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Catalytic Asymmetric Nitroaldol (Henry) Reaction with a Zinc-Fam Catalyst

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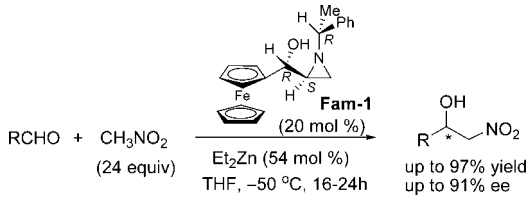

Ferrocenyl-substituted aziridinylmethanol (Fam-**1**) was used as a catalyst with zinc for the asymmetric nitroaldol (Henry) reaction. This catalyst worked with a variety of aldehydes (aromatic, aliphatic, α,β-unsaturated, and heteroaromatic) and α-ketoesters to give the nitroaldol product in up to 97% yield and 91% ee. The chiral ligand can be recovered and recycled without losing its activity.

The asymmetric nitroaldol or Henry reaction is one of the important carbon−carbon bond formation reactions.[1] The product obtained from this reaction is highly valuable as the starting material for 1,2-amino alcohols and β-hydroxy acids.[2] The development of new chiral catalysts for this important reaction has attracted the interest of many groups.[3] Although a reasonable number of catalysts having copper as the metal were reported to induce high enantiselectivity, only a few catalysts having zinc as the metal are known. Trost et al. reported the first efficient dinuclear ligand for the zinc catalyst for the asymmetric Henry reaction. This catalyst worked efficiently with aliphatic and aromatic aldehydes to give the nitroaldol products in up to 90% yield and 93% ee.[3d,e] Another zinc catalyst was reported by Palamo et al. They employed 30 mol % of $Zn(OTf)_2$ and 45 mol % of (+)-*N*-methylephedrine as the catalyst in the reaction of aliphatic and aromatic aldehydes to give nitroaldol products in 68−92% yields and with ee's of mostly above 90%.[3k] Another zinc catalyst, reported by Lin et al., gave the products in good yields but in low ee's, the highest ee being 74%.[3i] Very recently, Wolf et al. reported another efficient zinc catalyst for the asymmetric Henry reaction of aliphatic and aromatic aldehydes.[3y] This catalyst yields nitroaldol products in up to 99% yield and 95% ee. Two other zinc catalysts reported by Reiser et al.[3f] and Demirel et al.[3v] did not work very efficiently, and both the yields and ee's were quite low. We recently reported a new set of chiral ferrocenyl-substituted aziridinylmethanols Fam ligands **1**−**4** (Figure 1). These ligands were used for enantioselective asymmetric azomethine ylide cycloaddition reactions to produce pyrrolidines in up to 95% ee,[4] for enantioselective diethylzinc addition to enones to produce β-ethylated ketones in up to 80% ee,[5] for enantioselective diethylzinc addition to aldehydes to produce secondary alcohols in up to 99% ee,[6] and for alkynylzinc addition to aldehydes to produce propargylic alcohols in up to 98% ee.[7] The performance of these ligands has been tested for the zinc-catalyzed enantioselective Henry or nitroaldol reaction. Herein, we wish to report that ligand Fam-**1** serves as a good catalyst for the nitroaldol reaction.

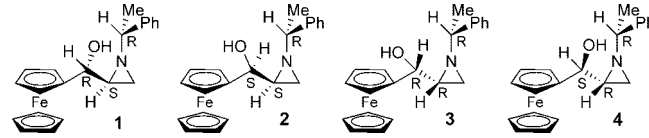

FIGURE 1. Structures of chiral ligands Fam **1**−**4**.

Chiral ligands Fam **1**−**4** (Figure 1) were prepared[4] in three easy steps starting with readily available acryloyl ferrocene[8] on gram scales in enantiomerically pure forms by employing

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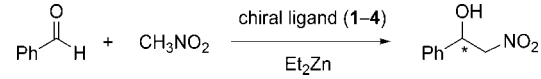
TABLE 1. Nitroaldol Reaction of Benzaldehyde and Nitromethane under Different Conditions



entry	ligand	ligand (mol %)	$MeNO_2$ (equiv)	Et_2Zn (mol %)	T (°C)	Et_3N (mol %)	solvent	concn (M)	% yield[a]	% ee[b]
1	**1**	10	6	18	−50	5	THF	0.24	78	59
2	**2**	10	6	18	−50	5	THF	0.24	57	27
3	**3**	10	6	18	−50	5	THF	0.24	72	15
4	**4**	10	6	18	−50	5	THF	0.24	77	41
5	**1**	10	6	18	−50	5	Et_2O	0.24	41	22
6	**1**	10	6	18	−50	5	DCM	0.24	33	32
7	**1**	10	6	18	−50	5	MeCN	0.24	22	11
8	**1**	10	3	18	−50	5	THF	0.24	23	26
9	**1**	10	12	18	−50	5	THF	0.24	82	29
10	**1**	10	6	9	−50	5	THF	0.24	27	5
11	**1**	10	6	36	−50	5	THF	0.24	62	59
12	**1**	10	6	18	−40	5	THF	0.10	49	71
13	**1**	10	9	18	−40	5	THF	0.10	63	77
14	**1**	5	9	18	−40	5	THF	0.10	62	57
15	**1**	15	9	18	−40	5	THF	0.10	61	45
16	**1**	10	6	18	−20	5	THF	0.10	90	64
17	**1**	10	6	18	−50	–	THF	0.24	29	57
18	**1**	10	12	18	−50	–	THF	0.24	54	45
19	**1**	10	12	54	−20	–	THF	0.10	36	65
20	**1**	15	6	54	−50	–	THF	0.24	35	88
21[c]	**1**	15	24	54	−50	–	THF	0.24	66	85
22	**1**	20	24	54	−50	–	THF	0.24	83	87
23[c]	**1**	20	24	54	−50	–	THF	0.24	87	86

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Reaction time was 24 h.

the Gabriel−Cromwell reaction.[9] First, ligands **1**−**4** were screened as catalysts for the enantioselective nitroaldol reaction between benzaldehyde and nitromethane in the presence of diethylzinc. Results of these studies are summarized in Table 1. As can be seen from this table, ligand **1** gave the highest ee (Table 1, entries 1−4). Therefore, we continued optimization studies with this ligand. Reactions using diethylether, dichloromethane, or acetonitrile in the place of THF gave the product in low yield and enantioselectivity (Table 1, entries 5−7). When the amount of nitromethane was lowered to 3 equiv, the yield and ee dropped to 23% and 26%, respectively (Table 1, entry 8). Increasing the amount of nitromethane to 12 equiv increased the yield to 82% while the ee remained almost the same (Table 1, entry 9). Optimization experiments at −40 °C and lower reaction concentration (Table 1, entries 12−15) were also not very successful, the highest enantioselectivity being 77% and the yield was around 60%. When the reaction was carried out at −20 °C, the highest yield was reached but again, the enantioselectivity was not satisfactory (Table 1, entry 16).

We have also carried out experiments without using amine (Table 1, entries 17−23). Under the same reaction conditions as in entry 1 but without the amine, the nitroaldol product was obtained in low yield with about the same ee (Table 1, entry 17). Doubling the amount of nitromethane to 12 equiv increased the yield as expected to 54% but lowered the ee to 45% (Table 1, entry 18). Further optimizations showed that good yields and ee's can be obtained for the enantioselective nitroaldol reaction by using 20 mol % of ligand **1**, 24 equiv of nitromethane, and 54 mol % of diethylzinc at −50 °C. Under these conditions, the reaction was also repeated in the presence of amine (5 mol %), giving the product in almost quantitative yield and 66% ee.

After determining the optimum conditions, the scope of the reaction was explored with different aldehydes. The results are summarized in Table 2. As can be seen from this table, the nitroaldol reaction with aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehydes gave the product in good yields and enantioselectivities. In the case of aromatic aldehydes, the substituents on the aromatic ring did not show a significant effect on the enantioselectivity, which varied between 82 and 91% except in the case of anisaldehyde (Table 2, entries 1−11). For most of the aromatic aldehydes, yields were above 80% and moderate for *p*-Br, *p*-CF_3, and *o*-Cl substituted ones. Extending the reaction time from 16 to 24 h had a significant effect on the yields for *o*-chlorobenzaldehyde and 1-naphthaldehyde (Table 2, entries 9 and 10). For the remaining aromatic aldehydes, this effect was not so significant. In the case of aliphatic, α,β-unsaturated, and heteroaromatic aldehydes (Table 2, entries 12−18), extending the reaction time increased the yield between 7 and 16%. However, the enantioselectivity remained almost the same except for isobutyraldehyde (Table 2, entry 14). The catalytic performance of the Fam-**1** ligand was also tested for α-ketoesters, which have been used as substrates for nitroaldol reactions in only a limited number of studies.[3r,9] Under the same reaction conditions, ethyl pyruvate and ethyl benzoylformate reacted with nitromethane to give nitroaldol products in 88% yield with 86% ee and 85% yield with 82%, respectively (Table 2, entries 19 and 20).

In conclusion, we have shown that a zinc complex with the Fam-**1** ligand serves as a good catalyst for the enantioselective nitroaldol or Henry reaction. It works for a wide spectrum of aldehydes including aromatic, aliphatic, α,β-unsaturated, and heteroaromatic aldehydes. For the aromatic aldehydes, in general, there is no significant effect of the substituents on the

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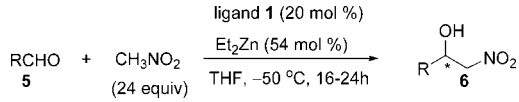
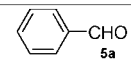
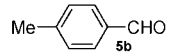
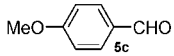
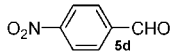
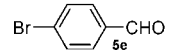
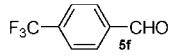
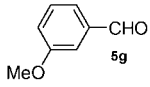
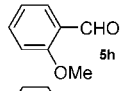
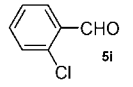
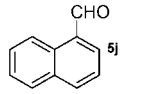
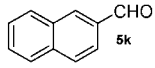
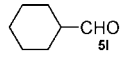
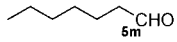
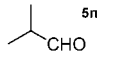
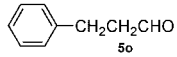
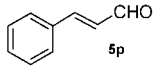
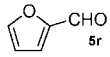
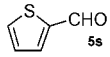
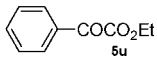
TABLE 2. Nitroaldol Reaction of Various Aldehydes and α-Ketoesters



entry	aldehyde	time (h)	% yield[a]	% ee[b]
1	 5a	16	83	87
		16	86[c]	87[c]
2	 5b	16	77	87
		24	80	86
3	 5c	16	92	75
		16	93[c]	76[c]
4	 5d	16	84	82
		16	82[c]	82[c]
		24	89	77
5	 5e	16	73	89
		24	79	91
6	 5f	16	76	86
		24	77	90
7	 5g	16	84	88
		24	84	83
8	 5h	16	82	82
		24	87	77
9	 5i	16	63	83
		24	75	83
10	 5j	16	77	90
		24	88	86
11	 5k	16	78	86
		16	77[c]	89[c]
		24	82	83
12	 5l	16	84	80
		24	91	78
13	 5m	16	74	71
		16	73[c]	72[c]
		24	88	73
14	 5n	16	71	87
		16	76[c]	86[c]
		24	85	79
15	 5o	16	81	74
		24	97	72
16	 5p	16	72	81
		24	85	78
17	 5r	16	72	85
		24	88	84
18	 5s	16	64	86
		24	73	85
19	$H_3C-COCO_2Et$ 5t	16	88	86
20	 5u	16	85	82

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Obtained from recovered ligand.

yield and enantioselectivity of the reaction. Besides aldehydes, the catalyst developed in this study also works efficiently in the asymmetric Henry reaction of α-ketoesters to give β-nitro-α-hydroxy esters in good yields and ee's. Up to now, no other catalyst has been reported to be effective for a wide variety of substrates. Although the asymmetric nitroaldol reaction requires 20 mol % of the Fam-**1** ligand, the ligand can be recovered in more than 90% yield and used without losing its activity. In addition, its antipode can easily be prepared by using (*S*)-methylbenzylamine at the aziridination step. This will allow the synthesis of nitroaldol products with the opposite configuration.

Experimental Section

General Procedure for the Nitroaldol Reaction. The chiral ligand (1.11 mL, used from a 0.1 M stock solution in THF) was added to a reaction flask under Ar. After cooling the reaction flask to 0 °C, Et_2Zn (0.3 mL, 1.0 M in hexane) was added. After stirring 30 min at this temperature, to this solution was added $MeNO_2$ (0.72 mL, 13.3 mmol). The resulting mixture was stirrred at this temperature for 2 h then cooled to −50 °C, and then benzaldehyde (56 μL, 0.55 mmol) was added (furfural and thiophenealdehyde were freshly distilled). The reaction mixture was stirred for 16 h at this temperature then quenched with a saturated solution of NH_4Cl. After separating the two layers, the aqueous layer was extracted with diethylether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, hexane:EtOAc, 7:1) to provide **6a** (76 mg, 0.46 mmol, 87% ee).

(*R*)-2-Nitro-1-phenylethanol (6a).[3g] ^1H NMR (400 MHz, CCl_4-CDCl_3, ppm): δ 7.35−7.20 (m, 5H), 5.32−5.25 (m, 1H), 4.46−4.40 (dd, 1H, J = 13.1, 9.9 Hz), 4.36−4.32 (dd, 1H, J = 13.1, 3.1 Hz), 3.07 (d, 1H, J = 3.6 Hz). ^{13}C NMR (100 MHz, CCl_4-CDCl_3, ppm): δ 138.3, 128.9, 128.8, 125.9, 81.2, 70.9. HPLC analysis (Chiralcel OD-H column, 0.8 mL/min, 15% *i*-PrOH in hexane). Retention times: 15.64 min [major (*R*)-enantiomer] and 19.56 min [minor (*S*)-enantiomer]. $[\alpha]^{23}_D$ = −37.0 (c = 3.55, $CHCl_3$).

(*R*)-2-Nitro-1-*p*-tolylethanol (6b).[3z] The title compound was prepared according to the general procedure as colorless oil (76.4 mg, 0.42 mmol, 86% ee). ^1H NMR (400 MHz, CCl_4-CDCl_3, ppm): δ 7.27 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz), 5.45−5.38 (m, 1H), 4.62−4.56 (dd, 1H, J = 13.3, 9.6 Hz), 4.50−4.46 (dd, 1H, J = 13.3, 3.0 Hz), 2.78 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 138.9, 135.3, 129.7, 125.9, 81.3, 70.9, 21.1. HPLC analysis (Chiralcel OD-H column, 0.8 mL/min, 15% *i*-PrOH in hexane). Retention times: 16.82 min [major (*R*)-enantiomer] and 21.22 min [minor (*S*)-enantiomer]. $[\alpha]^{23}_D$ = −75.7 (c = 5.30, $CHCl_3$).

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Supporting Information Available: Synthetic procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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