Supporting Information

A Novel Multicomponent Reaction for the Combinatorial Synthesis of 2-Imidazolines

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General Information: All reactions were carried out under an inert atmosphere of dry nitrogen. Standard syringe techniques were applied for transfer of air sensitive reagents and dry solvents. Melting points were measured using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained from CHCl₃ films on NaCl tablets (unless noted otherwise), using a Matteson Instruments 6030 Galaxy Series FT-IR spectrophotometer and wavenumbers (ν) are reported in cm⁻¹. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 (400.13 MHz and 100.61 MHz respectively) or a Bruker Avance 250 (250.13 MHz and 62.90 MHz respectively) with chemical shifts (δ) reported in ppm downfield from tetramethylsilane. MS and HRMS data were measured at the Laboratory of Organic Chemistry of the Wageningen University (NL) with a Finnigan MAT95 spectrometer. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and Baker 7024-02 silica gel (40 μ , 60 Å). Thin Layer Chromatography was performed using silica plates from Merck (Kieselgel 60 F₂₅₄ on aluminium with fluorescence indicator. Compounds on TLC were visualized by UV-detection. THF and Et₂O were dried and distilled from sodium benzophenone ketyl prior to use. CH₂Cl₂ was dried and distilled from CaH₂ prior to use. Petroleum ether (PE 40-65) was distilled prior to use. Triethylamine and isopropylamine were dried and distilled from KOH pellets. Furfural, isobutyraldehyde and benzaldehyde were distilled and stored over MS 4Å under a dry nitrogen atmosphere. Propionic acid was purified by drying with Na₂SO₄ and subsequent fractional distillation. Phosphoryl chloride was distilled from P₂O₅ and stored under a dry nitrogen atmosphere. Acetic formic anhydride was prepared by stirring 1 equiv. of acetic anhydride and 1.2 equiv. of formic acid for 2 h at 55°C used as such. Other commercially available reagents were used as purchased.

2-Imidazoline 9. Na₂SO₄ (2 g) and benzaldehyde **8** (0.51 mL, 5.0 mmol) were added to a stirring solution of benzylamine **7** (0.55 mL, 5.0 mmol) in 15 mL MeOH at rt,. After 2 h, methyl isocyanoacetate **6** (495 mg, 5.0 mmol) was added and stirring was continued for 18 h. The reaction mixture was filtered and concentrated *in vacuo*. Purification by column chromatography (PE:EtOAc:Et₃N = 2:1:0.01, gradient) afforded **9** as a single diastereomer (498 mg, 34%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.30-7.14 (m, 8H), 7.08-6.97 (m, 3H), 4.60 (d, J = 9.4 Hz, 1H), 4.50 (dd,

$J = 9.4, 1.8 \text{ Hz, 1H}$), $4.29 \text{ (d, } J = 14.9 \text{ Hz, 1H)}$, $3.84 \text{ (d, } J = 14.9 \text{ Hz, 1H)}$, 3.63 (s, 3H) ; ^{13}C NMR (101 MHz): δ (ppm) 172.5, 157.2, 140.0, 136.0, 129.4 (2C), 129.2 (2C), 128.7, 128.4 (2C), 128.3, 127.7 (2C), 78.4, 66.0, 52.8, 43.4; IR: 1740 (s), 1597 (s), 1221 (s).

Bisamide 13. Na_2SO_4 (1 g) and isobutyraldehyde **11** (144 mg, 2.0 mmol) were added to a stirred solution of isopropylamine **10** (118 mg, 2.0 mmol) in 3 mL CH_2Cl_2 at rt.. After stirring for 2 h, propionic acid **12** (148 mg, 2.0 mmol) was added. Stirring was continued for 0.5 h and methyl isocyanoacetate **6** (120 mg, 1.3 mmol) was added to the reaction mixture. After 18 h, the reaction mixture was poured into 4 mL water. The layers were separated and the aqueous layer extracted with 3 mL CH_2Cl_2 . The combined organic layers were washed with water (3 mL), brine (3 mL), dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (PE:EtOAc = 2:1) afforded the bisamide **13** (384 mg, 81%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.74 (br s, 1H), 4.09 (m, 1H), 4.04 (dd, $J = 17.8, 6.4 \text{ Hz, 1H}$), 3.87 (dd, $J = 17.8, 5.5 \text{ Hz, 1H}$), 3.70 (s, 3H), 3.20 (m, 1H), 3.02 (m, 1H), 2.44 (m, 2H), 1.23 (d, $J = 6.8 \text{ Hz, 3H}$), 1.20 (d, $J = 6.5 \text{ Hz, 3H}$), 1.17 (t, $J = 7.5 \text{ Hz, 3H}$), 0.99 (d, $J = 6.6 \text{ Hz, 3H}$), 0.81 (d, $J = 6.5 \text{ Hz, 3H}$); ^{13}C NMR (101 MHz): δ (ppm) 175.4, 173.9, 170.2, 68.0, 52.3, 50.0, 40.8, 28.3, 26.8, 21.1, 20.7, 20.3, 19.8, 9.7; IR: 3294 (s/br) 2972 (s), 1755 (s), 1672 (s), 1626 (s), 1537 (s), 1441 (s).

Formylamino-phenyl-acetic acid methyl ester 15. Acetic formic anhydride (25 mL) was added dropwise to a stirred solution of *D*-phenylglycine methyl ester **14** (11.33 g, 68.7 mmol) in 150 mL dry CH_2Cl_2 at 0°C . Stirring was continued for 1 h at rt. Evaporation of the solvent and acids at reduced pressure yielded the *N*-formamide **15** (12.1 g, 91%) as a yellow oil. ^1H NMR (250 MHz, CDCl_3): δ (ppm) 8.27 (br s, 1H), 7.43-7.32 (m, 5H), 6.67 (br s, 1H), 5.70 (d, $J = 12.4 \text{ Hz, 1H}$), 3.76 (s, 3H). $[\alpha]_{\text{D}}^{23} -237^\circ$ (c 1.00, CH_2Cl_2).

Isocyano-phenyl-acetic acid methyl ester 16. Et_3N was added (28.3 mL, 187.5 mmol) to a stirred solution of **15** (7.23 g, 37.5 mmol) in 100 mL dry THF at -78°C . After this POCl_3 (4.7 mL, 45 mmol) in 30 mL dry THF was added dropwise and the reaction mixture was allowed to warm to 0°C . After stirring for another 1 h, ice cold water

(100 mL) was added. The mixture was extracted with Et₂O (3 × 80 mL). The combined organic layers were extracted with brine (40 mL), dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (PE:EtOAc = 2:1, gradient). afforded **16** (4.0 g, 61%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.43-7.29 (m, 5H), 5.21 (s, 1H), 3.70 (s, 3H); ¹³C NMR (101 MHz): δ (ppm) 166.5, 161.9, 132.2, 130.0, 129.6, 127.1, 60.6 (broad signal), 54.1; IR: 2151 (s), 1757 (s).

9-formylamino-9H-fluorene 28 To a stirred solution of 9-amino-9H-fluorene **27** (3.33 g, 18.4 mmol) in 50 mL CH₂Cl₂ at 0°C, acetic formic anhydride (5 mL) was added dropwise. Stirring was continued for 1 h at rt. Evaporation of the solvent and acids at reduced pressure yielded the *N*-formamide **28** (3.77 g, 98%) as a white solid. ¹H NMR (250 MHz, CDCl₃): δ (ppm) 8.51 (s, 1H), 7.78-7.23 (m, 8H), 6.39 (d, *J* = 12.2 Hz, 1H), 5.75 (br s, 1H).

9-isocyano-9H-fluorene 29 To a stirred solution of **28** (3.94 g, 18.9 mmol) in 20 mL dry THF at -78°C, Et₃N was added (13.2 mL, 94.5 mmol). Then, POCl₃ (2.1 mL, 22.7 mmol) in 20 mL dry THF was added dropwise. The reaction mixture was allowed to warm to 0°C and stirred for 1 h. 40 mL ice cold water was added. The mixture was extracted with Et₂O (3 × 30 mL). The combined organic layers were extracted with brine (20 mL), dried with Na₂SO₄ and concentrated *in vacuo* to afford **29** (4.0 g, 61%) as dark red solid. Mp 87.1-91.4 °C; ¹H NMR (250 MHz, CDCl₃): δ (ppm) 7.76-7.69 (m, 4H), 7.55-7.38 (m, 4H), 5.66 (s, 1H); ¹³C NMR (63 MHz): δ (ppm) 140.1, 139.5, 129.8, 128.3, 124.8, 120.3, 56.7 (t, *J*_{C,N} = 6.8 Hz), The isocyanide carbon could not be observed; IR (KBr): 2141 (s), 1715 (m), 1451 (s).

General Procedure I for the Synthesis of 2-Imidazolines: All reactions were carried out at a concentration of 1 M of amine, 1 M of aldehyde and 0.5 M of isocyanide in dry CH₂Cl₂. Na₂SO₄ and the aldehyde were added, at rt, to a stirred solution of the amine. After stirring for 2 h, the isocyanide (1 equiv.) was added and the reaction mixture was stirred at for an additional 18 h. The reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (PE:EtOAc:Et₃N = 2:1:0.01, gradient, unless stated otherwise).

2-Imidazoline 17. According to General Procedure I, reaction between isopropylamine **10** (236 mg, 4.0 mmol), isobutyraldehyde **11** (288 mg, 4.0 mmol) and isocyanoacetate **16** (330 mg, 1.84 mmol), followed by column chromatography, afforded **17** (389 mg, 74%) as a 75:25 mixture of diastereomers as a yellow solid. ^1H NMR (250 MHz, CDCl_3): δ (ppm) 7.66 (d, $J = 7.2$ Hz, 2H) 7.45-7.17 (m, 6H + 4H), 4.46 (d, $J = 1.6$ Hz, 1H), 3.77 (d, $J = 2.2$ Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.49 (m, 1H), 3.31 (m, 1H), 2.54 (m, 1H), 1.61 (m, 1H), 1.40 (d, $J = 6.8$ Hz, 3H), 1.36 (d, $J = 6.9$ Hz, 3H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.09 (d, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 7.3$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.4$ Hz, 3H), 0.41 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 174.8, 172.9, 153.2, 153.1, 145.2, 137.6, 127.9, 127.8, 127.6, 127.3, 127.2, 126.3, 83.6, 80.9, 74.2, 67.7, 52.7, 52.4, 48.7, 48.2, 29.6, 28.9, 22.5, 22.4, 22.3, 21.9, 21.5, 21.4, 16.1, 15.4; IR: 2967 (s), 1722 (s), 1589 (s), 1576 (s), 1464 (s), 1447 (s), 1215 (s). Slow crystallisation from Et_2O afforded the pure diastereomer **17a** as white crystals. Mp 124.9-125.2 $^\circ\text{C}$; ^1H NMR (250 MHz, CDCl_3): δ (ppm) 7.47-7.25 (m, 5H), 7.18 (s, 1H), 4.46 (d, $J = 1.6$ Hz, 1H), 3.67 (s, 3H), 3.49 (m, 1H), 1.61 (m, 1H), 1.40 (d, $J = 6.8$ Hz, 3H), 1.21 (d, $J = 6.4$ Hz, 3H), 0.96 (d, $J = 7.3$ Hz, 3H), 0.41 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 175.2, 153.6, 138.0, 128.2, 128.0, 127.7, 84.0, 68.1, 55.5, 53.2, 48.6, 29.3, 22.9, 22.8, 21.9, 15.8; IR (KBr): 2969 (s), 1713 (s), 1587 (s), 1574 (s), 1129 (s), 1215 (s), 1198 (s); MS (EI, 70 eV): m/z (%) = 288 (0.5) $[\text{M}]^+$, 229 (100) $[\text{M}-\text{CO}_2\text{Me}]^+$, 187 (45), 145 (31); HRMS (EI, 70 eV) calculated for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$ (M^+) 288.1838, found 288.1835.

Crystallographic Data for 17a: $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$, fw = 288.38, Temp = 150(2) K; orthorhombic, Pbc_a (no. 61), a = 16.8620(2), b = 11.0458(1), c = 16.9723(2) Å, V = 3161.16(6) Å³, $D_x = 1.212$ g/cm³, 39712 measured refl., 3612 unique reflections (Nonius KappaCCD diffractometer, $\lambda = 0.71073$ Å). R1/wR2 [$I > 2 \sigma(I)$] = 0.0386/0.0986; R1/wR2 [all refl.] = 0.0537/0.1070; GoF = 1.085. Residual electron density between -0.19 and 0.25 e/Å³.

2-Imidazoline 18. According to General Procedure I, reaction between benzhydrylamine (733 mg, 4.0 mmol), isobutyraldehyde **11** (288 mg, 4.0 mmol) and isocyanoacetate **16** (330 mg, 1.84 mmol), followed by column chromatography (PE:EtOAc:Et₃N = 10:1:0.01, gradient), afforded **18** (99 mg, 13%) as a

66:34 mixture of diastereomers as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.47 (m, 2H), 7.35-6.95 (m, 15H + 11 H), 6.88 (s, 1H), 6.79 (s, 1H), 6.72 (m, 2H), 5.57 (s, 1H), 5.55 (s, 1H), 4.34 (d, $J = 1.5$ Hz, 1H), 3.78 (d, $J = 1.8$ Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 2.49 (m, 1H), 1.68 (m, 1H), 1.08 (d, $J = 7.2$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 4.5$ Hz, 3H), 0.48 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 175.1, 173.1, 155.6, 154.9, 145.4, 139.9, 139.5, 139.5, 139.1, 137.7, 129.3, 129.3, 129.2, 129.0, 128.9, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 126.9, 85.1, 82.8, 74.3, 68.8, 65.7, 65.7, 53.2, 52.9, 30.2, 29.2, 23.1, 22.9, 21.4, 21.3, 16.9, 16.2; IR: 2961 (m), 1726 (s), 1595 (s), 1221 (s).

2-Imidazoline 19. According to General Procedure I, reaction between *para*-methoxybenzylamine (274 mg, 2.0 mmol), isobutyraldehyde **11** (144 mg, 2.0 mmol) and isocyanoacetate **16** (191 mg, 1.1 mmol), followed by column chromatography, afforded **19** (292 mg, 73%) as a 76:24 mixture of diastereomers as an orange oil. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.45 (d, $J = 6.9$ Hz, 2H), 7.35 (d, $J = 7.2$ Hz, 2H), 7.25-7.12 (m, 3H + 3H), 7.09 (d, $J = 8.6$ Hz, 2H), 7.02 (s, 1H), 7.01 (s, 1H), 6.81 (d, $J = 8.6$ Hz, 2H), 6.72 (d, $J = 8.6$ Hz, 2H), 6.53 (d, $J = 8.6$ Hz, 2H), 4.45 (d, $J = 14.9$ Hz, 1H), 4.38 (d, $J = 15.0$ Hz, 1H), 4.26 (d, $J = 1.4$ Hz, 1H), 4.14 (d, $J = 14.9$ Hz, 1H), 4.02 (d, $J = 15.0$ Hz, 1H), 3.69 (s, 3H), 3.64 (d, $J = 2.0$ Hz, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.53 (s, 3H), 2.43 (m, 1H), 1.55 (m, 1H), 1.00 (d, $J = 7.3$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 7.4$ Hz, 3H), 0.38 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 174.2, 172.3, 158.8, 158.6, 156.3, 156.0, 144.5, 137.1, 128.6, 128.3, 128.0, 127.8, 127.5, 127.4, 127.2, 127.0, 126.9, 126.0, 113.7, 113.5, 83.7, 82.0, 72.3, 67.5, 54.8, 54.7, 52.4, 52.0, 50.5, 50.4, 29.3, 28.4, 22.3, 22.1, 16.0, 15.3; IR: 1726 (s), 1678 (m), 1599 (s), 1512 (s), 1462 (m), 1446 (m), 1246 (s), 1177 (s).

2-Imidazoline 20. According to General Procedure I, reaction between aniline (186 mg, 2.0 mmol), isobutyraldehyde **11** (144 mg, 2.0 mmol) and isocyanoacetate **16** (98 mg, 0.56 mmol), followed by column chromatography, afforded *anti*-**20** (70 mg, 39%) and *syn*-**20** (25 mg, 14%) as yellow oils. *anti*-**20**: ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.49 (d, $J = 7.4$ Hz, 2H), 7.49 (s, 1H), 7.30-7.19 (m, 5H), 7.15 (d, $J = 7.9$ Hz, 2H), 7.00 (t, $J = 7.0$ Hz, 1H), 5.30 (d, $J = 1.6$ Hz, 1H), 3.57 (s, 3H), 1.54 (m, 1H),

0.61 (d, $J = 7.3$ Hz, 3H), 0.40 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 174.7, 152.8, 140.6, 137.2, 129.4, 128.7, 128.1, 128.0, 124.3, 120.3, 84.1, 68.5, 53.5, 30.7, 23.0, 16.0; IR: 1723 (s), 1589 (s), 1609 (s), 1495 (m), 1210 (s); **syn-20**: ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.62 (d, $J = 7.3$ Hz, 2H), 7.47 (s, 1H), 7.29-7.17 (m, 5H), 6.96-6.93 (m, 3H), 4.66 (d, $J = 2.0$ Hz, 1H), 3.69 (s, 3H), 4.56 (m, 1H), 0.86 (d, 6.8 Hz, 3H), 0.78 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 172.5, 152.0, 144.4, 140.6, 129.9, 128.7, 128.2, 126.5, 124.0, 119.8, 73.8, 53.0, 31.4, 22.5, 17.0; IR: 1728 (s), 1592 (s), 1503 (s), 1249 (m), 1209 (m).

2-Imidazoline 21. According to General Procedure I, reaction between isopropylamine **10** (236 mg, 4.0 mmol), *para*-methoxybenzaldehyde (545 mg, 4.0 mmol) and isocyanoacetate **16** (322 mg, 1.84 mmol), followed by column chromatography, afforded **21** (479 mg, 77%) as a 70:30 mixture of diastereomers as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.65 (d, $J = 7.2$ Hz, 2H), 7.33 (s, 1H), 7.32-6.81 (m, 7H + 8H), 6.48 (br s, 2H), 5.46 (s, 1H), 4.86 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.61 (s, 1H), 3.16 (s, 1H), 3.11 (m, 1H), 3.04 (m, 1H), 1.22 (d, $J = 6.9$ Hz, 3H), 1.18 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 174.8, 171.8, 160.0, 159.2, 154.3, 153.5, 144.4, 138.2, 130.1, 129.9, 129.4, 128.1, 128.8, 128.5, 127.8, 127.6, 127.2, 127.1, 114.2, 113.5, 85.1, 84.4, 73.1, 68.9, 55.6, 55.5, 53.3, 52.3, 46.5, 22.2, 22.2, 21.7; IR: 2971 (m), 1726 (s), 1595 (s), 1578 (s), 1512 (s), 1246 (s).

2-Imidazoline 22. According to General Procedure I, reaction between *para*-methoxybenzylamine (274 mg, 2.0 mmol), *para*-methoxybenzaldehyde (272 mg, 2.0 mmol) and isocyanoacetate **16** (150 mg, 0.86 mmol), followed by column chromatography, afforded **22** (333 mg, 90%) as a 55:45 mixture of diastereomers as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.54 (m, 2H), 7.27 (s, 1H), 7.24-6.62 (m, 11H + 12H), 6.48 (m, 2H), 5.20 (s, 1H), 4.65 (s, 1H), 4.21 (dd, $J = 14.1, 14.0$ Hz, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.67 (dd, $J = 14.6, 10.6$ Hz, 2H), 3.63 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (101 MHz): δ (ppm) 173.8, 171.0, 159.4, 159.0, 158.9, 158.7, 156.3, 155.4, 143.2, 138.3, 129.2, 129.1, 128.9, 128.1, 127.9, 127.6, 127.4, 127.3, 127.0, 126.7, 126.5, 126.4, 113.9, 113.8, 113.562,

113.0, 84.9, 83.9, 72.0, 68.6, 55.0, 54.8, 52.6, 51.7, 48.4, 47.9; IR 1728 (s), 1610 (s), 1512 (s), 1248 (s).

2-Imidazoline 23. According to General Procedure I, reaction between isopropylamine **10** (236 mg, 4.0 mmol), 5-methylfurfural (432 mg, 4.0 mmol) and isocyanoacetate **16** (365 mg, 2.05 mmol), followed by column chromatography afforded **23** (359 mg, 54%) as a 76:24 mixture of diastereomers as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.74 (m, 2H), 7.39-7.10 (m, 6H + 4H), 6.26 (d, *J* = 3.0 Hz, 1H), 5.97 (d, *J* = 2.9 Hz, 1H), 5.94 (d, *J* = 3.0 Hz, 1H), 5.67 (s, 1H), 5.59 (d, *J* = 2.8 Hz, 1H), 4.98 (s, 1H), 3.74 (s, 3H), 3.48 (s, 3H), 3.31 (m, 1H + 1H), 2.31 (s, 3H), 1.91 (s, 3H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (101 MHz): δ (ppm) 174.4 170.9, 153.9, 153.7, 152.8, 152.6, 149.5, 148.2, 144.0, 138.9, 128.6, 127.9, 127.6, 127.3, 127.0, 126.8, 111.3, 110.4, 107.0, 105.9, 83.9, 83.1, 67.5, 63.0, 53.4, 52.7, 47.1, 46.9, 22.3, 22.0, 21.9, 21.9, 14.0, 13.5; IR (KBr): 2967 (s), 2949 (s), 1721 (s), 1593 (s), 1576 (s), 1287 (s), 1260 (s), 1231 (s), 1211 (s).

2-Imidazoline 24. According to General Procedure I, reaction between *para*-methoxybenzylamine (274 mg, 2.0 mmol), 5-methylfurfural (220 mg, 2.0 mmol) and isocyanoacetate **16** (163 mg, 0.93 mmol), followed by column chromatography afforded **24** (343 mg, 91%) as a 70:30 mixture of diastereomers as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.50 (d, *J* = 7.4 Hz, 2H), 7.18-6.93 (m, 6H + 4H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.08 (d, *J* = 3.0 Hz, 1H), 5.81 (m, 1H), 5.77 (d, *J* = 3.0 Hz, 1H), 5.44 (m, 1H), 5.31 (s, 1H), 4.64 (s, 1H), 4.21 (d, *J* = 14.8 Hz, 1H), 4.17 (d, *J* = 14.8 Hz, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.55 (s, 3H), 3.32 (s, 3H), 2.14 (s, 3H), 1.75 (s, 3H); ¹³C NMR (101 MHz): δ (ppm) 173.5, 171.2, 159.1, 159.1, 155.8, 155.6, 152.7, 152.4, 147.8, 146.6, 142.9, 138.4, 129.1, 129.1, 128.1, 128.0, 127.7, 127.5, 127.3, 126.9, 126.7, 126.4, 126.3, 114.0, 114.0, 111.8, 110.8, 106.5, 105.4, 84.1, 83.6, 67.0, 63.3, 55.2, 55.1, 52.9, 52.3, 48.6, 48.4, 13.6, 13.1; IR: 1728 (s), 1597 (s), 1512 (s), 1248 (s), 1175 (s).

2-Imidazoline 25. According to General Procedure I, reaction between isopropylamine **10** (236 mg, 4.0 mmol), pyridine-5-carboxaldehyde (428 mg, 4.0 mmol) and isocyanoacetate **16** (357 mg, 2.04 mmol), followed by column chromatography, afforded **25** (456 mg, 71%) as a 84:16 mixture of diastereomers as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.62 (d, $J = 4.6$ Hz, 1H), 8.31 (d, $J = 4.6$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 2H), 7.68 (m, 2H), 7.40-7.18 (m, 2H + 6H), 7.02-6.74 (m, 7H), 5.83 (s, 1H), 5.17 (s, 1H), 3.73 (s, 3H), 3.27 (m, 1H), 3.20 (m, 1H), 3.17 (s, 3H), 1.30 (d, $J = 6.7$ Hz, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.5$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 173.6, 171.3, 159.0, 157.5, 154.1, 153.7, 149.2, 148.6, 143.6, 138.0, 136.4, 135.5, 130.8, 128.7, 127.4, 127.3, 126.9, 126.8, 126.6, 123.2, 122.8, 121.9, 121.9, 85.0, 84.8, 74.3, 69.3, 53.0, 51.9, 47.0, 46.9, 21.8, 21.6, 21.6, 21.6; IR: 2972 (m), 1728 (s), 1591 (s), 1578 (s), 1223 (s). Slow crystallisation from hexanes/EtOAc (10:1) afforded the pure **anti-25** as white crystals. Mp 112.9-114.5 °C; ^1H NMR (250 MHz, CDCl_3): δ (ppm) 8.40 (m, 1H), 7.45 (s, 1H), 7.37-7.29 (m, 1H), 7.13-6.85 (m, 7H), 5.92 (s, 1H), 3.82 (s, 3H), 3.37 (m, 1H), 1.39 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (63 MHz): δ (ppm) 173.8, 157.7, 154.1, 148.7, 138.2, 135.4, 127.3, 127.0, 126.6, 123.2, 121.9, 85.0, 69.4, 53.0, 47.0, 21.8, 21.7; IR (KBr): 2971 (m), 1728 (s), 1589 (s), 1225 (s).

2-Imidazoline 26. According to General Procedure I, reaction between furfurylamine (194 mg, 2.0 mmol), ethyl-*trans*-4-oxo-buten-1-yl (256 mg, 2.0 mmol) and isocyanoacetate **16** (167 mg, 0.95 mmol), followed by column chromatography, afforded **anti-26** (115 mg, 32%) and **syn-26** (56 mg, 15%) as orange oils. **anti-26**: ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.36 (m, 1H), 7.29-7.22 (m, 5H), 7.14-7.11 (m, 2H), 6.31 (d, $J = 3.1, 1.9$ Hz, 1H), 6.20 (d, $J = 3.1$ Hz, 1H), 5.97 (dd, $J = 15.7, 8.4$ Hz, 1H), 5.87 (d, $J = 15.7$ Hz, 1H), 4.78 (d, $J = 8.4$ Hz, 1H), 4.34 (d, $J = 15.9$ Hz, 1H), 4.07 (m, 2H), 4.01 (d, $J = 15.9$ Hz, 1H), 3.73 (s, 3H), 1.17 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 173.0, 165.1, 156.4, 149.0, 142.9, 142.5, 136.3, 128.3, 127.9, 126.4, 125.0, 110.4, 109.0, 84.1, 65.8, 60.3, 53.0, 42.0, 14.0; IR: 1732 (s), 1672 (m), 1601 (m), 1254 (s), 1235 (s), 1181 (s); **syn-26**: ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.48 (m, 2H), 7.34-7.24 (m, 4H), 7.24 (s, 1H), 7.02 (dd, $J = 15.6, 8.6$ Hz, 1H), 6.24 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.11 (d, $J = 3.1$ Hz, 1H), 6.02 (dd, $J = 15.6, 0.7$ Hz, 1H), 4.35 (d, $J = 15.9$ Hz,

1H), 4.24 (q, $J = 7.1$ Hz, 2H), 4.16 (d, $J = 8.6$ Hz, 1H), 4.05 (d, $J = 15.9$ Hz, 1H), 3.65 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 170.8, 165.4, 156.7, 149.0, 143.0, 142.7, 142.2, 128.4, 127.8, 126.1, 125.3, 110.3, 109.1, 84.3, 70.6, 60.7, 52.6, 42.2, 14.2; IR: 1728 (s), 1669 (s), 1599 (s), 1256 (s), 1233 (s), 1181 (s).

2-Imidazoline 30. According to General Procedure I, reaction between benzhydrylamine (732 mg, 4.0 mmol), isobutyraldehyde **11** (288 mg, 4.0 mmol) and 9-isocyano-9H-fluorene **29** (315 mg, 1.6 mmol), followed by column chromatography (PE:EtOAc:Et₃N = 10:1:0.01, gradient), afforded **30** (137 mg, 20%) as a colorless oil. ^1H NMR (250 MHz, CDCl₃): δ (ppm) 7.56-6.76 (m, 19H), 5.64 (s, 1H), 3.58 (d, $J = 7.0$ Hz, 1H), 1.95 (m, 1H), 0.73 (d, $J = 6.9$ Hz, 3H), 0.38 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (63 MHz): δ (ppm) 158.1, 150.9, 145.8, 140.7, 140.4, 140.2, 137.6, 129.1, 129.0, 128.7, 128.4, 128.3, 128.2, 128.2, 127.8, 127.7, 126.8, 126.8, 124.4, 119.7, 119.5, 83.0, 72.8, 64.9, 28.8, 19.8, 19.8; IR: 3061 (s), 3030 (s), 2963 (s), 2930 (s), 2872 (s), 1599 (s), 1493 (s), 1448 (s), 1163 (s).

2-Imidazoline 31. According to General Procedure I, reaction between isopropylamine **10** (177 mg, 3.0 mmol), isobutyraldehyde **11** (216 mg, 3.0 mmol) and 9-isocyano-9H-fluorene **29** (216 mg, 1.13 mmol), followed by column chromatography, afforded **31** (285 mg, 84%) as a colorless oil. ^1H NMR (400 MHz, CDCl₃): δ (ppm) 7.58-7.08 (m, 9H), 3.62 (d, $J = 7.3$ Hz, 1H), 3.39 (m, 1H), 1.79 (m, 1H), 1.40 (d, $J = 7.0$ Hz, 3H), 1.21 (d, $J = 6.5$ Hz, 3H), 0.67 (d, $J = 6.9$ Hz, 3H), 0.29 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 156.8, 151.1, 145.7, 140.6, 140.5, 128.5, 128.2, 128.2, 127.7, 126.8, 126.7, 124.2, 119.7, 119.6, 82.6, 72.8, 29.2, 22.2, 20.0, 19.6, 16.5; IR: 2965 (s), 2930 (s), 1674 (s), 1605 (s), 1449 (s), 1238 (s).

2-Imidazoline 32. According to General Procedure I, reaction between *para*-methoxybenzylamine (274 mg, 2.0 mmol), isobutyraldehyde **11** (144 mg, 2.0 mmol) and 9-isocyano-9H-fluorene **29** (192 mg, 1.0 mmol), followed by column chromatography, afforded **32** (348 mg, 91%) as a brown oil. ^1H NMR (250 MHz, CDCl₃): δ (ppm) 7.69-7.00 (m, 13H), 4.64 (d, $J = 14.9$ Hz, 1H), 4.26 (d, $J = 14.9$ Hz, 1H), 3.88 (s, 3H), 3.55 (d, $J = 8.2$ Hz, 1H), 2.03 (m, 1H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.29 (d, $J =$

6.7 Hz, 3H); ^{13}C NMR (63 MHz): δ (ppm) 160.9, 159.2, 150.9, 145.8, 140.5, 140.2, 129.7, 128.1, 128.0, 127.9, 127.6, 126.8, 126.3, 126.0, 124.2, 119.6, 119.4, 114.1, 83.2, 71.9, 55.2, 52.6, 29.7, 20.7, 20.0; IR: 1609 (s), 1512 (s), 1449 (m), 1218(s).

2-Imidazoline 33. According to General Procedure I, reaction between tryptamine (320 mg, 2.0 mmol), isobutyraldehyde **11** (144 mg, 2.0 mmol) and 9-isocyano-9*H*-fluorene **29** (288 mg, 1.56 mmol), followed by column chromatography, afforded **33** (428 mg, 67%) as a yellow powder. Mp 234.0-234.5 °C (decomposes); ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.50 (br s, 1H), 7.57-7.53 (m, 3H), 7.35-7.06 (m, 10H), 6.92 (d, $J = 2.0$ Hz, 1H), 3.75 (d, $J = 7.5$ Hz, 1H), 3.57 (m, 2H), 3.12 (m, 2H), 1.88 (m, 1H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.28 (d, $J = 5.8$ Hz, 3H); ^{13}C NMR (101 MHz): δ (ppm) 160.2, 152.1, 145.8, 140.6, 140.5, 136.4, 128.3, 128.2, 127.7, 127.1, 126.9, 126.5, 124.3, 122.4, 122.1, 119.8, 119.7, 119.5, 118.4, 113.8, 111.5, 83.1, 73.5, 48.4, 29.6, 23.7, 20.4, 20.1; IR (KBr): 3420 (s/br), 1588 (s), 1449 (m), 735 (s); MS (EI, 70 eV) m/z (%) = 405 (53) $[\text{M}]^+$, 362 (1), 275 (4), 263 (6), 240 (33), 215 (65), 206 (15), 144 (100), 130 (23); HRMS (EI, 70 eV) calculated for $\text{C}_{28}\text{H}_{27}\text{N}_3$ (M^+) 405.2205, found 405.2207.

2-Imidazoline 34. According to General Procedure I, reaction between isopropylamine **10** (118 mg, 2.0 mmol), *para*-methoxybenzaldehyde (272 mg, 2.0 mmol) and 9-isocyano-9*H*-fluorene **29** (192 mg, 1.0 mmol), followed by column chromatography, afforded **34** (262 mg, 70%) as a yellow oil. ^1H NMR (250 MHz, CDCl_3): δ (ppm) 7.66 (s, 1H), 7.51-7.47 (m, 2H), 7.34-7.27 (m, 3H), 7.04-6.88 (m, 3H), 6.63 (d, $J = 8.6$ Hz, 2H), 6.47 (d, $J = 8.8$ Hz, 2H), 4.95 (s, 1H), 3.56 (s, 3H), 3.28 (m, 1H), 1.46 (d, $J = 6.9$ Hz, 3H), 1.18 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (63 MHz): δ (ppm) 158.5, 156.4, 150.1, 145.1, 140.8, 139.1, 128.3, 128.0, 127.8, 127.7, 126.6, 126.0, 123.9, 119.4, 119.2, 113.1, 84.1, 72.2, 55.0, 46.5, 22.1, 20.2; IR: 1592 (s), 1512 (s), 1246 (s).

2-Imidazoline 35. According to General Procedure I, reaction between *para*-methoxybenzylamine (548 mg, 4.0 mmol), *para*-methoxybenzaldehyde (544 mg, 4.0 mmol) and 9-isocyano-9*H*-fluorene **29** (382 mg, 2.0 mmol), followed by column chromatography, afforded **35** (714 mg, 80%) as a white solid. Mp

154.6-156.7 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.69 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.36-7.33 (m, 1H), 7.30-7.28 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.16-7.10 (m, 2H), 7.02 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.5 Hz, 2H), 4.78 (s, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.04 (d, *J* = 14.4 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H); ¹³C NMR (101 MHz): δ (ppm) 159.4, 159.2, 158.7, 149.7, 145.1, 140.9, 139.8, 129.9, 128.3, 127.9, 127.9, 127.7, 127.6, 126.9, 126.7, 126.1, 124.1, 119.4, 119.3, 114.2, 113.3, 84.6, 72.0, 55.3, 55.0, 49.8; IR: 1609 (s), 1593 (s), 1512 (s), 1248 (s).

2-Imidazoline 36. According to General Procedure I, reaction between *para*-methoxybenzylamine (548 mg, 4.0 mmol), *ortho*-methoxybenzaldehyde (544 mg, 4.0 mmol) and 9-isocyano-9*H*-fluorene **29** (382 mg, 2.0 mmol), followed by column chromatography, afforded **36** (714 mg, 80%) as a yellow oil. ¹H NMR (250 MHz, CDCl₃): δ (ppm) 7.63 (s, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.51-7.41 (m, 2H), 7.32-7.23 (m, 4H), 7.13-7.06 (m, 3H), 7.00-6.93 (m, 3H), 6.89-6.82 (m, 1H), 6.76-6.69 (m, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H), 4.69 (d, *J* = 14.5 Hz, 1H), 4.13 (d, *J* = 14.5 Hz, 1H), 3.88 (s, 3H), 2.88 (br s, 3H); ¹³C NMR (101 MHz): δ (ppm) 159.4, 157.9, 157.7, 151.7, 145.8, 140.4, 139.9, 129.9, 128.0, 128.0, 127.6, 127.5, 127.4, 126.3, 126.1, 126.0, 125.8, 123.3, 119.6, 118.7, 118.6, 114.2, 109.9, 84.5, 65.4, 55.3, 54.3, 49.9; IR: 1602 (s), 1512 (s), 1489 (s), 1462 (s), 1449 (s), 1248 (s).

2-Imidazoline 37. According to General Procedure I, reaction between *para*-methoxybenzylamine (548 mg, 4.0 mmol), furfural (388 mg, 4.0 mmol) and 9-isocyano-9*H*-fluorene **29** (288 mg, 1.5 mmol), followed by column chromatography, afforded **37** (361 mg, 60%) as dark brown crystals. Mp 67.1-70.0 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.61 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.36-7.13 (m, 8H), 7.08-7.03 (m, 1H), 6.95-6.91 (m, 2H), 6.12 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.92 (d, *J* = 4.2 Hz, 1H), 4.80 (s, 1H), 4.60 (d, *J* = 14.5 Hz, 1H), 4.07 (d, *J* = 14.5 Hz, 1H), 3.83 (s, 3H); ¹³C NMR (101 MHz): δ (ppm) 159.4, 158.1, 149.8, 149.5, 144.9, 142.0, 140.1 (2C), 129.7, 128.5, 128.3, 127.9, 127.6, 127.0, 125.7, 123.5, 119.6, 119.3, 114.2, 110.1, 108.6, 83.5, 65.8, 55.3, 49.7; IR (KBr): 1609 (s), 1512 (s), 1248 (s); MS (EI, 70 eV) *m/z* (%) = 406 (28) [M]⁺, 285 (100), 165 (39), 121 (27), HRMS (EI, 70 eV) calculated for C₂₇H₂₂N₂O₂ (M⁺) 406.1681, found 406.1684.

2-Imidazoline 38. According to General Procedure I, reaction between *para*-methoxybenzylamine (548 mg, 4.0 mmol), 5-methylfurfural (440 mg, 4.0 mmol) and 9-isocyano-9*H*-fluorene **29** (288 mg, 1.5 mmol), followed by column chromatography, afforded **38** (386 mg, 61%) as a dark brown oil. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.58 (s, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.31 (m, 1H), 7.26-7.19 (m, 6H), 7.10 (m, 1H), 6.93-6.90 (m, 2H), 5.75 (d, *J* = 3.1 Hz, 1H), 5.67 (m, 1H), 4.73 (s, 1H), 4.58 (d, *J* = 14.6 Hz, 1H), 4.08 (d, *J* = 14.6 Hz, 1H), 3.83 (s, 3H), 2.08 (s, 3H); ¹³C NMR (101 MHz): δ (ppm) 159.3, 158.0, 151.7, 149.8, 147.5, 145.2, 140.2, 140.1, 129.6, 128.3, 128.1, 127.9, 127.7, 126.7, 126.0, 123.4, 119.4, 119.1, 114.1, 109.7, 105.8, 83.5, 65.9, 55.3, 49.6, 13.4; IR: 1593 (s), 1512 (s), 1248 (s).

2-Imidazoline 39. According to General Procedure I, reaction between furfurylamine (291 mg, 3.0 mmol), ethyl-*trans*-4-oxo-butenoate (384 mg, 3.0 mmol) and 9-isocyano-9*H*-fluorene **29** (384 mg, 2.0 mmol), followed by column chromatography, afforded **39** (536 mg, 67%) as a light brown oil. ¹H NMR (250 MHz, CDCl₃): δ (ppm) 7.64 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 7.0 Hz, 2H), 7.50-7.18 (m, 6H), 6.48 (dd, *J* = 15.6, 7.9 Hz, 1H), 6.43 (m, 1H), 6.32 (d, *J* = 3.1 Hz, 1H), 5.67 (d, *J* = 15.7 Hz, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 4.26 (d, *J* = 8.0 Hz, 1H), 4.16 (d, *J* = 15.8 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (63 MHz): δ (ppm) 165.1, 158.9, 149.0, 148.2, 144.1, 142.9, 142.3, 140.8, 139.8, 128.7 (2C), 127.8, 127.4, 125.6, 124.1, 124.0, 120.0, 119.6, 110.4, 109.5, 83.9, 68.8, 60.3, 42.9, 14.0; IR: 1730 (s), 1715 (s), 1697 (s), 1682 (s), 1661 (s), 1182 (m).