Organocatalytic Direct Asymmetric Aldol Reaction in Water

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General. Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates (Merck 60 F₂₅₄) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash column chromatography was performed using KANTO silica gel 60N (particle size 63-210 μ m). ¹H NMR and ¹³C NMR spectra were recorded on JEOL JNM-AL spectrometer at ambient temperature. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in CDCl₃ as solvent at ambient temperature, TMS served as internal standard (δ = 0 ppm) for ¹H NMR and CDCl₃ was used as internal standard (δ = 77.0) for ¹³C NMR. Infrared spectra were recorded on a SHIMADZU FTIR-8200A spectrometer. Mass spectra were recorded on a SHIMADZU GCMS-QP5050 spectrometer. HPLC was carried out using a SHIMADZU LC-10AD intelligent pump, SPD-10A UV detector, and C-R8A integrator. Microanalyses were performed with a Thermo Finnigan FlashEA 1112. All aldol reactions were carried out under an atmosphere of air in a closed system.

Organic substrates cyclohexanone (**1a**, 108-94-1), cyclopentanone (**1b**, 120-92-3), cycloheptanone (**1c**, 502-42-1), acetone (**1d**, 67-64-1), butan-2-one (**1e**, 78-93-3), pentan-3-one (**1f**, 96-22-0), 4-nitrobenzaldehyde (**2a**, 555-16-8), 4-cyanobenzaldehyde (**2b**, 105-07-7), 4-(methoxycarbonyl)benzaldehyde (**2c**, 1571-08-0), 4-bromobenzaldehyde (**2d**, 1122-91-4), 4-chlorobenzaldehyde (**2e**, 104-88-1), benzaldehyde (**2f**, 100-52-7), 4-methoxybenzaldehyde (**2g**, 123-11-5), 3-nitrobenzaldehyde (**2h**, 99-61-6), 2-nitrobenzaldehyde (**2i**, 552-89-6), L-proline (**4**, 147-85-3), L-prolinol (**5**, 23356-96-9), and (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**8a**, 51207-66-0) were all commercially available and were used without any purification. Catalysts **6a**,¹ **6b**, **7**,² and **8b**³ were prepared by the methods previously described.⁴ Aldol adducts **3** are all known compounds except **3n**.

References

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Typical procedure for the aldol reaction using the diamine/acid bifunctional catalyst

in water: The following procedure for the reaction of cyclohexanone (**1a**) with *p*-nitrobenzaldehyde (**2a**) in water using the diamine **8b**/TFA bifunctional catalyst is representative. To a mixture of diamine **8a** (19.0 mg, 0.05 mmol) in water (1.0 mL) trifluoroacetic acid (3.9 μ L, 0.05 mmol) was added at 25 °C under air in a closed system. The reaction mixture was stirred for 3 min, then cyclohexanone (**1a**, 104 μ L, 1.0 mmol) and *p*-nitrobenzaldehyde (**2a**, 75.6 mg, 0.5 mmol) were added. The reaction mixture was stirred for 24 h. The reaction mixture was emulsion and the solid aldol product gradually formed from the emulsion mixture as shown in Figure 1. Water was removed by centrifugal separation. If extraction was needed, water phase was extracted with ethyl acetate (3 x 1 mL), and organic extracts were dried over Na₂SO₄. Diastereoselectivity and conversion were determined by ¹H NMR analysis of the crude aldol product after short column chromatography purification (SiO₂, 1 g) to remove the catalyst. Purification by flash column chromatography (silica gel, hexane/AcOEt) gave the aldol product **3a** as a colorless solid. The enantiomeric excess (ee) of **3a** was determined by chiral-phase HPLC analysis. The absolute configuration of aldol products **3** was extrapolated by comparison of the HPLC-data with those of **3a**, **3j**, **3l**, and **3o** whose absolute configuration is known.

Figure 1. A photograph of the reaction mixture at 24 h.

The absolute configuration of aldol products **3** was extrapolated by comparison of the HPLC-data with those of **3a**, **3j**, **3l**, and **3o** whose absolute configuration is known.

No.	structure	CAS No.	¹ H NMR (CDCl ₃ , -CH ₂ OH, δ)		HPLC ^a			
			<i>syn</i>	<i>anti</i>	column	eluent ^b	<i>syn</i> (min)	<i>anti</i> (min)
3a		(2 <i>R</i> ,1' <i>S</i>)-501417-31-8 (2 <i>S</i> ,1' <i>S</i>)-501417-28-3 (2 <i>S</i> ,1' <i>R</i>)-351533-35-2 (2 <i>R</i> ,1' <i>R</i>)-349628-69-9 rel-(2 <i>S</i> ,1' <i>R</i>)-71444-30-9 rel-(2 <i>R</i> ,1' <i>R</i>)-71444-29-6 racemic-61235-16-3	5.49 (d) (<i>J</i> = 1.8 Hz)	4.90 (d) (<i>J</i> = 8.4 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 80:20	21.767 (minor) 23.733 (major)	25.708 (2 <i>S</i> ,1' <i>R</i>) 32.875 (2 <i>R</i> ,1' <i>S</i>)
3b		rel-(2 <i>S</i> ,1' <i>R</i>)-175732-08-8 rel-(2 <i>R</i> ,1' <i>R</i>)-175732-07-7 racemic-862890-23-1	5.41 (d) (<i>J</i> = 2.6 Hz)	4.90 (d) (<i>J</i> = 8.1 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 90:10	34.592 (minor) 40.892 (major)	47.030 (2 <i>S</i> ,1' <i>R</i>) 59.042 (2 <i>R</i> ,1' <i>S</i>)
3c		rel-(2 <i>R</i> ,1' <i>R</i>)-187395-08-0 rel-(2 <i>R</i> ,1' <i>S</i>)-187394-99-6	5.44 (brs)	4.85 (d) (<i>J</i> = 8.6 Hz)	CHIRALPAK AS-H	Hexane:2-PrOH = 80:20	24.979 (minor) 60.973 (major)	34.496 (2 <i>S</i> ,1' <i>R</i>) 53.285 (2 <i>R</i> ,1' <i>S</i>)
3d		(2 <i>R</i> ,1' <i>S</i>)-281676-87-7 rel-(2 <i>R</i> ,1' <i>R</i>)-281676-85-5 rel-(2 <i>R</i> ,1' <i>S</i>)-119752-03-3 rel-(2 <i>S</i> ,1' <i>S</i>)-119752-02-2 racemic-73709-54-3	5.32 (d) (<i>J</i> = 2.6 Hz)	4.78 (d) (<i>J</i> = 8.6 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 90:10	19.483 (major) 23.050 (minor)	30.542 (2 <i>S</i> ,1' <i>R</i>) 35.742 (2 <i>R</i> ,1' <i>S</i>)
3e		rel-(2 <i>R</i> ,1' <i>S</i>)-13161-17-6 rel-(2 <i>S</i> ,1' <i>S</i>)-13161-16-5 racemic-61235-09-4	5.34 (d) (<i>J</i> = 2.4 Hz)	4.77 (d) (<i>J</i> = 8.7 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 90:10	17.983 (major) 20.950 (minor)	27.475 (2 <i>S</i> ,1' <i>R</i>) 31.508 (2 <i>R</i> ,1' <i>S</i>)
3f		(2 <i>R</i> ,1' <i>R</i>)-174173-20-7 (2 <i>R</i> ,1' <i>S</i>)-174173-19-4 (2 <i>S</i> ,1' <i>S</i>)-156197-79-4 (2 <i>S</i> ,1' <i>R</i>)-156039-16-6 rel-(2 <i>R</i> ,1' <i>S</i>)-42052-56-2 rel-(2 <i>S</i> ,1' <i>S</i>)-13161-18-7 racemic-56072-25-4	5.39 (d) (<i>J</i> = 2.4 Hz)	4.79 (d) (<i>J</i> = 8.8 Hz)	CHIRALPAK AS-H	Hexane:2-PrOH = 90:10	21.586 (minor) 25.805 (major)	27.161 (2 <i>S</i> ,1' <i>R</i>) 29.421 (2 <i>R</i> ,1' <i>S</i>)
3g		rel-(2 <i>S</i> ,1' <i>R</i>)-281676-92-4 rel-(2 <i>R</i> ,1' <i>R</i>)-281676-89-9 rel-(2 <i>R</i> ,1' <i>S</i>)-84624-42-0 rel-(2 <i>S</i> ,1' <i>S</i>)-84624-41-9 racemic-160084-47-9	5.33 (d) (<i>J</i> = 1.8 Hz)	4.75 (d) (<i>J</i> = 8.9 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 90:10	25.767 (minor) 29.492 (major)	42.792 (2 <i>S</i> ,1' <i>R</i>) 43.875 (2 <i>R</i> ,1' <i>S</i>)
3h		rel-(2 <i>R</i> ,1' <i>S</i>)-84624-44-2 rel-(2 <i>S</i> ,1' <i>S</i>)-84624-43-1 racemic-159208-44-3	5.48 (d) (<i>J</i> = 2.2 Hz)	4.90 (d) (<i>J</i> = 8.5 Hz)	CHIRALPAK AS-H	Hexane:2-PrOH = 95:5	30.761 (minor) 37.055 (major)	46.248 (2 <i>S</i> ,1' <i>R</i>) 48.803 (2 <i>R</i> ,1' <i>S</i>)
3i		rel-(2 <i>S</i> ,1' <i>R</i>)-590419-53-7 rel-(2 <i>R</i> ,1' <i>R</i>)-590419-49-1 racemic-29202-79-7	5.96 (d) (<i>J</i> = 2.1 Hz)	5.45 (d) (<i>J</i> = 7.1 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 95:5	19.333 (minor) 28.167 (major)	40.133 (2 <i>S</i> ,1' <i>R</i>) 43.008 (2 <i>R</i> ,1' <i>S</i>)

3j		(2 <i>R</i> ,1' <i>S</i>)-501417-30-7 (2 <i>S</i> ,1' <i>S</i>)-501417-27-2 (2 <i>S</i> ,1' <i>R</i>)-351533-04-5 (2 <i>R</i> ,1' <i>R</i>)-349628-52-0 rel-(2 <i>S</i> ,1' <i>S</i>)-71466-98-3 rel-(2 <i>R</i> ,1' <i>S</i>)-71466-97-2 racemic-205759-66-6	5.42 (brs)	4.86 (d) (<i>J</i> = 9.0 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 95:5	51.567 (minor) 71.550 (major)	91.683 (2 <i>S</i> ,1' <i>R</i>) 95.750 (2 <i>R</i> ,1' <i>S</i>)
3k		rel-(2 <i>R</i> ,1' <i>R</i>)-152700-01-1 rel-(2 <i>S</i> ,1' <i>R</i>)-152700-00-0	5.31 (brs)	5.00 (d) (<i>J</i> = 7.4 Hz)	CHIRALPAK AD-H	Hexane:2-PrOH = 90:10	32.667 (minor) 71.308 (major)	38.433 (2 <i>S</i> ,1' <i>R</i>) 90.100 (2 <i>R</i> ,1' <i>S</i>)
3l		(<i>R</i>)-264224-65-9 (<i>S</i>)-88958-64-9 racemic-57548-40-0	-	-	CHIRALPAK AS-H	Hexane:2-PrOH = 60:40	(<i>S</i>)-21.523	(<i>R</i>)-26.562
3m		(<i>R</i>)-349628-61-1 racemic-56072-29-8	-	-	CHIRALPAK AS-H	Hexane:2-PrOH = 60:40	(<i>S</i>)-15.697	(<i>R</i>)-17.300
3n		-	-	-	CHIRALPAK AS-H	Hexane:2-PrOH = 80:20	(<i>S</i>)-16.356	(<i>R</i>)-26.340
3o		(<i>S</i>)-727683-89-8 rac-620597-33-3	-	-	CHIRALPAK AS-H	Hexane:2-PrOH = 90:10	(<i>S</i>)-51.737	(<i>R</i>)-58.780

^a Flow rate = 0.5 mL/min, λ = 254 nm. ^b Hexane and 2-propanol were used as an eluent.

1-Hydroxy-1-(4-nitrophenyl)nonan-3-one (3n): $R_f = 0.38$ (hexane:AcOEt = 70:30); ^1H NMR (CDCl_3 , 300 MHz) $\delta = 0.88$ (t, $J = 6.6$ Hz, 3H, $-\text{CH}_3$), 1.14-1.37 (m, 6H, $3\times-\text{CH}_2-$), 1.44-1.84 (m, 2H, $-\text{CH}_2-$), 2.45 (t, $J = 7.4$ Hz, 2H, $-\text{COCH}_2\text{CH}_2-$), 2.79-2.86 (m, 2H, $-\text{COCH}_2\text{CH}-$), 3.77 (brs, 1H, $-\text{OH}$), 5.21-5.32 (m, $-\text{CHOH}$), 7.54 (d, $J = 8.7$ Hz, 2H, Ar), 8.20 (d, $J = 8.7$ Hz, 2H, Ar); ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 211.33$ ($\text{C}=\text{O}$), 150.21, 147.43, 126.47 (CH), 123.80 (CH), 69.02 (CHOH), 50.46, 43.60, 31.41, 28.66, 23.40, 22.32, 13.85 (CH_3); EI-MS 279 (M^+ , 8), 194 ($\text{M}^+ - n\text{-Hex}$, 72), 152 ($\text{M}^+ - n\text{-Hex-COCH}_2-$, 88), 113 ($\text{M}^+ - \text{CH}_2\text{CH}(\text{OH})\text{Ar}$, 83), 58 (100); Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4$; C, 64.50; H, 7.58; N, 5.01. Found: C, 64.30; H, 7.72; N, 5.20.