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Novel Primary Amine Organocatalysts Derived from Cinchona Alkaloids for Asymmetric Direct Aldol Reactions in Brine

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Abstract A series of Cinchona alkaloids derived organocatalysts have been developed and evaluated in the direct asymmetric intermolecular aldol reaction of 4-nitrobenzaldehyde and cyclohexanone. The catalyzed reactions of various aldehydes and ketones gave the corresponding aldol products with moderate to high enantioselectivities (up to 92%) and diastereoselectivities (up to >99/1, anti/syn) in the presence of 3e in brine.

Keywords Cinchona alkaloids · Primary amine · Aldol reaction · Brine

1 Introduction

The asymmetric aldol reaction is one of the most popular carbon–carbon bond-forming reactions [1–5] and plays an important role in medicinal chemistry and natural products synthesis. Development of organocatalysts for this reaction has attracted a great deal attention [6–8]. Since the pioneering work by List, Barbas, and their co-workers [9–11], numerous organocatalysts including proline-derived tetrazole [12], prolinol [13], proline *N*-sulfonyl amides [14], proline-derived diamines [15, 16], proline-based small peptides [17, 18] and proline amine alcohol amides [19, 20] have been developed for the direct asymmetric aldol reaction. Compared with the well-explored proline-based organocatalysts, the development of efficient primary amine organocatalysts is relatively sluggish. As we know, a secondary enamine is better stabilized by hyper-conjugation, whereas a primary amine gives the predominant imine form [21]. In a pioneering work by Amedikouh [22], L-valine was successfully applied to the direct asymmetric aldol reaction between aromatic aldehydes and acetone, albeit the enantioselectivity was not high. Córdova et al. [23] found that acyclic primary amine acids such as alanine, valine, and serine could efficiently catalyze the asymmetric aldol reaction between aromatic aldehydes and ketones with perfect enantioselectivity and moderate diastereoselectivity. From then on, more and more primary amino acids and primary amine-derived organocatalysts were applied to this reaction [24–29].

On the other hand, the development of asymmetric reactions in water is an attractive research field [30–33], mainly due to the low cost, safety and environmentally benign nature of water. Hayashi et al. [34, 35], Barbas et al. [36], Pericas co-workers[37] and Gong et al. [38] have reported proline-derived catalysts for the direct asymmetric aldol reactions in the presence of water. However, reports about primary amine catalyzed asymmetric aldol reaction in aqueous medium are limited [39–46] (Fig. 1).

Herein we report a series of novel primary amine organocatalysts 3a–3h for the asymmetric aldol reaction in brine. These catalysts were synthesized from primary amino acids and cinchona alkaloids derived amines. Cinchona alkaloids and their derivatives have tremendous applications [47–54] in asymmetric catalysis. As hydrogen bonding donor [16], the amide group of organocatalysts 3a–3h is crucial to the stabilization of the transition state according to the Houk–List [55–57] model. To achieve high stereo control, the incorporation of an appropriate

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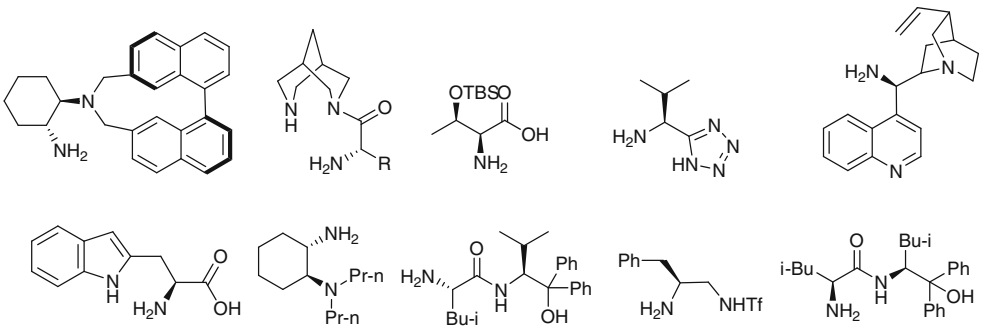


Fig. 1 Examples of primary amine organocatalysts for the asymmetric direct aldol reaction

hydrophobic group into the organic catalyst is necessary as it would generate a hydrophobic organocatalyst and diminish the contact between the reaction transition state and water. It was hypothesized that the cinchona alkaloids backbone of the catalysts would play a double role in the catalytic process. One role is to enhance steric shielding [58], and another role is to enhance the hydrophobicity of the catalysts to assembly with hydrophobic reactants and sequester the transition state from water [59–61]. Catalysts 3a–3h were effective in the direct asymmetric aldol reaction. Brine [62–66] was found to be the best solvent.

2 Experimental

2.1 Materials and Instruments

Cinchona alkaloids (cinchonine, quinine), solvent and *N-t*-butyloxycarbonyl protected amino acids were purchased from commercial suppliers. Cinchona alkaloids derived amines were synthesized according to literatures [47]. ^{1}H NMR spectra were recorded on a 300 MHz FT-NMR Mercury-300B (Varian) spectrometer with tetramethylsilane as an internal reference. Solvent for NMR is $CDCl_3$. ^{13}C NMR were recorded on 75 MHz. Elemental analyses (C, H, and N) were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD–H (4.6 × 250 mm^2), OD–H (4.6 × 250 mm^2) and AS–H (4.6 × 250 mm^2) column. Diastereoselectivities were determined by ^{1}H NMR analysis of the aldol product, Scheme 1.

2.2 Catalyst Preparation

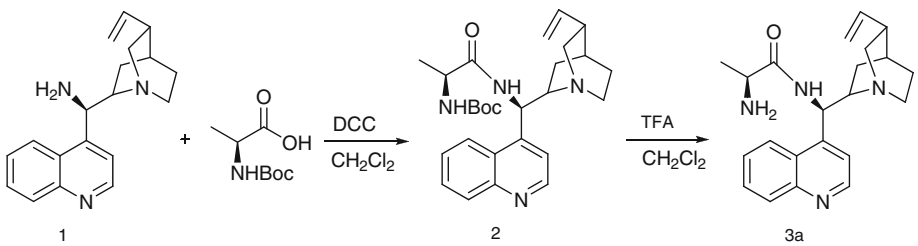
Organocatalysts 3a–3h were prepared from *N-t*-butyloxycarbonyl protected amino acids and cinchona alkaloids derived amines. Take the synthesis of 3a for example.

N-t-Butyloxycarbonyl-L-alanine (1.1 mmol) and DCC (1.1 mmol) were dissolved in 10 mL dichloromethane. Then the solution was cooled to 0 °C and stirred for 0.5 h. After that, 9-amino (9-deoxy) epicinchonine (1 mmol) was added and the reaction mixture was warmed to room temperature and stirred for another 12 h. After filtration and the removal of solvent under reduced pressure, the residue was purified through chromatography on silica gel column [eluent, *V* (ethyl acetate)/*V* (triethyl amine) =10/1] to afford compound 2 as a white solid.

Compound 2 was dissolved in 2 mL dichloromethane, to which 1 mL TFA was added. The solution was stirred for 5 h at room temperature. Then the reaction was quenched with concentrated ammonia solution and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel (eluent, methanol) to afford compound 3a as a white solid (Fig 2).

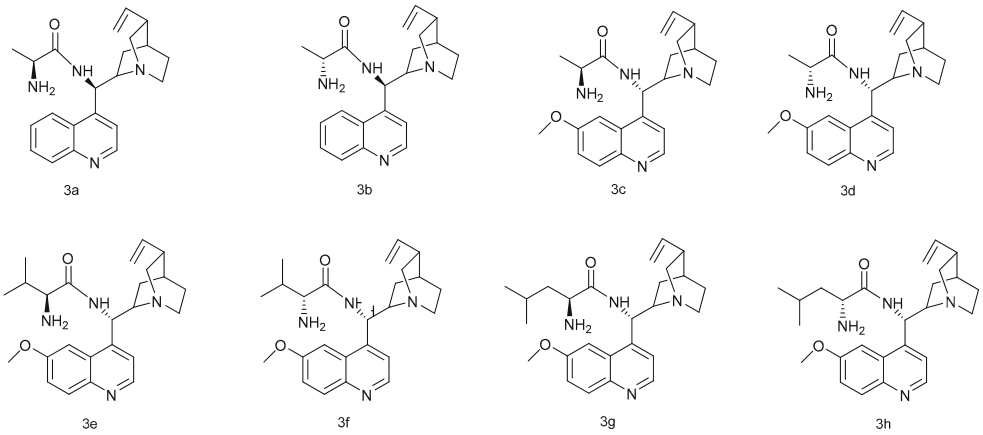
2.2.1 Catalyst 3a

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.89–1.01 (m, 1H), 1.30 (d, J = 6.9 Hz 3H), 1.38–1.57 (m, 3H), 2.28–2.33 (m, 1H), 2.92–3.14 (m, 5H), 3.47 (q, J = 6.9 Hz, 6.9 Hz, 1H), 5.11–5.16 (m, 2H), 5.39 (brs, 1H), 5.86–5.93 (m, 1H), 7.38



Scheme 1 Preparation of organocatalysts. Take the synthesis of 3a for example

Fig. 2 Organocatalysts evaluated in this study



(d, $J = 4.8$ Hz, 1H), 7.57–7.63 (m, 1H), 7.69–7.75 (m, 1H), 7.99 (brs, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 8.39 (d, $J = 8.1$ Hz, 1H), 8.87 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21.36, 25.36, 26.42, 27.09, 39.01, 46.85, 49.03, 50.49, 59.61, 114.56, 118.96, 123.19, 126.30, 127.04, 128.79, 130.06, 140.06, 147.01, 148.30, 149.67, 175.40; (EI) *m/z* 365 (rel. intensity) (M^++1); Analysis calculated for $C_{22}H_{28}N_4O$: C, 72.50; H, 7.74; N, 15.37. Found: C, 72.62; H, 7.66; N, 15.28.

2.2.2 Catalyst 3b

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.85–1.02 (m, 1H), 1.31 (d, $J = 6.9$ Hz 3H), 1.38–1.56 (m, 3H), 2.27–2.34 (m, 1H), 2.82–3.14 (m, 6H), 3.46 (q, $J = 6.9$ Hz, 6.9 Hz, 1H), 5.09–5.17 (m, 2H), 5.33 (brs, 1H), 5.85–5.97 (m, 1H), 7.41 (d, $J = 4.8$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz,1H), 7.74 (t, $J = 6.9$ Hz, 1H), 8.01 (brs, 1H), 8.14 (d, $J = 8.7$ Hz, 1H), 8.39 (d, $J = 8.4$ Hz, 1H), 8.88 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.99, 25.13, 26.12, 26.83, 38.69, 46.57, 48.76, 50.25, 59.31, 114.23, 118.65, 123.02, 126.01, 126.77, 128.54, 129.73, 139.83, 146.76, 148.01, 149.41, 175.17; (EI) *m/z* 365 (rel. intensity) (M^++1); Analysis calculated for $C_{22}H_{28}N_4O$: C, 72.50; H, 7.74; N, 15.37. Found: C, 72.58; H, 7.70; N, 15.42.

2.2.3 Catalyst 3c

^{1}H NMR (300 MHz, $CDCl_3$), δ:0.86–0.91 (m, 1H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.57–1.7 (m, 4H), 2.30–2.35 (m, 1H), 2.68–2.80 (m, 2H), 3.22–3.33 (m, 3H), 3.49 (q, $J = 5.6$, 5.6 Hz, 1H), 3.98 (s, 3H), 4.99–5.05 (m, 2H), 5.50 (brs, 1H), 5.74–5.86 (m, 1H), 7.29 (d, $J = 4.5$ Hz,1H), 7.35–7.39 (m, 1H), 7.68 (s, 1H), 7.86 (brs, 1H), 7.99 (d, $J = 9.3$ Hz, 1H), 8.73 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21.318, 26.56, 27.17, 27.48, 39.11, 40.86, 50.53, 55.44, 55.80, 59.04, 101.66, 114.31, 119.01, 121.69, 128.28, 131.36, 141.06, 144.55, 147.16, 157.71, 175.24; (EI) *m/z* 395 (rel. intensity) (M^++1); Analysis calculated for $C_{23}H_{30}N_4O_2$: C, 70.02; H, 7.66; N, 14.20. Found: C, 70.11; H, 7.59; N, 14.28.

2.2.4 Catalyst 3d

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.81–0.85(m, 1H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.52–1.65 (m, 4H), 2.26–2.30 (m, 1H), 2.63–2.76 (m, 2H), 3.17–3.28 (m, 3H), 3.47 (q, $J = 5.6$, 5.6 Hz, 1H), 3.93 (s, 3H), 4.94–5.01 (m, 2H), 5.43 (brs, 1H), 5.70–5.81 (m, 1H), 7.24 (d, $J = 4.5$ Hz,1H), 7.31–7.35 (m, 1H), 7.63 (s, 1H), 7.81 (brs, 1H), 7.95 (d, $J = 9.3$ Hz, 1H), 8.68 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21.575, 26.536, 27.374, 27.81, 39.43, 40.99, 50.75, 55.62, 56.06, 59.33, 101.93, 114.41, 119.30, 121.64, 128.37, 131.63, 141.33, 144.76, 147.40, 157.78, 175.37; (EI) *m/z* 395 (rel. intensity) (M^++1); Analysis calculated for $C_{23}H_{30}N_4O_2$: C, 70.02; H, 7.66; N, 14.20. Found: C, 70.15; H, 7.70; N, 14.18.

2.2.5 Catalyst 3e

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.56–0.59(d, $J = 6.9$ Hz 3H), 0.86–0.89 (d, $J = 6.$ 9 Hz 3H), 1.57–1.68 (m, 5H), 2.14–2.19 (m, 1H), 2.30–2.32 (m, 1H), 2.69–2.79 (m, 2H), 3.24–3.34 (m, 4H), 3.98 (s, 3H), 4.98–5.04 (m, 2H), 5.55 (brs, 1H), 5.73–5.85 (m, 1H), 7.30–7.31 (m, 1H), 7.35–7.39 (m, 1H), 7.72 (s, 1H), 8.02 (d, $J = 9$ Hz, 1H), 8.73 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.82, 19.48, 26.54, 27.21, 27.63, 30.91, 39.27, 40.93, 49.49, 55.49, 55.89, 59.43, 59.97, 101.6, 114.33, 118.36, 121.84, 128.52, 131.39, 141.25, 144.55, 147.20, 157.69, 174.21; (EI) *m/z* 423 (rel. intensity) (M^++1); Analysis calculated for $C_{25}H_{34}N_4O_2$: C, 71.06; H, 8.11; N, 13.26. Found: C, 71.21; H, 8.09; N, 13.33.

2.2.6 Catalyst 3f

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.82 (d, $J = 6.9$ Hz 3H), 0.91 (d $J = 6.9$ Hz 3H), 1.57–1.68 (m, 5H), 2.15–2.31

(m, 2H), 2.64–2.76 (m, 2H), 3.12–3.26 (m, 4H), 3.98 (s, 3H), 4.96–5.03 (m, 2H), 5.43 (brs, 1H), 5.72–5.84 (m, 1H), 7.32 (d, $J = 4.5$ Hz,1H), 7.35–7.39 (m, 1H), 7.72 (s, 1H), 7.99 (d, $J = 9.3$ Hz, 1H), 8.72 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ:16.22, 19.49, 26.56, 27.35, 27.72, 31.28, 39.34, 40.94, 50.27, 55.58, 55.90, 59.05, 60.42, 101.93, 114.34, 118.95,121.69, 128.41, 131.45, 141.30, 144.64, 147.25, 157.77, 173.99; (EI) *m/z* 423 (rel. intensity) (M^++1); Analysis calculated for $C_{25}H_{34}N_4O_2$: C, 71.06; H, 8.11; N, 13.26. Found: C, 71.18; H, 8.15; N, 13.45.

2.2.7 Catalyst 3g

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.84 (q, 6H), 1.13–1.22 (m, 1H), 1.52–1.68 (m, 7H), 2.31–2.32 (m, 1H), 2.68–2.78 (m, 2H), 3.22–3.44 (m, 4H), 3.98 (s, 3H), 4.98–5.04 (m, 2H), 5.48 (brs, 1H), 5.73–5.85 (m, 1H), 7.29–7.31 (d, $J = 4.5$ Hz,1H), 7.35–7.39 (m, 1H), 7.68 (s, 1H), 8.02 (d, $J = 9.3$ Hz, 1H), 8.74 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21.13, 23.01, 24.42, 26.51,27.15, 27.56, 39.21, 40.83, 43.80, 49.40, 53.24, 55.40, 55.83, 59.14, 101.54, 114.23, 118.54,121.68, 128.32, 131.31, 141.19, 144.47, 147.15, 157.61, 175.18; (EI) *m/z* 437 (rel. intensity) (M^++1); Analysis calculated for $C_{26}H_{36}N_4O_2$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.65; H, 8.17; N, 12.75.

2.2.8 Catalyst 3h

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.86 (q, 6H), 1.33–1.39 (m, 1H), 1.60–1.68 (m, 7H), 2.29–2.34 (m, 1H), 2.70–2.77 (m, 2H), 3.20–3.33 (m, 4H), 3.98 (s, 3H), 4.96–5.03 (m, 2H), 5.39 (brs, 1H), 5.72–5.83 (m, 1H), 7.32–7.33 (d, $J = 4.5$ Hz, 1H), 7.35–7.39 (m, 1H), 7.71 (s, 1H), 7.86(brs, 1H), 7.99 (d, $J = 9.3$ Hz, 1H), 8.72 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21.40, 23.14, 24.65, 26.55, 27.32, 27.69, 39.29, 40.95, 44.10, 51.03, 53.55, 55.62, 55.90, 59.16, 101.91, 114.46, 119.16, 121.75, 128.39, 131.49, 141.22, 144.66, 147.31, 157.84, 175.12; (EI) *m/z* 437 (rel. intensity) (M^++1); Analysis calculated for $C_{26}H_{36}N_4O_2$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.53; H, 8.18; N, 12.88.

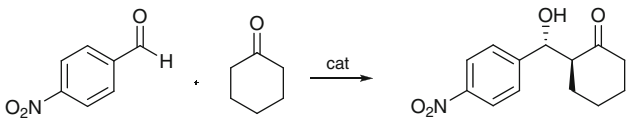
2.3 General Procedure for the Catalytic Direct Asymmetric Aldol Reaction

All solvents were refined according to standard methods. Aldehyde, cyclohexanone (freshly distilled), catalyst and 1.5 mL solvent were added to a 5 mL glass reactor. The reaction mixture was stirred until all the aldehyde has been consumed (monitored by TLC). Quenched with saturated ammonium chloride solution (5 mL), and extracted with ethyl acetate (10 mL × 3). Combined organic layer and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel [eluent, *V* (ethyl acetate)/*V* (petroleum ether) =3:1] to afford pure aldol product.

3 Results and Discussion

Initially catalysts 3a, 3b, 3c and 3d were prepared and their catalytic activities were evaluated in the model reaction between 4-nitrobenzaldehyde and cyclohexanone at room temperature. It was found that enantioselectivities and diastereoselectivities were low (Table 1, entries 1–4), the performance of catalysts 3b (derived from *R*-alanine and

Table 1 Aldol reaction of cyclohexanone and 4-nitrobenzaldehyde under various conditions



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Entry	Solvent	Catalyst	Time (h)	Yield (%)[A]	Anti/syn[B]	ee for anti (%)[C]
1	Neat	3a	12	91	89:11	40
2	Neat	3b	13	93	70:30	60
3	Neat	3c	13	90	92:8	75
4	Neat	3d	15	92	85:15	45
5	CH_2Cl_2	3c	45	82	78:22	54
6	$CHCl_3$	3c	47	85	86:14	48
7	Toluene	3c	52	88	90:10	57
8	DMF	3c	72	trace	–	–
9	Water	3c	15	90	87:13	74
10	Brine	3c	12	96	95:5	84
11[D]	Brine	3c	17	94	94:6	84
12[E]	Brine	3c	45	82	92:8	81
13[F]	Brine	3c	19	93	97:3	86
14[F]	Brine	3e	28	92	>99:1	92
15[F]	Brine	3f	30	88	94:6	76
16[F]	Brine	3g	27	85	97:3	89
17[F]	Brine	3h	28	87	95:5	82

Conditions: aldehyde (0.25 mmol), cyclohexanone (2.5 mmol), catalyst (5 mol%), 1.5 mL brine, RT

[A] Isolated yield

[B] Determined by chiral HPLC

[C] Determined by ^{1}H NMR

[D] 3 mol% of catalyst used

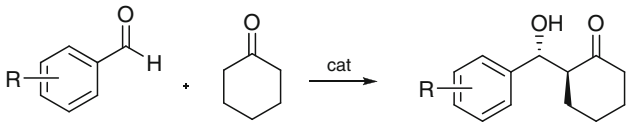
[E] 1 mol% of catalyst used

[F] Reaction temperature 5 °C, 3 mol% of catalyst used

cinchonine) and 3c (derive from *S*-alanine and quinine) was superior to 3a (derived from *S*-alanine and cinchonine) and 3d (derived from *R*-alanine and quinine), 3c gave the best result. We supposed that the match of chirality between amino acids and Cinchona alkaloids was crucial to enantioselectivity, the two chiral elements of catalysts 3b and 3c matched better over catalysts 3a and 3d [58], enhancing the stereo control of the organocatalyzed direct aldol reaction. Then, various solvents (entries 5–10) were screened with 3c at room temperature. Brine [61] was found to be the more suitable solvent, good yield and diastereoselectivity were obtained albeit the enantioselectivity was not satisfying (entry 10). Influence of catalyst loading was also examined. Reducing the amount of catalyst (entry 11) from 5 to 3 mol% did not cause the drop of yield and enantioselectivity. Further lowering the loading to 1 mol% resulted in decreased enantioselectivity and yield. The enantioselectivity increased (84–86%) slightly as the reaction temperature decreased from room temperature to 5 °C. The performance of catalyst 3c under optimized reaction condition (entry 13) was still not satisfying. Hence, analogues 3e, 3f, 3g and 3h were synthesized and applied to the model reaction under the optimized condition in the hope of achieving good enantioselectivity. Results were showed in Table 1 (entries 14–17). Catalyst 3e gave the best result (ee up to 92%, dr >99:1). Under the same conditions, catalysts 3e and 3g gave the desired product in higher enantioselectivity and diastereoselectivity, catalysts 3f and 3g gave the desired product in lower enantioselectivity and diastereoselectivity. The results indicated that *S*-amino acids matched better with Quinine, and the alkyl substituents at the chiral carbon atom influenced the enantioselectivity.

To further explore the scope of the reaction, the direct asymmetric aldol reactions of various aldehydes and cyclohexanone in the presence of 3e were examined as shown in Table 2. We selected methoxy substituent as a representative electron-donating group, nitro-, cyano-, fluoro-, and chloro- substituents as an electron-withdrawing group on the benzene ring. The benzaldehydes substituted by strong electron-withdrawing nitro- and cyano- groups (except 3-cyanobenzaldehyde) were converted to the corresponding aldol products in high yields, with moderate to high enantioselectivities (83–92% ee) and perfect diastereoselectivities (dr >99:1). Enantioselectivity was influenced by the position of substituent (entries 1 and 2), 4-nitrobenzaldehyde was converted to the corresponding aldol product with 92% ee value, however, 3-nitrobenzaldehyde only with 83% ee value. The aldol reactions of less reactive benzaldehydes which bearing chloro- and fluoro-substituents on the benzene ring (entries 7–11) were very sluggish, giving the corresponding aldol product in moderate yields with moderate enantioselectivities. Reactions

Table 2 Aldol reaction of various aldehydes and cyclohexanone in the presence of 3e



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Entry	R	Product	Time (h)	Yield (%)[A]	Anti/syn[B]	ee for anti (%)[C]
1	4-NO_2	6a	28	92	>99:1	92
2	3-NO_2	6b	30	90	>99:1	83
3	2-NO_2	6c	42	93	>99:1	90
4	4-CN	6d	32	93	>99:1	87
5	3-CN	6e	72	82	98:2	67
6	2-CN	6f	72	88	>99:1	83
7	4-Cl	6g	96	71	96:4	62
8	3-Cl	6h	96	68	>99:1	47
9	2-Cl	6i	96	65	>99:1	55
10	4-F	6j	96	68	90:10	60
11	2-F	6k	96	70	>99:1	45
12	H	6l	72	Trace	–	–
13	4-CH_3O	6m	72	Trace	–	–

Conditions: aldehyde (0.25 mmol), cyclohexanone (2.5 mmol), catalyst (3 mol%), 1.5 mL brine, reaction temperature 5 °C

[A] Isolated yield

[B] Determined by chiral HPLC

[C] Determined by chiral ^{1}HNMR

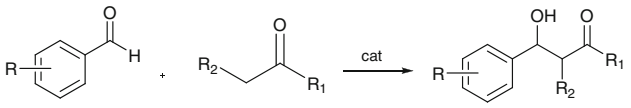
of benzaldehyde and 4-methoxybenzaldehyde with cyclohexanone afforded trace product under the same reaction condition.

We also examined the direct asymmetric aldol reactions between various ketones and aldehydes as shown in Table 3. The aldol reaction of cyclopentanone with 4-nitrobenzaldehyde gave the corresponding aldol product in moderate yield but with low enantioselectivity and diastereoselectivity. The reactions of acetone with 4-nitrobenzaldehyde and 3-nitrobenzaldehyde afforded the aldol product in moderate yield with low enantioselectivity.

4 Conclusion

In summary, a series of novel primary amine organocatalysts have been developed and applied to the asymmetric direct aldol reactions, 3e was found to be the best catalyst. 3 mol% of 3e is enough to efficiently promote the aldol reaction of various aromatic aldehydes and cyclohexanone with moderate to high enantioselectivities (up to 92%) and diastereoselectivities (up to >99:1) in brine. Applications of these catalysts in asymmetric transformations are in progress in our laboratory.

Table 3 Aldol reaction of aldehydes and various ketones in the presence of 3e



4 5 6

Entry	R	R^1	R^2	Product	Time (h)	Yield (%)[A]	anti/syn[B]	ee (%)[C]
1	4-NO_2	$-(CH_2)_{3-}$		6n	49	63	80:20	45
2	2-NO_2	CH_{3-}	H	6o	42	72	–	47
3	4-NO_2	CH_{3-}	H	6p	37	75	–	41

Conditions: aldehyde (0.25 mmol), ketone (2.5 mmol), catalyst (3 mol%), 1.5 mL brine, reaction temperature 5 °C

[A] Isolated yield

[B] Determined by chiral HPLC

[C] Determined by chiral ^{1}HNMR

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