

Palladium-Catalyzed [3+2] Cycloaddition via Two-Fold 1,3-C(sp³)-H Activation

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1. General Information

Solvents were obtained from Sigma-Aldrich, Alfa-Aesar, Oakwood, and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light. ^1H NMR was recorded on Bruker instrument (600 MHz). Chemical shifts were reported in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. ^{13}C NMR was recorded on Bruker instrument (150 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to 77.16 ppm for center line of chloroform. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, br = broad. Coupling constants, J , were reported in Hertz unit (Hz). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Enantiomeric excess value was determined on an Agilent 1260 Infinity SFC system using commercially available chiral columns.

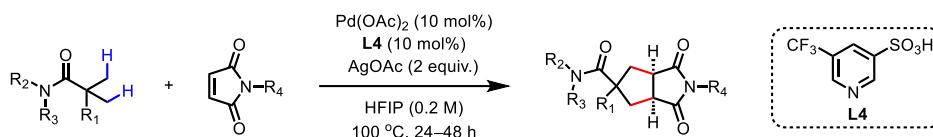
2. Experimental Section

2.1 Synthesis of substrates and ligands

1) Amide substrates were synthesized from corresponding carboxylic acids which were obtained from commercial sources or prepared following literature procedures.¹⁻³

2) Pyridine-3-sulfonic acid ligand **L4** was synthesized following literature procedures.³

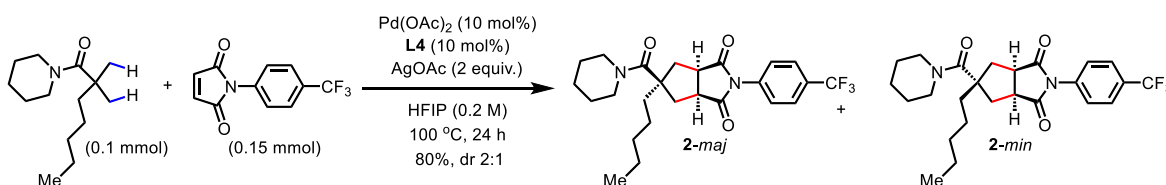
2.2 General procedure for Pd-catalyzed [3+2] reaction



A sealed tube with magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (10 mol%, 2.2 mg), **L4** (10 mol%, 2.3 mg), AgOAc (0.2 mmol, 33.4 mg), corresponding maleimide (0.15 mmol) and amide substrate (0.1 mmol). HFIP (0.5 mL) was added, and the reaction mixture was stirred at 100 °C for 24 to 48 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a celite plug, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography or pTLC to afford the desired products.

1) In most cases, both diastereomers were isolated separately and characterized. Otherwise, the product was isolated as a mixture of diastereomers. In these cases, if possible, analytical amount of the major diastereomer was purified for characterization.

2) Isolated yields are adjusted based on the amount of solvent observed in the ^1H NMR.



2-maj (24.7 mg) and **2-min** (12.5 mg) were isolated separately following the general procedure.

^1H NMR (**2-maj**, 600 MHz, CDCl_3) δ 7.70 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 3.46 (br s, 4H), 3.38 – 3.32 (m, 2H), 3.08 (d, J = 13.4 Hz, 2H), 1.87 (ddd, J = 13.7, 7.4, 2.5 Hz, 2H), 1.71 – 1.67 (m, 2H), 1.57 – 1.52 (m, 3H), 1.40 – 1.19 (m, 9H), 0.87 (t, J = 7.0 Hz, 3H).

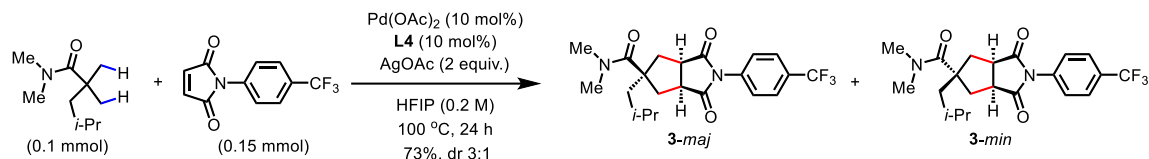
^{13}C NMR (**2-maj**, 151 MHz, CDCl_3) δ 178.65, 171.71, 135.82, 130.31 (q, J = 32.7 Hz), 127.05, 126.08 (q, J = 3.7 Hz), 123.97 (q, J = 272.1 Hz), 54.72, 47.98, 44.93, 40.44, 39.20, 32.26, 25.87, 25.51, 24.59, 22.52, 14.05.

HRMS (ESI-TOF): $\text{C}_{25}\text{H}_{32}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 465.2365, found 465.2368.

^1H NMR (**2-min**, 600 MHz, CDCl_3) δ 7.74 (d, $J = 8.3$ Hz, 2H), 7.46 (d, $J = 8.3$ Hz, 2H), 3.57 (t, $J = 5.5$ Hz, 4H), 3.47 – 3.41 (m, 2H), 2.89 (dd, $J = 13.4, 9.6$ Hz, 2H), 1.99 (dd, $J = 13.9, 5.5$ Hz, 2H), 1.71 – 1.66 (m, 2H), 1.64 – 1.53 (m, 6H), 1.31 – 1.18 (m, 6H), 0.86 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (**2-min**, 151 MHz, CDCl_3) δ 178.56, 171.73, 135.22, 130.59 (q, $J = 32.9$ Hz), 126.61, 126.39 (q, $J = 3.8$ Hz), 123.80 (q, $J = 272.4$ Hz), 57.13, 46.64, 44.98, 39.83, 38.37, 32.32, 26.38, 25.69, 24.68, 22.48, 14.06.

HRMS (ESI-TOF): $\text{C}_{25}\text{H}_{32}\text{F}_3\text{N}_2\text{O}_3$ [M+H] calculated 465.2365, found 465.2356.



3-maj (22.4 mg) and **3-min** (7.5 mg) were isolated separately following the general procedure.

^1H NMR (**3-maj**, 600 MHz, CDCl_3) δ 7.70 (d, $J = 8.2$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H), 3.39 – 3.32 (m, 2H), 3.16 (d, $J = 13.5$ Hz, 2H), 3.09 (br s, 3H), 2.73 (br s, 3H), 1.87 (ddd, $J = 13.7, 7.4, 2.5$ Hz, 2H), 1.71 (d, $J = 6.5$ Hz, 2H), 1.66 – 1.58 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 6H).

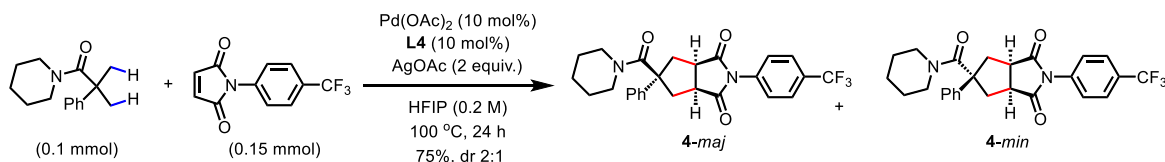
^{13}C NMR (**3-maj**, 151 MHz, CDCl_3) δ 178.62, 173.87, 135.78, 130.33 (q, $J = 33.0$ Hz), 127.07, 126.10 (q, $J = 3.8$ Hz), 123.96 (q, $J = 272.3$ Hz), 54.36, 48.41, 44.97, 41.21, 38.88, 37.93, 26.44, 23.68.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ [M+H] calculated 411.1896, found 411.1900.

^1H NMR (**3-min**, 600 MHz, CDCl_3) δ 7.74 (d, $J = 8.5$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 3.48 – 3.41 (m, 2H), 3.19 – 2.88 (m, 6H), 2.95 (dd, $J = 13.5, 9.3$ Hz, 2H), 1.96 (dd, $J = 13.8, 6.1$ Hz, 2H), 1.69 – 1.61 (m, 3H), 0.87 (d, $J = 6.1$ Hz, 6H).

^{13}C NMR (**3-min**, 151 MHz, CDCl_3) δ 178.46, 173.60, 135.20, 130.59 (q, $J = 98.6$ Hz), 126.64, 126.40 (q, $J = 3.7$ Hz), 123.81 (q, $J = 272.3$ Hz), 56.86, 47.05, 45.04, 40.69, 38.56, 37.96, 26.25, 23.75.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ [M+H] calculated 411.1896, found 411.1896.



4-maj (24.4 mg) and **4-min** (11.0 mg) were isolated separately following the general procedure.

^1H NMR (**4-maj**, 600 MHz, CDCl_3) δ 7.73 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.3$ Hz, 2H), 7.36 (t, $J = 7.7$ Hz, 2H), 7.27 (t, $J = 7.3$ Hz, 1H), 7.25 (dd, $J = 8.3, 1.3$ Hz, 2H), 3.51 – 3.46 (m, 2H), 3.39 (br s, 2H), 3.12 (d, $J = 13.5$ Hz, 2H), 3.02 (br s, 2H), 2.43 (ddt, $J = 13.4, 8.7, 6.2$ Hz, 2H), 1.40 (p, $J = 5.7$ Hz, 2H), 1.30 (br s, 2H), 1.04 (br s, 2H).

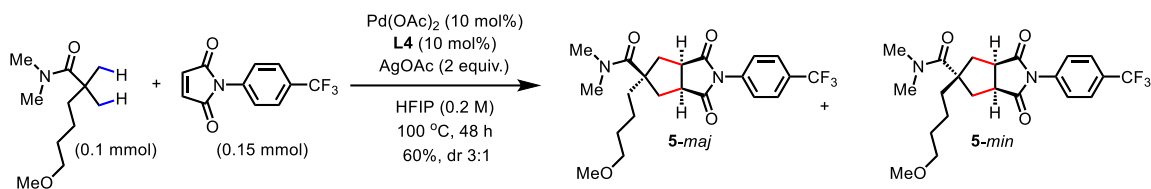
^{13}C NMR (**4-maj**, 151 MHz, CDCl_3) δ 178.40, 171.72, 141.71, 135.94, 130.37 (q, $J = 32.7$ Hz), 129.28, 127.34, 127.16, 126.17 (q, $J = 3.8$ Hz), 125.04, 123.99 (q, $J = 272.2$ Hz), 58.21, 47.66, 44.88, 44.28, 39.94, 25.11, 24.72, 24.34.

HRMS (ESI-TOF): $\text{C}_{26}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ [M+H] calculated 471.1896, found 471.1889.

^1H NMR (**4-min**, 600 MHz, CDCl_3) δ 7.68 (d, $J = 8.5$ Hz, 2H), 7.33 – 7.30 (m, 2H), 7.28 – 7.23 (m, 5H), 3.57 (td, $J = 5.5, 2.8$ Hz, 2H), 3.63 – 2.97 (m, 4H), 3.06 – 2.99 (m, 2H), 2.53 (dd, $J = 13.7, 5.7$ Hz, 2H), 1.54 – 1.31 (m, 4H), 0.89 (br s, 2H).

^{13}C NMR (**4-min**, 151 MHz, CDCl_3) δ 178.04, 171.30, 140.95, 134.98, 130.46 (q, $J = 33.0$ Hz), 129.32, 127.49, 126.66, 126.17 (q, $J = 3.6$ Hz), 125.61, 123.81 (q, $J = 272.4$ Hz), 60.58, 47.30, 44.95, 44.52, 39.91, 25.41, 24.35.

HRMS (ESI-TOF): $\text{C}_{26}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ [M+H] calculated 471.1896, found 471.1891.



5-maj (20.6 mg) and **5-min** (6.7 mg) were isolated separately following the general procedure.

(**5-maj** was isolated as an inseparable mixture with a small amount of *N*-demethylated substrate (0.7 mg), and the accurate yield was calculated accordingly)

$^1\text{H NMR}$ (**5-maj**, 600 MHz, CDCl_3) δ 7.70 (d, $J = 8.3$ Hz, 2H), 7.56 (d, $J = 8.2$ Hz, 2H), 3.38 – 3.35 (m, 2H), 3.34 (t, $J = 6.4$ Hz, 2H), 3.31 (s, 3H), 3.10 (d, $J = 13.6$ Hz, 2H), 3.06 (br s, 3H), 2.76 (br s, 3H), 1.89 (ddd, $J = 13.8, 7.4, 2.5$ Hz, 2H), 1.79 – 1.75 (m, 2H), 1.57 – 1.52 (m, 2H), 1.34 – 1.29 (m, 2H).

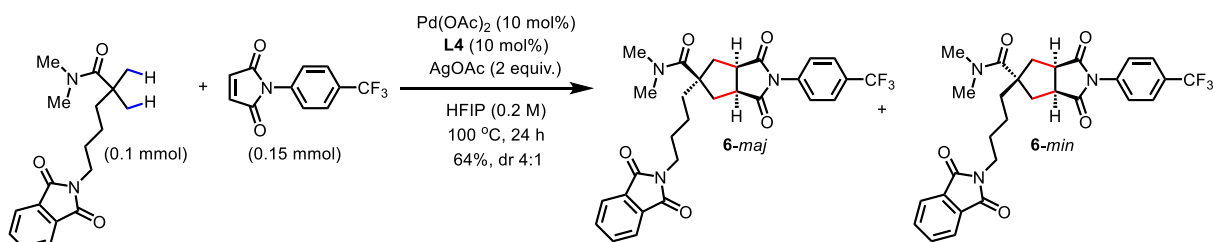
$^{13}\text{C NMR}$ (**5-maj**, 151 MHz, CDCl_3) δ 178.56, 173.45, 135.75, 130.34 (q, $J = 33.0$ Hz), 127.07, 126.11 (q, $J = 3.6$ Hz), 123.96 (q, $J = 272.3$ Hz), 72.51, 58.79, 54.76, 44.96, 40.20, 38.70, 38.64, 38.00, 30.06, 23.05.

HRMS (ESI-TOF): $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$] calculated 441.2001, found 441.1994.

$^1\text{H NMR}$ (**5-min**, 600 MHz, CDCl_3) δ 7.74 (d, $J = 8.2$ Hz, 2H), 7.47 (d, $J = 8.3$ Hz, 2H), 3.49 – 3.41 (m, 2H), 3.31 (t, $J = 6.4$ Hz, 2H), 3.28 (s, 3H), 3.05 (br s, 6H), 2.94 – 2.86 (m, 2H), 2.06 – 1.99 (m, 2H), 1.72 – 1.66 (m, 2H), 1.54 – 1.47 (m, 2H), 1.33 – 1.27 (m, 2H).

$^{13}\text{C NMR}$ (**5-min**, 151 MHz, CDCl_3) δ 178.48, 173.27, 135.20, 130.60 (q, $J = 32.8$ Hz), 126.60, 126.41 (q, $J = 3.8$ Hz), 123.79 (q, $J = 272.3$ Hz), 72.39, 58.74, 56.96, 45.00, 39.77, 38.14, 37.77, 30.05, 22.81.

HRMS (ESI-TOF): $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$] calculated 441.2001, found 441.2005.



6-maj (29.4 mg) and **6-min** (7.7 mg) were isolated separately following the general procedure.

(**6-maj** was isolated as an inseparable mixture with a small amount of *N*-demethylated substrate (1.5 mg), and the accurate yield was calculated accordingly)

$^1\text{H NMR}$ (**6-maj**, 600 MHz, CDCl_3) δ 7.84 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.72 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H), 3.68 – 3.63 (m, 2H), 3.39 – 3.35 (m, 2H), 3.22 – 2.99 (m, 5H), 2.74 (br s, 3H), 1.89 (ddd, $J = 13.7, 7.3, 2.5$ Hz, 2H), 1.83 – 1.79 (m, 2H), 1.68 (p, $J = 7.4$ Hz, 2H), 1.32 – 1.25 (m, 2H).

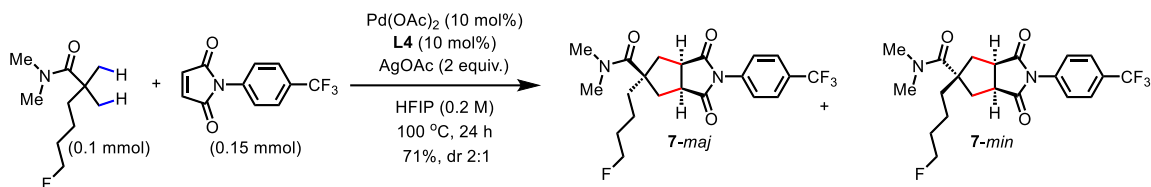
$^{13}\text{C NMR}$ (**6-maj**, 151 MHz, CDCl_3) δ 178.52, 173.17, 168.53, 135.70, 134.16, 132.17, 130.35 (q, $J = 33.0$ Hz), 127.05, 126.11 (q, $J = 3.8$ Hz), 123.95 (q, $J = 272.3$ Hz), 123.40, 54.60, 44.91, 40.13, 38.93, 38.07, 38.02, 37.35, 28.76, 23.08.

HRMS (ESI-TOF): $\text{C}_{29}\text{H}_{29}\text{F}_3\text{N}_3\text{O}_5$ [$\text{M}+\text{H}$] calculated 556.2059, found 556.2063.

$^1\text{H NMR}$ (**6-min**, 600 MHz, CDCl_3) δ 7.83 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.75 (d, $J = 8.1$ Hz, 2H), 7.71 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.47 (d, $J = 8.3$ Hz, 2H), 3.65 – 3.60 (m, 2H), 3.48 – 3.40 (m, 2H), 3.06 (br s, 6H), 2.94 – 2.87 (m, 2H), 2.00 (dd, $J = 13.5, 5.2$ Hz, 2H), 1.77 – 1.71 (m, 2H), 1.64 (p, $J = 7.4$ Hz, 2H), 1.33 – 1.27 (m, 2H).

$^{13}\text{C NMR}$ (**6-min**, 151 MHz, CDCl_3) δ 177.76, 172.43, 167.85, 134.56, 133.54, 131.58, 129.99 (d, $J = 33.0$ Hz), 126.06, 125.86 (q, $J = 3.7$ Hz), 123.22 (q, $J = 272.4$ Hz), 122.78, 56.37, 44.41, 39.16, 37.62, 36.81, 36.74, 28.25, 22.48.

HRMS (ESI-TOF): $\text{C}_{29}\text{H}_{29}\text{F}_3\text{N}_3\text{O}_5$ [$\text{M}+\text{H}$] calculated 556.2059, found 556.2063.



7-maj (21.7 mg) and **7-min** (9.0 mg) were isolated separately following the general procedure.

(**7-maj** was isolated as an inseparable mixture with a small amount of *N*-demethylated substrate (0.3 mg), and the accurate yield was calculated accordingly)

¹H NMR (**7-maj**, 600 MHz, CDCl₃) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 4.42 (dt, *J* = 47.3, 5.9 Hz, 2H), 3.39 – 3.35 (m, 2H), 3.19 – 2.96 (m, 5H), 2.77 (br s, 3H), 1.89 (ddd, *J* = 13.8, 7.4, 2.5 Hz, 2H), 1.83 – 1.78 (m, 2H), 1.73 – 1.64 (m, 2H), 1.40 – 1.34 (m, 2H).

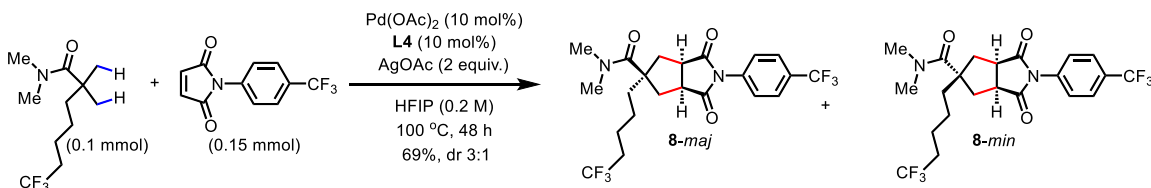
¹³C NMR (**7-maj**, 151 MHz, CDCl₃) δ 178.49, 173.27, 135.72, 130.36 (q, *J* = 32.5 Hz), 127.05, 126.12 (q, *J* = 3.7 Hz), 123.94 (q, *J* = 272.3 Hz), 83.77 (d, *J* = 165.1 Hz), 54.69, 44.93, 40.23, 38.81, 38.42, 38.09, 30.61 (d, *J* = 19.7 Hz), 22.23 (d, *J* = 4.8 Hz).

HRMS (ESI-TOF): C₂₁H₂₅F₄N₂O₃ [M+H] calculated 429.1801, found 429.1794.

¹H NMR (**7-min**, 600 MHz, CDCl₃) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 4.40 (dt, *J* = 47.3, 5.9 Hz, 2H), 3.49 – 3.43 (m, 2H), 3.06 (br s, 6H), 2.94 – 2.88 (m, 2H), 2.03 (dd, *J* = 13.8, 5.6 Hz, 2H), 1.74 – 1.70 (m, 2H), 1.69 – 1.59 (m, 2H), 1.41 – 1.34 (m, 2H).

¹³C NMR (**7-min**, 151 MHz, CDCl₃) δ 178.42, 173.11, 135.16, 130.63 (q, *J* = 32.5 Hz), 126.58, 126.42 (q, *J* = 3.6 Hz), 123.79 (q, *J* = 272.2 Hz), 83.72 (d, *J* = 165.6 Hz), 56.93, 44.99, 39.77, 38.14, 37.54, 30.63 (d, *J* = 19.8 Hz), 22.15 (d, *J* = 4.4 Hz).

HRMS (ESI-TOF): C₂₁H₂₅F₄N₂O₃ [M+H] calculated 429.1801, found 429.1797.



8-maj (24.1 mg) and **8-min** (9.2 mg) were isolated separately following the general procedure.

¹H NMR (**8-maj**, 600 MHz, CDCl₃) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 3.40 – 3.35 (m, 2H), 3.12 (d, *J* = 13.5 Hz, 2H), 3.09 (br s, 3H), 2.76 (br s, 3H), 2.10 – 2.01 (m, 2H), 1.87 (ddd, *J* = 13.7, 7.3, 2.5 Hz, 2H), 1.79 – 1.75 (m, 2H), 1.54 (p, *J* = 7.9 Hz, 2H), 1.34 – 1.28 (m, 2H).

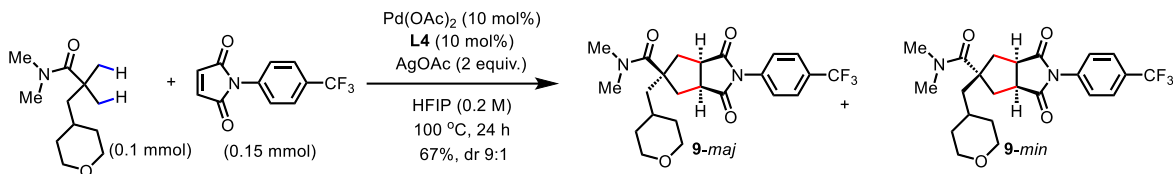
¹³C NMR (**8-maj**, 151 MHz, CDCl₃) δ 178.42, 173.10, 135.67, 130.39 (q, *J* = 32.9 Hz), 127.07 (q, *J* = 276.3 Hz), 127.03, 126.13 (q, *J* = 3.8 Hz), 123.94 (q, *J* = 272.3 Hz), 54.55, 44.89, 40.23, 38.80, 38.53, 38.07, 33.63 (q, *J* = 28.6 Hz), 25.38, 22.40 (q, *J* = 3.0 Hz).

HRMS (ESI-TOF): C₂₂H₂₅F₆N₂O₃ [M+H] calculated 479.1769, found 479.1773.

¹H NMR (**8-min**, 600 MHz, CDCl₃) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 3.49 – 3.43 (m, 2H), 3.06 (br s, 6H), 2.95 – 2.88 (m, 2H), 2.06 – 1.99 (m, 4H), 1.71 – 1.66 (m, 2H), 1.50 (p, *J* = 7.8 Hz, 2H), 1.35 – 1.29 (m, 2H).

¹³C NMR (**8-min**, 151 MHz, CDCl₃) δ 178.34, 172.95, 135.11, 130.67 (q, *J* = 33.0 Hz), 127.01 (q, *J* = 276.3 Hz), 126.51, 126.44 (q, *J* = 3.7 Hz), 123.77 (q, *J* = 272.3 Hz), 56.81, 44.94, 39.76, 38.16, 37.56, 33.56 (q, *J* = 28.6 Hz), 25.14, 22.39 (q, *J* = 2.8 Hz).

HRMS (ESI-TOF): C₂₂H₂₅F₆N₂O₃ [M+H] calculated 479.1769, found 479.1766.



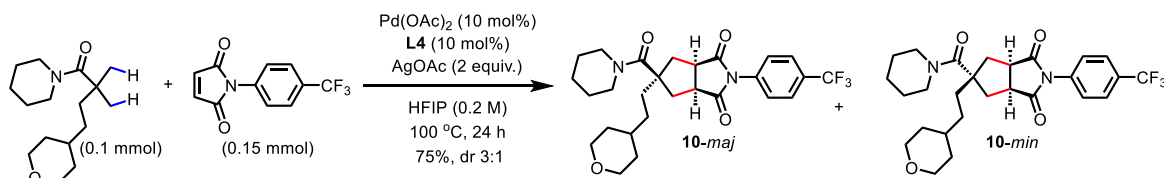
9-maj and **9-min** (31.2 mg) were isolated as mixture following the general procedure. Analytical amount of **9-maj** was purified for characterization.

(**9** was isolated as an inseparable mixture with a small amount of *N*-demethylated substrate (1.5 mg), and the accurate yield was calculated accordingly)

¹H NMR (**9-maj**, 600 MHz, CDCl₃) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 3.88 (dd, *J* = 11.3, 3.9 Hz, 2H), 3.40 – 3.35 (m, 2H), 3.35 – 3.30 (m, 2H), 3.17 (d, *J* = 13.5 Hz, 2H), 3.10 (br s, 3H), 2.73 br (s, 3H), 1.88 (ddd, *J* = 13.7, 7.4, 2.5 Hz, 2H), 1.75 (d, *J* = 5.8 Hz, 2H), 1.58 – 1.49 (m, 3H), 1.28 – 1.22 (m, 2H).

¹³C NMR (**9-maj**, 151 MHz, CDCl₃) δ 178.45, 173.72, 135.68, 130.37 (q, *J* = 32.7 Hz), 127.00, 126.11 (q, *J* = 3.8 Hz), 123.93 (q, *J* = 272.0 Hz), 67.92, 53.85, 46.68, 44.89, 41.15, 39.01, 38.02, 33.67, 33.25.

HRMS (ESI-TOF): C₂₃H₂₈F₃N₂O₄ [M+H] calculated 453.2001, found 453.2000.



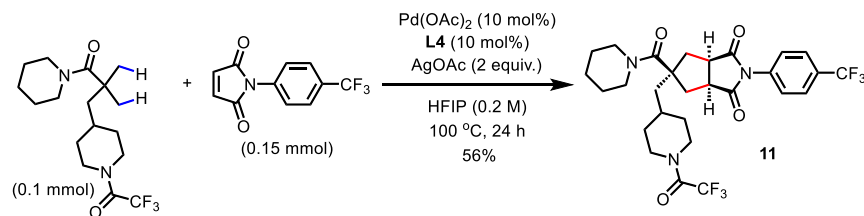
10-maj and **10-min** (38.2 mg) were isolated as mixture following the general procedure.

¹H NMR (**10-maj** + **10-min**, 600 MHz, CDCl₃) δ 7.74 (d, *J* = 8.5 Hz, 0.5H), 7.70 (d, *J* = 8.5 Hz, 1.5H), 7.55 (d, *J* = 8.3 Hz, 1.5H), 7.47 (d, *J* = 8.3 Hz, 0.5H), 3.96 – 3.90 (m, 2H), 3.59 – 3.28 (m, 8H), 3.09 (d, *J* = 13.2 Hz, 1.5H), 2.92 (dd, *J* = 13.5, 8.4 Hz, 0.5H), 1.96 (dd, *J* = 14.0, 5.6 Hz, 0.5H), 1.86 (ddt, *J* = 15.5, 8.1, 5.8 Hz, 1.5H), 1.77 – 1.62 (m, 3H), 1.61 – 1.48 (m, 5H), 1.45 – 1.32 (m, 2H), 1.29 – 1.18 (m, 5H).

¹³C NMR (**10-maj**, 151 MHz, CDCl₃) δ 178.52, 171.49, 135.77, 130.32 (q, *J* = 33.0 Hz), 127.01, 126.08 (q, *J* = 3.8 Hz), 123.95 (q, *J* = 272.4 Hz), 68.04, 54.51, 47.97, 44.87, 40.43, 35.93, 35.35, 33.09, 33.07, 25.48, 24.53.

¹³C NMR (**10-min**, 151 MHz, CDCl₃) δ 178.40, 171.49, 135.16, 130.59 (q, *J* = 33.0 Hz), 126.54, 126.35 (q, *J* = 3.7 Hz), 123.76 (q, *J* = 272.3 Hz), 67.98, 57.04, 46.36, 44.95, 39.82, 35.50, 35.17, 33.28, 33.06, 26.39, 24.62.

HRMS (ESI-TOF): C₂₇H₃₄F₃N₂O₄ [M+H] calculated 507.2471, found 507.2472.

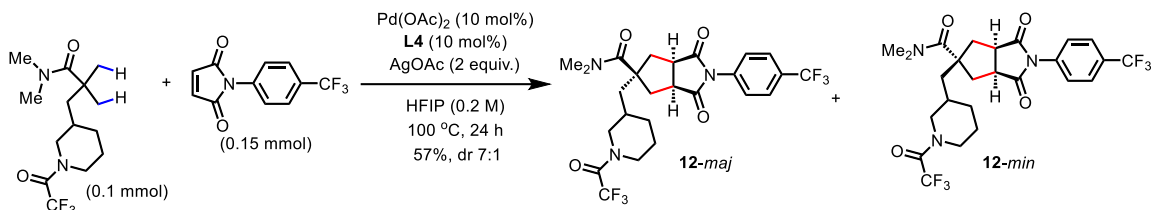


11-maj (33.1 mg) was isolated following the general procedure.

¹H NMR (**11-maj**, 600 MHz, CDCl₃) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 4.49 (ddt, *J* = 13.5, 4.7, 2.5 Hz, 1H), 3.94 (d, *J* = 14.3 Hz, 1H), 3.62 – 3.29 (m, 4H), 3.41 – 3.36 (m, 2H), 3.16 (br s, 2H), 3.08 – 3.02 (m, 1H), 2.67 (t, *J* = 12.3 Hz, 1H), 1.90 – 1.83 (m, 2H), 1.82 – 1.62 (m, 5H), 1.56 (br s, 4H), 1.24 – 1.09 (m, 4H).

¹³C NMR (**11-maj**, 151 MHz, CDCl₃) δ 178.34, 171.74, 155.37 (q, *J* = 35.7 Hz), 135.69, 130.43 (q, *J* = 32.9 Hz), 126.93, 126.11 (q, *J* = 3.6 Hz), 123.93 (q, *J* = 272.0 Hz), 116.68 (q, *J* = 288.2 Hz), 53.76, 48.31, 46.24, 46.01 (q, *J* = 3.5 Hz), 44.78, 43.88, 41.22, 34.30, 33.43, 32.45, 25.20, 25.09, 24.43.

HRMS (ESI-TOF): C₂₈H₃₂F₆N₃O₄ [M+H] calculated 588.2297, found 588.2300.

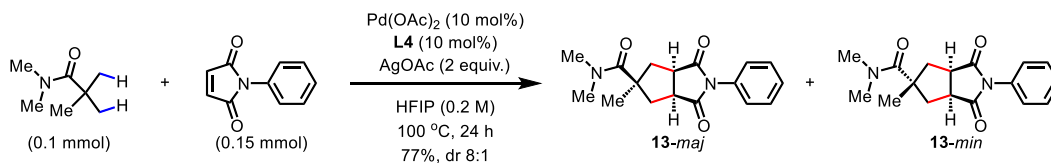


12-maj and **12-min** (31.2 mg) were isolated as mixture following the general procedure. Analytical amount of **12-maj** was purified for characterization.

¹H NMR (**12-maj**, 600 MHz, CDCl₃) (0.6:0.4 ratio of rotamers) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 4.40 (d, *J* = 13.2 Hz, 0.4H), 4.07 (d, *J* = 12.8 Hz, 0.6H), 3.81 – 3.74 (m, 1H), 3.41 – 3.35 (m, 2H), 3.23 (t, *J* = 15.3 Hz, 1.2H), 3.17 (ddd, *J* = 13.8, 10.8, 3.1 Hz, 0.8H), 3.14 – 2.93 (m, 4H), 2.80 – 2.69 (m, 4H), 2.02 – 1.62 (m, 6H), 1.58 – 1.43 (m, 1.8H), 1.28 – 1.12 (m, 1.2H).

¹³C NMR (**12-maj**, 151 MHz, CDCl₃) (major rotamer) δ 178.26, 173.05, 155.73 (q, *J* = 35.6 Hz), 135.64, 130.40 (q, *J* = 32.7 Hz), 126.99, 126.12 (q, *J* = 3.6 Hz), 123.92 (q, *J* = 272.3 Hz), 116.67 (q, *J* = 288.0 Hz), 53.83, 49.61, 46.48 (q, *J* = 3.7 Hz), 45.07, 44.53, 42.10, 41.62, 40.11, 38.91, 38.04, 33.71, 30.75, 25.11.

HRMS (ESI-TOF): C₂₅H₂₈F₆N₃O₄ [M+H] calculated 548.1984, found 548.1975.



13-maj (20.4 mg) and **13-min** (2.7 mg) were isolated separately following the general procedure.

¹H NMR (**13-maj**, 600 MHz, CDCl₃) δ 7.47 – 7.41 (m, 2H), 7.38 – 7.33 (m, 3H), 3.39 – 3.32 (m, 2H), 3.03 (d, *J* = 13.6 Hz, 2H), 3.17 – 2.69 (m, 6H), 1.98 – 1.89 (m, 2H), 1.42 (s, 3H).

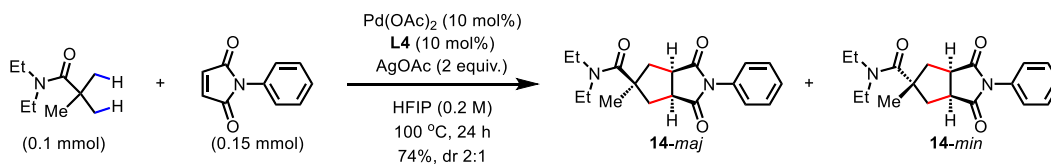
¹³C NMR (**13-maj**, 151 MHz, CDCl₃) δ 178.85, 174.31, 132.55, 129.06, 128.50, 126.72, 50.25, 45.09, 41.37, 38.75, 37.87, 24.18.

HRMS (ESI-TOF): C₁₇H₂₁N₂O₃ [M+H] calculated 301.1552, found 301.1559.

¹H NMR (**13-min**, 600 MHz, CDCl₃) δ 7.50 – 7.46 (m, 2H), 7.40 (ddt, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.29 – 7.27 (m, 2H), 3.48 – 3.40 (m, 2H), 3.04 (br s, 6H), 2.83 – 2.75 (m, 2H), 2.18 (ddd, *J* = 13.9, 2.6, 1.2 Hz, 2H), 1.37 (s, 3H).

¹³C NMR (**13-min**, 151 MHz, CDCl₃) δ 179.26, 174.90, 132.12, 129.36, 128.79, 126.34, 51.32, 44.92, 41.24, 38.07, 24.14.

HRMS (ESI-TOF): C₁₇H₂₁N₂O₃ [M+H] calculated 301.1552, found 301.1556.



14-maj and **14-min** (24.6 mg) were isolated as mixture following the general procedure.

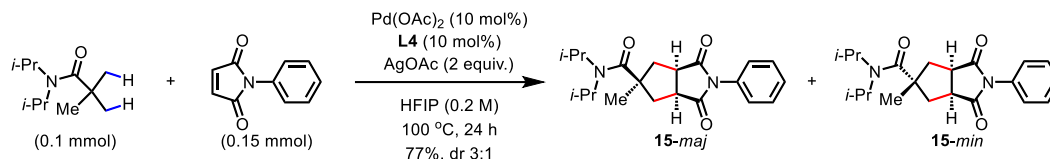
¹H NMR (**14-maj** + **14-min**, 600 MHz, CDCl₃) δ 7.50 – 7.46 (m, 0.67H), 7.45 – 7.42 (m, 1.33H), 7.41 – 7.38 (m, 0.33H), 7.38 – 7.36 (m, 1.33H), 7.36 – 7.33 (m, 0.67H), 7.29 – 7.27 (m, 0.67H), 3.48 – 3.18 (m, 6H), 2.96 (d, *J* = 13.6 Hz, 1.33H), 2.82 – 2.73 (m, 0.67H), 2.16 (ddd, *J* = 13.9, 2.4, 1.1 Hz, 0.67H), 2.00 – 1.91 (m, 1.33H), 1.41 (s, 2H), 1.34 (s, 1H), 1.24 – 1.06 (m, 4H), 0.91 (br s, 2H).

¹³C NMR (**14-maj**, 151 MHz, CDCl₃) δ 178.83, 173.69, 132.58, 129.01, 128.41, 126.69, 50.50, 45.13, 41.97, 41.60,

40.38, 24.80, 13.61, 12.33.

^{13}C NMR (**14-min**, 151 MHz, CDCl_3) δ 179.32, 174.10, 132.13, 129.34, 128.77, 126.33, 51.49, 44.85, 41.32, 40.95, 24.47, 14.37, 12.70.

HRMS (ESI-TOF): $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_3$ [M+H] calculated 329.1865, found 329.1869.



15-maj (21.1 mg) and **15-min** (6.5 mg) were isolated separately following the general procedure.

^1H NMR (**15-maj**, 600 MHz, CDCl_3) δ 7.48 (t, $J = 7.8$ Hz, 2H), 7.42 – 7.38 (m, 1H), 7.27 (dd, $J = 9.6, 1.3$ Hz, 2H), 4.16 (hept, $J = 6.7$ Hz, 1H), 3.45 – 3.40 (m, 2H), 3.33 (hept, $J = 6.7$ Hz, 1H), 2.79 – 2.71 (m, 2H), 2.16 (dd, $J = 12.9, 2.5$ Hz, 2H), 1.39 (d, $J = 6.7$ Hz, 6H), 1.33 (s, 3H), 1.22 (d, $J = 6.6$ Hz, 6H).

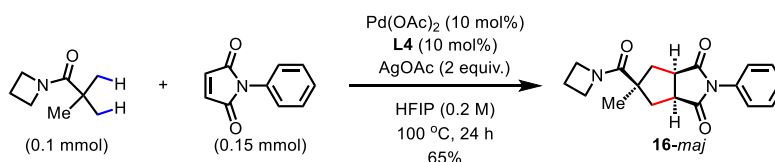
^{13}C NMR (**15-maj**, 151 MHz, CDCl_3) δ 179.43, 173.63, 132.16, 129.33, 128.75, 126.32, 52.02, 48.59, 46.77, 44.73, 41.19, 24.27, 20.79, 20.62.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3$ [M+H] calculated 357.2178, found 357.2177.

^1H NMR (**15-min**, 600 MHz, CDCl_3) δ 7.44 – 7.39 (m, 4H), 7.34 – 7.29 (m, 1H), 4.17 (hept, $J = 6.2, 5.7$ Hz, 1H), 3.39 – 3.34 (m, 2H), 3.18 (hept, $J = 6.8$ Hz, 1H), 2.93 (d, $J = 13.8$ Hz, 2H), 1.95 (ddd, $J = 14.0, 7.4, 2.5$ Hz, 2H), 1.40 (s, 3H), 1.19 (d, $J = 6.6$ Hz, 6H), 1.17 (d, $J = 6.8$ Hz, 6H).

^{13}C NMR (**15-min**, 151 MHz, CDCl_3) δ 178.86, 173.24, 132.39, 128.76, 128.11, 126.43, 51.35, 48.88, 46.72, 45.12, 41.33, 24.89, 20.68, 20.26.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3$ [M+H] calculated 357.2178, found 357.2177.

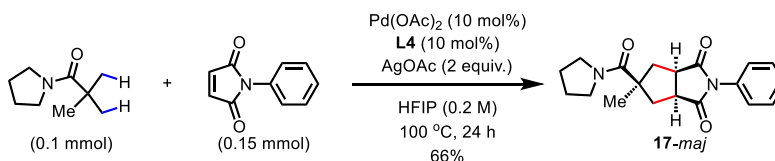


16-maj (20.4 mg) was isolated following the general procedure.

^1H NMR (**16-maj**, 600 MHz, CDCl_3) δ 7.45 (t, $J = 7.6$ Hz, 2H), 7.38 – 7.35 (m, 1H), 7.34 (dd, $J = 8.4, 1.2$ Hz, 2H), 4.32 (s, 2H), 3.87 (s, 2H), 3.39 – 3.32 (m, 2H), 2.89 (d, $J = 13.6$ Hz, 2H), 2.22 – 2.16 (m, 2H), 1.85 (ddd, $J = 14.1, 7.5, 2.7$ Hz, 2H), 1.32 (s, 3H).

^{13}C NMR (**16-maj**, 151 MHz, CDCl_3) δ 178.82, 174.28, 132.64, 129.14, 128.62, 126.91, 53.11, 49.77, 49.54, 45.25, 40.00, 23.15, 16.06.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$ [M+H] calculated 313.1552, found 313.1560.

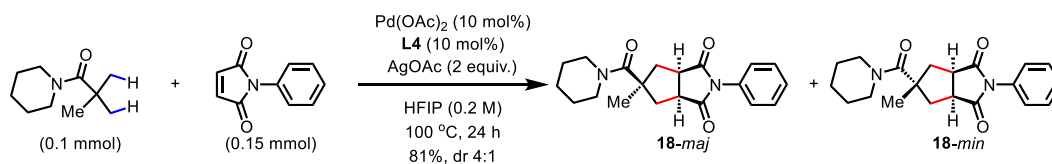


17-maj (21.4 mg) was isolated following the general procedure.

^1H NMR (**17-maj**, 600 MHz, CDCl_3) δ 7.47 – 7.41 (m, 2H), 7.38 – 7.33 (m, 3H), 3.53 (br s, 2H), 3.40 – 3.30 (m, 4H), 2.98 (d, $J = 13.6$ Hz, 2H), 1.93 (ddt, $J = 13.4, 8.6, 6.0$ Hz, 2H), 1.87 (br s, 2H), 1.71 (br s, 2H), 1.38 (s, 3H).

^{13}C NMR (**17-maj**, 151 MHz, CDCl_3) δ 178.88, 173.14, 132.63, 129.09, 128.52, 126.83, 50.83, 48.01, 45.16, 40.59, 27.05, 23.26, 23.07.

HRMS (ESI-TOF): $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_3$ [M+H] calculated 327.1709, found 327.1713.



18-maj (21.9 mg) and **18-min** (5.7 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**18-maj**, 600 MHz, CDCl_3) δ 7.45 – 7.41 (m, 2H), 7.35 (dd, $J = 9.0, 7.7$ Hz, 3H), 3.48 (br s, 4H), 3.37 – 3.33 (m, 2H), 3.04 (d, $J = 13.7$ Hz, 2H), 1.94 – 1.87 (m, 2H), 1.58 – 1.53 (m, 2H), 1.61 – 1.24 (m, 4H), 1.41 (s, 3H).

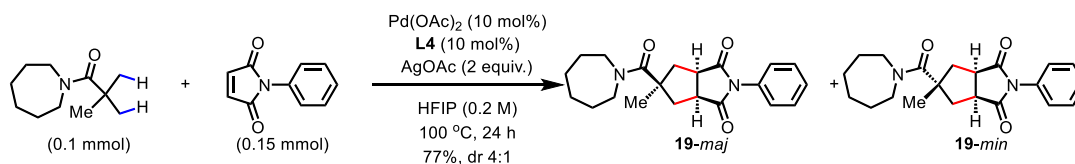
$^{13}\text{C NMR}$ (**18-maj**, 151 MHz, CDCl_3) δ 178.94, 172.62, 132.67, 129.04, 128.48, 126.73, 50.10, 45.11, 41.65, 25.43, 24.65, 24.55. (–N(CH₂)– peaks were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3$ [M+H] calculated 341.1865, found 341.1865.

$^1\text{H NMR}$ (**18-min**, 600 MHz, CDCl_3) δ 7.50 – 7.46 (m, 2H), 7.41 – 7.38 (m, 1H), 7.29 – 7.27 (m, 2H), 3.56 – 3.52 (m, 4H), 3.46 – 3.41 (m, 2H), 2.84 – 2.78 (m, 2H), 2.13 (ddd, $J = 13.8, 2.8, 1.2$ Hz, 2H), 1.70 – 1.65 (m, 2H), 1.59 – 1.54 (m, 4H), 1.36 (s, 3H).

$^{13}\text{C NMR}$ (**18-min**, 151 MHz, CDCl_3) δ 179.26, 173.35, 132.12, 129.34, 128.77, 126.37, 51.49, 44.93, 41.36, 26.28, 24.69, 24.46. (–N(CH₂)– peaks were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3$ [M+H] calculated 341.1865, found 341.1865.

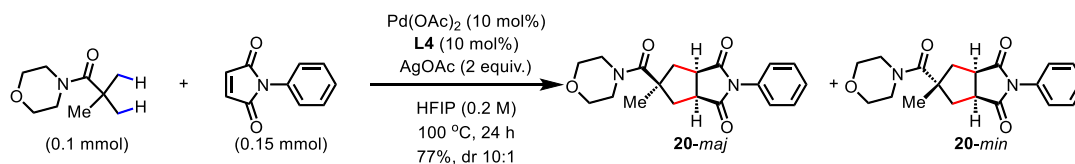


19-maj and **19-min** (27.5 mg) were isolated as mixture following the general procedure. Analytical amount of **19-maj** was purified for characterization.

$^1\text{H NMR}$ (**19-maj**, 600 MHz, CDCl_3) δ 7.45 – 7.41 (m, 2H), 7.39 – 7.36 (m, 2H), 7.36 – 7.32 (m, 1H), 3.55 (br s, 2H), 3.40 – 3.33 (m, 2H), 3.33 (br s, 2H), 3.00 (d, $J = 13.6$ Hz, 2H), 1.99 – 1.92 (m, 2H), 1.75 (br s, 2H), 1.58 – 1.38 (m, 6H), 1.43 (s, 3H).

$^{13}\text{C NMR}$ (**19-maj**, 151 MHz, CDCl_3) δ 178.85, 173.96, 132.55, 128.98, 128.40, 126.70, 50.70, 48.80, 47.79, 45.12, 41.66, 29.77, 28.21, 26.80, 25.49, 24.79.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_3$ [M+H] calculated 355.2022, found 355.2023.



20-maj (24.3 mg) and **20-min** (2.5 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**20-maj**, 600 MHz, CDCl_3) δ 7.44 (t, $J = 7.6$ Hz, 2H), 7.37 – 7.35 (m, 1H), 7.33 (dd, $J = 8.4, 1.2$ Hz, 2H), 3.55 (br s, 8H), 3.39 – 3.35 (m, 2H), 3.02 (d, $J = 13.8$ Hz, 2H), 1.96 – 1.89 (m, 2H), 1.41 (s, 3H).

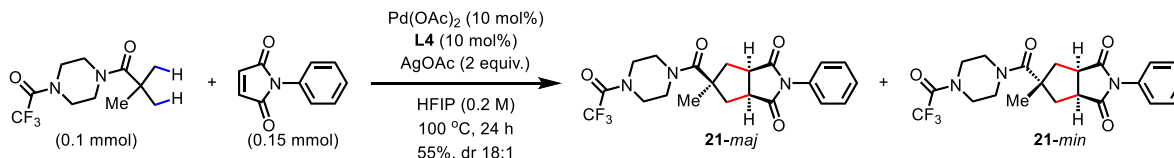
$^{13}\text{C NMR}$ (**20-maj**, 151 MHz, CDCl_3) δ 178.78, 173.12, 132.53, 129.08, 128.57, 126.53, 66.21, 49.96, 45.03, 41.54, 24.32. (–N(CH₂)– peaks were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_4$ [M+H] calculated 343.1658, found 343.1659.

$^1\text{H NMR}$ (**20-min**, 600 MHz, CDCl_3) δ 7.50 – 7.46 (m, 2H), 7.42 – 7.39 (m, 1H), 7.29 – 7.27 (m, 2H), 3.70 – 3.61 (m, 8H), 3.48 – 3.42 (m, 2H), 2.83 – 2.76 (m, 2H), 2.17 – 2.13 (m, 2H), 1.36 (s, 3H).

$^{13}\text{C NMR}$ (**20-min**, 151 MHz, CDCl_3) δ 179.06, 173.81, 132.04, 129.38, 128.85, 126.32, 66.94, 51.19, 44.84, 41.22, 24.48. (–N(CH₂)– peaks were not found due to weak intensity)

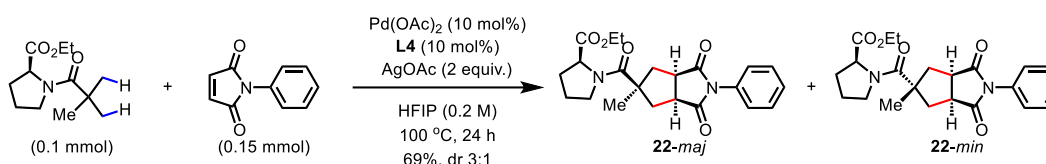
HRMS (ESI-TOF): C₁₉H₂₃N₂O₄ [M+H] calculated 343.1658, found 343.1660.



21-maj and **21-min** (24.5 mg) were isolated as mixture following the general procedure. Analytical amount of **21-maj** was purified for characterization.

¹H NMR (**21-maj**, 600 MHz, CDCl₃) δ 7.45 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.3 Hz, 2H), 3.81 – 3.19 (m, 8H), 3.41 – 3.37 (m, 2H), 3.04 (d, *J* = 13.6 Hz, 2H), 1.94 (ddt, *J* = 15.8, 8.6, 6.2 Hz, 2H), 1.43 (s, 3H).
¹³C NMR (**21-maj**, 151 MHz, CDCl₃) δ 178.83, 173.28, 155.66 (q, *J* = 36.1 Hz), 132.38, 129.18, 128.75, 126.31, 116.35 (q, *J* = 287.9 Hz), 49.96, 44.97, 44.91, 42.39, 41.58, 24.20.

HRMS (ESI-TOF): C₂₁H₂₃F₃N₃O₄ [M+H] calculated 438.1641, found 438.1638.

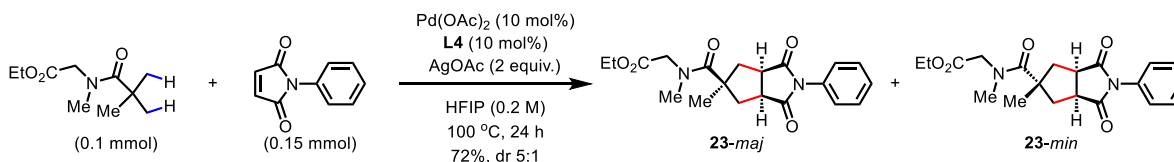


22-maj and **22-min** (27.4 mg) were isolated as mixture following the general procedure. Analytical amount of **22-maj** was purified for characterization.

¹H NMR (**22-maj**, 600 MHz, CDCl₃) δ 7.46 – 7.43 (m, 2H), 7.38 – 7.33 (m, 3H), 4.25 (dd, *J* = 8.1, 4.3 Hz, 1H), 4.12 – 4.03 (m, 2H), 3.74 – 3.64 (m, 2H), 3.42 – 3.34 (m, 2H), 3.02 (ddd, *J* = 13.5, 3.0, 1.6 Hz, 1H), 2.82 (dt, *J* = 13.9, 2.1 Hz, 1H), 2.06 – 1.99 (m, 3H), 1.96 (dd, *J* = 13.6, 10.0 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.83 – 1.76 (m, 1H), 1.43 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (**22-maj**, 151 MHz, CDCl₃) δ 178.95, 178.44, 173.81, 172.41, 132.54, 129.12, 128.54, 126.79, 60.97, 60.93, 50.84, 48.45, 45.77, 44.39, 41.69, 39.09, 28.09, 25.73, 23.02, 14.26.

HRMS (ESI-TOF): C₂₂H₂₇N₂O₅ [M+H] calculated 399.1920, found 399.1922.

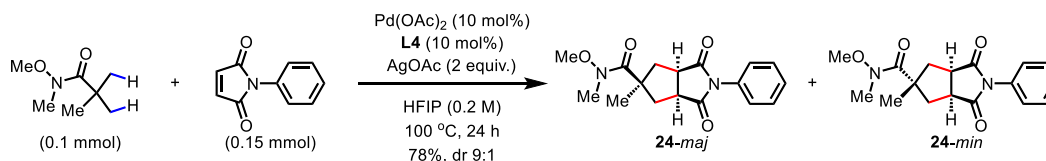


23-maj and **23-min** (26.9 mg) were isolated as mixture following the general procedure. Analytical amount of **23-maj** was purified for characterization.

¹H NMR (**23-maj**, 600 MHz, CDCl₃) δ 7.46 – 7.42 (m, 2H), 7.37 – 7.33 (m, 1H), 7.32 (d, *J* = 7.2 Hz, 2H), 4.29 – 3.74 (m, 4H), 3.40 – 3.36 (m, 2H), 3.26 – 2.79 (m, 3H), 3.00 (d, *J* = 13.3 Hz, 2H), 2.07 – 1.98 (m, 2H), 1.48 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (**23-maj**, 151 MHz, CDCl₃) δ 178.57, 175.38, 169.08, 132.48, 129.07, 128.45, 126.57, 61.20, 51.47, 50.32, 45.06, 41.37, 38.29, 24.00, 14.23.

HRMS (ESI-TOF): C₂₀H₂₅N₂O₅ [M+H] calculated 373.1763, found 373.1764.



24-maj (22.2 mg) and **24-min** (2.5 mg) were isolated separately following the general procedure.

¹H NMR (**24-maj**, 600 MHz, CDCl₃) δ 7.46 – 7.42 (m, 2H), 7.38 – 7.34 (m, 1H), 7.31 – 7.28 (m, 2H), 3.70 (s, 3H), 3.39 – 3.35 (m, 2H), 3.09 (s, 3H), 2.94 (d, *J* = 14.1 Hz, 2H), 1.99 – 1.93 (m, 2H), 1.39 (s, 3H).

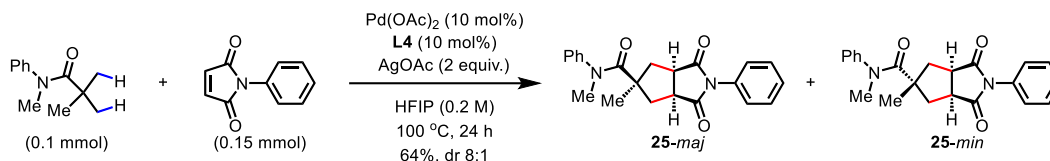
¹³C NMR (**24-maj**, 151 MHz, CDCl₃) δ 178.96, 176.14, 132.54, 129.15, 128.57, 126.69, 60.54, 51.25, 45.09, 40.31, 33.72, 22.95.

HRMS (ESI-TOF): C₁₇H₂₁N₂O₄ [M+H] calculated 317.1501, found 317.1508.

¹H NMR (**24-min**, 600 MHz, CDCl₃) δ 7.48 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 2H), 3.72 (s, 3H), 3.45 – 3.39 (m, 2H), 3.20 (s, 3H), 2.73 – 2.64 (m, 2H), 2.24 (dd, *J* = 13.9, 2.3 Hz, 2H), 1.32 (s, 3H).

¹³C NMR (**24-min**, 151 MHz, CDCl₃) δ 179.47, 176.53, 132.18, 129.35, 128.77, 126.34, 60.97, 51.49, 44.74, 40.06, 33.55, 23.66.

HRMS (ESI-TOF): C₁₇H₂₁N₂O₄ [M+H] calculated 317.1501, found 317.1508.



25-maj (20.9 mg) and **25-min** (2.8 mg) were isolated separately following the general procedure.

¹H NMR (**25-maj**, 600 MHz, CDCl₃) δ 7.45 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.31 (m, 6H), 7.24 (d, *J* = 5.4 Hz, 2H), 3.34 – 3.28 (m, 2H), 3.16 (s, 3H), 2.80 (d, *J* = 13.6 Hz, 2H), 1.75 (dd, *J* = 12.9, 8.3 Hz, 2H), 1.20 (s, 3H).

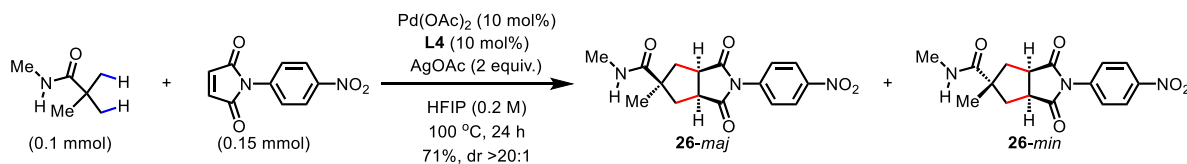
¹³C NMR (**25-maj**, 151 MHz, CDCl₃) δ 178.86, 174.91, 144.22, 132.50, 129.55, 129.15, 129.10, 128.57, 128.34, 126.82, 52.55, 45.03, 41.60, 41.35, 25.41.

HRMS (ESI-TOF): C₂₂H₂₃N₂O₃ [M+H] calculated 363.1709, found 363.1712.

¹H NMR (**25-min**, 600 MHz, CDCl₃) δ 7.45 – 7.41 (m, 4H), 7.39 – 7.34 (m, 2H), 7.23 – 7.18 (m, 4H), 3.36 – 3.31 (m, 2H), 3.24 (s, 3H), 2.60 – 2.53 (m, 2H), 1.84 (d, *J* = 14.0 Hz, 2H), 1.13 (s, 3H).

¹³C NMR (**25-min**, 151 MHz, CDCl₃) δ 179.35, 175.66, 143.99, 132.11, 129.83, 129.30, 128.72, 128.66, 126.19, 52.35, 44.68, 41.61, 40.96, 26.15.

HRMS (ESI-TOF): C₂₂H₂₃N₂O₃ [M+H] calculated 363.1709, found 363.1711.



26-maj (23.2 mg) and **26-min** (0.9 mg) were isolated separately following the general procedure.

¹H NMR (**26-maj**, 600 MHz, CDCl₃) δ 8.32 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 9.1 Hz, 2H), 5.63 (br s, 1H), 3.48 – 3.43 (m, 2H), 2.75 (d, *J* = 14.0 Hz, 2H), 2.67 (d, *J* = 4.7 Hz, 3H), 2.01 – 1.94 (m, 2H), 1.36 (s, 3H).

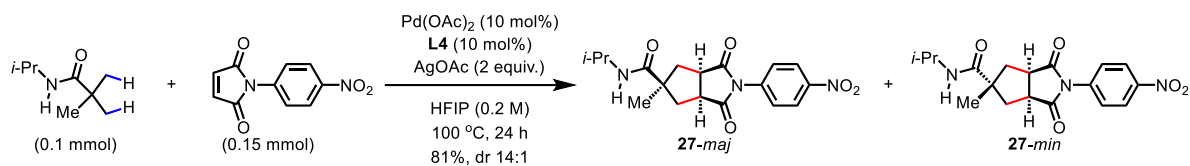
¹³C NMR (**26-maj**, 151 MHz, CDCl₃) δ 178.29, 176.81, 147.15, 138.46, 127.72, 124.36, 50.01, 45.83, 41.43, 26.83, 24.79.

HRMS (ESI-TOF): C₁₆H₁₈N₃O₅ [M+H] calculated 332.1246, found 332.1252.

¹H NMR (**26-min**, 600 MHz, CDCl₃) δ 8.34 (d, *J* = 9.1 Hz, 2H), 7.59 (d, *J* = 9.1 Hz, 2H), 5.63 (br s, 1H), 3.61 (ddd, *J* = 7.6, 5.1, 2.6 Hz, 2H), 2.85 (d, *J* = 4.8 Hz, 3H), 2.76 – 2.70 (m, 2H), 1.97 (ddd, *J* = 13.9, 3.5, 1.4 Hz, 2H), 1.31 (s, 3H).

¹³C NMR (**26-min**, 151 MHz, CDCl₃) δ 178.10, 176.03, 147.10, 137.60, 126.83, 124.55, 51.73, 45.79, 41.11, 26.95, 24.18.

HRMS (ESI-TOF): C₁₆H₁₈N₃O₅ [M+H] calculated 332.1246, found 332.1251.



27-maj (27.0 mg) and **27-min** (2.0 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**27-maj**, 600 MHz, CDCl_3) δ 8.32 (d, $J = 9.0$ Hz, 2H), 7.66 (d, $J = 9.1$ Hz, 2H), 5.34 (d, $J = 7.8$ Hz, 1H), 3.87 (dp, $J = 7.8, 6.5$ Hz, 1H), 3.48 – 3.41 (m, 2H), 2.75 (d, $J = 13.9$ Hz, 2H), 2.00 – 1.91 (m, 2H), 1.34 (s, 3H), 0.99 (d, $J = 6.6$ Hz, 6H).

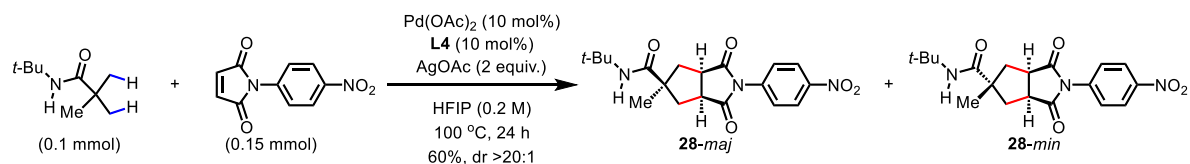
$^{13}\text{C NMR}$ (**27-maj**, 151 MHz, CDCl_3) δ 178.22, 175.27, 147.08, 138.50, 127.64, 124.31, 50.02, 45.76, 41.72, 41.29, 24.94, 22.51.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_5$ [M+H] calculated 360.1559, found 360.1565.

$^1\text{H NMR}$ (**27-min**, 600 MHz, CDCl_3) δ 8.34 (d, $J = 9.1$ Hz, 2H), 7.59 (d, $J = 9.1$ Hz, 2H), 5.35 (d, $J = 7.2$ Hz, 1H), 4.07 (dp, $J = 7.7, 6.5$ Hz, 1H), 3.62 – 3.56 (m, 2H), 2.74 – 2.68 (m, 2H), 1.96 – 1.92 (m, 2H), 1.30 (s, 3H), 1.17 (d, $J = 6.5$ Hz, 6H).

$^{13}\text{C NMR}$ (**27-min**, 151 MHz, CDCl_3) δ 178.08, 174.50, 147.09, 137.60, 126.84, 124.55, 51.81, 45.75, 41.88, 40.97, 24.23, 22.83.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_5$ [M+H] calculated 360.1559, found 360.1563.

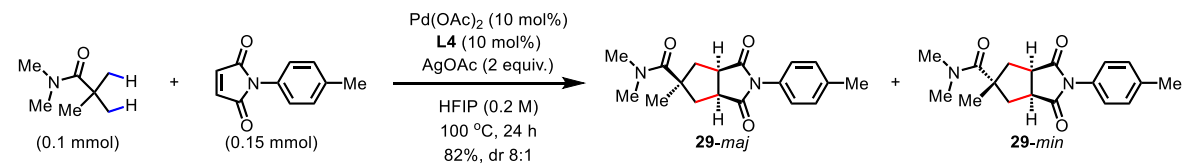


28-maj and **28-min** (22.4 mg) were isolated as mixture following the general procedure. Analytical amount of **28-maj** was purified for characterization.

$^1\text{H NMR}$ (**28-maj**, 600 MHz, CDCl_3) δ 8.31 (d, $J = 9.1$ Hz, 2H), 7.70 (d, $J = 9.1$ Hz, 2H), 5.30 (s, 1H), 3.46 – 3.41 (m, 2H), 2.73 (d, $J = 14.0$ Hz, 2H), 1.97 – 1.91 (m, 2H), 1.34 (s, 3H), 1.17 (s, 9H).

$^{13}\text{C NMR}$ (**28-maj**, 151 MHz, CDCl_3) δ 178.25, 175.73, 146.97, 138.50, 127.55, 124.22, 51.34, 50.61, 45.80, 41.35, 28.70, 25.40.

HRMS (ESI-TOF): $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_5$ [M+H] calculated 374.1716, found 374.1716.



29-maj (23.1 mg) and **29-min** (2.8 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**29-maj**, 600 MHz, CDCl_3) δ 7.26 – 7.21 (m, 4H), 3.36 – 3.32 (m, 2H), 3.02 (d, $J = 13.6$ Hz, 2H), 3.20 – 2.67 (m, 6H), 2.36 (s, 3H), 1.97 – 1.90 (m, 2H), 1.42 (s, 3H).

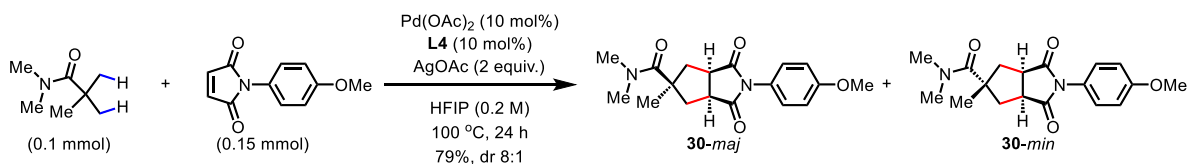
$^{13}\text{C NMR}$ (**29-maj**, 151 MHz, CDCl_3) δ 178.97, 174.30, 138.49, 129.89, 129.74, 126.50, 50.28, 45.05, 41.32, 38.56, 37.79, 24.18, 21.33.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3$ [M+H] calculated 315.1709, found 315.1711.

$^1\text{H NMR}$ (**29-min**, 600 MHz, CDCl_3) δ 7.28 (d, $J = 7.9$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 3.45 – 3.40 (m, 2H), 3.04 (br s, 6H), 2.82 – 2.75 (m, 2H), 2.38 (s, 3H), 2.19 – 2.15 (m, 2H), 1.36 (s, 3H).

$^{13}\text{C NMR}$ (**29-min**, 151 MHz, CDCl_3) δ 179.42, 174.94, 138.90, 130.01, 129.46, 126.14, 51.29, 44.90, 41.21, 38.11, 24.14, 21.36.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3$ [M+H] calculated 315.1709, found 315.1715.



30-maj (22.6 mg) and **30-min** (2.7 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**30-maj**, 600 MHz, CDCl_3) δ 7.27 (d, $J = 9.1$ Hz, 2H), 6.95 (d, $J = 9.1$ Hz, 2H), 3.81 (s, 3H), 3.37 – 3.30 (m, 2H), 3.02 (d, $J = 13.6$ Hz, 2H), 3.20 – 2.69 (m, 6H), 1.93 (ddt, $J = 13.3, 8.6, 6.0$ Hz, 2H), 1.42 (s, 3H).

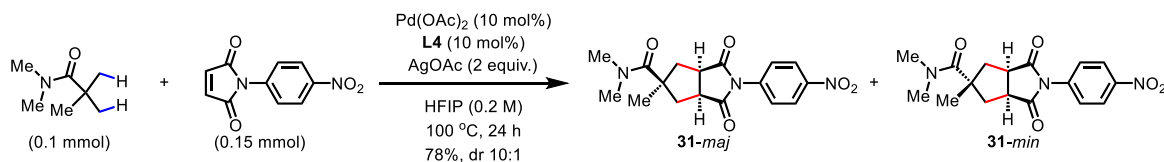
$^{13}\text{C NMR}$ (**30-maj**, 151 MHz, CDCl_3) δ 179.12, 174.32, 159.50, 127.91, 125.23, 114.42, 55.58, 50.25, 45.02, 41.34, 38.70, 37.81, 24.19.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_4$ [M+H] calculated 331.1658, found 331.1665.

$^1\text{H NMR}$ (**30-min**, 600 MHz, CDCl_3) δ 7.19 (d, $J = 9.0$ Hz, 2H), 6.98 (d, $J = 9.0$ Hz, 2H), 3.83 (s, 3H), 3.44 – 3.39 (m, 2H), 3.04 (br s, 6H), 2.81 – 2.75 (m, 2H), 2.17 (ddd, $J = 13.8, 2.5, 1.0$ Hz, 2H), 1.36 (s, 3H).

$^{13}\text{C NMR}$ (**30-min**, 151 MHz, CDCl_3) δ 179.53, 174.92, 159.67, 127.55, 124.74, 114.69, 55.66, 51.31, 44.86, 41.20, 38.09, 24.13.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_4$ [M+H] calculated 331.1658, found 331.1665.



31-maj (24.6 mg) and **31-min** (2.5 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**31-maj**, 600 MHz, CDCl_3) δ 8.30 (d, $J = 9.1$ Hz, 2H), 7.64 (d, $J = 9.1$ Hz, 2H), 3.42 – 3.37 (m, 2H), 3.07 (d, $J = 13.8$ Hz, 2H), 3.16 – 2.62 (m, 6H), 1.96 – 1.90 (m, 2H), 1.45 (s, 3H).

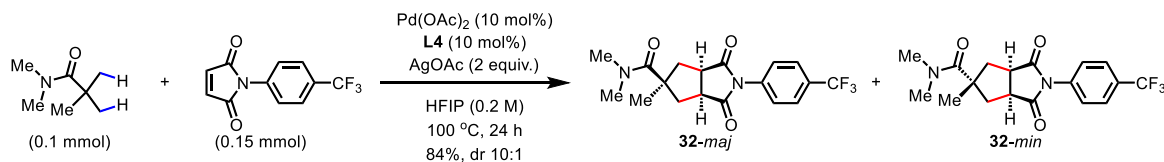
$^{13}\text{C NMR}$ (**31-maj**, 151 MHz, CDCl_3) δ 178.14, 174.34, 147.04, 138.18, 127.40, 124.27, 49.99, 45.19, 41.61, 38.96, 37.65, 24.07.

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_5$ [M+H] calculated 346.1403, found 346.1403.

$^1\text{H NMR}$ (**31-min**, 600 MHz, CDCl_3) δ 8.34 (d, $J = 9.0$ Hz, 2H), 7.59 (d, $J = 9.0$ Hz, 2H), 3.52 – 3.45 (m, 2H), 3.05 (br s, 6H), 2.88 – 2.82 (m, 2H), 2.14 – 2.11 (m, 2H), 1.37 (s, 3H).

$^{13}\text{C NMR}$ (**31-min**, 151 MHz, CDCl_3) δ 178.31, 174.48, 147.10, 137.62, 126.81, 124.56, 51.60, 45.02, 41.35, 38.17, 24.02.

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_5$ [M+H] calculated 346.1403, found 346.1404.



32-maj (27.9 mg) and **32-min** (2.9 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**32-maj**, 600 MHz, CDCl_3) δ 7.71 (d, $J = 8.4$ Hz, 2H), 7.55 (d, $J = 8.3$ Hz, 2H), 3.41 – 3.34 (m, 2H), 3.06 (d, $J = 13.6$ Hz, 2H), 3.20 – 2.62 (m, 6H), 1.97 – 1.88 (m, 2H), 1.44 (s, 3H).

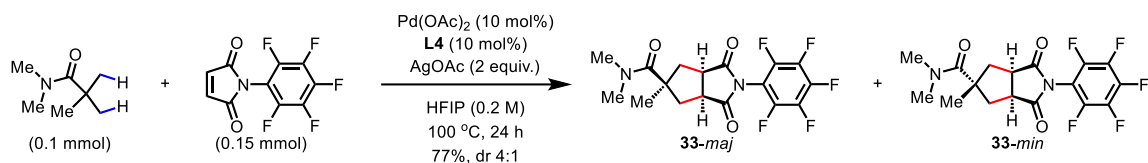
$^{13}\text{C NMR}$ (**32-maj**, 151 MHz, CDCl_3) δ 178.45, 174.33, 135.70, 130.36 (q, $J = 33.0$ Hz), 127.07, 126.14 (q, $J = 3.8$ Hz), 123.94 (q, $J = 272.3$ Hz), 50.07, 45.17, 41.51, 38.93, 37.74, 24.14.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3$ [M+H] calculated 369.1426, found 369.1429.

$^1\text{H NMR}$ (**32-min**, 600 MHz, CDCl_3) δ 7.75 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 2H), 3.50 – 3.44 (m, 2H), 3.05 (br s, 6H), 2.86 – 2.80 (m, 2H), 2.15 (ddd, $J = 13.9, 2.8, 1.0$ Hz, 2H), 1.37 (s, 3H).

^{13}C NMR (**32-min**, 151 MHz, CDCl_3) δ 178.69, 174.64, 135.20, 130.67 (q, $J = 32.8$ Hz), 126.57, 126.43 (q, $J = 3.8$ Hz), 123.79 (q, $J = 272.3$ Hz), 51.49, 44.98, 41.29, 38.12, 24.06.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 369.1426, found 369.1434.



33-maj and **33-min** (29.9 mg) were isolated as mixture following the general procedure.

^1H NMR (**33-maj** + **33-min**, 600 MHz, CDCl_3) δ 3.57 – 3.48 (m, 2H), 3.26 – 2.79 (m, 8H), 2.16 – 2.09 (m, 2H), 1.43 (s, 2.4H), 1.40 (s, 0.6H).

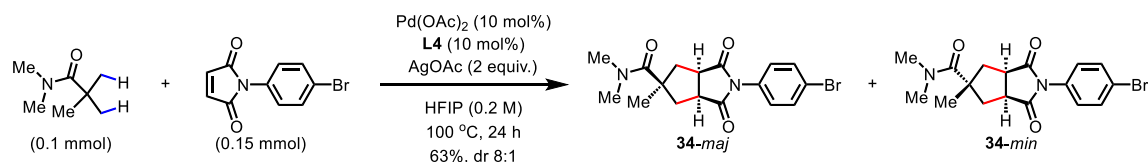
^{13}C NMR (**33-maj**, 151 MHz, CDCl_3) δ 176.06, 174.03, 143.73 (d, $J = 256.6$ Hz), 142.04 (d, $J = 243.4$ Hz), 138.05 (d, $J = 252.5$ Hz), 107.61, 51.17, 45.57, 41.04, 38.06, 24.10.

^{13}C NMR (**33-min**, 151 MHz, CDCl_3) δ 176.81, 174.45, 51.81, 45.61, 41.28, 23.92. (– NMe_2 and fluorinated aryl peaks and were not found due to weak intensity)

^{19}F NMR (**33-maj**, 376 MHz, CDCl_3) δ -142.03 (ddt, $J = 593.8, 22.5, 6.4$ Hz), -152.05 (t, $J = 21.4$ Hz), -161.47 (dtd, $J = 65.5, 22.0, 6.8$ Hz).

^{19}F NMR (**33-min**, 376 MHz, CDCl_3) δ -143.30 (ddt, $J = 202.5, 22.5, 6.5$ Hz), -151.03 (t, $J = 21.3$ Hz), -160.87 (dtd, $J = 111.4, 21.9, 6.9$ Hz).

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{16}\text{F}_5\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 391.1081, found 391.1078.



34-maj (21.1 mg) and **34-min** (2.8 mg) were isolated separately following the general procedure.

^1H NMR (**34-maj**, 600 MHz, CDCl_3) δ 7.56 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H), 3.38 – 3.31 (m, 2H), 3.04 (d, $J = 13.7$ Hz, 2H), 3.20 – 2.62 (m, 6H), 1.94 – 1.88 (m, 2H), 1.42 (s, 3H).

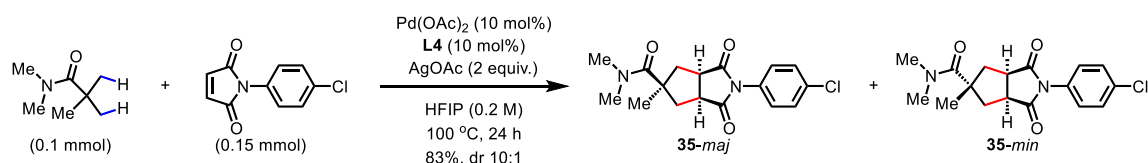
^{13}C NMR (**34-maj**, 151 MHz, CDCl_3) δ 178.56, 174.30, 132.23, 131.57, 128.35, 122.37, 50.10, 45.11, 41.45, 38.82, 37.79, 24.16.

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{20}\text{BrN}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 379.0657, found 379.0664.

^1H NMR (**34-min**, 600 MHz, CDCl_3) δ 7.60 (d, $J = 8.6$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 3.46 – 3.41 (m, 2H), 3.04 (br s, 6H), 2.83 – 2.77 (m, 2H), 2.14 (dd, $J = 13.4, 3.4$ Hz, 2H), 1.35 (s, 3H).

^{13}C NMR (**34-min**, 151 MHz, CDCl_3) δ 178.85, 174.72, 132.52, 131.09, 127.83, 122.60, 51.42, 44.93, 41.24, 38.11, 24.07.

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{20}\text{BrN}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 379.0657, found 379.0654.



35-maj (24.4 mg) and **35-min** (11.0 mg) were isolated separately following the general procedure.

^1H NMR (**35-maj**, 600 MHz, CDCl_3) δ 7.41 (d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 8.8$ Hz, 2H), 3.37 – 3.32 (m, 2H), 3.04 (d, $J = 13.6$ Hz, 2H), 3.20 – 2.65 (m, 6H), 1.95 – 1.88 (m, 2H), 1.42 (s, 3H).

^{13}C NMR (**35-maj**, 151 MHz, CDCl_3) δ 178.63, 174.30, 134.26, 131.05, 129.25, 128.05, 50.11, 45.10, 41.45, 38.83,

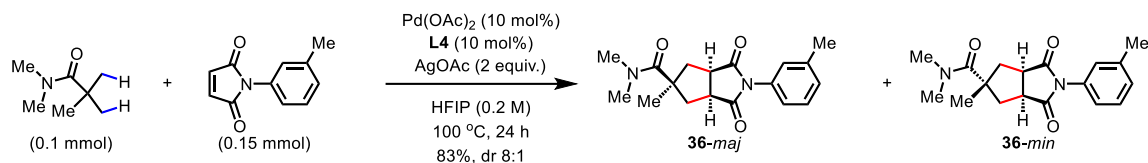
37.79, 24.16.

HRMS (ESI-TOF): C₁₇H₂₀ClN₂O₃ [M+H] calculated 335.1162, found 335.1161.

¹H NMR (**35-min**, 600 MHz, CDCl₃) δ 7.45 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 3.46 – 3.41 (m, 2H), 3.04 (br s, 6H), 2.82 – 2.78 (m, 2H), 2.14 (ddd, *J* = 13.8, 2.7, 1.0 Hz, 2H), 1.35 (s, 3H).

¹³C NMR (**35-min**, 151 MHz, CDCl₃) δ 178.93, 174.73, 134.56, 130.56, 129.54, 127.56, 51.41, 44.92, 41.24, 38.12, 24.08.

HRMS (ESI-TOF): C₁₇H₂₀ClN₂O₃ [M+H] calculated 335.1162, found 335.1170.



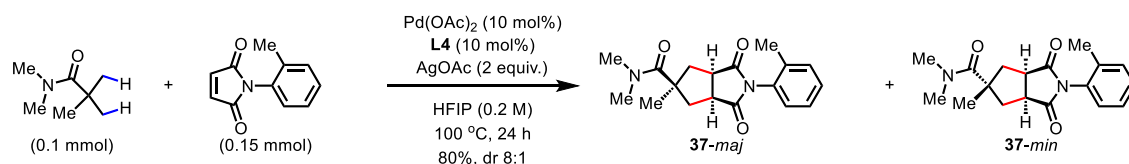
36-maj and **36-min** (26.0 mg) were isolated as mixture following the general procedure.

¹H NMR (**36-maj** + **36-min**, 600 MHz, CDCl₃) δ 7.36 (t, *J* = 7.8 Hz, 0.11H), 7.34 – 7.31 (m, 0.89H), 7.21 (d, *J* = 7.4 Hz, 0.11H), 7.16 (d, *J* = 8.5 Hz, 0.89H), 7.15 – 7.13 (m, 1.78H), 7.07 – 7.04 (m, 0.22H), 3.45 – 3.40 (m, 0.22H), 3.37 – 3.33 (m, 1.78H), 3.23 – 2.67 (m, 8H), 2.39 (s, 0.33H), 2.37 (s, 2.67H), 2.19 – 2.15 (m, 0.22H), 1.94 (ddt, *J* = 13.4, 8.7, 6.0 Hz, 1.78H), 1.42 (s, 2.67H), 1.37 (s, 0.33H).

¹³C NMR (**36-maj**, 151 MHz, CDCl₃) δ 178.95, 174.32, 139.07, 132.43, 129.44, 128.92, 127.32, 123.86, 50.30, 45.09, 41.35, 38.65, 37.91, 24.19, 21.47.

¹³C NMR (**36-min**, 151 MHz, CDCl₃) δ 179.36, 174.91, 139.43, 131.98, 129.69, 129.18, 126.93, 123.46, 51.29, 44.91, 41.20, 24.15, 21.47. (–NMe₂ peaks and were not found due to weak intensity)

HRMS (ESI-TOF): C₁₈H₂₃N₂O₃ [M+H] calculated 315.1709, found 315.1714.



37-maj (22.6 mg) and **37-min** (2.7 mg) were isolated separately following the general procedure.

¹H NMR (**37-maj**, 600 MHz, CDCl₃) (0.8:0.2 ratio of rotamers) δ 7.44 – 7.40 (m, 0.8H), 7.34 – 7.21 (m, 3H), 7.05 (d, *J* = 7.8 Hz, 0.2H), 3.49 – 3.43 (m, 0.4H), 3.42 – 3.37 (m, 1.6H), 3.25 – 2.79 (m, 7.6H), 2.52 – 2.36 (m, 0.8H), 2.14 (s, 0.6H), 2.11 (s, 2.4H), 1.94 (ddt, *J* = 13.2, 8.5, 6.2 Hz, 1.6H), 1.44 (s, 2.4H), 1.39 (s, 0.6H).

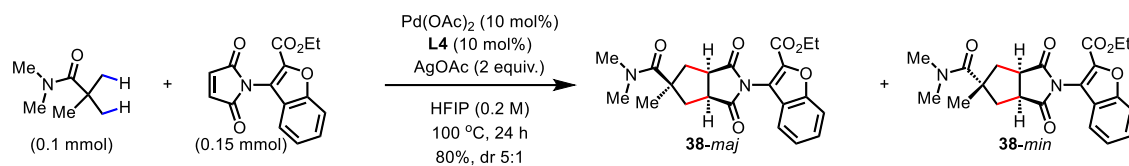
¹³C NMR (**37-maj**, 151 MHz, CDCl₃) (0.8:0.2 ratio of rotamers) δ 178.75, 178.25, 174.80, 174.39, 136.13, 135.34, 131.69, 131.37, 131.04, 130.88, 129.60, 129.29, 128.16, 128.05, 127.02, 126.88, 52.79, 50.31, 45.28, 44.81, 41.26, 40.41, 38.66, 37.92, 24.27, 23.21, 17.89, 17.81.

HRMS (ESI-TOF): C₁₈H₂₃N₂O₃ [M+H] calculated 315.1709, found 315.1713.

¹H NMR (**37-min**, 600 MHz, CDCl₃) (0.6:0.4 ratio of rotamers) δ 7.36 – 7.28 (m, 3H), 7.07 (d, *J* = 7.8 Hz, 0.4H), 7.02 (d, *J* = 7.7 Hz, 0.6H), 3.51 – 3.43 (m, 2H), 3.05 (br s, 6H), 3.01 – 2.96 (m, 0.8H), 2.82 – 2.76 (m, 1.2H), 2.20 (ddd, *J* = 13.8, 2.5, 1.2 Hz, 1.2H), 2.17 (s, 1.2H), 2.15 (s, 1.8H), 1.90 – 1.84 (m, 0.8H), 1.47 (s, 1.2H), 1.41 (s, 1.8H).

¹³C NMR (**37-min**, 151 MHz, CDCl₃) (0.6:0.4 ratio of rotamers) δ 178.72, 174.92, 174.29, 135.81, 135.66, 131.44, 131.38, 131.20, 131.06, 129.68, 129.66, 128.36, 127.31, 127.26, 127.03, 52.76, 51.35, 45.79, 45.11, 41.72, 41.13, 38.13, 24.27, 17.94, 17.88.

HRMS (ESI-TOF): C₁₈H₂₃N₂O₃ [M+H] calculated 315.1709, found 315.1715.

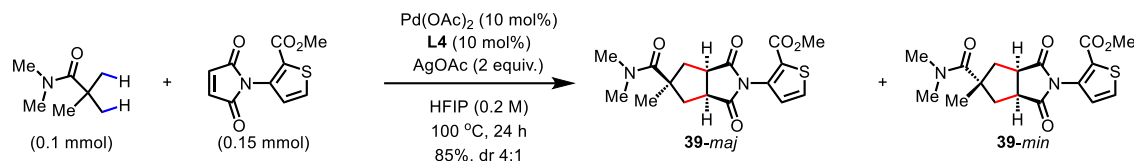


38-maj and **38-min** (33.0 mg) were isolated as mixture following the general procedure.

$^1\text{H NMR}$ (**38-maj** + **38-min**, 600 MHz, CDCl_3) δ 8.18 (s, 1H), 7.63 – 7.55 (m, 1H), 7.52 – 7.45 (m, 1H), 7.35 (ddd, J = 8.0, 7.1, 0.9 Hz, 1H), 4.43 – 4.35 (m, 2H), 3.55 (ddt, J = 7.9, 6.0, 2.6 Hz, 0.33H), 3.48 (d, J = 6.8 Hz, 1.67H), 3.23 – 2.63 (m, 8H), 2.33 – 1.80 (m, 2H), 1.50 (s, 0.5H), 1.45 (s, 2.5H), 1.41 – 1.36 (m, 3H).

$^{13}\text{C NMR}$ (**38-maj**, 151 MHz, CDCl_3) δ 177.24, 174.50, 158.46, 154.08, 139.52, 128.51, 124.30, 124.14, 123.49, 120.72, 112.44, 61.75, 50.42, 45.68, 40.82, 38.73, 38.00, 24.11, 14.41.

HRMS (ESI-TOF): $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_6$ [$\text{M}+\text{H}$] calculated 413.1713, found 413.1712.



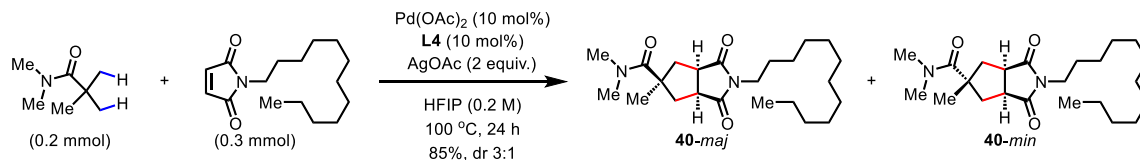
39-maj and **39-min** (30.8 mg) were isolated as mixture following the general procedure.

$^1\text{H NMR}$ (**39-maj** + **39-min**, 600 MHz, CDCl_3) δ 7.58 (d, J = 5.3 Hz, 0.2H), 7.55 (d, J = 5.3 Hz, 0.8H), 7.24 (d, J = 5.3 Hz, 0.8H), 7.02 (d, J = 5.3 Hz, 0.2H), 3.83 (s, 0.6H), 3.80 (s, 2.4H), 3.48 – 3.44 (m, 0.4H), 3.43 – 3.39 (m, 1.6H), 3.22 – 2.68 (m, 8H), 2.09 (dd, J = 13.3, 5.2 Hz, 0.4H), 2.00 – 1.95 (m, 1.6H), 1.45 (s, 0.6H), 1.42 (s, 2.4H).

$^{13}\text{C NMR}$ (**39-maj**, 151 MHz, CDCl_3) δ 177.81, 174.50, 160.81, 134.77, 130.25, 127.77, 126.81, 52.25, 50.62, 45.27, 40.93, 38.55, 38.02, 23.91.

$^{13}\text{C NMR}$ (**39-min**, 151 MHz, CDCl_3) δ 178.05, 174.69, 160.64, 134.31, 130.55, 127.49, 127.02, 52.44, 52.31, 45.59, 40.80, 23.84. (– NMe_2 peaks and were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_5\text{S}$ [$\text{M}+\text{H}$] calculated 365.1171, found 365.1166.

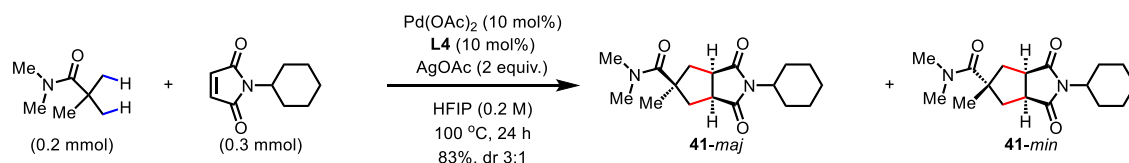


40-maj and **40-min** (66.5 mg) were isolated as mixture following the general procedure.

$^1\text{H NMR}$ (**40-maj** + **40-min**, 600 MHz, CDCl_3) δ 3.48 – 3.43 (m, 0.5H), 3.38 – 3.32 (m, 1.5H), 3.27 – 3.21 (m, 0.5H), 3.20 – 3.15 (m, 1.5H), 3.14 – 2.79 (m, 6H), 2.75 (d, J = 14.0 Hz, 1.5H), 2.73 – 2.67 (m, 0.5H), 2.00 (dd, J = 13.5, 3.4 Hz, 0.5H), 1.97 – 1.90 (m, 1.5H), 1.57 – 1.47 (m, 2H), 1.36 (s, 3H), 1.32 – 1.22 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H).

$^{13}\text{C NMR}$ (**40-maj** + **40-min**, 151 MHz, CDCl_3) δ 180.24, 179.67, 174.94, 174.28, 51.45, 50.74, 44.81, 44.72, 40.81, 40.74, 39.14, 39.08, 38.07, 32.01, 29.73, 29.72, 29.67, 29.67, 29.64, 29.61, 29.58, 29.44, 29.29, 29.24, 27.62, 27.58, 27.08, 27.08, 27.01, 24.05, 23.96, 22.79, 14.22.

HRMS (ESI-TOF): $\text{C}_{23}\text{H}_{41}\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 393.3117, found 393.3119.



41-maj and **41-min** (50.6 mg) were isolated as mixture following the general procedure.

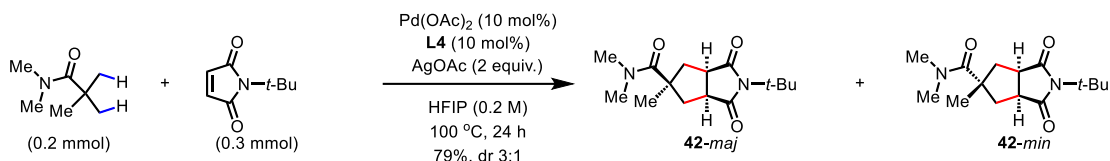
$^1\text{H NMR}$ (**41-maj** + **41-min**, 600 MHz, CDCl_3) δ 3.94 (tt, J = 12.3, 3.9 Hz, 0.25H), 3.87 (tt, J = 12.3, 3.9 Hz, 0.75H),

3.20 – 3.15 (m, 0.5H), 3.14 – 3.09 (m, 1.5H), 3.22 – 2.77 (m, 6H), 2.74 (ddd, $J = 13.8, 1.9, 0.9$ Hz, 1.5H), 2.68 – 2.61 (m, 0.5H), 2.13 (qd, $J = 12.4, 3.4$ Hz, 0.5H), 2.10 – 2.01 (m, 2H), 1.97 – 1.90 (m, 1.5H), 1.82 – 1.76 (m, 2H), 1.68 – 1.55 (m, 3H), 1.36 (s, 2.25H), 1.32 – 1.15 (m, 3H), 1.23 (s, 0.75H).

^{13}C NMR (**41-maj**, 151 MHz, CDCl_3) δ 179.74, 174.29, 51.73, 50.62, 44.51, 40.80, 38.04, 28.53, 25.93, 25.20, 24.23.

^{13}C NMR (**41-min**, 151 MHz, CDCl_3) δ 180.50, 175.19, 51.76, 50.90, 44.37, 40.86, 28.50, 25.86, 25.11, 24.21. (– NMe_2 peaks were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 307.2022, found 307.2026.



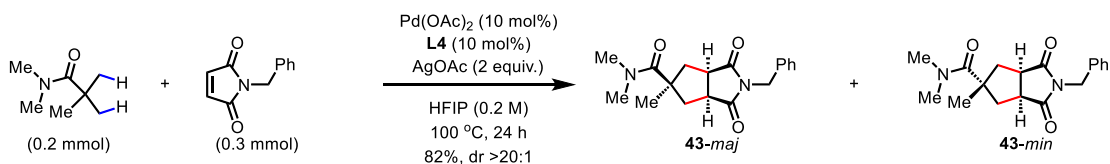
42-maj and **42-min** (44.6 mg) were isolated as mixture following the general procedure.

^1H NMR (**42-maj** + **42-min**, 600 MHz, CDCl_3) δ 3.17 – 2.83 (m, 8H), 2.73 (ddd, $J = 13.8, 1.9, 1.0$ Hz, 1.5H), 2.59 (ddd, $J = 13.9, 7.3, 2.3$ Hz, 0.5H), 2.12 (ddd, $J = 14.1, 1.8, 1.0$ Hz, 0.5H), 1.95 – 1.88 (m, 1.5H), 1.57 (s, 2.25H), 1.53 (s, 6.75H), 1.35 (s, 2.25H), 1.22 (s, 0.75H).

^{13}C NMR (**42-maj**, 151 MHz, CDCl_3) δ 180.66, 174.46, 58.11, 50.43, 44.73, 41.09, 38.02, 28.25, 24.25.

^{13}C NMR (**42-min**, 151 MHz, CDCl_3) δ 181.48, 175.37, 58.23, 50.46, 44.49, 41.01, 28.16, 24.04. (– NMe_2 peaks were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 281.1865, found 281.1864.

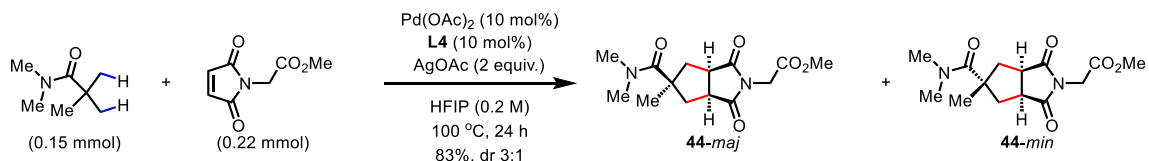


43-maj and **43-min** (51.8 mg) were isolated as mixture following the general procedure.

^1H NMR (**43-maj**, 600 MHz, CDCl_3) δ 7.39 – 7.37 (m, 2H), 7.29 (t, $J = 7.2$ Hz, 2H), 7.26 – 7.23 (m, 1H), 4.52 (s, 2H), 3.21 – 3.16 (m, 2H), 3.27 – 2.57 (m, 6H), 2.77 – 2.72 (m, 2H), 1.96 – 1.90 (m, 2H), 1.35 (s, 3H).

^{13}C NMR (**43-maj**, 151 MHz, CDCl_3) δ 179.28, 174.25, 136.02, 129.11, 128.62, 127.84, 50.77, 44.77, 42.61, 40.68, 38.35, 37.91, 23.80.

HRMS (ESI-TOF): $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 315.1709, found 315.1714.



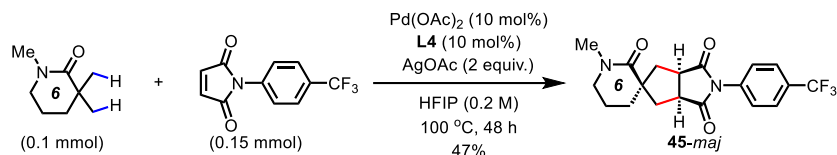
44-maj and **44-min** (36.9 mg) were isolated as mixture following the general procedure.

^1H NMR (**44-maj** + **44-min**, 600 MHz, CDCl_3) δ 4.23 (s, 0.5H), 4.14 (s, 1.5H), 3.76 (s, 0.75H), 3.73 (s, 2.25H), 3.38 – 3.29 (m, 2H), 3.22 – 2.70 (m, 8H), 2.03 – 1.95 (m, 2H), 1.37 (s, 0.75H), 1.37 (s, 2.25H).

^{13}C NMR (**44-maj**, 151 MHz, CDCl_3) δ 178.69, 174.38, 167.53, 52.65, 50.97, 44.83, 40.63, 39.56, 38.08, 23.69.

^{13}C NMR (**44-min**, 151 MHz, CDCl_3) δ 179.16, 174.86, 167.38, 52.74, 51.87, 45.17, 40.73, 39.49, 23.89. (– NMe_2 peaks were not found due to weak intensity)

HRMS (ESI-TOF): $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_5$ [$\text{M}+\text{H}$] calculated 297.1450, found 297.1456.

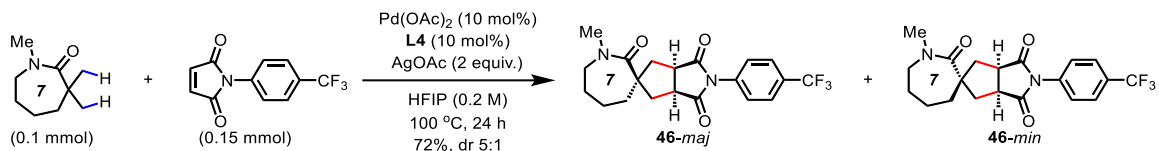


45-maj (24.4 mg) was isolated following the general procedure.

$^1\text{H NMR}$ (**45-maj**, 600 MHz, CDCl_3) δ 7.72 (d, $J = 8.5$ Hz, 2H), 7.62 (d, $J = 8.3$ Hz, 2H), 3.50 – 3.46 (m, 2H), 3.28 (t, $J = 5.8$ Hz, 2H), 2.84 (s, 3H), 2.68 (d, $J = 14.2$ Hz, 2H), 1.94 (ddd, $J = 14.4, 8.0, 2.6$ Hz, 2H), 1.88 – 1.81 (m, 4H).

$^{13}\text{C NMR}$ (**45-maj**, 151 MHz, CDCl_3) δ 179.22, 174.72, 136.55, 130.28 (q, $J = 32.5$ Hz), 127.83, 126.18 (q, $J = 3.8$ Hz), 124.06 (q, $J = 272.3$ Hz), 50.24, 49.62, 46.24, 41.52, 35.67, 34.90, 21.17.

HRMS (ESI-TOF): $\text{C}_{19}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 381.1426, found 381.1417.



46-maj (24.7 mg) and **46-min** (4.9 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**46-maj**, 600 MHz, CDCl_3) δ 7.70 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.2$ Hz, 2H), 3.45 – 3.37 (m, 4H), 3.02 (d, $J = 13.7$ Hz, 2H), 2.87 (s, 3H), 1.92 (ddd, $J = 13.8, 7.5, 2.5$ Hz, 2H), 1.78 – 1.69 (m, 4H), 1.65 – 1.60 (m, 2H).

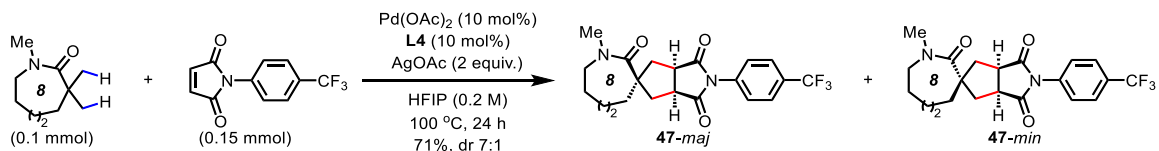
$^{13}\text{C NMR}$ (**46-maj**, 151 MHz, CDCl_3) δ 178.72, 175.91, 135.98, 130.30 (q, $J = 32.5$ Hz), 127.25, 126.13 (q, $J = 3.8$ Hz), 123.99 (q, $J = 272.4$ Hz), 54.52, 51.17, 45.41, 40.70, 39.07, 36.21, 27.80, 26.29.

HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 395.1583, found 395.1584.

$^1\text{H NMR}$ (**46-min**, 600 MHz, CDCl_3) δ 7.74 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 8.2$ Hz, 2H), 3.55 – 3.49 (m, 2H), 3.44 (dd, $J = 6.2, 3.7$ Hz, 2H), 3.02 (s, 3H), 2.90 – 2.83 (m, 2H), 2.08 (dd, $J = 13.5, 3.6$ Hz, 2H), 1.76 – 1.70 (m, 2H), 1.68 – 1.61 (m, 4H).

$^{13}\text{C NMR}$ (**46-min**, 151 MHz, CDCl_3) δ 178.67, 175.39, 135.22, 130.62 (q, $J = 32.9$ Hz), 126.62, 126.42 (q, $J = 3.7$ Hz), 123.80 (q, $J = 272.4$ Hz), 56.22, 50.54, 45.24, 39.70, 38.64, 34.95, 27.42, 25.53.

HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 395.1583, found 395.1577.



47-maj (26.6 mg) and **47-min** (3.6 mg) were isolated separately following the general procedure.

$^1\text{H NMR}$ (**47-maj**, 600 MHz, CDCl_3) δ 7.71 (d, $J = 8.1$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 3.58 (br s, 2H), 3.44 – 3.39 (m, 2H), 2.95 (br s, 2H), 2.77 (s, 3H), 2.04 – 1.93 (m, 4H), 1.71 (s, 2H), 1.67 – 1.59 (m, 2H), 1.39 (s, 2H).

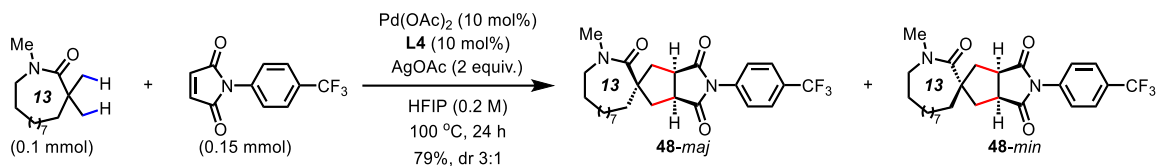
$^{13}\text{C NMR}$ (**47-maj**, 151 MHz, CDCl_3) δ 178.78, 177.27, 136.04, 130.27 (q, $J = 32.5$ Hz), 127.25, 126.15 (q, $J = 3.8$ Hz), 123.99 (q, $J = 272.2$ Hz), 54.73, 48.00, 45.64, 42.36, 41.55, 36.57, 26.13, 24.37, 20.72.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 409.1739, found 409.1729.

$^1\text{H NMR}$ (**47-min**, 600 MHz, CDCl_3) δ 7.74 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.3$ Hz, 2H), 3.58 (br s, 2H), 3.52 – 3.47 (m, 2H), 2.89 (s, 3H), 2.81 (br s, 2H), 2.23 (d, $J = 12.7$ Hz, 2H), 1.80 (t, $J = 6.1$ Hz, 2H), 1.71 (br s, 2H), 1.59 (br s, 2H), 1.40 (br s, 2H).

$^{13}\text{C NMR}$ (**47-min**, 151 MHz, CDCl_3) δ 178.87, 176.62, 135.25, 130.62 (q, $J = 32.8$ Hz), 126.55, 126.43 (q, $J = 3.8$ Hz), 123.79 (q, $J = 272.4$ Hz), 56.06, 47.23, 45.20, 41.25, 40.81, 35.90, 26.84, 23.47, 21.89.

HRMS (ESI-TOF): $\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 409.1739, found 409.1737.

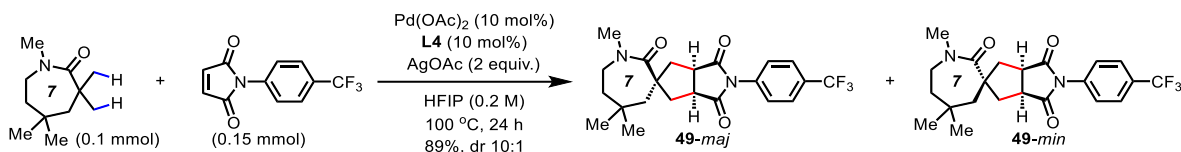


48-maj and **48-min** (37.8 mg) were isolated as mixture following the general procedure. Analytical amount of **48-maj** was purified for characterization.

^1H NMR (**48-maj**, 600 MHz, CDCl_3) (0.6:0.4 ratio of rotamers) δ 7.70 (d, $J = 8.5$ Hz, 2H), 7.61 – 7.49 (m, 2H), 4.27 – 4.22 (m, 0.8H), 3.48 – 3.37 (m, 1.2H), 3.36 – 3.25 (m, 2H), 3.23 – 3.04 (m, 2.8H), 2.99 (d, $J = 13.6$ Hz, 0.8H), 2.65 – 2.24 (m, 1.2H), 2.05 – 1.61 (m, 4.2H), 1.48 – 1.14 (m, 16H).

^{13}C NMR (**48-maj**, 151 MHz, CDCl_3) (0.6:0.4 ratio of rotamers) δ 178.86, 178.37, 173.56, 135.69, 130.32 (q, $J = 32.5$ Hz), 127.01, 126.11, 123.96 (q, $J = 272.3$ Hz), 55.45, 48.71, 48.10, 46.04, 44.87, 43.79, 41.71, 40.15, 38.64, 38.25, 37.81, 36.89, 32.91, 27.71, 27.59, 26.99, 26.83, 26.33, 26.09, 25.58, 25.26, 25.19, 24.82, 23.74, 23.50, 23.01, 22.30, 21.72.

HRMS (ESI-TOF): $\text{C}_{26}\text{H}_{34}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 479.2522, found 479.2522.

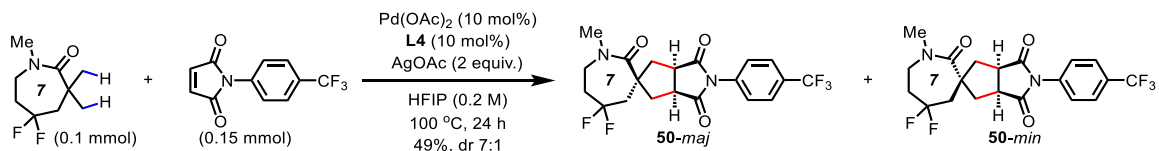


49-maj and **49-min** (37.4 mg) were isolated as mixture following the general procedure. Analytical amount of **49-maj** was purified for characterization.

^1H NMR (**49-maj**, 600 MHz, CDCl_3) δ 7.70 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.3$ Hz, 2H), 3.47 – 3.42 (m, 2H), 3.41 – 3.37 (m, 2H), 2.99 (d, $J = 13.7$ Hz, 2H), 2.87 (s, 3H), 1.98 (ddt, $J = 16.3, 8.5, 4.4$ Hz, 2H), 1.62 (s, 2H), 1.47 – 1.44 (m, 2H), 1.00 (s, 6H).

^{13}C NMR (**49-maj**, 151 MHz, CDCl_3) δ 178.82, 175.53, 136.12, 130.28 (q, $J = 32.7$ Hz), 127.35, 126.13 (q, $J = 3.8$ Hz), 124.02 (q, $J = 272.3$ Hz), 53.96, 49.08, 47.08, 45.52, 42.32, 39.52, 38.30, 33.95, 31.19.

HRMS (ESI-TOF): $\text{C}_{22}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 423.1896, found 423.1895.



50-maj (18.3 mg) and **50-min** (2.7 mg) were isolated separately following the general procedure.

^1H NMR (**50-maj**, 600 MHz, CDCl_3) δ 7.71 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 3.55 (br s, 2H), 3.45 – 3.41 (m, 2H), 3.00 (d, $J = 13.9$ Hz, 2H), 2.93 (s, 3H), 2.21 – 2.14 (m, 2H), 2.14 – 2.03 (m, 4H).

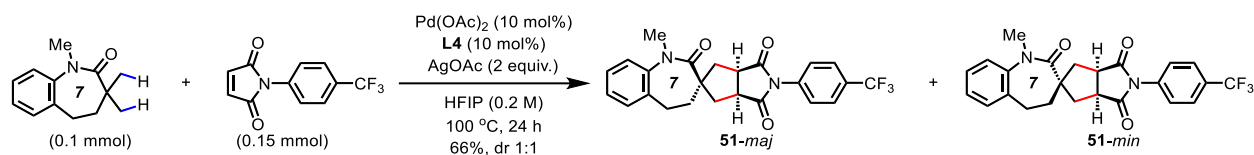
^{13}C NMR (**50-maj**, 151 MHz, CDCl_3) δ 178.24, 174.02, 135.82, 130.43 (q, $J = 32.8$ Hz), 127.15, 126.19 (q, $J = 3.8$ Hz), 123.95 (q, $J = 272.1$ Hz), 123.22 (t, $J = 239.9$ Hz), 50.65 (t, $J = 5.0$ Hz), 45.14, 44.70 (t, $J = 6.7$ Hz), 43.38 (t, $J = 25.8$ Hz), 40.58, 39.02, 36.18 (t, $J = 25.1$ Hz).

HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{20}\text{F}_5\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 431.1394, found 431.1394.

^1H NMR (**50-min**, 600 MHz, CDCl_3) δ 7.75 (d, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 3.62 – 3.56 (m, 2H), 3.56 – 3.51 (m, 2H), 3.09 (s, 3H), 2.92 (dd, $J = 12.4, 8.8$ Hz, 2H), 2.21 – 2.09 (m, 4H), 2.02 – 1.97 (m, 2H).

^{13}C NMR (**50-min**, 151 MHz, CDCl_3) δ 177.75, 173.34, 135.03, 130.71 (q, $J = 33.0$ Hz), 126.78, 126.44 (q, $J = 3.7$ Hz), 123.80 (q, $J = 272.7$ Hz), 123.01 (t, $J = 240.1$ Hz), 53.24 (t, $J = 4.9$ Hz), 45.26, 44.60 (t, $J = 6.6$ Hz), 42.51 (t, $J = 25.8$ Hz), 40.12, 38.83, 36.15 (t, $J = 25.2$ Hz).

HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{20}\text{F}_5\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] calculated 431.1394, found 431.1396.

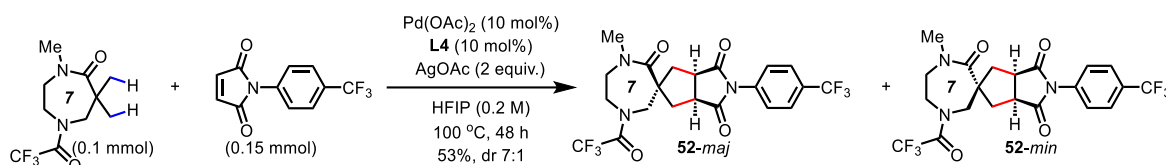


51-maj and **51-min** (29.0 mg) were isolated as mixture following the general procedure.

¹H NMR (**51-maj** + **51-min**, 600 MHz, CDCl₃) δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.20 – 7.13 (m, 2.5H), 7.08 (d, *J* = 8.0 Hz, 0.5H), 3.43 (s, 1.5H), 3.29 (br s, 1H), 3.21 – 3.17 (m, 1H), 3.17 (s, 1.5H), 3.04 – 2.35 (m, 4H), 2.20 (br s, 2H), 1.52 (br s, 2H).

¹³C NMR (**51-maj** + **51-min**, 151 MHz, CDCl₃) δ 178.30, 178.01, 174.24, 173.78, 143.91, 143.50, 135.75, 135.18, 135.11, 135.06, 130.54 (q, *J* = 33.0 Hz), 130.44 (d, *J* = 32.5 Hz), 129.22, 129.14, 128.61, 128.54, 127.13, 126.67, 126.61, 126.35 (q, *J* = 3.7 Hz), 126.23, 126.22 (q, *J* = 3.5 Hz), 123.97 (q, *J* = 272.3 Hz), 123.78 (q, *J* = 272.3 Hz), 122.57, 122.29, 56.32, 53.65, 44.87, 44.76, 44.46, 43.70, 40.91, 40.87, 37.62, 37.58, 30.18, 30.04.

HRMS (ESI-TOF): C₂₄H₂₂F₃N₂O₃ [M+H] calculated 443.1583, found 443.1585.



52-maj and **52-min** (26.2 mg) were isolated as mixture following the general procedure. Analytical amount of **52-maj** was purified for characterization.

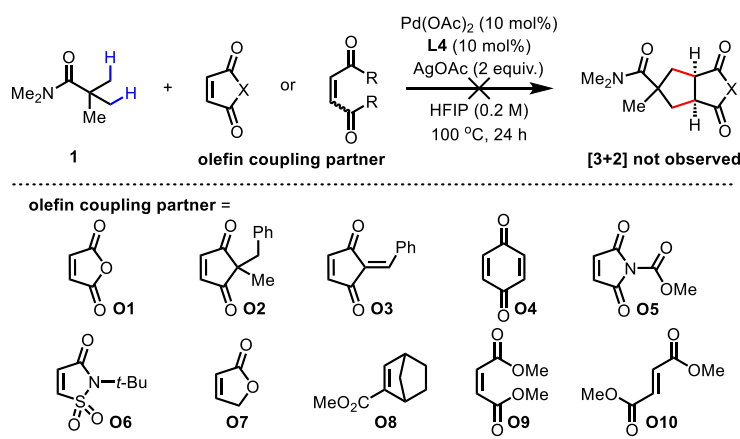
¹H NMR (**52-maj**, 600 MHz, CDCl₃) (0.85:0.15 ratio of rotamers) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 3.86 – 3.68 (m, 4H), 3.67 – 3.61 (m, 2H), 3.54 – 3.48 (m, 2H), 3.00 – 2.91 (m, 3.3H), 2.86 (d, *J* = 13.8 Hz, 1.7H), 2.18 (ddd, *J* = 13.9, 7.5, 2.5 Hz, 1.7H), 2.09 – 2.02 (m, 0.3H).

¹³C NMR (**52-maj**, 151 MHz, CDCl₃) (major rotamer) δ 178.10, 174.66, 156.96 (q, *J* = 36.5 Hz), 135.80, 130.52 (q, *J* = 33.1 Hz), 127.24, 126.25 (q, *J* = 3.8 Hz), 55.87, 50.88, 50.46, 48.27, 45.34, 39.11, 38.71. (–CF₃ peak was not found due to weak intensity)

HRMS (ESI-TOF): C₂₁H₂₀F₆N₃O₄ [M+H] calculated 492.1358, found 492.1356.

2.3 Evaluation of electron-deficient olefins

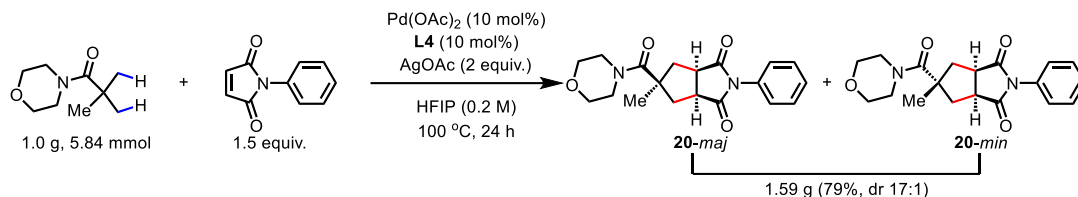
Table S1. Evaluation of electron-deficient cyclic olefins



Following the General Procedure above, various olefins (**O1**~**O10**) were tested as coupling partner. However, no formation of [3+2] product was observed in any case.

2.4 Procedure for gram-scale reaction & silver-free reaction

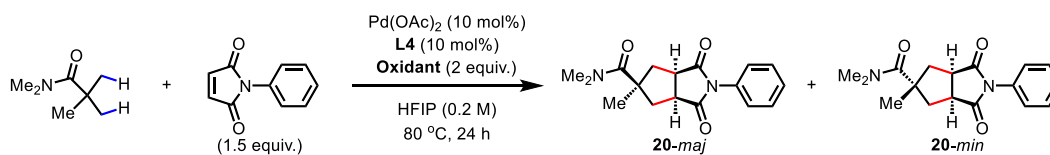
2.4.1 Gram-scale reaction with Ag oxidant



A 150 mL sealed vessel with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 131.1 mg), **L4** (10 mol%, 132.7 mg), AgOAc (11.68 mmol, 1.95 g), *N*-phenylmaleimide (8.76 mmol, 1.52 g), and substrate (5.84 mmol, 1.00 g) in air. Then, HFIP (30 mL) was added as solvent. The reaction tube was sealed and stirred at 100 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a plug of silica and celite, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography using hexanes/EtOAc as eluent to afford **20-maj** and **20-min** as mixture (1.59 g, 79% yield, dr 17:1).

2.4.2 Oxidant screening for silver-free [3+2] reaction

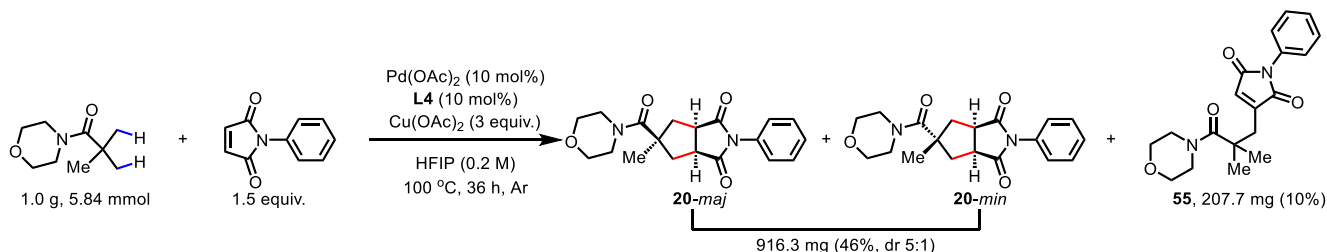
Table S2. Oxidant screening for silver-free [3+2] reaction



entry	Oxidant	Yield, dr
1	TBHP (5.0–6.0 M in Decane)	23%, 3:1
2	TBHP (70 wt. % in H ₂ O)	27%, 4:1
3	K ₂ S ₂ O ₈	21%, 3:1
4	DTBP	27%, 2:1
5	NFSI	<5%
6	Selecfleur	<10%
7	Cu(OAc) ₂	22%, 5:1
8	CuF ₂	24%, 2:1
9	Cu(OAc) ₂ (Under O ₂)	37%, 3:1 (significant substrate decomposition)
10	Cu(OAc) ₂ (100 °C, Under N ₂)	58%, 5:1

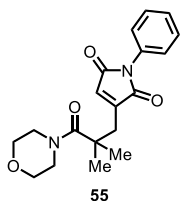
Conditions: substrate (0.1–0.2 mmol), Pd(OAc)₂ (10 mol%), **L4** (10 mol%), *N*-phenylmaleimide (1.5 equiv.), Oxidant (2 equiv.), HFIP (0.2 M), 80 °C, 24 h. Yields were determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

2.4.3 Gram-scale reaction with Cu oxidant



A 150 mL sealed vessel with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 131.1 mg), **L4** (10 mol%, 132.7 mg), Cu(OAc)₂ (17.52 mmol, 3.18 g), *N*-phenylmaleimide (8.76 mmol, 1.52 g), and substrate (5.84 mmol, 1.00 g) in air. Then, HFIP (30 mL) was added as solvent. The reaction tube was placed under vacuum and refilled with Argon for three times. The reaction tube was sealed and stirred at 100 °C for 36 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a plug of silica and celite, and concentrated *in vacuo*.

vacuo. The crude reaction mixture was purified by flash column chromatography using hexanes/EtOAc as eluent to afford **20-maj** and **20-min** as mixture (916.3 mg, 46% yield, dr 5:1). It is important to note that Heck product **55** was also isolated from the crude mixture (207.7 mg, 10% yield).

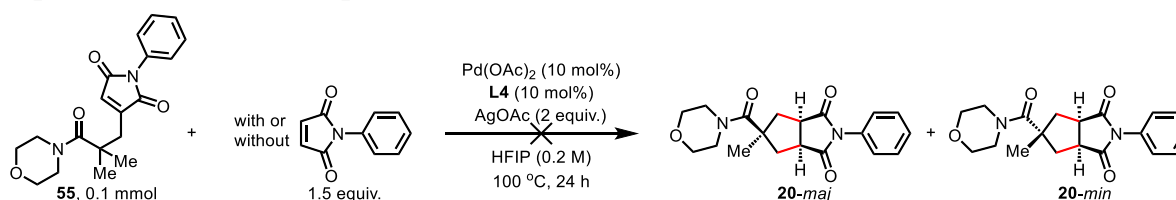


^1H NMR (600 MHz, CDCl_3) δ 7.47 – 7.43 (m, 2H), 7.37 – 7.33 (m, 3H), 6.56 (t, $J = 1.5$ Hz, 1H), 3.71 – 3.66 (m, 8H), 2.84 (d, $J = 1.5$ Hz, 2H), 1.39 (s, 6H).

^{13}C NMR (151 MHz, CDCl_3) δ 174.29, 171.16, 169.76, 146.32, 131.72, 129.44, 129.16, 127.81, 125.99, 66.90, 46.01, 43.14, 36.18, 26.22.

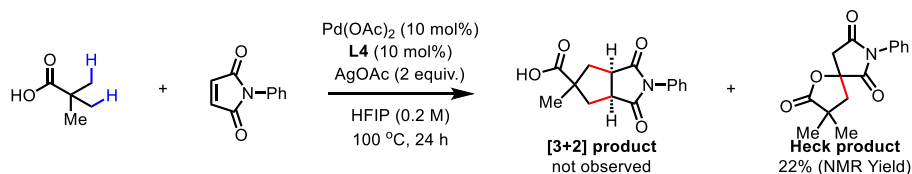
HRMS (ESI-TOF): $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_4$ [M+H] calculated 343.1658, found 343.1661.

2.5 Attempted reaction with Heck product **55**



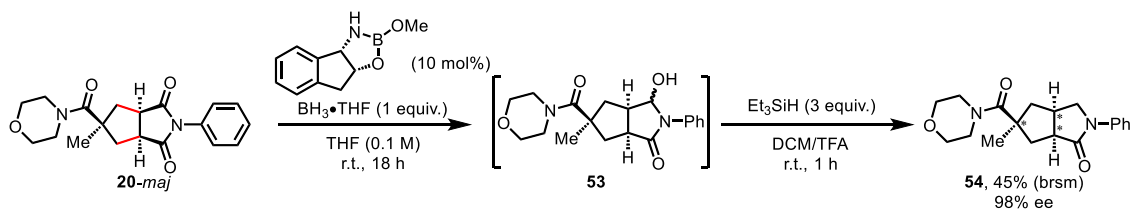
Following the General Procedure above, Heck product **55** was subjected into the reaction conditions with or without *N*-phenylmaleimide. ^1H NMR analysis revealed no formation of the [3+2] product **20**.

2.6 Attempted reaction with pivalic acid



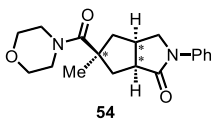
Following the General Procedure above, pivalic acid was subjected into the reaction conditions with *N*-phenylmaleimide. Only the Heck product lactone was observed through ^1H NMR analysis. The spectroscopic data of the lactone matched the reported data from reference 1.

2.7 Desymmetrization of **20**



Catalyst preparation⁴: To a solution of freshly recrystallized (1*S*,2*R*)-*cis*-1-aminoindan-2-ol (186.5 mg, 1.25 mmol) in THF (3 ml) was added trimethylborate (140 μL , 1.25 mmol) under N_2 atmosphere. The reaction mixture was stirred for 30 min at room temperature. 2 ml of THF was added to make a 2.5 M stock solution of the oxazaborolidine catalyst.

To a solution of **20-maj** (68.4 mg, 0.2 mmol) in THF (2 mL) was added the catalyst solution (40 uL, 10 mol%) and 1M BH₃·THF (200 uL, 0.2 mmol) under N₂ atmosphere. After stirring for 18 h at room temperature, the reaction was quenched with dropwise addition of 1 N HCl (aq), and was extracted with DCM. The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo* to give the crude hydroxylactam **53**. Without further purification, **53** was dissolved in DCM (2 mL) and treated with TFA (0.1 mL) and triethylsilane (0.1 mL). After stirring for 1 h at room temperature, sat. NaHCO₃ (aq) was added followed by extraction with DCM. The combined organic extracts were dried over MgSO₄, concentrated *in vacuo*, and purified via pTLC using hexanes/EtOAc as eluent to afford **54** (19.7 mg) along with substrate **20-maj** (22.3 mg). The ee value (98%) was determined by SFC analysis on a Chiralcel OD-3 column (20% isopropanol, 2.0 mL/min) with retention time of 8.159 min (major) and 11.497 min (minor).

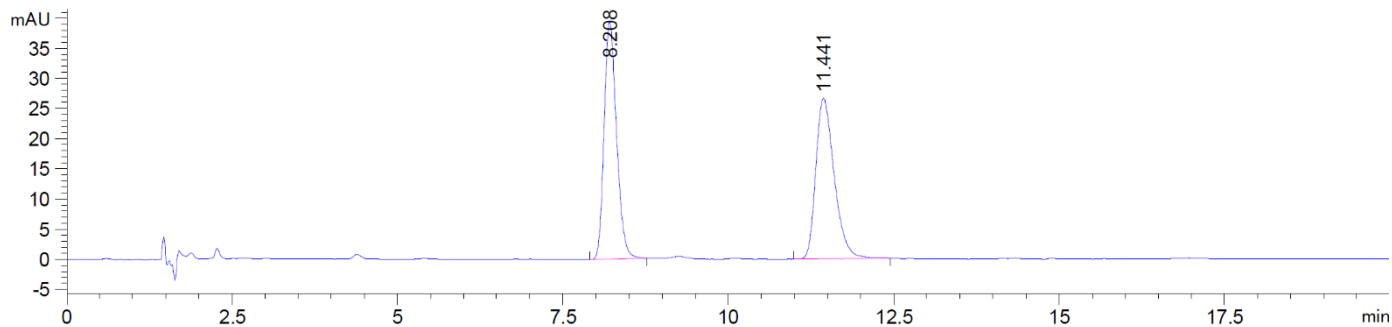


¹H NMR (600 MHz, CDCl₃) δ 7.59 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.02 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.72 – 3.52 (m, 9H), 3.20 (td, *J* = 9.5, 3.9 Hz, 1H), 2.89 – 2.81 (m, 1H), 2.53 (dd, *J* = 13.6, 3.9 Hz, 1H), 2.33 (dd, *J* = 13.4, 9.3 Hz, 1H), 2.11 (dd, *J* = 13.3, 10.3 Hz, 1H), 2.03 (dd, *J* = 13.4, 7.6 Hz, 1H), 1.34 (s, 3H).

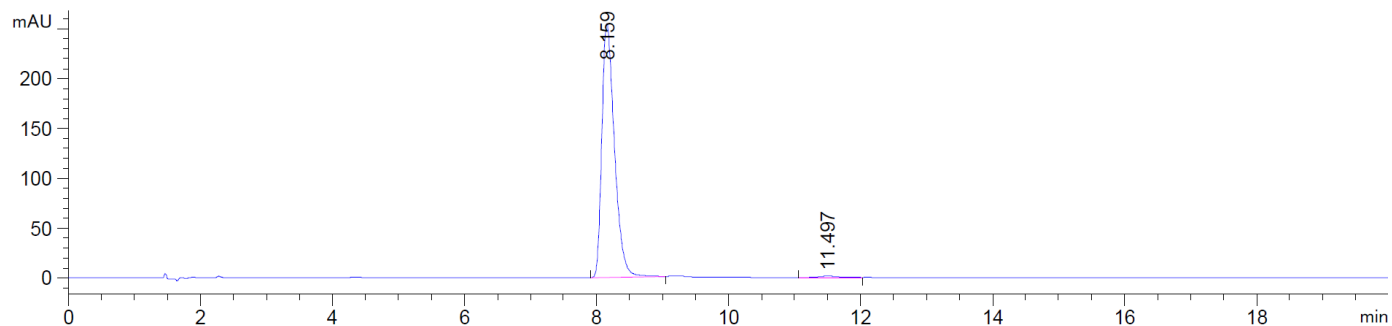
¹³C NMR (151 MHz, CDCl₃) δ 175.82, 175.06, 139.42, 128.95, 124.98, 120.62, 66.81, 52.68, 51.01, 48.44, 45.45, 39.64, 32.85, 25.35. (–N(CH₂)– peaks were not found due to weak intensity)

HRMS (ESI-TOF): C₁₉H₂₅N₂O₃ [M+H] calculated 329.1860, found 329.1866.

DAD1 A, Sig=250,4 Ref=360,100 (HP\HP 2020-02-11 20-16-37\003-6-HP_9_20_rac_OD_20%.D)



DAD1 A, Sig=250,4 Ref=360,100 (HP\HP 2020-02-11 20-16-37\004-7-HP_9_18_chiral_OD_20%.D)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.159	BB	0.2028	3383.66113	255.06105	99.1329
2	11.497	BB	0.2776	29.59540	1.39474	0.8671

2.8 X-Ray Crystallographic Data of *31-maj*, *31-min*, and *28-maj*

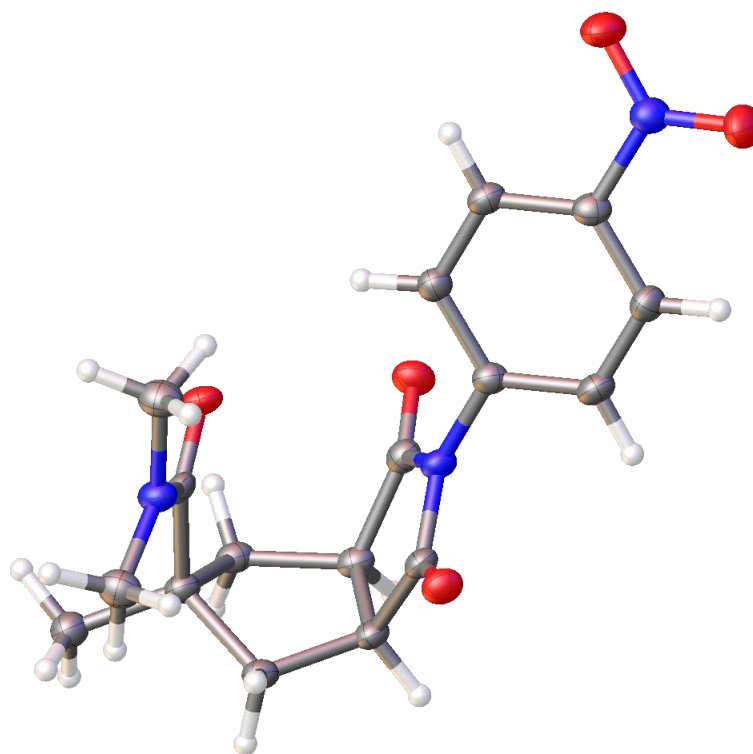


Table S3. Crystal data and structure refinement for **31-maj**. (CCDC1995507)

Empirical formula	C ₁₇ H ₁₉ N ₃ O ₅	
Formula weight	345.35	
Temperature	100.15 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 11.3909(6) Å	α = 90°.
	b = 6.6075(4) Å	β = 98.175(4)°.
	c = 22.1827(12) Å	γ = 90°.
Volume	1652.62(16) Å ³	
Z	4	
Density (calculated)	1.388 Mg/m ³	
Absorption coefficient	0.866 mm ⁻¹	
F(000)	728	
Crystal size	0.17 x 0.11 x 0.08 mm ³	
Theta range for data collection	4.026 to 70.066°.	
Index ranges	-13 ≤ h ≤ 13, -8 ≤ k ≤ 7, -27 ≤ l ≤ 26	
Reflections collected	15057	
Independent reflections	3051 [R(int) = 0.0610]	
Completeness to theta = 67.500°	97.9 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.5963
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3051 / 0 / 229
Goodness-of-fit on F ²	1.107
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1293
R indices (all data)	R1 = 0.0663, wR2 = 0.1362
Extinction coefficient	n/a
Largest diff. peak and hole	0.312 and -0.242 e.Å ⁻³

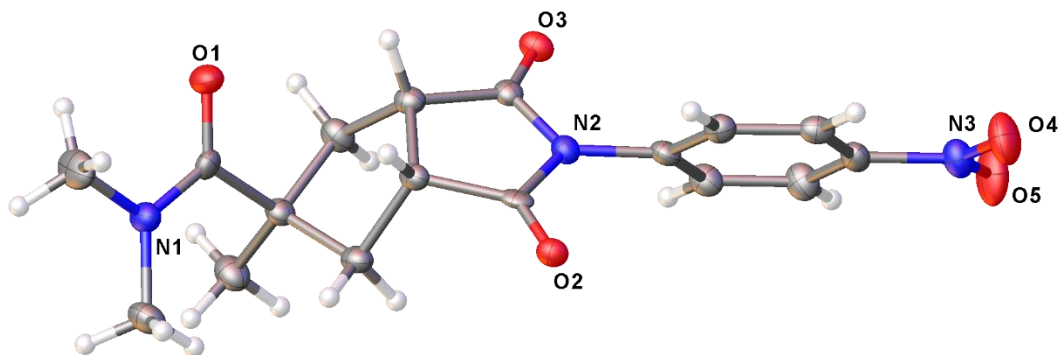


Table S4. Crystal data and structure refinement for **31-min.** (CCDC1995509)

Empirical formula	C17 H19 N3 O5 (racemic)	
Formula weight	345.35	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.548(4) Å	α = 109.288(16)°.
	b = 16.622(6) Å	β = 98.811(12)°.
	c = 22.118(8) Å	γ = 95.569(10)°.
Volume	3233(2) Å ³	
Z, Z'	8, 4	
Density (calculated)	1.419 Mg/m ³	
Absorption coefficient	0.106 mm ⁻¹	
F(000)	1456	
Crystal size	0.31 x 0.27 x 0.25 mm ³	
Theta range for data collection	1.314 to 25.427°.	
Index ranges	-11<=h<=10, -19<=k<=19, -26<=l<=26	
Reflections collected	31963	
Independent reflections	11851 [R(int) = 0.0799]	

Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6313
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	11851 / 0 / 978
Goodness-of-fit on F ²	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0594, wR2 = 0.1434
R indices (all data)	R1 = 0.0901, wR2 = 0.1664
Extinction coefficient	n/a
Largest diff. peak and hole	0.357 and -0.307 e.Å ⁻³

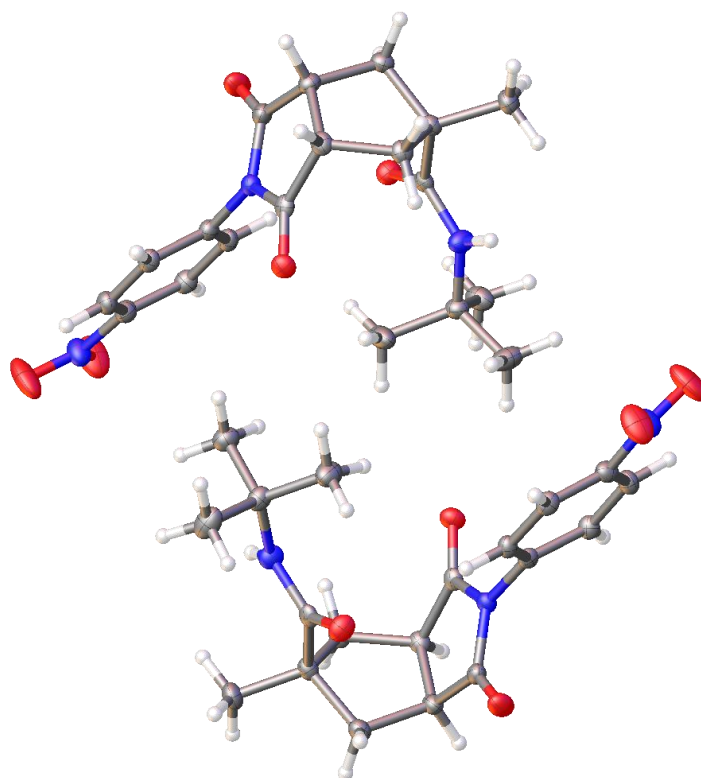


Table S5. Crystal data and structure refinement for **28-maj**. (CCDC1995508)

Empirical formula	C ₁₉ H ₂₃ N ₃ O ₅	
Formula weight	373.40	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pna2 ₁	
Unit cell dimensions	a = 25.8413(3) Å	α = 90°.
	b = 6.41810(10) Å	β = 90°.
	c = 22.5133(3) Å	γ = 90°.
Volume	3733.88(9) Å ³	

Z	8
Density (calculated)	1.328 Mg/m ³
Absorption coefficient	0.806 mm ⁻¹
F(000)	1584
Crystal size	0.8 x 0.161 x 0.13 mm ³
Theta range for data collection	3.420 to 70.817°.
Index ranges	-31<=h<=29, -7<=k<=7, -27<=l<=27
Reflections collected	40887
Independent reflections	7037 [R(int) = 0.0627]
Completeness to theta = 67.500°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7534 and 0.5303
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7037 / 1 / 495
Goodness-of-fit on F ²	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0332, wR2 = 0.0856
R indices (all data)	R1 = 0.0339, wR2 = 0.0863
Absolute structure parameter	0.06(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.253 and -0.169 e.Å ⁻³

3. References

- 1) Z. Zhuang *et al.*, *J. Am. Chem. Soc.* **140**, 10363–10367 (2018).
- 2) H. Park, N. Chekshin, P.-X. Shen, J.-Q. Yu, *ACS Catal.* **8**, 9292–9297 (2018).
- 3) H. Park, Y. Li, J.-Q. Yu, *Angew. Chem. Int Ed.* **58**, 11424–11428 (2019).
- 4) M. D. Barker, R. A. Dixon, S. Jones, B. J. Marsh, *Tetrahedron* **62**, 11663–11669 (2006).

4. ¹H and ¹³C NMR Spectra

