Synthesis of Substituted Imidazoles via Organocatalysis

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Supporting Information

General Methods: All reactions were performed under an atmosphere of nitrogen using dry solvents (KF < 300µg/mL). The starting α -amido sulfones were synthesized according to known procedures.¹ ¹H and ¹³C NMR data for compounds **4-8** was obtained in CD₃CN containing 1% trifluoroacetic acid (by volume) and in CDCl₃ for compounds **10-18** using a Bruker Advance 300 spectrometer with chemical shifts referenced to the internal solvent signal. Chromatographic purification of products was accomplished using forced flow chromatography on silica gel (230 mesh) according to the method of Stille.² Reactions were monitored by HPLC analysis on a HP 1100 system using a Waters Xterra RP₁₈ 5 µm 4.6mm X 250mm column and acetonitrile / 20mM KH₂PO₄ as eluents. Enantiomeric excesses for compounds **11** and **12** were determined by HPLC analysis using a Chiracel OJ-H column and heptane / isopropanol as eluents. Melting points were determined on a PerkinElmer Pyris 1 differential scanning calorimeter and are uncorrected.

General Procedure for the Synthesis of Substituted Imidazoles: A 50mL flask was charged with the α -amido sulfone (3.0 mmol, 1.0 eq) and the thiazolium catalyst (5-20 mol%)³ and purged with nitrogen for 15 min. To the flask was added solvent⁴ (20 mL) followed by the aldehyde (3.3 mmol, 1.1 eq) and the resulting mixture stirred and heated to 35 °C. Triethylamine (45 mmol, 15 eq) was added in one portion via syringe and the corresponding reaction was monitored by HPLC analysis for consumption of the amido sulfone. After the reaction was complete, the solvent was removed by simple concentration followed by the addition of EtOH (20mL), acetic acid (15 mmol, 5 equiv) and the appropriate amine (15 mmol, 5 equiv) in that order to the same reaction flask. *If the resulting amine salt precipitates from the reaction mixture, then enough ethanol was added to obtain a homogeneous reaction mixture.* The reaction was then heated to reflux and monitored by HPLC for consumption of the keto-amide. Once the reaction is complete (typical reaction times ~ 12-24 h), the corresponding substituted imidazole was isolated by either an aqueous workup followed by flash chromatography or by direct crystallization from the reaction mixture by the addition of water.

¹ Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696-9697.

² Still, W. C.; Ammon, H. L.; DeShong, P.J. *Am. Chem. Soc.* **1995**, *117*, 5166.

³ Aliphatic and electron-rich aromatic aldehydes typically require higher levels of thiazolium catalyst (15-20 mol%) due to lower reactivity.

⁴ Both CH₂Cl₂ and THF were found to be suitable solvents with the former being preferred in most cases.

4-(5-phenyl-1H-imidazole-4-yl)pyridine (4): Isolated in 76% yield by silica gel chromatography as a white crystalline solid, m.p. = 228.6 °C. ¹H NMR (300.13 MHz, 1% TFA in CD₃CN) δ 13.0 (br s, 1H), 8.57 (d, 2H, J = 7.1 Hz), 8.55 (s, 1H), 7.99 (d, 2H, J = 7.1 Hz), 7.62-7.49 (m, 5H); ¹³C NMR (75.48 MHz, 1% TFA in CD₃CN) δ 149.0, 142.3, 137.1, 134.8, 129.8, 129.7, 129.3, 128.9, 122.2.

4-phenyl-5-[(E)-2-phenylvinyl]-1H-imidazole (5): Isolated by direct crystallization from the reaction mixture in 47% yield and by flash chromatography in 68% yield as a light yellow crystalline solid, m.p. = 182.5. ¹H NMR (300.13 MHz, 1% TFA in CD₃CN) δ 12.3 (br s, 1H), 8.63 (s, 1H), 7.61-7.51 (m, 7H), 7.42-7.30 (m, 3H), 7.25 (d, 1H, J = 16.7 Hz), 7.07 (d, 1H, J = 16.7 Hz); ¹³C NMR (75.48 MHz, 1% TFA in CD₃CN) δ 135.9, 134.4, 132.7, 130.0, 129.4, 129.2, 128.8, 128.7, 128.3, 127.5, 127.3, 126.7, 112.7.

5-(4-fluorophenyl)-4-phenyl-1H-imidazole (6): Isolated by flash chromatography in 82% yield as a white crystalline solid, m.p. = 215.7 °C. ¹H NMR (300.13 MHz, 1% TFA in CD₃CN) δ 12.5 (br s, 1H), 8.65 (s, 1H), 7.50-7.38 (m, 7H), 7.22-7.13 (tt, 2H, J = 8.9 Hz, 2.2 Hz); ¹³C NMR (75.48 MHz, 1% TFA in CD₃CN) δ 166.1, 162.9, 135.1, 132.1, 132.0, 130.8, 130.4, 130.2, 129.6, 129.3, 128.7, 117.5, 117.2.

4-(2,4-diphenyl-1H-imidazole-5-yl)pyridine (7): Isolated by flash chromatography in 78% yield as an off-white crystalline solid, m.p. = 289.5 °C. ¹H NMR (300.13 MHz, 1% TFA in CD₃CN) δ 13.2 (br s, 1H), 8.51 (d, 2H, J = 7.0 Hz), 8.07 (d, 2H, J = 7.0 Hz), 8.06-8.01 (m, 2H), 7.62-7.51 (m, 8H); ¹³C NMR (75.48 MHz, 1% TFA in CD₃CN) δ 149.5, 149.1, 143.0, 138.1, 133.0, 132.0, 130.9, 130.8, 130.7, 129.2, 128.8, 128.3, 127.0, 125.1.

4-(2-cyclohexyl-4-phenyl-1H-imidazol-5-yl)pyridine (8): Isolated by direct crystallization from the reaction mixture in 55% yield and by flash chromatography in 82% yield as a white crystalline solid, m.p. = 254.5 °C. ¹H NMR (300.13 MHz, 1% TFA in CD₃CN) δ 11.1 (br s, 1H), 8.62 (d, 2H, J = 7.0 Hz), 7.95 (d, 2H, J = 7.0 Hz), 7.65-7.49 (m, 5H), 3.21-3.09 (tt, 1H, J = 12.1 Hz, 3.4 Hz), 2.15-2.06 (br d, 2H, J = 12.9 Hz), 1.94-1.84 (m, 2H), 1.80-1.60 (m, 3H), 1.52-1.24 (m, 3H); ¹³C NMR (75.48 MHz, 1% TFA in CD₃CN) δ 154.5, 145.1, 142.9, 134.1, 130.4, 129.4, 129.1, 127.1, 125.1, 123.5, 36.4, 30.6, 25.4, 25.1.

5-(4-fluorophenyl)-4-phenyl-1-(3-phenylpropyl)-1H-imidazole (9): Isolated by direct crystallization from the reaction mixture in 35% yield and by flash chromatography in 58% yield as a light yellow crystalline solid, m.p. = 118.2. ¹H NMR (300.13 MHz, CDCl₃) δ 7.62 (s, 1H), 7.48-7.42 (m, 2H), 7.31-7.10 (m, 10H), 7.06-7.01 (m, 2H), 3.80 (t, 2H, J = 7.3 Hz), 2.54 (t, 2H, 7.4 Hz), 1.91 (p, 2H, J = 7.6 Hz); ¹³C NMR (75.48 MHz, CDCl₃) δ

164.6, 161.3, 140.2, 138.5, 136.9, 134.4, 132.7, 132.6, 128.6, 128.3, 127.3, 126.8, 126.6, 126.5, 126.3, 116.5, 116.2, 44.5, 32.5, 32.0.

4-(4-fluorophenyl)-5-phenyl-1-(3-phenylpropyl)-1H-imidazole (10):

Isolated by direct crystallization from the reaction mixture in 42% yield and by flash chromatography in 61% yield as a white crystalline solid, m.p. = 116.4 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 7.59 (s, 1H), 7.48-7.40 (m, 5H), 7.34-7.15 (m, 5H), 7.07-7.01 (m, 2H), 6.89 (tt, 2H, J = 8.9 Hz, 2.1 Hz), 3.82 (t, 2H, J = 7.3 Hz), 2.53, (t, 2H, J = 7.5 Hz), 1.90 (p, 2H, J = 7.7 Hz); ¹³C NMR (75.48 MHz, CDCl₃) δ 163.3, 160.0, 140.3, 137.5, 136.8, 130.8, 130.7, 129.2, 128.8, 128.6, 128.2, 128.1, 126.3, 115.2, 114.9, 44.7, 32.5, 32.0.

4-{4-phenyl-1-[(1S)-1-phenylethyl]-1H-imidazol-5-yl}pyridine (11):

Isolated by flash chromatography in 83% yield and >98% ee as a white crystalline solid, m.p. = 157.5 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 8.59 (d, 2H, J = 6.0 Hz), 7.86 (s, 1H), 7.43 (m, 2H), 7.36-7.16 (m, 7H), 7.04 (d, 2H, J = 6.0 Hz), 6.99-6.94 (m, 2H), 5.15 (q, 1H, J = 7.1 Hz), 1.86 (d, 3H, J = 7.1 Hz); ¹³C NMR (75.48 MHz, CDCl₃) δ 150.4, 141.6, 139.7, 139.4, 135.6, 133.8, 129.0, 128.4, 128.1, 127.0, 126.0, 125.6, 55.2, 22.7. Enantiomeric excess determined by HPLC analysis using a Chiracel OJ-H column and heptane / isopropanol (85:15) as eluents (flow rate = 1.0 mL/min, 210 nm). Retention time of *R*-isomer = 6.08 min, *S*-isomer = 8.22 min).

(2S)-2-(4,5-diphenyl-1H-imidazol-1-yl)-3-phenylpropanoic acid (12):

Isolated by direct crystallization in 48% yield and by flash chromatography in 73% yield both in >98% ee as a viscous oil. ¹H NMR (300.13 MHz, CD₃OD) δ 8.21 (s, 1H), 7.38-7.02 (m, 11H), 6.93-6.90 (m, 2H), 6.75 (d, 2H, J = 7.0 Hz), 4.49 (dd, 1H, J = 11.3 Hz, 3.9 Hz), 3.47 (dd, 1H, J = 14.1 Hz, 3.9 Hz), 3.29-3.18 (m, 1H); ¹³C NMR (75.48 MHz, CD₃OD) δ 174.5, 137.7, 136.4, 135.1, 133.6, 131.0, 129.7, 129.6, 128.7, 128.6, 128.5, 128.2, 127.7, 126.5, 126.4, 126.2, 62.4, 40.0. Enantiomeric excess determined by HPLC analysis using a Chiracel AD column with isopropanol/heptane/TFA (25:75:0.1) as eluents (flow rate = 1.0 mL/min, 210 nm). Retention time of *S*-isomer at 6.2 min, *R*-isomer at 8.4 min.

3-({5-[(benzyloxy)methyl]-2-cyclohexyl-4-phenyl-1H-imidazol-1-yl}methyl)pyridine (13):

Isolated by flash chromatography in 22% yield as a white crystalline solid, m.p. = 90.4 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 8.53 (dd, 1H, J = 4.3 Hz, 2.2 Hz), 8.36 (s, 1H), 7.61 (m, 2H), 7.40-7.17 (m, 11H), 5.18 (s, 2H), 4.47 (s, 2H), 4.41 (s, 2H), 2.53 (m, 1H), 1.87-1.64 (m, 7H), 1.38-1.15 (m, 3H); ¹³C NMR (75.48 MHz, CDCl₃) δ 153.4, 149.1, 147.7, 141.1, 137.5, 134.7, 133.7, 133.0, 128.5, 128.4, 128.3, 128.0, 127.0, 123.8, 122.9, 72.3, 61.1, 44.5, 36.4, 32.1, 26.4, 25.7.

4-[4-(2-furyl)-2-phenyl-1-(3-phenylpropyl)-1H-imidazol-5-yl]pyridine (14):

Isolated by flash chromatography in 76% yield as a

light orange solid, m.p. = 114.7 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 8.70 (dd, 2H, J = 6.0 Hz, 2.8 Hz), 7.65-7.58 (m, 2H), 7.50-7.44 (m, 3H), 7.35 (dd, 2H, J = 6.0 Hz, 2.8 Hz), 7.20-7.15 (m, 3H), 6.84-6.78 (m, 2H), 6.44 (dd, 1H, J = 3.6 Hz, 0.7 Hz), 6.35 (dd, 1H, J = 3.4 Hz, 1.8 Hz), 3.95 (t, 2H, J = 7.8 Hz), 2.29 (t, 2H, J = 7.3 Hz), 1.64 (p, 2H, J = 7.5 Hz); ¹³C NMR (75.48 MHz, CDCl₃) δ 150.2, 149.6, 149.2, 141.5, 139.8, 138.7, 131.9, 130.5, 129.4, 129.2, 128.8, 128.5, 128.0, 126.2, 125.2, 111.1, 106.2, 44.5, 32.3, 31.5.

4-[1-(2,2-dimethoxyethyl)-2,4-diphenyl-1H-imidazol-5-yl]pyridine (15): Isolated by flash chromatography in 80% as a white crystalline solid, m.p. = 175.4 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 8.72 (br d, 2H, J = 5.9 Hz), 7.77-7.71 (m, 2H), 7.55-7.46 (m, 5H), 7.40 (d, 2H, J = 5.9 Hz), 7.28-7.20 (m, 3H), 4.11 (d, 2H, J = 5.5 Hz), 3.96 (t, 1H, J = 5.3 Hz), 3.05 (s, 6H); ¹³C NMR (75.48 MHz, CDCl₃) δ 150.6, 149.6, 139.7, 139.4, 133.8, 130.9, 129.5, 129.3, 128.8, 128.3, 127.5, 127.2, 127.1, 125.7, 103.0, 55.0, 46.9.

2-(2,4-diphenyl-5-pyridine-4-yl-1H-imidazol-1-yl)ethanol (16): Isolated by flash chromatography in 75% yield as a white crystalline solid, m.p. = 186.7 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 8.55 (dd, 2H, J = 6.1 Hz, 2.9 Hz), 7.62-7.57 (m, 2H), 7.48-7.39 (m, 5H), 7.33 (dd, 2H, J = 6.1 Hz, 2.9 Hz), 7.26-7.20 (m, 3H), 4.51-4.20 (br s, 1H), 4.02 (t, 2H, J = 6.0 Hz), 3.41 (t, 2H, J = 6.0 Hz); ¹³C NMR (75.48 MHz, CDCl₃) δ 150.1, 149.2, 139.9, 139.4, 133.5, 130.5, 129.4, 129.3, 128.8, 128.4, 127.6, 127.2, 126.9, 125.8, 60.8, 45.8.

4-(2-cyclohexyl-4-phenyl-1,3-oxazol-5-yl)pyridine (17): A 50mL flask was charged with the α-amido sulfone (3.0 mmol, 1.0 eq) and the thiazolium catalyst (0.15 mmol, 5 mol%) and purged with nitrogen for 15 min. To the flask was added CH₂Cl₂ (20 mL) followed by 4-pyridinecarboxaldehyde (3.3 mmol, 1.1 eq) and the resulting mixture stirred and heated to 35 °C. Triethylamine (45 mmol, 15 eq) was added in one portion via syringe and the corresponding reaction was monitored by HPLC analysis for consumption of the tosyl-amide. After the reaction was complete, it was cooled to 25 °C followed by the addition of I₂ (6.0 mmol, 2.0 equiv) and PPh₃ (6.0 mmol, 2.0 equiv).⁵ The resulting reaction was allowed to proceed overnight at ambient temperature. The reaction was quenched with aqueous Na₂S₂O₃ and the resulting organic layer dried over Na₂SO₄. The oxazole was isolated by flash chromatography in 77% yield as a white crystalline solid, m.p. = 82.7 °C. ¹H NMR (300.13 MHz, CDCl₃) δ 8.56 (dd, 2H, J = 4.5 Hz, 1.6 Hz), 7.65-7.61 (m, 2H), 7.46 (dd, 2H, J = 4.5 Hz, 1.6 Hz), 7.45-7.40 (m, 3H), 2.91 (tt, 1H, J = 11.4 Hz, 3.6 Hz), 2.21-2.12 (m, 2H), 1.95-1.83 (m, 2H), 1.80-1.62 (m, 3H), 1.50-1.26 (m, 3H); ¹³C NMR (75.48 MHz, CDCl₃) δ 168.3, 150.2, 142.0, 138.9, 136.4, 132.1, 128.9, 128.8, 128.4, 119.4, 37.7, 30.7, 25.8, 25.7.

⁵ Wipf, P.; Miller, C. P. *J. Org. Chem.* 1993, 58, 3604-3606.

4-(2-cyclohexyl-4-phenyl-1,3-thiazol-5-yl)pyridine (18): A 50mL flask was charged with the α -amido sulfone (3.0 mmol, 1.0 eq) and the thiazolium catalyst (0.15 mmol, 5 mol%) and purged with nitrogen for 15 min. To the flask was added CH_2Cl_2 (20 mL) followed by 4-pyridinecarboxaldehyde (3.3 mmol, 1.1 eq) and the resulting mixture stirred and heated to 35 °C. Triethylamine (45 mmol, 15 eq) was added in one portion via syringe and the corresponding reaction was monitored by HPLC analysis for consumption of the tosyl-amide. After the reaction was complete, the solvent was removed and the crude mixture dissolved in fresh toluene (20 mL). Lawesson's reagent (4.5 mmol, 1.5 equiv) was added and the resulting reaction was allowed to reflux overnight. The reaction was cooled to ambient temperature followed by an aqueous workup. The thiazole was isolated by flash chromatography in 50% yield as a white crystalline solids, m.p. = 146.8 °C. ^1H NMR (300.13 MHz, CDCl_3) δ 8.51 (dd, 2H, J = 4.6 Hz, 1.5 Hz), 7.51-7.48 (m, 2H), 7.35-7.32 (m, 3H), 7.22 (dd, 2H, J = 4.6 Hz, 1.5 Hz), 3.12-3.02 (tt, 1H, J = 11.4 Hz, 3.5 Hz), 2.28-2.18 (m, 2H), 1.93-1.72 (m, 3H), 1.68-1.27 (m, 5H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 176.6, 151.4, 150.1, 140.7, 134.6, 129.2, 128.6, 128.5, 128.4, 123.7, 43.0, 33.8, 26.1, 25.8.