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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1013–1016

Catalytic enantioselective addition of diethylzinc to aldehydes using aziridine based chiral ligands

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Received 28 March 2007; accepted 12 April 2007

Abstract—The readily available ferrocenyl substituted aziridinylmethanol **1** (FAM-**1**) was used as a chiral catalyst in the diethylzinc addition reaction to aromatic and aliphatic aldehydes to give secondary alcohols in high yields and up to 99% enantiomeric excess at room temperature. The catalyst can be recovered and used without losing its activity.

1. Introduction

Carbon–carbon bond forming reactions by the addition of organometallic reagents to carbonyl compounds in the presence of a chiral ligand are one of the most studied in the field of asymmetric synthesis. In this sense, asymmetric diethylzinc addition to prochiral aldehydes provides a general method for the preparation of chiral secondary alcohols.[1] After Oguni's first work[2] and Noyori's discovery of DAIB as an excellent catalyst[3] in diethylzinc additions to aldehydes, many catalysts have been reported in the literature. Chiral ligands with a ferrocenyl group[4] in the structure have gained much attention in recent years and some of these ligands have been tested in diethylzinc addition reactions to aldehydes.[1d] There are also a number of recent studies on the use of aziridine based chiral catalysts in diethylzinc addition reactions to aldehydes. For example, Tanner et al. have screened a number of aziridines including C-2 symmetric ones;[5] Zwanenburg et al. have used *N*-tritylaziridinyl(diphenyl)methanol and its polymer supported derivative;[6] Wang et al. have used *N*-ferrocenylmethyl aziridino alcohols as chiral catalysts;[7] Shi et al. have used a C-2 symmetric aziridine as a catalyst;[8] Finally, Page et al. studied aziridinylmethanols with different substituents on nitrogen.[9] Although many chiral ligands have been synthesized to induce asymmetry in these reactions, there is still a need to develop new chiral catalysts that are (1) easy to obtain as both enantiomers and (2) are efficient at low catalyst loading and at ambient temperature. It is also desirable to have a catalyst that does not require titanium isopropoxide used in more than 1 equiv.[10]

We recently reported a new set of chiral FAM ligands **1**–**4**, ferrocenyl substituted aziridinylmethanols, for enantioselective asymmetric azomethine ylide cycloaddition reactions. One of these ligands **2** produced pyrrolidines in up to 95% ee.[11] These ligands were also used in the enantioselective diethylzinc addition to enonones to obtain β-ethylated ketones in up to 80% ee.[12] The performance of these catalysts has also been tested in enantioselective diethylzinc addition reactions to aldehydes. Herein, we report that FAM-ligand **1** serves as an excellent catalyst for diethylzinc additions to aldehydes.

2. Results and discussion

Chiral FAM-ligands **1**–**4** (Fig. 1) were synthesized by using the literature procedure.[11]

First, the catalytic performances of these ligands were tested in diethylzinc addition reactions starting with ligand **1** (Table 1). Using *p*-anisidine and 15 mol % of this ligand with 2 equiv of Et_2Zn at 0 °C, 1-(4-methoxyphenyl)-1-propanol was obtained in 98% yield and 92% ee after 14 h reaction time. When the reaction was repeated with benzaldehyde under the same conditions, the product was obtained with 89% yield and 96% ee. Next we determined reaction conditions with regards to ligand loading and

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doi:10.1016/j.tetasy.2007.04.013

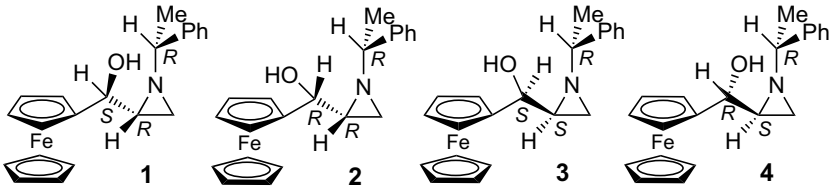
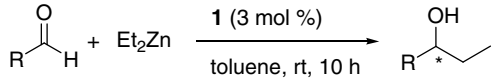


Figure 1. Chiral Fam-ligand **1**–**4**.

temperature using **1**. When the reaction was carried out at rt and 0.25 M concentration, the product was formed in about the same yield and ee (99% and 92%, respectively) after 5 h (entry 1). Upon lowering the ligand loading to 3 mol % and increasing the concentration to 0.3 M, the product was obtained in 93% yield and 90% ee at rt after 10 h (entry 2). Ligand **1** was also tested at 1 mol % but the reaction was slow. As a result, 3 mol % ligand, rt, and 10 h were determined as the standard set of reaction conditions. Ligand **1** was then used in a series of diethylzinc addition reactions to a standard set of aromatic, aliphatic, and α,β-unsaturated aldehydes. The results of diethylzinc addition to these aldehydes in the presence of chiral ligand **1** are shown in Table 1.

As can be seen from the results, ligand **1** catalyzes the enantioselective diethylzinc addition to aromatic aldehydes having electron-donating and electron-withdrawing groups on the aromatic ring in good to excellent yields (80–99%) and the enantioselectivities (86–98%). The same ligand **1** is also effective in enantioselective addition of diethylzinc to an α,β-unsaturated aldehyde by forming the product in 96% yield and 84% ee (entry 12). The catalytic effect of ligand **1** was also tested for aliphatic aldehydes. When heptanal was used, enantioselective diethylzinc addition reaction gave the product in 89% yield and 84% ee (entry 20). When cyclohexanecarbaldehyde was used as the aldehyde, secondary alcohol was obtained in low yield (52%) but excellent ee (94%, entry 22). Low yields for aliphatic aldehydes were also observed in previous studies.[6a,7b,10b] Ligand **1** can be recovered in more than 90% yield and used without losing its activity (entries 3, 15, and 18). Using the same reaction conditions, the catalytic performance of other ligands **2**–**4** was also tested. Ligands **2** and **3** were clearly inferior, for example with *p*-anisidine yields were 42% and 53%, ee's were 39% and 26%, respectively (entries 4 and 5). Quasie-

Table 1. Catalytic asymmetric diethylzinc addition to aldehydes[a]



Entry	aldehyde	Ligand	Yield[b] (%)	ee[c] (%)	Config[d]
1	*p*-$MeOC_6H_4CHO$	**1**[e]	99	92	*R*
2	*p*-$MeOC_6H_4CHO$	**1**	93	90	*R*
3	*p*-$MeOC_6H_4CHO$	**1**[f]	97	87	*R*
4	*p*-$MeOC_6H_4CHO$	**2**	42	39	*R*
5	*p*-$MeOC_6H_4CHO$	**3**	53	26	*S*
6	PhCHO	**1**	88	96	*R*
7	PhCHO	**4**	83	88	*S*
8	*p*-$CF_3C_6H_4CHO$	**1**	81	98	*R*
9	*p*-BrC_6H_4CHO	**1**	80	98	*R*
10	*p*-CNC_6H_4CHO	**1**	>99	93	*R*
11	*o*-$MeOC_6H_4CHO$	**1**	91	86	*R*
12	PhCH=CHCHO	**1**	96	84	*R*
13	PhCH=CHCHO	**4**	85	80	*S*
14	2-NaphthylCHO	**1**	>99	92	*R*
15	2-NaphthylCHO	**1**[f]	>99	94	*R*
16	2-NaphthylCHO	**4**	98	81	*S*
17	FcCHO	**1**	88	98	*R*
18	FcCHO	**1**[f]	93	>99	*R*
19	FcCHO	**4**	80	88	*S*
20[g]	*n*-$C_6H_{13}CHO$	**1**	89	84	*R*
21	*n*-$C_6H_{13}CHO$	**4**	85	82	*S*
22[g]	*c*-$C_6H_{11}CHO$	**1**	52	94	*R*

[a] All the reactions except for entry 1 were carried out at room temperature with 3 mol % catalyst loading.
[b] Yields are isolated yields.
[c] Determined by chiral HPLC except entry 10 which was based on the literature specific rotation value.[13]
[d] Determined by comparing with literature absolute optical rotation values.
[e] 5 mol % ligand loading.
[f] The recovered ligand was used.
[g] ee was determined by chiral HPLC using benzoate ester.

nantiomeric[14] ligand **4**, on the other hand, gave the products in good yields and enantioselectivities (entries 7, 13, 16, 19, and 21). In each case, the product was obtained with an opposite configuration when compared to the product obtained with ligand **1**.

The stereogenic center on the aziridine ring plays the main role in determining the configuration of the stereogenic center of the product. Chiral ligands **1** and **2** with an (*R*)-configuration at aziridine center gave the products with an (*R*)-configuration. Likewise, chiral ligands **3** and **4** with an (*S*)-configuration at the aziridine center gave the products with an (*S*)-configuration. These results are in line with the results of the previous enantioselective diethylzinc addition reactions carried out with aziridine based chiral ligands.

We propose the transition state in Figure 2 to account for the stereoselectivity observed with chiral ligand **1**. In this transition state, the ethyl group is delivered from the *re*-face of the aldehyde to give the product with an (*R*)-configuration. The R group of the aldehyde is farther away from the bulky group on the ligand nitrogen.

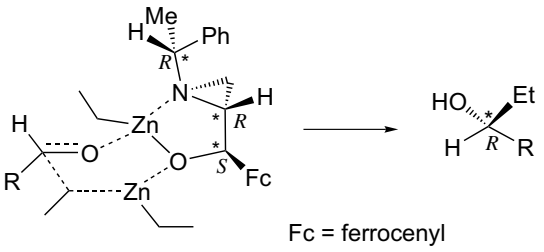


Figure 2. Proposed TS for the reaction involving (*R*,*R*,*S*)-Fam **1** ligand.

3. Conclusion

In conclusion, we have developed a highly effective, new chiral catalyst for the diethylzinc addition reactions to aldehydes. Using 3 mol % of this chiral catalyst, secondary alcohols can be obtained in up to 99% yields and 99% ee's. The sense of induction was found to be dependent on the configuration of the aziridine ring. Thus both enantiomers of the secondary alcohols can be obtained with the desired configuration by choosing the appropriate ligand. The advantages of these catalysts are ease of preparation[11] (prepared on a gram scale), efficiency at low catalyst loading, and high enantioselectivities at ambient temperatures. Another advantage of these catalysts is that their antipodes can be easily synthesized starting from (*S*)-methylbenzylamine. The catalytic effect of these ligands for other asymmetric reactions is currently under investigation in our laboratory and will be reported in due course.

4. Experimental

4.1. General

All of the reactions were performed in flame-dried glassware under an atmosphere of argon. Toluene was dried and distilled over sodium prior to use. Products were purified by flash column chromatography on silica gel 60 (MERCK Co.) (230–400 mesh ASTM). TLC analyses were performed on 250 μm Silica Gel 60 F254 plates and visualized by quenching of UV fluorescence ($\lambda_{max} = 254$ nm). Optical rotations were measured by using a Rudolph Autopol III polarimeter. ^{1}H NMR samples were prepared in $CDCl_3$–CCl_4 (1:1 mixture) and recorded at 400 MHz on Brucker Spectrospin Avance DPX-400 Ultra shield instrument. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$ ppm) for ^{1}H NMR (7.26 ppm). Optical rotation was obtained on a Perkin–Elmer 241 polarimeter. Enantioselectivities were determined by HPLC analysis and performed with a Dionex HPLC device equipped with an P-680A pump, UVD 170U UV detector.

4.2. Representative procedure for catalytic enantioselective diethylzinc addition to aldehydes (Table 1, entry 6)

Diethylzinc (1.1 mL, 1 M solution in hexane) was added to a stirred solution of chiral ligand (0.017 mmol, 560 μL used from 0.03 M stock solution in toluene) in toluene (1.0 mL) under Ar at room temperature. After stirring the resulting reaction mixture at this temperature for 30 min, benzaldehyde (0.05 mL, 0.55 mmol) was added. Stirring was continued for 10 h at room temperature. At the end of this period, the reaction mixture was diluted with EtOAc (10 mL), quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the two layers were separated. The aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography on silica gel using 7:1 hexane/EtOAc. 1-Phenyl-1-propanol was obtained in 88% yield (66 mg, 0.484 mmol). Chiral HPLC was used to determine the ee.

4.2.1. 1-(4-Methoxyphenyl)-1-propanol (Table 1, entry 2). (Chiralcel OD-H column, 1.0 mL/min, 5% *i*-PrOH in hexane); retention times: 13.64 min [major (*R*)-enantiomer] and 16.10 min [minor (*S*)-enantiomer] $[\alpha]_D^{20} = +34.0$ (*c* 2.60 $CHCl_3$) for (*R*)-enantiomer with ee = 90%. Lit.[15] $[\alpha]_D^{24} = -28.3$ (*c* 2.20, C_6H_6) for (*S*)-enantiomer with ee = 87%.

4.2.2. 1-Phenyl-1-propanol (Table 1, entry 6). (Chiralcel OD column, 1.0 mL/min, 2% *i*-PrOH in hexane); retention times: 19.35 min (major (*R*)-enantiomer) and 21.73 min [minor (*S*)-enantiomer] $[\alpha]_D^{20} = +30.2$ (*c* 2.20, $CHCl_3$) for (*R*)-enantiomer with ee = 96%. Lit.[15] $[\alpha]_D^{24} = -36.6$ (*c* 0.99, $CHCl_3$) for (*S*)-enantiomer with ee = 81%.

4.2.3. 1-(*p*-Trifluoromethylphenyl)-1-propanol (Table 1, entry 8). (Chiralcel OJ-H column, 1.0 mL/min, 2% *i*-PrOH in hexane); retention times: 17.97 min (major (*R*)-enantiomer) and 16.40 min [minor (*S*)-enantiomer] $[\alpha]_D^{20} = +18.6$ (*c* 3.4, $CHCl_3$) for (*R*)-enantiomer with ee = 98%. Lit.[16] $[\alpha]_D = +19.5$ (*c* 3.2, CH_3OH) for (*R*)-enantiomer with ee = 78%.

4.2.4. 1-(4-Bromophenyl)-1-propanol (Table 1, entry 9). (Chiralcel OB column, 0.3 mL/min, 3% *i*-PrOH in hexane); retention times: 33.19 min (major (*R*)-enantiomer) and

29.18 min [minor (*S*)-enantiomer] $[\alpha]_D = +26.7$ (*c* 1.50, $CHCl_3$) for (*R*)-enantiomer with ee = 98%. Lit.[17] $[\alpha]_D^{20} = +15.8$ (*c* 1.49, C_6H_6) for (*R*)-enantiomer with ee = 90.3%.

4.2.5. 1-(4-Cyanophenyl)-1-propanol (Table 1, entry 10). $[\alpha]_D^{20} = +31.6$ (*c* 0.5, $CHCl_3$) for (*R*)-enantiomer with ee = 93%. Lit.[13] $[\alpha]_D^{23} = +23.2$ (*c* 11.0, $CHCl_3$) for (*R*)-enantiomer with ee = 69%.

4.2.6. 1-(2-Methoxyphenyl)-1-propanol (Table 1, entry 11). (Chiralcel OD column, 0.5 mL/min, 3% *i*-PrOH in hexane); retention times: 27.36 min [major (*R*)-enantiomer] and 24.77 min [minor (*S*)-enantiomer] $[\alpha]_D^{20} = +17.6$ (*c* 4.1, $CHCl_3$) for (*R*)-enantiomer with ee = 86%. Lit.[15] $[\alpha]_D^{22} = -36.0$ (*c* 0.71, $C_6H_5CH_3$) for (*S*)-enantiomer with ee = 59%.

4.2.7. (*E*)-1-Phenyl-1-penten-3-ol (Table 1, entry 12). (Chiralcel OD column, 1.0 mL/min, 5% *i*-PrOH in hexane); retention times: 13.65 min [major (*R*)-enantiomer] and 23.95 min [minor (*S*)-enantiomer] $[\alpha]_D^{20} = +4.3$ (*c* 2.1, $CHCl_3$) for (*R*)-enantiomer with ee = 84%. Lit.[15] $[\alpha]_D^{24} = -6.3$ (*c* 1.73, $CHCl_3$) for (*S*)-enantiomer with ee = 88%.

4.2.8. 1-(2-Naphthyl)-1-propanol (Table 1, entry 14). (Chiralcel OD column, 0.5 mL/min, 10% *i*-PrOH in hexane); retention times: 27.72 min [major (*R*)-enantiomer] and 25.81 min (minor (*S*)-enantiomer) $[\alpha]_D^{20} = +35.1$ (*c* 2.4, $CHCl_3$) for (*R*)-enantiomer with ee = 92%. Lit.[15] $[\alpha]_D^{24} = -19.2$ (*c* 1.79, C_6H_6) for (*S*)-enantiomer with ee = 91%.

4.2.9. 1-Ferrocenyl-1-propanol (Table 1, entry 17). (Chiralcel OD column, 0.5 mL/min, 10% *i*-PrOH in hexane); retention times: 13.67 min [major (*R*)-enantiomer] and 14.55 min (minor (*S*)-enantiomer) $[\alpha]_D^{20} = -66.5$ (*c* 4.9, $CHCl_3$) for (*R*)-enantiomer with ee = 98%. Lit.[18] $[\alpha]_D^{20} = +56$ (*c* 1.4, C_6H_6) for (*S*)-enantiomer with ee = 94%.

4.2.10. 3-Nonanol (as benzoate) (Table 1, entry 20). (Chiralcel OD-H column, 1.0 mL/min, hexane); retention times: 15.20 min (major (*R*)-enantiomer) and 14.38 min [minor (*S*)-enantiomer].

4.2.11. 1-Cyclohexyl-1-propanol (as benzoate) (Table 1, entry 22). (Chiralpak AD column, 1.2 mL/min, 3% *i*-PrOH in hexane); retention times: 11.44 min (major (*R*)-enantiomer) and 12.61 min [minor (*S*)-enantiomer].

Acknowledgments

The authors thank Scientific and Technical Research Council of Turkey (TUBITAK, Grant No. 106T071), the Middle East Technical University, and Kirikkale University Research Foundations for the financial support.

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