A Versatile Synthesis of Fluorinated Uracils in Solution and on Solid-Phase.

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SUPPORTING INFORMATION

Preparation of compounds 8.

General procedure. *N*-butyllithium (10.5 mmol, 2.5 M in hexane) was slowly added to a solution of diisopropylamine (10.5 mmol) in THF (15 mL) at -30 °C. The mixture was stirred at that temperature for 30 min, after which time the temperature was lowered to -50 °C. A solution of the ester (8.4 mmol) in THF (10 mL) was then added dropwise and the reaction mixture was stirred until it took on a yellow color, which indicated the complete formation of the enolate. The temperature was then lowered to -78 °C and a solution of the nitrile (7.0 mmol) in THF (10 mL) was slowly added. The progress of the reaction was monitored by means of TLC, and after *ca.* 1 - 1.5 h it was quenched with satd. aq. NH₄Cl solution and extracted with AcOEt (3 x 20 mL). The organic layers were pooled together, washed with brine, dried over anhydrous Na₂SO₄, and concentrated to give crude product **8**, which was purified in each case as described below.

Ethyl 3-amino-4,4-difluoro-4-phenyl-2-butenate (8a). Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (2% Et₃N in hexane) gave a yellow oil (97%). ¹H NMR (300 MHz, CDCl₃) δ 1.15 (t, *J* = 7.2 Hz, 2H), 4.03 (c, *J* = 7.6 Hz, 2H), 4.82 (s, 1H), 7.30-7.35 (m, 3H), 7.45-7.48 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.3 (c), 58.4 (t), 84.6 (t, ³*J*_{CF} = 5.5 Hz), 116.6 (t, ¹*J*_{CF} = 245.4 Hz), 124.4 (t, ³*J*_{CF} = 5.7 Hz), 127.6 (d), 129.7 (d), 133.4 (t, ²*J*_{CF} = 27.0 Hz), 154.2 (t, ²*J*_{CF} = 28.7 Hz), 168.7 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -99.8 (s, 2F). HRMS calcd for C₁₂H₁₃F₂NO₂ 241.0914, found 241.0902.

Ethyl 3-amino-4,4-difluoro-4-phenyl-2-methyl-2-butenate (8b). Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (2% Et₃N in hexane) gave a yellow oil (87% yield). ¹H NMR (300 MHz, CDCl₃) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.45 (t, *J* = 2.2 Hz, 3H), 4.10 (c, *J* = 7.1 Hz, 2H), 6.79 (br s, 2H), 7.36-7.41 (m, 3H), 7.51-7.55 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 12.5 (c), 14.8 (c), 60.2 (t), 92.8 (t, ³*J*_{CF} = 2.9 Hz), 118.7 (t, ¹*J*_{CF} = 244.3 Hz), 125.9 (t, ³*J*_{CF} = 5.2 Hz), 129.0 (d), 131.1 (t, ⁴*J*_{CF} = 2.0 Hz), 135.3 (t, ²*J*_{CF} = 26.4 Hz), 151.4 (t, ²*J*_{CF} = 24.7 Hz), 171.5 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -92.3 (s, 2F). HRMS calcd for C₁₃H₁₅F₂NO₂ 255.1071, found 255.1078.

Ethyl 3-amino-4,4-difluoro-4-phenyl-2-phenyl-2-butenate (8c). Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (2% Et₃N in hexane) gave a yellow oil (93% yield). ¹H NMR (300 MHz, CDCl₃) δ 1.12 (t, *J* = 7.2, 3H), 4.17 (c, *J* = 7.0, 2H), 7.40-7.48 (m, 3H), 7.69-7.90 (m, 2H), 7.98 (br s, 1H), 8.15 (br s, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.3 (c), 58.4 (t), 84.6 (t, ³*J*_{CF} = 5.5), 116.6 (t, ¹*J*_{CF} = 245.4), 124.4 (t, ³*J*_{CF} = 5.7), 127.6 (d), 129.7 (d), 133.4 (t, ²*J*_{CF} = 27.0), 154.2 (t, ²*J*_{CF} = 28.7), 168.7 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -96.2 (s, 2F). HRMS calcd for C₁₈H₁₇F₂NO₂ 317.1227, found 317.1209.

Ethyl 3-amino-4,4-difluoro-4-(1-naphtyl)-2-phenyl-2-butenate (8d). Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (2% Et₃N in hexane) gave a yellow oil (70% yield). ¹H NMR (300 MHz, CDCl₃) δ 1.12 (t, *J* = 7.2, 3H), 4.17 (c, *J* = 7.0, 2H), 7.40-7.48 (m, 3H), 7.69-7.90 (m, 2H), 7.98 (br s, 1H), 8.15 (br s, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.3 (c), 59.7 (t), 85.1 (t, ³*J*_{CF} = 5.1), 115.9 (t, ¹*J*_{CF} = 244.7), 122.6 (t, ⁴*J*_{CF} = 3.1), 123.3 (d), 125.2 (t, ³*J*_{CF} = 9.5), 125.2 (t, ²*J*_{CF} = 21.9), 125.6 (d), 127.1 (d), 128.0 (s), 128.6 (d), 131.6 (d), 132.2 (s), 147.8 (t, ²*J*_{CF} = 29.6), 163.2 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -96.2 (s, 2F). HRMS calcd for (M-1) C₁₆H₁₄F₂NO₂ 290.0992, found 290.1008.

Ethyl 3-amino-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluoro-dec-2-enoate (8e). Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (4:1)] on deactivated silica gel (2% Et₃N in hexane) gave a colorless oil (91% yield). ¹H NMR (300 MHz, CDCl₃) δ 1.16 (t, *J* = 7.1, 3H), 4.06 (c, *J* = 7.1, 2H), 4.97 (s, 1H), 6.30 (br s, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.0 (c), 60.0 (t), 88.5 (t, ³*J*_{CF} = 6.3), 104.3-123.6 (the signals from the C₇F₁₅ group were obscured due to their low intensity), 147.3 (t, ²*J*_{CF} = 24.4), 169.3 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -82.1-(-82.2) (m, 3H), -119.5-(-119.6) (m, 2H), -122.3-(-122.5) (m, 2H), 122.9 (m, 2H), 123.3-(-123.4) (m, 2H), 123.6-(-123.7) (m, 2H), 127.1-(-127.3) (m, 2H). HRMS calcd for C₁₂H₈F₁₅NO₂ 483.0315, found 483.0245.

Preparation of compounds 5.

General procedure. NaH (3.6 mmol) was slowly added to a solution of β -enaminoester **8** (2.0 mmol) in DMF (3 ml) at 0°C. The mixture was stirred at that temperature for 30 min, after which time the isocyanate or isotiocyanate (2.4 mmol) was added. The mixture was then stirred at room temperature. The progress of the reaction was monitored by means of TLC and after *ca.* 30 min it was quenched with H₂O and the solvent was removed under vacuum. The resulting crude mixture was taken up in H₂O (10 ml) and then extracted with CH₂Cl₂ (3 x 10 ml). The uracils and tiouracils **8** proved to be soluble in H₂O and insoluble in CH₂Cl₂. The aqueous layer was concentrated to a volume of 2 ml and then extracted with AcOEt (3 x 10ml). The organic layers were pooled together, dried over anh. Na₂SO₄, and concentrated to give crude product **5**, which was purified in each case as described below.

6-(Difluoromethylphenyl)-3-(4-fluorophenyl)-2,4-pyrimidindione (5a). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5a** as a white solid (90% yield): mp 166-168°C. ¹H NMR (300 MHz, CDCl₃) δ 5.87 (s, 1H), 7.04-7.07 (m, 4H), 7.32-7.35 (m, 3H), 7.52-7.55 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 95.8 (t, ³J_{CF}=5.2), 117.1 (d, ²J_{CF}=23.0), 119.7 (t, ¹J_{CF}=244.0), 127.2 (t, ³J_{CF}=6.0), 129.8 (d), 131.5 (d), 132.0 (d, ³J_{CF}=9.2), 135.2 (d, ⁴J_{CF}=2.8), 138.0 (t, ²J_{CF}=27.3), 161.9 (s), 163.8 (d, ¹J_{CF}=244.8), 164.8 (t, ²J_{CF}=29.6), 169.7 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -101.6 (s, 2F), -117.4 (m, 1F). HRMS calcd for C₁₇H₁₁F₃N₂O₂ 332.0772, found 332.0760.

6-(Difluoromethylphenyl)-3-(4-methoxyphenyl)-2,4-pyrimidindione (5b). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5b** as a white solid (84% yield): mp 175-177°C. ¹H NMR (300 MHz, CDCl₃) δ 3.70 (s, 3H), 5.88 (s, 1H), 6.88 (d, *J* = 9.0, 2H), 6.97 (d, *J* = 9.0, 2H), 7.34-7.36 (m, 3H), 7.54-7.57 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 56.3 (c), 96.1 (t, ³J_{CF} = 4.9), 115.8 (d), 119.6 (t, ¹J_{CF} = 244.0), 127.2 (t, ³J_{CF} = 6.0), 129.8 (d), 130.9 (d), 131.5 (d), 131.6 (d), 137.9 (t, ²J_{CF} = 27.3), 161.0 (s), 161.7 (s), 163.6 (t, ²J_{CF} = 29.9), 169.7 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -101.4 (s, 2F). HRMS calcd for C₁₈H₁₄F₂N₂O₃ 344.0972, found 344.0987.

6-(Difluoromethylphenyl)-3-(3-trifluoromethylphenyl)-2,4-pyrimidindione (5c). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5c** as a white solid (76% yield): mp 165-167°C. ¹H NMR (300 MHz, CDCl₃) δ 5.89 (s, 1H), 7.35-7.49 (m, 5H), 7.50-7.57 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ 97.9 (t, ³J_{CF} = 5.2), 119.2 (t, ¹J_{CF} = 244.5), 125.7 (c, ¹J_{CF} = 271.3), 126.4 (c,

$^3J_{\text{CF}} = 4.9$), 127.2 (t, $^3J_{\text{CF}} = 6.0$), 127.4 (c, $^3J_{\text{CF}} = 3.8$), 130.1 (d), 131.4 (d), 132.1 (d), 132.9 (c, $^2J_{\text{CF}} = 32.5$), 134.2 (d), 136.7 (t, $^2J_{\text{CF}} = 26.7$), 138.9 (s), 158.1 (s), 159.1 (t, $^2J_{\text{CF}} = 30.7$), 167.7 (s); ^{19}F NMR (282 MHz, CDCl_3) δ -64.4 (s, 3F), -101.0 (s, 2F). HRMS calcd for $\text{C}_{18}\text{H}_{11}\text{F}_5\text{N}_2\text{O}_2$ 382.0740, found 382.0749.

6-(Difluoromethylphenyl)-3-(3-trifluoromethylphenyl)-2,4-pyrimidindione (5d). The crude reaction product was washed with *n*-hexane- CH_2Cl_2 (5:1) to give pure **5d** as a white solid (86% yield): mp 214-216°C. ^1H NMR (300 MHz, CDCl_3) δ 6.03 (s, 1H), 7.25-7.28 (m, 2H), 7.36-7.46 (m, 3H), 7.55-7.58 (m, 3H), 7.74-7.76 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 99.1 (t, $^3J_{\text{CF}} = 5.2$), 116.9 (t, $^1J_{\text{CF}} = 245.7$), 126.1 (t, $^3J_{\text{CF}} = 5.7$), 128.5 (d), 129.1 (d), 129.2 (d), 129.3 (d), 131.8 (d), 133.5 (t, $^2J_{\text{CF}} = 26.7$), 135.6 (s), 148.0 (t, $^2J_{\text{CF}} = 33.0$), 151.6 (s), 162.8 (s); ^{19}F NMR (282 MHz, CDCl_3) δ -97.3 (s, 2F). HRMS calcd for $\text{C}_{17}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_2$ 314.0866, found 314.0876.

3-sec-Butyl-6-(difluoromethylphenyl)-2,4-pyrimidindione (5e). Flash chromatography [*n*-hexane:EtOAc (2:1)] of the crude reaction mixture on silica gel gave **5e** as a white solid (71% isolated yield): mp 116-118°C. ^1H NMR (300 MHz, CDCl_3) δ 0.72 (t, $J = 7.4$, 3H), 1.30 (d, $J = 7.0$, 3H), 1.58-1.72 (m, 1H), 1.89-2.05 (m, 1H), 4.69-4.61 (m, 1H), 5.64 (s, 1H), 7.39-7.54 (m, 5H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 11.9 (c), 17.9 (c), 27.2 (t), 52.9 (d), 100.9 (d), 118.2 (t, $^1J_{\text{CF}} = 244.8$), 127.1 (t, $^3J_{\text{CF}} = 6.0$), 130.5 (d), 132.9 (d), 134.8 (t, $^2J_{\text{CF}} = 26.4$), 149.4 (t, $^2J_{\text{CF}} = 32.7$), 153.1 (s), 165.9 (s); ^{19}F NMR (282 MHz, CDCl_3) δ -100.2 (s, 2F). HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_2$ 294.1179, found 294.1190.

The structure of compound **5e** was determined by means of single crystal X-ray diffraction techniques. The structure shows three independent molecules in the asymmetric unit with the *sec*-butyl group bonded to the N(1) atom (Figures 1 and 3). The heterocyclic ring is planar for all three independent molecules (mean deviation 0.004-0.016). N-H...O=C hydrogen bonds are present in the crystal packing. *Crystal data for 5e*: $\text{C}_{15}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_2$, $M = 294.11$, colorless prism of 0.40 x 0.32 x 0.10 mm size, triclinic, $P -1$, $a = 11.2061(2)$, $b = 111.3867(2)$, $c = 18.0052(3)$ Å, $\alpha = 106.934(1)$, $\beta = 106.934(1)$, $\gamma = 106.934(1)$, $V = 2151.70(6)$ Å³, $Z = 6$, $D_c = 1.363$ gcm⁻³, $\theta_{\text{max}} = 30.0^\circ$, diffractometer Kappa CCD, Mo $K\alpha$ ($\lambda = 0.71073$ Å), ω -scan, $T = 173(2)$ K, 9964 reflections collected of which 8759 were independent ($R_{\text{int}} = 0.025$), direct primary solution and refinement on F² (SHELXL-97, G.M. Sheldrick, University of Göttingen, 1997), 637 refined parameters, free NH, other hydrogen atoms riding, the *sec*-Bu group of two independent molecules is disordered over two sites, $R_1[I > 2\sigma(I)] = 0.0630$, wR_2 (all data) = 0.2055.

Figure 3. Ellipsoid plot of compound **5e** (50% probability level). See Figure 1 in the main text for an additional view.

Figure 4. Crystal packing of compound **5e** through N-H...O=C and C-H...O=C hydrogen bonds.

6-(Difluoromethylphenyl)-3-ethyl-2,4-pyrimidindione (5f). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5f** as a white solid (78% yield): mp 135-137°C. ¹H NMR (300 MHz, CDCl₃) δ 1.07 (t, *J* = 7.1, 3H), 3.85 (c, *J* = 7.0, 2H), 5.74 (s, 1H), 7.32-7.35 (m, 3H), 7.47-7.50 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.4 (c), 37.0 (t), 96.6 (t, ³*J*_{CF} = 4.9), 119.4 (t, ¹*J*_{CF} = 243.9), 127.1 (t, ³*J*_{CF} = 5.7), 129.8 (d), 131.7 (d), 137.5 (t, ²*J*_{CF} = 27.3), 160.2 (s), 160.9 (t, ²*J*_{CF} = 30.0), 168.5 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -101.0 (s, 2F). HRMS calcd for C₁₃H₁₂F₂N₂O₂ 266.0866, found 266.0864.

(+)-(S)-6-(Difluoromethylphenyl)-3-(1-phenylethyl)-2,4-pyrimidindione (5g). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5g** as a white solid (90% yield): mp 168-170°C. [α]_D²⁵ +168.5° (*c* 1.04, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 1.76 (d, *J* = 7.2, 3H), 5.78 (s, 1H), 6.15 (c, *J* = 7.1, 1H), 7.15-7.22 (m, 3H), 7.30-7.34 (m, 4H), 7.38-7.45 (m, 3H), 10.7 (s, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 15.9 (c), 50.7 (d), 100.9 (t, ³*J*_{CF} = 4.9), 116.5 (t, ¹*J*_{CF} = 246.8), 125.9 (t, ³*J*_{CF} = 6.0), 127.7 (d), 127.9 (d), 128.5 (d), 129.4 (d), 131.7 (d), 133.2 (t, ²*J*_{CF} = 26.7), 139.8 (s), 147.4 (t, ²*J*_{CF} = 33.3), 152.7 (s), 163.1 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -100.4 (s, 2F). HRMS calcd for C₁₃H₁₂F₂N₂O₂ 342.1179, found 342.1190.

6-(Difluoromethylphenyl)-3-(4-ethoxycarbonylphenyl)-2,4-pyrimidindione (5h). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) and then subjected to flash chromatography [*n*-hexane:EtOAc (2:1)] on silica gel to give **5h** as a white solid (75% yield): mp 140-142°C. ¹H NMR (300 MHz, CDCl₃) δ 1.37 (t, *J* = 7.1, 3H), 4.38 (c, *J* = 7.1, 2H), 5.82 (s, 1H), 7.34 (d, *J* = 8.5, 2H), 7.54-7.57 (m, 3H), 7.68-7.71 (m, 2H), 8.02 (d, *J* = 8.5, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.5 (c), 61.0 (t), 93.9 (d), 118.3 (t, ¹*J*_{CF} = 243.9), 125.9 (t, ³*J*_{CF} = 6.0), 128.2 (t, ²*J*_{CF} = 31.0), 128.5 (d), 128.7 (d), 129.6 (d), 129.8 (d), 130.6 (d), 135.9 (t, ²*J*_{CF} = 27.0), 143.0 (s), 156.7 (s), 165.0 (s), 165.8 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -98.3 (s, 2F). HRMS calcd for C₂₀H₁₆F₂N₂O₄ 386.1078, found 386.1072.

Ethyl [4-(difluoromethylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1-yl]-acetate (5i). Flash chromatography [*n*-hexane:EtOAc (2:1)] on silica gel of the washed product from *n*-hexane-CH₂Cl₂ (5:1) gave **5i** as a white solid (73% yield): mp 98-100°C. ¹H NMR (300 MHz, CDCl₃) δ 1.15 (t, *J* = 7.2, 3H), 4.07 (c, *J* = 7.1, 2H), 4.54 (s, 2H), 5.79 (s, 1H), 7.34-7.35 (m, 3H), 7.49-7.52 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.8 (c), 43.3 (t), 62.7 (t), 95.9 (t, ³*J*_{CF} = 5.2), 119.5 (t, ¹*J*_{CF} = 243.9), 127.2 (t, ³*J*_{CF} = 6.0), 129.8 (d), 131.7 (d), 137.5 (t, ²*J*_{CF} = 27.3), 160.1 (s), 162.0 (t, ²*J*_{CF} = 28.7), 168.2 (s), 170.9 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -101.0 (s, 2F). HRMS calcd for C₁₅H₁₄F₂N₂O₄ 324.0921, found 324.0928.

6-(Difluoromethylphenyl)-3-(4-fluorophenyl)-2-tioxo-2,3-dihydropyrimidin-4-one (5j). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5j** as a yellowish solid (64% yield): mp 176-178°C. ¹H NMR (300 MHz, CDCl₃) δ 6.07 (s, 1H), 7.08-7.11 (m, 4H), 7.46-7.49 (m, 3H), 7.60-7.61 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 104.8 (t, ³J_{CF} = 5.5), 117.5 (d, ²J_{CF} = 23.6), 118.1 (t, ¹J_{CF} = 247.1), 127.4 (t, ³J_{CF} = 5.7), 130.1 (t, ²J_{CF} = 28.4), 130.5 (d), 132.0 (d, ³J_{CF} = 9.2), 133.1 (d), 134.6 (t, ²J_{CF} = 26.1), 136.6 (d, ⁴J_{CF} = 3.4), 163.1 (s), 164.3 (d, ¹J_{CF} = 246.6), 180.5 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -99.2 (s, 2F), -115.9 (m, 1F). HRMS calcd for C₁₇H₁₁F₃N₂O₂S 348.0544, found 348.0544.

6-(Difluoromethylphenyl)-3-(4-methylphenyl)-2-tioxo-2,3-dihydropyrimidin-4-one (5k). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5k** as a yellowish solid (68% yield): mp 180-182°C. ¹H NMR (300 MHz, CDCl₃) δ 2.29 (s, 3H), 6.09 (s, 1H), 6.97 (d, *J* = 8.1, 2H), 7.18 (d, *J* = 8.1, 2H), 7.47-7.65 (m, 5H); ¹³C NMR (75.5 MHz, CDCl₃) δ 21.9 (c), 105.1 (t, ³J_{CF} = 5.5), 118.2 (t, ¹J_{CF} = 245.1), 127.2 (t, ³J_{CF} = 6.0), 129.8 (d), 130.3 (t, ²J_{CF} = 30.4), 130.7 (d), 131.5 (d), 133.3 (s), 134.7 (t, ²J_{CF} = 26.4), 138.2 (s), 140.1 (s), 162.8 (s), 180.5 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -98.4 (s, 2F). HRMS calcd for C₁₈H₁₄F₂N₂O₂S 344.0794, found 344.0778.

6-(Difluoromethylphenyl)-3-(4-nitrophenyl)-2-tioxo-2,3-dihydropyrimidin-4-one (5l). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) and then subjected to flash chromatography [*n*-hexane:EtOAc (2:1)] on silica gel to give **5l** as a yellowish solid (70% yield): mp 187-189°C. ¹H NMR (300 MHz, CDCl₃) δ 6.06 (s, 1H), 7.19-7.24 (m, 5H), 7.37-7.40 (m, 2H), 7.91-7.94 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 103.9 (t, ³J_{CF} = 5.7), 116.5 (t, ¹J_{CF} = 246.0), 124.8 (d), 126.4 (t, ³J_{CF} = 5.5), 129.2 (d), 130.9 (d), 131.9 (d), 133.2 (t, ²J_{CF} = 26.4), 145.3 (s), 147.5 (s), 148.0 (t, ²J_{CF} = 33.6), 160.3 (s), 178.1 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -95.7 (s, 2F). HRMS calcd for C₁₇H₁₁F₂N₃O₃S 375.0489, found 375.0463.

6-(Difluoromethylphenyl)-3-ethyl-2-tioxo-2,3-dihydropyrimidin-4-one (5m). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) and then subjected to flash chromatography [*n*-hexane:EtOAc (2:1)] on silica gel to give **5m** as a yellowish solid (66% yield): mp 110-112°C. ¹H NMR (300 MHz, CDCl₃) δ 1.16 (t, *J* = 7.0, 3H), 4.42 (c, *J* = 6.3, 2H), 6.05 (s, 1H), 7.29-7.47 (m, 5H); ¹³C NMR (75.5 MHz, CDCl₃) δ 12.8 (c), 43.5 (t), 102.1 (d), 119.3 (t, ¹J_{CF} = 243.9), 127.3 (t, ³J_{CF} = 5.7), 129.8 (d), 131.6 (d), 137.6 (t, ²J_{CF} = 27.6), 159.9 (t, ²J_{CF} = 29.6), 166.8 (s), 182.2 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -100.8 (s, 2F). HRMS calcd for C₁₃H₁₂F₂N₂O₂S 282.0638, found 282.0635.

6-(Difluoromethylphenyl)-3-(4-fluorophenyl)-5-methyl-2,4-pyrimidindione (5n). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5n** as a white solid (82% yield): mp 179-181°C. ¹H NMR (300 MHz, CDCl₃) δ 1.83 (s, 3H), 7.26-7.28 (m, 4H), 7.57-7.73 (m, 5H); ¹³C NMR (75.5 MHz, CDCl₃) δ 10.9 (c), 103.7 (s), 115.5 (t, ²J_{CF} = 20.4), 115.6 (d, ²J_{CF} = 22.4), 119.2 (t, ¹J_{CF} = 244.3), 125.8 (t, ³J_{CF} = 5.2), 129.0 (d), 130.9 (d), 131.1 (d, ³J_{CF} = 8.6), 134.3 (d, ⁴J_{CF} = 2.9), 135.7 (t, ²J_{CF} = 27.0), 154.6 (s), 161.4 (d, ¹J_{CF} = 243.1), 165.8 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -90.7 (s, 2F), -116.0 (t, J_{FH} = 6.7, 1F). HRMS calcd for C₁₈H₁₃F₃N₂O₂ 346.0929, found 346.0928.

6-(Difluoromethylphenyl)-3-(3-trifluoromethylphenyl)-2,4-pyrimidindione (5o). The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) to give pure **5o** as a white solid (79% yield): mp 158-160°C. ¹H NMR (300 MHz, CDCl₃) δ 1.72 (t, J = 2.3, 3H), 7.45-7.47 (m, 4H), 7.58-7.64 (m, 5H); ¹³C NMR (75.5 MHz, CDCl₃) δ 11.2 (c), 110.6 (s), 119.3 (t, ¹J_{CF} = 245.4), 126.9 (c, ³J_{CF} = 4.0), 127.0 (t, ³J_{CF} = 5.2), 127.5 (c, ³J_{CF} = 3.8), 130.6 (d), 131.6 (d), 133.0 (c, ²J_{CF} = 32.8), 133.1 (t, ⁴J_{CF} = 1.6), 134.2 (d), 135.6 (t, ²J_{CF} = 26.4), 137.8 (s), 144.3 (t, ²J_{CF} = 29.0), 152.4 (s), 166.5 (s), (the signal from the CF₃ group was obscured due to its low intensity); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.1 (s, 3F), -93.1 (s, 2F). HRMS calcd for C₁₉H₁₃F₅N₂O₂ 396.0897, found 396.0891.

6-(Difluoromethylphenyl)-3-(4-fluorophenyl)-5-phenyl-2,4-pyrimidindione (5p). Flash chromatography of the crude reaction product [*n*-hexane:EtOAc (2:1)] on deactivated silica gel (2% Et₃N in hexane) gave **5p** as a white solid (85% yield): mp 210-212°C. ¹H NMR (300 MHz, CDCl₃) δ 6.98-7.02 (m, 2H), 7.24-7.36 (m, 5H), 7.42-7.56 (m, 7H), 11.8 (br s, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 114.0 (t, ³J_{CF} = 1.7), 116.0 (d, ²J_{CF} = 22.9), 117.5 (t, ¹J_{CF} = 247.1), 125.8 (t, ³J_{CF} = 5.2), 127.6 (d), 127.9 (d), 128.9 (d), 131.1 (d), 131.2 (d, ³J_{CF} = 9.2), 131.4 (d), 132.0 (s), 134.4 (t, ²J_{CF} = 26.4), 142.9 (t, ²J_{CF} = 29.0), 150.7 (s), 160.2 (s), 162.4 (d, ¹J_{CF} = 216.1), 163.5 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -87.7 (s, 2F), -114.4 (m, 1F). HRMS calcd for C₂₃H₁₅F₃N₂O₂ 408.1085, found 408.1080.

5-Bromo-6-(difluoromethylphenyl)-3-(4-fluorophenyl)-2,4-pyrimidindione (5q).¹ The crude reaction product was washed with *n*-hexane-CH₂Cl₂ (5:1) and then subjected to flash chromatography [*n*-hexane:EtOAc (2:1)] to give **5q** as a yellowish solid (78% yield): mp 165-167°C. ¹H NMR (300 MHz, CDCl₃) δ 7.06-7.21 (m, 4H), 7.40-7.43 (m, 3H), 7.62-7.65 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ 96.7 (s), 117.4 (d, ²J_{CF} = 23.0), 118.9 (t, ¹J_{CF} = 247.1), 127.3 (t, ³J_{CF} = 5.2), 130.2 (d), 132.0

¹ The brominated enamino ester necessary for the preparation of **5q** was prepared through NBS bromination of the corresponding enamino ester **8a**. See: Fustero, S.; Salavert, E.; Sanz-Cervera, J. F.; Román, R.; Fernández-Gutiérrez, B.; Asensio, A. *Lett. Org. Chem.* **2004**, *1*, 93-98.

(d, $^3J_{\text{CF}} = 8.6$), 132.7 (d), 133.4 (d, $^4J_{\text{CF}} = 3.4$), 135.2 (t, $^2J_{\text{CF}} = 26.1$), 150.1 (t, $^2J_{\text{CF}} = 29.0$), 153.8 (s), 163.0 (s), 164.3 (d, $^1J_{\text{CF}} = 246.0$); ^{19}F NMR (282 MHz, CDCl_3) δ -94.6 (s, 2F), -115.6 (m, 1F). HRMS calcd for $\text{C}_{17}\text{H}_{10}\text{BrF}_3\text{N}_2\text{O}_2$ 409.9877, found 409.9872.

6-[(1-Naphthyl)difluoromethyl]-3-(4-fluorophenyl)-2,4-pyrimidindione (5r). The crude reaction product was washed with *n*-hexane- CH_2Cl_2 (5:1) and then subjected to flash chromatography [*n*-hexane:EtOAc (2:1)] to give pure **5r** as a white solid (64% yield): mp 205-207°C. ^1H NMR (300 MHz, CDCl_3) δ 5.90 (s, 1H), 7.06-7.14 (m, 4H), 7.36-7.42 (m, 1H), 7.50-7.54 (m, 2H), 7.74-7.77 (m, 1H), 7.86-7.98 (m, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 100.8 (t, $^3J_{\text{CF}} = 5.2$), 115.5 (d, $^2J_{\text{CF}} = 23.0$), 116.2 (t, $^1J_{\text{CF}} = 243.7$), 122.9 (t, $^4J_{\text{CF}} = 2.9$), 123.4 (d), 124.9 (t, $^3J_{\text{CF}} = 8.9$), 125.3 (t, $^2J_{\text{CF}} = 23.6$), 125.7 (d), 126.9 (d), 128.1 (s), 128.3 (d), 128.5 (d, $^4J_{\text{CF}} = 3.4$), 129.0 (d, $^3J_{\text{CF}} = 8.6$), 132.1 (d), 133.1 (s), 145.6 (t, $^2J_{\text{CF}} = 31.6$), 150.1 (s), 161.3 (s), 161.6 (d, $^1J_{\text{CF}} = 248.9$); ^{19}F NMR (282 MHz, CDCl_3) δ -101.6 (s, 2F), -117.4 (m, 1F). HRMS calcd for $\text{C}_{21}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$ 382.0929, found 382.0941.

3-(4-Fluorophenyl)-6-pentadecafluoroheptil-2,4-pyrimidindione (5s). The crude reaction product was washed with *n*-hexane- CH_2Cl_2 (5:1) to give pure **5s** as a white solid (82% yield): mp 195-197°C. ^1H NMR (300 MHz, CDCl_3) δ 6.14 (s, 1H), 7.33-7.36 (m, 4H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 102.0 (d), 115.8 (d, $^2J_{\text{CF}} = 22.3$), 131.1 (d, $^3J_{\text{CF}} = 8.6$), 160.0 (s), 163.3 (s), (the signals from the C_7F_{15} group were obscured due to their low intensity); ^{19}F NMR (282 MHz, CDCl_3) -80.6 (m, 3H), -115.2 (s, 1F), -115.8 (t, $J_{\text{FF}} = 11.3$, 2H), -121.7 (s, 4H), 122.2 (s, 2H), 122.9 (s, 2H), 126.9 (s, 2H). HRMS calcd for $\text{C}_{17}\text{H}_6\text{F}_{16}\text{N}_2\text{O}_2$ 574.0173, found 574.0159.

3-Phenyl-6-pentadecafluoroheptil-2,4-pyrimidindione (5t). The crude reaction product was washed with *n*-hexane- CH_2Cl_2 (5:1) to give pure **5t** as a white solid (84% yield): mp 192-194°C. ^1H NMR (300 MHz, CDCl_3) δ 5.70 (s, 1H), 7.13-7.16 (m, 2H), 7.32-7.47 (m, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 95.0 (d), 126.9 (d), 128.6 (d), 129.2 (d), 138.8 (s), 158.0 (s), 165.4 (s), (the signals from the C_7F_{15} group were obscured due to their low intensity); ^{19}F NMR (282 MHz, CDCl_3) -80.7 (m, 3H), -115.9 (t, $J_{\text{FF}} = 97.6$, 2H), -121.6-(-121.8) (m, 4H), 122.2 (m, 2H), 122.9 (m, 2H), 126.1-(-126.2) (m, 2H). HRMS calcd for $\text{C}_{17}\text{H}_7\text{F}_{15}\text{N}_2\text{O}_2$ 556.0268, found 556.0290.

Preparation of acetylated Wang resin 11.

Acetic anhydride (2.5mmol) and pyridine (2.5mmol) were added dropwise to a suspension of Wang resin **10** (0.83mmol) in CH_2Cl_2 (5 ml). The mixture was stirred for 15 h and then filtered and

washed with DMF (3 x 5ml), CH₂Cl₂ (3 x 5ml), and MeOH (3 x 5ml). The solvent was then removed under vacuum.

Acetylated Wang resin (11). Yellowish solid. IR (cm⁻¹): 1730.

Preparation of the compound resin-bound β -enaminoester 12.

N-butyllithium (2.5 mmol, 2.5 M in hexane) was slowly added to a solution of diisopropylamine (2.4 mmol) in THF (5 mL) at 0°C. The mixture was stirred at that temperature for 20 min, after which time the acetylated resin (0.8 mmol) was slowly added. The temperature was maintained at 0°C for 1.5 h more and then a solution of the nitrile (2.4 mmol) in THF (2 mL) was slowly added dropwise. After 3 h the reaction was quenched with satd. aq. NH₄Cl solution and filtered. The resin was washed with DMF (3 x 5ml), CH₂Cl₂ (3 x 5ml), and MeOH (3 x 5ml) and then dried under vacuum.

Wang resin bound to 3-amino-4,4-difluoro-4-phenyl-2-butenate (12). Yellow solid. IR (cm⁻¹): 1679, 1731, 3417, 3523.

Preparation of compounds **5** from the resin-bound β -enaminoester **12**.

General procedure. NaH (0.4 mmol) was slowly added to a suspension of Wang resin bound to β -enaminoester **12** (0.11 mmol) in DMF (2 ml) at 0°C. The mixture was stirred at that temperature for 1 h after which time the isocyanate or isotiocyanate (0.27 mmol) was added. After additional stirring at room temperature for 15 h, the reaction was quenched with H₂O, then filtered and washed with THF/H₂O (1:1) (3 x 3ml). The aqueous layers were pooled together and extracted with CH₂Cl₂ (3 x 3 ml) to remove CH₂Cl₂-soluble impurities. The uracils and tiouracils **5** were both soluble in H₂O, but insoluble in CH₂Cl₂. The aqueous layer was reduced to a volume of 1 ml under vacuum and then extracted with AcOEt (3 x 3ml). The organic layers were pooled together, dried over anh. Na₂SO₄, and concentrated to give crude product **5**, which was purified in the same manner as described above. The uracils and tiouracils obtained from this method were identical in their physical and spectroscopic data to those obtained in solution.