Asymmetric Henry Reaction Catalyzed by a Chiral Dinuclear Nickel Complex

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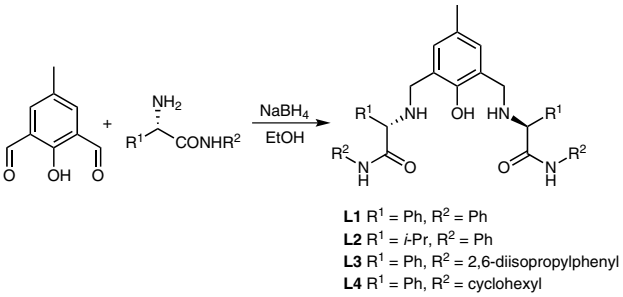
Abstract: Several chiral polyfunctional ligands were conveniently synthesized from L-amino acids and used to prepare the dinuclear complex in situ. A novel bimetallic catalyst containing dinuclear nickel was developed and applied to the asymmetric Henry reaction. With the assistance of *N*-methylmorpholine, good enantioselectivities (up to 91% ee) and moderate yields (up to 72%) were obtained for aryl, heteroaryl, and aliphatic aldehydes. The pathway was air tolerant and easily manipulated, and the reagents were readily available.

Key words: asymmetric catalysis, bimetallic catalyst, nickel, Henry reaction, nitroaldol reaction

The catalytic asymmetric nitroaldol (Henry) reaction is a useful carbon–carbon bond-forming reaction.[1] It affords enantiomerically enriched β-hydroxynitroalkanes which are key intermediates and building blocks.[2] Due to its synthetic utility, increasing efforts have been directed towards developing an efficient catalytic asymmetric Henry reaction. Since the pioneering application of Shibasaki's heterometallic catalyst system[3] in the Henry reaction, various types of catalyst systems have been studied containing metal complexes[4–9] and organocatalysts.[10] Among these systems, the multimetallic systems (such as Shibasaki's multimetallic complex,[11] Trost's dinuclear zinc complex,[5a,12] Savoia's dinuclear copper complex[13]) are very attractive for the high efficiency and easy modification. Herein, we report our preliminary results on the development of a dinuclear nickel complex for the asymmetric Henry reaction.

Chiral polyfunctional ligands **L1**–**L4** were easily prepared from L-amino acids (Scheme 1). We began our studies by examining the Henry reaction of benzaldehyde and nitromethane in the presence of **L1** and various metal salts (Table 1, entries 1–8). The commonly used Zn(II), Cu(I), and Cu(II) did not work well in this reaction (Table 1, entries 5, 7, and 8). High activity was obtained when Mn(II) was used as the central metal with low chiral induction (Table 1, entries 3 and 4), while it was difficult for Mn(III) to catalyze this reaction (Table 1, entry 6). Fortunately, Ni(II) showed good inductive potential in this reaction and 48% enantiomeric excess was achieved when $Ni(OAc)_2{\cdot}4H_2O$ was used to prepare the dinuclear catalyst (Table 1, entries 1 and 2).



Scheme 1 Synthesis of ligands

Subsequently, the effect of ligands was examined. The studies on the effect of the amide moiety (R^2 substituent, Scheme 1) demonstrated that the phenyl group was superior to the cyclohexyl group and the 2,6-diisopropylphenyl group (Table 1, entries 1, 10, and 11). When the R^1 substituent of the ligands (Scheme 1) varied from aryl group to aliphatic group, the enantiomeric excess slightly decreased.

In order to enhance the reactivity, a series of additives were examined to optimize the catalyst system with the results shown in Table 2. *tert*-Amine, pyridine, and *p*-*tert*-butylphenol could obviously increase the reactivity but reduce the enantioselectivity (Table 2, entries 1–5). When a more acidic one, *p*-nitrophenol, was added to the system, the reactivity decreased (Table 2, entry 6). Based on the reactivity and enantioselectivity, *N*-methylmorpholine was selected as the additive for the next optimization.

We continued to carry out the optimization of the reaction conditions with the results given in Table 3. When the reaction temperature was lowered to 0 °C, the enantioselectivity was increased from 41% to 71% enantiomeric excess (Table 3, entry 1). When the amount of nitromethane was decreased from 0.2 mL to 107 μL (10 equiv) and the amount of *N*-methylmorpholine was increased from ten mol% to ten equivalents, both of the reactivity and the enantioselectivity were improved (Table 3, entry 2). Further reducing the amount of nitromethane could increase the enantioselectivity, while the activity decreased too (Table 3, entries 3 and 4). We tried to further reduce the reaction temperature to –10 °C, and 92% enantiomeric ex-

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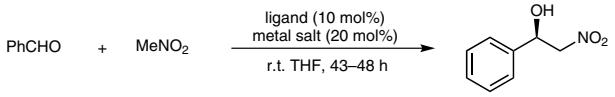
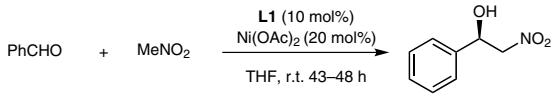
Table 1 The Screening of Ligands and Metal Salts[a]



Entry	Ligand	Metal salts	Yield (%)[b]	ee (%)[c]
1	**L1**	$Ni(OAc)_2{\cdot}4H_2O$	35	48
2	**L1**	$Ni(acac)_2$	40	15
3	**L1**	$Mn(acac)_2$	77	3
4	**L1**	$Mn(OAc)_2{\cdot}4H_2O$	26	3[d]
5	**L1**	$Zn(OAc)_2{\cdot}2H_2O$	20	9[d]
6	**L1**	$Mn(acac)_3$	trace	n.d.[e]
7	**L1**	$CuOTf{\cdot}0.5C_6H_6$	n.r.[f]	–
8	**L1**	$Cu(OTf)_2$	n.r.[f]	–
9	**L2**	$Ni(OAc)_2{\cdot}4H_2O$	40	43
10	**L3**	$Ni(OAc)_2{\cdot}4H_2O$	50	21
11	**L4**	$Ni(OAc)_2{\cdot}4H_2O$	27	6

[a] Reactions were carried out on a 0.2 mmol scale (benzaldehyde) with nitromethane (0.2 mL) in THF (0.8 mL) in the presence of a ligand (10 mol%) and a metal salt (20 mol%) at r.t. for 43–48 h.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by HPLC analysis on a Chiralcel OD-H column; the absolute configuration was established as *R* by comparison with literature data.
[d] The absolute configuration of the major product was inverse compared with the others by the analysis of HPLC on a Chiralcel OD-H column.
[e] Not determined.
[f] No reaction.

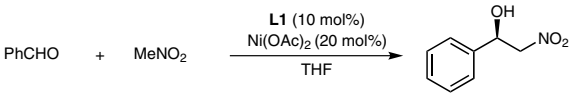
Table 2 The Screening of Additives[a]



Entry	Additive	Yield (%)[b]	ee (%)[c]
1	Et_3N (10 mol%)	64	34
2	pyridine (10 mol%)	57	38
3	*i*-Pr_2NEt (10 mol%)	53	40
4	*N*-methylmorpholine (10 mol%)	48	41
5	*p-tert*-butylphenol (10 mol%)	47	29
6	*p*-nitrophenol (10 mol%)	20	24

[a] Reactions were carried out on a 0.2 mmol scale (benzaldehyde) with nitromethane (0.2 mL) in THF (0.8 mL) in the presence of **L1** (10 mol%), $Ni(OAc)_2{\cdot}4H_2O$ (20 mol%), and the specified additive at r.t. for 43–48 h.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by HPLC analysis on a Chiralcel OD-H column.

Table 3 Further Optimization of Reaction Conditions[a]



Entry	Temp (°C)	The amount of $MeNO_2$ (equiv)	Additive (equiv)	Reaction time (h)	Yield (%)[b]	ee (%)[c]
1	0	200 μL	NMM[d] (1)	89	45	71
2	0	107 μL (10)	NMM[d] (10)	96	66	85
3	0	54 μL (5)	NMM[d] (10)	92	36	89
4	0	21 μL (2)	NMM[d] (10)	92	trace	88
5	–10	107 μL (10)	NMM[d] (10)	92	32	92

[a] Reactions were carried out on a 0.2 mmol scale (benzaldehyde) with nitromethane in THF (0.8 mL for entry 1 and 1.0 mL for entries 2–5) in the presence of **L1** (10 mol%), $Ni(OAc)_2{\cdot}4H_2O$ (20 mol%), and the specified additive.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by HPLC analysis on a Chiralcel OD-H column.
[d] *N*-Methylmorpholine.

cess was achieved, but only 32% isolated yield was obtained (Table 3, entry 5). Currently, the optimized reaction conditions were established: 10 mol% **L1**–$[Ni(OAc)_2]_2$ complex, ten equivalents *N*-methylmorpholine, ten equivalents nitromethane, and 0.2 mmol aldehyde in 1.0 mL THF at 0 °C (Table 3, entry 2). It should be noted that the process is air- and moisture-tolerant.

With the optimized reaction conditions in hand, the substrate scope was explored. The results were summarized in Table 4. No matter aryl aldehydes with a *meta* substituent or a *para* substituent or an electron-withdrawing substituent as well as heteroaryl aldehyde afforded the corresponding product in moderate yields with good enantioselectivities (Table 4, entries 3–6). The bulkier aldehyde, such as 2-naphthaldehyde, also gave good yield and enantioselectivity (Table 4, entry 2). It is worth mentioning that the aliphatic aldehyde (Table 4, entry 7) was suitable for this catalyst system, providing high enantioselectivity (91% ee) which was higher than the corresponding product of benzaldehyde.

In summary, several chiral polyfunctional ligands were conveniently synthesized from L-amino acids and they were used to prepare the dinuclear complex in situ. Finally, a novel bimetallic catalyst containing dinuclear nickel was developed and applied to the asymmetric Henry reaction with good enantioselectivities (up to 91% ee) and moderate yield (up to 72%). The pathway was air-tolerant and easily manipulated, and the reagents were readily available. Further investigations are under way in our laboratory including the exploration of the dinuclear catalyst, the detailed mechanism, and the extending of the substrate scope.

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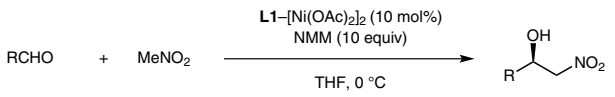
Table 4 Enantioselective Nitroaldol Reactions between Aldehydes and Nitromethane[a]



Entry	Aldehyde	Reaction time (h)	Yield (%)[b]	ee (%)[c]
1	PhCHO	96	66	85
2	2-naphthaldehyde	96	71	84
3	4-MeC_6H_4CHO	120	65	82
4	3-MeC_6H_4CHO	120	65	72
5	4-ClC_6H_4CHO	96	58	84
6	2-furaldehyde	96	72	85
7	hexanal	96	63	91

[a] Reactions were carried out with the aldehydes (0.2 mmol) and nitromethane (10 equiv) in THF (1.0 mL) in the presence of **L1** (10 mol%), $Ni(OAc)_2·4H_2O$ (20 mol%), and *N*-methylmorpholine.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by HPLC analysis.

MS Analysis of the L1–$[Ni(OAc)_2]_2$ Complex

The mixture of ligand **L1** (11.7 mg, 0.02 mmol) and $Ni(OAc)_2·4H_2O$ (10.0 mg, 0.04 mmol) was stirred in THF (0.5 mL) at 35 °C under air atmosphere for 1 h to generate the catalyst. The mixture was analyzed by ESI-MS (pos.): *m/z* calcd for $C_{41}H_{41}N_4Ni_2O_7$ $[M_{\mathbf{L1}} – H + Ni_2(OAc)_2]^+$: 817.17; found: 817.26.

Typical Experimental Procedure for the Henry Reaction

The mixture of ligand **L1** (11.7 mg, 0.02 mmol) and $Ni(OAc)_2·4H_2O$ (10.0 mg, 0.04 mmol) was stirred in THF (0.5 mL) at 35 °C under air atmosphere for 1 h to generate the catalyst. $Ni(OAc)_2$ was dissolved in THF, and a green solution was obtained. Then the nitromethane (107 μL) was added to the solution, and the stirring was continued for 0.5 h. After that, the reaction mixture was cooled to 0 °C followed by the addition of the benzaldehyde (0.2 mmol), *N*-methylmorpholine, and THF (0.5 mL). The stirring was continued for 96 h at 0 °C. The products were isolated by using column chromatography on silica gel (EtOAc–PE = 1:8, v/v) as a colorless oil, 66% yield, 85% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.37 (m, 5 H), 5.38 (dd, 1 H, *J* = 9.60 Hz, 2.85), 4.52–4.57 (m, 1 H), 4.46–4.43 (m, 1 H), 3.24 (br s, 1 H). $[\alpha]_D^{20}$ –44.8 (*c* 0.40, CH_2Cl_2). HPLC (Chiralcel OD-H column, hexane–2-propanol = 90:10, flow 1.0 mL/min, detection at 215 nm): t_R (major) = 14.4 min and t_R (minor) = 17.9 min.

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