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# Practical synthesis of four different pseudoenantiomeric organocatalysts with both *cis*- and *trans*-substituted 1,2-cis-cyclohexanediamine structures from a common intermediate

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ABSTRACT

A new and convenient approach has been deviced for the practical synthesis of structurally robust, four different pseudoenantiomeric amino Tf-amido organocatalysts with the unique *cis*- and *trans*-substituted 1,2-cis-cyclohexanediamine structures. These pseudoenantiomeric organocatalysts are easily prepared by the Diels-Alder strategy of 2-phenyl-1,3-butadiene and maleic anhydride, and their chemical behavior was investigated by their application to asymmetric aldol synthesis for the practical synthesis of both enantiomeric aldols.



## 1. Introduction

The chiral phenomenon plays an crucially important role not only in nature but also in pharmaceutical, agrochemical and other chemical industries.[1] A variety of compounds associated with living organisms are chiral, and enantiomers of such compounds may possess distinctly different biological activity. Those include DNA, enzymes, hormones, antibodies, etc. Thus, the biology is quite sensitive to the chirality, and the biological activity of drugs depends on which enantiomer is used. In fact, in pharmaceutical industries, about half of the drugs currently in use are known to be chiral products, and its number is steadily increasing.[2] Accordingly, it is important to synthesize both enantiomeric products, and to promote the chiral separation and analysis of racemic drugs in pharmaceutical industries as well as in clinical use in order to eliminate the unwanted enantiomer from the preparation. The most traditional way for obtaining both enantiomeric products is the proper use of both enantiomeric catalysts,[3–6] although the preparation of both enantiomeric catalysts in a separate manner is often time-consuming. In a practical viewpoint, the use of two different pseudoenantiomeric catalysts derived from the common chiral compounds or intermediates seems to be more convenient for the synthesis of both enantiomeric products. In this context, we are interested in the design of new pseudoenantiomeric organocatalysts from the common chiral source for efficient asymmetric transformations. Indeed, we previously reported the facile synthesis of two different pseudoenantiomeric organocatalysts **2** and **3** from the common chiral compound **1** with the unique *cis*-diamine structure via 3-step sequence (Scheme 1).[7] The synthetic application of these pseudoenantiomeric organocatalysts **2** and **3** is illustrated by asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde **4a**, leading to both enantiomeric aldol products, *anti*-**5a** and *anti*-**6a**, respectively.[8,9]

## 2. Results and discussion

Although this asymmetric strategy is highly practical, there still

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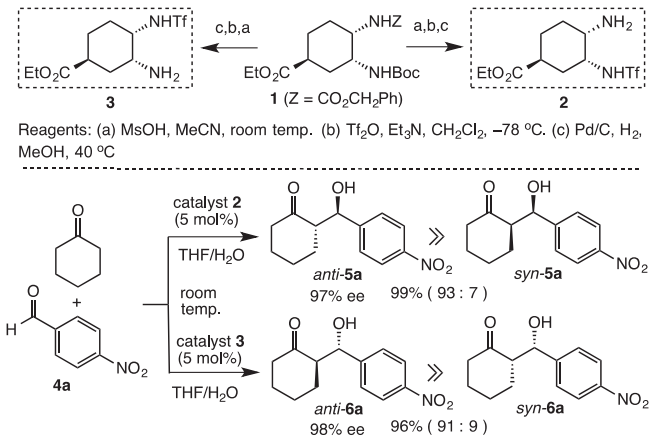
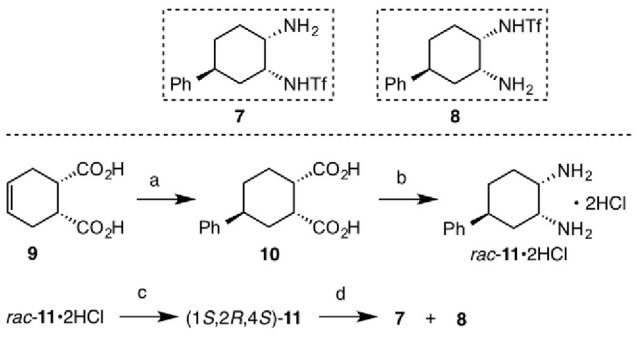



**Scheme 1.** Synthesis of two different pseudoenantiomeric organocatalysts **2** and **3**, and the application to asymmetric aldol synthesis.

needs some improvements on the design of pseudoenantiomeric organocatalysts **2** and **3**. Namely, the common chiral source **1** is not commercially available, and the synthesis of **1** generally requires some more steps from an easily available starting material.[10] In addition, the ester functionality in **1** is labile under acidic or basic conditions. Apparently, more robust pseudoenantiomeric organocatalysts of type **7** and **8** would be desirable for the wide variety of asymmetric transformations (Scheme 2). Accordingly, pseudoenantiomeric organocatalysts **7** and **8** can be prepared from commercially available *cis*-4-cyclohexene-1,2-dicarboxylic acid **9** in 4-step sequence as shown in Scheme 2. Thus, the Friedel-Crafts alkylation of *cis*-4-cyclohexene-1,2-dicarboxylic acid **9** in benzene furnished 4-phenyl-1,2-cyclohexanedicarboxylic acid **10** in 81% yield.[11] The Curtius rearrangement of diacid **10** afforded **11** as hydrogen chloride salt.[12] This racemic salt was then resolved with optically pure (*S*,*S*)-benzoyltartaric acid to furnish optically pure (1*S*,2*R*,4*S*)-**11**.[13] Mono-triflation of (1*S*,2*R*,4*S*)-**11** gave a mixture of amino Tf-amido organocatalysts **7** and **8**, which were easily separated by column chromatography to furnish optically pure **7** and **8**.[14]

We then compared the reactivity and selectivity of robust organocatalysts **7** and **8** in comparison with the original organocatalysts **2** and **3** in asymmetric aldol reaction of cyclohexanone with substituted benzaldehyde derivatives as shown in Table 1.[15,16]




**Scheme 2.** Synthetic route of two different, robust pseudoenantiomeric organocatalysts **7** and **8** from *cis*-4-cyclohexene-1,2-dicarboxylic acid **9**.

**Table 1**
Asymmetric direct aldol reaction of cyclohexanone and substituted benzaldehydes catalyzed by pseudoenantiomeric organocatalysts **2**, **3**, **7**, **8**, **12** or **13**.[a]

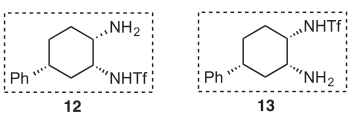
| entry | catalyst | major aldol | % yield[b] | anti/syn ratio[c] | % ee[d] |
|---|---|---|---|---|---|
| | | 4a; catalyst, THF/H2O, room temp. | *anti*-**5a** or *anti*-**6a** | | |
| 1 | **2** | *anti*-**5a** | 99 | 93: 7 | 97 |
| 2 | **3** | *anti*-**6a** | 96 | 91: 9 | 98 |
| 3[e] | **7** | *anti*-**5a** | 96 | 81: 19 | 95 |
| 4 | **8** | *anti*-**6a** | 96[f] | 93: 7 | 99 |
| 5 | **12** | *anti*-**5a** | 94[f] | 91: 9 | 99 |
| 6 | **13** | *anti*-**6a** | 48[e] | 52: 48 | 67 |
| | | 4b; catalyst, THF/H2O, room temp. | *anti*-**5b** or *anti*-**6b** | | |
| 7 | **2** | *anti*-**5b** | 99 | 89: 11 | 93 |
| 8 | **3** | *anti*-**6b** | 96 | 85: 15 | 94 |
| 9[e] | **7** | *anti*-**5b** | 95 | 82: 18 | 93 |
| 10 | **8** | *anti*-**6b** | 97[f] | 93: 7 | 99 |
| 11 | **12** | *anti*-**5b** | 95[f] | 90: 10 | 99 |
| 12 | **13** | *anti*-**6b** | 46 | 51: 49 | 54 |
| | | 4c; catalyst, THF/H2O, room temp. | *anti*-**5c** or *anti*-**6c** | | |
| 13 | **2** | *anti*-**5c** | 53[g] | 96: 4 | 98 |
| 14 | **3** | *anti*-**6c** | 27[g] | 89: 11 | 76 |
| 15[e] | **7** | *anti*-**5c** | 42[g] | 81: 19 | 83 |
| 16 | **8** | *anti*-**6c** | 61[f,g] | 94: 6 | 98 |
| 17 | **12** | *anti*-**5c** | 66[f,g] | 91: 9 | 98 |
| 18 | **13** | *anti*-**6c** | 20[g] | 51: 49 | 58 |

[a] Unless otherwise specified, asymmetric direct aldol reaction of cyclohexanone and substituted benzaldehyde in the presence of 5 mol% of catalyst **2**, **3**, **7**, **8**, **12** or **13** at room temperature for three days.
[b] Isolated yield.
[c] The *anti*/*syn* ratio was determined by $^1$H NMR analysis.
[d] Enantiopurity of *anti*-aldol products was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H and AS-H] with hexane-isopropanol as solvent.
[e] DMSO/$H_2O$ was used as solvent.
[f] Reaction for one day.
[g] The reaction was not complete under the standard conditions.

With three different benzaldehyde substrates, there is a general tendency among four different pseudoenantiomeric organocatalysts **2**, **3**, **7**, and **8**. In the asymmetric aldol synthesis of *anti*-**5**, the robust organocatalyst **7** exhibited lower reactivity and selectivity (both *trans*- and enantioselectivity) than **2** (entries 3, 9, 15 vs. 1, 7, 13), while pseudoenantiomeric organocatalyst **8** showed better reactivity and selectivity than **3** (entries 4, 10, 16 vs. 2, 8, 14).

So far, we studied the reactivity and selectivity of *trans*-substituted 1,2-cis-diamine-derived organocatalysts **2**, **3**, **7**, and **8**. However, we are also interested in the chemical behavior of the corresponding *cis*-substituted 1,2-cis-diamine-derived organocatalysts **12** and **13** (Scheme 3).

The intermediary 4-phenyl-4-cyclohexene-1,2-cis-dicarboxylic




**Scheme 3.** Robust *cis*-substituted pseudoenantiomeric organocatalysts **12** and **13**.

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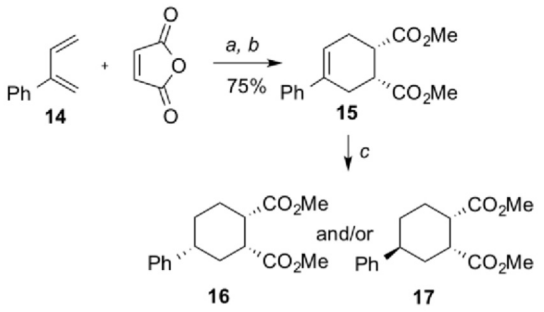
ester **15** can be easily prepared from 2-phenyl-1,3-butadiene **14** and maleic anhydride by the Diels-Alder reaction and subsequent transformation of the resulting Diels-Alder adduct to the corresponding dimethyl ester **15** (Scheme 4). Indeed, the Diels-Alder reaction of 2-phenyl-1,3-butadiene **14** and maleic anhydride in toluene at 100 °C for 48 h,[17] and subsequent treatment of the Diels-Alder adduct with catalytic sulfuric acid in MeOH at 50 °C for 10 h gave rise to the dimethyl ester **15** in 75% yield.[18] We then studied the catalytic hydrogenation of the unsaturated dimethyl ester **15** to either *cis*- or *trans*-substituted dimethyl ester **16** or **17**, respectively. The selected results are shown in Table 2. As shown in Table 2, Rh/C and Pd/C catalysts showed good *cis*-selectivity (entries 2 and 3), and the use of Pt/C significantly enhanced the *cis*-selectivity (entry 4). $Pd/Ba_2SO_4$ catalyst also exhibited high *cis*-selectivity (entries 6–10), and the use of THF solvent for $Pd/Ba_2SO_4$ catalyst gave the best *cis*-selectivity (entry 8). In contrast to such *cis*-selectivity, the use of Crabtree's catalyst afforded the opposite *trans*-selectivity almost exclusively (entry 11).[19]

With the desired cis and trans isomers **16** and **17** selectively, our approach provides a facile way to synthesize four different pseudoenantiomeric amino Tf-amido organocatalysts **7**, **8**, **12** and **13** after hydrolysis of diesters **16** and **17** (Scheme 5). Thus, the hydrolysis of the resulting *trans*-isomer **17** with aqueous LiOH at 40 °C for 10 h provided 4-phenyl-1,2-cis-cyclohexanedicarboxylic acid **10** in 82% yield.[20] The transformation of **10** to pseudoenantiomeric amino Tf-amido catalysts **7** and **8** can be effected as shown in Scheme 2. In a similar manner, *cis*-substituted diacid **18** was converted to the corresponding pseudoenantiomeric amino Tf-amido catalysts **12** and **13**, respectively.[21]

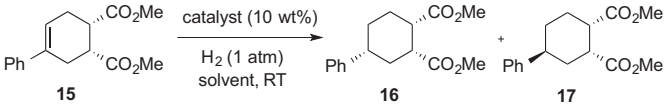
With new pseudoenantiomeric organocatalysts **12** and **13**, we carried out asymmetric aldol synthesis, and selected results are included in Table 1. As shown in Table 1, the robust organocatalyst **12** exhibited similar reactivity and selectivity to **2** and **7** (entries 5, 11, 17 vs. 1, 3, 7, 9, 13, 15), while pseudoenantiomeric organocatalyst **13** showed much lower reactivity and selectivity than **3** and **8** (entries 6, 12, 18 vs. 2, 4, 8, 10, 14, 16). Since the organocatalysts **2**, **7** and **12** gave the same aldol *anti*-**5a** preferentially, preferred conformations of these organocatalysts would be **2A**, **7A** and **12A** rather than **12B** which has the conformationally stable equatorial phenyl group. In a similar manner, the organocatalysts **3**, **8** and **13** gave the same aldol *anti*-**6a** preferentially, preferred conformations of these organocatalysts would be **3A**, **8A** and **13A** rather than **13B** which has the conformationally stable equatorial phenyl group. Interestingly, both organocatalysts **12** and **13** have preferred conformations with axial phenyl groups. The low anti/syn selectivity probably originated from the severe steric hindrance by the 1,3-diaxial interaction between phenyl and 1-cyclohexenylamino moieties in the cyclohexanone enamine of **13A** (see Scheme 6).




Reagents and conditions: (a) toluene, 100 °C; (b) $H_2SO_4$, MeOH, 50 °C; (c) catalytic hydrogenation (see Table 2).

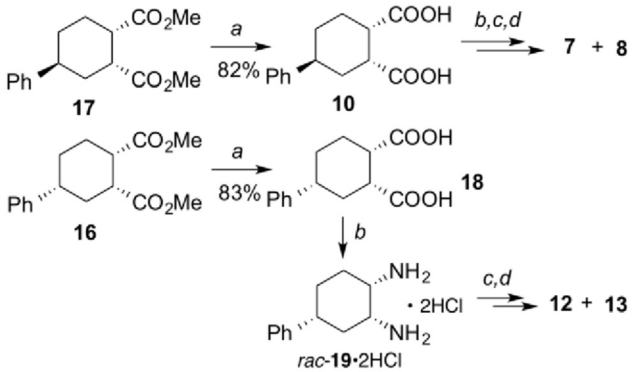
**Scheme 4.** Synthesis of *cis*- and *trans*-substituted diesters **16** and **17**.

**Table 2**
Optimization of reaction condition[a].




| entry | catalyst | solvent, time | % yield[b] | ratio of 16:17[c] |
|---|---|---|---|---|
| 1 | Raney Ni | EtOH, 20 h | – | – |
| 2 | Rh/C | EtOH, 2 h | 83 | 6.5: 1 |
| 3 | Pd/C | EtOH, 2 h | 94 | 7.0: 1 |
| 4 | Pt/C | EtOH, 1 h | 84 | 19.2: 1 |
| 5 | $Pd(OH)_2/C$ | EtOH, 2 h | 86 | 6.7: 1 |
| 6 | $Pd/BaSO_4$ | EtOH, 2 h | 93 | 15.3: 1 |
| 7 | $Pd/BaSO_4$ | EtOAc, 2 h | 94 | 15.2: 1 |
| 8 | $Pd/BaSO_4$ | THF, 2 h | 93 | 20.2:1 |
| 9 | $Pd/BaSO_4$ | $CH_2Cl_2$, 2 h | 94 | 15.8: 1 |
| 10 | $Pd/BaSO_4$ | cyclohexane, 2 h | 93 | 15.0: 1 |
| 11 | Crabtree's Catalyst | $CH_2Cl_2$, 72 h | 89 | 1: >20 |

[a] Unless otherwise specified, the stereoselective hydrogenation of unsaturated diester **15** in the presence of 10 wt% of hydrogenation catalyst at room temperature for 1–20 h.
[b] Isolated yield.
[c] The cis/trans ratio was determined by $^1H$ NMR analysis.




Reagents and conditions: (a) (i) 2 M LiOH aq., THF, 40 °C; (ii) 6 M HCl aq., room temp. (b) (i) DPPA, $Et_3N$, THF, room temp.; (ii) toluene, reflux then 6 M HCl aq. (c) (i) NaOH, $H_2O$, room temp.; (ii) (*S,S*)-DBTA, MeOH, EtOH, room temp.; (iii) 2 M NaOH aq., $CH_2Cl_2$, room temp. (d) TfCl, $Et_3N$, $CH_2Cl_2$, room temp.

**Scheme 5.** General synthesis of robust pseudoenantiomeric organocatalysts **7**, **8**, **12**, and **13**.

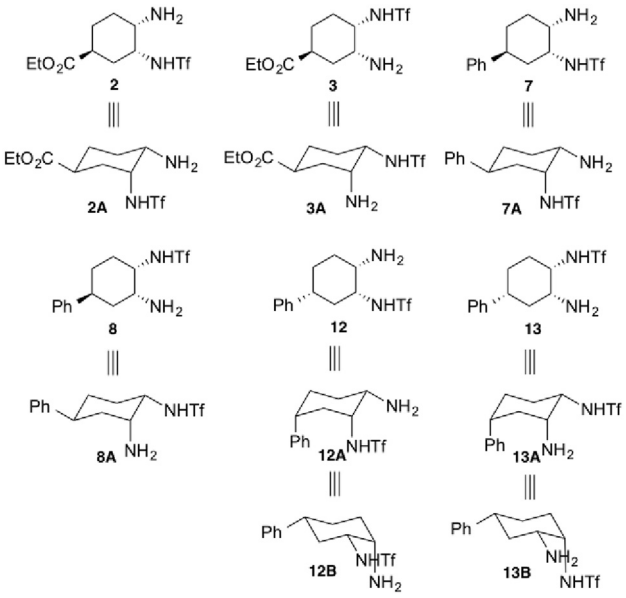
## 3. Conclusions

In summary, we have succeeded in preparing four different pseudoenantiomeric organocatalysts **7**, **8**, **12**, and **13**, which are easily derived from common source **15** in 5-step sequence. The Diels-Alder strategy of 2-substituted-1,3-butadiene and maleic anhydride would provide a general approach to the facile synthesis of various pseudoenantiomeric organocatalysts. These robust catalysts are in principle applicable to other catalytic systems, and further effort to this end is currently underway in our laboratory.

## 4. Experimental section

### 4.1. General

$^1H$ NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer and a JEOL JNM-ECA500 (500 MHz)



**Scheme 6.** Conformations of pseudoenantiomeric organocatalysts **2**, **3**, **7**, **8**, **12**, and **13**.

spectrometer. The data were reported as follows: chemical shifts in ppm from tetramethylsilane (TMS) as the internal standard, integration, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constants (Hz), and assignment. $^{13}$C NMR spectra were measured on a JEOL JNM-ECA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. High performance liquid chromatography (HPLC) was performed on Shimadzu 10 A instruments using 4.6 mm × 250 mm Daicel Chiralpak and Chiralcel. High-resolution mass spectra (HRMS) were performed on Brucker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. The reactions were monitored by thin-layer chromatography (Merck precoated TLC plates; silica gel 60 GF-254, 0.25 mm). The products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh). Commercially available chemicals were used without further purification.

### 4.2. Synthesis of cis-diamine catalysts *7*, *8*, *12* and *13*

#### 4.2.1. Friedel-Crafts alkylation of cis-4-cyclohexene-1,2-dicarboxylic acid *9*

To a solution of *cis*-4-cyclohexene-1,2-dicarboxylic acid **9** (1.70 g, 10 mmol) in benzene (7.7 mL) was added $AlCl_3$ (2.93 g, 22 mmol). The mixture was stirred at 50 °C for 24 h and concentrated in vacuo. The residue was treated with a 6 M aqueous solution of HCl (7.7 mL) at 0 °C and stirred there for 10 min. Then, water (66 mL) was added and the stirring was continued at room temperature for 30 min. The precipitate was filtered off and washed with $CH_2Cl_2$. The solid was dissolved in acetone and filtered. After the concentration of the filtrate, crude 4-phenylcyclohexane-1,2-dicarboxylic acid **10** was obtained as a white solid (2.01 g, 81% yield): M.p. 191–192 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.14 (brs, 2H), 7.28 (t, $J$ = 7.6 Hz, 2H), 7.20–7.16 (m, 3H), 3.18–3.16 (m, 1H), 2.48–2.42 (m, 2H), 2.16–2.01 (m, 1H), 1.97–1.88 (m, 2H), 1.84–1.76 (m, 2H), 1.45 (qd, $J$ = 12.4, 4.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 177.8, 177.0, 147.5, 129.4, 127.7, 127.2, 43.8, 43.3, 41.2, 37.0, 34.4, 25.5; IR (neat) 3021, 2864, 2567, 1678, 1447, 1417, 1326, 1259, 939, 825, 739, 696 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{16}O_4Na$: 271.0941 ($[M + Na]^+$), found: 271.0943.

#### 4.2.2. Curtius rearrangement of *10*

To a solution of crude diacid **10** (1.24 g, 5.0 mmol) in THF (12.5 mL) was added $Et_3N$ (2.1 mL, 15 mmol) and diphenylphosphoryl azide (2.2 mL, 10.5 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After quenched with $NaHCO_3$, the mixture was extracted with $Et_2O$ and washed with brine. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The oil was dissolved in toluene (12.5 mL) and stirred at 80 °C for 30 min. After refluxed at 120 °C for 1 h, the mixture was concentrated in vacuo and treated with a 6 M aqueous solution of HCl (25 mL) at 0 °C. The mixture was stirred at 90 °C for 12 h and then concenterated in vacuo. The residue was dissolved in ethyl acetate and the precipitate was filtered off. After the dryness, crude *rac*-**11**•2HCl was obtained as a white solid (1.14 g, 87% yield): M.p. decomp. >270 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.64 (brs, 6H), 7.30 (t, $J$ = 8.0 Hz, 2H), 7.22–7.18 (m, 3H), 3.81–3.80 (m, 1H), 3.54–3.50 (m, 1H), 3.16–3.10 (m, 1H), 2.08–1.91 (m, 4H), 1.84–1.81 (m, 1H), 1.68–1.58 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 114.6, 128.4, 126.7, 126.3, 50.1, 48.8, 34.5, 34.2, 30.8, 23.9; IR (neat) 3020, 2840, 2588, 1560, 1502, 1451, 1156, 1051, 1024, 742, 699 cm$^{-1}$.

#### 4.2.3. Resolution of rac-*11*•*2HCl*

To a solution of crude *rac*-**11**•2HCl (1.31 g, 5.0 mmol) in water (12.5 mL) was added NaOH (0.66 g, 16.5 mmol) at room temperature. The mixture was extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and concentrated in vacuo. The solid was dissolved in MeOH (25 mL) and added to a solution of (*S*,*S*)-benzoyltartaric acid (1.79 g, 5.0 mmol) in EtOH (25 mL) at 0 °C. The mixture was stirred at room temperature for overnight. Then, the precipitate was filtered off and washed with cold EtOH. The white solid was re-suspended in MeOH/$CHCl_3$ (1:2) and the mixture was stirred at 70 °C for 1 h. After cooled to 0 °C, the precipitate was filtered off and washed with $CHCl_3$. The process was repeated three times, and the optically pure (1*S*,2*R*,4*S*)-**11**•(*S*,*S*)-DBTA was obtained as a white solid. This solid was suspended in $CH_2Cl_2$ (100 mL), basified with 2 M aqueous solution of NaOH (25 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to afford optically pure (1*S*,2*R*,4*S*)-4-phenylcyclohexane-1,2-diamine (**11**) as a white solid (0.29 g, 31% yield): M.p. 78.5–79.5 °C; $[\alpha]_D^{23} = -25.9$ (c = 0.5, MeOH; 99% ee); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.16–7.10 (m, 4H), 7.03 (t, $J$ = 7.0 Hz, 1H), 2.97 (brs, 1H), 2.73–2.66 (m, 2H), 1.81 (dd, $J$ = 13.5, 2.0 Hz, 1H), 1.74–1.64 (m, 2H), 1.59–1.55 (m, 1H), 1.52–1.38 (m, 2H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 147.6, 129.4, 127.9, 127.0, 53.5, 52.4, 40.9, 37.5, 34.0, 29.4; IR (neat) 3289, 3024, 2919, 2426, 1600, 1449, 1375, 754, 697 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{19}N_2$: 191.1543 ($[M + H]^+$), found: 191.1543.

#### 4.2.4. Triflation of (1S,2R,4S)-*11*

To a solution of (1*S*,2*R*,4*S*)-**11** (0.19 g, 1.0 mmol) in $CH_2Cl_2$ (15 mL) was added $Et_3N$ (0.14 mL, 1.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then, TfCl (0.12 mL, 1.2 mmol) was added and the stirring was continued at the same temperature for 1 h. The solution was stirred at room temperature for overnight. After quenched with water, the mixture was extracted with $CH_2Cl_2$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography (MeOH/$CH_2Cl_2$ = 1/20 as eluent) to afford **7** and **8**.

*4.2.4.1. N-((1R,2S,5S)-2-amino-5-phenylcyclohexyl)-1,1,1-trifluoromethanes-ulfonamide (7).* (20% yield): White solid; M.p. 252–253 °C; $[\alpha]_D^{24} = -15.8$ (c = 0.5, DMSO); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.26–7.23 (m, 2H), 7.20–7.18 (m, 2H), 7.15–7.12 (m, 1H),

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3.81–3.79 (m, 1H), 3.20 (dt, $J$ = 12.5, 4.0 Hz, 1H), 3.07 (tt, $J$ = 12.5, 3.0 Hz, 1H), 2.00–1.87 (m, 3H), 1.77–1.67 (m, 2H), 1.62–1.53 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 146.6, 128.2, 126.6, 125.7, 122.3 (q, $^{1}J_{C,F}$ = 334.0 Hz), 52.0, 51.9, 35.6, 35.6, 31.4, 25.0; IR (neat) 3085, 2948, 1591, 1509, 1449, 1221, 1197, 1147, 1065, 999, 803, 746, 696 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{18}O_2N_2F_3S$: 323.1036 ([M + H]$^+$), found: 323.1044.

*4.2.4.2. N-((1S,2R,4S)-2-amino-4-phenylcyclohexyl)-1,1,1-trifluoromethanes-ulfonamide (**8**).* (47% yield): White solid; M.p. 84.5–85.5 °C; $[\alpha]_D^{23} = -39.4$ (c = 0.8, MeOH); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.28–7.22 (m, 4H), 7.16 (t, $J$ = 7.0 Hz, 1H), 3.58–3.54 (m, 1H), 3.42–3.40 (m, 1H), 2.81–2.74 (m, 1H), 2.06–1.92 (m, 2H), 1.89–1.81 (m, 2H), 1.71–1.58 (m, 2H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 146.3, 129.5, 127.8, 127.4, 123.1 (q, $^{1}J_{C,F}$ = 327.5 Hz), 55.8, 55.2, 37.4, 36.8, 33.3, 30.3; IR (neat) 3087, 2933, 1602, 1495, 1453, 1372, 1189, 1079, 973, 754, 698 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{18}O_2N_2F_3S$: 323.1036 ([M + H]$^+$), found: 323.1030.

*4.2.5. Synthesis of **15***

To a solution of maleic anhydride (0.98 g, 10 mmol) in toluene (33 mL) was added 2-phenyl-1,3-butadiene **14** (1.30 g, 10 mmol) at room temperature. The mixture was stirred at 100 °C for 48 h and concentrated in vacuo. The residue was dissolved in MeOH (16 mL) and treated with conc. $H_2SO_4$ (0.67 mL). The mixture was stirred at 50 °C for 10 h and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:9 as eluent) to afford dimethyl ester **15** as colorless oil (2.05 g, 75% yield): $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39–7.38 (m, 2H), 7.31 (t, $J$ = 7.5 Hz, 2H), 7.23 (t, $J$ = 7.5 Hz, 2H), 6.07–6.05 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.22–3.19 (m, 1H), 3.13–3.10 (m, 1H), 3.01–2.96 (m, 1H), 2.79–2.72 (m, 2H), 2.58–2.53 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.5, 173.5, 141.2, 135.0, 128.2, 127.0, 125.1, 122.2, 51.9, 51.8, 40.3, 39.4, 27.9, 26.4; IR (neat) 3023, 2950, 1728, 1434, 1199, 1167, 1025, 994, 746, 695 cm$^{-1}$; HRMS (ESI) calcd for $C_{16}H_{18}O_4Na$: 297.1097 ([M + Na]$^+$), found: 297.1101.

*4.2.6. Catalytic hydrogenation for cis-isomer **16***

To a solution of **15** (55 mg, 0.2 mmol) in THF (2.0 mL) was added Pd/$BaSO_4$ (6 mg) at room temperature. The mixture was stirred under 1 atm of hydrogen gas for 2 h. The catalyst was filtered through a pad of celite. After removal of the solvent, purification by silica gel column chromatography (ethyl acetate/hexane = 1:10 as eluent), **16** was obtained as colorless oil (51 mg, 93% yield, 20.2:1 dr): $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30–7.27 (m, 2H), 7.22–7.17 (m, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.32–3.29 (m, 1H), 2.63–2.59 (m, 1H), 2.57–2.51 (m, 1H), 2.36–2.32 (m, 1H), 2.25–2.20 (m, 1H), 2.10–2.03 (m, 1H), 1.80–1.74 (m, 1H), 1.73–1.68 (m, 1H), 1.48 (dq, $J$ = 12.5, 3.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.9, 173.7, 146.0, 128.3, 126.7, 126.1, 51.7, 51.6, 43.9, 43.5, 40.7, 31.3, 29.6, 28.3; IR (neat) 3026, 2949, 1727, 1600, 1494, 1434, 1196, 1145, 1022, 778, 700 cm$^{-1}$; HRMS (ESI) calcd for $C_{16}H_{20}O_4Na$: 299.1254 ([M + Na]$^+$), found: 299.1252.

*4.2.7. Catalytic hydrogenation for trans isomer **17***

To a solution of **15** (55 mg, 0.2 mmol) in $CH_2Cl_2$ (2.0 mL) was added Crabtree's catalyst (24 mg, 0.03 mmol) at room temperature. The mixture was stirred under 1 atm of hydrogen gas for 72 h. After removal of the solvent and purification by silica gel column chromatography (ethyl acetate/hexane = 1:15 as eluent), **17** was obtained almost exclusively as colorless oil (49 mg, 89% yield): $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.21–7.18 (m, 3H), 3.71 (s, 6H), 3.41–3.39 (m, 1H), 2.63–2.56 (m, 1H), 2.54–2.49 (m, 1H), 2.41–2.36 (m, 1H), 2.19–2.14 (m, 1H), 2.06–1.97 (m, 2H), 1.75 (td, $J$ = 13.0, 5.0 Hz, 1H), 1.52–1.43 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.7, 145.7, 128.3, 126.6, 126.2, 51.7, 51.7, 43.7, 41.9, 39.3, 35.2, 33.0, 24.3; IR (neat) 3026, 2949, 1727, 1601, 1494, 1434, 1194, 1156, 1023, 898, 756, 699 cm$^{-1}$; HRMS (ESI) calcd for $C_{16}H_{20}O_4Na$: 299.1254 ([M + Na]$^+$), found: 299.1256.

*4.2.8. Hydrolysis of dimethyl ester **16** and **17***

To a solution of **17** (0.14 g, 0.5 mmol) in THF (2.0 mL) was added a 2 M aqueous solution of LiOH (2.5 mL, 10 mmol) at room temperature. The mixture was stirred at 40 °C for 10 h. The solution was diluted with water and extracted with $CH_2Cl_2$. The aqueous layer was acidified to pH 2 with 6 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The solid was washed with cold $CH_2Cl_2$. After the dryness, crude **10** was obtained as a white solid (0.10 g, 82% yield). For the cis isomer **18**: (83% yield): White solid; M.p. 188–189 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.14 (brs, 2H), 7.27 (t, $J$ = 7.5 Hz, 2H), 7.18–7.15 (m, 3H), 3.09–3.06 (m, 1H), 2.59–2.52 (m, 2H), 2.15 (dq, $J$ = 13.0, 3.0 Hz, 1H), 1.99–1.87 (m, 2H), 1.74–1.62 (m, 2H), 1.45 (qd, $J$ = 13.0, 3.0 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.7, 174.6, 146.6, 128.3, 126.5, 126.0, 42.5, 42.4, 40.2, 31.5, 29.3, 28.0; IR (neat) 3029, 2955, 2594, 1694, 1447, 1422, 1345, 1223, 922, 749, 697 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{16}O_4Na$: 271.0941 ([M + Na]$^+$), found: 271.0942.

*4.2.9. Curtius rearrangement of **18***

To a solution of **18** (1.24 g, 5.0 mmol) in THF (12.5 mL) was added $Et_3N$ (2.1 mL, 15 mmol) and diphenylphosphoryl azide (2.2 mL, 10.5 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After quenched with $NaHCO_3$, the mixture was extracted with $Et_2O$ and washed with brine. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The oil was dissolved in toluene (12.5 mL) and stirred at 80 °C for 30 min. After refluxed at 120 °C for 1 h, the mixture was concentrated in vacuo and treated with a 6 M aqueous solution of HCl (25 mL) at 0 °C. The mixture was stirred at 90 °C for 12 h and then concenterated in vacuo. The residue was dissolved in ethyl acetate and the precipitate was filtered off. After the dryness, crude desired product was obtained as a white solid (1.06 g, 81% yield): M.p. 236–237 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.66 (brs, 6H), 7.35–7.28 (m, 4H), 7.22–7.19 (m, 1H), 3.76–3.74 (m, 1H), 3.57–3.53 (m, 1H), 2.75–2.69 (m, 1H), 2.08–2.04 (m, 1H), 2.00–1.84 (m, 4H), 1.59–1.55 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 144.8, 128.3, 126.9, 126.4, 50.5, 47.7, 41.5, 31.0, 27.2, 25.1; IR (neat) 3417, 2924, 2606, 1601, 1518, 1452, 1159, 1057, 1030, 760, 700 cm$^{-1}$.

*4.2.10. Resolution of rac-**19**•2HCl*

To a solution of crude *rac*-**19**•2HCl (1.31 g, 5.0 mmol) in water (12.5 mL) was added NaOH (0.66 g, 16.5 mmol) at room temperature. The mixture was extracted with $CH_2Cl_2$, dried over $Na_2SO_4$ and concentrated in vacuo. The solid was dissolved in MeOH (25 mL) and added to a solution of (*S*,*S*)-benzoyltartaric acid (1.79 g, 5.0 mmol) in EtOH (25 mL) at 0 °C. The mixture was stirred at room temperature for overnight. Then, the precipitate was filtered off and washed with cold EtOH. The white solid was re-suspended in MeOH/$CHCl_3$ (1:2) and the mixture was stirred at 70 °C for 1 h. After cooled to 0 °C, the precipitate was filtered off and washed with $CHCl_3$. The process was repeated three times, and the optically pure (1*S*,2*R*,4*R*)-**19**•(*S*,*S*)-DBTA was obtained as a white solid. This solid was suspended $CH_2Cl_2$ (100 mL), basified with 2 M aqueous solution of NaOH (25 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to afford optically pure (1*S*,2*R*,4*R*)-4-phenylcyclohexane-1,2-diamine (**19**) as a colorless oil (0.794 g, 29% yield): $[\alpha]_D^{23} = +9.9$ (c = 0.5, MeOH; 99% ee); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.27–7.21 (m, 4H), 7.16–7.11 (m, 1H), 3.02–3.00 (m, 1H), 2.85 (dt, $J$ = 12.0, 3.5 Hz, 1H), 2.61–2.54 (m, 1H),

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1.97–1.88 (m, 1H), 1.76–1.54 (m, 5H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 147.8, 129.3, 127.8, 127.0, 54.2, 51.3, 44.8, 37.1, 32.9, 27.7; IR (neat) 3283, 3025, 2920, 2854, 1599, 1448, 1389, 754, 698 $cm^{-1}$; HRMS (ESI) calcd for $C_{12}H_{19}N_2$: 191.1543 ($[M + H]^+$), found: 191.1546.

*4.2.11. Triflation of (1S,2R,4R)-**19***

To a solution of (1*S*,2*R*,4*R*)-**19** (0.19 g, 1.0 mmol) in $CH_2Cl_2$ (15 mL) was added $Et_3N$ (0.14 mL, 1.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then, TfCl (0.12 mL, 1.2 mmol) was added and the stirring was continued at same temperature for 1 h. The solution was stirred at room temperature for overnight. After quenched with water, the mixture was extracted with $CH_2Cl_2$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography ($MeOH/CH_2Cl_2 = 1/20$ as eluent) to afford **12** and **13**.

*4.2.11.1. N-((1R,2S,5R)-2-amino-5-phenylcyclohexyl)-1,1,1-trifluoromethanesulfonamide (**12**).* (44% yield): White solid; M.p. 174–175 °C; $[\alpha]_D^{26} = -31.2$ (c = 1.0, DMSO); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.29–7.24 (m, 4H), 7.18–7.15 (m, 1H), 3.62 (dt, $J = 12.5$, 4.0 Hz, 1H), 3.38–3.36 (m, 1H), 2.66 (tt, $J = 12.5$, 3.5 Hz, 1H), 2.07–2.01 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.81 (m, 1H), 1.72–1.57 (m, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 146.9, 129.4, 127.8, 127.3, 123.1 (q, $^1J_{C,F} = 328.0$ Hz), 56.4, 54.4, 44.0, 37.8, 29.1, 27.3; IR (neat) 3268, 2948, 1601, 1494, 1448, 1403, 1272, 1189, 1083, 982, 758, 699 $cm^{-1}$; HRMS (ESI) calcd for $C_{13}H_{18}O_2N_2F_3S$: 323.1036 ($[M + H]^+$), found: 323.1042.

*4.2.11.2. N-((1S,2R,4R)-2-amino-4-phenylcyclohexyl)-1,1,1-trifluoromethanesulfonamide (**13**).* (15% yield): White solid; M.p. 223–224 °C; $[\alpha]_D^{24} = +8.2$ (c = 0.6, MeOH); $^1$H NMR (500 MHz, $CD_3OD$) δ 7.21–7.15 (m, 4H), 7.08–7.04 (m, 1H), 3.66–3.64 (m, 1H), 3.16 (dt, $J = 12.0$, 3.5 Hz, 1H), 2.52 (tt, $J = 12.5$, 3.5 Hz, 1H), 1.94–1.82 (m, 3H), 1.65–1.55 (m, 2H), 1.46–1.43 (m, 1H); $^{13}$C NMR (125 MHz, $CD_3OD$) δ 147.1, 129.4, 128.0, 127.3, 123.2 (q, $^1J_{C,F} = 326.7$ Hz), 54.5, 53.2, 44.3, 33.6, 33.1.1, 28.0; IR (neat) 3264, 3102, 2929, 1619, 1474, 1454, 1216, 1194, 1148, 1045, 995, 788, 754, 699 $cm^{-1}$; HRMS (ESI) calcd for $C_{13}H_{18}O_2N_2F_3S$: 323.1036 ($[M + H]^+$), found: 323.1041.

*4.3. General procedure for the aldol reaction using the cis-diamine catalyst*

To a mixture of catalyst **2**, **3**, **7, 8, 12** or **13** (3.2 mg, 5 mol%) in THF (0.6 mL) and $H_2O$ (0.6 mL) was added an aldehyde (0.2 mmol) and cyclohexanone (0.6 mL, 6.0 mmol). The resulting homogeneous mixture was stirred at room temperature for the appropriate time until the reaction was completed by TLC. Then, saturated $NH_4Cl$ solution and ethyl acetate were added with vigorous stirring. The residue was then purified by column chromatography on silica gel (mixture of ethyl acetate/hexane) to give the corresponding aldol adducts. The enantiomeric excess (ee) was determined by chiral-phase HPLC analysis and the absolute configuration of aldol products was determined by comparison with that in the literature.[16]

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.035.

## References

1. Review: Mitra S, Chopra P *Indian J Anaesth*. 2011;55:556–562.
2. Reviews: . (a) Calcaterra A, D'Acquarica I. *J Pharmaceut Biomed Anal*. 2018;147:323–340;
(b) Sanganyado E, Lu Z, Fu Q, Schlenk D, Gan J. *Water Res*. 2017;124:527–542;
(c) Sekhon BS. *J Mod Med Chem*. 2013;1:1–36;
(d) Nguyen LA, He H, Chuong P-H. *Int J Biomed Sci*. 2006;2:85–100.
3. Mikami K, Lautens M. *New Frontiers in Asymmetric Catalysis*. Weinheim: Wiley-VCH; 2007.
4. Recent reviews: . (a) Heravi MM, Zadsirjan V, Dehghani M, Hosseintash N. *Tetrahedron: Asymmetry*. 2017;28:587–707;
(b) Bhowmick S, Mondal A, Ghosh A, Bhowmick KC. *Tetrahedron: Asymmetry*. 2015;26:1215–1244;
(c) Mlynarski J, Bas S. *Chem Soc Rev*. 2014;43:577–587;
(d) Dondoni A, Massi A. *Angew Chem Int Ed*. 2008;47:4638–4660.
5. Enantiodivergent catalysis: . (a) Neel J, Milo A, Sigman MS, Toste FD. *J Am Chem Soc*. 2016;138:3863–3875;
(b) Sohtome Y, Yamaguchi T, Tanaka S, Nagasawa K. *Org Biomol Chem*. 2013;11:2780–2786;
(c) Yamamoto T, Suzuki Y, Ito E, Tokunaga E, Shibata N. *Org Lett*. 2011;13:470–473;
(d) Sohtome Y, Tanaka S, Takada K, Yamaguchi T, Nagasawa K. *Angew Chem Int Ed*. 2010;49:9254–9257;
(e) Lutz F, Igarashi T, Kinoshita T, et al. *J Am Chem Soc*. 2008;130:2956–2958;
(f) Lutz F, Igarashi T, Kawasaki T, Soai K. *J Am Chem Soc*. 2005;127:12206–12207;
(g) Arseniyadis S, Subhash PV, Valleix A, et al. *J Am Chem Soc*. 2005;127:6138–6139;
(h) Arseniyadis S, Valleix A, Wagner A, Mioskowski C. *Angew Chem Int Ed*. 2004;43:3314–3317;
(i) Sculimbrene R, Morgan AJ, Miller SJ. *J Am Chem Soc*. 2002;124:11653–11656.
6. Reviews on the use of chiral primary amines in asymmetric organocatalysis: .
(a) Duan J, Li P. *Catal Sci Technol*. 2014;4:311–320;
(b) Serdyuk OV, Heckel CM, Tsogoeva SB. *Org Biomol Chem*. 2013;11:7051–7071;
(c) Xu L-W, Luo J, Lu Y. *Chem Commun*. 2009:1807–1821;
(d) Xu L, Lu Y. *Org Biomol Chem*. 2008;6:2047–2053.
7. Nakayama K, Maruoka K. *J Am Chem Soc*. 2008;130:17666–17667.
8. For a review of direct asymmetric aldol reactions, see: Trost BM, Brindle CS *Chem Soc Rev*. 2010;39:1600–1632. Recent selected examples;
(a) Liu J, Yang Z, Wang Z, et al. *J Am Chem Soc*. 2008;130:5654–5655;
(b) Luo S, Xu H, Zhang L, Li J, Cheng J-P. *Org Lett*. 2008;10:653–656;
(c) Ramasastry SSV, Albertshofer K, Utsumi N, Barbas III CF. *Org Lett*. 2008;10:1621–1624;
(d) Luo S, Xu H, Chen L, Cheng J-P. *Org Lett*. 2008;10:1775–1778;
(e) Hayashi Y, Itoh T, Aratake S, Ishikawa H. *Angew Chem Int Ed*. 2008;47:2082–2084;
(f) Ramasastry SSV, Zhang H, Tanaka F, Barbas III CF. *J Am Chem Soc*. 2007;129:288–289;
(g) Luo S, Xu H, Li J, Zhang L, Cheng J-P. *J Am Chem Soc*. 2007;129:3074–3075;
(h) Guizzetti S, Benaglia M, Raimondi L, Celentano G. *Org Lett*. 2007;9:1247–1250;
(i) Xu X-Y, Wang Y-Z, Gong L-Z. *Org Lett*. 2007;9:4247–4249;
(j) Wu X, Jiang Z, Shen H-M, Lu Y. *Adv Synth Catal*. 2007;349:812–816;
(k) Jiang Z, Liang Z, Wu X, Lu Y. *Chem Commun*. 2006:2801–2803;
(l) Mase N, Nakai Y, Ohara N, et al. *J Am Chem Soc*. 2006;128:734–735.
9. (a) Moteki SA, Maruyama H, Nakayama K, et al. *Chem Asian J*. 2015;10:2112–2116;
(b) Kano T, Sakamoto R, Maruoka K. *Org Lett*. 2014;16:944–947;
(c) Moteki SA, Han J, Arimitsu S, Akakura M, Maruoka K. *Angew Chem Int Ed*. 2012;51:1187–1190;
(d) Kano T, Song S, Maruoka K. *Chem Commun*. 2012;48:7037–7039;
(e) Kano T, Noishiki A, Sakamoto R, Maruoka K. *Chem Commun*. 2011;47:10626–10628;
(f) Kano T, Sugimoto H, Maruoka K. *J Am Chem Soc*. 2011;133:18130–18133;
(g) Kano T, Yamaguchi Y, Maruoka K. *Chem Eur J*. 2009;15:6678–6687;
(h) Kano T, Yamaguchi Y, Tanaka Y, Maruoka K. *Angew Chem Int Ed*. 2007;46:1738–1740;
(i) Kano T, Tokuda O, Takai J, Maruoka K. *Chem Asian J*. 2006;1–2:210–215;
(j) Kano T, Tokuda O, Maruoka K. *Tetrahedron Lett*. 2006;47:7423–7426. See also;
(k) Kano T, Takai J, Tokuda O, Maruoka K. *Angew Chem Int Ed*. 2005;44:3055–3057.
10. (a) Wang X, Ma M, Reddy AGK, Hu W. *Tetrahedron*. 2017;73:1381–1388;
(b) Nagata T, Yoshino T, Hainoya N, et al. *Bioorg Med Chem*. 2009;17:1193–1206;
(c) Yoshino T, Nagata T, Hagionya N, Yoshikawa K, Kanno H, Nagamochi M. *PCT Int Appl*. 2001. WO2001074774;
(d) Poll T, Sobczak A, Hartmann H, Helmchen. *G Tetrahedron Lett*. 1985;26:3095–3098.

Please cite this article in press as: Lee H-J, et al., Practical synthesis of four different pseudoenantiomeric organocatalysts with both *cis*- and *trans*-substituted 1,2-cis-cyclohexanediamine structures from a common intermediate, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.035

11. (a) Kolobov AV, Borlsov PV, Panfilov ST, Ovchinnikov KL, Krasovskaya GG, Kofanov ER. *Izv Vyssh Uchebn Zaved Khim Khim Tekhnol*. 2007;50:56–58;
(b) Salvati ME, Attar RM, Gottardis MM, et al. *PTC Int Appl*. 2002. WO2002067939;
(c) Guo Q, Liu M-L, Feng L-S, et al. *Arch Pharm*. 1979;312:982–994.
12. (a) Gee YS, Goertz NJM, Gardiner MG, Hyland CJT. *Org Biomol Chem*. 2016;14:2498–2503;
(b) Ling P-X, Fang S-L, Yin X-S, Chen K, Sun B-Z, Shi B-F. *Chem Eur J*. 2015;21:17503–17507;
(c) Zhang Y, Vaidyanathan S, Garnes K, Schildknegt K. *J Label Compd Radiopharm*. 2012;55:166–170.
13. (a) Moteki SA, Xu S, Arimitsu S, Maruoka K. *J Am Chem Soc*. 2010;132:17074–17076;
(b) Seiji M, Toshihiro F, Haruyo S. *PTC Int Appl*. 2004. WO2004063141;
(c) Ryoda A, Yajima N, Haga T, et al. *J Am Chem Soc*. 2002;124:14631–14641.
14. (a) Tang Y, Xiang J, Cun L, et al. *Tetrahedron: Asymmetry*. 2010;21:1900–1905;
(b) Martins JED, Wills M. *Tetrahedron*. 2009;65:5782–5786;
(c) Xue D, Chen Y-C, Cui X, Wang Q-W, Zhu J, Deng J-G. *J Org Chem*. 2005;70:3584–3591.
15. (a) Brogan AP, Dickerson TJ, Janda KD. *Angew Chem Int Ed*. 2006;45:8100–8102;
(b) Hayashi Y. *Angew Chem Int Ed*. 2006;45:8103–8104. See also related references therein.
16. The absolute and relative configuration of the aldol products **5** and **6** was determined by comparison with that in ref 8l. See also: . (a) Gryko D, Lipiński R. *Eur J Org Chem*. 2006:3864–3876;
(b) Suri JT, Ramachary DB, Barbas III CF. *Org Lett*. 2005;7:1383–1385.
17. (a) Matuszek K, Chrobok A, Latos P, et al. *Catal Sci Technol*. 2016;6:8129–8137;
(b) Erfurt K, Wandzik I, Walczak K, Matuszek K, Chrobok A. *Green Chem*. 2014;16:3508–3514;
(c) Brown PA, Bonnert RV, Jenkins PR, Lawrence NJ, Selim MR. *J Chem Soc Perkin Trans*. 1991;1:1893–1900;
(d) Hall HK, Nogues Jr P, Rhoades JW, Sentman RC, Detar M. *J Org Chem*. 1982;47:1451–1455.
18. (a) Ralph MJ, Harrowven DC, Gaulier S, Ng S, Booker-Milburn KI. *Angew Chem Int Ed*. 2015;54:1527–1531;
(b) Ralph MJ, Harrowven DC, Gaulier S, et al. *J Org Chem*. 2007;72:9597–9603;
(c) Applequist DE, Werner ND. *J Org Chem*. 1963;28:48–54.
19. (a) Brown JM. *Angew Chem Int Ed*. 1987;26:190–203;
(b) Crabtree RH, Davis MW. *J Org Chem*. 1986;51:2655–2661;
(c) Brown JM, Hall SA. *J Organomet Chem*. 1985;285:333–341.
20. (a) Wang H, Yan L, Wu Y, Lu Y, Chen F. *Org Lett*. 2015;17:5452–5455;
(b) White JD, Shaw S. *Org Lett*. 2011;13:2488–2491;
(c) Luethi E, Nguyen KT, Bürzle M, et al. *J Med Chem*. 2010;53:7236–7250.
21. The absolute configuration of catalyst **12** was determined with x-ray structure of 4-bromobenzenesulfonamide derivative of **12**. The data has been deposited with the Cambridge crystallographic data centre, and can be obtained free of charge via www.ccdc.cam.ac.uk/structures. CCDC 1838928 contains the supplementary crystallographic data for this paper.

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