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A Highly Diastereo- and Enantioselective Copper(I)-Catalyzed Henry Reaction Using a Bis(sulfonamide)−Diamine Ligand

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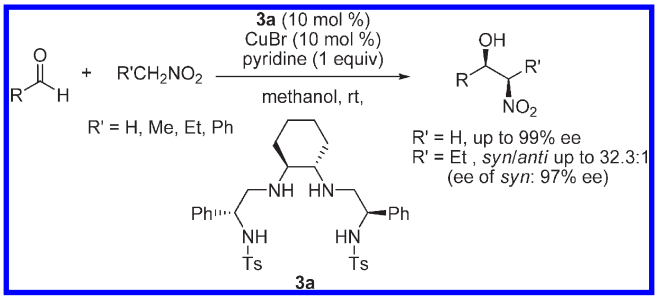

A series of bis(sulfonamide)−diamine (BSDA) ligands were synthesized from commercially available chiral α-amino alcohols and diamines. The chiral BSDA ligand **3a**, coordinated with Cu(I), catalyzes the enantioselective Henry reaction with excellent enantioselectivity (up to 99%). Moreover, with the assistance of pyridine, a CuBr−**3a** system promotes the diastereoselective Henry reaction with various aldehyde substrates and gives the corresponding *syn*-selective adduct with up to a 99% yield and 32.3:1 *syn*/*anti* selectivity. The enantiomeric excess of the *syn* adduct was 97%.

Introduction

The nitroaldol (Henry) reaction is one of the most atom-economic C−C bond-forming reactions.[1] The resulting products, β-nitroalcohols, are widely used organic intermediates because of the many possible transformations of the nitro group into other functional groups.[2] Thus, the development of catalytic, asymmetric protocols for this reaction has gained particular attention. Efforts aimed at achieving an asymmetric version of the process by using chiral, metallic (such as rare-metal,[3] Cu,[4] Zn,[5] Co,[6] Cr,[7] Mg[8]) and organic catalysts[9] as well as biocatalysts[10] have been extensively explored in recent years, and the most prominent results have been obtained with a copper-based catalyst system. The design and development of the ligand plays a pivotal role in the development of efficient metal-catalyzed asymmetric reactions. In a recent communication, we developed a chiral

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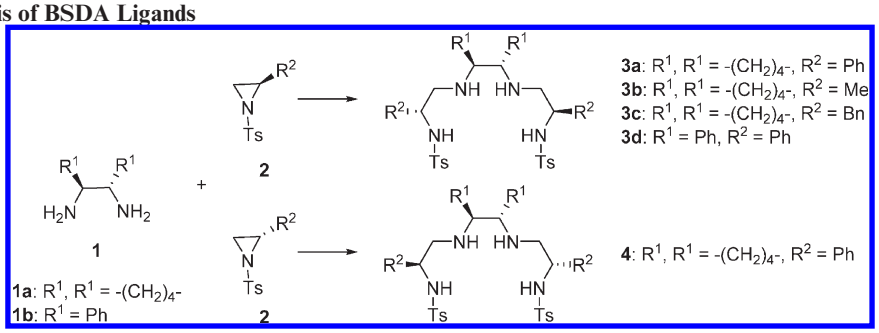
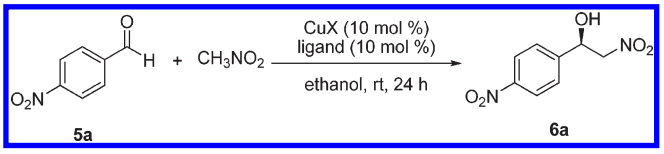
SCHEME 1. Synthesis of BSDA Ligands



bis(sulfonamide)−diamine (BSDA) skeleton for the $Cu(OAc)_2$-catalyzed enantioselective Henry reaction.[11] Although a high yield and high enantioselectivity were observed when nitromethane was used as the nucleophile, the diastereo- and enantioselective Henry reactions of nitroethane or other nitroalkanes remain less explored. Even after the Shibasaki group reported the first *syn*-selective Henry reaction using modified heterometallic complexes,[12] examples of effective reactions are still quite limited.[13,14] Moreover, limitations, such as low reaction temperature and a multistep synthetic procedure for ligand preparation, still need to be addressed. Therefore, in this paper, we fully delineate the details of our findings on the highly diastereo- and enantioselective Henry reaction using the BSDA−CuBr system as the catalyst.

TABLE 1. Screening of Central Metals and BSDA Ligand Structures[a]



entry	ligand	CuX	yield (%)	ee (%)[b]
1	**3a**	CuI	76	78
2	**3a**	CuBr	95	94
3	**3a**	CuCl	55	89
4	**3a**	CuCN	84	20
5	**3a**	CuOAc	84	83
6	**3b**	CuBr	54	11
7	**3c**	CuBr	59	77
8	**3d**	CuBr	48	87
9	**4**	CuBr	33	87
10	**1a**	CuBr	99	rac
11	**1b**	CuBr	99	rac

[a]Reactions were carried out using 0.25 mmol of *p*-nitrobenzaldehyde, ethanol (1 mL), and nitromethane (10 equiv) at room temperature. [b]Enantiomeric excesses were determined by HPLC analysis on a chiral OD-H column.

Results and Discussion

Ligands **3** and **4** were prepared via a one-step reaction between commercially available chiral diamines **1** and the corresponding aziridines **2**[15] (Scheme 1).[16] Pure products were obtained with satisfactory yields. These ligands are stable for months in air.

Before examining the diastereoselective Henry reaction, it is reasonable to test the potential of the BSDA ligands in an enantioselective nitroaldol model reaction using *p*-nitrobenzaldehyde and nitromethane. The results are summarized in Table 1. At the outset, a series of Cu(I) catalysts, such as CuI, CuCl, CuCN, and CuOAc, were screened in the presence of ligand **3a** in ethanol (Table 1, entries 1−5), and the corresponding products of the Henry reaction were obtained with relatively low yields and moderate ee values (Table 1, entries 1 and 3−5). CuBr turned out to be the best copper catalyst for the reaction (Table 1, entry 2). The sequential investigations on the steric and electronic effects of the BSDA ligands showed that the reactivity and enantioselectivity were closely related to the chiral backbone and the substituents of the

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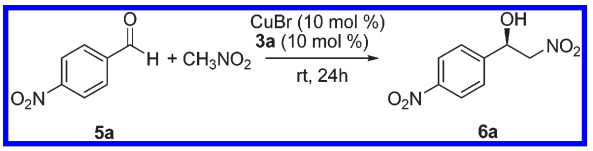
TABLE 2. Effect of Solvents on the Asymmetric Henry Reaction[a]



entry	solvent	yield (%)	ee (%)[b]
1	ethanol	95	94
2	methanol	98	95
3	acetonitrile	36	77
4	dichloromethane	27	66
5	toluene	32	61
6	THF	79	79
7	2-propanol	70	90

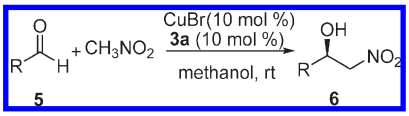
[a]Reactions were carried out using 0.25 mmol of *p*-nitrobenzaldehyde, CuBr (10 mol %), **3a** (10 mol %), and nitromethane (10 equiv) in solvent (1 mL) at room temperature for 24 h. [b]Enantiomeric excesses were determined by HPLC analysis on a chiral OD-H column.

ligand moiety. The result obtained with ligand **3a** was superior to that with ligands **3d** and **4** in terms of yield and enantioselectivity (Table 1, entries 2, 8, and 9). The R^2 substituent of the sulfonamide moiety of the BSDA ligand significantly affected the yield and enantioselectivity (Table 1, entries 2, 6, and 7). In control experiments, the known chiral diamines **1a** and **1b** were also tested in the reaction.[4k] In terms of ee values, ligands **1a** and **1b** produced inferior results compared with those of ligand **3a**. Therefore, we conclude that the weak coordination of the additional sulfonamide fragment is necessary for further acceleration and stereocontrol in the addition reaction as compared to reactions with the chiral diamines.

The solvent effects on enantioselectivity were examined in the presence of 10 mmol % CuBr−**3a**, and the results are shown in Table 2. Among the screened solvents, ethanol, methanol, and 2-propanol were superior in terms of enantioselectivity (Table 2, entries 1, 2, and 7). The best enantioselectivity, as well as an excellent yield, was observed when the reaction was performed in methanol (Table 2, entry 2).

Given the above-mentioned optimal results, the complex of CuBr−**3a** was used in the asymmetric addition of nitromethane to a variety of other aldehydes (Table 3). The reactions worked well to generate the Henry adduct in high yields with excellent enantioselectivities. For aromatic aldehydes, the present system tolerated both electron-withdrawing and electron-donating substituents (Table 3, entries 3−8). Interestingly, the position of the substituent on the phenyl ring had a limited effect on the enantioselectivity (Table 3, entries 4−6). Aldehydes with a large sterical hindrance, such as 1-naphthaldehyde and 2-naphthaldehyde, could also give the corresponding adducts with good yield and high enantioselectivity (Table 3, entries 9 and 10). Aliphatic aldehydes were found to be good substrates, affording the corresponding adducts with excellent selectivities. High yields and excellent enantioselectivities were achieved with the addition of nitromethane to linear and branched aldehydes. For linear aldehydes, the length of the alkyl carbon chain had little effect on the enantioselectivity (Table 3, entries 13, 17, and 18), and the size of the alkyl group also had no effect on the enantioselectivity (Table 3, entries 14 and 20). Excellent reactivity and enantioselectivity were observed with α-branched aliphatic aldehydes, such as

TABLE 3. Henry Reaction of Various Aromatic and Aliphatic Aldehydes[a]



entry	R	product	time (h)	yield (%)	ee (%)[b]
1	4-NO_2-C_6H_4	**6a**	24	98	95 (*R*)
2	Ph	**6b**	48	93	96 (*R*)
3	2-Me-C_6H_4	**6c**	48	92	97 (*R*)
4	2-MeO-C_6H_4	**6d**	60	75	96 (*R*)
5	3-MeO-C_6H_4	**6e**	48	77	94 (*R*)
6	4-MeO-C_6H_4	**6f**	60	74	92 (*R*)
7	4-Cl-C_6H_4	**6g**	36	85	95 (*R*)
8	4-Br-C_6H_4	**6h**	36	80	95 (*R*)
9	1-naphthyl	**6i**	24	85	93 (*R*)
10	2-naphthyl	**6j**	24	70	95 (*R*)
11	$PhCH_2CH_2$	**6k**	24	83	96 (*R*)
12	$(CH_3)_2CH$	**6l**	36	83	99 (*R*)
13	$CH_3(CH_2)_4$	**6m**	30	99	98 (*R*)
14	*c*-hexyl	**6n**	36	99	98 (*R*)
15	$PhCH_2$	**6o**	48	99	97 (*R*)
16	$(CH_3)_2CHCH_2$	**6p**	36	99	97 (*R*)
17	$CH_3(CH_2)_3$	**6q**	36	93	97 (*R*)
18	$CH_3(CH_2)_8$	**6r**	36	99	98 (*R*)
19	$(CH_3CH_2)_2CH$	**6s**	36	97	99 (*R*)
20	*c*-C_5H_9	**6t**	36	99	98 (*R*)

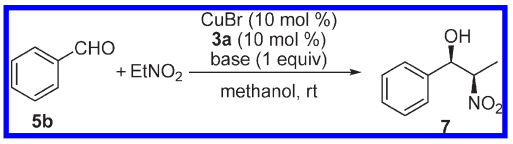
[a]Reactions were carried out using 0.25 mmol of aldehyde, CuBr (10 mol %), **3a** (10 mol %), and nitromethane (10 equiv) in methanol (1 mL) at room temperature. [b]Enantiomeric excesses were determined by HPLC analysis, and the absolute configuration was assigned by comparison to literature values.[17]

*iso*butyraldehyde and 2-ethylbutyraldehyde. In the most successful reactions, up to a 99% ee was obtained (Table 3, entries 12 and 19).

Finally, the optimized catalyst system was applied to the diastereoselective Henry reaction. The initial results indicated that the reaction between the benzaldehyde (**5b**) and nitroethane required an extended reaction time (Table 4, entry 1) to reach completion. Because the Henry reaction is considered to employ basicity to generate the nitronate, base was added to the reaction system to increase the reactivity of the catalyst.[13c] A series of bases were tested in a model reaction between nitroethane and benzaldehyde (**5b**) in the presence of ligand **3a** and CuBr. The results are summarized in Table 4. As expected, the reactivity of the catalyst and the yield of the nitroaldol products were significantly improved when a series of bases were added (Table 1, entries 2−9). Variation of the base slightly affected the *syn*/*anti* ratio while greatly influencing the yield and enantioselectivity. Among the screened bases, morpholine gave a negative result (Table 4, entry 7). Bulky amines, such as Et_3N, DIPEA, and DBU, gave the nitroaldol adduct in moderate to good yields with low enantioselectivities (Table 4, entries 1, 2, and 4). The strong coordinating bases DMAP and 2,6-diaminopyridine gave poor enantioselectivities (Table 4, entries 3 and 5). In contrast to morpholine, *N*-methylmorpholine exhibited good reactivity and moderate enantioselectivity for the *syn* product (Table 4, entry 8). When pyridine was employed, the enantioselectivity of the *syn* diastereomer improved substantially to 87% (Table 4, entry 9).

After the optimal base was determined, the scope of the catalytic diastereoselective Henry reaction was evaluated, and the results are summarized in Table 5. When nitroethane

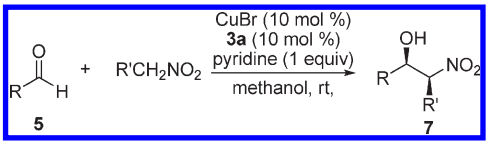
TABLE 4. Effect of Bases on the Diastereoselective Henry Reaction[a]



entry	base	yield (%)	*syn*/*anti*[b]	ee of *syn* (%)[c]
1[d]	no	55	2.0:1	80
2	Et_3N	77	1.9:1	< 1
3	DIPEA	91	1.9:1	5
4	DMAP	87	2.1:1	13
5	DBU	88	1.8:1	17
6	2,6-diaminopyridine	30	2.0:1	19
7	morpholine	0		
8	*N*-methylmorpholine	86	2.1:1	25
9	pyridine	95	2.2:1	87

[a]Reactions were carried out using 0.25 mmol of benzaldehyde, CuBr (10 mol %), **3a** (10 mol %), base (1 equiv), and nitroethane (10 equiv) in methanol (1 mL) at room temperature for 24 h. [b]Determined by NMR analysis. [c]Determined by HPLC analysis of the crude product. [d]Reaction was run for 7 days.

TABLE 5. Asymmetric Henry Reaction of Nitroalkanes and Aldehydes Catalyzed by CuBr−3a[a]



entry	R	R′	product	yield (%)	*syn*/*anti*[b]	ee of *syn* (%)[c]
1	Ph	Me	**7a**	95	2.2:1	87
2[d]	2-MeO-C_6H_4	Me	**7b**	86	8.1:1	92
3[d]	4-MeO-C_6H_4	Me	**7c**	99	3.9:1	77
4	4-Cl-C_6H_4	Me	**7d**	98	2.2:1	72
5	1-naphthyl	Me	**7e**	88	13.3:1	82
6	$PhCH_2CH_2$	Me	**7f**	81	4.3:1	93
7	*c*-hexyl	Me	**7g**	71	8.1:1	94
8	Ph	Et	**7h**	88	4.3:1	80
9	2-MeO-C_6H_4	Et	**7i**	82	24:1	94
10	4-Cl-C_6H_4	Et	**7j**	57	15.1:1	81
11	$PhCH_2CH_2$	Et	**7k**	90	2.1:1	98
12	*c*-hexyl	Et	**7l**	72	32.3:1	97
13[e]	*c*-hexyl	Ph	**7m**	90	5.7:1	77

[a]Reactions were carried out using 0.25 mmol of aldehyde, CuBr (10 mol %), **3a** (10 mol %), pyridine (1 equiv), and nitroalkane (10 equiv) in methanol (1 mL) at room temperature. [b]Determined by HPLC analysis. [c]Enantiomeric excesses were determined by HPLC analysis of the crude product. [d]The reaction was run for 60 h. [e]The reaction was run for 36 h.

was used, the reaction of aromatic and aliphatic aldehydes proceeded well to afford the desired product in moderate to good yields, accompanied by the predominant *syn* diastereomer, and good to excellent enantioselectivities. Interestingly, the reaction with an *ortho*-substituted benzaldehyde as the substrate provided much higher diastereoselectivity than that with a *para*-substituted benzaldehyde. For instance, the reaction with 2-methoxybenzaldehyde afforded the corresponding product with a *syn*/*anti* diastereoselectivity of 8.1:1, while the reaction with 4-methoxybenzaldehyde gave a ratio of 3.3:1 (Table 5, entries 2 and 3). Interestingly, use of a bulky aldehyde, such as 1-naphthaldehyde, resulted in high

(17) The absolute configuration was assigned by comparison to literature values; see the Experimental Section.

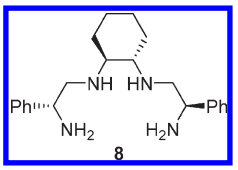


FIGURE 1. Ligand **8**.

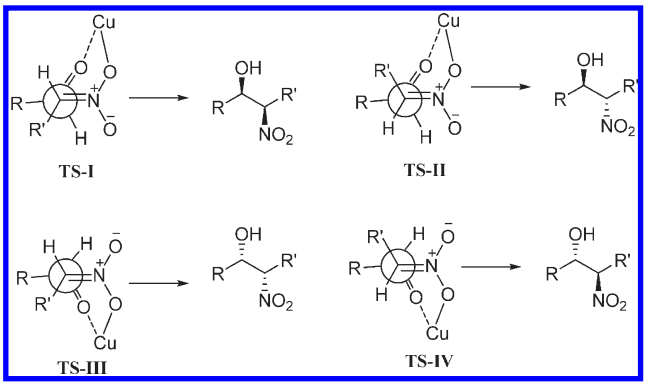


FIGURE 2. Plausible transition state for the diastereoselective Henry reaction.

diastereoselectivity 13.3:1 (Table 5, entry 5). In general, diastereoselectivity was dramatically improved when 1-nitropropane was used. 4-Chlorobenzaldehyde reacted with 1-nitropropane to afford the corresponding product in good diastereoselectivity (15.7:1). In contrast, the reaction between 4-chlorobenzaldehyde and nitroethane only gave a ratio of 2.2:1 (Table 5, entries 4 and 10). Moreover, the addition of 1-nitropropane and cyclohexanecarboxaldehyde gave the corresponding adduct with a 97:3 *syn* selectivity. The enantioselectivity of the *syn* product was 97% (Table 5, entry 12). Furthermore, we found that the catalyst system of CuBr−**3a**−pyridine was also effective for the diastereoselective Henry reaction between (nitromethyl)benzene and cyclohexanecarboxaldehyde. The *syn* adduct was furnished with a good *syn*/*anti* ratio of 5.7:1, and the ee value of the *syn* diastereomer was 77% (Table 5, entry 13).

To investigate the function of the sulfonamide moiety, ligand **8** was synthesized and explored in the Henry reaction (Figure 1). Ligand **8** turned out to be inefficient in the copper-catalyzed Henry reaction. This result suggests that the nitrogen atom from the sulfonamide serves as a weak coordinating site in the molecule because it is a poor electron donor.[18] On the basis of the observed *syn* selectivity of the reaction, a possible transition state model of Cu with **3a** is depicted in Figure 2. After accounting for the steric hindrance of the Cu-containing transition state, the structure **TS-I** is most favored and results in a *syn* adduct.

Conclusion

The bis(sulfonamide)−diamine ligand **3a**, containing both diamine and bis-sulfonamide moieties, together with CuBr, was able to promote a highly enantioselective Henry reaction between nitromethane and a wide range of aromatic and aliphatic aldehydes, providing high yields and excellent enantioselectivities. Notably, with the assistance of pyridine,

(18) Pritchett, S.; Gantzel, P.; Walsh, P. J. *Organometallics* **1997**, *16*, 5130–5132.

this catalyst system was able to promote a highly *syn*-selective Henry reaction of an aldehyde with nitroalkanes with up to a 97% ee of the *syn* adduct in 99% yield. The effectiveness of this catalyst system and the simplicity of the reaction procedure make our catalyst widely applicable. Further work is in progress with the aim of expanding the applications of these inexpensive chiral ligands to other enantioselective catalytic processes.

Experimental Section

General Procedure for the Preparation of the Bis(sulfonamide)−Diamines 3 and 4. Chiral diamines **1a** or **1b** and the corresponding aziridines **2**[5] were dissolved in dry acetonitrile, and the mixture was stirred under reflux for 3 days. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on a silica gel using petroleum ether and ethyl acetate as eluent.

Characterization of 3a: white solid; 70% yield; mp 74−76 °C; $[\alpha]^{25}_D = -12.9$ (*c* 1.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.76 (m, 2H), 7.59−7.57 (m, 2H), 7.28−7.20 (m, 5H), 7.22−7.05 (m, 9H), 4.39 (t, J = 7.44 Hz, 1H), 3.81−3.78 (m, 1H), 3.06−3.03 (m, 1H), 2.91−2.87 (m, 2H), 2.68 (m, 1H), 2.39 (s, 1H), 2.31 (s, 3H), 2.29 (m, 1H), 1.85−1.84 (m, 2H), 1.57−1.54 (m, 2H), 0.89−0.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.1, 141.2, 139.6, 137.9, 137.2, 129.9, 129.4, 128.9, 128.5, 127.9, 127.6, 127.4, 127.2, 126.98, 126.7, 61.7, 58.4, 58.1, 57.7, 52.5, 49.8, 31.95, 31.4, 24.97, 24.8, 21.7, 21.6; HRMS (APCI) calculated for $C_{36}H_{44}N_4O_4S_2$ (M + H^+) 661.2882, found 661.2862.

Characterization of 3b: yellow oil; 35% yield; $[\alpha]^{25}_D = -31.0$ (*c* 0.91, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.79 (m, 4H), 7.29−7.27 (m, 4H), 3.40−3.36 (m, 2H), 2.75−2.71 (m, 2H), 2.40−2.36 (m, 8H), 2.10−2.08 (m, 2H), 2.04 (b, 2H), 1.84−1.80 (m, 2H), 1.63−1.61 (m, 2H), 1.12−1.09 (m, 2H), 0.99−0.91 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 138.5, 129.6, 127.0, 61.1, 51.7, 50.2, 31.8, 24.9, 21.5, 19.1; HRMS (APCI) calculated for $C_{26}H_{40}N_4O_4S_2$ (M + H^+) 537.2569, found 537.2567.

Characterization of 3c: white solid; 44% yield; mp 128−129 °C; $[\alpha]^{25}_D = -53.9$ (*c* 1.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.59 (m, 4H), 7.16−7.12 (m, 10H), 6.99−6.97 (m, 4H), 3.62 (m, 2H), 2.85−2.82 (m, 2H), 2.70−2.62 (m, 4H), 2.54−2.30 (m, 8H), 1.83 (m, 2H), 1.65 (m, 2H), 1.15−1.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 138.3, 137.8, 129.8, 129.4, 128.7, 127.0, 126.5, 59.8, 56.1, 48.5, 39.5, 31.7, 25.2, 21.7; HRMS (APCI) calculated for $C_{38}H_{48}N_4O_4S_2$ (M + H^+) 689.3195, found 689.3178.

Characterization of 3d: white solid; 74% yield; mp 83−85 °C; $[\alpha]^{25}_D = +18.4$ (*c* 0.63, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.58 (m, 2H), 7.44−7.42 (m, 2H), 7.41−7.20 (m, 10H), 7.18−7.12 (m, 3H), 7.09−7.00 (m, 5H), 6.83 (m, 4H), 6.74−6.72 (m, 2H), 5.74 (b, 1H), 5.07 (b, 1H), 4.33 (m, 1H), 3.43−3.41 (m, 1H), 3.21−3.19 (m, 2H), 2.97−2.86 (m, 2H), 2.67−2.63 (m, 1H), 2.52-δ 2.36 (m, 1H), 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 143.0, 140.8, 140.4, 140.2, 139.6, 129.8, 129.5, 128.9, 128.6, 128.3, 128.2, 128.0, 127.8, 127.6, 127.4, 127.3, 127.2, 126.9, 69.2, 65.4, 58.8, 57.4, 52.6, 49.6, 21.7, 21.6; HRMS (APCI) calculated for $C_{44}H_{46}N_4O_4S_2$ (M + H^+) 759.3039, found 759.3010.

Characterization of 4: white solid; 42% yield; mp 69−71 °C; $[\alpha]^{25}_D = +51.9$ (*c* 0.86, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.78−7.76 (m, 2H), 7.65−7.63 (m, 2H), 7.40−7.38 (m, 2H), 7.29−7.18 (m, 12H), 4.43 (t, J = 7.88 Hz, 1H), 3.74 (t, J = 6 Hz, 1H), 3.00−2.85 (m, 3H), 2.65 (m, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 2.06−1.99 (m, 2H), 1.89−1.55 (m, 2H), 1.07−1.05 (m, 2H), 0.85−0.83 (m, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 144.0, 143.1, 142.8, 140.9, 138.9, 138.3, 129.8, 129.4, 128.9, 128.3, 127.4, 127.2, 127.1, 60.8, 60.5, 57.8, 52.5, 49.4, 32.6, 31.1, 25.0, 24.6, 20.7; HRMS (APCI) calculated for $C_{36}H_{44}N_4O_4S_2$ (M + H^+) 661.2882, found 661.2865.

General Procedure for the Addition of Nitromethane to Aldehydes. Under an argon atmosphere, the ligand **3a** (16.5 mg, 0.025 mmol, 10 mmol %) and CuBr (3.6 mg, 0.025 mmol, 10 mmol %) were suspended in anhydrous methanol (1.0 mL). After stirring for 1 h at room temperature, nitromethane (0.27 mL, 10 mmol) and the aldehyde (0.025 mmol) were added and the reaction was stirred for a specified amount of time at room temperature. The volatile components were then removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the pure product. The enantiomeric purity of the product was determined by HPLC analysis. The absolute configurations of the products were assigned by comparison to literature values.

Characterization of the Enantioselective Henry Products. (*R*)-(-)-2-Nitro-1-(4-nitrophenyl)ethanol (6a).[4e] 98% yield; 95% ee; yellow solid; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 22.00 min, t_r (minor) = 27.69 min; $[\alpha]^{25}_D = -39.1$ (*c* 0.98, CH_2Cl_2, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 2H), 7.65 (d, J = 2.4 Hz, 2H), 5.62 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 4.56−4.64 (m, 2H), 3.15 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 145.1, 127.2, 124.4, 80.8, 70.2.

(*R*)-(-)-2-Nitro-1-phenylethanol (6b).[4e] 93% yield; 96% ee; yellow oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 13.24 min, t_r (minor) = 16.33 min; $[\alpha]^{25}_D = -53.1$ (*c* 1.01, CH_2Cl_2, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.40 (m, 5H), 5.39 (dd, J_1 = 2.86 Hz, J_2 = 9.6 Hz, 1H), 4.55 (dd, J_1 = 9.6 Hz, J_2 = 13.2 Hz, 1H), 4.44 (dd, J_1 = 2.86 Hz, J_2 = 13.2 Hz, 1H), 3.20 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 129.1, 129.0, 126.1, 81.3, 71.1.

(*R*)-(-)-2-Nitro-*o*-tolylethanol (6c).[4e] 92% yield; 97% ee; colorless oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 11.27 min, t_r (minor) = 16.33 min; $[\alpha]^{25}_D = -48.4$ (*c* 1.10, CH_2Cl_2, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.49 (m, 1H), 7.21−7.25 (m, 2H), 7.17−7.15 (m, 1H), 5.62 (dd, J_1 = 2.4 Hz, J_2 = 9.68 Hz, 1H), 4.49 (dd, J_1 = 9.68 Hz, J_2 = 13.28 Hz, 1H), 4.39 (dd, J_1 = 2.4 Hz, J_2 = 13.28 Hz, 1H), 3.02 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 134.6, 130.98, 128.8, 126.9, 125.8, 80.4, 68.1, 18.98.

(*R*)-(-)-2-Nitro-1-(2-methoxyphenyl)ethanol (6d).[14d] 75% yield; 96% ee; colorless oil; HPLC (Chiralcel OD-H, 90/10 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 15.84 min, t_r (minor) = 19.20 min; $[\alpha]^{25}_D = -48.9$ (*c* 0.99, CH_2Cl_2, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 7.32 (td, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H), 7.02 (dd, J_1 = J_2 = 8 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.61 (dd, J_1 = 3.2 Hz, J_2 = 9.2 Hz, 1H), 4.63 (dd, J_1 = 3.2 Hz, J_2 = 12.8 Hz, 1H), 4.55 (dd, J_1 = 9.2 Hz, J_2 = 12.8 Hz, 1H), 3.87 (s, 3H), 3.26 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 129.95, 127.3, 126.1, 121.3, 110.7, 80.0, 67.96, 55.6.

(*R*)-(-)-2-Nitro-1-(3-methoxyphenyl)ethanol (6e).[4e] 77% yield; 94% ee; colorless oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 20.03 min, t_r (minor) = 29.22 min; $[\alpha]^{25}_D = -38.8$ (*c* 0.99, CH_2Cl_2, 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 8 Hz, 1H), 6.95−6.94 (m, 2H), 6.88 (dd, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 1H), 5.41 (dd, J_1 = 2.4 Hz, J_2 = 9.6 Hz, 1H), 4.58 (dd, J_1 = 9.6 Hz, J_2 = 13.2 Hz, 1H), 4.49 (dd, J_1 = 2.4 Hz, J_2 = 13.2 Hz, 1H), 3.81 (s, 3H), 3.05 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 139.96, 130.3, 118.3, 114.6, 111.7, 81.4, 71.1, 55.5.

(*R*)-(-)-2-Nitro-1-(4-methoxyphenyl)ethanol (6f).[14d] 74% yield; 92% ee; colorless oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 17.77 min, t_r (minor) = 22.15 min; $[\alpha]^{25}_D = -47.1$ (*c* 1.00, CH_2Cl_2, 92% ee);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.30 (m, 2H), 6.94−6.90 (m, 2H), 5.40 (dd, J_1 = 3 Hz, J_2 = 9.6 Hz, 1H), 4.60 (dd, J_1 = 9.6 Hz, J_2 = 13.6 Hz, 1H), 4.47 (dd, J_1 = 3 Hz, J_2 = 13.6 Hz, 1H), 3.81 (s, 3H), 2.79 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 130.4, 127.5, 114.6, 81.4, 70.7, 55.6.

(*R*)-(-)-2-Nitro-1-(4-chlorophenyl)ethanol (6g).[4e] 85% yield; 95% ee; colorless oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 14.40 min, t_r (minor) = 18.74 min; $[\alpha]^{25}_D$ = −48.1 (*c* 1.01, CH_2Cl_2, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 4H), 5.41 (dd, J_1 = 3.24 Hz, J_2 = 9.36 Hz, 1H), 4.55 (dd, J_1 = 9.36 Hz, J_2 = 13.28 Hz, 1H), 4.47 (dd, J_1 = 3.24 Hz, J_2 = 13.28 Hz, 1H), 3.30 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.9, 129.3, 127.5, 81.1, 70.4.

(*R*)-(-)-2-Nitro-1-(4-bromophenyl)ethanol (6h).[5d] 80% yield; 95% ee; colorless oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 14.54 min, t_r (minor) = 18.97 min; $[\alpha]^{25}_D$ = −48.0 (*c* 0.95, CH_2Cl_2, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.36 Hz, 2H), 7.26 (d, *J* = 8.36 Hz, 2H), 5.41−5.38 (m, 1H), 4.55 (dd, J_1 = 9.36 Hz, J_2 = 13.32 Hz, 1H), 4.47 (dd, J_1 = 3.2 Hz, J_2 = 13.32 Hz, 1H), 3.23 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 132.3, 127.8, 123.1, 81.1, 70.5.

(*R*)-(-)-2-Nitro-1-(1-naphthyl)ethanol (6i).[4e] 85% yield; 93% ee; yellow oil; HPLC (Chiralcel OD-H, 85/15 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 16.53 min, t_r (minor) = 27.01 min; $[\alpha]^{25}_D$ = −30.6 (*c* 1.01, CH_2Cl_2, 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.49−7.61 (m, 3H), 6.24 (t, *J* = 4 Hz, 1H), 4.66−4.64 (m, 2H), 2.93 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 133.7, 129.6, 129.5, 127.3, 126.3, 125.7, 124.1, 122.0, 80.97, 68.5.

(*R*)-(-)-2-Nitro-1-(2-naphthyl)ethanol (6j).[4e] 70% yield; 95% ee; yellow solid; HPLC (Chiralcel OD-H, 80/20 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm): t_r (major) = 22.71 min, t_r (minor) = 32.29 min; $[\alpha]^{25}_D$ = −51.5 (*c* 1.11, CH_2Cl_2, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.83 (m, 4H), 7.55−7.45 (m, 3H), 5.63 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 4.69 (dd, J_1 = 9.6 Hz, J_2 = 13.6 Hz, 1H), 4.59 (dd, J_1 = 3.2 Hz, J_2 = 13.6 Hz, 1H), 2.90 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.6, 133.4, 129.3, 128.3, 128.0, 126.9, 125.6, 123.4, 81.4, 71.4.

(*R*)-(+)-1-Nitro-4-phenyl-2-butanol (6k).[4g] 83% yield; 96% ee; off-white solid; HPLC (Chiralcel AD-H, 90/10 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm): t_r (major) = 11.69 min, t_r (minor) = 14.88 min; $[\alpha]^{25}_D$ = +15.8 (*c* 0.89, CH_2Cl_2, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2H), 7.25−7.19 (m, 3H), 4.40−4.27 (m, 3H), 2.85−2.82 (m, 1H), 2.78−2.69 (m, 2H), 1.87−1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 128.8, 128.6, 126.5, 80.7, 67.95, 35.3, 34.5.

(*R*)-(-)-3-Methyl-1-nitro-2-butanol (6l).[4c] 83% yield; 99% ee; yellow oil; HPLC (Chiralcel OD-H, 98/2 *n*-hexane/*i*-PrOH, 0.2 mL/min, 20 °C, 215 nm): t_r (major) = 100.40 min, t_r (minor) = 112.97 min; $[\alpha]^{25}_D$ = −29.9 (*c* 0.57, CH_2Cl_2, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, J_1 = 2.88 Hz, J_2 = 12.72 Hz, 1H), 4.41 (dd, J_1 = 9.36 Hz, J_2 = 12.72 Hz, 1H), 4.10−4.06 (m, 1H), 3.42 (b, 1H), 1.79 (td, J_1 = 6.72 Hz, J_2 = 13.4 Hz, 1H), 0.97 (t, *J* = 6.72 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.4, 73.5, 31.7, 18.2, 17.3.

(*R*)-(-)-1-Nitro-2-heptanol (6m).[4h] 99% yield; 97% ee; colorless oil; HPLC (Chiralcel AD-H, 97/3 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm): t_r (major) = 20.29 min, t_r (minor) = 29.66 min; $[\alpha]^{25}_D$ = −10.0 (*c* 1.01, CH_2Cl_2, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46−4.28 (m, 3H), 2.68 (b, 1H), 1.57−1.47 (m, 3H), 1.39−1.31 (m, 5H), 0.90 (t, *J* = 6.72 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.9, 68.9, 33.9, 31.6, 25.0, 22.6, 14.0.

(*R*)-(-)-2-Nitro-(1-cyclohexyl)ethanol (6n).[4c] 99% yield; 98% ee; colorless oil; HPLC (Chiralcel AD-H, 97/3 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm): t_r (major) = 30.16 min, t_r (minor) = 32.90 min; $[\alpha]^{25}_D$ = −19.0 (*c* 0.66, CH_2Cl_2, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51−4.40 (m, 2H), 4.12−4.07 (m, 1H), 2.55 (b, 1H), 1.82−1.77 (m, 3H), 1.69−1.68 (m, 2H), 1.52−1.43 (m, 1H), 1.25−1.08 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.5, 73.0, 41.6, 28.98, 28.1, 26.3, 26.1, 25.9.

(*R*)-(+)-1-Nitro-3-phenyl-2-propanol (6o).[4n] 99% yield; 97% ee; colorless oil; HPLC (Chiralcel OD-H, 90/10 *n*-hexane/*i*-PrOH, 0.5 mL/min, 20 °C, 220 nm): t_r (major) = 39.20 min, t_r (minor) = 51.70 min; $[\alpha]^{25}_D$ = +15.7 (*c* 1.05, CH_2Cl_2, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 4.53 (b, 1H), 4.43−4.33 (m, 2H), 2.90−2.78 (m, 2H), 2.63−2.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 129.5, 129.1, 127.5, 79.9, 69.7, 40.5.

(R)-(+)-4-Methyl-1-nitro-2-pentanol (6p).[4h] 99% yield; 97% ee; colorless oil; HPLC (Chiralcel OJ-H, 97/3 *n*-hexane/*i*-PrOH, 0.8 mL/min, 20 °C, 215 nm): t_r (major) = 21.82 min, t_r (minor) = 23.85 min; $[\alpha]^{25}_D$ = −2.62 (*c* 0.99, CH_2Cl_2, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43−4.33 (m, 3H), 1.85−1.82 (m, 1H), 1.52−1.49 (m, 1H), 1.27−1.20 (m, 1H), 0.96 (t, *J* = 6.36 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.9, 67.2, 42.6, 24.5, 23.4, 21.9.

(*R*)-(-)-1-Nitro-2-pentanol (6q).[4h] 93% yield; 97% ee; colorless oil; HPLC (Chiralcel OJ-H, 97/3 *n*-hexane/*i*-PrOH, 0.6 mL/min, 20 °C, 215 nm): t_r (major) = 38.21 min, t_r (minor) = 40.12 min; $[\alpha]^{25}_D$ = −9.04 (*c* 1.04, CH_2Cl_2, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46−4.37 (m, 2H), 4.35−4.30 (m, 1H), 2.78 (b, 1H), 1.59−1.46 (m, 3H), 1.45−1.35 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.9, 68.9, 33.6, 27.4, 22.6, 14.0.

(*R*)-(-)-1-Nitro-2-decanol (6r).[14d] 99% yield; 98% ee; colorless oil; HPLC (Chiralcel AD-H, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm): t_r (major) = 11.02 min, t_r (minor) = 16.23 min; $[\alpha]^{25}_D$ = −5.5 (*c* 1.01, CH_2Cl_2, 98% ee); ^{1}H NMR (400 MHz, CDCl3) δ 4.45−4.29 (m, 2H), 2.77 (b, 1H), 1.58−1.47 (m, 3H), 1.38−1.27 (m, 13H), 0.88 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 80.9, 68.9, 33.9, 33.0, 29.6, 29.6, 29.5, 29.4, 25.3, 22.8, 14.3.

(*R*)-(-)-3-Ethyl-1-nitro-2-pentanol (6s).[14c] 97% yield; 99% ee; colorless oil; HPLC (Chiralcel AD-H, 99/1 *n*-hexane/*i*-PrOH, 0.5 mL/min, 20 °C, 220 nm): t_r (major) = 62.53 min, t_r (minor) = 70.29 min; $[\alpha]^{25}_D$ = −18.9 (*c* 0.88, CH_2Cl_2, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46−4.42 (m, 2H), 4.37 (m, 1H), 2.51 (b, 1H), 1.52−1.27 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.7, 70.4, 44.9, 21.99, 21.5, 11.6, 11.6.

(*R*)-(-)-2-Nitro-(1-cyclopentan)ethanol (6t).[9h] 93% yield; 97% ee; colorless oil; HPLC (Chiralcel OD-H, 98/2 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm): t_r (major) = 24.88 min, t_r (minor) = 26.85 min; $[\alpha]^{25}_D$ = −3.18 (*c* 1.02, CH_2Cl_2, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (dd, J_1 = 12.8 Hz, J_2 = 2.4 Hz, 1H), 4.39 (dd, J_1 = 8.8 Hz, J_2 = 12.8 Hz, 1H), 4.13 (t, *J* = 7.6 Hz, 1H), 2.72 (b, 1H), 1.95−1.90 (m, 2H), 1.71−1.57 (m, 5H), 1.28−1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.5, 72.9, 43.3, 29.1, 28.7, 25.8, 25.5.

General Procedure for the Diastereoselective Henry Reaction. A solution of **3a** (0.025 mmol, 16.5 mg, 10 mol %) and CuBr (0.025 mmol, 3.6 mg, 10 mol %) in methanol (1.0 mL) was stirred for 1 h at room temperature to generate the catalyst. The nitroalkane (2.5 mmol, 10 equiv), pyridine (0.25 mmol, 20 μL, 1 equiv), and the aldehyde (0.25 mmol) were then added. After the reaction was stirred for a specified amount of time at room temperature, the volatile components were removed under reduced pressure and the residue was purified by column chromatography (using neutral silica gel, petroleum ether/ethyl acetate = 6:1) to afford the corresponding adduct as the product. The diastereoselectivity was determined by NMR analysis. The enantiomeric excess was determined by HPLC analysis.

Characterization of the Diastereoselective Henry Products.

(1*R*,2*R*)-2-Nitro-1-phenyl-1-propanol (7a).[14d] colorless oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.26 (m, 5H), 5.38 (d,

J = 3.6 Hz, 0.31H) (*anti*), 5.02 (d, J = 8.8 Hz, 0.69H) (*syn*), 4.80−4.68 (m, 1H), 2.73 (b, 0.31H) (*anti*), 2.62 (b, 0.69H) (*syn*), 1.49 (d, J = 6.8 Hz, 0.93H) (*anti*), 1.31 (d, J = 6.8 Hz, 2.07H) (*syn*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 129.4, 129.2, 128.9, 128.7, 127.1, 126.2, 88.6, 87.6, 76.5, 74.1, 16.7, 12.3. The ee (87%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 22.75 min, t_r (*syn*, minor) = 20.21 min, t_r (*anti*, major) = 16.27 min, t_r (*anti*, minor) =14.50 min. *syn* isomer $[\alpha]^{25}_D = -25.9$ (*c* 0.89, CH_2Cl_2, 87% ee); *anti* isomer $[\alpha]^{25}_D = -0.2$ (*c* 0.22, CH_2Cl_2, 65% ee).

(1*R*,2*R*)-1-(2-Methoxyphenyl)-2-nitro-1-propanol (7b).[14d] colorless oil; 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 2H), 7.02−6.92 (m, 2H), 5.15−5.14 (m, 1H), 5.04−4.99 (m, 1H), 3.90 (s, 3H), 3.28−3.26 (b, 1H), 1.34 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 130.3, 129.2, 126.1, 121.4, 110.2, 87.8, 74.5, 55.6, 16.8. The ee (92%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 32.16 min, t_r (*syn*, minor) = 30.44 min, t_r (*anti*, major) = 22.28 min, t_r (*anti*, minor) = 16.05 min.

(1*R*,2*R*)-1-(4-Methoxyphenyl)-2-nitro-1-propanol (7c).[14d] colorless oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.28 (m, 2H), 6.93−6.89 (m, 2H), 5.30 (d, J = 3.6 Hz, 0.21H) (*anti*), 4.98 (d, J = 9.2 Hz, 0.79H) (*syn*), 3.82 (s, 3H), 2.65 (b, 0.21H) (*anti*), 2.53 (b, 0.79H) (*syn*), 1.52 (d, J = 6.4 Hz, 0.63H) (*anti*), 1.30 (d, J = 6.8 Hz, 2.37H) (*syn*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 130.6, 128.4, 127.5, 114.6, 114.4, 88.7, 87.8, 76.1, 55.6, 16.7, 12.7. The ee (77%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 90/10 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm: t_r (*syn*, major) = 19.89 min, t_r (*syn*, minor) = 17.15 min, t_r (*anti*, major) = 13.70 min, t_r (*anti*, minor) = 11.97 min.

(1*R*,2*R*)-1-(4-Chlorophenyl)-2-nitro-1-propanol (7d).[14d] colorless oil; 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (m, 2H), 7.32−7.30 (m, 2H), 5.38 (d, J = 8.8 Hz, 0.31H) (*anti*), 5.02 (d, J = 8.8 Hz, 0.69H) (*syn*), 4.74−4.72 (m, 0.69H) (*syn*), 4.71−4.64 (m, 0.93H) (*syn*), 2.79 (b, 0.31H) (*anti*), 2.70 (b, 0.69H) (*syn*), 1.49 (d, J = 8.4 Hz, 0.63H) (*anti*), 1.33 (d, J = 6.8 Hz, 2.07H) (*syn*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.96, 135.3, 134.6, 129.4, 129.2, 128.5, 127.6, 88.4, 87.4, 75.7, 73.4, 16.6, 12.2. The ee (72%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 22.85 min, t_r (*syn*, minor) = 25.64 min, t_r (*anti*, major) = 17.26 min, t_r (*anti*, minor) = 15.64 min.

(1*R*,2*R*)-1-(Naphthalen-1-yl)-2-nitro-1-propanol (7e).[14g] colorless oil; 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.4 Hz, 1H), 7.92−7.87 (m, 2H), 7.61−7.48 (m, 4H), 5.81 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 5.17−5.10 (m, 1H), 2.68−2.67 (b, 1H), 1.44 (d, J=6.8 Hz, 0.21H) (*anti*), 1.28 (d, J=6.8 Hz, 2.79 H) (*syn*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 131.0, 130.0, 129.4, 127.1, 126.3, 125.9, 123.4, 88.7, 73.97, 17.1. The ee (82%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AS-H column, 98/2 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 215 nm: t_r (*syn*, major) = 53.92 min, t_r (*syn*, minor) = 46.70 min, t_r (*anti*, major) = 33.95 min, t_r (*anti*, minor) = 32.11 min.

(3*R*,4*R*)-4-Nitro-1-phenyl-3-pentanol (7f).[13a,b] colorless oil; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 4.56−4.50 (m, 1H), 3.91−3.89 (m, 1H), 2.89−2.84 (m, 1H), 2.78−2.72 (m, 1H), 2.44−2.42 (b, 1H), 1.84−1.68 (m, 2H), 1.55 (d, J = 5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 128.8, 128.6, 126.5, 87.9, 86.6, 72.3, 71.4, 34.9, 34.8, 32.1, 31.6, 16.4, 12.7. The ee (93%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 20.07 min, t_r (*syn*, minor)=21.90 min, t_r (*anti*, major) = 16.07 min, t_r (*anti*, minor) = 15.02 min.

(1*R*,2*R*)-1-Cyclohexyl-2-nitro-1-propanol (7g).[13c] colorless oil; 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75−4.63 (m, 1H), 3.95 (dd, J_1 = 3.0 Hz, J_2 = 8.2 Hz, 0.11H) (*anti*), 3.65 (dd, J_1 = J_2 = 5.3 Hz, 0.89H) (*syn*), 2.43 (b, 1H), 1.78−1.16 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.7, 84.5, 76.9, 76.5, 40.4, 30.1, 29.1, 26.4, 26.3, 26.0, 25.8, 16.7. The ee (94%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 97/3 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 25.96 min, t_r (*syn*, minor) = 17.65 min, t_r (*anti*, major) = 16.42 min, t_r (*anti*, minor) = 19.19 min.

(1*R*,2*R*)-2-Nitro-1-phenyl-1-butanol (7h).[14d] colorless oil; 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.32 (m, 5H), 5.16 (dd, J_1 = J_2 = 2.0 Hz, 0.19H) (*anti*), 5.02 (dd, J_1 = 9.0 Hz, J_2 = 3.1 Hz, 0.81H) (*syn*), 4.64−4.56 (m, 1H), 2.76−2.75 (b, 0.19H) (*anti*), 2.58−2.57 (b, 0.81H) (*syn*), 1.89−1.81 (m, 1H), 1.44−1.39 (m, 1H), 0.93 (t, J = 7.4 Hz, 0.57H) (*anti*), 0.87 (t, J = 7.4 Hz, 2.43H) (*syn*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 129.4, 129.2, 128.9, 127.1, 126.4, 95.4, 94.9, 75.7, 74.4, 24.1, 21.5, 10.6, 10.3. The ee (80%) was determined by chiral HPLC analysis on a DAICEL Chiralcel OD-H + AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 38.57 min, t_r (*syn*, minor)=34.48 min, t_r (*anti*, major) = 26.31 min, t_r (*anti*, minor) = 22.19 min.

(1*R*,2*R*)-1-(2-Methoxyphenyl)-2-nitro-1-butanol (7i).[14d] colorless oil; 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 1H), 7.27−7.25, (m, 1H), 7.01−6.92 (m, 2H), 5.14 (dd, J_1 = J_2 = 8.5 Hz, 1H), 4.87−4.81 (m, 1H), 3.90 (s, 3H), 3.29−3.20 (b, 1H), 1.96−1.88 (m, 1H), 1.45−1.39 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 130.3, 129.1, 126.4, 121.4, 111.2, 94.6, 73.7, 55.7, 24.3, 10.4. The ee (94%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 43.81 min, t_r (*syn*, minor) = 40.88 min, t_r (*anti*, major) = 27.82 min, t_r (*anti*, minor) = 24.81 min.

(1*R*,2*R*)-1-(4-Chlorophenyl)-2-nitro-1-butanol (7j).[14d] colorless oil; 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 4H), 5.18 (d, J = 4.8 Hz, 0.94H) (*syn*), 5.03 (d, J = 8.8 Hz, 0.06H) (*anti*), 4.56−4.51 (m, 1H), 3.02−3.00 (b, 0.06H) (*anti*), 2.77 (b, 0.94H) (*syn*), 2.46 (m, 0.06H) (*anti*), 2.17−2.11 (m, 0.94H) (*syn*), 1.91−1.85 (m, 1H), 0.98−0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 134.8, 129.2, 127.8, 94.7, 73.8, 21.5, 10.6. The ee (81%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 18.38 min, t_r (*syn*, minor)=23.21 min, t_r (*anti*, major) = 13.85 min, t_r (*anti*, minor) = 12.66 min.

(3*R*,4*R*)-4-Nitro-1-phenyl-3-hexanol (7k).[14b] colorless oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H), 4.41−4.35 (m, 1H), 3.89 (m, 1H), 2.88−2.85 (m, 1H), 2.75−2.73 (m, 1H), 2.03−2.00 (b, 1H), 1.87−1.82 (m, 1H), 1.81−1.74 (m, 3H), 0.99−0.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 128.8, 128.6, 126.4, 94.5, 94.0, 71.6, 71.2, 35.6, 34.9, 31.96, 31.7, 24.0, 21.7, 10.7, 10.3. The ee (98%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 95/5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 18.80 min, t_r (*syn*, minor) = 18.01 min, t_r (*anti*, major) = 13.83 min, t_r (*anti*, minor) = 12.98 min.

(1*R*,2*R*)-1-Cyclohexyl-2-nitro-1-butanol (7l).[4h] colorless oil; 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60−4.50 (m, 1H), 3.80 (dd, J_1 = J_2 = 5.6 Hz, 0.03H), 3.63 (m, 0.97H), 2.18 (b, 1H), 2.09−2.04 (m, 1H), 1.89−1.86 (m, 1H), 1.85−1.66 (m, 5H), 1.24−1.13 (m, 6H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 92.1, 76.2, 40.5, 30.0, 27.1, 26.3, 26.2, 25.97, 24.3, 10.4. The ee (97%) was determined by chiral HPLC analysis on a DAICEL Chiralcel OJ-H column, 99/1 *n*-hexane/*i*-PrOH, 0.3 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 60.83 min, t_r (*syn*, minor) = 58.31 min, t_r (*anti*, major) = 44.74 min, t_r (*anti*, minor) = 47.10 min.

(1*R*,2*R*)-1-Cyclohexyl-2-nitro-2-phenylethanol (7m).[13a,13h] colorless oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.26 (m, 5H), 5.53 (d, J = 9.9 Hz, 1H), 4.43 (dd, J_1 = 10 Hz, J_2 = 1.5 Hz, 0.85H) (*syn*), 4.33 (dd, J = 6 Hz, 0.15H) (*anti*), 2.17 (b, 1H), 1.71−0.95 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 130.4, 129.6, 129.4, 129.2, 128.3, 94.96, 91.8, 76.4, 39.9, 38.7, 30.5, 29.8, 26.96, 26.3, 26.2, 25.9, 24.9. The ee (77%) was determined by chiral HPLC analysis on a DAICEL Chiralcel AD-H column, 97/3 *n*-hexane/*i*-PrOH, 1.0 mL/min, 20 °C, 220 nm: t_r (*syn*, major) = 32.67 min, t_r (*syn*, minor) = 28.58 min, t_r (*anti*, major) = 38.40 min, t_r (*anti*, minor) = 24.35 min.

General Procedure for Preparation of 8. A mixture of bis-(sulfonamide)−diamine **3a** (661 mg, 1 mmol), phenol (1.93 mg, 6.4 mmol), and HBr (8.39 mL, 48% in water) was refluxed for 48 h. Water (37 mL) and 2 M NaOH (16 mL) were carefully added at room temperature to adjust the pH to about 1. The aqueous phase was washed with EtOAc (3 × 21 mL), and its pH was then adjusted to 13 with 2 M NaOH (about 148 mL). The aqueous phase was then extracted with CH_2Cl_2 (5 × 42 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography to give **8** as a yellow oil with 73% yield: $[\alpha]^{25}_D$ = +17.0 (*c* 0.96, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 10H), 4.11−4.08 (m, 2H), 3.84 (b, 4H), 3.12−3.09 (m, 2H), 2.69−2.66 (m, 4H), 2.40−2.38 (m, 2H), 2.06−2.04 (m, 2H), 1.15−1.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 128.9, 127.8, 126.7, 63.92, 61.81, 55.74, 53.75, 46.28, 30.97, 24.82; HRMS (APCI) calculated for $C_{22}H_{32}N_4$ ($M + H^+$) 353.2700, found 353.2699.

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Supporting Information Available: General experimental methods as well as ^{1}H NMR, ^{13}C NMR, and HRMS spectra for the characterization of compounds are reported. This material is available free of charge via the Internet at http://pubs.acs.org.