1-Proline Nitrate: A Recyclable and Green Catalyst for the Synthesis of Highly Functionalized Piperidines

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Figure S1. Energetics of the reaction via L-proline mediated aniline enamine pathway

Figure S2. Energetics of the reaction via L-proline mediated iminium activation of the aldehydes
### Table S1. Absolute energies of reactants, intermediates and transition states at B3LYP/6-31G(d)

<table>
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<th>Absolute Energy (PCM) (^b)</th>
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<td>Aniline</td>
<td>-287.6017597</td>
<td>-287.6083904</td>
<td>73.67215</td>
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<td>Methyl Acetoacetate</td>
<td>-421.025418</td>
<td>-421.0334358</td>
<td>80.61808</td>
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<td>Methyl Acetoacetate-enol</td>
<td>-421.0205123</td>
<td>-421.0274342</td>
<td>81.27901</td>
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<td>MeOH</td>
<td>-115.7144051</td>
<td>-115.7192461</td>
<td>32.30035</td>
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<tr>
<td>Proline</td>
<td>-401.037168</td>
<td>-401.1567542</td>
<td>91.22973</td>
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<td>Benzaldehyde</td>
<td>-345.573442</td>
<td>-345.579287</td>
<td>69.16718</td>
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<td>Enamine</td>
<td>-632.2083078</td>
<td>-632.2153068</td>
<td>140.14109</td>
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<tr>
<td>Water</td>
<td>-76.4089533</td>
<td>-76.4160764</td>
<td>-76.41607</td>
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TS and Intermediates of pathway a

- Aniline+Acetoacetate+MeOH TS

\[
\text{Aniline+Acetoacetate Product}
\]

\[
\text{Aniline Enamine}
\]

\[
\text{AnilineEnamine+Benzaldehyde+MeOH TS}
\]

\[
\text{AnilineEnamine+Benzaldehyde Product}
\]

\[
\text{AnilineEnamine+Benzaldehyde-H2O Product}
\]
TS and Intermediates of pathway b

Acetoacetate+Proline+MeOH TS

Acetoacetate+Prolineadduct

Proline enamine product

ProlineEnamine+Benzaldehyde+MeOH TS

ProlineEnamine+Benzaldehyde+MeOH Product

BenzelideneAcetoacetate Product
TS and Intermediates of L-proline mediated aniline enamine pathway

Acetoacetate+Aniline+Proline TS

Acetoacetate+Aniline+Proline Product

AnilineEnamine+Aldehyde+Proline TS
TS and Intermediates of L-proline mediated iminium activation of aldehyde

AnilineEnamine+Aldehyde+Proline Product

-1378.934508  -1378.958308  304.40079

Aldehyde + Proline+ MeOH TS

-862.4388175  -862.454731  193.95554

Benzaldehyde+Proline+MeOH iminium

-786.0109137  -786.0375646  178.97453

Iminium +acetoacetate+MeOH TS

-1207.0370152  -1207.0540376  261.40103

Iminium +acetoacetate product

-1091.3290846  -1091.3425379  228.35161

Iminium +acetoacetate+Aniline TS

-1378.9097971  -1378.9444223  302.81736
Calculation of green chemistry metrics \[1\]

### 1. E factor:

The E factor of organic conversion can be calculated as mass of waste i.e. the total mass of raw materials minus the total mass of product, all divided by the total mass of product. The ideal value for E factor should be zero.\[2\]

\[
E\text{-}factor = \frac{\text{mass of waste}}{\text{mass of product}}
\]

Where mass of waste = total mass of raw materials minus the total mass of product = [0.331 g (aniline) + 0.371 g (benzaldehyde) + 0.203 g (methyl acetoacetate) + 0.0312 g (proline nitrate) + 0.395 g (methanol) - 0.721 g (product)]

Mass of waste = 0.6107 g

E-factor = 0.6107/0.721

**E-factor = 0.8469** (including mass of methanol and proline nitrate)

As methanol and proline nitrate can be recycled, E-factor excluding mass of methanol and proline nitrate is
Mass of waste = [0.331 g (aniline) + 0.371 g (benzaldehyde) + 0.203 g (methyl acetoacetate) - 0.721 g (product)] = 0.184 g

**E-factor = 0.184/0.721 = 0.255** (excluding the mass of methanol)

2. **Atom economy (AE):** AE serves to determine the efficiency of a chemical reaction with regard to how many atoms from the starting materials reside within the product. The ideal value for AE should be 100%.\(^3\)

\[
AE = \frac{\text{MW of product}}{\sum (\text{MW of stoichiometric reactants})} \times 100
\]

\[
AE = \frac{460.57 \text{ (product)}}{[2(93.12) \text{ (aniline)} + 2(106.12) \text{ (benzaldehyde)} + 116.11 \text{(MAA)}]} \times 100
\]

**AE = 89.50\%**

3. **Process mass intensity (PMI):** PMI is defined as the total mass used in a process divided by the mass of product. The ideal value for PMI should be 1.\(^4\)

\[
\text{PMI} = \frac{\sum (\text{mass of stoichiometric reactants} + \text{solvents used in the process})}{\text{mass of product}}
\]

\[
\text{PMI} = \frac{[0.331 g \text{ (aniline)} + 0.371 g \text{ (benzaldehyde)} + 0.203 g \text{ (methyl acetoacetate)} + 0.0312g \text{ (proline nitrate)} + 0.395 g \text{ (methanol + 1 g (water) + 0.0867 g (toluene))}]}{0.721 g \text{ (product)}}
\]

**PMI = 3.354**

4. **Reaction mass efficiency (RME):** RME is defined as the mass of product divided by the sum of total mass of stoichiometric reactants. The ideal value for RME should be 100%.\(^4\)

\[
\text{RME} = \frac{\text{mass of product}}{\sum (\text{mass of stoichiometric reactants})} \times 100
\]

\[
\text{RME} = \frac{0.721 g \text{ (product)}}{[0.331 g \text{ (aniline)} + 0.371 g \text{ (benzaldehyde)} + 0.203 g \text{ (methyl acetoacetate)}]} \times 100
\]

**RME = 79.66\%**
General experimental details

All solvents and chemicals were obtained commercially and were used as received. Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded using a Spectrum-60 spectrometer instrument. NMR spectra were taken with a Bruker Avance II at 400 MHz / Bruker DMX spectrometer at 500 MHz (1H) and 125 MHz (13C) using CDCl3 or DMSO-d6 as the solvent with TMS as internal standard. The crystal data were collected with SuperNova, X-ray diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at 100 K. The structure was solved by direct methods using using SHELXS97 software. All of the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F² using SHELXL97. All H atoms were allowed to ride on the parent atom in the model during refinement.

General procedure for the preparation of functionalized piperidines:
A mixture of 1,3-dicarbonyl (1.75 mmol), amine (3.5 mmol), aldehyde (3.5 mmol) and L-proline nitrate (31.2 mg, 0.175 mmol) in MeOH (0.5 mL) was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC, solid obtained was filtered under suction to get product of sufficient purity. To recover the catalyst, initially methanol from the filtrate was removed under reduced pressure and residue was washed with a little quantity of water to get an aqueous solution of the catalyst as a filtrate. Water from the filtrate was removed under reduced pressure and the last traces of water were removed by forming azeotrope with a very little amount of toluene to get the catalyst which was then available for the next run.

Scheme S1: Functionalised piperidine depicting different types of hydrogen
Methyl 1,2,6-triphenyl-4-(phenlamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4a)\textsuperscript{5}

![Chemical Structure](image)

White solid; (Yield 0.721g; 90%); mp: 165-167 °C; IR (cm\textsuperscript{-1}): 3258, 1660, 1586, 1504, 1251, 1078; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 2.78-2.85 (m, 2H, H\textsubscript{5a} H\textsubscript{5b}), 3.93 (s, 3H, OCH\textsubscript{3}), 5.14 ( brs,1H, H\textsubscript{6}), 6.28-7.31 (m, 21H, H\textsubscript{2}+Ar-H), 10.25 (s, 1H, NH); HRMS (ESI): m/z [M+Na]\textsuperscript{+} calc. for C\textsubscript{31}H\textsubscript{28}N\textsubscript{2}NaO\textsubscript{2} 483.2048, found 483.2036.

Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenlamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4b)\textsuperscript{5}

![Chemical Structure](image)

White solid; (Yield 0.737g; 81%); mp 174-176 °C; IR (cm\textsuperscript{-1}): 3058, 1651, 1592, 1245, 1189, 1070 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ ppm: 2.77-2.83 (m, 2H, H\textsubscript{5a} H\textsubscript{5b}), 3.78 (m, 6H, OCH\textsubscript{3}), 3.92 (s, 3H, OCH\textsubscript{3}), 5.0 ( brs,1H, H\textsubscript{6}), 6.36-7.26 (m, 19H, H\textsubscript{2}+Ar-H), 10.26 (s, 1H, NH); HRMS (ESI): m/z [M+Na]\textsuperscript{+} calc. for C\textsubscript{33}H\textsubscript{32}N\textsubscript{2}NaO\textsubscript{4} 543.2260, found 543.1450.
Methyl 2,6-bis(4-isopropylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4e)

White solid; (Yield 0.753g; 79%); mp 160-162 °C; IR (cm⁻¹): 3231, 1654, 1589, 1501, 1261, 1074 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm (syn:anti = 10:90); 1.20-1.22 (m, 1.2H, CH (CH₃)₂), 1.27-1.35 (m, 10.8H, CH (CH₃)₂), 2.72-2.83 (m, 0.46H, [CH (CH₃)₂], 2.86-2.98 (m, 1.54H, [CH (CH₃)₂], 3.77(s, 0.44H, OCH₃), 3.97(s, 2.56H, OCH₃), 5.15 (br s, 1H, H₆), 6.22-7.61 (m, 19.7H, H₂+Ar-H), 10.29 (s, 0.9H, NH); 10.7 (s, 0.1H, NH); ¹³C NMR (100 MHz,CDCl₃): 23.91, 24.03, 24.07, 24.20, 33.63, 33.75, 33.84, 50.99, 54.80, 98.00, 112.90, 115.20, 115.93, 123.88, 125.78, 126.11, 126.26, 126.57, 126.70, 126.90, 128.76, 128.87, 129.30, 137.91, 140.38, 141.09, 146.68, 147.11, 147.85, 156.53, 168.70; HRMS (ESI): m/z [M+Na]+ calc. for C₃₇H₄₀N₂NaO₅ 567.2987, found 567.2107.

Methyl 1-phenyl-4-(phenylamino)-2,6-bis(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4f)⁶

White solid (Yield 0.863g; 77%); mp 145-147 °C; IR (cm⁻¹): 3241, 2996, 2938, 2835, 1656, 1592, 1502, 1461, 1416, 1323, 1256, 1126, 1006 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ppm: 2.77-3.00 (m, 2H, H₅a +H₅b), 3.69-3.73 (m, 12H, OCH₃a, OCH₃c), 3.83-3.84 (m, 9H, OCH₃b+ OCH₃d), 5.06 (brs, 1H, H₆), 6.34-7.15 (m, 15H, H₂+Ar-H), 10.25 (s, 1H, NH); HRMS (ESI): m/z [M+Na]+ calc. for C₃₇H₄₀N₂NaO₈ 663.2682, found 662.9989.
Methyl 26-bis(4-hydroxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4h)

White solid; (Yield 0.673 g; 78%); mp 170-172 °C; IR (cm⁻¹): 3290, 1594, 1319, 1247, 1074 cm⁻¹; ¹H NMR (500 MHz, DMSO- d₆) δ ppm: 2.74-2.86 (m, 2H, H₅a+H₅b), 3.84 (s, 3H, OCH₃), 5.19 (br s, 1H, H₆), 6.17 (s, 1H, H₂), 6.65-7.17 (m, 18H, Ar-H), 9.24 (s, 1H, OHₐ), 9.28 (s, 1H, OHₖ), 10.17 (s, 1H, NH); ¹³C NMR (125 MHz, DMSO- d₆): 33.20, 51.01, 54.05, 56.12, 98.02, 115.14, 124.62, 127.08, 127.17, 128.97, 134.03, 137.62, 154.69, 156.23, 167.52; HRMS (ESI): m/z [M+Na]⁺ calc. for C₃₁H₂₈N₂NaO₄ 515.1174, found 515.1947.

Methyl 2,6-bis(2-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4i)

White solid; (Yield 0.722 g; 78%); mp 166-168 °C; IR (cm⁻¹): 3249, 1660, 1595, 1327, 1246, 1046 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm: (syn:anti 13:87) 2.8 (dd, J=16.06, 8.04 Hz, 1H, H₅a), 3.06 (dd, J= 16.04, 8 Hz, 1H, H₅b), 3.73 (s, 0.4H, OCH₃), 3.89 (s, 2.6H, OCH₃), 5.46 (brs, 0.87H, H₆), 5.46 (brs, 0.13H, H₆), 6.508 (s, 1H, H₂), 6.40-7.45 (m, 19H, H₂+Ar-H), 10.10 (s, 0.87H, NH), 10.77 (s, 0.13H, NH); ¹³C NMR (100 MHz,CDCl₃): 29.55, 34.42, 50.80, 51.11, 99.20, 114.25, 117.65, 122.00, 124.78, 125.92, 126.11, 127.16, 128.03, 128.52, 128.72, 128.98, 129.01, 129.18, 129.28, 129.32, 129.65, 131.11, 132.39, 133.37, 137.88, 138.72, 140.09, 146.32, 155.54, 168.87; HRMS (ESI): m/z [M+Na]⁺ calc. for C₃₁H₂₆Cl₂N₂NaO₂ 551.1269, found 551.0179.
Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j)\n
White solid; (Yield 0.664g; 80%); mp 171-172 °C; IR (cm$^{-1}$): 3059, 3018, 2980, 2872, 1651, 1504, 1454, 1371, 1255, 1070 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ ppm: 1.47 (t, 3H, OCH$_2$CH$_3$), 2.78-2.86 (m, 2H, H$_{5a}$ + H$_{5b}$), 4.33-4.44 (m, 2H, OCH$_2$CH$_3$), 5.14 (brs, 1H, H$_6$), 6.27-7.33 (m 21H, H$_2$+Ar-H), 10.29 (s, 1H, NH); HRMS (ESI): m/z [M-H]$^+$ calc. for C$_{32}$H$_{29}$N$_2$O$_2$ 473.2229, found 473.2400.

Ethyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4k)\n
White solid; (Yield 0.645g, 69%); mp 165-167°C; IR (cm$^{-1}$): 3750, 2988, 2902, 2819, 2029, 1974, 1496, 1417, 1240, 687, 667 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ ppm: 1.46 (t, J=6.88 Hz, 3H, OCH$_2$CH$_3$), 2.77- 2.84 (m,2H, H$_{5a}$, H$_{5b}$), 3.78 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 4.33-4.45 (m, 2H, OCH$_2$(a+b)CH$_3$), 5.09 (brs, 1H, H$_6$), 6.37-7.09 (m, 19H, H$_2$+ Ar-H ) 10.31 (s, 1H, NH); HRMS (ESI): m/z [M-H]$^+$ calc. for C$_{32}$H$_{29}$N$_2$O$_2$ 533.2440, found 533.1925.
Ethyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4m)

![Chemical Structure]

White solid; (Yield 0.643g; 72%); mp 204-205 °C; IR (cm\(^{-1}\)) : 3671, 2996, 2981, 2815, 2187, 2053, 1970, 1648, 1607, 1499, 1251, 751 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ ppm: 1.44-1.46 (t, 3H, J= 7.0 Hz, OCH\(_2\)CH\(_3\)), 2.72-2.85 (dd, 2H, J= 15.1, 7.52 Hz, H\(_{5a}+H_{5b}\)), 4.30 (m, 1H, OCH\(_2\)CH\(_3\)), 4.33 (m, 1H, OCH\(_2\)CH\(_3\)), 5.10 (d, 1H, H\(_6\)), 6.38-7.31 (m, 19H, H\(_2\)+Ar-H), 10.31 (s, 1H, NH); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)): 14.83, 33.82, 54.63, 59.85, 98.06, 113.03, 114.94, 115.15, 115.39, 115.61,116.60, 125.68, 125.90, 127.89, 127.97, 128.11, 128.19, 128.88, 129.0, 129.04, 129.39,137.77, 138.11, 138.14,139.51,139.52, 146.65, 155.93, 160.32, 160.78, 162.75, 163.22, 168.09; HRMS (ESI): m/z [M+Na\(^{+}\)] calc. for C\(_{32}\)H\(_{28}\)F\(_2\)N\(_2\)NaO\(_2\) 533.2017, found 533.1345.

Ethyl 2,6-bis(4-isopropylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n)

![Chemical Structure]

White solid; (Yield 0.782g; 80%); mp 169-170 °C; IR (cm\(^{-1}\)) : 3230. 1653, 1577, 1261, 1190, 1076 cm\(^{-1}\); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) δ ppm (syn:anti = 09:91): 1.20-1.22 (m, 1.1H, CH (CH\(_3\))\(_2\)), 1.27-1.35 (m, 10.9H, CH (CH\(_3\))\(_2\)), 1.50-1.53 (t, 3H, J= 7.12 Hz, OCH\(_2\)CH\(_3\)), 2.72 -2.76 (m, 0.47H, H\(_{5a}+H_{5b}\)), 2.86 -2.97 (m, 1.53H, H\(_{5a}+H_{5b}\)), 2.86-3.00 (m, 2H, CH(CH\(_3\))\(_2\), CH(CH\(_3\))\(_2\)), 4.34-4.54 (m, 2H, OCH\(_2\)CH\(_3\)), 5.16 (brs, 1H, H\(_6\)), 6.22-7.32 (m, 19H, H\(_2\)+Ar-H), 10.34 (s, 0.91H, NH), 10.7 (s, 0.09H, NH); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)): 14.85, 23.91, 24.06, 24.20, 24.29, 33.63, 33.74, 33.84, 54.77, 59.20, 98.29, 112.92, 115.27, 115.90, 123.80, 125.68, 126.05, 126.27, 126.45, 126.58, 126.70, 126.94,
128.74, 128.88, 129.28, 137.99, 140.43, 141.21, 146.63, 147.15, 147.84, 156.34, 168.39; HRMS (ESI): m/z [M+Na]+ calc. for C_{33}H_{42}N_{2}NaO_{2} 581.3144, found 581.2186.

**Ethyl 1-phenyl-4-(phenylamino)-2,6-bis(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4o)**

![Chemical structure of 1-phenyl-4-(phenylamino)-2,6-bis(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4o)](image)

White solid; (Yield 0.824g; 72%); mp 175-176 °C; IR (cm⁻¹): 3401, 2971, 2942, 2194, 1954, 1648, 1508, 1247, 1106, 718 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm: 1.43-1.47 (t, 3H, OCH₂CH₃), 2.77-2.80 (dd, J= 14.9, 7.4 Hz, 1H, H₅a), 2.95-3.00 (dd, J= 14.9, 7.4 Hz, 1H, H₅b), 3.70-3.75 (m, 12H, OCH₃), 3.86-3.88 (m, 6H, OCH₃), 4.29-4.50 (m, 2H, OCH₂CH₃), 5.06 (s, 1H, H₆), 6.39-7.28 (m, 13H, H₂+ Ar-H), 10.34 (s, 1H, NH); ¹³C NMR (100 MHz,CDCl₃): 15.05, 33.70, 55.43 55.97, 56.02, 56.46, 58.42, 59.56, 60.88, 60.94, 97.50, 103.12, 103.83, 113.02, 116.49, 125.99, 126.17, 128.82, 128.97, 129.40, 136.44, 136.97, 137.84, 138.53, 139.72, 146.94, 152.99,153.37, 156.76, 168.09; HRMS (ESI): m/z [M+Na]+ calc. for C_{37}H_{40}N_{2}NaO_{7} 677.2839, found 677.1614.

**Ethyl 2,6-bis(4-hydroxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)**

![Chemical structure of 2,6-bis(4-hydroxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)](image)

White solid; (Yield 0.78g; 88%); mp 175-177 °C; IR (cm⁻¹): 3012, 2868, 2673, 1578, 1288, 1164 cm⁻¹; ¹H NMR (500 MHz, DMSO- d₆) δ ppm: 1.37 (t, 3H, J= 7.0 Hz, OCH₂CH₃), 2.73-2.89 (m, 2H, H₅a+...
H\textsubscript{5b}), 4.27- 4.37 (m, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 5.20 (brs, 1H, H\textsubscript{6}), 6.17 (s, 1H, H\textsubscript{2}), 6.64-7.17 (m, 18H, Ar-H), 9.24(s, 1H, OH\textsubscript{a}), 9.28 (s, 1H, OH\textsubscript{b}), 10.25 (s, 1H, NH); \textsuperscript{13}C NMR (120 MHz, DMSO- d\textsubscript{6}): 14.59, 33.61, 54.24, 59.33, 98.44, 115.13, 124.45, 127.09, 129.00, 134.16, 137.77, 154.73, 156.23, 167.20; HRMS (ESI): m/z [M+Na]\textsuperscript{+} calc. for C\textsubscript{32}H\textsubscript{30}N\textsubscript{2}NaO\textsubscript{4} 529.2103, found 529.1274.

**Ethyl 2,6-bis(2-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r)**

![Image of ethyl 2,6-bis(2-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r)](image)

White solid; (Yield 0.618g; 65%); mp 158-160 °C; IR (cm\textsuperscript{-1}): 3509, 2926, 2859, 2111, 1962, 1751, 1619, 1255, 1173, 743 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ ppm: 1.36 (t, J= 6.88 Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}), 2.88-3.0 (m, 2H, H\textsubscript{5a} +H\textsubscript{5b}), 4.29-4.32 (m, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 5.41 (brs, 1H, H\textsubscript{6}), 6.41-7.22 (m, 19H, H\textsubscript{2}+Ar-H), 10.12 (s, 1H, NH); HRMS (ESI): m/z [M+H]\textsuperscript{+} calc. for C\textsubscript{32}H\textsubscript{29}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{2} 543.1606, found 543.0548.

**Ethyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4t)\textsuperscript{9}**

![Image of ethyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4t)](image)

White solid; (Yield 0.962g; 87%); mp 221-222 °C; IR (cm\textsuperscript{-1}): 3034, 1650, 1594, 1499, 1250, 1178, 1065 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ ppm: 1.45 (t, J=5.52Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}), 2.75-2.81 (m, 2H, H\textsubscript{5a}+H\textsubscript{5b}), 4.32-4.44 (m, 2H, OCH\textsubscript{2}CH\textsubscript{b}), 5.07 (brs , 1H, H\textsubscript{6}) 6.34 (s, 1H, H\textsubscript{2}), 6.41-7.40 (m, 18H, Ar-H), 10.28 (s, 1H, NH)
Ethyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4u)

White solid; (Yield 0.599g, 63%); mp 204-206 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ ppm 1.47 (t, J= 7.64 Hz, 3H, OCH$_2$CH$_3$), 2.71-2.84 (m, 2H, H$_{5a}$+H$_{5b}$), 4.34-4.37 (m, 2H, OCH$_2$CH$_3$), 5.11 (brs, 1H, H$_6$), 6.16-7.30 (m, 19H, H$_2$+Ar-H), 10.24 (s, 1H, NH); HRMS (ESI): m/z [M+Na]$^+$ calc. for C$_{32}$H$_{28}$Cl$_2$N$_2$NaO$_2$ 565.1426, found 565.0034.

Ethyl 1-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4v)

White solid; (Yield 0.802g; 76%); mp 179-181 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ ppm: 1.46 (t, 3H, OCH$_2$CH$_3$), 2.67-2.82 (m, 2H, H$_{5a}$+H$_{5b}$), 3.75-3.80 (m, 6H, OCH$_3$), 4.33-4.45 (m, 2H, OCH$_2$CH$_3$), 5.05 (brs, 1H, H$_6$), 6.25-7.07 (m, 17H, H$_2$+Ar-H) 10.26 (s, 1H, NH); HRMS (ESI): m/z [M+Na]$^+$ calc. for C$_{34}$H$_{32}$Cl$_2$N$_2$NaO$_4$ 625.1637, found 624.9412.
$^1$H Spectrum of 4a

Mass Spectrum of 4a
$^1$H Spectrum of 4b

Mass Spectrum of 4b
$^1$H Spectrum of 4e (Diasterotropic ratio syn:anti = 10:90)

$^{13}$C Spectrum of 4e
Mass Spectrum of 4e

\[ \text{Mass Spectrum of } 4e \]

\[ \text{H Spectrum of } 4f \]
Mass Spectrum of 4f

1H Spectrum of 4h
$^{13}$C Spectrum of 4h

Mass Spectrum of 4h
$^1$H Spectrum of 4i (Diasterotropism ratio syn:anti = 13:87)

$^{13}$C Spectrum of 4i
Mass Spectrum of 4i

\[ \text{Mass Spectrum of } 4i \]

\[ \text{^1H Spectrum of } 4j \]
Mass Spectrum of 4j

$^1$H Spectrum of 4k
Mass Spectrum of 4k

1H Spectrum of 4m
$^{13}$C Spectrum of 4m

Mass Spectrum of 4m
$^1$H Spectrum of 4n (Diastereotopic ratio syn:anti = 09:91)

$^{13}$C Spectrum of 4n

Mass Spectrum of 4n
$^1$H Spectrum of 4o
$^{13}$C Spectrum of 4o

Mass Spectrum of 4o
$^1$H Spectrum of 4q

$^{13}$C Spectrum of 4q
Mass Spectrum of 4q

$^1$H Spectrum of 4r
Mass Spectrum of 4r

^1H Spectrum of 4t
$^1$H Spectrum of 4u

Mass Spectrum of 4u
$^1$H Spectrum of 4v

Mass Spectrum of 4v
X-Ray Structure of 4o (CCDC 1047298)

Figure S3. Twin molecules in the unit cell of 4o

References