Enantioselective Alkylation of Aldehydes with Diethylzinc Using a New Catalyst System, ((*R*)-Thiolan-2-yl)diphenylmethanol and Metal Alkoxides

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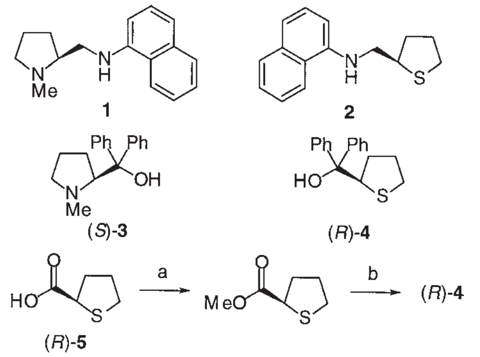
(Received November 2, 2001; CL-011100)

Various optically active secondary alcohols are obtained by asymmetric alkylation of aldehydes with diethylzinc by way of a new catalyst system, ((*R*)-thiolan-2-yl)diphenylmethanol and several metal alkoxides. The transition states are also discussed in terms of experimental results and theoretical calculation.

Synthesis of optically active secondary alcohols is one of the most important subjects in producing chiral organic molecules. Asymmetric reductions of ketones and asymmetric additions of alkyl metal reagents to aldehydes are the two general methods for obtaining such compounds, and the latter method using dialkylzinc has extensively been studied in these two decades. In 1984, Oguni *et al.* found that natural L-amino acid derived-amino alcohols accelerated the addition reaction of diethylzinc to aldehydes to yield the corresponding alcohols with moderate enantioselectivities.[1] After that report, several effective asymmetric catalysts including modified amino alcohols, diols, sulfonamides and metal salts of these compounds were developed for the synthesis of optically active secondary alcohols.[2] While almost all the chiral catalysts which gave rigid transition states contained nitrogen to coordinate to the metal part, there were few that contained sulfur in place of nitrogen.[3]

In 1991, Mukaiyama *et al.* reported an asymmetric aldol reaction by using tin(II) trifluoromethanesulfonate which coordinated with [((*R*)-thiolan-2-yl)methyl]naphthylamine (**2**),[4] an analogue of chiral diamine **1**. On the other hand, Soai *et al.* found that ((*S*)-1-methylpyrrolidin-2-yl)diphenylmethanol (**3**) worked effectively as a catalyst in the enantioselective alkylation of aldehydes with diethylzinc.[5] In this communication, we would like to describe synthesis of a novel chiral ligand having sulfur followed by asymmetric ethylation of aldehydes by using metal alkoxides derived from the sulfur ligand.

As shown in Scheme 1, ((*R*)-thiolan-2-yl)diphenylmethanol (**4**)[6] was synthesized from the corresponding optically active carboxylic acid **5** which was prepared by Claeson *et al.* in 1966.[7] Enantiomeric purity of **4** was determined by HPLC.



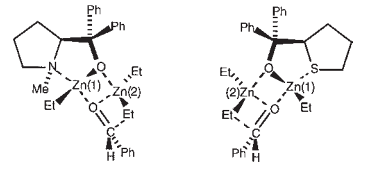
Scheme 1. Synthesis of chiral ligand **4**: a) MeI, DBU, Et_2O, RT, 89%; b) PhMgBr, THF, 0 °C, 81%, HPLC (CHIRALCEL OJ, ^{i}PrOH/ hexane = 1/39, flow rate = 0.5 mL/min): $t_R = 22.6$ min (<0.5%), $t_R = 30.8$ min (>99.5%).

At first, a solution of diethylzinc in hexane was added to a solution of benzaldehyde in hexane in the presence of 20 mol% of **4**. The alkylation proceeded slowly at 0 °C, and 1-phenylpropanol (**6**) was obtained in 69% yield after 20 h. Although the ee was not high (22%), an interesting result was observed; that is, the sense of optical rotation of **6** showed that the carbinol carbon in the adduct had *S*-configuration and it was of the opposite stereochemistry of C2 in chiral ligand **4**. It was already known that the asymmetric alkylation of benzaldehyde with diethylzinc using chiral amino alcohol **3** gave **6** with high enantioselectivity and that the carbinol carbon in the product had the same absolute stereochemistry of C2 in **3**.[5] Therefore, it was assumed that there was a distinctive difference of the transition states between the reactions using **3** and **4**.

Transition structure of the reaction of dimethylzinc with formaldehyde in the presence of zinc alkoxide of 2-aminoethanol (**7**) was calculated by Yamasaki and Noyori at HF/3-21G* level in 1995.[8] Here, so-called *anti*-ts included two zinc atoms and was proved to be the most stable structure of all, which led other theoretical examinations using QM/MM method to develop and apply the results into advanced complex molecules.[9] We also found several transition states to give ethanol by the addition of dimethylzinc to formaldehyde in the presence of a catalyst generated from 2-methylthioethanol (**8**) as a model ligand.[10] The existence of only one imaginary frequency for each structure and the analysis of these vibration sequences showed that these are certainly the transition structure to give ethanol. Similarly, it was calculated that the lowest energy structure of transition state among these conformers was *anti*-ts ($\nu_\mathrm{i} = 195.15\,\mathrm{cm}^{-1}$) when **8** was used, and so-called *syn*-ts ($\nu_\mathrm{i} = 189.75\,\mathrm{cm}^{-1}$) was the second stable ts.[8] However, the energy difference in the case of using **8** between *anti*-ts and *syn*-ts was smaller (1.4 kcal/mol) compared to that of using **7** (3.4 kcal/mol). The above observation showed that the structure of the complex consisted of **8**, formaldehyde and dimethylzinc was too flexible to give high ee for the enantio-face selective alkylation since the bond length between sulfur and zinc was very long (S–Zn = 2.690 Å, N–Zn = 2.054 Å).

Based on the above hypothesis, it was considered that the transition structure (**4**-*anti*-ts) generated from diethylzinc, benzaldehyde and zinc alkoxide of sulfur ligand **4** would be looser than that of **3**-*anti*-ts generated from diethylzinc, benzaldehyde and zinc alkoxide of amino alcohol **3** (Scheme 2). Therefore, it was assumed that the flexibility of **4**-*anti*-ts may allow the reaction to proceed *via* several other transition states to give the corresponding adducts at random.

In order to attain satisfactory enantioselectivity using the above mentioned ligand **4**, it was planned for Zn(1) or Zn(2) to be replaced with different element by using other metal alkoxides except zinc



3-*anti*-ts **4**-*anti*-ts

Scheme 2.

salt. Actually, (*R*)-**6** was obtained with moderate enantioselectivity (37% ee) when the reaction of diethylzinc with benzaldehyde was carried out in the presence of a titanium alkoxide generated from 20 mol% of **4** with 20 mol% of $Ti(O^iPr)_4$ in refluxed toluene for 2 h prior to use. After examining the solvents and the molar ratios of $Ti(O^iPr)_4$ to **4**, the desired (*R*)-**6** was obtained with good ee (74%) at 0 °C in a mixed solvent (*o*-xylene/hexane=3/2) by using 20 mol% of **4** and 10 mol% of $Ti(O^iPr)_4$.

Since there was a possibility for metal salts other than ziac alkoxide of **4** also to be utilized for the asymmetric alkylation of aldehydes,[11] various commercially available metal salts were tried in the enantioselective alkylation. It was then found that the reaction using some kinds of metal alkoxides with 20 mol% of **4** at 0 °C gave good to high enantioselectivities as shown in Table 1.[12]

Table 1. Synthesis of optically active **6** using several alkoxides

Entry	$M(O^iPr)_n$ (mol%)	Yield/%	ee/%	Configuration
1[a]	none	69	22	*S*
2[b]	$B(O^iPr)_3$ (10)	52 (32)[e]	92 (91)[e]	*R*
3[b]	$Sc(O^iPr)_3$ (20)	58	89	*R*
4[b]	$Ge(O^iPr)_4$ (20)	44	90	*R*
5[b]	$Sn(O^iPr)_4$ (20)	42	90	*R*
6[c]	$Ti(O^iPr)_4$ (10)	41	74	*R*
7[d]	$Zr(O^iPr)_4$ (10)	68	90	*R*

[a]Hexane was used as a solvent. [b]A mixture of toluene and hexane (3 : 2) was used as a solvent. [c]A mixture of *o*-xylene and hexane (3 : 2) was used as a solvent. [d]A mixture of mesitylene and hexane (3 : 2) was used as a solvent. [e]20 mol% of $B(O^iPr)_3$ was used.

Next, the transition states that form ethanol were calculated by the reaction of formaldehyde with dimethylzinc in the presence of boron alkoxide generated from **8** and $B(OMe)_3$ (See Figure 1). It was assumed that this complex was formed after the ligand exchange between dimethylzinc and boron alkoxide of **8**.[13] In this structure, zinc chelated by sulfur and oxygen was located inside the complex, and migration of methyl group proceeded *via* 4-membered ring transition structure. On the other hand, boron was coordinated with oxygen in zinc alkoxide of **8** to form stable 4-membered ring structure which included two oxygens and two metallic species.

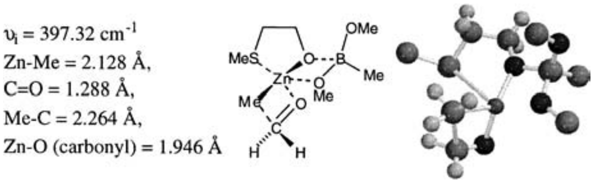


Figure 1. Calculated transition structure forming ethanol by methylation of formaldehyde. Some hydrogens have been omitted for clarity.

Several examples of the synthesis of optically active secondary alcohols *via* the reaction of the corresponding aldehydes with diethylzinc using 20 mol% of **4** and 10 mol% of $B(O^iPr)_3$ are shown as follows; (yield/%, ee/% (configuration)), $4\text{-}ClC_6H_4CHO$ (62, 85 (*R*)), $4\text{-}CF_3C_6H_4CHO$ (61, 87 (*R*)), (*E*)-PhCH = CHCHO (61, 69 (*R*)), $PhCH_2CH_2CHO$ (49, 66 (*R*)), $^nC_8H_{17}CHO$ (40, 72 (*R*)). As a result, it was proved that the present catalyst system efficiently promoted the reaction not only of aromatic aldehydes but also of aliphatic aldehydes to form the desired alcohols with good to high ee.

Thus, asymmetric alkylation of aldehydes to give the corresponding optically active secondary alcohols by using a new ligand **4** combined with several metal alkoxides was developed. The hypothesis that the reaction using **4** proceeded *via* the transition state that possesses zinc chelated by sulfur and oxygen was supported experimentally as the similar enantioselectivities were observed with the use of various metal alkoxides. Other applications and further studies on mechanism of the present reaction are now in progress.

We dedicate this paper to Professor Teruaki Mukaiyama on the celebration of his 75th birthday.

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