A New Approach to the Synthesis of Optically Active Norephedrine, Norpseudoephedrine and Cathinone *via* Double Asymmetric Induction

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New and facile synthetic routes for preparation of optically active norephedrine, norpseudoephedrine and cathinone with high optical purities via double asymmetric induction by employing asymmetric reduction of 2-*N*-protected amino (or azido)-1-phenylpropanone and 2-methanesulfonyloxy-1-phenylpropanone with CBS-catalyzed-borane and $^{d}Ipc_2BCl$ as chiral reducing agents are described.

Key Words : Asymmetric reduction, Norephedrine, Norpsedorephedrine, Cathinone

Introduction

Optically active norephedrine **1**, norpseudoephedrine **2** and cathinone **3** are naturally occurring alkaloids possessing amphetamine-like pharmacological activity which are used as anorexic drugs (Figure 1). Among those, **1** and **2** are of great importance as chiral auxiliaries, ligands, bases and catalysts in a variety of asymmetric reaction,[1,2] such as enolate alkylation,[3a] aldol reaction,[3b-d] α or β-amino acid synthesis,[3e-g] rearrangement of epoxides to allylic alcohols,[3h-j] oxazaborolidine reduction,[3k] hydrogen transfer reaction,[3l-m] and alkynylation to aldehydes.[3n-p] Moreover, these compounds are widely used as very useful starting materials for preparation of chiral 2-oxazoline,[4] piperidines,[5] aziridines,[6] and imidazolines.[7] Accordingly, the development of a simple and convenient synthetic methods for these compounds is of great interest. For the synthesis of these compounds, a number of methods including optical resolution of racemic mixtures,[8] bioreduction of 2-azido-1-phenylpropanone,[9] regioselective azidolysis of chiral *cis*-β-methylstyrene oxides,[10] diastereoselective reduction of chiral 2-hydroxyamino-1-phenylpropanone[11] or 1-hydroxy-1-phenyl-2-propanone-2-*O*-methyloxime,[12] diastereoselective phenylation of *N*-protected alaninal derivatives,[13] and diastereoselective methylation of chiral *O*-protected cyanohydrin[14] or α-hydroxy aldehyde hydrazones[15] have been presented. However, these methods except for resolution of racemic mixture and bioreduction of 2-azido-1-phenylpropanone need mostly chiral substrates as starting materials. Recently a number of highly efficient asymmetric reductions of prochiral ketones using catalytic and stoichiometric chiral reducing agents to give high enantioselectivity have been reported.[16] Of such chiral reducing agents, it has been realized that CBS-oxazaborolidine-catalyzed borane and (–)-*B*-chlorodiisopinocampheylborane ($^{d}Ipc_2BCl$) are highly effective for asymmetric reduction of various α-functionalized ketones, leading to the corresponding alcohols with high enantioselectivity.[17] It was expected that asymmetric reductions of 2-*N*-protected amino (or azido)-1-phenylpropanone using these reducing agents and the same reductions of 2-methanesulfonyloxy-1-phenylpropanone followed by S_N2 type amination might be one of the most convenient methods for preparation of optically active **1**-**3**, if the double asymmetric inductions[18] and/or kinetic resolutions are included in these reductions. However, to our knowledge, there have been no reports of such reductions. We report here new and facile synthetic routes for the preparation of chiral **1**-**3** using this methodology.

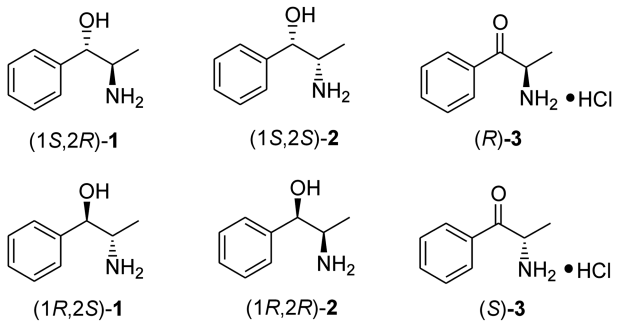

Figure 1

Results and Discussion

The synthetic routes of **1**-**3** are outlined in Scheme 1. First we studied the enantioselective synthesis of **1**-**3** *via* asymmetric reductions of 2-*N*-Boc and *N*-Cbz-amino-1-phenylpropanone (**7a** and **7b**) with (*S*)-MeCBS-oxazaborolidine-catalyzed borane (CBS-reagent) (route 1). Thus the reduction was carried out by slow addition of *N*-protected amino ketones **7** over 1.5 h to a solution of 1.0 equiv. (3.0 equiv. as hydride) of the reagent **5** in the presence of 0.1 equiv. of **4** in THF at 25 °C (method A). As shown in Table 1, the reduction of **7a** afforded a 60 : 40 diastereomeric mixture of product alcohols, the *anti* isomer (**8a** + *ent*-**8a**) and the *syn* isomer (**9a** + *ent*-**9a**), in 96% yield within 10 min (entry 2). In the case of **7b**, the ratio was 65:35 (entry 4). The diastereomeric ratios of products alcohols (**8** and **9**) were determined by HPLC analysis using a 25 cm Whelk-O1 chiral column. With respect to enantioselectivies, the reductions provided **8a** with 48% ee, **9a** with 70% ee, **8b** with

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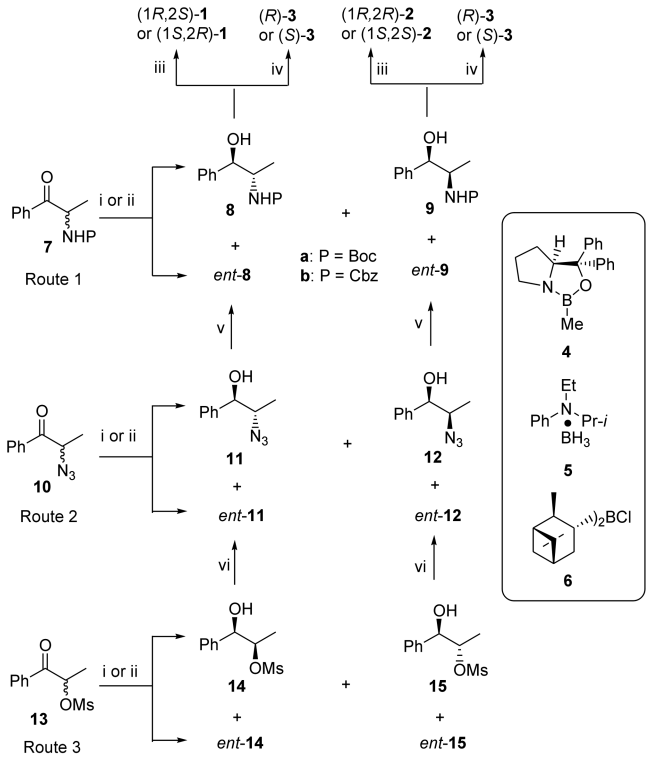


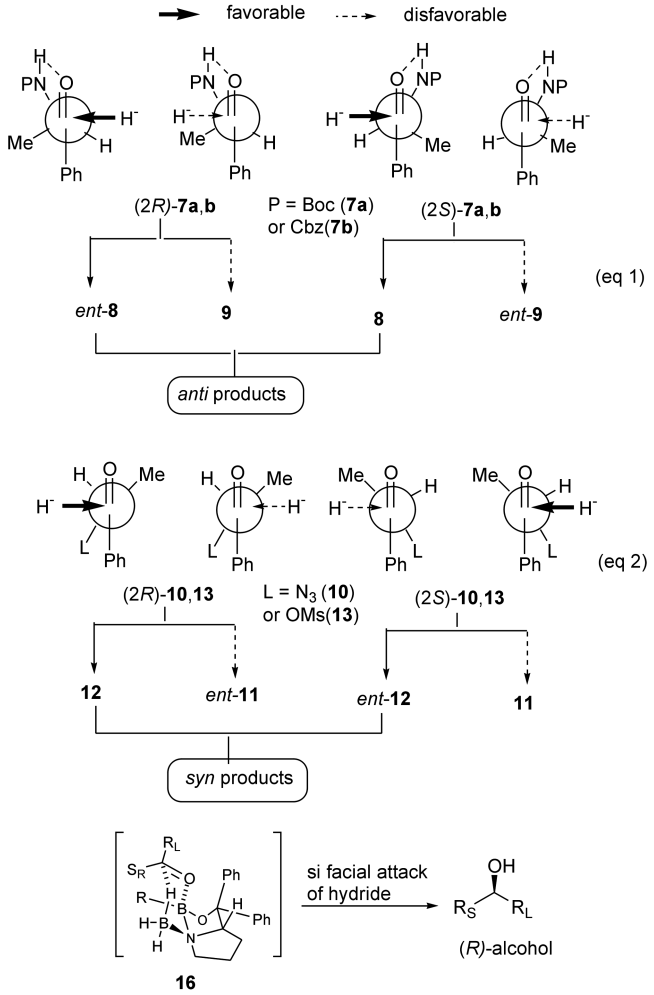
Scheme 1. Reaction conditions: i. **4** (0.1 eq), **5** (1.0 eq), THF, 25 °C (Method A). ii. **6** (1.2 eq), THF, 0 °C (Method B). iii. For **8a** and **9a**, 3 N HCl, AcOEt, r.t., 88%; for **8b** and **9b**, 6 N HCl, reflux, 89%. iv. PCC (1.5 eq), CH_2Cl_2, r.t., then 3 N or 6 N HCl, 74-76% v. 10% Pd/C, H_2, Boc_2O, AcOEt, r.t., 89%, vi. NaN_3 (1.1 eq), DMSO, 80 °C, 82%.

26% ee and **9b** with 55% ee, which. were easily separated by a flash column chromatography on silica gel. *N*-Boc and *N*-Cbz groups of **8** and **9** were deprotected with 3 *N* HCl solution at room temperature and 6 *N* HCl solution under reflux condition, respectively.[19] Subsequently the reaction mixtures were basified with 6 *N* NaOH and extracted with dichloromethane to give norephedrine **1** and norpseudoephedrine **2**. Using this procedure, we obtained (1*R*,2*S*)-**1** with 48% ee from **8a** and (1*R*,2*R*)-**2** with 70% ee from **9a** in 88-90% yields. When **9a** with 70% ee was oxidized with PCC in dichloromethane at room temperature, followed by deprotection with hydrochloric acid, (*R*)-cathinone **3** with 70% ee was produced in 80% yields.[9a] Comparing optical rotation values for optically active **1**, **2** and **3** reported with those obtained, we found that no racemization occurs in the course of deprotection and oxidation. On the other hand, the same reductions of 2-azido-1-phenylpropanone **10** (route 2) and 2-methanesulfonyloxy-1-phenylpropanone **13** using CBS reagent (route 3) provided inseparable diastereomeric mixtures of azido alcohols (**11** and **12**) and 1,2-diol monomesylates (**15** and **14**). To separate the diastereomeric mixtures and to determine their ratios and enantioselectivities, the product alcohols were converted into **8a** (or *ent*-**8a**) and **9a** (or *ent*-**9a**) in the following manners. The azido alcohols **11** and **12** obtained were hydrogenated on 10% Pd/C under atmospheric pressure in the presence of excess Boc_2O in ethyl acetate at room temperature. The product alcohols **15** and **14** produced from route 3 were converted into **8a** (or *ent*-**8a**) and **9a** (or *ent*-**9a**) by the S_N2 type reaction with sodium azide in DMSO at 80 °C, followed by catalytic hydrogenation in the presence of excess Boc_2O as described above. HPLC analysis of the *N*-Boc amino alcohols obtained from route 2 and 3 showed the formation of *ent*-**8a** with 76% ee from *ent*-**11**, *ent*-**9a** with 26% ee from *ent*-**12**, *ent*-**8a** with

Table 1. Enantioselective synthesis of **1-3** *via* asymmetric reduction using method A[a]

Entry	Cpd	Method[a] (cpd:**5**)	Yield[b] (%)	Ratio (%)[c] anti		Ratio (%)[c] syn		Products, % ee[c,d] **1** and **2**	Products, % ee[c,d] ketones
1	**7a**	A	40	**8a**	64	**9a**	20	(1*R*,2*S*)-**1**, 74	(*R*)-**7a**,[e] 27 (26)[j]2[j]
		(1:0.17)		*ent*-**8a**	10	*ent*-**9a**	6	(1*R*,2*R*)-**2**, 54	
2	**7a**	A	96	**8a**	44 (46)[i]	**9a**	34 (33)	(1*R*,2*S*)-**1**, 48	
		(1:1)		*ent*-**8a**	16 (17)	*ent*-**9a**	6 (4)	(1*R*,2*R*)-**2**, 70	(*R*)-**3**, 70
3	**7b**	A	45	**8b**	57	**9b**	19	(1*R*,2*S*)-**1**, 60	(*R*)-**7b**,[f] 26 (26)[j]
		(1:0.17)		*ent*-**8b**	15	*ent*-**9b**	9	(1*R*,2*R*)-**2**, 36	
4	**7b**	A	95	**8b**	41 (43)[i]	**9b**	27 (28)	(1*R*,2*S*)-**1**, 26	
		(1:1)		*ent*-**8b**	24 (22)	*ent*-**9b**	8 (7)	(1*R*,2*R*)-**2**, 55	
5	**10**	A	43	**11**	10	**12**	19	(1*S*,2*R*)-**1**, 38	(*R*)-**10**,[g] 18 (14)[j]
		(1:0.17)		*ent*-**11**	22	*ent*-**12**	49	(1*S*,2*S*)-**2**, 44	
6	**10**	A	97	**11**	5 (8)[i]	**12**	24 (23)	(1*S*,2*R*)-**1**, 76	
		(1:1)		*ent*-**11**	26 (27)	*ent*-**12**	45 (42)	(1*S*,2*S*)-**2**, 26	
7	**13**	A	40	**15**	6	**14**	20	(1*S*,2*R*)-**1**, 44	(*R*)-**13**,[h] 9 (10)[j]
		(1:0.17)		*ent*-**15**	22	*ent*-**14**	52	(1*S*,2*S*)-**2**, 57	
8	**13**	A	98	**15**	3 (5)[i]	**14**	25 (24)	(1*S*,2*R*)-**1**, 30	
		(1:1)		*ent*-**15**	26 (26)	*ent*-**14**	46 (45)	(1*S*,2*S*)-**2**, 78	

[a]Method A: Reduction was carried out with 1.0 or 0.17 equiv. of **5** in the presence of 0.1 equiv of **4** in THF at 25 °C. [b]Isolated yields of diastereomeric mixtures. [c]% Ees of **7**, **8**, **9** and **13** were determined by HPLC analysis using a 25 cm Whelk-O1 chiral column. Using the same column, enantioselectivities of **10**, **11**, **12**, **14** and **15** were determined after conversion of these compounds to **7a**, **8a** or **9a**. [d]Determined by comparison with their known absolute configurations and optical rotation values. [e]53% of unreacted ketone **7a** was recovered. [f]47% of unreacted ketone **7b** was recovered. [g]50% of unreacted ketone **10** was recovered. [h]54% of unreacted ketone **13** was recovered. [i]The figures in parentheses indicated the values calculated from each of kinetic resolution data of the corresponding ketones **7**, **10** and **13**. [j]The values calculated from diastereomeric ratios of the corresponding product alcohols.



Scheme 2

30% ee from *ent*-**14** and *ent*-**9a** with 78% ee from *ent*-**15**, which could be converted into (1*S*,2*R*)-**1** and (1*S*,2*S*)-**2** with no loss of enantiomeric purity, respectively (entries 6 and 8). To find out that these reductions were included with kinetic resolution or not, the same reductions of **7**, **10**, and **13** using 0.17 equiv. (0.5 equiv. as hydride) of the reagent **5** were carried out. The reduction of **7a** and **7b** afforded product alcohols, which were **8a** with 74% ee and **9a** with 54% ee in 40% yield and **8b** with 60% ee and **9b** with 36% ee in 45% yield. The *anti*/*syn* rations of the product alcohols obtained were 74 : 26 for **7a** and 72 : 28 for **7b**. From the reductions, (*R*)-**7a** with 27% ee and 47% yield and (*R*)-**7b** with 26% ee in 53% yield were recovered (entries 1 and 3). The reduction of **10** under the same condition, followed by hydrogenation provided *ent*-**8a** with 38% ee and *ent*-**9a** with 44% ee in 43% yield with the unreacted ketone (*R*)-**10** with 18% ee recovered in 50% yield (entry 5). In the case of **13**, *ent*-**8a** with 44% ee and *ent*-**9a** with 57% ee in 40% yield were obtained with recovery of the unreacted ketone (*R*)-**13** with 9% ee in 54% yield (entry 7). In contrast to those of **7**, the reductions of **10** and **13** favorably afforded the *syn* products, as the *anti*/*syn* ratios were 32 : 68 and 28 : 72 for **10** and **13**, respectively. Such different diastereoselectivities can be explained by Crams rule which predicts the steric outcome in the reduction of acyclic ketones having one asymmetric carbon atom adjacent to the carbonyl group.[20] According to this rule, distereoselectivities for **7** were controlled by the Cram-chelating model favoring the *anti* products (eq. 1 in Scheme 2), whereas the *syn* products for **10** and **13** were preferentially formed by the Cram open-chain model where hydride approaches electrophilic carbon from the side of the smallest substituent (hydrogen) when azide and mesyloxy groups occupy the largest substituent in transition state (eq 2). The Cram-chelating model for **7** can be rationalized by intramolecular hydrogen bonding between hydrogen of *N*-Boc or Cbz amide and the carbonyl, since such hydrogen bonding stabilizes their conformations in the transition states. With respect to enantioselectivity, it has been known that asymmetric induction by (*S*)-CBS-oxazaborolidine-catalyzed borane reduction (CBS reduction) of prochiral ketones comes from *si* facial attack of hydride on carbonyl of the ketone R_LCOR_S in the transition state **16** to produce (*R*)-alcohol.[16f] Interestingly, phenyl group behaves as the large group in the reduction of **10** and **13** in contrast to the same reduction of **7**, wherein the phenyl group behaved as the small group, although the reason is so far unclear. The values of enantiomeric excess of unreacted ketones recovered under the kinetic conditions are in good correspondences with those calculated from diasteromeric ratios of product alcohols obtained. Also, all the diastereomeric ratios of the

Table 2. Enantioselective synthesis of **1**-**3** *via* asymmetric reduction using method B[a]

Entry	Cpd	Method[a] (cpd:**6**)	Yield[b] (%)	Ratio (%)[c]				Products, % ee[c,d]	
				anti		syn		**1** and **2**	ketones
1	**7a**	B	48	**8a**	31	**9a**	52	(1*R*,2*S*)-**1**, 38	(*S*)-**7a**,[e] 31(30)[i]
		(1:1.2)		*ent*-**8a**	14	*ent*-**9a**	3	(1*R*,2*R*)-**2**, 89	
2	**7b**	B	40	**8b**	30	**9b**	60	(1*R*,2*S*)-**1**, 58	(*S*)-**7b**,[f] 19 (18)[i]
		(1:1.2)		*ent*-**8b**	8	*ent*-**9b**	2	(1*R*,2*R*)-**2**, 93	(*R*)-**3**, 93
3	**10**	B	60	**11**	17	**12**	64.7	(1*R*,2*S*)-**1**, 96	(*S*)-**10**,[g] 46 (45)[i]
		(1:1.2)		*ent*-**11**	0.3	*ent*-**12**	18	(1*R*,2*R*)-**2**, 56	(*S*)-**3**, 96
4	**13**	B	55	**15**	0	**14**	89	(1*R*,2*S*)-**1**, 78	(*S*)-**13**,[h] 95 (95)[i]
		(1:1.2)		*ent*-**15**	0	*ent*-**14**	11		

[a]Method B: Reduction was carried out with 1.2 equiv. of **6** in THF at 0 °C for 72 h. [b-d]See the corresponding footnotes in Table 1. [e]46% of unreacted ketone **7a** was recovered. [f]52% of unreacted ketone **7b** was recovered. [g]33% of unreacted ketone **10** was recovered. [h]38% of unreacted ketone **13** was recovered. [i]The values calculated from diastereomeric ratios of the corresponding product alcohols.

product alcohols obtained from route 1-3 using method A under non-kinetic conditions are good agreements with those calculated from the ratios obtained under kinetic conditions. From these results, we realized that the reductions by method A were included with double asymmetric induction via partial kinetic resolution.

Next, we examined synthesis of optically active **1**-**3** via asymmetric reduction of **7**, **10** and **13** with 1.2 equiv. of ^{d}Ipc$_2$BCl **6** in THF at 0 °C (method B). As shown in Table 2, all the reduction examined proceeded more slowly to afford the product alcohols in 40-60% yields after 72 h. Unreacted ketones were recovered in 33-52% yields. With respect to enantioselectivity, the reduction of **7** provided **8a** with 38% ee, **9a** with 89% ee, **8b** with 58% ee and **9b** with 93% ee. Enantiomeric purities of unreacted ketones recovered are 31% ee for **7a** and 19% ee for **7b** with the (*S*)-configuration (entries 1-2). The reductions of **10** and **13**, followed by deprotection, oxidation, S_N2 type azidation and catalytic hydrogenation according to the same procedure described in route 1-3 using method A afforded (1*R*,2*R*)-**2** with 89% ee from **9a**, (1*R*,2*R*)-**2** with 93% ee and (*R*)-**3** with 93% ee from **9b**, (1*R*,2*S*)-**1** with 96% ee and (*S*)-**3** with 96% ee from **11** and (1*R*,2*S*)-**1** with 78% ee from **14**. In this reduction, unreacted ketones which are (*S*)-**10** with 46% ee and (*S*)-**13** with 95% ee were recovered in 33% and 38% yields, respectively (entries 3 and 4). With the same manner described in method A, (*R*)-**3** with 93% ee and (S)-**3** with 96% ee were obtained in 82 and 89% yields by oxidation of **9b** and **8a**, followed by deprotection. All the reductions using method B produced the *syn* products preferentially, such as the *anti*/*syn* ratios 45 : 55 for **7a**, 38 : 62 for **7b**, 17.3 : 82.7 for **10** and 0 : 100 for **13**. Especially, it is noteworthy in a practical aspect that the reduction of **13** afforded only the *syn* products. In general, it has been known that reductions with **6** proceed through a cyclic, six-membered transition-state reminiscent of the Meerwein-Pondorf-Verley (MPV) processes and their enantioselectivities are induced by stereodifferential control of the methyl group at the 2-position of a-pinene to prochiral ketones (Figure 2).[21] Based on this proposed mechanism, preferential formation of the *syn* products can be explained by the Cram open-chain model shown in Scheme 3 where hydride more favorably approaches the carbon of the carbonyl group from the least hindered side in both (2*R*)- and (2*S*)-prochiral ketones. Unlike CBS reduction, formation of the *syn* products as the major product from **7** might be attributable to a strong coordination of Lewis acid-typed reducing agent **6** on oxygen of the carbonyl. The enantiomeric purities of the unreacted ketones recovered are in good correspondences with those calculated from diastereomeric ratios of the corresponding product alcohols. This indicates that all the reductions by method B are also included with double asymmetric induction via partial kinetic resolutions.

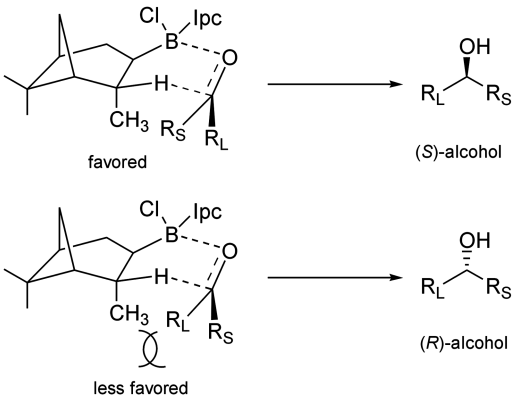
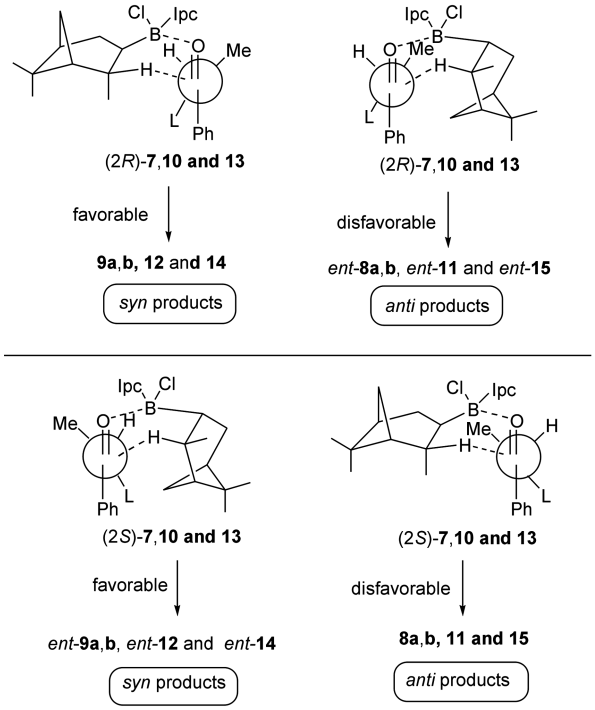


Figure 2



Scheme 3

Conclusion

We have developed a new synthetic route for preparation of optically active norephedrine **1**, norpseudoephedrine **2** and cathinone **3** by employing asymmetric reduction of *N*-protected 2-amino-1-phenylpropanone **7**, 2-azido-1-phenylpropanone **10** and 2-methanesulfonyloxy-1-phenylpropanone **13** using CBS-reagent (method A) and ^{d}Ipc$_2$BCl (method B) as chiral reducing agents under kinetic and non-kinetic conditions and found out that the reductions were included with double asymmetric induction via partial kinetic resolution. To our best knowledge, this is the first example for kinetic resolution of acyclic racemic ketones using these chiral reducing agents. The best results from method A were achieved by reduction of **10** and **13** to give (1*S*,2*R*)-**1** with 76% ee and (1*S*,2*S*)-**2** with 78% ee. Method B notably provided (1*R*,2*S*)-**1** and (*S*)-**3** with 96% ee from **11** and (1*R*,2*R*)-**2** and (*R*)-**3** with 93% ee from **9b**. Especially, only single isomer (1*R*,2*S*)-**1** with 78% ee was obtained from reduction of **13** using method B. This methodology provides alternative routes for preparation of chiral **1**-**3**, which are of

great importance as biologically active substances and chiral auxiliaries, ligands and catalysts for a variety of asymmetric synthesis.

Experimental Section

General. All operations with air-sensitive materials were carried out under a nitrogen atmosphere with oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by a flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 200, 300 or 400 MHz for ^{1}H and 50, 75 or 100 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$, CD_3OD or D_2O-DCl. *J*-values are given in Hz. Optical rotations were measured with a high resolution digital polarimeter. $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were uncorrected. Enantiomeric excesses (e.e.s) of the products were determined with a HPLC apparatus fitted with a 25 cm Whelk-O1 (Regis) chiral column.

Materials. Most of organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. THF was distilled over sodium benzophenone ketyl and stored in ampules under nitrogen atmosphere. The (*S*)-MeCBS reagent **4**, *N*-ethyl-*N*-isopropylaniline-borane complex **5** and (−)-*B*-chlorodiisopinocampheylborane (^{d}Ipc$_2$BCl, **6**) were purchased from the Aldrich Chemical Company.

General procedure for asymmetric reduction of 7, 10 and 13 using (*S*)-MeCBS-oxazaborolidine-catalyzed borane (method A) and (−)-*B*-chlorodiisopinocampheyl-borane (^{d}Ipc$_2$BCl; method B). Method A: To a solution of **4** (0.2 mmol; 0.2 M, 1.0 cm^3) in THF was added a solution of *N*-ethyl-*N*-isopropylaniline-borane complex **5** [2.0 mmol; 2.0 M, 1.0 mL for non-kinetic condition; or 0.34 mmol; 0.34 M, 1 mL for kinetic condition] in THF. To this was added slowly 2 mL of THF solution of ketones **7**, **10** or **13**, (2 mmol) over a period of 1.5 h using a syringe pump at 25 °C. After the addition, the reaction mixture was stirred for 10 min, quenched cautiously with methanol (0.5 cm^3), and stirred for additional 30 min. The solvent was evaporated under reduced pressure. The crude product alcohols obtained were further purified by a flash column chromatography on silica gel (230-400 mesh) using appropriate solvents as eluent.

Method B: An oven-dried, 10 mL round bottom flask equipped with a septum-capped side arm, magnetic stirring bar, and a connecting tube was cooled to room temperature in a stream of nitrogen. ^{d}Ipc$_2$BCl (**6**, 786 mg, 2.4 mmol) was transferred to the flask in a glove bag and dissolved in THF (0.5 mL). The solution was cooled to 0 °C and 2 mL of THF solution of **7**, **10**, or **13** (2.0 mmol) was added. The reaction mixture was maintained at 0 °C. After 72 h, to this was added acetaldehyde (160 mg, 3.6 mmol) dropwise at the same temperature. The mixture was warmed to room temperature and stirred for 4 h. After solvent was evaporated under reduced pressure, the residue was purified by a flash column chromatography on silica gel (230-400 mesh) using appropriate solvents as eluent. All the reductions examined in this study proceeded incompletely under these reaction conditions to be recovered 33-52% of starting materials from the reaction mixtures.

To determine absolute configuration of product alcohols, authentic **8a**, **8b**, **9a** and **9b** were prepared by treating (1*R*,2*S*)-norephedrine **1** and (1*R*,2*R*)-norpseudoephedrine **2** with Boc_2O and Cbz-Cl according to the literature.[19] **8a**: mp 91-92 °C (lit.[9a] 91-93 °C); $[\alpha]_D^{20}$ = -68.97 (*c* 1.02, $CHCl_3$), >99% ee {lit.[9a] $[\alpha]_J^{25}$ = -63 (*c* 0.06, $CHCl_3$), 95% ee}. **8b**: mp 94-95 °C; $[\alpha]_D^{20}$ = -44.6 (*c* 1.06, $CHCl_3$), >99% ee. **9a**: mp 84-85 °C (lit.[9a] 85-87°C); $[\alpha]_D^{20}$ = 37.58 (*c* 1.02, $CHCl_3$), >99% ee {lit.[9a] $[\alpha]_J^{25}$ = -32 (*c* 0.05, $CHCl_3$), 1*R*,2*R*}. **9b**: mp 62-63 °C; $[\alpha]_D^{20}$ = -40.51 (*c* 1.21, $CHCl_3$), >99% ee.

A) Reduction of 7 by method A.

A1) Reduction of 7a (non-kinetic conditions: use of 1.0 equiv. of 5): 96% yield (as diastereomeric mixture); white solid; HPLC analysis using a 25 cm Whelk-O1 chiral column showed a composition of 44% **8a**, 16% *ent*-**8a**, 34% **9a** and 6% *ent*-**9a** [analytical conditions: *iso*-PrOH/hexane: 1/99; flow rate: 0.7 mL/min; detector: 254 nm; t_R 25.99 min for **8a**, t_R 29.60 min for *ent*-**8a**, t_R 32.63 min for **9a** and t_R 38.12 min for *ent*-**9a**], which exhibited the formation of **8a** with 48% ee and **9a** with 70% ee.

A2) Reduction of 7a (kinetic conditions: use of 0.17 equiv. of 5): 40% yield (as diastereomeric mixture); white solid; HPLC analysis under the same analytical conditions as described above showed a composition of 64% **8a**, 10% *ent*-**8a**, 20% **9a** and 6% *ent*-**9a**. Unreacted ketone **7a** was recovered in 53% yield. R_f 0.25; white solid; mp 68-70 °C (lit.[9a] 70-72 °C); IR (KBr, cm^{-1}) 3336, 2973, 1710, 1682; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (3 H, d, *J* = 7.3, C*H*$_3$), 1.46 (9H, s, C(C*H*$_3$)$_3$), 5.30 (1H, quintet, *J* = 7.0, C*H*NH), 5.55 (1H, br s, N*H*), 7.49-7.61 (3H, m), 7.98 (2H, d, *J* = 8.2) (Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.51 (*C*H$_3$), 29.02 (C(*C*H$_3$)$_3$), 51.85 (*C*HNH), 80.40 (*C*Me$_3$), 129.43, 134.45, 135.02, 135.10 (Ar-*C*), 155.93 (NH*C*O), 200.20 (Ph*C*O); Its enantiomeric purty determined by HPLC analysis using the same column [*iso*-PrOH/hexane: 1/9; flow rate: 0.5 mL/min; detector: 254 nm; t_R (2*S*) 9.84 min and t_R (2*R*) 13.23 min] showed it to be 27% ee with the (*R*)-configuration.

A3) Reduction of 7b (non-kinetic conditions: use of 1.0 equiv. of 5): 95% yield (as diastereomeric mixture); white solid; HPLC analysis using a 25 cm Whelk-O1 chiral column showed a composition of 41% **8b**, 24% *ent*-**8b**, 27% **9b** and 8% *ent*-**9b** [analytical conditions: *iso*-PrOH/hexane: 1/40; flow rate: 0.7 mL/min; detector: 254 nm; t_R 44.50 min for **8b**, t_R 48.04 min for *ent*-**8b**, t_R 55.08 min for *ent*-**9b** and t_R 57.62 min for **9b**], which exhibited the formation of **8b** with 26% ee and **9b** with 55% ee.

A4) Reduction of 7b (kinetic conditions: use of 0.17 equiv. of 5): 45% yield (as diastereomeric mixture); white solid; HPLC analysis under the same analytical conditions as described above showed a composition of 57% **8b**, 15% *ent*-**8a**, 19% **9a** and 9% *ent*-**9a**. Unreacted ketone **7b** was recovered in 47% yield; R_f 0.54 (eluent: EtOAc/hexane 1 :

2); white solid; mp 88-89 °C; IR (KBr, cm^{-1}) 3378, 1707, 1696; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 7.0, CH_3), 5.14 (2H, s,PhCH_2), 5.33 (1H, quintet, J = 7.2, C*H*NH), 5.89 (1H, br s, CHN*H*), 7.26-8.00 (10H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.62 (*C*H$_3$), 52.32 (*C*HNH), 67.50 (Ph*C*H$_2$), 128.80, 129.38, 134.58, 134.68, 137.10 (Ar-*C*), 156.33 (NH*C*O), 199.61 (Ph*C*O). Its enantiomeric purty determined by HPLC analysis using the same column [*iso*-PrOH/hexane: 1/4; flow rate: 1.1 mL/min; detector: 254 nm; t_R (2*S*) 6.62 min and t_R (2*R*) 13.82 min] showed it to be 26% ee with the (*R*)-configuration.

B) Reduction of 10.

B1) Reduction of 10 (non-kinetic conditions: use of 1.0 equiv. of 5): The reduction of **10** provided an inseparable mixture of product alcohols **11**, *ent*-**11**, **12** and *ent*-**12** in 97% yield by a flash column chromatography on silica gel; oil; IR (neat, cm^{-1}) 3424, 2978, 2102; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (2.1H, d, J = 6.7, CH^A_3), 1.20 (0.9H, d, J = 6.4, CH^B_3), 2.20 (0.3H, d, J = 3.4, OH^A), 2.49 (0.7H, d, J = 3.1, OH^B), 3.68 (1H, m, C*H*N$_3$), 4.47 (0.7H, dd, J = 3.1, 7.3, CH^AOH), 4.75 (0.3H, t, J = 4.0, CH^BOH), 7.26-7.36 (5H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.90 (C^AH$_3$), 16.34 (C^BH$_3$), 62.77 (C^AHN$_3$), 63.95 (C^BHN$_3$), 76.81 (C^AHOH), 78.54 (C^BHOH), 126.85, 127.18, 128.52, 128.86, 129.02, 140.51 (Ar-*C*); A mixture of the azido alcohol (2 mmol), Boc_2O (2.4 mmol) and 10% Pd/C (40 mg) in EtOAc (2 cm^3) was hydrogenated using hydrogen balloon at room temperature for 24 h, filtered on a celite pad and the filtrate was concentrated to give a mixture of **8a** or *ent*-**8a** and **9a** or *ent*-**9a** in 89% yield. HPLC analysis of the product *N*-Boc amino alcohols displayed a composition of 5% **8a**, 24% *ent*-**8a**, 26% **9a** and 45% *ent*-**9a**.

B2) Reduction of 10 (kinetic conditions: use of 0.17 equiv. of 5): 43% yield (as diastereomeric mixture); oil; After the mixture of product alcohols were converted into *N*-Boc amino alcohols according to the procedure previously mentioned, HPLC analysis showed a composition of 10% **8a**, 22% *ent*-**8a**, 19% **9a** and 49% *ent*-**9a**. Unreacted ketone **10** was recovered in 50% yield; R_f 0.63 (eluent: EtOAc/hexane 1 : 2); oil; IR (neat, cm^{-1}) 2986, 2123, 1698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (3H, d, J = 6.9, CH_3), 4.70 (1H, q, J = 7.0, C*H*N$_3$), 7.47-7.59 (3H, m), 7.90-7.93 (2H, m, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 16.89 (*C*H$_3$), 58.87 (*C*HN$_3$), 128.83, 129.12, 134.12, 134.40 (Ar-*C*), 196.80 (Ph*C*O); Anal. calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.53; H, 5.14; N, 24.04%. After **10** was converted into **7a**,[9a] its enantiomeric purity determined by HPLC analysis with the same analytical condition described above was found to be 18% ee with the (*R*)-configuration.

C) Reduction of 13.

C1) Reduction of 13 (non-kinetic conditions: use of 1.0 equiv of 5): The reduction of **13** provided a mixture of 1,2-diol monomesylates **14**, *ent*-**14**, **15** and *ent*-**15** in 98% yield, which were not separated by a flash column chromatography on silica gel; white solid; IR (KBr, cm^{-1}) 3499, 1344, 1173; δ_H NMR (400 MHz, $CDCl_3$) 1.25 (2.16 H, d, J = 6.46, CH^A_3), 1.34 (0.84H, d, J = 6.30, CH^B_3), 2.58 (0.28H, br s, OH^A), 2.73 (0.72H, d, J = 3.52, OH^B), 2.81 (0.84H, s, CH^A_3SO$_2$), 2.94 (2.16H, s, CH^B_3SO$_2$), 4.66 (0.72H, dd, J = 3.30, 7.10, CH^AOH), 4.84 (1H, quintet, J = 6.65, C*H*OMs), 4.89 (0.28H, d, J = 4.29, CH^BOH), 7.26-7.38 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.84 (C^AH$_3$), 18.16 (C^BH$_3$), 38.20 (C^AH$_3$SO$_2$), 38.29 (C^BH$_3$SO$_2$), 77.57 (*C*HOMs), 82.50 (C^AHOH), 83.50 (C^BHOH), 126.75, 126,90, 128.37, 128.53, 128.74, 128.78, 139.09, 139.32 (Ar-$C^{A,B}$); Anal. cald. for $C_{10}H_{14}O_4S$: C, 52.16; H, 6.13; S, 13.92. Found: C, 52.33; H, 6.24; S, 14.04%; A mixture of 1,2-diol monomesylates (1 mmol) and sodium azide (1.2 mmol) in DMSO (2 mL) was heated at 80 °C for 2 h and then cooled to room temperature. To this was added water (2 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product obtained was further purified by a flash column chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane (1/2) as eluent to give a mixture of 2-azido-1-phenylpropanols in 82% yield. According to the procedure described above, the azido alcohols obtained were converted into *N*-Boc amino alcohols, **8a**, *ent*-**8a**, **9a** and *ent*-**9a**. HPLC analysis of these showed a composition of 25% **8a**, 46% *ent*-**8a**, 3% **9a** and 26% *ent*-**9a**.

C2) Reduction of 13 (kinetic conditions: use of 0.17 equiv of 5): 40% yield (as diastereomeric mixture); white solid; After the mixture of product alcohols were converted into *N*-Boc amino alcohols, its HPLC analysis showed a composition of 20% **8a**, 52% *ent*-**8a**, 6% **9a** and 22% *ent*-**9a**. Unreacted ketone **13** was recovered in 54% yield. R_f 0.31 (eluent: EtOAc/hexane 1 : 2); white solid; mp 92-94 °C; IR (KBr, cm^{-1}) 3016, 1696, 1357, 1175; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (3H, d, J = 7.2, CH_3), 3.14 (3H, s, CH_3SO$_2$), 6.04 (1 H, q, J = 7.0, C*H*OMs), 7.47-7.65 (3H, m), 7.90-7.94 (2H, m, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.14 (*C*H$_3$), 39.79 (*C*H$_3$SO$_2$), 77.45 (*C*HOMs), 128.81, 129.21, 133.82, 134.39 (Ar-*C*), 195.37 (Ph*C*O); Anal. calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.05. Found: C, 52.33; H, 5.41; S, 14.04%; Its enantiomeric purty determined by HPLC analysis [analytical conditions: *iso*-PrOH/hexane: 1/9; flow rate: 1.0 mL/min; detector: 254 nm; t_R (2*S*) 13.13 min and t_R (2*R*) 24.48 min] showed it to be 9% ee with (*R*)-configuration.

D) Reduction of 7 by method B.

D1) Reduction of 7a: 48% yield (as diastereomeric mixture); white solid; HPLC analysis showed a composition of 31% **8a**, 14% *ent*-**8a**, 52% **9a** and 3% *ent*-**9a,** which exhibited the formation of **8a** with 38% ee and **9a** with 89% ee. (*S*)-**7a** with 31% ee was recovered in 46% yield.

D2) Reduction of 7b: 40% yield (as diastereomeric mixture); white solid; HPLC analysis showed a composition of 30% **8b**, 8% *ent*-**8b**, 60% **9b** and 2% *ent*-**9b,** which exhibited the formation of **8b** with 58% ee and **9b** with 93% ee. (*S*)-**7b** with 19% ee was recovered in 52% yield.

E) Reduction of 10. 60% yield (as diastereomeric mixture); oil; After product alcohols were converted into *N*-Boc amino alcohols, HPLC analysis showed a composition of 17% **8a**, 0.3% *ent*-**8a**, 64.7% **9a** and 18% *ent*-**9a**, which

exhibited the formation of **8a** with 96% ee and **9a** with 56% ee. (*S*)-**10** with 46% ee was recovered in 33% yield. R_f 0.63 (eluent: EtOAc/hexane 1 : 2); oil; $[\alpha]_D^{20}$ = +65.92 (*c* 1.09, $CHCl_3$).

F) Reduction of 13. 55% yield as only **14**; R_f 0.25 (eluent: EtOAc/hexane 1 : 2); white solid; mp 81-82 °C; IR (KBr, cm^{-1}) 3524, 1337, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3 H, d, *J* = 6.46, C*H*$_3$), 2.73 (1 H, d, *J* = 3.52, O*H*), 2.94 (3 H, s, C*H*$_3$SO$_2$), 4.66 (1 H, dd, *J* = 3.30, 7.10, C*H*OH), 4.84 (1 H, quintet, *J* = 6.65, C*H*OMs), 7.26-7.38 (5 H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.16 (*C*H$_3$), 38.29 (*C*H$_3$SO$_2$), 77.57 (*C*HOMs), 83.50 (*C*HOH), 126,90, 128.53, 128.74, 139.32 (Ar-*C*); $[\alpha]_D^{18}$ = -39.29 (*c* 1.06, $CHCl_3$); HPLC analysis of **8a** prepared from **14** showed it to be 78% ee. (*S*)-**13** with 95% ee was recovered in 38% yield; $[\alpha]_D^{18}$ = -106.92 (*c* 0.99, $CHCl_3$).

Isolation of optically active 8 and 9.

A) (1*R*,2*S*)-*N*-Boc-norephedrine 8a. Reductions of **7a** using method A and **10** using method B are representative (Table 1, entry 2 and Table 2, entry 3). 57% yield from **7a** and 9% yield from **10** by catalytic hydrogenation according to aforementioned procedure; R_f 0.39 (eluent: EtOAc/hexane 1 : 2); white solid; mp 85-86 °C (lit.[9a] 91-93 °C); IR (KBr, cm^{-1}) 3403, 3375, 2980, 1684; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (3 H, d, *J* = 6.7, C*H*$_3$), 1.46 (9 H, s, C(C*H*$_3$)$_3$), 3.31 (1 H, br s, N*H*), 4.0 (1 H, m, C*H*NH), 4.67 (1 H, br s, O*H*), 4.85 (1 H, m, C*H*OH), 7.26-7.36 (5 H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.43 (*C*H$_3$), 29.00 (C(*C*H$_3$)$_3$), 52.78 (*C*HNH), 77.40 (*C*Me$_3$), 80.47 (*C*HOH), 127.14, 128.19, 128.96, 141.61 (Ar-*C*), 157.08 (NH*C*O); Their optical purities determined by HPLC analysis were found to be 48% ee from **7a** by method A and 96% ee from **10** by method B with the (1*R*,2*S*)-configuration [t_R (1*R*,2*S*) 25.99 min and t_R (1*S*,2*R*) 29.60 min]; $[\alpha]_D^{20}$ = -30.5 (*c* 1.12, $CHCl_3$), 48% ee and $[\alpha]_D^{20}$ = -67.28 (*c* 1.09, $CHCl_3$), 96% ee {lit.[9a] $[\alpha]_J^{25}$ =-63 (*c* 0.06, $CHCl_3$), 95% ee}.

(1*R*,2*S*)-*N*-Cbz-norephedrine 8b. Reduction of **7b** using method B is representative (Table 2, entry 2). 15% yield; R_f 0.28 (eluent: EtOAc/hexane 1 : 2); white solid; mp 92-93 °C; IR (KBr, cm^{-1}) 3438, 3326, 1686, 1660; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (3 H, d, *J* = 6.7, C*H*$_3$), 2.89 (1 H, br s, N*H*), 4.04 (1 H, m, C*H*NH), 4.87 (1 H, br s, O*H*), 5.00 (1 H, d, *J* = 7.9, C*H*OH), 5.11 (2 H, s, PhC*H*$_2$), 7.25-7.35 (10 H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.09 (*C*H$_3$), 53.09 (*C*HNH), 61.48 (Ph*C*H$_2$), 67.55 (*C*HOH), 126.90, 128.32, 128.93, 137.13, 141.41 (Ar-*C*), 157.18 (NH*C*O); HPLC analysis showed it to be 58% ee with the (1*R*,2*S*)-configuration [t_R (1*R*,2*S*) 44.50 min and t_R (1*S*,2*R*) 48.04 min].

B) (1*R*,2*R*)-*N*-Boc-norpseudoephedrine 9a. Reduction of **7a** using method B is representative (Table 2, entry 1). 26% yield; R_f 0.32 (eluent: EtOAc/hexane 1 : 2); white solid; mp 83-85 °C (lit.[9a] 85-87 °C); IR (KBr, cm^{-1}) 3409, 3367, 2971, 1671; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (3 H, d, *J* = 6.7, C*H*$_3$), 1.41 (9 H, s, C(C*H*$_3$)$_3$), 3.31 (1 H, br s, N*H*), 3.88 (1 H, m, C*H*NH), 4.55 (1 H, dd, *J* = 3.82, 5.96, C*H*OH), 4.66 (1 H, br s, O*H*), 7.27-7.35 (5 H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.28 (*C*H$_3$), 29.00 (C(*C*H$_3$)$_3$), 53.18 (*C*HNH), 78.81 (*C*Me$_3$), 80.47 (*C*HOH), 127.14, 128.19, 128.96, 142.41 (Ar-*C*), 157.19 (NH*C*O); HPLC showed it to be 89% ee with the (1*R*,2*R*)-configuration [t_R (1*R*,2*R*) 32.63 min and t_R (1*S*,2*S*) 38.12 min]; $[\alpha]_D^{20}$ = -33.42 (*c* 0.99, $CHCl_3$) for 89% ee {lit.[9a] $[\alpha]_J^{25}$ = -32 (*c* 0.05, $CHCl_3$), 1*R*,2*R*}.

C) (1*R*,2*R*)-*N*-Cbz-norpseudoephedrine 9b. Reduction of **7b** using method B is representative (Table 2, entry 2). 24% yield; R_f 0.24 (eluent: EtOAc/hexane 1 : 2); white solid; mp 61-62 °C; IR (KBr, cm^{-1}) 3421, 3303, 1690, 1542; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (3 H, d, *J* = 6.7, C*H*$_3$), 2.89 (1 H, br s, N*H*), 3.95 (1 H, m, C*H*NH), 4.59 (1 H, d, *J* = 5.5, O*H*), 5.00 (1 H, d, *J* = 7.9, C*H*OH), 5.05 (2 H, s, PhC*H*$_2$), 7.25-7.35 (10 H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.32 (*C*H$_3$), 36.93 (*C*HNH), 53.43 (Ph*C*H$_2$), 67.45 (*C*HOH), 127.19, 128.79, 129.17, 137.16, 142.06 (Ar-*C*), 157.31 (NH*C*O); HPLC analysis showed it to be 93% ee with the (1*R*,2*R*)-configuration [t_R (1*S*,2*S*) 55.08 min and t_R (1*R*,2*R*) 57.62 min]; $[\alpha]_D^{20}$ = 37.60 (*c* 1.35, $CHCl_3$).

Preparation of (1*R*,2*S*)-norephedrine (1*R*,2*S*)-1 from 8a.

To a solution of **8a** with 96% ee (1 mmol) in EtOAc (4 mL) was added 3 *N* HCl solution (2 mL) and stirred at room temperature for 1 h. The mixture was basified with 6 *N* NaOH solution and extracted with CH_2Cl_2 (3 × 5 mL). The combined extract was dried over anhydrous Na_2SO_4, filtered, concentrated and crystallized with ether-hexane to give (1*R*,2*S*)-**1** in 90% yield; white solid; mp 49-51 °C (lit.[22] 51-52 °C); IR (KBr, cm^{-1}) 3338, 3063, 1605, 1452; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (3 H, d, 3H, *J* = 6.7, C*H*$_3$), 2.40 (3 H, br s, N*H*$_2$ + O*H*), 3.13 (1 H, quintet, *J* = 5.7, C*H*NH$_2$), 4.50 (1 H, d, *J* = 4.6, C*H*OH), 7.23-7.37 (5 H, m, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.62 (*C*H$_3$), 52.64 (*C*HNH$_2$), 77.06 (*C*HOH), 127.23, 128.11, 128.85, 142.16 (Ar-*C*); HPLC analysis of **8a** obtained from treatment of this product with Boc_2O showed it to be 96% ee; $[\alpha]_D^{20}$ = -14.71 (*c* 1.83, EtOH){lit.[9b] $[\alpha]_D^{20}$ = -14.6 (*c* 3.4, EtOH), 1*R*,2*S*}.

Preparation of (1*R*,2*R*)-norpseudoephedrine (1*R*,2*R*)-2 from 9b.

A mixture of **9b** with 93% ee (0.5 mmol) in 6 *N* HCl solution (2 mL) was heated to reflux for 1 h. The mixture was basified with 6 *N* NaOH solution and extracted with CH_2Cl_2 (3 × 5 mL). The combined extract was dried over anhydrous Na_2SO_4, filtered, concentrated and crystallized with ether-hexane to give (1*R*,2*R*)-**2** in 89% yield; white solid; mp 60-61 °C; IR (KBr, cm^{-1}) 3354, 3032, 1584, 1448; ^{1}H NMR (200 MHz, D_2O-1 *N* DCl)) δ 0.71 (3 H, *J* = 7.0, C*H*$_3$), 3.19 (1 H, m, C*H*NH$_2$), 4.25 (1 H, d, *J* = 8.6, C*H*OH), 6.99-7.02 (5 H, m, Ar*H*); ^{13}C NMR (50 MHz, D_2O-1 *N* DCl) δ 14.73 (*C*H$_3$), 52.88 (*C*HNH$_2$), 74.95 (*C*HOH), 127.11, 129.14. 139.40 (Ar-*C*); [a] 30.29 (*c* 1.29, EtOH){lit.[9b] $[\alpha]_D^{20}$ = -32.6 (*c* 3.5, EtOH), 1*R*,2*R*}; For (1*R*,2*R*)-**2**·HCl: $[\alpha]_D^{20}$ = -37.67 (*c* 1.02, H_2O){lit.[15] $[\alpha]_D$= -38.9 (*c* 1.0, H_2O), 1*R*,2*R*.}.

Preparation of (*S*)-2-amino-1-phenylpropanone hydrochloride [(S)-cathinone·HCl] (*S*)-3·HCl from 8a.

According to the literature procedure,[9a] a solution of **8a** (1 mmol) with 96% ee was added to a suspension of PCC (1.5

mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 2 h. After ether (10 mL) was added, the mixture was filtered on a celite short column. The column was washed with ether (3 × 10 mL). The combined filtrate was dried over anhydrous $MgSO_4$, filtered and concentrated. Crude product was further purified by a flash column chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane (1/2) as eluent to give (*S*)-2-*N*-Boc-amino-1-phenylpropanone **7a** in 82% yield; R_f 0.25; white solid; mp 68-70 °C (lit.[9a] 70-72 °C); $[\alpha]_D^{20}$ -2.25 (*c* 1.15, $CHCl_3$) {lit.[9a] $[\alpha]_J^{25}$ 2 (*c* 0.03, $CHCl_3$), *S*, >95% ee}; HPLC analysis [*iso*-PrOH/hexane: 1/9; flow rate: 0.5 cm^3/min; detector: 254 nm; t_R (2*S*) 9.84 min and t_R (2*R*) 13.23 min] showed it to be 96% ee with (*S*)-configuration; All of IR, ^1H and ^{13}C NMR spectra of this compound were identical with those of its (*R*)-isomer. A solution of (*S*)-**7a** (1 mmol) with 96% ee in EtOAc (4 cm^3) was treated with 3 *N* HCl solution at room temperature for 1 h. The mixture was concentrated and the residue was recrystallized from *iso*-PrOH-Et_2O to give (*S*)-**3**·HCl in 89% yield: white solid; mp 179-181 °C (lit.[9a] 180-182 °C); IR (KBr/cm^{-1}) 3442, 3005, 1688, 1497; ^1H NMR (400 MHz, CD_3OD) δ 1.57 (3 H, d, J = 6.6, CH_3), 5.14 (1 H, q, J = 6.7, C$H$$NH_2$), 7.58-7.61 (2 H, m), 7.73 (1 H, m), 8.06 (2 H, d, J 7.5) (ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.20 (CH_3), 53.33 (CHNH_2), 130.37, 130.76, 134.61, 136.22 (Ar-*C*), 197.68 (Ph*C*O); These NMR spectra data were identical with those of literature values.[9a]; $[\alpha]_D^{20}$ = -45.2 (*c* 1.20, H_2O), 96% ee {lit.[9a] $[\alpha]_J^{25}$ = -48 (*c* 0.02, H_2O), >95% ee}.

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