Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

Efficient Organocatalytic Chiral Synthesis of (*R*)-Pipecolic Acid

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Abstract
Aldehyde obtained from unsymmetrical cleavage of cyclohexene by ozonolysis is subjected to L-proline catalyzed asymmetric α-amination reaction to obtain chiral amino alcohol with >99% ee which is subsequently converted into (*R*)-6-(hydroxymethyl)piperidin-2-one and (*R*)-pipecolic acid. Overall, a short and efficient asymmetric synthesis of (*R*)-pipecolic acid is described employing organocatalytic asymmetric α-amination of aldehyde as key step.

Keywords: organocatalysis; α-amination of aldehyde, pipecolic acid; unsymmetrical ozonolysis

1. Introduction

Functionalized piperidine derivatives are versatile building blocks for synthesis of various natural and unnatural bioactive molecules (Figure 1) [1,2]. (*R*)-Pipecolic acid (**1**) is one of the simplest members of substituted piperidine family. As it provides foundation for extension [3-9] to more complex and functionalized biologically active derivatives, it attracted synthetic chemists around the globe. This resulted in number of asymmetric synthesis [10-36] of (*R*)- and/or (*S*)-pipecolic acids based on enzymatic transformations, asymmetric hydrogenation, auxiliary directed alkylation, ring closing metathesis, and from chiral building blocks. Recently Greck et al. [26] synthesized (*R*)-pipecolic acid (**1**) using L-proline catalyzed α-amination of aldehyde derived from cyclohexene via ozonolysis. (*R*)-6-(Hydroxymethyl) piperidin-2-one (**2**), another member of piperidine family, is part of an important class of antitumor agents and is useful for the synthesis of pipecolic acid derivatives [37-41]. Recently Kumar et al. reported synthesis of **3** starting from L-aspartic acid [41]. In general, design and synthesis of conformationally constrained α-amino acids has attracted considerable attention from the synthetic and medicinal chemistry communities.

In the recent years, the area of asymmetric organocatalysis has provided several new transformations for obtaining chiral building blocks [42-47]. In this context, proline, a naturally occurring α-amino acid with secondary amine functionality, cheap and available in both enantiomeric forms and because of utility in different reactions, has emerged as the most practical and versatile organocatalyst [48]. Proline has also been found to be an excellent asymmetric catalyst for α-amination [49-53] of aldehydes and ketones.

As a part of our research program aimed at achieving asymmetric synthesis of biologically active molecules using organocatalysis [54-57], we wish to report organocatalytic asymmetric synthesis of (*R*)-pipecolic acid via (*R*)-6-(hydroxymethyl)piperidin-2-one using L-proline catalyzed α-amination of aldehyde as the key step.

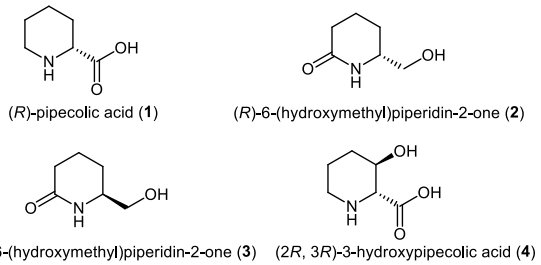

Figure 1 Structure of various piperidine derivatives

2. Results and discussion

From retrosynthetic analysis (Scheme 1), it was envisaged that (*R*)-pipecolic acid (**1**) and (*R*)-6-

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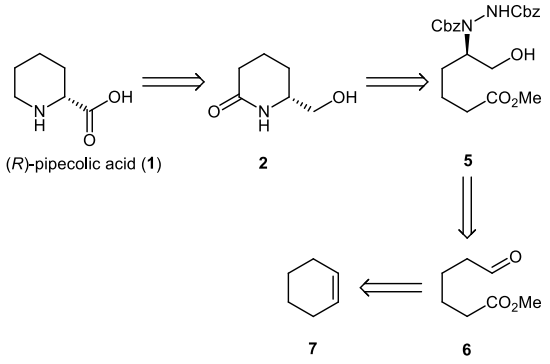
Receive Date: 10 March 2022, **Revise Date:** 10 April 2022, **Accept Date:** 10 June 2022, **First Publish Date:** 10 June 2022
DOI: 10.21608/EJCHEM.2022.126431.5609

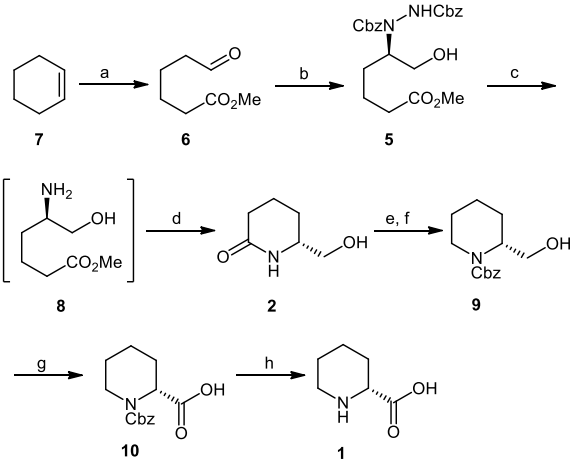
(hydroxymethyl)piperidin-2-one (**2**) could be synthesized from the aldehyde **6** using L-proline catalyzed α-amination to install required chirality. The aldehyde **6** could be derived from cyclohexene **7** using unsymmetrical ozonolysis.



Scheme 1 Retrosynthetic analysis of (*R*)-pipecolic acid

The synthetic approach began with commercially available cyclohexene **7** as outlined in Scheme 2. Ozonolysis [58-59] of cyclohexene **7** in CH_2Cl_2/MeOH in the presence of sodium bicarbonate at -78 °C followed by treatment with acetic anhydride and triethylamine afforded unsymmetrically cleaved functionalized aldehyde **6** in 82% yield [57]. Aldehyde **6** was subjected to α-amination with dibenzyl azodicarboxylate and L-proline (10 mol %) at 0 °C in CH_3CN followed by reduction with sodium borohydride in methanol at 0 °C (List protocol [49]) to furnish chiral amino alcohol **5** in 79% yield. The chiral purity of amino alcohol **5**, as determined by chiral HPLC analysis [60] was found to be >99%. The compound **5** was then subjected to W2 Raney Nickel-catalyzed hydrogenation in methanol with catalytic glacial acetic acid for benzylcarbamate deprotection and *N-N* bond cleavage affording crude aminoalcohol ester **8**. The crude aminoalcohol ester **8** on reflux in ethanol for 5h in presence of catalytic pyridine afforded (*R*)-6-(hydroxymethyl)piperidin-2-one (**2**) in 81% yield over two steps. The spectroscopic data of compound **2** was in accordance with data reported in the literature [40].

The hydroxylactam **2** on reduction with $BH_3.Me_2S$ in presence of $BF_3.Et_2O$ in THF under reflux condition for 24h afforded aminoalcohol which was immediately protected as benzyl carbamate using benzyl chloroformate and $NaHCO_3$ in dioxane: H_2O (1:1) at 0 °C affording compound **9** in 86% yield. Alcohol **9** on treatment with pyridinium dichromate in DMF at room temperature for 5h afforded acid **10** in 71% yield. Palladium-on-carbon catalyzed hydrogenation of benzyl carbamate **10** afforded (*R*)-pipecolic acid (**1**) in 93% yield. The physical and spectroscopic data of pipecolic acid **1** were in full agreement with the literature data [16]. Although Greck's approach [26] for (*R*)-pipecolic acid (**1**) also involves ozonolysis and L-proline catalyzed amination of aldehyde, but our approach is different one.



Scheme 2 *Reagents and conditions*: (a) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, -78 °C then Ac_2O, Et_3N, 0 °C, 82%; (b) dibenzyl azodicarboxylate, L-proline, CH_3CN, 0 °C, 2h and rt, 1h then $NaBH_4$, MeOH, 0 °C, 5 min, 79%; (c) Raney Ni, H_2 (60 psi), cat. AcOH, MeOH, rt, 24h; (d) EtOH, reflux, 5h, 81% over two steps; (e) $BH_3.Me_2S$, $BF_3.Et_2O$, THF, reflux, 24h; (f) CbzCl, $NaHCO_3$, dioxane:H_2O (1:1), 0 °C, 86% over two steps; (g) pyridinium dichromate, DMF, rt, 5h, 71%; (h) Pd/C, MeOH, H_2 (20 psi), 4h, 93%.

3. Conclusion

In conclusion, proline-catalyzed α-amination approach has been successfully applied to the synthesis of (*R*)-6-(hydroxymethyl)piperidin-2-one and (*R*)-pipecolic acid. The present method is easily amenable for the synthesis of a variety of piperidine alkaloids. Currently, studies in this direction are in progress.

4. Experimental

4.1. General information

All reagents and solvents were of analytical grade or were purified by standard procedures prior to use. IR spectra were recorded on a Perkin-Elmer 68B infrared spectrophotometer. The ^1H (200 MHz/ 400 MHz) and ^{13}C (50 MHz/ 100 MHz) NMR spectra were recorded on a Bruker AC-200/ AC-400 spectrometers using TMS as internal standard. In ^{13}C NMR spectra, the carbon resonances were assigned by use of DEPT

experiments. Mass spectra were recorded at an ionization energy 70 eV on API Q STARPULSAR spectrometer using electrospray ionization. Elemental analysis data were obtained on a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Optical rotations were measured on Jasco P-1020 polarimeter. Progress of the reactions was monitored by TLC on Merck silica gel 60 F254 precoated plates, and compounds were visualized by fluorescence quenching, by use of I_2, or by charring after treatment with a *p*-anisaldehyde–AcOH–H_2SO_4 mixture in EtOH. Column chromatography was performed on flash silica gel (230–400 mesh size).

4.2. Methyl 6-oxohexanoate 6

Yield: 8.871 g (82%); colourless liquid; IR ($CHCl_3$) ν_{max}2987, 2952, 1735, 1714, 1252, 678 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 1.60-1.67 (m, 4H), 2.28-2.35 (m, 2H), 2.41-2.47 (m, 2H), 3.64 (s, 3H), 9.74 (t, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 21.2, 24.0, 33.4, 43.1, 51.3, 173.5, 202.0 ppm.

4.3. (5*R*)-Methyl-5-(N,N´-(dibenzyloxycarbonyl) hydrazinyl)-6-hydroxyhexanoate 5

To a cooled solution of dibenzyl azodicarboxylate (90%, 8.25 g, 25 mmol, 1 equiv) and L-proline (287 mg, 2.49 mmol, 10 mol %) in CH_3CN (200 mL) at 0 °C, aldehyde **6** (3.600 g, 25 mmol) was added and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 °C within 1 h. After the reaction mixture became colourless, it was cooled to 0 °C, treated with EtOH (20 mL) and $NaBH_4$ (1.2 g), and was stirred for 5 min at 0 °C. The reaction mixture was worked up by adding aqueous ammonium chloride solution and extracting with ethyl acetate (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pet. ether–ethyl acetate = 85:15).

Yield: 8.769 g (79%); viscous liquid; $[\alpha]_D^{25}$ = +27.6 (*c* 1.16, $CHCl_3$); ee >99% [50]; IR ($CHCl_3$) ν_{max} 3453, 2997, 1733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ ppm 1.52-1.72 (m, 4H), 2.31 (t, *J* = 8 Hz, 2H), 3.50 (s, 3H), 4.13-4.24 (m, 2H), 4.67-4.83 (m, 1H), 5.15 (s, 4H), 7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.3, 28.0, 34.5, 51.5, 58.6, 60.5, 67.8, 68.2, 127.7, 127.9, 128.1, 128.4, 135.5, 155.4, 156.6, 166.1 ppm; Elemental Anal. Calced for $C_{23}H_{28}N_2O_7$: C, 62.15; H, 6.35; N, 6.30. Found: C, 62.18; H, 6.29; N, 6.27.

4.4. (*R*)-6-(Hydroxymethyl)piperidin-2-one 2

The solution of **5** (6.0 g, 13.51 mmol) in MeOH (100 mL) and acetic acid (10 drops) was treated with Raney nickel (6 g, excess) under H_2 (80 psi) atmosphere for 24 h. The reaction mixture was filtered over celite and concentrated to give crude γ-amino ester **8** which on stirring in EtOH (20 mL) in presence of catalytic pyridine at 50 °C for 5h to furnish crude cyclized product. Purification by silica gel column chromatography afforded lactam **2**.

Yield: 1.289 g (74%); white solid; mp 73 °C (Lit. 74 °C [40]); $[\alpha]_D^{25}$ = -22.5 (*c* 1.05, $CHCl_3$) {Lit. for *S*-isomer $[\alpha]_D^{25}$ = +22.2 (*c* 1.0, $CHCl_3$) [40]}; IR ($CHCl_3$) ν_{max} 3351, 2954, 1668, 1461, 1377, 1112, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.33-1.52 (m, 1H), 1.64-1.76 (m, 1H), 1.81-1.97 (m, 2H), 2.28-2.46 (m, 2H), 3.21 (broad s, 1H), 3.41-3.52 (m, 1H), 3.55-3.71 (m, 2H), 6.40 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 24.9, 31.3, 54.7, 65.7, 171.1 ppm; ESI-MS: *m*/*z* = 152.21 $[M + Na]^+$.

4.5. (*R*)-1-(Benzyloxycarbonyl)-2-(hydroxymethyl) piperidine 9

To the solution of lactam 2 (0.516 g, 4 mmol) in THF (20 mL) under argon atmosphere was added $BF_3.Et_2O$ (0.564 g, 4 mmol, 1 equiv) and boron-dimethyl sulfide (0.304 g, 4 mmol, 1 equiv) drop wise. Once H_2 evolution ceased, the solution was refluxed for 24h. The reaction mixture, washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the residue as crude amino alcohol which was used in the next reaction without further purification.

To cooled solution of amino alcohol and $NaHCO_3$ (0.403 g, 4.8 mmol, 1.2 equiv) in 1,4-dioxane: water (1:1, 20 mL) was added benzyl chloroformate (0.818 g, 4.8 mmol) at 0 °C and stirred at that temperature for 2h. The pH of reaction mixture was adjusted to 2 with dilute HCl and extracted with diethyl ether (2 x 50 mL), washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. Purification by column chromatography afforded carbamate **9**.

Yield: 0.856 g (86%); mp 53 °C (Lit. 49-52 °C [16]); $[\alpha]_D^{25}$ = -30.4 (*c* 1.15, $CHCl_3$). {Lit. $[\alpha]_D^{25}$ = +30.3 (*c* 1.15, $CHCl_3$) for *S*-isomer [16]}; ^1H NMR (200 MHz, $CDCl_3$): δ ppm 1.39-1.68 (m, 6H), 1.82 (broad s, 1H), 2.85-3.06 (m, 1H), 3.59-3.68 (m, 1H), 3.80-3.85 (m, 1H), 4.07 (d, *J* = 12.6 Hz, 1H), 4.32-4.46 (m, 1H), 5.14 (s, 2H), 7.25-7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3, 24.8, 25.0, 40.0, 52.8, 60.5, 66.7, 127.5, 127.7, 128.4, 136.6, 156.3 ppm; ESI-MS: *m*/*z* = 272.34 $[M + Na]^+$.

4.6. (*R*)-N-(benzyloxycarbonyl)-pipecolic acid 10

To a solution of alcohol **9** (0.400 g, 1.60 mmol) in DMF (10 mL) was added pyridinium dichromate

(2.416 g, 6.4 mmol, 4 equiv) at room temperature and stirred at that temperature for 5h. After completion of reaction, as seen by TLC analysis, reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 30 mL), washed with water, brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography to obtain pure acid **10**.

Yield: 0.299 g (71%); mp 83 °C (Lit. 84 °C [13]) $[\alpha]_D^{25}$ = +76.8 (*c* 0.2, CH_2Cl_2) {Lit. $[\alpha]_D$ = +77.6 (*c* 0.2, CH_2Cl_2) [13]}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.33-1.47 (m, 2H), 1.65-1.72 (m, 3H), 2.24-2.33 (m, 1H), 2.98-3.13 (m, 1H), 4.08 (dd, *J*= 8 Hz, 11 Hz, 1H), 4.89-5.02 (m, 1H), 5.16 (s, 2H), 7.32 (m, 5H), 10.63 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 24.5, 26.5, 41.7, 54.3, 67.5, 127.7, 127.9, 128.6, 136.4, 156.6, 177.3 ppm.

4.7. (*R*)-Pipecolic acid 1

A solution of acid **10** (0.200 g, 0.76 mmol) in ethyl acetate (20 mL) was stirred under H_2 (20 psi) in presence of catalytic 10% Pd/C (50 mg) for 4h. The catalyst was filtered through a bed of celite. The celite bed was again washed with water. The combined filtrate was concentrated under vacuum to obtain (*R*)-pipecolic acid **1**.

Yield: 0.091 g (93%); mp 271 °C (Lit. 271-274 °C [22]); $[\alpha]_D^{25}$ = +26.9 (*c* 1.15, water) {Lit. $[\alpha]_D^{25}$ = +26.3 (*c* 1, water) [22]}; ^{1}H NMR (400 MHz, D_2O): δ ppm 1.61-1.73 (m, 3H), 1.85-1.92 (m, 2H), 2.26-2.30 (m, 1H), 2.99-3.06 (m, 1H), 3.43-3.46 (m, 1H), 3.89 (dd, *J* = 8 Hz, 10 Hz, 1H); ^{13}C NMR (100 MHz, D_2O): δ = 21.30, 21.32, 25.7, 43.7, 57.0, 172.0 ppm; Elemental Anal. Calced for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.81; H, 8.55; N, 10.81.

5. Acknowledgements

SPP thanks Department of Science and Technology for funding to K. M. C. College Khopoli under DST-FIST scheme.

6. Conflicts of interest

There are no conflicts to declare.

7. References

[1] Strunz, G. M.; Findlay, J. A. "The Alkaloids" Brossi, A., Ed.; *Academic Press: San Diego* **26** (1986): 89.

[2] Fodor, G. B.; Colasanti, B. "Alkaloids: Chemical and Biological Properties" Pelletier, S. W., Ed.; *Wiley: New York*, **3** (1986); 1.

[3] Pinder, A. R. 1989. Pyrrole, pyrrolidine, piperidine, and azepine alkaloids. *Natural Product Reports*, ***6***, 67-78.

[4] Pinder, A. R. 1992. Pyrrole, pyrrolidine, piperidine, and azepine alkaloids. *Natural Product Reports*, ***9***, 17-23.

[5] Pinder, A. R. 1992. Azetidine, pyrrole, pyrrolidine, piperidine, and pyridine alkaloids. *Natural Product Reports*, ***9***, 491-504.

[6] Nadin, A. 1997. Saturated nitrogen heterocycles. *Contemporary Organic Synthesis*, ***4***, 387-414.

[7] Bailey, P.D., Millwood, P.A., Smith, P.D. 1998. Asymmetric routes to substituted piperidines. *Chemical Communications*, 633-640.

[8] Bols, M. 1998. 1-Aza Sugars, apparent transition state analogues of equatorial glycoside formation/cleavage. *Accounts of Chemical Research*, ***31***, 1-8.

[9] Mitchinson, A., Nadin, A. 1999. Saturated nitrogen heterocycles. *Journal of the Chemical Society, Perkin Transactions 1*, 2553-2582.

[10] For review see: Kadouri-Puchot, C., Comesse, S. 2005. Recent Advances in asymmetric synthesis of pipecolic acid and derivatives. *Amino Acids*, ***29***, 101-130.

[11] Aketa, K., Terashima, S., Yamada, S. 1976. Stereochemical studies. XL. A biomimetic Conversion of L-lysine into optically active 2-substituted piperidines. Synthesis of D- and L-pipecolic acid, and (*S*)-(+)-coniine from L-lysine. *Chemical & Pharmaceutical Bulletin*, ***24***, 621-631.

[12] Meyers, A. G., Gleason, J. L., Yoon, T. 1995. Practical method for the synthesis of D- and L-alpha amino acids by the alkylation of (+)- or (-)-pseudoephedrine glycinamide. *Journal of American Chemical Society*, ***117***, 8488-8489.

[13] Fernández-García, C, MaKervey, M. A. 1995. A short enantioselective synthesis of pipecolic acid. *Tetrahedron: Asymmetry*, ***6***, 2905-2906.

[14] Greek, C., Ferreira, F., Genet, G. P. 1996. Synthesis of both enantiomers of trans 3-hydroxypipecolic acid *Tetrahedron Letters*, ***37***, 2031-2034.

[15] Chenevert, R., Morin, M.-P. 1996. Chemoenzymatic synthesis of both enantiomers of cis-6-hydroxymethylpipecolic acid. *Tetrahedron: Asymmetry*, ***7***, 2161-2164.

[16] Sànchez-Sancho, F., Herradón, B. 1998. Short syntheses of (*S*)-pipecolic acid, (*R*)-coniine, (*S*)-δ-coniceine using biocatalytically-generated chiral building blocks. *Tetrahedron: Asymmetry*, ***9***, 1951-1965.

[17] Wilkinson, T. J., Stehle, N. W., Beak, P. 2000. Enantioselective synthesis of 2-alkyl- and 2,6-dialkylpiperidine alkaloids: preparations of the hydrochlorides of (-)-coniine, (-)-solenopsin A, and (-)-dihydropinidine. *Organic Letters*, ***2***, 155-158.

[18] Teoh, E., Campi, E. M., Jackson, W. R., Robinson, A. J. 2002. A highly enantioselective synthesis of cyclic *α*-amino acids involving a one-pot, single catalyst, tandem hydrogenation-hydroformylation sequence. *Chemical Communications*, 978-979.

[19] Pal, B., Ikeda, S., Kominami, H., Kera, Y., Ohtani, B. 2003. Photocatalytic redox-combined synthesis of L-pipecolinic acid from L-lysine by suspended titania particles: effect of noble metal loading on the selectivity and optical purity of the product. *Journal of Catalysis*, ***217***, 152-159.

[20] Calmes, M., Escale, F., Rolland, M., Martinez, J. 2003. Diastereoselective esterification of (±)-*N*-trifluoroacetyl pipecolic acid using (*S*)-α-methyl pantolactone: synthesis of (*S*)-*N*-Boc pipecolic acid and (*S*)-*N*-Boc-2-piperidinemethanol. *Tetrahedron: Asymmetry*, ***14***, 1685-1689.

[21] Rogers, L. M.-A., Rouden, J., Lecomte, L., Lasne, M.-C. 2003. Enantioselective decarboxylation-reprotonation of an α-amino malonate derivatives as a route to optically enriched cyclic α-amino acid. *Tetrahedron Letters*, ***44***, 3047-3050.

[22] Watanabe, L.A., Haranaka, S., Jose, B., Yoshida, M., Kato, T., Moriguchi, M., Soda, K., Nishino, N. 2005. An efficient access to both enantiomers of pipecolic acid. *Tetrahedron: Asymmetry*, ***16***, 903-908.

[23] Hou, D.-R., Hung, S.-Y., Hu, C.-C. 2005. An efficient, asymmetric synthesis of pipecolic acid and 2-alkyl pipecolic acids. *Tetrahedron: Asymmetry*, ***16***, 3858-3864.

[24] Fadel, A., Lahrache, N. 2007. An efficient synthesis of enantiomerically pure (*R*)-pipecolic acid, (*S*)-proline, and their N-alkylated derivatives. *Journal of Organic Chemistry*, ***72***, 1780-1784.

[25] Chattopadhyay, S. K., Biswas, T., Biswas, T. 2008. Complementary routes to both enantiomers of pipecolic acid and 4,5-dihydroxypipecolic acid derivatives. *Tetrahedron Letters*, ***49***, 1365-1369.

[26] Kalch, D., Rycke, N. D., Moreau, X., Greck, C. 2009. Efficient syntheses of enantioenriched (*R*)-pipecolic acid and (*R*)-proline via electrophilic organocatalytic amination. *Tetrahedron Lett*ers, ***50***, 492-494.

[27] Lemire, A., Charette, A. B. 2010, Stereoselective synthesis of L-pipecolic acid and (2*S*, 3*S*)-3-hydroxypipecolic acid from a chiral *N*-imino-2-phenyl-1,2-dihydropyridine intermediate. *Journal of Organic Chemistry*, ***75***, 2077-2080.

[28] Beng, T. K., Gawley, R. E. 2010. Highly enantioselective catalytic dynamic resolution of *N*-boc-2-lithiopiperidine: synthesis of (*R*)-(+)-*N*-boc-pipecolic acid, (*S*)-(-)-coniine, (*S*)-pellotierine, (+)-β-conhydrine, and (*S*)-(-)-ropivacaine and formal synthesis of (-)-lasubine II and (+)-cermizine C. *Journal of American Chemical Society*, ***132***, 12216-12217.

[29] Cant, A. A., Sutherland, A. 2012. Asymmetric synthesis of pipecolic acid and derivatives. *Synthesis*, ***44***, 1935-1950.

[30] Fernandes, R. A., Nallasivam, J. L. 2012. Enantioselective allylation of imines catalyzed by newly developed (-)-β-pinene-based-π-allylpalladium catalyst: an efficient synthesis of (*R*)-α-propylpiperonylamine and (*R*)-pipecolic acid. *Organic and Biomolecular Chemistry*, ***10***, 7789-7800.

[31] Chattopadhyay, S. K., Mukherjee, J. P. 2014. Asymmetric synthesis of D-proline and D-pipecolic acid, (2*R*, 3*S*, 4*R*)-3,4-dihydroxyproline, and 1,4-dideoxy-1,4-imino-D-talitol from a common precursor. *Synthesis*, ***46***, 2481-2488.

[32] Chavan, S. P., Khairnar, L. B., Pawar, K. P., Chavan, P. N., Kalbhor, D. B. 2014. A short enantioselective total synthesis of (*R*)- and (*S*)-pipecolic acid. *Tetrahedron: Asymmetry*, ***25***, 1246-1251.

[33] Chavan, S. P., Khairnar, L. B., Pawar, K. P., Chavan, P. N., Kawale, S. A. 2015. Enantioselective synthesis of (*R*)-pipecolic acid, (2*R*, 3*R*)-3-hydroxypipecolic acid, β-(+)-conhydrine and (-)-swainsonine using an aziridine derived common chiral synthon. *RSC Advances*, ***5***, 50580-50590.

[34] Zhai, Y., Chuang, S. S. C. 2018. Photocatalytic synthesis of pipecolic acid from lysine on TiO_2: effects of the structure of catalysts and adsorbed species on chiral selectivity. *Organic Process Research & Development*, ***22***, 1636-1643.

[35] Chavan, S. P., Kadam, A. L., Shinde, S. S., Gonnade, R. G. 2020. Furan derived chiral bichoaziridino lactone synthon: collective syntheses of oseltamivir phosphate (tamiflu), (*S*)-pipecolic acid and its 3-hydroxy derivatives. *Chemistry - An Asian Journal*, ***15***, 415-424.

[36] Yang, Y., Li, H.; You, Z., Zhang, X. 2021. A convenient and highly enantioselective synthesis of (*S*)-2-pipecolic acid: an efficient access to caine anesthetics. *Synthetic Communications*, ***51***, 3084-3089.

[37] Hermitage, S. A., Moloney, M. G. 1994. Short approach to functionalized homochiral piperidinones. *Tetrahedron: Asymmetry*, ***5***, 1463-1464.

[38] Davies, C. E., Heightman, T. D., Hermitage, S. A., Moloney, M. G. 1996. Convenient preparations of racemic and enantiopure methyl

6-oxopipecolate. *Synthetic Communications*, ***26***, 687-696.

[39] Ezquerra, J., Pedregal, C., Escribano, A., Carreno, M. C., Ruano, J.L.G. 1995. Stereoselective functionalization of *N*-Boc pyroaminoadipic acid: synthesis of 5-substituted aminoadipic and pipecolic acids. *Tetrahedron Letters*, ***36***, 3247-3250.

[40] Huang, S.-B., Nelson, J. S., Weller, D. D. 1989. Preparation of optically pure ω-hydroxymethyl lactams. *Synthetic Communications*, ***19***, 3485-3496.

[41] Upadhyay, P. K., Kumar, P. 2010. A short and efficient synthesis of (*S*)-(+)-2-(hydroxymethyl)-6-piperidin-2-one. *Synthesis*, 2512-2514.

[42] Dalko, P. I., Moisan, L. 2001. Enantioselective organocatalysis. *Angewandte Chemie International Edition*, ***40***, 3726-3748.

[43] Dalko, P. I., Moisan, L. 2004. In the golden age of organocatalysis. *Angewandte Chemie International Edition*, ***43***, 5138-5175.

[44] Houk, K. N., List, B. 2004. Asymmetric Organocatalysis. *Accounts of Chemical Research*, ***37***, 487-487.

[45] List, B. 2004. Organocatalysis: a complimentary catalysis strategy advances organic synthesis. *Advanced Synthesis & Catalysis*, **346**, 1021-1021.

[46] List, B., Seayad, J. 2005. Asymmetric Organocatalysis. *Organic & Biomolecular Chemistry*, ***3***, 719-724.

[47] MacMillian, D. W. C. 2008. The advent and development of organocatalysis. *Nature*, ***455***, 304-308.

[48] For a review of proline-catalyzed asymmetric reactions, see: List, B. Proline-catalyzed asymmetric reactions. 2002. *Tetrahedron*, ***58***, 5573-5590.

[49] List, B. 2002. Direct catalytic asymmetric α-amination of aldehydes. *Journal of American Chemical Society*, ***125***, 5656-5657.

[50] Bogevig, A., Juhl, K., Kumaragurubaran, N., Zhuang, W., Jorgensen, K. A. 2002. Direct organo-catalytic asymmetric α-amination of aldehydes-a simple approach to optically active α-amino aldehydes, α-amino alcohols, and α-amino acids. *Angewandte Chemie International Edition*, ***41***, 1790-1793.

[51] Kumaragurubaran, N., Juhl, K., Zhuang, W., Bogevig, A., Jorgensen, K. A. 2002. Direct L-proline-catalyzed asymmetric α-amination of ketones. *Journal of American Chemical Society*, ***124***, 6254-6255.

[52] Vogt, H., Vanderheiden, S., Brase, S. 2003. Proline-catalysed asymmetric amination of α,α-disubstituted aldehydes: synthesis of configurationally stable enantioenriched α-aminoaldehydes. *Chemical Communications*, 2448-2449.

[53] Iwamura, H., Mathew, S. P., Blackmond, D. G. 2004. In situ catalyst improvement in the proline-mediated α-amination of aldehydes. *Journal of American Chemical Society*, ***126***, 11770-11771.

[54] Panchgalle, S. P., Gore, R. G., Chavan, S. P., Kalkote, U. R. 2009. Organocatalytic enantioselective synthesis of β-blockers: (*S*)-propranolol and (*S*)-naftopidil. *Tetrahedron: Asymmetry*, ***20***, 1767-1770.

[55] Panchgalle, S. P., Jogdand, G. F., Chavan, S. P., Kalkote, U. R. 2010. Enantioselective synthesis of (*R*)-(+)-α-lipoic acid via proline-catalyzed sequential α-aminoxylation and HWE olefination of aldehyde. *Tetrahedron Letters*, ***51***, 3587-3589.

[56] Panchgalle, S. P., Kunte, S. S., Chavan, S. P., Kalkote, U. R. 2011. Exploration of L-proline-catalyzed α-aminoxylation of aldehyde to (*S*)-guifenesin-related drug molecules. *Synthetic Communications*, ***41***, 1938-1946.

[57] Panchgalle, S. P., Bidwai, H. B., Chavan, S. P., Kalkote, U. R. 2010. Organocatalytic asymmetric synthesis of (-)-δ-coniceine based on sequential proline-catalyzed asymmetric α-amination-HWE olefination. *Tetrahedron: Asymmetry*, ***21***, 2399-2401.

[58] Schreiber, S. L., Claus, R. E., Reagan, J. 1982. Ozonolytic cleavage of cycloalkenes of terminally differentiated products. *Tetrahedron Letters*, ***23***, 3867-3870.

[59] Claus, R. E., Schreiber, S. L. 1986. Ozonolytic cleavage of cyclohexene to terminally differentiated products: methyl 6-oxohexanoate, 6,6-dimethoxyhexanal, methyl 6,6-dimethoxyhexanoate. *Organic Synthses.* ***64***, 150.

[60] Chiral HPLC analysis: Chiracel OD-H (250 x 4.6 mm) column; eluent: 2- Propanol :petroleum ether 05:95; flow rate : 0.5 ml/min., detector 260 nm t_R = 61.56 min., t_S = 69.41 min.