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## Zirconium-catalyzed enantiotopic group-selective synthesis of hydrindanes

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Abstract—When a THF solution of 12b and (S)-(EBTHI)ZrBINOL (10 mol%) was refluxed in the presence of BuMgCl (4 equiv.) for 4 h, zirconium-catalyzed enantiotopic group-selective cyclization proceeded and hydrindane 13b with 87% ee was obtained in 35% yield. © 2003 Published by Elsevier Science Ltd.

Zirconium-mediated or -catalyzed reaction is very useful because carbon–carbon bonds are formed between multiple bonds.<sup>1</sup> Since Negishi and Takahashi found a method for preparing dibutylzirconocene,<sup>2</sup> many interesting carbon–carbon bond forming reactions have been reported. These reactions have been extended to catalytic reactions in the presence of Grignard reagent,<sup>3</sup> and asymmetric reactions<sup>4</sup> using a chiral zirconium complex have been developed.<sup>5</sup> Asymmetric cyclization was developed by our group, and carbo- and heterocyclic compounds having more than one stereo center were synthesized in high enantiomeric excesses.<sup>6</sup> Here we report the synthesis of hydrindane using zirconium-catalyzed enantiotopic group-selective cyclization. Our plan is shown in Scheme 1.

When triene I is treated with zirconocene dichloride in the presence of a Grignard reagent, for example, zirconacycle II and *ent*-II would be formed. However, if zirconocene having a chiral ligand is used for this reaction, enantiotopic group-selective cyclization should proceed, and chiral cyclized compound having three stereo centers should be produced after hydrolysis. The triene **5a** was synthesized from **2**, whose hydroxyl group was protected by a silyl group. Deprotection of enol ethers **3** followed by Wittig reaction gave triene **5a**. When a THF solution of triene **5a**, 10 mol% of (*S*)-(EBTHI)ZrBINOL (Cp<sup>\*</sup><sub>2</sub>ZrBINOL, **1**)<sup>5a</sup> and an excess amount of BuMgCl (8 equiv.) was refluxed for 64 h, bicyclic compounds **6a** and **6b** were obtained in 13 and 24% yields, respectively (Scheme 2).

Desilylation of **6a** gave **6b** in high yield. From an NOE experiment of **6a**, *trans*-fused 5-5-membered zirconacycle **7a** should be formed as an intermediate. After conversion of **6a** and **6b** into (S)-MTPA ester **6c**, enantiomeric excesses (ee) were determined to be -12 and 59% ee by <sup>1</sup>H NMR spectra, respectively.<sup>7</sup> Since compounds **6a** and **6b** had different ees, kinetic resolution would occur during the reaction or cyclization of **5b** would occur after desilylation. The reaction was carried out under various conditions to improve the ee and the yield, and the results are shown in Table 1. BuMgCl, EtMgCl, and Bu<sub>2</sub>Mg as Grignard reagents were used and BuMgCl gave good results. Dioxane can be used as a solvent.



Scheme 1. Plan for an enantiotopic group selective cyclization.

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Scheme 2. Zirconium-catalyzed cyclization of triene 5.

The protecting groups of the hydroxyl group were changed to TBDPS (Si'BuPh<sub>2</sub>), benzyl, and methyl groups, but good results were not obtained. Next, compound **5b** was used as a substrate. Although the

Table 1. Enantioselective zirconium-catalyzed cyclization

cyclized compound **6b** was obtained in high yield, it was almost racemic (Scheme 3). Since the amount of a Grignard reagent affects the ee of the product in zirconium-catalyzed asymmetric cyclization,<sup>6</sup> the amounts of a Grignard reagent were changed (Table 2). It was interesting that a decrease in the amount of BuMgCl resulted in an increase in the ee of **6b**, although the ees were moderate (runs 1–5). When 1.2 equiv. of BuMgCl was used for this reaction, **6b** with 54% ee was obtained in 46% yield (run 6). The reaction proceeded in a similar manner when **5b** was treated with BuLi or NaH, and in each case, the different ee was obtained (runs 7–8).



Scheme 3. Reaction of 5b with 1.

The possible reaction course is shown in Scheme 4. Treatment of triene 5 with 1 gives tricyclic zirconacycle 7 (route a). In the presence of BuMgCl, it is converted into ate-complex 8 (route b), which is in a state of equilibrium with 9 or 9' (routes c and c') From 9 or 9',  $\beta$ -hydrogen elimination occurs to give 10 or 10'. After hydrolysis, each complex affords hydrindane 6. According to this scheme, the reaction of 5 with 1 also affords *ent-7*, which should give *ent-6*.

Entry	RMgX (equiv.)	Solvent	Time (h)	<b>6a</b> (%)		<b>6b</b> (%)		5a (%)
				Yield	ee	Yield	ee	_
1	BuMgCl (8)	THF	64	13	-12	24	59	33
2	EtMgBr (8)	THF	91	19	14	30	41	5
3	$Bu_2Mg(4)$	THF/heptane <sup>b</sup>	87.5	11	_	19	30	9
4	BuMgCl (8)	Bu <sub>2</sub> O <sup>a</sup>	15.5	37	25	23	25	_
5	BuMgCl (8)	THF/THP <sup>a,c</sup>	40	_	_	45	47	_
6	BuMgCl (8)	THF/dioxane <sup>a,c</sup>	63.5	41	32	13	53	_

<sup>a</sup> Reaction temp., 80°C.

<sup>b</sup> Ratio of 3 to 2.

<sup>c</sup> Ratio of 2 to 3.

 Table 2. Results for different amounts of BuMgCl

Entry	R		BuMgCl (equiv.) <sup>a</sup>	Time (h)	Yield (%)	ee (%)	
1	MgCl	5c	15	1.5	85	-9	
2	MgCl	5c	8	13	83	0	
3	MgCl	5c	7	10	95	12	
4	MgCl	5c	4	11.5	98	17	
5	MgCl	5c	2	16	88	34	
6	MgCl	5c	1.2	48	46 <sup>b</sup>	54	
7	Lic	5d	8	12.5	77	-21	
8	Na <sup>c</sup>	5e	8	3	90	-19	

<sup>a</sup> Since 1 equiv. of BuMgCl is consumed by the hydroxyl group, the other amount of BuMgCl was described.

<sup>b</sup> **5b** was recovered in 23% yield.

<sup>c</sup> 1 equiv. of BuLi or NaH was added and the reaction was carried out.



Scheme 4. Possible reaction course.

It was thought that the reaction proceeds through either route c or c'. To determine the route, compound 5b was treated with rac-1 in a similar manner in the presence of BuMgCl, and then the formed magnesium complex was treated with oxygen to give compound 11 in 70% yield (Scheme 5). This means that the reaction proceeds via route c. When the reaction of 5d with a stoichiometric amount of (S)-1 was carried out at room temperature for 48 h, 6b was obtained in 57% yield with -36% ee after hydrolysis. In a catalytic reaction, **6b** with -21% ee was obtained from 5d (Table 2, run 7). These results indicate that enantioselection should occur at both steps, i.e. when zirconacycle is formed (step a) and when ate-complex 8 is formed by RMgX (step b). The effects of protecting group, including metals, on the hydroxyl group are not clear at this stage.



Scheme 5. Confirmation of the reaction course.

OR OF 1. (S)-1 (10 mol %) **BuMgCl** THF, reflux 2. sat. NH<sub>4</sub>Cl aq. 13 12 13b Bu₄NF, THF NOE OBz OMgCl MgCl ŻrCp MgCl 17 13d 14 16 1. (S)-1 (10 mol %) OH BuMgCI (5 equiv.) THF, reflux, 4 h 2. O<sub>2</sub> 12b OН 15 35%, 85% ee

**Scheme 6.** Synthesis of hydrindane using zirconium-catalyzed asymmetric cyclization.

Subsequently, triene 12 was used as a substrate. When a THF solution of triene 12a, 10 mol% of (S)-1, and BuMgCl (8 equiv.) was refluxed for 5 h, cyclized compounds 13a and 13b were obtained in 22 and 15% yields, respectively. Treatment of the former compound with Bu<sub>4</sub>NF afforded compound 13b in high yield. The results of an NOE experiment of benzoate 13d, obtained from 13b, indicate that trans-fused 5-5-membered zirconacycle 14 was formed. The ees were determined by HPLC using a chiral column to be 78 and 80%, respectively.<sup>8,9</sup> The effects of protecting groups were examined, and the results are shown in Table 3. In the case of a TBDPS group, the desired compound 13c with 78% ee was obtained in 48% yield, and in the case of a hydroxyl group, 13b with 87% ee was obtained in 35% yield. Compound 12b was treated in a similar manner followed by treatment with oxygen to give diol 15 with 85% ee in 35% yield. This means that  $\beta$ -hydrogen elimination<sup>10</sup> from 16 should occur during the reaction to give 17 (Scheme 6).

The results indicate that functionalized hydrindane having a high ee can be obtained using zirconium-catalyzed enantiotopic group-selective cyclization, although the yield is moderate. Further studies are in progress.

Run	R		BuMgCl (equiv.)	Time (h)	13		13b	
					Yield (%)	ee (%)	Yield (%)	ee (%)
1	TBDMS	12a	8	5	22	78	15	80
2	TBDMS	12a	4	10	23	75	10	78
3	<b>TBDPS</b> <sup>a</sup>	12c	4	23.5	48	78	_	_
4	Н	12b	5	4	_	_	35	87

Table 3. Reaction of 12 with (S)-1 in the presence of BuMgCl

<sup>a</sup> Si<sup>t</sup>BuPh<sub>2</sub>.

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- 7. The ees of 6a and 6b were determined by conversion of

**6b** into (S)-MTPA ester using DCC. The methylene protons connected to the acyloxy group on a <sup>1</sup>H NMR spectrum of a mixture of (S)-MTPA esters of **6a** and *ent*-**6a** appeared at 4.16 and 4.11 ppm for **6** and *ent*-**6**, respectively, as <sup>1</sup>H protons of quartets of AB type. The ee was determined from the ratio of the area. Since the absolute configuration was not determined, the ee obtained from 4.16 ppm is shown as a positive value and that obtained from 4.11 ppm is shown as a negative value.

- The ees were determined by HPLC using DAICEL CHIRALCEL OD eluted with hexane/2-propanol=95/5.
- 9. 13b was converted into 19, and the absolute configuration was determined using the CD exciton chirality method.<sup>11</sup> Since the CD spectrum of 19 showed first the negative Cotton effect at 273 nm and secondly the positive Cotton effect at 247 nm, the absolute configuration of 19 was determined to be *S* as shown in Scheme 7.



Scheme 7. Determination of absolute configuration.

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