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Convenient Method for Synthesis of *N*-Protected α-Amino Epoxides: Key Intermediates for HIV Protease Inhibitors

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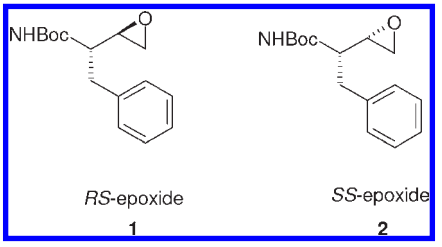
Supporting Information

ABSTRACT: A convenient method for synthesis of 2*R*,3*S* and 2*S*,3*S* *N*-Boc phenylalanine epoxides using readily available allylamine is described. Previous methods employed multistep synthetic routes from L-phenyl alanine that include use of *m*-chloroperbenzoic acid (*m*-CPBA) and a chromatographic method for purification of the desired diastereomers. Column purification could be eliminated by bringing in much improvement in the existing process. The process was further enhanced by replacing *m*-CPBA with oxone, an ecofriendly reagent advantageous for commercial application. The overall green process discussed involves the recovery and recycling of enantiomers of chiral allyl amines and judicial separation of diastereomers of the epoxides using simple economical methods.

1. INTRODUCTION

Optically active α-amino alkyl epoxides are key building blocks for the synthesis of active pharmaceutical ingredients. In particular, the two diastereomers 2*R*,3*S* and 2*S*,3*S* *N*-Boc phenylalanine epoxides (**1** and **2** respectively) form essential intermediates for HIV protease inhibitors viz. Atazanavir[1] (involves 2*R*,3*S*) as well as Saquinavir,[2b] Nelfanavir,[3] and Fosamprenavir[4] (involves 2*S*,3*S*). Several synthetic approaches reported in literature[5a] (Figure 1) start from L-phenyl alanine and build up to synthons such as aldehyde (**I**),[5b,5c] 1,2-diols (**II**),[5d,5e] halomethyl derivatives (**III**),[5f−5h] or α-substituted allyl amines (**IV**).[5i]



Difficulties associated with the industrial application of these methods include the multistep transformations from the amino acid and use of expensive reagents. Our approach was to use an alternative route with a minimum number of steps, starting from easily available raw material other than an amino acid and then adopting a green synthetic process along the pathway. Compound **IV** was chosen as the preferred precursor. Retrosynthetic analysis of **IV** (Scheme 1) suggested commercially available allyl amine, as a possible starting raw material.

α-Alkylation of allyl amine is enabled by its conversion to a Schiff base. Stereoselective alkylation reaction is possible at this stage using sterically hindered or chiral allyl imines.[6] Use of such

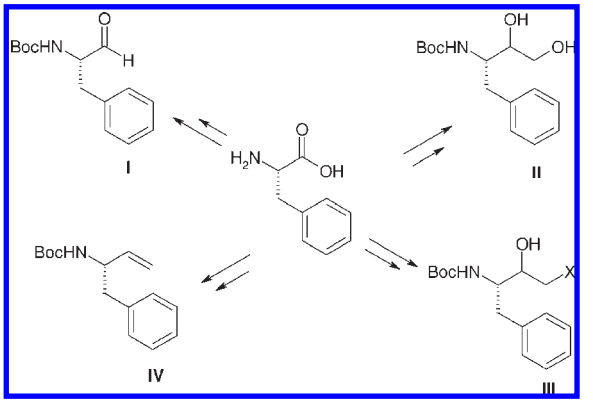


Figure 1. Conversion of amino acid to intermediates required for synthesis of epoxides.

a technique adds not only to the number of steps but also to the cost. This led us to consider classical resolution, and the scheme intended was for making racemic α-alkyl allyl amine. A route was designed (Scheme 2) using a simple ketone such as benzophenone for making a Schiff base of allyl amine **3** which on alkylation with benzyl halide and subsequent hydrolysis would form racemic α-benzyl allyl amine **5**. A "low waste green process" approach was followed using diastereomeric crystallization coupled with racemisation. The final step of epoxidation leads to the desired diastereomers **1** and **2**. Literature describes epoxidation using *m*-chloroperbenzoic (*m*-CPBA) acid and use of a chromatographic method for separation of the diastereomers. The hazards associated with *m*-CPBA and cost ineffectiveness of column

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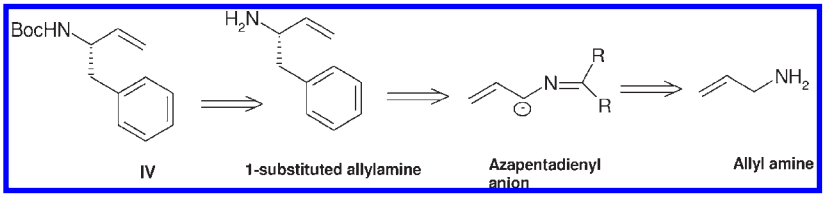
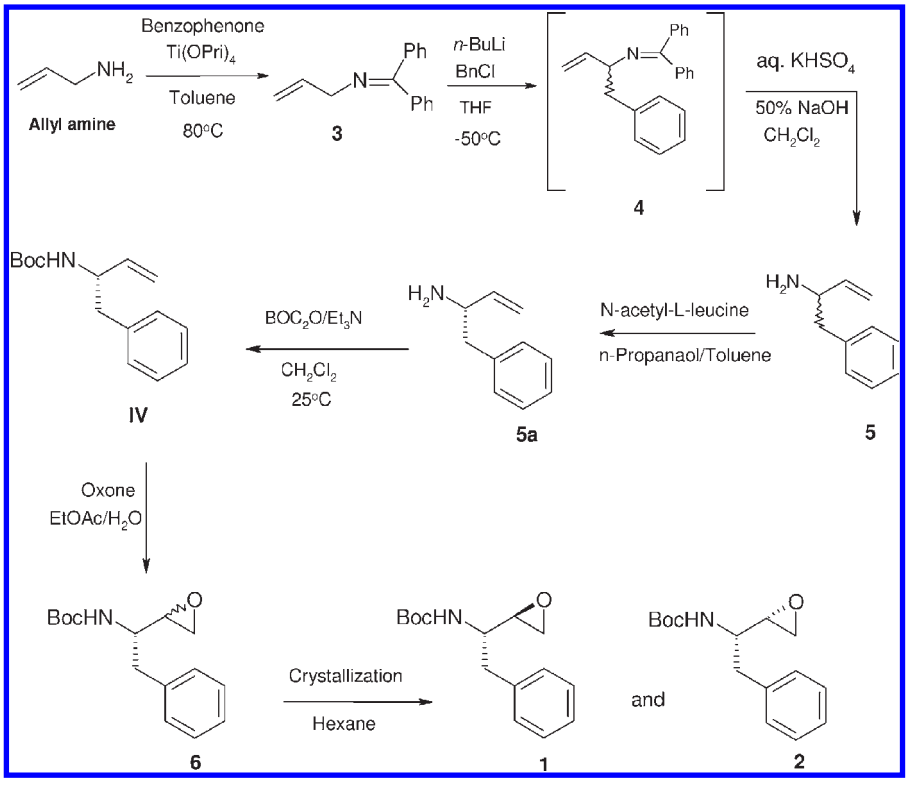
Scheme 1. Retrosynthetic analysis for *N*-protected 1-substituted amine



Scheme 2. Synthetic route for the synthesis of 1 and 2



chromatography for an industrial large scale process incited us to look for an alternate reagent and an effective separation method. Thus herein we report a green industrially feasible process for preparation of pharmaceutically important 2*S*,3*S* and 2*R*,3*S* *N*-Boc phenylalanine epoxides using a single synthetic route.

2. RESULTS AND DISCUSSION

Reaction of allyl amine with benzophenone is described in literature in the presence of $TiCl_4$ with a reaction time of 48 h. Replacing $TiCl_4$ with a cheaper reagent such as $Ti(OPri)_4$ resulted in the reduction of reaction time to 6 h and an increase in yield from 88−92%[7,8] to >98% (purity >96% GC a/a). Another obvious advantage was easy handling of $Ti(OPri)_4$ which enhanced the scope of application of the reaction on a commercial scale (Scheme 2). The benzophenone used was recovered in the subsequent reaction and purified for further reuse.

As alkylation of allyl imine at the C-3 position is known to be kinetically controlled, all reactions were carried out at −50 °C. The nature of the alkylating reagent was also a significant factor, and the yield improved from 50% using benzyl bromide to 74% with the chloride derivative. A number of bases were screened for the reaction (Figure 2). Bases such as $LiNH_2$, PhLi, and LiHMDS showed practically no formation of alkylated imine **4** and a disproportionate presence of only ∼60% unreacted imine **3**. On the other hand moving from *sec*-BuLi, to a mixture of *n*-BuLi and *t*-BuOK, to only *n*-BuLi, a >40% increase in formation of **4** (44% to 84%) was observed. The studies led to the choice of *n*-BuLi as the base for alkylation.

A subsequent solvent selection screening (Figure 3) showed THF to be the best solvent for the reaction. Thus with benzyl chloride in the presence of *n*-BuLi in THF, amine **5** could be isolated in 74% yield with ≥97% purity (GC, a/a).

To develop a method for resolution of the racemic amine **5**, readily available chiral resolving agents, such as L-tartaric acid (TA), L-ditolyl tartaric acid (DTTA), and *N*-acetyl-L-leucine (NAL) were tried. The tartrate salt of amine (±)-**5** was found to be highly soluble in various alcoholic solvents viz. methanol, isopropanol, and *n*-propanol, thereby making crystallization ineffective. A fruitful result was obtained with DTTA in methanol whereby the DTTA salt of **5a** was isolated with 90% *ee* (corresponding to free base) in 27% yield (Table 1). Efforts to

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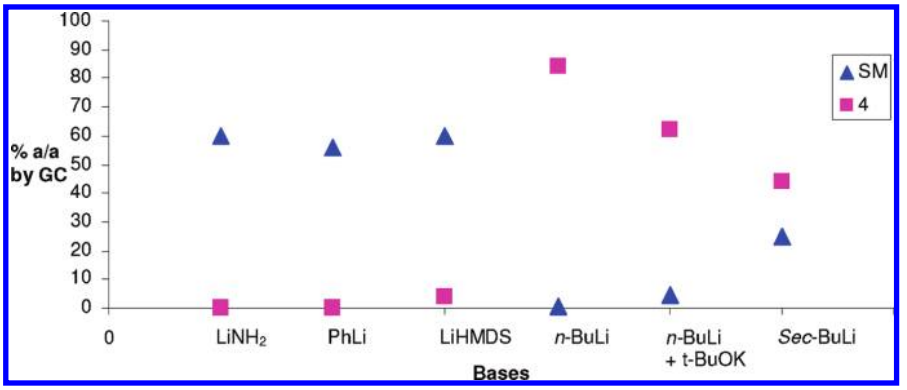

Figure 2. Benzylation of **3** with benzyl chloride at −50 °C in THF using different bases. Compound **3** (1 equiv) in THF (5 v/w) was cooled to −50 °C. A respective base (1 equiv) was added at −50 °C over a period of 1 h. The reaction mixture was maintained at −50 °C for an additional 1 h, followed by addition of benzyl chloride (1 equiv) in THF (1 v/w). The reaction mass was then stirred for 1 h, quenched in EtOH, and analysed on GC.

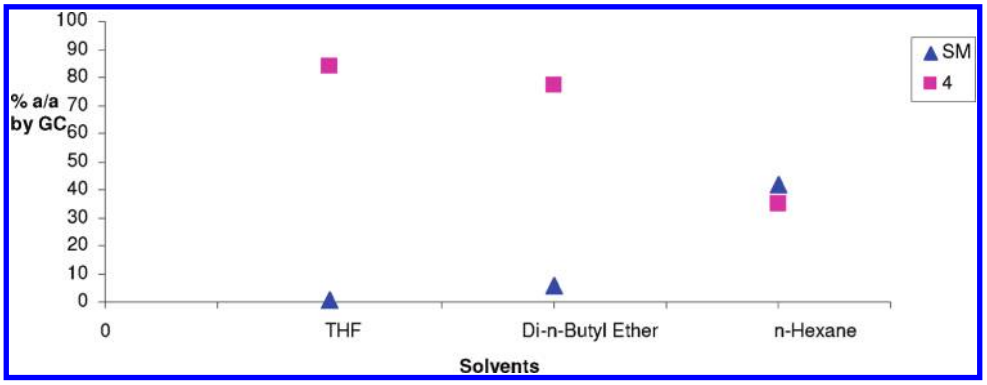

Figure 3. Benzylation of **3** with benzyl chloride at −50 °C in different solvents; *n*-BuLi was used as a base. Compound **3** (1 equiv) in respective solvent (5 v/w) was cooled to −50 °C. *n*-BuLi (1.6 M, 1 equiv) was added at −50 °C over a period of 1 h. The reaction mixture was maintained at −50 °C for an additional 1 h, followed by addition of benzyl chloride (1 equiv) in respective solvent (1 v/w). The reaction mass was then stirred for 1 h, quenched in EtOH, and analysed on GC.

Table 1. Resolution using chiral reagent (0.55 equiv) in methanol

Sr. No	Reagent	Volume (w/v)	%ee (S)	Yield[a]
1	TA	5	-	0
2	DTTA	25	90	27
3	NAL	12	82	28

[a] The yields are of the isolated products, based on racemate.

Table 2. Resolution using DTTA (0.55 equiv) in different solvents

Sr. No	Solvent	Volume (w/v)	%ee (S)	Yield[a]
1	MeOH	25	90	27
2	MeOH/water	15/2	50	33
3	MeOH/*n*-BuOH	20/6	0	38
4	IPA	12	0.1	100
5	IPA/water	13/2	17	90

[a] The yields are of the isolated products, based on racemate.

improve the yield further by using different solvents (Table 2) or upgrade *ee* by a second crystallization were not successful.

N-Acetyl-L-leucine was then revisited and a subsequent solvent selection screen showed *n*-PrOH/Toluene to be the best solvent for this resolution (Table 3). In two crystallizations NAL salt of **5a** having 98% *ee* (corresponding to free base) was obtained in 35% overall yield. Recovery and reuse of binary solvent was also studied. Binary solvent was recovered in 80% yield; the desired ratio was readjusted and reused to achieve reproducible results.

Table 3. Resolution using NAL (0.55 equiv) in different solvents

Sr. No	Solvent	Volume (w/v)	%ee (S)	Yield[a]
1	MeOH	5	82	28
2	*n*-PrOH	20	80	35
3	IPA	5	–	Salt highly soluble
4	*n*-BuOH	20	68	33
5	MeOH/Toluene	3/20	80	35
6	*n*-PrOH/Toluene	7/20	84	40
7	*n*-PrOH/Toluene	10/10	80	36

[a] The yields are of the isolated products, based on racemate.

Thus *N*-acetyl-L-leucine (NAL) seems to be the chiral reagent of choice for the resolution of racemic amine **5**. Operating through a combination of two crystallizations with maximizing yield in the first and chiral purity in the second, an efficient resolution process with NAL has thus been developed.

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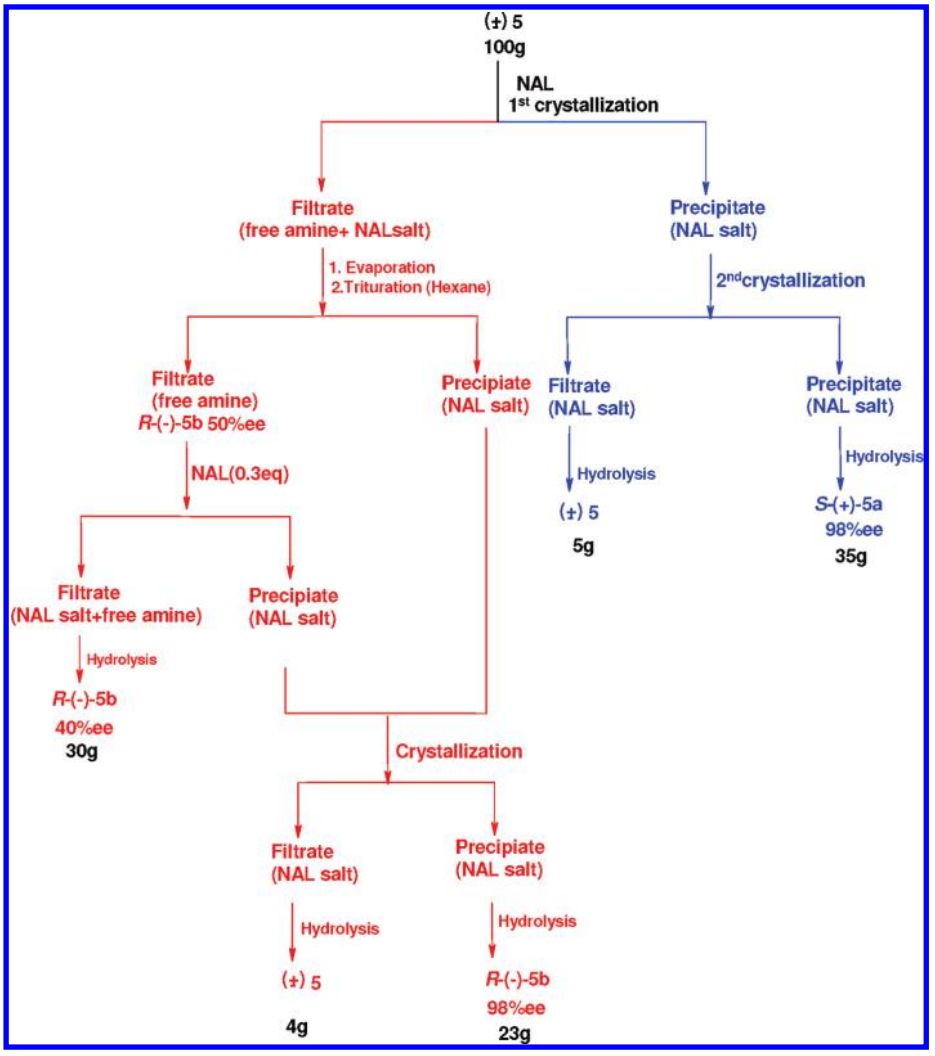


Figure 4. Resolution of racemic allyl amine (±)-**5** using NAL.

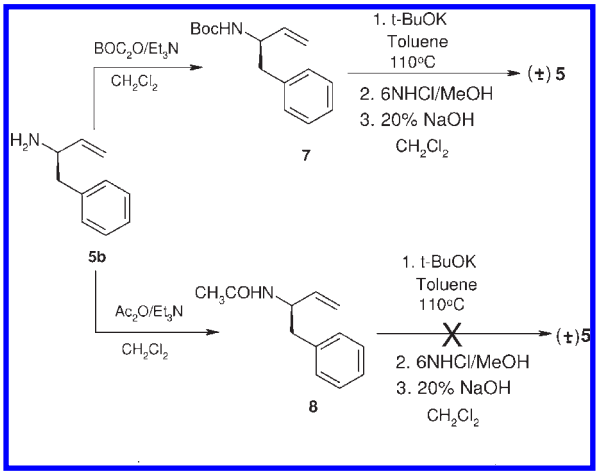
As depicted in Figure 4 additional experimentation with the filtrate of resolved *S* isomer **5a** resulted in (i) recovery of the racemic mixture, (ii) isolation of the *R* isomer **5b** (Scheme 3) having 98% *ee*, (iii) recovery of *R*-isomer **5b** having 40% *ee*, (iv) a 97% material balance. The racemic mixture was recycled into the process.

A scheme was designed for recycling of the *R*-isomer based on racemisation of the *N*-acetyl or *N*-Boc derivative, followed by extraction of the chiral proton using an alkoxide base such as *t*-BuOK (Scheme 3). *N*-Acetyl derivative **8** was found to be unstable in the presence of *t*-BuOK, whereas *N*-Boc derivative **7** racemised effectively to a 60:40 ratio of *R*/*S*.

The scheme was then integrated into a semicontinuous "resolution−recycle" process as depicted in Figure 5.

Epoxidation of allyl amine (*S* isomer) reported in literature makes use of *m*-CPBA[9] to form selectively the *RS*-isomer with 74% *de*. With long reaction hours and excess *m*-CPBA, the minor *SS* epoxide is preferentially decomposed improving the *de* of *RS*-epoxide to >98%. Disadvantages of the route include (i) a low purity of the desired product and (ii) use of chromatographic method for purification. These factors are due to generation of byproducts oxazolidinones **9** and **10** formed from the decomposition of epoxides (Figure 6).[10]

Scheme 3. Racemization of 5b



Investigation of the process revealed that other than oxazolidinones excess *m*-CPBA also led to formation of a byproduct viz. bis-benzoyl peroxide **11**. It was observed that reducing the molar equivalents from 4 to 1.5 enhanced the purity of the *RS*-isomer

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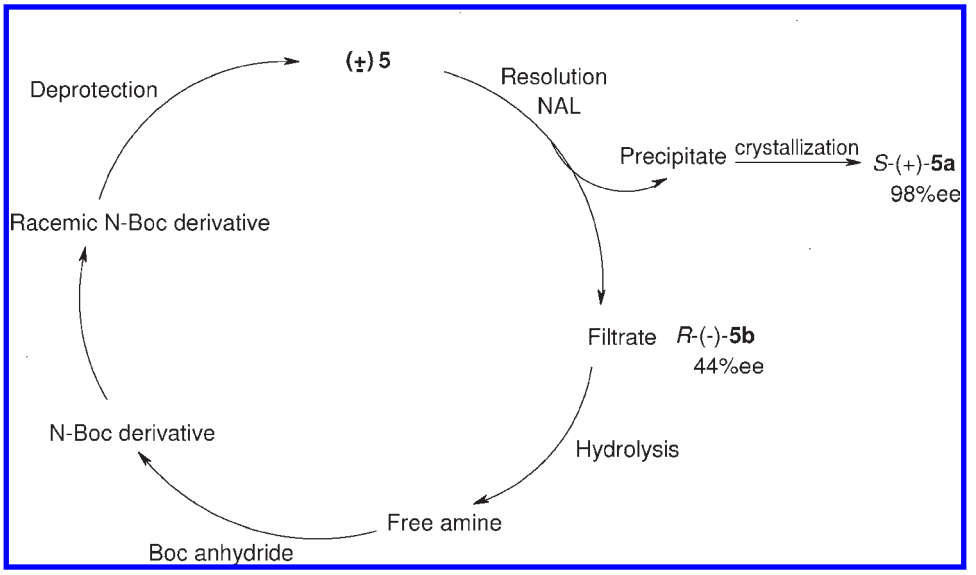

Figure 5. "Resolution−recycle" process of amine (±)-**5**.

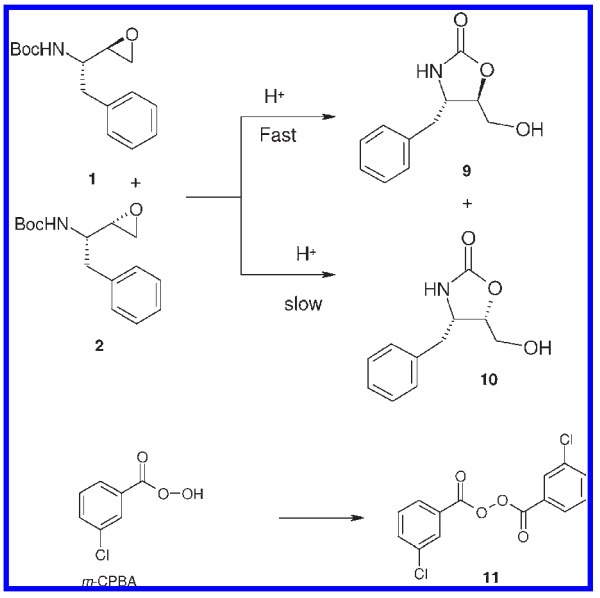

Figure 6. Impurities formed during *m*-CBPA epoxidation.

while maintaining its *de* of >99% (Table 4). Reducing the quantity of *m*-CPBA further to 1.0 mol equiv increased the reaction time required to decompose the *SS*-isomer to <1% which again affected the purity of the *RS*-isomer. Thus keeping a balance between the reaction time and quantity of *m*-CPBA, 1.5 mol equiv of *m*-CPBA was derived as the optimal condition for epoxidation. But even under these conditions purification by any method other than column chromatography failed to succeed.

An approach was needed which would allow formation of the *RS*-isomer with the desired *de* while sustaining its purity, which as a corollary would facilitate the purification. Due to the fact that the differential rate of decomposition of the diastereomers was acid initiated, the search for a mild acid which would generate minimal byproduct was a viable option. Experiments were planned where *m*-CPBA was used only to the point of completion of

Table 4. Epoxidation[10] of 6 using *m*-CPBA in MDC at 40 °C

Sr. No	*m*-CPBA (equivalent)	Time (h)	IV	HPLC (a/a) Purity of epoxide (%)	*RS*/*SS*
1	4	8	–	67	99:1
2	1.5	11	–	79	99:1
3	1	23	–	65	99.6:0.4

the epoxidation reaction, and the reaction was terminated just as the allyl amine **IV** was consumed. Screening various solvents suitable for isolation led to hexane, and *RS*-epoxide was isolated in hexane in 90% purity (HPLC, a/a) and 80% *de*. Differential decomposition of the isomers was then tried with benzoic acid, acetic acid, and formic acid. In benzoic acid and acetic acid the rate of decomposition was very slow. A comparable result with *m*-CPBA (1.5 equiv) was obtained by using formic acid (1.0 equiv) whereby in 8 h the *de* of *RS*-epoxide was >99% with 80% HPLC purity (Table 5). Optimization with molar equivalents of formic acid and reaction temperature (Table 6) resulted in a sustained purity of the *RS*-epoxide of ~90% (HPLC, a/a) with *de* > 99.5%! The results enabled us to circumvent chromatographic purification which was not possible earlier and use crystallization to obtain *RS*-epoxide with ≥97% purity and 99.6% *de* albeit at 25% yield (based on the diastereomeric mixture).

In pursuit of a greener process with "no decomposition" and consequently a commendable yield, we were encouraged to investigate other oxidizing reagents milder than *m*-CPBA viz. H_2O_2[11] and oxone.[12] The reaction rate was found to be very slow in H_2O_2, and epoxidation remained incomplete. Reaction with oxone was found to be much cleaner with no impurity formation (even after a lengthy reaction time) and most importantly with little difference in selectivity achieved with *m*-CPBA. As a result epoxide **6** was isolated in quantitative yield with an *RS*/*SS* ratio of 73:27 (Figure 7). Triturating the above mixture with hexane at low temperature allowed precipitation of a solid enriched in the *SS* isomer. The *RS* isomer was subsequently isolated from the filtrate in 71% yield (91% yield based on diastereomeric purity) with 97% purity (HPLC, a/a) and 94% *de*. Thus by utilizing

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epoxidation with oxone rather than *m*-CPBA, significant improvements were achieved: (i) decomposition and formation of byproducts were avoided; (ii) a high yield was achieved; (iii) column chromatography was circumvented; (iv) the process was simplified by use of crystallization for purification. A further added benefit was the isolation of the *SS*-epoxide **2** in 90% *de* and 98% purity (HPLC, a/a) in 18% yield. This amounts to an overall 89% recovery of combined diastereomers. Thus an ultimate green process was developed, which allowed judicial segregation of the two respective 2*R*,3*S* and 2*S*,3*S* *N*-Boc phenylalanine epoxides of equal pharmaceutical importance.

Table 5. Decomposition[a] of epoxides in different acids (1 mol equiv) in MDC at 40 °C

Sr. No	Acid	pK_a	Time (h)	HPLC (a/a) Purity of epoxide (%)	*RS*/*SS*
1	*m*-CBPA	3.82	23	65	99.6:0.4
2	Benzoic acid	4.2	24	84	94:6
3	Acetic acid	4.76	63	88	97:3
4	Formic acid	3.77	8	80	99:1

[a] Crude epoxide (*RS*/*SS* 90:10) purity 90% (HPLC, a/a) was taken in MDC. To this respective acid, 1 equiv was added and heated to 40 °C.

Table 6. Decomposition[a] study of epoxide in formic acid in MDC

Sr. No	Mol equiv	Temp (°C)	Time (h)	HPLC (a/a) Purity of **1** (%)	*RS*
1	2	40	4	86	99.9
2	3	40	2	86	99.9
3	3	25	8	89	99.8

[a] Crude epoxide (1 equiv) was taken in MDC. To this formic acid, 1 equiv was added and heated to 40 °C.

3. CONCLUSIONS

In conclusion, by employing readily available allylamine and an ecofriendly reagent, a convenient industrially feasible method for the synthesis of the amino epoxides in high diastereomeric purity has been developed. The scheme includes resolution at two stages: (i) enantiomers of allylamine and (ii) diastereomers of epoxide. In recognition of the necessity for favorable process economics, an approach of "minimal loss and maximum exploitation" in resolution was adapted. This led to (1) the recycling of waste enantiomer and (2) a process for making optically pure chiral building blocks: (i) *S*-allyl amine **5a**, (ii) *R*-allyl amine **5b**, (iii) *RS*-amino epoxide **1**, and (iv) *SS*-amino epoxide **2**.

4. EXPERIMENTAL SECTION

Instrumentation and Materials. *^{1}H NMR.* A Bruker 300 MHz instrument with tetramethylsilane as reference was used. Chemical shifts were reported as (δ) values in parts per million. The following abbreviations were used: s, singlet; d, doublet; m, multiplet; dd, doublet of doublets; and br s, broad signal.

^{13}C NMR. Spectra were recorded at 75 MHz.

MS. A Shimadzu QP 2010 instrument was used.

Melting Points. A Lab India MR-V/S melting point apparatus was used, and the measurements are uncorrected.

FT-IR. Perkin-Elmer spectrophotometer.

Optical Rotations. Jasco P-1020 polarimeter at λ 589 nm and 25 °C.

Techniques. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under nitrogen.

Solvents. THF (anhydrous), MTBE (methyl tertiary butyl ether), toluene, MeOH, CH_2Cl_2, EtOAc, and *n*-propanol were purchased from RFCL Ltd.

Reagents. Allyl amine, benzophenone, titanium isopropoxide, *N*-acetyl-L-leucine, and DTTA were purchased commercially from Arrow Biochem. Benzyl bromide was purchased from Spectrochem. *n*-BuLi was purchased from ACROS ORGANICS.

GC Analytical Method. For the GC analysis of allyl amine, **3**, **4**, **5**, **IV**, and **7**, a Perkin-Elmer Clarus 500 GC chromatograph

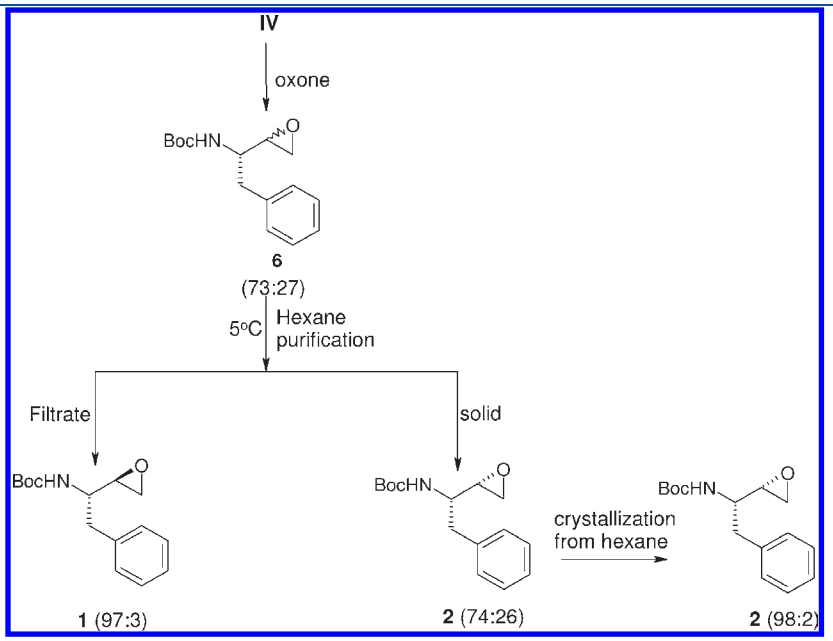

Figure 7. Schematic presentations for isolation of epoxides.

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equipped with an FID detector was used. The GC method used included the following: capillary column, DB-1 30 m × 0.32 mm, 1.0 μm with USP G1 packing; carrier gas, nitrogen with inlet pressure of 12 psi; temperature of injector and detector, 250 °C; oven programme, 50 °C, 5 min hold, ramped to 300 °C @10 °C/min, 10 min hold. Retention times of the compounds observed were as follows: Allyl amine, R_t 1.8 min; **3**, R_t 24.5 min; **4**, R_t 29.8 min; **5**, R_t 16.2 min; **IV** and **7**, R_t 22.0 min.

HPLC Analytical Methods. *HPLC Method for Achiral Analysis for 1 and 2.* Column, Eclipse XDB 4.6 mm × 15 cm, 5 μm, with USP L1 packing; flow rate, 1.5 mL/min; mobile phase, water—acetonitrile; programme, 40% acetonitrile kept for 15 min and then increased to 80% in next 15 min, then kept constant for 7 min, and re-equilibrate for 5 min. Sample was prepared at 1000 ppm concentration in acetonitrile. Retention times of the compounds observed were as follows: **1**, R_t 10.9 min; **2**, R_t 10.1 min; **IV** and **7**, R_t 21.5 min.

HPLC Method for Chiral Analysis. Column, Chiralcel OD-H 4.6 mm × 25 cm, 5 μm; flow rate, 0.5 mL/min. Mobile phase used for compound **5a** and **5b**, *n*-hexane/methyl *tert*-butyl ether/trifluoroacetic acid (800:200:2), 960 mL of this solvent mixture with 40 mL of EtOH, and 1.0 mL of diethyl amine; retention times of **5a** and **5b**, R_t 15.1 and 16.2 min. Mobile phase used for compounds **1**, **2**, **IV**, and **8**, *n*-hexane/IPA (98:2); flow rate for **1** and **2**, 0.9 mL/min and that for **IV** and **7**, 0.5 mL/min; retention times as follows: **1**, R_t 11.0 min; **2**, R_t 12.0 min; **IV**, R_t 13.5 min; **7**, R_t 13.0 min. Mobile phase used for compound **7**, *n*-hexane/EtOH/diethylamine (920:80:0.1); flow rate, 0.4 mL/min; retention time of **8**, R_t 15.3 min.

Preparation of 1,1-Diphenyl-2-aza-1,4-pentadiene (3). To a solution of benzophenone (300.0 g, 1.64 mol) in toluene (1500 mL) was added allyl amine (140.7 g, 2.46 mol) followed by titanium isopropoxide (300.3 g, 1.05 mol). After heating at 80 °C for 6 h, the mass was cooled to 25−26 °C, and water (35 mL) and toluene (1200 mL) were added. The reaction mass was stirred for 0.5 h, and the white suspension formed (of TiO_2) was filtered through Celite. The residue was washed with toluene (2 × 750 mL). The combined organic layer was concentrated under vacuum at 60−65 °C to give 356 g (98%) of **3** as a yellow oil: 97% GC (a/a) purity (R_t 24 min). IR (neat): 3080, 1661, 1622, 1597, 1313, 1287 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78−7.76 (m, 2H, Ar—H), 7.44−7.28 (m, 6H, Ar—H), 7.18−7.15 (m, 2H, Ar—H), 6.20−6.07 (m, 1H, =N—CH=CH_2), 5.25 (dd, 1H, J = 1.5, 9.6 Hz, =N—CH=CH_2), 5.15 (dd, 1H, J = 1.5, 9.6 Hz, =N—CH=CH_2), 4.10 (d, 2H, J = 5.4 Hz, —CH_2—Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 138.7, 129.3, 128.3, 126.2, 113.5, 55.3, 44.1 ppm. MS m/z 221 $[M]^+$.

Preparation of (±)3-Amino-4-phenyl-1-butene (5). A solution of compound **3** (336 g, 1.52 mol) in THF (1680 mL) was cooled to −50 °C, and *n*-BuLi (953 mL, 1.52 mol) was added dropwise over a period of 1 h. During the addition a wine red colored suspension was formed. The reaction mass was stirred at −50 °C for an additional 1 h. Benzyl chloride (192 g, 1.52 mol) in THF (192 mL) was then added to the mixture, over a period of 10 min. The reaction mass was stirred for an additional 1 h, and the formation of compound **4** was monitored by GC. The reaction was quenched with ethanol (60 mL). $KHSO_4$ solution (20%, 1700 mL) was added to the reaction mass at a rate that maintains the internal temperature below −30 °C. The mixture was warmed to room temperature and stirred for 9−10 h (for hydrolysis). During this period two layers were formed. Jthe organic layer (THF) was separated, and the aqueous layer containing the product was washed with methyl *tert*-butyl ether (350 mL) followed by CH_2Cl_2 (2 × 350 mL). The aqueous layer was cooled to 0 °C and basified with 50% NaOH solution (412 mL) to pH 9−10. The product was extracted in CH_2Cl_2 (2 × 350 mL). The combined CH_2Cl_2 layer was washed with brine (2 × 350 mL), dried over Na_2SO_4, and concentrated in vacuum to give 164 g (74%) of **5** as a light brown colored oil: 96% GC(a/a) purity (R_t 16.2 min.), enantiomeric ratio *S*/*R* 55:45. IR (neat): 3367, 3289, 1642, 1602, 1584 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.03−7.16 (m, 5H, Ar—H), 5.67−5.79 (m, 1H, CH_2=CH—C*H*—), 5.01 (dd, 1H, J = 1.2, 10.5 Hz, —N—CH=CH_2), 4.90 (d, 1H, J = 1.2, 10.5 Hz, —N—CH=CH_2), 3.4 (q, 1H, J = 6, 13.2, —N—C*H*=CH_2), 2.6 (dd, 1H, J = 5.4, 13.2 Hz, —CH_2Ph), 2.46 (dd, 1H, J = 8.1, 13.2 Hz, —CH_2Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 138.7, 129.3, 128.3, 126.2, 113.5, 55.3, 44.1 ppm. MS m/z 147 $[M]^+$.

Procedure for Recovery of Benzophenone. The methyl *tert*-butyl ether extract was combined with the organic layer (THF) and concentrated to obtain 345 g of a brown colored oil containing 80% benzophenone (GC, a/a). The oil was distilled under reduced pressure (0.5 mm) at 160 °C. The fraction distilling out at 117−125 °C was collected to give 250 g of benzophenone with 96% purity (GC, a/a).

General Procedure for Resolution. To a solution of 1 equiv of amine **5** in toluene (20 volumes) and *n*-PrOH (7 volumes) was added *N*-acetyl-L-leucine (0.55 equiv). The reaction mixture was heated to 95 °C and then cooled slowly at 5 °C/h to 20 °C. The reaction mass was stirred for 2−3 h at 20 °C. The filtered solid (NAL salt) was dried under vacuum and underwent a second crystallization following the above procedure. The solid thus obtained was hydrolyzed with 10% NaOH, and the free base was extracted in CH_2Cl_2 to afford optically pure amine.

Resolution of (*S*)-3-Amino-4-phenyl-1-butene (5a). Compound **5** (100 g, 0.680 mol) was resolved with *N*-acetyl-L-leucine (64 g, 37.4 mmol) in 2000 mL of toluene and 700 mL of *n*-PrOH as per procedure mentioned above to give 35g (35%) of **5a** as a colorless oil: 98% GC(a/a) purity (R_t 16.2 min), *ee* 98% (Chiral HPLC). $[\alpha]^{25}_D$ = +15.1 (*c* 1, $CHCl_3$).

Resolution of (*R*)-3-Amino-4-phenyl-1-butene (5b). The mother liquour from the first crystallization was concentrated to obtain 80 g of residue. The residue was stirred in hexane (300 mL) and filtered to obtain the NAL salt of (*R*)-3-amino-4-phenyl-1-butene in 82% ee (32 g). The hexane filtrate was evaporated to obtain the free amine of *R*-isomer **5b** in 50% ee, which on resolution with NAL afforded the NAL salt of the *R*-isomer (27 g) in 85% ee. The combined NAL salt (59 g) was underwent a second crystallization followed by hydrolysis. (*R*)-3-Amino-4-phenyl-1-butene (**5b**) was obtained as a colorless oil (23.2 g, yield 23%); purity 98% (GC a/a, R_t 15.1 min), *ee* 98% (HPLC); $[\alpha]^{25}_D$ = −15.3 (*c* 1, $CHCl_3$).

General Procedure for Preparation of *N*-Boc Derivative. To a stirred solution of amine (1 equiv) in CH_2Cl_2 (5 volumes) was added triethylamine (1.25 equiv) followed by the dropwise addition of di-*tert*-butyl dicarbonate (1.25 equiv) over a period of 1 h. The reaction was monitored by GC. After 28 h the reaction mixture was quenched with 5% $KHSO_4$ solution. The organic layer was washed with water followed by brine, dried over Na_2SO_4, and concentrated. Hexane was added to the residue, and the product was isolated from hexane.

Preparation of (*S*)-2-(*t*-Boc-amino)-1-phenylbut-3-ene (IV). White solid; 55 g (95% yield), 98% GC (a/a, R_t 22 min); mp = 67−68 °C, $[\alpha]^{25}_D$ = +36.9 (*c* 1, $CHCl_3$).

Preparation of (*R*)-2-(*t*-Boc-amino)-1-phenylbut-3-ene (7). White solid; yield 54.5 g (94%), purity 98% (GC a/a, R_t 22 min); mp 67−68 °C, $[\alpha]^{25}_D$ = −34.8 (*c* 1, $CHCl_3$).

Racemization of 7. To a stirred solution of 7 (20 g, 0.081 mol) in toluene (200 mL) was added *t*-BuOK (4.5 g, 0.041 mol). The reaction mixture was heated to reflux for 48 h. The reaction was monitored by chiral HPLC. On completion of racemization after 48 h, the toluene layer was washed with water and dried over Na_2SO_4. The toluene evaporated to obtain a crude residue which was then hydrolysed using 6 N HCl (120 mL) in MeOH (30 mL). The reaction was monitored by TLC. After 4 h the aqueous layer was washed with CH_2Cl_2 (150 mL) and basified with 20% NaOH (450 mL). The product was extracted with CH_2Cl_2 (3 × 150 mL). All CH_2Cl_2 layers were combined and washed with a brine solution (200 mL), dried over Na_2SO_4, and evaporated to dryness affording 6 g (67%) of racemic **5** as an oil: 98% GC (a/a) purity.

Preparation of *N*-((*S*)-1-Benzyl-allyl)-acetamide (8). To a stirred solution of amine **5b** (20 g, 0.136 mol) in dichloromethane (100 mL) was added triethylamine (17.1 g, 0.17 mol) followed by acetic anhydride (15.2 g, 0.145 mol) dropwise over a period of 1 h. The reaction was monitored by GC. After 28 h the reaction mixture was quenched with 5% $KHSO_4$ solution. The organic layer was washed with water and a brine solution, dried over Na_2SO_4, and evaporated. The crude solid was stirred with hexane (60 mL) and filtered to obtain 20.6 g (80%) compound **8** as a white solid: 99% GC (a/a) purity (R_t 15.9 min). Mp = 116−117 °C, $[\alpha]^{25}_D$ = −49.5 (*c* 1, $CHCl_3$).

Preparation of (2*R*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1,2-epoxy-4-phenylbutane (1) and (2*S*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1,2-epoxy-4-phenylbutane (2). A solution of compound **IV** (20 g, 8.1 mmol) in acetone (235 g, 8.1 mol) was added to sodium bicarbonate (340 g, 4.05 mol) solution in mixture of water (3400 mL) and ethyl acetate (1700 mL). Oxone (797 g, 1.296 mol) was added to this biphasic mixture in 8 lots (each lot 99.6 g) at intervals of 1 h. The reaction was monitored by HPLC. The reaction mixture was filtered after 16 h, and the inorganic residue was washed with ethyl acetate (2 × 200 mL). The combined organic layer was washed with brine (2 × 200 mL), dried over Na_2SO_4, and concentrated under vacuum. Hexane (40 mL) was added to the residue and was filtered to give 21.5 g (100%) of **6** as a white solid: 96% HPLC (a/a) purity; diastereomeric ratio *RS*/*SS* 73:27 (HPLC). The solid was taken in hexane (160 mL) and heated to 45 °C. The solution was then cooled to 5 °C, stirred for 1 h, and filtered. Both the solid (7.3 g) and the filtrate were treated separately. The filtrate was concentrated to 75% of the volume, cooled to −5 °C, and filtered to give 14.2 g (71%) of **1** as a white solid: 97.2% HPLC (a/a) purity (R_t 12.7 min); diastereomeric ratio ratio *RS*/*SS* 97:3 (HPLC).

The solid (7.3 g) was recrystallized thrice from 45 mL of hexane to give 3.0 g (14%) of **2** as a white solid: 99% HPLC (a/a) purity (R_t 11.7 min): diastereomeric ratio *SS*/*RS* 98:2 (HPLC).

■ ASSOCIATED CONTENT

Supporting Information. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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DISCLOSURE

⊥This manufacturing unit for Piramal has been closed.

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■ NOTE ADDED AFTER ASAP PUBLICATION

In the version published September 23, 2010, there was an author omitted, and the affiliation for one of the other authors was not clear. These have been corrected in the version posted February 10, 2011.