Carboxylic Acids as a Traceless Activation Group for Conjugate Additions: A
Three-Step Synthesis of (±)-Lyrica

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1. General Information

Commercial reagents were purchased from Sigma Aldrich and purified prior to use following the guidelines of Perrin and Armarego (1). All solvents were purified by passage through columns of activated alumina. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an acetone-dry ice bath for volatile compounds. Chromatographic purification of products was accomplished by flash chromatography on silica gel (Fluka, 230-400 mesh). Thin layer chromatography (TLC) was performed on Analtech Uniplate 250 m silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching, p-anisaldehyde, potassium permanganate, or ceric ammonium molybdate stain. ¹H and ¹³C NMR spectra were recorded on a Bruker 500 (500 and 125 MHz) instrument, and are internally referenced to residual protio solvent signals (note: CDCl₃ referenced at 7.26 and 77.0 ppm respectively). Data for ¹H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz) and assignment. Data for ¹³C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. High resolution mass spectra were obtained at Princeton University mass spectrometry facilities. All amino acids were used from commercial suppliers or prepared using standard literature procedures. All olefins were used from commercial suppliers or prepared using standard literature procedures.

2. Experimental Procedures and Characterization of the Decarboxylative Michael Products
General Procedure for the Decarboxylative Michael: An oven-dried 8 mL vial equipped with a Teflon septum and magnetic stir bar was charged with Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2 µmol, 0.01 equiv), Cbz-Pro-OH (0.2 mmol, 1.0 equiv), diethyl ethylenediamino, (0.2 mmol, 1.0 equiv), K₂HPO₄ (0.24 mmol, 1.2 equiv), and 0.5 mL of DMF. The reaction mixture was degassed by bubbling nitrogen stream for 15 min, then irradiated with a 26 W fluorescent lamp (at approximately 2 cm away from the light source). After 36 h, the reaction mixture was diluted with saturated aqueous NaHCO₃ solution, extracted with Et₂O (3 × 50 mL). The combined organic extracts were washed with water and brine, dried over MgSO₄ and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.

(±)-Benzyl 2-(3-oxocyclopentyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), 2-cyclopenten-1-one (16.4 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (51 mg, 88%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 7.37-7.30 (m, 5H), 5.16-5.10 (m, 2H), 4.06-3.96 (m, 1H), 3.62-3.52 (m, 1H), 3.38 (br, 1H), 2.35-1.79 (m, 10H), 1.69-1.64 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 218.79, 218.42, 155.93, 155.85, 155.62, 155.45, 136.97,
136.55, 128.57, 128.41, 128.25, 128.02, 127.84, 60.76, 60.27, 60.18, 66.82, 66.53, 66.48, 66.49, 56.4, 56.2, 55.64, 51.09, 50.89, 50.39, 46.45, 46.25, 45.76, 40.15, 39.58, 39.05, 31.77, 31.41, 31.26, 30.99, 23.83,

(±)-Benzyl 2-(3-oxo-2,3-diphenylpropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF3)ppy]2(dtbbpy)PF6 (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (49.9 mg, 0.2 mmol, 1.0 equiv.), CsF (36.5 mg, 0.24 mmol, 1.2 equiv.), 1,2-diphenylprop-2-en-1-one (41.7 mg, 0.2 mmol, 1.0 equiv.) and DMF (0.5 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a colourless powder (67 mg, 81%). 1H NMR (500 MHz, CDCl3) mixture of diastereomers and rotamers: δ 8.06-7.84 (m, 2H), 7.50-7.14 (m, 13H), 5.20-5.03 (m, 1.2H), 5.03-4.90 (m, 0.6H), 4.82-4.75 (m, 0.2H), 4.74-4.67 (m, 0.2H), 4.67-4.58 (m, 0.6H), 4.41 (d, J = 12.5 Hz, 0.2H), 4.26-4.18 (m, 0.4H), 4.05-3.94 (m, 0.35H), 3.94-3.85 (m, 0.25H), 3.55-3.20 (m, 2H), 2.79-2.67 (m, 0.5H), 2.41-2.32 (m, 0.15H), 2.30-2.21 (m, 0.2H), 2.21-1.71 (m, 4.5H), 1.55-1.44 (m, 0.65H); 13C NMR (125 MHz, CDCl3) mixture of diastereomers and rotamers: δ 199.40, 199.15, 198.95, 198.57, 155.43, 155.28, 154.93, 139.86, 139.70, 139.52, 139.31, 137.28, 136.87, 136.79, 136.60, 136.46, 136.40, 132.87, 132.73, 132.60, 129.05, 128.96, 128.88, 128.77, 128.63, 128.52, 128.47, 128.38, 128.24, 128.14, 128.06, 127.86, 127.81, 127.69, 127.11, 126.99, 66.86, 66.53, 66.48, 56.49, 56.2, 55.64, 51.09, 50.89, 50.39, 46.45, 46.25, 45.76, 40.15, 39.58, 39.05, 31.77, 31.41, 31.26, 30.99, 23.83,
23.55, 22.90; HRMS (ESI) m/z calcd for C_{27}H_{28}NO_3 [(M+H)^+] 414.20637, found 414.20623. IR (film) 2958, 1686, 1407, 1353, 1206, 1177, 1096, 953, 747, 694 cm^{-1};

![Chemical Structure Image]

(±)-Benzyl 2-(4-oxobutan-2-yl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6 (11 mg, 10.0 µmol, 0.01 equiv), Cbz-Pro-OH (250.0 mg, 1.0 mmol, 1.0 equiv), crotonaldehyde (70.9 mg, 1.0 mmol, 1.0 equiv), K_2HPO_4 (210.0 mg, 1.2 mmol, 1.2 equiv), and 2.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (253 mg, 92%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) mixture of diastereomers and rotamers: \(\delta\) 9.70 (br, 0.3H), 9.59-9.57 (m, 0.5H), 9.50 (br, 0.2H), 7.37-7.30 (m, 5H), 5.16-5.09 (m, 2H), 3.90 (br, 0.55H), 3.81 (br, 0.45H), 3.65-3.48 (m, 1H), 3.31-3.26 (m, 0.45H), 3.22-3.17 (m, 0.55H), 2.95 (br, 0.3H), 2.69 (br, 0.2H), 2.59-2.49 (m, 0.6H), 2.39-2.34 (m, 0.6H), 2.26-2.11 (m, 0.9H), 1.93-1.63 (m, 4.4H), 0.96-0.86 (m, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) mixture of diastereomers and rotamers: \(\delta\) 202.10, 201.83, 201.61, 201.42, 155.43, 155.38, 155.16, 136.78, 136.52, 128.32, 127.93, 127.76, 127.60, 66.87, 66.54, 61.91, 61.66, 61.00, 47.93, 47.66, 47.20, 47.08, 46.61, 46.16, 45.77, 31.06, 30.98, 30.96, 30.37, 27.19, 26.82, 25.79, 24.18, 23.85, 23.55, 23.24, 16.91, 15.68, 15.25; HRMS (ESI) m/z calcd for C_{16}H_{21}NNaO_3 [(M+Na)^+] 298.1419, found 298.1422. IR (film) 2962, 1692, 1404, 1097, 697 cm\(^{-1}\);
(±)-2-Benzyl-3-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)propanoic acid: According to the general procedure, Ir[dF(CF₃ppy)]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), 2-benzylacrylic acid (32.4 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (50% ethyl acetate/hexane) as a pale yellow solid (42 mg, 57%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 7.41-7.08 (m, 10H), 5.23-5.01 (m, 2H), 4.16-4.12 (m, 0.6H), 3.98-3.92 (m, 0.4H), 3.46-3.42 (m, 1H), 3.32-3.27 (m, 1H), 3.12-2.60 (m, 3H), 2.20-1.53 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 179.80, 179.56, 177.13, 157.21, 155.39, 155.22, 139.26, 139.05, 138.75, 138.70, 136.90, 136.36, 129.37, 129.16, 129.04, 128.96, 128.71, 128.57, 128.53, 128.42, 128.34, 128.17, 128.04, 127.97, 126.62, 126.53, 126.45, 67.82, 67.11, 66.97, 56.24, 55.93, 55.63, 46.66, 46.45, 46.28, 44.89, 44.58, 44.43, 38.85, 38.56, 38.42, 36.75, 36.37, 36.04, 31.53, 31.24, 30.82, 30.40, 29.83, 23.71, 23.47, 23.16, 22.93; HRMS (ESI) m/z calcd for C₂₂H₂₆NO₄ [(M+H)⁺] 368.1862, found 368.1868. IR (film) 2957, 1700, 1419, 1105, 698 cm⁻¹;

(±)-Benzy1 2-(4-benzamido-4-oxobutan-2-yl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF₃ppy)]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-
Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), (E)-N-(but-2-enoyl)benzamide (37.8 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (30% ethyl acetate/hexane) as a pale yellow solid (67 mg, 85%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 9.41 (s, 0.2H), 9.03 (s, 0.4H), 8.45 (s, 0.14H), 8.39 (m, 0.26H), 7.91-7.78 (m, 2H), 7.62-7.56 (m, 1H), 7.51-7.45 (m, 2H), 7.37-7.22 (m, 5H), 5.16-5.00 (m, 2H), 4.04 (br, 0.2H), 3.92-3.91 (m, 0.8H), 3.68-3.59 (m, 0.6H), 3.55-3.50 (m, 0.4H), 3.36-3.29 (m, 1H), 3.09-2.88 (m, 1H), 2.81-2.68 (m, 1H), 2.61-2.49 (m, 1H), 2.00-1.73 (m, 4H), 1.02-0.93 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 175.46, 175.21, 174.58, 174.23, 165.63, 165.57, 156.11, 155.93, 155.76, 155.57, 136.98, 136.89, 133.25, 133.03, 129.02, 128.86, 128.57, 128.52, 128.46, 128.12, 127.96, 127.84, 127.77, 67.00, 66.91, 66.81, 62.15, 61.37, 61.32, 47.83, 47.32, 46.80, 41.74, 41.40, 40.01, 34.02, 32.73, 32.50, 27.82, 27.71, 27.45, 24.42, 24.02, 23.77, 23.51, 17.00, 16.59, 15.84, 15.60; HRMS (ESI) m/z calcd for C$_{23}$H$_{27}$N$_2$O$_4$ [(M+H)$^+$] 395.1971, found 395.1961. IR (film) 2964, 1686, 1411, 1242, 1102, 705 cm$^{-1}$;

![Chemical Structure](image)  

(±)-Benzy1 2-(2-(phenylsulfonyl)ethyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), phenyl vinylsulfone (33.6 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (50% ethyl acetate/hexane) as a pale yellow solid.
(52 mg, 69%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 7.90 (d, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 7.0$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.57-7.52 (m, 2H), 7.33-7.30 (m, 4H), 7.26-7.22 (m, 1H), 5.09-5.04 (m, 2H), 3.96-3.89 (m, 1H), 3.49-3.35 (m, 2H), 3.20 (d, $J = 8.0$ Hz, 1H), 3.03-3.02 (m, 1H), 2.09-1.94 (m, 2H), 1.90-1.82 (m, 3H), 1.65-1.62 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 155.47, 155.00, 139.20, 139.02, 136.81, 136.39, 133.78, 129.37, 128.64, 128.57, 128.22, 128.10, 128.06, 127.87, 67.20, 66.85, 56.49, 55.87, 53.93, 53.60, 46.87, 46.48, 31.14, 30.68, 27.90, 27.83, 23.75, 23.02; HRMS (ESI) m/z calcd for C$_{20}$H$_{24}$NO$_4$S [(M+H)$^+$] 374.1426, found 374.1431. IR (film) 2956, 1691, 1408, 1304, 1143, 1086, 742 cm$^{-1}$;

(±)-Diethyl 2-(1-(1-benzoylpyrrolidin-2-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), dimethyl maleate (28.8 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (25% ethyl acetate/hexane) as a pale yellow oil (65 mg, 93%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 7.41-7.29 (m, 5H), 5.21-5.08 (m, 2H), 4.31-4.28 (m, 0.55H), 4.17-4.09 (m, 0.45H), 3.69-3.64 (m, 6.8H), 3.56-3.47 (m, 0.8H), 3.37-3.33 (m, 0.8H), 3.28-3.22 (m, 0.6H), 2.81-2.70 (m, 1H), 2.54-2.29 (m, 1H), 1.95-1.72 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 173.60, 173.27, 173.03, 172.37, 172.30, 172.14, 155.40,
155.03, 136.89, 136.77, 136.56, 128.52, 128.22, 128.08, 128.03, 127.99, 127.86, 67.22, 66.86, 59.02, 58.35, 58.24, 57.42, 52.13, 52.11, 51.92, 51.86, 47.79, 47.19, 46.96, 46.60, 44.57, 44.31, 44.13, 43.65, 33.60, 31.15, 30.54, 28.14, 28.10, 27.42, 24.17, 23.64, 23.57, 22.85; HRMS (ESI) m/z calcd for C_{18}H_{24}NO_{6} [(M+H)^+] 350.1604, found 350.1600. IR (film) 2953, 1697, 1732, 1408, 1165, 1110, 699 cm\(^{-1}\);

(\pm)-Benzyl 2-(3-(benzyloxy)-3-oxopropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF\(_3\))ppy]\(_2\)(dtbbpy)PF\(_6\) (2.2 mg, 2 \(\mu\)mol, 0.01 equiv.), Cbz-Pro-OH (49.9 mg, 0.2 mmol, 1.0 equiv.), benzyl acrylate (32.4 mg, 0.2 mmol, 1.0 equiv.), K\(_2\)HPO\(_4\) (41.8 mg, 0.24 mmol, 1.2 equiv.) and DMF (0.5 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a colorless oil (55 mg, 75%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) mixture of rotamers: \(\delta\) 7.31-7.19 (m, 10H), 5.08-4.94 (m, 4H), 3.89-3.80 (m, 1H), 3.46-3.26 (m, 2 H), 2.40-2.22 (m, 2H), 2.05-1.95 (m, 0.5H), 1.95-1.62 (m, 4.5H), 1.60-1.50 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) mixture of rotamers: \(\delta\) 173.25, 173.03, 155.14, 137.03, 136.84, 136.01, 135.94, 128.54, 128.46, 128.26, 128.20, 127.97, 127.88, 127.85, 66.84, 66.59, 66.28, 57.25, 56.54, 46.65, 46.32, 31.36, 31.17, 30.75, 30.05, 29.80, 29.44, 23.77, 23.00; HRMS (ESI) m/z calcd for C\(_{22}\)H\(_{26}\)NO\(_4\) [(M+H)^+] 368.18563, found 368.18568. IR (film) 2957, 1733, 1695, 1455, 1409, 1355, 1165, 1151, 1098, 743, 697 cm\(^{-1}\);
(±)-Benzyl 2-(3-butoxy-2-methyl-3-oxopropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), butyl methacrylate (28.4 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (48 mg, 69%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 7.39-7.26 (m, 5H), 5.18-5.07 (m, 2H), 4.06-3.91 (m, 3H), 3.49-3.33 (m, 2H), 2.56-2.38 (m, 1H), 2.18-1.60 (m, 6H), 1.39-1.31 (m, 3H), 1.24-1.20 (m, 1.4H), 1.10-1.09 (m, 2H), 0.95-0.90 (m, 3.6H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 176.76, 176.38, 155.28, 155.02, 154.69, 137.25, 137.17, 136.94, 128.55, 128.53, 128.29, 128.07, 128.01, 127.96, 127.94, 127.93, 127.83, 66.95, 66.91, 66.90, 66.65, 66.61, 64.65, 64.33, 64.31, 55.92, 55.45, 46.57, 46.45, 46.28, 46.26, 46.20, 38.98, 38.52, 37.49, 37.17, 30.73, 30.71, 30.69, 30.57, 23.89, 23.81, 22.99, 19.37, 19.25, 19.24, 17.95, 17.80, 13.89, 13.86, 13.85; HRMS (ESI) m/z calcd for C₂₀H₃₀NO₄ [(M+H)⁺] 348.2175, found 348.2183. IR (film) 2959, 1698, 1408, 1110, 697 cm⁻¹;

(±)-Benzyl 2-(3-methoxy-3-oxo-2-phenylpropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 10.0 µmol, 0.01 equiv), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), methyl 2-phenylacrylate (32.4
mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (65 mg, 89%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 7.46-7.15 (m, 10H), 5.15-5.03 (m, 2H), 3.99-3.31 (s, 7H), 2.59-2.55 (br, 0.7H), 2.34-2.22 (m, 0.3H), 2.10-2.05 (m, 0.3H), 1.91-1.70 (m, 3.7H), 1.57-1.48 (m, 0.8H), 1.27-1.20 (m, 0.2H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 174.25, 174.00, 173.91, 155.26, 155.12, 155.01, 139.40, 139.12, 138.57, 138.14, 137.04, 136.90, 136.82, 128.71, 128.53, 128.43, 128.38, 128.36, 128.06, 127.94, 127.84, 127.39, 127.31, 126.67, 67.04, 66.96, 66.65, 66.59, 56.52, 56.06, 55.97, 55.24, 56.52, 56.06, 55.97, 55.24, 52.14, 52.09, 48.97, 48.75, 46.60, 46.35, 46.05, 38.68, 38.60, 37.62, 37.24, 31.15, 30.80, 30.70, 30.15, 23.88, 23.72, 23.07, 22.90; HRMS (ESI) m/z calcd for C₂₂H₂₆NO₄ [(M+H)⁺] 368.1862, found 368.1869. IR (film) 2952, 2693, 1408, 1097, 697 cm⁻¹;

(±)-Benzyl 2-(3-methoxy-2-(4-methoxyphenyl)-3-oxopropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (49.9 mg, 0.2 mmol, 1.0 equiv.), CsF (36.5 mg, 0.24 mmol, 1.2 equiv.), methyl 2-(4-methoxyphenyl)acrylate (38.4 mg, 0.2 mmol, 1.0 equiv.) and DMF (0.5 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a colorless oil (60 mg, 76%). ¹H NMR (500 MHz, CDCl₃)
mixture of diastereomers and rotamers: δ 7.50-7.28 (m, 6H), 7.16 (d, J = 7.5 Hz, 0.8H), 7.08 (d, J = 7.5 Hz, 0.2H), 6.90-6.81 (m, 1.8H), 6.71 (d, J = 8.5 Hz, 0.2H), 5.21-5.05 (m, 2H), 4.04-3.89 (m, 0.8H), 3.85-3.75 (m, 3.5H), 3.75-3.52 (m, 3.5H), 3.52-3.30 (m, 2.2H), 2.62-2.49 (m, 0.8H), 2.43-2.33 (m, 0.1H), 2.29-2.20 (m, 0.1H), 2.10-1.42 (m, 5H); 13C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 174.48, 174.22, 174.15, 158.79, 155.20, 155.04, 154.99, 153.96, 136.99, 136.86, 136.77, 131.36, 131.09, 129.03, 128.80, 128.00, 127.88, 127.78, 114.00, 66.97, 66.60, 56.43, 55.93, 55.26, 55.23, 55.10, 52.07, 52.00, 48.06, 47.81, 46.55, 46.29, 46.02, 38.69, 38.58, 37.36, 36.96, 31.20, 30.79, 30.53, 29.99, 23.84, 23.69, 23.03, 22.86; HRMS (ESI) m/z calcd for C₂₃H₂₈NO₅ [(M+H)⁺] 398.1962, found 398.19642. IR (film) 2952, 1731, 1694, 1511, 1409, 1351, 1248, 1178, 1161, 1097, 1032, 698 cm⁻¹;

(±)- Benzyl 2-(2-(2-bromophenyl)-3-methoxy-3-oxopropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (49.9 mg, 0.20 mmol, 1.0 equiv.), K₂HPO₄ (41.8 mg, 0.24 mmol, 1.2 equiv.), methyl 2-(2-bromophenyl)acrylate (48.2 mg, 0.2 mmol, 1.0 equiv.) and DMF (0.5 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a colorless oil (77 mg, 87%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 7.60-7.53 (m, 1H), 7.52-7.25 (m, 6.5H), 7.18-6.98 (m, 1.5H), 5.23-5.03 (m, 2H), 4.37-4.20 (m, 1H), 4.12-4.03 (m, 0.65H), 3.90-
3.83 (m, 0.16H), 3.77-3.75 (m, 0.19H), 3.74-3.55 (m, 3H), 3.54-3.33 (m, 2H), 2.71-2.62 (m, 0.3H), 2.57-2.47 (m, 0.3H), 2.37-2.28 (m, 0.2H), 2.23-2.16 (m, 0.2H), 2.12-1.60 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: $\delta$ 173.61, 173.45, 173.30, 173.18, 155.13, 154.99, 154.94, 138.94, 138.67, 138.05, 137.74, 137.04, 136.85, 136.78, 133.07, 132.95, 128.97, 128.93, 128.77, 128.72, 128.66, 128.49, 128.44, 128.32, 128.29, 128.00, 127.81, 124.82, 124.79, 124.34, 66.95, 66.53, 56.61, 55.96, 55.73, 55.08, 55.22, 47.73, 47.55, 47.23, 47.06, 46.57, 46.33, 46.27, 46.11, 38.20, 37.51, 37.34, 36.89, 30.94, 30.71, 30.27, 30.12, 23.81, 23.76, 22.98, 22.88; HRMS (ESI) $m/z$ calcd for C$_{22}$H$_{25}$BrNO$_4$ [(M+H)$^+$] 446.09615, found 446.09693. IR (film) 2951, 1734, 1694, 1408, 1350, 1187, 1166, 1096, 1022, 748, 697 cm$^{-1}$;

(±)-Benzyl 2-(2-(2,4-difluorophenyl)-3-methoxy-3-oxopropyl)pyrrolidine-1-carboxylate: According to the general procedure, Ir[dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (2.2 mg, 2 µmol, 0.01 equiv.), Cbz-Pro-OH (74.8 mg, 0.30 mmol, 1.5 equiv.), K$_2$HPO$_4$ (52.3 mg, 0.3 mmol, 1.5 equiv.), methyl 2-(2,4-difluorophenyl)acrylate (39.6 mg, 0.2 mmol, 1.0 equiv.) and DMF (0.5 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a colorless oil (73 mg, 90%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers and rotamers: $\delta$ 7.55-7.23 (m, 5.9H), 7.11-7.03 (m, 0.3H), 6.89-6.70 (m, 1.6H), 6.54 (t, $J$ = 8.0 Hz, 0.2H), 5.22-5.03 (m, 2H), 4.14-4.06 (m,
0.3H), 4.06-3.93 (m, 1H), 3.93-3.86 (m, 0.2H), 3.82-3.74 (m, 0.2H), 3.70-3.57 (m, 3H), 3.54-3.31 (m, 2H), 2.69-2.61 (m, 0.3H), 2.58-2.50 (m, 0.3H), 2.45-2.35 (m, 0.2H), 2.28-2.19 (m, 0.2H), 2.11-1.52 (m, 5H); 13C NMR (125 MHz, CDCl3) mixture of diastereomers and rotamers: δ 173.32, 173.22, 173.04, 163.06, 162.95, 162.87, 161.53, 161.44, 161.35, 161.20, 160.97, 159.56, 159.46, 159.37, 159.27, 155.13, 155.01, 154.91, 136.92, 136.76, 136.59, 130.37, 130.12, 129.82, 129.66, 128.46, 128.27, 128.13, 127.93, 127.83, 127.80, 127.70, 122.56, 122.44, 122.27, 122.15, 121.32, 121.20, 120.95, 120.82, 111.85, 111.66, 111.50, 111.36, 104.08, 103.95, 103.87, 103.75, 103.67, 103.54, 67.06, 66.61, 56.32, 55.76, 54.96, 52.30, 52.24, 46.58, 46.31, 46.14, 41.06, 40.48, 40.23, 40.09, 37.76, 37.19, 36.45, 35.89, 31.00, 30.36, 29.82, 23.82, 23.75, 23.01, 22.87; HRMS (ESI) m/z calcd for C22H24F2NO4 [(M+H)+] 404.16679, found 404.16672. IR (film) 2954, 2883, 1736, 1694, 1503, 1409, 1352, 1098, 964, 850, 698 cm⁻¹;

(±)-Diethyl 2-(1-(1-benzoylpyrrolidin-2-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF3)ppy]2(dtbbpy)PF6 (2.2 mg, 20.0 µmol, 0.01 equiv), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), diethyl 2-(3-phenylpropylidene)malonate (55.5 mg, 0.2 mmol, 1.0 equiv), K2HPO4 (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (25% ethyl acetate/hexane) as a pale yellow oil (89 mg, 92%). 1H NMR (500 MHz, CDCl3) mixture of diastereomers and rotamers: δ 7.45-7.29 (m, 5H), 7.27-7.23 (m, 2H), 7.18-7.04 (m, 3H), 5.20-5.05 (m, 2H), 4.22-3.99 (m, 5H), 3.76-3.57 (m, 1H), 3.50-3.47 (m, 0.5H), 3.40-3.36 (m, 0.5H), 3.25-
3.14 (m, 1H), 3.07 (br, 0.6H), 2.72-2.38 (m, 2.4H), 2.00-1.95 (m, 1H), 1.91-1.84 (m, 1H), 1.82-1.58 (m, 4H), 1.27-1.19 (m, 6H); $^1$H NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: $\delta$ 169.02, 168.93, 168.76, 168.61, 155.67, 155.35, 142.35, 142.23, 142.00, 141.92, 136.83, 136.76, 136.64, 136.40, 128.52, 128.46, 128.40, 128.37, 128.29, 128.22, 128.15, 128.00, 127.92, 127.79, 125.89, 67.43, 67.31, 66.93, 66.80, 61.63, 61.42, 61.36, 60.50, 59.79, 59.56, 58.88, 54.13, 53.73, 53.37, 52.86, 48.16, 47.74, 47.49, 47.01, 42.22, 41.93, 40.58, 34.53, 34.25, 33.04, 32.75, 31.87, 31.75, 31.25, 29.77, 29.49, 27.47, 27.24, 24.32, 23.75, 23.65, 23.00, 14.13, 14.09, 14.02; HRMS (ESI) m/z calcd for C$_{28}$H$_{36}$NO$_6$ [(M+H)$^+$] 482.2543, found 482.2557. IR (film) 2947, 1697, 1405, 1096, 749, 698 cm$^{-1}$;

(±)-Diethyl 2-((1-((benzyloxy)carbonyl)pyrrolidin-2-yl)(cyclohexyl)methyl)malonate:

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 mg, 10.0 µmol, 0.01 equiv), Cbz-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), diethyl 2-(cyclohexylmethylene)malonate (50.8 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (25% ethyl acetate/hexane) as a pale yellow oil (80 mg, 87%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers and rotamers: $\delta$ 7.47-7.29 (m, 5H), 5.22-5.01 (m, 2H), 4.21-4.06 (m, 4H), 3.96-3.87 (m, 0.25H), 3.70-3.53 (m, 1.75H), 3.29-3.17 (m, 1H), 3.07-3.00 (m, 1H), 1.97-1.56 (m, 11H), 1.27 (d, $J = 7.0$ Hz, 3H), 1.20 (d, $J = 7.0$ Hz, 3H), 1.13-0.96 (m, 5H); $^1$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and
rotamers: \(\delta 169.69, 169.63, 169.53, 169.03, 168.73, 156.83, 155.73, 155.68, 155.47, 137.04, 136.74, 136.64, 136.06, 129.35, 128.53, 128.31, 127.98, 127.90, 127.75, 67.87, 67.36, 67.00, 66.66, 61.60, 61.43, 61.31, 61.05, 58.35, 57.85, 57.55, 57.05, 52.98, 52.71, 51.20, 50.80, 49.67, 49.26, 47.83, 47.72, 47.33, 47.22, 45.83, 45.19, 40.27, 40.21, 38.96, 38.70, 33.85, 33.27, 32.02, 31.49, 30.86, 28.28, 27.68, 27.63, 27.43, 27.37, 27.05, 26.86, 26.71, 26.59, 26.48, 24.40, 23.82, 23.33, 22.42, 14.22, 14.12, 14.00; \) HRMS (ESI) m/z calcd for \(\text{C}_{26}\text{H}_{38}\text{NO}_6\) \([\text{M+H}]^+\) 460.2699, found 460.2697. IR (film) 2926, 1698, 1404, 1097, 698 cm\(^{-1}\);

(\(\pm\))-Diethyl 2-(1-(tetrahydro-2\(H\)-pyran-2-yl)ethyl)malonate: According to the general procedure, \(\text{Ir}[\text{dF(CF}_3\text{ppy})_2(\text{dtbbpy})\text{PF}_6\) (2.2 mg, 2 \(\mu\)mol, 0.01 equiv.), tetrahydro-2\(H\)-pyran-4-carboxylic acid (26 mg, 0.2 mmol, 1.0 equiv), diethyl ethyldienemalonate (37.3 mg, 0.20 mmol, 1.0 equiv), \(\text{K}_2\text{HPO}_4\) (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (50 mg, 90%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) mixture of diastereomers: \(\delta 4.23-4.15\) (m, 4H), 3.94 (d, \(J = 10.5\) Hz, 1H), 3.73 (d, \(J = 5.5\) Hz, 0.4H), 3.51 (d, \(J = 9.0\) Hz, 0.6H), 3.37-3.26 (m, 1.6H), 3.16 (t, \(J = 9.5\) Hz, 0.4H), 2.33-2.27 (m, 1H), 1.87-1.84 (m, 1H), 1.74 and 1.72 (2 brs, 0.4H), 1.53-1.42 (m, 4H), 1.28-1.17 (m, 6.6H), 1.00-0.97 (m, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) mixture of diastereomers: \(\delta 169.66, 169.11, 169.05, 168.88, 79.27, 78.47, 68.69, 68.54, 61.13, 61.08, 60.98, 60.79, 54.94, 52.92, 39.03, 38.14, 29.16, 28.65, 26.02, 26.00, 23.71, 23.46, 14.16,
14.11, 14.08, 12.88, 11.70; HRMS (ESI) m/z calcd for C_{14}H_{25}O_5 [(M+H)^+] 273.1702, found 273.1703. IR (film) 2939, 1749, 1729, 1088, 1029, 895 cm\(^{-1}\);

(±)-Diethyl 2-(1-(tetrahydrofuran-2-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6 (2.2 mg, 2 \(\mu\)mol, 0.01 equiv.), tetrahydro-2-furoic acid (24 mg, 0.2 mmol, 1.0 equiv), diethyl ethylidenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K_2HPO_4 (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (47.5 mg, 92%). \(^1\)H NMR (500 MHz, CDCl_3) mixture of diastereomers: \(\delta\) 4.24-4.16 (m, 4H), 3.86-3.68 (m, 3H), 3.61 (d, \(J = 6.0\) Hz, 0.55H), 3.42 (d, \(J = 9.0\) Hz, 0.45H), 2.52-2.45 (m, 0.45H), 2.33-2.26 (m, 0.55H), 2.03-1.82 (m, 3H), 1.64-1.57 (m, 1H), 1.28-1.25 (m, 6H), 0.98 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl_3) mixture of diastereomers: \(\delta\) 169.31, 168.86, 168.83, 168.77, 81.25, 80.35, 68.32, 67.75, 61.22, 61.17, 61.09, 61.00, 54.93, 54.42, 39.09, 37.36, 30.00, 28.46, 25.98, 25.86, 14.13, 14.09, 14.06, 14.05, 13.49, 12.31; HRMS (ESI) m/z calcd for C_{13}H_{23}O_5 [(M+H)^+] 259.1545, found 259.1525. IR (film) 2978, 1748, 1728, 1153, 1065, 1030 cm\(^{-1}\);

(±)-Diethyl 2-(1-cyclohexylethyl)malonate [known compound (2)]: According to the general procedure, Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6 (2.2 mg, 2 \(\mu\)mol, 0.01 equiv.),
cyclohexanecarboxylic acid (26 mg, 0.2 mmol, 1.0 equiv), diethyl ethyldienemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), 0.5 mL of DMF and 34 W Blue LED (instead of 26 W fluorescent light bulb) were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (41 mg, 75%). ¹H NMR (500 MHz, CDCl₃) δ 4.23-4.16 (m, 4H), 3.39 (d, J = 9.5 Hz, 1H), 2.21-2.14 (m, 1H), 1.76-1.71 (m, 2H), 1.67-1.57 (m, 3H), 1.30-1.08 (m, 11H), 0.98-0.92 (m, 1H), 0.90 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.30, 169.05, 61.14, 61.06, 55.81, 40.24, 38.56, 31.52, 27.37, 26.73, 26.53, 26.46, 14.13, 12.89; HRMS (ESI) m/z calcd for C₁₅H₂₆NaO₄ [(M+Na)⁺] 293.1729, found 293.1727. IR (film) 2925, 1753, 1729, 1147, 1031 cm⁻¹;

(±)-Diethyl 2-(1-cyclobutylethy)lmalonate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), cyclobutanecarboxylic acid (20 mg, 0.2 mmol, 1.0 equiv), diethyl ethyldienemalonate (54 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.3 mmol, 1.2 equiv), 0.5 mL of DMF and 34 W Blue LED (instead of 26 W fluorescent light bulb) were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (33 mg, 68%). ¹H NMR (500 MHz, CDCl₃) δ 4.20-4.14 (m, 4H), 3.22 (d, J = 6.5 Hz, 1H), 2.27-2.13 (m, 2H), 2.01-1.89 (m, 2H), 1.83-1.74 (m, 1H), 1.72-1.62 (m, 3H), 1.27 (t, J = 7.5 Hz, 6H), 0.91 (d, J = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.26, 168.71, 61.16, 60.96, 55.03, 40.10, 39.95, 27.28, 27.05, 17.50, 14.14, 14.06, 13.96; HRMS (ESI) m/z calcd for
C_{13}H_{22}NaO_{4} [(M+Na)^+] 265.1416, found 265.1400. IR (film) 2970, 1750, 1729, 1148, 1032 cm^{-1}.

(±)-Diethyl 2-(1-cyclopentylethyl)malonate: According to the general procedure, Ir[dF(CF_{3})ppy]_{2}(dtbbpy)PF_{6} (2.2 mg, 2 µmol, 0.01 equiv.), cyclopentanecarboxylic acid (24 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenediamonate (37.3 mg, 0.2 mmol, 1.0 equiv), K_{2}HPO_{4} (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of 1,4-dioxane were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (30 mg, 58%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.19 (q, \(J = 7.5\) Hz, 4H), 3.41 (d, \(J = 6.5\) Hz, 1H), 2.17-2.10 (m, 1H), 1.79-1.71 (m, 3H), 1.64-1.58 (m, 2H), 1.53-1.50 (m, 2H), 1.27 (td, \(J = 7.5\) Hz, \(J = 2.5\) Hz, 6H), 1.19-1.13 (m, 2H), 1.02 (d, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.48, 168.86, 61.15, 60.91, 56.32, 43.82, 38.48, 30.96, 29.66, 25.32, 25.28, 14.61, 14.16, 14.10; HRMS (ESI) m/z calcd for C_{14}H_{25}O_{4} [(M+H)^+] 257.1753, found 257.1770. IR (film) 2952, 1750, 1728, 1124, 1150, 1030 cm\(^{-1}\);

(±)-Diethyl 2-(nonan-2-yl)malonate: According to the general procedure, Ir[dF(CF_{3})ppy]_{2}(dtbbpy)PF_{6} (2.2 mg, 2 µmol, 0.01 equiv.), octanoic acid (29 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenediamonate (37.3 mg, 0.2 mmol, 1.0 equiv), K_{2}HPO_{4} (42.0 mg, 0.24 mmol, 1.2 equiv), 0.5 mL of DMF and 34 W Blue LED (instead of 26 W
fluorescent light bulb) were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a colorless oil (22 mg, 38%). \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.19 (q, \( J = 7.0 \) Hz, 4H), 3.22 (d, \( J = 8.0 \) Hz, 1H), 2.27-2.19 (m, 1H), 1.42-1.18 (m, 18H), 0.98 (d, \( J = 7.0 \) Hz, 3H), 0.87 (t, \( J = 7.0 \) Hz, 3H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 169.05, 168.89, 61.12, 61.06, 57.84, 34.34, 33.39, 31.83, 29.59, 29.24, 26.81, 22.66, 16.96, 14.14, 14.12, 14.11; HRMS (ESI) m/z calcd for C\(_{16}\)H\(_{30}\)NaO\(_4\) [(M+Na)\(^+\)] 309.2036, found 309.2026. IR (film) 2927, 1753, 1731, 1148, 1031 cm\(^{-1} \).

(±)-Diethyl 2-(3-hexylundecan-2-yl)malonate: According to the general procedure, Ir[dF(CF\(_3\)ppy)]\(_2\)(dtbbpy)PF\(_6\) (2.2 mg, 2 \( \mu \)mol, 0.01 equiv.), 2-hexyldecanoic acid (52 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenedimalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K\(_2\)HPO\(_4\) (42.0 mg, 0.24 mmol, 1.2 equiv), 0.5 mL of DMF and 34 W Blue LED (instead of 26 W fluorescent light bulb) were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (42 mg, 53%). \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.21-4.16 (m, 4H), 3.34 (d, \( J = 10.5 \) Hz, 1H), 2.46-2.38 (m, 1H), 1.36-1.17 (m, 30H), 1.00-0.94 (m, 1H), 0.88 (t, \( J = 7.0 \) Hz, 6H), 0.81 (t, \( J = 7.0 \) Hz, 3H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 169.12, 168.97, 61.16, 56.63, 39.69, 35.09, 31.93, 31.89, 31.79, 30.32, 30.09, 29.96, 29.75, 29.64, 29.59, 29.38, 29.31, 28.06, 28.02, 27.42, 27.39, 22.70, 14.13, 11.61; HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{46}\)NaO\(_4\) [(M+Na)\(^+\)] 421.3294, found 421.3293. IR (film) 2924, 2855, 1757, 1733, 1175, 1032 cm\(^{-1} \);
(±)-Diethyl 2-((3r,5r,7r)-adamantan-1-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), 1-adamantane-carboxylic acid (36 mg, 0.2 mmol, 1.0 equiv), diethyl ethylidenemalonate (37.7 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), 0.5 mL of DMF and 34 W Blue LED (instead of 26 W fluorescent light bulb) were used. The product was isolated by flash chromatography (10% ethyl acetate/hexane) as a pale yellow oil (60 mg, 93%). ¹H NMR (500 MHz, CDCl₃) δ 4.21-4.14 (m, 4H), 3.57 (d, J = 5.5 Hz, 1H), 2.09-2.04 (m, 1H), 1.98-1.95 (m, 3H), 1.69-1.67 (m, 3H), 1.61-1.59 (m, 3H), 1.53-1.47 (m, 6H), 1.27 (q, J = 7.0 Hz, 6H), 0.98 (d, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.38, 169.79, 169.32, 60.89, 61.32, 51.83, 43.08, 39.36, 37.02, 35.23, 28.61, 14.09, 14.05, 10.40; HRMS (ESI) m/z calcd for C₁₉H₃₀NaO₄ [(M+Na)⁺] 345.2042, found 345.2024. IR (film) 3001, 2848, 1728, 1218, 1148, 1137, 1031 cm⁻¹;

(±)-Diethyl 2-((tert-butoxycarbonyl)amino)-4-phenylbutan-2-yl)malonate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Phe-OH (53.0 mg, 0.2 mmol, 1.0 equiv), diethyl ethylidenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (15% ethyl acetate/hexane)
as a pale yellow oil (77 mg, 94%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers: δ 7.29-7.25 (m, 2H), 7.21-7.15 (m, 3H), 4.49 (d, $J = 9.5$ Hz, 0.43H), 4.32-3.98 (m, 5H), 3.86-3.72 (m, 0.57H), 3.51-3.46 (m, 0.55H), 3.39-3.33 (m, 0.45H), 2.99-2.95 (m, 0.6H), 2.81-2.73 (m, 0.8H), 2.66-2.61 (m, 0.6H), 2.50-2.39 (m, 1H), 1.32-1.19 (m, 15H), 1.15 (d, $J = 6.5$ Hz, 1.7H), 0.95 (d, $J = 7.0$ Hz, 1.3H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers: δ 169.67, 169.01, 168.43, 155.56, 155.34, 138.03, 137.97, 129.41, 129.17, 128.51, 128.48, 126.48, 79.30, 79.21, 61.60, 61.48, 61.46, 61.43, 55.65, 55.26, 54.28, 52.81, 39.93, 39.08, 37.18, 35.76, 28.36. 15.12, 14.20, 14.18, 14.12, 11.15; HRMS (ESI) m/z calcd for C$_{22}$H$_{34}$NO$_6$ [(M+H)$^+$] 408.2386, found 408.2388. IR (film) 2978, 1704, 1365, 1165, 1026, 699 cm$^{-1}$;

![Chemical Structure Image]

(±)-Diethyl 2-(6-amino-3-((tert-butoxycarbonyl)amino)-6-oxohexan-2-yl)malonate:

According to the general procedure, Ir[dF(CF$_3$ppy)$_2$(dtbbpy)]$_2$ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Gln-OH (49 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenediamononate (37.3 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (60% ethyl acetate/hexane) as a pale yellow solid (65 mg, 84%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers: δ 6.35 (s, 0.5H), 6.14 (s, 0.5H), 5.40 (s, 1H), 4.76 (d, $J = 10.0$ Hz, 0.5H), 4.46 (d, $J = 10.5$ Hz, 0.5H), 4.23-4.17 (m, 4H), 3.87-3.81 (m, 0.5H), 3.64-3.59 (m, 0.5H), 3.44 (d, $J = 6.5$ Hz, 0.5H), 3.20 (d, $J = 10.0$ Hz, 0.5H), 2.46-2.34 (m, 1H), 2.29-2.24 (m, 2H), 2.02-1.96 (m, 0.5H), 1.83-1.77 (m, 2H), 1.63-1.55 (m, 0.5H), 1.42 (s, 9H), 1.29-1.24
(m, 6H), 1.06 (d, $J = 7.0$ Hz, 1.5H), 0.91 (d, $J = 7.0$ Hz, 1.5H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers: $\delta$ 175.61, 175.55, 169.42, 168.91, 168.81, 168.52, 156.35, 156.30, 79.56, 79.49, 61.64, 61.53, 61.48, 61.47, 55.53, 54.25, 53.49, 51.50, 37.90, 36.96, 32.96, 32.65, 29.75, 29.28, 28.39, 28.36, 14.73, 14.13, 14.09, 14.03, 11.14; HRMS (ESI) m/z calcd for C$_{18}$H$_{33}$N$_2$O$_7$ [(M+H)$^+$] 389.2288, found 389.2296. IR (film) 3347, 2978, 1670, 1165, 1026, 735 cm$^{-1}$; 

(±)-5-Benzyl 1,1-diethyl 3-((tert-butoxycarbonyl)amino)-2-methylpentane-1,1,5-tricarboxylate: According to the general procedure, Ir[dF(CF$_3$)ppy)]$_2$(dtbbpy)PF$_6$ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Glu(OBzl)-OH (67 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (89 mg, 93%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers: $\delta$ 7.38-7.31 (m, 5H), 5.15-5.08 (m, 2H), 4.52 (d, $J = 10.0$ Hz, 0.4H), 4.31 (d, $J = 10.5$ Hz, 0.4H), 4.22-4.16 (m, 4.2H), 3.86-3.74 (m, 0.5H), 3.62-3.49 (m, 0.5H), 3.42 (d, $J = 7.0$ Hz, 0.5H), 3.28 (d, $J = 10.0$ Hz, 0.5H), 2.50-2.34 (m, 3H), 2.03-1.96 (m, 0.5H), 1.85-1.74 (m, 1H), 1.65-1.60 (m, 0.5H), 1.41 (m, 5H), 1.40 (s, 4H), 1.27 (qd, $J = 7.0$ Hz, $J = 3.0$ Hz, 6H), 1.05 (d, $J = 7.0$ Hz, 1.6H), 0.89 (d, $J = 7.0$ Hz, 1.4H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers: $\delta$ 173.23, 173.20, 169.45, 168.82, 168.78, 168.38, 155.70, 155.51, 135.90, 135.89, 128.56, 128.24, 128.21, 128.20, 79.37, 79.26, 66.37, 66.34, 61.56, 61.43, 61.37, 55.41, 54.26, 53.59,
(±)-Diethyl 2-(3-((tert-butoxycarbonyl)amino)-5-(methylthio)pentan-2-yl)malonate:

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Met-OH (50.0 mg, 0.2 mmol, 1.0 equiv), diethyl ethylidenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (74 mg, 94%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers: δ 4.56 (d, J = 9.5 Hz, 0.5H), 4.31 (d, J = 10.5 Hz, 0.3H), 4.23-4.17 (m, 4.2H), 3.92-3.87 (m, 0.4H), 3.68-3.63 (m, 0.6H), 3.42 (d, J = 7.0 Hz, 0.6H), 3.29 (d, J = 10.0 Hz, 0.4H), 2.59-1.67 (m, 8H), 1.43 (s, 5H), 1.42 (s, 4H), 1.29-1.25 (m, 6H), 1.05 (d, J = 7.0 Hz, 1.7H), 0.89 (d, J = 7.0 Hz, 1.3H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers: δ 169.53, 168.90, 168.45, 155.74, 155.58, 79.46, 79.32, 61.64, 61.53, 61.46, 55.49, 54.33, 53.58, 51.41, 37.66, 36.80, 34.02, 33.02, 31.16, 30.85, 28.42, 28.39, 15.76, 15.74, 14.81, 14.17, 14.14, 14.08, 11.20; HRMS (ESI) m/z calcd for C₁₈H₃₃NNaO₆S [(M+Na)⁺] 414.1926, found 414.1940. IR (film) 2978, 1715, 1366, 1168, 1031 cm⁻¹;
(±)-Diethyl 2-(4-(benzyloxy)-3-((tert-butoxycarbonyl)amino)butan-2-yl)malonate:

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Ser(Bzl)-OH (59 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenediamonate (37.3 mg, 0.2 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (25% ethyl acetate/hexane) as a pale yellow oil (83 mg, 94%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers: δ 7.36-7.27 (m, 5H), 4.94 (d, $J$ = 9.5 Hz, 0.5H), 4.68 (d, $J$ = 9.5 Hz, 0.5H), 4.53-4.46 (m, 2H), 4.23-4.14 (m, 4H), 4.04-3.92 (m, 0.5H), 3.78-3.75 (m, 0.5H), 3.63-3.55 (m, 1.5H), 3.50-3.46 (m, 1H), 3.41 (d, $J$ = 9.0 Hz, 0.5H), 2.61-2.56 (m, 1H), 1.43 (s, 4.3H), 1.42 (s, 4.7H), 1.26 (td, $J$ = 7.0 Hz, $J$ = 2.5 Hz, 6H), 1.05 (d, $J$ = 7.0 Hz, 1.6H), 0.96 (d, $J$ = 7.0 Hz, 1.4H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers: δ 169.76, 168.99, 168.88, 168.76, 155.80, 155.61, 138.11, 128.50, 128.49, 127.81, 127.76, 127.69, 79.45, 79.35, 73.29, 73.06, 70.96, 70.20, 61.48, 61.38, 61.26, 55.12, 53.89, 53.50, 51.23, 34.94, 34.91, 28.46, 14.41, 14.21, 14.18, 14.14, 12.31; HRMS (ESI) m/z calcd for C$_{23}$H$_{36}$NO$_7$ [(M+H)$^+$] 438.2492, found 438.2496. IR (film) 2978, 1715, 1164, 1028, 698 cm$^{-1}$;
(±)-Diethyl 2-(3-((tert-butoxycarbonyl)amino)-4-(1H-indol-3-yl)butan-2-yl)malonate:

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Trp-OH (61 mg, 0.2 mmol, 1.0 equiv), diethyl ethlylidenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow solid (51 mg, 57%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers: δ 8.02 (br, 1H), 7.60 (dd, J = 17.5 Hz, J = 8.0 Hz, 1H), 7.60 (dd, J = 8.0 Hz, J = 3.5 Hz, 1H), 7.20-7.16 (m, 1H), 7.13-7.05 (m, 2H), 4.59 (d, J = 9.5 Hz, 0.3H), 4.41 (d, J = 9.5 Hz, 0.3H), 4.30-4.28 (m, 0.4H), 4.22-4.15 (m, 4.5H), 3.95 (br, 0.5H), 3.54 (d, J = 6.5 Hz, 0.5H), 3.39 (d, J = 10.0 Hz, 0.5H), 3.10-3.06 (m, 0.5H), 2.95-2.78 (m, 1.5H), 2.62-2.56 (m, 0.5H), 2.48 (q, J = 7.0 Hz, 0.5H), 1.35-1.33 (m, 6H), 1.29-1.17 (m, 9H), 1.10-1.03 (m, 1.5H), 0.97 (d, J = 7.0 Hz, 1.5H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers: δ 169.80, 169.20, 169.12, 168.65, 155.85, 155.63, 136.57, 136.27, 128.07, 127.82, 127.54, 122.78, 122.63, 122.46, 121.97, 121.88, 119.40, 119.30, 118.86, 118.69, 111.98, 111.47, 111.25, 79.31, 79.11, 61.57, 61.51, 61.45, 55.77, 54.56, 54.16, 52.07, 36.86, 36.42, 35.76, 28.36, 27.73, 15.15, 14.18, 14.14, 14.05, 11.09; HRMS (ESI) m/z calcd for C₂₄H₃₅N₂O₆ [(M+H)⁺] 447.2495, found 447.2498. IR (film) 3387, 2978, 1721, 1169, 1027, 741 cm⁻¹;
(±)-Diethyl 2-(1-((((benzyloxy)carbonyl)glycyl)pyrrolidin-2-yl)ethyl)malonate:

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 mg, 2 μmol, 0.01 equiv.), Z-Gly-Pro (61.1 mg, 0.2 mmol, 1.0 equiv), diethyl ethyldienemalonate (37.3 mg, 0.20 mmol, 1.0 equiv), K$_2$HPO$_4$ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow solid (79 mg, 88%). $^1$H NMR (500 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 7.36-7.22 (m, 5H), 5.80-5.59 (m, 1H), 5.14-5.09 (m, 2H), 4.31-4.28 (m, 0.4H), 4.23-4.13 (m, 4H), 4.09-4.00 (m, 0.6H), 4.00 (d, J = 4.0 Hz, 0.15H), 3.96 (dd, J = 7.0 Hz, J = 7.0 Hz, 0.55H), 3.91 (q, J = 4.5 Hz, 0.6H), 3.87 (d, J = 4.0 Hz, 0.3H), 3.81 (d, J = 4.0 Hz, 0.2H), 3.78 (q, J = 4.5 Hz, 0.2H), 3.64 (q, J = 9.5 Hz, 0.4H), 3.50-3.47 (m, 0.6H), 3.46-3.44 (m, 0.4H), 3.32-3.18 (m, 1.6H), 2.70-2.65 (m, 1H), 2.10-1.76 (m, 4H), 1.29-1.19 (m, 6H), 1.01 (d, J = 7.0 Hz, 0.2H), 0.95 (d, J = 6.5 Hz, 1.3H), 0.92 (d, J = 7.0 Hz, 0.2H), 0.88 (d, J = 7.0 Hz, 1.3H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 169.01, 168.84, 168.67, 168.46, 168.37, 168.11, 168.05, 167.92, 167.70, 167.58, 156.25, 156.21, 136.56, 136.54, 128.55, 128.12, 128.03, 66.86, 62.04, 62.00, 61.81, 61.79, 61.51, 61.38, 61.36, 61.07, 60.26, 60.05, 59.05, 55.70, 55.09, 53.30, 46.93, 46.82, 46.39, 46.06, 43.78, 43.48, 43.37, 37.25, 36.78, 36.35, 36.16, 29.14, 27.60, 24.47, 23.84, 22.73, 22.32, 14.26, 14.17, 14.11, 14.05, 13.38; HRMS (ESI) m/z calcd for C$_{23}$H$_{33}$N$_2$O$_7$ [(M+H)$^+$] 449.2288, found 449.2278. IR (film) 2976, 1721, 1647, 1243, 1028, 698 cm$^{-1}$;
(±)-Diethyl 2-(3-((benzyloxy)carbonyl)amino)acetamido)-4-phenylbutan-2-yl)malonate: According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Z-Gly-Phe (71.3 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 1.0 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow solid (90 mg, 90%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 7.37-7.30 (m, 5H), 7.27-7.24 (m, 2H), 7.21-7.17 (m, 1H), 7.16-7.12 (m, 2H), 6.44 (d, J = 9.0 Hz, 0.6H), 5.92 (d, J = 8.0 Hz, 0.4H), 5.21 (br, 1H), 5.13 (s, 2H), 4.47 (q, J = 8.0 Hz, 0.4H), 4.24-4.14 (m, 4.6H), 3.76-3.67 (m, 2H), 3.50 (d, J = 6.5 Hz, 0.6H), 3.29 (d, J = 9.5 Hz, 0.4H), 2.93-2.89 (m, 0.6H), 2.84-2.80 (m, 0.4H), 2.75-2.71 (m, 1H), 2.53-2.41 (m, 1H), 1.27-1.22 (m, 6H), 1.14 (d, J = 6.5 Hz, 1.7H), 0.94 (d, J = 7.0 Hz, 1.3H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 169.24, 168.99, 168.82, 168.48, 168.38, 156.73, 156.51, 137.73, 137.57, 136.27, 136.21, 129.24, 128.97, 128.60, 128.57, 128.50, 128.48, 128.29, 128.24, 128.03, 126.62, 126.58, 67.12, 67.07, 61.72, 61.64, 61.53, 61.43, 55.59, 53.95, 53.59, 51.67, 44.62, 44.47, 39.32, 38.14, 36.23, 35.91, 15.01, 14.12, 14.07, 14.06, 11.14; HRMS (ESI) m/z calcd for C₂₇H₃₅N₂O₇ [(M+H)⁺] 449.2444, found 449.2420. IR (film) 3321, 2980, 1722, 1230, 1027, 733, 697 cm⁻¹;
(±)-Diethyl 2-(1-(1-((benzyloxy)carbonyl)pyrrolidin-2-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF\textsubscript{3})ppy]\textsubscript{2}(dtbbpy)PF\textsubscript{6} (2.2 mg, 2 µmol, 0.01 equiv.), Z-Pro-OH (50.0 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K\textsubscript{2}HPO\textsubscript{4} (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (72 mg, 92%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) mixture of diastereomers and rotamers: δ 7.42-7.29 (m, 5H), 5.21-5.03 (m, 2H), 4.20-3.84 (m, 5H), 3.69-3.36 (m, 2H), 3.24-3.17 (m, 1H), 2.80-2.73 (m, 0.6H), 2.68-2.63 (m, 0.4H), 2.02-1.72 (m, 4H), 1.28-1.18 (m, 6H), 0.96-0.87 (m, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) mixture of diastereomers and rotamers: δ 169.05, 168.93, 168.87, 168.81, 168.71, 168.56, 168.47, 155.95, 155.85, 155.70, 155.27, 136.87, 136.81, 136.72, 136.65, 128.44, 128.20, 128.14, 127.92, 127.83, 127.77, 67.11, 66.79, 61.70, 61.46, 61.23, 60.56, 60.47, 59.96, 55.58, 55.13, 55.00, 54.50, 47.95, 47.66, 47.26, 46.76, 37.13, 37.05, 29.15, 28.78, 28.27, 28.16, 24.41, 23.79, 23.65, 23.19, 14.22, 14.12, 14.06, 14.02, 13.87, 13.68, 13.48; HRMS (ESI) m/z calcd for C\textsubscript{21}H\textsubscript{30}NO\textsubscript{6} [(M+H)\textsuperscript{+}] 392.2073, found 392.2066. IR (film) 2977, 1695, 1405, 1096, 1027, 697 cm\textsuperscript{-1};
(±)-Diethyl 2-(1-(1-tert-butoxycarbonyl)pyrrolidin-2-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF₃ppy)]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Pro-OH (43.0 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (69 mg, 97%). ^1H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 4.22-4.11 (m, 4H), 3.97-3.30 (m, 3H), 3.17-3.12 (m, 0.55H), 3.11-3.06 (m, 0.45H), 2.75-2.71 (m, 0.83H), 2.60-2.53 (m, 0.17H), 2.00-1.67 (m, 4H), 1.46 (s, 9H), 1.28-1.23 (m, 6H), 0.94-0.88 (m, 3H); ^13C NMR (125 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 168.88, 168.73, 168.36, 168.36, 155.43, 155.20, 154.79, 79.77, 79.07, 61.29, 61.12, 60.52, 60.26, 59.91, 55.52, 54.74, 54.00, 47.72, 47.14, 46.95, 46.81, 37.00, 36.77, 28.45, 28.42, 24.37, 23.77, 23.48, 23.26, 14.08, 14.02; HRMS (ESI) m/z calcd for C₁₈H₃₂NO₆ [(M+H)^+] 358.2230, found 358.2235. IR (film) 2975, 1729, 1689, 1381, 1365, 1162, 1105, 1030, 773 cm⁻¹; 

(±)-Diethyl 2-(1-(1-benzylopyrrolidin-2-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF₃ppy)]₂(dtbbpy)PF₆ (5.5 mg, 5 µmol, 0.01 equiv.), Benzoyl-L-proline (110 mg, 0.5 mmol, 1.0 equiv.), K₂HPO₄ (105 mg, 0.6 mmol, 1.2 equiv.), diethyl 2-ethylenemalonate (93 mg, 0.5 mmol, 1.0 equiv.) and DMF (1.25 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a pale yellow oil (150 mg, 83%). ^1H NMR (500 MHz, CDCl₃) mixture of diastereomers and
rotamers: δ 7.56-7.48 (m, 2H), 7.44-7.34 (m, 3H), 4.57 (td, J = 8.0, 3.0 Hz, 0.4H), 4.48-4.42 (m, 0.6H), 4.30-4.10 (m, 4H), 3.82 (d, J = 10.0 Hz, 0.4H), 3.54-3.47 (m, 1H), 3.44-3.36 (m, 1.6H), 3.02-2.93 (m, 0.6H), 2.80-2.71 (m, 0.4 H), 2.26-2.17 (m, 0.4H), 2.20-1.56 (m, 3.6 H), 1.29-1.19 (m, 6H), 1.01-0.99 (m, 3H); 13C NMR (125 MHz, CDCl3) mixture of diastereomers and rotamers: δ 171.51, 170.63, 169.34, 169.20, 168.88, 168.68, 136.88, 136.82, 130.24, 130.14, 128.16, 128.10, 127.69, 127.61, 61.37, 61.25, 61.21, 61.17, 59.92, 59.05, 55.48, 51.99, 50.81, 37.31, 35.29, 29.42, 26.82, 25.40, 25.12, 14.12, 14.09, 14.02, 14.00, 12.97, 12.49; HRMS (ESI) m/z calcd for C20H28NO5 [(M+H)+] 362.1962, found 362.19642. IR (film) 2977, 1747, 1726, 1627, 1394, 1265, 1174, 1150, 1027, 792, 700 cm−1.

**(+)-Diethyl 2-(1-(tert-butoxycarbonyl)piperidin-2-yl)ethylmalonate:** According to the general procedure, Ir[dF(CF3)ppy]2(dtbbpy)PF6 (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Pip-OH (45.8 mg, 0.2 mmol, 1.0 equiv), diethyl ethylidenemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K2HPO4 (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (70 mg, 94%). 1H NMR (500 MHz, CDCl3) mixture of diastereomers: δ 4.26-3.95 (m, 6H), 3.43 (d, J = 4.5 Hz, 1H), 2.79-2.68 (m, 2H), 1.80-1.78 (m, 0.4H), 1.71-1.69 (m, 0.6H), 1.58-1.49 (m, 5H), 1.44 (s, 9H), 1.30-1.24 (m, 6H), 1.07 (d, J = 6.5 Hz, 1.3H), 0.99 (d, J = 7.0 Hz, 1.7H); 13C NMR (125 MHz, CDCl3) mixture of diastereomers: δ 169.87, 169.24, 168.52, 168.24, 155.16, 155.14, 79.50, 79.39, 61.49, 61.39, 61.17, 60.91,
53.37, 53.14, 31.97, 31.70, 28.49, 28.45, 26.18, 25.39, 19.04, 18.89, 14.21, 14.14, 14.11, 13.80, 12.90; HRMS (ESI) m/z calcd for C_{19}H_{33}NNaO_6 [(M+Na)^+] 394.2206, found 394.2192. IR (film) 2977, 2935, 1687, 1150, 1028, 866 cm^{-1};

(±)-Diethyl 2-(1-(4-(tert-butoxycarbonyl)morpholin-3-yl)ethyl)malonate: According to the general procedure, Ir[dF(CF_3)ppy)]_2(dtbbpy)PF_6 (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Morph-OH (46.2 mg, 0.2 mmol, 1.0 equiv), diethyl ethyldienemalonate (37.3 mg, 0.20 mmol, 1.0 equiv), K_2HPO_4 (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (71 mg, 95%). ^1H NMR (500 MHz, CDCl_3) mixture of diastereomers: δ 4.23-4.10 (m, 4H), 4.01-3.78 (m, 4H), 3.51-3.44 (m, 3H), 3.13-3.03 (m, 1H), 2.93-2.85 (m, 1H), 1.46 (s, 4.5H), 1.45 (s, 4.5H); 1.30-1.25 (m, 6H), 1.16 (d, J = 7.0 Hz, 1.5H), 1.05 (d, J = 7.0 Hz, 1.5H); ^13C NMR (125 MHz, CDCl_3) mixture of diastereomers: δ 168.83, 168.26, 168.22, 154.76, 154.59, 80.28, 67.21, 67.14, 61.48, 61.27, 60.97, 52.90, 52.66, 31.21, 28.40, 28.36, 14.21, 14.16, 14.14, 14.09, 13.67, 12.80; HRMS (ESI) m/z calcd for C_{18}H_{31}NNaO_7 [(M+Na)^+] 396.1998, found 396.1995. IR (film) 2978, 1729, 1690, 1103, 866 cm^{-1};
(±)-Diethyl 2-(1-((tert-butoxycarbonyl)amino)propan-2-yl)malonate: According to the general procedure, Ir[dF(CF₃ppy)]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Gly-OH (35.0 mg, 0.2 mmol, 1.0 equiv), diethyl ethylenediamonemalonate (37.3 mg, 0.2 mmol, 1.0 equiv), K₂HPO₄ (42.0 mg, 0.24 mmol, 1.2 equiv), and 0.5 mL of DMF were used. The product was isolated by flash chromatography (25% ethyl acetate/hexane) as a pale yellow oil (60 mg, 94%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers: δ 4.71 (s, 1H), 4.20 (qd, J = 7.0 Hz, J = 2.0 Hz, 4H), 3.31 (d, J = 7.5 Hz, 1H), 3.22-3.12 (m, 2H), 2.48-2.43 (m, 1H), 1.43 (s, 9H), 1.27 (d, J = 7.5 Hz, 6H), 1.01 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) mixture of diastereomers: δ 168.78, 168.56, 155.96, 79.21, 61.41, 61.35, 55.02, 44.18, 34.08, 28.37, 15.52, 14.09, 14.06; HRMS (ESI) m/z calcd for C₁₅H₂₇NNaO₆ [(M+Na)⁺] 340.1736, found 340.1739. IR (film) 2978, 1714, 1515, 1246, 1164, 1030 cm⁻¹;

3. Synthetic Procedures and Characterization of (±)-Lyrica
(±)-Dimethyl 2-(1-((tert-butoxycarbonyl)amino)-4-methylpentan-2-yl)malonate:
According to the general procedure of decarboxylative alkylation, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.2 mg, 2 µmol, 0.01 equiv.), Boc-Gly-OH (35 mg, 0.2 mmol, 1.0 equiv.), K₂HPO₄ (41.8 mg, 0.24 mmol, 1.2 equiv.), dimethyl 2-(3-methylbutylidene)malonate (42.4 mg, 0.2 mmol, 1.0 equiv.) and DMF (0.5 mL) were used. The product was isolated by flash chromatography (30% ethyl acetate in hexanes) as a pale yellow oil (64 mg, 96%). ¹H NMR (500 MHz, CDCl₃) mixture of rotamers: δ 4.80 (br, 0.8H), 4.66 (br, 0.2H), 3.66 (d, J = 2.5 Hz, 6H), 3.36 (d, J = 6.5 Hz, 1H), 3.23-3.18 (m, 1H), 3.22-3.19 (m, 1H), 3.11-3.01 (m, 1H), 2.40-2.33 (m, 1H), 1.65-1.54 (m, 1H), 1.45 (s, 9H), 1.19-1.13 (m, 1H), 1.06-0.99 (m, 1H), 0.82 (m, 6H); ¹³C NMR mixture of rotamers (125 MHz, CDCl₃): δ 169.29, 155.83, 79.01, 53.62, 52.36, 52.33, 41.51, 39.14, 36.96, 28.31, 25.26, 23.21, 21.85; HRMS (ESI) m/z calcd for C₁₆H₂₉NNaO₆ [(M+Na)⁺] 354.1887, found 354.1888. IR (film) 2956, 1732, 1713, 1509, 1435, 1366, 1246, 1159, 1018 cm⁻¹;

(±)-4-Isobutyl-2-oxopyrrolidine-3-carboxylic acid: A flask was charged with (±)-Dimethyl 2-(1-((tert-butoxycarbonyl)amino)-4-methylpentan-2-yl)malonate (450 mg, 1.36 mmol) and KOH (229 mg, 4.07 mmol, 3 equiv.) solution in water (2 mL) and the mixture
was heated to reflux for 20 h and then cooled to room temperature. The pH of the solution was adjusted to 2 with conc. HCl and diluted with ethyl acetate. The solution was extracted twice with ethyl acetate and concentrated. The residue was purified by column chromatography (3% methanol in dichloromethane then 10% methanol in dichloromethane) to give a colorless powder (200 mg, 80%). $^1$H NMR (500 MHz, CDCl$_3$): δ 9.87 (br, 1H), 7.47 (s, 1H), 3.52 (t, $J$ = 9.0 Hz, 1H), 3.02 (t, $J$ = 9.0 Hz, 1H), 2.97 (t, $J$ = 8.0 Hz, 1H), 2.88-2.79 (m, 1H), 1.57-1.47 (m, 2H), 1.35-1.26 (m, 1H), 0.86 (d, $J$ = 6.0 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 175.24, 172.14, 53.81, 47.18, 43.18, 36.87, 25.94, 22.90, 22.19; HRMS (ESI) $m/z$ calcd for C$_9$H$_{16}$NO$_3$ [(M+H)$^+$] 186.1125, found 186.1125;

(±)-3-(Aminomethyl)-5-methylhexanoic acid [known compound (3)]: A flask was charged with (±)-4-isobutyl-2-oxopyrrolidine-3-carboxylic acid (200 mg, 1.08 mmol), solution of conc. HCl (240 mg, 2.37 mmol, 2.2 equiv.) in water (2 mL) and acetic acid (20 mg, 0.33 mmol, 0.31 equiv.). The mixture was heated to reflux for 48 h and then cooled to room temperature. The solution was concentrated and the residue was purified by ion-exchange chromatography on Dowex 50W-8 (H$^+$) (H$_2$O until pH 7 and then 0.5 mol/L NH$_4$OH). Fractions containing product were concentrated and crystallized from ethanol and water to give a colorless powder (121 mg, 70%). mp 166.5-167.7 °C. $^1$H NMR (500 MHz, D$_2$O): δ 2.93-2.82 (m 2H), 2.24-2.05 (m, 3H), 1.58-1.53 (m, 1H), 1.12 (t, $J$ = 7.5 Hz, 2H), 0.79 (dd, $J$ = 6 Hz, 6H); $^{13}$C NMR (125 MHz, D$_2$O): δ 181.18, 43.63,
4. Synthetic Procedures and Characterization of Pyrrolizidine

(±)-tert-Butyl-2-(3-chlorobenzyl)-2-(4-oxobutan-2-yl)pyrrolidine-1-carboxylate:

According to the general procedure of decarboxylative alkylation, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (4.4 mg, 4 µmol, 0.01 equiv.), 1-(tert-butoxycarbonyl)-2-(3-chlorobenzyl)pyrrolidine-2-carboxylic acid (136.0 mg, 0.4 mmol, 1.0 equiv), crotonaldehyde (28.0 mg, 0.4 mmol, 1.0 equiv), K₂HPO₄ (84.0 mg, 0.48 mmol, 1.2 equiv), and 1.4 mL of DMF were used. The product was isolated by flash chromatography (20% ethyl acetate/hexane) as a pale yellow oil (135 mg, 92%). ¹H NMR (500 MHz, CDCl₃) mixture of diastereomers and rotamers: δ 9.79-9.77 (m, 0.3H), 9.74-9.73 (m, 0.3H), 9.61 (t, J = 2.5 Hz, 0.4H), 7.22-7.12 (m, 3H), 7.05-7.02 (m, 0.7H),
7.00-6.98 (m, 0.3H), 3.65-3.62 (m, 0.6H), 3.49-3.45 (m, 0.4H), 3.36-3.22 (m, 1H), 3.11-2.90 (m, 2H), 2.75-2.56 (m, 1.4H), 2.42-2.05 (m, 1.6H), 1.88-1.68 (m, 2H), 1.58-1.15 (m, 8H), 1.34-1.28 (m, 1H), 1.05-1.03 (m, 1.7H), 0.91-0.86 (m, 1.3H), 0.68-0.45 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) mixture of diastereomers and rotamers: δ 202.48, 202.31, 201.37, 201.29, 153.93, 153.89, 153.81, 153.77, 140.64, 140.55, 140.38, 140.20, 134.05, 134.02, 133.98, 133.96, 130.46, 130.42, 130.32, 130.24, 129.59, 129.57, 129.22, 128.57, 128.43, 128.25, 126.76, 126.73, 126.54, 80.66, 80.42, 79.51, 79.25, 69.48, 69.02, 68.92, 68.48, 49.43, 49.39, 49.29, 49.10, 47.70, 47.33, 47.14, 46.13, 41.62, 41.28, 40.52, 40.26, 34.59, 34.51, 34.50, 34.09, 32.47, 32.07, 31.07, 30.82, 28.76, 28.69, 28.65, 28.54, 21.73, 21.51, 21.11, 20.87, 16.74, 16.58, 14.66, 14.56; HRMS (ESI) m/z calcd for C$_{20}$H$_{28}$ClINaO$_3$ [(M+Na)$^+$] 388.1655, found 388.1657.

![Chemical Structure](image)

**7a-(3-Chlorobenzyl)-1-methylhexahydro-1H-pyrrolizine**: To a stirring solution of (+)-tert-Butyl-2-(3-chlorobenzyl)-2-(4-oxobutan-2-yl)pyrrolidine-1-carboxylate (80 mg, 0.2 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (2 mL) at room temperature was added 4N HCl in dioxane (1 mL). The reaction mixture was stirred at room temperature for 4 hours, and then evaporated in vacuo. The crude aldehyde was dissolved in THF/H$_2$O (3 mL, 2:1) and added NaCNBH$_4$ (42 mg, 0.6 mmol, 3.0 equiv.). The reaction mixture was stirred at room temperature until the reaction was completed (judged by TLC). Saturated aqueous
NaHCO$_3$ solution was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO$_4$, and concentrated. The residue was purified by flash chromatography (5% MeOH/CH$_2$Cl$_2$). Two separated isomers were isolated (23 mg and 12 mg, 71% yield in total). Major isomer: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.37 (s, 1H), 7.23-7.20 (m, 1H), 7.17-7.14 (m, 2H), 3.24 (t, $J$ = 8.0 Hz, 1H), 2.58-2.56 (m, 1H), 2.49-2.36 (m, 4H), 1.93-1.88 (m, 1H), 1.84-1.76 (m, 1H), 1.64-1.45 (m, 4H), 1.19-1.15 (m, 1H), 1.06 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 142.00, 133.10, 131.41, 129.68, 128.53, 125.73, 56.15, 54.67, 44.60, 40.86, 35.02, 34.20, 29.85, 25.00, 14.39; Minor isomer: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.29 (br, 1H), 7.19-7.18 (m, 3H), 3.25-3.21 (m, 1H), 2.84-2.79 (m, 1H), 2.67 (s, 2H), 2.56-2.48 (m, 2H), 2.02-1.94 (m, 1H), 1.77-1.71 (m, 1H), 1.66-1.50 (m, 4H), 1.44-1.37 (m, 1H), 0.81 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 141.49, 133.58, 130.66, 129.03, 128.93, 126.24, 56.88, 53.67, 46.13, 40.79, 32.30, 31.40, 29.85, 25.42, 15.17; HRMS (ESI) m/z calcd for C$_{15}$H$_{21}$ClN [(M+H)$^+$] 250.1363, found 250.1359. IR (film) 2942, 1471, 1081, 780, 708 cm$^{-1}$;

References

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