Molecular-Sieves Controlled Diastereo- and Enantioselectivity: Unexpected Effect in the Organocatalyzed Direct Aldol Reaction

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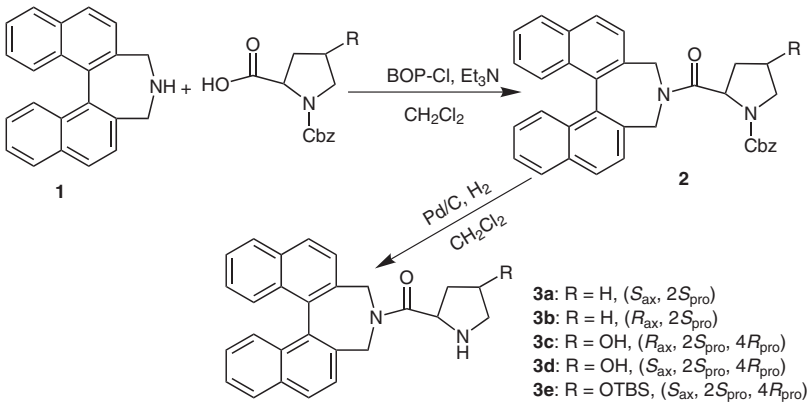
Abstract: An efficient asymmetric organocatalyst was developed for the direct aldol reaction between ketones and aldehydes to afford β-hydroxy ketones in high stereoselectivity (*anti*/*syn* up to 92:8, ee up to >99%). The key of the success was the use of activated molecular sieves (4 Å MS), which acted as a water scavenger. The influence of additives such as water or different types of molecular sieves on the reactivity and stereoselectivity of the reaction was also studied.

Key words: asymmetric catalysis, aldol reaction, stereoselectivity, molecular sieves, aldehyde

The asymmetric aldol condensation is one of the most powerful tools for the carbon–carbon bond formation in synthetic organic chemistry.[1] Asymmetric organocatalysis, where small organic molecules catalyze the reactions without the presence of any metal, has become an attractive strategy for the direct aldol reactions.[2] The major breakthrough came from a pioneering work by List[3] and Barbas[4] that L-proline could act as a catalyst in intermolecular direct aldol reaction where an enamine generated in situ from a chiral amine and carbonyl compound underwent an enantioselective nucleophilic attack on the electrophilic aldehyde center. Since then, great emphases have been given to the design of new chiral organocatalysts, and many proline derivatives have become popular organocatalysts in this field.[5] During our studies of enantioselective direct aldol condensation of cyclohexanone and 4-nitrobenzaldehyde catalyzed by the use of new chiral prolinamide derivatives, we found, quite unexpectedly, that the addition of molecular sieves (MS) resulted in markedly enhanced diasteroselectivity as well as enantioselectivity. To our knowledge, this is the first time that such an effect has been observed in organocatalytic synthesis.[6] Herein, we wish to present this intriguing finding and disclose the origin of the favorable influence of the molecular sieves.

The chiral organic catalysts **3a**–**e**[12] were prepared as shown in Scheme 1. Reaction of Cbz-L-proline and *trans*-4-hydroxy-L-proline with binaphthyl-based axially chiral amine **1** provided intermediate **2**, subsequent deprotection of the Cbz group then gave compound **3** in good yields. The catalytic activities of these new organocatalysts were then evaluated in a direct enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde (Scheme 2).

In our initial experiment, the direct aldol reaction was performed in the presence of 4 Å molecular sieves using a catalytic amount (10 mol%) of the prolinamides **3a**–**e** (Table 1). The two diastereomeric organocatalysts **3a** and **3b** maintained moderate reactivity, yet high diastereo- and enantioselectivities were obtained, with catalyst **3b** better than **3a** (entries 1 and 2). It was noteworthy that *trans*-4-hydroxy-L-proline-derived organocatalysts **3c** and **3d** gave the opposite sense of asymmetric induction (entries 3 and 4). Interestingly, both the yield and stereoselectivity of the aldol reaction were decreased when the hydroxyl group of **3d** was replaced by a siloxy group (entry 5).



Scheme 1 Synthesis of new organocatalysts

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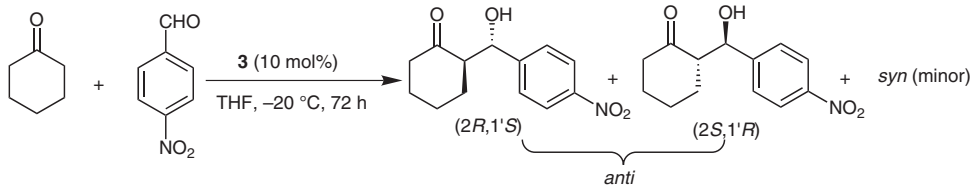


Scheme 2 Model reaction for screening of organocatalysts

Among these small organic molecules, compound **3d** exhibited a superior level of reactivity and stereoselectivity.[7] In the absence of molecular sieves, it was quite unexpectedly found that the the aldol reactions proceeded more quickly (within 16 h) with excellent yields, but the diastereo- and enantioselectivities decreased dramatically (entry 6 vs. entry 2, and entry 7 vs. entry 4). Different kinds of molecular sieves were also used in the presence of organocatalyst **3d**, and their influence on the stereoselectivities of the aldol reaction was observed (entries 8–10). In addition, diminishing the amount of 4 Å molecular sieves from 60 to 50 mg led to a slight decrease in the selectivities (entry 11). The yields became poor when the amount of molecular sieves was increased (entry 12 and 13). At 0 °C, although the reaction was complete within 24 hours without loss of enantioselectivity, the dr value was slightly lower (entry 14).

It is well known that adventitious water often results in a less-than-satisfactory stereoselectivity for some transition-metal-catalyzed asymmetric reactions.

In contrast, organocatalytic aldol reactions can usually be performed under an aerobic atmosphere with wet solvents, and even in aqueous medium.[8,9] However, water might be the culprit for the lowering of diastereo- and enantioselectivities in our organocatalytic system. Therefore, the influence of water on the selectivity was investigated in order to ascertain if the molecular sieves served to eliminate moisture, and prevented water-mediated background reactions. Significantly, we found that the presence of water had a remarkable effect on the catalytic activity and stereoselectivity (Table 2). With added water, the reaction proceeded quickly but in moderate diastereoselectivities. Furthermore, the enantioselectivity tended to decrease with increasing amount of water (entries 1–7). Performing the same reaction in neat water leads to *syn* product as the major diastereomer with 26% ee (entry 8).

In the presence of 4 Å molecular sieves, a representative selection of cyclic ketones and aromatic aldehydes was evaluated under the optimized conditions (Scheme 3) and the results obtained are shown in Table 3. The direct aldol reactions of ketones with the aldehydes bearing an electron-withdrawing group on the benzene ring took place smoothly and were catalyzed by 10 mol% **3d** to afford aldol adducts in moderate to high yields with high stereoselectivities (*anti*/*syn* up to 97:3, ee up to >99%; entries 1–11).

Interestingly, 4-*tert*-butylcyclohexanone, a conformationally anchored substrate, also showed complete progress after 9 days to give the aldol product with excellent diastereo- and enantioselectivities (entry 12). For aromatic aldehydes with electron-neutral (H) or electron-donating

Table 1 Evaluation of Organocatalysts and Effect of Molecular Sieves in the Direct Aldol Reaction[a]

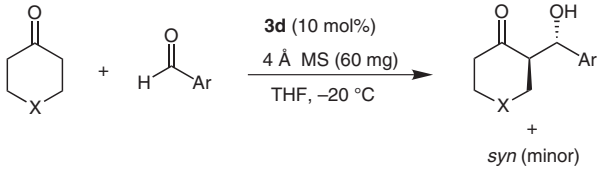
Entry	Catalyst	Additive	Yield (%)[b]	Ratio *anti*/*syn*[c]	ee (*anti*)[c]
1	**3a**	4 Å MS (60 mg)	35	89:11	80 (2*S*,1′*R*)
2	**3b**	4 Å MS (60 mg)	31	93:7	>99 (2*S*,1′*R*)
3	**3c**	4 Å MS (60 mg)	42	87:13	91 (2*R*,1′*S*)
4	**3d**	4 Å MS (60 mg)	>99	92:8	>99 (2*R*,1′*R*)
5	**3e**	4 Å MS (60 mg)	67	84:16	77 (2*R*,1′*S*)
6[d]	**3b**	–	95	53:47	46 (2*S*,1′*R*)
7[d]	**3d**	–	>99	66:34	72 (2*R*,1′*S*)
8	**3d**	3 Å MS (60 mg)	64	81:19	82 (2*R*,1′*S*)
9	**3d**	5 Å MS (60 mg)	48	89:11	48 (2*R*,1′*S*)
10	**3d**	13X MS (60 mg)	86	83:17	85 (2*R*,1′*S*)
11	**3d**	4 Å MS (50 mg)	98	89:11	95 (2*R*,1′*S*)
12	**3d**	4 Å MS (100 mg)	33	–	–
13	**3d**	4 Å MS (120 mg)	13	–	–
14[e]	**3d**	4 Å MS (60 mg)	>99	87:13	>99 (2*R*,1′*S*)

[a] The reactions were carried out with **3** (10 mol%), cyclohexanone (5.0 mmol), 4-nitrobenzaldehyde (1.0 mmol), and MS in THF at –20 °C for 72 h.
[b] Yield of isolated product.
[c] Determined by HPLC analysis with a chiral column. The absolute configuration was determined by comparison of the optical rotation with the literature value.
[d] Reaction time: 16 h
[e] Reaction temperature and time: 0 °C, 24 h.

Table 2 Effect of the Amount of Water on the Direct Aldol Reaction[a]

Entry	H_2O–THF (vol.)	Yield (%)[b]	*anti*/*syn*[c]	ee (*anti*)[c]
1	1:100,000	72	61:39	85
2	1:10,000	83	54:46	82
3	1:1,000	93	55:45	85
4	1:100	>99	66:34	72
5	10:90	>99	83:17	38
6	40:60	>99	56:44	66
7	70:30	>99	64:36	63
8	100:0	>99	42:58	54:26 (*syn*)

[a] The reactions were carried out with **3d** (0.1 mmol), cyclohexanone (5.0 mmol), aldehyde (1.0 mmol) in THF at –20 °C.
[b] Yield of isolated product.
[c] Determined by HPLC analysis with a chiral column.



Scheme 3 The reaction of different ketones and aromatic aldehydes catalyzed by **3d** in the presence of 4 Å MS

substituents (such as Me, MeO, and Cl), the desired aldol adducts were not obtained.[13]

The stereochemical outcome in the above direct aldol reaction catalyzed by **3d** could be explained by the transition state as depicted in Figure 1, which was based on the previous model supported by DFT calculations.[5o,10] The aldehyde was activated and oriented by hydrogen bonding with the OH of the catalyst in a manner such that enamine attacked the aldehyde from the *re* face, leading to the formation of the major stereoisomer. In addition, the π–π stacking interaction might also play an important role in stabilizing the transition state. In the presence of water, the hydrogen-bonding interaction between water and aldehyde could result in a decrease of stereoselectivities.

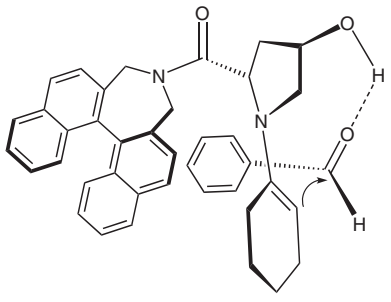


Figure 1 Transition-state model

Table 3 Screening of Different Ketones and Aromatic Aldehydes in the Presence of 4 Å MS

Entry	Ar	X	Yield (%)[a]	*anti*/*syn*[b]	ee (*anti*)[b]
1[c]	2-naphthyl	CH_2	37	78:22	>99
2	4-$O_2NC_6H_4$	CH_2	>99	92:8	>99
3	3-$O_2NC_6H_4$	CH_2	45	94:6	94
4	2-$O_2NC_6H_4$	CH_2	79	91:9	87
5[d]	4-NCC_6H_4	CH_2	90	80:20	93
6	4-$F_3CC_6H_4$	CH_2	84	87:12	83
7	4-$O_2NC_6H_4$	O	78	65:35	92
8	3-$O_2NC_6H_4$	O	95	56:44	84
9	4-NCC_6H_4	O	34	82:18	84
10	4-$O_2NC_6H_4$	S	35	60:40	89
11	3-$O_2NC_6H_4$	S	43	97:3	96
12	4-$O_2NC_6H_4$	*t*-$BuCH_2$	>99	98:2	95

[a] Yield of isolated product.
[b] Determined by HPLC analysis with a chiral column.
[c] Reaction temperature: r.t.
[d] Reaction temperature: 0 °C.

In summary, we found that the presence of 4 Å molecular sieves increased the diastereo- and enantioselectivity in the direct aldol reaction of cyclic ketones and various aromatic aldehydes using of a series of L-prolinamide organocatalysts. The beneficial influence of the molecular sieves could be due to their water-trapping properties. Further investigations of the effect of the molecular sieves in other organocatalytic reactions are in progress and the results will be communicated in due course.

Acknowledgment

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(12) **Typical Procedure for the Preparation of Organocatalyst**
To a stirred solution of the corresponding *N*-(benzyloxycarbonyl)proline (2.5 mmol) and Et_3N (0.9 mL, 6.8 mmol) in anhyd CH_2Cl_2 (10 mL) and under an argon atmosphere, were added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 0.63 g, 2.6 mmol) at 0 °C. After 30 min of stirring, the corresponding chiral amine (2.5 mmol) was added, and the mixture was further stirred for 24 h. It was diluted with 10 mL of CH_2Cl_2 and washed once with HCl (1 N), H_2O, and brine. Then, it was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford a residue. The resulting residue was dissolved in EtOAc (10 mL) and Pd/C (10 wt%) was added. The mixture was stirred at r.t. under hydrogen atmosphere (1 atm) overnight. Then, the mixture was filtered through Celite and the solvent evaporated under reduced pressure to afford the title compounds, which were purified over silica gel flash column chromatography [Et_3N–EtOAc–PE, 1:20:100 (vol.)].
Compound **3a**:[11] yield 97%, mp 146–147 °C; $[\alpha]_D^{20}$ –162.5 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.82–1.89 (m, 1 H, pyrrolidine-H), 1.95–2.02 (m, 2 H, pyrrolidine-H), 2.50–2.57 (m, 1 H, pyrrolidine-H), 3.03–3.07 (m, 1 H, pyrrolidine-H), 3.16 (br, 1 H, NH), 3.27–3.32 (m, 1 H, pyrrolidine-H), 3.56 (d, *J* = 13.5 Hz, 1 H, NCH), 3.97 (d, *J* = 12.5 Hz, 1 H, NCH), 4.19–4.22 (m, 1 H, pyrrolidine-H), 4.65 (d, *J* = 13.0 Hz, 1 H, NCH), 5.46 (d, *J* = 13.0 Hz, 1 H, NCH), 7.28–7.33 (m, 2 H, binaphthyl-H), 7.43 (d, *J* = 9.0 Hz, 1 H, binaphthyl-H), 7.49–7.54 (m, 4 H, binaphthyl-H), 7.62 (d, *J* = 8.5 Hz, 1 H, binaphthyl-H), 7.93–8.00 (m, 4 H, binaphthyl-H). ^{13}C NMR (125 MHz, DMSO): δ = 171.6, 135.2, 135.0, 133.6, 133.0, 132.9, 131.4, 131.3, 130.6, 129.9, 129.1, 128.9, 128.5, 128.3, 127.8, 127.5, 127.3, 127.2, 126.6, 126.3, 126.2, 59.1, 48.9, 47.9, 47.5, 30.9, 26.6. IR (KBr): ν = 2927, 1641, 1508, 1453, 1398, 1249, 1211, 821, 752 cm^{-1}. ESI-MS: *m*/*z* = 393.5 [M^+ + 1]. ESI-HRMS: *m*/*z* calcd for [$C_{27}H_{24}N_2O$ + H]: 393.1961; found: 393.1960.
Compound **3b**:[11] yield 94%, mp 127–129 °C; $[a]_D^{20}$ +20.3 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.84–1.88 (m, 1 H, pyrrolidine-H), 1.96–2.02 (m, 2 H, pyrrolidine-H), 2.51–2.55 (m, 1 H, pyrrolidine-H), 3.00–3.07 (m, 1 H, pyrrolidine-H), 3.10 (br, 1 H, NH), 3.27–3.32 (m, 1 H, pyrrolidine-H), 3.56 (d, *J* = 13.5 Hz, 1 H, NCH), 3.96 (d, *J* = 12.5 Hz, 1 H, NCH), 4.19–4.22 (m, 1 H, pyrrolidine-H), 4.65 (d, *J* = 13.0 Hz, 1 H, NCH), 5.46 (d, *J* = 13.0 Hz, 1 H, NCH), 7.27–7.33 (m, 2 H, binaphthyl-H), 7.42 (d, *J* = 9.0 Hz, 1 H, binaphthyl-H), 7.47–7.54 (m, 4 H, binaphthyl-H), 7.61 (d, *J* = 8.5 Hz, 1 H, binaphthyl-H), 7.95–8.00 (m, 4 H, binaphthyl-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 135.9, 135.1, 133.7, 133.6, 132.4, 131.7, 131.5, 131.4, 129.8, 129.6, 128.6, 128.5, 127.9, 127.7, 127.4, 126.7, 126.6, 126.5, 126.4, 126.2, 58.5, 48.8, 47.6, 47.0, 31.6, 26.3. IR (KBr): ν = 3049, 2924, 1639, 1456, 1406, 1211, 1024, 819, 752 cm^{-1}. ESI-MS: *m*/*z* = 393.5

[M^+ + 1]. ESI-HRMS: *m/z* calcd for [$C_{27}H_{24}N_2O$ + H]: 393.1961; found: 393.1965.

Compound **3c**: yield 81%, mp 123–125 °C; $[\alpha]_D^{20}$ +52.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (br, 1 H, NH), 1.95–2.00 (m, 1 H, pyrrolidine-H), 2.82–2.87 (m, 1 H, pyrrolidine-H), 3.28–3.36 (m, 2 H, pyrrolidine-H), 3.48 (d, *J* = 13.5 Hz, 1 H, NCH), 3.92 (d, *J* = 13.0 Hz, 1 H, NCH), 4.54–4.71 (m, 3 H, NCH, 2 × pyrrolidine-H), 5.35 (d, *J* = 13.0 Hz, 1 H, NCH), 6.89 (br, 1 H, OH), 7.20–7.28 (m, 2 H, binaphthyl-H), 7.34 (d, *J* = 8.5 Hz, 1 H, binaphthyl-H), 7.40–7.48 (m, 3 H, binaphthyl-H), 7.53–7.59 (m, 2 H, binaphthyl-H), 7.86–7.94 (m, 4 H, binaphthyl-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 135.6, 135.3, 133.7, 133.6, 131.9, 131.6, 131.5, 131.4, 129.8, 129.7, 128.6, 127.8, 127.6, 127.4, 126.7, 126.5, 126.4, 126.2, 57.6, 54.9, 48.8, 47.1, 46.0, 40.4. IR (KBr): ν = 3227, 2944, 1640, 1445, 1335, 1250, 1076, 820, 753 cm^{-1}. ESI-MS: *m/z* 409.2 [M^+ + 1]. ESI-HRMS: *m/z* calcd for [$C_{27}H_{24}N_2O_2$ + H]: 409.1911; found: 409.1907.

Compound **3d**: yield 82%, mp 212–215 °C; $[\alpha]_D^{20}$ –119.4 (*c* 1.0, DMSO). ^{1}H NMR (500 MHz, DMSO): δ = 1.86–1.92 (m, 1 H, pyrrolidine-H), 2.47–2.51 (m, 1 H, pyrrolidine-H), 3.32–3.35 (m, 1 H, pyrrolidine-H), 3.37–3.41 (m, 1 H, pyrrolidine-H), 3.62 (d, *J* = 14.0 Hz, 1 H, NCH), 3.93 (d, *J* = 13.0 Hz, 1 H, NCH), 4.57 (t, 1 H, *J* = 4.0 Hz, pyrrolidine-CHNH), 4.81 (d, *J* = 13.0 Hz, 1 H, NCH), 5.11–5.15 (m, 1 H, pyrrolidine-CHOH), 5.36 (d, *J* = 13.5 Hz, 1 H, NCH), 7.27–7.30 (m, 2 H, binaphthyl-H), 7.37–7.40 (m, 2 H, binaphthyl-H), 7.49–7.52 (m, 2 H, binaphthyl-H), 7.58 (d, *J* = 8.5 Hz, 1 H, binaphthyl-H), 7.76 (d, *J* = 8.0 Hz, 1 H, binaphthyl-H), 7.97–8.07 (m, 4 H, binaphthyl-H). ^{13}C NMR (125 MHz, DMSO): δ = 168.5, 134.5, 134.4, 133.0, 132.9, 132.0, 131.9, 130.7, 130.6, 129.4, 129.3, 128.5, 127.7, 127.0, 126.6, 126.5, 126.4, 126.2, 126.1, 70.3, 57.0, 54.2, 47.9, 46.1, 45.2. IR (KBr): ν = 3300, 2845, 1652, 1459, 1372, 1212, 1085, 814, 753 cm^{-1}. ESI-MS: *m/z* = 409.2 [M^+ + 1]. ESI-HRMS: *m/z* calcd for [$C_{27}H_{24}N_2O_2$ + H]: 409.1911; found: 409.1909.

Compound **3e**: yield 51%, mp 84–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.88 [s, 9 H, $SiC(CH_3)_3$], 2.04 (br, 1 H, NH), 2.95–3.00 (m, 1 H, pyrrolidine-H), 3.35–3.38 (m, 1 H, pyrrolidine-H), 3.57 (d, *J* = 13.5 Hz, 1 H, NCH), 3.90 (d, *J* = 13.0 Hz, 1 H, NCH), 4.41–4.44 (m, 1 H, pyrrolidine-H), 4.69 (t, *J* = 8.0 Hz, 1 H, pyrrolidine-H), 4.80 (d, *J* = 13.0 Hz, 1 H, NCH), 5.39–5.45 (m, 3 H, NCH, 2 × pyrrolidine-H), 7.27–7.31 (m, 2 H, binaphthyl-H), 7.43–7.51 (m, 4 H, binaphthyl-H), 7.59 (d, *J* = 8.0 Hz, 1 H, binaphthyl-H), 7.69 (d, *J* = 8.5 Hz, 1 H, binaphthyl-H), 7.95–8.01 (m, 4 H, binaphthyl-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 135.4, 133.7, 133.6, 132.7, 131.9, 131.6, 131.5, 129.7, 129.6, 128.6, 128.5, 127.8, 127.7, 127.6, 127.4, 126.5, 126.4, 126.3, 126.2, 73.0, 57.5, 54.9, 48.9, 47.2, 40.1, 26.0, 18.2, –4.6, –4.5. IR (KBr): ν = 2927, 1639, 1460, 1393, 1252, 1097, 827, 775 cm^{-1}. ESI-MS: *m/z* = 523.6 [M^+ – 1]. ESI-HRMS: *m/z* calcd for [$C_{33}H_{38}N_2O_2Si$ + H]: 523.2775; found: 523.2771.

(13) **Representative Procedure for Organoatalyzed Direct Aldol Reaction**

The mixture of L-prolinamide derivative **3d** (0.1 mmol), cyclohexanone (5.0 mmol), 4-nitrobenzaldehyde (1.0 mmol), and MS in THF (1 mL) was stirred at –20 °C under an argon atmosphere for 72 h. The reaction mixture was directly purified through flash column chromatography on silica gel [gradient increasing from 20 → 25 → 30% EtOAc in PE (60–90 °C)] to give the adduct product; yield >99%; *anti/syn* = 92:8.

anti-Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.87 (m, 6 H), 2.09–2.13 (m, 2 H), 2.47–2.51 (m, 1 H), 4.08 (s, 1 H), 4.89 (d, *J* = 8.4 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 27.4, 31.5, 42.0, 57.2, 73.9, 123.5, 127.6, 147.8, 148.5, 213.5. HPLC analysis Daicel Chiralpak AD-H, *i*-PrOH–hexane (20:80), 254 nm, 0.5 mL/min, t_R = 25.7 min (minor), 32.8 min (major); ee: >99%.

syn-Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.89 (m, 6 H), 2.35–2.43 (m, 2 H), 2.57–2.62 (m, 1 H), 3.18 (s, 1 H), 5.48 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.4 Hz, 1 H), 8.21 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 26.0, 28.4, 42.6, 57.0, 70.2, 123.4, 126.8, 147.0, 149.1, 213.8. HPLC analysis Daicel Chiralpak AD-H, *i*-PrOH–hexane (20:80), 254 nm, 0.5 mL/min, t_R = 21.7 min and 23.7 min.