Supporting Information

Highly efficient and selective phosphorylation of amino acid derivatives and polyols catalysed by 2-aryl-4-(dimethylamino)pyridine-N-oxides– towards kinase-like reactivity

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1. General Directions:

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in flame-dried glassware. Yields refer to chromatographically and spectroscopically (1H-NMR) homogenous materials, unless otherwise indicated. **Solvents and reagents:** Solvents were dried as follows: MeCN, CH₂Cl₂ and MeOH were distilled over CaH₂, CH₃Cl over MgSO₄, THF and Et₂O over Na-benzophenone ketyl and toluene over Na. Otherwise MeCN, CH₂Cl₂, THF, Et₂O and toluene were dried and deoxygenated with a Grubbs Pure-Solv 400 solvent purification system. The moisture content of the solvents was monitored by Karl Fischer coulometric titration (Mettler-Toledo DL39). All other materials were obtained from commercial suppliers and used without further purification. **Chromatography:** Flash chromatography (FC) was always performed on silica gel (Merck Kieselgel 60 F₂₅₄ 230-400 mesh) according to the method of W.C. Still,¹ unless otherwise stated. Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F₂₅₄) which were visualized either by quenching of ultraviolet fluorescence (λ_max = 254 and 366 nm) or by charring with 10% KMnO₄ in 1 M H₂SO₄. **Melting points:** These were determined on a Khofler hot stage. **Infra red spectra:** These were recorded as KBr discs on Perkin-Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (υ_max) are reported. **¹H NMR spectra:** These were recorded on a Bruker DRX-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (J) are reported to the nearest 0.1 Hz. **¹³C NMR spectra:** These were recorded at 400 MHz on Bruker AMX-400 instrument. Chemical shifts (δ_C) are quoted in ppm, referenced to the appropriate residual solvent peak. Degenerate peaks are suffixed by the number of carbons. **Optical rotations:** These were recorded at 589 nm (Na D-line) with a path length of 1 dm. Concentrations (c.) are quoted in g/100 mL and specific rotations, [α]_D T, are quoted in units of 10⁻¹ deg cm² g⁻¹ at the specified temperature, T. **Mass spectra:** Low and high resolution non-peptidic mass spectra (m/z) were recorded on Micromass Autospec Premier spectrometer with magnetic sector detector. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5ppm. **Peptide LCMS and LCUV:** These were performed using a Waters LCT Premier Es-ToF mass spectrometer operating in ES+ mode [Capillary Voltage: 2000V, Cone Voltage 30V, Desolvation Temperature 350 degrees, Source Temperature 120 degrees, Cone Gas Flow 10 L/hr, Desolvation Gas Flow 400 L/hr], coupled to a Waters Aquity UPLC system [Column: BEH C18 50mm x 2.1 mm, 1.7um at 40 degrees, Flow: 0.5 ml/min, 10µL injection, Mobile Phase: Water A (0.1% Formic acid), Acetonitrile B (0.1% formic acid) with the following gradient: t = 0 (A = 95%, B = 5%) → t = 3.2 min (A = 5%, B = 95%) → t = 3.5min (A = 95%, B = 5%), total run time 4min, PDA operating between 210nm and 280 nm]. **MS-MS (MS²) studies:** These were performed on a Thermo Scientific Q-Exactive instrument [Sample was directly infused via syringe pump at 5µL/min, Spray Voltage: 4kV, Capillary temperature 325 degrees, Sheath Gas Flow: 20 (arbitrary unit)]. **Chiral Stationary phase (CSP) HPLC:** Analytical CSP-HPLC was performed using a CHIRALCEL OD-H column (size: 0.46 cm I.D. × 25 cm L) eluting with n-hexane/i-propanol (55:45) at 1 ml/min (25 °C) and detecting at UV 210 nm (injection volume 5 µL; sample conc. 10 mg/mL).
2. General Method 1: Synthesis of protected amino acid substrates by esterification

Acetyl chloride (5 mL) was added dropwise to dry MeOH (40 mL) at 0 °C. The resulting solution was allowed to stir at this temperature for 5 min before the addition of the N-Cbz protected amino acid (12-16 mmol). The resulting solution was heated to 70 °C and stirred at this temperature for 12 h. The reaction mixture was then allowed to cool before being concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (50 mL) and the organic phase washed with sat. NaHCO₃ (3 × 50 mL) before being dried over MgSO₄ and concentrated in vacuo to afford the product.

(S)-N-Cbz-Ser(OH)-OMe (1)²

According to General Method 1, (S)-N-Cbz-Ser(OH)-OH (4.0 g, 16.7 mmol) afforded methyl ester 1 as a pale brown oil (3.64 g, 14.4 mmol, 86%). ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.39-7.28 (m, 5H), 5.74 (br d, J = 6.3 Hz, 1H), 5.16 (s, 2H), 4.49 (s, 1H), 4.05-3.94 (m, 2H), 3.81 (s, 3H). ¹H NMR (400 MHz, methanol-d₄, ppm): δ 7.41-7.29 (m, 5H), 5.12 (s, 2H), 4.34 (t, J = 4.5 Hz, 1H), 3.91-3.75 (m, 2H), 3.75 (s, 3H). Spectroscopic data in agreement with the literature.²

(S)-N-Cbz-(α-Me)Ser(OH)-OMe (5)³

To a solution of (S)-α-MeSer(OH)-OH (0.75 g, 6.3 mmol) in 10% Na₂CO₃ (18 ml) was added N-(Benzyloxy carbonyloxy)succinimide (3.14 g, 12.6 mmol) followed by 1,4-dioxane (12 ml). The resulting mixture was stirred at RT for 24 h at which time it was extracted with Et₂O (3 × 10 mL). The aqueous phase was then acidified to pH 3 before being extracted with EtOAc (4 × 15 mL). The combined organic phases were then washed with brine and dried over MgSO₄ before being concentrated in vacuo to afford crude (S)-N-Cbz-α-MeSer(OH)-OH (1.1 g, 6.7 mmol) which was used directly in the following esterification reaction. Using a diazomethane distillation kit, Diazald® (2.7 g, 12.6 mmol) in ether (20 ml) was added dropwise to a mixture of KOH (2 g) in water (15 mL), carbitol® (25 mL) and ether (20 mL) at 85 °C. The resulting diazomethane was distilled through the diazomethane distillation apparatus into a solution of crude N-Cbz-α-MeSer(OH)-OH (1.1 g, 6.7 mmol) in CH₂Cl₂ (25 mL). The reaction mixture was allowed to stand for 12 h to allow evaporation of any excess diazomethane before being concentrated in vacuo to afford the methyl ester 5 as a brown oil (1.12 g, 4.2 mmol, 67%). ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.47-7.35 (m, 5H), 5.72 (br s, 1H), 5.12 (s, 2H), 4.01-3.83 (m, 1H), 3.83-3.75 (m, 1H), 3.75 (s, 3H), 3.10 (s, 1H), 1.49 (s, 3H, Me). Spectroscopic data in agreement with the literature.³

(S)-N-Cbz-Thr(OH)-OMe (8)⁴

According to General Method 1, (S)-N-Cbz-Thr(OH)-OH (4.0 g, 15.8 mmol) afforded methyl ester 8 as an off white solid (3.42 g, 12.8 mmol, 81%). ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.40-7.34 (m, 5H), 5.65 (br d, J = 8.5 Hz, 1H), 4.36 (br d, J = 6.9 Hz, 2H), 5.16 (s, 2H), 3.80 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H). ¹H NMR (400 MHz, methanol-d₄, ppm): δ 7.42-7.32 (m, 5H), 5.14 (s, 2H), 4.29 (dd, J = 6.4, 3.1 Hz, 1H), 4.24 (br d, J = 2.9 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 1H), 2.63 (br s, 1H), 1.22 (d, J = 6.4 Hz, 3H). Spectroscopic data in agreement with the literature.⁴

(S)-N-Cbz-Tyr(OH)-OMe (10)⁵

3
3. General Method 2: Synthesis of phosphorylated amino acid derivatives using DMAP-
N-oxide derived catalysis

To a solution of (S)-N-Cbz-Xxx(OH)-OMe (1 eq.) in dry CH₂Cl₂ (0.2 M) was added base (2 eq.),
diphenylphosphoryl chloride (1.2 eq.) followed by catalyst (5 mol %) under nitrogen. The reaction was
allowed to stir at RT and reaction progress monitored by ¹H NMR (sample aliquots quenched in
methanol-d₄). At the appropriate time point, CH₂Cl₂ (2 mL) was added and the organic phase washed
with 2 M HCl (2 × 5 mL), dried over MgSO₄ and concentrated in vacuo. The crude reaction mixture
was purified by flash chromatography (eluents: EtOAc/hexanes) to afford phosphate 3 as a white solid (271
mg, 0.56 mmol, 95%). M.p. 50-51 °C. IR (νmax/cm⁻¹): 3313, 3067, 3039, 2957, 1721, 1590, 1514, 1488,
1456, 1288, 1185, 1163, 948, 754, 688. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.37-7.21 (m, 15H), 5.67
(d, J = 7.6 Hz, 1H), 5.12 (s, 2H), 4.70-4.64 (m, 2H), 4.59-4.55 (m, 1H), 3.72 (s, 3H). ¹H NMR (400
MHz, methanol-d₄, ppm): δ 7.39-7.21 (m, 15H), 5.11 (s, 2H), 4.64-4.60 (m, 3H), 3.71 (s, 3H). ¹³C
NMR (100 MHz, CDCl₃, ppm): δ 169.0, 155.7, 150.3, 150.2, 135.9, 129.9, 128.6, 128.1, 125.6, 120.0,
120.0, 110.0, 68.6, 67.3, 54.3, 53.0. ³¹P NMR (161 MHz, CDCl₃, ppm): δ -12.28. HRMS (m/z +ES):
Found: 486.1327 (M⁺ C₂H₆NO₃P Requires: 486.1328). [α]D²³ + 79 (c 1.04, CHCl₃); > 99% ee by
CSP-HPLC – see section 4, below.

(2S)-Methyl 2-[[((benzoxycarbonyl)amino)-3-[(diphenoxophosphoryl)oxy]propanoate (3)
Representative procedure using cat. 2i and propylene oxide (Table 1, Entry 13):

According to General Method 2, (S)-N-Cbz-Ser(OH)-OMe (1, 150 mg, 0.59
mmol), propylene oxide (0.082 mL, 1.2 mmol), diphenylphosphoryl chloride (0.147
mL, 0.71 mmol) and cat. 2i (9.9 mg, 0.03 mmol) after 8 h and following flash
chromatography (0-30% EtOAc/hexanes) afforded phosphate 3 as a white solid (271
mg, 0.56 mmol, 95%). M.p. 50-51 °C. IR (νmax/cm⁻¹): 3313, 3067, 3039, 2957, 1721, 1590, 1514, 1488,
1456, 1288, 1185, 1163, 948, 754, 688. ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.37-7.21 (m, 15H), 5.67
(d, J = 7.6 Hz, 1H), 5.12 (s, 2H), 4.70-4.64 (m, 2H), 4.59-4.55 (m, 1H), 3.72 (s, 3H). ¹H NMR (400
MHz, methanol-d₄, ppm): δ 7.39-7.21 (m, 15H), 5.11 (s, 2H), 4.64-4.60 (m, 3H), 3.71 (s, 3H). ¹³C
NMR (100 MHz, CDCl₃, ppm): δ 169.0, 155.7, 150.3, 150.2, 135.9, 129.9, 128.6, 128.1, 125.6, 120.0,
120.0, 110.0, 68.6, 67.3, 54.3, 53.0. ³¹P NMR (161 MHz, CDCl₃, ppm): δ -12.28. HRMS (m/z +ES):
Found: 486.1327 (M⁺ C₂H₆NO₃P Requires: 486.1328). [α]D²³ + 79 (c 1.04, CHCl₃); > 99% ee by
CSP-HPLC – see section 4, below.

(S)-Methyl 2-[[((benzoxycarbonyl)amino)-3-[(diphenoxophosphoryl)oxy]-2-methylpropanoate
(7)
Representative procedure using cat. 2i and Proton Sponge® (Table 2, Entry 4)

According to General Method 2, (S)-N-Cbz-α-MeSer(OH)-OMe (5, 15, 100 mg,
0.40 mmol), Proton Sponge® (172 mg, 0.80 mmmol), diphenylphosphoryl chloride
(0.1 mL, 0.48 mmol) and cat. 2i (7.0 mg, 0.02 mmol) after 2 h and following flash
chromatography (0-40% EtOAc/hexanes) afforded phosphate 7 as a colourless oil (174 mg, 0.35 mmol,
87%). IR (νmax/cm⁻¹): 3308, 3070, 3040, 2955, 1721, 1590, 1488, 1286, 1218, 1186, 1162, 1047, 947, 754, 689. ¹H NMR (400 MHz, methanol-d₄, ppm): δ 7.41-7.20 (m, 15H), 5.07-4.95 (m, 2H), 4.84-4.51 (m, 2H), 3.71 (s, 3H), 1.47 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, ppm): δ 171.8, 154.5, 150.4, 150.4, 129.8, 128.5, 128.2, 120.1, 69.4, 66.7, 59.9, 53.1, 20.0. ³¹P NMR (161 MHz, methanol-d₄, ppm): δ -12.47. HRMS (m/z +ES): Found: 522.1268 (M+ C₂₅H₂₆NO₅P Na Requires: 522.1294). [α]D° = 115 (c 1.01, CHCl₃).

(2S, 3S)-Methyl 2-[(benzlyoxy)carbonyl]amino]-3-[(diphenoxyphosphoryl)oxy]butanoate (9)

Representative procedure using cat. 2l and Proton Sponge® (Table 3, Entry 6)

According to General Method 2, (S)-N-Cbz-Thr(OH)-OMe (8, 100 mg, 0.4 mmol), Proton Sponge® (171 mg, 0.8 mmol), diphenylphosphoryl chloride (0.088 mL, 0.48 mmol) and cat. 2l (6.7 mg, 0.02 mmol) after 24 h and following flash chromatography (0-40% EtOAc/hexanes) afforded phosphate 9 as a colourless oil (179 mg, 0.36 mmol, 96%). IR (νmax/cm⁻¹): 3315, 3077, 3038, 2955, 1718, 1498, 1294, 1215, 1162, 1009, 947, 754, 689. ¹H NMR (400 MHz, methanol-d₄, ppm): δ 7.64 (br d, J = 9.4 Hz, 1H), 7.40-7.21 (m, 15H), 5.31-5.28 (m, 1H), 5.14 (s, 2H), 4.60 (t, J = 2.9 Hz, 1H), 3.59 (s, 3H), 1.41 (d, J = 6.4 Hz, 3H). ¹³C NMR (100 MHz, methanol-d₄, ppm): δ 160.7, 157.7, 150.3, 136.7, 129.7, 128.1, 127.5, 125.5, 119.9, 119.8, 77.6, 66.6, 58.5, 51.8, 17.3. ³¹P NMR (161 MHz, methanol-d₄, ppm): δ -12.87. HRMS (m/z +ES): Found: 500.1043 (M+H⁺ C₂₅H₂₆NO₅P Requires: 500.1074). [α]D° = 85 (c 0.98, CHCl₃).

(2S)-Methyl 2-[(benzlyoxy)carbonyl]amino]-3-[(diphenoxyphosphoryl)oxy]phenylpropanoate (11)

Representative procedure using cat. 2l and NEt₃ (Table 3, Entry 10)

According to General Method 2, (S)-N CBz-Tyr(OH)-OMe (7, 100 mg, 0.30 mmol), NEt₃ (0.083 mL, 0.60 mmol), diphenylphosphoryl chloride (0.074 mL, 0.36 mmol) and cat. 2l (5.2 mg, 0.02 mmol) after 2 h and following flash chromatography (0-20% EtOAc/hexanes) afforded phosphate 11 as a colourless oil (165 mg, 0.29 mmol, 95%). IR (νmax/cm⁻¹): 3324, 3072, 3038, 2955, 1720, 1590, 1488, 1291, 1184, 1161, 954, 754, 688. ¹H NMR (400 MHz, methanol-d₄, ppm): δ 7.44-7.22 (m, 17H), 7.15 (d, J = 8.7 Hz, 2H), 5.03 (s, 1H), 4.48-4.44 (m, 1H), 3.71 (s, 3H), 3.20-2.92 (m, 2H). ¹³C NMR (100 MHz, methanol-d₄, ppm): δ 172.2, 156.9, 150.3, 149.0, 136.8, 135.1, 130.6, 129.8, 128.0, 127.6, 127.3, 125.7, 119.7, 66.2, 60.1, 55.4, 51.4. ³¹P NMR (161 MHz, methanol-d₄, ppm): δ -17.41. HRMS (m/z +ES): Found: 563.1632 (M+H⁺ C₂₃H₂₅NO₅P Requires: 562.1631). [α]D° = 176 (c 1.09, CHCl₃).

4. Checking the stereochemical integrity of phosphoryl serine 3.

To ascertain whether there had been any racemisation during the phosphorylation of serine derivative 1, the products of the using PPO, Proton Sponge®, and PMP (Table 2, entries 2, 4 and 5) were analysed by CSP-HPLC [For each of the chromatography conditions see ‘General Directions’ (page 2, above)]. Moreover, the products of each of these reactions were also resubjected to the reaction conditions for
24 h in the absence of phosphorylating agent and re-analysed. In all cases, the products were enantiomerically pure within the limits of detection (~98% ee), see below.

Racemic phosphoryl serine 3 (control).

Phosphoryl serine 3 from reaction using PPO.

Phosphoryl serine 3 following resubjection to the PPO reaction conditions [5 mol% cat. 2l, PPO (2 eq.), CH₂Cl₂ (0.2 M), 24 h].

Phosphoryl serine 3 from reaction using Proton Sponge°.
Phosphoryl serine 3 following resubjection to the Proton Sponge© reaction conditions [5 mol% cat. 2l, Proton Sponge© (2 eq.), CH₂Cl₂ (0.2 M), 24 h].

Phosphoryl serine 3 from reaction using PMP.

Phosphoryl serine 3 following resubjection to the PMP reaction conditions [5 mol% cat. 2l, PMP (2 eq.), CH₂Cl₂ (0.2 M), 24 h].
5. Use of alternative solvents in place of CH₂Cl₂ for the phosphorylation of Serine derivative 1. See below.

![Chemical structure](image)

<table>
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<th>Entry</th>
<th>Solvent</th>
<th>Base/H⁺ scavenger</th>
<th>Yield[^a]</th>
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<tr>
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</table>

[^a]: Isolated yield after chromatographic purification.  
[^b]: Corresponds to entry 1, Table 2 in main manuscript.  
[^c]: Corresponds to entry 2, Table 2 in main manuscript.

6. Synthesis of 3-(p-hydroxyphenyl)-1,2-propanediol (12)^6

6-1: ([S]-3-[4-(Benzyloxy)phenyl]-2-hydroxypropanoic acid)^7

To an ice-cooled solution of (S)-2-amino-3-[4-(benzyloxy)phenyl]propanoic acid (0.5 g, 1.8 mmol) in H₂SO₄ (1M, 5 mL) and DMF (2.8 mL) was added dropwise NaNO₂ (635 mg, 9.2 mmol) in water (1.5 mL). After 1 h, H₂SO₄ (3 M, 2 mL) was added and the resulting solution stirred at RT for 12 h. The reaction mixture was then extracted with EtOAc (3 × 50 mL), brine (6 × 50 mL) and dried over MgSO₄ before being concentrated in vacuo to afford a yellow liquid, to which was added EtOAc (20 mL) and washed with LiCl solution (7.5%, 3 × 25 mL) followed by brine and dried over MgSO₄ before being concentrated in vacuo to afford (S)-2-amino-3-[4-(benzyloxy)phenyl]propanoic acid as a yellow solid (300 mg, 1.1 mmol, 62%).[^1]  
[^1]: H NMR (400 MHz, methanol-d₄, ppm): δ 7.43 (d, J = 7.1 Hz, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.31 (t, J = 7.1 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 5.03 (s, 2H), 4.51 (dd, J = 7.1, 4.3 Hz, 1H), 3.18 (dd, J = 14.6, 4.3 Hz, 1H), 2.96 (dd, J = 14.6, 7.6 Hz, 1H), 2.60 (br s, 2H). Spectroscopic data in agreement with literature.^[7]

6-2: (S)-3-[4-(Benzyloxy)phenyl]propane-1,2-diol^8

To a stirred solution of NaBH₄ (125 mg, 3.3 mmol) in dry THF (5 mL) at 0 °C was added iodine (420 mg, 1.6 mmol) in dry THF (2 mL) in a dropwise manner. To this solution was added (S)-3-[4-(benzyloxy)phenyl]-2-hydroxypropanoic acid (300 mg, 1.1 mmol) in dry THF (3 mL) in a dropwise manner. The resulting solution was heated to 60 °C for 12 h. To the reaction mixture was added MeOH (2 mL) before being concentrated in vacuo. The residue was then dissolved in EtOAc (5 mL) and the organic phase washed with sat. NaHCO₃ (3 × 5 mL) before being dried over MgSO₄ and concentrated.
in vacuo to afford a yellow oil which was purified by flash chromatography (50-100% EtOAc/hexanes) to afford (S)-3-[4-(benzyl oxy)phenyl]propane-1,2-diol as yellow solid (140 mg, 0.54 mmol, 49%). \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): \(\delta\) 7.47-7.39 (m, 5H), 7.17 (d, \(J = 8.6\) Hz, 2H), 6.96 (d, \(J = 8.6\) Hz, 2H), 5.08 (s, 2H), 3.96 - 3.91 (m, 1H), 3.74-3.71 (m, 1H), 3.57-3.54 (m, 1H), 2.80-2.69 (m, 2H), 1.83 (br s, 2H). LRMS (m/z +ES): Found: 259 (M+H\(^+\) C\(_{10}\)H\(_{10}\)O\(_3\) Requires: 259). Spectroscopic data in agreement with literature.\(^8\)

### 6-3: (S)-3-(4-Hydroxyphenyl)propane-1,2-diol (12)\(^6\)

To a solution of (S)-3-[4-(benzyl oxy)phenyl]propane-1,2-diol (150 mg, 0.59 mmol) in MeOH (4 mL) and AcOH (0.1 mL) was added Pd/C (3 mg, 0.03 mmol). The reaction vessel was evacuated and refilled with hydrogen (× 3) and the reaction mixture stirred under at RT for 12 h. The reaction mixture was then concentrated in vacuo and the residue purified by flash chromatography (50-100% EtOAc/hexanes) to afford (S)-3-(4-hydroxyphenyl)propane-1,2-diol (12) as a pale brown oil that solidified over a period of 12 h to form an off white solid (96 mg, 0.57 mmol, 99%). \(^1\)H NMR (400 MHz, methanol-\(d_4\), ppm): \(\delta\) 7.07 (d, \(J = 8.5\) Hz, 2H), 6.72 (d, \(J = 8.5\) Hz, 2H), 3.78-3.71 (m, 1H), 3.53-3.41 (m, 2H), 2.76-2.58 (m, 2H). Spectroscopic data in agreement with literature.\(^6\)

### 7. Synthesis of ortho-xylene phosphoryl chloride (14, \(o-XPCl\))\(^9\)

To a solution of POCl\(_3\) (1.22 mL, 13.0 mmol) in CH\(_2\)Cl\(_2\) (50 mL) at 0 °C was added NEt\(_3\) (3.63 mL) dropwise. To the resulting yellow suspension was added a solution of phthalalcohol (1.80 g, 13.0 mmol) in CH\(_2\)Cl\(_2\) (25 mL) dropwise. The resulting reaction mixture was allowed to warm to RT and stirred at this temperature for a further 2 h. The reaction mixture was then washed with citric acid (1 M, 3 × 50 mL). The organic phase was then dried over MgSO\(_4\) and concentrated in vacuo to afford ortho-xylene phosphoryl chloride (14) as an off white solid (1.72 g, 7.93 mmol, 61%). \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): \(\delta\) 7.50-7.37 (m, 4H), 5.49 (dd, \(J = 13.4, 10.1\) Hz, 2H), 5.11 (dd, \(J = 13.4, 10.1\) Hz, 2H). \(^3\)P NMR (161 MHz, CDCl\(_3\), ppm): \(\delta\) 3.00. Spectroscopic data in agreement with literature.\(^9\)

### 8. General Method 3: Chemoselective phosphorylation of (S)-3-(p-hydroxyphenyl)-1,2-propanediol (12) and Chloramphenicol \(^0\) (16)

To a solution of hydroxyl-containing substrate (1 eq.) in dry CH\(_2\)Cl\(_2\):MeCN (9:1, 0.2 M) was added base, phosphorylating agent followed by catalyst (5 mol %) under nitrogen. The reaction was allowed to stir at RT for the time indicated. At the appropriate time point, MeOH (2 mL) was added and the reaction mixture concentrated in vacuo concentrated in vacuo. The crude reaction mixture was purified by flash chromatography (EtOAc/hexanes) to afford product.

\((S)-2\text{-Hydroxy-3-(4-hydroxyphenyl)propyl diphenyl phosphate [13a, } R^3 = P(O)(OPh)_2]\) (Table 4, Entry 1)

According to General Method 4, (S)-3-(4-hydroxyphenyl)propane-1,2-diol (12, 100 mg, 0.59 mmol), propylene oxide (0.083 mL, 1.19 mmol),
(S)-3-(2-Hydroxy-3-(4-hydroxyphenyl)propoxy)-1,5-dihydrobenzo[e][1,3,2]dioxaphosphepine 3-oxide (13a, R^3 = o-XP) (Table 4, Entry 1)

According to General Method 4, (S)-3-(4-hydroxyphenyl)propane-1,2-diol (12, 100 mg, 0.59 mmol), propylene oxide (0.083 mL, 1.19 mmol), ortho-xylene phosphoryl chloride (14, 155 mg, 0.71 mmol) and catalyst 2l (10 mg, 0.03 mmol) in CH2Cl2/DMF (9:1, 0.2 M) at RT for 8 h. Flash chromatography (50-75% EtOAc/hexanes) afforded mono-phosphate derivative 13a [R^3 = P(O)(OPh)_2] as a pale yellow oil (221 mg, 0.55 mmol, 94%). ^1H NMR (400 MHz, CDCl3, ppm): δ 7.37-7.15 (m, 10H), 7.03 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.54-4.46 (m, 2H), 3.82 (d, J = 5.5 Hz, 2H), 3.11-3.09 (m, 1H). ^13C NMR (100 MHz, CDCl3, ppm): δ 155.6, 150.3, 129.9, 129.3, 125.6, 120.1, 115.7, 69.6, 62.9, 47.3, 31.0. ^31P NMR (161 MHz, CDCl3, ppm): δ -11.44. HRMS (m/z +ES): Found: 401.1155 (M^+ C_{21}H_{30}O_{3}P Requires: 401.1154). [α]_D^{23} - 135 (c 1.01, CHCl3).

(S)-3-(4-(2,3-Dihydroxypropyl)phenoxo)-1,5-dihydrobenzo[e][1,3,2]dioxaphosphepine 3-oxide (13b, R^3 = o-XP) (Table 4, Entry 2)

According to General Method 4, (S)-3-(4-hydroxyphenyl)propane-1,2-diol (12, 100 mg, 0.59 mmol), pentamethylpiperidine (0.108 mL, 0.59 mmol), ortho-xylene phosphoryl chloride (14, 129 mg, 0.59 mmol) and catalyst 2l (10 mg, 0.03 mmol) in CH2Cl2/DMF (9:1, 0.2 M) at RT for 1 h. Flash chromatography (50-75% EtOAc/hexanes) afforded mono-phosphate derivative 13b [R^3 = P(O)(OPh)_2] as a colourless oil (169 mg, 0.48 mmol, 81%). ^1H NMR (400 MHz, CDCl3, ppm): δ 7.44-7.41 (m, 2H), 7.38-7.34 (m, 2H), 7.27-7.23 (m, 4H), 5.44-5.37 (m, 2H), 5.29-5.20 (m, 2H), 4.29-4.27 (m, 1H), 4.15-4.12 (m, 2H), 2.85-2.78 (m, 2H). ^13C NMR (100 MHz, CDCl3, ppm): δ 135.1, 134.2, 130.9, 129.5, 129.2, 120.0, 70.3, 69.0, 67.0, 39.1. ^31P NMR (161 MHz, CDCl3, ppm): δ -7.09. HRMS (m/z +ES): Found: 351.1003 (M^+ C_{17}H_{29}O_{3}P Requires: 351.0998). [α]_D^{23} -187 (c 0.98, CHCl3).

4-[(2S)-3-[(Diphenoxophosphoryl)oxy]-2-hydroxypropyl]phenyl diphenylphosphate (13c, R^2 & R^3 = P(O)(OPh)_2) (Table 4, Entry 3)

According to General Method 4, (S)-3-(4-hydroxyphenyl)propane-1,2-diol (12, 100 mg, 0.59 mmol), pentamethylpiperidine (0.258 mL, 1.43 mmol), diphenylphosphoryl chloride (0.283 mL, 1.37 mmol) and catalyst 2l (10 mg,
0.03 mmol) stirred at RT for 4 h. Flash chromatography (50-70% EtOAc/hexanes) afforded di-phosphate derivative 13c [R² & R³ = P(O)(OPh)₂] as a colourless oil (321 mg, 0.51 mmol, 86%). ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.41-7.16 (m, 24H), 4.60-4.50 (m, 2H), 3.83 (d, J = 6.0 Hz, 1H), 3.16-3.13 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, ppm): δ 150.4, 150.3, 129.9, 125.7, 120.4, 120.1, 115.3, 68.8, 62.3, 47.5. ³¹P NMR (161 MHz, CDCl₃, ppm): δ -10.86, -17.61. HRMS (m/z +ES): Found: 633.1453 (M⁺ C₃₃H₅₁O₈P₂ Requires: 633.1443). [α]D²⁵ - 197 (c 1.00, CHCl₃).

4-[(2S)-2,3-bis[(Diphenoxyporphosphoryl)oxy]propyl]phenyl diphenyl phosphate [13d, R¹, R² & R³ = P(O)(OPh)₂] (Table 4, Entry 4)

According to General Method 4: (S)-3-(4-hydroxyphenyl)propane-1,2-diol (12, 100 mg, 0.59 mmol), Proton Sponge⁵ (383 mg, 1.78 mmol), diphenylphosphoryl chloride (0.394 mL, 1.90 mmol) and catalyst 2l (10 mg, 0.03 mmol) stirred at RT for 24 h. Flash chromatography (25-50% EtOAc/hexanes) afforded tri-phosphate derivative 13d [R¹, R² & R³ = P(O)(OPh)₂] as a colourless oil (487 mg, 0.56 mmol, 96%). ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.39-6.96 (m, 32H), 4.51-4.46 (m, 1H), 4.39-4.23 (m, 2H), 3.02 (d, J = 6.1 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃, ppm): δ 150.4, 149.5, 132.4, 131.0, 130.6, 129.9, 129.8, 125.7, 125.5, 120.3, 120.1, 120.0, 119.9, 68.0, 60.4, 36.9. ³¹P NMR (161 MHz, CDCl₃, ppm): δ -12.2, -12.6, -17.4. HRMS (m/z +ES): Found: 865.1738 (M⁺ C₄₅H₂₆O₁₂P₃ Requires: 865.1735). [α]D²⁵ - 162 (c 0.96, CHCl₃).

Chloramphenicol⁶ diphenyl phosphate (17)

According to General Method 4, chloramphenicol⁶ (16, 200 mg, 0.62 mmol), pentamethylpiperidine (0.224 mL, 1.24 mmol), diphenylphosphoryl chloride (0.154 mL, 0.75 mmol) and catalyst 2l (10 mg, 0.03 mmol) in CH₂Cl₂:MeCN (9:1, 0.2 M) at RT for 4 h. Flash chromatography (50-75% CH₂Cl₂/MeCN) afforded mono-phosphate derivative 17 as a colourless oil (317 mg, 0.57 mmol, 92%). ¹H NMR (400 MHz, methanol-d₄, ppm): δ 8.19 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.45-7.25 (m, 10H), 6.21 (s, 1H), 5.10 (d, J = 2.7 Hz, 1H), 4.64-4.58 (m, 1H), 4.49 (td, J = 6.6 Hz, 5.6 Hz, 2.8 Hz, 1H), 4.41-4.37 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, ppm): δ 164.4, 150.0, 147.5, 147.1, 130.1, 126.7, 126.1, 123.6, 120.2, 120.0, 69.1, 65.9, 54.6, 54.5. ³¹P NMR (161 MHz, methanol-d₄, ppm): δ -12.12. HRMS (m/z +ES): Found: 555.0484 (M⁺ H⁺ C₂₅H₂₃N₂O₉Cl₂P Requires: 555.0491). [α]D²⁵ + 42 (c 1.01, CHCl₃).

Chloramphenicol⁶ ortho-xylene phosphate (18)

According to General Method 4, chloramphenicol⁶ (16, 200 mg, 0.62 mmol), pentamethylpiperidine (0.224 mL, 1.24 mmol), ortho-xylene phosphoryl chloride (161 mg, 0.75 mmol) and catalyst 2l (10 mg, 0.03 mmol) in CH₂Cl₂:MeCN (9:1, 0.2 M) at RT for 4 h. Flash chromatography (25-75% CH₂Cl₂/MeCN) afforded mono-phosphate derivative 18 as pale yellow oil (302 mg, 0.60 mmol, 96%). ¹H NMR (400 MHz, CDCl₃, ppm):
δ 8.21 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.62-7.60 (m, 2H), 7.46-7.44 (m, 2H), 5.78 (s, 1H), 5.39-5.13 (m, 4H), 4.52-4.45 (m, 2H), 4.34-4.30 (m, 1H), 3.98-3.96 (m, 1H).

13C NMR (100 MHz, CDCl₃, ppm): δ 164.5, 147.4, 134.8, 129.8, 129.4, 129.3, 126.8, 123.6, 69.2, 66.0, 60.4, 54.7.

31P NMR (161 MHz, CDCl₃, ppm): δ 0.76.

HRMS (m/z +ES): Found: 505.0332 (M⁺ C₂₀H₂₀N₂O₈³⁵Cl₂P Requires: 505.0334).

[α]D²³ + 63 (c 0.95, CHCl₃).

9. Deprotection of ortho-xylene phosphates

(S)-4-(2,3-Dihydroxypropyl)phenyl dihydrogen phosphate (15)

To a solution of ortho-xylene phosphates 13b (R³ = o-XP, 10 mg, 0.029 mmol) in MeOH (2 mL) was added Pd/C (1 mg, 10 mol%). The resulting reaction mixture was stirred under an atmosphere of hydrogen for 2 h. The reaction mixture was then filtered through a pad of Celite® to remove Pd/C before being concentrated in vacuo. The resulting crude product was left under a flow of nitrogen for 12 h to remove the ortho-xylene byproduct and afforded mono-phosphate 15 as a colourless oil (7 mg, 0.028 mmol, 99%).

1H NMR (400 MHz, methanol-d₄, ppm): δ 7.25 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 3.82-3.79 (m, 1H), 3.54-3.44 (m, 2H), 2.88-2.64 (m, 2H).

13C NMR (125 MHz, methanol-d₄, ppm): 149.9, 135.0, 130.1, 119.7, 73.0, 65.1, 38.7.

31P NMR (201 MHz, methanol-d₄, ppm): δ 0.24.

HRMS (m/z +ES): Found: 497.0973 [(2M+H)⁺ C₁₈H₂₇O₁₃P₂ Requires: 497.0978].

[α]D²³ + 63 (c 0.95, CHCl₃).

Chloramphenicol dihydrogen phosphate (19)

To a solution of chloramphenicol ortho-xylene phosphate (18, 10 mg, 0.02 mmol) in AcOH (0.2 mL) at RT, was added a solution of HBr (0.2 mL, 48% w/v in AcOH). The reaction mixture was stirred for 1 h at this temperature before being concentrated in vacuo. To the residue was added MeOH and this was removed under a flow of nitrogen repeatedly until no ortho-xylene byproduct remained, affording mono-phosphate 19 as a white solid (8 mg, 0.02 mmol, 99%). M.p. 102-103 °C. 1H NMR (400 MHz, methanol-d₄, ppm): δ 8.19 (d, J = 7.7 Hz, 2H, H¹), 7.68 (d, J = 7.7 Hz, 2H, H¹), 6.25 (s, 1H, H₆), 5.26-5.24 (m, 1H, H³), 4.38-4.17 (m, 1H, H₅), 4.15-4.11 (m, 1H, H₅). 13C NMR (125 MHz, methanol-d₄, ppm): 166.5, 151.2, 148.6, 128.5, 124.8, 124.1, 116.0, 70.8, 67.3, 64.7, 57.0.

31P NMR (201 MHz, methanol-d₄, ppm): δ -0.24.

10. Chemoselective phosphorylation of Ac-Ala-Tyr-Ala-Ser-Ala-Thr-Ala-OMe (20)

Peptide 20 was purchased from ChinaPeptides Co., Ltd, 365 Chuanhong Road, Chuansha, Pudong new area, Shanghai, China, 201202 (www.chinapeptides.com).

To a solution of peptide 20 (10 μL, 0.14 μmol, 0.14 M solution in CH₂Cl₂) in CH₂Cl₂ (40 μL) was added cat. 21 (10 μL, 7.1 nmol, 7.1 mM in CH₂Cl₂) and pentamethylpiperidine (10 μL, 0.16 μmol, 0.15 M solution in CH₂Cl₂) followed by ortho-xylenyl phosphoryl chloride (14, 10 μL, 0.17 μmol, 0.17 M solution in CH₂Cl₂). The reaction vessel was sealed and the reaction mixture agitated for 24 h. To the reaction mixture was added MeOH (0.1 mL) and the solvent evaporated under a flow of nitrogen to afford crude product which was analysed by LC-MS. Integration of the TIC chromatogram indicates ~21% recovered unreacted peptide (Rₜ = 0.92 min) and ~49% phosphorylated product (Rₜ = 1.55 min) (see below).

LC-MS chromatogram of crude reaction mixture.
MS traces for the indicated peaks.

MS-MS analysis of the product peak at $R_t = 1.55$ min confirmed this as having the ortho-xylenyl phosphate moiety attached at the tyrosine residue (see below).
MS/MS of purified product: RT: 1.55, MS [P + H]^+ = 892, MS [P + Na]^+ = 914

\[ \text{[Ac-A-Y(P)-A-S-A-T+H]^+} \]

\[ \text{[Ac-A-Y(P)-A-S-A+H]^+} \]

\[ \text{[Ac-A-Y(P)A+H]^+} \]
11. Synthesis of 2-aryl-pyridine/DMAP-N-oxide derived catalysts

11a. General Method 4-1: Synthesis of (2-aryl)pyridines via Suzuki coupling

A procedure modified from that described by Bob-Egbe\textsuperscript{10} was developed in which 2,4-dichloropyridine/2-chloropyridine (1 eq.), boronic acid (1.5 eq.) and tetrakis(triphenylphosphine)palladium (5 mol\%) in degassed THF (10 mL) were stirred at RT under a purged nitrogen atmosphere. After 5 min, K$_2$CO$_3$ (2 eq.) in degassed H$_2$O (5 mL) was added and the resulting biphasic orange solution heated to reflux for 16 h. The reaction mixture was allowed to cool to RT and diluted with EtOAc (20 mL) and the organic layer washed with brine, separated and dried over MgSO$_4$ before being concentrated \textit{in vacuo}. The crude reaction mixture was purified by flash chromatography and the appropriate fractions concentrated \textit{in vacuo} to afford the desired product.

2-[3,5-bis(Trifluoromethyl)phenyl]pyridine\textsuperscript{11}

According to General Method 4-1, 2-chloropyridine (1 g, 8.8 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (3.4 g, 13.2 mmol, 1.5 eq.), K$_2$CO$_3$ (2.44 g, 17.7 mmol, 2 eq.) and tetrakis(triphenylphosphine)palladium (493 mg, 0.4 mmol, 5 mol\%) followed by flash chromatography (0-20\% CH$_2$Cl$_2$/hexanes) afforded 2-[3,5-bis(trifluoromethyl)phenyl]pyridine as an off white solid (1.9 g, 0.7 mmol, 83\%). M.p. 42-44 °C. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.79 (d, $J = 5.0$ Hz, 1H), 8.52 (s, 2H), 7.95 (s, 1H), 7.90-7.84 (m, 2H), 7.40-7.33 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 154.1, 150.1, 141.2, 137.3, 133.8, 132.3, 127.8, 127.0, 123.6, 122.4, 120.7. HRMS (m/z +ES): Found: 292.0575 (M$^+$ C$_{13}$H$_6$NF$_6$ Requires: 292.0561). Spectroscopic data in agreement with the literature.\textsuperscript{11}

2-[3,5-bis(Trifluoromethyl)phenyl]-4-chloropyridine

According to General Method 4-1, 2,4-dichloropyridine (0.8 g, 5.4 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (2.09 g, 8.1 mmol, 1.5 eq.), K$_2$CO$_3$ (1.86 g, 13.5 mmol, 2.5 eq.) and tetrakis(triphenylphosphine)palladium (624 mg, 0.5 mmol, 5 mol\%) followed by flash chromatography (0-20\% EtOAc/hexanes) afforded 2-[3,5-bis(trifluoromethyl)phenyl]-4-chloropyridine as an off white solid (1.51 g, 0.69 mmol, 86\%). M.p. 45-47 °C. IR (v$_{max}$/cm$^{-1}$): 1637, 1376, 1281, 1177, 1133. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 7.39 (d, $J = 8$ Hz, 1H), 7.85 (s, 1H), 7.98 (s, 1H), 8.50 (s, 2H), 8.68 (d, $J = 8.0$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 155.6, 150.9, 145.5, 140.0, 132.5, 132.2, 127.0, 123.8, 123.1, 121.1. HRMS (m/z +ES): Found: 325.0098 (M$^+$ C$_{13}$H$_6$NF$_6$Cl Requires: 325.0093).

4-Chloro-2-(p-tolyl)pyridine

According to General Method 4-1, 2,4-dichloropyridine (1.5 g, 10.2 mmol), 4-methylbenzeneboronic acid (2.08 g, 15.2 mmol, 1.5 eq.), K$_2$CO$_3$ (3.45 g, 25.5 mmol, 2.5 eq.) and tetrakis(triphenylphosphine)palladium (352 mg, 0.30 mmol, 5 mol\%) followed by Flash chromatography (0-20\% ether/hexanes) afforded 4-chloro-2-(p-tolyl)pyridine as an off white solid (1.44 g, 7.2 mmol, 70\%). M.p. 53-54 °C. IR (v$_{max}$/cm$^{-1}$): 3034, 2922, 1574, 1552, 1513, 1460, 1381, 1106, 909, 818, 733. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.59 (d, $J = 5.7$ Hz), 7.90 (d, $J = 7.9$ Hz), 7.74 (d, $J = 1.9$ Hz), 7.31 (d, $J = 7.9$ Hz), 7.24 (dd, $J = 5.7, 1.9$ Hz), 2.44
(s, 3H, Me). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 159.0, 150.4, 144.7, 139.8, 135.3, 129.6, 126.9, 122.0, 120.5, 21.3. HRMS (m/z +EI): Found: 203.0507 (M$^+$ C$_{12}$H$_{10}$NO$_3$Cl Requires: 203.0502).

**4-Chloro-2-(4-methoxyphenyl)pyridine**

According to General Method 4-1, 2,4-dichloropyridine (1.0 g, 6.76 mmol), 4-methoxybenzenearboxylic acid (1.23 g, 10.14 mmol, 1.5 eq.), K$_2$CO$_3$ (2.33 g, 16.9 mmol, 2.5 eq.) and tetrakis(triphenylphosphine)palladium (236 mg, 0.33 mmol, 5 mol%) followed by flash chromatography (0-20% ether/hexanes) afforded 4-chloro-2-(4-methoxyphenyl)pyridine as an off white solid (1.05 g, 4.8 mmol, 71.1%). M.p. 118-120 °C. IR ($\nu_{\max }$/cm$^{-1}$): 3016, 1608, 1574, 1514, 1458, 1249, 1176, 820, 696. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.56 (d, $J = 5.7$ Hz, 1H), 7.94-7.9 (m, 2H), 7.69 (d, $J = 2.3$ Hz, 1H), 7.21 (dd, $J = 5.7$ Hz, 2.3 Hz, 1H), 7.04-7.0 (m, 2H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 161.0, 158.6, 150.3, 144.7, 130.7, 128.3, 121.6, 120.0, 114.2, 55.4. HRMS (m/z +EI): Found: 219.0460 (M+ C$_{13}$H$_{10}$NO$_3$Cl Requires: 219.0451).

**2-[2,4-bis(Trifluoromethyl)phenyl]-4-chloropyridine**

According to General Method 4-1, 2,4-dichloropyridine (1.0 g, 6.76 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (2.61 g, 10.14 mmol, 1.5 eq.), K$_2$CO$_3$ (2.33 g, 16.9 mmol, 2.5 eq.) and tetrakis(triphenylphosphine)palladium (780 mg, 0.68 mmol, 5 mol%) followed by flash chromatography (0-20% EtOAc/hexanes) afforded 2-[2,4-bis(trifluoromethyl)phenyl]-4-chloropyridine as an off white solid (2.15 g, 6.62 mmol, 98%). M.p. 44-46 °C. IR ($\nu_{\max }$/cm$^{-1}$): 1673, 1401, 1254, 1204, 1137. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.64 (d, $J = 5.4$ Hz, 1H), 8.06 (s, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.48 (s, 1H), 7.42 (dd, $J = 5.4$, 1.9 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 157.7, 150.2, 144.3, 142.2, 132.3, 128.5, 127.2, 124.5, 124.2, 123.8, 123.5, 121.8, 119.0. HRMS (m/z +ES): Found: 326.0175 (M+ C$_{13}$H$_{10}$NF$_3$Cl Requires: 326.0171).

**11b. General Method 4-2: Synthesis of (2-aryl)pyridines by hydrogenation of (2-aryl)-4-chloropyridines**

To a solution of (2-aryl)-4-chloropyridine (1 eq.) in MeOH (5 mL) was added Pd/C (10 mol%). The reaction vessel was evacuated and refilled with hydrogen ($\times$5). The reaction mixture was then allowed to stir under an atmosphere of hydrogen at RT for 12 h before being filtered through a pad of Celite® and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexanes).

**2-(para-Tolyl)pyridine**

According to General Method 4-2, 4-chloro-2-(p-tolyl)pyridine (500 mg, 2.46 mmol) and Pd/C (26 mg, 0.25 mmol) followed by flash chromatography (0-25% EtOAc/hexanes) afforded 2-(para-tolyl)pyridine as white solid (353 mg, 2.09 mmol, 85%). $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.66 (d, $J = 4.4$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 2H), 7.70 (m, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.17 (m, 1H), 2.39 (s, 3H). HRMS (m/z +EI): Found: 169.0887 (M$^+$ C$_{12}$H$_{11}$N Requires: 169.0891). Spectroscopic data in agreement with literature.\(^{12}\)
2-(para-Methoxyphenyl)pyridine\textsuperscript{13}

According to General Method 4-2, 4-chloro-2-(4-methoxyphenyl)pyridine (500 mg, 2.28 mmol) and Pd/C (24 mg, 0.22 mmol) followed by flash chromatography (0-25% EtOAc/hexanes) afforded 2-(para-methoxyphenyl)pyridine as an off-white solid (333 mg, 1.80 mmol, 79%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta 8.65 (d, J = 4.5 \text{ Hz}, 1H)\), \(7.96 (d, J = 8.5 \text{ Hz}, 2H)\), \(7.73-7.68 (m, 2H)\), \(7.20-7.16 (m, 1H)\), \(7.01 (d, J = 8.5 \text{ Hz}, 2H)\), \(3.87 (s, 3H, OMe)\). HRMS (m/z +EI): Found: 185.0834 (M\textsuperscript{+} C\textsubscript{12}H\textsubscript{11}N Requires: 185.0841). Spectroscopic data in agreement with literature.\textsuperscript{13}

11c. General Method 4-3: Synthesis of (2-aryl)pyridine-N-oxides via mCPBA oxidation

A procedure modified from that described by Bob-Egbe\textsuperscript{10} was developed in which a solution (2-aryl)(4-chloro)pyridine (1 eq.) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) at 0 °C was added mCPBA (2.5 eq.) and NaHCO\textsubscript{3} (1 eq. in 4 mL H\textsubscript{2}O). The resulting solution was heated to 40 °C for 12 h. The reaction mixture was allowed to cool to RT and quenched with sat. sodium sulfate solution. The reaction mixture was extracted into CH\textsubscript{2}Cl\textsubscript{2} and the combined organic phases washed with sat. NaHCO\textsubscript{3} followed by brine before being dried over MgSO\textsubscript{4} and concentrated in vacuo. The product was purified by flash chromatography and the appropriate fractions concentrated in vacuo to afford product. N.B. Only starting material and product present in each reaction. Recovered starting material was re-isolated and further oxidised where required.

4-Chloropyridine-N-oxide (2b)\textsuperscript{14}

According to General Method 4-3, 4-chloropyridine (2 g, 17.7 mmol), mCPBA (4.16 g, 44.2 mmol) and NaHCO\textsubscript{3} (1.48 g, 17.7 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded N-oxide 2b as a white solid (1.58 g, 12.2 mmol, 69%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta 8.15 (d, J = 3.4 \text{ Hz}, 2H)\), \(7.28 (d, J = 3.4 \text{ Hz}, 2H)\). Spectroscopic data in agreement with the literature.\textsuperscript{14}

2-Chloropyridine-N-oxide (2c)\textsuperscript{15}

According to General Method 4-3, 2-chloropyridine (1 g, 8.8 mmol), mCPBA (3.8 g, 22.1 mmol) and NaHCO\textsubscript{3} (0.966 g, 11.5 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded N-oxide 2c as a white solid (730 mg, 5.6 mmol, 64%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta 8.39-8.37 (m, 1H)\), \(7.53-7.51 (m, 1H)\), \(7.25-7.23 (m, 2H)\). Spectroscopic data in agreement with the literature.\textsuperscript{15}

2,4-Dichloropyridine-N-oxide

According to General Method 4-3, 2,4-dichloropyridine (2 g, 13.5 mmol), mCPBA (5.8 g, 33.7 mmol) and NaHCO\textsubscript{3} (1.25 g, 14.8 mmol) were employed. flash chromatography (100% EtOAc) afforded 2,4-dichloropyridine-N-oxide as a yellow oil (774 mg, 4.7 mmol, 34%). M.p. 56-57 °C. IR (\(v_{\text{max}}/\text{cm}^{-1}\)): 3434, 3056, 3013, 1446, 1392, 1257, 1107, 1072, 865,
822, 753, 668. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.30 (d, $J = 7.1$ Hz, 1H), 7.53 (d, $J = 2.8$ Hz, 1H), 7.22 (dd, $J = 7.1$, 2.8 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 142.6, 140.7, 131.2, 126.9, 124.5. HRMS (m/z +EI): Found: 162.9584 (M$^+$ C$_{3}$H$_{3}$NO$^{35}$Cl Requires: 162.9592).

2-[3,5-bis(Trifluoromethyl)phenyl]pyridine-N-oxide (2j)

According to General Method 4-3, 2-[3,5-bis(trifluoromethyl)phenyl]chloropyridine (758 mg, 2.6 mmol), mCPBA (1.12 g, 6.5 mmol) and NaHCO$_3$ (284 mg, 3.4 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded N-oxide 2j as a yellow oil solidified over time to form a yellow solid (627 mg, 2.04 mmol, 79%). M.p. 156-157 °C. IR ($\nu_{\text{max}}$/cm$^{-1}$): 2976, 1552, 1453, 1280, 1161, 1127. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.39 (dd, $J = 5.9$, 1.5 Hz, 1H), 8.34 (s, 2H), 7.97 (s, 1H), 7.76-7.71 (m, 1H), 7.58-7.46 (m, 1H), 7.43-7.35 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 146.3, 140.7, 134.4, 132.0, 129.7, 128.6, 128.6, 127.3, 126.0, 124.5, 123.3. HRMS (m/z +ES): Found: 308.0522 (M+H$^+$ C$_{13}$H$_{12}$NO Requires: 308.0510).

2-[3,5-bis(Trifluoromethyl)phenyl]-4-chloropyridine-N-oxide

According to General Method 4-3, 2-[3,5-bis(trifluoromethyl)phenyl]-4-chloropyridine (1.6 g, 4.9 mmol), mCPBA (2.12 g, 12.3 mmol) and NaHCO$_3$ (454 mg, 5.4 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded 2-[3,5-bis(trifluoromethyl)phenyl]-4-chloropyridine-N-oxide as a yellow oil which solidified over time to form a yellow solid (912 mg, 2.68 mmol, 55%). M.p. 141-143 °C. IR ($\nu_{\text{max}}$/cm$^{-1}$): 2925, 1574, 1280, 1178, 1136. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.33-8.31 (m, 3H), 8.02 (s, 1H), 7.52 (d, $J = 2.6$ Hz, 1H), 7.37 (d, $J = 6.9$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 147.1, 141.3, 133.3, 131.9, 129.7, 127.2, 126.2, 124.3, 123.9, 121.6. HRMS (m/z +ES): Found: 342.0121 (M C$_{13}$H$_{12}$NO$^{35}$Cl Requires: 342.0120).

4-Chloro-2-(para-tolyl)pyridine-N-oxide

According to General Method 4-3, 4-chloro-2-(p-tolyl)pyridine (1.0 g, 4.9 mmol), mCPBA (2.12 g, 12.3 mmol) and NaHCO$_3$ (455 mg, 5.4 mmol) followed by flash chromatography (100% EtOAc) afforded 4-chloro-2-(para-tolyl)pyridine-N-oxide as a white solid (880 mg, 4.0 mmol, 82%). M.p. 110-112 °C. IR ($\nu_{\text{max}}$/cm$^{-1}$): 2942, 1607, 1515, 1458, 1392, 1302. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta$ 8.24 (d, $J = 7.0$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 3.0$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.17 (dd, $J = 7.0$, 3.0 Hz, 1H), 2.41 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 150.1, 141.1, 140.5, 131.5, 129.1, 128.6, 127.0, 124.8 (2C), 21.5. HRMS (m/z +EI): Found: 219.0465 (M$^+$ C$_{13}$H$_{10}$NO$^{35}$Cl Requires: 219.0451).

4-Chloro-2-(4-methoxyphenyl)pyridine-N-oxide

According to General Method 4-3, 4-chloro-2-(4-methoxyphenyl)pyridine (432 mg, 2.0 mmol), mCPBA (858 mg, 4.9 mmol) and NaHCO$_3$ (182 mg, 2.1 mmol) followed by flash chromatography (100% EtOAc) afforded 4-chloro-2-(4-methoxyphenyl)pyridine-N-oxide as a white solid (272 mg, 1.2 mmol, 59%). M.p. 98-100 °C. IR ($\nu_{\text{max}}$/cm$^{-1}$): 2952, 1608, 1574, 1547, 1514, 1458, 1249, 1176, 820, 672. $^1$H NMR (400
MHZ, CDCl₃, ppm): δ 8.26 (d, J = 7.0 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 3.0 Hz, 1H), 7.16 (dd, J = 7.0, 3.0 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 3.87 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, ppm): δ 161.0, 149.8, 141.2, 131.7, 130.8, 126.7, 124.0, 123.7, 113.8, 55.4. HRMS (m/z +ES): Found: 236.0460 (M+H⁺ C₁₃H₁₁NO₃Cl Requires: 236.0478).

2-[2,4-bis(Trifluoromethyl)phenyl]-4-chloropyridine-N-oxide

According to General Method 4-3. 2-(2,4-bis(trifluoromethyl)phenyl)-4-chloropyridine (125 mg, 0.4 mmol), mCPBA (165 mg, 1.0 mmol) and NaHCO₃ (35 mg, 0.4 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded 2-[2,4-bis(trifluoromethyl)phenyl]-4-chloropyridine-N-oxide as an off white solid (47 mg, 0.15 mmol, 36%). M.p. 143-145 °C. IR (νmax/cm⁻¹): 2957, 1614, 1287, 1195, 1236. ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.29 (d, J = 7.0 Hz, 1H), 8.09 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 7.0, 2.9 Hz, 1H), 7.33 (d, J = 2.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, ppm): δ 147.6, 140.9, 132.4, 131.2, 130.7, 130.4, 129.0, 127.3, 126.4, 124.2, 121.6, 121.4. HRMS (m/z +ES): Found: 342.0110 (M+H⁺ C₁₃H₁₀NO₃Cl Requires: 342.0120).

2-(para-Tolyl)pyridine-N-oxide (2h)¹⁶

According to General Method 4-3. 2-(p-tolyl)pyridine (411 mg, 2.4 mmol), mCPBA (1.05 g, 6.08 mmol) and NaHCO₃ (224 mg, 2.68 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded N-oxide 2h as an off white solid (364 mg, 0.2 mmol, 81%). ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.25 (1H, m), 7.81 (d, J = 8.5 Hz, 2H), 7.56 (m, 1H), 7.33 (m, 2H), 7.27 (d, J = 8.5 Hz), 2.38 (s, 3H). HRMS (m/z +EI): Found: 185.0485 (M+ C₁₂H₁₁NO Requires: 185.0841). Spectroscopic data in agreement with literature.¹⁶

2-(para-Methoxy)pyridine-N-oxide (2f)¹⁶

According to General Method 4-3. 2-(p-methoxyphenyl)pyridine (417 mg, 2.25 mmol), mCPBA (972 mg, 6.64 mmol) and NaHCO₃ (208 mg, 2.50 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded N-oxide 2f as off white solid (303 mg, 1.5 mmol, 67%). ¹H NMR (400 MHz, DMSO-d₆, ppm): δ 8.26-8.24 (m, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.56 (dd, J = 7.5, 3.5 Hz, 1H), 7.28-7.35 (m, 2H), 7.04 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H). Spectroscopic data in agreement with literature.¹⁶

11d. General Method 4-4: Synthesis of (2-aryl)-4-DMAP-N-oxides via Sₐ-Ar substitution

(2-Aryl)-4-chloropyridine-N-oxide (1 eq.) was dissolved in MeCN (2 mL). HNMe₂ (40% w/w in H₂O, 4 mL) was added and the resulting yellow solution heated to 110 °C in a Biotage Initiator microwave for 90 min. The reaction mixture was then diluted with CH₂Cl₂ (5 mL) and washed with NaHCO₃ (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic extracts were dried over MgSO₄ and concentrated in vacuo to afford product.
4-Dimethylaminopyridine-N-oxide (2d)\(^1\)

According to General Method 4-4, 4-chloropyridine-N-oxide (2c, 500 mg, 3.8 mmol) afforded 4-DMAP-N-oxide (2d) as a pale brown solid (479 mg, 3.5 mmol, 90\%). \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 8.06 (d, J = 7.9 Hz, 2H), 6.61 (d, J = 7.9 Hz, 2H), 3.10 (s, 6H, NMe\(_2\)). Spectroscopic data in agreement with the literature.\(^1\)

2-Chloro-4-dimethylaminopyridine-N-oxide (2e)

According to General Method 4-4, 2,4-dichloropyridine-N-oxide (200 mg, 1.2 mmol) followed by flash chromatography (0-10\% MeOH/EtOAc) afforded dimethylamine 2e as an off white solid (45 mg, 0.3 mmol, 22\%). M.p. 76-78 °C. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)): 3371, 2960, 2859, 1601, 1546, 1502, 1398, 1206, 1179, 1105, 986, 765, 672. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 8.06 (d, J = 7.6 Hz, 1H), 6.79-6.78 (m, 2H), 3.05 (s, 6H). \(^13\)C NMR (100 MHz, CDCl\(_3\), ppm): δ 155.5, 140.8, 133.0, 117.1, 114.4, 40.5. HRMS (m/z +ES): Found: 172.0399 (M\(^+\) C\(_7\)H\(_9\)N\(_2\)O\(^{35}\)Cl Requires: 172.0403).

2-[3,5-bis(Trifluoromethyl)phenyl]-4-dimethylaminopyridine-N-oxide (2k)

According to General Method 4-4, 2-(3,5-bis(trifluoromethyl)phenyl)-4-chloropyridine-N-oxide (100 mg, 0.3 mmol) afforded dimethylamine 2k as a yellow solid (102 mg, 0.29 mmol, 99\%). M.p. 118-119 °C. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)): 1574, 1361, 1280, 1136. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 8.29 (s, 2H), 8.15 (d, J = 7.4 Hz, 1H), 7.93 (s, 1H), 6.49 (dd, J = 7.4, 3.5 Hz, 1H), 6.55 (d, J = 3.5 Hz, 1H), 3.10 (s, 6H). \(^13\)C NMR (100 MHz, CDCl\(_3\), ppm): δ 148.4, 145.8, 140.4, 135.5, 129.9, 124.5, 123.1, 121.8, 108.5, 108.3, 39.9. HRMS (m/z +ES): Found: 351.0921 (M\(^+\) C\(_{15}\)H\(_{13}\)N\(_2\)O\(^{6}\) Requires: 351.0932).

2-(para-Tolyl)-4-dimethylaminopyridine-N-oxide (2i)

According to General Method 4-4, 4-chloro-2-(p-tolyl)pyridine-N-oxide (500 mg, 2.3 mmol) afforded dimethylamine 2i as a yellow solid (516 mg, 2.2 mmol, 99\%). M.p. 78-79 °C. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)): 2922, 1601, 1546, 1502, 1448, 987, 817. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 8.12 (d, J = 7.4 Hz, 1H), 7.71 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.54 (d, J = 3.5 Hz, 1H), 6.49 (dd, J = 7.4, 3.6 Hz, 1H), 3.06 (s, 6H), 2.41 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\), ppm): δ 148.9, 148.1, 140.2, 139.3, 130.9, 129.3, 128.8, 108.7, 107.0, 39.8, 21.4. HRMS (m/z +ES): Found: 229.1331 (M+H\(^+\) C\(_{15}\)H\(_{17}\)N\(_2\)O Requires: 229.1341).

2-(4-Methoxyphenyl)-4-dimethylaminopyridine-N-oxide (2g)

According to General Method 4-4, 4-chloro-2-(4-methoxyphenyl)pyridine-N-oxide (500 mg, 2.3 mmol) afforded dimethylamine 2g as a yellow solid (550 mg, 2.2 mmol, 99\%). M.p. 75-76 °C. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)): 3171, 3104, 2924, 1630, 1512, 1439, 1252, 1201, 1179, 1022, 818, 798, 762. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): δ 8.09 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.58
(d, J = 3.5 Hz, 1H), 6.47 (dd, J = 7.5, 3.5 Hz, 1H), 3.85 (s, 3H, OMe), 3.06 (s, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), ppm): \(\delta\) 160.4, 148.6, 148.4, 140.2, 130.9, 125.9, 113.6, 108.4, 106.8, 55.4, 39.8. HRMS (m/z +ES): Found: 245.1228 (M+H\(^+\)) C\(_{14}\)H\(_{17}\)N\(_2\)O\(_2\) Requires: 245.1290.

2-[2,4-bis(Trifluoromethyl)phenyl]-4-dimethylaminopyridine-N-oxide (2I)

According to General Method 4-4 2-[2,4-bis(trifluoromethyl)phenyl]-4-chloropyridine-N-oxide (340 mg, 1.0 mmol) afforded dimethylamine 2I as a yellow solid (330 mg, 0.94 mmol, 94%). M.p. 115-116 °C. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)): 1617, 1382, 1271, 1096. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): \(\delta\) 8.16 (d, \(J = 7.5\) Hz, 1H), 8.07 (s, 1H), 7.96 (d, \(J = 8.1\) Hz, 1H), 7.78 (d, \(J = 8.1\) Hz, 1H), 6.65 (dd, \(J = 7.5, 3.5\) Hz, 1H), 6.49 (d, \(J = 3.5\) Hz, 1H), 3.11 (s, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), ppm): \(\delta\) 147.6, 145.5, 139.9, 135.8, 132.6, 130.3, 128.7, 123.8, 123.8, 121.6, 108.9, 103.8, 39.8. HRMS (m/z +ES): Found: 351.0919 (M+H\(^+\)) C\(_{14}\)H\(_{17}\)N\(_2\)OF\(_2\) Requires: 351.0932.

12. Synthesis of histidine-based pentapeptide catalyst 6 (Miller catalyst)\(^{18}\)

This peptide corresponds to the catalyst numbered ‘24’ in ref 18 and was synthesized by SPPS using commercially available Wang polystyrene resin preloaded with (S)-Phe. Couplings were performed using 4 eq. of appropriate amino acid derivative, HBTU (4 eq.) and Hünig’s base (8 eq.) in DMF. Deprotections were performed using 20\% piperidine in DMF for 20 min. The peptide was then cleaved from the solid support using a 9:1:1 mixture of MeOH:DMF:NEt\(_3\) for 4 days. The solvent was removed at RT under a flow of nitrogen to afford crude product (121 mg; still traces of DMF present). The peptide was purified using reverse phase LCMS, performed using a RP-18 X Terra (Waters) column. Preparative LCMS was performed over 18 min by eluting with 50-75% MeOH in water to afford the desired peptide 6 (57 mg, 0.06 mmol, 13%). \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): \(\delta\) 7.37 (s, 1H), 7.23-7.06 (m, 9H), 6.85-6.82 (m, 3H), 6.67 (s, 1H), 5.18 (d, \(J = 6.6\) Hz, 1H), 4.76 (q, \(J = 7\) Hz, 1H), 4.50-4.47 (m, 2H), 4.32 (t, \(J = 7.5\) Hz, 1H), 4.24 (s, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.25-3.09 (m, 2H), 3.08-2.97 (m, 2H), 2.95-2.81 (m, 2H), 2.36-2.24 (m, 1H), 2.08-1.91 (m, 2H), 1.87-1.83 (m, 1H), 1.77-1.67 (m, 5H), 1.58-1.52 (m, 3H), 1.41 (s, 9H), 1.26 (s, 9H), 1.16 (s, 9H). LRMS (m/z +ES): Found: 930.5 (M+H\(^+\)) C\(_{53}\)H\(_{57}\)N\(_3\)O\(_{10}\) Requires: 930.1). Spectroscopic data in agreement with the literature.\(^{18}\)

13. References
