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Enantioselective synthesis of 1,2,5,6-tetrahydropyridines (THPs) via proline-catalyzed direct Mannich-cyclization/domino oxidation-reduction sequence: Application for medicinally important *N*-heterocycles

Panduga Ramaraju,^a Nisar A. Mir,^a Deepika Singh^b and Indresh Kumar^{*a}

An enantioselective multi-component synthesis of 1,2,5,6-tetrahydropyridines (THPs) has been developed through a onepot domino-process. This transformation proceeds through proline-catalyzed direct Mannich reaction-cyclization of glutaraldehyde with in situ generated imines, followed by site-selective oxidation-reduction sequence under mild conditions. Chiral 1,2,5,6-THPs are obtained in good to high yields (up to 80%) and with the excellent enantioselectivity (up to 98:2 er). The usefulness of this operationally simple method is also shown to synthesize other medicinally important nitrogen-heterocycles.

Introduction

Functionalized piperidine and polyhydropyridines are an integral part of numerous natural products.¹ In particular, 1,2,5,6-tetrahydropyridine (THP) is an important structural motif present in many biologically important synthetic pharmaceuticals as well as natural products; such as haouamine's (I, II),^{2a,b} anhydrocannabisativine (III),^{2c} compounds (IV, V)^{2d,e} and (VI),^{3a} guvacine (VII),^{3b} (–)-205B (VIII),^{3c} and SKF 100330-A (IX)^{3d} (Fig. 1). Due to the medicinal significance of this aforementioned scaffold, several fascinating methods found in the literature to synthesize 1,2,5,6-THPs⁴ which includes; hetero-Diels-Alder reaction,⁵ involvement of imine,⁶ and reduction of dihydropyridine.⁷ Despite of few advances for the asymmetric synthesis of 1,2,5,6-THPs,⁸ the development of a simple, convenient and environmentally friendly approach for optically pure THPs is highly desirable.

The development of "one-pot domino process" for chemical transformations that run with the ultimate aim of "to complete an entire multi-step, multi-reaction synthesis in a single pot" is not only considered as a sustainable strategy but also support the basis of the green chemistry philosophy.⁹ One way to achieve this task is to add substrates/reagents sequentially at different time intervals, without workup and product isolation at an intermediate stage, which further

increases the "pot economy" of the overall process. $^{\mathbf{10}}$ In addition, multi-



Fig. 1 Biologically important compounds having tetrahydropyridine (THP) moiety

component reactions (MCRs) is an alternative way to achieve multiple bond formations in a one pot operation,¹¹ however the development of asymmetric MCRs are still infancy.¹² In this direction, organocatalysis¹³ have contributed significantly to the recent growth of asymmetric domino¹⁴ and MCRs,¹⁵ under mild conditions due to the increasing demand of chiral scaffolds in pharmaceuticals. Recently, two parallel chiral phosphoric acid catalyzed MCRs of aromatic aldehydes, anilines, and β -ketoesters were reported by Xufeng Lin *et al.*^{16a} and Shi and Tu *et al.*^{16b} to synthesize 1,2,5,6-THPs in asymmetric fashion (eq 1, Scheme 1). A multi-component reaction will be more cost-effective by linking through a domino-process of three or even four consecutive steps in one pot operation in such a way that the product of initial step

^{a.} Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, (Rajasthan) India, E-mail: indresh.chemistry@gmail.com,

indresh.kumar@pilani.bits-pilani.ac.in

^{b.} Instrumentation Division, IIIM-CSIR Lab, Jammu 180 001, India

⁺ Footnotes relating to the title and/or authors should appear here

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later become the substrate for next reaction until dissolution leads to stable product. Therefore, we present a highly enantioselective synthesis of 1,2,5,6-tetrahydropyridines (THPs) through proline-catalyzed multi-component Mannich reaction-cyclization followed by site-selective oxidationreduction sequence as a domino-process in a single flask (eq 2, Scheme 1).

Earlier work: (organocatalytic asymmetric multicomponent approach) ref (16)



Present work: (organocatalytic asymmetric multicomponent one-pot domino process)



Scheme 1 Overview of present work for pyrrole-3-methanols synthesis

Results and discussion

Linear dialdehydes have recently being shouted as suitable bifunctionalized substrates for amine catalyzed asymmetric and non-asymmetric transformations.¹⁷ In this direction, Xu and co-workers have earlier utilized glutaraldehyde and imines for the asymmetric synthesis of 1,2,3,4-tetrahydropyridines (THPs).¹⁸ Our group has independently developed prolinecatalyzed [4+2] annulation between glutaraldehyde and imines for the asymmetric synthesis of piperidines,¹⁹ and 1,2dihydropyridines (DHPs).²⁰ Next, we become fascinated to extend our idea of the synthesis of 1,2,5,6-THPs and that is quite feasible if we selectively reduce the in situ generated 1,2-DHPs without isolation so that a one pot domino process will be realized. Although the use of preformed imines was an option, the whole process will be greener and more economical if imines could be generated in situ. This reaction could conveniently follow multi-component pathway through in situ formation of imine (step 1), proline-catalytic Mannich reaction-cyclization (step 2), in situ site-selective oxidation with IBX (step 3) and finally acid mediated selective NaBH₄ reduction (step 4) as one pot domino-approach to furnish 1,2,5,6-THPs with high stereoselectivity without any isolation at intermediate stage. By keeping this idea in mind and the previous experience in this direction, we quickly established the reaction conditions by taking p-nitrobenzaldehyde 2c as a model substrate along with *p*-anisidine **3** and glutaraldehyde **4** as shown in Table 1.

During our experimental studies, we initially carried out all steps of the multi-component/domino-reaction at room temperature with proline **1** (20 mol %) in DMSO as preferred solvent and obtained 1,2,5,6-THP **5c** exclusively in moderate yield (65%) and enantioselectivity (88:12 er) (entry 1, Table 1). We did not alter the amine catalyst or solvent as they turn out

to be best in our previous studies. However, by changing the reaction temperature at individual steps, we could obtain our product with 80% yield and excellent enantioselectivity (97:3 er) (entry 2, Table 1). A further change in the reaction conditions (entry 3, Table 1), and catalyst loading (entry 4, Table 1), resulted a loss in the overall yield. Thus, we choose to perform this one pot protocol of sequential multi-component amine catalyzed [4+2] annulation/IBX oxidation/acid mediated NaBH₄ reduction through preferred conditions (entry 2, Table 1).





^{*a*}Unless otherwise indicated, the reaction was carried out with: (*step 1*) **2c** (0.3 mmol), **3** (0.3 mmol), DMSO (3.0 mL), (*step 2*) glutaraldehyde **4** (25% aqueous sol., 0.9 mmol), L-Proline **1** (20 mol %), (*step 3*) IBX (120 mol %), and (*step 4*) MeOH (3.0 mL), NaBH₄ (excess), CH₃CO₂H (200 mol %). ^{*b*}Isolated yield of **5c**. ^{*c*}Determined using stationary chiral columns. ^{*d*}CH₃CO₂H (200 mol %), and MeOH (3.0 mL) were not added during step 4. ^{*c*}Catalyst **1** (10 mol %).

Once we established the reaction conditions for this one pot domino sequence, we turn our attention to check the substrate scope with respect to a variety of aromatic aldehydes 2 having various substituents. This one pot protocol advance well in almost all cases when aromatic aldehydes 2 were decorated with electron withdrawing groups (EWG) (e.g. -NO2, -F, -Cl, -Br and -CN) at the ortho-, meta-, or parapositions, and furnished corresponding 1,2,5,6-DHPs 5a-5p (Table 2) with good yields and high enantioselectivity's. In all the cases, aromatic aldehyde 2 was stirred with p-anisidine 3 at rt for about 3 h (step 1) for in situ generation of imine, which subsequently used for further steps. The amine catalyzed Mannich reaction-cyclization (step 2) was rather slow in case of imines generated from aldehydes substituted at ortho-position (5a, 5d, 5g, and 5i, Table 2). A similar observation of slow reaction was made for 5q (Table 2) when benzaldehyde 2q was used for this one-pot sequence. Pleasantly, compound 5r-5v (Table 2) were also obtained in good yields and high enantiomeric ratio, when heteroaromatic aldehydes were employed under standardized conditions. This reaction failed to give desired product 5w (Table 2) when electronically rich aryl-aldehydes was employed.

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chiral columns.



5v, 8 h, 63% er = 86:14

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Synthetic applications 1,2,5,6-THPs **5**, carrying a double bond and alcohol functionality as well as some functional groups at the aromatic ring, are interesting scaffolds for further functionalization. Therefore, we

^aUnless otherwise indicated, the reaction was carried out with (*step* 1) 2 (0.3 mmol), **3** (0.3 mmol), DMSO (3.0 mL), 3 h, (*step* 2) glutaraldehyde 4 (25% aqueous sol., 0.9 mmol), L-Proline 1 (20 mol %), ^btime required (h), (*step* 3) IBX

(120 mol %), 40 °C, 4 h, and (step 4) NaBH₄ (excess), MeOH (3.0 mL), CH₃CO₂H

(200 mol %) in single flask. ^cisolated yield of 5. ^dDetermined using stationary

initially developed a rapid synthesis of chromeno-[4,3b]pyridine 7 from compound 5j to demonstrate the synthetic potential of these compounds. Pd-catalyzed intramolecular C-O coupling reaction of in situ generated syn-alcohol (Scheme 2a) via Pd/C reduction of 5j, furnished polycyclic alkaloid-type product 6 having syn-stereochemistry at two chiral centers. Subsequent PMP-cleavage (PMP = p-methoxyphenyl) resulted highly functionalized hexahydrochromeno[4.3-b]pyridine 7. This polycyclic chromeno-[4,3-b]pyridine compound 7 and similar ring systems are present as core skeletons in many interesting bioactive compounds, like- 8 and 9.21 Moreover, derivatization of the double-bond present in the ring through diastereoselective epoxidation/dihydroxylation reactions could lead to saturated piperidines. Initially, 5c underwent diastereoselective epoxidation with m-CPBA (metachloroperbenzoic acid) in CH₂Cl₂ at rt to corresponding epoxycompound 10. Whereas, corresponding dihydroxylated compound 11 was obtained with good yield and selectivity (dr ≥95:5) under standard dihydroxylation conditions (Scheme 2b). These polyhydroxyl-piperidines and similarly functionalized compounds are important glycosidase inhibitors categorized as iminosugars.²²



Scheme 2 Applications for the synthesis of hexahydrochromeno[4,3-*b*]pyridine and important polyfunctionalized piperidines

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Interestingly, direct oxidation of primary alcohol functionality of 5q to corresponding carboxylic acid provide a rapid access to guvacine derivatives 12 (Scheme 3a). Further, we also showed the synthetic utility of our approach to synthesize ent-5q by just changing the stereochemistry of catalyst used under with standardized conditions similar vields and enantioselectivity (18:82 er). The resulting product ent-5q was next used for the synthesis of syn-nipecotic acid derivative 14 with 66% yield (after two steps, Scheme 3b) through reduction-oxidation sequence. Nipecotic acid 15, a cyclic amino acid and considered as a conformationally restricted βalanine analog, shows high in vitro activity as an inhibitor of [³H]GABA uptake.²³



Scheme 3 Quick synthesis of guyacine and nipecotic acid derivative



Synthetic application of this method was also shown to synthesize structural analog 19 of (-)-CP-99 994 20 as this compound carries interesting biological activity.²⁴ In this context, firstly Pd/C catalyzed hydrogenation of THPcompound 5q gave syn-2,3-substituted-piperidine 16 in 90% yield and with high diastereoselectivity (dr ≥95:5). The alcoholic group was converted into -OTs under standard condition, the crude 17 was further subjected to nucleophilic substitution with 2-methoxyaniline 18 under heating condition resulted in compound 19 (68% yield from 20, Scheme 4).

Conclusions

In summary, we have developed an efficient multi-component domino-sequence for the asymmetric synthesis of functionalized 1,2,5,6-tetrahydropyridines (THPs) in a single flask. This method proceeds through proline-catalyzed Mannich reaction-cyclization of glutaraldehyde with in situ generated imines, followed by sequential selective IBXoxidation/NaBH₄-reduction under mild conditions, without any isolation at intermediate stages. Further applications of this developed method were also shown for the synthesis of; (i) hexahydrochromeno[4,3-b]pyridine (ii) polyhydroxy-piperidine (iii) guvacine and nipecotic acid derivatives, and (iv) structural analog of (-)-CP 99 994, as medicinally important scaffolds. Further efforts are underway to synthesize other important polyhydropyridines through this one-pot method and results will be presented later.

Experimental

General Remarks: Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. All reactions under standard conditions were monitored by thinlayer chromatography (TLC) on Merck silica gel 60 F254 precoated plates (0.25 mm). The column chromatography was performed on silica gel (100-200) using a mixture of hexane/EtOAc. Chemical yields refer to pure isolated substances. ¹H-NMR spectra were recorded on a BRUKER-AV400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃= δ 7.26 for ¹H, and 77.00 for ¹³C-NMR). Data are reported as follows: chemical shift, multiciplity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ¹³C-NMR spectra were recorded on a BRUKER-AV400 (75 MHz) spectrometer with complete proton decoupling. High-resolution mass spectra were recorded using the quadrupole electrospray ionization (ESI) technique. HPLC was performed on Water-2998-instrument with CHIRALPAK-IA and IB columns using hexane/2-propanol.

Typical procedure for the synthesis of THPs (5)

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To a stirred solution of aryl aldehyde 2 (0.3 mmol) in DMSO (3.0 mL) at rt was added p-anisidine 3 (0.3 mmol) and stirred for additional 3 hr at same temperature. To this mixture, was added glutaraldehyde 4 (25 % sol. in water, 0.360 mL, 0.9 mmol), and L-proline 1 (6.9 mg, 0.06 mmol) and taken to 10 °C. This reaction mixture was further stirred at the same temperature until the in situ generated imine was consumed completely as monitored by TLC. IBX (2-lodoxybenzoic acid) (1.2 equiv, 0.36 mmol) was added into the same flask and further heated to 40 °C for 4 hrs. This reaction mixture was then cooled to 0 °C and methanol (3.0 mL) was added followed by NaBH₄ (in excess and portion wise) along with CH₃CO₂H (200 mol %) until the dark red color of the solution turned into pale reddish yellow. The reaction was quenched slowly with saturated NaHCO₃ (5.0 mL, 20% sol.) and stirred with ethyl acetate (10 mL) for 10 min. at rt and organic layer was separated out. The aqueous layer was further extracted with ethyl acetate (10 mL) and the combined organic extracts were washed with brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure after filtration. Purification was performed by a silica gel column and eluted with hexane/EtOAc to give product 5 (58-80% yields). The enantiomeric ratios (er) of the products were determined by stationary chiral phase HPLC analysis.

(*R*)-(1-(4-Methoxyphenyl)-2-(2-nitrophenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5a).

Yellow viscous oil, (64 mg, 63% yield), ¹H NMR (400 MHz, CDCl₃) δ 1.77–1.79 (bs, 1H), 2.18–2.23 (m, 1H), 2.25-2.32 (m, 1H), 3.00–3.07 (m, 1H), 3.15–3.19 (m, 1H), 3.73 (s, 3H), 4.06 (s, 2H), 5.80 (s, 1H), 6.16 (t, *J* = 4.2 Hz, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.32–7.36 (m, 1H), 7.50–7.51 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 23.70, 44.50, 55.35, 55.57, 64.91, 114.20 (2C), 121.40 (2C), 124.16, 125.61, 128.02, 130.13, 131.66, 135.19, 136.73, 143.78, 150.57, 154.65; IR (KBr)/cm⁻¹ 3448, 2924, 2854, 1520, 1466, 1350, 1242, 1180, 1034; HRMS (ESI): Calcd for C₁₉H₂₀N₂O₄ (MH⁺) 341.1501; Found: 341.1504. $[\alpha]_D^{25} = - 81.4$ (*c* 0.1, CH₂Cl₂). HPLC analysis: 97:3 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 94/06), flow rate (0.8 mL/min), *t* (minor) = 15.224 min, *t* (major) = 22.808 min].

(*R*)-(1-(4-Methoxyphenyl)-2-(3-nitrophenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5b).

Pale yellow viscous liquid, (75 mg, 74% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.33–2.47 (m, 2H), 3.10–3.22 (m, 2H), 3.73 (s, 3H), 3.86 (d, *J* = 12.8 Hz, 1H), 4.01 (d, *J* = 12.8 Hz, 1H), 5.20 (s, 1H), 6.16 (t, *J* = 3.1 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 8.02–8.08 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.68, 43.00, 55.40, 61.64, 64.78, 114.24 (2C), 121.24 (2C), 122.41, 123.23, 125.30, 128.76, 135.14, 136.77, 141.61, 143.76, 147.90, 154.34; IR (KBr)/cm⁻¹ 3418, 2924, 2847, 1605, 1520, 1458, 1342, 1250, 1188, 1034; HRMS (ESI): Calcd for C₁₉H₂₀N₂O₄ (MH⁺) 341.1501; Found: 341.1508. $[\alpha]_D^{25} = -173$ (*c* 0.5, CH₂Cl₂). HPLC analysis: 94:6 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 29.538 min, *t* (major) = 33.207 min].

(*R*)-(1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5c).

Yellowish viscous oil, (82 mg, 80% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.32–2.47 (m, 2H), 3.11–3.22 (m, 2H), 3.74 (s, 3H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.99 (d, *J* = 12.8 Hz, 1H), 5.18 (s, 1H), 6.14 (t, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.79, 42.96, 55.32, 61.74, 66.59, 114.15 (2C), 121.20 (2C), 122.98 (2C), 124.84, 129.48 (2C), 136.81, 143.68, 146.82, 147.80, 154.28; IR (KBr)/cm⁻¹ 3446, 2925, 2854,1522, 1468, 1350, 1241, 1180, 1034; HRMS (ESI Calcd for C₁₉H₂₀N₂O₄ (MH⁺) 341.1501; Found: 341.1495. [α]₀²⁵ = -198 (c 1.0, CH₂Cl₂). HPLC analysis: 97:3 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (1.0 mL/min), *t* (minor) = 17.932 min, *t* (major) = 22.037 min].

(S)-(2-(2-Fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5d).

Reddish viscous oil, (57 mg, 61% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.17–2.22 (m, 1H), 2.27–2.32 (m, 1H), 3.28–3.31 (m, 2H), 3.74 (s, 3H), 3.94 (s, 2H), 5.48 (s, 1H), 6.11 (t, *J* = 3.9 Hz, 1H), 6.77 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.17–7.22 (m, 2H), 7.32–7.34 (m, 1H) 7.39–7.41(m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 23.38, 44.79, 55.37, 57.34, 64.71, 114.08 (2C), 120.67 (2C), 124.84, 126.43, 128.51, 129.81, 129.96, 135.32, 137.64, 138.39, 144.27, 153.89; IR (KBr)/cm⁻¹ 3140, 2916, 2850,1660, 1508, 1246, 1178; HRMS (ESI): Calcd for C₁₉H₂₀FNO₂ (MH⁺) 314.1556; Found: 314.1559. [α]_D²⁵ = – 46.1 (*c* 0.8, CH₂Cl₂). HPLC analysis: 98:2 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 11.835 min, *t* (major) = 14.871 min].

(*R*)-(2-(3-Fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5e).

Yellow viscous liquid, (62 mg, 66% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.26–2.31 (m, 1H), 2.39–2.47 (m, 1H), 3.18–3.21 (m, 2H), 3.74 (s, 3H), 3.91 (d, *J* = 12.4 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 5.08 (s, 1H), 6.10 (t, *J* = 4.3 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 3H), 6.90–6.92 (m, 2H), 7.14–7.20 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.62, 42.63, 55.44, 61.87, 64.97, 114.15 (2C), 114.33, 115.41, 115.62, 120.88 (2C), 124.39, 124.67, 129.27, 129.35, 137.59, 144.24, 153.99; IR (KBr)/cm⁻¹ 3420, 2924, 2848, 1655, 1589, 1247, 1170; HRMS (ESI Calcd for C₁₉H₂₀FNO₂ (MH⁺) 314.1556; Found: 314.1562. $[\alpha]_D^{25} = -41.3$ (*c* 0.6, CH₂Cl₂). HPLC analysis: 81:19 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 17.480 min, *t* (major) = 20.078 min].

(*R*)-(2-(4-Fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5f).

Yellowish viscous liquid, (64 mg, 68% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.25–2.26 (m, 1H), 2.39–2.47 (m, 1H), 3.14–3.17 (m, 2H), 3.74 (s, 3H), 3.93 (m, 2H), 5.07 (s, 1H), 6.09 (t, *J* = 4.4 Hz, 1H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.89 (t, *J* = 8.7 Hz, 2H), 7.07 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.76, 42.35, 55.43, 61.80, 65.02, 114.10 (2C), 114.62, 114.83, 121.16 (2C), 124.14, 130.35, 130.43, 134.74, 137.93, 144.31, 154.04, 160.83; IR (KBr)/cm⁻¹ 3426, 2924, 2854, 1643, 1597, 1512, 1242, 1034, 825, 725; HRMS (ESI): Calcd for C₁₉H₂₀FNO₂ (MH⁺) 314.1556; Found: 314.1549. [α]_D²⁵ = – 101 (*c* 0.2, CH2Cl₂).

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HPLC analysis: 83:17 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 18.826 min, *t* (major) = 20.510 min].

(S)-(2-(2-Chlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5g).

Dark red viscous liquid, (64 mg, 65% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.16–2.23 (m, 1H), 2.25–2.34 (m, 1H), 3.28–3.31 (m, 2H), 3.74 (s, 3H), 3.93 (s, 2H), 5.48 (s, 1H), 6.11 (t, *J* = 3.8 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.15–7.22 (m, 2H), 7.32–7.34 (m, 1H), 7.37–7.41 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 23.35, 44.76, 55.38, 57.30, 64.75, 114.07 (C), 120.64 (2C), 124.90, 126.44, 128.53, 129.83, 129.96, 153.33, 137.62, 138.38, 144.25, 153.87; IR (KBr)/cm⁻¹ 3418, 2924, 2862, 1659, 1512, 1458, 1250, 1188, 1095, 1034; HRMS (ESI): Calcd for C₁₉H₂₀CINO₂ (MH⁺) 330.1261; Found : 330.1255. [α]_D²⁵ = – 76.6 (*c* 0.3, CH₂Cl₂). HPLC analysis: 97:3 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 90/10), flow rate (0.6 mL/min), *t* (minor) = 8.278 min, *t* (major) = 11.601 min].

(*R*)-(2-(3-Chlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5h).

Pale yellow liquid, (67 mg, 68% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.19 (bs, 1H), 2.25–2.30 (m, 1H), 2.40–2.46 (m, 1H), 3.17–3.20 (m, 2H), 3.78 (s, 3H), 3. 89 (d, *J* = 12.8 Hz, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 5.06 (s, 1H), 6.09 (t, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 6.98–7.01 (m, 1H), 7.08–7.13 (m, 1H), 7.15–7.19 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.47, 42.47, 55.42, 6180, 64.76, 114.14 (2C), 120.87 (2C), 124.36, 127.25, 127.46, 128.64, 129.12, 133.79, 137.33, 141.36, 144.03, 154.01; IR (KBr)/cm⁻¹ 3464, 2924, 2947, 1643, 1512, 1242, 1188, 1088, 1034; HRMS (ESI): Calcd for C₁₉H₂₀CINO₂ (MH⁺) 330.1261; Found : 330.1267. [α]_D²⁵ = – 97.6 (*c* 0.8, CH₂Cl₂). HPLC analysis: 85:15 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 17.376 min, *t* (major) = 19.863 min].

(*R*)-(2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5i).

Colorless viscous liquid, (69 mg, 70% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.25–2.30 (m, 1H), 2.38–2.46 (m, 1H), 3.12–3.17 (m, 2H), 3.74 (s, 3H), 3.87 (d, *J* = 13.1 Hz, 1H), 3.95 (d, *J* = 12.8 Hz, 1H), 5.06 (s, 1H), 6.08 (t, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.71, 42.31, 55.38, 61.76, 64.78, 114.08 (2C), 121.09 (2C), 124.11, 127.99 (2C), 130.16 (2C), 133.02, 137.42, 137.60, 144.12, 154.02; IR (KBr)/cm⁻¹ 3418, 2916, 2847, 1651, 1597, 1594, 1242, 1188, 1095, 1026; HRMS (ESI): Calcd for C₁₉H₂₀CINO₂ (MH⁺) 330.1261; Found : 330.1263. [α]_D²⁵ = – 143.2 (*c* 0.7, CH₂Cl₂). HPLC analysis: 86:14 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 20.054 min, *t* (major) = 23.154 min].

(S)-(2-(2-Bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5j).

Reddish viscous liquid, (65 mg, 58% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.30–2.35 (m, 2H), 3.14–3.19 (m, 1H), 3.23–3.30 (m, 2H), 3.52 (d, *J* = 13.9 Hz, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 3.76 (s, 3H), 5.55 (s, 1H), 5.91 (bs, 1H), 6.82 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 7.14–7.18 (m, 1H), 7.33–7.39 (m, 1H), 7.53–

7.55 (m, 1H), 7.59–7.61 (m, 1H); 13 C NMR (75 MHz, CDCl₃) δ 23.36, 45.13, 55.36, 59.75, 64.72, 114.04 (2C), 121.06 (2C), 124.97, 126.17, 127.03, 128.78, 130.19, 133.18, 137.67, 140.09, 144.35, 153.98; IR (KBr)/cm⁻¹ 3317, 3055, 2916, 2847, 1512, 1450, 1242, 1180, 1034; HRMS (ESI): Calcd for C₁₉H₂₀BrNO₂ (MH⁺) 374.0755; Found: 374.0759. [α]_D²⁵ = – 32.3 (*c* 0.6, CH₂Cl₂). HPLC analysis: 98:2 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 10.465 min, *t* (major) = 13.302 min].

(R)-(2-(3-Bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5k).

Yellow viscous liquid, (75 mg, 67% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.27–2.28 (m, 1H), 2.41–2.48 (m, 1H), 3.19–3.22 (m, 2H), 3.77 (s, 3H), 3.92 (d, *J* = 12.9 Hz, 1H), 4.01 (d, *J* = 12.8 Hz, 1H), 5.07 (s, 1H), 6.12 (t, *J* = 4.2 Hz, 1H), 6.79 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 9.1 Hz, 2H), 7.05–7.12 (m, 2H), 7.34–7.37 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.44, 42.35, 55.40, 61.75, 64.69, 114.12 (2C), 120.86 (2C), 122.09, 124.34, 127.66, 129.40, 130.34, 131.49, 137.24, 141.57, 144.01, 153.98; IR (KBr)/cm⁻¹ 3302, 3055, 2916, 2839, 1566, 1512, 1458, 1242, 1180, 1034; HRMS (ESI): Calcd for C₁₉H₂₀BrNO₂ (MH⁺) 374.0755; Found: 374.0762. [α]_D²⁵ = – 113.3 (*c* 1.5, CH₂Cl₂). HPLC analysis: 90:10 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 17.692 min, *t* (major) = 19.870 min].

(*R*)-(2-(4-Bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (5l).

Colorless viscous liquid, (77 mg, 69% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.25–2.30 (m, 1H), 2.38–2.46 (m, 1H), 3.13–3.16 (m, 2H), 3.74 (s, 3H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.96 (d, *J* = 12.9 Hz, 1H), 5.04 (s, 1H), 6.08 (t, *J* = 4.2 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.99 (d, *J* = 9.6 Hz, 2H), 7.33 (d, *J* = 9.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.70, 42.31, 55.37, 61.79, 64.70, 114.09 (2C), 121.05 (2C), 121.24, 124.07, 130.51 (2C), 130.91 (2C), 137.52, 137.94, 144.08, 154.01; IR (KBr)/cm⁻¹ 3418, 2916, 2908, 1659, 1504, 1242, 1188, 1026, 818; HRMS (ESI): Calcd for C₁₉H₂₀BrNO₂ (MH⁺) 374.0755; Found: 374.0757. [α]_D²⁵ = - 187.5 (*c* 0.8, CH₂Cl₂). HPLC analysis: 92:8 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 21.191 min, *t* (major) = 25.148 min].

(*R*)-(2-(3-Bromo-4-fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (5m).

Pale yellow viscous liquid, (83 mg, 71% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.26–2.31 (m, 1H), 2.37–2.45 (m, 1H), 3.09–3.17 (m, 2H), 3.75 (s, 3H), 3.86–3.89 (d, *J* = 12.3 Hz, 1H), 3.98 (d, *J* = 12.9 Hz, 1H), 5.04 (s, 1H), 6.10 (t, *J* = 3.0 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.2 Hz, 2H), 6.92–6.96 (m, 1H), 6.98–7.02 (m, 1H), 7.32–7.34 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.56, 42.35, 55.40, 61.31, 64.64, 114.16 (2C), 121.18 (2C), 124.50, 129.45, 129.52, 133.41, 136.46, 137.22, 143.84, 154.21, 156.91, 159.36; IR (KBr)/cm⁻¹ 3279, 3047, 2914, 2847, 1558, 1504, 1242, 1180, 1034; HRMS (ESI): Calcd for C₁₉H₁₉BrFNO₂ (MH⁺) 392.0661; Found: 392.0667. [α]_D²⁵ = – 95.4 (*c* 1.2, CH₂Cl₂). HPLC analysis: 87:13 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 17.880 min, *t* (major) = 20.715 min].

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(*R*)-3-(3-(Hydroxymethyl)-1-(4-methoxyphenyl)-1,2,5,6tetrahydropyridin-2-yl)benzonitrile (5n).

Yellow viscous liquid, (71 mg, 74% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.29–2.38 (m, 1H), 2.40–2.45 (m, 1H), 3.07–3.21 (m, 2H), 3.74 (s, 3H), 3.82–3.85 (m, 1H), 3.98 (d, *J* = 13.0 Hz, 1H), 5.11 (s, 1H), 6.13 (t, *J* = 3.1 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 7.28–7.32 (m, 1H), 7.34–7.37 (m, 1H), 7.47–7.50 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.55, 42.70, 55.33, 61.53, 64.50, 111.65, 114.15 (2C), 118.85 121.11 (2C), 124.84, 128.62, 130.92, 132.02, 133.46, 136.75, 140.74, 143.70, 154.20; IR (KBr)/cm⁻¹ 3418, 2924, 2947, 2230, 1605, 1512, 1458, 1242, 1188, 1034; HRMS (ESI): Calcd for C₂₀H₂₀N₂O₂ (MH⁺) 321.1603; Found: 321.1609. [α]₀²⁵ = – 143.3 (*c* 0.8, CH₂Cl₂). HPLC analysis: 88:12 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 85/15), flow rate (0.5 mL/min), *t* (major) = 16.913 min, *t* (minor) = 21.912 min].

(*R*)-4-(3-(Hydroxymethyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-2-yl)benzonitrile (50).

Pale yellow viscous liquid, (74 mg, 78% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.28–2.34 (m, 1H), 2.38–2.47 (m, 1H), 3.08–3.17 (m, 2H), 3.74 (s, 3H), 3.84 (d, *J* = 12.3 Hz, 1H), 3.97 (d, *J* = 12.9 Hz, 1H), 5.12 (s, 1H), 6.12 (t, *J* = 3.1 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.62, 42.77, 55.28, 61.88, 64.42, 110.77, 114.09 (2C), 118.70, 121.02 (2C), 124.58, 129.36 (2C), 131.55 (2C), 136.78, 143.73, 144.74, 154.13; IR (KBr)/cm⁻¹ 3418, 2924, 2862, 2230, 1659, 1512, 1458, 1250, 1188, 1095, 1034; HRMS (ESI): Calcd for C₂₀H₂₀N₂O₂ (MH⁺) 321.1603; Found: 321.1605. [α]_D²⁵ = - 182.4 (*c* 1.5, CH₂Cl₂). HPLC analysis: 90:10 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (0.5 mL/min), *t* (minor) = 16.974 min, *t* (major) = 18.771 min].

(*R*)-(2-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (5p).

Orange liquid, (76 mg, 70% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.25–2.30 (m, 1H), 2.36–2.44 (m, 1H), 3.08–3.17 (m, 2H), 3.73 (s, 3H), 3.85 (d, *J* = 12.3 Hz, 1H), 3.97 (d, *J* = 12.9 Hz, 1H), 5.03 (s, 1H), 6.09 (t, *J* = 3.1 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.93 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 7.23–7.25 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.56, 42.53, 55.36, 61.33, 61.51, 114.19 (2C), 121.04 (2C), 124.49, 128.29, 129.70, 130.39, 131.13, 131.86, 137.03, 139.51, 143.81, 154.18; IR (KBr)/cm⁻¹ 3410, 3055, 2916, 2839, 1605, 1512, 1458, 1396, 1242, 1188, 1034; HRMS (ESI): Calcd for C₁₉H₁₉Cl₂NO₂ (MH⁺) 364.0871; Found: 364.0876. $[\alpha]_D^{25} = -193$ (*c* 1.3, CH₂Cl₂). HPLC analysis: 93:7 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 17.848 min, *t* (major) = 21.804 min].

(*R*)-(1-(4-Methoxyphenyl)-2-phenyl-1,2,5,6tetrahydropyridin-3-yl)methanol (5q).

Yellow viscous oil, (51 mg, 58% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.23–2.28 (m, 1H), 2.40–2.45 (m, 1H), 3.17–3.21 (m, 2H), 3.73 (s, 3H), 3.93 (m, 2H), 5.09 (s, 1H), 6.07 (bs, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 7.12–7.15 (m, 2H), 7.20–7.22 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 24.54, 42.22, 55.39, 62.31, 64.94, 114.03 (2C), 120.73 (2C), 123.79, 127.27, 127.88 (2C), 128.87 (2C), 137.95, 139.10, 144.41, 153.73; IR

(KBr)/cm⁻¹ 3394, 2924, 2854, 1736, 1512, 1458, 1381, 1242, 1180, 1034, 875; HRMS (ESI): Calcd for $C_{19}H_{21}NO_2$ (MH⁺) 296.1650; Found: 296.1658. [α]_D²⁵ = - 140.5 (*c* 0.5, CH₂Cl₂). HPLC analysis: 85:15 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 88/12), flow rate (0.5 mL/min), *t* (minor) = 13.505 min, *t* (major) = 15.262 min].

(S)-(1-(4-Methoxyphenyl)-2-phenyl-1,2,5,6-

tetrahydropyridin-3-yl)methanol (ent-5q).

 $[\alpha]_{D}^{25}$ = + 42.3 (*c* 0.1, CH₂Cl₂). HPLC analysis: 18:82 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 88/12), flow rate (0.5 mL/min), *t* (major) = 13.397 min, *t* (minor) = 15.273 min].

(S)-(1-(4-Methoxyphenyl)-2-(pyridin-2-yl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5r).

Dark red viscous liquid, (56 mg, 63% yield), ¹H NMR ¹H NMR (400 MHz, CDCl₃) δ 2.33–2.37 (bs, 2H), 3.19–3.25 (m, 1H), 3.34-3.40 (m, 1H), 3.74 (s, 3H), 4.08 (m, 2H), 5.27 (s, 1H), 5.99 (t, *J* = 3.9 Hz, 1H), 6.76-6.80 (m, 2H), 6.82-6.83 (m, 2H), 7.16–7.19 (m, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 8.50 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 23.81, 43.93, 55.49, 63.71, 65.88, 114.48 (2C), 117.45 (2C), 120.86, 122.50, 124.11, 124.93, 136.86, 137.42, 148.07, 159.26, 161.77; IR (KBr)/cm⁻¹ 3294, 3055, 2924, 2839, 1466, 1242, 1034; HRMS (ESI): Calcd for C₁₈H₂₀N₂O₂ (MH⁺) 297.1603; Found: 297.1608. [α]₀²⁵ = –111.5 (*c* 0.8, CH₂Cl₂). HPLC analysis: 91:9 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 85/15), flow rate (0.5 mL/min), *t* (minor) = 22.747 min, *t* (major) = 28.847 min].

(*R*)-(1-(4-Methoxyphenyl)-2-(pyridin-3-yl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5s).

Red viscous liquid, (64 mg, 72% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.27–2.32 (m, 1H), 2.40–2.50 (m, 1H), 3.09–3.17 (m, 2H), 3.73 (s, 3H), 3.87 (d, *J* = 13.0 Hz, 1H), 3.99 (d, *J* = 12.9 Hz, 1H), 5.12 (s, 1H), 6.13 (s, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.13–7.15 (m, 1H), 7.42–7.44 (m, 1H), 8.32 (s, 1H), 8.41 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.70, 42.52, 55.37, 60.18, 64.41, 141.18 (2C), 121.29 (2C), 123.07, 124.44, 135.00, 136.63, 136.92, 143.86, 148.23, 149.69, 154.24; IR (KBr)/cm⁻¹ 3410, 2924, 2862, 1651, 1582, 1512, 1242, 1034; HRMS (ESI): Calcd for C₁₈H₂₀N₂O₂ (MH⁺) 297.1603; Found: 297.1605. [α]_D²⁵ = – 103 (*c* 0.4, CH₂Cl₂). HPLC analysis: 81:19 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (1.0 mL/min), *t* (minor) = 19.082 min, *t* (major) = 22.508 min].

(R)-(1-(4-Methoxyphenyl)-2-(pyridin-4-yl)-1,2,5,6-

tetrahydropyridin-3-yl)methanol (5t).

Yellow viscous liquid, (67 mg, 76% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.26–2.31 (m, 1H), 2.39–2.47 (m, 1H), 3.08–3.22 (m, 2H), 3.73 (s, 3H), 3.87 (d, *J* = 12.7 Hz, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 5.08 (s, 1H), 6.12 (t, *J* = 3.2 Hz, 1H), 6.74 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 7.05 (d, *J* = 6.0 Hz, 2H), 8.41 (d, *J* = 5.9 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 24.60, 42.79, 55.38, 61.26, 64.38, 114.17 (2C), 115.35, 118.22, 120.82 (2C), 123.89, 124.57, 136.73, 143.87, 148.52, 149.08, 154.08; IR (KBr)/cm⁻¹ 3711, 3040, 2916, 2847, 1512, 1458, 1260, 1188; HRMS (ESI): Calcd for C₁₈H₂₀N₂O₂ (MH⁺) 297.1603; Found: 297.1611. [α]₀²⁵ = - 105.9 (*c* 0.7, CH₂Cl₂). HPLC analysis: 96:4 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (1.0 mL/min), *t* (minor) = 20.044 min, *t* (major) = 24.477 min].

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(S)-(1-(4-Methoxyphenyl)-2-(thiophen-2-yl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5u).

Reddish viscous oil, (48 mg, 53% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.24–2.29 (m, 1H), 2.43–2.52 (m, 1H), 3.21–3.24 (m, 2H), 3.75 (s, 3H), 4.02–4.09 (m, 2H), 5.41 (s, 1H), 6.03–6.05 (m, 1H), 6.66–6.68 (m, 1H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.83–6.84 (m, 1H), 6.87 (d, *J* = 9.2 Hz, 2H), 7.12–7.13 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.98, 41.06, 55.41, 57.89, 64.97, 114.13 (2C), 120.69 (2C), 123.85, 124.81, 126.12, 126.64, 138.29, 141.57, 144.02, 153.97; IR (KBr)/cm⁻¹ 3493, 2924, 2854, 1651, 1512, 1242, 1034; HRMS (ESI): Calcd for C₁₇H₁₉NO₂S (MH⁺) 302.1214; Found: 302.1219. [α]_D²⁵ = – 123 (*c* 0.2, CH₂Cl₂). HPLC analysis: 86:14 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), *t* (minor) = 30.484 min, *t* (major) = 36.166 min].

(*S*)-(1-(4-Methoxyphenyl)-2-(5-nitrofuran-2-yl)-1,2,5,6tetrahydropyridin-3-yl)methanol (5v).

Dark red viscous liquid, (62 mg, 63% yield), ¹H NMR (400 MHz, CDCl₃) δ 2.28–2.35 (m, 2H), 3.22–3.25 (m, 2H), 3.64 (s, 2H), 3.77 (s, 3H), 4.11 (s, 1H), 5.86 (bs, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.98 (m, 2H), 7.27–7.30 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 25.03, 41.22, 55.48, 57.96, 65.05, 114.22 (2C), 120.89 (2C), 123.91, 124.84, 126.16, 126.63, 138.40, 141.83, 144.13, 154.04; IR (KBr)/cm⁻¹ 3420, 2924, 2848, 1512, 1458, 1404, 1250, 1188; HRMS (ESI): Calcd for C₁₇H₁₈N₂O₅ (MH⁺) 331.1294; Found: 331.1298. [α]₀²⁵ = – 146 (*c* 0.4, CH₂Cl₂). HPLC analysis: 86:14 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 85/15), flow rate (0.5 mL/min), *t* (minor) = 25.996 min, *t* (major) = 30.493 min].

(4aR,10bS)-1-(4-Methoxyphenyl)-1,3,4,4a,5,10bhexahydro-2*H*-chromeno[4,3-*b*]pyridine (6).

To a stirred solution of compound 5j (160 mg, 0.43 mmol) in dry EtOH (4 mL) was added 10% Pd/C (10 wt %) and purged with H_2 and stirred under H_2 at room temperature for 4 hrs. Reaction mixture was filtered through celite and washed with ethanol. Solvent was evaporated under vacuo and crude material was used for further oxidation without purification at this stage. This crude material was taken in DMF (3.0 mL) and added Pd(OAc)₂ (18 mg, 20 mol%) and KO^tBu (94 mg, 0.42 mmol) and PPh₃ (44 mg, 0.4 equivalents) and degassed the reaction mixture with nitrogen for 20 minutes. This reaction mixture was heated at 110 °C for 4 hrs and monitored by TLC. The reaction was quenched with saturated NaHCO₃ solution (5.0 mL) and extracted with EtOAc (2 × 8 mL). The combined organic layer was washed with brine and dried over Na₂SO₄ and concentrated under reduced pressure to give crude mass which was purified by silica gel column chromatography by using hexane:EtOAc, gave 6 (62 mg, 61% yield) as colorless viscous liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.47–1.59 (m, 1H), 1.84-1.87 (m, 2H), 2.03-2.07 (m, 1H), 2.77 (m, 1H), 3.29-3.40 (m, 3H), 3.66 (s, 3H), 4.31 (d, J = 3.9 Hz, 1H), 6.63 (d, J = 9.1 Hz, 2H), 6.94-7.00 (m, 3H), 7.08 (m, 1H), 7.13-7.16 (m, 1H), 7.52-7.54 (m, 1H); 13 C NMR (75 MHz, CDCl₃) δ 25.85, 27.62, 47.45, 55.15, 58.37, 61.89, 64.56, 113.65 (2C), 125.39 (2C), 127.11, 127.80, 128.61 (2C), 129.95 (2C), 133.70 (2C); IR (KBr)/cm⁻¹ 2932, 1597, 1298, 1180, 1034; HRMS (ESI): Calcd for C₁₉H₂₁NO₂ (MH^{+}) 296.1650; Found: 296.1655. $[\alpha]_{D}^{25} = -31.7$ (c 0.4, CH₂Cl₂).

(4a*R*,10b*S*)-1,3,4,4a,5,10b-Hexahydro-2*H*-chromeno[4,3*b*]pyridine (7).

To a stirred solution of ceric ammonium nitrate (CAN) (441 mg, 0.8 mmol) in distilled H₂O (2.0 mL) at 0 °C was added compound 6 (95 mg, 0.32 mmol) in CH₃CN (3.0 mL) dropwise for 10 minutes. This reaction mixture was further stirred at rt for 1 hr and monitored by TLC. Once, compound 6 was consumed completely, reaction was quenched with saturated NaHCO₃ (5.0 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic layer was dried over Na2SO4 and concentrated under reduced pressure after filtration. The crude mas was purified through a small pad of silica gel column using hexane:acetone as eluting solvent, afforded 7 (46 mg, 75% yield) as colorless viscous liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.41–1.52 (m, 2H), 2.02–2.07 (m, 2H), 2.62 (s, 1H), 2.76-2.83 (m, 1H), 3.16-3.20 (m, 1H), 3.27-3.38 (m, 2H), 3.58-3.65 (m, 1H), 4.07 (d, J = 3.8 Hz, 1H), 7.18-7.22 (m, 1H), 7.28-7.30 (m, 1H), 7.35 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.61 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 26.31, 28.04, 48.15, 58.59, 64.95, 70.16, 125.23, 128.05, 128.56, 130.85, 132.36, 156.15; IR (KBr)/cm⁻¹ 3433, 2932, 1597, 1350, 1103; HRMS (ESI): Calcd for C₁₂H₁₅NO (MH⁺) 190.1232; Found: 190.1235 $[\alpha]_{D}^{25} = -29.2$ (*c* 0.1, CH₂Cl₂).

((1*S*,2*R*,6*S*)-3-(4-Methoxyphenyl)-2-(4-nitrophenyl)-7-oxa-3-azabicyclo[4.1.0] heptan-1-yl)methanol (10).

To a stirred solution of compound 5c (64 mg, 0.19 mmol) in CH₂Cl₂ (2.0 mL) at 0 °C was added m-CPBA (56 mg, 0.38 mmol) predissolved in CH₂Cl₂ (1.0 mL) through syringe. This reaction mixture was further stirred for 3 hr at the same temperature and monitored by TLC. Once, compound 5c was consumed, reaction was stirred with NaHCO₃ solution (3.0 mL, 10 mol % sol.) for 10 minutes. This reaction mixture was extracted with CH₂Cl₂ (5.0 mL) and combined organic layer was washed with brine solution and dried over Na₂SO₄. The crude mass after concentrated under vacuo was purified through column chromatography by unsing hexane/EtOAc as eluting solvents, which afford compound 10 (50 mg, 75% yield) as a colorless viscous liquid. ¹H NMR (400 MHz, CDCl₃) δ 2.44 (d, J = 4.2 Hz, 1H), 3.23 (d, J = 11.6 Hz, 1H), 3.44 (d, J = 11.7 Hz, 1H), 3.69-3.78 (m, 6H), 4.63-4.70 (m, 1H), 5.02 (s, 1H), 5.40 (s, 1H), 6.68 (d, J = 9.4 Hz, 2H), 7.03 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.84–7.95 (m, 3H); 13 C NMR (75 MHz, CDCl₃) δ 25.17, 32.70, 43.34, 55.70, 58.15, 69.66, 72.58, 114.92 (2C), 121.97 (2C), 123.75 (2C), 130.25 (2C), 137.58, 144.45, 147.76, 155.05; IR (KBr)/cm⁻¹ 3433, 2916, 2854, 1713, 1574, 1381, 1257, 1080, 756; HRMS (ESI): Calcd for C₁₉H₂₀N₂O₅ (MH⁺) 357.1450; Found: 357.1455. $[\alpha]_D^{25} = +43.8$ (*c* 0.2, CH₂Cl₂).

(2*R*,3*S*,4*S*)-3-(Hydroxymethyl)-1-(4-methoxyphenyl)-2-(4nitrophenyl) piperidine-3,4-diol (11).

To a stirred solution of compound **5c** (60 mg, 0.18 mmol) in acetone (2.5 mL) and H_2O (0.5 mL) was added 4-Methylmorpholine *N*-oxide (NMO) (32 mg, 0.27 mmol) and OsO₄ (20 mol %, 1.76 mL, 0.02 M solution in *tert*-BuOH). This reaction mixture was stirred at room temperature for 12 hrs and monitored by TLC. The reaction mixture was evaporated

under reduced pressure, once 5c was completely consumed. The resulting mass was stirred with EtOAc (10 ml) and saturated NaHCO₃ (8.0 mL) for 10 minutes. Organic layer was separated and the aqueous layer was again extracted with EtOAc (2 \times 10 mL). The combined organic layer was dried over Na₂SO₄ and evaporated under reduced pressure after filtration. The resulting mass was purified through column chromatography using hexane/EtOAc as eluting solvents, which afforded 11 (42 mg, 65 % yield). ¹H NMR (400 MHz, CDCl₃) δ 1.94–1.98 (m, 1H), 2.27–2.35 (m, 1H),3.11–3.21 (m, 2H), 3.56 (d, J = 11.6 Hz, 1H), 3.67 (s, 3H), 3.73 (bs, 1H), 3.75-3.79 (m, 1H), 4.19 (t, J = 3.7 Hz, 1H), 4.65 (s, 1H), 6.65 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H); 13 C NMR (75 MHz, CDCl₃) δ 29.44, 51.47, 55.22, 63.94, 67.55, 69.20, 73.56, 114.14 (2C), 122.67 (2C), 125.11 (2C), 130.69 (2C), 144.11, 145.21, 146.74, 156.02; IR (KBr)/cm⁻¹ 3441, 2939, 1597, 1520, 1350, 1250, 1103; HRMS (ESI): Calcd for C₁₉H₂₂N₂O₆ (MH⁺) 375.1556; Found: 375.1560. $[\alpha]_{D}^{25} = -61.5 (c \ 0.15, CH_{2}Cl_{2}).$

(R)-1-(4-Methoxyphenyl)-2-phenyl-1,2,5,6tetrahydropyridine-3-carboxylic acid (12).

To a stirred solution of compound 5q (81 mg, 0.2 mmol) in acetonitrile (1.5 mL) and H₂O (0.5 mL) at 0 °C, was added slowly a freshly prepared solution (1.5 mL) of oxidizing agents [prepared through reported procedure, 25 (2.3 mg of CrO₃ and 1.14 grams of H_5IO_6), in H_2O (12.0 mL)] over a period of 30 minutes. The combined mixture was further stirred for additional 1 hr at rt and monitored by the TLC. The reaction was extracted with CH_2Cl_2 (2 × 10 mL), once 5q was over. The combined organic fractions are passed through a small pad of Na₂SO₄ and concentrated under reduced pressure. The crude mass was purified through preparative TLC technique by eluting with CH₂Cl₂, to afford **12** (57 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ 2.38 (m, 1H), 2.60–2.73 (m, 1H), 3.20–3.28 (m, 1H), 3.30-3.35 (m, 1H), 3.76 (s, 3H), 5.23 (s, 1H), 6.12 (s, 1H), 6.76 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 7.01 (dd, J = 8.0, 1.4 Hz, 2H), 7.18–7.26 (m, 3H); 13 C NMR (75 MHz, CDCl₃) δ 29.65, 44.12, 55.54, 63.54, 114.61 (2C), 123.49 (2C), 127.98, 128.67, 129.16, 130.46, 131.40, 131.74, 133.31, 134.18, 141.74, 160.01, 171.00; IR (KBr)/cm⁻¹ 3441-3061 (br), 2939, 1690, 1582, 1512, 1126; HRMS (ESI): Calcd for C₁₉H₁₉NO₃ (MH⁺) 310.1443; Found: 310.1439. $[\alpha]_{D}^{25} = -127.4$ (*c* 0.25, CH₂Cl₂).

(2R,3S)-1-(4-Methoxyphenyl)-2-phenylpiperidine-3carboxylic acid (14).

To a stirred solution of compound ent-5q (96 mg, 0.32 mmol) in dry EtOH (4 mL) was added 10% Pd/C (10 wt %) and purged with H_2 and stirred under H_2 at room temperature for 4 hrs. Reaction mixture was filtered through celite and washed with ethanol. Solvent was evaporated under vacuo and crude material was used for further oxidation without purification at this stage. The oxidation of crude saturated syn-alcohol to corresponding acid was carried out by following the previous procedure, similar to compound 12, to afford 14 (66 mg, 66% yield) after two steps. ¹H NMR (400 MHz, CDCl₃) δ 1.86–1.94 (m, 1H), 2.01-2.08 (m, 2H), 3.25-3.30 (m, 2H), 3.43-3.46 (m, 2H), 3.66 (s, 3H), 3.92 (d, J = 3.9 Hz, 1H), 6.63 (d, J = 9.1 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 7.15 (m, 3H), 7.38-7.42 (m, 2H);

¹³C NMR (75 MHz, CDCl₃) δ 22.68, 27.19, 29.68, 42.65, 55.24, 64.90, 113.85 (2C), 124.83, 127.32, 127.90 (2C), 128.28, 128.73, 131.23, 132.44, 135.92, 141.29, 170.16; IR (KBr)/cm⁻¹ 3433-3063 (br), 2939, 1690, 1589, 1173, 1034; HRMS (ESI): Calcd for $C_{19}H_{21}NO_3$ (MH⁺) 312.1599; Found: 312.1592 $[\alpha]_D^{25}$ = + 49.4 (c 0.1, CH₂Cl₂).

((2S,3R)-1-(4-Methoxyphenyl)-2-phenylpiperidin-3yl)methanol (16).

Compound 5q (140 mg, 0.32 mmol), was reduced by following procedure and purified through previous column chromatography to afford 16 as colorless viscous liquid with 90% yield (126 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.62–1.69 (m, 2H), 1.83 (d, J = 6.4 Hz, 2H), 2.61-2.70 (m, 2H), 3.00-3.09 (m, 2H), 3.50-3.55 (m, 2H), 3.75 (s, 3H), 3.76-3.83 (m, 1H), 6.56 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 7.16-7.22 (m, 3H), 7.29 (t, J = 6.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 25.51, 27.42, 45.96, 55.18, 56.60, 65.27, 67.46, 113.66 (2C), 125.11, 126.72 ,128.02 (2C) ,128.47 (2C), 139.24 , 142.13, 146.05, 155.21; HRMS (ESI): Calcd for $C_{19}H_{23}NO_2$ (MH⁺) 298.1808, Found: 298.1813. $[\alpha]_{D}^{25} = -56.3$ (c 0.1, CH₂Cl₂).

2-Methoxy-N-(((25,35)-1-(4-methoxyphenyl)-2phenylpiperidin-3-yl)methyl) aniline (19).

To a stirred solution of 16 (90 mg, 0.3 mmol) in dry CH₂Cl₂ (2.0 mL) at rt was added $Et_{3}N$ (168 $\mu\text{L},$ 1.2 mmol) and TsCl (69 mg, 0.36 mmol) in dry CH₂Cl₂ (1.5 mL) by syringe. The resulting mixture was further stirred for 6 hrs at the same temperature and monitored by TLC. The reaction was quenched with saturated NaHCO₃ (3.0 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over Na₂SO₄ and concentrated in reduced pressure to give the crude product, which was used further without isolation. The crude mass was taken in dry EtOH (3 mL) and added o-anisidine 18 (74 mg, 0.6 mmol) and further refluxed for additional 4 hrs. Once the reaction is over by TLC, EtOH was evaporated under reduced pressure and resulting residue was purified by column chromatography to afforded 19 (83 mg, 68% yield) as a colorless viscous liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.58–1.75 (m, 4H), 2.10-2.13 (m, 1H), 2.93-3.00 (m, 1H), 3.12-3.16 (m, 1H), 3.49-3.57 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 5.04 (d, J = 3.6, 1H), 6.47-6.49 (m, 1H), 6.56-6.60 (m, 1H), 6.72-6.76 (m, 2H), 6.78–6.81 (m, 2H), 6.84 (d, J = 9.2, 2H), 6.91(d, J = 9.2 Hz, 2H), 6.99–7.03 (m, 1H), 7.14 (d, J = 7.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 24.28, 24.51, 31.47, 42.12, 46.55, 55.39, 55.75, 56.69, 110.37, 113.62, 114.80 (2C), 115.00, 115.94, 117.00, 118.46, 120.11, 121.03, 127.61 (2C), 128.07, 136.08, 144.81, 145.62, 147.28, 151.61; IR (KBr)/cm⁻¹ 3393, 2932, 2831, 1598, 1512, 1366, 1180, 1034; Calcd for $C_{26}H_{30}N_2O_2$ (MH⁺) 403.2385; Found: 403.2389. $[\alpha]_D^{25} = -54.6$ (*c* 0.15, CH₂Cl₂).

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Abstract: An enantioselective multi-component synthesis of 1,2,5,6-tetrahydropyridines (THPs) has been developed through a one-pot domino-process. This transformation proceeds through proline-catalyzed direct Mannich reaction-cyclization of glutaraldehyde with in situ generated imines, followed by site-selective oxidation-reduction sequence under mild conditions. Chiral 1,2,5,6-THPs are obtained in good to high yields (up to 80%) and with the excellent enantioselectivity (up to 98:2 er). The usefulness of this operationally simple method is also shown to synthesize other medicinally important nitrogen-heterocycles.

