*Technical Note*

# An alternative synthesis of (±)-phenylephrine hydrochloride

**Wipanoot Baison, Aphiwat Teerawutgulrag\*, Pakawan Puangsombat and Nuansri Rakariyatham**

Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai 50200, Thailand

\* Corresponding author, e-mail: aphiwattee@yahoo.co.uk

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**Abstract:** This study presents alternative synthetic pathways and reagents for the preparation of racemic phenylephrine hydrochloride. Using *m*-hydroxybenzaldehyde as starting material, two separate pathways─epoxidation and bromohydrin formation─are presented. Both routes provide good yields (overall of 71% and 66% respectively) and can be performed at mild conditions.

**Keywords:** phenylephrine, phenylephrine hydrochloride, m-hydroxybenzaldehyde, alpha adrenergic receptor agonist

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## INTRODUCTION

Phenylephrine hydrochloride (PE) or 3-(1-hydroxy-2-(methylamino)ethyl)phenol hydro-chloride (**1**: Figure 1) is an alpha$_1$-adrenergic receptor agonist [1] used as a topical nasal decongestant and in eye drops to dilate the pupil. Recently, PE has been marketed in the optically active *(R)*-form as a substitute for pseudoephedrine, a precursor in the production of methamphetamine, a notorious narcotic drug [2]. Various methods for the synthesis of PE have been documented in the literature. Legerlotz [3-5] reported the classical industrial synthetic pathway. Racemic PE was resolved using tartaric acid in order to obtain the *(R)*-form [6].
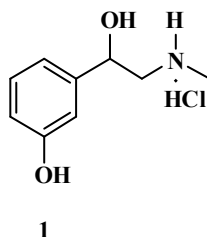


**1**

**Figure 1.** Phenylephrine hydrochloride

Nonchiral synthesis of PE was reported in 1951 by Bergmann and Sulzbacher [7], who used m-hydroxybenzaldehyde as starting material and a Curtius rearrangement of a beta-hydroxyl acid azide as the key step (Scheme 1). In 1961, Russell and Childress [8] used the same starting material for the synthesis of racemic PE, employing the reduction of mandelamide with lithium aluminium hydride as the key step (Scheme 2). Takeda *et al.* [9] reported an asymmetric synthesis of chiral PE using (*2R,4R*)-dicyclohexylphosphino-2-diphenylphosphinomethyl-1-(*N*-methycarbonyl)-pyrolidine (MCCPM)-rhodium as chiral catalyst, producing *(R)*-PE as a product with 85% ee (Scheme 3).
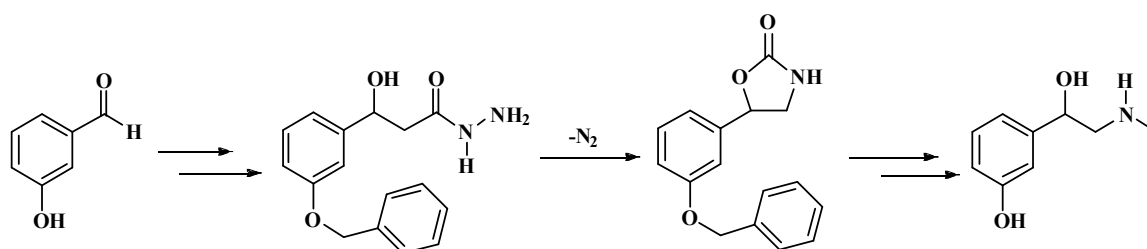


**Scheme 1.** Synthesis of phenylephrine by Curtius rearrangement of beta-hydroxyl acid azide
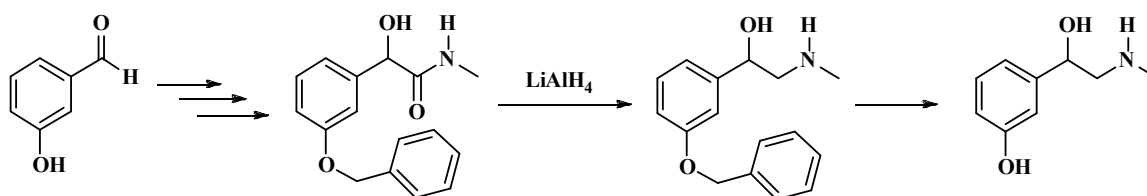


**Scheme 2.** Synthesis of phenylephrine using reduction of mandelamide with lithium aluminium hydride as key step
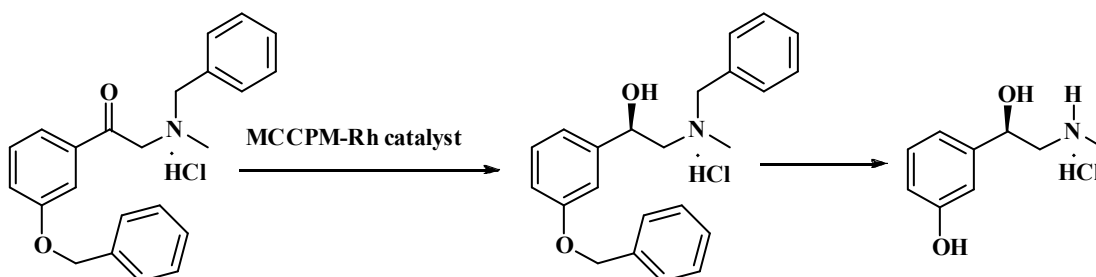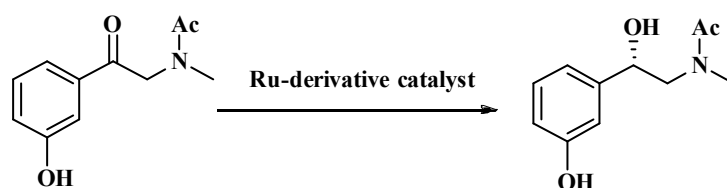


**Scheme 3.** Synthesis of *(R)*-PE using MCCPM-rhodium catalyst

McGarrity and Zanotti-Gerosa [10] reported a feasibility study on a new route to *(R)*-PE based on ruthenium-derivative-catalysed asymmetric hydrogenation of an *N*-protected aminoketone precursor (Scheme 4). The direct and fast asymmetric reduction of *N*-protected aminoketone was highly enantioselective (>95% ee) but the *(S)*-PE was the main product in most conditions.

Gurjar *et al.* [11] studied the hydrolytic kinetic resolution of a styrene oxide derivative. They used *(R,R)*-SalenCo$^{III}$OAc complex to induce racemic styrene epoxide to *(R)*-form at 45% yield (97% ee) as shown in Scheme 5 [11]. In 2003, Pandey *et al.* [13] reported *(R)*-PE synthesis via Sharpless asymmetric dihydroxylation with 98% ee, yielding the desired product in seven steps
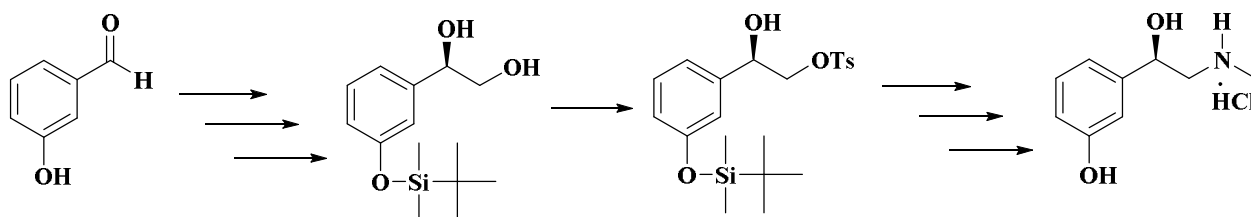
(Scheme 6). In this paper, we report a variation of the route and reagents for preparing PE in high yields using mild conditions.



**Scheme 4.** Asymmetric hydrogenation of *N*-protected aminoketone



A = (-)-*N,N*-bis(3,5-di-tert-butylsalicylidene)-
1,2-cyclohexadiaminocobalt(III)acetate
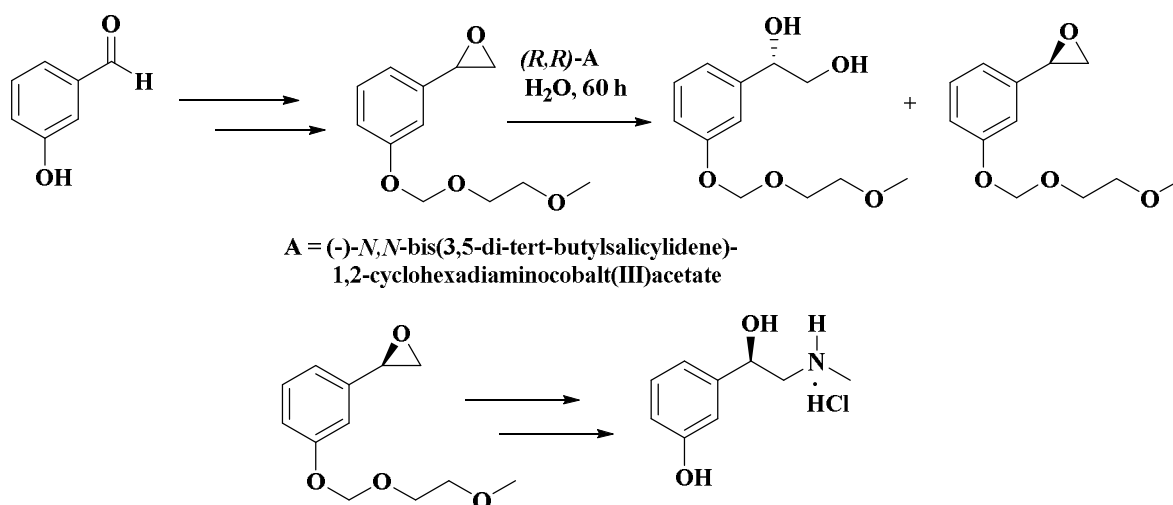


**Scheme 5.** Synthesis of *(R)*-PE via hydrolytic kinetic resolution



**Scheme 6.** Synthesis of *(R)*-PE via Sharpless asymmetric dihydroxylation

**DISCUSSION**

Synthesis of PE **(1)** was initiated from *m*-hydroxybenzaldehyde **(2)**, as illustrated in Scheme 7. The protection of **2** with *t*-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of imidazole produced the silyl compound **3** in quantitative yield. The Wittig olefination of **3** with methyltriphenylphosphonium iodide and *t*-BuOK in THF at ambient temperature furnished styrene **4** in 97% yield. After these steps, the synthesis could be performed using two pathways. The epoxidation of **4** with *m*-chloroperoxybenzoic acid (MCPBA) in $CH_2Cl_2$ at room temperature produced epoxide **5** in 81% yield, while treatment of **4** with *N*-bromosuccinimide (NBS) in the presence of $H_2O$ and DMSO at room temperature produced bromohydrin **6** in 80% yield. The epoxide **5** and bromohydrin **6** was treated with methylamine in methanol at room temperature and

the TBDMS group deprotected with 6M hydrochloric acid solution at room temperature to produce **1** in 90% (from epoxide **5**) and 85% (from bromohydrin **6**). The overall yields of **1** via epoxide **5** and bromohydrin **6** were 71% and 66% respectively.
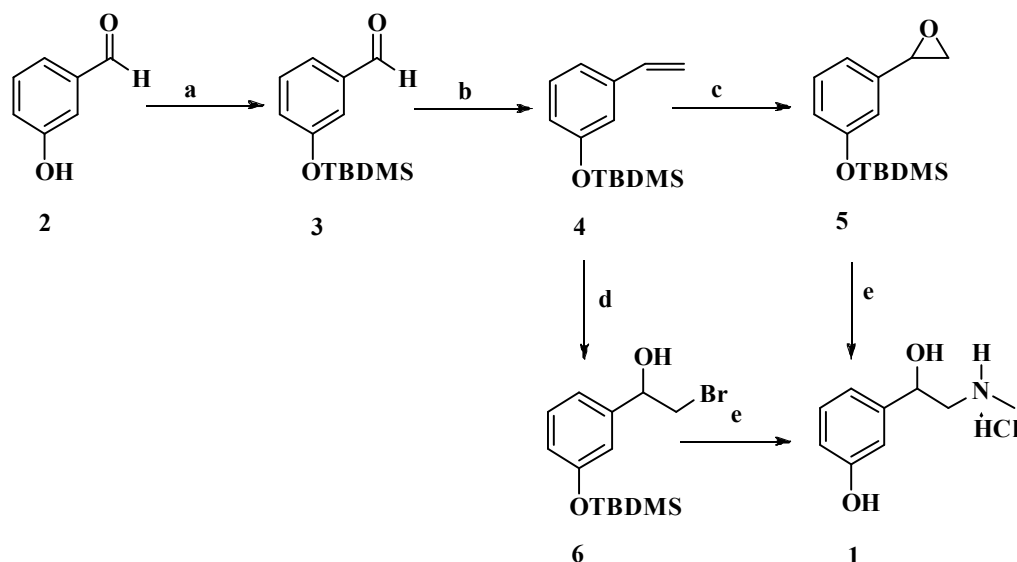


**Scheme 7.** Synthesis of PE (**1**). Reagents and condition: (a) TBDMS-Cl, imidazole, $0^o$; (b) $CH_3P^+Ph_3I^-$, *t*-BuOK, $0^o$; (c) MCPBA, RT; (d) NBS, $H_2O$, DMSO, $0^o$; (e) i. $MeNH_2$, RT  ii. HCl, RT

**CONCLUSION**

A practical and alternative method for the synthesis of racemic phenylephrine hydrochloride has been performed using mild conditions with good overall yields.

**EXPERIMENTAL**

*m*-Hydroxybenzaldehyde, TBDMS-Cl, MCPBA, imidazole, potassium *tert*-butoxide and methylamine were purchased from Aldrich. Methyltriphenylphosphonium iodide was prepared from triphenylphosphine and methyl iodide. *N*-Bromosuccinimide was recrystallised in water at $90^o$ and dried in oven at $60^o$ for 2 hr. All solvents were distilled prior to use. Thin-layer chromatography (TLC) was performed on silica 60 $F_{264}$ plates and column chromatography was carried out on silica gel (0.063-0.20 mm).

^{1}H-NMR spectra were recorded on a 400-MHz or 500-MHz Bruker Avance using trimethyl-silane as the internal standard in $CDCl_3$ or DMSO-$d_6$. ^{13}C-NMR spectra were recorded on a 100-MHz or 125-MHz Bruker Avance using trimethylsilane as the internal standard in $CDCl_3$ or DMSO-$d_6$. Mass spectra were recorded on ESI-Q-TOF-MS (Micromass, Manchester, UK). IR spectra were recorded on a FT-IR spectrometer (Tensor 27) as neat film or KBr disc. Melting point was determined on MEL-TEMP (Laboratory Devices Inc., USA) and used without correction.

**3-(*tert*-Butyldimethylsilyloxy)benzaldehyde (3)**

Imidazole (4.21 g, 61.8 mmol) and TBDMS-Cl (9.31 g, 61.7 mmol) was added to a stirred solution of *m*-hydroxybenzaldehyde (**2**) (5.04 g, 41.3 mmol) in dry dichloromethane (50 mL) at $0^o$. The mixture was then allowed to warm up to room temperature. After 24 hr, water (30 mL) was

added and the organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified on silica gel by eluting with EtOAc-hexane (1:4) to give compound **3** as a pale yellow liquid (10.13 g, quantitative yield): IR 2958, 2927, 2860, 1705, 1581, 1275, 840 cm$^{-1}$; $^1$H-NMR δ 9.94 (s, 1H), 7.46 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 2.3, 1.6 Hz, 1H), 7.10 (m, 1H), 0.99 (s, 9H), 0.22 (s, 6H); $^{13}$C-NMR δ 191.85, 156.27, 137.85, 129.95, 126.37, 123.43, 119.69, 25.52, 18.05, -4.58; HRMS calculated for C$_{13}$H$_{21}$O$_2$Si [M+H]$^+$ 237.1311, found 237.1313.

### *tert*-Butyldimethyl(3-vinylphenoxy)silane (4)

Potassium *tert*-butoxide (2.90 g, 25.9 mmol) was added to a stirred suspension of methyltriphenylphosphonium iodide (10.32 g, 25.5 mmol) in dry THF (50 mL) at 0°. The mixture was stirred at room temperature for 1 hr; then aldehyde **3** (5.01 g, 21.2 mmol) was added portionwise. The mixture was stirred for 2 hr at room temperature and diluted with water (40 mL). The aqueous layer was extracted with ethyl acetate (2×40 mL). The combined organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified on silica gel by eluting with EtOAc-hexane (1:19) to furnish, after concentration, compound **4** (4.82 g, 97%) as a colourless liquid: IR 2957, 2930, 2858, 1578, 1485, 1279, 839 cm$^{-1}$; $^1$H-NMR δ 7.27 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.6 Hz), 7.02 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.77 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 1.12 (s, 9H), 0.33 (s, 6H); $^{13}$C-NMR δ 155.84, 139.06, 136.75, 129.36, 119.51, 119.49, 117.72, 113.78, 25.69, 18.17, -4.42; HRMS calculated for C$_{14}$H$_{23}$O$_2$Si [M+H]$^+$ 235.1518, found 235.1512.

### *tert*-Butyldimethyl(3-oxiranylphenoxy)silane (5)

MCPBA (1.01 g, 5.83 mmol) was added to a stirred solution of compound **4** (0.65 g, 2.76 mmol) in CH$_2$Cl$_2$ (15 mL) at room temperature. After 3 hr, the reaction mixture was washed with saturated sodium thiosulfate solution (5 mL) and saturated NaHCO$_3$ solution (5 mL). The organic layer was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified on silica gel by eluting with EtOAc-hexane (1:19) to produce, after concentration, compound **5** (0.56 g, 81%) as a colourless liquid: IR 3048, 2931, 2858, 1606, 1486, 1284, 957, 833 cm$^{-1}$; $^1$H-NMR δ 7.20 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 2H), 3.79 (dd, *J* = 4.0, 2.6 Hz, 1H), 3.09 (dd, *J* = 5.6, 4.1 Hz, 1H), 2.74 (dd, *J* = 5.6, 2.5 Hz, 1H), 1.03 (s, 9H), 0.23 (s, 6H); $^{13}$C-NMR δ 155.80, 139.24, 129.30, 119.64, 118.42, 116.74, 51.87, 50.82, 25.51, 17.99, -4.60; HRMS calculated for C$_{14}$H$_{23}$O$_2$Si [M+H]$^+$ 251.1467, found 251.1465.

### 2-Bromo-1-(3-(*tert*-butyldimethylsilyloxy)phenyl)ethanol (6)

NBS (1.14 g, 6.43 mmol) and water (0.25 mL) were added to a stirred solution of compound **4** (0.52 g, 2.22 mmol) in DMSO (8 mL) at 0°C. After 45 min., ice-cooled water (10 mL) was added. The aqueous phase was extracted with ethyl acetate (2×10 mL). The combined organic layer was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified on silica gel by eluting with EtOAc-hexane (1:19) to produce, after concentration, compound **6** (0.59 g, 80%) as a colourless liquid: IR 3422, 2956, 2858, 1602, 1485, 1065, 1278, 835 cm$^{-1}$; $^1$H-NMR δ 7.22 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.88 (br, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.85 (d, *J* = 8.3 Hz, 1H), 3.61 (d, *J* = 9.1, Hz, 1H), 3.51 (t, *J* = 9.7 Hz, 1H), 2.77 (s, 1H), 1.00 (s, 9H), 0.21 (s, 6H); $^{13}$C-NMR δ 155.85, 141.89, 129.59, 119.98, 118.79, 117.69, 73.51,

40.04, 25.62, 18.12, -4.45; HRMS calculated for $C_{14}H_{23}O_1SiBr$ [M+H-OH]$^+$ 315.0630, found 315.0346.

**Phenylephrine hydrochloride (1)**

*Via epoxide compound 5*

A solution of **5** (0.51 g, 2.05 mmol) in dry methanol (5 mL) was saturated with methylamine gas and left stirred at room temperature for 2 hr. The solution was concentrated to give the crude mixture. Hydrochloric acid (6M, 0.50 mL) was added to the solution of the crude mixture in methanol (5 mL). The resulting solution was stirred at room temperature for 2 hr and then concentrated under reduced pressure. The residue was purified on silica gel by eluting with methanol:dichloromethane (1:19) to produce, after concentration, PE (**1**) (0.38 g, 90%) as a white solid: m.p.141-143° (Lit.141° [11]); IR 3419, 2963, 2798, 1593, 1462, 1274, 1083, 879 cm$^{-1}$; $^1$H-NMR δ 9.56 (s, 1H), 8.99 (br, 1H), 7.15 (t, $J$ = 7.8 Hz, 1H), 6.81 (br, 1H), 6.78 (d, $J$ = 7.7 Hz, 1H), 6.70 (d, $J$ = 8.0 Hz, 1H), 6.11 (s, 1H), 4.83 (d, $J$ = 8.3 Hz, 1H), 3.05 (d, $J$ = 12.5 Hz, 1H), 2.11 (t, $J$ = 12.4 Hz, 1H), 2.53 (s, 3H); $^{13}$C-NMR δ 157.99, 143.71, 129.78, 116.74, 115.12, 113.22, 68.49, 55.37, 33.14; HRMS calculated for $C_9H_{14}NO_2$ [M+H]$^+$ 168.0980, found 168.1019.

*Via bromohydrin compound 6*

A solution of bromohydrin **6** (0.53 g, 1.60 mmol) in dry methanol (5 mL) was processed under the same procedure as above to produce **1** (0.29 g, 85%).

**REFERENCES**

1.  H. J. Roth, A. Kleemann and T. Beisswenger, "Pharmaceutical Chemistry, Volume 1: Drug Synthesis", Halstead Press/Ellis Horwood Ltd., Chisherter, **1988**, p. 44.
2.  D. Reynolds, "Federal legislation leads to new drugs", **2007**, http://www.dnronline.com/ (Accessed: February 2007).
3.  H. Legerlotz, "Optically active monohydroxyphenylalkylamines", *German Patent DE 543529* (**1929**).
4.  H. Legerlotz, "Monohydric amino alcohols and their derivatives", *German Patent DE 566578* (**1932**).
5.  H. Legerlotz, "Optically active amino alcohols", *German Patent DE 585164* (**1933**).
6.  F. D. Klingler, "Asymmetric hydrogenation of prochiral amino ketones to amino alcohols for pharmaceutical use", *Acc. Chem. Res.*, **2007**, *40*, 1367-1376.
7.  E. D. Bergamann and M. Sulzbacher, "A new synthesis of 1-(*m*- and *p*-hydroxyphenyl)-2-methylaminoethanol (*m*- and *p*-sympathol)", *J. Org. Chem.*, **1951**, *16*, 84-89.
8.  P. B. Russel and S. J. Childress, "New route to phenylephrine", *J. Pharm. Sci.*, **1961**, *50*, 713-714.

9. H. Takeda, T. Tachninami and M. Aburatuni, "Practical Asymmetric synthesis of *(R)- (-)*-phenylephrine hydrochloride catalyzed by (*2R, 4R*)-MCCPM-rhodium complex", *Tett. Lett.*, **1989**, *30*, 367-370.

10. J. F. McGarrity and A. Zanotti-Gerosa, "A feasibility study on the synthesis of phenylephrine via ruthenium-catalyzed homogeneous asymmetric hydrogenation", *Tettrhedron Asym.*, **2010**, *21*, 2479-2486.

11. M. K. Gurjar, L. M. Krishna, B. V. N. B. S. Sarma and M. S. Chorghade, "A practical synthesis of *(R)-(-)*-phenylephrine hydrochloride", *Org. Process Res. Develop.*, **1998**, *2*, 422-424.

12. R. K. Pandey, P. K. Upadhyay and P. Kumar, "Enantioselective synthesis of *(R)*-phenylephrine hydrochloride", *Tetrahedron Lett.*, **2003**, *44*, 6245-6246.