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Salicylhydrazone ligands for enantioselective addition of diethylzinc to aldehydes

Takayoshi Arai,[a,*] Yoko Endo[b] and Akira Yanagisawa[a]

[a]*Department of Chemistry, Faculty of Science, Chiba University, Inage, Chiba 263-8522, Japan*
[b]*Graduate School of Science and Technology, Chiba University, Inage, Chiba 263-8522, Japan*

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Abstract—A family of chiral salicylhydrazones was designed and synthesized for application in asymmetric catalysis. The ability of newly prepared binaphthyl-containing salicylhydrazones as the chiral ligand was examined in the addition of diethylzinc to aldehyde, with the desired product obtained in up to 80% ee.

1. Introduction

Since efficient catalytic asymmetric synthesis is an ideal technology in modern chemistry, many chiral ligands have been introduced aimed at high stereoselectivity.[1] Among the various types of chiral ligands reported, a series of Schiff base derived from salicylaldehydes has been employed as the core function to construct the catalytic site of metal complexes, as symbolized by the famous example of salen ligands.[2] Inspired by the successful use of Schiff base, we herein report a diversity-oriented design and synthesis of chiral salicylhydrazones, and demonstrate an application in asymmetric catalysis.

Hydrazones have been widely utilized for the derivatization, characterization, and protection of carbonyl compounds. Enders' anion chemistry using RAMP and/or SAMP represents the usefulness of chiral hydrazones in asymmetric synthesis.[3] Recently, Enders and Mino independently reported pioneering work on *P*,*N*-hydrazone ligands for the palladium-catalyzed asymmetric allylic alkylation.[4] Since it is possible for the hydrazones to have a stereogenic center at either end (nitrogen atom and/or carbon atom) of the structure, a new family of chiral salicylhydrazones was designed as depicted in Figure 1.

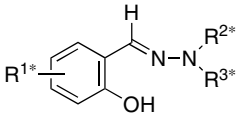

Figure 1. Chiral salicylhydrazones (*: showing the chirality).

2. Results and discussion

Toward the development of a chiral salicylaldehydes, we decided to adopt a binaphthyl skeleton as the origin of chirality, which has been well employed to create a promising chiral reaction sphere.[5]

The synthesis of chiral binaphthyl-consisting salicylhydrazones **L1** was readily achieved by way of reaction of salicylaldehyde with a chiral binaphthyl moiety in the hydrazone-forming reaction (Scheme 1). Thus, after the dehydrating condensation of salicylaldehydes and hydrazine, continuous alkylation by dibromomethyl-1,1′-binaphthyl[6] provided the desired ligands **L1a**–**L1d**.

Moreover, the idea of employing a binaphthyl moiety as the origin of chirality led us to the synthesis of a different type of ligand **L2** as shown in Scheme 2. In this classification, **L1** consists of the binaphthyl skeleton at the end of the nitrogen atom of hydrazone, while **L2** has it on the carbon atom.

The synthesis of **L2** was also achieved very readily by the formation of hydrazone from 3,3′-diformyl-2,2′-binaphthol[7] and *N*,*N*-dialkyl hydrazine; the target hydrazones **L2a** and **L2b** were obtained in quantitative yields.

* Corresponding author. Tel./fax: +81 43 290 2889; e-mail: tarai@faculty.chiba-u.jp

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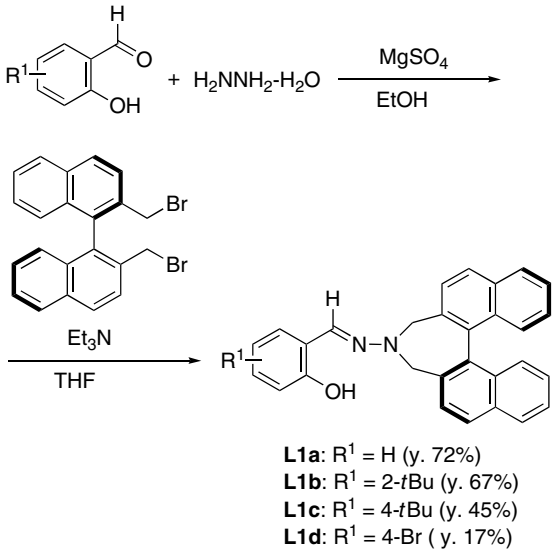
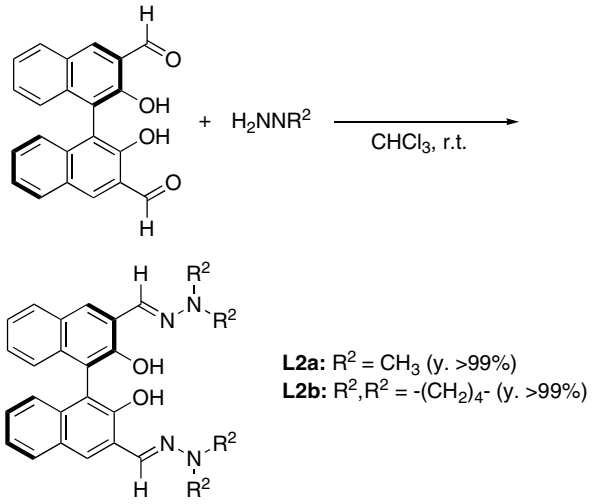


Scheme 1. Synthesis of chiral salicylhydrazone **L1**.

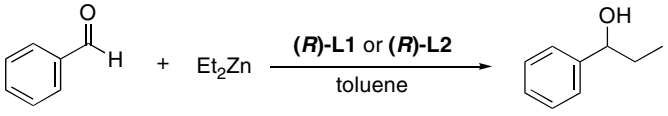


Scheme 2. Synthesis of chiral hydrazone **L2**.

With two types of chiral ligands **L1** and **L2** in hand, examination of their ability as the chiral ligand was started in the well-studied nucleophilic addition of diethylzinc to benzaldehyde, in which chiral β-amino alcohols have been successfully utilized.[8,9] Although a number of Schiff base ligands derived from salicylaldehydes have produced elegant applications in asymmetric catalysis, the typical Schiff base derived from the aldehyde, reacts with diethylzinc.[10] Based on the aforementioned hydrazone-related anion chemistry, we envisioned that the stability of the hydrazone would allow the use of the N,O-framework of salicylhydrazone in the nucleophilic addition of diethylzinc.

When the newly prepared hydrazone **L1a** was examined in the nucleophilic addition of diethylzinc to benzaldehyde at room temperature, the target product was obtained in 48% yield with 52% ee (Table 1, entry 1). Although the reaction at −20 °C caused a reduction of the catalyst efficiency (entry 3), the reaction at 0 °C gave the adduct in moderate yield with 58% ee (entry 2). With regards to the effects of the substituents, the bulky *t*-Bu at the 3-position drastically diminished the enantioselectivity (entry 4). On the other hand, the reaction using **L2** proceeded smoothly even at −20 °C to give the adduct with improved enantioselectivity. For example, the reaction using **L2a** provided the product in 61% yield with 71% ee under similar conditions with those of entry 3.[11] When the amount of **L2a** was increased to 15 mol %, the adduct was obtained in 75% yield with up to 80% ee (entry 9). The use of the 5-membered ring of pyrrolidine **L2b** showed similar results to those obtained by **L2a**. Regarding the relationship of the absolute configuration of the products with the chirality of ligands, an (*R*)-enriched product was obtained by (*R*)-binaphthyl-containing **L1**, and an (*S*)-enriched product was obtained via the use of (*R*)-binaphthyl-consisting **L2**.

Table 1. Enantioselective diethylzinc addition to benzaldehyde[a]



Entry	Ligand	Amount of ligand (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)	Absolute configuration[d]
1	**L1a**	5	rt	5	48	52	(*S*)
2	**L1a**	5	0	22	40	58	(*S*)
3	**L1a**	5	−20	22	16	49	(*S*)
4	**L1b**	5	0	22	28	14	(*S*)
5	**L1c**	5	0	22	31	56	(*S*)
6	**L1d**	5	0	22	36	48	(*S*)
7	**L2a**	5	0	6	57	45	(*R*)
8	**L2a**	5	−20	6	61	71	(*R*)
9	**L2a**	15	−20	6	75	80	(*R*)
10	**L2b**	5	−20	6	51	72	(*R*)
11	**L2b**	15	−20	6	80	76	(*R*)

[a] The reaction was performed using 0.8 mmol of benzaldehyde and 1.6 mmol of diethylzinc in 0.9 mL of toluene.
[b] Isolated yield.
[c] ee was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralcel OD).
[d] Absolute configuration was determined by specific rotation reported in Ref. [10b].

For accessing the catalyst structure and the reaction mechanism, the non-linear effects were examined in Figure 2.[12]

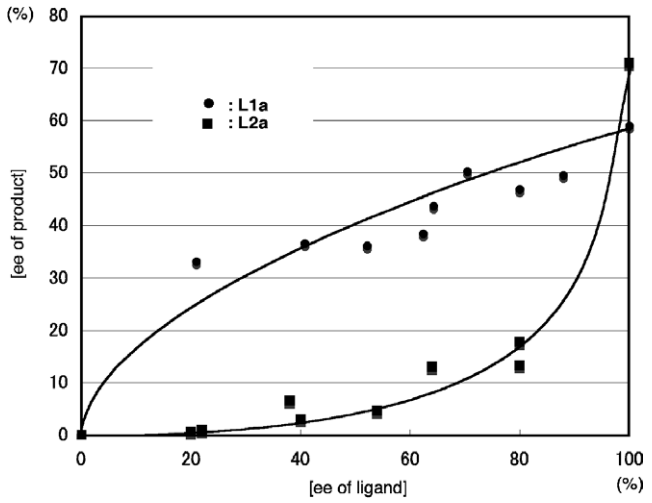
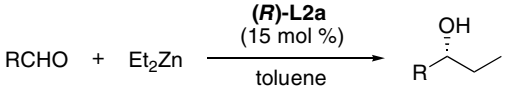


Figure 2. Non-linear effect in the addition of diethylzinc to benzaldehyde.

The catalysis using **L1a** showed moderately positive non-linear effects of asymmetric amplification as normally observed in the nucleophilic addition of diethylzinc to aldehyde.[13] In contrast, the reaction using **L2a** showed negative non-linear effect of asymmetric depletion. This result would shows us that the catalysis using the relatively bulky **L2a** still proceeds with keeping the aggregated structure.

Other catalytic enantioselective additions of diethylzinc to aldehydes were also examined in Table 2. The reaction of aliphatic aldehyde was also catalyzed to provide the adduct in moderate enantiomeric excess, although the chemical yield was decreased.

Table 2. (*R*)-**L2a**-catalyzed diethyl zinc addition to aldehydes[a]



Entry	RCHO	Temperature (°C)	Time (h)	Yield (%)	ee[b] (%)
1[c]	4-$MeOC_6H_4CHO$	0	96	Quant.	31
2[c]	4-ClC_6H_4CHO	−10	24	74	36
3[c]	PhCHCHCHO	−20	24	89	42
4[d]	2-Naphthaldehyde	0	96	81	37
5[c]	$PhCH_2CH_2CHO$	−10	42	38	58

[a] The reaction was performed using 0.2 mmol of aldehyde and 0.4 mmol of diethylzinc in 250 μL of toluene.
[b] ee was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralcel OD).
[c] The absolute configuration was based on Ref. 10b.
[d] The absolute configuration was based on Ref. 14.

3. Conclusion

In conclusion, a series of binaphthyl-containing salicylhydrazones was synthesized, and their potential as chiral ligand was examined in the nucleophilic addition of diethylzinc to aldehydes (up to 80% ee). Since various *N*,*N*-dialkyl hydrazines and substituted salicylaldehydes are readily accessible, the synthesis of a large number of binaphthyl-consisting salicylhydrazones is possible. Further application of the chiral salicylhydrazones to various asymmetric catalyses is now in progress.

4. Experimental

4.1. General

Analytical TLC was carried out on pre-coated (0.25 mm) silica gel plates. Column chromatography was conducted with 100–210 μm silica gel 60 N (Spherical, neutral). Infrared (IR) spectra were recorded on a FTIR spectrometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometers. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane (δ 0) or chloroform (δ 7.26). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on 100 MHz spectrometers. Chemical shifts of ^{13}C NMR spectra were reported relative to $CDCl_3$ (δ 77.0).

4.2. 2-((*E*)-((*R*)-6,7-Dihydro-5*H*-dinaphtho[2,1-*c*;1′,2′-*e*]-azepin-6-ylimino)methyl)phenol L1a

To a mixture of salicylaldehyde (1 mmol, 106 μL) and hydrazine monohydrate (1.0 equiv, 51 μL) in ethanol (2 mL) was added $MgSO_4$ (2.0 equiv, 250 mg), and the resulting suspension stirred at 50 °C for 30 min. Then, Et_3N (2.2 equiv, 330 μL) and 2,2′-bromomethyl binaphthalene (1.1 equiv, 484 mg) in THF (2 mL) were added to the mixture. After being stirred at 50 °C for 19 h, the insoluble residue was removed by filtration, and concentrated in vacuo. To the residue was added saturated $NaHCO_3$ (30 mL), and the solution was extracted with CH_2Cl_2 (15 mL × 4). The combined extract was dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on neutral silica gel (AcOEt/hexane, 1:15) to give **L1a** (29.9 mg, 72%) as a solid. R_f 0.6 (AcOEt/hexane = 1:4); ^{1}H NMR ($CDCl_3$) δ: 11.68 (s, 1H), 7.94–7.91 (m, 4H), 7.58 (d, J = 8.5 Hz, 2H), 7.50–7.43 (m, 5H), 7.28–7.22 (m, 2H), 7.16–7.11 (m, 1H), 7.00–6.94 (m, 2H), 6.80–6.75 (m, 1H), 4.47 (d, J = 12.3 Hz, 2H), 3.76 (d, J = 12.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.6, 77.2, 116.4, 119.0, 119.5, 125.9, 126.1, 127.2, 127.4, 128.4, 129.0, 129.1, 131.4, 132.5, 133.3, 134.8, 139.9, 157.3; IR (ATR): 3050, 3010, 2927, 2854, 1267, 746 cm^{-1}; FAB-HRMS calcd for $C_{29}H_{22}ON_2$ 414.1732, found 414.1723.

4.3. 2-*tert*-Butyl-6-((*E*)-((*R*)-6,7-dihydro-5*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]azepin-6-ylimino)methyl)phenol L1b

To a mixture of 3-*tert*-butyl-2-hydroxybenzaldehyde (0.3 mmol, 51.4 μL) and hydrazine monohydrate (1.05 equiv, 15.3 μL) in ethanol (0.6 mL) was added $MgSO_4$ (2.0 equiv, 74 mg), and the resulting suspension was stirred at 30 °C for 2 h. Then, Et_3N (2.0 equiv, 90 μL) and 2,2′-bromomethyl binaphthalene (1.0 equiv,

132 mg) in THF (1.5 mL) was added to the mixture. After being stirred at 60 °C for 8 h, insoluble residue was removed by filtration, and concentrated in vacuo. The residue was purified by column chromatography on neutral silica gel (AcOEt/hexane, 1:15) to give **L1b** (94.6 mg, 67%) as a solid. R_f 0.28 (AcOEt/hexane = 1:15); ^{1}H NMR ($CDCl_3$) δ: 12.15 (s, 1H), 7.97–7.93 (m, 4H), 7.62 (d, $J = 8.2$ Hz, 2H), 7.56 (s, 1H), 7.50–7.45 (m, 4H), 7.3–7.26 (m, 2H), 7.18 (dd, $J = 1.5$, 7.8 Hz, 1H), 6.89 (dd, $J = 1.6$, 7.7 Hz, 1H), 6.74 (t, $J = 15.3$ Hz, 1H), 4.52 (d, $J = 12.3$ Hz, 2H), 3.78 (d, $J = 12.3$ Hz, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 29.5, 34.9, 56.4, 118.2, 119.4, 125.8, 126.1, 126.6, 127.3, 127.4, 127.7, 128.4, 129.0, 131.4, 132.6, 133.4, 134.8, 136.7, 141.1, 156.7; IR (ATR): 3052, 3008, 2958, 2864, 1495, 752 cm^{-1}; FAB-HRMS calcd for $C_{33}H_{30}N_2O$ 470.2358, found 470.2338.

4.4. 4-*tert*-Butyl-2-((*E*)-((*R*)-6,7-dihydro-5*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]azepin-6-ylimino)methyl)phenol L1c

To a mixture of 5-*tert*-butyl-2-hydroxybenzaldehyde (0.2 mmol, 34.3 μL) and hydrazine monohydrate (1.0 equiv, 9.7 μL) in ethanol (0.4 mL) was added $MgSO_4$ (2.0 equiv, 48 mg), and the resulting suspension stirred at rt for 2 h. Then, Et_3N (2.0 equiv, 60.2 μL) and 2,2′-bromomethyl binaphthalene (1.0 equiv, 88 mg) in THF (0.4 mL) was added to the mixture. After being stirred at 60 °C for 26 h, the insoluble residue was removed by filtration, and concentrated in vacuo. The residue was purified by column chromatography on neutral silica gel (AcOEt/hexane, 1:15) to give **L1c** (42.3 mg, 45%) as a solid. R_f 0.55 (AcOEt/hexane = 1:4); ^{1}H NMR ($CDCl_3$) δ: 11.48 (s, 1H), 7.95 (dd, $J = 3.5$, 8.3 Hz, 4H), 7.60 (d, $J = 8.5$ Hz, 2H), 7.56 (s, 1H), 7.49–7.45 (m, 4H), 7.30–7.25 (m, 2H), 7.19 (dd, $J = 2.3$, 8.6 Hz, 1H), 7.02 (d, $J = 2.2$ Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 4.50 (d, $J = 12.1$ Hz, 2H), 3.78 (d, $J = 12.3$ Hz, 2H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 31.4, 33.9, 56.6, 116.0, 118.7, 125.8, 125.9, 126.1, 126.3, 127.2, 127.4, 128.4, 129.0, 131.4, 132.6, 133.4, 134.8, 140.6, 141.7, 155.1; IR (ATR): 3052, 2954, 2870, 1431, 750 cm^{-1}; FAB-HRMS calcd for $C_{33}H_{30}N_2O$ 470.2358, found 470.2326.

4.5. 4-Bromo-2-((*E*)-((*R*)-6,7-dihydro-5*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]azepin-6-ylimino)methyl)phenol L1d

To a mixture of 5-bromosalicylaldehyde (2 mmol, 402 mg) and hydrazine monohydrate (1.0 equiv, 97 μL) in THF (4 mL) was added $MgSO_4$ (5.0 equiv, 600 mg). After being stirred at rt for 21 h, the insoluble residue was removed by filtration, and the residue was purified by column chromatography on neutral silica gel (AcOEt/hexane, 1:4) to give the corresponding hydrazone (97.4 mg, 22% yield). Then, the hydrazone (0.45 mmol, 97 mg) and Et_3N (2 equiv, 135 μL) in THF (1.8 mL) were added to 2,2′-bromomethyl binaphthalene (1.0 equiv, 198 mg). After being stirred at 40 °C for 24 h, the insoluble residue was removed by filtration, and the residue was purified by column chromatography on neutral silica gel (AcOEt/hexane, 1:15) to give **L1d** (44.4 mg, 19% yield). R_f 0.3 (AcOEt/hexane = 1:10); ^{1}H NMR ($CDCl_3$) δ: 11.55 (s, 1H), 7.90–7.80 (m, 4H), 7.48 (d, $J = 8.5$ Hz, 2H), 7.41–7.36 (m, 4H), 7.28 (s, 1H), 7.20–7.10 (m, 3H), 7.00 (d, $J = 2.5$ Hz, 1H), 6.75 (d, $J = 8.7$ Hz, 1H), 4.4 (d, $J = 12.4$ Hz, 2H), 3.7 (d, $J = 12.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 56.5, 110.7, 118.2, 121.3, 126.0, 126.1, 126.7, 127.1, 127.4, 128.4, 129.1, 131.1, 131.4, 131.4, 132.2, 133.3, 134.7, 156.2; IR (ATR): 3055, 3010, 2924, 2852, 1477, 1267, 754 cm^{-1}; FAB-HRMS calcd for $C_{29}H_{21}BrN_2O$ (M^+) 492.0837, found 492.0777.

4.6. (*R*)-3,3′-Diformyl-2,2′-binaphthol bis-*N*-(dimethylamino)imine L2a

To a solution of 3,3′-diformyl binaphthol (0.3 mmol, 103 mg) in $CHCl_3$ (6 mL) was added 1,1-dimethyl hydrazine (2.2 equiv, 51 μL). After being stirred at rt for 16 h, the reaction mixture was concentrated in vacuo to give **L2a** (133.1 mg, 99%) as a yellow solid. R_f 0.25 (AcOEt/hexane = 1:2); ^{1}H NMR ($CDCl_3$) δ: 11.75 (s, 2H), 7.82–7.76 (m, 4H), 7.66 (s, 2H), 7.28–7.15 (m, 6H), 2.95 (s, 12H); ^{13}C NMR ($CDCl_3$) δ: 42.6, 116.6, 121.9, 123.1, 124.7, 126.7, 128.0, 128.2, 129.0, 133.4, 136.8, 152.3; IR (ATR): 3055, 3001, 2956, 2871, 2792, 1435, 750 cm^{-1}; FAB-HRMS calcd for $C_{26}H_{26}O_2N_4$ 426.2056, found 426.2021.

4.7. (*R*)-3,3′-Diformyl-2,2′-binaphthol bis-*N*-(pyrrolidinyl)-imine L2b

To a solution of 3,3′-diformyl binaphthol (0.23 mmol, 80 mg) in $CHCl_3$ (4 mL) was added 60% aq *N*-aminopyrolizine (4.0 equiv, 150 μL). After being stirred at rt for 6 h, the reaction was quenched by adding saturated $NaHCO_3$ (30 mL), and the aqueous layer was extracted with $CHCl_3$ (15 mL × 4). The combined extract was dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on neutral silica gel (AcOEt/hexane, 1:2) to give **L2b** (110 mg, 99%) as a white solid in yield. R_f 0.4 (AcOEt/hexane = 1:2); ^{1}H NMR ($CDCl_3$) δ: 11.69 (s, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.73 (s, 2H), 7.55 (s, 2H), 7.26–7.15 (m, 6H), 3.33–3.29 (m, 8H), 1.97–1.90 (m, 8H); ^{13}C NMR ($CDCl_3$) δ: 23.4, 50.8, 116.5, 122.4, 123.0, 124.7, 126.4, 127.8, 128.2, 128.2, 133.2, 135.7, 152.1; IR (ATR): 3055, 2958, 2924, 2854, 1435, 1340, 750 cm^{-1}; FAB-HRMS calcd for $C_{30}H_{30}O_2N_4$ 478.2369, found 478.2366.

4.8. General procedure for the asymmetric addition of diethylzinc to benzaldehyde

To a solution of **L2a** (17 mg, 0.04 mmol) in anhydrous toluene was added diethylzinc (1.6 mL 1.0 M solution in hexane) under Ar and stirred for 10 min at room temperature. The solution was cooled at −20 °C, and benzaldehyde (81.3 μL, 0.8 mmol) was added slowly. After being stirred for 6 h at −20 °C, the reaction was quenched with 1 M aqueous HCl (20 mL). The mixture was extracted with Et_2O, and the combined organic layer dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford 1-phenyl-1-propanol (81.7 mg, 75%) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralcel OD, Hex/*i*-PrOH = 9:1).

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