaBH_4$ to give alcohol **12** in 66% yield. The NOE experiment with **12** indicated that the ring junction of **12** is cis.



(15) One explanation for why magnesium complex **14** was formed from the ate complex **13** may involve steric release between the methyl group and the Cp* group or the butyl group on ate-complex **13**. Presumably, the reaction rate for the cyclization of **4** is faster than that of **2** for the same reason; the zirconacycle or ate-complex formed from **2** is more stable than that formed from **4**.

(16) Aza-spiro compound (**24**, R = CH_2Ph) was synthesized by zirconium-promoted cyclization. Negishi, E.; Maye, J. P.; Choueiry, D. *Tetrahedron* **1995**, *51*, 4447.