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Chemoenzymatic synthesis of enantiopure geminally dimethylated cyclopropane-based C_2- and pseudo-C_2-symmetric diamines

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Abstract—Enantiopure (−)-(1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxamide **2** and (+)-(1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid **3** were easily obtained from a multigram scale biotransformation of racemic amide or nitrile in the presence of *Rhodococcus erythropolis* AJ270 whole cell catalyst under very mild conditions. Coupled with efficient and convenient chemical manipulations, comprising mainly of the Curtius rearrangement, oxidation, and reduction reactions, chiral C_2-symmetric (1*S*,2*S*)-3,3-dimethylcyclopropane-1,2-diamine **6** and ((1*R*,3*R*)-3-(aminomethyl)-2,2-dimethylcyclopropyl)methanamine **8** and pseudo-C_2-symmetric (1*S*,3*S*)-3-(aminomethyl)-2,2-dimethylcyclopropanamine **11** were prepared. These were also transformed into the corresponding chiral salen derivatives **12**, **13**, and **14**, respectively, in almost quantitative yields.

1. Introduction

Chiral vicinal diamines and their derivatives have been extensively used as ligands and catalysts in asymmetric synthesis.[1] For example, 1,2-diaminocyclohexane-derived salen-metal complexes[2] and thioureas[3] are powerful Lewis acid catalysts and organocatalysts, respectively, which catalyze a variety of organic reactions. While the effort in developing new structurally diverse chiral diamine catalysts and, particularly, in modifying chiral 1,2-diaminocyclohexane-based catalysts is still increasing,[1,4] it is surprising that the design of diamine catalysis based on a chiral cyclopropane structure has been overlooked until now. As the smallest ring, cyclopropane provides a structural scaffold of unique bond angles and well-defined configurations of the substituents. Indeed, several cyclopropane-derived chiral phosphorus and phosphorus/sulfur ligands have been reported,[5] and one phosphorus/sulfur ligand has shown an excellent catalytic activity with a very good enantioselectivity in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate. Very recently, a (−)-*trans*-1,2-diaminocyclopropane-derived salen-Cu complex has been prepared,[6] and no asymmetric induction was observed, however, in the catalytic benzylation of an alanine enolate. These reports[5,6] have prompted us to disclose our synthetic study of enantiomerically pure geminally dimethylated cyclopropane-based C_2- and pseudo-C_2-symmetric diamines.[7]

2. Results and discussion

We have previously found that, when catalyzed by *Rhodococcus erythropolis* AJ270,[8,9] a robust and a highly enantioselective nitrile hydratase/amidase containing whole cell catalyst, racemic chrysanthemic nitriles, and amides undergo effective hydrolysis to yield the corresponding optically active chrysanthemic acids and amides.[10] Having considered the polyfunctionality of chrysanthemic acid and amide structures, we envisioned that these enantiomerically pure cyclopropane derivatives are ideal chiral pool materials for the construction of chiral C_2- and pseudo-C_2-symmetric diamines.

To start our synthesis, we first investigated the preparative biotransformations of nitrile and amide. After being incubated with *R. erythropolis* AJ270 at room temperature, racemic *trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarbonitrile **1** (10 mM) was converted into (1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxamide **2** and (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid **3** in a high yield

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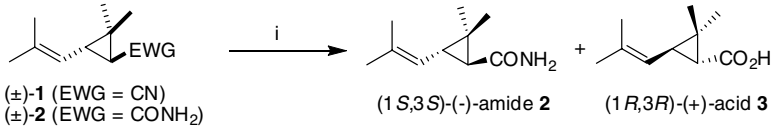
with an excellent enantioselectivity (Scheme 1, entry 1 in Table 1). However, the conversion became sluggish and incomplete when the substrate concentration was doubled (Table 1, entries 1–3). When racemic amide (±)-**2** was employed as the substrate, the biocatalytic kinetic resolution proceeded effectively to afford the desired enantiomerically pure amide and acid products, even with the substrate concentration up to 40 mM (Table 1, entries 4–6). Therefore, a multigram-scale biocatalytic preparation of pure (1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxamide **2** and (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid **3** was readily achieved in our laboratory via the biotransformation of racemic amide (±)-**2** in a parallel fashion.

To synthesize chiral C_2-symmetric diamines **6** and **8**, C_2-symmetric 3,3-dimethylcyclopropane-1,2-dicarboxylic acid (1*R*,3*R*)-(−)-**5** was chosen as a key intermediate. The synthesis of (1*R*,3*R*)-(−)-**5** was then attempted from the direct oxidation reaction of (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid **3**. Interestingly, upon treatment of **3** with $KMnO_4$ under alkaline conditions at an ambient temperature, α-hydroxy ketone **4** was obtained as the sole oxidation product in a high yield. Further oxidation of **4** using $NaIO_4$ afforded diacid **5** in a good yield. Following the Curtius rearrangement procedure, diacid **5** was transformed into enantiomerically pure C_2-symmetric (1*S*,2*S*)-3,3-dimethylcyclopropane-1,2-diamine dihydrochloride **6** in a yield of 68%. The synthesis of ((1*R*,3*R*)-3-(aminomethyl)-2,2-dimethylcyclopropyl)methanamine **8** was also very straightforward and efficient. Thus, the reaction of **5** with $ClCO_2Et$ in the presence of Et_3N followed by treatment with ammonia produced a good yield of dicarboxamide intermediate **7** that underwent reduction with $LiAlH_4$ to furnish ((1*R*,3*R*)-3-(aminomethyl)-2,2-dimethylcyclopropyl)methanamine dihydrochloride **8** in a 70% yield (Scheme 2).

Taking the advantage of nitrile and amide biotransformations, the resulting biotransformation product (1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxamide **2** was directly applied in the synthesis of pseudo-C_2-

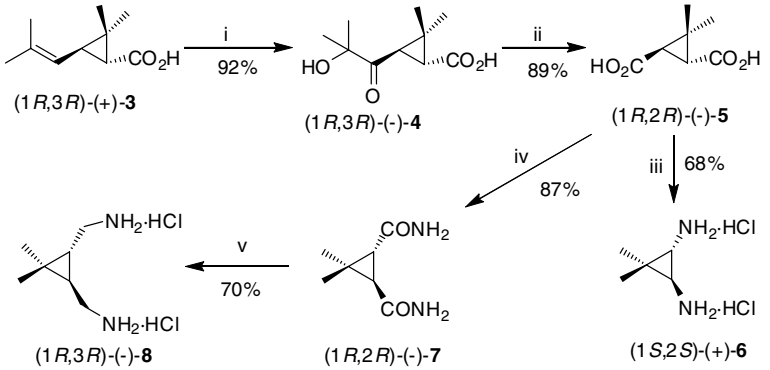


Scheme 1. Preparative biotransformations of nitrile and amide. Reagents and conditions: (i) *R. erythropolis* AJ270, phosphate buffer (0.1 M, pH 7.0), 30 °C.

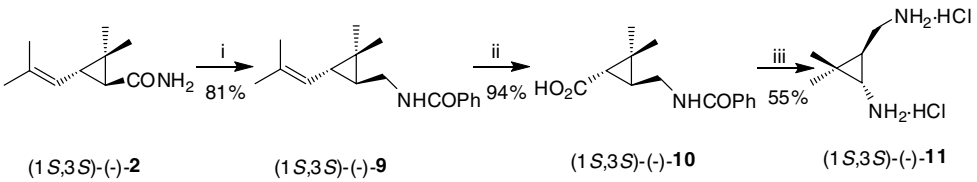
Table 1. Preparative biotransformations of (±)-**1** and (±)-**2**

Entry	Substrate	Concentration (mM)	Time[a] (h)	(1*S*,3*S*)-**2** Yield[b] (%)	(1*S*,3*S*)-**2** ee[c] (%)	(1*R*,3*R*)-**3** Yield[b] (%)	(1*R*,3*R*)-**3** ee[c] (%)
1	(±)-**1**	10	82	48	>99	49	>99
2	(±)-**1**	20	58	68	37	27	>99
3	(±)-**1**	20	95	64	45	32	>99
4	(±)-**2**	10	73	48	>99	51	97
5	(±)-**2**	20	90	46	>99	50	99
6	(±)-**2**	40	162	48	>99	49	>99

[a] Racemic nitrile or amide was incubated with *R. erythropolis* AJ270 (2 g wet weight) in phosphate buffer (0.1 M, pH 7.0, 50 ml).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.



Scheme 2. Synthesis of C_2-symmetric diamines **6** and **8**. Reagents and conditions: (i) $KMnO_4$, aq KOH (10%), rt, 1 h. (ii) $NaIO_4$, rt, 1 h. (iii) (a) $ClCO_2Et$, Et_3N in acetone, 0 °C, 0.5 h; (b) NaN_3, 1 h; (c) toluene, reflux 6 h; (d) HCl, reflux 2.5 h. (iv) (a) $ClCO_2Et$, Et_3N in acetone, 0 °C, 0.5 h; (b) concd $NH_3{\cdot}H_2O$, 0 °C–rt, 2 h. (v) (a) $LiAlH_4$, THF, under Ar, reflux 12 h; (b) 2 N hydrochloric acid.



Scheme 3. Synthesis of pseudo-C_2-symmetric diamine **11**. Reagents and conditions: (i) (a) $LiAlH_4$, THF, under Ar, reflux 4 h; (b) PhCOCl, Et_3N, 0 °C, 2 h. (ii) (a) O_3, −5 °C; (b) 30% aq H_2O_2, CH_3CO_2H, 0 °C, 15 min, rt, 1.5 h. (iii) (a) $ClCO_2Et$, Et_3N in acetone, 0 °C, 0.5 h; (b) NaN_3, 1 h; (c) toluene, reflux 3 h; (d) HCl, reflux 8 h.

symmetric diamine **11**. As depicted in Scheme 3, the reduction of cyclopropanecarboxamide **2** followed by the protection of the amino group using benzoyl chloride yielded amide intermediate **9** in a good yield. Ozonolysis of olefin **9** followed by further oxidation with aqueous hydrogen peroxide solution, led to the formation of amino acid derivative **10** in an almost quantitative yield. The synthesis of pseudo-C_2-symmetric diamine compound, (1*S*,3*S*)-3-(aminomethyl)-2,2-dimethylcyclopropanamine dihydrochloride **11** was accomplished by performing the Curtius rearrangement of **10** followed by a deprotection reaction.

Chiral C_2-symmetric diamines **6** and **8** and pseudo-C_2-symmetric diamine **11**, which are stable in the form of a dihydrochloride salt, were very efficiently and conveniently converted into the corresponding salen ligands **12**–**14** (Fig. 1) in almost quantitative yields when they reacted with two equivalents of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde.

3. Conclusion

In conclusion, we have developed a chemoenzymatic synthesis of chiral geminally dimethylated cyclopropane-based C_2- and pseudo-C_2-symmetric diamines **6**, **8**, and **11**. The combination of a highly enantioselective biotransformation and the straightforward and convenient chemical manipulations using inexpensive reagents under mild conditions render these syntheses very practical. Since the (1*S*,3*S*)-**3** and (1*R*,3*R*)-**2** enantiomers of starting cyclopropanecarboxylic acid and amide are readily available from the chemical interconversion of (1*S*,3*S*)-**2** and (1*R*,3*R*)-**3**, respectively,[10] the chemoenzymatic methods developed in the current study should also be applicable to the synthesis of all antipodes of chiral diamines **6**, **8**, and **11** if (1*S*,3*S*)-**3** and (1*R*,3*R*)-**2** enantiomers are employed. The C_2- and pseudo-C_2-symmetric diamines and their salen derivatives synthesized provide a set of novel and unique bidentate ligands with defined structures, and their applications in asymmetric organic synthesis and chiral recognition warrant extensive investigation.

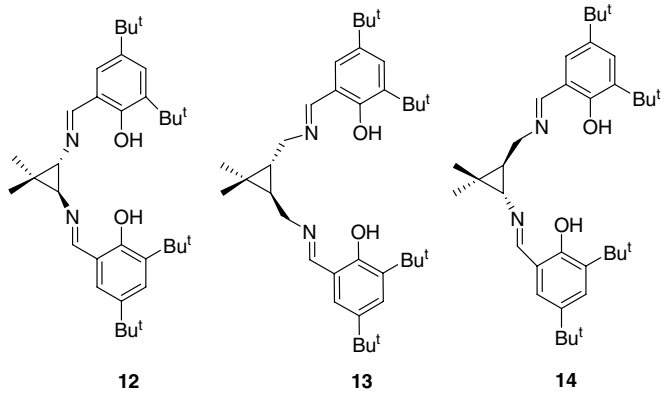


Figure 1. Salen ligands derived from chiral geminally dimethylated cyclopropane-based C_2- and pseudo-C_2-symmetric diamines.

4. Experimental

4.1. A multigram-scale preparation of enantiopure amide (−)-(1*S*,3*S*)-2 and acid (+)-(1*R*,3*R*)-3

To each of 14 Erlenmeyer flasks (150 ml) in parallel was added *R. erythropolis* AJ270 cells (2 g wet weight), which can be readily obtained from fermentation,[8,9q] and potassium phosphate buffer (0.1 M, pH 7.25, 50 ml), and the resting cells were activated at 30 °C for 0.5 h with orbital shaking. Racemic amide **2** (4.683 g, 28 mmol) as a fine powder was added evenly in one portion to each of the flasks and the mixture (concentration of racemic amide was 40 mM) was incubated at 30 °C using an orbital shaker (200 rpm). The reaction was quenched after 162 h by removing the biomass through a Celite pad via filtration. The combined filtrate was basified to pH 12 with aqueous NaOH (2 M). Extraction with ethyl acetate gave, after drying and concentration, (−)-(1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxamide **2**[10] as a white solid (2.24 g, 48%, ee >99%). The aqueous solution was then acidified to pH 2 using aqueous HCl (2 M) and extracted with ethyl acetate. (+)-(1*R*,3*R*)-2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid **3**[10] (2.30 g, 49%, ee >99%) was obtained as a colorless oil after removal of the solvent.

4.2. Synthesis of chiral C_2-symmetric diamine product 6 and its salen derivative 12

4.2.1. Oxidation of (1*R*,3*R*)-(+)-3. To a mixture of (+)-(1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic acid **3** (1.008 g, 6 mmol, ee >99%, HPLC) with aqueous KOH solution (10%, 8 ml) and water (50 ml) was added $KMnO_4$ (3.5 g). The mixture was stirred at room temperature for 1 h. After filtration through a Celite pad, the filtrate was first treated with a small amount of dilute $NaHSO_3$ solution until the purple color had vanished.

The aqueous solution was then acidified to pH 1 using hydrochloric acid (2 M) and saturated with NaCl. After extraction with ethyl acetate, drying over anhydrous $MgSO_4$ and removal of organic solvent, α-hydroxy ketone product **4** (1.10 g, yield 92%) was obtained as a colorless solid: mp 144–145 °C; $[\alpha]_D^{25} = -10$ (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (br s, 1H, COOH), 2.72 (d, 1H, $J = 5.7$, CH), 2.50 (d, 1H, $J = 5.7$, CH), 1.48 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.19 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 175.9, 36.7, 34.5, 33.8, 26.5, 25.4, 20.3, 19.8; IR (KBr) 3423 (OH), 2800–3450 (br s, COOH), 1729, 1690 cm^{-1}; MS (FAB, NBA) *m/z* 199 (M^+-1). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.84; H, 8.18.

4.2.2. Preparation of 5. A mixture of **4** (1.10 g, 5.5 mmol) with $NaIO_4$ (2.57 g) in water (30 ml) was stirred at room temperature for 1 h. The resulting mixture was acidified to pH 1 and saturated with NaCl. Extraction with ethyl acetate, dried over anhydrous $MgSO_4$, and removal of organic solvent led to the isolation of crude diacid product **5** (790 mg). Recrystallization from a mixture of ethyl acetate and petroleum ether gave pure (−)-(1*R*,2*R*)-3,3-dimethylcyclopropane-1,2-dicarboxylic acid **5** (770 mg, 89%) as colorless crystals: mp 200–202 °C; $[\alpha]_D^{25} = -38.7$ (*c* 1.5, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 2.15 (s, 2H, 2CH), 1.18 (s, 6H, $2CH_3$); ^{13}C NMR (75 MHz, D_2O) δ 174.3 (2C), 33.5 (2C), 30.5, 19.6 (2C); IR (KBr) 2400–3600 (br s, COOH), 1688, 1621, 1421; MS (FAB, NBA) *m/z* 157 (M^+-1). Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.17; H, 6.46.

4.2.3. Preparation of (+)-(1*S*,2*S*)-3,3-dimethylcyclopropane-1,2-diamine dihydrochloride 6. To an ice water bath cooled solution of (−)-(1*R*,2*R*)-3,3-**5** (790 mg, 5 mmol), Et_3N (1.6 ml) in acetone (10 ml) was added $ClCO_2Et$ (1.23 ml) very slowly. A white solid precipitated immediately from the solution when $ClCO_2Et$ was added. After 0.5 h, NaN_3 (985 mg, 15.2 mmol) solution in water (4 ml) was added and the mixture was stirred for 1 h. Ice water (10 ml) was added and the mixture extracted with ether and dried with anhydrous $MgSO_4$. The residue, after removal of organic solvent, was refluxed in toluene (6 ml) for 6 h. After cooling to room temperature, the solvent was removed and the residue was refluxed again for 2.5 h with concentrated hydrochloric acid (10 ml) and water (15 ml) to give a brown solution. Most of the water was removed under reduced pressure and the resulting residue was subjected to chromatography using an active carbon column with water as an eluent to give a colorless solid product. Recrystallization in a mixture of ethyl acetate and methanol afforded pure (+)-(1*S*,2*S*)-3,3-dimethylcyclopropane-1,2-diamine dihydrochloride **6** (590 mg, 68%): $[\alpha]_D^{25} = +5.5$ (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 2.81 (s, 2H, 2CH), 1.24 (s, 6H, $2CH_3$); ^{13}C NMR (75 MHz, D_2O) δ 35.75 (2C), 21.0 (2C), 17.27 (2C); IR (KBr) 3445 ($-NH_3^+$), 1637, 1400, 1385 cm^{-1}; MS (FAB, GLY) *m/z* 193 ($M^+-2HCl+92$), 101 (M^+-2HCl).

4.2.4. Preparation of chiral C_2-symmetric salen ligand 12. A mixture of **6** (34.6 mg, 0.2 mmol), K_2CO_3 (56 mg), and water (1.5 ml) was stirred for 10 min. Ethanol (8 ml) was added and the mixture was heated at reflux. A solution of 2-hydroxy-3,5-di-*tert*-butylbenzaldehyde (93.8 mg, 0.4 mmol) in ethanol (4 ml) was then added dropwise to give a bright yellow solution. After another 2 h, the mixture was cooled to below 5 °C and ice water (10 ml) was added. The precipitate was filtered, washed with ethanol (95%), and dried to give pure chiral C_2-symmetric salen ligand **12** (92%) as a pale yellow solid: mp 248–250 °C; $[\alpha]_D^{25} = +560$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 13.0 (s, 2H, 2OH), 8.48 (s, 2H, 2CH=N), 7.37 (s, 2H, Ar–H), 7.08 (s, 2H, Ar–H), 3.18 (s, 2H, 2CH), 1.57 (s, 3H, CH_3), 1.45 (s, 18H, $6CH_3$), 1.38 (s, 3H, CH_3), 1.31 (s, 18H, $6CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (2C), 157.3 (2C), 140.3 (2C), 136.5 (2C), 126.6 (2C), 125.6 (2C), 118.3 (2C), 61.5 (2C), 35.0 (2C), 34.1 (2C), 31.5 (6C), 29.4 (6C), 29.3 (6C), 20.6 (2C); IR (KBr) 1617, 1465, 1247; MS (EI) *m/z* 532 (M^+, 4%), 517 (2), 299 (5), 289 (22), 288 (100), 270 (15), 244 (50), 219 (16), 216 (28); MS (FAB, NBA) *m/z* 533 $(M+1)^+$. Anal. Calcd for $C_{35}H_{52}N_2O_2$: C, 78.90; H, 9.84; N, 5.26. Found: C, 78.93; H, 9.87; N, 5.23.

4.3. Synthesis of chiral C_2-symmetric diamine product 8 and its salen derivative 13

4.3.1. Preparation of (−)-(1*R*,2*R*)-3,3-dimethylcyclopropane-1,2-dicarboxamide 7. To a mixture of diacid (−)-(1*R*,2*R*)-**5** (400 mg, 2.53 mmol), triethylamine (820 μl) in acetone (20 ml), cooled with an ice water bath, was added slowly $ClCO_2Et$ (620 μl) and the mixture was stirred at 0 °C for 0.5 h. The precipitate was filtered off and the filtrate concentrated. The residue was dissolved in a small amount of ether and then was added slowly, while stirring, to a cold ammonia solution. After another 2 h reaction, the mixture was concentrated to give white solids. Crystallization in acetone by adding ether afforded pure (−)-(1*R*,2*R*)-3,3-dimethylcyclopropane-1,2-dicarboxamide **7** (342 mg, 87%): mp 249–251 °C; $[\alpha]_D^{25} = -12$ (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 2.09 (s, 2H, 2CH), 1.28 (s, 6H, $2CH_3$); ^{13}C NMR (75 MHz, D_2O) δ 177.5 (2C), 35.7 (2C), 30.9, 22.2 (2C); IR (KBr) 3404, 3361, 3199, 1686, 1653, 1627, 1413 cm^{-1}; MS (FAB, NBA) *m/z* 157 (M^++1). Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 54.11; H, 7.91; N, 17.78.

4.3.2. Preparation of (−)-((1*R*,3*R*)-3-(aminomethyl)-2,2-dimethylcyclopropyl)methanamine dihydrochloride 8. To a solution of diamide **7** (230 mg, 1.47 mmol) in anhydrous THF (40 ml) was added $LiAlH_4$ (300 mg) and the resulting mixture was refluxed for 12 h under an argon atmosphere. The reaction was quenched by adding ice after cooling down to room temperature. The mixture was then filtered through a Celite pad, washed with THF, and the filtrate was concentrated. The residue was mixed with hydrochloric acid (2 N, 15 ml) to give, after removal of the solvent, a brown solid. The crude product was dissolved in a small amount of methanol, and acetone was slowly added to precipitate pure (−)-((1*R*,3*R*)-3-(aminomethyl)-2,2-dimethylcyclopropyl)methanamine dihydrochloride **8** as a pale gray solid (206 mg, 70%): $[\alpha]_D^{25} = -5$ (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 2.98 (m, 4H, $2CH_2$), 1.03 (s,

6H, $2CH_3$), 0.80 (m, 2H, 2CH); ^{13}C NMR (75 MHz, D_2O) δ 39.41 (2C), 26.15 (2C), 21.25, 19.85 (2C); IR (KBr) 3430 ($-NH_3^+$), 1636, 1401, 1385 cm^{-1}. MS (FAB, GLY) m/z 129 (M^+-2HCl).

4.3.3. Preparation of C_2-symmetric salen ligand 13. Following the procedure for the synthesis of salen **12**, diamine **8** (202 mg, 0.1 mmol) was converted into chiral C_2-symmetric salen ligand **13** (90%) as pale yellow solids: mp 64–66 °C; $[\alpha]_D^{25} = -40$ (c 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 14.04 (s, 2H, 2OH), 8.39 (s, 2H, 2CH=N), 7.41 (d, 2H, $J = 2.25$, Ar–H), 7.11 (d, 2H, $J = 2.2$, Ar–H), 3.77 (dd, 2H, $J = 5.18$, 13.4, 2NCH*H*), 3.57 (dd, 2H, $J = 7.4$, 13.2, 2NC*H*H), 1.48 (s, 18H, $6CH_3$), 1.34 (s, 3H, CH_3), 1.34 (s, 18H, $6CH_3$), 1.23 (s, 6H, $2CH_3$), 0.88 (dd, 2H, $J = 5.58$, 5.59, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (2C), 158.2 (2C), 139.8 (2C), 136.6 (2C), 126.7 (2C), 125.7 (2C), 117.9 (2C), 59.1 (2C), 35.0 (2C), 34.1 (2C), 31.5 (6C), 29.9 (6C), 29.4 (6C), 21.7 (2C), 20.5 (1C); IR (KBr) 3437, 1632, 1597, 1470, 1441; MS (EI) m/z 561 (M^++1, 24), 560 (M^+, 54%), 545 (10), 327 (11), 315 (23), 314 (100), 294 (15), 293 (19), 266 (15), 265 (28), 248 (19), 247 (95), 246 (25), 244 (10), 232 (37), 219 (21), 218 (31), 190 (51), 57 (97). Anal. Calcd for $C_{37}H_{56}N_2O_2$: C, 79.24; H, 10.06; N, 4.99. Found: C, 79.16; H, 10.11; N, 4.95.

4.4. Synthesis of chiral pseudo-C_2-symmetric diamine product 11 and its salen derivative 14

4.4.1. Preparation of (+)-*N*-(((1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)methyl)benzamide 9. To a solution of (−)-(1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxamide **2** (334 mg, 2 mmol, ee >99%) in anhydrous THF (10 ml) was added slowly $LiAlH_4$ (200 mg), and the resulting mixture gently refluxed for 4 h under argon. Ice was added to quench the reaction after cooling to room temperature and the mixture was filtered through a basic aluminum pad. The filtrate was mixed with cold water (25 ml) and extracted with ether. The combined organic phase was dried with anhydrous $MgSO_4$ and then concentrated to a volume of about 10 ml. After cooling with an ice water bath, the resulting solution was consecutively mixed with triethylamine (350 μl) and benzoyl chloride (290 μl) slowly while stirring. The reaction was stopped after 2 h by adding ice water, and the mixture was basified with 2 M NaOH solution. Extraction with ether, drying over anhydrous $MgSO_4$, and concentration under vacuum gave an oily residue. Chromatography on a silica gel column yielded pure (+)-*N*-(((1*S*,3*S*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropyl)methyl)benzamide **9** (415 mg, 81%) as a colorless oil: $[\alpha]_D^{25} = +16$ (c 2.5, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, $J = 7.5$, Ar–H), 7.39–7.48 (m, 3H, Ar–H), 6.34 (br s, 1H, NH), 4.86 (d, 1H, $J = 7.9$, =CH), 3.45–3.56 (m, 2H, CH_2N), 1.70 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.16 (d, 1H, $J = 9.9$, CH), 1.05 (s, 3H, CH_3), 0.81 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 134.8, 133.3, 131.3, 128.5, 126.9, 123.3, 40.8, 32.0, 29.2, 25.7, 22.6, 22.2, 21.6, 18.3; IR (KBr) 3310, 3064, 1635, 1603, 1578, 1541, 1295, 694; MS (EI) m/z 257 (M^+, 5%), 214 (2), 134 (13), 124 (10), 123 (100), 121 (17), 106 (6), 105 (85), 93 (11), 91 (11), 81 (38), 77 (45). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.54; H, 9.03; N, 5.52.

4.4.2. Conversion of 9 into (+)-(1*S*,3*S*)-3-((benzamido)methyl)-2,2-dimethylcyclopropanecarboxylic acid 10. To a solution of **9** (80 mg, 0.31 mmol) in ethyl acetate (30 ml) was bubbled into O_3 at −5 °C. After consumption of the starting material (about 20 min), which was monitored by TLC, oxygen was bubbled into the solution to remove O_3 in the system. Acetic acid (200 μl) and aqueous hydrogen peroxide (30%, 200 μl) were added, and the mixture was stirred at 0 °C for 15 min and then at room temperature for 1.5 h. After reaction, the mixture was poured into ice water (20 ml), extracted with ethyl acetate, and dried over anhydrous $MgSO_4$. Removal of solvent under vacuum gave the crude product as a glass solid. Precipitation from acetone solution by adding ether afforded pure (+)-(1*S*,3*S*)-3-((benzamido)methyl)-2,2-dimethylcyclopropanecarboxylic acid **10** (72 mg, 94%) as a white solid: mp 162–164 °C; $[\alpha]_D^{25} = +46$ (c 1.0, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 8.56 (br s, 1H, COOH), 7.70 (d, 2H, $J = 7.47$, Ar–H), 7.32–7.43 (m, 3H, Ar–H), 4.82 (br s, 1H, NH), 3.32–3.40 (m, 2H, CH_2), 1.59 (m, 1H, CH), 1.38 (d, 1H, $J = 5.4$, CH), 1.18 (s, 3H, CH_3), 1.14 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 174.4, 168.7, 134.1, 131.1 (2C), 128.0 (2C), 126.7, 38.4, 32.0, 31.6, 26.8, 20.5, 19.5; IR (KBr) 3337 (NH), 2600–3600 (COOH), 1705, 1628, 1601, 1575, 1555, 1183; MS (EI) m/z 247 (M^+, 10%), 229 (5), 202 (7), 147 (16), 146 (10), 134 (13), 122 (8), 105 (100), 96 (3), 77 (46). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.14; H, 6.96; N, 5.62.

4.4.3. Preparation of (−)-(1*S*,3*S*)-3-(aminomethyl)-2,2-dimethylcyclopropanamine dihydrochloride 11. To a solution of **10** (124 mg, 0.5 mmol) in acetone (3 ml) were added consecutively triethylamine (0.16 ml) and $ClCO_2Et$ (0.125 ml) while stirring. After 0.5 h, a solution of NaN_3 (100 mg) in water (0.35 ml) was added and the mixture kept stirring at 0 °C for 1 h. The reaction was quenched by the addition of ice water (10 ml), extracted with ether, and dried with anhydrous $MgSO_4$. After removal of the solvent, the residue was refluxed in toluene (3 ml) for 3 h. The solvent was then removed again under vacuum and the residue refluxed for 8 h in a mixture of concentrated hydrochloric acid (2 ml) and water (3 ml). After cooling to room temperature, ice water (5 ml) was added and the resulting brown solution washed with ethyl acetate. The aqueous solution was concentrated to dryness under vacuum, and the solid residue dissolved in a small amount of methanol. The slow addition of acetone, while stirring, gave pure product (−)-(1*S*,3*S*)-3-(aminomethyl)-2,2-dimethylcyclopropanamine dihydrochloride **11** (51 mg, 55%) as a pale gray precipitate: $[\alpha]_D^{25} = -6$ (c 1.0, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 2.91 (d, 2H, $J = 7.5$, CH_2), 2.29 (d, 2H, $J = 4.0$, CH), 1.10 (m, 1H, CH), 1.06 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (75 MHz, D_2O) δ 37.79, 36.99, 25.48, 20.74, 18.87, 18.09; IR (KBr) 3430 (NH_3^+), 1636, 1401, 1385; MS (FAB, GLY) m/z 207 ($M^+-2HCl+92$), 115 (M^+-2HCl).

4.4.4. Preparation of chiral pseudo-C_2-symmetric salen ligand 14. Following the procedure for the synthesis of salen **12**, diamine **11** (20.1 mg, 0.1 mmol) was converted into chiral pseudo-C_2-symmetric salen ligand **14** (51.6 mg, 92%) as a pale yellow solid: mp 82–84 °C; $[\alpha]_D^{25} = +16$ (*c* 1.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 13.90 (s, 1H, OH), 13.14 (s, 1H, OH), 8.48 (s, 1H, CH=N), 8.40 (s, 1H, CH=N), 7.39 (d, 1H, $J = 1.68$, Ar–H), 7.34 (d, 1H, $J = 1.29$, Ar–H), 7.08 (s, 2H, Ar–H), 3.74 (dd, 2H, $J = 6.42$, 6.86, CH_2), 2.69 (d, 1H, $J = 3.3$, CH), 1.59 (s, 3H, CH_3), 1.46 (s, 9H, $3CH_3$), 1.44 (s, 9H, $3CH_3$), 1.34 (s, 3H, CH_3), 1.32 (d, 1H, $J = 7.7$, CH), 1.31 (s, 9H, $3CH_3$), 1.309 (s, 9H, $3CH_3$), 1.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.0, 158.2, 157.3, 140.1, 140.0, 136.6, 136.4, 126.9, 126.3, 125.8, 125.4, 118.3, 117.9, 57.8, 57.2, 35.1, 35.0, 34.7, 34.1, 31.5 (6C), 29.4 (6C), 25.2, 22.2, 20.4; IR (KBr) 3435, 1630, 1469, 1441, 1390, 1362, 1273, 1251; MS (EI) *m*/*z* 546 (M^+, 22%), 531 (3), 461 (3), 434 (5), 357 (4), 315 (24), 314 (100), 313 (72), 303 (14), 302 (64), 301 (22), 300 (81), 298 (21), 274 (11), 258 (16), 244 (32), 234 (52), 233 (36), 232 (10), 218 (21), 190 (16), 69 (14), 57 (95), 41 (20), 32 (50). Anal. Calcd for $C_{36}H_{54}N_2O_2$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.79; H, 9.96; N, 4.95.

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