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Enantioselective Synthesis of Cyclopentane Derivatives Using Zirconium-Catalyzed Asymmetric Cyclization

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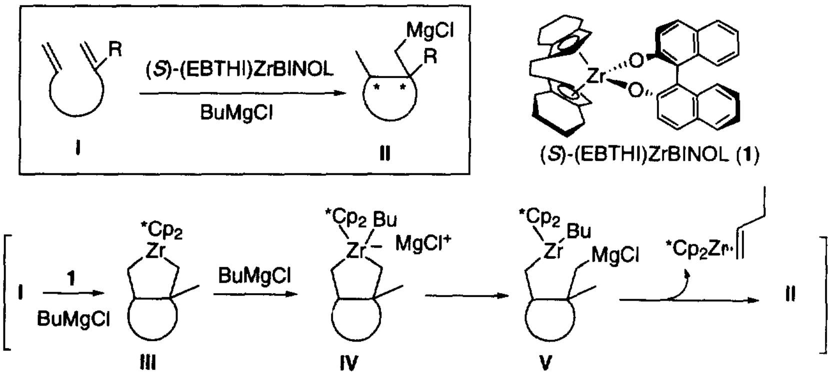
Abstract: Cyclization of diene **2a** using (*S*)-(EBTHI)ZrBINOL (**1**) (10 mol %) and BuMgCl in THF upon heating gave cyclopentane derivative *trans*-**3a** with 99% ee and *cis*-**3a** with 86% ee in 69% and 31% yields, respectively. In a similar manner, diene **10** gave cyclopentane derivative *cis*-**11** with 94% ee in 81% yield as a sole product. © 1999 Elsevier Science Ltd. All rights reserved.

Key Words: Asymmetric Cyclzation, (EBTHI)ZrBINOL, Diene, Zirconium.

Zirconium-promoted diene, enyne, and diyne cyclizations, which were developed by Negishi[1] and Nugent[2], independently, are useful for the synthesis of cyclic compounds. Diene cyclization was further developed to the catalytic reaction in regard to the zirconium complex using Grignard reagent.[3] As a results, asymmetric synthesis of homoallyl alcohols and kinetic resolution of furan and pyran[4] derivatives were achieved using (EBTHI)ZrCl$_2$[5] and other chiral zirconium complex.[6] Recently, we succeeded in the asymmetric cyclization[7] from diene using (EBTHI)ZrBINOL (**1**).[5c] These results prompted us to synthesize cyclopentane derivatives from dienes.

Scheme 1 Plan for a catalytic asymmetric synthesis of cyclopentane derivative



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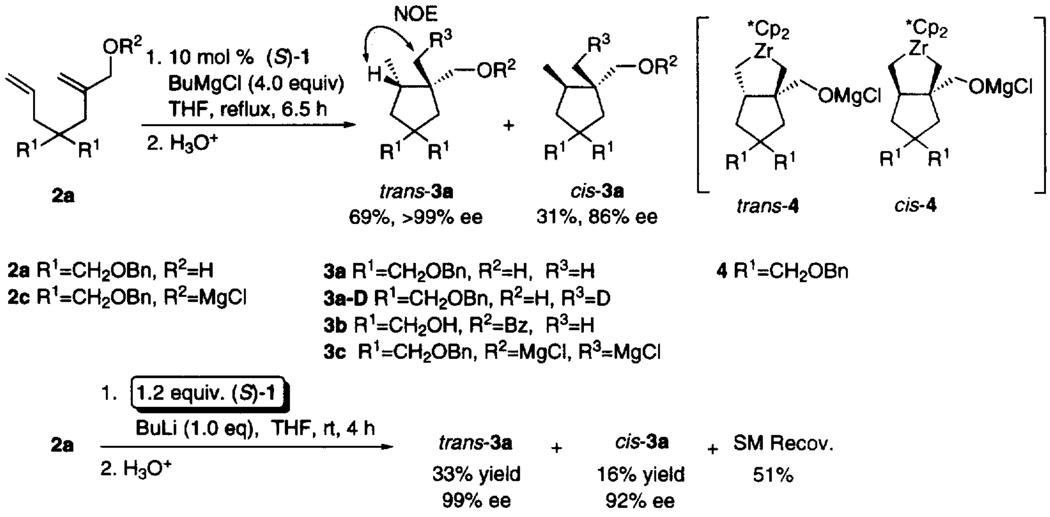
Synthesis of chiral cyclopentane derivatives is very important for the synthesis of naturally occurring products or biologically active substances. Our plan is shown in Scheme 1.

When diene **I** is treated with Grignard reagent and a catalytic amount of **1**, cyclized product **II** would be formed *via* zirconacycle **III**. In this reaction, BuMgCl reacts with zirconacycle **III** to produce ate-complex **IV**, whose carbon-zirconium bond-fission occurs to give **V**. Then it produces **II**. When a THF solution of diene **2a**, (*S*)-(EBTHI)ZrBINOL (**1**) (10 mol %), and BuMgCl (4.0 equiv) was refluxed for 6.5 h and then the reaction mixture was hydrolyzed, a mixture of two isomers was obtained in quantitative yield. From the NOE experiment of the major product, *trans*-**3a**[8,12] with 99% ee,[9] which was derived from *trans*-zirconacycle **4**, was obtained in 69% yield. The minor product was *cis*-**3a**[8,12] with 86% ee,[9] which was derived from *cis*-**4**. This product was obtained in 31 % yield. To determine which methyl group was connected with magnesium chloride during the reaction, the reaction mixture was treated with 10% DCl-D_2O. As a result, *trans*-**3a-D** with 97% ee (D-content; 84%) and *cis*-**3a-D** with 86% ee (D-content, 91%) were obtained in 62% and 30% yields, respectively. These results indicate that *trans*-**3c** and *cis*-**3c** were formed during the reaction. In a previous study,[7] we found that enantioselection did not occur upon the formation of zirconacyle but at the stage of the reaction of zirconacycle with BuMgCl. If enantioselection occurs upon the formation of zirconacycle, *trans*- and *cis*-**3a**, which are produced from **2a** and an equimolar amount of (*S*)-(EBTHI)ZrBINOL (**1**), should afford the same ees, obtained by the catalytic reaction. When the reaction of **2a** with an equimolar amount of (*S*)-**1** was carried out at room temperature, *trans*-**3a** with 99% ee and *cis*-**3a** with 92% ee were obtained in 33% and 16% yields, respectively.



Scheme 2

On the basis of these results, the possible reaction course is shown in Scheme 3.[10] In a stoichiometric reaction, the ee of *trans*-**3a** gave the same ee and the ee of *cis*-**3a** slightly increased compared with the corresponding ee obtained by a catalytic reaction. This means that the enantioselection of **3a** would occur upon the formation of zirconacycle.[11] Since the ee of *cis*-**3a** obtained by a catalytic reaction is lower than that obtained by a stoichiometric reaction, the reaction of zirconacycle with BuMgCl would also affect the enantioselectivity of **3**. From the deuterium experiment, the carbon-zirconium bond was cleaved at the position of B in *trans*-**6**, because of the cancellation of the steric hindrance in *trans*-**6**.

To examine whether the amount of zirconium complex (*S*)-**1** affects the ees of the products, reactions of **2a** with various amounts of (*S*)-**1** were carried out, and the results are shown in Table 1. The reaction proceeded using only 1 mol % of (*S*)-**1** (run 3), but the ee of *trans*-**3** decreased to 83%, while the ee of *cis*-**3** was not affected by the amount of **1**. The reason for this is not clear. In this reaction, the decrease in the amount of BuMgCl increased the ee of *trans*-**3** (run 4).

Scheme 3 Possible Reaction Course

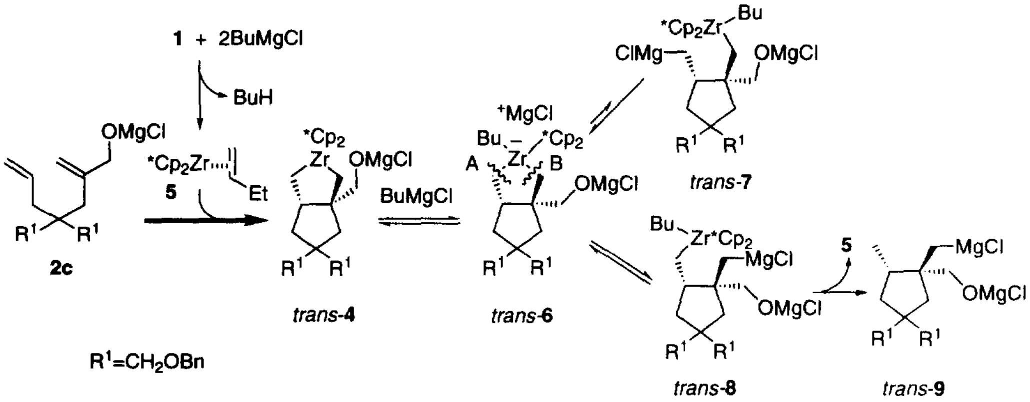


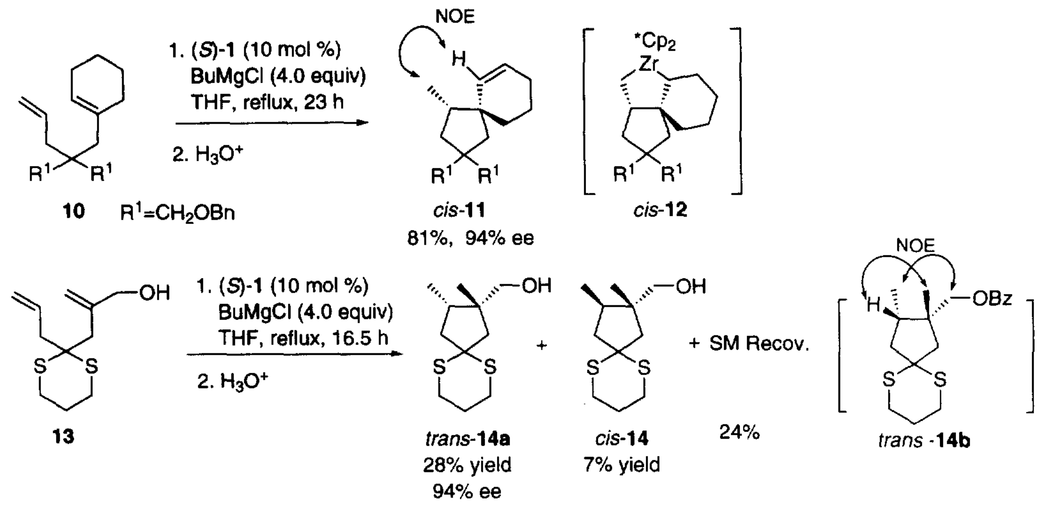
Table 1 Effect of amount of (*S*)-**1**[a]

run	(*S*)-**1** (mol %)	BuMgCl (eq)	*trans*-**3** yield (%)	*trans*-**3** ee (%)	*cis*-**3** yield (%)	*cis*-**3** ee (%)
1	10	4.0	69	>99	31	86
2	5.0	4.0	59	88	27	85
3	1.0	4.0	64	83	27	86
4[b]	1.0	2.5	14	96	10	84

[a] All reactions were carried out in THF upon heating. [b] The starting material was recovered in 52% yield.

The reaction was further developed for the synthesis of other chiral cyclopentane derivatives. It was quite interesting that the spiro-compound *cis*-**11**,[12] which was derived from *cis*-zirconacycle **12**, was obtained as a sole product with 94% ee (81% yield). Although diene **13** having a thioketal moiety is considered to be troublesome,[13] **13** gave *trans*-**14**[12] with 94% ee in 28% yield. Each stereochemistry was determined by NOE experiments.

Scheme 4 Synthesis of Various Chiral Cyclopentane Derivatives



Further studies for zirconium-catalyzed asymmetric cyclization are in progress.

References and Notes

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8. 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.
9. The ees of *trans*-**3a** and *cis*-**11** were determined by HPLC analyses (DAICEL CHIRALCEL OJ, hexane:^{i}PrOH=9:1 and DAICEL CHIRALCEL OJ-R, CH_3CN:H_2O=7:3, respectively), and the ees of *cis*-**3a** and *trans*-**14a** were determined by HPLC analyses after conversion into *cis*-**3b** and *trans*-**14b** (DAICEL CHIRALPAK AD, hexane:^{i}PrOH=9:1).
10. In this scheme, the course from **2c** to *trans*-**3c** is shown and that from **2c** to *cis*-**3c** is omitted.
11. This is not a special case. In the asymmetric synthesis of spiro-compound having nitrogen,[7] it was found that the enantioselection would occur upon the formation of zirconacycle (unpublished result).
12. The absolute configuration was not determined.
13. It is known that the reaction of thioketal with a low-valent titanium complex gives titanium-carbene complex, see: Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.