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Highly Enantioselective Henry Reaction Catalyzed by C_2-Symmetric Modular BINOL-Oxazoline Schiff Base Copper(II) Complexes Generated in Situ

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A 16-member library of C_2-symmetric modular chiral BINOL-oxazoline Schiff base copper(II) complex catalysts generated in situ was easily generated in a one-pot, three-component manner. This approach avoided the need for isolation and characterization of ligands and greatly improved the catalyst screening efficiency. This modular catalyst library was evaluated in the asymmetric Henry reaction, for which good yields (up to 98 %) and good to excellent enantioselectivities (up to 98 % *ee*) were obtained under mild conditions.

Introduction

The Henry or nitroaldol reaction is one of the most general and versatile methods for new carbon–carbon bond formation in organic synthesis. The Henry reaction generates β-nitro alcohol, which can further be converted into various valuable structural motifs.[1] Since the first asymmetric version of the Henry reaction was reported by Shibasaki in 1992,[2] catalytic asymmetric Henry reactions have gained particular attention, and great effort has been devoted to the development of more selective and efficient catalytic systems for this synthetically useful transformation.[3–5] Although good to excellent results have been achieved by using these systems, the design and development of efficient and flexible synthetic strategies involving chiral ligands or catalysts is still needed.

In recent years, modular and combinatorial approaches have been applied to generate a combinatorial library of modular chiral ligands or catalysts in asymmetric catalysis.[6] As efficient and flexible synthetic strategies, these approaches enable new, highly efficient and enantioselective catalysts to be developed. Meanwhile, the modular approach also offers a powerful tool to synthesize new ligands by combining classical ligands. Modular synthesis based on "privileged ligand" architectures is an efficient method that can be used to develop new prominent ligands. For example, modular phosphite–phosphoroamidites libraries have been used in asymmetric palladium-catalyzed allylic substitution reactions and Cu-catalyzed asymmetric 1,4-addition to enones.[7] Modular oxazoline ligands have also been developed and applied in various asymmetric catalytic reactions.[8]

Due to excellent axial chirality, enantiomerically pure 1,1′-bi-2-naphthol (BINOL) derivatives play an important role in ligand design for asymmetric catalysis.[9] Oxazoline is also a type of "privileged ligand" owing to its ready accessibility, modular nature, and proven success in various catalytic asymmetric reactions. The design and application of chiral oxazoline ligands has gained much attention in recent years.[10] Our group has focused on the design, synthesis, and applications of the C_2-symmetric oxazoline ligands in various asymmetric reactions in recent years.[5,11] Schiff-base ligands have also been recognized as "privileged ligands" because they are able to coordinate with various metals in a large variety of useful catalytic transformations; they can be easily prepared through condensation of various aldehydes with primary amines.[12] In our preliminary report,[5a] we succeeded in developing C_1-symmetric modular ligands and catalysts by facile combination of salicylaldehyde derivatives and oxazoline through Schiff base formation in situ. As a rational extension and update, we now report on the design of new C_2-symmetric modular BINOL-oxazoline Schiff-base ligands, which are the combinatorial ligands of BINOLs and the oxazoline moieties by Schiff-base formation. We envisioned that the new C_2-symmetric modular BINOL-oxazoline Schiff-base ligands would possess features of the former privileged ligands. Herein, we report on the formation of a library of new C_2-symmetric modular BINOL-oxazoline Schiff-base copper(II) complex catalysts, which were easily obtained in one pot from the combination of BINOL-dicarboxaldehydes, oxazoline moieties, and copper(II) acetate. This modular library of complex catalysts formed in situ was screened in the asymmetric Henry reaction of various aldehydes with nitromethane; good yields (62–98 %) and good to excellent enantioselectivies (81–98 % *ee*) were obtained.

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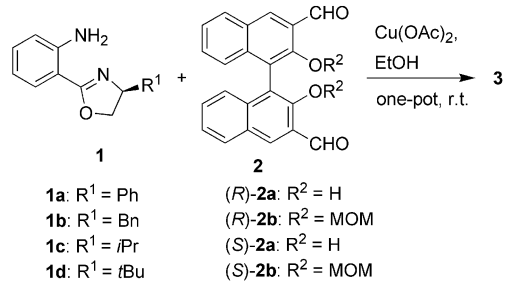
Results and Discussion

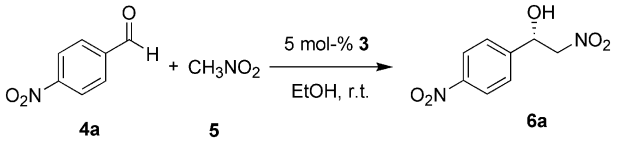
Initially, 2-aminophenyl oxazolines **1** and BINOL dicarboxaldehydes **2** were synthesized for the preparation of catalysts following the literature procedures.[5a,13] A small library of chiral C_2-symmetric modular BINOL-oxazoline Schiff-base copper(II) complex catalysts was then easily built in a one-pot, three-component way (Scheme 1). The library was screened in situ in the asymmetric Henry reaction of 4-nitrobenzaldehyde with nitromethane. The screening results are presented in Table 1. During the screening of complex catalysts **3a**–**p**, the reaction was performed in ethanol, in the presence of 5 mol-% complex **3**, at room temperature. Reactions reached completion within 8 hours in almost quantitative yields and variable enantioselectivities (41–88% *ee*). The complex **3p**, generated from **1d**, (*R*)-**2b**, and $Cu(OAc)_2$, was clearly the best catalyst for this reaction, giving good enantioselectivity (88% *ee*) (Table 1, entry 16). The data obtained (illustrated in Figure 1), clearly demonstrates the effect of each chiral component. It can be seen that the (*R*) isomer of the BINOL component is better for asymmetric induction than the corresponding (*S*) isomer; substitutes on the oxazoline ring had little effect on asymmetric induction. Clearly, the above approach, which avoids the need for isolation and characterization of ligands, was effective for rapid screening of catalysts.



Scheme 1. Preparation of complex catalysts **3**.

To optimize the reaction conditions, the effect of solvent, catalyst loading, temperature and the ratio of **1d/2b**/$Cu(OAc)_2$ was screened. The results are shown in Table 2. Under otherwise identical conditions, use of methanol and 2-propanol as solvent gave slightly lower enantioselectivity (Table 2, entries 2 and 3), whereas using dichloromethane, toluene, tetrahydrofuran (THF), or Et_2O as solvent gave only trace amounts of product (Table 2, entries 4–7). When the complex **3p** was formed in EtOH, but the Henry reaction was carried out in a second solvent, modest yields and enantioselectivities were obtained after 24 h (Table 2, entries 8–11). The above results indicated that ethanol was the best solvent for this Henry reaction. The product was obtained in excellent yield but with a decrease in enantioselectivity when Et_3N or 4-Å MS was used as an additive (79 and 80% *ee*, respectively). The effect of catalyst loading was further explored and it was found that with 10 or 2.5 mol-% catalyst loadings, lower enantioselectivities were obtained (83 and 71% *ee*, respectively). When the reaction was performed at 0 °C, much lower yield and lower enantioselectivity (Table 2, entry 16) was obtained. We also adjusted the ratio of **1d/2b**/$Cu(OAc)_2$, but no improved results were obtained. After the optimization, 5 mol-% complex catalyst **3p** in EtOH at room temperature were established as the standard conditions.

Table 1. Screening of complexes generated in situ for the Henry reaction of 4-nitrobenzaldehyde with nitromethane.[a]



Entry	Complex catalyst {source components}	Yield[b] [%]	*ee*[c] [%]
1	**3a** {**1a** + (*S*)-**2a** + $Cu(OAc)_2$}	95	41
2	**3b** {**1b** + (*S*)-**2a** + $Cu(OAc)_2$}	96	47
3	**3c** {**1c** + (*S*)-**2a** + $Cu(OAc)_2$}	96	50
4	**3d** {**1d** + (*S*)-**2a** + $Cu(OAc)_2$}	95	52
5	**3e** {**1a** + (*S*)-**2b** + $Cu(OAc)_2$}	94	41
6	**3f** {**1b** +(*S*)-**2b** + $Cu(OAc)_2$}	98	66
7	**3g** {**1c** + (*S*)-**2b** + $Cu(OAc)_2$}	95	47
8	**3h** {**1d** + (*S*)-**2b** +$Cu(OAc)_2$}	97	77
9	**3i** {**1a** + (*R*)-**2a** + $Cu(OAc)_2$}	95	42
10	**3j** {**1b** + (*R*)-**2a** + $Cu(OAc)_2$}	97	62
11	**3k** {**1c** + (*R*)-**2a** + $Cu(OAc)_2$}	96	51
12	**3l** {**1d** + (*R*)-**2a** + $Cu(OAc)_2$}	99	64
13	**3m** {**1a** + (*R*)-**2b** + $Cu(OAc)_2$}	96	73
14	**3n** {**1b** + (*R*)-**2b** + $Cu(OAc)_2$}	97	80
15	**3o** {**1c** + (*R*)-**2b** + $Cu(OAc)_2$}	97	81
16	**3p** {**1d** + (*R*)-**2b** + $Cu(OAc)_2$}	98	88

[a] Reagents and conditions: 4-nitrobenzaldehyde (0.5 mmol), nitromethane (5.0 mmol), EtOH (2 mL), complex catalysts **3** (5 mol-%), room temperature, 8 h. [b] Isolated yield after the column chromatographic purification. [c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column (*n*-hexane/2-propanol, 80:20; 1.0 mL/min; 254 nm).

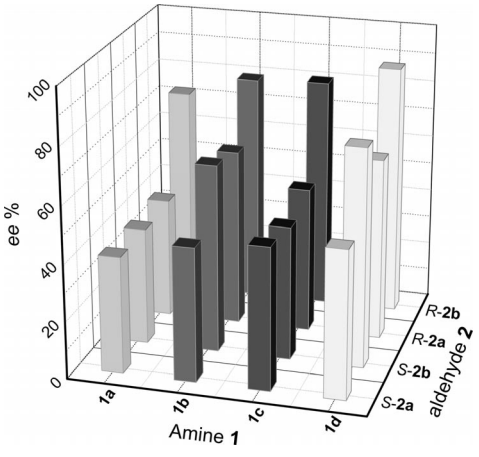
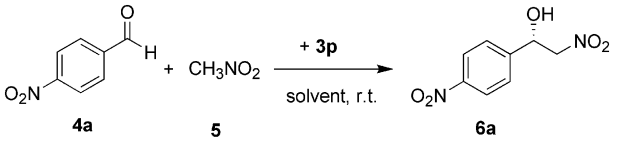


Figure 1. Screening of complexes generated in situ.

Under the optimal reaction conditions, a series of aldehydes were tested, and good to excellent yields and enantioselectivities (up to 98% *ee*) were achieved in most cases (Table 3). Benzaldehydes with strong electron-withdrawing nitro substitutions gave high yields and good enantioselectivities (Table 3, entries 1–3). Benzaldehyde and benzal-

Table 2. Optimization of the reaction conditions.[a]



4a 5 6a

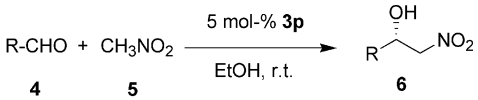
Entry	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	EtOH	8	98	88
2	MeOH	8	95	67
3	*i*PrOH	8	88	54
4	CH_2Cl_2	8	trace	–
5	toluene	8	trace	–
6	THF	8	trace	–
7	Et_2O	8	trace	–
8[d]	CH_2Cl_2	24	73	46
9[d]	toluene	24	72	49
10[d]	THF	24	78	78
11[d]	Et_2O	24	70	50
12[e]	EtOH	4	98	79
13[f]	EtOH	6	97	80
14[g]	EtOH	6	98	83
15[h]	EtOH	8	85	71
16[i]	EtOH	48	40	81
17[j]	EtOH	8	97	69
18[k]	EtOH	8	97	83

[a] Reagents and conditions: 4-nitrobenzaldehyde (0.5 mmol), nitromethane (5.0 mmol), complex **3p** (5 mol-% formed in situ), solvent (2 mL), room temperature. [b] Isolated yield after column chromatography. [c] Determined by HPLC using a Chiralcel OD-H column (*n*-hexane/2-propanol, 80:20; 1.0 mL/min; 254 nm). [d] Complex **3p** was formed in EtOH, whereas the Henry reaction was carried out in the solvent shown. [e] Et_3N (10 mol-%) was used as additive. [f] Molecular sieves (4 Å, 100 mg) was used as additive. [g] Complex **3p** (10 mol-%) was employed. [h] Complex **3p** (2.5 mol-%) was employed. [i] The Henry reaction was performed at 0 °C. [j] The ratio of **1d**/**2b**/$Cu(OAc)_2$ was adjusted to 6:3:5 (**1d**; 0.06 mmol). [k] The ratio of **1d**/**2b**/$Cu(OAc)_2$ was adjusted to 2:1:3 (**1d**; 0.05 mmol).

dehyde derivatives with weak electron-withdrawing or even electron-donating substitutions also gave good yields and comparable enantioselectivities, but required more prolonged reaction times (Table 3, entries 4–7). *ortho*-Methoxy-substitution of benzaldehyde resulted a low reactivity and slightly lower yield and enantioselectivity (Table 3, entry 8), whereas *para*- or *meta*-methoxy-substituted benzaldehydes gave only trace amounts of product under the same reaction conditions. In the case of cinnamaldehyde and other aromatic aldehydes, such as 1-naphthaldehyde and 2-furaldehyde, moderate yields and good enantioselectivities were obtained (Table 3, entries 9–11). Most remarkably, excellent results were obtained when aliphatic aldehydes were used as substrates. When aliphatic unbranched and even branched or sterically hindered aldehydes were tested, good yields and excellent enantioselectivities (96–98% *ee*) were achieved (Table 3, entries 12–16).

To verify the role of the C_2-symmetric feature in the above complex catalytic system, control experiments were carried out. When the copper(II) complex catalyst **8**, formed from BINOL monocarboxaldehyde **7**[14] instead of dicarboxaldehyde (*R*)-**2b**, was tested in the Henry reaction

Table 3. Enantioselective Henry reactions of various aldehydes with nitromethane.[a]

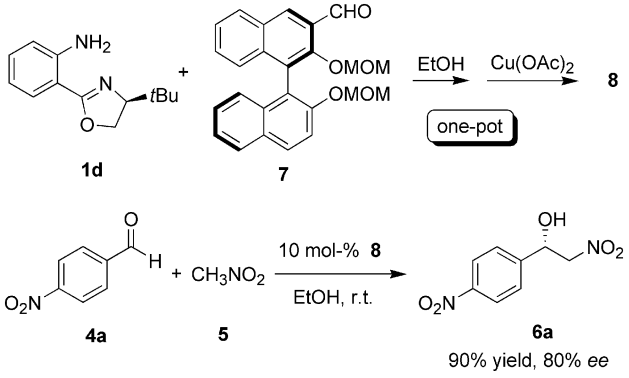


4 5 6

Entry	R	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	4-NO_2Ph	**6a**	8	98	88 (*S*)[d]
2	3-NO_2Ph	**6b**	8	95	81 (*S*)
3	2-NO_2Ph	**6c**	12	93	87 (*S*)
4	4-ClPh	**6d**	24	81	93 (*S*)
5	4-BrPh	**6e**	24	76	81 (*S*)
6	Ph	**6f**	48	85	82 (*S*)
7	4-MePh	**6g**	48	78	85 (*S*)
8	2-MeOPh	**6h**	72	56	72 (*S*)
9	1-naphthyl	**6i**	48	65	81 (*S*)
10	2-furyl	**6j**	48	62	92 (*R*)
11	PhCH=CH	**6k**	48	78	87 (*S*)
12	$PhCH_2CH_2$	**6l**	48	69	98 (*S*)
13	cyclohexyl	**6m**	48	92	98 (*S*)
14	isopropyl	**6n**	48	87	98 (*S*)
15	*t*Bu	**6o**	48	80	98 (*S*)
16	nonyl	**6p**	48	79	96 (*S*)

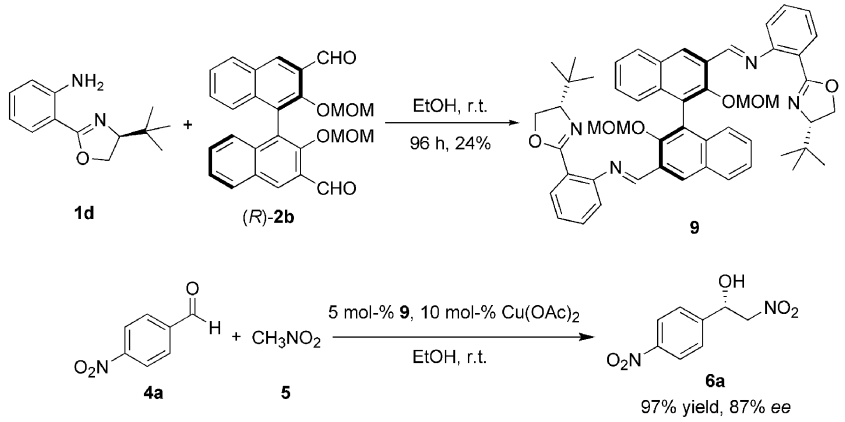
[a] Reagents and conditions: aldehyde (0.5 mmol), nitromethane (5.0 mmol), EtOH (2 mL), complex catalysts **3p** (5 mol-%), room temperature. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on Daicel Chiralcel OD-H, OF or Chiralpak IA column. [d] By comparison with the literature data.[4]

of 4-nitrobenzaldehyde and nitromethane with 10 mol-% catalyst loading, the desired product was obtained with 90% yield and 80% *ee* (Scheme 2). Whereas, when the corresponding Henry reaction of 4-nitrobenzaldehyde and nitromethane was conducted with 5 mol-% C_2-symmetric catalyst, the desired product was obtained with 98% yield and 88% *ee* (Table 3, entry 1) [this comparison was based on the same amount of $Cu(OAc)_2$]. This result demonstrated that the three-component C_2-symmetric catalysts generated in situ were slightly better than C_1-symmetric equivalents.



Scheme 2. One-pot, three-component synthesis of C_1-symmetric chiral oxazoline Schiff-base copper complex and its application in the Henry reaction of 4-nitrobenzaldehyde with nitromethane.

Many attempts were made to isolate and characterize the three-component complex catalysts **3p** or **8** generated in situ, however, no pure material was obtained and, thus, no clear structure of the catalytic complex could be determined. High-resolution mass spectra also did not give any



Scheme 3. Synthesis of oxazoline Schiff-base ligand **9** and its application in the Henry reaction of 4-nitrobenzaldehyde with nitromethane.

useful composition information. In our previous report, we demonstrated that aminophenyl oxazoline moieties **1a**–**d** were not effective ligands in the catalysis of the model Henry reaction of 4-nitrobenzaldehyde.[5a] The mixture of aldehyde (*S*)-**2b** and $Cu(OAc)_2$ did not catalyze the Henry reaction. We further synthesized the Schiff-base ligand **9** from **1d** and (*S*)-**2b**, but the product was only obtained in 24% yield. The corresponding Henry reaction of 4-nitrobenzaldehyde with nitromethane catalyzed by 5 mol-% ligand **9** and 10 mol-% $Cu(OAc)_2$ gave the desired Henry product with 97% yield and 87% *ee* (Scheme 3). This result is similar to that obtained by using catalyst **3p** generated in situ (Table 3, entry 1), which demonstrated that the three-component catalysts generated in situ were equivalent to those generated by using pure oxazoline Schiff-base ligand and $Cu(OAc)_2$. Although the mechanism of this catalyst system cannot be resolved at the present time owing to the uncertainty of the complex catalyst structure, this in situ approach can avoid the isolation and characterization of ligands and greatly improves the efficiency of catalyst screening.

Conclusions

We have developed a library of new C_2-symmetric modular BINOL-oxazoline Schiff base copper(II) complex catalysts in an efficient, one-pot, three-component method that enables rapid evaluation of ligands and catalysts. The BINOL-oxazoline Schiff base copper(II) complex **3p** was found to be an efficient catalyst that can catalyze the asymmetric Henry reaction of various aldehydes and nitromethane under mild reaction conditions. Good yields and excellent enantioselectivities (96–98% *ee*) were observed, especially when aliphatic aldehydes were used as substrates. Furthermore, this new library of C_2-symmetric modular BINOL-oxazoline Schiff base copper(II) complex catalysts are more efficient than the C_1-symmetric modular oxazoline-Schiff base copper(II) catalysts formed by saciylaldehyde derivatives and corresponding oxazolines developed previously.[5a] Further studies are in progress in our laboratory to expand the scope of this approach to other asymmetric reactions.

Experimental Section

General Methods: Melting points were measured with a XT-4 melting point apparatus. ^{1}H NMR spectra were recorded with a Varian Mercury 200 or 300 MHz spectrometer. Infrared spectra were obtained with a Perkin–Elmer Spectrum One spectrometer. The ESI-MS spectra were obtained with a Bruker APEX IV mass spectrometer. Optical rotations were measured with a Perkin–Elmer 341 LC or WZZ-3 polarimeter. The enantiomeric excesses of the products were determined by chiral HPLC with an Agilent 1200 LC instrument and Daicel Chiralcel OD-H, OF and Chiralpak IA columns. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was carried out using silica gel (200–300 mesh).

Compounds **1a**–**d** were prepared according to our previous paper.[5a] Compounds (*R*)-**2a**, (*R*)-**2b**, (*S*)-**2a**, (*S*)-**2b** and **7** were prepared following literature procedures.[13,14]

General Procedure for Asymmetric Henry Reaction with Complex Catalyst Generated in Situ: A solution of (*S*)-2-(4-*tert*-butyl-4,5-dihydrooxazol-2-yl)aniline (**1d**; 10.9 mg, 0.05 mmol), (*R*)-2,2′-bis-(methoxymethoxy)-1,1′-binaphthyl-3,3′-dicarboxaldehyde [(*R*)-**2b**; 10.8 mg, 0.025 mmol], and EtOH (2 mL) was stirred for 1 h at room temperature. Anhydrous $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) was added and the mixture was stirred for another 1 h, during which time the reaction mixture turned brown. Aldehyde (0.5 mmol) and nitromethane (5.0 mmol, 0.26 mL) were added and the mixture was stirred for 8–48 h at room temperature. The reaction mixture was concentrated and purified by silica gel column chromatography.

Synthesis of Oxazoline Schiff-Base Ligand 9: To a solution of (*R*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl-3,3′-dicarbaldehyde [(*R*)-**2b**; 108 mg, 0.25 mmol] in EtOH (2 mL), was added (*S*)-2-(2-aminophenyl)-4-*tert*-butyloxazoline (**1d**; 109 mg, 0.50 mmol). The reaction mixture was stirred for 96 h at room temperature, during which time some white precipitate was formed. The product was obtained through filtration as a white solid (101 mg, 24%). M. p. 152–154 °C. $[\alpha]_D^{25} = -114.3$ ($c = 0.56$, CH_2Cl_2). IR: $\tilde{\nu}$ = 2957, 2902, 2869, 1637, 1589, 1524, 1453, 1359, 1328, 1285, 1262, 1241, 1159, 1062, 969, 908, 752 cm^{-1}. ^{1}H and ^{13}C NMR could not be obtained owing to its decomposition in solvent. HRMS (ESI): calcd.

for $C_{52}H_{55}N_4O_6$ $[M + H]^+$ 831.41161; found 831.41331. $C_{52}H_{54}N_4O_6 \cdot 2C_2H_5OH$ (923.15): C 72.86, H 7.21, N 6.07; found C 73.00, H 7.18, N 6.02.

Asymmetric Henry Reaction Using Pure Oxazoline Schiff-Base Ligand 9 and $Cu(OAc)_2$: A mixture of oxazoline Schiff-base pure ligand **9** (20.8 mg, 0.025 mmol) and anhydrous $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) were stirred for 30 min in EtOH. 4-Nitrobenzaldehyde (**4a**; 75.6 mg, 0.5 mmol) and nitromethane (5.0 mmol, 0.26 mL) were added and the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate, 5:1) to give **6a** (101 mg, 97%) with 87% *ee*.

Supporting Information (see footnote on the first page of this article): Data of well-known compounds, HPLC diagrams of Henry products, IR and HRMS of new ligands.

Acknowledgments

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