Titanium-Catalyzed Stereoselective Geminal Heterodihalogenation of α -Ketoesters.

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Supporting Information

General considerations: Reactions were carried out under an argon atmosphere. Substrates **1a**, **1h**, **1j**, **1k** were purchased from Fluka. F-TEDA and NCS were obtained from Aldrich. Column chromatography was performed using silicagel 60 (Fluka, particle size 40-63 μ m). NMR spectra were recorded on Bruker AVANCE spectrometers AC-200, DPX-250, DPX-300. ^1H and ^{13}C positive chemical shifts in ppm are downfield of TMS. ^{19}F NMR spectra were referenced against CFCl_3 as internal standard. EI-MS spectra were measured by the MS service of the Laboratory of Organic Chemistry of the ETH Zürich). Elemental analyses were carried out by the Laboratory of Microelemental Analysis (ETH Zürich). The enantiomeric excesses (ee's) were determined by HPLC or GC analyses. HPLC analysis were performed on Agilent HPLC 1100 *Series* system, column DAICEL CHIRALCEL OJ, mobile phase, hexane / 2-propanol. GC analysis were performed on ThermoQuest GC TRACE 2000 Series, column SUPELCO α -DEX 120 (30 m), helium carrier (1.4 ml/min), split injector (42 ml/min, 200 °C), FID detector (Air/ H_2 350/35 ml/min, 250 °C).

Preparation of α -ketoesters

Substrates **1b-1g**, **1i** were prepared according to the literature procedures: Nudelman, A. Kelner, R. Broida, N. Gottlieb, H. E. *Synthesis* **1989**, 387-388.

Diphenylmethyl-3-oxobutanoate (**1b**):

TLC (TBME/Hexane 1 : 2): R_f = 0.46 (UV/Mostaine) ^1H -NMR (300.1 MHz, CDCl_3): Keto form: δ 7.37-7.20 (m, Ar-H), 6.92 (s, Ar-CH), 3.50 (s, αCH_2), 2.16 (s, CH_3) ; Enol form: δ 11.97 (s, OH), 5.14 (s, H-C=), 1.92 (s, CH_3) ^{13}C -NMR (75.5 MHz, CDCl_3): Keto form: δ 200.0, 166.0, 139.4, 128.4, 128.0, 127.0, 77.8, 50.1, 29.9 ; Enol form: δ 176.1, 171.5, 140.0, 128.5, 128.4, 127.8, 126.9, 89.6, 76.3, 21.1; MS (EI⁺): 268 (M⁺), 250, 224, 208, 183, 167, 152; EA calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_3$: C: 76.10, H: 6.01, found: C: 75.92, H: 6.14.

Diphenylmethyl-3-oxopentanoate (**1c**):

TLC (TBME/Hexane 1 : 2): R_f = 0.54 (UV) ; ^1H -NMR (300.1 MHz, CDCl_3): Keto form: δ 7.37-7.27 (m, Ar-H), 6.92 (s, Ar-CH), 3.54 (s, αCH_2), 2.52 (q, J = 7.3 Hz, CH_2), 1.05 (t, J = 7.3, CH_3) ; Enol form: δ 11.95 (OH) ; ^{13}C -NMR (75.5 MHz, CDCl_3): δ 202.9, 166.3, 139.6, 128.5, 128.1, 127.1, 77.9, 49.2, 36.3, 7.5 ; MS (EI⁺): 282 (M⁺), 183 ([$\text{Ph}_2\text{C}(\text{H})\text{O}$]⁺), 167 (Ph_2CH^+), 166, 165, 105, 77 (Ph^+); EA calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_3$: C: 76.57, H: 6.43, found C: 76.69, H: 6.55.

Benzyl-3-oxobutanoate (1d):

¹H-NMR (250.1 MHz, CDCl₃): Keto form: δ 7.39-7.32 (m, Ar-H), 5.18 (s, Ar-CH₂), 3.50 (s, $\square$ CH₂), 2.25 (s, CH₃) ; Enol form: δ 12.02 (OH) ; **¹³C-NMR (62.9 MHz, CDCl₃):** δ 200.4, 166.9, 135.2, 128.6, 128.5, 128.4, 67.1, 50.0, 30.1 ; **RN: 5396-89-4, 54565-08-1** (Enol form).

Benzyl-3-oxopentanoate (1e):

TLC (TBME/Hexane 1 : 5): R_f = 0.36 (UV/Mostaine) **¹H-NMR (250.1 MHz, CDCl₃):** δ 7.35 (s, 5H, Ar-H), 5.18 (s, 2H, Ar-CH₂), 3.50 (s, 2H, $\square$ CH₂), 2.55 (q, *J* = 7.25 Hz, 2H, CH₂), 1.11 (t, *J* = 7.2 Hz, 3H, CH₃) **¹³C-NMR (62.9 MHz, CDCl₃):** δ 203.0, 167.1, 135.2, 128.5, 128.4, 128.3, 67.0, 48.9, 36.3, 7.5 **RN: 4949-45-5**

(2',4',6'-Triisopropylbenzyl)-3-oxobutanoate (1f):

TLC (TBME/Hexane 1 : 5): R_f = 0.44 (UV/Mostaine) **¹H-NMR (250.1 MHz, CDCl₃):** δ 7.07 (s, 2H, Ar-H), 5.33 (s, 2H, Ar-CH₂), 3.48 (s, 2H, $\square$ CH₂), 3.21 (h, *J* = 6.8 Hz, 2H, CH), 2.91 (h, *J* = 6.9 Hz, 1H, CH), 2.26 (s, 3H, CH₃), 1.27 (d, *J* = 6.9 Hz, 6H, CH₃), 1.26 (d, *J* = 6.9 Hz, 12H, CH₃) **¹³C-NMR (50.3 MHz, CDCl₃):** δ 199.7, 166.7, 149.4, 148.3, 125.3, 120.7, 59.8, 49.6, 33.8, 29.6, 28.9, 23.8, 23.4 ; **MS**(EI⁺): 318.2 (M⁺), 303.2 ([M $\square$ CH₃]⁺), 275.2 ([M $\square$ CH₃CH₂]⁺); **EA** calcd. for C₂₀H₃₀O₃: C: 75.43, H: 9.49, found: C: 75.56, H: 9.31.

(2',4',6'-Triisopropylbenzyl)-3-oxopentanoate (1g):

TLC (TBME/Hexane 1 : 20): R_f = 0.20 (UV/Mostaine) **¹H-NMR (250.1 MHz, CDCl₃):** Keto form: δ 7.05 (s, Ar-H), 5.30 (s, Ar-CH₂), 3.45 (s, $\square$ CH₂), 3.19 (h, *J* = 6.8 Hz, CH), 2.90 (h, *J* = 6.8 Hz, CH), 2.54 (q, *J* = 7.25 Hz, CH₂), 1.26 (d, *J* = 6.9 Hz, CH₃-CH), 1.24 (d, *J* = 6.9 Hz, CH₃-CH), 1.06 (t, *J* = 7.25 Hz, CH₃-CH₂) **Enol form:** δ 12.12 (s, OH), 4.97 (s, H-C=), 2.24 (q, *J* = 7.5 Hz, CH₂), 1.12 (t, *J* = 7.5 Hz, CH₃-CH₂) **¹³C-NMR (75.5 MHz, CDCl₃):** Keto form: δ 202.6, 167.2, 149.6, 148.6, 125.6, 120.9, 87.8, 59.9, 48.7, 34.1, 31.3, 24.0, 23.6, 13.8, 7.2 **Enol form:** δ 179.9, 172.6, 149.4, 148.5, 126.2, 58.4, 36.0, 31.3, 27.8, 22.3, 10.1; **MS**(EI⁺): 332.3 (M⁺), 288.3 ([M $\square$ ⁱPr]⁺), 234.2, 216.2, 201.1, 173.1; **EA** calcd. for C₂₁H₃₂O₃: C: 75.86, H: 9.70, found: C: 76.01, H: 9.75.

($\square$)-Menthyl-3-oxobutanoate (1i):

TLC (TBME/Hexane 1 : 10): R_f = 0.27 (UV/Mostaine) **¹H-NMR (250.1 MHz, CDCl₃):** Keto form: δ 4.75 (td, *J* = 10.8 Hz, *J* = 4.4 Hz, CHOCO), 3.44 (s, $\square$ CH₂), 2.27 (s, CH₃CO), 2.07 (m, CH), 1.96-1.60 (m, CH and CH₂), 1.40-1.33 (m, CH₂), 1.04-0.96 (m, CH₂), 0.91 (d, *J* = 6.5 Hz, CH₃), 0.90 (d, *J* = 6.5 Hz, CH₃), 0.78 (d, *J* = 6.9 Hz, CH₃) **Enol form:** δ 12.20 (s, OH) **¹³C-NMR (50.3 MHz, CDCl₃):** Keto form: δ 200.1, 166.18, 74.9, 50.0, 46.3, 40.1, 33.6, 29.5, 25.6, 23.0, 21.4, 20.2, 15.6 **Enol form:** δ 174.7, 166.2, 89.5, 46.5, 40.5, 33.7, 31.0, 25.8, 23.0, 22.1, 21.5, 15.8 **MS**(EI⁺): 240.3 (M⁺), 155.2, 138.1, 123.1, 95.0, 81.0; **EA** calcd. for C₁₄H₂₄O₃: C: 69.96, H: 10.06, found: C: 70.05, H: 9.89.

General procedure for the Catalytic Stereoselective Heterodihalogenation of α -ketoesters

F α Cl sequence: F-TEDA (0.28 mmol) was added to a solution of α -ketoester (0.25 mmol) and the titanium complex (0.0125 mmol) in CH₃CN (3 mL) at room temperature. The completion of the first halogenation reaction was monitored by ¹H NMR. A second portion of the catalyst (0.0125 mmol) and NCS (0.28 mmol) were then added and the reaction mixture was stirred until complete conversion. After the addition of TBME, the mixture was filtered, the liquid phase concentrated, and the residue was chromatographed on silica to afford the product in analytical pure form as an oily material in 40-70% yield.

Monohalogenated compounds:

Ethyl-2-fluoro-3-oxo-3-phenylpropanoate (2aF):

TLC (TBME/Hexane 1 : 5): R_f = 0.39 (UV/Mostaine) α ¹H-NMR (300.1 MHz, CDCl₃): α 8.04 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.63 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.3 Hz, 2H, Ar-H), 5.87 (d, *J*_{FH} = 48.9 Hz, 1H, α CHF), 4.30 (q, *J* = 7.1 Hz, 2H, CH₂), 1.26 (t, *J* = 7.1 Hz, 3H, CH₃) α ¹³C-NMR (75.5 MHz, CDCl₃): α 189.2 (d, *J* = 22.7 Hz, C_{keto}), 164.6 (d, *J* = 30.2 Hz, C_{ester}), 134.2, 133.1, 129.2, 128.5, 89.8 (d, *J* = 196.3 Hz, α CHF), 62.4, 13.6 ; ¹⁹F-NMR (282.4 MHz, CDCl₃): α α 190.75 (d, *J* = 50.8 Hz) ; RN: 1479-22-7.

Diphenylmethyl-2-fluoro-3-oxobutanoate (2bF):

TLC (TBME/Hexane 1 : 10): R_f = 0.48 (UV/Mostaine) α ¹H-NMR (300.1 MHz, CDCl₃): Keto form: α 7.42-7.27 (m, Ar-H), 6.98 (s, Ar-CH), 5.28 (d, *J*_{FH} = 49.6 Hz, α CHF), 2.28 (d, *J*_{FH} = 4.2 Hz, CH₃); Enol form: α 10.00 (d, *J*_{FH} = 4.1 Hz, OH), 2.06 (dd, *J* = 4.2 Hz, *J* = 0.7, CH₃COH); ¹³C-NMR (50.3 MHz, CDCl₃): α 198.7 (d, *J* = 24 Hz, C_{keto}), 163.1 (d, *J* = 24 Hz, C_{ester}), 138.8, 138.8, 128.7-126.8, 91.7 (d, *J* = 199 Hz, α CHF), 79.2 (d, *J* = 1 Hz), 26.0 ; ¹⁹F-NMR (188.3 MHz, CDCl₃): α α 193.2 (dq, *J* = 49.5 Hz, *J* = 4.2 Hz); MS (HR-MALDI): calcd. for [C₁₇H₁₅O₃F + Na]⁺: 309.090, found: 309.089.

Diphenylmethyl-2-fluoro-3-oxopentanoate (2cF):

TLC (TBME/Hexane 1 : 5): R_f = 0.50 (UV); ¹H-NMR (500.2 MHz, CDCl₃): α 7.37-7.28 (m, 10 H, Ar-H), 6.97 (s, 1H, Ar-CH), 5.30 (d, *J*_{FH} = 49.4 Hz, 1H, α CHF), 2.73-2.53 (m, 2H, CH₃CH₂), 1.04 (t, *J* = 7.2 Hz, 3H, CH₃CH₂) ; ¹³C-NMR (125.8 MHz, CDCl₃): 201.63 (d, *J* = 23.0 Hz, C_{keto}), 163.28 (d, *J* = 24.2 Hz, C_{ester}), 138.82, 128.66, 128.61, 128.43, 128.28, 127.22, 126.85, 91.42 (d, *J* = 199.4 Hz, α CHF), 79.08, 31.89, 6.70 ; ¹⁹F-NMR (282.4 MHz, CDCl₃): α α 195.4 (dt, *J* = 49.4 Hz, *J* = 2.6 Hz) ; MS (EI⁺): 300 (M⁺), 210, 183 (Ph₂C(H)O⁺), 167 (Ph₂CH⁺), 166, 165; EA calcd. for C₁₈H₁₇FO₃: C: 71.99, H: 5.71, found: C: 71.96, H: 5.80.

Benzyl-2-fluoro-3-oxo-butanoate (2dF):

¹H-NMR (250.1 MHz, CDCl₃): α 7.37 (m, 5H, Ar-H), 5.27 (s, 2H, CH₂), 5.24 (d, *J*_{FH} = 49.3 Hz, 1H, α CHF), 2.32 (d, *J*_{FH} = 4.3 Hz, 3H, CH₃) ; ¹³C-NMR (75.5 MHz, CDCl₃): α 198.8 (d, *J* = 23.8 Hz, C_{keto}), 163.9 (d, *J* = 24.1 Hz, C_{ester}), 134.4, 128.8, 128.7, 128.4, 91.4

(d, $J = 198.6$ Hz, $\square$ CHF), 68.1, 26.0; **^{19}F -NMR (282.4 MHz, CDCl_3)**: $\square$ 193.55 (dq, $J = 49.3$ Hz, $J = 4.1$ Hz); **MS** (EI^+): 210.3 (M^+), 182.2, 107.0 (PhCH_2O^+), 91.0 (PhCH_2^+); **EA** calcd. for $\text{C}_{11}\text{H}_{11}\text{O}_3\text{F}$: C: 62.85, H: 5.27, found: C: 62.78, H: 5.32.

Benzyl-2-fluoro-3-oxopentanoate (2eF):

TLC (TBME/Hexane 1 : 5): $R_f = 0.35$ (UV/Mostaine) **^1H -NMR (200.1 MHz, CDCl_3)**: $\square$ 7.38 (s, 5H, Ar-H), 5.28 (s, 2H, CH_2 -Ar), 5.27 (d, $J_{\text{FH}} = 49.3$ Hz, 1H, $\square$ CHF), 2.67 (m, 2H, CH_2), 1.09 (t, $J = 7.2$ Hz, 3H, CH_3); **^{13}C -NMR (75.5 MHz, CDCl_3)**: $\square$ 201.3 (d, $J = 22.7$ Hz, C_{keto}), 163.7 (d, $J = 22.7$ Hz, C_{ester}), 134.1, 128.5, 128.4, 128.1, 91.0 (d, $J = 196.3$ Hz, $\square$ CHF), 67.7, 31.6, 13.6; **^{19}F -NMR (188.3 MHz, CDCl_3)**: $\square$ 195.38 (d, $J = 49.3$ Hz) **MS** (EI^+): 224.1 (M^+), 196.1, 107.0 (PhCH_2O^+), 91.0 (PhCH_2^+); **EA** calcd. for $\text{C}_{12}\text{H}_{13}\text{FO}_3$: C: 64.28, H: 5.84, found: C: 64.10, H: 5.68.

(2',4',6'-Triisopropylbenzyl)-2-fluoro-3-oxobutanoate (2fF):

TLC (TBME/Hexane 1 : 10): $R_f = 0.26$ (UV/Mostaine) **^1H -NMR (250.1 MHz, CDCl_3)**: $\square$ 7.06 (s, 2H, Ar-H), 5.51 (H_A , $J_{AB} = 12.2$ Hz, 1H, Ar-CH), 5.41 (H_B , $J_{AB} = 12.2$ Hz, 1H, Ar-CH) (5.19 (d, $J_{\text{FH}} = 49.4$ Hz, 1H, $\square$ CHF), 3.18 (h, $J = 6.8$ Hz, 2H, CH), 2.91 (h, $J = 6.9$ Hz, 1H, CH), 2.34 (d, $J_{\text{FH}} = 4.0$ Hz, 3H, CH_3), 1.27 (d, $J = 6.9$ Hz, 6H, CH_3 -CH), 1.26 (d, $J = 6.9$ Hz, 12H, CH_3 -CH) **^{13}C -NMR (62.9 MHz, CDCl_3)**: $\square$ 198.7 (d, $J = 18.9$ Hz, C_{keto}), 163.1 (d, $J = 25.1$ Hz, C_{ester}), 150.2, 149.0, 124.9, 121.3, 91.4 (d, $J = 198.7$ Hz, $\square$ CHF), 61.5, 34.4, 29.4, 26.0, 24.5, 24.3, 23.9 **^{19}F -NMR (188.3 MHz, CDCl_3)**: $\square$ 192.95 (dq, $J = 49.3$ Hz, $J = 4.0$ Hz) **MS** (EI^+): 336.2 (M^+), 277.2, 216.2, 201.1, 91.0 (PhCH_2^+); **EA** calcd. for $\text{C}_{20}\text{H}_{29}\text{FO}_3$: C: 71.40, H: 8.69, found: C: 71.54, H: 8.50.

(2',4',6'-Triisopropylbenzyl)-2-fluoro-3-oxopentanoate (2gF):

TLC (TBME/Hexane 1 : 20): $R_f = 0.28$ (UV/Mostaine) **^1H -NMR (200.1 MHz, CDCl_3)**: $\square$ 7.06 (s, 2H, Ar-H), 5.47 (H_A , $J_{AB} = 12.2$ Hz, 1H, Ar-CH), 5.36 (H_B , $J_{AB} = 12.2$ Hz, 1H, Ar-CH), 5.21 (d, $J_{\text{FH}} = 49.4$ Hz, 1H, $\square$ CHF), 3.21 (h, $J = 6.8$ Hz, 1H, CH), 2.90 (h, $J = 6.8$ Hz, 1H, CH), 2.73 (m, 2H, CH_2), 1.27 (d, $J = 6.9$ Hz, 6H, CH_3 -CH), 1.26 (d, $J = 6.9$ Hz, 6H, CH_3 -CH), 1.24 (d, $J = 6.9$ Hz, 6H, CH_3 -CH), 1.09 (t, $J = 7.25$ Hz, 3H, CH_3 - CH_2); **^{13}C -NMR (50.3 MHz, CDCl_3)**: $\square$ 201.0 (d, $J = 23.0$ Hz, C_{keto}), 163.9 (d, $J = 23.6$ Hz, C_{ester}), 149.7, 148.5, 124.4, 120.7, 90.8 (d, $J = 198.3$ Hz, $\square$ CHF), 60.8, 33.8, 31.4, 28.9, 23.8, 23.4; **^{19}F -NMR (188.3 MHz, CDCl_3)**: $\square$ 194.94 (dt, $J = 50.8$ Hz, $J = 3.8$ Hz) **MS** (EI^+): 350.2 (M^+), 335.2 ($[\text{M} - \text{CH}_3]^+$), 307.2 ($[\text{M} - \text{Pr}]^+$), 234.2, 216.2, 201.2, 173.2, 91.1; **EA** calcd. for $\text{C}_{21}\text{H}_{31}\text{FO}_3$: C: 71.97, H: 8.92, found: C: 72.07, H: 8.97.

(2',4',6'-Trichlorophenyl)-2-fluoro-3-oxobutanoate (2hF):

Moisture sensitive.

^1H -NMR (300.1 MHz, CDCl_3): $\square$ 7.41 (s, 2H, Ar-H), 5.53 (d, $J_{\text{FH}} = 49.1$, 1H, $\square$ CHF), 2.48 (d, $J_{\text{FH}} = 4.2$, 3H, CH_3); **^{19}F -NMR (282.4 MHz, CDCl_3)**: $\square$ 193.6 (dq, $J_{\text{FH}} = 49.1$, 4.1 Hz). Decomposition.

[Selected ^{13}C : 197.22 (d, $J = 23.8$ Hz), 160.35 (d, $J = 25.3$ Hz), 90.94 (d, $J = 201.3$ Hz).

(*S*)-Menthyl-2-fluoro-3-oxobutanoate (2iF):

TLC (TBME/Hexane 1 : 20): R_f = 0.17 (UV/Mostaine) **$^1\text{H-NMR}$ (200.1 MHz, CDCl_3):** first diastereoisomer: δ 5.20 (d, $J_{\text{FH}} = 49.7$ Hz, $\square\text{CHF}$), 4.88 (m, CH-O), 2.35 (d, $J_{\text{FH}} = 4.0$ Hz, CH_3), 0.93 (d, $J = 6.9$ Hz, CH_3), 0.91 (d, $J = 6.9$ Hz, CH_3), 0.78 (d, $J = 6.9$ Hz, CH_3) **$^{13}\text{C-NMR}$ (50.3 MHz, CDCl_3):** first diastereoisomer: δ 198.6 (d, $J = 24.0$ Hz, C_{keto}), 163.1 (d, $J = 23.8$ Hz, C_{ester}), 91.1 (d, $J = 198.0$ Hz, $\square\text{CHF}$), δ 6.6, 46.2, 39.9, 33.4, 30.9, 25.3, 22.7, 21.4, 20.1, 15.6; second diastereoisomer: δ 198.4 (d, $J = 24.0$ Hz, C_{keto}), 163.0 (d, $J = 23.8$ Hz, C_{ester}), 90.9 (d, $J = 198.0$ Hz, $\square\text{CHF}$), δ 6.5, 46.1, 39.8, 33.4, 30.8, 25.3, 22.5, 21.3, 20.0, 15.3 **$^{19}\text{F-NMR}$ (188.3 MHz, CDCl_3):** δ 192.95 (dq, $J = 49.0$ Hz, $J = 4.0$ Hz), δ 192.63 (dq, $J = 49.0$ Hz, $J = 4.0$ Hz) **$\text{MS}(\text{EI}^+)$:** 259.2 ($[\text{M} + \text{H}]^+$), 243.1 ($[\text{M} - \text{CH}_3]^+$), 155.2, 138.2, 123.1, 95.1; **EA** calcd. for $\text{C}_{14}\text{H}_{23}\text{FO}_3$: C: 65.09, H: 8.97, found: C: 65.20, H: 8.88.

Ethyl-2-fluoro-3-oxo-3-*tert*-butyl-propanoate (2kF):

$^1\text{H-NMR}$ (300.1 MHz, CDCl_3): δ 5.42 (d, $J_{\text{FH}} = 48.9$ Hz, 1H, $\square\text{CHF}$), 4.28 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 1.31 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.24 (s, 9H, $(\text{CH}_3)_3\text{CO}$) ; **$^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3):** δ 204.9 (d, $J = 17.7$ Hz, C_{keto}), 164.8 (d, $J = 23.8$ Hz, C_{ester}), 89.0 (d, $J_{\text{FC}} = 198.3$, $\square\text{CHF}$), 62.2, 25.6 (d, $J = 2.4$ Hz, CH_3), 13.8 ; **$^{19}\text{F-NMR}$ (282.4 MHz, CDCl_3):** δ 191.2 (d, $J = 49.0$ Hz). **RN: 118460-47-2.**

Ethyl-2-chloro-3-oxo-3-phenylpropanoate (2aCl):

TLC (TBME/Hexane 1 : 9): R_f = 0.26 (UV/Mostaine) **$^1\text{H-NMR}$ (250.1 MHz, CDCl_3):** δ 8.02 (d, $J = 7.5$ Hz, 2H, Ar-H), 7.58 (m, 3H, Ar-H), 5.61 (s, 1H, $\square\text{CHCl}$), 4.28 (q, $J = 7.5$ Hz, 2H, CH_2), 1.25 (t, $J = 7.5$ Hz, 3H, CH_3) **$^{13}\text{C-NMR}$ (62.9 MHz, CDCl_3):** δ 188.1 (s, C_{keto}), 165.2 (s, C_{ester}), 134.3, 133.3, 129.2, 128.8, 63.1 (s, $\square\text{CHCl}$), 57.9, 13.6 **RN: 41381-97-9.**

Diphenylmethyl-2-chloro-3-oxobutanoate (2bCl):

TLC (TBME/Hexane 1 : 5): R_f = 0.48 (UV/Mostaine) **$^1\text{H-NMR}$ (250.1 MHz, CD_2Cl_2):** Keto form: δ 7.39 (b.s, Ar-H), 6.93 (s, $\text{Ar}_2\text{-CH}$), 4.94 (s, $\square\text{CHCl}$), 2.22 (s, CH_3) ; Enol form: δ 12.14 (s, OH), 2.32 (s, CH_3) ; **$^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3):** δ 195.8 (s, C_{keto}), 163.7 (s, C_{ester}), 139.5, 138.7, 128.3, 128.0, 127.8, 127.1, 126.6, 126.4, 126.0, 79.3 ($\square\text{CHCl}$), 78.0, 26.0 **Enol form:** δ 173.1, 168.1 ; **$\text{MS}(\text{EI}^+)$:** 301.1 ($[\text{M} - \text{H}]^+$), 267.1 ($[\text{M} - \text{Cl}]^+$), 183.1 ($\text{Ph}_2\text{CH-O}^+$), 167.1 (Ph_2CH^+); **EA** calcd. for $\text{C}_{17}\text{H}_{15}\text{ClO}_3$: C: 67.44, H: 4.99, found: C: 67.16, H: 5.04.

Benzyl-2-chloro-3-oxo-butanoate (2dCl):

$^1\text{H-NMR}$ (300.1 MHz, CDCl_3): Keto form: δ 7.38-7.34 (m, Ar-H), 5.26 (s, CH_2), 4.80 (s, $\square\text{CHCl}$), 2.34 (s, CH_3); Enol form: δ 12.24 (s, OH), 7.41-7.37 (m, Ar-H), 5.28 (s, CH_2), 2.19 (s, CH_3) ; **$^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3):** δ Keto form: δ 196.4 (s, C_{keto}), 164.8 (s, C_{ester}), 134.4, 128.8, 128.7, 128.4, 68.6, 61.3 (s, $\square\text{CH}$), 26.2; Enol form: δ 173.0, 169.1, 135.2, 128.6, 128.4, 128.0, 67.2, 19.8; **MS** (EI^+): 226.1 (M^+), 191.1 ($[\text{M} - \text{Cl}]^+$), 107.1 (PhCH_2O^+), 91.1 (PhCH_2^+); **EA** calcd. for $\text{C}_{11}\text{H}_{11}\text{ClO}_3$: C: 58.29, H: 4.89, found: C: 58.13, H: 4.95.

Benzyl-2-chloro-3-oxopentanoate (2eCl):

TLC (TBME/Hexane 1 : 9): $R_f = 0.44$ (UV/Mostaine) $^1\text{H-NMR}$ (250.1 MHz, CDCl_3): Keto form: δ 7.36 (s, Ar-H), 5.25 (s, $\text{CH}_2\text{-Ar}$), 4.84 (s, CHCl), 2.71 (q, $J = 7.5$ Hz, CH_2), 1.08 (t, $J = 7.5$ Hz, CH_3) $^1\text{H-NMR}$ (250.1 MHz, CDCl_3): Enol form: δ 12.33 (s, OH), 5.28 (s, $\text{CH}_2\text{-Ar}$), 2.68 (q, $J = 7.5$ Hz, CH_2), 1.19 (t, $J = 7.5$ Hz, CH_3); $^{13}\text{C-NMR}$ (62.9 MHz, CDCl_3): δ 199.4 (s, C_{keto}), 164.9 (s, C_{ester}), 134.4, 128.5, 128.4, 127.9, 68.5 (s, CHCl), 60.7, 32.4, 7.5; **MS** (EI^+): 240.1 (M^+), 205.1 ($[\text{M} - \text{Cl}]^+$), 91.1 (PhCH_2^+); **EA** calcd. for $\text{C}_{12}\text{H}_{13}\text{ClO}_3$: C: 59.88, H: 5.44, found: C: 59.84, H: 5.35.

Chlorofluorinated compounds:**Ethyl-2-chloro-2-fluoro-3-phenyl-3-oxopropanoate (2aClF):**

TLC (TBME/Hexane 1 : 5): $R_f = 0.51$ (UV/Mostaine) $^1\text{H-NMR}$ (300.1 MHz, CDCl_3): δ 8.08 (d, $J = 7.3$ Hz, 2H, Ar-H), 7.66 (t, $J = 7.3$ Hz, 1H, Ar-H), 7.51 (t, $J = 7.3$ Hz, 2H, Ar-H), 4.35 (q, $J = 7.1$ Hz, 2H, CH_2), 1.28 (t, $J = 7.1$ Hz, 3H, CH_3) $^{13}\text{C-NMR}$ (62.9 MHz, CDCl_3): δ 184.6 (d, $J = 26$ Hz, C_{keto}), 162.9 (d, $J = 28$ Hz, C_{ester}), 134.7, 130.9 (d, $J = 3$ Hz), 130.1 (d, $J = 4$ Hz), 128.8, 103.0 (d, $J = 265$ Hz, CClF), 64.2, 13.7; $^{19}\text{F-NMR}$ (282.4 MHz, CDCl_3): δ -117.07; **MS** (EI^+): 244.2 (M^+), 198.9, 171.0 (PhCOCClF^+), 125.0, 105.0 (PhCO^+); **EA** calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{ClF}$: C: 54.00, H: 4.12, found: C: 54.98, H: 4.43.

Diphenylmethyl-2-chloro-2-fluoro-3-oxobutanoate (2bClF):

TLC (TBME/Hexane 1 : 10): $R_f = 0.32$ (UV/Mostaine) $^1\text{H-NMR}$ (300.1 MHz, CDCl_3): δ 7.33 (bs, 10H, Ar-H), 6.97 (s, Ar-CH, 1H, CH), 2.38 (q, $J_{\text{FH}} = 2.70$ Hz, 3H, CH_3) $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 192.8 (d, $J = 22.7$ Hz, C_{keto}), 161.1 (d, $J = 30.2$ Hz, C_{ester}), 137.9, 128.4, 128.3, 126.8, 126.7, 100.6 (d, $J = 264.3$ Hz, CClF), 80.5, 23.5; $^{19}\text{F-NMR}$ (282.4 MHz, CDCl_3): δ -123.36 (q, $J = 2.82$ Hz); **MS** (EI^+): 320.0 (M^+), 285.1 ($[\text{M} - \text{Cl}]^+$), 183.1, 167.1, 152.1; **EA** calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_3\text{ClF}$: C: 63.66, H: 4.40, found: C: 63.60, H: 4.59; **HPLC**: 14.8, 18.1 min (OJ, 93:7 Hexane/iPrOH, 0.5 ml/min).

Diphenylmethyl-2-chloro-2-fluoro-3-oxopentanoate (2cClF):

TLC (TBME/Hexane 1 : 10): $R_f = 0.42$ (UV); $^1\text{H-NMR}$ (300.1 MHz, CDCl_3): δ 7.39-7.29 (m, 10H, Ar-H), 6.96 (s, 1H, Ar-CH), 2.86-2.61 (m, 2H, CH_2), 1.10 (t, $J = 7.1$ Hz, 3H, CH_3); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 196.5 (d, $J = 26.2$ Hz, C_{keto}), 161.6 (d, $J = 28.0$ Hz, C_{ester}), 138.2, 128.7, 128.6, 128.5, 127.1, 127.0, 101.2 (d, $J = 264.4$ Hz, CClF), 80.7, 29.9 (d, $J = 1$ Hz, CH_2), 7.3; $^{19}\text{F-NMR}$ (282.4 MHz, CDCl_3): δ -123.8 (t, $J = 1.8$ Hz); **MS** (EI^+): 334 (M^+), 299 ($[\text{M} - \text{Cl}]^+$), 183 ($[\text{Ph}_2\text{C}(\text{H})\text{O}]^+$), 167 (Ph_2CH^+), 57 ($\text{CH}_3\text{CH}_2\text{CO}^+$); **EA**: calcd. for $\text{C}_{18}\text{H}_{16}\text{ClFO}_3$: C: 64.58, H: 4.82, found: C: 64.52, H: 5.01; $[\alpha]_D^{25} = +6.8$ ($c = 1.26$, MeOH, F $\rightarrow$ Cl sequence).

Benzyl-2-chloro-2-fluoro-3-oxobutanoate (2dClF):

$^1\text{H-NMR}$ (300.1 MHz, CDCl_3): δ 7.39-7.34 (m, 5H, Ar-H), 5.32 (s, 2H, CH_2), 2.40 (d, $J = 2.6$ Hz, 3H, CH_3); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 193.3 (d, $J = 27.1$ Hz, C_{keto}), 162.2

(d, $J = 27.7$ Hz, C_{ester}), 133.8, 128.9, 128.7, 128.3, 100.8 (d, $J = 264.7$ Hz, $\square\text{CClF}$), 69.4, 23.7 ; **^{19}F -NMR (282.4 MHz, CDCl_3)**: $\square$ 123.4 (q, $J = 2.6$ Hz); **MS** (EI⁺): 244 (M^+), 209 ($[\text{M} - \text{Cl}]^+$), 107 ($[\text{Ph}_2\text{C}(\text{H})\text{O}]^+$), 91 (PhCH_2^+), 43 (CH_3CO^+); **EA** calcd. for $\text{C}_{11}\text{H}_{10}\text{ClFO}_3$: C: 54.00, H: 4.12, found: C: 54.02, H: 4.25; **GC**: 89.9, 91.6 min ($\square$ -dex, 120 °C isotherm).

Benzyl-2-chloro-2-fluoro-3-oxopentanoate (2eClF):

TLC (TBME/Hexane 1 : 10): $R_f = 0.39$ (UV/Mostaine) **^1H -NMR (200.1 MHz, CDCl_3)**: $\square$ 7.38 (s, 5H, Ar-H), 5.34 (s, 2H, CH_2 -Ar), 2.80 (m, 2H, CH_2), 1.14 (t, $J = 7.2$ Hz, 3H, CH_3); **^{13}C -NMR (50.3 MHz, CDCl_3)**: $\square$ 196.2 (d, $J = 26.6$ Hz, C_{keto}), 162.4 (d, $J = 27.8$ Hz, C_{ester}), 133.3, 128.4, 128.2, 127.8, 100.1 (d, $J = 226.5$ Hz, $\square\text{CClF}$), 68.9, 29.2, 6.7; **^{19}F -NMR (188.3 MHz, CDCl_3)**: $\square$ 123.65 ; **MS** (EI⁺): 258.2 (M^+), 223.2 ($[\text{M} - \text{Cl}]^+$), 218.1, 166.1, 107.0 (PhCH_2O^+), 91.0 (PhCH_2^+); **EA** calcd. for $\text{C}_{12}\text{H}_{12}\text{ClFO}_3$: C: 55.72, H: 4.68, found: C: 55.88, H: 4.63; **GC**: 124.2, 128.4 ($\square$ -dex, 122 °C isotherm).

(2',4',6'-Triisopropylbenzyl)-2-chloro-2-fluoro-3-oxobutanoate (2fClF):

TLC (TBME/Hexane 1 : 20): $R_f = 0.37$ (UV/Mostaine) **^1H -NMR (200.1 MHz, CDCl_3)**: $\square$ 7.06 (s, Ar-H, 2H), 5.45 (s, 2H, CH_2 -Ar), 3.17 (h, $J = 6.8$ Hz, 2H, CH), 2.91 (h, $J = 6.9$ Hz, 1H, CH), 2.43 (d, $J_{\text{FH}} = 2.6$ Hz, 3H, CH_3), 1.27 (d, $J = 6.9$ Hz, 6H, CH_3 -CH), 1.26 (d, $J = 6.9$ Hz, 6H, CH_3 -CH), 1.26 (d, $J = 6.9$ Hz, 6H, CH_3 -CH) **^{13}C -NMR (75.5 MHz, CDCl_3)**: $\square$ 193.2 (d, $J = 30.2$ Hz, C_{keto}), 162.2 (d, $J = 30.2$ Hz, C_{ester}), 150.2, 148.9, 124.1, 121.0, 100.6 (d, $J = 264.1$ Hz, $\square\text{CClF}$), 62.8, 34.1, 29.2, 26.0, 24.1, 24.0, 23.9, 23.6 **^{19}F -NMR (188.3 MHz, CDCl_3)**: $\square$ 122.89 (q, $J = 2.6$ Hz) ; **MS** (EI⁺): 370.3 (M^+), 327.2 ($[\text{M} - \text{Pr}]^+$), 252.1, 234.1, 216.2, 91.0 (PhCH_2^+); **EA** calcd. for $\text{C}_{20}\text{H}_{28}\text{ClFO}_3$: C: 64.77, H: 7.61, found: C: 64.84, H: 7.71.

($\square$)-Menthyl-2-chloro-2-fluoro-3-oxobutanoate (2iClF):

TLC (TBME/Hexane 1 : 10): $R_f = 0.55$ (UV/Mostaine) **^1H -NMR (250.1 MHz, CDCl_3)**: $\square$ 4.84 (tdd, $J = 10.9$ Hz, $J = 4.8$ Hz, $J = 1.5$ Hz, 1H, CHOCO), 2.43 (d, $J_{\text{FH}} = 2.5$ Hz, 3H, CH_3), 2.04 (m, CH), 1.75-1.60 (m, 3H, CH and CH_2), 1.52-1.49 (m, 2H, CH_2), 1.11-1.05 (m, 2H, CH_2), 0.93 (d, $J = 6.5$ Hz, 3H, CH_3), 0.91 (d, $J = 6.5$ Hz, 3H, CH_3), 0.78 (d, $J = 7.0$ Hz, 3H, CH_3) **^{13}C -NMR (62.9 MHz, CDCl_3)**: first diastereoisomer: $\square$ 193.6 (d, $J = 25.1$ Hz, C_{keto}), 161.9 (d, $J = 25.1$ Hz, C_{ester}), 101.0 (d, $J = 257.9$ Hz, $\square\text{CClF}$), 99.1, 46.7, 40.0, 34.0, 31.4, 26.0, 23.3, 21.9, 20.6, 16.0; second diastereoisomer: $\square$ 193.4 (d, $J = 25.1$ Hz, C_{keto}), 161.8 (d, $J = 25.1$ Hz, C_{ester}), 100.8 (d, $J = 251.6$ Hz, $\square\text{CClF}$), 99.0, 46.6, 39.9, 33.9, 31.4, 26.0, 23.2, 21.8, 20.6, 15.9 ; **^{19}F -NMR (188.3 MHz, CDCl_3)**: $\square$ 122.77 (q, $J = 4.0$ Hz), $\square$ 122.89 (q, $J = 4.0$ Hz).

Ethyl-2-chloro-2-fluoro-3-oxobutanoate (2jClF):

^{19}F -NMR (188.3 MHz, CDCl_3): $\square$ 123.44; **GC**: 23.7, 25.0 ($\square$ -dex, 70 °C isotherm).

RN: 135664-26-5

2bF

2hF

2iClF