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Enantiopure azetidine-2-carboxamides as organocatalysts for direct asymmetric aldol reactions in aqueous and organic media

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ABSTRACT

A family of enantiopure azetidine-2-caboxamides was asymmetrically synthesized, and was examined as organocatalyst in direct aldol reactions. A well chosen chiral azetidine-2-caboxamide was found to smoothly catalyze the direct aldol reaction of various benzaldehydes with acetone in brine, and β-hydroxy ketones were produced with enantiomeric excess up to 96%. The reaction of benzaldehydes with cyclic ketones also led to the formation of anti-products in diastereomeric ratio up to 99:1 and enantiomeric excess up to 99%.

1. Introduction

Because of the remarkable biological activities of azetidines, the interest in the four-membered constrained aza-heterocyclic compounds in organic syntheses and pharmaceutical chemistry has increased dramatically over the years.[1,2] Although numerous efficient methodologies have been developed to assemble the strained ring systems,[3] it is still difficult to synthesize enantiopure forms with general approaches.[4] The difficulty renders it uncommon to integrate enantioenriched azetidine scaffold in the framework of chiral catalysts. As early as in 1998, Zwanenburg and co-workers successfully applied *N*-alkyl azetidine-2-tertiary alcohols in asymmetric boron catalyzed Diels–Alder reactions.[5] The same group also demonstrated enantioselective diethylzinc addition to aldehydes using the similar azetidine-derived chiral ligands.[6] Meanwhile, chiral C_2-symmetric 2,4-disubstituted azetidines were developed by Shi and co-workers, and were examined in the catalytic asymmetric induction reactions.[7] Recently, we highlighted a three-step, one-pot protocol for a facile and practical preparation of enantiopure *N*-ferrocenylmethyl azetidine-2-ylmethanol, which served as a general ligand for asymmetric addition of various organozinc species (alkylzinc, arylzinc, and alkynylzinc) to the prochiral aldehydes with excellent enantioselectivities.[8] As illustrated in these examples, azetidine-based chiral ligands usually afforded improved asymmetric induction compared with pyrrolidine- or aziridine-based counterparts. As a result, the enantiopure four-membered aza-heterocyclic scaffold should be introduced into the building block arsenal for chiral catalysts, and await broad application and further elaboration.

Compared with its higher homologues, such as pyrrolidine and piperidine, azetidine has found little application as an effective aminocatalyst.[9] In infantile era of organocatalysis, List and co-workers brought out the concept of enamine catalysis of the proline-catalyzed direct asymmetric aldol reaction.[10] In this pioneer work, L-azetidinecarboxylic acid showed similar catalytic ability, but gave an inferior stereoselectivity of 40% ee comparing with 76% ee of L-proline. Interestingly, the higher homologue, pipecolic acid was ineffective for the reaction. Barbas III and co-workers also demonstrated the unique catalytic ability of L-azetidinecarboxylic acid in the asymmetric Mannich-type reaction.[11] The azetidine-based catalyst afforded a major *syn*-product with an enantioselectivity of 80% ee, while its pyrrolidine counterpart induced *anti*-selectivity. Enders and co-workers developed an efficient asymmetric syntheses of 3-substituted azetidine-2-carboxylic acids and 2-substituted azetidine-3-carboxylic acids, but neither of these amino acids produced

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matchable enantioselectivity in aldol reaction as simple L-proline.[12] In some other cases, L-azetidinecarboxylic acid could produce similar asymmetric induction comparable to that of L-proline.[13] Moreover, Greck and co-workers described the asymmetric α-amination of carbonyls, in which L-azetidinecarboxylic acid induced better enantioselectivity than L-proline.[14]

The proline amides are believed to be one type of the most effective organocatalysts for stereoselective direct aldol reaction.[15] The Gong's and Singh's research group have independently developed L-proline amino alcohol amides as catalysts for direct aldol reactions.[16,17] Substitution the pyrrolidine scaffold in proline amides with azetidine would lead to a kindred family of organocatalysts. The study of enantiopure azetidine amides would pose a useful complement to the five-membered-aza-heterocycle-dominated aminocatalysis, and gain deeper insight as well as broader perspective in the organocatalysis. In this paper, we reported the practical asymmetric syntheses of a series of chiral azetidine-2-caboxamides (Fig. 1, **1**, **2**, and **3**), and the studies of these compounds in the asymmetric catalysis of direct aldol reaction.

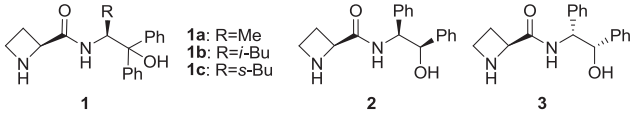


Fig. 1. Azetidine-2-carboxamides used for direct aldol reactions in this study.

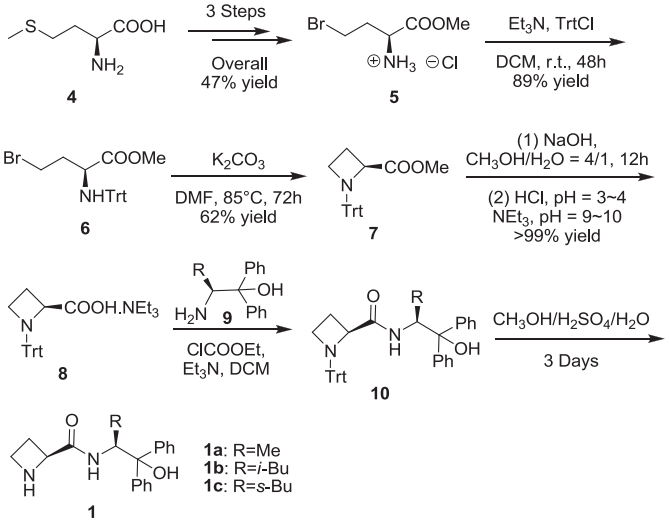
2. Results and discussion

2.1. Preparation of azetidine-based novel organocatalysts

The synthetic route leading to chiral azetidine-2-carboxamides (**1**, **2**, and **3**), was based on our previously developed approach to the enantiopure azetidine-2-carboxylate (Scheme 1).[8b]

Starting from the cheap and commercially available L-(+)-methionine **4**, which contained the source of chirality, the methyl L-2-amino-4-bromobutanoate **5** was obtained in the overall yield of 47% after three-steps. After the treatment of compound **5** with triethylamine and triphenylmethyl (trityl, or Trt) chloride in dichloromethane at room temperature for two days, the amino group was protected with trityl to afford the compound **6** in 89% yield. The aza-heterocyclic compound **7** was directly constructed from acyclic compound **6** via intramolecular nucleophilic substitution. The cyclization was carried out at an elevated temperature of 85 °C for 3 days with the efficiency of 52% yield.

The carboxylic acid was obtained after the hydrolysis of the methyl ester **7**, and was stabilized in the form of triethylamine salt **8**. The salt could react with various 2-aminoethanol **9** in the presence of stoichiometric amount of ClCOOEt and triethylamine to give the corresponding amides **10**. Upon the de-protection of *N*-trityl group under acidic condition, the chiral azetidine-2-carboxamides **1** were produced in decent yields. Following the similar route, the chiral amides **2** and **3** were also synthesized.

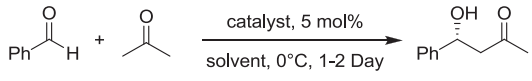


Scheme 1. Representative asymmetric synthetic route of chiral azetidine-2-carboxamide **1**.

2.2. The direct asymmetric aldol reaction of acetone with aldehydes catalyzed by azetidine-2-carboxamide 1a

The aldol reaction of benzaldehydes with acetone was used as a model reaction to test the catalytic efficiency of various azetidine-2-carboxamides (Table 1). The organocatalyst **1a**, which contains methyl as steric hindrance group on 2-aminoethanol moiety, was submitted to the model reaction in brine at room temperature (26 °C), and received 47% yield and 93% ee (Table 1, entry 1). The dehydration of aldol adduct was observed, and (*E*)-4-phenylbut-3-en-2-one was isolated as a major side product. Decreasing the reaction temperature to 0 °C would increase the yield to 71% by suppression of dehydration process (Table 1, entry 2). When azetidine amide **1b** or **1c**, which bears larger steric hindrance group on the side arm, was used as catalyst, decreased enantioselectivity was observed (Table 1, entries 3 and 4). The observation was contrary to our expectation. In Singh's work, the pyrrolidine counterpart of **1b** was found as the optimal catalyst.[17e] Similar effect was also observed with chiral amides **2** and **3** (Table 1, entries 5 and 6). Keeping **1a** as the optimal catalyst, when other organic solvents were screened, both reaction yield and stereoselectivity were decreased (Table 1, entries 7–12). When the catalyst loading was decreased from 5% mol to 3%, 2%, or even 1% mol, the catalytic efficiency was diminished, and decreased yield as well as extended reaction time was observed (not shown in Table 1).

Table 1
Direct aldol reaction of benzaldehyde with acetone catalyzed by **1**–**3**[a]

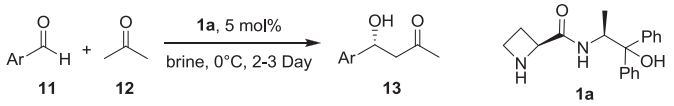


Entry	Catalyst (mol %)	Solvent	Yield (%)[b]	ee (%)[c,d]
1[e]	**1a**	Brine	47	93
2	**1a**	Brine	71	93
3	**1b**	Brine	72	84
4	**1c**	Brine	67	86
5	**2**	Brine	49	69
6	**3**	Brine	63	53
7[f]	**1a**	Neat	45	90
8	**1a**	*i*-PrOH	55	92
9	**1a**	MeOH	40	26
10	**1a**	CH_2Cl_2	57	87
11	**1a**	$CHCl_3$	53	90
12	**1a**	THF	42	69

[a] Unless specified, aldehyde **11a** (1 mmol), acetone **12** (5 mmol), and catalyst (5 mol %) were dissolved in solvent (2 mL, 0.5 M) and stirred at 0 °C for 1–2 days.
[b] Isolated yield calculated based on benzaldehyde.
[c] The ee values were determined by HPLC using the Chiralcel AD column.
[d] The absolute configuration of **13a** was assigned as *R* by comparison of retention times of known compounds.
[e] The reaction was carried out at the room temperature of 26 °C.
[f] The reaction was carried out in neat acetone with a concentration of 0.5 M.

The substrate scope and limitation of the aldol reaction were scrutinized (Table 2). A wide range of aromatic aldehydes reacted with acetone in brine under the optimal conditions, and the aldol adducts were produced with moderate to good yields (from 38% to 88%) and good to excellent enantioselectivities (from 67% to 96% ee). When aliphatic aldehydes, such as butanal and pentanal, were used as substrate, no desired aldol product was observed (not shown in Table 2). This might be the formation of aldehyde hydrate in the aqueous media.

Table 2
Direct aldol reaction of various aldehydes with acetone catalyzed by **1a**[a]



Entry	Ar	Product	Yield (%)[b]	ee (%)[c,d]
1	Ph	**13a**	71	93
2	4-MeC_6H_4	**13b**	85	83
3	3-MeC_6H_4	**13c**	78	90
4	2-MeC_6H_4	**13d**	69	89
5	4-MeOC_6H_4	**13e**	42	83
6	2-MeOC_6H_4	**13f**	71	82
7	2,3,4-$(MeO)_3C_6H_2$	**13g**	47	67
8	2-Naphthyl	**13h**	73	78
9	1-Naphthyl	**13i**	88	79
10	4-ClC_6H_4	**13j**	80	95
11	3-ClC_6H_4	**13k**	88	86
12	2-ClC_6H_4	**13l**	62	86
13	4-BrC_6H_4	**13m**	82	83
14	3-BrC_6H_4	**13n**	75	93
15	2-BrC_6H_4	**13o**	70	93
16	4-$NO_2C_6H_4$	**13p**	<5	n.d.[e]
17	3-$NO_2C_6H_4$	**13q**	38	90
18	2-$NO_2C_6H_4$	**13r**	71	96

[a] Unless specified, aldehyde **11** (1 mmol), acetone **12** (5 mmol), and catalyst **1a** (5 mol %) were dissolved in brine (2 mL, 0.5 M) and stirred at 0 °C for 2–3 days.
[b] Isolated yield calculated based on aldehyde **11**.
[c] The ee values were determined by HPLC using chiral columns.
[d] The absolute configuration of **13** was assigned as *R* by comparison of retention times of known compounds.
[e] Not determined.

Comparing the enantioselective outcomes of *para*-substituted benzaldehydes (Table 2, entries 2, 5, 10, 13, and 16), a weak electronic effect was observed. The substrates **11** bearing electronic donating groups on *para*-position (Table 2, entries 2 and 5) produced diminished stereoselectivities comparing with unsubstituted benzaldehyde (Table 2, entry 1). Among weak electronic withdrawing groups, only chloro brought out elevated enantioselectivity of 95% ee (Table 2, entry 10), while bromo gave the same ee of 83% as electronic donation groups (Table 2, entry 13). Surprisingly, when *para*-nitrobenzaldehyde was used as substrate, no desired aldol product was observed (Table 2, entry 16). For instead, the (*E*)-4-(4-nitrophenyl)but-3-en-2-one was isolated as a major product, because of fast dehydration of the aldol adduct.

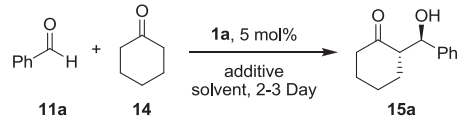
A strong steric hindrance effect was identified by comparing the stereoselective outcomes of the same substituent group at different substituted positions on benzaldehyde. The *ortho*- and *meta*-methyl benzaldehydes rendered better stereocontrol over *para*-substituted one (Table 2, entries 3 and 4 vs 2). The benzaldehydes bearing bromo (Table 2, entries 13, 14, and 15) and nitro (Table 2, entries 16, 17, and 18) substituents, also demonstrated the same effect. But the steric effect did not prevail in methoxy substituted benzaldehydes (Table 2, entries 6 and 7 vs 5) or chloro substituted ones (Table 2, entry 10, 11, and 12).

Although 2-naphthaldehyde reacted smoothly with acetone to generate aldol adduct in 73% yield, the enantioselectivity decreased from 93% ee of benzaldehyde to 78% ee (Table 2, entry 8). The bulkier 1-naphthaldehyde did not gain improved stereocontrol, and retained the enantioselectivity of 79% ee (Table 2, entry 9).

2.3. The direct asymmetric aldol reaction of cyclohexanone with aldehydes catalyzed by azetidine-2-carboxamide 1a

The donor of the aldol reaction was extended from acyclic acetone to cyclohexanone in order to further explore the catalytic ability of azetidine-2-carboxamide **1a**. Under the previously optimized reaction conditions, the aldol adduct **15a** was obtained with excellent diastereoselectivity favoring *anti*-product but in moderate enantioselectivity of 81% ee (Table 3, entry 1). The reaction conditions were screened to gain better results (Table 3). In the enamine catalysis, the presence of additional proton might promote the rapid formation of reactive enamine species and strengthen the intramolecular hydrogen bonding in transition state, and subsequently accelerate the reaction speed and elevate the stereoselectivity.[18] As a result, different proton source was used as additive, but no improved result was observed (Table 3, entries 2 and 3). Various solvents were encouragingly screened, and improved results were noticed in some of the cases (Table 3, entries 4, 5, and 6). When the reaction temperature was decreased to −20 °C, a boost in enantioselectivity from 86% to 97% ee was identified (Table 3, entry 7).

Table 3
Direct aldol reaction of benzaldehyde with cyclohexanone catalyzed by **1a**[a]



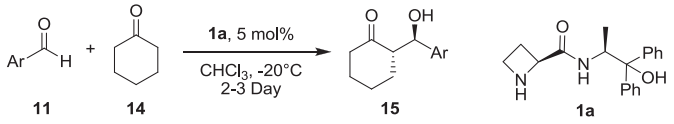
Entry	Solvent	Additive	Yield (%)[b]	d.r.[c]	e.e. (%)[c]
1	Brine	—	75	99:1	81
2	Brine	TFA	<5	n.d.[d]	n.d.[d]
3	Brine	TsOH	84	99:1	54
4	*i*-PrOH	—	76	94:6	86
5	CH_2Cl_2	—	83	95:5	86
6	$CHCl_3$	—	87	93:7	86
7[e]	$CHCl_3$	—	68	99:1	97

[a] Unless specified, aldehyde **11a** (1 mmol), cyclohexanone **14** (5 mmol), catalyst **1a** (5 mol %), and additive (1 mmol) were dissolved in solvent (2 mL, 0.5 M) and stirred at the room temperature of 26 °C for 2–3 days.
[b] Isolated yield calculated based on aldehyde **11**.
[c] The d.r. values and the ee values of the major *anti*-isomers were determined by HPLC using the Chiralcel OD column. The d.r. value as *anti*/*syn*, and the major isomer was the *anti*-isomer. The configuration of **15** was assigned by comparison of retention times of known compounds.
[d] Not determined.
[e] The experiment was carried out at −20 °C.

Furthermore, a variety of aromatic aldehydes were reacted with cyclohexanone under the refined reaction conditions (Table 4). Catalyzed by azetidine-2-carboxamide **1a**, the direct aldol reaction produced the *anti*-products in diastereomeric ratio up to 99:1 and enantiomeric excess up to 99%.

By comparison of the enantioselectivities of *para*-substituted benzaldehydes (Table 4, entries 2, 5, 9, 12, and 15), a strong reversed electronic effect was disclosed, which was contrary to the effect in the abovementioned aldol reaction with acetone as nucleophile (Table 2). While benzaldehydes bearing electronic donating groups produced similar enantioselectivities as unsubstituted benzaldehyde (Table 4, entries 2 and 5), electronic withdrawing groups afforded decreased stereoselectivities in two cases (Table 4, entries 12 and 15).

Table 4
Direct aldol reaction of benzaldehyde with cyclohexanone catalyzed by **1a**[a]

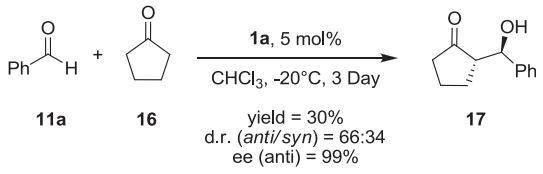


Entry	Ar	15	Yield (%)[b]	d.r.[c]	e.e.[c]
1	Ph	**15a**	68	99:1	97
2	4-MeC_6H_4	**15b**	46	77:23	>99
3	3-MeC_6H_4	**15c**	69	99:1	91
4	2-MeC_6H_4	**15d**	63	84:16	89
5	4-MeOC_6H_4	**15e**	69	80:20	96
6	3-MeOC_6H_4	**15f**	65	81:19	93
7	2-Naphthyl	**15h**	39	88:12	96
8	1-Naphthyl	**15i**	79	87:13	99
9	4-ClC_6H_4	**15j**	61	93:7	99
10	3-ClC_6H_4	**15k**	44	82:18	83
11	2-ClC_6H_4	**15l**	80	96:4	96
12	4-BrC_6H_4	**15m**	56	92:8	75
13	3-BrC_6H_4	**15n**	88	89:11	99
14	2-BrC_6H_4	**15o**	71	98:2	99
15	4-$NO_2C_6H_4$	**15p**	63	75:25	52
16	3-$NO_2C_6H_4$	**15q**	55	94:6	44
17	2-$NO_2C_6H_4$	**15r**	71	75:25	97

[a] Unless specified, aldehyde **11** (1 mmol), cyclohexanone **14** (5 mmol), and catalyst **1a** (5 mol %) were dissolved in chloroform (2 mL, 0.5 M) and stirred at 0 °C for 2–3 days.
[b] Isolated yield calculated based on aldehyde **11**.
[c] The d.r. values and the ee values of the major *anti*-isomers were determined by HPLC using chiral columns. The d.r. value as *anti*/*syn*, and the major isomer was the *anti*-isomer. The configuration of **15** was assigned by comparison of retention times of known compounds.

When bromo and nitro were used as substituent groups of benzaldehyde (Table 4, entries 12–14, entries 15–17, respectively), the similar steric effect was clearly received, which was consistent with the trend observed in Table 2. But the effect did not persist for methyl, methoxy, or chloro substituted benzaldehydes (Table 4, entries 2–4, entries 5–6, entries 9–11, respectively). This might be an overall outcome of the domination of electronic effect over steric effect in these cases. In addition, the bulkier 1-naphthaldehyde did induce a better enantioselectivity of 99% ee than 96% ee of 2-napthaldehyde (Table 4, entries 7 and 8).

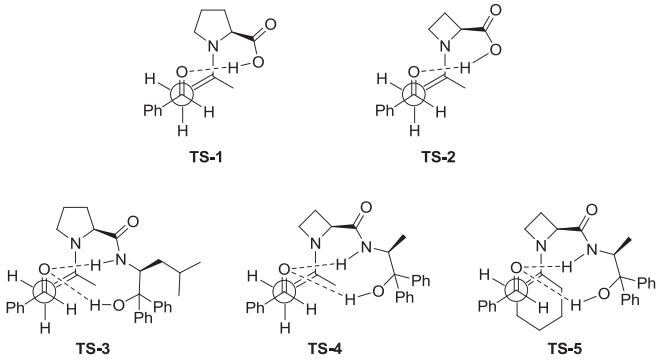
The five-membered cyclopentanone **16** was also employed as a donor in the asymmetric aldol reaction (Scheme 2). Catalyzed by azetidine-based organocatalyst **1a**, the aldol reaction was carried out without impediment, but the isolated yield was as low as 30%. The aldol adduct **17** was identified with an *anti* versus *syn* ratio of 66:34, and the enantiomeric excess of the major *anti*-isomer was 99%.



Scheme 2. Direct aldol reaction of benzaldehyde with cyclopentanone catalyzed by **1a**.

2.4. Proposition and consideration of transition states

The transition states for aldol reaction of benzaldehyde with acetone catalyzed by L-proline, L-azetidinecarboxylic acid, and Singh's organocatalyst were proposed previously on the bases of the DFT calculation (**TS-1**, **TS-2**, and **TS-3** in Scheme 3).[16,17,19] The calculated transition state **TS-2** of L-azetidinecarboxylic acid was about 2 kcal/mol lower in energy than the most populated transition state **TS-1** of L-proline. As a result, the abilities of stereocontrol of the five-membered aza-heterocycle and the four-membered counterpart should be on the same level.[19]



Scheme 3. Proposed transition states for aldol reaction of benzaldehyde.

Based on a formally developed transition state **TS-3** of Singh's organocatalyst,[18] the transition state **TS-4** of the azetidine-2-carboxamide **1a** was proposed to explain the stereochemical outcome of the asymmetric aldol reaction. The benzaldehyde was activated by hydrogen bonding with the NH and OH of the amide branch of the catalyst **1a**, and was attacked from its *re*-face by acetone-derived enamine species, which was synergetically activated by the azetidine moiety of the same catalyst **1a**. Likewise, the transition state of **1a** catalyzed aldol reaction of benzaldehyde with cyclohexanone was also proposed in model **TS-5**, which explained the preferential formation of the *anti*-diastereoisomer.

3. Conclusion

In summary, a family of enantiopure azetidine-2-carboxamides was asymmetrically synthesized, and was examined as organocatalyst in direct aldol reactions. The azetidine-2-caboxamide **1a**, with methyl as steric hindrance group on 2-aminoethanol moiety, was found as the optimal catalyst. The presence of 5 mol % **1a** could smoothly catalyze the direct aldol reaction of various benzaldehydes with acetone in brine, to afford β-hydroxy ketones with enantioselectivities up to 96% ee. The aldol reaction of benzaldehydes with cyclohexanone produced *anti*-products as major isomers in diastereomeric ratio up to 99:1 and enantioselectivities of more than 90% ee in most cases. In addition, cyclopentanone also reacted with benzaldehyde to afford the major *anti*-adduct in 99% ee. The unprecedented application of enantiopure azetidine-2-carboxamides as organocatalysts in asymmetric aldol reaction posed a useful complement to the five-membered-aza-heterocycle-dominated aminocatalysis. The chiral azetidine scaffold was demonstrated as an efficient chiral unit for organocatalysis. The transition states of **1a** catalyzed aldol reaction were proposed to gain insight for further development of the azetidine-based organocatalysts.

4. Experimental

4.1. General methods

NMR Spectra (^1H and ^{13}C) were performed on a commercial spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using solution in $CDCl_3$ (referenced internally to Me_4Si); *J* values are given in Hertz. IR Spectra were determined on a commercial spectrophotometer. TLC was performed on dry silica gel plates developed with petroleum (60–90 °C) and ethyl acetate. Mass spectra were

obtained using a commercial instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. Methanol was dried with $Mg(OCH_3)_2$. The ionization method for HRMS is electrospray ionization (ESI), and the mass analyzer type is the time of flight (TOF). Melting points were determined using melting point apparatus. Optical rotations were measured on a commercial polarimeter at 20 °C in $CHCl_3$. All other reagents were commercially available and used as received.

4.2. Procedure of preparation of catalysts 1a, 1b, 1c, 2, and 3

4.2.1. Synthesis of L-homoserine. L-(+)-Methionine **4** (75 g, 0.5 mol) was suspended in H_2O/MeOH (1400 mL/200 mL), and methyl iodide (75 mL, 1.21 mol) was added. The resulting two-phase system was stirred vigorously for 48 h. The volume of the solvent was then reduced to one-third by evaporation to remove excess amount of methyl iodide. Water was added to reach a total volume of 1.0 L, and $NaHCO_3$ (42 g, 0.5 mol) was added. This solution was refluxed for 15 h and cooled, and the solvent was evaporated under reduced pressure to yield thick syrup. This residue was dissolved in a minimum quantity of water (140 mL), with heating. The addition of acetone (270 mL) and ethanol (3.0 L) caused immediate precipitation of L-homoserine as a white solid (37 g, 62%); mp=202–203 °C (dec.) [lit.: mp=203 °C (dec.)]; $[\alpha]_D^{20}$=8.2 (*c* 3.08, H_2O) [lit.: $[\alpha]_D^{26}$=8.0 (*c* 5, H_2O)]; ^1H NMR (400 MHz, D_2O) δ ppm: 3.66 (dd, *J*=7.4, 4.8 Hz, 1H), 3.54–3.58 (m, 2H), 1.92–2.01 (m, 1H), 1.79–1.87 (m, 1H).

4.2.2. Synthesis of L-2-amino-4-bromobutanoic acid hydrobromide. L-Homoserine (1.6 g, 13.3 mmol) and AcOH (36 mL, saturated with HBr) were placed in an autoclave, which was immersed in an oil bath, and then the temperature was raised to 75–80 °C. After stirring for 5 h, the temperature was gradually lowered to room temperature overnight. The precipitated was collected by suction filtration on a Büchner funnel and was washed with Et_2O. Recrystallization of the product from C_2H_5OH–Et_2O afforded L-2-amino-4-bromobutanoic acid hydrobromide (3.1 g, 85%); mp=187–188 °C [lit.: mp=188–190 °C]; $[\alpha]_D^{20}$ +11.8 (*c* 0.21, DMF) [lit.: $[\alpha]_D$ +11.8 (*c* 0.20, DMF)]; ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 8.33 (s, 3H), 4.00 (d, *J*=5.6 Hz, 1H), 3.59–3.71 (m, 2H), 2.22–2.41 (m, 2H).

*4.2.3. Synthesis of methyl L-2-amino-4-bromobutanoate hydrochloride (**5**).* L-2-Amino-4-bromobutanoic acid hydrobromide (4.2 g, 15.6 mmol) was suspended in methanol (120 mL), dry HCl was passed for 2 h at such a rate that the temperature of the reaction mixture was maintained at 35–40 °C. The solution was evaporated to dryness, the residue was dissolved in methanol and the solution was again evaporated to dryness; the same procedure was repeated once more, the residual oil was dried in vacuo over sodium hydroxide and the resulting crystals were triturated with ether, collected, and washed with diethyl ether. Recrystallization of the product from C_2H_5OH–Et_2O gave methyl L-2-amino-4-bromobutanoate hydrochloride **5** as white solid (3.3 g, 89%); mp=100.3–102.1 °C [lit.: mp=98–99 °C]; $[\alpha]_D^{20}$ +29.1 (*c* 0.83, CH_3OH).

*4.2.4. Representative procedure for the synthesis of catalysts **1**–**3**.* In a 100 mL round bottom flask, a reaction mixture of 0.5 g (1.33 mmol) (*S*)-methyl 1-tritylazetidine-2-carboxylate **7** and 0.213 g (5.33 mmol) sodium hydroxide was dissolved in 40 mL methanol and 10 mL distilled water, and was stirred at 50 °C for 12 h. When MeOH was distilled out, white solid precipitated. The solid was dissolved in about 50 mL THF, and the pH was tuned to 3–4 by addition of 1 M HCl. When the pH was tuned to 9–10 with the treatment of triethylamine, white solid precipitated again. The solid was collected by vacuum filtration, and was submitted to following reaction without purification. The triethylamine (*S*)-1-tritylazetidine-2-carboxylate **8** was received in quantitative yield (0.59 g).

The compound **8** obtained from abovementioned reaction was dissolved in 30 mL dichloromethane, and was treated with 3 equiv triethylamine. The ClCOOEt (1 equiv) was added dropwise at 0 °C, and the mixture was stirred for 1 h. The corresponding amino alcohol **9** (1.2 equiv) was added, and the mixture was stirred at rt for 10 h. After reactants were totally consumed (determined by TLC analysis), the solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and petroleum. The compound **10** was received as solid with isolated yield ranging from 42% to 63%.

The mixture of compound **10** (1 mmol), 8 mL distilled water, 3 mL concentrated sulfuric acid, and 60 mL MeOH was stirred at rt for 3 days. After reactant **10** was totally consumed, 40 mL water was added, and white solid was filtrated. The pH of the filtrate was tuned to basic using 25% NaOH aqueous solution. The mixture was extracted three times by ethyl acetate. The combined organic phase was washed by saturated NaCl, and was concentrated before purification by column chromatography, eluting with a mixture of ethyl acetate and petroleum. After the de-protection process, the azetidine-based organocatalysts **1**–**3** were isolated as white solids. For copies of ^1H and ^{13}C NMR spectra of the synthetic key intermediate **10** and catalysts **1**–**3**, please refer to Supplementary data.

4.3. Characterization of the synthetic key intermediate 10 and catalysts 1–3

*4.3.1. (S)-N-((S)-1-Hydroxy-1,1-diphenylpropan-2-yl)-1-tritylazetidine-2-carboxamide (**10a**).* Light yellow solid, 0.38 g, yield 51%; mp=94–96 °C; $[\alpha]_D^{25}$ −63.7 (*c* 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.82 (d, *J*=8.9 Hz, 1H), 7.60–7.58 (m, 2H), 7.56–7.54 (m, 2H), 7.30–7.19 (m, 9H), 7.18–7.17 (m, 11H), 4.87 (m, 1H), 4.74 (s, 1H), 4.09 (m, 1H), 3.73 (m, 1H), 3.40 (m, 1H), 3.02–2.98 (m, 1H), 1.68–1.63 (m, 1H), 1.09 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.5, 146, 145.1, 143.3, 129.2, 128.3, 128.2, 126.8, 126.7, 125.9, 125.7, 80.3, 75.6, 61.7, 53.5, 47.5, 21.8, 15.1; IR (KBr pellet) ν cm^{-1}: 3388, 2924, 2854, 1654, 1525, 1494, 1448, 1381, 1062, 747, 700; MS (EI) *m*/*z*: 553.4 $(M+H)^+$, 243.4 $(CPh_3)^+$; HRMS (ESI-TOF) *m*/*z*: $(M+Na)^+$ calcd for $C_{38}H_{36}N_2O_2Na$ 575.2674, found 575.2680.

*4.3.2. (S)-N-((S)-1-Hydroxy-1,1-diphenylpropan-2-yl)azetidine-2-carboxamide (**1a**).* Light yellow solid, 126 mg, yield 60%; mp=151–153 °C; $[\alpha]_D^{25}$ −129.3 (*c* 1.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.78 (d, *J*=9.0 Hz, 1H), 7.54–7.51 (m, 4H), 7.30–7.23 (m, 4H), 7.18–7.14 (m, 2H), 4.91 (m, 1H), 3.99 (m, 1H), 3.48 (m, 1H), 3.05 (m, 1H), 2.34 (m, 1H), 1.77 (m, 1H), 1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.8, 145.8, 145.0, 128.1, 127.9, 126.7, 126.6, 125.8, 125.6, 80.2, 58.8, 51.8, 43.3, 26.0, 15.5; IR (KBr pellet) ν cm^{-1}: 3324, 2927, 1650, 1529, 1493, 1449, 1375, 1178, 1127, 750, 701, 642; MS (EI) *m*/*z*: 311.4 $(M+H)^+$, 293.5 $(M-OH)^+$; HRMS (ESI-TOF) *m*/*z*: $(M+Na)^+$ calcd for $C_{19}H_{22}N_2O_2Na$ 333.1579, found 333.1582.

*4.3.3. (S)-N-((S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-1-tritylazetidine-2-carboxamide (**10b**).* Light yellow solid, 0.44 g, yield 55%; mp=98–100 °C; $[\alpha]_D^{25}$ −74.0 (*c* 1.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.64 (m, 2H), 7.55 (m, 2H), 7.31–7.15 (m, 21H), 4.81 (m, 1H), 4.11 (m, 1H), 3.70 (m, 1H), 3.30 (m, 1H), 2.92 (m, 1H), 1.90–1.91 (m, 1H), 1.51–1.60 (m, 2H), 1.09 (m, 2H), 0.92 (m, 3H), 0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.8, 146.1, 145.6, 145.5, 145.1, 143.1, 129.1, 128.7, 128.2 (×3), 128.0, 127.9, 127.7, 126.7,

126.6 (×2), 125.9, 125.8, 125.5, 125.4, 81.1, 60.4, 55.4, 47.1, 38.5, 26.9, 24.7, 24.0, 21.4; IR (KBr pellet) ν cm^{-1}: 3354, 2954, 2868, 1649, 1519, 1492, 1468, 1447, 1369, 1262, 1170, 1097, 1060, 772, 746, 703, 657; MS (EI) *m/z*: 594.7 $(M+H)^+$, 242.8 $(CPh_3)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{41}H_{42}N_2O_2Na$ 617.3144, found 617.3150.

*4.3.4. (S)-N-((S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)azetidine-2-carboxamide (**1b**).* Light yellow solid, 152 mg, yield 59%; mp=136–138 °C; $[\alpha]_D^{25}$ −64.2 (*c* 1.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.72 (d, *J*=8.9 Hz, 2H), 7.55 (m, 4H), 7.31–7.13 (m, 6H), 4.76 (m, 1H), 4.01 (m, 1H), 3.49 (m, 1H), 3.02 (m, 1H), 2.35 (m, 1H), 1.79 (m, 1H), 1.60–1.69 (m, 2H), 1.21 (m, 2H), 0.88 (m, 3H), 0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.5, 146.2, 144.5, 128.2, 127.8, 126.7, 126.5, 125.8, 125.6, 80.8, 58.9, 55.6, 43.3, 38.1, 26.2, 25.2, 23.8, 21.5; IR (KBr pellet) ν cm^{-1}: 3323, 2953, 2926, 2871, 1652, 1527, 1447, 1367, 1316, 1167, 1063, 744, 700; MS (EI) *m/z*: 353.8 $(M+H)^+$, 334.8 $(M-OH)^+$, 378.8 $(M+Na)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{22}H_{28}N_2O_2Na$ 375.2048, found 375.2061.

*4.3.5. (S)-N-((2S,3R)-1-Hydroxy-3-methyl-1,1-diphenylpentan-2-yl)-1-tritylazetidine-2-carboxamide (**10c**).* Light yellow solid, 0.48 g, yield 61%; mp=115–118 °C; $[\alpha]_D^{25}$ −105.5 (*c* 1.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.42 (m, 4H), 7.30–7.03 (m, 21H), 4.93 (m, 1H), 3.99–3.95 (m, 1H), 3.18–3.12 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.60–1.53 (m, 2H), 1.07 (m, 1H), 0.91 (m, 3H), 0.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.1, 147.0, 146.1, 143.5, 129.1, 128.6, 128.2, 127.7, 127.0, 126.7, 126.6, 126.4, 125.6, 81.8, 75.5, 62.0, 58.5, 47.9, 36.6, 23.6, 23.0, 18.5, 12.2; IR (KBr pellet) ν cm^{-1}: 3377, 2961, 2929, 2873, 1654, 1512, 1446, 1376, 1063, 746, 703, 631; MS (EI) *m/z*: 595.5 $(M+H)^+$, 243.4 $(CPh_3)^+$, 617.5 $(M+Na)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{41}H_{42}N_2O_2Na$ 617.3144, found 617.3153.

*4.3.6. (S)-N-((2S,3R)-1-Hydroxy-3-methyl-1,1-diphenylpentan-2-yl) azetidine-2-carboxamide (**1c**).* Light yellow solid, 217 mg, yield 76%; mp=112–113 °C; $[\alpha]_D^{25}$ −104.8 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.55–7.52 (m, 4H), 7.30–7.12 (m, 6H), 4.76 (m, 1H), 4.01 (m, 3H), 3.53 (m, 1H), 3.16–3.14 (m, 1H), 2.44–2.39 (m, 1H), 1.86–1.76 (m, 3H), 1.09–1.05 (m, 1H), 0.83 (m, 3H), 0.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.3, 147.2, 145.8, 128.3, 128.2, 128.1, 126.6, 125.9, 125.6, 125.5, 81.6, 59.7, 59.1, 43.6, 35.8, 26.5, 24.7, 18.8, 12.0; IR (KBr pellet) ν cm^{-1}: 3352, 2960, 2927, 2873, 1638, 1526, 1448, 1377, 1283, 1178, 1065, 747, 701, 642; MS (EI) *m/z*: 353.4 $(M+H)^+$, 335.5 $(M-OH)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{22}H_{28}N_2O_2Na$ 375.2048, found 375.2057.

*4.3.7. (S)-N-((1S,2R)-2-Hydroxy-1,2-diphenylethyl)-1-tritylazetidine-2-carboxamide (**10d**).* Light yellow solid, 0.45 g, yield 63%; mp=214–216 °C; $[\alpha]_D^{25}$ −78.6 (*c* 1.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36–7.02 (m, 25H), 5.21–5.18 (m, 1H), 4.92 (m, 1H), 4.16 (m, 1H), 3.68 (m, 1H), 3.28 (m, 1H), 1.90–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.7, 143.5, 139.8, 137.3, 129.5, 128.0, 127.9 (×2), 127.7 (×2), 126.6 (×2), 127.5, 126.9, 126.5, 126.4, 126.3, 76.2, 75.5, 62.1, 58.7, 48.2, 21.7; IR (KBr pellet) ν cm^{-1}: 3318, 2987, 2882, 1646, 1529, 1492, 1448, 1344, 1159, 1033, 998, 895, 772, 701, 641; MS (EI) *m/z*: 539.6 $(M+H)^+$, 243.7 $(CPh_3)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{37}H_{34}N_2O_2Na$ 561.2518, found 561.2523.

*4.3.8. (S)-N-((1S,2R)-2-Hydroxy-1,2-diphenylethyl)azetidine-2-carboxamide (**2**).* Light yellow solid, 104 mg, yield 42%; mp=94–97 °C; $[\alpha]_D^{25}$ −123.0 (*c* 0.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36–7.30 (m, 10H), 5.29–5.17 (m, 1H), 4.96 (m, 1H), 4.07 (m, 1H), 3.37–3.28 (m, 1H), 3.07–3.05 (m, 1H), 2.29–2.23 (m, 1H), 2.06–2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.1, 137.7, 137.0, 128.2, 128.1 (×2), 128.0 (×2), 127.9, 127.8, 127.7 (×2), 127.4 (×2), 77.4, 61.8, 60.4, 45.3, 23.1; IR (KBr pellet) ν cm^{-1}: 3396, 2923, 2853, 1652, 1524, 1452, 1382, 1098, 1061, 761, 703; MS (EI) *m/z*: 296.8 $(M+H)^+$, 279.0 $(M-OH)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{18}H_{20}N_2O_2Na$ 319.1422, found 319.1437.

*4.3.9. (S)-N-((1R,2S)-2-Hydroxy-1,2-diphenylethyl)-1-tritylazetidine-2-carboxamide (**10e**).* Light yellow solid, 0.30 g, yield 42%; mp=76–79 °C; $[\alpha]_D^{25}$ −76.3 (*c* 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27–7.04 (m, 25H), 5.33–5.30 (m, 1H), 4.99 (m, 1H), 3.87 (m, 1H), 3.57 (m, 1H), 3.08 (m, 1H), 1.90–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.0, 143.1, 139.5, 137.6, 129.3, 129.2 (×2), 128.3, 127.9, 127.8, 127.7 (×2), 127.6 (×2), 126.9, 126.7, 77.3, 75.7, 61.8, 58.9, 47.5, 21.8; IR (KBr pellet) ν cm^{-1}: 3376, 2978, 2934, 1645, 1522, 1447, 1373, 1130, 1072, 764, 702, 643; MS (EI) *m/z*: 539.4 $(M+H)^+$, 243.5 $(CPh_3)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ calcd for $C_{37}H_{34}N_2O_2Na$ 561.2518, found 561.2529.

*4.3.10. (S)-N-((1R,2S)-2-Hydroxy-1,2-diphenylethyl)azetidine-2-carboxamide (**3**).* Light yellow solid, 124 mg, yield 75%; mp=74–75 °C; $[\alpha]_D^{25}$ −12.0 (*c* 0.32, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19–6.92 (m, 10H), 5.23–5.15 (m, 1H), 5.01 (m, 1H), 4.01 (m, 1H), 3.20–3.10 (m, 1H), 3.04–3.02 (m, 1H), 2.06 (m, 1H), 1.96–1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.9, 136.7, 136.6, 127.2, 127.0 (×2), 126.9 (×2), 126.8 (×2), 126.7, 126.6, 126.5, 78.9, 61.8, 59.4, 43.6, 25.2; IR (KBr pellet) ν cm^{-1}: 3392, 2923, 2853, 1647, 1520, 1455, 1280, 1054, 698, 601, 529; MS (EI) *m/z*: 296.5 $(M+H)^+$, 279.2 $(M-OH)^+$; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{18}H_{20}N_2O_2Na$ 319.1422, found 319.1435.

4.4. Representative procedure for the direct aldol reaction of aldehydes with acetone in brine catalyzed by azetidine-based organocatalyst 1a

An aldehyde (1.0 mmol) was added to a mixture of acetone (5 mmol) and the catalyst **1a** in brine at 0 °C. The reaction mixture was stirred, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and petroleum ether. The enantiomeric excess (ee) of the aldol adduct was determined by chiral HPLC analysis. For HPLC spectra of compounds **13a**–**r**, please refer to Supplementary data.

4.5. Representative procedure for the direct aldol reaction of aldehydes with cyclohexanone or cylcopentanone in Chloroform catalyzed by azetidine-based organocatalyst 1a

An aldehyde (1.0 mmol) was added to a mixture of cyclohexanone or cyclopentanone (5 mmol) and the catalyst **1a** in chloroform at −20 °C. The reaction mixture was stirred, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and petroleum ether. The diastereomeric ratio (d.r.) and the enantiomeric excess (ee) of the aldol adduct were determined by chiral HPLC analysis. For HPLC spectra of compounds **15a**–**r** and **17**, please refer to Supplementary data.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of **1a**–**c**, **3**, **10a**, and **10c**, and copies of chiral HPLC spectra of **13a**–**r**, **15a**–**r**, and **17** are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.081.

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