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C2-Alkenylation of N-Heteroaromatic Compounds
via Brønsted Acid Catalysis

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**General Experimental Details**

All materials were purchased from commercial sources (Acros, Aldrich, Alfa Aesar, Fluorochem and Strem) and used without any further treatment. Reagents requiring purification were purified using standard laboratory techniques according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966). Catalytic reactions were carried out in Young-type re-sealable tubes. Anhydrous solvents were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. Anhydrous DMSO and NMP employed in the catalytic reactions were purchased form Aldrich and they were employed in a 50:1 v/v mixture with deionized water, in order to maintain the water amount constant. High-boiling solvents were removed from the reaction crudes employing rotary evaporators connected with high-vacuum pumps. Heteroarene N-oxides were stored and handled under inert atmosphere (glovebox), due to their hygroscopicity, to facilitate their use. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 µm, 230-400 mesh). Thin layer chromatography was performed using aluminium backed 60 F\textsubscript{254} silica plates. Visualization was achieved by UV fluorescence or a basic KMnO\textsubscript{4} solution and heat. Proton nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz or 500 MHz. 13\textsuperscript{C} NMR spectra were recorded at 100 MHz or 125 MHz as stated. Chemical shifts (\(\delta\)) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m) and broad (br.). Coupling constants (\(J\)) are quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data (DEPT\textsuperscript{135}, COSY, HSQC and HMBC). In situ yields were determined by employing 1,3,5-trimethoxybenzene as internal standard. Mass spectra were recorded using a VG Autospec (Cl\textsuperscript{+} mode), a Brüker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS (ESI\textsuperscript{+} mode) and Shimadzu GCMS QP2010+ (EI\textsuperscript{+} mode). Infrared spectra were recorded on a Perkin Elmer Spectrum Two FTIR spectrometer as thin films or solids compressed on a diamond plate. Melting points were determined using Stuart SMP30 melting point apparatus and are reported uncorrected. Enantiomeric excess was determined by integration of chromatograms peaks. Chiral HPLC was performed on an Agilent 1260 Infinity SFC Control Module system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified.
Experimental Procedures and Data

Substrates Synthesis

**General Procedure A** for the preparation of N-oxide substrates employing m-CPBA as oxidant:
To a stirred, ice-cooled (0 °C) solution of heteroarene derivate (100 mol%) in CH₂Cl₂ (0.2 M) was added portion-wise m-CPBA (130 mol%). The reaction was warmed to room temperature and stirred overnight. Saturated aq. NaHCO₃ (5 mL/mmol) was slowly added and the mixture was extracted with CH₂Cl₂ (3 × 5 mL/mmol). The organic extracts were combined, washed with brine (2 mL/mmol), dried over Na₂SO₄, filtered and concentrated in vacuo to provide the crude product. Purification by FCC (EtOAc → 10% MeOH/EtOAc) afforded pure N-oxide product.

**General Procedure B** for the preparation of N-oxide substrates employing hydrogen peroxide-urea adduct as oxidant: To a stirred solution of heteroarene derivate (100 mol%) in CH₂Cl₂ (0.3 M) was added portion-wise hydrogen peroxide-urea adduct (300 mol%). The mixture was cooled to 0 °C and trifluoroacetic anhydride (270 mol%) was added dropwise. The reaction was warmed to room temperature and stirred for 3 hours. The reaction was quenched with a 1M aq. solution of Na₂S₂O₅ (5 mL/mmol) and the mixture was extracted with CH₂Cl₂ (3 × 5 mL/mmol). The organic portions were combined, washed with brine (2 mL/mmol), dried over Na₂SO₄, filtered and concentrated in vacuo to provide the crude product. Purification by FCC (EtOAc → 5% MeOH/EtOAc) afforded pure N-oxide product.

Substrates 1a (83% yield), 1b (48% yield), 1c (90% yield), 1d (85% yield), 1e (85% yield), 1f (86% yield), 1g (42% yield), 1h (86% yield), 1i (78% yield), 1j (80% yield), 1l (91% yield) and 1n (84% yield) were synthesized according to **General Procedure A** from the corresponding commercially available quinoline, isoquinoline and pyridine precursors (yields reported in parenthesis for each compound). Substrates 1k (87% yield) and 1o (58% yield) were synthesized according to **General Procedure B** from the corresponding commercially available pyridine precursors (yields reported in parenthesis for each compound). The spectroscopic proprieties of all compounds were consistent with the data available in literature. Substrates 1q and 1r were purchased from commercial sources (Aldrich, Alfa-Aesar) and used without any further treatment.
3-Bromo-5-phenylpyridine N-oxide (1m)

**Step 1:** The title compound was prepared following a literature procedure.² To a solution of 3,5-dibromopyridine (1.00 g, 4.22 mmol, 110 mol%) in DME (13 mL) was added Pd(PPh₃)₄ (125 mg, 0.08 mmol, 2 mol%) and the mixture was stirred for 10 minutes. A solution of potassium carbonate (1.75 g, 12.7 mmol, 330 mol%) in water (7 mL) was added, followed by phenylboronic acid (463 mg, 3.79 mmol, 100 mol%), and the mixture was heated at reflux for 4 hours. The reaction was cooled to room temperature and quenched with 1M aq. NaOH (6 mL). The mixture was extracted with Et₂O (3 × 20 mL). The organic portions were collected, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by FCC (10% EtOAc/hexane) afforded 3-bromo-5-phenylpyridine (586 mg, 66% yield) as a colorless solid; ¹H NMR (CDCl₃, 400 MHz): δ 8.76 (1H, d, J = 2.0 Hz), 8.65 (1H, d, J = 2.0 Hz), 8.02 (1H, dd, J = 2.0, 2.0 Hz), 7.60-7.53 (2H, m), 7.53-7.46 (2H, m), 7.46-7.40 (1H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 149.3, 146.4, 138.3, 136.9, 136.3, 129.2, 128.7, 127.2, 120.9. The spectroscopic properties were consistent with the data available in literature.²

**Step 2:** To a stirred, ice-cooled (0 °C) solution of 3-bromo-5-phenylpyridine (580 mg, 2.48 mmol, 100 mol%) in CH₂Cl₂ (15 mL) was added portion-wise m-CPBA (556 mg, 3.22 mmol, 130 mol%). The reaction was warmed to room temperature and stirred overnight. Saturated aq. NaHCO₃ (10 mL) was slowly added and the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic extracts were combined, washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to provide the crude product. Purification by FCC (EtOAc → 10% MeOH/EtOAc) afforded 3-bromo-5-phenylpyridine N-oxide (580 mg, 94% yield) as a colorless solid; m.p. = 114-116 °C [hexane/CH₂Cl₂]; νmax / cm⁻¹: 3098 (m), 3048 (s), 2922 (s), 2852 (m), 1591 (s), 1543 (s), 1397 (s), 1191 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.40-8.34 (1H, m, C5-H), 8.34-8.28 (1H, m, C1-H), 7.62-7.55 (1H, m, C3-H), 7.55-7.41 (5H, m, 2×C7-H, 2×C8-H and C9-H); ¹³C NMR (CDCl₃, 100 MHz): δ 140.6 (C4), 138.9 (C1), 136.4 (C5), 134.0 (C6), 129.9 (C9), 129.5 (C8), 127.5 (C3), 126.9 (C7), 120.4 (C2); HRMS: (ESI⁺) Calculated for C₁₁H₈(⁷⁹Br)NNaO: 271.9681. Found [M+Na]⁺: 271.9677.
Methyl 3-bromoisonicotinate N-oxide (1p)

To a stirred solution of 3-bromoisonicotinic acid (250 mg, 1.24 mmol, 100 mol%) in toluene (5 mL) and MeOH (2 mL) was added dropwise a solution of (trimethylsilyl)diazomethane (2.0 M in Et2O, 1.24 mL, 2.47 mmol, 200 mol%). The mixture was stirred for 2 hours at room temperature. The volatiles were removed under reduced pressure and the crude material was re-dissolved in in CH2Cl2 (7 mL). The solution was cooled to 0 °C and m-CPBA (278 mg, 1.61 mmol, 130 mol%) was added portion-wise. The reaction was warmed to room temperature and stirred overnight. Saturated aq. NaHCO3 (5 mL) was slowly added and the mixture was extracted with CH2Cl2 (3 × 10 mL). The organic extracts were combined, washed with brine (2 mL), dried over Na2SO4, filtered and concentrated in vacuo to provide the crude material. Purification by FCC (EtOAc → 10% MeOH/EtOAc) afforded methyl 3-bromoisonicotinate N-oxide (185 mg, 64% yield) as a colorless solid; m.p. = 134-135 °C [hexane/CH2Cl2]; νmax / cm⁻¹: 3105 (m), 3065 (m), 3027 (s), 2922 (s), 2851 (m), 1724 (s), 1596 (s), 1438 (s), 1244 (s), 1149 (s), 1052 (s); ¹H NMR (CDCl3, 400 MHz): δ 8.43 (1H, d, J = 2.0 Hz, C1-H), 8.11 (1H, dd, J = 2.0, 7.0 Hz, C5-H), 7.80 (1H, d, J = 7.0 Hz, C4-H), 3.94 (3H, s, C7-H3); ¹³C NMR (CDCl3, 100 MHz): δ 162.9 (C6), 142.7 (C1), 137.9 (C5), 127.3 (C4), 126.9 (C3), 120.8 (C2), 53.0 (C7); HRMS: (ESI⁺) Calculated for C7H6(79Br)NNaO3: 253.9423. Found [M+Na⁺]: 253.9416.

Alkene Synthesis

General Procedure C for the preparation of alkene partner from aldehydes: To a stirred, ice-cooled (0 °C) solution of the appropriate aldehyde (100 mol%) in anhydrous Et2O (1 M) was added dropwise a solution of (trimethylsilyl)methylmagnesium chloride (0.5 M in 2-Me-THF, 110 mol%). The reaction was maintained stirring at 0 °C for 10 hours. Saturated aq. NH4Cl (5 mL/mmol) was slowly added and the mixture was extracted with Et2O (3 × 5 mL/mmol). The organic extracts were combined, washed with saturated aq. NaHCO3 (2 mL/mmol), dried over Na2SO4, filtered and concentrated in vacuo to provide the corresponding 2-(trimethylsilyl)ethanol. The crude material was re-dissolved in Et2O (1 M) and stirred with 1M aq. HCl (1.3 mL/mmol) at room temperature, monitoring the reaction by TLC. The mixture was extracted with Et2O (3 × 5 mL/mmol). The organic extracts were combined, dried over Na2SO4, filtered and the solvent was removed under reduced pressure [N.B. many alkenes tent to be really volatile, pay attention before putting the flask into the heating-bath of the rotary evaporator or on the high-vacuum line]. Purification by either distillation or FCC (10%EtOAc/hexane) afforded pure terminal olefins.
**4-Vinylthiazole** (34% yield), **2-vinylfuran** (61% yield) and **3-vinylthiophene** (51% yield) were synthesized according to **General Procedure C** from the corresponding commercially available aldehyde precursors (yields reported in parenthesis for each compound). The spectroscopic proprieties of all compounds were consistent with the data available in literature. All the other olefinic partners were purchased from commercial sources (Aldrich, Alfa-Aesar) and used without any further treatment.

**5-Phenyl-3-vinylisoxazole**

To a stirred, ice-cooled (0 °C) solution of 5-phenylisoxazole-3-carboxaldehyde (210 mg, 1.21 mmol, 100 mol%) in anhydrous Et₂O (2 mL) was added dropwise a solution of (trimethylsilyl)methylmagnesium chloride (0.5 M in 2-Me-THF, 2.67 mL, 1.33 mmol, 110 mol%). The reaction was maintained stirring at 0 °C for 10 hours. Saturated aq. NH₄Cl (5 mL/mmol) was slowly added and the mixture was extracted with Et₂O (3 × 5 mL). The organic extracts were combined, washed with saturated aq. NaHCO₃ (1 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to provide the corresponding 2-(trimethylsilyl)ethanol. The crude material was re-dissolved in Et₂O (1.5 mL) and stirred with conc. H₂SO₄ (0.1 mL) at room temperature, monitoring the reaction by TLC. The mixture was extracted with Et₂O (3 × 5 mL). The organic extracts were combined, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. Purification by FCC (20% EtOAc/hexane → 30% EtOAc/hexane) afforded 5-phenyl-3-vinylisoxazole (182 mg, 92% yield) as a colorless solid; m.p. = 49-51 °C [hexane/CH₂Cl₂] (Lit.⁴ 55-56 °C [no solvent quoted]);¹ H NMR (CDCl₃, 400 MHz): δ 7.85-7.73 (2H, m), 7.55-7.39 (4H, m), 6.82 (1H, dd, J = 11.0, 18.0 Hz), 5.93 (1H, dd, J = 1.0, 18.0 Hz), 5.65 (1H, dd, J = 1.0, 11.0 Hz);¹³C NMR (CDCl₃, 100 MHz): δ 184.8, 169.8, 162.3, 130.2, 128.9, 126.0, 125.8, 121.4, 96.2. The spectroscopic proprieties were consistent with the data available in literature.⁵

**C2-Alkenylation Reactions**

**General Procedure D** for Brønsted-acid catalysed C2-alkenylation reactions:

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with N-oxide substrate (0.143 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of the appropriate alkene (300-500 mol%) and acid catalyst (5 mol%) in the appropriate solvent (50:1 v/v mixture with H₂O, 1.5 M concentration with respect to substrate) was added via syringe and the tube was sealed with a Young’s tap. The reaction vessel was placed into a pre-heated heating block at 120-140 °C and stirred for 24-48 hours. The reaction mixture was cooled to room
temperature and concentrated in vacuo. Purification of the residue by FCC (10% EtOAc/hexane \(\rightarrow\) 30% EtOAc/hexane) afforded pure (\(E\))-2-alkenylated heteroaromatic product.

\((E\))-2-Styrylquinoline (2a)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (450 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 2a (31.8 mg, 96% yield) as an off-white solid; m.p. = 99-100 °C [hexane/CH₂Cl₂] (Lit.⁶ 98-100 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (1H, d, \(J = 8.5\) Hz), 8.07 (1H, d, \(J = 8.5\) Hz), 7.78 (1H, d, \(J = 8.0\) Hz), 7.72-7.63 (5H, m), 7.49 (1H, dd, \(J = 7.5, 7.5\) Hz), 7.43-7.38 (3H, m), 7.34-7.32 (1H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 156.0, 148.3, 136.5, 136.3, 134.4, 129.7, 129.2, 129.0, 128.8, 128.6, 127.5, 127.3, 127.2, 126.1, 119.2. The spectroscopic proprieties were consistent with the data available in literature.⁷

\((E\))-3-Bromo-2-styrylquinoline (2b)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (300 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 2b (30.2 mg, 68% yield) as a yellow solid; m.p. = 125-126 °C [hexane/CH₂Cl₂]; ν max / cm⁻¹: 3055 (m), 3026 (m), 2922 (s), 2851 (s), 1726 (s), 1631 (s), 1575 (s), 1484 (s), 1309 (s), 1017 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.35 (1H, s, C₃-H), 8.13-8.01 (2H, m, C₈-H and C₁₁-H), 7.82 (1H, d, \(J = 16.0\) Hz, C₁₀-H), 7.75-7.65 (4H, m, C₅-H, C₇-H and 2 × C₁₃-H), 7.54-7.46 (1H, m, C₆-H), 7.42 (2H, dd, \(J = 7.5, 7.5\) Hz, 2 × C₁₄-H), 7.35 (1H, t, \(J = 7.5\) Hz, C₁₅-H); ¹³C NMR (CDCl₃, 100 MHz): δ 152.9 (C₁), 146.9 (C₉), 139.3 (C₃), 137.1 (C₁₁), 136.7 (C₁₂), 130.1 (C₇), 129.4 (C₈), 129.0 (C₁₅), 128.9 (C₁₄), 128.5 (C₄), 127.8 (C₁₃), 127.0 (C₆), 126.6 (C₅), 125.1 (C₁₀), 118.6 (C₂); HRMS: (ESI⁺) Calculated for C₁₇H₁₃Br: 310.0226. Found [M+H]^⁺: 310.0224. The regiochemistry of compound 2b was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C₁₀-H [\(J = 16.0\) Hz].
(E)-6-Methoxy-2-styrylquinoline (2c)

General Procedure D: TsOH-H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded quinoline 2c (28.2 mg, 76% yield) as a yellow solid; m.p. = 147-149 °C [hexane/CH₂Cl₂] (Lit.5 147-149 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.04-7.96 (2H, m), 7.66-7.58 (4H, m), 7.43-7.28 (5H, m), 7.05 (1H, d, J = 2.5 Hz), 3.93 (3H, s); ¹³C NMR (CDCl₃, 100 MHz): δ 157.8, 153.8, 144.4, 136.8, 135.2, 133.2, 130.8, 129.2, 128.9, 128.5, 128.4, 127.2, 122.4, 119.7, 105.4, 55.7. The spectroscopic proprieties were consistent with the data available in literature.⁷

Methyl (E)-2-styrylquinoline-6-carboxylate (2d)

General Procedure D: TsOH-H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 2d (37.7 mg, 91% yield) as an off-white solid; m.p. = 185-186 °C [hexane/CH₂Cl₂]; νₘₐₓ / cm⁻¹: 3027 (m), 3003 (m), 2952 (s), 2941 (m), 2872 (m), 1660 (s), 1650 (s), 1610 (s), 1590 (s), 1580 (s), 1570 (s), 1520 (s), 1490 (s), 1480 (s), 1470 (s), 1460 (s), 1450 (s), 1440 (s), 1430 (s), 1420 (s), 1410 (s), 1400 (s), 1390 (s), 1380 (s), 1370 (s), 1360 (s), 1350 (s), 1340 (s), 1330 (s), 1320 (s), 1310 (s), 1300 (s), 1290 (s), 1280 (s), 1270 (s), 1260 (s), 1250 (s), 1240 (s), 1230 (s), 1220 (s), 1210 (s), 1200 (s), 1190 (s), 1180 (s), 1170 (s), 1160 (s), 1150 (s), 1140 (s), 1130 (s), 1120 (s), 1110 (s), 1100 (s), 1090 (s), 1080 (s), 1070 (s), 1060 (s), 1050 (s), 1040 (s), 1030 (s), 1020 (s), 1010 (s), 1000 (s), 990 (s), 980 (s), 970 (s), 960 (s), 950 (s), 940 (s), 930 (s), 920 (s), 910 (s), 900 (s), 890 (s), 880 (s), 870 (s), 860 (s), 850 (s), 840 (s), 830 (s), 820 (s), 810 (s), 800 (s), 790 (s), 780 (s), 770 (s), 760 (s), 750 (s), 740 (s), 730 (s), 720 (s), 710 (s), 700 (s), 690 (s), 680 (s), 670 (s), 660 (s), 650 (s), 640 (s), 630 (s), 620 (s), 610 (s), 600 (s), 590 (s), 580 (s), 570 (s), 560 (s), 550 (s), 540 (s), 530 (s), 520 (s), 510 (s), 500 (s), 490 (s), 480 (s), 470 (s), 460 (s), 450 (s), 440 (s), 430 (s), 420 (s), 410 (s), 400 (s), 390 (s), 380 (s), 370 (s), 360 (s), 350 (s), 340 (s), 330 (s), 320 (s), 310 (s), 300 (s), 290 (s), 280 (s), 270 (s), 260 (s), 250 (s), 240 (s), 230 (s), 220 (s), 210 (s), 200 (s), 190 (s), 180 (s), 170 (s), 160 (s), 150 (s), 140 (s), 130 (s), 120 (s), 110 (s), 100 (s), 90 (s), 80 (s), 70 (s), 60 (s), 50 (s), 40 (s), 30 (s), 20 (s), 10 (s), 9 (s), 8 (s), 7 (s), 6 (s), 5 (s), 4 (s), 3 (s), 2 (s), 1 (s), 0.9 (s), 0.8 (s), 0.7 (s), 0.6 (s), 0.5 (s), 0.4 (s), 0.3 (s), 0.2 (s), 0.1 (s), 0.0 (s).

The regiochemistry of compound 2d was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C11-H [J = 16.5 Hz].
(E)-6-Methyl-2-styrylquinoline (2e)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 2e (28.6 mg, 82% yield) as an off-white solid; m.p. = 136-137 °C [hexane/CH₂Cl₂] (Lit.6 136-138 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.06-7.95 (2H, m), 7.69-7.59 (4H, m), 7.56-7.51 (2H, m), 7.44-7.36 (3H, m), 7.36-7.29 (1H, m), 2.53 (3H, s); ¹³C NMR (CDCl₃, 100 MHz): δ 155.2, 146.9, 136.7, 136.2, 135.8, 134.0, 132.1, 129.2, 129.0, 128.9, 128.6, 127.5, 127.3, 126.5, 119.3, 119.7. The spectroscopic properties were consistent with the data available in literature.⁷

(E)-1-Styrylisoquinoline (2f)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (300 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded isoquinoline 2f (20.5 mg, 62% yield) as a yellow solid; m.p. = 102-103 °C [hexane/CH₂Cl₂] (Lit.⁶ 107-109 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.57 (1H, d, J = 5.5 Hz), 8.38 (1H, dd, J = 1.0, 8.5 Hz), 8.06-7.96 (2H, m), 7.83 (1H, dd, J = 1.5, 8.0 Hz), 7.77-7.60 (4H, m), 7.57 (1H, dd, J = 1.0, 5.5 Hz), 7.48-7.39 (2H, m), 7.39-7.31 (1H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 154.5, 142.5, 136.9, 136.7, 135.8, 129.9, 128.8, 128.6, 127.4, 127.3, 127.2, 126.7, 124.4, 122.8, 120.0. The spectroscopic properties were consistent with the data available in literature.⁷

(E)-1-Styrylisoquinoline-3-carbonitrile (2g)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (300 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24
hours and afforded isoquinoline 2g (27.6 mg, 75% yield) as an off-white solid; m.p. = 126-128 °C [hexane/CH₂Cl₂]; ν<sub>max</sub> / cm⁻¹: 3060 (m), 3024 (m), 2922 (s), 2852 (m), 2228 (s), 1629 (s), 1550 (s), 1360 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.46-8.36 (1H, m, C3-H), 8.09 (1H, d, J = 15.5 Hz, C11-H), 7.98 (1H, s, C8-H), 7.94-7.85 (2H, m, C6-H and C10-H), 7.85-7.77 (2H, m, C4-H and C5-H), 7.74-7.65 (2H, m, 2 × C13-H), 7.48-7.35 (3H, m, 2 × C14-H and C15-H); ¹³C NMR (CDCl₃, 100 MHz): δ 156.4 (C1), 138.7 (C11), 136.3 (C12), 135.9 (C7), 131.5 (C5), 130.3 (C4), 129.4 (C15), 129.0 (C14), 128.0 (C6), 127.9 (C13), 127.5 (C2), 126.6 (C9), 126.3 (C8), 124.9 (C3), 121.0 (C10), 118.5 (C16); HRMS: (ESI⁺) Calculated for C₁₅H₁₁N₂: 257.1073. Found [M+H⁺]: 257.1066. The regiochemistry of compound 2g was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C11-H [J = 15.5 Hz].

(Œ)-5-Nitro-1-strylisoquinoline (2h)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded isoquinoline 2h (23.1 mg, 59% yield) as a yellow solid; m.p. = 117-119 °C [hexane/CH₂Cl₂]; ν<sub>max</sub> / cm⁻¹: 3056 (m), 2922 (s), 2855 (m), 1517 (s), 1313 (s), 1033 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.77-8.68 (2H, m, C3-H and C9-H), 8.46 (1H, dd, J = 1.0, 8.0 Hz, C5-H), 8.30 (1H, dd, J = 1.0, 6.0 Hz, C8-H), 8.04 (1H, d, J = 15.5 Hz, C11-H), 7.94 (1H, d, J = 15.5 Hz, C10-H), 7.74-7.65 (3H, m, C4-H and 2 × C13-H), 7.48-7.33 (3H, m, 2 × C14-H and C15-H); ¹³C NMR (CDCl₃, 100 MHz): δ 155.5 (C1), 145.8 (C9), 145.7 (C6), 138.1 (C11), 136.4 (C12), 131.4 (C3), 129.3 (2 signals, C7 and C15), 129.0 (C14), 127.8 (C5), 127.7 (C13), 127.2 (C2), 125.5 (C4), 122.0 (C10), 114.5 (C8); HRMS: (ESI⁺) Calculated for C₁₇H₁₃N₂O₂: 277.0972. Found [M+H⁺]: 277.0977. The regiochemistry of compound 2h was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C10-H and C11-H [J = 15.5 Hz].
(E)-4-Bromo-1-styrylisoquinoline (2i)

![HMBC analysis](image)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded isoquinoline 2i (32.4mg, 73% yield) as a yellow solid; m.p. = 88-90 °C [hexane/CH₂Cl₂]; νₘₐₓ / cm⁻¹: 3057 (m), 3025 (m), 2923 (s), 2856 (m), 1681 (s), 1625 (s), 1446 (s), 1383 (s), 1225 (s), 1032 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.73 (1H, s, C9-H), 8.35 (1H, dd, J = 1.0, 8.5 Hz, C3-H), 8.19 (1H, dd, J = 1.5, 8.5 Hz, C6-H), 7.99 (1H, d, J = 15.5 Hz, C11-H), 7.92 (1H, d, J = 15.5 Hz, C10-H), 7.79 (1H, ddd, J = 1.0, 7.0, 8.5 Hz, C5-H), 7.75-7.64 (3H, m, C4-H and 2 × C13-H), 7.43 (2H, dd, J = 7.5, 7.5 Hz, 2 × C14-H), 7.39-7.33 (1H, m, C15-H); ¹³C NMR (CDCl₃, 100 MHz): δ 154.0 (C1), 144.2 (C9), 136.7 (C12), 136.6 (C11), 135.2 (C7), 131.1 (C5), 128.8 (2 signals, C14 and C15), 128.0 (C4), 127.8 (C2), 127.5 (C13), 126.6 (C6), 124.8 (C3), 122.1 (C10), 118.3 (C8); HRMS: (ESI⁺) Calculated for C₁₁H₁₃BrN: 310.0226. Found [M+H]⁺: 310.0213. The regiochemistry of compound 2i was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C10-H and C11-H [J = 15.5 Hz].

(E)-3-Bromo-2-styrylpyridine (2j)

![HMBC analysis](image)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine 2j (16.8 mg, 45% yield) as a yellow oil; νₘₐₓ / cm⁻¹: 3051 (m), 2926 (s), 1631 (s), 1418 (s), 1264 (s), 1021 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.54 (1H, dd, J = 1.5, 4.5 Hz, C5-H), 7.89-7.80 (2H, m, C3-H and C7-H), 7.68-7.56 (3H, m, C6-H and 2 × C9-H), 7.39 (2H, dd, J = 6.5, 8.0 Hz, 2 × C10-H), 7.36-7.30 (1H, m, C11-H), 7.03 (1H, dd, J = 4.5, 8.0 Hz, C4-H); ¹³C NMR (CDCl₃, 100 MHz): δ 153.4 (C1), 148.2 (C5), 140.9 (C3), 136.6 (C8), 136.0 (C7), 128.9 (2 signals, C10 and C11), 127.7 (C9), 124.9 (C6), 123.2 (C4), 121.2 (C2); HRMS: (ESI⁺) Calculated for
C_{13}H_{11}(^{79}\text{Br})\text{N}: 260.0069. Found [M+H]^+: 260.0066. The regiochemistry of compound 2j was confirmed by HMBC analysis (as indicated above).

\textit{(E)-6-Styryl-4-((trifluoromethyl)nicotinonitrile (2k) and \textit{iso}-2k isomer}

### General Procedure D:
TsOH-H\textsubscript{2}O was employed as the catalyst. A solution of styrene (500 mol\%) in DMSO/H\textsubscript{2}O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours. Purification by FCC afforded pyridine 2k (14.8 mg, 38% yield) as an off-white solid. Continued elution provided regioisomer \textit{iso}-2k (9.2 mg, 23% yield) as an off-white solid.

\textit{Data for 2k: m.p. = 107-109 °C [hexane/CH\textsubscript{2}Cl\textsubscript{2}]; \nu_{\text{max}} l \text{ cm}^{-1}: 3060 (m), 3026 (m), 2923 (s), 2855 (m), 2231 (s), 1591 (s), 1384 (s), 1291 (s), 1144 (s); ¹H NMR (CDCl\textsubscript{3}, 400 MHz): \delta 8.99 (1H, s, C5-H), 7.93 (1H, d, J = 16.0 Hz, C7-H), 7.66 (1H, s, C2-H), 7.63 (2H, dd, J = 1.5, 8.0 Hz, 2 × C9-H), 7.47-7.38 (3H, m, 2 × C10-H and C11-H), 7.22 (1H, d, J = 16.0 Hz, C6-H); ¹C NMR (CDCl\textsubscript{3}, 125 MHz): \delta 160.4 (C1), 154.6 (C5), 140.6 (q, 2J\textsubscript{CF} = 34.0 Hz, C3), 139.5 (C7), 135.3 (C8), 130.2 (C11), 129.2 (C10), 128.1 (C9), 125.2 (C6), 121.4 (q, 1J\textsubscript{CF} = 275.0 Hz, C13), 118.1 (q, 3J\textsubscript{CF} = 4.5 Hz, C2), 114.2 (C12), 103.3 (q, 3J\textsubscript{CF} = 2.0 Hz, C4); HRMS: (ESI\textsuperscript{+}) Calculated for C_{13}H_{10}F_{2}N_{2}: 297.0610. Found [M+Na\textsuperscript{+}]: 297.0609. The regiochemistry of compound 2k was confirmed by HMBC analysis (as indicated above) and by the multiplicity of C5-H and C2-H signals in ¹H NMR (singlets). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 16.0 Hz].

\textit{Data for \textit{iso}-2k: m.p. = 86-88 °C [hexane/CH\textsubscript{2}Cl\textsubscript{2}]; \nu_{\text{max}} l \text{ cm}^{-1}: 3024 (m), 2922 (s), 2855 (m), 2230 (s), 1632 (s), 1397 (s), 1338 (s), 1179 (s), 1138 (s); ¹H NMR (CDCl\textsubscript{3}, 400 MHz): \delta 8.93 (1H, d, J = 5.0 Hz, C5-H), 8.14 (1H, d, J = 15.5 Hz, C7-H), 7.71-7.67 (2H, m, 2 × C9-H), 7.64 (1H, d, J = 15.5 Hz, C6-H), 7.50 (1H, d, J = 5.0 Hz, C4-H), 7.47-7.38 (3H, m, C2-H, 2 × C10-H and C11-H); ¹C NMR (CDCl\textsubscript{3}, 125 MHz): \delta 159.5 (C1), 153.2 (C5), 141.3 (q, 2J\textsubscript{CF} = 34.0 Hz, C3), 140.3 (C7), 135.2 (C8), 130.1 (C11), 129.0 (C10), 128.2 (C9), 121.6 (C6), 121.4 (q, 1J\textsubscript{CF} = 275.0 Hz, C2), 117.5 (q, 3J\textsubscript{CF} = 4.5 Hz, C4), 113.4 (C12), 103.2 (q, 3J\textsubscript{CF} = 2.0 Hz, C2); HRMS: (ESI\textsuperscript{+}) Calculated for C_{13}H_{10}F_{2}N_{2}: 275.0791. Found [M+H\textsuperscript{+}]: 275.0801. The regiochemistry of compound \textit{iso}-2k was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 15.5 Hz].
(E)-6-Methyl-2-styrylnicotinonitrile (2l)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine 2l (16.7 mg, 53% yield) as a yellow oil; ν_{max} / cm⁻¹: 3053 (m), 2982 (s), 2921 (m), 2225 (s), 1581 (s), 1494 (s), 1264 (s), 1053 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.03 (1H, d, J = 15.5 Hz, C7-H), 7.79 (1H, d, J = 8.0 Hz, C3-H), 7.69-7.63 (2H, m, 2 × C9-H), 7.50 (1H, d, J = 15.5 Hz, C6-H), 7.45-7.33 (3H, m, 2 × C10-H and C11-H), 7.09 (1H, d, J = 8.0 Hz, C4-H), 2.66 (3H, s, C13-H); ¹³C NMR (CDCl₃, 100 MHz): δ 162.6 (C5), 156.8 (C1), 140.3 (C3), 137.4 (C7), 135.8 (C8), 129.3 (C11), 128.8 (C10), 127.8 (C9), 123.0 (C6), 121.3 (C4), 117.2 (C12), 104.5 (C2), 25.3 (C13); HRMS: (ESI⁺) Calculated for C₁₅H₁₃N₂: 221.1073. Found [M+H]+: 221.1070. The regiochemistry of compound 2l was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 15.5 Hz].

(E)-3-Bromo-5-phenyl-2-styrylpyridine (2m) and iso-2m isomer

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded a 0.8:0.2 mixture of pyridine 2m and iso-2m (25.8 mg, 54% yield) as a yellow solid; ν_{max} / cm⁻¹: 3055 (m), 3025 (m), 2922 (m), 2845 (m), 1628 (s), 1576 (s), 1448 (s), 1440 (s), 1033 (s), 1013 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.79 (0.8H, d, J = 2.0 Hz, C5-H, 2m), 8.67 (0.2H,
d, $J = 2.0$ Hz, C5-H, iso-2m), 8.07 (0.8H, d, $J = 2.0$ Hz, C3-H, 2m), 7.89 (0.8H, d, $J = 15.5$ Hz, C7-H, 2m), 7.82 (0.2H, d, $J = 15.5$ Hz, C7-H, iso-2m), 7.75 (0.2H, d, $J = 2.0$ Hz, C3-H, iso-2m), 7.70-7.24 (10.8H, m, C6-H for 2m and CAr-H for 2m and iso-2m), 7.11 (0.2H, d, $J = 15.5$ Hz, C6-H, iso-2m); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 151.7 (C1, 2m), 151.0 (C1, iso-2m), 149.3 (C5, iso-2m), 146.4 (C5, 2m), 140.0 (C3, iso-2m), 138.6 (C3, 2m), 137.6 (2 signals, C2 and C12, iso-2m), 136.7 (C8, iso-2m), 136.5 (C8, 2m), 136.2 (C4, 2m), 136.1 (C12, 2m), 135.7 (C7, 2m), 134.2 (C7, iso-2m), 129.5 (CAr-H, iso-2m), 129.2 (CAr-H, 2m), 128.8 (CAr-H, 2m), 128.7 (CAr-H, iso-2m), 128.5 (CAr-H, 2m), 128.4 (CAr-H, iso-2m), 128.2 (CAr-H, iso-2m), 127.5 (CAr-H, 2m), 127.3 (CAr-H, iso-2m), 126.9 (CAr-H, 2m), 124.4 (2 signals, C6, 2m and iso-2m), 121.1 (C2, 2m), 118.3 (C4, iso-2m); HRMS: (ESI$^+$) Calculated for C$_{19}$H$_{15}$$(^{79}$Br)N: 336.0382. Found [M+H]$^+$: 336.0382. The regiochemistry of compounds 2m and iso-2m was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C7-H [$J = 15.5$ Hz] for 2m and for C6-H and C7-H [$J = 15.5$ Hz] for iso-2m.

(E)-3,5-Dibromo-2-styrylpyridine (2n)

General Procedure D: TsOH·H$_2$O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H$_2$O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine 2n (33.2 mg, 69% yield) as an off-white solid; m.p. = 112-113 °C [hexane/CH$_2$Cl$_2$]; $v_{max}$ / cm$^{-1}$: 3080 (m), 3056 (m), 3025 (s), 2853 (s), 1628 (s), 1429 (s), 1207 (s), 1020 (s); $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.57 (1H, d, $J = 2.0$ Hz, C5-H), 8.01 (1H, d, $J = 2.0$ Hz, C3-H), 7.84 (1H, d $J = 15.5$ Hz, C7-H), 7.65-7.59 (2H, m, 2 × C9-H), 7.52 (1H, d $J = 15.5$ Hz, C6-H), 7.43-7.30 (3H, m, 2 × C10-H and C11-H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 152.0 (C1), 149.1 (C5), 142.5 (C3), 136.6 (C7), 136.4 (C8), 129.1 (C11), 128.9 (C10), 127.7 (C9), 123.7 (C6), 120.8 (C2), 118.1 (C4); HRMS: (ESI$^+$) Calculated for C$_{18}$H$_{15}$$(^{79}$Br)$_3$N: 377.9127. Found [M+H]$^+$: 377.9127. The regiochemistry of compound 2n was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [$J = 15.5$ Hz].

(E)-5-Bromo-6-styrylpyrrolidinonitrile (2o)
An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with 5-bromo-2-cyanopyridine N-oxide (28.4 mg, 0.143 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of styrene (82.1 µL, 0.710 mmol, 500 mol%) and TsOH·H₂O (1.36 mg, 7.14 µmol, 5 mol%) in 0.1 mL of a 50:1 v/v mixture of DMSO and H₂O was added via syringe and the tube was sealed with a Young’s tap. The reaction vessel was placed into a pre-heated heating block at 120 °C and stirred for 16 hours. The tube was cooled to room temperature and the tap was replaced with a rubber septum. Acetic anhydride (13.5 µL, 0.143 mmol, 100 mol%) was added to the solution and the vessel was re-sealed with the tap. The reaction was stirred for further 16 hours at 120 °C. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue by FCC (10% EtOAc/hexane → 30% EtOAc/hexane) afforded pyridine 2o (27.3 mg, 67% yield) as a yellow solid; m.p. = 147-148 °C [hexane/CH₂Cl₂]; νmax / cm⁻¹: 3026 (m), 3054 (m), 2922 (s), 2851 (m), 2238 (s), 1624 (s), 1549 (s), 1418 (s), 1012 (s); ¹H NMR (CDCl₃, 400 MHz): δ 7.98 (1H, d, J = 8.0 Hz, C3-H), 7.96 (1H, d, J = 15.5 Hz, C7-H), 7.67-7.63 (2H, m, 2 × C9-H), 7.55 (1H, d, J = 15.5 Hz, C6-H), 7.45-7.34 (4H, m, C4-H, 2 × C10-H and C11-H); ¹³C NMR (CDCl₃, 100 MHz): δ 155.3 (Cl), 141.7 (C3), 138.9 (C7), 135.7 (C8), 132.1 (C5), 129.5 (C11), 128.9 (C10), 127.9 (C9), 126.4 (C4), 124.2 (C2), 122.6 (C6), 116.8 (C12); HRMS: (ESI⁺) Calculated for C₁₄H₁₀(⁷⁵Br)N₂: 285.0022. Found [M+H]⁺: 285.0024. The regiochemistry of compound 2o was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 15.5 Hz].

Data for 5-Bromo-6-(2-hydroxy-2-phenylethyl)picolinonitrile intermediate

When the Ac₂O step was omitted, this compound was isolated by FCC (10% EtOAc/hexane → 30% EtOAc/hexane) as a yellow oil; νmax / cm⁻¹: 3326 (s), 2942 (s), 2831 (m), 2222 (s), 1451 (s), 1270 (s), 1023 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.02 (1H, d, J = 8.0 Hz, C3-H), 7.50-7.43 (3H, m, C4-H and 2 × C9-H), 7.43-7.35 (2H, m, 2 × C10-H), 7.35-7.28 (1H, m, C11-H), 5.34 (1H, dt, J = 3.0, 6.5 Hz, C7-H), 3.71 (1H, d, J = 3.0 Hz, OH), 3.36 (2H, d, J = 6.5 Hz, C6-H₂); ¹³C NMR (CDCl₃, 100 MHz): δ 160.5 (Cl), 143.0 (C8), 141.4 (C3), 131.3 (C5), 128.6 (C10), 127.8 (C11), 127.2 (C4), 126.6 (C2), 125.8 (C9), 116.5 (C12), 71.8 (C7), 45.6 (C6); HRMS: (ESI⁺) Calculated for C₁₄H₁₁(⁷⁵Br)N₂NaO:
Methyl (E)-3-bromo-2-styrylisonicotinate (2p)

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine 2p (21.9 mg, 48% yield) as a yellow oil; ν_max/cm⁻¹: 3053 (m), 2986 (s), 1739 (s), 1629 (s), 1577 (s), 1264 (s), 1111 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.59 (1H, d, J = 4.5 Hz, C5-H), 7.87 (1H, d, J = 15.5 Hz, C7-H), 7.75 (1H, d, J = 15.5 Hz, C6-H), 7.67-7.61 (2H, m, 2 × C9-H), 7.44-7.37 (2H, m, 2 × C10-H), 7.37-7.32 (1H, m, C11-H), 7.30 (1H, d, J = 4.5 Hz, C4-H), 3.98 (3H, s, C13-H); ¹³C NMR (CDCl₃, 100 MHz): δ 166.1 (C12), 155.0 (C1), 147.9 (C5), 142.1 (C3), 137.1 (C7), 136.3 (C8), 129.0 (C11), 128.8 (C10), 127.6 (C9), 124.5 (C6), 121.6 (C4), 117.6 (C2), 53.0 (C13); HRMS: (ESI⁺) Calculated for C₁₅H₁₃BrN₂O₂: 318.0124. Found [M+H]⁺: 318.0125. The regiochemistry of compound 2p was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 15.5 Hz].

(E)-2-Styrylnicotinonitrile (2q) and iso-2q isomer

General Procedure D: TsOH·H₂O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours. Purification by FCC afforded pyridine iso-2q (6.3 mg, 21% yield) as an off-white solid. Continued elution provided regioisomer 2q (18.7 mg, 64% yield) as an off-white solid.
Data for 2q: m.p. = 99-101 °C [hexane/CH₂Cl₂]; ν_max / cm⁻¹: 3057 (m), 3024 (m), 2922 (s), 2845 (m), 2222 (s), 1632 (s), 1573 (s), 1425 (s), 1032 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.77 (1H, dd, J = 2.0, 5.0 Hz, C3-H), 8.04 (1H, d, J = 15.5 Hz, C7-H), 7.92 (1H, dd, J = 2.0, 8.0 Hz, C5-H), 7.69-7.63 (2H, m, 2 × C9-H), 7.53 (1H, d, J = 15.5 Hz, C6-H), 7.47-7.32 (3H, m, 2 × C10-H and C11-H), 7.25 (1H, dd, J = 5.0, 8.0 Hz, C4-H); ¹³C NMR (CDCl₃, 100 MHz): δ 157.4 (C1), 152.7 (C3), 140.5 (C5), 138.0 (C7), 135.6 (C8), 129.5 (C11), 128.9 (C10), 127.9 (C9), 122.6 (C6), 121.3 (C4), 116.7 (C12), 107.5 (C2); HRMS: (ESI⁺) Calculated for C₁₄H₁₂N₂: 207.0917. Found [M+H⁺]: 207.0914. The regiochemistry of compound 2q was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 15.5 Hz].

Data for iso-2q: m.p. = 102-104 °C [hexane/CH₂Cl₂]; ν_max / cm⁻¹: 3024 (m), 2921 (s), 2845 (m), 2221 (s), 1582 (s), 1475 (s), 1033 (s); ¹H NMR (CDCl₃, 500 MHz): δ 8.84 (1H, d, J = 2.0 Hz, C5-H), 7.90 (1H, dd, J = 8.0, 2.0 Hz, C3-H), 7.81 (1H, d, J = 16.0 Hz, C7-H), 7.61 (2H, dd, J = 7.5, 2.0 Hz, 2 × C9-H), 7.47-7.33 (4H, m, C2-H, 2 × C10-H and C11-H), 7.17 (1H, d, J = 16.0 Hz, C6-H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.1 (C1), 152.6 (C5), 139.8 (C3), 137.2 (C7), 135.8 (C8), 129.6 (C11), 129.1 (C10), 127.8 (C9), 126.3 (C6), 121.8 (C2), 117.3 (C12), 107.4 (C4); HRMS: (ESI⁺) Calculated for C₁₄H₁₁N₂: 207.0917. Found [M+H⁺]: 207.0912. The regiochemistry of compound iso-2q was confirmed by HMBC analysis (as indicated above) and by the multiplicity of C5-H signal in ¹H NMR (doublet, J = 2.0 Hz). The geometry of the double bond was confirmed by the coupling constants observed for C6-H and C7-H [J = 16.0 Hz].

(E)-2-(2-Bromostyryl)quinoline (3a)

General Procedure D: TsOH-H₂O was employed as the catalyst. A solution of 2-bromostyrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3a (35.2 mg, 80% yield) as an off-white solid; m.p. = 58-60 °C [hexane/CH₂Cl₂]; ¹H NMR (CDCl₃, 400 MHz): δ 8.14 (1H, d, J = 8.5 Hz) 8.10 (1H, dd, J = 1.0, 8.5 Hz), 7.99 (1H, d, J = 16.5 Hz), 7.83-7.74 (3H, m), 7.71 (1H, ddd, J = 1.5, 7.0, 8.5 Hz), 7.62 (1H, dd, J = 1.5, 8.5 Hz), 7.51 (1H, ddd, J = 1.0, 7.0, 8.0 Hz), 7.41-7.30 (2H, m), 7.17 (1H, ddd, J = 1.5, 7.0, 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 155.8, 148.3, 136.5, 136.4, 133.3, 133.0, 132.1, 129.9, 129.8, 129.4, 127.8, 127.6, 127.5, 127.3, 126.5, 124.8, 119.0. The spectroscopic proprieties were consistent with the data available in literature.⁹

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**General Procedure D:** TsOH·H₂O was employed as the catalyst. A solution of 3-chlorostyrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3b (38.3 mg, quantitative yield) as an off-white solid; m.p. = 91-93 °C [hexane/CH₂Cl₂] (Lit.9 96-99 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.12 (1H, d, J = 8.5 Hz), 8.09 (1H, dd, J = 1.0, 8.5 Hz), 7.78 (1H, dd, J = 1.0, 8.5 Hz), 7.75-7.67 (1H, m), 7.66-7.58 (3H, m), 7.54-7.46 (2H, m), 7.38 (1H, d, J = 16.5 Hz), 7.35-7.26 (2H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 155.5, 148.4, 138.6, 136.6, 134.9, 132.9, 130.4, 130.1, 129.4, 128.6, 127.6 (2 signals), 127.2, 126.5, 125.5, 119.6. The spectroscopic properties were consistent with the data available in literature.⁹

**General Procedure D:** TsOH·H₂O was employed as the catalyst. A solution of 4-fluorostyrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3c (32.6 mg, 92% yield) as an off-white solid; m.p. = 121-123 °C [hexane/CH₂Cl₂] (Lit.10 123-125 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.11 (1H, d, J = 8.5 Hz), 8.08 (1H, d, J = 8.5 Hz), 7.77 (1H, dd, J = 1.0, 8.0 Hz), 7.74-7.56 (5H, m), 7.49 (1H, ddd, J = 1.0, 7.0, 8.0 Hz), 7.31 (1H, d, J = 16.0 Hz), 7.15-7.02 (2H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 163.0 (d, ¹JC-F = 248.5 Hz), 155.9, 148.4, 136.5, 133.2, 132.8 (d, ¹JC-F = 3.5 Hz), 129.9, 129.3, 128.9 (d, ¹JC-F = 8.0 Hz), 128.8 (d, ¹JC-F = 2.5 Hz), 127.6, 127.4, 126.3, 119.4, 115.9 (d, ²JC-F = 3.5 Hz). The spectroscopic properties were consistent with the data available in literature.¹⁰

**General Procedure D:** TsOH·H₂O was employed as the catalyst. A solution of 4-methoxystyrene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3d (29.1 mg, 78% yield) as an off-white solid; m.p. = 120-122 °C [hexane/CH₂Cl₂] (Lit.6 125-127 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.10-8.03
(2H, m), 7.75 (1H, dd, J = 1.5, 8.0 Hz), 7.71-7.54 (5H, m), 7.46 (1H, ddd, J = 1.0, 7.0, 8.0 Hz), 7.27 (1H, d, J = 16.5 Hz), 6.95-6.89 (2H, m), 3.83 (3H, s); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 160.2, 156.4, 148.4, 136.3, 134.2, 129.8, 129.4, 129.2, 128.7, 127.6, 127.3, 126.9, 126.0, 119.2, 114.4, 55.4. The spectroscopic properties were consistent with the data available in literature.\(^7\)

(E)-2-(2-Phenylprop-1-en-1-yl)quinoline (3e)

General Procedure D: TsOH-H\(_2\)O was employed as the catalyst. A solution of \(\alpha\)-methylstyrene (500 mol\%) in DMSO/H\(_2\)O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3e (9.5 mg, 27% yield) as off-white solid; m.p. = 96-98 °C [hexane/CH\(_2\)Cl\(_2\)]; \(\nu\)\(_{\text{max}}\) / cm\(^{-1}\): 3053 (m), 2922 (s), 2863 (m), 2845 (m), 1594 (s), 1444 (s), 1032 (s); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.17-8.08 (2H, m, C3-H and C8-H), 7.80 (1H, ddd, J = 1.5, 8.0 Hz, C5-H), 7.71 (1H, ddd, J = 1.5, 7.0, 8.0 Hz, C7-H), 7.65-7.59 (2H, m, 2 × C13-H), 7.55-7.48 (1H, m, C6-H), 7.46 (1H, d, J = 8.5 Hz, C2-H), 7.41 (2H, dd, J = 7.0, 8.0 Hz, 2 × C14-H), 7.37-7.31 (1H, m, C15-H), 7.02 (1H, s, C10-H), 2.65 (3H, s, C16-H\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 157.4 (C1), 148.0 (C9), 143.9 (C11), 143.6 (C12), 135.8 (C3), 129.5 (C7), 129.3 (C8), 128.4 (C14), 127.8 (C15), 127.4 (C5), 127.1 (C10), 126.4 (C4), 126.2 (C13), 126.1 (C6), 123.0 (C2), 18.0 (C16); HRMS: (ESI\(^+\)) Calculated for C\(_{18}\)H\(_{16}\)N: 246.1277. Found [M+H]\(^+\): 246.1273. The regiochemistry of compound 3e was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by 1D gradient nOe analysis (as shown above). Selective irradiation of signal for C16-H\(_3\) revealed a positive peak for C2-H signal.

(E)-4-(2-(Quinolin-2-yl)vinyl)thiazole (3f)

General Procedure D: TFA was employed as the catalyst. A solution of 4-vinylthiazole (500 mol\%) in NMP/H\(_2\)O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3f (19.3 mg, 57% yield) as off-white solid; m.p. = 81-82 °C [hexane/CH\(_2\)Cl\(_2\)]; \(\nu\)\(_{\text{max}}\) / cm\(^{-1}\): 3062 (m), 3045 (m), 2965 (s), 2922 (s), 2844 (m), 1595 (s), 1503 (s), 1428 (s), 1315 (s),
1033 (s); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.85 (1H, d, \(J = 2.0\) Hz, C13-H), 8.12 (1H, d, \(J = 8.5\) Hz, C3-H), 8.09 (1H, d, \(J = 8.5\) Hz, C8-H), 7.87 (1H, d, \(J = 16.0\) Hz, C11-H), 7.78 (1H, dd, \(J = 1.5, 8.0\) Hz, C5-H), 7.75-7.66 (2H, m, C7-H and C10-H), 7.57 (1H, d, \(J = 8.5\) Hz, C2-H), 7.49 (1H, dd, \(J = 7.0, 8.0\) Hz, C6-H), 7.42 (1H, d, \(J = 2.0\) Hz, C14-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 155.4 (C1), 154.5 (C12), 153.2 (C13), 148.3 (C9), 136.4 (C3), 131.2 (C10), 129.7 (C7), 129.3 (C8), 127.5 (2 signals, C4 and C5), 126.4 (C11), 126.2 (C6), 120.6 (C2), 117.1 (C14); HRMS: (ESI\(^+\)) Calculated for C\(_{14}\)H\(_{11}\)N\(_2\)S: 239.0637. Found [M+H]\(^+\): 239.0635. The regiochemistry of compound 3f was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the constant observed for C11-H \(J = 16.0\) Hz.

2-(1H-Inden-2-yl)quinoline (3g)

\[\text{HMBC analysis}\]

General Procedure D: TFA was employed as the catalyst. A solution of indene (500 mol\%) in NMP/H\(_2\)O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3g (13.6 mg, 39% yield) as off-white solid; m.p. = 133-135 °C [hexane/CH\(_2\)Cl\(_2\)]; \(\nu_{\text{max}}\) / cm\(^{-1}\): 3057 (m), 3038 (m), 2922 (s), 2844 (m), 1596 (s), 1427 (s), 1203 (s), 1149 (s); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.14-8.07 (2H, m, C3-H and C8-H), 7.83 (1H, d, \(J = 8.5\) Hz, C2-H), 7.78 (1H, dd, \(J = 1.5, 8.0\) Hz, C5-H), 7.74-7.66 (2H, m, C7-H and C11-H), 7.57 (1H, dd, \(J = 1.5, 7.0\) Hz, C16-H), 7.54-7.46 (2H, m, C6-H and C13-H), 7.36-7.25 (2H, m, C14-H and C15-H), 4.12 (2H, d, \(J = 1.5\) Hz, C18-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 154.4 (C1), 148.3 (C9), 147.7 (C10), 144.7 (C12), 144.4 (C17), 135.9 (C3), 131.8 (C11), 129.6 (C8), 129.5 (C7), 127.4 (C5), 127.2 (C4), 126.6 (C14), 126.1 (C15), 125.9 (C6), 124.0 (C16), 121.9 (C13), 118.8 (C2), 39.1 (C18); HRMS: (ESI\(^+\)) Calculated for C\(_{18}\)H\(_{14}\)N: 244.1121. Found [M+H]\(^+\): 244.1123. The regiochemistry of compound 3g was confirmed by HMBC analysis (as indicated above).

\((E)-5\text{-Phenyl}-3\text{-(2-(quinolin-2-yl)vinyl)}\text{isoazole (3h)}\)

\[\text{HMBC analysis}\]

General Procedure D: TFA was employed as the catalyst. A solution of 5-phenyl-3-vinylisoxazole (500 mol\%) in NMP/H\(_2\)O mixture was added to the reaction tube. The reaction was conducted at 120
°C for 24 hours and afforded quinoline 3h (24.4 mg, 63% yield) as a colourless solid; m.p. = 175-176 °C [hexane/CH₂Cl₂]; ν_max / cm⁻¹: 2981 (m), 2938 (s), 2922 (s), 2844 (m), 2253 (s), 1615 (s), 1574 (s), 1430 (s), 1033 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.17 (1H, d, J = 8.5 Hz, C3-H), 8.09 (1H, d, J = 8.5 Hz, C8-H), 7.85-7.77 (3H, m, C5-H and 2 × C16-H), 7.77-7.64 (3H, m, C2-H, C7-H and C11-H), 7.58-7.41 (5H, m, C6-H, C10-H, 2 × C17-H and C18-H), 6.84 (1H, s, C13-H); ¹³C NMR (CDCl₃, 100 MHz): δ 170.1 (C14), 161.9 (C12), 154.5 (C1), 148.2 (C9), 136.7 (C3), 136.3 (C10), 130.3 (C18), 130.0 (C7), 129.5 (C8), 129.0 (C17), 127.7 (C4), 127.6 (C5), 127.2 (C15), 126.9 (C6), 125.9 (C16), 121.6 (C11), 118.9 (C2), 96.7 (C13); HRMS: (ESI⁺) Calculated for C₂₉H₁₅N₂O: 299.1179. Found [M+H]⁺: 299.1184. The regiochemistry of compound 3h was confirmed by HMBC analysis (as indicated above).

(E)-2-(2-(Furan-2-yl)vinyl)quinoline (3i)

General Procedure D: TFA was employed as the catalyst. A solution of 4-vinylfuran (500 mol%) in NMP/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3i (15.9 mg, 50% yield) as a yellow oil; ¹H NMR (CDCl₃, 400 MHz): δ 8.09 (1H, d, J = 8.5 Hz), 8.06 (1H, d, J = 8.5 Hz), 7.76 (1H, dd, J = 1.5, 8.0 Hz), 7.69 (1H, ddd, J = 1.5, 7.0, 8.5 Hz), 7.61-7.44 (4H, m), 7.28 (1H, d, J = 16.0 Hz), 6.54 (1H, d, J = 3.5 Hz), 6.47 (1H, dd, J = 2.0, 3.5 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 155.5, 152.8, 148.3, 143.2, 136.3, 129.7, 129.2, 127.5, 127.3, 126.8, 126.0, 121.7, 119.9, 112.0, 111.1. The spectroscopic proprieties were consistent with the data available in literature.²

(E)-2-(2-(Thiophen-3-yl)vinyl)quinoline (3j)

General Procedure D: TsOH-H₂O was employed as the catalyst. A solution of 3-vinylthiophene (500 mol%) in DMSO/H₂O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3j (27.3 mg, 80% yield) as brown solid; m.p. = 125-127 °C [hexane/CH₂Cl₂]; ν_max / cm⁻¹: 3104 (m), 3007 (m), 2922 (s), 2865 (m), 1590 (s), 1550 (s), 1412 (s), 1116 (s), 1055 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.09 (1H, d, J = 8.5 Hz, C3-H), 8.06 (1H, d, J = 8.5 Hz, C8-H), 7.76 (1H, dd, J = 1.5, 8.0 Hz, C5-H), 7.73-7.65 (2H, m, C7-H and C11-H), 7.62 (1H, d, J = 8.5 Hz, C2-H), 7.53-7.41 (3H, m, C6-H, C14-H and C15-H), 7.35 (1H, dd, J = 3.0, 5.0 Hz, C13-H),

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7.24 (1H, d, J = 16.0 Hz, C10-H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 156.1 (C1), 148.2 (C9), 139.5 (C12), 136.3 (C3), 129.7 (C7), 129.1 (C8), 128.9 (C10), 128.4 (C11), 127.5 (C5), 127.3 (C4), 126.5 (C13), 126.1 (C6), 125.1 (C14), 124.7 (C15), 119.0 (C2); HRMS: (ESI$^+$) Calculated for C$_{13}$H$_{12}$NS: 238.0685. Found [M+H]$^+$: 238.0682. The regiochemistry of compound 3j was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C10-H [J = 16.0 Hz].

2-((1E,3E)-4-Phenylbuta-1,3-dien-1-yl)quinoline (3k)

General Procedure D: TFA was employed as the catalyst. A solution of trans-1-phenyl-1,3-butadiene (500 mol%) in NMP/H$_2$O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3k (18.7 mg, 51% yield) as an off-white solid; m.p. = 107-109 °C [hexane/CH$_2$Cl$_2$] (Lit. 8 110-112 °C [no solvent quoted]); $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.12-8.02 (2H, m), 7.76 (1H, dd, J = 1.5, 8.0 Hz), 7.69 (1H, ddd, J = 1.5, 7.0, 8.5 Hz), 7.61-7.43 (5H, m), 7.41-7.32 (2H, m), 7.32-7.24 (1H, m), 7.06 (1H, ddd, J = 1.0, 10.5, 15.5 Hz), 6.96 (1H, d, J = 15.5 Hz), 6.86 (1H, d, J = 15.5 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 156.0, 148.3, 136.9, 136.2, 136.0, 134.9, 132.8, 129.7, 129.2, 128.7, 128.6, 128.1, 127.5, 127.3, 126.8, 126.1, 119.4. The spectroscopic proprieties were consistent with the data available in literature.7

Methyl (E)-3-(quinolin-2-yl)acrylate (3l)

General Procedure D: TsOH-H$_2$O was employed as the catalyst. A solution of methyl acrylate (500 mol%) in DMSO/H$_2$O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline 3l (5.1 mg, 17% yield) as a yellow solid; m.p. = 75-76 °C [hexane/CH$_2$Cl$_2$] (Lit. 11 79-80 °C [no solvent quoted] [MeOH]); $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.19 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 16.0 Hz), 7.85-7.80 (1H, m), 7.74 (1H, ddd, J = 1.5, 7.0, 8.5 Hz), 7.62 (1H, d, J = 8.5 Hz), 7.57 (1H, ddd, J = 1.0, 7.0, 8.0 Hz), 7.01 (d, J = 16.0 Hz), 3.86 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 167.0, 153.1, 148.3, 144.3, 136.8, 130.1, 129.9, 128.1, 127.5, 127.3, 123.2, 120.4, 51.9. The spectroscopic proprieties were consistent with the data available in literature.12

8-Phenylquinoline N-oxide (4)
The title compound was prepared following a literature procedure. An oven-dried sealed tube was charged with quinoline N-oxide (145 mg, 1.00 mmol, 100 mol%), Ag₃PO₄ (dried overnight at 90 °C under high-vacuum, 209 mg, 0.50 mmol, 50 mol%) and Pd(OAc)₂ (11.2 mg, 0.05 mmol, 5 mol%). The vessel was fitted with a rubber septum and flushed with argon. Degassed glacial acetic acid (1.72 mL, 30.0 mmol, 3000 mol%) and degassed deionized water (0.720 mL, 40.0 mmol, 4000 mol%) were added to the vessel followed by iodobenzene (0.336 mL, 3.00 mmol, 300 mol%). The tube was sealed with a Young’s tap, placed into a pre-heated heating-block at 120 °C and stirred for 16 hours. The reaction was then cooled to room temperature and diluted with 5 mL of a 1:3 v/v mixture of 30% aq. NH₃ and saturated aq. NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ (5 × 5 mL). The organic portions were combined, dried over Na₂SO₄, filtered and the solvent removed in vacuo. Purification of the crude material by FCC (EtOAc → 10% MeOH/EtOAc) afforded quinoline N-oxide 4 (222 mg, quantitative yield) as a brown wax; νmax/cm⁻¹: 3054 (m), 2981 (s), 2922 (s), 2844 (m), 1569 (s), 1421 (s), 1306 (s), 1264 (s), 1033 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.35 (1H, d, J = 1.0, 6.0 Hz, C₁-H), 7.88 (1H, d, J = 1.5, 7.5 Hz, C₅-H), 7.76 (1H, dd, J = 1.0, 8.5 Hz, C₃-H), 7.61 (1H, dd, J = 7.5, 7.5 Hz, C₆-H), 7.53 (1H, dd, J = 1.5, 7.5 Hz, C₇-H), 7.42-7.25 (6H, m, C₂-H, 2 × C₁₁-H, 2 × C₁₂-H and C₁₃-H); ¹³C NMR (CDCl₃, 100 MHz): δ 142.7 (C₁₀), 139.2 (C₉), 136.9 (C₁), 136.4 (C₈), 134.2 (C₇), 132.0 (C₄), 128.4 (C₅), 128.0 (C₁₂), 127.6 (C₆), 126.9 (C₁₁), 126.2 (C₃), 125.9 (C₁₃), 121.2 (C₂); HRMS: (ESI⁺) Calculated for C₁₅H₁₂NO: 222.0913. Found [M+H]⁺: 222.0920. The regiochemistry of compound 4 was confirmed by HMBC analysis (as indicated above). The product structure was further confirmed by the presence of the characteristic C₁-H peak at 136.9 ppm in ¹³C-NMR spectrum.

(E)-2-(3-Methylstyryl)-8-phenylquinoline (5)

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with 8-Phenylquinoline N-oxide 4 (74.4 mg, 0.336 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of 3-methylstyrene (0.223 mL, 1.68 mmol, 500 mol%) and TsOH·H₂O (3.19 mg, 0.0168 mmol, 5 mol%) in 0.2 mL of a 50:1 v/v mixture of DMSO and H₂O was added via syringe and
the tube was sealed with a Young’s tap. The reaction vessel was placed into a pre-heated heating block at 140 °C and stirred for 24 hours. Purification of the residue by FCC (10% EtOAc/hexane 30% EtOAc/hexane) afforded quinoline 5 (69.8 mg, 65% yield) as a brown wax; νmax / cm⁻¹: 2981 (m), 2973 (m), 2938 (s), 2922 (s), 2865 (m), 2844 (m), 1598 (s), 1499 (s), 1379 (s), 1033 (s); ¹H NMR (CDCl₃, 400 MHz): δ 8.16 (1H, d, J = 8.5 Hz, C3-H), 7.93-7.87 (2H, m, 2 × C20-H), 7.82-7.76 (2H, m, C5-H and C7-H), 7.66 (1H, d, J = 16.0 Hz, C11-H), 7.64 (1H, d, J = 8.5 Hz, C2-H), 7.61-7.54 (3H, m, C6-H and 2 × C21-H), 7.52-7.46 (1H, m, C22-H), 7.46-7.39 (2H, m, C13-H and C17-H), 7.35 (1H, d, J = 16.0 Hz, C10-H), 7.30 (1H, dd, J = 7.5, 7.5 Hz, C16-H), 7.19-7.13 (1H, m, C15-H), 2.42 (3H, s, C18-H); ¹³C NMR (CDCl₃, 100 MHz): δ 155.5 (C1), 145.7 (C9), 140.3 (C8), 139.5 (C19), 138.3 (C14), 136.6 (C12), 136.5 (C3), 134.3 (C11), 131.2 (C20), 130.5 (C7), 129.3 (C15), 129.2 (C10), 128.6 (C16), 127.9 (C13), 127.8 (C4), 127.7 (C21), 127.2 (2 signals, C5 and C22), 125.9 (C6), 124.6 (C17), 119.5 (C2), 21.5 (C18); HRMS: (ESI⁺) Calculated for C₂₉H₂₆NO: 322.1590. Found [M+H⁺]: 322.1595. The regiochemistry of compound 5 was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C10-H and C11-H [J = 16.0 Hz].

(E)-2-(3,4-Dimethoxystyril)quinoline (7)

\[
\text{TsOH·H₂O} \quad \text{DMSO/H₂O, 140 °C, 24 h} \quad \text{N₂} \rightarrow
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An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with quinoline N-oxide (88.4 mg, 0.609 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of 3,4-dimethoxystyrene (0.298 mL, 2.03 mmol, 330 mol%) and TsOH·H₂O (8.69 mg, 0.0457 mmol, 7.5 mol%) in 0.5 mL of a 50:1 v/v mixture of DMSO and H₂O was added via syringe and the tube was sealed with a Young’s tap. The reaction vessel was placed into a pre-heated heating block at 140 °C and stirred for 24 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue by FCC (10% EtOAc/toluene 30% EtOAc/toluene) afforded quinoline 7 (160 mg, 90% yield) as an orange solid; m.p. = 101-102 °C [hexane/CH₂Cl₂] (Lit.¹⁴ 104-105 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.12 (1H, d, J = 8.5 Hz), 8.06 (1H, d, J = 8.5 Hz), 7.78 (1H, dd, J = 1.5, 8.0 Hz), 7.73-7.66 (2H, m), 7.61 (1H, d, J = 16.5 Hz), 7.49 (1H, ddd, J = 1.0, 7.0, 8.0 Hz), 7.30 (1H, d, J = 16.5 Hz), 7.24 (1H, d, J = 2.0 Hz), 7.17 (1H, dd, J = 2.0, 8.5 Hz), 6.90 (1H, d, J = 8.5 Hz), 3.96 (3H, s), 3.93 (3H, s); ¹³C NMR (CDCl₃, 100 MHz): δ 156.3, 149.8, 149.2, 148.2, 136.3, 134.2, 129.7, 129.6, 129.0, 127.5, 127.2, 127.1, 126.0, 121.3, 118.9, 111.1, 108.8, 55.9 (2 signals). The spectroscopic proprieties were consistent with the data available in literature.¹⁴

(-)-Cuspareine
The title compound was prepared following a modified literature procedure. An oven-dried autoclave, equipped with a magnetic follower, was charged with \([\text{Ir(cod)Cl}]_2\) (1.68 mg, 2.50 μmol, 1 mol%), (S)-SegPhos (3.36 mg, 5.50 μmol, 2.2 mol%) and anhydrous benzene (1 mL) under nitrogen atmosphere. The solution was stirred 10 minutes at room temperature and then a solution of iodine (6.34 mg, 0.025 mmol, 10 mol%) and (E)-2-(3,4-dimethoxystyryl)quinoline 7 (72.8 mg, 0.250 mmol, 100 mol%) in anhydrous benzene (2 mL) was added to the vessel in one portion. The reaction was let stir for further 10 minutes at room temperature. The autoclave was pressurised with H\(_2\) (750 psi) and stirred for 16 hours at room temperature. H\(_2\) was carefully released and a solution of formaldehyde (37% wt. sol. in H\(_2\)O, 0.609 mL, 7.50 mmol, 3000 mol%) in MeOH (5 mL) was added to the reaction. The autoclave was re-pressurised with H\(_2\) (750 psi) and the reaction was stirred overnight at room temperature. The solvent was then removed in vacuo. The crude material was re-suspended in water (2 mL) and washed with CH\(_2\)Cl\(_2\) (3 × 5 mL). The organic portions were collected, dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification of the residue by FCC (20% EtOAc/hexane → 30% EtOAc/hexane) afforded enanti-enriched (-)-cuspareine (61.3 mg, 79% yield, 94% e.e. as colourless oil; \([\alpha]_D^{24} = -25.6 \text{ (c 2.0, CHCl}_3\), [Lit.\(^{16}\) \([\alpha]_D^{24} = -30.2 \text{ (c 0.95, CHCl}_3\), \([\alpha]_D^{25} = -22.8 \text{ (c 1.0, CHCl}_3\), (-)-cuspareine isolated from Galipea officinalis (Hancock)].\(^{17}\) **SFC conditions:** column: CHIRALPACK IB, elute: 5% MeOH/CO\(_2\), detector: 250 nm, flow rate: 3.5 mL/min, temperature: 40 °C, retention times: (R) \(t_1 = 7.86 \text{ min}, (S) t_2 = 8.41 \text{ min}; \) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.12-7.07 \text{ (1H, m)}, 6.99 \text{ (1H, dd, } J = 1.5, 7.0 \text{ Hz)}, 6.80 \text{ (1H, d, } J = 8.0 \text{ Hz)}, 6.76-6.70 \text{ (2H, m)}, 6.61 \text{ (1H, ddd, } J = 1.0, 7.5, 7.5 \text{ Hz)}, 6.54 \text{ (1H, d, } J = 8.0 \text{ Hz)}, 3.88 \text{ (3H, s)}, 3.87 \text{ (3H, s)}, 3.30 \text{ (1H, dq, } J = 4.5, 8.5 \text{ Hz)}, 2.93 \text{ (3H, s)}, 2.86 \text{ (1H, ddd, } J = 6.0, 12.0, 17.5 \text{ Hz)}, 2.75-2.63 \text{ (2H, m)}, 2.55 \text{ (1H, ddd, } J = 6.5, 10.0, 14.0 \text{ Hz)}, 2.02-1.87 \text{ (3H, m)}, 1.75 \text{ (1H, dddd, } J = 5.5, 9.0, 10.0, 14.0 \text{ Hz}); \) \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 148.9, 147.2, 145.3, 134.6, 128.7, 127.1, 121.7, 120.0, 115.4, 111.6, 111.3, 110.6, 58.4, 55.9 \text{ (2 signals); \(38.1, 33.1, 31.9, 24.4, 23.6. \) The spectroscopic properties were consistent with the data available in literature.}\(^{16}\) 1-Phenyl-2-(quinolin-2-yl)ethan-1-ol (9)

The title compound was prepared following a literature procedure. An oven-dried two-necked flask equipped with a magnetic follower was charged with CeCl\(_3\)-7H\(_2\)O (3.73 g, 10.0 mmol, 100 mol%). The solid was heated to 140 °C under high vacuum for 3 hours. The flask was flushed with nitrogen.
and anhydrous THF was added at -78 °C. The colourless suspension was stirred at the same temperature for 1 hour. A solution of lithiated quinaldine, previously prepared by slow addition of n-BuLi (1.6M in hexanes, 6.25 mL, 10.0 mmol, 100 mol%) to a solution of quinaldine (1.35 mL, 10.0 mmol, 100 mol%) in anhydrous THF (20 mL) at -20 °C after stirring for 1 hour, was added in one portion to the mixture at -78 °C and the reaction was maintained stirred at the same temperature for 1 hour. Benzaldehyde (1.21 mL, 12.0 mmol, 120 mol%) was added dropwise to the suspension and the solution was maintained stirring at -78 °C for further 15 minutes. The reaction was quenched with water (50 mL) and Et₂O (20 mL) and 2M HCl aq. sol. was added to the mixture to adjust the pH to ≈ 8. The organic phase was separated and the aqueous phase was extracted with Et₂O (3 × 50 mL). The organic portions were collected, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by FCC (50% Et₂O/hexane → 60% Et₂O/hexane) afforded quinoline 9 (1.85 g, 74% yield) as an off-white solid; m.p. = 125-126 °C [hexane/EtOAc] (Lit. 19 124-125 °C [no solvent quoted]); ¹H NMR (CDCl₃, 400 MHz): δ 8.17-7.98 (2H, m), 7.89-7.63 (2H, m), 7.60-7.45 (3H, m), 7.45-7.11 (4H, m), 6.24 (1H, br. s), 5.43-5.27 (1H, m), 3.44-3.22 (2H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 160.5, 147.1, 144.0, 136.8, 129.8, 128.7, 128.4, 127.6, 127.3, 126.9, 126.2, 125.9, 122.1, 73.0, 46.2. The spectroscopic properties were consistent with the data available in literature. 18
Copies of 1H and 13C NMR
References