Application of Aziridino Alcohols as Chiral Ligands in Zinc-catalyzed Enantioselective Henry Reaction

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Abstract A pair of diastereoisomeric aziridino alcohols which could be readily prepared from the reaction between (*S*)-α-methylbenzyl amine and methyl acrylate has been used as chiral ligands in zinc-catalyzed enantioselective Henry reaction between nitromethane and arylaldehydes. A moderate enantioselectivity of β-nitroalcohol, up to 64% *ee* value, could be achieved in this catalytic reaction. The possible transition states of the reaction were proposed.

Keywords Henry reaction, zinc catalyst, aziridino alcohol ligand
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The nitro-aldol(Henry) reaction is a carbon-carbon bond-forming reaction in a high atom-economy that facilitates the synthesis of β-hydroxy nitroalkanols which can be readily converted into valuable building blocks, such as conjugate nitroalkenes, α-nitro ketones and β-amino alcohols[1-2]. Thus, its catalytic asymmetric transformation is highly desirable. The breakthrough was made by Shibasaki group by using chiral rare earth complexes as catalysts[3-5]. Since then the development of highly enantioselective catalysts for Henry reaction has been the focus of extensive investigation. Inspired by this, many metal-based catalysts and organocatalysts have been developed and applied into this reaction[6-8]. Among these, copper-based catalysts have been intensively studied by many researchers leading to high levels of stereocontrol with a wide variety of ligands[9-15]. More recently, catalyst systems involving other metals such as cobalt or chromium with chiral salen derivatives afforded β-nitroalcohol in satisfactory yields and enantioselectivities[16-18]. Despite these excellent metal-based catalysts, zinc based catalysts, which is a kind of relatively cheap and non-toxicity complexes, hold a promising position in asymmetric Henry reaction. Trost *et al*[19-20] have designed the first efficient zinc-based catalyst, a dinuclear zinc complex with a chiral semi-aza-crown ligand (**1**), which catalyzed the nitro-aldol reaction with broad substrate scope and afforded the products with a high enantioselectivity. Subsequently, the dinuclear zinc complex catalyzed asymmetric nitroaldol reaction was applied to synthesize β-receptor agonists (*R*)-(−)-denopamine and (*R*)-(−)-arbutamine. Another zinc based catalyst developed by Dogan *et al*[21], with the newly designed ferrocenyl-substituted aziridinylmethanol(**2**) as ligand and zinc as central metal, has proved to be a good catalyst for the enantioselective Henry reaction with broad substrate scope(aromatic, aliphatic, α,β-unsaturated, and heteroaromatic) generating the products with 97% yield, 91% *ee* value. The diketone-derived C_2-symmetric bisoxazolidine ligand(**3**) was developed by

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Wolf et al and has been successfully utilized in the zinc catalyzed asymmetric Henry reaction[22]. This catalyst gave the β-hydroxy nitroalkanes in excellent yields and enantioselectivities for the aromatic as well as aliphatic aldehydes. Two other organozinc catalysts reported by Martell *et al*[23-24] and Lin *et al*[25] (Fig. 1, **4**) gave the adducts in good yields and moderate enantioselectivities. Recently, Bian′s chiral cyclopropane-based 1,4-amino alcohol 6-Zn showed moderate catalytic capability and afforded moderate to good enantiomeric excesses[26-27]. Although many attempts have been made, only a few catalysts having zinc as the metal are known. Therefore, it is of importance to develop new efficient, cheap and easily obtained ligands to this catalytic enantioselective reaction.

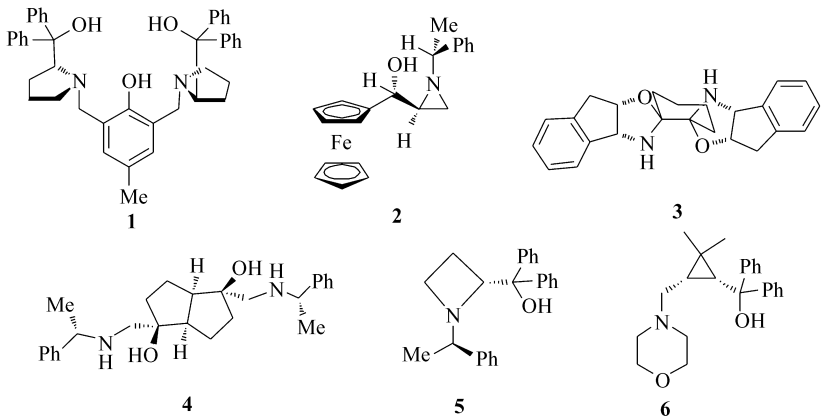
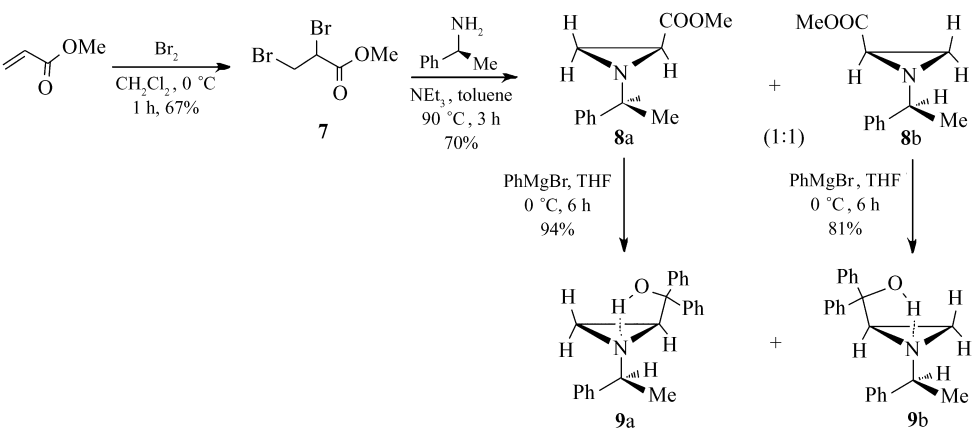


Fig. 1 Chiral amino alcohol ligands for the zinc-catalyzed Henry reaction

In recent years, our group has paid continuing attentions to the synthesis and application of the chiral small-ring nitrogen heterocyclic ligands containing a β-amino alcohol scaffold in the catalytic asymmetric addition reaction. In our previous work[28-29], a series of chiral azetidino amino alcohol ligands(**5**) bearing an additional stereogenic center was prepared and used as catalysts for the asymmetric addition of alkynylzinc to aromatic aldehydes. The experimental results show that the enantioselective level of the reaction is greatly influenced by the second stereogenic centre out of azetidine ring. In addition, ferrocenyl-substituted aziridinylmethanol(**2**)[21] was reported and its structural features accounting for its superior performance had been elucidated. Therefore, in accordance with the above two facts and from the viewpoint of practical usage, the development of a convenient access from a readily available compound as a common chiral source to get a pair of chiral ligands would be very useful and necessary[30-31]. Bearing this in mind, we synthesized a pair of diastereomers(**9**) in only two steps from a single common chiral source according to the concept of conformation design(Scheme 1). The ligands were used in the asymmetric addition of diethylzinc to aldehydes



Scheme 1 Synthetic pathway for the preparation of ligands **9**

affording secondary alcohol in similarly outstanding enantioselectivities and high yields[32]. Herein, we report their application to the asymmetric Henry reaction between aldehydes and nitromethane.

1 Experimental

1.1 General

Except for diethylzinc purchased from Aldrich. Other reagents were purchased in China. Toluene and THF were predried over calcium chloride and then distilled from sodium/benzophenone before use. Melting points were determined using YRT-3 melting point apparatus (Tianjin Tianda Tianfa Technology Co., Led., China) without correction. Optical rotations were measured with model 341 Polarimeter (PerkinEImer, USA) at 20 ℃ in $CHCl_3$. The enantiomeric purity was determined by HPLC using a chiral column with hexane/propan-2-ol (ratio as indicated) as the eluent. The chromatographic system consisted of a model PU-1580 intelligent HPLC pump and a model UV-1575 intelligent UV-Vis detector (254 nm) (JASCO, Japan). The injection loop has a 20 μL capacity. The column used was a Chiralcel OD (250 mm × 4.6 mm) (Daicel Chemical Ind., Ltd, Japan). The column was operated at ambient temperature. TLC was performed on dry silica gel plates developed with hexane/ethyl acetate. NMR spectra (^1H and ^{13}C) were performed on a Bruker DPX 400 (400 MHz) spectrometer (Switzer) using solutions in $CDCl_3$ (referenced internally to Me_4Si). *J* values are given in Hz. IR spectra were determined on a IR 200 spectrophotometer (Thermo Nicolet, America). Mass spectra were obtained using a Bruker esquire-3000 instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. Elemental analyses were determined with a Carlo Erba 1160 elemental analyzer (Switzer).

Compounds **7**, **8**a and **8**b were synthesized according to the literature[33-36].

1.2 Synthesis of ligands 9a and 9b

To the Grignard reagent solution prepared from 0.33 mL (3.12 mmol) bromobenzene in 2 mL THF and 76 mg (3.12 mmol) magnesium in 5 mL THF was gradually added 80 mg (0.39 mmol) compound **8** dissolved in 1 mL THF at 0 ℃ over a period of 30 min. The mixture was then allowed to reach room temperature. After stirring for 6 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 ℃. The organic phase of reaction mixture was separated and the aqueous phase extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by the preparative TLC with Hexane/EtOAc (4∶1, volume ratio) as the developing solvent to give the ligand.

1.2.1 *Diphenyl-(l-((1S)-phenylethyl)aziridin-(2S)-yl)-methanol* (**9***a*) White solid, yield 94%, mp 127 ~ 127.7 ℃. $[\alpha]_D^{20} = +49.0$ (*c* 0.502, in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$), δ: 0.91 (d, *J* = 6.8 Hz, CH_3, 3H), 1.60 (d, *J* = 6.4 Hz, NCH_2, 1H), 1.99 (d, *J* = 3.6 Hz, NCH_2, 1H), 2.55 (dd, *J* = 9.6, 3.6 Hz, NCH, 1H), 2.77 (q, *J* = 6.4 Hz, PhCH, 1H), 4.14 (br, OH, 1H), 7.25 ~ 7.39 (m, PhH, 15H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 23.53 (NCH_2), 30.65 (CH_3), 47.39 (NCH), 68.10 (PhCH), 73.89 (COH), 125.94, 126.67, 126.74, 127.15, 127.22, 128, 128.17, 128.36, 144.20, 144.91, 147.92. IR (KBr pellet), σ/cm^{-1}: 3356, 3084, 3026, 2969, 2828, 1599, 1491, 1448, 1366, 1172, 1032, 991, 932, 748, 697, 642. MS: *m*/*z* (ESI): 329.9 $(M+H)^+$, 351.9 $(M+Na)^+$. Elemental anal. calcd. for $C_{23}H_{23}NO$/%: C 83.85, H 7.04, N 4.25, Found: C 83.68, H 7.351, N 4.225.

1.2.2 *Diphenyl-(l-((1S)-phenylethyl)aziridin-(2R)-yl)-methanol* (**9***b*) White solid, yield 81%, mp 91.4 ~ 92 ℃. $[\alpha]_D^{20} = -50.4$ (*c* 0.660, in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$), δ: 1.41 (d, *J* = 6.8 Hz, CH_3, 3H), 1.52 (d, *J* = 6.4 Hz, NCH_2, 1H), 2.02 (d, *J* = 3.2 Hz, NCH, 1H), 2.48 (dd, *J* = 10, 3.6 Hz, NCH_2, 1H), 2.76 (q, *J* = 6.4 Hz, PhCH, 1H), 3.82 (br, OH, 1H), 6.88 ~ 7.36 (m, PhH, 15H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 22.98 (NCH_2), 30.15 (CH_3), 45.50 (NCH), 69.00 (PhCH), 73.88 (COH), 126.02,

126.21, 126.42, 126.85, 127.02, 127.24, 127.55, 127.95, 128.26, 143.46, 145.43, 146.87. IR (KBr pellet), σ/cm^{-1}: 3356, 3084, 3027, 2969, 2854, 1599, 1491, 1449, 1356, 1170, 1028, 985, 932, 749, 697, 640. MS: m/z (ESI): 329.9 $(M+H)^+$. Elemental anal. calcd. for $C_{23}H_{23}NO$/%: C 83.85, H 7.04, N 4.25, Found: C 83.75, H 7.411, N 4.221.

1.3 General procedure for the asymmetric Henry reaction of arylaldehydes catalyzed by 9a

Under nitrogen atmosphere, the chiral ligand **9**a (16 mg, 20 mol%), DiMPEG (50 mg, 10 mol%, M_w = 2000) were added to a dried Schlenk tube containing THF (0.3 mL). After cooling the Schlenk tube to 0 ℃, diethylzinc (0.3 mL, 120 mol%, 1.0 mol/L in hexane) was added. The resulting mixture was stirred for 0.5 h at room temperature, to this solution was added $MeNO_2$ (0.32 mL, 6 mmol). The resulting mixture was stirring at this temperature for 2 h then cooling to −50 ℃, and then aldehyde (0.25 mmol) was added (freshly distilled). The reaction mixture was stirred for 20 h at −50 ℃. The reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The mixture was extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (Hexane/EtOAc) afforded the pure nitroaldol product. The *ee* value was determined by HPLC analyses using a Chiralcel OD column. In all cases, the product chromatograms were compared against a known racemic mixture.

(*R*)-2-nitro-1-phenylethanol (entry 6 in Table 1)[21]. 62% isolated yield, 60% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 10% *i*-PrOH in hexane). Retention times: 14.1 min [major (*R*)-enantiomer] and 17.2 min [minor (*S*)-enantiomer].

(*R*)-1-(2-methoxyphenyl)-2-nitroethanol (entry 1 in Table 2)[21]. 61% isolated yield, 45% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 10% *i*-PrOH in hexane). Retention times: 11.3 min [major (*R*)-enantiomer] and 13.3 min [minor (*S*)-enantiomer].

(*R*)-1-(3-methoxyphenyl)-2-nitroethanol (entry 2 in Table 2)[21]. 57% isolated yield, 56% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 10% *i*-PrOH in hexane). Retention times: 23.6 min [major (*R*)-enantiomer] and 31.0 min [minor (*S*)-enantiomer].

(*R*)-1-(4-methoxyphenyl)-2-nitroethanol (entry 3 in Table 2)[21]. 55% isolated yield, 45% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 15% *i*-PrOH in hexane). Retention times: 11.3 min [major (*R*)-enantiomer] and 13.3 min [minor (*S*)-enantiomer].

(*R*)-1-(2-chlorophenyl)-2-nitroethanol (entry 4 in Table 2)[21]. 57% isolated yield, 36% *ee* by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 5% *i*-PrOH in hexane). Retention times: 32.5 min [major (*R*)-enantiomer] and 34.8 min [minor (*S*)-enantiomer].

(*R*)-1-(3-chlorophenyl)-2-nitroethanol (entry 5 in Table 2)[21]. 72% isolated yield, 58% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 10% *i*-PrOH in hexane). Retention times: 13.7 min [major (*R*)-enantiomer] and 17.3 min [minor (*S*)-enantiomer].

(*R*)-1-(4-chlorophenyl)-2-nitroethanol (entry 6 in Table 2)[21]. 45% isolated yield, 58% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 10% *i*-PrOH in hexane). Retention times: 13.9 min [major (*R*)-enantiomer] and 17.6 min [minor (*S*)-enantiomer].

(*R*)-1-(2-bromophenyl)-2-nitroethanol (entry 7 in Table 2)[21]. 32% isolated yield, 62% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 5% *i*-PrOH in hexane). Retention times: 35.5 min [major (*R*)-enantiomer] and 38.7 min [minor (*S*)-enantiomer].

(*R*)-1-(3-bromophenyl)-2-nitroethanol (entry 8 in Table 2)[21]. 34% isolated yield, 60% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 15% *i*-PrOH in hexane). Retention times: 10.3 min [major (*R*)-enantiomer] and 13.1 min [minor (*S*)-enantiomer].

(*R*)-1-(4-bromophenyl)-2-nitroethanol (entry 9 in Table 2)[21]. 50% isolated yield, 60% *ee* value by

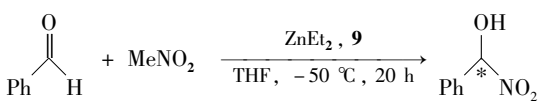
HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 15% *i*-PrOH in hexane). Retention times: 10.8 min [major (*R*)-enantiomer] and 13.8 min [minor (*S*)-enantiomer].

(*R*)-2-nitro-1-*p*-tolylethanol (entry 10 in Table 2)[21]. 58% isolated yield, 64% *ee* value by HPLC analysis (Chiralcel OD column, 254 nm, 1 mL/min, 15% *i*-PrOH in hexane). Retention times: 10.0 min [major (*R*)-enantiomer] and 12.3 min [minor (*S*)-enantiomer].

2 Results and Discussion

Firstly, ligands **9**a and **9**b were screened as catalysts for the enantioselective Henry reaction between benzaldehyde and nitromethane in the presence of diethylzinc. Results of these studies are summarized in Table 1. As can be seen from Table 1, ligand **9**a afforded the desired β-nitroalcohol with 20% *ee* value in 25% isolated yield when the reaction was performed at −50 ℃ in the absence of any additive (Table 1, entry 1). Increasing of the amount of ligand allowed an enhancement in the reaction selectivity (Table 1, entries 2 and 3). When the reaction was carried out in the presence of 0.1 equiv. of triethylamine, a moderate yield was reached. However the enantioselectivity was not successful (Table 1, entry 4). Under similar reaction conditions, the addition of triphenylphosphine sulfide increased the turnover frequency rather slow, while the enantioselectivity was only increased a little bit (Table 1, entry 5), whereas dimethyl poly (ethylene glycol) (DiMPEG) led to a good efficient catalytic system (Table 1, entry 6). So, the use of additive had an important effect on both the activity and enantioselectivity of the transformation. As far as the enantioselectivitiy was concerned, ligand **9**a was more effective within the pair of diastereoisomeric aziridino amino alcohols. Optimizations show that moderate yields and *ee* values can be obtained for the enantioselective nitroaldol reaction by using 20% molar fraction of ligand **9**a, 24 equiv. of nitromethane, and 120% molar fraction of diethylzinc at −50 ℃. These results suggest that the absolute configuration of the addition products is only determined by the configuration of the aziridine ring. Meanwhile, these results also indicate that the match of the configuration of the aziridine ring with the configuration of the additional chiral centre is crucial to obtain moderate enantioselectivity.

Table 1　Henry reaction of benzaldehyde and nitromethane under different conditions[a]



Entry	Molar fraction of ligand/%	Additive	Yield[b]/%	*ee*[c]/%	Config.[d]
1	**9**a(5)	None	25	20	R
2	**9**a(10)	None	57	20	R
3	**9**a(20)	None	55	50	R
4	**9**a(20)	Et_3N[e]	59	18	R
5	**9**a(20)	$Ph_3P{=}S$[e]	62	53	R
6	**9**a(20)	DiMPEG[e]	62	60	R
7	**9**a(15)	DiMPEG[e]	60	55	R
8	**9**b(20)	DiMPEG[e]	57	40	S

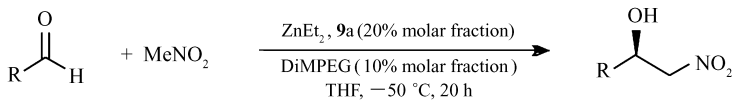
a. All the reactions were processed under argon at −50 ℃ for 20 h; *b*. isolated yields; *c*. determined by HPLC using a Chiralcel OD column, the product chromatograms were compared against a known racemic mixture; *d*. absolute configuration assigned by known elution order from a Chiralcel OD column according to the literature; *e*. using 10% molar fraction, DiMPEG: dimethyl poly (ethylene glycol), $Ph_3P{=}S$: triphenylphosphine sulfide, Et_3N: triethylamine.

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 Table 2, the reactions of nitromethane with aromatic aldehydes give the products in moderate yields and enantioselectivities. In the case of aromatic aldehydes, the substituents on the aromatic ring did not show a significant effect on the enantioselectivity. The

best asymmetric induction (as high as 64% ee value) was found by using *p*-methyl benzaldehyde as the substrate (Table 2, entry 10).

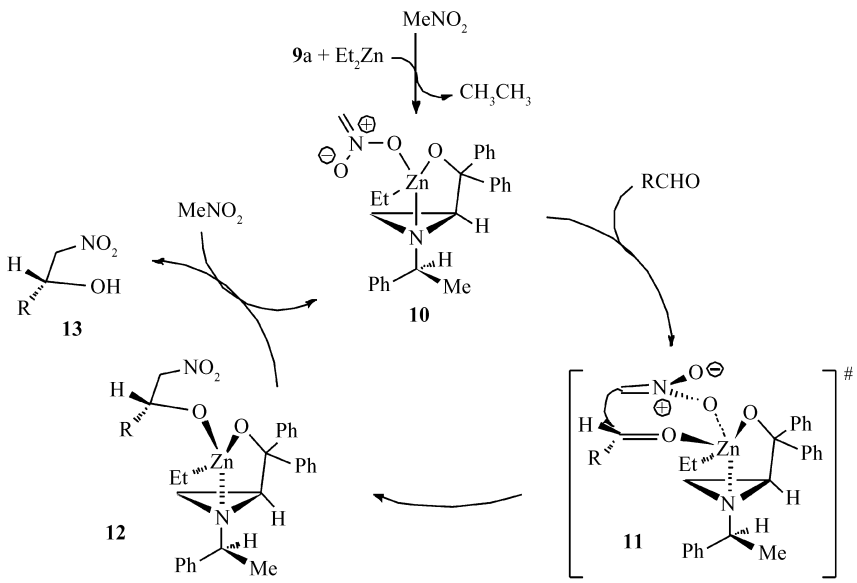
The reaction probably involves zinc-mediated dual activation of the nitronate and the aldehyde substrate (Scheme 2). Deprotonation of nitromethane by diethylzinc in the presence of ligand **9**a is expected to generate zinc complex **10**. Coordination of the aldehyde then sets the stage for enantioselective carbon-carbon bond formation *via* transition state intermediate **11**. Replacement of the formed alkoxide from complex **12** by another prenucleophilic reagent finally produces the nitroaldol product **13** and regenerates the loaded catalyst **10**.

Table 2 Enantioselective Henry reaction between aldehydes and nitromethane [a]



Entry	R	Yield/% [b]	*ee*/% [c]	Config. [d]
1	*o*-$MeOC_6H_4$	61	45	*R*
2	*m*-$MeOC_6H_4$	57	56	*R*
3	*p*-$MeOC_6H_4$	55	45	*R*
4	*o*-ClC_6H_4	57	36	*R*
5	*m*-ClC_6H_4	72	58	*R*
6	*p*-ClC_6H_4	45	58	*R*
7	*o*-BrC_6H_4	32	62	*R*
8	*m*-BrC_6H_4	34	60	*R*
9	*p*-BrC_6H_4	50	60	*R*
10	*p*-MeC_6H_4	58	64	*R*

a. All the reactions were processed under argon at −50 ℃ for 20 h; *b*. isolated yields; *c*. determined by HPLC using a Chiralcel OD column. In all cases, the product chromatograms were compared against a known racemic mixture; *d*. absolute configuration assigned by known elution order from a Chiralcel OD column according to the literature.



Scheme 2 Proposed catalytic cycle using **9**a as ligand

3 Conclusion

In summary, new categories of β-amino alcohols with aziridine ring scaffold were synthesized using a common chiral source, and the application of chiral ligands in combination with Et_2Zn and DiMPEG to the asymmetric addition of $MeNO_2$ to various aromatic aldehydes has been investigated, moderate enantioselectivities

were obtained for the aromatic aldehydes (up to 64% *ee* value). An investigation on the ligand structure and the result of the reaction confirmed that the catalytic activities of the ligands are governed by subtle structural features, and the stereochemical outcome of the reaction was determined by the configuration of the azetidine ring. Possible transition states of the reaction were proposed. Further application of chiral ligands **9** for other asymmetric reactions is under investigation in our laboratory.

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氮杂醇手性配体在锌催化的不对称 Henry 反应中的应用

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摘 要 以(*S*)-苯乙胺和丙烯酸甲酯为原料,方便地合成了一对非对映的氮杂醇手性配体,研究了它们在锌催化的不对称的 Henry 反应中不对称催化效果,*β*-硝醇的加成产物达到中等的催化效果(高达 64% 的 ee 值)。同时探讨了可能的催化机理。

关键词 Henry 反应,锌催化,氮杂醇配体

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