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Article

A Straightforward Synthesis of Enantiopure (1*S*,2*R*)-Ephenamine

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An enantioselective six-step synthesis of (1*S*,2*R*)-ephenamine starting from readily available chiral amino acid is disclosed presenting 26% overall yield and high optical purity. The use of chiral phenylglycine as starting material was also studied and did not present satisfactory results due to a very sensitive α-carbonyl/benzylic stereogenic center that, in our hands, led to racemization.

Keywords: chiral auxiliary, chiral amino alcohols, (1*S*,2*R*)-ephenamine

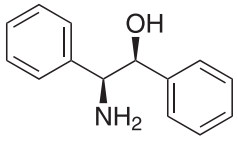
Introduction

Chiral amino alcohols are very versatile compounds used in organic chemistry as chiral auxiliaries, chiral ligands and synthetic intermediates.[1] They also present high biological activity,[2,3] and take part in the structure of valuable drugs.[4-7] *Syn* and *anti* 1,2-diphenyl-2-aminoethanol, **1** and **2** (Figure 1), have been used widely as part of designed ligands for asymmetric transformations including α-arylation of α-aminoacids,[8] synthesis of enantiomerically enriched 1,2-diaryl carbonyl compounds,[9] asymmetric Baeyer-Villiger oxidation,[10] asymmetric epoxidation of alkylidenemalononitriles,[11] among others.[12-16]

(1*S*,2*S*)-Pseudoephenamine **3** and (1*S*,2*R*)-ephenamine **4** (Figure 1) are known chiral auxiliaries used in diastereoselective alkylations which provide alcohols, ketones and carboxylic acids with high enantiomeric purity.[17,18] Several synthetic methods have been reported for the synthesis of (1*S*,2*R*)-ephenamine **4**,[19-22] as well as the respective (1*S*,2*R*)-1,2-aminoalcohol **2**,[23-27] however, to the best of our knowledge, none of these methods starts from readily available chiral amino acid.

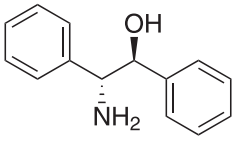
Zhou *et al.*[28,29] has described the synthesis of enantiopure *syn N*-Boc-protected-1,2-amino alcohols in good yields from readily available L-amino acids in four reaction steps (Scheme 1).

Ghorai *et al.*[30] has described the synthesis of *anti N*-Boc-protected-1,2-amino alcohols starting from *N*-Boc-(*S*)-phenylglycine on a similar approach, nevertheless none chiral ephenamine **4** precursor had been synthesized (Scheme 2).



1

(1*S*,2*S*)-1,2-diphenyl-2-aminoethanol



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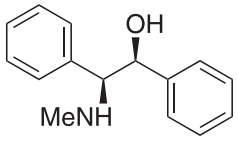
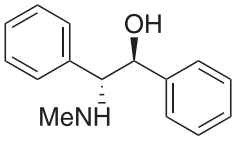
(1*S*,2*R*)-1,2-diphenyl-2-aminoethanol



3

(1*S*,2*S*)-pseudoephenamine



4

(1*S*,2*R*-ephenamine)

Figure 1. Structures of 1,2-diphenyl-2-aminoethanol derivatives.

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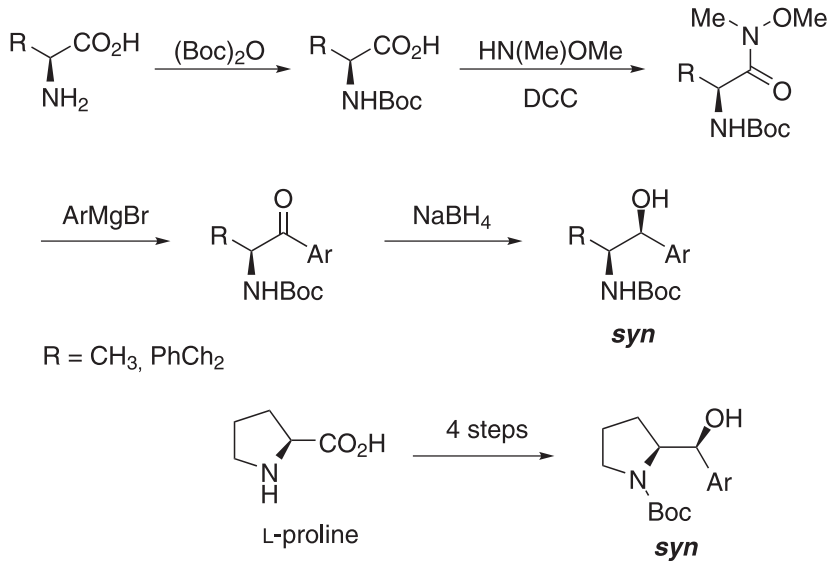
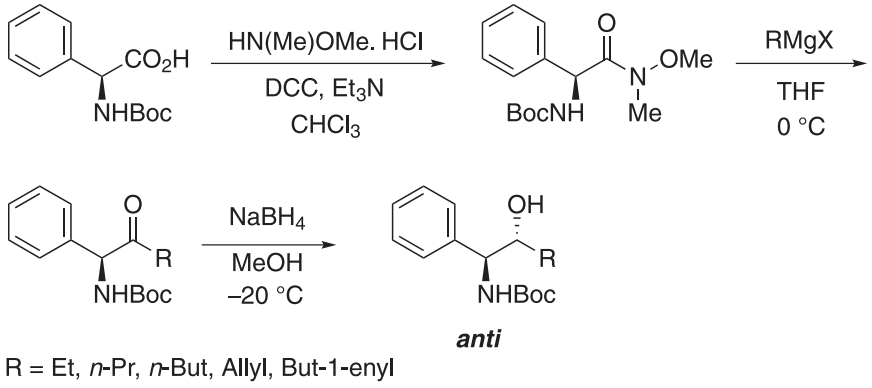
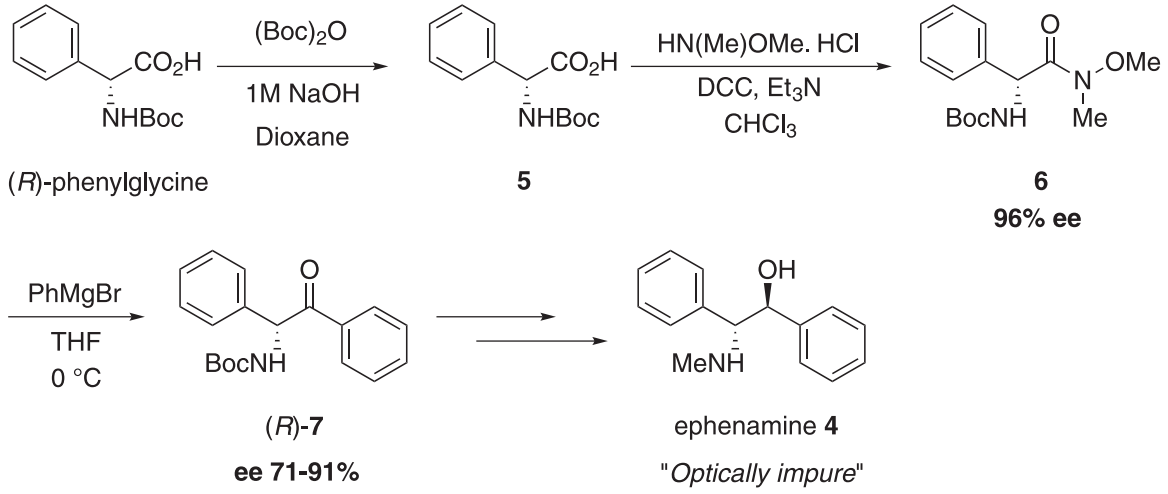


Scheme 1. Synthesis of *syn*-*N*-Boc-protected-1,2-amino alcohols from L-amino acids.



Scheme 2. Synthesis of *anti*-*N*-Boc-protected-1,2-amino alcohols from chiral phenylglycine derivative.

Inspired by these findings we decided to synthesize (1*S*,2*R*)-ephenamine **4** starting from (*R*)-phenylglycine using Ghorai *et al*.[30] approach described above, however, in our hands, most attempts furnished the optically impure ephenamine **4** suggesting partial racemization during the process (Scheme 3). Further studies have revealed that the synthesis of ketone (*R*)-**7** from the Weinreb amide **6**, through Grignard addition, was the critical step providing,



Scheme 3. Synthesis of ephenamine **4** from (*R*)-phenylglycine.

in our hands, the ketone (*R*)-**7** with fluctuating enatiomeric excess (ee) values (71-91%).

The acidic α-carbonyl/benzylic stereogenic center on the starting materials (Scheme 3) demands highly mild conditions in each step in order to avoid racemization as previously observed by Hultin and co-workers.[31] In order to overcome this obstacle we developed a new approach for the synthesis of such important chiral auxiliary starting from commercially available chiral glycine derivative which is less suitable for racemization.

Results and Discussion

The proposal begins with the synthesis of key intermediate **10** through previously described methodology[28-30] in three reaction steps (Scheme 4). The Boc protection of commercially available (*R*)-2-(2,5-dihydrophenyl)-glycine provided the carbamate **8** in 91% yield.[32] The treatment of **8** with pivaloyl chloride followed by addition of *N*,*O*-dimethylhydroxylamine hydrochloride and *N*,*N*-diisopropylethylamine (DIPEA) afforded the Weinreb amide **9** in 85% yield.[33] The chiral ketone **10** was obtained in 87% yield by means of Grignard addition to **9**.[30]

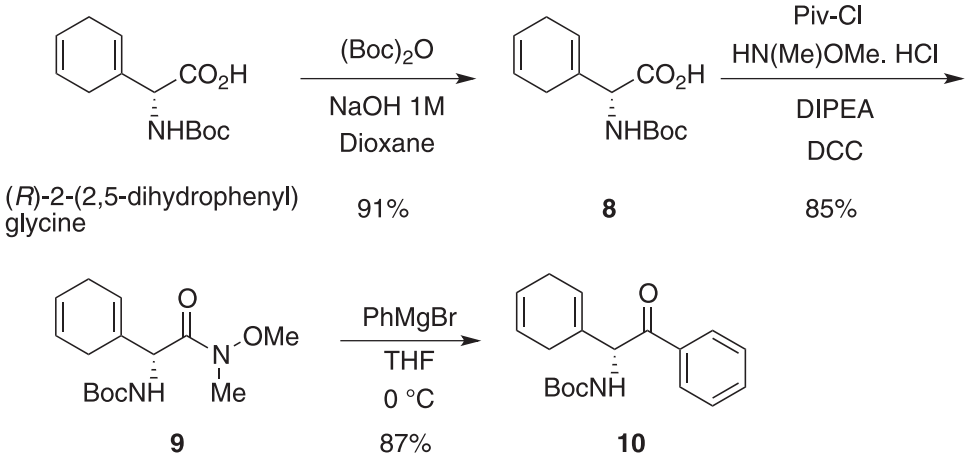
Zhou and co-workers[34] have described the stereoselective reduction of chiral α-aminoketone (*S*)-**7**, which was obtained by means of asymmetric N–H insertion at α-diazoketones (Scheme 5). The reduction provided the *anti*-1,2-amino alcohol **12** with high stereoselectivity (> 20:1) suggesting a Felkin-Anh control,[35-39] where the phenyl group has priority (bulkier) over the NHBoc group (Scheme 6).

The high hindrance provided by the Boc group combined with the sodium poor chelation ability makes a chelation control unlikely in this case.[40]

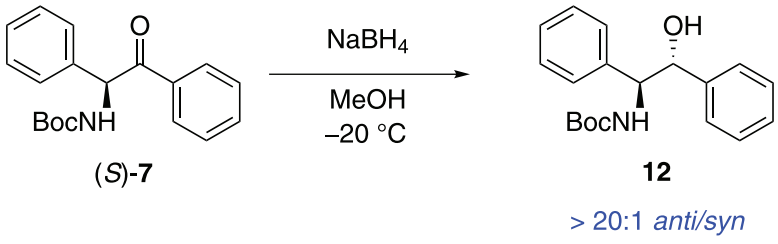
Inspired by these results, we decided to investigate the stereoselective reduction of ketone **10**, which presents slightly structural resemblance with (*S*)-**7**,[34] over several conditions (Table 1).

As illustrated on Table 1, the use of $NaBH_4$ presented slightly better selectivity for the alcohol *anti*-**11** (Table 1, entry 1). Even when using highly chelating reagent as $Zn(BH_4)_2$ (entry 4) or very bulky ones (entries 5 to 7) it was not observed any considerable diastereoselectivity. The results on Table 1 (entry 1) suggest the Felkin-Anh model for the stereoselective reduction of ketone **10** (Scheme 7a) is similar to that suggested for reduction of ketone (*S*)-**7** (Scheme 6). The 1,4-cyclohexadienyl group on **10** has slightly higher priority (bulkier) over the NHBoc group providing the alcohol *anti*-**11** as the major stereoisomer (Scheme 7a).

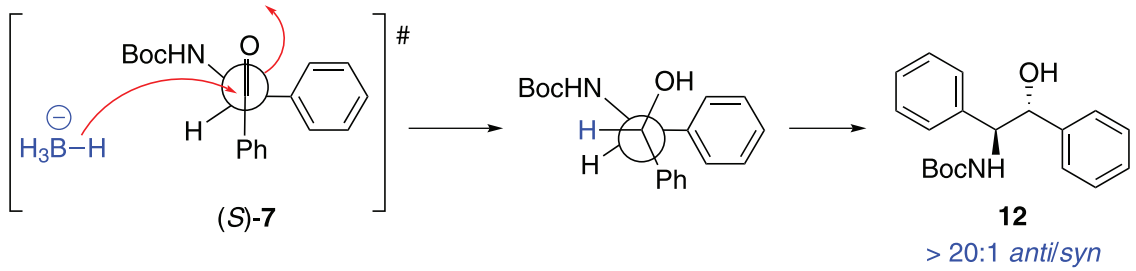
In contrast, when using L-selectride as reducing agent (Table 1, entry 5) a modest shift in diastereoselectivity was observed providing a slight excess of alcohol *syn*-**11**. In this case, the bulkiness of both L-selectride and NHBoc group



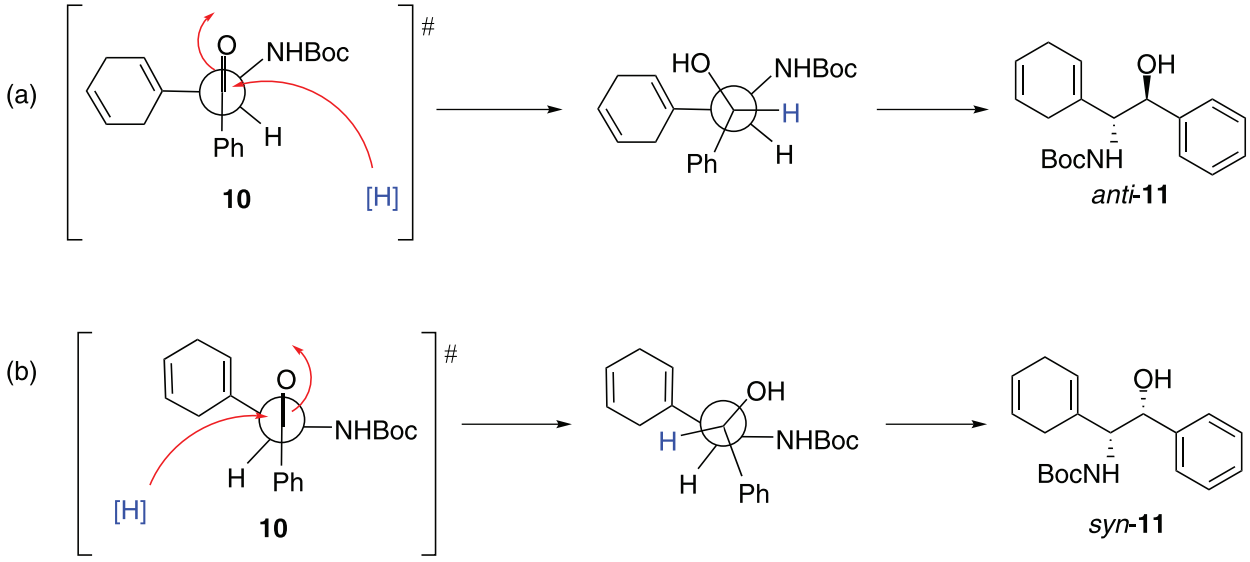
Scheme 4. Synthesis of ketone **10** from commercial chiral glycine derivative.



Scheme 5. Stereoselective reduction of ketone (*S*)-**7**.

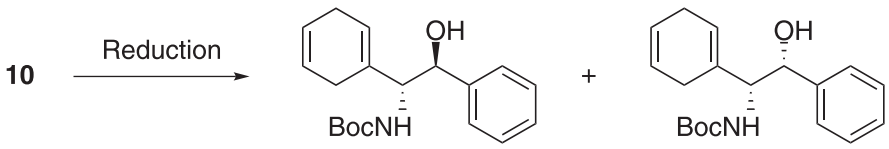


Scheme 6. Felkin-Anh approach for stereoselective reduction of (*S*)-**7**.



Scheme 7. Felkin-Anh approach for stereoselective reduction of **10**: (a) synthesis of *anti*-**11**; (b) synthesis of *syn*-**11**.

Table 1. Diastereoselective reduction of ketone **10**

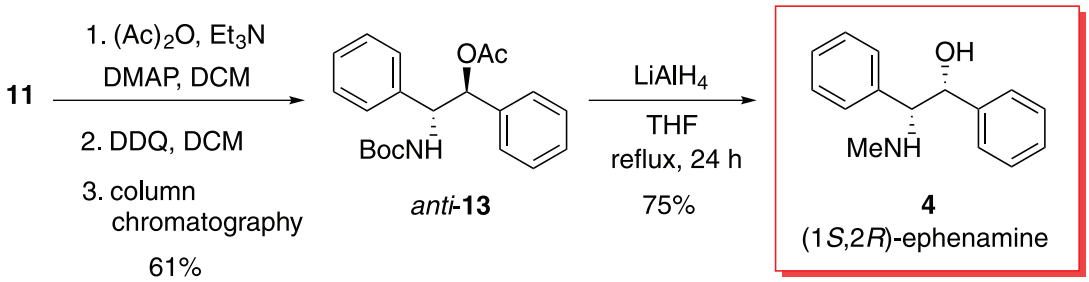


entry	Reagent (equiv.)	Solvent	Temperature / °C	time / h	Yield / %	*anti*/*syn*[a]
1	$NaBH_4$ (3.0)	MeOH	–40	6	86	3.0/1
2	$NaBH_4$ (3.0)	EtOH	–78	4	95	1.1/1
3	$NaBH_4$ (3.0)	MeOH	rt	16	90	1/1
4	$Zn(BH_4)_2$ (2.0)	THF	–78	6	88	1.2/1
5	L-selectride (2.0)	THF	–78	6	90	1/1.6
6	$LiAlH(OtBu)_3$ (2.0)	THF	–78	4	90	1.1/1
7	DIBAL-H (2.0)	THF	–78	4	92	1/1

[a]The ratio was determined by ^1H NMR spectra from 1,2-amino alcohol obtained through Boc deprotection of **11**. THF: tetrahydrofuran; DIBAL-H: diisobutylaluminium hydride; rt: room temperature.

may contribute to elevate the energy of transition state that leads to alcohol *anti*-**11** (Scheme 7a) slightly favoring the synthesis of *syn* stereoisomer (Scheme 7b).

The protection of crude alcohol **11**[41] (3:1 *anti*/*syn* ratio) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated aromatization afforded the aromatic



Scheme 8. Synthesis of (1*S*,2*R*)-ephenamine **4** from alcohol **11**.

ester **13** (3:1 *anti*/*syn* ratio) which upon chromatographic column afforded the pure *anti*-**13** stereoisomer in 61% yield (Scheme 8). The nuclear magnetic resonance (NMR) spectra of all NHBoc-derivatives corroborate the respective structures despite presenting a complex pattern due to the presence of Boc group rotamers.[42,43]

The (1*S*,2*R*)-ephenamine **4** was obtained by the reduction of *anti*-**13** using a large excess of lithium aluminium hydride (LAH) in 75% yield (Scheme 8).[19] The physical and spectroscopic data of compound **4** were in full agreement with those reported in the literature.[19,21]

Conclusions

In this work we described a simple and efficient six-step synthesis of (1*S*,2*R*)-ephenamine **4**, an important chiral auxiliary, from commercially available chiral glycine derivative through straightforward procedures with 26% overall yield and high optical purity. The use of chiral phenylglycine as starting material was not satisfactory due to the presence of a very sensitive α-carbonyl/benzylic stereogenic center which, in our hands, led to partial racemization. When starting from (*R*)-2-(2,5-dihydrophenyl)-glycine instead this problem was suppressed consisting in an excellent strategy for the synthesis of similar chiral molecules in high optical purity.

Experimental

Unless indicated otherwise, all reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich Corp., St. Louis, USA) and used without further purification. Melting points were measured on a Stuart Scientific melting point apparatus. NMR spectra were measured with a VARIAN 400.1 MHz in $CDCl_3$ or CD_3OD solutions (Sigma-Aldrich Corp., St. Louis, USA). Chemical shifts are expressed as δ (ppm) relative to tetramethylsilane (TMS) as an internal standard and the *J* values are given in hertz. Infrared spectra (IR) (neat) were recorded with a Bruker Alpha ATR (attenuated total reflection) spectrometer. Optical rotations were measured with a Jasco P-2000 Polarimeter. High resolution mass spectra (HRMS) were recorded with a Bruker Impact II UHPLC-QTOF (ultra-high performance liquid chromatography-quadrupole time-of-flight) mass spectrometer. HPLC analysis was performed on a Shimadzu LC-20AT chromatograph. Column chromatography was performed by using silica gel (230-400 mesh) according to the methods described by Still *et al.*[44] Thin layer chromatography (TLC) was performed by using silica gel 60 with fluorescent indicator UV_{254} (0.20 mm thickness). For visualization, TLC plates were either placed under ultraviolet light, iodine cell or treated with vanillin or ninhydrin followed by heating. Air and moisture sensitive reactions were conducted in flame or oven dried glassware equipped with tightly fitted rubber septa and under a positive pressure of dry nitrogen. Solvents were purified when necessary using standard procedures.[45]

(*R*)-2-(*tert*-Butoxycarbonylamino)-2-(cyclohexa-1,4-dienyl) acetic acid (**8**)

Adapted from literature.[32] To a solution of (*R*)-2-(2,5-dihydrophenyl)-glycine (1.0 equiv., 2.0 g, 13.0 mmol) in 1 M aqueous NaOH (2.0 equiv., 26 mL, 26.0 mmol) at 0 °C was added a solution of $(Boc)_2O$ (1.1 equiv., 3.1 g, 14.3 mmol) in dioxane (15 mL) dropwise over 30 min. The resulting mixture was stirred at 0 °C for another 30 min, then allowed to warm to room temperature and stirred overnight. The organic solvent was removed under reduced pressure. The remaining aqueous solution was acidified to pH ca. 4 with 1 M $KHSO_4$ and the aqueous solution was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous K_2CO_3, and concentrated by rotary evaporation to afford carbamate **8** (3.0 g, 91% yield) as light yellow oil (mixture of rotamers) which was used without further purification. $[\alpha]_D^{20}$ −69.7 (*c* 0.5, MeOH); IR (ATR) ν / cm^{-1} 3391, 3310, 2976, 2930, 1688, 1599, 1494, 1380, 1248, 1163, 1047, 1022, 752, 696; ^1H NMR (400.1 MHz, $CDCl_3$) δ 5.62-5.55 (brs, 3H), 5.05-4.93 (brs, 0.7H), 4.75-4.66 (brs, 0.3H), 2.68-2.57 (brs, 4H), 1.38 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 176.8, 157.1, 141.8, 129.2, 128.1, 125.1, 124.6, 80.3, 61.1, 28.7, 27.6; HRMS

(Fourier transform mass spectrometry (FTMS) + probe electrospray ionization (pESI)) *m/z*, calcd. for $C_{13}H_{20}NO_4$ $[M + H]^+$: 254.1386, found: 254.1385.

(*R*)-*tert*-Butyl 1-(cyclohexa-1,4-dienyl)-2-(methoxy(methyl) amino)-2-oxoethylcarbamate (**9**)

Adapted from literature.[33] To an ice cold solution of carbamate **8** (1.0 equiv., 1.2 g, 4.7 mmol), in dry dichloromethane (DCM, 50 mL) was added DIPEA (1.1 equiv., 0.9 mL, 5.1 mmol). After stirring for 15 min, pivaloyl chloride was added (1.1 equiv., 0.6 mL, 5.1 mmol). The solution was stirred at room temperature for two hours and then *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 equiv., 0.5 g, 5.1 mmol) and DIPEA (2.0 equiv., 1.6 mL, 9.6 mmol) were added. The reaction mixture was stirred overnight, washed with 5% HCl solution (20 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous K_2CO_3, and concentrated by rotary evaporation. Flash chromatography on a short pad silica gel (0 → 30% v/v ethyl acetate/hexane) afforded Weinreb amide **9** (1.2 g, 85%) as light yellow oil (mixture of rotamers). $[\alpha]_D^{20}$ −81.4 (*c* 1.0, EtOAc); IR (ATR) ν / cm^{-1} 2975, 2935, 2822, 1707, 1656, 1481, 1390, 1365, 1248, 1160, 1046, 1025, 993, 961, 865; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 5.73-5.60 (m, 3H), 5.41 (brs, 1H), 5.11 (brs, 1H), 3.70 (s, 3H), 3.46 (brs, 1H), 3.21 (s, 3.0H), 2.70 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.1, 155.2, 137.8, 131.4, 128.6, 127.9, 127.5, 123.7, 123.4, 79.5, 61.1, 61.0, 55.6, 54.8, 32.1, 28.2, 26.5; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{15}H_{24}N_2NaO_4$ $[M + Na]^+$: 319.1628, found: 319.1636.

(*R*)-*tert*-Butyl 1-(cyclohexa-1,4-dienyl)-2-oxo-2-phenyl-ethylcarbamate (**10**)

To an ice cold solution of 1.0 M phenylmagnesium bromide in tetrahydrofuran (THF, 4.0 equiv., 18.2 mL, 18.2 mmol), under N_2 atmosphere, was added dropwise a solution of Weinreb amide **9** (1.0 equiv., 1.3 g, 4.4 mmol) in THF (15 mL). The system was stirred at room temperature for five hours and quenched by addition of saturated solution of NH_4Cl (20 mL). The reaction mixture was extracted with diethyl ether (3 × 40 mL) and the combined organic layers were washed with brine (50 mL), dried over anhydrous K_2CO_3, and concentrated by rotary evaporation. Silica gel flash chromatography (0 → 20% v/v ethyl acetate/hexane) afforded the ketone **10** (1.2 g, 87%) as a light yellow solid (mixture of rotamers). $[\alpha]_D^{20}$ −183.0 (*c* 1.0, EtOAc); mp 76-79 °C; IR (ATR) ν / cm^{-1} 3346, 2978, 1672, 1486, 1448, 1364, 1247, 1155, 1055, 877, 754, 692; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 8.00-7.91 (m, 2H), 7.60-7.18 (m, 3H), 6.30-5.55 (m, 5H), 2.76-2.48 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.8, 196.1, 155.2, 154.9, 137.4, 134.8, 134.5, 133.5, 129.0, 128.9, 128.7, 128.6, 128.2, 128.0, 123.6, 123.4, 79.8, 79.7, 60.8, 59.7, 28.3, 26.8; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{24}NO_3$ $[M + H]^+$: 314.1750, found: 314.1724.

tert-Butyl (1*R*,2*S*)-1-(cyclohexa-1,4-dienyl)-2-hydroxy-2-phenylethylcarbamate (**11**)

A solution of ketone **10** (1.0 equiv., 0.64 g, 2.0 mmol) in dry MeOH (30 mL) was cooled to −40 °C and stirred for 10 min. $NaBH_4$ (3.0 equiv., 0.23 g, 6.1 mmol) was added in one portion and the mixture was stirred at −40 °C for seven hours under N_2 atmosphere. The methanol was removed under reduced pressure and a 3% HCl solution (30 mL) was added to the crude solid. The aqueous phase was extracted with DCM (3 × 40 mL) and the organic layers were combined, washed with brine, dried over anhydrous K_2CO_3 and concentrated under reduced pressure affording the alcohol **11** (3:1 *anti*/*syn* ratio) as white solid that was used in the next step without further purification (0.5 g, 86%). IR (ATR) ν / cm^{-1} 3380, 3062, 2978, 2935, 1682, 1518, 1289, 1250, 1169, 995, 752, 699, 603; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.34-6.98 (m, 5H), 5.67-4.75 (m, 5H), 4.30 (brs, 1H), 2.90 (brs, 1H), 2.80-2.39 (m, 4H), 1.20-1.00 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 157.3, 143.3, 129.2, 128.8, 128.4, 128.1, 125.2, 124.7, 123.9, 80.22, 77.6, 61.6, 28.7, 27.5, 26.9; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{19}H_{26}NO_3$ $[M + H]^+$: 316.1907, found: 316.1913.

(1*S*,2*R*)-2-(*tert*-Butoxycarbonylamino)-1,2-diphenylethyl acetate (*anti*-**13**)

To a stirred solution of diastereomeric mixture (3:1 *anti*/*syn* ratio) of **11** (1.0 equiv., 0.49 g, 1.55 mmol) in DCM (35 mL) were added acetic anhydride (1.1 equiv., 0.17 mL, 1.8 mmol), triethylamine (1.1 equiv., 0.26 mL, 1.8 mmol) and catalytic 4-dimethyl-aminopyridine (DMAP). The solution was stirred for 16 h at room temperature and then a 5% HCl solution was added. The organic phase was separated, and the aqueous layer was extracted with DCM (3 × 30 mL). The organic extracts were washed with water (20 mL), dried over anhydrous K_2CO_3 and concentrated under reduced pressure providing a light yellow oil that was immediately dissolved in dry DCM (25 mL) and treated with DDQ (2.0 equiv., 0.7 g, 3.2 mmol). The system was stirred at room temperature for 18 h under N_2 atmosphere and then the solution was filtered through a short pad of celite. The solvent was evaporated affording a crude yellow solid that was purified by silica gel flash chromatography (0 → 20% v/v ethyl acetate/hexane) affording pure compound *anti*-**13** (0.33 g, 61%) as a pale yellow solid (mixture of rotamers).

$[\alpha]_D^{20}$ +19.5 (*c* 1.1, EtOAc); mp 145-148 °C; IR (ATR) ν / cm^{-1} 3389, 2977, 1736, 1682, 1518, 1364, 1238, 1165, 1016, 755, 699; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.29-7.22 (m, 6H), 7.12-7.03 (m, 4H), 6.05 (d, *J* 4.9 Hz, 1H), 5.18 (brs, 1H), 5.00 (brs, 1H), 2.07 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.9, 154.9, 137.8, 135.9, 128.2, 128.1, 127.3, 127.0, 79.8, 77.7, 77.6, 57.9, 28.3, 28.2, 21.1, 21.0; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{21}H_{26}NO_4$ $[M + H]^+$: 356.1856, found: 356.1851.

(1*S*,2*R*)-2-(Methylamino)-1,2-diphenylethanol (**4**)

To a solution of Boc-protected-amino ester *anti*-**13** (1 equiv., 0.3 g, 0.84 mmol) in dry THF (16 mL) at 0 °C under N_2 atmosphere was added dropwise 1 M $LiAlH_4$ solution in THF (10 equiv., 8.4 mL, 8.4 mmol). The resulting solution was refluxed under nitrogen atmosphere for 24 h. The solution was quenched with 10% NaOH (2 mL) and then ethyl acetate (30 mL) was added and the system was stirred for 1 h. The organic extract was separated and washed with brine (20 mL), dried over anhydrous K_2CO_3 and evaporated under reduced pressure. Silica gel flash chromatography (0 → 10% v/v MeOH/DCM) afforded the pure (1*S*,2*R*)-ephenamine **4** (0.14 g, 75%) as a white solid. $[\alpha]_D^{20}$ +32.5 (*c* 0.47, EtOH) [lit.[21] $[\alpha]_D^{20}$ +32.8 (*c* 0.5, EtOH)]; mp 134-136 °C, lit.[21] mp 135-136 °C; IR (ATR) ν / cm^{-1} 3379, 3320, 3028, 2919, 1452, 1055, 885, 695; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.28-7.10 (m, 10H), 4.82 (d, *J* 5.77 Hz, 1H), 3.74 (d, *J* 5.77 Hz, 1H), 2.58 (brs, 2H), 2.24 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.5, 138.7, 128.3, 128.1, 128.0, 127.6, 127.5, 126.7, 76.4, 70.9, 34.2; HRMS (FTMS + pESI) *m/z*, calcd. for $C_{15}H_{17}NO$ $[M + H]^+$: 228.1382, found: 228.1381.

Supplementary Information

Supplementary information (NMR, infrared and HRMS spectra from all the compounds) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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