Intermolecular Coupling of Alkenes to Heterocycles via C-H Bond Activation

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Supporting Information

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Spectroscopic and Analytical Data

General Experimental.

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All solvents were distilled under nitrogen from the following drying agents immediately prior to use: ether and tetrahydrofuran (THF) from sodium/benzophenone ketyl, and dichloromethane (CH_2Cl_2) from calcium hydride. All reagent solutions were handled under an inert nitrogen atmosphere using syringe and cannula techniques. All reactions unless otherwise noted were carried out in flame or oven-dried glassware under an inert nitrogen atmosphere. Reaction progress was monitored with thin layer chromatography on Merck 60 F₂₅₄ 0.25 micron silica plates. Unless otherwise specified, extracts were dried over Na_2SO_4 and solvents were removed with a rotary evaporator. Flash column chromatography was carried out using Merck 60 230-400 mesh silica gel. All infrared (IR) spectra were recorded either on a Mattson Galaxy 3000 fourier transform spectrometer using thin film on NaCl plates or KBr pellets, or on a Nicolet Avatar 370 DTGS spectrometer using single bounce HATR on a ZnSe crystal. Only partial data are listed. ^1H NMR spectra were obtained on a Bruker AMX-400, AM-500 FT, or AMX-300 spectrometers. Unless otherwise noted, all NMR spectra were obtained in CDCl_3 ; chemical shifts are reported in ppm relative to internal standard CDCl_3 . Coupling constants are reported in Hz. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) and the University of California, Berkeley elemental analysis facility. Mass spectrometry was performed by the University of California, Berkeley mass spectrometry facility. For GC analysis yields were determined relative to internal standard, hexamethylbenzene, using a response

factor (RF) to normalize the values. GC analysis was performed on an Agilent Technologies 6890NGC system with an Agilent Ultra 2 column (140 °C –1 min; 80 °C/min, 220 °C-1 min; 80 °C/min, 300 °C-4 min). $t_R(\text{benzthiazole}) = 2.854 \text{ min}$, $RF = 1.91$; $t_R(\text{hexamethylbenzene}) = 3.663 \text{ min}$; $t_R(2\text{-hexylbenzthiazole}) = 4.893 \text{ min}$, $RF = 1.05$). Analytical data and synthetic protocols have been reported for the following compounds in the literature: $[\text{RhCl}(\text{coe})_2]_2$,¹ *tert*-butyldiphenylsilyl 5-hexen-1-yl ether,² 4,4,5,5-tetramethyl-2-vinyl-[1,3] dioxolane,³ PtBu_2Et ,⁴ PCy_2Me ,⁴ PCy_2Et ,⁴ PtBu_2iPr ,⁴ and PCy_2tBu .⁵ Phosphonium salts were obtained by treatment of the corresponding free base with HCl in ether using the procedure prescribed for the preparation of $\text{PCy}_3\bullet\text{HCl}$.

General procedure coupling of heterocycles to alkenes.

Method A. In air, to an oven dried vessel with a Kontes stopper, was added $[\text{RhCl}(\text{coe})_2]_2$ (5 mol % Rh) (coe = *cis*-cyclooctene), tricyclohexylphosphine (7.5 mol %), lutidinium chloride (5 mol %) , and the heterocycle. The vessel was placed under nitrogen. Under a positive pressure of nitrogen, THF (diluted to 0.1M in heterocycle) and the alkene (5 equiv) were added to the vessel. The vessel was closed with the Kontes stopper and subjected to three successive freeze pump thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO_2 and purified by flash chromatography.

Method B. In air, to an oven dried vessel with a Kontes stopper, was added $[\text{RhCl}(\text{coe})_2]_2$ (5 mol % Rh) (coe = *cis*-cyclooctene), tricyclohexylphosphine (7.5 mol %), and lutidinium chloride (5 mol %). The vessel was placed under nitrogen. Under a positive pressure of nitrogen, THF, the alkene (5 equiv), and the heterocycle (0.1M) were added to the vessel. The vessel was closed with the Kontes stopper and was

subjected to three successive freeze pump thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO₂ and purified by flash chromatography.

Method C. In air, to an oven dried vessel with a Kontes stopper, was added [RhCl(coe)₂]₂ (10 mol % Rh) (coe = *cis*-cyclooctene), tricyclohexylphosphine (15 mol %), lutidinium chloride (5 mol %) , and the heterocycle. The vessel was placed under nitrogen. Under a positive pressure of nitrogen, THF (diluted to 0.1M in heterocycle) and alkene (5 equiv) were added to the vessel. The vessel was closed with the Kontes stopper and was subjected to three successive freeze pump thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO₂ and purified by flash chromatography.

Method D. In air, to an oven dried vessel with a Kontes stopper, was added [RhCl(coe)₂]₂ (10 mol % Rh) (coe = *cis*-cyclooctene), tricyclohexylphosphine (15 mol %), and lutidinium chloride (5 mol %). The vessel was placed under nitrogen. Under a positive pressure of nitrogen, THF, the alkene (5 equiv), and the heterocycle (0.1M) were added to the vessel. The vessel was closed with the Kontes stopper and was subjected to three successive freeze pump thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO₂ and purified by flash chromatography.

Method E. In air, to an oven dried vessel with a Kontes stopper, was added [RhCl(coe)₂]₂ (5 mol % Rh) (coe = *cis*-cyclooctene), tricyclohexylphosphonium chloride (5 mol %), and the heterocycle. The vessel was placed under nitrogen. Under a positive pressure of nitrogen, THF (diluted to 0.1M in heterocycle) and the alkene (5

equiv) were added to the vessel. The vessel was closed with the Kontes stopper and was subjected to three successive freeze pump thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO₂ and purified by flash chromatography.

Method F. In air, to an oven dried vessel with a Kontes stopper, was added [RhCl(coe)₂]₂ (10 mol % Rh) (coe = *cis*-cyclooctene), tricyclohexylphosphonium chloride (10 mol %), and the heterocycle. The vessel was placed under nitrogen. Under a positive pressure of nitrogen, THF (diluted to 0.1M in heterocycle) and the alkene (5 equiv) were added to the vessel. The vessel was closed with the Kontes stopper and was subjected to three successive freeze pump thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO₂ and purified by flash chromatography.

Typical procedure for optimization screens. In a Braun glove box, a solution of benzthiazole (0.1M), [RhCl(coe)₂]₂ (5 mol % Rh dimer, 10 mol % Rh), PCy₃ (10 mol %), hexamethylbenzene (internal standard), and 1-hexene (5 equiv relative to benzthiazole) in THF was made. To glass vials (Kimble Article No. 60700-2) were distributed the additives (10 mol %) and the above solution (0.5 mL). The vessels were closed (Kontes Article No. 410119-2015 open cap with Kimble Article No. 749110-0022 valve) and were heated for 16 h at 75 °C (in a Pierce No. 18935 heating block). The crude reaction mixtures were loaded onto a silica plug, eluted with 40% EtOAc/hexanes, and analyzed by GC or ¹H NMR spectroscopy.

Tricyclohexylphosphonium Chloride.⁶ To an oven dried round bottom flask under nitrogen was added PCy₃ (273 mg, 0.975 mmol) in ether (25 mL). To this was

added 4N HCl in dioxane (0.5 mL), causing immediate precipitation of a white solid. After 20 min of stirring the solid was collected by filtration and quickly washed with ether, in order to avoid exposure to moisture. After filtration the solid was dried under high vacuum with P₂O₅ as a desiccant to afford a white solid (270 mg, 87%). ¹H NMR in CD₃OD (400 MHz): δ 2.65 (q, 3H, *J* = 12.0), 2.10-1.95 (m, 6H), 1.90-1.85 (m, 6H), 1.80-1.70 (m, 3H), 1.70-1.55 (m, 6H), 1.55-1.25 (m, 9H). ¹³C NMR in CD₃OD (100 MHz): δ 27.5 (d, *J* = 3.6), 27.4 (d, *J* = 39.9), 25.8 (d, *J* = 12.9), 24.8. ³¹P NMR in CD₃OD (162 MHz): δ 33.8 (t, *J* = 69.9). . HRMS (FAB): Calc'd for C₁₈H₃₄P (M⁺): 281.2398. Found: 281.2396. (Note: using this procedure 1-2 equiv of HCl is incorporated; however, this does not appear to affect the efficiency of the reaction.)

2-(3,3-Dimethyl-butyl)-1*H*-benzimidazole (1). Reaction of benzimidazole (154 mg, 1.31 mmol) with neo-hexene (810 μL, 6.30 mmol) according to method **A** yielded the product (254 mg, 96%) as a white solid after column chromatography (10-25% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO₂ and purified by column chromatography. M.p. = 217-218.5 °C. IR(KBr): 3057.2 (br, s), 1415.8, 1273.5, 736.7 cm⁻¹. ¹H NMR (CD₃OD, 500 MHz): δ 0.99 (s, 9H), 1.8-1.65 (m, 2H), 2.9-2.8 (m, 2H), 7.2-7.1 (m, 2H), 7.5-7.4 (m, 2H). ¹³C NMR (CD₃OD, 125 MHz): δ 156.1, 121.6, 41.9, 29.8, 28.0, 24.0 (Note: two carbons were not observed due the slow exchange of the N-H proton, which causes these signals to be broadened). Anal. Calcd for C₁₃H₁₈N₂: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.04; H, 9.06; N, 13.77. EI: Calc'd for C₁₃H₁₈N₂ (M⁺): 202. Found: 202.

2-(3,3-Dimethyl-butyl)-benzothiazole (2). Reaction of benzothiazole (145 μL , 1.28 mmol) with neo-hexene (810 μL , 6.30 mmol) according to method **B** yielded the product (272 mg, 97%) as a brown/orange solid after column chromatography (2.5% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO_2 and purified by column chromatography. IR(NaCl): 2954.7, 2905.1, 2864.9, 758.4, 728.6 cm^{-1} . ^1H NMR (500 MHz): δ 1.00 (s, 9H), 1.9-1.7 (m, 2H), 3.2-3.0 (m, 2H), 7.34 (app. triplet, 1H, J = 7.5), 7.44 (app. triplet, 1H, J = 7.5), 7.83 (d, 1H, J = 8), 7.96 (d, 1H, J = 8). ^{13}C NMR (125 MHz): δ 173.0, 153.2, 135.1, 125.8, 124.5, 122.4, 121.4, 43.7, 30.6, 30.1, 29.1. Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NS}$: C, 71.18; H, 7.81; N, 6.39. Found: C, 71.19; H, 7.89; N, 6.52.

2-(3,3-Dimethyl-butyl)-1H-benzoxazole (3). Reaction of benzoxazole (154 mg, 1.27 mmol) with neo-hexene (810 μL , 6.30 mmol) according to method **A** yielded the product (199 mg, 77%) as a white solid after column chromatography 2.5-10% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO_2 and purified by column chromatography. IR(NaCl): 3055.5, 2955.7, 2867.1, 1572.7, 1455.3, 1242.8, 744.8 cm^{-1} . ^1H NMR (500 MHz): δ 0.97 (s, 9H), 1.9-1.8 (m, 2H), 3.0-2.8 (m, 2H), 7.3-7.2 (m, 2H), 7.5-7.4 (m, 1H), 7.7-7.6 (m, 1H). ^{13}C NMR (125 MHz): δ 167.9, 150.7, 141.3, 124.3, 124.0, 119.4, 110.1, 40.5, 30.3, 29.0, 24.3. Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}$: C, 76.81; H, 8.43; N, 6.89 Found: C, 76.42; H, 8.80; N, 6.95.

2-(3,3-Dimethyl-butyl)-4, 5-dimethyl-thiazole (4). Reaction of 4, 5-dimethylthiazole (140 μL , 1.32 mmol) with neo-hexene (810 μL , 6.30 mmol) according to

method **B** yielded the product (257 mg, 99%) as a red/orange liquid after column chromatography (5% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO₂ and purified by column chromatography. IR(NaCl): 2954.0, 2866.1, 1477.8, 1365.0, 1121.5 cm⁻¹. ¹H NMR (500 MHz): δ 0.93 (s, 9H), 1.7-1.6 (m, 2H), 2.26 (s, 3H), 2.28 (s, 3H), 2.9-2.8 (m, 2H). ¹³C NMR (125 MHz): δ 167.5, 147.0, 124.7, 44.3, 30.5, 29.1, 29.0, 14.5, 11.2. Anal. Calcd for C₁₁H₁₉NS: C, 66.95; H, 9.70; N, 7.10 Found: C, 66.61; H, 9.58; N, 7.22.

8-(3,3-Dimethyl-butyl)-7H-purine (5). Reaction of purine (152 mg, 1.27 mmol) with neo-hexene (810 μL, 6.30 mmol) according to method **A** (with the exception that the reaction mixture was heated for only 4.5 h) yielded the product (197 mg, 76%) as a white solid after column chromatography (50-100% EtOAc/hexanes). M.p. = 179-180 °C. IR(KBr): 2926.5 (br, s), 1616.7, 1592.1, 920.8, 648.6, 614.1 cm⁻¹. ¹H NMR (CD₃OD, 500 MHz): δ 1.00 (s, 9H), 1.8-1.7 (m, 2H), 3.0-2.9 (m, 2H), 8.83 (s, 1H), 8.90 (s, 1H). ¹³C NMR (125 MHz): δ 151.3, 41.3, 29.9, 27.9, 24.6 (Note: two carbons were not observed due the slow exchange of the N-H proton, which causes these signals to be broadened). Anal. Calcd for C₁₁H₁₆N₄: C, 64.68; H, 7.89; N, 27.43. Found: C, 64.48; H, 7.91; N, 27.04. EI: Calc'd for C₁₁H₁₆N₄ (M⁺): 204. Found: 204.

6,8-Bis-(3, 3-Dimethyl-butyl)-7H-purine (6). Reaction of purine (152 mg, 1.27 mmol) with neo-hexene (810 μL, 6.30 mmol) according to method **A** (with the exception that the reaction mixture was only heated for 4.5 h) yielded the product (61 mg, 17%) as a white solid after column chromatography (50-100% EtOAc/hexanes). M.p. = 180-

181.7 °C. IR(KBr): 2960.2 (br, s), 1594.9, 983.4, 653.1 cm^{-1} . ^1H NMR (400 MHz): δ 1.00 (s, 9H), 1.02 (s, 9H), 1.9-1.7 (m, 4H), 3.1-3.0 (m, 2H), 3.3-3.1 (m, 2H), 8.84 (s, 1H). ^{13}C NMR (100 MHz): δ 162.5, 157.9, 152.5, 150.2, 133.3, 42.2, 41.9, 30.7, 30.6, 29.3, 29.2, 28.6, 25.9. Anal. Calcd for $\text{C}_{17}\text{H}_{28}\text{N}_4$: C, 70.79; H, 9.78; N, 19.42. Found: C, 70.88; H, 9.86; N, 19.50.

2-(3,3-Dimethyl-butyl)-1-methyl-benzimidazole (7). Reaction of 1-methylbenzimidazole (132 mg, 1.00 mmol) with neo-hexene (643 μL , 5 mmol) according to method **C** yielded the product (144 mg, 67%) as a white solid after column chromatography (10-30% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO_2 and purified by column chromatography. M.p. = 98.5-99.4 °C. IR(NaCl): 2953.9, 2864.7, 745.0 cm^{-1} . ^1H NMR (500 MHz): δ 1.02 (s, 9H), 1.79-1.75 (m, 2H), 2.85-2.82 (m, 2H), 3.71 (s, 3H), 7.30-7.20 (m, 3H), 7.72-7.70 (m, 1H). ^{13}C NMR (500 MHz): δ 155.8, 142.5, 135.8, 121.9, 121.7, 119.0, 108.7, 41.4, 30.4, 29.6, 29.1, 23.0. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.39; H, 9.54; N, 12.63.

8-(3,3-Dimethyl-butyl)-1, 3-dimethyl-3, 9-dihydro-purine-2, 6-dione (8). Reaction of theophylline (100 mg, 0.555 mmol) with neo-hexene (360 μL , 2.79 mmol) according to method **F** yielded the product (22 mg, 15%) as a white solid after column chromatography (30-50% EtOAc/hexanes). M.p. = 233.4-234.5 °C. IR (ZnSe): 3188.0, 2955.4, 1719.6, 1627.8 (s), 1497.6, 754.3, 740.2 cm^{-1} . ^1H NMR (500 MHz): δ 12.87 (br s, 1H), 3.63 (s, 3H), 3.46 (s, 3H), 2.88-2.85 (m, 2H), 1.74-1.70 (m, 2H), 0.98 (s, 9H). ^{13}C NMR (125 MHz): δ 156.9, 155.7, 151.5, 149.5, 106.4, 42.2, 30.4, 30.2, 29.0, 28.3,

24.8. Anal. Calcd for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.63; N, 21.20. Found: C, 58.84; H, 7.84; N, 20.99.

2-Hexyl-1H-benzimidazole (9). Reaction of benzimidazole (151 mg, 1.28 mmol) with 1-hexene (538 mg, 6.40 mmol) according to method **A** yielded the product (209 mg, 80%) as a white solid after column chromatography (20-50% EtOAc/hexanes). M.p. = 134.7-135.1 °C. IR(KBr): 2930.1 (br, s), 1420.7, 1027.0, 750.2 cm^{-1} . 1H NMR (CD_3OD , 500 MHz): δ 0.87 (t, 3H, J = 6.5), 1.4-1.2 (m, 6H), 1.85-1.75 (m, 2H), 2.85 (t, 2H, J = 7.5), 7.19-7.13 (m, 2H), 7.5-7.45 (m, 2H). ^{13}C NMR (CD_3OD , 125 MHz): δ 155.5, 121.6, 31.2, 28.5, 28.3, 27.9, 22.1, 12.9 (Note: two carbons were not observed due the slow exchange of the N-H proton, which causes these signals to be broadened). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.36; H, 9.03; N, 13.68. EI: Calc'd for $C_{13}H_{18}N_2$ (M^+): 202. Found: 202.

2-[6-(*tert*-Butyl-diphenyl-silanyloxy)-hexyl]-1H-benzimidazole (10). Reaction of benzimidazole (70 mg, 0.591 mmol) with *tert*-butyl-hex-5-enyloxy-diphenyl-silane (1 g, 2.95 mmol) according to method **A** yielded the product (207 mg, 77%) as a white solid after column chromatography (25-50% EtOAc/hexanes). M.p. = 113.4-115 °C. IR(KBr): 2926.5 (br, s), 1426.2, 1273.8, 1109.3, 744.4, 701.0 cm^{-1} . 1H NMR (CD_3OD , 500 MHz): δ 0.99 (s, 9H), 1.36-1.30 (m, 2H), 1.44-1.38 (m, 2H), 1.56-1.51 (m, 2H), 1.82-1.77 (m, 2H), 2.84 (t, 2H, J = 7.5), 3.62 (t, 2H, J = 6.5), 7.2-7.15 (m, 2H), 7.4-7.3 (m, 6H), 7.5-7.45 (m, 2H), 7.7-7.6 (m, 4H). ^{13}C NMR (CD_3OD , 125 MHz): δ 155.4, 135.2, 133.6, 129.3, 127.3, 121.7, 63.4, 32.0, 28.5, 28.3, 27.8, 25.9, 25.1, 18.5 (Note: two carbons were not observed due the slow exchange of the N-H proton, which causes these signals to be broadened). Anal. Calcd for $C_{29}H_{36}N_2OSi$: C, 76.27; H, 7.95; N, 6.13.

Found: C, 76.16; H, 8.10; N, 6.06. FAB: Calc'd for $C_{29}H_{36}N_2OSi$ (M+1): 457. Found: 457.

4-(1*H*-Benzimidazol-2-yl)-butyric acid isobutyl ester (11). Reaction of benzimidazole (150 mg, 1.27 mmol) with isobutyl vinylacetate (903 mg, 6.35 mmol) according to method **C** (with the exception that the reaction mixture was heated for only 8 h) yielded the product (288 mg, 87%) as a white solid after column chromatography (40-75% EtOAc/hexanes). M.p. = 96.3-100 °C. IR(KBr): 2947.8 (br, s), 1732.9 (s), 749.3 cm^{-1} . 1H NMR (CD_3OD , 500 MHz): δ 0.89 (d, 6H, J = 6.5), 1.90-1.82 (m, 1H), 2.15-2.10 (m, 2H), 2.41 (t, 2H, J = 7.5), 2.93 (t, 2H, J = 7.5), 3.80 (d, 2H, J = 6.5), 7.18-7.16 (m, 2H), 7.49-7.46 (m, 2H). ^{13}C NMR (CD_3OD , 125 MHz): δ 173.2, 154.4, 138.0 (br), 121.8, 113.9 (br), 70.2, 32.8, 27.6, 27.5, 23.0, 17.9. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.14; H, 7.86; N, 10.73. EI: Calc'd for $C_{15}H_{20}N_2O_2$ (M+): 260. Found: 260.

2-Phenethyl-1*H*-benzimidazole (12). Reaction of benzimidazole (100 mg, 0.847 mmol) with styrene (491 μL , 4.24 mmol) according to method **C** yielded the product (36 mg, 19%) as a white solid after column chromatography (25-50% EtOAc/hexanes). The THF used in this reaction was dried over 4 Å molecular sieves instead of being distilled from Na^0 /benzophenone. GCMS analysis of the crude reaction mixture showed a linear:branched ratio of 25:1. M.p = 187.5-188.9 °C. IR(KBr): 2866.8 (br, s), 1420.2, 1280.1, 749.3, 696.2 cm^{-1} . 1H NMR (CD_3OD , 500 MHz): δ 3.2-3.05 (m, 4H), 7.3-7.1 (m, 7H), 7.5-7.43 (m, 2H). ^{13}C NMR (CD_3OD , 125 MHz): δ 154.5, 140.3, 128.1, 127.9, 125.9, 121.7, 34.0, 30.5 (Note: two carbons were not observed due the slow exchange

of the N-H proton, which causes these signals to be broadened). HRMS (EI): Calc'd for $C_{15}H_{14}N_2$ (M⁺): 222.1158. Found: 222.1157.

2-[2-(4,4,5,5-Tetramethyl-[1,3]dioxolan-2-yl)-ethyl]-1H-benzimidazole (13).

Reaction of benzimidazole (150 mg, 1.27 mmol) with 4, 4, 5, 5-tetramethyl-2-vinyl-[1, 3]dioxolane (992 mg, 6.35 mmol) according to method **C** yielded the product (209 mg, 60%) as a white solid after column chromatography (25-75% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO₂ and purified by column chromatography. M.p. = 202.5-204.3 °C. IR(KBr): 2976.2 (br, s), 1547.7, 1164.3, 1131.4, 758.9 cm⁻¹. ¹H NMR (DMSO-d₆, 500 MHz): δ 1.12 (s, 6H), 1.14 (s, 6H), 2.01-1.97 (m, 2H), 2.85 (t, 2H, *J* = 8), 5.04 (t, 1H, *J* = 5), 7.09-7.08 (m, 2H), 7.47-7.40 (m, 2H), 12.20-12.05 (m, 1H). ¹³C NMR (DMSO-d₆, 125 MHz): δ 154.8, 121.5 (br), 99.6, 81.8, 34.4, 24.5, 24.0, 22.3 (Note: two carbons were not observed due the slow exchange of the N-H proton, which causes these signals to be broadened). Anal. Calcd for C₁₆H₂₂N₂O₂: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.99; H, 8.33; N, 10.06. FAB: Calc'd for C₁₆H₂₂N₂O₂ (M+1): 275. Found: 275.

2-[2-(1H-Benzimidazol-2-yl)-ethyl]isoindole-1,3-dione (14). Benzimidazole (50 mg, 0.42 mmol) was treated with *N*-vinylphthalimide (367 mg, 2.12 mmol) according to method **F**. However, the work-up was modified to remove excess alkene. Upon completion of the reaction the mixture was diluted with EtOAc (40 mL). The organic layer was extracted with 1N HCl (3 x 15 mL). The aqueous layer was basified with K₂CO₃ and extracted with CH₂Cl₂ (3 x 15 mL), and the CH₂Cl₂ layers were combined, concentrated, and purified by SiO₂ column chromatography (50-75% EtOAc/hexanes).

The product was isolated as a white solid (78 mg, 63%). M.p. = 192.7-194.3 °C. IR (ZnSe): 3322.1 (br), 2946.1, 1769.6, 1705.6 (s), 1396.2, 714.3 cm^{-1} . ^1H NMR (500 MHz, CD_3OD) δ 7.73-7.68 (m, 4H), 7.43-7.41 (m, 2H), 7.14-7.12 (m, 2H), 4.08 (t, 2H, J = 6.9), 3.21 (t, 2H, J = 6.9). ^{13}C NMR (125 MHz, CD_3OD): δ 169.3, 153.2, 139.6 (br), 135.2, 133.2, 124.1, 123.3, 115.5 (br), 37.5, 29.0. HRMS (FAB): Calc'd for $\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}_2$ ($M+1$): 292.1086. Found: 292.1085.

3-(4,5-Dimethyl-thiazol-2-yl)-propionic acid *tert*-butyl ester (15). Reaction of 4, 5-dimethylthiazole (97% pure, 135 μL , 1.24 mmol) with *tert*-butyl acrylate (930 μL , 6.35 mmol) according to method **D** yielded the product (278 mg, 93%) as a red-orange liquid after column chromatography (5-10% EtOAc/hexanes). Before chromatography triethylamine was added to neutralize the lutidinium chloride. The crude solution was dry loaded on to SiO_2 and purified by column chromatography. IR(NaCl): 2978.9, 2924.5, 1729.1, 1366.88, 1154.65 cm^{-1} . ^1H NMR (500 MHz): δ 1.42 (s, 9H), 2.25 (s, 3H), 2.29 (s, 3H), 2.66 (t, 2H, J = 7.5), 3.14 (t, 2H, J = 7.5). ^{13}C NMR (125 MHz): δ 171.4, 164.3, 147.3, 125.2, 80.6, 35.1, 28.5, 28.0, 14.5, 11.2. Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2\text{S}$: C, 59.72; H, 7.93; N, 5.80. Found: C, 59.75; H, 7.79; N, 6.00.

3-(4,5-Dimethyl-thiazol-2-yl)-propionitrile (16). Reaction of 4, 5-dimethylthiazole (97% pure, 135 μL , 1.24 mmol) with acrylonitrile (418 μL , 6.35 mmol) according to method **D** yielded the product (134 mg, 65% linear product) as a yellow liquid after column chromatography (10-30% EtOAc/hexanes). GCMS analysis of the crude reaction mixture showed a linear:branched ratio of 4.3:1. IR(NaCl): 2922.8, 2864.8, 2249.3, 1439.7, 1134.8 cm^{-1} . ^1H NMR (400 MHz): δ 2.27 (s, 3H), 2.30 (s, 3H),

2.80 (t, 2H, $J = 7.6$), 3.19 (t, 2H, $J = 7.6$). ^{13}C NMR (100 MHz): δ 160.6, 148.2, 126.5, 118.6, 28.9, 17.3, 14.6, 11.2. Anal. Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{S}$: C, 57.80; H, 6.06; N, 16.85. Found: C, 57.81; H, 6.05; N, 17.04.

2-(3,3-Dimethyl-butyl)-6-methoxy-1*H*-benzimidazole (17). Reaction of 5-methoxybenzimidazole (100 mg, 0.675 mmol) with neo-hexene (283 μL , 2.20 mmol) according to method E yielded the product (148 mg, 94%) as a yellow solid after column chromatography (25-50% EtOAc/hexanes). M.p. = 94.6-96 °C IR(ZnSe): 3300-2600 (br), 1156.6 cm^{-1} . ^1H NMR (500 MHz): δ 9.30 (s, br, 1H), 7.41 (d, 1H, $J = 8.7$), 7.01 (d, 1H, $J = 2.2$), 6.83 (dd, 1H, $J = 2.3, 8.7$), 3.79 (s, 3H), 2.88-2.85 (m, 2H), 1.77-1.73 (m, 2H), 0.84 (s, 9H). ^{13}C NMR (125 MHz): δ 156.0, 155.8, 138.7 (br), 133.4 (br), 115.2 (br), 111.2, 97.5 (br), 55.8, 42.2, 30.3, 29.0, 24.8. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.09; H, 8.96; N, 11.76.

2-(3,3-Dimethyl-butyl)-3*H*-benzimidazole-5-carboxylic acid (18). Reaction of 5-benzimidazole carboxylic acid (100 mg, 0.617 mmol) with neo-hexene (397 μL , 3.08 mmol) according to method E yielded the product (101 mg, 66%) as a pale yellow solid after column chromatography (5-10% MeOH/ CH_2Cl_2). IR(ZnSe): 3300-2600 (br), 1683.1 (w), 1365.7, 776.5 cm^{-1} . ^1H NMR (500 MHz, CD_3OD): δ 8.19 (s, 1H), 7.90 (d, 1H, $J = 8.4$), 7.48 (d, 1H, $J = 8.4$), 2.87-2.84 (m, 2H), 1.72-1.69 (m, 2H), 0.95 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ 171.2, 160.2, 142.5, 139.2, 126.8, 125.3, 118.0, 114.8, 43.3, 31.4, 29.6, 25.7. HRMS (FAB): Calc'd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$ ($M+1$): 247.1449. Found: 247.1447.

2-(3,3-Dimethyl-butyl)-3*H*-benzimidazole-5-carboxylic acid methyl ester (19).

Reaction of 5-benzimidazole carboxylic acid methyl ester (100 mg, 0.568 mmol) with neo-hexene (365 μ L, 2.84 mmol) according to method E yielded the product (132 mg, 89%) as a yellow oil after column chromatography (EtOAc/hexanes). IR(ZnSe): 3300-2600 (br), 1715.8 (s), 1285.4, 771.9 cm^{-1} . ^1H NMR (500 MHz): δ 10.0-9.0 (br, s, 1H), 8.30 (s, 1H), 7.93 (d, 1H, $J = 8.5$), 7.54 (d, 1H, $J = 8.5$), 3.89 (s, 3H), 2.96-2.92 (m, 2H), 1.79-1.75 (m, 2H), 0.79 (s, 9H). ^{13}C NMR (125 MHz): δ 167.9, 159.0 (br), 141.9 (br), 138.1 (br), 123.9, 123.8, 116.8 (br), 114.1 (br), 52.1, 42.2, 30.3, 28.8, 24.9. HRMS (FAB): Calc'd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$ ($M+1$): 261.1603. Found: 261.1603.

6-Chloro-2-(3,3-dimethyl-butyl)-1*H*-benzimidazole (20). Reaction of 5-chlorobenzimidazole (100 mg, 0.655 mmol) with neo-hexene (421 μ L, 3.28 mmol) according to method E yielded the product (143 mg, 93%) as a yellow solid after column chromatography (25 % EtOAc/hexanes). M.p. = 159-163 $^{\circ}\text{C}$. IR (ZnSe): 3300-2600 (br), 1410.7, 801.3 cm^{-1} . ^1H NMR (500 MHz): δ 13.0-12.5 (br s, 1H), 7.55 (s, 1H), 7.46 (d, 1H, $J = 8.5$), 7.20 (d, 1H, $J = 8.5$), 2.97-2.94 (m, 2H), 1.81-1.78 (m, 2H), 0.82 (s, 9H). ^{13}C NMR (125 MHz): 157.8, 139.3, 137.0, 127.7, 122.6, 115.1, 114.5, 42.5, 30.3, 28.9, 24.9. Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{ClN}_2$: C, 65.95; H, 7.24; N, 11.83. Found: C, 65.75; H, 7.31; N, 11.88.

2-(3,3-Dimethyl-butyl)-6-trifluoromethyl-1*H*-benzimidazole (21). Reaction of 5-trifluoromethylbenzimidazole (100 mg, 0.543 mmol) with neo-hexene (350 μ L, 2.72 mmol) according to method E yielded the product (139 mg, 95%) as a yellow solid after column chromatography (25 % EtOAc/hexanes). M.p. = 174-179 $^{\circ}\text{C}$. IR (ATIR): 3300-

2600, 2924.5, 1327.6, 1112.6, 812.9 cm^{-1} . ^1H NMR (500 MHz, CD_3OD): δ 7.77 (s, 1H), 7.58 (d, 1H J = 8.4), 7.42 (d, 1H, J = 7.5), 2.88-2.85 (m, 2H), 1.73-1.70 (m, 2H), 0.96 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ 160.4, 141.2 (br), 139.7 (br), 126.4 (q, J = 271), 125.3 (q, J = 32), 119 (q, J = 3.6), 115.4 (br), 113.3 (br), 43.2, 31.2, 29.4, 25.6. ^{19}F NMR (376 MHz): δ -61.2. Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{F}_3$: C, 62.21; H, 6.34; N, 10.36. Found: C, 62.17; H, 6.48; N, 9.97.

2-Hexylbenzthiazole (22).⁷ Reaction of benzthiazole (55 mg, 0.407 mmol) with 1-hexene (231 μL , 1.85 mmol) according to method E yielded the product (46 mg, 52%) as a red oil after column chromatography (2.5 % EtOAc/hexanes). IR(ZnSe): 2926.5, 2856.1, 1520.0, 757.2, 727.7 cm^{-1} . ^1H NMR (500 MHz): δ 7.96 (d, 1H, J = 8.1), 7.82 (d, 1H, J = 7.9), 7.43 (t, 1H, J = 7.4), 7.32 (t, 1H, J = 7.5), 3.10 (t, 2H, J = 7.7), 1.88-1.83 (m, 2H), 1.45-1.43 (m, 2H), 1.33-1.25 (m, 4H), 0.90-0.87 (m, 3H). ^{13}C NMR (125 MHz): δ 172.4, 153.2, 135.1, 125.8, 124.5, 122.4, 121.4, 34.3, 31.4, 29.7, 28.8, 22.5, 14.0.

Selected Spectra

^1H NMR of **12**

¹HNMR of **14**

¹H NMR of HCIPCy₃

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