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Diastereoselective reductive N-alkylation of (*R*,*R*)-*trans*-1,2-diaminocyclohexane with prochiral ketones using the Ti(O^{i}Pr)$_4$/NaBH$_4$ system

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ABSTRACT

A simple and convenient one-pot method for the reductive N-alkylation of (*R*,*R*)-*trans*-1,2-diaminocyclohexane by prochiral ketones using a Ti(O^{i}Pr)$_4$/NaBH$_4$ system to obtain the corresponding alkyl amine derivatives in 76–95% yields with good diastereoselectivity (dr = up to 23:1:1) is reported.

1. Introduction

Amines and their derivatives are highly versatile building blocks for various organic molecules and are essential precursors for the synthesis of a variety of biologically active compounds such as pharmaceuticals[1] and agrochemicals.[2] Over the last 10 years, numerous different methods have emerged for the preparation of amines such as hydrogenations,[3–6] hydrosilylations of imines or imine derivatives, and nucleophilic 1,2-additions of organometallic reagents to the C=N double bond.[7–10] The reductive alkylation of amines is a very convenient and important tool for chemists to target the synthesis of primary, secondary, and tertiary amines. *trans*-1,2-Diaminocyclohexane derivatives have been shown to be useful chiral reagents and ligands for catalysis with applications in asymmetric synthesis.[11] In continuation of our research efforts toward the synthesis of various chiral secondary amines[12,13] and macrocycles[14] containing the *trans*-1,2-diaminocyclohexyl moiety, we were looking for a convenient method of N-alkylation of this readily accessible[15] versatile C_2-symmetric chiral amine with prochiral ketones. Recently, there have been reports on the reductive mono-N-alkylation of primary amines with ketones using the Ti(O^{i}Pr)$_4$ and NaBH$_4$ reagent system.[16–20] Accordingly, we have examined the use of this reagent system for the synthesis of chiral secondary diamines **4a**–**4i** containing the *trans*-1,2-diaminocyclohexane moiety. Herein we report the results of this investigation (Scheme 1).

2. Results and discussion

Initially, the titanium(IV)-reductive N-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **1** with acetophenone was carried out using the Ti(O^{i}Pr)$_4$/NaBH$_4$ system[16] (Table 1, entry 1). Acetophenone was reacted with the chiral primary diamine **1** and Ti(O^{i}Pr)$_4$, followed by reaction with NaBH$_4$ under ambient conditions (Scheme 1). After completion of the reaction followed by extraction of the product, the crude N-alkylated diamine **4a** was obtained in an 8:1:1 diastereomeric ratio. The separation of the major diastereomer was achieved by flash column chromatography (silica gel, 230–400 mesh, hexane/EtOAc 97/3) in 61% chemical yield. The configuration of this major diastereomer was assigned as 1*R*,2*R*,1′*R*,1″*R* by comparison with the reported specific rotation value.[22] The absolute configuration at the newly formed stereogenic centers of the major diastereomer **4a** was further confirmed by single-crystal X-ray analysis of its trifluoroacetamide derivative **5** (Fig. 1).[23] The absolute configuration at the newly formed stereogenic centers of the major diastereomer **4c** was confirmed to be (1*R*,2*R*,1′*R*,1″*R*) by single-crystal X-ray analysis (Fig. 2).[24]

We next examined the titanium(IV)-reductive N-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **1** with various prochiral ketones under the experimental conditions. The results are summarized in Table 1. The expected three diastereomeric products were obtained in good to excellent chemical yields (76–95%), with diastereomeric ratios (dr) of 2:1:0 to 23:1:1. For example, the reaction of chiral amine **1** with α-tetralone gave the corresponding N-alkylated product **4d** in a 13:1:1 diastereomeric ratio (Table 1, entry 4). One major diastereomer and two minor diastereomers of the alkylated product **4d** were separated by column chromatography. The best diastereoselectivity was achieved with 2-acetylthiophene (Table 1, entry 5, dr 23:1:1). The separation of the major diastereomer was achieved via column chromatography in 84% yield. Also, in the case of *p*-nitro and *p*-chloroacetophenones, the corresponding N-alkylated products were obtained in 4:1:1 and 7:1:1 dr, respectively (Table 1, entries 2 and 3). In these cases, the major diastereomers were isolated in pure form by column chromatography. In the case of the reaction with ketones such as 2-acetylnaphthalene, *p*-methyl acetophenone, and *p*-methoxyacetophenone, only the major diastereomers were obtained in pure form for identification by column chromatography besides the mixture of diastereomers. In the reaction with 2-acetylpyridine

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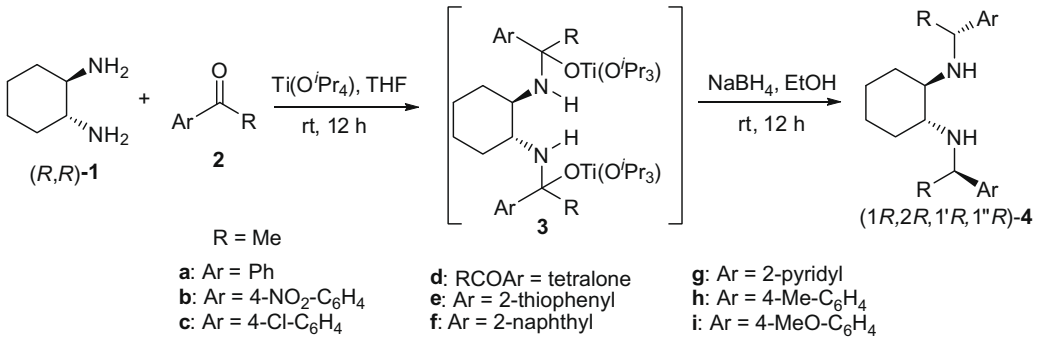


Scheme 1.

the major diastereomer could not be isolated in pure form by column chromatography and the diastereoselectivity for this reaction was poor (Table 1, entry 7). The configurations of the major diastereomers of the *N*-alkylated products **4b, 4d**, and **4e** were assigned as 1*R*,2*R*,1′*R*,1″*R* by comparison with the specific rotation value of the known diamine **4a**.[22]

We have also studied the effect of solvents and temperature on the diastereoselective titanium(IV)-reductive N-alkylation reaction

Table 1
Ti(IV)-reductive N-alkylation reaction of (*R*,*R*)-*trans*-1,2-diaminocyclohexane **1** with various prochiral ketones[a]

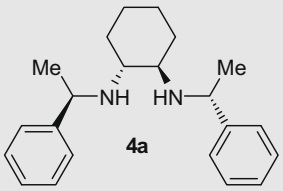
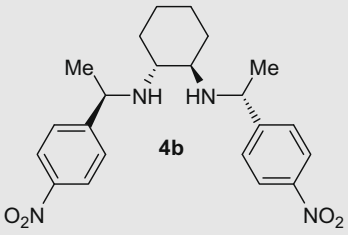
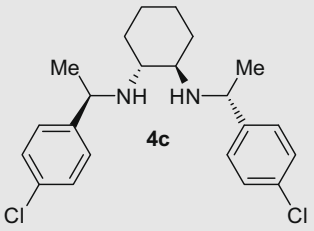
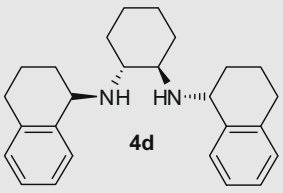
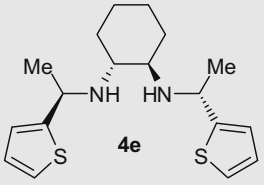
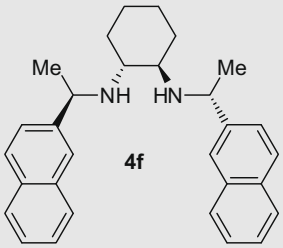
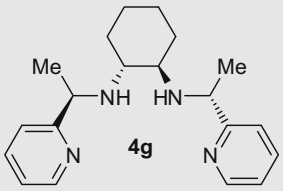
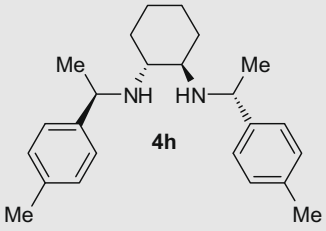
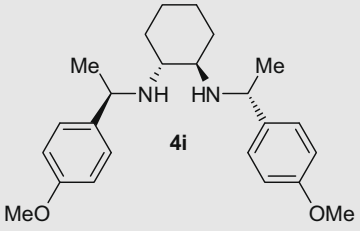
Entry	Starting ketone		Product amine[b]	Yield[c] (%)	dr[d]
	Ar	R			
1	Ph	Me	 **4a**	87	8:1:1
2	4-NO_2–C_6H_4	Me	 **4b**	80	4:1:1
3	4-Cl–C_6H_4	Me	 **4c**	89	7:1:1
4	α-Tetralone		 **4d**	94	13:1:1
5	2-Thiophenyl	Me	 **4e**	89	23:1:1

Table 1 (*continued*)

Entry	Starting ketone		Product amine[b]	Yield[c] (%)	dr[d]
	Ar	R			
6	2-Naphthyl	Me	 **4f**	76	7:1:1
7	2-Pyridyl	Me	 **4g**	90	2:1:0[e]
8	4-Me–C_6H_4	Me	 **4h**	95	4:1:0
9	4-MeO–C_6H_4	Me	 **4i**	79	8:1:1

[a] All reactions were carried out using 1.0 mmol of diamine **1**, 2.2 mmol of ketone **2**, and 4.0 mmol of $Ti(OiPr)_4$ in 5.0 mL of dry THF at room temperature for 12 h and for in situ reduction, 5.0 mmol of $NaBH_4$ in 5.0 mL of absolute EtOH was used at rt and stirred for 12 h.
[b] Products were identified using spectroscopic data (IR and ^1H and ^{13}C NMR).
[c] Yields are of the isolated product and correspond to the three diastereomers.
[d] Diastereomeric ratio (dr) was determined by ^1H NMR analysis of the crude product mixture. The major diastereomer was obtained in pure form by column chromatography of the crude diastereomeric products **4a**, **4b**, **4c**, **4d**, and **4e**.
[e] A mixture containing the major diastereomer (87.5%) and the minor diastereomer (12.5%) was isolated by column chromatography for spectroscopic analysis.

of (*R*,*R*)-*trans*-1,2-diaminocyclohexane with α-tetralone (Scheme 2). The results are given in Table 2. When the reaction was carried out in absolute MeOH at room temperature, the chemical yield and diastereoselectivity of the product diamine **4d** decreased (Table 2, entry 1). When absolute EtOH was used as the solvent, the chemical yield decreased from 94% to 73%. When CH_2Cl_2 was used, there was a significant decrease in the chemical yield from 94% to 41% (Table 2, entry 4). In THF, the reaction proceeded well and the product diamine **4d** was obtained in 94% chemical yield with 13:1:1 dr (Table 2, entry 3). When the reaction was carried out at −78 °C in THF, both the chemical yield and the diastereoselectivity decreased (Table 2, entry 5).

The transformations reported here may be rationalized by considering the steps and stereochemical models shown in Scheme 3 and Figure 3. The initially formed titanium(IV) complex **3** (Scheme 1 and 2) would undergo further elimination to give the chiral diimine intermediate **6** or **7**.[17] The (*E*,*E*) intermediate **6** is expected to be more favorable in which the aryl group is far away from the cyclohexyl moiety.

Since the *re* face is more hindered, the borohydride prefers to approach intermediate **6** through the *si* face (Fig. 3).

The formation of a titanium complex of the diimine intermediate **8** before reduction cannot be ruled out (Fig. 3). However, such an intermediate would also lead to the same stereochemical outcome (Fig. 3).

3. Conclusion

In conclusion, we have developed a one-pot method for the synthesis of chiral diamines **4a**–**4i** containing an (*R*,*R*)-*trans*-1,2-diaminocyclohexyl moiety via a Ti(IV) isopropoxide-mediated reductive N-alkylation reaction of chiral diamine **1** with prochiral ketones in good to excellent yields with moderate to good diastereoselectivities. The secondary chiral *N*-alkyl amines have been used as ligands for asymmetric deprotonation of epoxides.[21] Previously, the 1,2-diaminocyclohexane derivative **4a** containing a chiral *N*-alkyl group was prepared by the opening of an aziridine with (*S*)-α-

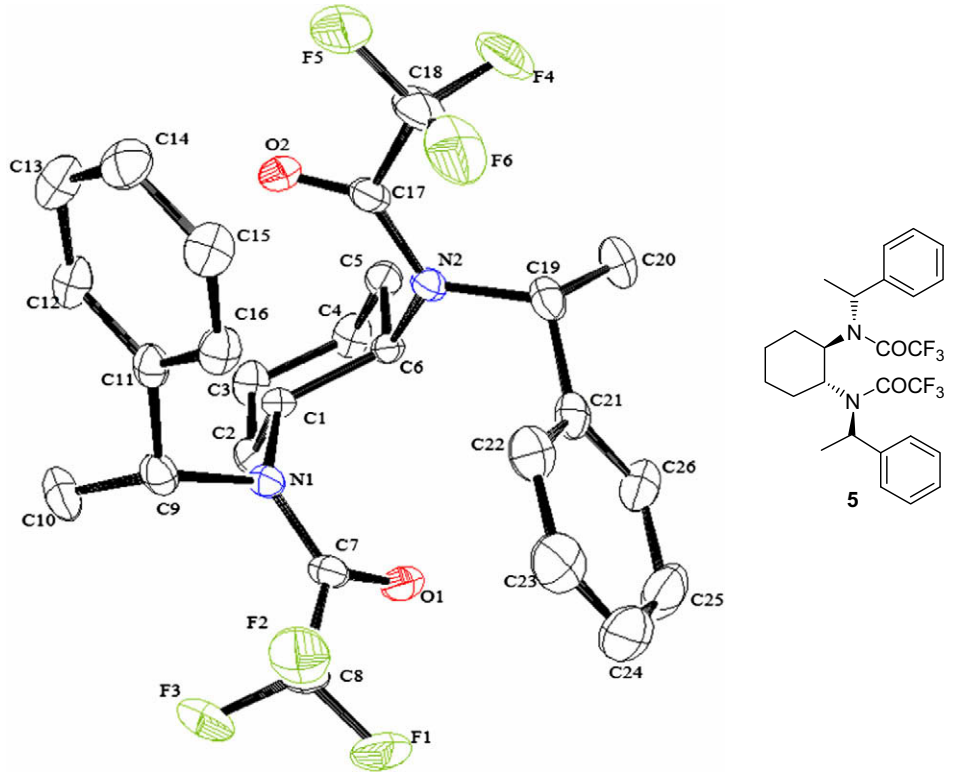


Figure 1. ORTEP diagram of compound **5**.

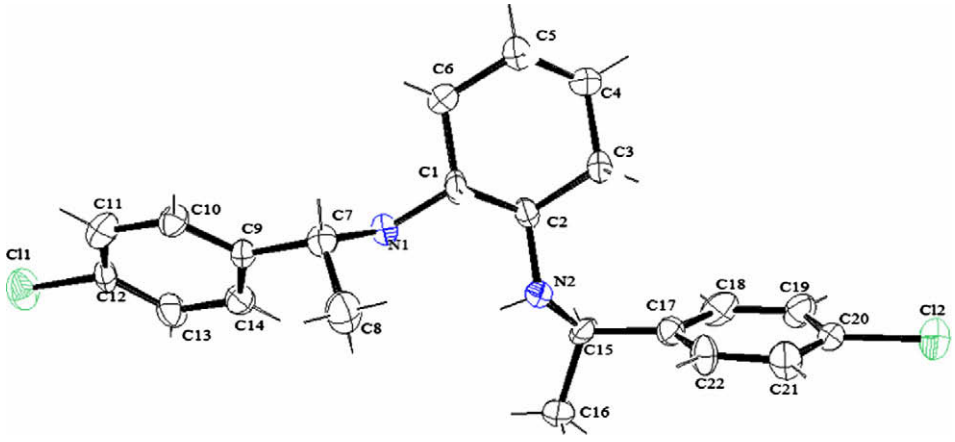
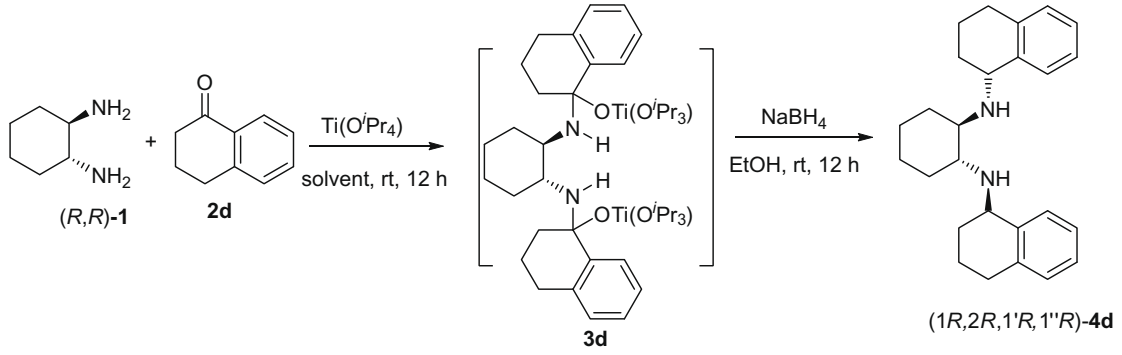


Figure 2. ORTEP diagram of the compound **4c**.



Scheme 2.

Table 2
Ti(IV)-reductive N-alkylation reaction of (*R,R*)-*trans*-1,2-diaminocyclohexane **1** with α-tetralone under various experimental conditions[a]

Entry	Solvent	Temperature	Product[b]	Yield[c] (%)	dr[d]
1	MeOH	rt	**4d**	64	12:1:1
2	EtOH	rt	**4d**	73	13:1:1
3	THF	rt	**4d**	94	13:1:1
4	CH_2Cl_2	rt	**4d**	41	12:1:1
5	THF	−78 °C	**4d**	66	12:1:1

[a] All reactions were carried out using 1.0 mmol of diamine **1**, 2.2 mmol of α-tetralone, and 4.0 mmol of $Ti(O^iPr)_4$ in 5.0 mL of dry solvent at rt for 12 h and for in situ reduction, 5.0 mmol of $NaBH_4$ in 5.0 mL of absolute EtOH was used at rt and stirred for 12 h.
[b] The products were identified using spectroscopic data (IR and ^1H and ^{13}C NMR).
[c] Yields are of the isolated product and correspond to the three diastereomers.
[d] Diastereomeric ratio (dr) was determined by ^1H NMR analysis of the crude product mixture.

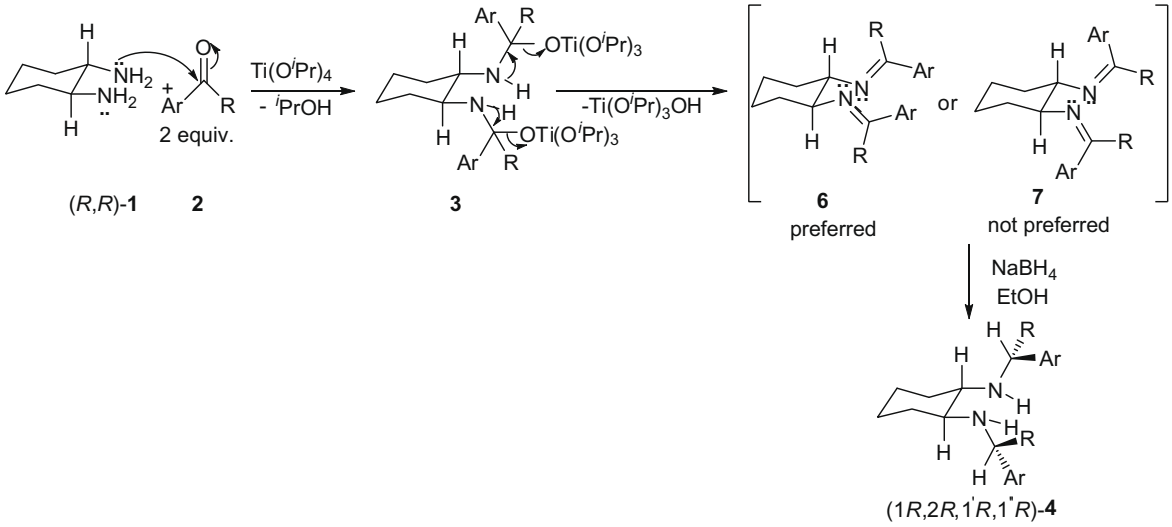
phenylethylamine catalyzed by lithium perchlorate in a three-step reaction sequence in moderate chemical yield and diastereoselectivity.[22] Easy access to the chiral amines **4a**–**4i** following the method described here should be helpful for further synthetic exploitations.

4. Experimental

Infrared spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometers with chloroform-*D* as a solvent and TMS as the reference ($\delta = 0$ ppm). Coupling constants *J* are given in hertz. Elemental analyses were carried out on a Flash EA 1112 series analyzer. Optical rotations were measured in an AUTOPOL-IV automatic polarimeter (readability ± 0.001). Chromatography was carried out using Acme's silica gel (100–200 mesh and 230–400 mesh). Solvents were dried using the standard procedures. The reagents were used as received after further distillation. The commercial *cis/trans* mixture of 1,2-diaminocyclohexane was resolved following a literature procedure.[15]

4.1. General procedure for the N-alkylation reaction of (*R,R*)-*trans*-1,2-diaminocyclohexane 1

A mixture of the (*R,R*)-*trans*-1,2-diaminocyclohexane **1** (0.12 mL, 1 mmol), ketone **2** (2.2 mmol), and $Ti(O^iPr)_4$ (1.2 mL, 4 mmol) in dry THF (5 mL) was stirred for 12 h at room temperature



Scheme 3.

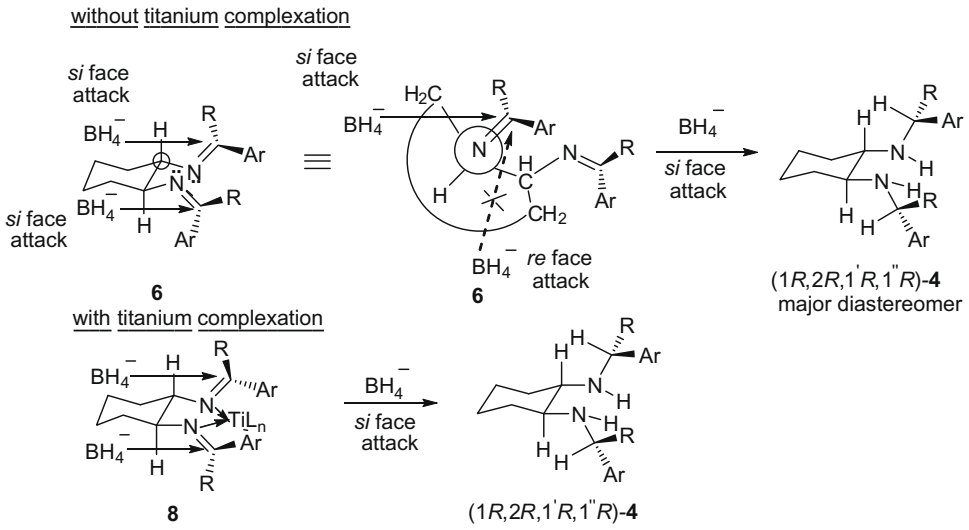


Figure 3. Stereochemical models.

under a N_2 atmosphere. Then $NaBH_4$ (190 mg, 5 mmol) and absolute EtOH (5 mL) were added at 0 °C under a N_2 atmosphere and the resulting mixture was stirred for an additional 12 h at room temperature. The reaction mixture was then quenched by adding water (1 mL). The solvent was evaporated and the residue was stirred with Et_2O (15 mL) for 15 min. The resulting inorganic precipitate was filtered and washed with Et_2O (10 mL). Next, H_2O (10 mL) was added to the filtrate and the organic layer was separated and the remaining aqueous layer was extracted with Et_2O (10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and the solvent was removed at reduced pressure. The crude product was purified by column chromatography on silica gel.

4.2. (1*R*,2*R*,1′*R*,1″*R*) -*N*,*N*′-Di(1-phenylethyl)-1,2-cyclohexanediamine 4a

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) was 8:1:1. The mixture containing three diastereomeric products was isolated in 87% yield by flash column chromatography. The major diastereomer was isolated in pure form by flash column chromatography (silica gel; 230–400 mesh, hexane/EtOAc 97/3) as a colorless liquid. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4a**: Yield: 61% (0.196 g); $[\alpha]_D^{25} = -40.4$ (*c* 1.1, $CHCl_3$), lit.[22] for (1*S*,2*S*,1′*S*,1″*S*)-isomer $[\alpha]_D^{25} = +40.5$ (*c* 1.0, $CHCl_3$); IR (neat) (cm^{-1}): 3308, 3061, 2926, 1602, 1493, 1448, 1122, 700; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.29–7.10 (m, 10H), 3.76 (q, *J* = 6.6 Hz, 2H), 2.23–2.17 (m, 2H), 1.77–1.74 (m, 4H), 1.51–1.48 (m, 2H), 1.26 (d, *J* = 6.6 Hz, 6H), 1.06–1.02 (m, 2H), 0.88–0.78 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 147.6, 128.3, 126.7, 126.6, 60.4, 56.1, 32.6, 25.0, 24.0.

4.3. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(4-nitrophenyl)ethyl]-1,2-cyclohexanediamine 4b

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 4:1:1. The mixture containing three diastereomeric products was isolated in 80% yield by column chromatography. The major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4b** was isolated in pure form by column chromatography (silica gel; 100–200 mesh, hexane/EtOAc, 90/10) as a colorless liquid and the two minor diastereomers were obtained together as a 1:1 mixture using hexane/EtOAc (75/15) as eluent in 19% yield. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4b**: Yield: 61% (0.25 g); $[\alpha]_D^{25} = -21.0$ (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}); 3306, 3930, 1601, 1516, 1344, 1109, 856; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 8.22 (d, *J* = 8.4 Hz, 4H), 7.48 (d, *J* = 8.4 Hz, 4H), 4.00 (q, *J* = 6.6 Hz , 2H), 2.17 (br s, 2H), 1.82–1.84 (m, 4H), 1.63–1.50 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 6H), 1.12–0.96 (m, 2H), 0.92–0.81 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 155.5, 146.8, 127.4, 123.6, 60.8, 55.9, 32.6, 24.8, 24.1; CHN calcd: C, 64.06; H, 6.8; N, 13.5; O, 15.6; found: C, 64.07; H, 6.9; N, 14.6; O, 14.5.

4.4. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(4-chlorophenyl)ethyl]-1,2-cyclohexanediamine 4c

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 7:1:1. The mixture containing three diastereomeric products was isolated in 89% yield by column chromatography. The major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4c** was isolated in pure form by column chromatography (silica gel; 100–200 mesh, hexane/EtOAc, 93/7) as a colorless liquid which solidifies slowly. The two minor diastereomers were obtained together as a 1:1 mixture using hexane/EtOAc (85/15) as an eluent in 20% yield; major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4c**: yield: 69% (0.269 g); Mp: 70–72 °C; $[\alpha]_D^{25} = -17.5$ (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3306, 2924, 1595, 1489, 1369, 1091, 829; ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.30–7.25 (m, 8H), 3.79 (q, *J* = 6.6 Hz, 2H), 2.26–2.22 (m, 2H), 1.79–1.75 (m, 2H), 1.56–1.54 (m, 2H), 1.46 (br s, 1H), 1.44 (br s, 1H), 1.28 (d, *J* = 6.6 Hz, 6H), 1.12–1.07 (m, 2H), 0.92–0.83 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 146.2, 132.2, 128.5, 128.4, 127.9, 126.8, 60.5, 55.6, 32.7, 24.9, 24.1.

4.5. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2-cyclohexanediamine 4d

^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 13:1:1. The mixture containing three diastereomeric products was isolated in 94% yield by column chromatography. The major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4d** was isolated in pure form by column chromatography (silica gel; 100–200 mesh, hexane/EtOAc, 90/10) as a colorless liquid and the two minor diastereomers were obtained together as a 1:1 mixture using hexane/EtOAc (85/15) as an eluent in 9% yield. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4d**: yield: 85% (0.32 g); $[\alpha]_D^{25} = -115.1$ (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3301, 3059, 2930, 2855, 1603, 1578, 1489, 739; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.34 (d, *J* = 6.6 Hz, 2H), 7.14–7.10 (m, 4H), 7.04 (d, *J* = 6.6 Hz, 2H), 3.77 (br s, 2H), 2.77–2.60 (m, 4H), 2.33–2.30 (m, 4H), 1.86–1.66 (m, 10H), 1.33–1.12 (m, 6H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 140.3, 137.4, 129.2, 128.8, 126.3, 125.7,59.2, 51.8, 32.6, 29.3, 28.0, 25.3, 18.5; CHN calcd: C, 83.4; H, 9.1; N, 7.5; found: C, 83.2; H, 9.1; N, 7.8.

4.6. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(2-thienyl)ethyl]-1,2-cyclohexanediamine 4e

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 23:1:1. The mixture containing three diastereomeric products was isolated in 89% yield by column chromatography. The major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4e** was isolated in pure form by column chromatography (silica gel; 100–200 mesh, hexane/EtOAc, 90/10) as a colorless liquid and the two minor diastereomers were obtained together as a 1:1 mixture using (75/15) hexane/EtOAc in 5% yield. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4e**: Yield: 84% (0.28 g); $[\alpha]_D^{25} = -27.9$ (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3299, 3073, 2969, 2926, 2855, 1510, 1449; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.18–7.16 (m, 2H), 6.95–6.93 (m, 4H), 4.20 (q, *J* = 6.4 Hz, 2H), 2.33–2.31 (m, 2H), 2.00 (br s, 2H), 1.92–1.89 (m, 2H), 1.65–1.62 (m, 2H), 1.43 (d, *J* = 6.4 Hz, 6H), 1.20–1.15 (m, 2H), 1.05–1.00 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 152.7, 126.4, 123.4, 122.5, 60.1, 51.5, 32.5, 25.0, 24.4; CHN calcd: C, 64.6; H, 7.8; N, 8.4; S, 19.2; found: C, 64.8; H, 7.9; N, 8.2; S, 19.1.

4.7. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(2-naphthyl)ethyl]-1,2-cyclohexanediamine 4f

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 7:1:1. The mixture of three diastereomeric products was isolated by column chromatography (silica gel; 100–200 mesh, hexane/EtOAc, 90/10). Yield: 76% (0.32 g). A small quantity (0.030 g) of the major isomer was obtained in pure form as a colorless liquid which solidified on standing. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4f**: Mp: 73–75 °C; $[\alpha]_D^{25} = -9.1$ (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}): 3306, 3053, 2926, 2854, 1601, 1508, 1367, 746; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.87 (d, *J* = 8.4 Hz, 6H), 7.83 (s, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.50 (m, 4H), 4.06 (q, *J* = 6.4 Hz, 2H), 2.43–2.37 (m, 2H), 1.89 (br s, 1H), 1.85 (br s, 1H), 1.62–1.53 (m, 4H), 1.48 (d, *J* = 6.4 Hz, 6H), 1.16–1.11 (m, 2H), 1.02–0.91 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 147.7, 136.2, 135.4, 130.7, 130.4, 130.3, 128.5, 128.0, 127.9, 127.5, 63.3, 59.1, 35.4, 27.6, 26.8; CHN calcd: C, 85.3; H, 8.1; N, 6.6; found: C, 85.1; H, 8.2; N, 6.7.

4.8. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(2-pyridyl)ethyl]-1,2-cyclohexanediamine 4g

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 2:1:0. The mixture of diastereomeric products was isolated by column chromatography (silica gel; 100–200 mesh, $CHCl_3$/MeOH, 98/2) as a brownish liquid **4g** which solidified on standing. Yield: 90% (0.29 g). Upon further purification a small quantity (0.050 g) of product containing major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4g** (87.5%) and the minor diastereomer (12.5%) was obtained. Mp: 88–90 °C (for the mixture of diastereomeric products, dr = 87.5:12.5:0): $[\alpha]_D^{25} = -10.3$ (*c* 1.0, $CHCl_3$) (for the mixture of diastereomeric products, dr = 87.5:12.5:0); IR (KBr, cm^{-1}): 3294, 2934, 1593,1375, 856, 787; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 8.40 (d, *J* = 4.6 Hz, 2H), 7.58–7.54(m, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.10–7.07 (m, 2H), 4.16 (q, *J* =6.8 Hz, 2H), 2.57–2.55 (m, 2H), 1.67–1.64 (m, 2H), 1.5 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.13–1.06 (m, 2H), 1.03–0.95 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 161.1, 148.8, 136.9, 122.6, 121.5, 59.1, 56.1, 30.2, 24.2, 21.1; CHN calcd: C, 74.0; H, 8.7; N, 17.2; found: C, 74.1; H, 8.7; N, 18.0.

4.9. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(4-methylphenyl)ethyl]-1,2-cyclohexanediamine 4h

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 4:1:0. A mixture of two diastereomeric products was isolated by column chromatography (silica gel; 100–200 mesh, hexane/EtOAc, 90/10) as a colorless liquid. Yield: 95% (0.33 g). A small quantity (0.065 g) of the major diastereomer was obtained in pure form. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4h**: $[\alpha]_D^{25} = -29.2$ (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}): 3306, 3015, 2961, 2924, 2857,1613, 1514, 1447, 1109, 818; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.24 (d, *J* = 8.0 Hz, 4H), 7.12 (d, *J* = 8.0 Hz, 4H), 3.8 (q, *J* = 6.4 Hz, 2H), 2.33 (s, 6H), 2.27–2.21 (m, 2H), 1.85 (br s, 1H), 1.81 (br s, 1H), 1.59–1.55 (m, 4H), 1.30 (d, *J* = 6.4 Hz, 6H), 1.14–1.08 (m, 2H), 0.95–0.83 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 144.6, 136.2, 129.0, 126.5, 60.4, 55.8, 32.7, 25.0, 24.0, 21.1; CHN calcd: C, 82.2; H, 9.8; N, 8.0; found: C, 82.3; H, 9.7; N, 7.6.

4.10. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di[1-(4-methoxyphenyl)ethyl]-1,2-cyclohexanediamine 4i

The ^{1}H NMR analysis of the crude product mixture revealed that the diastereomeric ratio (dr) is 8:1:1. A mixture of three diastereomeric products was isolated by column chromatography (silica gel; 100–200 mesh, $CHCl_3$/MeOH, 98/2) as a colorless liquid. Yield: 79% (0.30 g). A small quantity (0.035 g) of the major diastereomer was obtained in pure form. Major diastereomer (1*R*,2*R*,1′*R*,1″*R*)-**4i**: $[\alpha]_D^{25} = +10.7$ (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}): 3293, 2932, 2857, 1610, 1512, 1248, 1033, 833; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.27 (d, *J* = 8.8 Hz, 4H), 6.86 (d, *J* = 8.8 Hz, 4H), 3.8 (s, 8H), 2.28–2.20 (m, 2H), 1.97 (br s, 2H), 1.86–1.77(m, 2H), 1.59–1.54 (m, 2H), 1.31(d, *J* = 6.4 Hz, 6H), 1.16–1.09 (m, 2H), 0.97–0.85 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 158.5, 139.7, 127.6, 113.8, 60.4, 55.5, 55.3, 32.7, 25.1, 24.0.

5. Representative procedure for the synthesis of (1*R*,2*R*,1′*R*,1″*R*)-2,2,2-trifluoro-*N*-(1-phenyl-ethyl)-*N*-{2-[(1-phenyl-ethyl)-(2,2,2-trifluoro-acetyl)-amino]-cyclohexyl}-acetamide 5

To a solution of (1*R*,2*R*,1′*R*,1″*R*) diamine **4a** (0.32 g, 1 mmol) in solvent DCE (5 mL) under N_2 atmosphere, Et_3N (0.3 mL, 2.1 mmol) and DMAP (0.2 mmol) were added and the solution was stirred for 5 min. To this excess trifluoroacetic anhydride (TFAA) (2 mL) was added slowly at 0 °C and the reaction mixture was stirred at room temperature for 48 h. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The product was purified by column chromatography (silica gel, hexane/EtOAc, 99/1). The product was obtained as a white solid. Yield: 68% (0.35 g); $[\alpha]_D^{25} = +34.7$ (*c* 1.2, $CHCl_3$) Mp: 150–152 °C; IR (neat, cm^{-1}): 3065, 2984, 2937, 1699, 1442, 1140, 744; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.43–7.30 (m, 10H), 4.92 (q, *J* = 8 Hz, 2H), 4.27 (q, *J* = 4 Hz, 2H), 2.30–2.28 (m, 2H), 1.69–1.66 (m, 4H), 1.54 (d, *J* = 8 Hz, 6H), 1.33–1.28 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 155.6 (q, *J* = 34 Hz), 137.1, 128.7, 128.6, 128.4, 116.0 (q, *J* = 288 Hz), 56.5, 55.4, 29.0, 24.9, 18.4.

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23. *Crystal data for the compound* **5**: Molecular formula: $C_{26}H_{28}F_6N_2O_2$, *Mw* = 514.5, trigonal, space group: *P*3(1), *a* = 9.7315(3) Å, *b* = 9.7315(3) Å, *c* = 22.5776(17) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 120°$, *V* = 1851.69(16) Å^3, *Z* = 3, $\rho_c = 1.384$ mg m^{-3}, $\mu = 0.118$ mm^{-1}, *T* = 298(2) K. Of the 4787 reflections collected, 4206 reflections were unique ($R_{int} = 0.0198$). Refinement on all data converged at $R_1 = 0.0451$, $wR_2 = 0.1068$ (CCDC deposition number 720608).
24. *Crystal data for the compound* **4c**: Molecular formula: $C_{22}H_{28}N_2Cl_2$, *Mw* = 391.36, orthorhombic, space group: *P*2(1)2(1)2(1), *a* = 5.7190(11) Å, *b* = 16.311(3) Å, *c* = 23.291(5) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, *V* = 2172.5(7) Å^3, *Z* = 4, $\rho_c = 1.197$ mg m^{-3}, $\mu = 0.307$ mm^{-1}, *T* = 293(2) K. Of the 6359 reflections collected, 4630 reflections were unique ($R_{int} = 0.1134$). Refinement on all data converged at $R_1 = 0.0414$, $wR_2 = 0.0997$ (CCDC deposition number 720607).