Synthesis of medium ring heterocycles using an intramolecular Heck reaction

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Supporting information

1. Materials described in Scheme 1.

Scheme A. Synthesis of ethyl 2-[2-(bromomethyl)phenyl]acrylate **11**.

(S1) Ethyl (2-methylphenyl)acetate: To a solution of *o*-tolylacetic acid (60 mmol, 9 g) in ethanol (30 ml) is added conc. H₂SO₄ (2 ml) and molecular sieves 4 Å (5 g). The reaction mixture was refluxed for 3 hours and poured into NH₄Cl (aq), diluted with ethylacetate (30 ml) and the organic layer was separated. The aqueous layer was extracted two times with EtOAc (20 ml) and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product **S1** 9.85 g (92%) is a colorless liquid. Bp.: 110°C/15 mm; ¹H-NMR (400 MHz) δ = 7.16 (m, 4H), 4.13 (q, *J* =

6.0 Hz, 2H), 3.61 (s, 3H), 2.30 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C -NMR (100 MHz) $\delta = 171.4, 136.7, 132.8, 130.2, 130.0, 127.2, 126.0, 60.7, 39.2, 19.5, 14.1$; Ms (EI) for $\text{C}_{10}\text{H}_{12}\text{O}_2$: $m/z = 178.1$ (M^+); HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$ 178.0993 found 178.0995.

(S2) Ethyl 2-(2-methylphenyl)acrylate¹: To a solution of **S1** (40 mmol, 9.5 g), paraformaldehyde (800 mmol, 24 g), TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine) (4 mmol, 1.29 g) and K_2CO_3 (200 mmol, 27.6 g) in 300 ml dry toluene was stirred in a pressure vessel (350 ml) at 85°C . Full conversion, indicated by TLC, was achieved after five days. The cooled solution was filtered, washed thoroughly with water, dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 ethylacetate/hexane, 1:25, $R_f = 0.27$) gave 5.8 g (76%) of **S2** as a colorless oil. ^1H -NMR (400 MHz) $\delta = 7.25\text{--}7.15$ (m, 4H), 6.51 (d, $J = 1.6$ Hz, 1H), 5.70 (d, $J = 1.6$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 2.24 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C -NMR (100 MHz) $\delta = 166.5, 142.1, 137.3, 136.0, 129.7, 129.4, 128.1, 128.0, 125.5, 60.9, 19.7, 14.1$; Ms (EI) for $\text{C}_{12}\text{H}_{14}\text{O}_2$: $m/z = 190.2$ (M^+); HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$ 190.0993, found 190.988.

(11) Ethyl 2-[2-(bromomethyl)phenyl]acrylate: To a solution of **S2** (30 mmol, 5.7 g) in CCl_4 (30 ml) was added NBS (33 mmol, 5.9 g) and benzoyl peroxide (2 mmol, 48 mg) and the reaction mixture was refluxed for 12h. The cooled solution was poured into water, separated and the water phase was extracted again with diethyl ether. The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 ethylacetate/hexane, 1:8, $R_f = 0.38$) gave 7.6 g (88%) of **4** as a colorless oil. ^1H -NMR (400 MHz) $\delta = 7.43\text{--}7.13$ (m, 4H), 6.63 (s, 1H), 5.88 (s, 1H), 4.42 (s, 2H), 4.24 (q, $J = 6.8$ Hz, 2H), 1.26 (t, $J = 6.8$ Hz, 3H); ^{13}C -NMR (100 MHz) $\delta = 166.2, 139.6, 137.0, 135.6, 130.4, 130.2, 129.8, 128.6, 128.3, 61.3, 31.6, 14.1$; Ms (EI) for $\text{C}_{12}\text{H}_{13}\text{BrO}_2$: $m/z = 189.2$ ($\text{M}^+ - \text{HBr}$); HRMS not possible because of instability.

(1) 2,2,2-Trifluoro-N-(2-iodo-phenyl)-acetamide: To a solution of 2-iodoaniline (4.38 g, 20 mmol) and Et_3N (4.2 ml, 30 mmol) in CH_2Cl_2 (15 ml) was added slowly trifluoroacetic anhydride (3.4 ml, 24 mmol) at 0°C . After stirring the reaction mixture for 1 h at the same temperature it was poured into NH_4Cl (aq), diluted with ethylacetate (30 ml) and the organic layer was separated. The aqueous layer was extracted two times with ethylacetate (20 ml) and the combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by crystallization from H_2O gave 5.17 g (82%) of **1** as brownish solid (mp $102\text{--}103^\circ\text{C}$). ^1H -NMR (400 MHz) $\delta = 8.28$ (s, broad, 1H (NH)), 8.21 (d, $J = 7.6$ Hz, 1H), 7.84 (d, $J = 7.6$ Hz, 1H), 7.42 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 1H), 6.98 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 1H); ^{13}C -NMR (100 MHz) $\delta = 154.7$ (q, $^2J(\text{C},\text{F}) = 37$ Hz), 139.1, 135.6, 129.5, 127.8, 122.2, 115.5 (q, $^2J(\text{C},\text{F}) = 289$ Hz), 90.3 Ms (EI) for $\text{C}_8\text{H}_5\text{F}_3\text{INO}$: $m/z = 315.1$ (M^+); HRMS calcd for $\text{C}_8\text{H}_5\text{F}_3\text{INO}$ 314.9368, found 314.9370.

(2) 2,2,2-Trifluoro-N-(2-bromo-phenyl)acetamide: To a solution of 2-bromoaniline (5 mmol, 860 mg) and Et_3N (7.5 mmol, 1.04 ml) in CH_2Cl_2 (10 ml) was added slowly

¹ Carvotto, G.; Goivenzana, G.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447.

trifluoroacetic anhydride (5.5 mmol, 776 μ l) at 0° C. After stirring the reaction mixture for 1 h at the same temperature it was poured into NH₄Cl (aq), diluted with ethylacetate (30 ml) and the organic layer was separated. The aqueous layer was extracted two times with ethylacetate (20 ml) and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo* to give 1.27 g (88%) of crude **2** as a brownish solid (mp 57-59°C). ¹H-NMR (400 MHz) δ = 8.45 (s, broad, 1H (NH)), 8.24 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H); ¹³C-NMR (100 MHz) δ = 154.6 (q, ²*J*(C,F) = 37 Hz), 133.1, 132.6, 128.7, 128.6, 127.2, 122.1, 119.9, 117.0, 115.6 (q, ²*J*(C,F) = 289 Hz), 114.2; Ms (EI) for C₈H₅F₃INO: *m/z* = 315.1 (M⁺); HRMS calcd for C₈H₅F₃INO 314.9368, found 314.9370.

(5) Ethyl 2-(2-[(2-iodo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl)-phenyl)-acrylate: To a solution of **1** (12 mmol, 3.78 g) and **11** (10.5 mmol, 2.82 g) in acetone (100 ml) was added K₂CO₃ (55 mmol, 7.6 g) and the reaction mixture was refluxed for 18 h. The cooled solution was filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂ ethylacetate/hexane, 1:8, R_f = 0.32) gave 4.28 g (71%) of **5** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.88 (d, *J* = 8.0 Hz, 1H), 7.28-7.00 (m, 6H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 5.75 (d, *J* = 14.4 Hz, 1H), 5.16 (d, *J* = 1.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 4.14 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz) δ = 165.7, 156.4 (q, ²*J*(C,F) = 37 Hz), 139.9, 139.7, 139.5, 137.8, 133.0, 131.3, 130.4, 130.0, 129.9, 129.2, 128.4, 128.3, 128.0, 115.5 (q, ²*J*(C,F) = 287 Hz), 99.4, 61.0, 49.6, 14.0. Ms (CI) for C₂₀H₁₇F₃INO₃: *m/z* = 503.3 (M⁺); HRMS calcd for C₂₀H₁₇F₃INO₃ 503.0205, found 503.1095.

(6) Ethyl 2-(2-[(2-bromo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl)-phenyl)-acrylate: To a solution of **2** (2.5 mmol, 787 mg) and **11** (3 mmol, 804 mg) in acetone (30 ml) was added K₂CO₃ (15 mmol, 2.07 g) and the reaction mixture was refluxed for 18 h. The cooled solution was filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂ ethylacetate/hexane, 1:10, R_f = 0.33) gave 694 mg (77%) of **6** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.60 (d, *J* = 7.8 Hz, 1H), 7.25-7.04 (m, 6H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.32 (d, *J* = 1.4 Hz, 1H), 5.73 (d, *J* = 14.5 Hz, 1H), 5.19 (d, *J* = 1.4 Hz, 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 4.13 (d, *J* = 14.4 Hz, 1H), 1.24 (t, *J* = 6.9 Hz, 3H); ¹³C-NMR (100 MHz) δ = 165.8, 156.6 (q, ²*J*(C,F) = 36 Hz), 140.0, 137.8, 136.3, 133.2, 133.1, 131.8, 130.5, 130.1, 130.0, 129.2, 128.3, 128.0, 127.5, 116.1 (q, ²*J*(C,F) = 289 Hz), 61.1, 49.4, 14.0. Ms (CI) for C₂₀H₁₇BrF₃NO₃: *m/z* = 456.1 (M + H⁺); HRMS calcd for C₂₀H₁₇BrF₃NO₃ (+H⁺) 456.0417, found 456.0405.

(7) Ethyl 2-{2-[(2-iodophenoxy)methyl]phenyl}acrylate: To a solution of 2-Iodophenol (2 mmol, 538 mg) and **11** (2 mmol, 440 mg) in acetone (10 ml) was added K₂CO₃ (5 mmol, 690 mg) and the reaction mixture was refluxed for 6h. The cooled solution was filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂ ethylacetate/hexane, 1:12, R_f = 0.20) gave 725 mg (84%) of **7** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.76 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 6.7 Hz, 1H), 7.31 (t, *J* = 6.5 Hz, 1H), 7.20 (t, *J* = 6.9 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.69 (t, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 5.83 (d, *J* = 1.9 Hz, 1H), 5.03 (s, 2H), 4.21 (q, *J* = 6.9 Hz, 2H), 1.25 (t, *J* = 6.8 Hz, 3H); ¹³C-NMR (100 MHz) δ = 166.2, 157.0,

140.3, 139.5, 135.9, 134.5, 129.8, 129.6, 129.3, 128.4, 127.7, 127.6, 122.7, 112.5, 86.5, 68.8, 61.3, 14.1. HRMS calcd for $C_{20}H_{17}IO_3$ ($+Na^+$) 431.0120, found 431.0110.

(8) Ethyl 2-{2-[(2-bromophenoxy)methyl]phenyl}acrylate: To a solution of **11** (2.5 mmol, 432 mg) and 2-bromophenol (3 mmol, 804 mg) in acetone (20 ml) was added K_2CO_3 (15 mmol, 2.07 g) and the reaction mixture was reflux for 18 h. The cooled solution was filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 ethylacetate/hexane, 3:40, R_f = 0.35) gave 784 mg (69%) of **8** as a colorless oil. 1H -NMR (400 MHz) δ = 7.63 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 6.7 Hz, 1H), 7.34 (t, J = 6.5 Hz, 1H), 7.20 (m, 2H), 6.82 (m, 2H), 6.57 (d, J = 1.9 Hz, 1H), 5.83 (d, J = 1.9 Hz, 1H), 5.05 (s, 2H), 4.23 (q, J = 6.9 Hz, 2H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C -NMR (100 MHz) δ = 166.1, 157.7, 140.3, 136.0, 134.4, 133.3, 129.8, 129.4, 128.4, 128.3, 127.7, 127.6, 122.0, 113.5, 112.2, 68.7, 61.2, 14.1. HRMS calcd for $C_{18}H_{17}BrO_3$ ($+Na^+$) 383.0253, found 383.0269.

(9) Ethyl 5-(trifluoroacetyl)-5,6-dihydrodibenzo[b,f]azocine-11-carboxylate: Under argon atmosphere: To a solution of **5** (0.33 mmol, 166 mg) in dimethylacetamide (4 ml) was added Et_4NCl (0.3 mmol, 50 mg), N-methylcyclohexylamine (0.45 mmol, 96 μ l) and $Pd(OAc)_2$ (0.0165 mmol, 3.7 mg). After stirring reaction mixture for 4 h at 95°C the reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO_2 ethylacetate/hexane, 1:8, R_f = 0.29) to give 89 mg (72%) of **8** as colorless oil. 1H -NMR (400 MHz) δ = 7.91 (s, 1H), 7.23-7.01 (m, 8H), 5.07 (d, J = 14.3 Hz, 1H), 4.55 (d, J = 14.3 Hz, 1H), 4.29 (q, J = 6.9 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C -NMR (100 MHz) δ = 165.4, 156.2 (q, $^2J(C,F)$ = 36 Hz), 140.2, 137.2, 137.1, 136.4, 135.1, 131.3, 130.5, 129.5, 129.4, 129.1, 128.9, 128.4, 128.2, 127.9, 127.0, 115.8 (q, $^2J(C,F)$ = 287 Hz), 61.6, 55.2, 14.1; HRMS calcd for $C_{20}H_{17}F_3INO_3$ 375.1082, found 375.1079.

(10) Ethyl 6H-dibenzo[b,f]oxocine-11-carboxylate: Under argon atmosphere: To a solution of **7** (0.33 mmol, 134 mg) in dimethylacetamide (4 ml) was added Et_4NCl (0.3 mmol, 50 mg), N-methylcyclohexylamine (0.45 mmol, 96 μ l) and $Pd(OAc)_2$ (0.0165 mmol, 3.7 mg). After stirring reaction mixture for 4 h at 95°C the reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO_2 ethylacetate/hexane, 1:12, R_f = 0.27) to give 76 mg (82%) of **10** as colorless oil. 1H -NMR (400 MHz) δ = 7.94 (s, 1H), 7.48 (m, 1H), 7.31 (m, 3H), 7.01 (m, 2H), 6.82 (m, 2H), 5.33 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.8 Hz, 3H); ^{13}C -NMR (100 MHz) δ = 166.7, 154.8, 141.7, 136.6, 134.8, 132.1, 131.1, 130.4, 129.9, 129.8, 128.4, 128.2, 122.1, 120.9, 120.4, 70.2, 61.3, 14.2; Ms (CI) for $C_{18}H_{16}O_3$: m/z = 281.1 ($M + H^+$); HRMS calcd for $C_{18}H_{16}O_3$ 280.1099, found 280.1099.

1. Materials described in Scheme 2.

(12) 2-Iodo-benzenesulfonyl chloride²: ¹H-NMR (400 MHz) CDCl₃ δ = 8.21 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), ¹³C-NMR (100 MHz) δ = 164.1, 146.7, 135.5, 130.3, 128.8, 92.0; HRMS calcd for C₆H₄ClIO₂S [(M-HCl)] 266.8971, found 266.8975.

(14) Ethyl 2-(2-((4-iodophenyl)sulfonyl)methyl)phenyl)acrylate: Na₂HPO₄ (4 mmol, 567 mg), Na₂SO₃ (8 mmol, 1 g) and **12** (4 mmol, 1.21 g) were dissolved water (4 ml) and stirred for 16h at 60°C. **11** (2 mmol, 538 mg) in acetone (1 ml) was added stirring was continued for 16h. The reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO₂ ethylacetate/hexane, 1:2, R_f = 0.41) to give **14** 420 mg (46%) as a colorless oil. ¹H-NMR (400 MHz) δ = 8.07 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.80 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.39-7.20 (m, 7H), 7.10 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 6.51 (d, *J* = 1.6 Hz, 1H), 5.52 (d, *J* = 1.6 Hz, 1H), 4.62 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz) δ = 165.7, 142.5, 140.7, 139.3, 138.6, 134.3, 132.1, 131.8, 131.1, 130.4, 128.5, 128.4, 128.0, 125.8, 93.4, 61.1, 56.5, 14.1; HRMS calcd for C₁₈H₁₇IO₄S (M+Na)⁺ 456.9965, found 456.9960.

(15) Ethyl 2-(2-((3-bromophenyl)sulfonyl)methyl)phenyl)acrylate: Na₂HPO₄ (2 mmol, 284 mg), Na₂SO₃ (4 mmol, 504 mg) and **13** (2 mmol, 511 mg) were dissolved water (2 ml) and stirred for 16h at 60°C. **11** (2 mmol, 538 mg) in acetone (1 ml) was added stirring was continued for 16h. The reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO₂ ethylacetate/hexane, 1:2, R_f = 0.42) to give **A30** 290 mg (35%) as a colorless oil. ¹H-NMR (400 MHz) δ = 7.83 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.74 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.45-7.35 (m, 4H), 7.31-7.26 (m, 3H), 7.12 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 6.51 (d, *J* = 1.6 Hz, 1H), 5.59 (d, *J* = 1.6 Hz, 1H), 4.66 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz) δ = 165.8, 139.4, 138.7, 137.9, 135.3, 134.7, 132.5, 131.8, 131.1, 130.5, 128.6, 128.1, 127.7, 125.8, 121.4, 61.2, 57.2, 14.1; HRMS calcd for C₁₈H₁₇BrO₄S (M+Li) 415.1915, found 415.200.

(16) Ethyl 6H-dibenzo[d][thiocine-11-carboxylate 5,5-dioxide: Under argon atmosphere: To a solution of **14** (0.26 mmol, 119 mg) in dimethylacetamide (3 ml) was added Et₄NCl (0.3 mmol, 50 mg), N-methylcyclo-hexylamine (0.45 mmol, 0.115 ml) and Pd(OAc)₂ (0.013 mmol, 2.9 mg). After stirring reaction mixture for 18 h at 100°C the reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO₂ ethylacetate/hexane, 1:2 R_f = 0.41) to

² Chau, M. M., Kice, J. L. *J. Org. Chem.* **1977**, *42*, 3265.

give 59 mg (69%) of **16** as a colorless oil. $^1\text{H-NMR}$ (400 MHz) δ = 8.23 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.43-7.18 (m, 5H), 7.07 (d, J = 7.6 Hz, 1H), 4.74 (d, J = 13.6 Hz, 1H), 4.58 (d, J = 13.6 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz) δ = 165.3, 140.9, 138.3, 136.7, 136.1, 133.7, 132.4, 129.8, 129.1, 129.0, 128.9, 128.7, 128.4, 127.1, 64.7, 61.9, 14.1; HRMS calcd for $\text{C}_{18}\text{H}_{16}\text{O}_4\text{S}$ ($\text{M}+\text{Li}$) 335.0929, found 335.0930.

1. Materials described in Scheme 3.

Scheme B. Synthesis of **S4**.

(S3) 2-[2-(2Bromophenyl)ethoxy]tetrahydro-2H-pyran: To a stirred solution of 2-bromophenethyl alcohol (21g, 105 mmol) and 10-camphorsulfonic acid (500 mg, 2 mmol) in DCM (250 ml) was added 3,4-dihydro-2H-pyran (13.7 ml, 150 mmol) in DMC (20ml) at rt. After stirring over night the solvent was evaporated and the residue was purified by column chromatography (SiO_2 ethylacetate/hexane, 1:15, R_f = 0.35) to give 28.22 g **S3** (99%) as a colorless liquid. $^1\text{H-NMR}$ (400 MHz) δ = 7.50 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 4.61 (m, 1H), 3.96 (m, 1H), 3.76 (m, 1H), 3.64 (m, 1H), 3.46 (m, 1H), 3.06 (t, J = 7.3 Hz, 3H), 1.83-1.46 (m, 6H); $^{13}\text{C-NMR}$ (100 MHz) δ = 132.6, 131.4, 128.2, 127.8, 127.2, 124.6, 98.5, 66.3, 62.0, 36.4, 30.6, 25.4, 19.4; HRMS calcd for $\text{C}_{13}\text{H}_{17}\text{BrO}_2$ (Na^+) 310.0310 found 310.0323.

(S4) Ethyl 2-[2-(2-hydroxyethyl)phenyl]acrylate: To a solution of **S3** (104 mmol, 28 g) in THF (300ml) was added n-BuLi (44 ml, 2.5M in hexanes) over a period of 1 h at -78°C followed by the addition of ethyl pyruvate (120 mmol, 13.3 ml) over a period of 1 h at the same temperature. The reaction mixture was warmed up to rt and stirred for an additional 3h, poured into NH_4Cl (aq) and extracted with ethyl acetate two times. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and

concentrated *in vacuo*. The crude product was dissolved in pyridine (200 ml) and POCl₃ (150 mmol, 22 ml) was added at 0°C. The reaction mixture was warmed up to 50°C and stirred over night. After evaporation of the solvent the residue was dissolved in ethyl acetate and washed with NH₄Cl (aq), brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was further dissolved in MeOH followed by the addition of p-TsOH (300 mg). The reaction mixture was stirred over night rt and the solvent was evaporated. Purification of the residue by column chromatography (SiO₂ ethyl acetate/hexane, 1:2, R_f = 0.24) gave 5.74g (25% over three steps) of **S4** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.31-7.23 (m, 2H), 7.22 (dt, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 7.14 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 6.53 (d, *J* = 1.8 Hz, 1H), 5.72 (d, *J* = 1.5 Hz, 1H), 4.23 (q, *J* = 6.8 Hz, 2H), 3.78 (t, *J* = 6.8 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 1.27 (t, *J* = 6.8 Hz, 3H); ¹³C-NMR (100 MHz) 166.7, 141.3, 137.2, 136.4, 129.7, 129.2, 128.7, 128.0, 126.0, 62.1, 61.0, 36.2, 13.9; HRMS calcd for C₁₃H₁₆O₃ 221.1172 found 221.1174.

(17) Ethyl 2-{2-[2-(2-iodophenoxy)ethyl]phenyl}acrylate: To a solution of **S4** (1 mmol, 220 mg), 2-iodophenol (1 mmol, 219 mg) and PPh₃ (1.3 mmol, 342 mg) in THF (10 ml) was added DIAD (1.2 mmol, 0.236 ml) at 0°C. After stirring for 15 min the reaction mixture was warmed up to rt and stirred for an additional 3h. The solvent was evaporated and the residue was purified by column chromatography (SiO₂ ethyl acetate/hexane, 1:8, R_f = 0.36) to give 333 mg of **17** (79%) as a colorless oil. ¹H-NMR (400 MHz) δ = 7.74 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.23 (m, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 1.4 Hz, 1H), 5.76 (d, *J* = 1.4 Hz, 1H), 4.22 (d, *J* = 6.9 Hz, 2H), 4.12 (t, *J* = 6.9 Hz, 2H), 3.07 (d, *J* = 6.9 Hz, 2H), 1.26 (t, *J* = 6.9 Hz, 3H); ¹³C-NMR (100 MHz) δ = 166.5, 157.3, 141.4, 139.4, 137.2, 135.8, 130.1, 129.9, 129.3, 129.1, 128.4, 128.2, 126.5, 122.5, 112.1, 86.5, 74.3, 61.2, 32.9, 14.1; HRMS calcd for C₁₉H₁₉IO₃ 422.0379 found 422.0382.

(18) 2-[1-(Ethoxycarbonyl)vinyl]benzyl 2-iodobenzoate: A mixture of 2-iodobenzoic acid (2 mmol, 496 mg), CsF (3 mmol, 453 mg), **A6** (2 mmol, 538 mg), and DMF (5 ml) was stirred at rt for 24h. the reaction mixture was combined with NaHCO₃ (aq) and extracted two times with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂ ethylacetate/hexane, 1:14, R_f = 0.13) gave 668 mg (95%) of **A15** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.99 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 6.6 Hz, 1H), 7.40-7.36 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 2.2 Hz, 1H), 5.82 (d, *J* = 2.2 Hz, 1H), 5.31 (s, 2H), 4.18 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.7 Hz, 3H). ¹³C-NMR (100 MHz) δ = 165.9, 165.8, 141.2, 140.2, 137.0, 134.4, 133.4, 132.6, 130.9, 129.9, 129.2, 129.0, 128.2, 128.1, 127.7, 94.1, 65.2, 61.1, 14.0; HRMS calcd for C₁₉H₁₇IO₄ 436.0171 found 436.0172.

1. Materials described in Scheme 3.

(19) *t*-Butyl (2-iodophenyl)carbamate: To a solution of 2-iodoaniline (15 mmol, 3.28 g) in THF (10 ml) was added a 1M solution of NaHMDS in THF (32 ml). After 15 min, a solution of methyl chloroformate (15 mmol, 1.16 ml) in THF (5 ml) was added and the reaction mixture was stirred for an additional 12 h, poured into NH₄Cl (aq), diluted with ethyl acetate (30 ml) and the organic layer was separated. The aqueous layer was extracted two times with ethyl acetate (20 ml) and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂ ethylacetate/hexane, 1:25, R_f = 0.24) gave 4.22 g of **19** (88%) as a slightly yellow oil. ¹H-NMR (400 MHz) δ = 8.03 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 6.81 (s, 1H(NH)), 6.71 (t, *J* = 7.8 Hz, 1H), 1.51 (s, 9H); ¹³C-NMR (100 MHz) δ = 152.5, 138.8, 129.1, 129.1, 124.6, 120.1, 88.7, 80.7, 28.1; HRMS calcd for C₁₁H₁₄INO₂ 320.0142, found 320.0136.

(20) Ethyl 2-[2-(bromophenyl)acrylate: A solution of (40 mmol, 9.7 g), paraformaldehyde (333 mmol, 10 g), TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine) (10 mmol, 3.22 g) and K₂CO₃ (58 mmol, 8 g) in 300 ml dry toluene was stirred in a pressure vessel (350 ml) at 85°C. Full conversion, indicated by TLC, was achieved after three days. The cooled solution was filtered, washed thoroughly with water, dried over MgSO₄, filtered and concentrated *in vacuo*. Colorless oil **20**, 9.99 g (78%) was obtained as pure oil and used without further purification. (SiO₂ ethylacetate /hexane, 1:8, R_f = 0.41). ¹H-NMR (400 MHz) δ = 7.54 (d, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.49 (s, 1H), 5.72 (s, 1H), 4.23 (q, *J* = 6.6 Hz, 2H), 1.25 (t, *J* = 6.6 Hz, 3H); ¹³C-NMR (100 MHz) δ = 165.5, 142.0, 138.5, 132.2, 130.7, 129.3, 128.5, 127.1, 123.1, 61.0, 13.9; Ms (EI) for C₁₁H₁₁BrO₂ m/z = 175.1 (M⁺-HBr); HRMS (253.9) not possible because of instability.

(21) Ethyl (2E)-2-(2-bromophenyl)-3-{2-[butoxycarbonyl]amino]phenyl}acrylate: Under argon atmosphere: To a solution of **19** (2.96 mmol, 820 mg) and **20** (2.6 mmol, 663 mg) in dimethylacetamide (10 ml) was added Et₄NCl (4 mmol, 662 mg), N-methylcyclohexylamine (6 mmol, 1.54 ml) and Pd(OAc)₂ (0.1 mmol, 22 mg). After stirring reaction mixture for 18 h at 100°C the reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO₂ ethylacetate/hexane, 1:3, R_f = 0.35) to give 860 mg (82%) of **21** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.91 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H(br)), 7.55 (d, *J* = 7.8 Hz, 1H), 7.20-7.09 (m, 3H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.41 (s, (NH)), 4.25 (m, 2H), 1.51 (s, 3H), 1.25 (t, *J* = 6.9 Hz, 3H); ¹³C-NMR (100 MHz) δ = 166.3, 152.6, 136.8, 136.5, 135.1, 132.4, 131.5, 129.6, 129.4, 129.3, 127.6, 124.3, 123.8, 121.6, 61.5, 52.4, 14.08;

Ms (CI) for $C_{17}H_{15}BrO_3$: $m/z = 403.8$ ($M+H^+$); HRMS calcd for $C_{20}H_{20}BrNO_3$ (Na^+) 426.0317 found 426.0328.

(22) Ethyl (2E)-3-(2-aminophenyl)-2-(2-bromophenyl)acrylate: To a solution of **A38** (0.72 mmol, 320 mg) in DCM (10 ml) was added TFA (8 mmol, 0.616 ml). The reaction mixture was stirred at rt for 14 h, evaporate to dryness and purified by column chromatography (SiO_2 ethylacetate/hexane, 1:2, $R_f = 0.39$) to give 251 mg (99%) of **22** as a colorless oil. 1H -NMR (400 MHz) $\delta = 7.98$ (s, 1H), 7.59 (dd, $J = 7.69$ Hz, $J = 1.46$ Hz, 1H), 7.18-7.15 (m, 2H), 7.08-7.05 (m, 2H), 6.82 (dd, $J = 7.69$ Hz, $J = 1.46$ Hz, 1H), 6.64 (d, $J = 7.69$ Hz, 1H), 6.58 (t, $J = 7.69$ Hz, 1H), 5.28 (m, 2H(NH_2)), 4.25 (m, 2H), 1.27 (t, $J = 6.9$ Hz, 3H); ^{13}C -NMR (100 MHz) $\delta = 166.9, 141.9, 137.0, 136.4, 134.0, 132.5, 131.6, 130.2, 129.8, 129.3, 127.5, 124.6, 122.1, 120.5, 117.7, 61.5, 14.1$; HRMS calcd for $C_{17}H_{16}BrNO_2$ 346.0437, found 346.0429.

(23) Ethyl (2E)-2-(2-bromophenyl)-3-(4-hydroxyphenyl)acrylate: Under argon atmosphere: To a solution of 2-iodophenol (3.5 mmol, 770 mg) and **20** (3 mmol, 765 mg) in dimethylacetamide (10 ml) was added Et_4NCl (4 mmol, 662 mg), N-methylcyclohexylamine (6 mmol, 1.54 ml) and $Pd(OAc)_2$ (0.1 mmol, 22 mg). After stirring reaction mixture for 18 h at $100^\circ C$ the reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO_2 ethylacetate/hexane, 1:3, $R_f = 0.25$) to give 850 mg (82%) of **22** as a colorless oil. 1H -NMR (400 MHz) $\delta = 8.27$ (s, 1H), 7.63 (dd, $J = 7.7$ Hz, $J = 1.9$ Hz, 1H), 7.25-7.17 (m, 2H), 7.11-7.05 (m, 2H), 6.77 (dd, $J = 7.7$ Hz, $J = 1.9$ Hz, 1H), 6.61 (m, 2H), 5.74 (bs, OH, 1H), 4.28 (m, 2H), 1.27 (t, $J = 6.9$ Hz, 3H); ^{13}C -NMR (100 MHz) $\delta = 167.8, 155.6, 137.4, 135.5, 132.5, 131.5, 131.3, 130.7, 129.6, 129.3, 127.6, 124.6, 121.4, 119.7, 115.8, 61.1, 13.9$; Ms (CI) for $C_{17}H_{15}BrO_3$: $m/z = 347.0$ ($M+H^+$); HRMS calcd for $C_{17}H_{15}BrO_3$, 347.0283 found 347.0292.

(24) Ethyl 5H-dibenzo[b,f]azepine-10-carboxylate: Under argon atmosphere: A solution of **A39** (0.64 mmol, 220 mg), K_3PO_4 (1.3 mmol, 275 mg) and $Pd(t-Bu_3P)_2$ (0.032 mmol, 16.3 mg) in toluene (10 ml) was heated for 16h at $90^\circ C$. The reaction mixture was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 ethylacetate/hexane, 1:3, $R_f = 0.40$) give 125 mg (74%) of **23** as a red oil. 1H -NMR (400 MHz) $\delta = 7.72$ (s, 1H), 7.24 (d, $J = 7.8$ Hz, 1H), 7.17-7.13 (m, 3H), 6.99 (t, $J = 7.8$ Hz, 1H), 6.92 (t, $J = 7.8$ Hz, 1H), 6.71-6.66 (m, 2H), 5.15 (s, (NH)), 4.33 (m, 2H), 1.35 (t, $J = 6.8$ Hz, 3H); ^{13}C -NMR (100 MHz) $\delta = 167.6, 150.6, 150.2, 140.8, 133.6, 131.8, 130.9, 130.8, 129.5, 127.8, 127.7, 123.4, 123.2, 120.7, 119.5, 61.1, 14.2$; HRMS calcd for $C_{17}H_{15}NO_2$ 266.1176, found 266.1178.

(25) Ethyldibenzo[b,f]oxepine-10-carboxylate: Under argon atmosphere: To a mixture of K_3PO_4 (1.61 mmol, 341mg), $Pd(OAc)_2$ (0.081 mmol, 18 mg) and 2-(di-tert-butylphosphino)biphenyl (0.121 mmol, 36 mg) was added a solution of **23** (0.8 mmol,

280 mg) in toluene (3 ml). The reaction mixture was stirred at 100°C for 14 h and was poured into water (10 ml) and the extracted with ethylacetate (2x20 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. Purified by column chromatography (SiO₂ ethylacetate/hexane, 1:6, R_f = 0.64) give 129 mg (60%) of **24** as a colorless oil. ¹H-NMR (400 MHz) δ = 7.90 (s, 1H), 7.52 (dd, *J* = 7.7 Hz, *J* = 1.9 Hz, 1H), 7.38-7.30 (m, 3H), 7.22 (m, 2H), 7.16 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100MHz) δ = 166.8, 159.0, 158.8, 137.7, 131.6, 131.5, 130.7, 130.2, 128.8, 127.7, 124.9, 124.6, 121.3, 121.1, 61.3, 14.9; HRMS calcd for C₁₇H₁₄O₃ (M+Li) 273.1103, found 273.1103.

8.282
8.221
8.201
7.856
7.836
7.441
7.421
7.401
7.260
7.001
6.983
6.964

(1) 2,2,2-Trifluoro-N-(2-iodo-phenyl)-acetamide

(1) 2,2,2-Trifluoro-N-(2-iodo-phenyl)-acetamide

8.436
8.247
8.223
7.571
7.551
7.363
7.341
7.324
7.101
7.081
7.062

(2) 2,2,2-Trifluoro-N-(2-bromo-phenyl)acetamide

(2) 2,2,2-Trifluoro-N-(2-bromo-phenyl)acetamide

(5) Ethyl 2-(2-[[[(2-iodo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl]-phenyl]-acrylate

(5) Ethyl 2-(2-[[2-(2-iodo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl]-phenyl)-acrylate

(6) Ethyl 2-(2-[[2-bromo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl]-phenyl)-acrylate

(6) Ethyl 2-(2-[(2-bromo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl)-phenyl)-acrylate

(7) Ethyl 2-{2-[(2-iodophenoxy)methyl]phenyl}acrylate

(8) Ethyl 2-{2-[(2-bromophenoxy)methyl]phenyl}acrylate

(8) Ethyl 2-{2-[(2-bromophenoxy)methyl]phenyl}acrylate

(9) Ethyl 5-(trifluoroacetyl)-5,6-dihydrodibenzo[b,f]azocine-11-carboxylate

(9) Ethyl 5-(trifluoroacetyl)-5,6-dihydrodibenzo[b,f]azocine-11-carboxylate

(10) Ethyl 6H-dibenzo[b,f]oxocine-11-carboxylate

(10) Ethyl 6H-dibenzo[b,f]oxocine-11-carboxylate

(5) Ethyl 2-(2-[[2-(2-iodo-phenyl)-(2,2,2-trifluoro-acetyl)-amino]-methyl]-phenyl)-acrylate

8.234
8.214
8.194
7.616
7.595
7.576
7.379
7.374
7.359
7.339

(12) 2-Iodo-benzenesulfonyl chloride

(12) 2-Iodo-benzenesulfonyl chloride

(14) Ethyl 2-(2-[[2-(2-iodophenyl)sulfonyl]methyl]phenyl)acrylate

(14) Ethyl 2-(2-[[2-iodophenyl)sulfonyl]methyl]phenyl)acrylate

(15) Ethyl 2-(2-[[2-(bromophenyl)sulfonyl]methyl]phenyl)acrylate

(15) Ethyl 2-(2-[[2-bromophenyl)sulfonyl]methyl}phenyl)acrylate

8.228
7.942
7.922
7.588
7.571
7.431
7.412
7.385
7.368
7.326
7.309
7.262
7.238
7.219
7.197
7.179
7.084
7.069

4.760
4.728
4.594
4.560
4.332
4.313
4.303

1.353
1.334
1.317

(16) Ethyl 6H-dibenzo[b,f]thiocine-11-carboxylate 5,5-dioxide

(16) Ethyl 6H-dibenzo[b,f]thiocine-11-carboxylate 5,5-dioxide

(17) Ethyl 2-{2-[2-(2-iodophenoxy)ethyl]phenyl}acrylate

(17) Ethyl 2-{2-[2-(2-iodophenoxy)ethyl]phenyl}acrylate

(18) 2-[1-(Ethoxycarbonyl)vinyl]benzyl 2-iodobenzoate

(18) 2-[1-(Ethoxycarbonyl)vinyl]benzyl 2-iodobenzoate

8.039
8.020
7.695
7.675
7.281
7.260
7.243
6.812
6.729
6.710
6.688

(19) t-Butyl (2-iodophenyl)carbamate

(19) t-Butyl (2-iodophenyl)carbamate

(20) Ethyl 2-[2-(bromophenyl)]acrylate

(20) Ethyl 2-[2-(bromophenyl)acrylate

(21) Ethyl (2E)-2-(2-bromophenyl)-3-{2-[(tert-butoxycarbonyl)amino]phenyl}acrylate

(21) Ethyl (2E)-2-(2-bromophenyl)-3-{2-[(tert-butoxycarbonyl)amino]phenyl}acrylate

(22) Ethyl (2E)-3-(2-aminophenyl)-2-(2-bromophenyl)acrylate

(22) Ethyl (2E)-3-(2-aminophenyl)-2-(2-bromophenyl)acrylate

8.274

7.641

7.622

7.253

7.243

7.223

7.204

7.180

7.165

7.114

7.088

7.070

7.052

6.786

6.767

6.617

6.602

6.568

6.552

6.532

4.281

1.295

1.275

1.258

(23) Ethyl (2E)-2-(2-bromophenyl)-3-(2-hydroxyphenyl)acrylate

(23) Ethyl (2E)-2-(2-bromophenyl)-3-(2-hydroxyphenyl)acrylate

(24) Ethyl 5H-dibenzo[b,f]azepine-10-carboxylate

(24) Ethyl 5H-dibenzo[b,f]azepine-10-carboxylate

(25) Ethyl dibenzo[b,f]oxepine-10-carboxylate

(25) Ethyl dibenzo[b,f]oxepine-10-carboxylate

(S1) Ethyl (2-methylphenyl)acetate

(S1) Ethyl (2-methylphenyl)acetate

(S2) Ethyl 2-(2-methylphenyl)acrylate

(S2) Ethyl 2-(2-methylphenyl)acrylate

7.540
7.520
7.286
7.282
7.259
7.245
7.229
7.225
7.088
7.083
7.069
7.064
7.050

4.618
4.611
4.600

3.977
3.960
3.953
3.942

3.936
3.917
3.757
3.676
3.658
3.651
3.640
3.634
3.616
3.493
3.479

3.466
3.450
3.439
3.082
3.064
3.045
1.798
1.699
1.690
1.518
1.514
1.507
1.504
1.495

(S3) 2-[2-(2-Bromophenyl)ethoxy]tetrahydro-2H-pyran

(S3) 2-[2-(2-Bromophenyl)ethoxy]tetrahydro-2H-pyran

(S4) Ethyl 2-[2-(2-hydroxyethyl)phenyl]acrylate

(S4) Ethyl 2-[2-(2-hydroxyethyl)phenyl]acrylate