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ORIGINAL PAPER

Direct asymmetric aldol reaction of cyclohexanone with aldehydes catalyzed by chiral *trans*-cyclohexanediamine L-tartrate salt

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Abstract The stable and commercially available catalyst (1*R*,2*R*)-(+)-1,2-cyclohexanediamine L-tartrate complex was used for asymmetric aldol reaction in high yields (up to 99 %) and enantioselectivities [up to 94 % enantiomeric excess (ee)]. The catalyst was obtained easily and reused three times.

Keywords Chiral resolution · Asymmetric aldol condensation · Green chemistry · Cyclohexanediamine catalyst · Stable and recoverable

Introduction

Asymmetric direct aldol reactions have tremendous synthetic utility and have received considerable attention as one of the most ubiquitous C–C bond-forming reactions in modern organic synthesis [1–4]. They provide an atom-economic approach to access chiral β-hydroxycarbonyl compounds, which are versatile synthetic motifs for biologically active natural products and pharmaceutical intermediates. Since List and co-workers [5] reported an L-proline-catalyzed direct asymmetric intermolecular aldol reaction, a large number of secondary amine derived catalysts, such as **1** (Fig. 1), have been developed for this reaction with the aim of increasing reactivity and stereoselectivity [6].

Recently, primary amine based organocatalysts have also been investigated as effective tools in asymmetric aldol condensation [7–11]. Among them, chiral cyclohexanediamine catalysts with diverse functional features have been designed, with excellent results. For example, Luo and Cheng [12] reported the primary–tertiary diamine catalyst **2**, which showed excellent selectivity in cross aldol condensation; the Shao group [13] synthesized the catalyst **3** in combination of binaphthyl unit; the primary amine–thiourea catalysts **4** and **5** were introduced by Jacobsen [14] and Tsogoeva [15], respectively. However, most of these catalysts need multi-step and time-consuming preparation, or were generated in situ with unstable properties.

In 2006, the List group introduced asymmetric counteranion-directed catalysis (ACDC) as a new concept in organocatalysis [16–18]. They demonstrated that salts made from a chiral primary amine and a chiral phosphoric acid could function as highly enantioselective iminium catalysts in the reduction of α,β-unsaturated aldehydes with Hantzsch esters. Recently, chiral diaminocyclohexane itself, with different acids as additives generating ion pair salts such as **6**, in aldol or other reactions were also reported [12, 19–22]. However, in view of the rules of green chemistry, it is necessary to develop a stable and recoverable catalyst to overcome the major drawbacks associated with the exorbitant cost and technical difficulty of large-scale production. As is well known, racemic *trans*-cyclohexane-1,2-diamine was resolved easily by L-tartaric acid giving ditartrate (*R*,*R*)-**7** [23]. This salt is stable, cheap, and easy to prepare on a large scale. Herein, we report (1*R*,2*R*)-(+)-1,2-cyclohexanediamine L-tartrate ((*R*,*R*)-**7**, Scheme 1) as an efficient counteranion-directed catalyst for direct asymmetric aldol reaction.

Electronic supplementary material The online version of this article (doi:10.1007/s00706-012-0821-6) contains supplementary material, which is available to authorized users.

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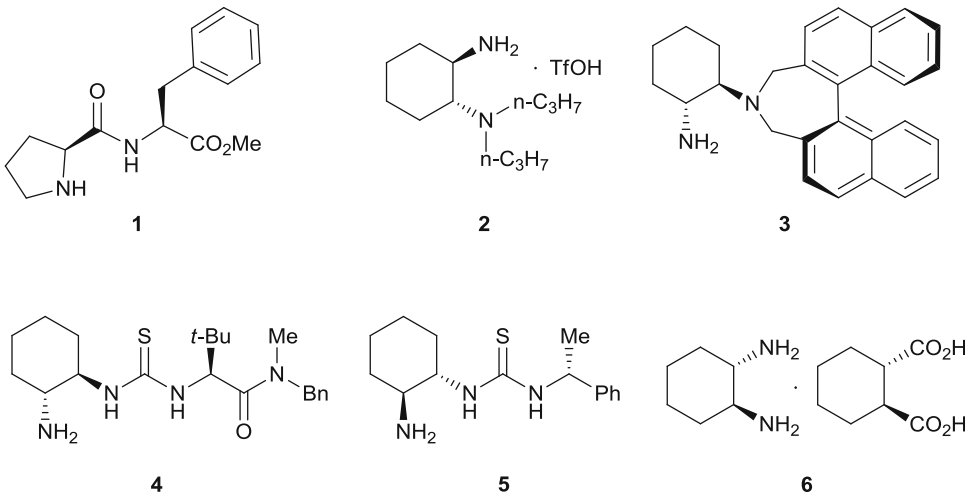
Fig. 1 Examples of chiral catalysts for asymmetric aldol reaction



Scheme 1

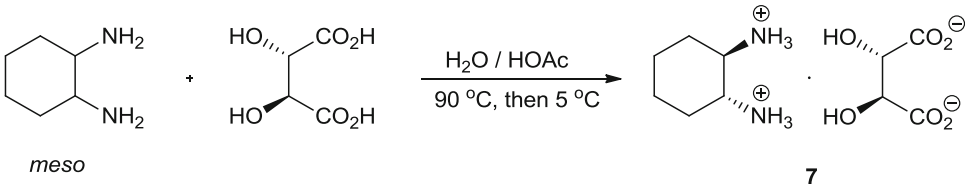
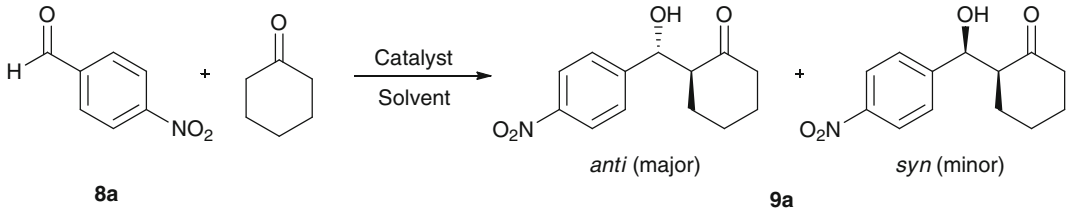


Table 1 Influence of the solvent on the asymmetric template-aldol reaction



Entry	Solvent	Time/h	Yield/%[a]	ee % (*anti*)	ee % (*syn*)	dr (*anti*/*syn*[b])
1	H_2O	24	>99	24	4	50/50
2	EtOH	24	>99	43	32	55/45
3	EtOH/H_2O = 4/1	24	>99	58	38	67/33
4	Neat	72	83	69	40	75/25
5	DCM	120	n.r.	–	–	–
6	DMF	120	n.r.	–	–	–
7	THF	120	n.r.	–	–	–
8	Brine[c]	12	>99	76	21	74/26

Reaction conditions: aldehyde (0.5 mmol) and cyclohexanone (2 mmol) in the presence of **7** (0.1 mmol) in different solvents (1 cm^3) at room temperature

ee Enantiomeric excess

[a] Isolated combined yields of *anti*- and *syn*-*β*-hydroxyketones

[b] Determined by ^1H NMR

[c] Saturated brine

Results and discussion

L-Tartaric acid combining cyclohexanediamine might be suitable for the activation of ketones due to their double hydroxyl group on the molecule, which could act with hydrogen bonding. Therefore, we studied tartrate salt **7** (Scheme 1) in the aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde. First, we prepared (*R*,*R*)-**7** from

Table 2 Screening of alcohol-brine co-solvent systems

Entry	Solvent	Yield/%[a]	ee % (*anti*)	ee % (*syn*)	dr (*anti*/*syn*[b])
1	EtOH/brine = 4/1	>99	85	63	70/30
2	EtOH/brine = 3/2	>99	83	55	67/33
3	EtOH/brine = 1/1	>99	83	58	70/30
4	EtOH/brine = 2/3	>99	82	47	72/28
5	EtOH/brine = 1/4	>99	78	44	67/33
6	*i*-PrOH/brine = 4/1	>99	72	45	58/42
7	*t*-BuOH/brine = 4/1	>99	75	57	67/33
8	EtOH/$CaCl_2$ = 4/1	>99	80	40	70/30
9	EtOH/NH_4Cl = 4/1	>99	83	60	70/30
10	EtOH/Na_2SO_4 = 4/1	>99	70	30	63/37
11	EtOH/Na_2CO_3 = 4/1	>99	Racemic	52	33/67

Reaction conditions: aldehyde (0.5 mmol) and cyclohexanone (2 mmol) in the presence of **7** (0.1 mmol) in alcohol/brine (1 cm^3) co-solvent at room temperature (25 °C) for 12 h

[a] Isolated combined yields of *anti*- and *syn*-*β*-hydroxyketones

[b] Determined by ^1H NMR

Table 3 Optimization of catalyst loading

Entry	Catalyst amount/%	Time/h	Yield/%[a]	ee % (*anti*)	ee % (*syn*)	dr (*anti*/*syn*[b])
1	40	5	97	82	45	66/34
2	20	12	>99	85	63	70/30
3	10	24	>99	91	80	70/30
4	7	48	>99	92	81	74/26
5	5	120	>99	88	78	71/29

Reaction conditions: aldehyde (0.5 mmol) and cyclohexanone (2 mmol) in the presence of **7** in EtOH-brine (4/1, 1 cm^3) at room temperature

[a] Isolated combined yields of *anti*- and *syn*-*β*-hydroxyketones

[b] Determined by ^1H NMR

cyclohexanediamine and L-tartaric acid by stirring in water/acetic acid (Scheme 1). With catalyst **7** in hand, initially we investigated water as a reaction medium, because of its favorable characteristics, such as non-toxic, safe, economic, and environmentally benign nature. Gratifyingly, (*R*,*R*)-**7** was found to act as a catalyst to give the desired product **9a** in nearly quantitative yield (Table 1, entry 1). Unfortunately, the diastereoselectivity and enantioselectivity were very low [*anti*/*syn* ratio = 50/50, enantiomeric excess (ee) = 24 %/4 %]. Then, ethanol was tried as a solvent, which led to increased enantioselectivity still with excellent yield (*anti*/*syn* ratio = 55/45, ee = 43 %/32 %). The reaction proceeded rather slowly under neat conditions, and no product was found in the case of DCM, DMF, and THF (Table 1, entries 4–7). As reported previously [24–26], brine was found to be a suitable solvent in the aldol condensation. Thus, we conducted the reaction in brine to afford improved enantioselectivity and diastereoselectivity (*anti*/*syn* = 74/26, ee = 76 %/21 %; Table 1, entry 8).

Subsequently, to improve selectivity of the aldol reaction, the reaction was carried out in EtOH/brine co-solvent, screening different ratios of EtOH/brine. As shown in Table 2, a ratio of 4/1 (EtOH/brine) was found to be the most suitable (*anti*/*syn* ratio = 70/30, ee = 85 %/63 %; Table 2, entry 1). A variety of alcohols with brine as co-solvents, as well as ethanol with several saturated aqueous solutions of inorganic salts, were also studied and no better selectivities were observed (Table 2, entries 6–11). Notably, in the case of saturated aqueous sodium carbonate solution and ethanol as co-solvent, a reverse effect on diastereoselectivity was observed, and *syn*-**9a** was obtained as the main product in 52 % ee (Table 2, entry 11).

Having established ethanol and brine (4/1) as a good solvent system, we then investigated catalyst loading. Dropping catalyst loading resulted in a longer reaction time for full conversion of *p*-nitrobenzaldehyde, and the ee value of the product was slightly improved (Table 3, entries 1–4). We were delighted to find that 7 mol % catalyst loading resulted in the best result after 48 h reaction (99 % yield, *anti*/*syn* ratio = 74/26, ee = 92 %/81 %; Table 3, entry 4). Decreasing the catalyst loading to 5 mol % led to decreased enantioselectivity and diastereoselectivity (Table 3, entry 5).

Next, the temperature effect was also examined, as shown in Table 4. Dropping the reaction temperature did not have a significant effect on the ee value; however, the reaction became sluggish. For simplicity, room temperature was used in all further experiments (Table 4, entry 6).

Table 4 Temperature effect catalyzed with 7 mol % of catalyst

Entry	*T*/°C	Time/h	Yield/%[a]	ee % (*anti*)	ee % (*syn*)	dr (*anti*/*syn*[b])
1	−10	120	64	84	52	72/28
2	−5	96	73	89	45	82/18
3	0	80	78	86	50	72/28
4	5	72	85	87	20	65/35
5	10–15	60	99	88	71	74/26
6	r.t.	48	>99	92	81	70/30

Reaction conditions: aldehyde (0.5 mmol), and cyclohexanone (2 mmol) in the presence of **7** (0.035 mmol) in EtOH/brine (1 cm^3) co-solvent at different temperatures

[a] Isolated combined yields of *anti*- and *syn*-*β*-hydroxyketones

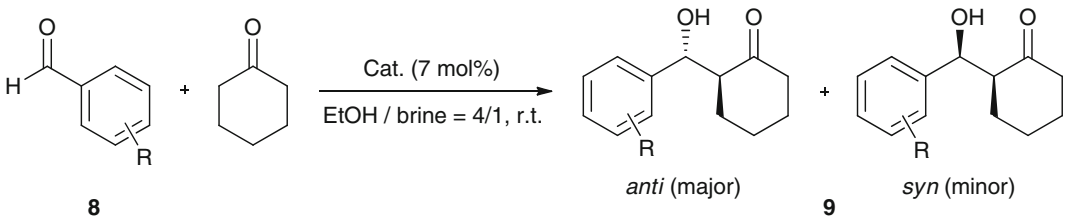
[b] Determined by ^1H NMR

With the optimized conditions in hand, the scope of the reaction was then explored and the results are shown in Table 5 (entries 1–5). It appears that aromatic aldehydes **8** with electron-withdrawing groups could react with cyclohexanone affording the corresponding products **9** in good yields (73–99 %) with moderate-to-high diastereoselectivity and good enantioselectivity.

Based on previous studies [27–30], the recycling and reuse of the catalyst was also desired on account of high catalyst loading. The L-tartrate complex has weak solubility in EtOH-brine as co-solvent; the reaction proceeded in the heterogeneous system. The catalyst could be recycled by simple filtration and reused three times without significant loss of reactivity and enantioselectivity (Table 5, entry 6).

To gain a better understanding of the reaction, the following experiments were carried out: (1) L-tartaric acid with cyclohexylamine as an achiral primary amine, and (2) the chiral diamine in combination with malonic acid as an achiral carboxylic acid. The results are shown in Table 6. Both cases were effective in giving the desired product; however, the yields and enantioselectivities were lower

Table 5 Substrate scope for enantioselective organocatalytic aldol reaction



Entry	R[a]	Yield/%[b]	ee % (*anti*)	ee % (*syn*)	dr (*anti*/*syn*[c])
1	2-NO_2	>99	91	75	99/1
2	3-NO_2	96	84	70	74/26
3	4-CN	89	81	81	60/40
4	4-CF_3	84	70	31	61/39
5	2-CF_3	73	94	75	>99/1
6[d]	4-NO_2	96 (81, 67)	90 (87, 83)	80 (76, 70)	70/30 (71/29, 68/32)

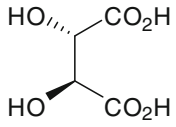
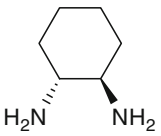
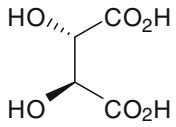
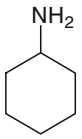
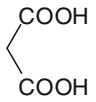
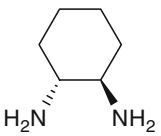
[a] Reaction conditions: aldehyde (0.5 mmol) and cyclohexanone (2 mmol) in the presence of **7** (0.035 mmol) in EtOH/brine (4/1, 1 cm^3) co-solvent at room temperature

[b] Isolated combined yields of *anti*- and *syn*-*β*-hydroxyketones

[c] Determined by ^1H NMR

[d] Recycled and reused for three times

Table 6 Catalyst screening of aldol reaction

Entry	Acid	Amine	Yield/%[c]	ee % (*anti*)	ee % (*syn*)	dr (*anti*/*syn*[d])
1[a]			>99	92	81	70/30
2[b]			95	83	70	68/32
3[a]			92	73	60	60/40

Reaction conditions: aldehyde (0.5 mmol) and cyclohexanone (2 mmol) in the presence of the catalyst (0.035 mmol) in EtOH-brine (4/1, 1 cm^3) at room temperature for 48 h

[a] Generated in situ

[b] Catalyst **7**

[c] Isolated combined yields of *anti*- and *syn*-*β*-hydroxyketones

[d] Determined by ^1H NMR

than the value catalyzed by the titled L-tartrate salt (Table 6, entries 1–3).

In conclusion, we developed (1*R*,2*R*)-(+)-1,2-cyclohexanediamine L-tartrate for an efficient direct asymmetric aldol reaction in EtOH/brine (4/1) as co-solvent, giving the products in good enantiomeric excess (up to 94 %) and excellent diastereoselectivities (up to 99 %). The diamine tartrate solid is stable, easy to handle, and commercially available, and could be a powerful catalyst in amino-catalyzing reactions in the future.

Experimental

Unless otherwise stated, materials were purchased from commercial suppliers and used without purification. ^1H NMR spectra were recorded on a Varian 400 (400 MHz) spectrometer. Flash column chromatography was performed using 200–300 mesh silica gel. Chiral HPLC was performed on Waters 2487 series with chiral columns (Chiralcel AD-H/OD-H). (1*R*,2*R*)-(+)-1,2-Cyclohexanediamine L-tartrate was prepared following reported procedures [23]. All products are known compounds; ^1H NMR and other characterization data matched data reported in literature [19–30]. All the detailed data and spectra are shown in the supplementary material.

General procedure for asymmetric aldol reaction

Aromatic aldehyde (0.5 mmol) was introduced to a mixture of a catalytic amount of catalyst (0.05 mmol, 10 mol %) and neat cyclohexanone (2.0 mmol) in 0.1 cm^3 EtOH-brine (4/1) co-solvent. The reaction mixture was stirred at room temperature for the time indicated in Table 3. The catalyst was recycled by simple filtration. The reaction mixture was subsequently filtered, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The organic layers were evaporated under reduced pressure. The crude aldol product was purified by flash column chromatography on silica gel to afford the aldol adducts as a white or pale yellow solids, and then analyzed by ^1H NMR spectroscopy and chiral HPLC.

General procedure for racemic samples

Electron-withdrawing aromatic aldehyde (0.5 mmol), neat ketone, and weak base additives (TEA, EDA, or K_2CO_3 if necessary) were mixed in EtOH-brine (4/1) co-solvent and

stirred magnetically at room temperature for 48 h. The reaction mixture was filtered and extracted with ethyl acetate, and then dried over anhydrous Na_2SO_4. The organic layers were evaporated under reduced pressure. The crude residue was purified by flash column chromatography and analyzed by chiral HPLC.

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