L-Proline Diamides with an Axially Chiral Binaphthylene Backbone as Efficient Organocatalysts for Direct Asymmetric Aldol Reactions: The Effect of Acetic Acid

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Abstract: A series of L-proline diamides derived from optically active 1,1'-binaphthyl-2,2'-diamines have been synthesized in good yields and their catalytic abilities as organocatalysts in direct asymmetric aldol reactions have been evaluated. Among these organocatalysts, bis(prolinamides) exhibit higher catalytic abilities. The aldol reaction of arylaldehydes with acetone or cyclohexanone proceeds smoothly using the organocatalyst (10 mol%) in the presence of acetic acid (10 mol%) as an additive in toluene at -40 °C for 48–72 hours to give the corresponding aldol products in high yields (<90%) and with good to high enantioselectivities (<98%) and high *anti*-diastereoselectivities (<98:2).

Key words: 1,1'-binaphthyl-2,2'-diamine, organocatalysts, direct asymmetric aldol reactions, L-proline diamides, acetic acid

Asymmetric organocatalysis has recently attracted much attention in asymmetric catalysis. This has resulted in a new field of research and the exploration of the fundamental chemical parameters of asymmetric organocatalysis, such as reactivity, selectivity, and mechanism, has lead to the discovery of many novel reactions and catalysts.¹ In this endeavor, the design and synthesis of multifunctional chiral organocatalysts is of great importance. The ability of simple, small organic compounds from readily available homochiral compounds to act as catalysts, as if an enzyme, represents a remarkable synthetic alternative to many established asymmetric reactions. Among the various enantiomerically pure small organic molecules available, amino acids and peptides, as well as cinchona alkaloids, are extremely interesting asymmetric organocatalysts, with useful levels of enantioselectivity for a wide range of transformations.²

The aldol reaction is the most important carbon–carbon bond-forming reactions in organic synthesis.³ Several efficient asymmetric methodologies for this reaction using organocatalysts have been developed, of which the most remarkable advances in the domain of L-proline and its derivative catalysts have been made by List and Barbas et al.⁴ On the other hand, the groups of MacMillan,⁵ Jørgensen,⁶ and Yamamoto⁷ are also pioneering workers in this field. These catalysts are believed to catalyze aldol reactions by stabilizing the transition state through hydrogen bonding by proline and its derivatives. Thus far, it has been realized that a subtle change in the backbone of the catalyst may affect the strength of hydrogen bonding, such that a dramatic enhancement of activity and selectivity may be anticipated. Recently, various organocatalysts derived from L-proline and diamines have exhibited very high catalytic activity and stereoselectivity in direct aldol reactions. For example, Zhao and co-workers synthesized several C_2 -symmetric bisamide organocatalysts from Lproline and 1,2-diphenylethylenediamine. They found that the enantioselectivities achieved in the aldol reaction catalyzed by C_2 -symmetric bis(prolinamides) were strongly influenced by the chiral backbone of the catalysts. Using (1S,2S)-1,2-diphenylethylenediamine as a chiral backbone, <98% ee can be achieved with small loading of the catalyst (10 mol%).⁸ Xiao and co-workers revealed that unsymmetric bisamides derived from (1R,2R)-cyclohexane-1,2-diamine and L-proline are effective catalysts for the aldol reaction of cyclohexanone with arylaldehydes affording the corresponding aldol products in good yields and with <97% ee and diastereoselectivity anti/syn <99:1.9 Furthermore, Gryko and coworkers recently synthesized bis(prolinamides) derived from L-proline and racemic 1,1'-binaphthyl-2,2'-diamine and used them as organocatalysts in the direct asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde to give the corresponding aldol reaction product in moderate vield (<79%) and enantioselectivity (<88%). In addition, moderate diastereoselectivity (anti/syn <70:30) and low enantioselectivity (<17~45% ee) have been attained in the aldol reaction of cyclopentanone or cyclohexanone with 4-nitrobenzaldehyde after prolonged reaction times (68 h) at 4 °C.10

Thus far, we have been working on the design and synthesis of chiral ligands based on axially chiral 1,1'-binaphthyl-2,2'-diamine and we have been examining their ability to induce chirality in asymmetric catalysis.¹¹ Hence, we attempted to synthesize chiral L-proline diamide organocatalysts derived from optically active 1,1'-binaphthyl-2,2'-diamine so that we could assess their efficacy in direct asymmetric aldol reactions. We found that the aldol reaction of arylaldehydes with acetone or cyclohexanone proceeds smoothly using a chiral bis(prolinamide) catalyst (10 mol%) in the presence of acetic acid (10 mol%) as an additive in toluene at -40 °C for 48–72 hours to give

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the corresponding aldol products in high yields (<90%), and good to high enantioselectivities (<98%) as well as high *anti*-diastereoselectivities (<98:2). Herein, we report the details.

Since optically active (S)- and (R)-1,1'-binaphthyl-2,2'diamines (S)- and (R)-2 have been widely used in transition-metal-catalyzed asymmetric reactions, we believed that if an optically active diamine (S)- or (R)-2 was used as the backbone of a bis(prolinamide), the efficiency of the corresponding organocatalysts in direct asymmetric aldol reactions could be improved.¹² Thus, we attempted to synthesize some chiral monoprolinamides and bis(prolinamides) directly from optically active diamines (S)- or (R)-2. An optically active diamine (S)-2 or (R)-2 (284 mg, 1.0 mmol), prepared according to the literature,¹³ was coupled with 1-(tert-butoxycarbonyl)-L-proline (1, 454 mg, 2.2 mmol) in the presence of N,N'-dicyclohexylcarbodiimide (474 mg, 2.20 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol),⁹ affording the corresponding N-(tert-butoxycarbonyl)-protected bis(prolinamide) (S)-3 or (R)-3 in good yield. Next, these compounds were treated with excess trifluoroacetic acid to remove the tert-butoxycarbonyl protecting group, leading to the formation of the corresponding pure bis(prolinamide) (S)-4a or (R)-4a in good yield (Scheme 1).

N-tert-Butoxycarbonyl-protected monoprolinamides (*S*)-**3b** and (*R*)-**3b** bearing an *N*-acetyl group and *N-tert*-butoxycarbonyl-protected monoprolinamides (*S*)-**3c** and (*R*)-**3c** bearing an *N*-tosyl group were prepared from the corresponding optically active N-monoacetylated diamines (*S*)- and (*R*)-**5** and N-monotosylated diamines (*S*)- and (*R*)-**6** in the same manner as that described for (*S*)- and

(*R*)-**3a** (Schemes 2 and 3). Removal of the *tert*-butoxycarbonyl protecting group by treatment with excess trifluoroacetic acid produced the desired monoprolinamides (*S*)and (*R*)-**4b** and (*S*)- and (*R*)-**4c** in good yields (Schemes 2 and 3).

The catalytic abilities of these organocatalysts 4a-c (Figure 1) were evaluated in the direct asymmetric aldol reaction of 4-nitrobenzaldehyde (7a) with acetone at room temperature (25 °C). The results are summarized in Table 1. The organocatalyst (S)-4a (10 mol%), derived from L-proline with (S)-1,1'-binaphthyl-2,2'-diamine, produced the corresponding aldol reaction product (R)-8a with higher enantiomeric excess than its diastereomer (R)-4a (10 mol%) in the presence of acetic acid (10 mol%) under identical conditions (Table 1, entries 1 and 2). In general, under identical conditions monoprolinamides (S)-4b, (R)-4b, (S)-4c, and (R)-4c were not as effective as the bis(prolinamides) (S)-4a and (R)-4a (Table 1, entries 3–6). Using a combination of (S)-4a and (R)-4a as the organocatalyst in the same reaction produced the aldol reaction product (R)-8a in 60% ee under the standard conditions (Table 1, entry 7).

In order to improve the yield and enantioselectivity of 8a, the effects of temperature, solvent, and additive on the aldol reaction were investigated using (*S*)-4a as the organocatalyst. The results are given in Table 2. It was found that the enantioselectivity was highly dependent on the temperature and the solvent employed. The enantiomeric excess value of 8a increased to 84% when the reaction temperature was lowered to -40 °C in neat acetone (Table 2, entries 2–5). We also found that acetic acid as an additive has a remarkable effect on the catalytic ability of



Scheme 1 Synthesis of bis(prolinamides) (S)-4a and (R)-4a.

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Scheme 2 Synthesis of monoprolinamides (S)-4b and (R)-4b.



Scheme 3 Synthesis of monoprolinamides (S)-4c and (R)-4c.

(*S*)-**4a**, since reaction proceeded slowly at 0 °C when it was performed without the addition of acetic acid (Table 2, entries 1 and 3). Increasing the amount of acetic acid to 40 mol% did not significantly affect the reaction rate (Table 2, entries 2 and 3). The solvent employed significantly affected the enantiomeric excess of (*R*)-**8a** at -40 °C. We found the use of 1,2-dichloroethane, chloroform, *N*,*N*-dimethylformamide, and dichloromethane as the solvent under identical conditions gave the desire al-

dol product (*R*)-**8a** in good yields and with 34–86% ee (Table 2, entries 6–9). In toluene, (*R*)-**8a** was obtained in 82% yield and with 93% ee in the presence of acetic acid (10 mol%) and 50% yield and with 92% ee in the presence of acetic acid (5 mol%) (Table 2, entries 10 and 12), but in the absence of acetic acid (*R*)-**8a** was still obtained in 75% yield and with 90% ee thus the isolated yield and the enantiomeric excess value decreased slightly under identical conditions in the absence of acetic acid (Table 2, en-



Figure 1 C_2 -Symmetric bis(prolinamide) catalysts 4a and C_1 -symmetric monoprolinamide catalysts 4b,c.

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 Table 1
 Direct Asymmetric Aldol Reaction of Acetone and 4-Nitrobenzaldehyde (7a) Using Various L-Proline Amide Organocatalysts 4a-c^a

	O +	O ₂ N 7a	catalyst (<i>S</i>)- and (<i>R</i>)-4 AcOH (10 mol%), r.t	a–c (10 mol%) → O₂N ^{<}	OH O (<i>R</i>)-8a	
Entry	Catalyst	Temp (°C)	Time (h)	Yield ^b (%)	ee ^c (%)	Config ^d
1	(S)- 4a	25	12	89	60	R
2	(<i>R</i>)-4a	25	12	90	50	R
3	(<i>S</i>)- 4 b	25	24	78	54	R
4	(<i>R</i>)-4b	25	24	68	44	R
5	(<i>S</i>)-4c	25	24	75	54	R
6	(<i>R</i>)-4c	25	24	77	54	R
7	(S)-4a + (R)-4a	25	18	80	60	R

^a Conditions: **7a** (75.6 mg, 0.5 mmol), acetone (2.0 mL), catalyst (10 mol%), AcOH (10 mol%), 8–24 h.

^b Isolated yields.

^c Determined by chiral HPLC analysis using a Chiralpak AS-H column.

^d The absolute configuration was determined by comparing the sign of the specific rotation with an authentic sample.

tries 10 and 11). We also examined various organic acids as additives in this reaction. We found that **8a** was formed in trace amounts in the presence of trifluoroacetic acid or trifluoromethanesulfonic acid under identical conditions (Table 2, entries 13 and 14). With the addition of 4-toluenesulfonic acid, benzoic acid, or formic acid, (*R*)-**8a** was obtained in moderate yields and 68-91% ee (Table 2, entries 15–17). Therefore, the optimized reaction conditions use (*S*)-**4a** (10 mol%) as the organocatalyst in toluene with the addition of 10 mol% of acetic acid at -40 °C.

Table 2 Direct Asymmetric Aldol Reaction of Acetone and 4-Nitrobenzaldehyde (7a) Using L-Prolinamide Organocatalyst (S)-4a underVarious Conditions^a

	,	O ₂ N 73	H (S)-4a (10 mol%)				
Entry	Additive	Solvent	Temp (°C)	Time (h)	Yield ^b (%)	ee ^c (%)	
1	_	d	0	72	58	65	-
2	AcOH (40 mol%)	d	0	48	90	61	
3	AcOH (10 mol%)	d	0	48	88	60	
4	AcOH (10 mol%)	d	-20	72	85	77	
5	AcOH (10 mol%)	d	-40	72	79	84	
6	AcOH (10 mol%)	DCE	-40	48	96	34	
7	AcOH (10 mol%)	CHCl ₃	-40	72	77	65	
8	AcOH (10 mol%)	DMF	-40	72	67	74	
9	AcOH (10 mol%)	CH ₂ Cl ₂	-40	72	67	86	
10	AcOH (10 mol%)	toluene	-40	72	82	93	
11	_	toluene	-40	72	75	90	
12	AcOH (5 mol%)	toluene	-40	72	50	92	

 Table 2
 Direct Asymmetric Aldol Reaction of Acetone and 4-Nitrobenzaldehyde (7a) Using L-Prolinamide Organocatalyst (S)-4a under Various Conditions^a (continued)

	O +	O ₂ N Ta	(<i>S</i>)- 4a (10 mol%) ➤	OH O O ₂ N (<i>R</i>)-8a		
Entry	Additive	Solvent	Temp (°C)	Time (h)	Yield ^b (%)	ee ^c (%)
13	TFA (10 mol%)	toluene	-40	96	trace	n.d. ^e
14	TfOH (10 mol%)	toluene	-40	96	trace	n.d. ^e
15	TsOH (10 mol%)	toluene	-40	96	25	68
16	PhCO ₂ H (10 mol%)	toluene	-40	96	58	90
17	HCO ₂ H (10 mol%)	toluene	-40	96	50	91

^a Conditions: **7a** (75.6 mg, 0.5 mmol), acetone (0.5 mL), (S)-**4a** (10 mol%), 48–96 h.

^b Isolated yields.

^c Determined by chiral HPLC using a Chiralpak AS-H column.

^d Acetone was the solvent.

^e Not determined.

To test the substrate generality of this interesting organocatalyst, the aldol reaction of various aldehydes with acetone was examined under these optimized conditions. The results are summarized in Table 3. As shown, we found that arylaldehydes with a strongly electron-withdrawing group, such as a nitro group, on the benzene ring gave the corresponding aldol products (R)-**8a–c** in good yields with 92–98% ee (Table 3, entries 1, 3, and 4). For arylaldehydes bearing a halogen atom on the benzene ring the corresponding aldol products were produced in moderate yields and with 67–92% ee (Table 3, entries 5–8). Furthermore, it is noteworthy that even using 5 mol% of (S)- **4a** and 5 mol% of acetic acid, the reaction also proceeded smoothly to give the corresponding aldol product (*R*)-**8a** in 55% yield and with 92% ee, which is comparable to those results obtained using of 10 mol% of (*S*)-**4a** and 10 mol% of acetic acid under identical conditions (Table 3, entries 1 and 2).

Moreover, we also examined the direct aldol reaction of cyclohexanone and cyclopentanone with arylaldehydes under these optimized reaction conditions. The results using cyclohexanone as a substrate are summarized in Table 4. For various arylaldehydes bearing an electron-

Table 3 Scope of Arylaldehydes 7 for the Direct Aldol Reaction with Acetone under Optimal Conditions^a

	Ŭ +	R H (S)-4a (10 mol%) toluene, -40	s), AcOH (10 mol%) ℃, 48–72 h R	OH O (<i>R</i>)-8	
Entry	R	Product	Yield ^b (%)	ee ^c (%)	Config ^d
1	$4-O_2NC_6H_4$	8a	83	93	R
2	$4-O_2NC_6H_4$	8a	55 ^e	92	R
3	$3-O_2NC_6H_4$	8b	86	95	R
4	$2-O_2NC_6H_4$	8c	86	98	R
5	4-ClC ₆ H ₄	8d	67	81	R
6	2-ClC ₆ H ₄	8e	91	92	R
7	$4-BrC_6H_4$	8f	60	76	R
8	$4-FC_6H_4$	8g	57	67	R

^a Conditions: **7a–g** (0.5 mmol), acetone (0.5 mL), (S)-**4a** (10 mol%), AcOH (10 mol%), toluene (3.0 mL), -40 °C, 48–72 h.

^b Isolated yields.

^c Determined by chiral HPLC using a Chiralpak AS-H or AD-H or a Chiralcel OD-H or OJ-H column.

^d The absolute configuration was determined by comparing the sign of the specific rotation with an authentic sample.

^e In the presence of (S)-4a (5 mol%) and AcOH (5 mol%).

 Table 4
 Scope of Aldehyde 7 for the Direct Aldol Reaction with Cyclohexanone under Optimal Conditions^a

	+	$\begin{array}{c} O \\ H \\ R \\ H \end{array} \qquad \begin{array}{c} (S) - 4a (10 \text{ mod}) \\ AcOH (10 \text{ mod}) \\ \hline toluene, -40 ^{\circ}C, \end{array}$	01%), 01%) 48–72 h	+ R H O	
		7	anti- 9	syn- 9	
Entry	R	Product	Yield ^b (%)	dr ^c (anti/syn)	ee ^d (%) anti
1	$4-O_2NC_6H_4$	9a	90	98:2	95
2	$3-O_2NC_6H_4$	9b	83	98:2	95
3	$2-O_2NC_6H_4$	9c	83	98:2	90
4	$4-ClC_6H_4$	9d	71	97:3	98
5	$4-BrC_6H_4$	9e	70	95:5	96
6	$4-FC_6H_4$	9f	61	92:8	92
7	C ₆ H ₅	9g	45	97:3	80

^a Conditions: **7a–g** (0.5 mmol), cyclohexanone (0.5 mL), (*S*)-**4a** (10 mol%), AcOH (10 mol%), toluene (3.0 mL), -40 °C, 48–72 h. ^b Isolated yields.

^c Determined by analysis of *anti/syn* mixtures by ¹H NMR and chiral HPLC.

^d Determined by chiral HPLC using a Chiralpak AS-H or AD-H or a Chiralcel OD-H, or OJ-H column.

withdrawing group, such as a nitro group or a halogen atom, on the benzene ring the reaction with cyclohexanone proceeded smoothly to furnish the corresponding aldol adducts **9a–f** with excellent *anti*-diastereoselectivity (<92:8–98:2) and high enantioselectivity (<90–98% ee) (Table 4, entries 1–6). Only in the case of the aldol reaction of cyclohexanone with benzaldehyde was the corresponding aldol product **9g** obtained with lower enantiomeric excess (80% ee), although with excellent *anti*-diastereoselectivity, presumably due to its electronrich character (Table 4, entry 7).

The reaction of 4-nitrobenzaldehyde (**7a**) with cyclopentanone was also investigated to examine the scope of the aldol donors. The corresponding aldol product **10** was produced in 84% yield with an *anti/syn* ratio of 30:70 and with 98% ee for the *anti*-diastereomer and with 81% ee for the *syn*-diastereomer (Scheme 4). Comparing the result for cyclopentanone with that of cyclohexanone, it is interesting to note that organocatalyst (*S*)-**4a** has the opposite performance for these two substrates in terms of diastereoselectivity.

The mechanism of the diamide–Brønsted acid catalyzed aldol addition is the subject of an extensive ongoing investigation, but it remains unsolved.^{14–16} For the purpose of the detailed discussion, we give a proposed mechanism as shown in Scheme 5 based on a prolinamide-catalyzed process through a six-membered, chairlike transition state, which is derived from a generally accepted iminium ion and enamine intermediate found in proline-catalyzed direct asymmetric aldol reactions, locating the *re*-face of the acceptor proximate to the attack by the enamine to give the corresponding aldol product with *R*-configuration. Acetic acid as an additive is also indispensable in this catalysis process, as it provides a proton to accelerate the

formation of the enamine intermediate, but excessive acetic acid may have a negative effect on the hydrogen bonding of the diamide, which in turn depresses the catalytic efficacy.⁹

In conclusion, we have synthesized a series of L-prolinamide organocatalysts bearing an axially chiral binaphthylene backbone and their catalytic activity has been examined using direct asymmetric aldol reactions. We found that bis(prolinamide) organocatalysts are superior to monoprolinamide organocatalysts in reactivity and stereoselectivity. Under these optimized reaction conditions, good to excellent enantioselectivities (<98% ee) can be achieved in the aldol reaction of arylaldehydes with acetone in good yields in the presence of acetic acid in toluene at -40 °C. On the other hand, good to high enantioselectivities (<98%) as well as high *anti*-diastereoselectivities (<98:2) can be realized in the aldol reaction of cyclohexanone with arylaldehydes in toluene at -40 °C. Further work on determining the reaction mecha-



Scheme 4 Reaction of 4-nitrobenzaldehyde (7a) with cyclopentanone.



six-membered transition state

Scheme 5 Plausible enamine mechanism of the direct asymmetric aldol reaction catalyzed by bis(prolinamide) (S)-4a.

nism and exploration of direct asymmetric Michael additions using these L-prolinamide organocatalysts are currently underway.

Unless otherwise stated, materials were purchased from commercial suppliers and used without further purification. CH₂Cl₂ and 1,2dichloroethane were freshly distilled from CaH₂; THF and toluene were distilled from Na under argon; hexane, petroleum ether, and EtOAc for flash column chromatography and recrystallization were distilled before use. Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin-Elmer 341 MC digital polarimeter; $[\alpha]_D$ values are given in units of 10 deg⁻¹·cm²·g⁻¹. ¹H NMR spectra were recorded on a Bruker AM-300 (300 MHz). Chemical shifts are reported from the solvent resonance as the internal standard (CDCl₃: δ = 7.26). ¹³C NMR spectra were recorded on a Bruker AM-300 (75 MHz) with complete proton decoupling (CDCl₃: δ = 77.0). IR spectra were recorded on a Bio-Rad FTS-185. Flash column chromatography was performed using silica gel (300-400 mesh). For TLC, silica gel plates (Huanghai GF254) were used and compounds were visualized by irradiation with UV light and/or by treatment with phosphomolybdic acid in EtOH soln followed by heating. Chiral HPLC was performed on a Shimadzu SPD-10A series with chiral columns [Chiralpak AS-H or AD-H or Chiralcel OD-H or OJ-H columns 4.6×250 mm (Daicel Chemical Ind., Ltd.)]. Elementary analysis (CHN) was taken on a Carlo-Erba 1106 analyzer. MS spectra were recorded by EI and HRMS was measured on a HP-5989 instrument. All aldol reactions were carried out under an atmosphere of air in a closed system. Racemic aldol products were synthesized by treatment of the corresponding substrates with aq NaOH (1% w/v) at 0 °C.

N,*N*'-1,1'-Binaphthalene-2,2'-diylbis[1-(*tert*-butoxycarbon-yl)prolinamides] (*S*)-3a and (*R*)-3a; General Procedure

Boc-L-proline 1 (454 mg, 2.2 mmol), DCC (474 mg, 2.2 mmol), and DMAP (20 mg, 0.16 mmol) were dissolved in CH_2Cl_2 (10 mL) and

the soln was cooled to 0 °C and stirred for 30 min. A soln of (*S*)- or (*R*)-1,1'-binaphthyl-2,2'-diamine [(*S*)-**2** or (*R*)-**2**] (284 mg, 1.0 mmol) in CH₂Cl₂ (10 mL) was added dropwise over 15 min. When the addition was complete, the mixture was warmed to r.t. and stirred for a further 12 h. Dicyclohexylurea was filtered off and the solvent was removed under reduced pressure. Then, H₂O (5 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed consecutively with 1.0 M KHSO₄ (1 × 25 mL), H₂O (1 × 25 mL), 10% aq NaHCO₃ (1 × 25 mL), and H₂O (1 × 25 mL) and dried (anhyd Na₂SO₄). The solvent was evaporated to provide (*S*)-**3a** and (*R*)-**3a** were obtained by recrystallization (CH₂Cl₂, hexane).

Bis[1-(tert-butoxycarbonyl)prolinamide] (S)-3a

White solid; yield: 610 mg (91%); mp 238–240 °C.

 $[\alpha]_{D}^{20}$ –199.4 (*c* 1.025, CHCl₃).

IR (film): 3320, 2925, 2848, 1622, 1435 1087, 1039, 641 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): $\delta = 0.80-1.15$ (m, 4 H, CH₂), 1.30 [s, 18 H, C(CH₃)₃], 1.50-1.95 (series of m, 6 H, CH₂), 2.60-2.80 (m, 2 H, CH₂), 4.05-4.10 (m, 2 H, CH), 7.11-7.20 (m, 2 H, ArH), 7.24-7.36 (m, 2 H, ArH), 7.38-7.48 (m, 2 H, ArH), 7.88-8.00 (m, 4 H, ArH), 8.06-8.15 (m, 2 H, ArH), 8.82 (br s, 2 H, NHCO).

MS (EI): *m*/*z* (%) = 678.5 (3.67) [M⁺], 408.2 (9.29), 267.2 (10.52), 70.1 (100).

Bis[1-(*tert*-butoxycarbonyl)prolinamide] (*R*)-3a

White solid; Yield: 600 mg (88%); mp 221-223 °C.

 $[\alpha]_{\rm D}{}^{20}\,{-}26.4\;(c\;1.045,\,{\rm CHCl}_3).$

IR (film): 3320, 2925, 2848, 1622, 1435, 1087, 1039, 641 cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ [s, 18 H, $C(CH_3)_3$], 1.00–1.30 (m, 2 H, CH_2), 1.42–1.90 (series of m, 6 H, CH_2), 2.30–2.65 (m, 2 H, CH_2), 2.80–3.10 (m, 2 H, CH_2), 3.90–4.20 (m, 2 H, CH_2), 7.05–

7.18 (m, 2 H, ArH), 7.20–7.35 (m, 2 H, ArH), 7.40–7.55 (m, 2 H, ArH), 7.65–8.13 (m, 6 H, ArH), 8.82 (br s, 2 H, NHCO).

MS (EI): *m*/*z* (%) = 678.4 (1.67) [M⁺], 409.2 (6.31), 267.1 (10.57), 70.1 (100).

2'-Acetamido-1,1'-binaphthalen-2-ylamine (S)-5 and (R)-5;¹⁷ General Procedure

Ac₂O (208 μ L, 2.2 mmol) was added to a mixture of (*S*)- or (*R*)-1,1'binaphthyl-2,2'-diamine [(*S*)-**2** or (*R*)-**2**] (568 mg, 2.0 mmol), AcOH (1.2 mL, 20 mmol), and CH₂Cl₂ (20 mL) with ice-cooling. The mixture was stirred at r.t. overnight, and 2 M NaOH (0.2 mL) was added until pH >7. The mixture was extracted with CH₂Cl₂ and the combined organic extracts were dried (anhyd MgSO₄). The residue obtained upon evaporation was purified by column chromatography to afford (*S*)-**5** or (*R*)-**5**¹⁷ as white solids.

2'-(4-Tolyl
sulfonamido)-1,1'-binaphthalen-2-ylamine(S)-6 and
 (R)-6;'' General Procedure

To a mixture of (*S*)- or (*R*)-1,1'-binaphthyl-2,2'-diamine [(*S*)-**2** or (*R*)-**2**] (568 mg, 2.0 mmol) and pyridine (2.0 mL, 24 mmol) in CH₂Cl₂ (15 mL) was added dropwise a soln of TsCl (420 mg, 2.2 mmol) in CH₂Cl₂ (5 mL). The mixture was stirred at r.t. for 12 h and then it was washed with 5% HCl (3 × 10 mL) and the separated organic layer was dried (anhyd MgSO₄). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give (*S*)-**6** or (*R*)-**6**¹⁷ as white solids.

N-(2'-Acetamido-1,1'-binaphthalen-2-yl)-1-(*tert*-butoxycarbon-yl)prolinamides (*S*)-3b and (*R*)-3b; General Procedure

Boc-L-proline 1 (258 mg, 1.2 mmol), DCC (248 mg, 1.2 mmol), and DMAP (20 mg, 0.16 mmol) were dissolved in CH_2Cl_2 (10 mL) and the soln was cooled to 0 °C and stirred for 30 min. A soln of (*S*)-5 or (*R*)-5 (325 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 30 min. When the addition was complete, the mixture was warmed to r.t. and stirred for a further 12 h. Dicyclohexylurea was filtered off and the solvent was removed under reduced pressure. Then, H_2O (5 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed consecutively with 1.0 M KHSO₄ (1 × 25 mL), H_2O (1 × 25 mL), aq 10% NaHCO₃ (1 × 25 mL), and H_2O (1 × 25 mL) and dried (anhyd Na₂SO₄). The solvent was evaporated to provide (*S*)-**3b** and (*R*)-**3b**, which were used in the next reaction without further purification.

$N'\mbox{-}Acetyl\mbox{-}Substituted$ 1-($tert\mbox{-}Butoxycarbonyl)$ prolinamide (S)-3b

White solid; yield: 490 mg (91%); mp 186-189 °C.

 $[\alpha]_{D}^{20}$ –52.5 (*c* 0.33, CHCl₃).

IR (film): 3262, 3055, 2977, 2932, 2879, 1690, 1394, 1163, 1124, 1089, 818, 735 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.10–1.50 (m, 2 H, CH₂), 1.30 [s, 9 H, C(CH₃)₃], 1.50–2.00 (m, 2 H, CH₂), 1.74 (s, 3 H, CH₃), 2.50–2.70 (s, 1 H, CH), 2.92–3.10 (m, 1 H, CH), 4.11–4.13 (m, 1 H, CH), 6.98–7.10 (m, 2 H, ArH), 7.20–7.45 (m, 4 H, ArH), 7.45–7.58 (m, 2 H, ArH), 7.93–8.09 (m, 4 H, ArH), 8.48 (br s, 1 H, NHCO).

MS (EI): *m*/*z* (%) = 523.3 (4.04) [M⁺], 423.2 (4.91), 267.2 (57.04), 70.1 (100).

N'-Acetyl-Substituted 1-(*tert*-Butoxycarbonyl)prolinamide (R)-3b

White solid; yield: 454 mg (86%); mp 222-224 °C.

 $[\alpha]_{D}^{20}$ +7.9 (*c* 0.90, CHCl₃).

IR (film): 3442, 3321, 2915, 2848, 1622, 1580, 1535, 1088, 1046, 892, 641 $\rm cm^{-1}.$

 $^1\mathrm{H}$ NMR (300 MHz, CDCl₃): δ = 0.85–1.10 (m, 2 H, CH₂), 1.38 [s, 9 H, C(CH₃)₃], 1.50–2.00 (m, 2 H, CH₂), 1.79 (s, 3 H, CH₃), 2.50–2.65 (m, 1 H, CH), 2.85–3.10 (m, 1 H, CH), 3.90–4.20 (m, 1 H, CH), 6.98–7.35 (m, 4 H, ArH), 7.38–7.47 (m, 2 H, ArH), 7.80–8.00 (m, 4 H, ArH), 8.03–8.15 (m, 2 H, ArH), 8.45 (br s, 1 H, NHCO).

MS (EI): *m*/*z* (%) = 523.3 (8.10) [M⁺], 423.2 (6.77), 267.2 (59.51), 70.1 (100).

1-(*tert*-Butoxycarbonyl)-*N*-[2'-(tosylamino)-1,1'-binaphthalen-2-yl]prolinamides (*S*)-3c and (*R*)-3c; General Procedure

Boc-L-proline 1 (258 mg, 1.2 mmol), DCC (248 mg, 1.2 mmol), and DMAP (20 mg, 0.16 mmol) were dissolved in CH_2Cl_2 (10 mL) and the soln was cooled to 0 °C and stirred for 30 min. Then a soln of compound (*S*)-6 or (*R*)-6b (438 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 30 min. When the addition was complete, the mixture was warmed to r.t. and stirred for a further 12 h. Dicyclohexylurea was filtered off and the solvent was removed under reduced pressure. Then, H_2O (5 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed consecutively with 1.0 M KHSO₄ (1 × 25 mL), H_2O (1 × 25 mL), aq 10% NaHCO₃ (1 × 25 mL), and H_2O (1 × 25 mL) and dried (anhyd Na₂SO₄). The solvent was evaporated to provide (*S*)-**3c** and (*R*)-**3c**, which were used for the next reaction without further purification.

N'-Tosyl-Substituted 1-(*tert*-Butoxycarbonyl)prolinamide (*S*)-3c

White solid; yield: 360 mg (57%); mp 165-168 °C.

 $[\alpha]_{D}^{20}$ –69.1 (*c* 1.045, CHCl₃).

IR (film): 3333, 2977, 1697, 1621, 1502, 1476, 1452, 1367, 1163, 1091, 984, 814, 744, 662 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.32 [s, 9 H, C(CH₃)₃], 1.50–2.00 (m, 4 H, CH₂), 2.37 (s, 3 H, CH₃), 2.75–2.98 (m, 1 H, CH), 3.20–3.70 (m, 1 H, CH), 4.00–4.20 (m, 1 H, CH), 6.25–6.54 (m, 2 H, ArH), 6.85–7.24 (m, 2 H, ArH), 7.38–7.51 (m, 6 H, ArH), 7.80–8.00 (m, 4 H, ArH), 8.03 (d, *J* = 8.7 Hz, 1 H, ArH), 8.46 (d, *J* = 8.7 Hz, 1 H, ArH), 8.67 (br s, 1 H, NHCO).

MS (EI): *m/z* (%) = 635.2 (2.73) [M⁺], 438.1 (10.27), 311.1 (100), 267.1 (27.69), 70.1 (33.72).

N'-Tosyl-Substituted 1-(*tert*-Butoxycarbonyl)prolinamide (R)-3c

White solid; yield: 570 mg (89%); mp 203-204 °C.

 $[\alpha]_{D}^{20}$ –46.7 (*c* 1.175, CHCl₃).

IR (film): 3356, 2977, 1697, 1596, 1501, 1429, 1400, 1367, 1164, 1091, 976, 815, 748, 662 cm⁻¹.

¹H NMR (300 Hz, CDCl₃): δ = 1.32 [s, 9 H, C(CH₃)₃], 1.69–2.06 (m, 4 H, CH₂), 2.38 (s, 3 H, CH₃), 2.60–2.84 (m, 1 H, CH), 2.95–3.20 (m, 1 H, CH), 3.95–4.20 (m, 1 H, CH), 6.25–6.54 (m, 2 H, ArH), 6.85–7.24 (m, 2 H, ArH), 7.38–7.51 (m, 6 H, ArH), 7.85–8.05 (m, 4 H, ArH), 8.08 (d, *J* = 8.7 Hz, 1 H, ArH), 8.58 (d, *J* = 8.7 Hz, 1 H, ArH), 8.67 (br s, 1 H, NHCO).

MS (EI): *m/z* (%) = 635.3 (0.34) [M⁺], 438.2 (12.95), 311.1 (100), 267.1 (35.94), 70.1 (41.18).

Removal of the *tert*-Butoxycarbonyl Protecting Group; General Procedure

Compounds **3a–c** (1.0 mmol) were dissolved in a mixed soln of TFA–CH₂Cl₂ (1:4, 8.0 mL), and the resulting soln was stirred at r.t. for 2 h. The mixture was basified with concd NH₃ soln (pH >8) and extracted with CH₂Cl₂ (3×10 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, EtOAc–MeOH, 5:1) to yield compounds **4a–c**. All

these pure compounds 4a-c were obtained by recrystallization (CH₂Cl₂, hexane).

(*S*)-*N*,*N*'-1,1'-Binaphthalene-2,2'-diylbis(prolinamide) [(*S*)-4a] White solid; yield: 420 mg (89%); mp 240–241 °C.

 $[\alpha]_{D}^{20}$ –167.3 (*c* 1.02, CHCl₃).

IR (film): 3338, 3215, 2965, 2869, 1678, 1594, 1501, 1426, 1344, 1332, 1150, 868, 818, 776, 750 $\rm cm^{-1}.$

¹H NMR (300 MHz, CDCl₃): $\delta = 0.82-0.96$ (m, 2 H, CH₂), 1.20– 1.30 (m, 2 H, CH₂), 1.55–1.68 (m, 2 H, CH₂), 1.76–1.86 (m, 4 H, CH), 2.10–2.38 (m, 2 H, CH₂), 3.54 (dd, J = 4.2, 9.6 Hz, 2 H, CH), 7.17 (d, J = 8.4 Hz, 2 H, ArH), 7.25 (t, J = 7.5 Hz, 2 H, ArH), 7.39 (t, J = 7.5 Hz, 2 H, ArH), 7.91 (d, J = 8.4 Hz, 2 H, ArH), 8.03 (d, J = 9.0 Hz, 2 H, ArH), 8.80 (d, J = 9.0 Hz, 2 H, ArH), 9.69 (s, 2 H, NHCO).

¹³C NMR (75 MHz, CDCl₃): δ = 25.6, 30.5, 46.0, 60.4, 119.0, 119.4, 124.8, 125.1, 126.8, 128.1, 129.5, 130.7, 132.2, 134.9, 173.9. MS (EI): *m/z* (%) = 478.2 (2.57) [M⁺], 409.2 (13.78), 284.1 (13.21), 70.1 (100).

Anal. Calcd for $C_{30}H_{30}N_4O_2$: C, 75.29, H, 6.32, N, 11.71. Found: C, 75.12, H, 6.38, N, 11.54.

(*R*)-*N*,*N*'-1,1'-Binaphthalene-2,2'-diylbis(prolinamide) [(*R*)-4a] White solid; yield: 383 mg (80%); mp 225–228 °C.

 $[\alpha]_{D}^{20}$ –3.7 (*c* 0.55, CHCl₃).

IR (film): 3339, 3212, 2914, 2867, 1685, 1595, 1502, 1453, 1428, 1261, 1089, 821, 750 cm $^{-1}$.

¹H NMR (300 MHz, CDCl₃): δ = 1.25–1.30 (m, 2 H, CH₂), 1.35–1.55 (m, 2 H, CH₂), 1.60–1.80 (m, 4 H, CH₂), 2.20–2.28 (m, 2 H, CH₂), 2.52–2.61 (m, 2 H, CH), 3.52 (dd, *J* = 4.2, 9.3 Hz, 2 H, CH), 7.13 (d, *J* = 8.4 Hz, 2 H, ArH), 7.26 (t, *J* = 7.5 Hz, 2 H, ArH), 7.41 (t, *J* = 7.5 Hz, 2 H, ArH), 7.93 (d, *J* = 7.5 Hz, 2 H, ArH), 8.04 (d, *J* = 9.0 Hz, 2 H, ArH), 8.77 (d, *J* = 9.0 Hz, 2 H, ArH), 9.69 (s, 2 H, NHCO).

¹³C NMR (75 MHz, CDCl₃): δ = 25.6, 30.6, 46.6, 60.5, 119.6, 119.7, 124.8, 125.1, 126.8, 128.1, 129.5, 130.8, 132.6, 135.0, 173.6.

MS (EI): m/z (%) = 478.2 (2.21) [M⁺], 409.2 (7.84), 284.1 (9.50), 70.1 (100).

HRMS (EI): m/z [M⁺] calcd for $C_{30}H_{30}N_4O_2$: 478.2369; found: 478.2357.

(S)-N-(2'-Acetamido-1,1'-binaphthalen-2-yl)prolinamide [(S)-4b]

White solid; yield: 380 mg (90%); mp 166-167 °C.

 $[\alpha]_{D}^{20}$ –124.0 (*c* 1.04, CHCl₃).

IR (film): 3252, 2956, 2926, 1671, 1594, 1500, 1449, 1426, 1276, 819, 749 $\rm cm^{-1}.$

¹H NMR (300 MHz, CDCl₃): δ = 0.82–0.95 (m, 1 H, CH₂), 1.20– 1.35 (m, 1 H, CH₂), 1.68–1.74 (m, 2 H, CH₂), 1.76 (s, 3 H, CH₃), 1.79–1.96 (m, 1 H, CH₂), 1.80 (s, 1 H, NH), 2.30–2.45 (m, 1 H, CH₂), 3.52 (dd, *J* = 4.5, 9.6 Hz, 1 H, CH), 7.01 (s, 1 H, NHCOCH₃), 7.03 (d, *J* = 8.7 Hz, 1 H, ArH), 7.16 (d, *J* = 8.7 Hz, 1 H, ArH), 7.18– 7.32 (m, 2 H, ArH), 7.36–7.45 (m, 2 H, ArH), 7.91 (dd, *J* = 4.8, 7.8 Hz, 2 H, ArH), 8.03 (dd, *J* = 6.0, 9.0 Hz, 2 H, ArH), 8.50 (d, *J* = 9.0 Hz, 1 H, ArH), 8.70 (d, *J* = 9.0 Hz, 1 H, ArH), 9.74 (s, 1 H, NHCO).

¹³C NMR (75 MHz, CDCl₃): δ = 24.2, 25.1, 30.4, 46.0, 60.3, 119.0, 120.0, 120.6, 121.3, 124.6, 124.9, 125.2, 126.8, 127.1, 127.9, 128.2, 129.2, 129.8, 130.7, 130.9, 132.10, 132.12, 134.8, 135.0, 168.7, 174.1.

MS (EI): m/z (%) = 423.2 (10.79) [M⁺], 326.1 (12.33), 267.1 (66.19), 143.1 (9.88), 70.1 (100).

HRMS (EI): m/z [M⁺] calcd for C₂₇H₂₅N₃O₂: 423.1947; found: 423.1947.

(R) - N - (2' - Acetamido-1,1'-binaphthalen-2-yl) prolinamide [(R) - 4b]

White solid; yield: 360 mg (85%); mp 125–127 °C.

 $[\alpha]_{D}^{20}$ +69.9 (*c* 1.02, CHCl₃).

IR (film): 3274, 2970, 1686, 1677, 1655, 1597, 1500, 1460, 1276, 820, 750 $\rm cm^{-1}.$

¹H NMR (300 MHz, CDCl₃): $\delta = 0.95-1.10$ (m, 1 H, CH₂), 1.25–1.35 (m, 1 H, CH₂), 1.40–1.55 (m, 1 H, CH₂), 1.65 (s, 3 H, CH₃), 1.68–1.82 (m, 1 H, CH₂), 1.74 (s, 1 H, NH), 1.95–2.08 (m, 1 H, CH₂), 2.35–2.50 (m, 1 H, CH₂), 3.43 (dd, J = 4.5, 9.6 Hz, 1 H, CH), 6.91 (d, J = 8.4 Hz, 1 H, ArH), 7.04 (s, 1 H, NH), 7.05 (d, J = 8.7 Hz, 1 H, ArH), 7.08–7.20 (m, 2 H, ArH), 7.25–7.35 (m, 2 H, ArH), 7.81 (t, J = 8.1 Hz, 2 H, ArH), 7.92 (dd, J = 9.0 Hz, 1 H, ArH), 9.51 (br s, 1 H, NHCO).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 24.3, 25.5, 30.4, 46.4, 60.3, 120.5, 121.1, 121.3, 121.7, 124.8, 124.96, 124.98, 125.3, 126.7, 127.1, 127.9, 128.1, 129.1, 129.9, 130.8, 131.2, 132.2, 132.3, 134.6, 134.9, 168.4, 174.3.

MS (EI): m/z (%) = 423.2 (9.61) [M⁺], 326.1 (11.24), 267.1 (52.63), 143.1 (8.66), 70.1 (100).

HRMS (EI): m/z [M⁺] calcd for C₂₇H₂₅N₃O₂: 423.1947; found: 423.1948.

(S)-N-[2'-(Tosylamino)-1,1'-binaphthalen-2-yl]prolinamide [(S)-4c]

White solid; yield: 470 mg (88%); mp 191-192 °C.

 $[\alpha]_{D}^{20}$ –205.2 (*c* 1.04, CHCl₃).

IR (film): 3333, 3193, 3053, 2876, 1687, 1501, 1468, 1429, 1166, 1092, 976, 814, 748, 663 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 0.82–0.95 (m, 1 H, CH₂), 1.00–1.35 (m, 1 H, CH₂), 1.40–1.65 (m, 1 H, CH), 1.57 (br s, 1 H, NH), 1.78–2.05 (m, 2 H, CH₂), 2.34 (s, 3 H, CH₃), 2.50–2.60 (m, 1 H, CH₂), 3.50 (dd, *J* = 4.5, 9.3 Hz, 1 H, CH), 6.50 (d, *J* = 8.4 Hz, 1 H, ArH), 6.85–7.05 (m, 4 H, ArH), 7.15–7.25 (m, 1 H, ArH), 7.35–7.42 (m, 4 H, ArH), 7.83–7.95 (m, 2 H, m ArH), 7.98 (d, *J* = 9.3 Hz, 1 H, ArH), 8.03 (d, *J* = 9.3 Hz, 1 H, ArH), 8.14 (d, *J* = 8.7 Hz, 1 H, ArH), 8.78 (d, *J* = 8.7 Hz, 1 H, ArH), 9.69 (br s, 1 H, NHCO).

 13 C NMR (75 MHz, CDCl₃): δ = 21.4, 25.8, 30.5, 46.6, 60.5, 117.5, 118.7, 119.7, 120.0, 124.4, 124.6, 125.1, 125.3, 126.9, 127.2, 127.9, 128.1, 129.4, 129.9, 130.3, 130.6, 130.8, 132.1, 132.6, 133.6, 135.4, 135.9, 143.7, 173.9.

MS (EI): *m*/*z* (%) = 535.2 (1.09) [M⁺], 438.1 (7.97), 311.1 (100), 283.1 (14.84), 267.1 (26.05), 70.1 (51.57).

HRMS (EI): m/z [M⁺] calcd for $C_{32}H_{29}N_3O_3S$: 535.1930; found: 535.1927.

(*R*)-*N*-[2'-(Tosylamino)-1,1'-binaphthalen-2-yl]prolinamide [(*R*)-4c]

White solid; yield: 430 mg (81%); mp 152-155 °C.

 $[\alpha]_{D}^{20}$ –4.7 (*c* 1.045, CHCl₃).

IR (film): 3333, 3193, 3052, 2911, 1682, 1594, 1504, 1454, 1469, 1429, 1315, 1166, 1091, 976, 814, 664 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.25–1.30 (m, 1 H, CH₂), 1.45– 1.70 (m, 1 H, CH₂), 1.60 (br s, 1 H, NH), 1.80–2.03 (m, 2 H, CH₂), 2.30–2.50 (m, 1 H, CH₂), 2.34 (s, 3 H, CH₃), 2.55–2.68 (m, 1 H, CH₂), 3.50 (dd, *J* = 4.5, 9.0 Hz, 1 H, CH), 6.54 (d, *J* = 8.4 Hz, 1 H, ArH), 6.85–7.05 (m, 4 H, ArH), 7.15–7.25 (m, 1 H, ArH), 7.30–7.45 (m, 4 H, ArH), 7.85–7.90 (m, 2 H, ArH), 7.99 (d, *J* = 9.3 Hz, 1 H,

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ArH), 8.05 (d, *J* = 9.3 Hz, 1 H, ArH), 8.16 (d, *J* = 9.0 Hz, 1 H, ArH), 8.77 (d, *J* = 9.0 Hz, 1 H, ArH), 9.64 (br s, 1 H, NHCO).

 ^{13}C NMR (75 MHz, CDCl₃): δ = 21.4, 25.8, 30.5, 46.6, 60.5, 117.5, 118.7, 119.7, 120.0, 124.4, 124.6, 125.1, 125.3, 126.9, 127.2, 127.9, 128.1, 129.4, 129.9, 130.3, 130.6, 130.8, 132.1, 132.6, 133.6, 135.4, 135.9, 143.7, 173.9.

MS (EI): *m*/*z* (%) = 535.2 (3.96) [M⁺], 438.1 (12.10), 311.1 (100), 283.1 (13.60), 267.1 (9.48), 70.1 (6.26).

HRMS (EI): m/z [M⁺] calcd for $C_{32}H_{29}N_3O_3S$: 535.1930; found: 535.1934.

Aldol Products 8a-g, 9a-g, and 10; General Procedure

Bis(prolinamide) (*S*)-**4a** (24.0 mg, 0.05 mmol) was stirred in toluene (3.0 mL), ketone (such as acetone, cyclopentanone, or cyclohexanone) (0.5 mL), then AcOH (4.0 μ L) were added into the soln. The mixture was stirred at -40 °C for 30 min. The corresponding arylaldehyde **7** (0.5 mmol) was added and the mixture was stirred for 48–72 h. The reaction was quenched with sat. NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (anhyd Na₂SO₄), filtered, and concentrated under reduced pressure to give pure aldol adducts **8a–g**, **9a–g**, and **10** after flash chromatography (silica gel, petroleum ether–EtOAc, 5:1~3:1).

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (8a)

Yield: 86.0 mg (83%). HPLC analysis (Chiralpak AS-H, hexane– *i*-PrOH, 80:20, 1.0 mL/min, 254 nm, 20 °C): $t_{\rm R}$ (*R*, major) = 25.91 min and $t_{\rm R}$ (*S*, minor) = 41.02 min; 93% ee.

 $[\alpha]_{D}^{20}$ +59.4 (*c* 1.02, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 2.21 (s, 3 H, CH₃), 2.80–2.89 (m, 2 H, CH₂), 3.64 (br s, 1 H, OH), 5.26 (dd, *J* = 4.5, 7.5 Hz, 1 H, CH), 7.53 (d, *J* = 9.0 Hz, 2 H, ArH), 8.21 (d, *J* = 9.0 Hz, 2 H, ArH).

4-Hydroxy-4-(3-nitrophenyl)butan-2-one (8b)

Yield: 90.0 mg (86%). HPLC analysis (Chiralcel OJ-H, hexane– *i*-PrOH, 80:20, 1.0 mL/min, 254 nm, 20 °C): $t_{\rm R}$ (*R*, major) = 18.10 min and $t_{\rm R}$ (*S*, minor) = 21.09 min; 95% ee.

$[\alpha]_{D}^{20}$ +73.7 (*c* 1.05, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 2.23 (s, 3 H, CH₃), 2.87–2.89 (m, 2 H, CH₂), 3.66 (br s, 1 H, OH), 5.26 (dd, *J* = 4.5, 7.5 Hz, 1 H, CH), 7.53 (t, *J* = 8.1 Hz, 1 H, ArH), 7.70 (d, *J* = 7.5 Hz, 1 H, ArH), 8.13 (d, *J* = 8.1 Hz, 1 H, ArH), 8.24 (s, 1 H, ArH).

4-Hydroxy-4-(2-nitrophenyl)butan-2-one (8c)

Yield: 90.0 mg (86%). HPLC analysis (Chiralpak AS-H, hexane– *i*-PrOH, 70:30, 1.0 mL/min, 254 nm, 20 °C): $t_{\rm R}$ (*R*, major) = 10.92 min and $t_{\rm R}$ (*S*, minor) = 9.98 min; 98% ee.

 $[\alpha]_{D}^{20}$ +72.9 (*c* 1.02, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 2.22 (s, 3 H, CH₃), 2.85–2.90 (m, 2 H, CH₂), 3.71 (br s, 1 H, OH), 5.26 (dd, *J* = 3.6, 7.2 Hz, 1 H, CH), 7.52 (t, *J* = 7.8 Hz, 1 H, ArH), 7.70 (d, *J* = 7.8 Hz, 1 H, ArH), 8.10–8.14 (m, 1 H, ArH), 8.24 (m, 1 H, ArH).

4-(4-Chlorophenyl)-4-hydroxybutan-2-one (8d)

Yield 68.0 mg (67%). HPLC analysis (Chiralpak AS-H, hexane– *i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ (*R*, major) = 25.91 min and $t_{\rm R}$ (*S*, minor) = 41.02 min; 81% ee.

 $[\alpha]_{D}^{20}$ +98.8 (*c* 1.035, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 2.19 (s, 3 H, CH₃), 2.75–2.85 (m, 2 H, CH₂), 3.07 (br s, 1 H, OH), 5.11 (dd, *J* = 3.9, 8.4 Hz, 1 H, CH), 7.26–7.33 (m, 4 H, ArH).

4-(2-Chlorophenyl)-4-hydroxybutan-2-one (8e)

Yield: 89.0 mg (91%). HPLC analysis (Chiralpak AD-H, hexane– *i*-PrOH, 98:2, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ (*R*, major) = 14.84 min and $t_{\rm R}$ (*S*, minor) = 11.01 min; 92% ee.

 $[\alpha]_{D}^{20}$ +97.4 (*c* 1.15, CHCl₃).

¹H NMR (300 MHz, CDCl₃): $\delta = 2.21$ (s, 3 H, CH₃), 2.68 (dd, J = 9.6, 17.7 Hz, 1 H, CH₂), 2.96 (d, J = 9.6 Hz, 1 H, CH₂), 3.45 (dd, 1 H, OH), 5.50 (d, J = 9.6 Hz, 1 H, CH), 7.15–7.40 (m, 3 H, ArH), 7.61 (d, J = 7.8 Hz, 1 H, ArH).

4-(4-Bromophenyl)-4-hydroxybutan-2-one (8f)

Yield: 73.0 mg (60%). HPLC analysis (Chiralpak AS-H, hexane– *i*-PrOH, 80:20, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ (*R*, major) = 17.20 min and $t_{\rm R}$ (*S*, minor) = 23.19 min; 76% ee.

 $[\alpha]_{D}^{20}$ +31.0 (*c* 0.525, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 2.01 (s, 3 H, CH₃), 2.57 (dd, J = 3.6, 17.4 Hz, 1 H, CH₂), 2.70 (dd, J = 9.0, 17.4 Hz, 1 H, CH₂), 3.87 (br s, 1 H, OH), 4.93 (dd, J = 3.6, 9.0 Hz, 1 H, CH), 7.07 (d, J = 8.7 Hz, 2 H, ArH), 7.30 (d, J = 8.7 Hz, 2 H, ArH).

4-(4-Fluorophenyl)-4-hydroxybutan-2-one (8g)

Yield: 54.0 mg (57%). HPLC analysis (Chiralpak AD-H, hexane– *i*-PrOH, 98:2, 1.0 mL/min, 220 nm, 20 °C): t_R (*R*, major) = 11.02 min and t_R (*S*, minor) = 12.78 min; 67% ee.

 $[\alpha]_{D}^{20}$ +20.4 (*c* 0.50, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 2.18 (s, 3 H, CH₃), 2.78 (dd, *J* = 3.6, 17.4 Hz, 1 H, CH₂), 2.86 (dd, *J* = 8.7, 17.4 Hz, 1 H, CH₂), 3.16 (br s, 1 H, OH), 5.10–5.14 (dd, *J* = 3.6, 8.7 Hz, 1 H, CH), 6.95–7.08 (m, 2 H, ArH), 7.25–7.38 (m, 2 H, ArH).

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (9a)

Yield: 112.0 mg (90%); ratio anti/syn 98:2.

 $[\alpha]_{D}^{20}$ +10.2 (*c* 1.00, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiralcel OJ-H, hexane–*i*-PrOH, 70:30, 1.0 mL/ min, 254 nm, 20 °C): $t_{\rm R}$ (major) = 8.84 min and $t_{\rm R}$ (minor) = 10.67 min; 95% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.30–1.85 (series of m, 5 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.25–2.55 (m, 2 H, CH₂), 2.58–2.68 (m, 1 H, CH), 4.09 (br s, 1 H, OH), 4.89 (d, *J* = 8.4 Hz, 1 H, CH), 7.49 (d, *J* = 8.7 Hz, 2 H, ArH), 8.19 (d, *J* = 8.7 Hz, 2 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralcel OJ-H, hexane–*i*-PrOH, 70:30, 1.0 mL/ min, 254 nm, 20 °C): $t_{\rm R}$ = 9.85 min and $t_{\rm R}$ = 15.14 min.

¹H NMR (300 MHz, CDCl₃): $\delta = 1.30-1.85$ (series of m, 5 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.25–2.55 (m, 2 H, CH₂), 2.58–2.68 (m, 1 H, CH), 5.47 (d, J = 1.5 Hz, 1 H, CH), 7.48 (d, J = 8.8 Hz, 2 H, ArH), 8.20 (d, J = 8.8 Hz, 2 H, ArH).

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone (9b)

Yield: 103.0 mg (83%); ratio anti/syn 98:2.

 $[\alpha]_{D}^{20}$ +29.6 (*c* 1.06, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/ min, 254 nm, 20 °C): t_R (major) = 31.95 min and t_R (minor) = 41.13 min; 95% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.30–1.85 (series of m, 5 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.30–2.55 (m, 2 H, CH₂), 2.58–2.68 (m, 1 H, CH), 4.12 (br s, 1 H, OH), 4.89 (d, *J* = 8.4 Hz, 1 H, CH), 7.52 (t,

J = 8.1 Hz, 1 H, ArH), 7.67 (d, J = 8.1 Hz, 1 H, ArH), 8.16 (d, J = 8.1 Hz, 1 H, ArH), 8.20 (s, 1 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 254 nm, 20 °C): $t_{\rm R} = 25.48$ min and $t_{\rm R} = 28.74$ min.

¹H NMR (300 MHz, CDCl₃): δ = 1.46–1.90 (series of m, 5 H, CH₂), 2.05–2.18 (m, 1 H, CH₂), 2.30–2.55 (m, 2 H, CH₂), 2.60–2.70 (m, 1 H, CH), 3.20 (br s, 1 H, OH), 5.48 (d, *J* = 2.4 Hz, 1 H, CH), 7.53 (t, *J* = 7.8 Hz, 1 H, ArH), 7.68 (d, *J* = 7.8 Hz, 1 H, ArH), 8.13 (d, *J* = 7.8 Hz, 1 H, ArH), 8.19 (s, 1 H, s, ArH).

2-[Hydroxy(2-nitrophenyl)methyl]cyclohexanone (9c)

Yield: 103.0 mg (83%); ratio anti/syn 98:2.

 $[\alpha]_{D}^{20}$ +25.4 (*c* 1.02, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 254 nm, 20 °C): $t_{\rm R}$ (major) = 21.24 min and $t_{\rm R}$ (minor) = 31.18 min; 90% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.35–1.85 (series of m, 5 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.30–2.50 (m, 2 H, CH₂), 2.55–2.68 (m, 1 H, CH), 4.09 (br s, 1 H, OH), 4.89 (d, *J* = 8.4 Hz, 1 H, CH), 7.53 (t, *J* = 7.8 Hz, 1 H, ArH), 7.68 (d, *J* = 7.8 Hz, 1 H, ArH), 8.15–8.19 (m, 1 H, ArH), 8.17–8.21 (m, 1 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 254 nm, 20 °C): $t_{\rm R}$ = 18.15 min and $t_{\rm R}$ = 18.75 min.

¹H NMR (300 MHz, CDCl₃): δ = 1.45–1.90 (series of m, 5 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.30–2.55 (m, 2 H, CH₂), 2.60–2.70 (m, 1 H, CH), 3.20 (br s, 1 H, OH), 5.47 (d, *J* = 2.1 Hz, 1 H, CH), 7.51 (t, *J* = 7.8 Hz, 1 H, ArH), 7.65 (d, *J* = 7.8 Hz, 1 H, ArH), 8.09–8.11 (m, 1 H, ArH), 8.12–8.18 (m, 1 H, ArH).

2-[(4-Chlorophenyl)(hydroxy)methyl]cyclohexanone (9d)

Yield: 85.0 mg (71%); ratio anti/syn 97:3.

 $[\alpha]_{D}^{20}$ +22.6 (*c* 1.005, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ (minor) = 12.78 min and $t_{\rm R}$ (major) = 14.73 min; 98% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.25–1.85 (series of m, 5 H, CH₂), 2.00–2.15 (m, 1 H, CH₂), 2.25–2.50 (m, 2 H, CH₂), 2.55–2.65 (m, 1 H, CH), 4.00 (br s, 1 H, OH), 4.76 (d, *J* = 8.7 Hz, 1 H, CH), 7.24 (d, *J* = 8.4 Hz, 2 H, ArH), 7.31 (d, *J* = 8.4 Hz, 2 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ 8.39 min and $t_{\rm R}$ 9.82 min.

¹H NMR (300 MHz, CDCl₃): δ = 1.25–1.85 (series of m, 5 H, CH₂), 2.00–2.15 (m, 1 H, CH₂), 2.25–2.50 (m, 2 H, CH₂), 2.55–2.65 (m, 1 H, CH), 5.36 (d, *J* = 2.4 Hz, 1 H, CH), 7.24 (d, *J* = 8.4 Hz, 2 H, ArH), 7.31 (d, *J* = 8.4 Hz, 2 H, ArH).

2-[(4-Bromophenyl)(hydroxy)methyl]cyclohexanone (9e)

Yield: 98.0 mg (70%); ratio anti/syn 95:5.

 $[\alpha]_{D}^{20}$ +17.3 (*c* 1.03, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ (minor) = 14.80 min and $t_{\rm R}$ (major) = 17.37 min; 96% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.20–1.35 (m, 1 H, CH₂), 1.40–1.85 (m, 4 H, CH₂), 2.00–2.15 (m, 1 H, CH₂), 2.25–2.50 (m, 2 H, CH₂), 2.55–2.65 (m, 1 H, CH), 3.99 (br s, 1 H, OH), 4.74 (d, *J* = 8.4 Hz, 1 H, CH), 7.17 (d, *J* = 8.4 Hz, 2 H, ArH), 7.47 (d, *J* = 8.4 Hz, 2 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/ min, 220 nm, 20 °C): $t_{\rm R} = 9.17$ min and $t_{\rm R} = 10.92$ min.

¹H NMR (300 MHz, CDCl₃): δ = 1.40–2.05 (series of m, 5 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.30–2.65 (m, 3 H, CH), 3.09 (br s, 1 H, OH), 5.33 (d, *J* = 2.1 Hz, 1 H, CH), 7.18 (d, *J* = 8.4 Hz, 2 H, ArH), 7.45 (d, *J* = 8.4 Hz, 2 H, ArH).

2-[(4-Fluorophenyl)(hydroxy)methyl]cyclohexanone (9f)

Yield: 68.0 mg (61%); ratio anti/syn 92:8.

 $[\alpha]_{D}^{20}$ +17.7 (*c* 1.045, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/min, 220 nm, 20 °C): $t_{\rm R}$ (minor) = 12.29 min and $t_{\rm R}$ (major) = 13.50 min; 92% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.15–1.35 (m, 1 H, CH₂), 1.40– 1.85 (m, 4 H, CH₂), 2.05–2.15 (m, 1 H, CH₂), 2.30–2.65 (m, 3 H, CH), 4.01 (br s, 1 H, OH), 4.77 (d, *J* = 8.7 Hz, 1 H, CH), 7.03 (t, *J* = 8.7 Hz, 2 H, ArH), 7.27–7.31 (m, 2 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralpak AD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/ min, 220 nm, 20 °C): $t_{\rm R} = 8.23$ min and $t_{\rm R} = 9.42$ min.

¹H NMR (300 MHz, CDCl₃): δ = 1.45–1.75 (series of m, 5 H, CH₂), 2.05–2.18 (m, 1 H, CH₂), 2.30–2.50 (m, 2 H, CH₂), 2.55–2.65 (m, 1 H, CH), 3.06 (br s, 1 H, OH), 5.36 (d, *J* = 2.1 Hz, 1 H, CH), 7.03 (t, *J* = 8.7 Hz, 2 H, ArH), 7.24–7.29 (m, 2 H, ArH).

2-[Hydroxy(phenyl)methyl]cyclohexanone (9g)

Yield: 46 mg (45%); ratio *anti/syn* 97:3. $[\alpha]_D^{20} + 26.5$ (*c* 0.40, CHCl₃).

anti-Diastereomer

HPLC analysis (Chiracel OD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/ min, 220 nm, 20 °C): $t_{\rm R}$ (minor) = 18.5 min and $t_{\rm R}$ (major) = 27.5 min; 80% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.20–1.40 (m, 1 H, CH₂), 1.45– 1.82 (m, 4 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.30–2.58 (m, 2 H, CH), 2.60–2.70 (m, 1 H, CH), 4.79 (d, *J* = 8.7 Hz, 1 H, CH), 7.31– 7.36 (m, 5 H, ArH).

syn-Diastereomer

HPLC analysis (Chiralcel OD-H, hexane–*i*-PrOH, 90:10, 1.0 mL/ min, 220 nm, 20 °C): $t_{\rm R} = 14.8$ min and $t_{\rm R} = 16.3$ min.

¹H NMR (300 MHz, CDCl₃): δ = 1.40-1.80 (m, 4 H, CH₂), 2.05–2.20 (m, 1 H, CH₂), 2.30–2.58 (m, 2 H, CH), 2.60–2.70 (m, 1 H, CH), 5.39 (d, J = 2.4 Hz, 1 H, CH), 7.30–7.35 (m, 5 H, ArH).

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentanone (10)

Yield: 100.0 mg (84%); ratio anti/syn 30:70.

 $[\alpha]_{D}^{20}$ +98.2 (*c* 1.025, CHCl₃).

syn-Diastereomer

HPLC analysis (Chiralpak AS-H, hexane–*i*-PrOH, 85:15, 0.8 mL/ min, 254 nm, 20 °C): $t_{\rm R}$ (major) = 24.49 min and $t_{\rm R}$ (minor) = 79.12 min; 81% ee. ¹H NMR (300 MHz, $CDCl_3$): $\delta = 1.47-2.52$ (series of m, 7 H, CH_2), 2.87 (br s, 1 H, OH), 5.41 (d, J = 3.0 Hz, 1 H, CH), 7.53 (d, J = 8.7 Hz, 2 H, ArH), 8.21 (d, J = 8.7 Hz, 2 H, ArH).

anti-Diastereomer

HPLC analysis (Chiralpak AS-H, hexane–*i*-PrOH, 85:15, 0.8 mL/min, 254 nm, 20 °C): $t_{\rm R}$ (minor) = 27.45 min and $t_{\rm R}$ (major) = 37.17 min; 98% ee.

¹H NMR (300 MHz, CDCl₃): δ = 1.67–2.54 (series of m, 7 H, CH₂), 4.78 (s, 1 H, OH), 4.84 (d, *J* = 9.0 Hz, 1 H, CH), 7.54 (d, *J* = 8.7 Hz, 2 H, ArH), 8.21 (d, *J* = 8.7 Hz, 2 H, ArH).

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