

Enantioselective addition of methyl group to aldehydes catalyzed by titanium complex of fluorous ligand

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Received 7 February 2007; revised 23 February 2007; accepted 28 February 2007

Available online 2 March 2007

Abstract—Titanium complex of fluorous axially dissymmetric ligand ((*Ra*^{*})-2,2'-bis(*R*^{*})-perfluoro-1*H*-1-hydroxyoctyl]biphenyl, ((*Ra*^{*})-(*R*^{*})₂-**1**) having perfluoroheptyl carbinol moieties catalyzed enantioselective addition of a methyl group to aldehydes. Dimethylzinc prepared in situ by mixing ZnCl₂ and methyl magnesium bromide without removal of magnesium salt was more reactive for addition of methyl group than dimethylzinc without magnesium salt, and gave up to 99% ee of the products. The high fluorine content of **1** enables it to be recoverable by the selective extraction with perfluorohexane.

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The rapidly growing field of asymmetric synthesis has provided new methodologies for easy access to chiral compounds. Among them, a variety of asymmetric reactions with a chiral ligand have been developed. In recent years, development of recyclable ligands has received a great deal of attention in this area from economical and ecological points of view.¹ We have synthesized a new type of recyclable ligand, (*Ra*)-(*R*)₂-**1**.^{2,3} (*Ra* indicates the axial configuration and *R* is the configurations of the side chains Fig. 1). Fluorine content of 60% by weight in **1** affords its recoverability by fluorous technique.^{3b} A high stability of the hydroxyl groups toward oxidation and racemization given by the adjacent perfluoroheptyl groups also contributes to its recycled use. The Ti-catalyst prepared by mixing **1** and Ti(O*i*Pr)₄ cat-

alyzed the asymmetric addition of R₂Zn (R = CH₃ and C₂H₅) to aldehydes, and gave the products in high ee's. However, the addition of (C₂H₅)₂Zn proceeded quantitatively, but that of (CH₃)₂Zn resulted in a 49% yield because of inherent low reactivity of the latter zinc reagent. Despite many efforts, the successful asymmetric addition of a methyl group to aldehyde has not been attained easily, although there are many natural products with a chiral methyl carbinol moiety.^{4,5} To solve this problem, we concentrated on developing a useful method to synthesize a chiral methyl carbinol moiety.

This Letter describes a successful asymmetric methylation of aldehyde using (CH₃)₂Zn generated from ZnCl₂ and CH₃MgBr in situ catalyzed by **1**.

Titanium complex of **1** catalyzed the reaction of aldehyde with (CH₃)₂Zn to give 1-phenylethanol in high ee as well as the reaction with (C₂H₅)₂Zn, but the chemical yield was not satisfactory (Table 1, entries 1 and 2).

In order to increase a nucleophilicity of a methyl anion, we used more reactive CH₃MgBr instead of (CH₃)₂Zn. However, the reaction of benzaldehyde with CH₃MgBr catalyzed by titanium complex of **1** gave the product with lower yield and ee (Table 2, entries 1 and 2). Raising the temperature resulted in better chemical yield, but decrease of ee (entry 3). For the asymmetric methylation, Seebach had already reported effective method using (CH₃)₂Zn generated from ZnCl₂ and CH₃MgBr

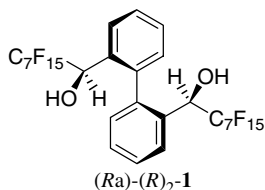


Figure 1. Structure of (*Ra*)-(*R*)₂-**1**.

Keywords: Axial dissymmetric ligand; Fluorous; Chiral; Enantioselective; Methyl addition; Recyclable; Recycle; Fluorine; Perfluoroalkyl.

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Table 1. A symmetric alkylation reaction with R_2Zn

$$\text{PhCHO} + R_2Zn \xrightarrow[\text{(Ra)-(R)}_2\text{-1 (5 mol\%)}]{\text{Ti(OiPr)}_4 \text{ (1.2 eq)}} \text{Ph-CH(OH)-R}$$

Entry	R	Yield ^a (%)	ee (%)
1	C ₂ H ₅	96	97
2	CH ₃	49	95

^a Isolated yield.

in situ.⁶ They removed magnesium salts by precipitation of their complexes with dioxane followed by filtration. Although they obtained the product of 94% ee, the chemical yield was only 55%. According to this report, we tried to add ZnCl₂ for producing (CH₃)₂Zn in the reaction mixture but to use it without separation of magnesium salts for easy handling. The addition of ZnCl₂ improved the reaction considerably. The methylation was successful when ZnCl₂ and CH₃MgBr were used in a ratio of 1:2 and gave the product of 92% ee in 81% yield (entry 5). Interestingly, the yield exceeded the reaction of commercially available (CH₃)₂Zn significantly with slight decrease of the ee (Table 1, entry 2). We thought that coexisting magnesium salts activated the catalytic reactivity without any effect on the asymmetric environment produced by **1**. Equimolar mixture

of ZnCl₂ and CH₃MgBr did not afford the product at all. On the other hand, excess of Grignard reagent decreased both reactivity and enantioselectivity (entry 7), though the ee was better than that obtained only by Grignard reagent (entry 3). Removal of magnesium salts by precipitation of their complex with dioxane followed by filtration to give pure (CH₃)₂Zn resulted in a similar result as entry 2 in Table 1. The best result was obtained by keeping the reaction temperature at –30 °C, and gave the product of 94% ee in 89% yield. Thus, high enantioselective methylation was attained using (CH₃)₂Zn formed from CH₃MgBr and ZnCl₂ in situ without removal of magnesium salts. Magnesium might activate the carbonyl group by coordination, methyl group by ate complex formation, or both. Study on the detailed mechanism is now on progress.

Based on this result, we investigated the applicability of this asymmetric methylation. Results of the reaction of several aldehydes with a variety of properties are shown in Table 3. The reaction condition that gave the best result in Table 2 was used as the standard. Namely, the titanate of **1** was prepared by mixing **1** (20 mol % to the aldehyde) and Ti(OiPr)₄ (2.4 equiv to the aldehyde) for 30 min in toluene at room temperature. The titanate was transferred to a solution of ZnCl₂ and

Table 2. Asymmetric methylation of benzaldehyde catalyzed by **1**

$$\text{PhCHO} + \text{CH}_3\text{MgBr} \xrightarrow[\text{Ti(OiPr)}_4 \text{ (2.4 eq), } \mathbf{1} \text{ (20 mol\%)}]{\text{ZnCl}_2} \text{Ph-CH(OH)-CH}_3 \quad \mathbf{2a}$$

Entry	ZnCl ₂	CH ₃ MgBr	Reaction temperature	Yield ^a (%)	ee ^b (%)
1	—	1.5 equiv	–78 to –30 °C	30	81
2	—	2.0 equiv	–78 to –30 °C	46	80
3	—	2.0 equiv	–78 to 0 °C	86	66
4	2.2 equiv	2.2 equiv	–78 to –30 °C	NR	—
5	2.2 equiv	4.4 equiv	–78 to –30 °C	81	92
6 ^c	2.2 equiv	4.4 equiv	–78 to –30 °C	41	95
7	2.2 equiv	6.6 equiv	–78 to –30 °C	70	77
8	2.2 equiv	4.4 equiv	–30 °C	89	94

^a Isolated yield.^b Determined by GLC analysis.^c Mg salt was precipitated by adding dioxane and the salt was filtered off before use.**Table 3.** Asymmetric methylation of R-CHO (**2b–l**) catalyzed by **1** (20 mol %)

Entry	R	Substrate	Product	Yield ^a (%)	ee ^b (%) (configuration) ^c
1	<i>p</i> -CH ₃ -C ₆ H ₄	2b	3b	95	90 (<i>S</i>)
2	<i>p</i> -iPr-C ₆ H ₄	2c	3c	86	92 (<i>S</i>)
3	<i>p</i> -CH ₃ O-C ₆ H ₄	2d	3d	18	12 (<i>S</i>)
4	<i>n</i> C ₇ H ₁₅	2e	3e	64	99 (<i>S</i>)
5	PhC ₂ H ₄	2f	3f	51	99 (<i>S</i>)
6	<i>p</i> -Cl-C ₆ H ₄	2g	3g	82	91 (<i>S</i>)
7	<i>m</i> -Cl-C ₆ H ₄	2h	3h	99	91 (<i>S</i>)
8	<i>o</i> -Cl-C ₆ H ₄	2i	3i	95	58 (<i>S</i>)
9	<i>o</i> -F-C ₆ H ₄	2j	3j	45	88 (<i>S</i>)
10	<i>p</i> -CH ₃ OCO-C ₆ H ₄	2k	3k	77	90 (<i>S</i>)
11	<i>p</i> -CH ₃ CO-C ₆ H ₄	2l	3l	82	81 (<i>S</i>)

^a Isolated yield.^b Determined by GLC analysis.^c Estimated by the sign of the optical rotation.

CH₃MgBr (2.2 and 4.4 equiv to the aldehyde, respectively) in toluene stirred for 30 min at room temperature in advance. After stirring for 30 min at room temperature, the mixture was chilled to –78 °C and then a solution of the aldehyde in toluene was added slowly at –78 °C. The reaction mixture was warmed up to –30 °C over two hours. In most cases, the reaction completed within 12 h but every reaction was quenched after stirring for 24 h. The enantioselectivity was highly affected by the slight change of the reaction temperature and reactivity of the aldehyde itself. For instance, in case of aromatic aldehydes substituted with electron-withdrawing groups, the initial temperature must be kept at –78 °C to acquire the best enantioselectivity. In case of alkylated aromatic aldehydes, the reaction gave the products of more than 90% ee and in good yield (entries 1 and 2). Anisaldehyde gave **3d** with 12% ee in 18% yield. It is likely that this aldehyde was deactivated by *p*-methoxy group, leading to the low yield. Further, the oxygen atom of the methoxy group might concern with low ee by its coordination. Extremely high enantioselective methylation was attained with aliphatic aldehydes. Chemical yields were fairly good, and **3e** and **3f** were obtained in both 99% ee. The reaction of halogenated benzaldehyde proceeded in good yields except for *ortho*-fluorinated aldehyde **2j**. *ortho*-Chlorinated one **2i** gave high chemical yield, but low ee probably due to steric hindrance. Ester or ketone groups did not disturb this reaction, and gave **3k** and **3l** in good yields and ee's.

For the recovery of **1**, fluoruous phase separation technique was applied to this reaction. After the reaction using aldehyde (0.25 mmol) and **1** (0.05 mmol), the reaction mixture was quenched with 10% HCl (more than 5 mL), then hexane (3 mL) and perfluorohexane (5 mL) were added. The resulting mixture was shaken vigorously for the efficient extraction. After collection of bottom phase, further 5 mL of perfluorohexane was added for the next extraction. For the complete recovery of **1**, three times extraction in total were necessary. Evaporation of the collected perfluorohexane phase under vacuum gave **1** in 93% recovery and 98% purity. From the upper organic phase, the product was obtained by usual work-up. The use of the recovered ligand without purification gave **1** in 86% yield with 92% ee. We have reported similar seven times recycled use of **1** on the reaction of diethylzinc,^{3b} and believe **1** can be used for this methylation repeatedly without loss of any activity.

In conclusion, titanate complex of **1** prepared by mixing **1** and Ti(O^{*i*}Pr)₄ induced high enantioselective methylation of aldehyde. In this reaction, (CH₃)₂Zn prepared from ZnCl₂ and CH₃MgBr in a mixing ratio of 1:2 was effective. This provided the same enantioselectivity as pure (CH₃)₂Zn but in better chemical yield. Namely, magnesium salts must have increased the reactivity of **1** without disturbing the asymmetric inductivity. This methylation was applicable to a variety of aldehydes. The detailed study of mechanism is now under investigation.

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