Supporting Information

Highly Selective Rhodium-Catalyzed Conjugate Addition Reactions of 4-Oxobutenamides

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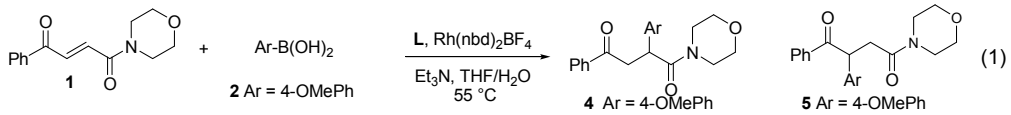
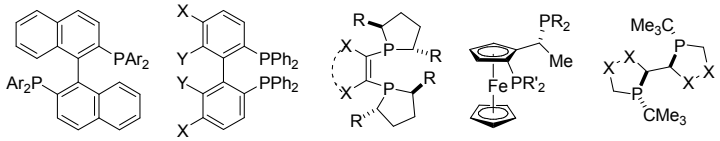


(1)

Table 1. Effect of ligand structure on conversion, product distribution and enantioselectivity in the reaction of 1 with **2** (eq 1)[a]

entry	L =	conv.[b]	regioselectivity[c]	%ee [d]	entry	L =	conv.	regioselc.	% ee
1	L1a: Ar = Ph	100	89:11	88	12	L3a: X= 1,2-benzene; R = Et	94	99 : 1	50
2	L1b: Ar = 4-MePh	100	89:11	85	13	L3b: X= 2,3-benzo[b]thiophene; R = Me	100	96 : 4	2
3	L1c: Ar = 3,5-Me_2Ph	100	89:11	84	14	L3c: X= 2,3-benzo[b]thiophene; R = Et	99	99 : 1	79
4	L2a: X = Cl; Y = OMe	100	88:12	92	15	L3d: X = 2,3-benzo[b]thiophene; R = *i*Pr	99	98 : 2	30
5	L2b: X = H; Y = -OCH_2O-	100	90:10	82	16	L3e: X = O=COC=O; R = Me	100	96 : 4	17
6	L2c: X = H; Y = -$O(CH_2)_2O$-	100	90:10	79	17	L3f: X = O=C(NMe)C=O; R = Me	100	98 : 2	55
7	L2d: X = H; Y = -$O(CH_2)_3O$-	100	89:11	85	18	L3g: X = O=C(N3,5-Me_2Ph)C=O; R = Me	100	99 : 1	60
8	L2e: X = H; Y = -$O(CH_2)_4O$-	100	89:11	85	19	L3h: X = O=C(N3,5-$(CF_3)_2$Ph)C=O; R = Me	88	99 : 1	61
9	L2f: X = H; Y = -$O(CH_2)_5O$-	100	89:11	83	21	L4a: X = $(CH_2)_2$; Tangphos	100	99.7 : 0.3	95
10	L2g: X = H; Y = -$O(CH_2)_3O$-	100	89:11	85	22	L4b: X = 1,2-benzene; Duanphos	100	99.6 : 0.4	98
11	L2h; X = Y = -$O(CH_2)_2O$-	100	90:10	87	23	L5a: R = *c*-Hex; R' = Ph	80	97 : 3	65
					24	L5b: R = *c*-Hex; R' = *c*-Hex	12	99 : 1	56
					25	L5c: R = *c*-Hex; R' = 3,5-$(CF_3)_2$Ph	90	99 : 1	57
					26	L5d: R = CMe_3, R' = 2-MePh	7	90 : 10	44
					27	L5e: R = Ph, R' = CMe_3	21	94 : 6	36

[a] The reactions were conducted at 55 - 60°C for 24h using 1.5 equiv of **2**, 1.5 equiv of Et_3N, 2 mol% $Rh(nbd)_2BF_4$ and 2.2 mol% ligand **L** in 10:1 THF:H_2O. [b] As measured by HPLC: PA% Σ Regioisomers/Σ(PA% SM,regioisomers). [c] HPLC PA% **4** : **5**. [d]Determined by chiral HPLC analysis (see supporting information)



L1 **L2** **L3** **L4** **L5**

II. General Methods:

Flash chromatography was performed on silica gel 60 (230-400 mesh) in glass columns or pre-packed cartridges (Biotage) using HPLC grade solvents. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, potassium permanganate stain or phosphomolybdic acid. Commercial reagents and solvents were used as received and were not purified unless otherwise stated. All air and moisture sensitive reactions were performed under a nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ using a Bruker DX 400 mHz spectrometer unless

otherwise stated. Chemical shifts are reported in ppm relative to internal tetramethylsilane (δ 0.00 ppm) for ^{1}H and CDCl3 for ^{13}C. All Electrospray FTMS (ESI) data were acquired on a Bruker Q-FTMS operating at 7 tesla. IR spectra are recorded using an ATR sampling unit. Optical rotations were measured using a polarimeter using the sodium D line (589 nm) using spectrophotometric grade solvents at the concentrations (g/100 mL) indicated. Melting points recorded were determined on a Stanford Research Systems Opti-Melt melting point apparatus and are uncorrected. Analytical HPLC was performed on an Agilent 1100 instrument using a diode array detector.

X-ray crystal structure data were collected using a Bruker SMART CCD (charge coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 193 K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3 ° per frame for 10 seconds, such that a hemisphere was collected. A total of 1271 frames were collected with a maximum resolution of 0.76 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART[1] software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software[2] which corrects for Lp and decay. Absorption corrections were applied using SADABS[3] multiscan technique, supplied by George Sheldrick. The structures are solved by the direct method using the SHELXS-97[4]

[1] SMART V 5.625 (NT) *Software for the CCD Detector System*; Bruker Analytical X-ray Systems, Madison, WI (2001).
[2] SAINT V 6.22 (NT) *Software for the CCD Detector System* Bruker Analytical X-ray Systems, Madison, WI (2001).
[3] SADABS. Program for absorption corrections using Siemens CCD based on the method of Robert Blessing; Blessing, R.H. *Acta Cryst. A51* **1995**, 33-38.
[4] Sheldrick, G. M. SHELXS-90, *Program for the Solution of Crystal Structure*, University of Göttingen, Germany, 1990.

program and refined by least squares method on F^2, SHELXL-97, [5] incorporated in SHELXTL-PC V 6.10.[6]

III. Chromatographic Methods:

Method #	Type	Column	Solvent A	Solvent B	Method Info
A	HPLC	Zorbax Ecplipse XDB-C18	0.1% HClO4 in water	Acetonitrile	90:10 A:B to 10:90 A:B over 5 min, hold 1 min, 35 °C, 3 mL/min flow
B	SFC	Chiralcel® OD-H, 5 μm, 4.6x250 mm	CO_2	Methanol	85:15 A:B isocratic, 10 min, 4 mL/min 30 °C 100 psi outlet pressure
C	SFC	Chiralcel® OD-H, 5 μm, 4.6x250 mm	CO_2	0.1% iPrNH2 in 2-propanol	85:15 A:B isocratic, 10 min, 4 mL/min 30 °C 100 psi outlet pressure
D	SFC	Chiralcel® OD-H, 5 μm, 4.6x250 mm	CO_2	0.1% iPrNH2 in 2-propanol	95:5 A:B isocratic, 10 min, 4 mL/min 30 °C 100 psi outlet pressure
E	HPLC	Chiralpak® AD-H, 5	Hexanes	2-propanol	85:15 A:B isocratic,

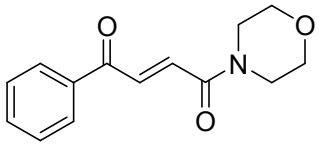
[5] Sheldrick, G. M. SHELXL-97, *Program for the Refinement of Crystal Structure,* University of Göttingen, Germany, 1997.
[6] SHELXTL 6.1 (PC-Version), *Program library for Structure Solution and Molecular Graphics*; Bruker Analytical X-ray Systems, Madison, WI (2000).

		µm, 4.6x250 mm			10 min, 1.6 mL/min 25 °C
F	HPLC	Chiralcel® OJ-H, 5 µm, 4.6x250 mm	Hexanes	Ethanol	90:10 A:B isocratic, 20 min 1.6 mL/min 25 °C,
G	HPLC	Chiralcel® OJ-H, 5 µm, 4.6x250 mm	Hexanes	Ethanol	97:3 A:B isocratic, 25 min 2 mL/min 25 °C,
H	SFC	Chiralpak® AD-H, 5 µm, 4.6x250 mm	CO_2	Methanol	94:6 A:B Isocratic, 6 min 4 mL/min 35 °C 100 psi outlet pressure
I	HPLC	Chiralpak® AD-H, 5 µm, 4.6x250 mm	Hexanes	2-propanol	85:15 A:B Isocratic, 20 min 1 mL/min 25 °C
J	SFC	Chiralpak® AD-H, 5 µm, 4.6x250 mm	CO_2	Methanol	90:10 A:B Isocratic, 6 min 4 mL/min 35 °C 100 psi outlet pressure
K	SFC	Chiralpak® AD-H, 5 µm, 4.6x250 mm	CO_2	0.1% $iPrNH_2$ in 2-propanol	75:25 A:B Isocratic, 6 min 4 mL/min 35 °C 100 psi outlet pressure
L	HPLC	Chiralcel®	Hexanes	Ethanol	88:12 A:B

		AS-H, 5 μm, 4.6x250 mm			isocratic, 40 min 1.6 mL/min 25 °C,
M	SFC	Chiralcel® OD-H, 5 μm, 4.6x250 mm	CO_2	Methanol (0.1% *i*-$PrNH_2$)	95:5 A:B to 65:35 A:B gradient over 6 min 4 mL/min flow 100 psi outlet pressure 35 °C
N	SFC	Chiralpak® AD-H, 5 μm, 4.6x250 mm	CO_2	Methanol (0.1% *i*-$PrNH_2$)	95:5 A:B to 50:50 A:B gradient over 6 min 4 mL/min flow 100 psi outlet pressure 35 °C
O	SFC	Chiralcel® AD-H, 5 μm, 4.6x250 mm	CO_2	Methanol (0.1% *i*-$PrNH_2$)	95:5 A:B to 65:35 A:B gradient over 6 min 4 mL/min 100 psi outlet pressure 35 °C
P	SFC	Chiralcel® AD-H, 5 μm, 4.6x250 mm	CO_2	Methanol (0.1% *i*-$PrNH_2$)	95:5 A:B Isocratic 6 min run 4 mL/min 100 psi outlet pressure 35 °C

IV. General Procedures:

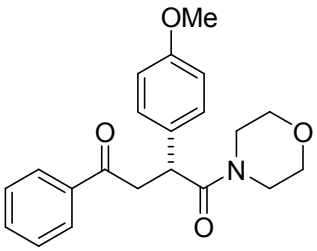
General procedure for generation of 4-oxobutenamides:



(*E*)-1-phenyl-4-morpholinobut-2-ene-1,4-dione (1a): A 500 mL 3-necked round-bottomed flask was charged with (E)-4-oxo-4-phenylbut-2-enoic acid (10g; 56.8 mmol) and 100 mL of anhydrous tetrahydrofuran. The solution was cooled to an internal temperature of -25 to -30 °C whereupon *N*-methylmorpholine (6.9 mL, 62.4 mmol, 1.1 equiv) was added. Isobutyl chloroformate (7.7 mL; 59.6 mmol; 1.05 equiv) was added drop-wise maintaining the reaction temperature below -20 °C to form a thick precipitate. The reactor contents were warmed to 0 °C and stirred 1 hour whereupon the reaction was chilled to -20 °C. Morpholine (5.9 mL; 68.1 mmol; 1.2 equiv) was added and the reaction was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 50 mL of 1N hydrochloric acid and partitioned into 50 mL of ethyl acetate. The aqueous layer was extracted with 50 mL of methyl-*tert*-butyl ether and the combined organic extracts were washed with 50 mL of 10% aqueous sodium carbonate and then dried over anhydrous magnesium sulfate. The organics were filtered and concentrated to a solid. The solid was then suspended in 100 mL of 2:1 methyl-*tert*-butyl ether and hexane. The suspension was stirred 16 hours at ambient temperature, filtered and then dried to afford 11.1g (*E*)-1-phenyl-4-morpholinobut-2-ene-1,4-dione **1a** of a pale yellow solid (80% yield). mp (124-126 °C). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.05 (d, *J*=8.53 Hz, 2 H); 7.98 (d, *J*=15.06 Hz, 1 H), 7.45 (d, *J*=14.56 Hz, 1 H), 6.99 (d, *J*=9.03 Hz, 2 H), 3.90 (s, 3 H), 3.69 - 3.83 (m, 6 H), 3.59 - 3.69 (m, 2 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 187.6, 164.2, 134.7, 131.3, 131.0, 129.9, 114.1, 66.8, 55.6, 46.4,

42.6; HRMS calcd for $C_{15}H_{17}NO_4$ [M+Na] 298.1055 found 298.1067; IR (neat) 2968, 2866, 1667, 1628, 1603, 1448, 1263, 1167, 1032, 831, 761 cm^{-1}.

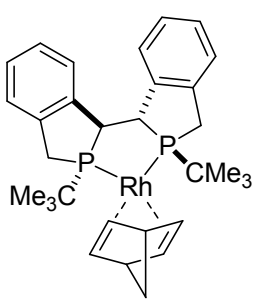
General Method for Rhodium-catalyzed conjugate addition reaction to 4-oxo-butenamides.



Preparation of *(R)*-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutane-1,4-dione 2a: A 20 mL scintillation vial was charged with (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (0.5 g, 2.0 mmol), 4-methoxyphenylboronic acid (456 mg, 3.0 mmol), Rh catalyst **5** (27 mg, 0.04 mmol), triethylamine (0.42 mL, 3.0 mmol), and tetrahydrofuran:water (19:1, 5 mL). The reaction mixture was warmed to 65 °C and stirred for 16h. Upon completion the reaction was poured into 20 mL of ethyl acetate and washed with 10 mL of saturated sodium bicarbonate. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was analyzed by HLPC (Method A: T_{ret} **2a** = 4.3 min; T_{ret} **3a** = 4.1 min; >99:1; Method B: T_{ret} *R*-**2a** = 1.08 min; T_{ret} *S*-**2a** = 1.47 min = 98% ee) and then purified by flash column chromatography (30 % to 100 % ethyl acetate in hexanes) to afford the product as a colorless solid (701 mg, 96 %). A duplicate reaction afforded **2a** in 97% isolated yield (96% yield average). Analytical data for **2a**: mp (133-135 °C). $[\alpha]^{25}_{D}$ = - 157.4 ° (c = 1.2 in dichloromethane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.99 (d, *J*=7.53 Hz, 2 H), 7.44 (t, *J*=7.53 Hz, 2 H), 7.55 (t, *J*=7.28 Hz, 2 H), 7.16 - 7.31 (m, 2 H), 6.89 (d, *J*=8.53 Hz, 2 H), 4.49 (dd, *J*=9.79, 3.76 Hz, 1 H), 4.10 (dd, *J*=17.82, 9.79 Hz, 1 H), 3.81 (s, 3 H), 3.76 - 3.33 (m, 7 H), 3.30 - 3.12 (m, 1 H), 3.06 (dd, *J*=17.57, 3.51 Hz, 1

H), ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 198.7, 171.1, 158.8, 136.6, 133.1, 131.2, 128.7, 128.5, 128.2, 114.5, 66.8, 66.4, 55.3, 46.2, 44.3, 43.2, 42.6; HRMS calcd' for $C_{21}H_{24}NO_4$ [M]+: 354.1699 found 354.1748; IR (neat) 2972, 2856, 1698, 1628, 1606, 1502, 1441, 1231, 1024, 829 cm^{-1}.

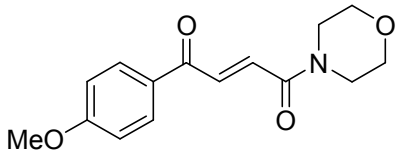
Procedure for scale-up of *(R)*-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutane-1,4-dione (2a). A 250 mL round-bottomed flask was charged with (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (3.0 g, 12.2 mmol), 4-methoxyphenylboronic acid (3.0g , 19.6 mmol, 1.6 equiv), Rh catalyst **5** (162 mg, 0.24 mmol, 0.02 equiv), triethylamine (2.7mL, 19.6 mmol, 1.6 equiv), and tetrahydrofuran:water (19:1, 30 mL). The reaction mixture was vacuum degassed (3X vacuum/argon cycles) and reaction mixture was warmed to 65 °C and stirred for 16h. HPLC analysis of this solution indicated reaction was complete and afforded >99:1 regioselectivity HLPC (Method A: T_{ret} **2a** = 4.3 min; T_{ret} **3a** = 4.1 min; >99:1; Method B: T_{ret} *R*-**2a** = 1.08 min; T_{ret} *S*-**2a** = 1.47 min = 98% ee). . Upon completion the reaction was poured into 100 mL of ethyl acetate and washed with 50 mL of saturated sodium bicarbonate. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to a yellow solid (4.1g). The crude material was purified by recrystallization from 20 mL of 5:1 2-propanol/heptane to afford 3.6g of colorless solid (84%). The isolated material was analyzed by HLPC (Method A: T_{ret} **2a** = 4.3 min; T_{ret} **3a** = 4.1 min; >99:1 **2a:3a**) (Method B: T_{ret} *R*-**2a** = 1.08 min; T_{ret} *S*-**2a** = 1.47 min = 99% ee)**.** Loss to mother liquors was calculated to be 346 mg (9% of theoretical mass based upon HPLC using an external standard.



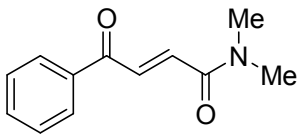
[(Bicyclo[2.2.1]hepta-2,5-diene) rhodium (I) ((1S,1'S,2R,2'R)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole)] tetrafluoroborate (5): In an inert-atmosphere glove box, a 100 mL Schlenk flask was charged with [bis-(bicyclo[2.2.1]hepta-2,5-dienyl)rhodium (I)] tetrafluoroborate (3.56g, 9.52 mmol, 1.0 equiv) and 40 mL of dichloromethane. To this solution was added (1S,1'S,2R,2'R)-2,2'-bis(1,1-dimethylethyl)-2,2',3,3'-tetrahydro-1,1'-bi-1H-isophosphindole (3.92g , 10 mmol, 1.05 equiv) in 15 mL of dichloromethane portion-wise. The orange solution was stirred at ambient temperature and the flask was sealed and removed from the glove-box. The dichloromethane was removed *in vacuo* and dissolved in 20 mL of fresh dichloromethane. This solution was then layered with 40 mL of methyl-*tert*-butyl ether and left to crystallize for 12 hours. The supernatant was decanted and the crystals were rinsed with 2X 5 mL of methyl-*tert*-butyl ether. A suitable crystal was selected for single crystal x-ray diffraction analysis. The remaining crystals were dried in vacuo. Compound **5** (5.9g) was isolated as deep red prisms. An appropriate crystal was selected for single crystal x-ray diffraction analysis (See section VII in supporting information). Analytical data for **5**: mp >230 °C (decomposes); $[\alpha]^{25}_{D}$ = 18.5 ° (c = 0.10 in dichloromethane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.47 (d, *J*=7.53 Hz, 2 H), 7.29 - 7.42 (m, 6 H), 5.81 (d, *J*=25.60 Hz, 4 H), 4.24 - 4.32 (m, 3 H), 4.19 (s, 1 H), 3.85 (d, *J*=17.57 Hz, 2 H), 3.41 (dd, *J*=17.82, 10.79 Hz, 2 H), 1.89 (s, 2 H), 0.81 (d, *J*=14.56 Hz, 18 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 139.1, 137.9, 128.6, 128.4, 128.2, 128.1, 126.5, 92.3, 85.2, 85.2, 72.4, 55.7, 52.1, 51.9, 51.7, 32.4, 29.6, 29.4,

26.6; ^{31}P NMR (100 MHz, CHLOROFORM-*d*) δ ppm 103.3 (d, J_{Rh-P} =152.5 Hz); IR (neat) 2956, 1737, 1579, 1462, 1403, 1368, 1311, 1183, 1033, 829, 789, 769, 754, 677 cm^{-1}.

IV. Compound Syntheses and Data:

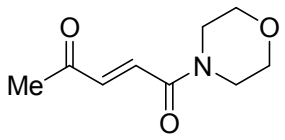


(*E*)-1-(4-methoxyphenyl)-4-morpholinobut-2-ene-1,4-dione (1b): According to the general procedure for preparation of 4-oxobutenamides: (*E*)-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid (10g, 48.5 mmol) was treated with isobutyl chloroformate (6.6 mL, 50.9 mmol, 1.05 equiv), *N*-methylmorpholine (7.3 mL, 53.4 mmol, 1.1 equiv) and morpholine (5.1 mL, 58.2 mmol, 1.2 equiv) in tetrahydrofuran (100 mL) . The crude reaction mixture was concentrated in vacuo to a solid which was suspended in 100 mL of 2:1 ethyl acetate:hexanes. Isolated 7.0g of pale yellow solid (52% yield), mp (124-126 °C). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.05 (d, *J*=8.53 Hz, 2 H); 7.98 (d, *J*=15.06 Hz, 1 H), 7.45 (d, *J*=14.56 Hz, 1 H), 6.99 (d, *J*=9.03 Hz, 2 H), 3.90 (s, 3 H), 3.69 - 3.83 (m, 6 H), 3.59 - 3.69 (m, 2 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 187.6, 164.2, 134.7, 131.3, 131.0, 129.9, 114.1, 66.8, 55.6, 46.4, 42.6; HRMS calcd for $C_{15}H_{17}NO_4$ [M+Na] 298.1055 found 298.1067; IR (neat) 2968, 2866, 1667, 1628, 1603, 1448, 1263, 1167, 1032, 831, 761 cm^{-1}.

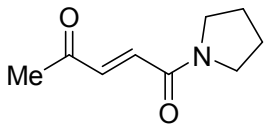


(*E*)-*N*,*N*-dimethyl-4-oxo-4-phenylbut-2-enamide (1f): According to the general procedure for preparation of 4-oxobutenamides: (E)-4-oxo-4-phenylbut-2-enoic acid (10g; 56.8 mmol) was treated with isobutyl chloroformate (8.1 mL, 62.44 mmol), *N*-

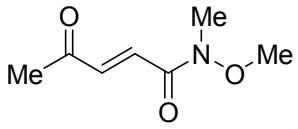
methylmorpholine (6.5 mL, 62.44 mmol) and dimethylamine, as a 2.0M solution in THF, (57 mL, 113.5 mmol) in tetrahydrofuran (100 mL) . The crude material which was purified by recrystallization (4:1 hexanes:methyl-*tert*-butyl ether; 60 mL) to afford the product as a pale-yellow solid (8.2 g, 70 %), mp: 66-70 °C: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.03 (d, *J*=7.53 Hz, 2 H), 7.94 (d, *J*=15.06 Hz, 1 H), 7.61 (t, *J*=7.28 Hz, 1 H), 7.45 - 7.55 (m, 3 H), 3.17 (s, 3 H), 3.08 (s, 3 H); ^{13}C NMR (100 MHz, CHLOROFORM-*d*) δ 185.6, 165.1, 136.9, 133.8, 133.6, 132.5, 128.8, 37.5, 35.9; HRMS (ESI) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$, 204.1025. Found 204.1072. IR (neat) 1667, 1629, 1611, 1593, 1394, 1288, 1114, 979, 902 cm^{-1}



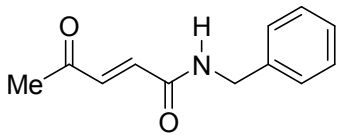
(*E*)-1-morpholinopent-2-ene-1,4-dione (1c): According to the general procedure for preparation of 4-oxobutenamides: (*E*)-4-oxopent-2-enoic acid (1.0 g, 8.76 mmol) was treated with isobutyl chloroformate (1.2 mL, 9.20 mmol), *N*-methylmorpholine (1.06 mL, 9.64 mmol) and morpholine (0.92 mL, 10.5 mmol) in tetrahydrofuran (15 mL) . The crude material which was purified by flash column chromatography (5 % to 85 % acetone in hexanes) to afford the product as a white solid (0.90 g, 56 %), mp: 48-52 °C: ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.2 (d, *J*=15.4 Hz, 1 H), 7.0 (d, *J*=15.4 Hz, 1 H), 3.7 (m, 6 H), 3.6 (m, 2 H), 2.3 (s, 3 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ 197.3, 163.9, 137.6, 130.4, 66.7, 46.4, 42.5, 29.4; HRMS (ESI) calc'd for $C_9H_{13}NO_3$ $[M+H]^+$, 184.0968. Found 184.0976. IR (neat) 1664, 1642, 1605, 1439, 1268, 1252, 1111, 971, 859 cm^{-1}



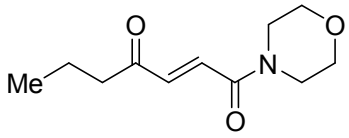
(*E*)-1-(pyrrolidin-1-yl)pent-2-ene-1,4-dione (1d): According to the general procedure for preparation of 4-oxobutenamides: (*E*)-4-oxopent-2-enoic acid (1.5 g, 13.2 mmol) was treated with isobutyl chloroformate (1.8 mL, 13.8 mmol), *N*-methylmorpholine (1.6 mL, 14.5 mmol) and pyrrolidine (1.3 mL, 15.8 mmol) in tetrahydrofuran (23 mL) . The crude material was purified by flash column chromatography (5 % to 85 % acetone in hexanes) to afford the product as a white solid (1.02 g, 46 %), mp: 76-82 °C; ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.1 (d, *J*=15.4 Hz, 1 H), 7.0 (d, *J*=15.4 Hz,1 H), 3.6 (dd, *J*=16.0, 6.7 Hz, 4 H), 2.4 (s, 3 H), 2.0 (m, 4 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ 197.8, 162.9, 136.8, 131.9, 46.8, 46.3, 29.5, 26.1, 24.2; HRMS calcd' for $C_9H_{13}NO_2$ $[M+H]^+$, 168.1019, Found 168.1041, IR (neat) 1663, 1646, 1604, 1428, 1368, 1252, 976 cm^{-1}



(*E*)-N-methoxy-N-methyl-4-oxopent-2-enamide (1e): According to the general procedure for preparation of 4-oxobutenamides, (*E*)-4-oxopent-2-enoic acid (1.5 g, 13.2 mmol) was reacted with isobutyl chloroformate (1.8 mL, 13.8 mmol), *N*-methylmorpholine (1.6 mL, 14.5 mmol), *N,O*-dimethylhydroxylamine (1.2mL, 15.8 mmol) in tetrahydrofuran (23 mL) . The crude material was purified by flash column chromatography (5% to 85% acetone in hexanes) to afford the product as a pale yellow oil (2.07 g, 82 %); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.3 (d, *J*=15.7 Hz, 1 H), 7.1 (d, *J*=15.7 Hz, 1 H), 3.7 (s, 3 H), 3.3 (s, 3 H), 2.4 (s, 3 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ 197.7, 165.0, 138.5, 129.2, 62.2, 32.4, 29.1; HRMS calcd for $C_7H_{11}NO_3$ $[M+H]^+$, 158.0818. Found 158.0819. IR (neat) 1650, 1627, 1417, 1383, 1247, 996, 977 cm^{-1}.



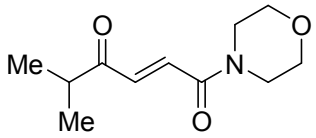
(*E*)-N-benzyl-4-oxopent-2-enamide (1f): According to the general procedure for preparation of 4-oxobutenamides, (*E*)-4-oxopent-2-enoic acid (1.0 g, 8.76 mmol) was reacted with isobutyl chloroformate (1.2 mL, 9.20 mmol), *N*-methylmorpholine (1.06 mL, 9.64 mmol), benzylamine (1.15 mL, 10.5 mmol), in tetrahydrofuran (15 mL). The crude material was purified by flash column chromatography (5 % to 85 % acetone in hexanes) to afford the product as a white solid (0.49 g, 27 %) mp: 107-115 °C; ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.3 (m, 5 H), 7.1 (d, *J*=15.5 Hz, 1 H), 6.7 (d, *J*=15.5 Hz, 1 H), 6.4 (s, 1 H), 4.5 (d, *J*=5.7 Hz, 2 H), 2.3 (s, 3 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ 197.7, 163.9, 137.3, 136.7, 133.7, 128.8, 127.9, 127.8, 44.1, 29.1; HRMS calcd for $C_{12}H_{13}NO_2$ $[M+H]^+$, 204.1019. Found 204.1026.IR (neat) 1693, 1641, 1628, 1548, 1361, 1321, 1289, 1163, 996, 675 cm^{-1};



(*E*)-1-morpholinohept-2-ene-1,4-dione (1g)[7]: To a solution of diethylzinc (1 M in hexanes, 25 mL, 25.0 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added methylene iodide (2.14 mL, 26 mmol).The resulting white suspension was stirred at 0 °C for 10 min. In a single portion, 1-morpholinohexane-1,3-dione (1.0 g, 5.0 mmol) was added, and the reaction was stirred at 0 °C for 30 min. Iodine (6.35 g, 25.0 mmol) was added and after stirring at 0 °C for 10 min, the reaction remained colorless. Additional iodine (2.0 g, 7.88 mmol) in dichloromethane (40 mL) was added and stirred for 35 min to achieve a pink color that

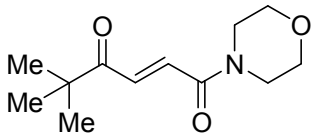
[7] Prepared in analogy to Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68*, 4535-4538.

persisted. A solution of saturated sodium thiosulfate (50 mL) was added and the suspension was stirred for 10 min until the pink color disappeared. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (7.48 mL, 50.0 mmol) was added and the mixture was stirred vigorously for 2 h. A solution of saturated ammonium chloride (100 mL) was added and the mixture was extracted with diethyl ether (3 X 100 mL). The combined extracts were dried (anhydrous magnesium sulfate) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (12 % - 100 % ethyl acetate in hexanes) to afford the product as a pale yellow solid (480 mg, 45 %) mp: 43-48 °C; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.2 (d, *J*=15.3 Hz, 1 H), 7.1 (d, *J*=15.4 Hz, 1 H), 3.7 (m, 6 H), 3.6 (m, 2 H), 2.6 (t, *J*=7.2 Hz, 2 H), 1.7 (td, *J*=14.6, 7.3 Hz, 2 H), 0.9 (t, *J*=7.4 Hz, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 199.6, 164.0, 137.2, 129.6, 66.7, 46.4, 44.6, 42.5, 17.1, 13.6; HRMS calc'd for $C_{11}H_{17}NO_3$ $[M+H]^+$, 212.1281. Found 212.1280 IR (neat) 1699, 1640, 1618, 1435, 1259, 1109, 967 cm^{-1}



(*E*)-5-methyl-1-morpholinohex-2-ene-1,4-dione (1h)[1]: To a solution of diethylzinc (1 M in hexanes, 75 mL, 75.0 mmol) in CH_2Cl_2 (225 mL) at 0 °C was added methylene iodide (6.42 mL, 78 mmol). The resulting white suspension was stirred at 0 °C for 20 min. In a single portion, 4-methyl-1-morpholinopentane-1,3-dione (3.0 g, 15.0 mmol) was added, and the reaction was stirred at 0 °C for 30 min. A solution of iodine (6.35 g, 25.0 mmol) in dichloromethane (50 mL) and tetrahydrofuran (20 mL) was added over 5 min and the reaction remained colorless. Additional iodine (2.0 g, 7.88 mmol) was added in one portion and the mixture was stirred for 2 h to achieve a pink color that persisted. A solution of saturated sodium

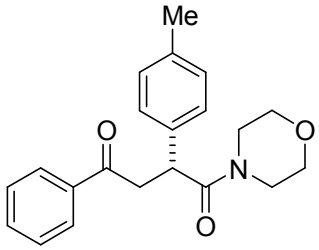
thiosulfate (300 mL) was added and the suspension was stirred until the pink color disappeared. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (22.4 mL, 150.0 mmol) was added and the mixture was stirred vigorously for 2 h. A solution of saturated ammonium chloride (300 mL) was added and the mixture was extracted with diethyl ether (3 X 300 mL). The combined extracts were dried (anhydrous magnesium sulfate) and concentrated in vacuo. The crude material was purified by flash column chromatography (12 % - 100 % ethyl acetate in hexanes) to afford the product as a yellow solid (1.48g, 47 %) mp: 32-35 °C; ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.3 (d, *J*=15.1 Hz, 1 H), 7.2 (d, *J*=15.1 Hz, 1 H), 3.7 (m, 6 H), 3.6 (m, 2 H), 2.8 (m, 1 H), 1.1 (d, *J*=6.9 Hz, 6 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 202.9, 163.9, 136.1, 129.9, 66.7, 46.4, 42.5, 40.8, 17.7; HRMS calc'd for $C_{11}H_{17}NO_3$ $[M+H]^+$, 212.1281. Found 212.1289. IR (neat) 1695, 1635, 1603, 1440, 1266, 1256, 1116, 1053, 968 cm^{-1}.



(*E*)-5,5-dimethyl-1-morpholinohex-2-ene-1,4-dione (1i):

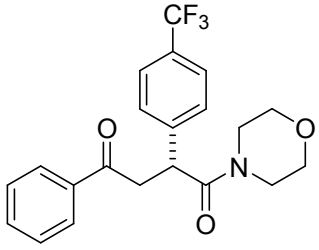
(*E*)-methyl 5,5-dimethyl-4-oxohex-2-enoate[1] (1.61 g, 9.46 mmol) was dissolved in a solvent mixture of tetrahydrofuran/water (1:1, 300 mL). The solution was cooled to 5 °C and solid lithium hydroxide was added (340 mg, 14.2 mmol). After stirring at 5 °C for 5 h, the reaction was quenched at 5 °C with 1 N hydrochloric acid (100 mL) and extracted with diethyl ether (3 X 200 mL). The combined extracts were dried (anhydrous magnesium sulfate) and concentrated in vacuo to afford (*E*)-5,5-dimethyl-4-oxohex-2-enoic acid as a yellow solid. The crude material was used directly in the next step.

According to the general procedure for preparation of 4-oxobutenamides: (*E*)-5,5-dimethyl-4-oxohex-2-enoic acid (1.43 g, 9.16 mmol) was reacted with isobutyl chloroformate (1.26 mL, 9.61 mmol), *N*-methylmorpholine (1.1 mL, 10.1 mmol), morpholine (0.96 mL, 11.0 mmol) in tetrahydrofuran (16 mL) . The crude material was purified by flash column chromatography (60 % to 100 % ethyl acetate in hexanes) to afford the product as a yellow solid (1.66 g, 80 %) mp: 59-62 °C; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.5 (d, *J*=14.9 Hz, 1 H), 7.3 (d, *J*=14.9 Hz, 1 H), 3.7 (m, 6 H), 3.6 (m, 2 H), 1.2 (s, 9 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 204.1, 164.0, 133.9, 130.4, 66.7, 46.3, 43.6, 42.5, 25.8; HRMS calc'd for $C_{12}H_{19}NO_3$ $[M+H]^+$, 226.1437. Found 226.1445. IR (neat) 1686, 1635, 1610, 1435, 1250, 1110, 1074, 971, 904 cm^{-1}.



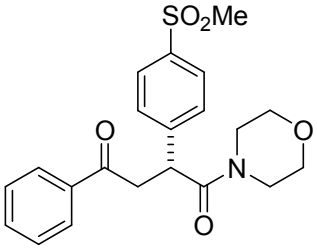
1-morpholino-4-phenyl-2-*p*-tolylbutane-1,4-dione (2b): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with *p*-tolylboronic acid (416 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2b** = 3.94 min; T_{ret} **3b** = 4.07 min; >99:1; Method O: T_{ret} *R*-**2b** = 5.6 min; T_{ret} *S*-**2b** = 6.7 min = 98% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as an off-white solid (685 mg, 99%). A duplicate experiment afforded 99% yield of **2b** with an average yield of 99%: Analytical data for **2b**: mp (89-90 °C); $[\alpha]^{25}_{D}$ = -162.9 ° (c = 2.1 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.94 -

8.02 (m, 2 H), 7.50 - 7.57 (m, 1 H), 7.43 (t, *J*=7.63 Hz, 2 H), 7.18 - 7.24 (m, 2 H), 7.13 - 7.18 (m, 2 H), 2.34 (s, 3 H) 4.50 (dd, *J*=9.98, 3.72 Hz, 1 H), 4.07 - 4.17 (m, 1 H), 3.48 - 3.76 (m, 6 H), 3.36 - 3.45 (m, 1 H), 3.14 - 3.23 (m, 1 H), 3.04 (dd, *J*=17.80, 3.52 Hz, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.6, 171.0, 137.0, 133.1, 129.8, 128.5, 128.2, 127.5, 66.8, 66.4, 60.4, 46.2, 44.3, 43.6, 42.6, 21.1, 14.2; HRMS calcd for $C_{21}H_{23}NO_3$ $[M+H]^+$ 338.1751 found 338.1798; IR (neat) 2860, 1691, 1627, 1509, 1439, 1390, 1355, 1317, 1266, 1232, 1174, 1112, 1068, 1028, 989, 839, 802, 768, 745, 717, 695, 655, 567, 503, 460, 424, 401 cm^{-1}.



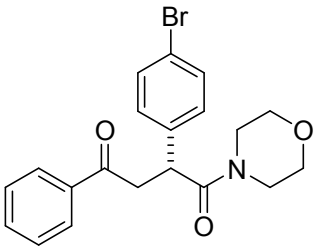
1-Morpholino-4-phenyl-2-(4-(trifluoromethyl)phenyl)butane-1,4-dione (2c): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 4-(trifluoromethyl)phenylboronic acid (581 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2c** = 4.38 min; T_{ret} **3c** = 4.27 min; >99:1; Method M: T_{ret} *R*-**2c** = 2.94 min; T_{ret} *S*-**2c** = 3.57 min = >99% ee) and then purified by flash column chromatography (40% ethyl acetate in hexanes) to afford the product as a colorless solid (785 mg, 98 % yield). A duplicate experiment afforded 96% isolated yield of **2c** for an average yield of 97%. Analytical data for **2c**: mp (108-109 °C); $[\alpha]^{25}_D$ = -135.4 ° (c = 2.2 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.97 (d, *J*=8.03 Hz, 2 H), 7.62 (d, *J*=8.53 Hz, 2 H), 7.56 (t, *J*=7.53 Hz, 1 H), 7.41 - 7.51 (m, 4 H), 4.62 (dd,

J=9.79, 3.76 Hz, 1 H), 4.08 - 4.20 (m, 1 H), 3.59 - 3.76 (m, 5 H), 3.51 - 3.59 (m, 1 H), 3.33 - 3.43 (m, 1 H), 3.21 - 3.32 (m, 1 H), 3.10 (dd, *J*=17.82, 3.76 Hz, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 197.9, 170.1, 143.3, 136.3, 133.4, 128.6, 128.1, 126.2, 66.8, 66.4, 46.2, 44.0, 43.6, 42.7, 14.2; HRMS calcd for $C_{21}H_{20}F_3NO_3$ $[M+H]^+$ 392.1468 found 392.1474; IR (neat) 1683, 1639, 1435, 1321, 1234, 1163, 1109, 1067, 1018, 845, 748, 690, 614 cm^{-1}.



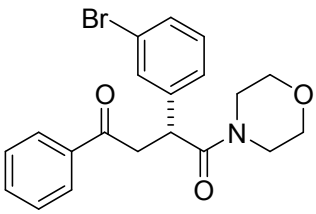
2-(4-(methylsulfonyl)phenyl)-1-morpholino-4-phenylbutane-1,4-dione (2d): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 4-(methylsulfonyl)phenylboronic acid (618 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethyalmine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water(19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2d** = 2.97 min; T_{ret} **3d** = 2.85 min; >99:1; Method M: T_{ret} *R*-**2d** = 6.51 min; T_{ret} *S*-**2d** = 8.61 min = 99 % ee) and then purified by flash column chromatography (70 % ethyl acetate in hexanes) to afford the product as an off-white solid (804 mg, 98 % yield). A duplicate experiment afforded **2d** in 99% isolated yield with an average yield of 98%. Analytical data for **2d**: mp (75-76 °C); $[\alpha]^{25}_D$ = -117.3 ° (c = 2.1 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.96 (dd, *J*=13.05, 8.03 Hz, 4 H), 7.57 (t, *J*=7.78 Hz, 3 H), 7.45 (t, *J*=7.53 Hz, 2 H), 4.67 (dd, *J*=9.03, 4.02 Hz, 1 H), 4.08 - 4.20 (m, 1 H), 3.53 - 3.78 (m, 6 H), 3.27 - 3.44 (m, 2 H), 3.14 (dd, *J*=17.57, 4.02 Hz, 1 H), 3.07 (s, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 197.6, 169.9,

145.6, 139.7, 136.2, 133.5, 128.8, 128.3, 128.1, 46.3, 44.5, 66.7, 43.9, 43.5, 42.8; HRMS calcd for $C_{21}H_{23}NO_5S$ $[M+H]^+$ 402.1369 found 402.1363; IR (neat) 1680, 1638, 1596, 1439, 1301, 1232, 1145, 1111, 1089, 1028, 956, 843, 767, 690, 630, 569, 523 cm^{-1}.



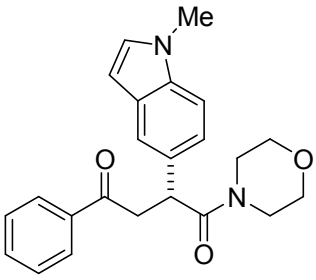
2-(4-bromophenyl)-1-morpholino-4-phenylbutane-1,4-dione (2e): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 4-bromophenylboronic acid (615 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2e** = 4.30 min; T_{ret} **3e** = 4.21 min; 98.6:1.4; Method O: T_{ret} *R*-**2e** = 7.88 min; T_{ret} *S*-**2e** = 8.81 min = 98% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as a pale yellow solid (597 mg, 73 % yield). A duplicate experiment afforded **2e** in 80% isolated yield for an average yield of 76%. A small sample of **2e** was dissolved in hot methanol and slowly cooled to ambient temperature. A suitable crystal was chosen for x-ray diffraction analysis (See section VII in supplemental information). Analytical data for **2e:** mp (137-138 °C); $[\alpha]^{25}_D$ = -110.8 ° (c = 2.2 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.97 (d, *J*=7.53 Hz, 2 H), 7.55 (t, *J*=7.53 Hz, 1 H), 7.40 - 7.51 (m, 4 H), 7.22 (d, *J*=8.53 Hz, 2 H), 4.51 (dd, *J*=9.54, 3.51 Hz, 1 H), 4.04 - 4.16 (m, 1 H), 3.49 - 3.76 (m, 6 H), 3.35 - 3.45 (m, 1 H), 3.21 - 3.31 (m, 1 H), 3.07 (dd, *J*=17.82, 3.76 Hz, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.2, 170.4, 138.3, 136.4, 133.3, 132.3, 129.4, 128.6, 128.2, 121.3, 66.8, 66.4,

60.4, 46.2, 44.0, 43.3, 42.7, 21.1, 14.2; HRMS calcd for $C_{20}H_{20}BrNO_3$ $[M+H]^+$ 402.0699 found 402.0720; IR (neat) 2854, 1682, 1636, 1486, 1433, 1358, 1231, 1203, 1111, 1069, 1027, 1010, 835, 780, 748, 689, 543, 496, 418 cm^{-1}.



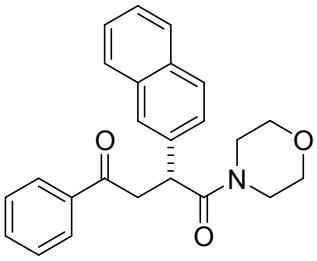
2-(3-bromophenyl)-1-morpholino-4-phenylbutane-1,4-dione(2f): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 3-bromophenylboronic acid (615 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2f** = 4.26 min; T_{ret} **3f** = 4.16 min; 99:1; Method N: T_{ret} *R*-**2f** = 5.36 min; T_{ret} *S*-**2f** = 6.98 min = 93% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as an off-white solid (820 mg, 99%). A duplicate experiment afforded **2f** in 98% isolated yield with and average yield of 98%. A small portion of this material was dissolved in warm methanol and allowed to cool and evaporate. A suitable crystal was selected for single crystal X-ray crystallographic analysis (See supplemental information section VII). Analytical data for **2f:** mp (137-138 °C). $[\alpha]^{25}_D$ = -147.8 ° (c = 2.1 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.95 - 8.00 (m, 2 H), 7.52 - 7.59 (m, 1 H), 7.50 (t, *J*=1.76 Hz, 1 H), 7.40 - 7.48 (m, 3 H), 7.28 (d, *J*=1.57 Hz, 0.4 H), 7.22 (t, *J*=7.63 Hz, 1 H), 4.51 (dd, *J*=9.88, 3.62 Hz, 1 H), 4.07 - 4.17 (m, 2 H), 3.51 - 3.74 (m, 6 H), 3.41 (dd, *J*=5.87, 2.74 Hz, 1 H), 3.24 - 3.32 (m, 1 H), 3.07 (dd, *J*=17.80, 3.72 Hz, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.1, 170.2, 141.6, 136.4, 133.3, 130.7,

128.6, 128.2, 126.4, 123.2, 66.8, 66.4, 60.4, 46.2, 44.1, 43.5, 42.7, 14.2, ; HRMS calcd for $C_{20}H_{20}BrNO_3$ $[M+H]^+$ 402.0699 found 402.0712; IR (neat) 1687, 1628, 1446, 1358, 1263, 1227, 1175, 1108, 1026, 988, 837, 781, 754, 693, 583, 539, 435, 404 cm^{-1}.



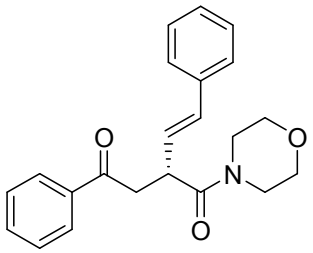
2-(1-methyl-1*H*-indol-5-yl)-1-morpholino-4-phenylbutane-1,4-dione (2g): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 1-(*tert*-butyoxycarbonyl)-1*H*-indol-2-ylboronic acid (535 mg, 3.06 mmol), Rh catalyst (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2g** = 3.93 min; T_{ret} **3g** = 3.85 min; 90:10; Method O: T_{ret} *R*-**2g** = 7.29 min; T_{ret} *S*-**2g** = 9.0 min = 97% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as a pink solid (548 mg, 71 % yield). A duplicate experiment afforded **2g** in 82% isolated yield with an average yield of 76%. Analytical data for **2g**: mp (156-157 °C); $[\alpha]^{25}_D$ = -158.5 ° (c = 2.4 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.99 (d, *J*=7.03 Hz, 2 H), 7.49 - 7.59 (m, 2 H), 7.42 (t, *J*=7.53 Hz, 2 H), 7.30 (d, *J*=8.53 Hz, 1 H), 7.17 (d, *J*=8.53 Hz, 1 H), 7.07 (d, *J*=3.01 Hz, 1 H), 6.45 (d, *J*=3.01 Hz, 1 H), 4.62 (dd, *J*=10.04, 3.51 Hz, H), 4.20 (dd, *J*=17.57, 10.04 Hz, H), 3.80 (s, H), 3.39 - 3.77 (m, 12 H), 3.05 - 3.16 (m, 2 H), 1.56 (s, 2 H) ; ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 190.0, 171.6, 136.8, 136.0, 133.1, 130.1, 129.6, 129.0, 128.5, 121.2, 119.8, 110.0, 100.9, 66.8, 66.5, 46.2, 44.9, 44.2, 42.7, 33.0; HRMS calcd for $C_{23}H_{24}N_2O_3$ $[M+H]^+$ 377.1860 found 377.1915 ; IR (neat) 3519, 2958, 2895, 2843, 1685, 1638, 1567, 1581, 1510, 1491, 1459, 1434,

1396, 1358, 1338, 1300, 1269, 1238, 1211, 1185, 1157, 1113, 1084, 1067, 1031, 1001, 989, 941, 920, 907, 892, 847, 819, 787, 771, 763, 749, 730, 689, 675, 647, 638, 595, 578, 553, 537, 497, 476, 454, 437, 418, 401 cm^{-1}.

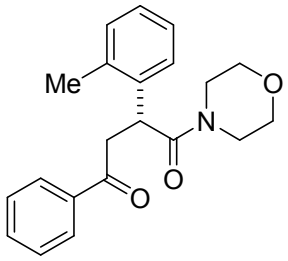


1-morpholino-2-(naphthalene-2-yl)-4-phenylbutane-1,4-dione (2h): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with naphthalen-2-ylboronic acid (526 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2h** = 4.38 min; T_{ret} **3h** = 4.24 min; 99:1; Method N: T_{ret} *R*-**2h** = 6.60 min; T_{ret} *S*-**2h** = 8.02 min = 98% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as a light yellow solid (458 mg, 60 % yield). A duplicate experiment afforded **2h** in 54% isolated yield with an average yield of 57%. Analytical data for **2h:** mp (138-140 °C); $[\alpha]^{25}_{D}$ = 160.8 ° (c = 2.2 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.96 - 8.02 (m, 2 H), 7.76 - 7.88 (m, 4 H), 7.40 - 7.58 (m, 6 H), 4.71 (dd, *J*=9.88, 3.62 Hz, 1 H), 4.23 (dd, *J*=17.90, 9.88 Hz, 1 H), 3.49 - 3.78 (m, 6 H), 3.39 - 3.47 (m, 1 H), 3.10 - 3.20 (m, 2 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.5, 170.8, 136.7, 136.6, 133.6, 133.2, 132.5, 129.1, 128.5, 128.2, 127.7, 126.5, 126.4, 126.1, 125.7, 66.8, 66.4, 60.4, 46.2, 44.3, 44.2, 42.7, 21.1, 14.2; HRMS calcd for $C_{24}H_{23}NO_3$ $[M+H]^+$ 374.1751 found 374.1779**;** IR (neat) 2841,

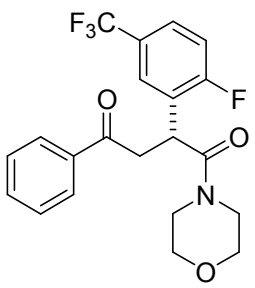
1689, 1627, 1460, 1445, 1392, 1359, 1322, 1264, 1223, 1175, 1111, 1067, 1026, 990, 859, 841, 823, 789, 764, 741, 696, 656, 583, 566, 550, 501, 478, 416 cm^{-1}.



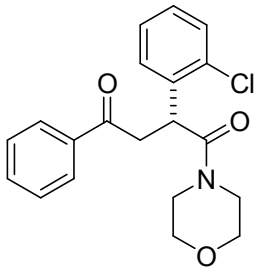
(*R*,*E*)-1-Morpholino-4-phenyl-2-styrylbutane-1,4-dione (2i): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with (*E*)-styrylboronic acid (452 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2i** = 4.87 min; T_{ret} **3i** = 4.67 min; 96:4; Method N: T_{ret} *R*-**2i** = 6.76 min; T_{ret} *S*-**2i** = 8.07 min = >99% ee) and then purified by flash column chromatography (10-40 % ethyl acetate in hexanes) to afford the product as an off-white solid (555 mg, 92%). A duplicate experiment afforded **2i** in 99% isolated yield with with an average yield of 96%. Analytical data for **2i**: mp (140-141 °C); $[\alpha]^{25}_{D}$ = -93.2 ° (c = 2.0 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.01 (d, *J*=7.53 Hz, 8 H), 7.57 (t, *J*=7.28 Hz, 4 H), 7.47 (t, *J*=7.53 Hz, 8 H), 7.30 - 7.40 (m, 16 H), 7.28 - 7.30 (m, 1 H), 7.23 - 7.26 (m, 1 H), 6.56 (d, *J*=15.56 Hz, 4 H), 6.28 (dd, *J*=16.06, 8.53 Hz, 4 H), 4.14 - 4.24 (m, 4 H), 3.96 (dd, *J*=17.57, 9.54 Hz, 4 H), 3.59 - 3.88 (m, 33 H), 3.09 (dd, *J*=17.82, 3.76 Hz, 4 H), 1.61 (s, 3 H) ; ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.3, 171.0, 136.6, 136.4, 133.2, 132.5, 128.6, 128.6, 128.1, 127.9, 127.0, 126.4, 66.9, 66.7, 46.3, 42.6, 41.9, 40.9; HRMS calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$ 350.1750 found 350.1787; IR (neat) 2906, 2839, 1687, 1633, 1596, 1577, 1497, 1445, 1387, 1358, 1332, 1300, 1286, 1269, 1249, 1235, 1219, 1176, 1114, 1068, 1029, 999, 990, 971, 939, 928, 907, 846, 801, 776, 758, 742, 720, 664 cm^{-1}.



1-morpholino-4-phenyl-2-*o*-tolylbutane-1,4-dione (2j): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with *o*-tolylboronic acid (416 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2j** = 4.01 min; T_{ret} **3j** = 3.83 min; >99:1; Method N: T_{ret} *R*-**2j** = 5.39 min; T_{ret} *S*-**2j** = 6.38 min = >99% ee) and then purified by flash column chromatography (40 % ethyl acetate in hexanes) to afford the product as a thick colorless oil (640 mg, 93 %). A duplicate experiment afforded **2j** in 99% isolated yield with an average yield of 96%. Analytical data for **2j:** $[\alpha]^{25}_{D}$ = -181.5 ° (c = 2.4 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.97 - 8.03 (m, 2 H), 7.51 - 7.57 (m, 1 H), 7.41 - 7.47 (m, 2 H), 7.17 - 7.25 (m, 4 H), 4.65 (dd, *J*=10.56, 2.74 Hz, 1 H), 4.05 - 4.16 (m, 2 H), 3.79 (dd, *J*=9.98, 5.67 Hz, 1 H), 3.65 - 3.74 (m, 1 H), 3.48 - 3.60 (m, 3 H), 3.36 - 3.45 (m, 1 H), 3.03 - 3.17 (m, 2 H), 2.82 (dd, *J*=17.80, 2.74 Hz, 1 H), 2.38 (s, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.6, 171.2, 137.5, 134.4, 133.1, 131.1, 128.5, 128.3, 127.0, 66.8, 66.2, 45.8, 42.7, 42.4, 40.9, 21.1, 19.4, 14.2; HRMS calcd for $C_{21}H_{23}NO_3$ $[M+H]^+$ 338.1751 found 338.1789**;** IR (neat) 2855, 1682, 1640, 1431, 1357, 1298, 1233, 1112, 1027, 990, 845, 743, 726, 689, 595, 451 cm^{-1}.

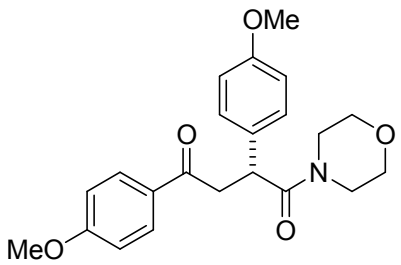


2-(2-fluoro-5-(trifluoromethyl)phenyl)-1-morpholino-4-phenylbutane-1,4-dione (2k): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 2-fluoro-5-(trifluoromethyl)phenylboronic acid (636 mg, 3.06 mmol), Rh catalyst **5**(21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2k** = 4.39 min; T_{ret} **3k** = 4.27 min; >99:1; Method P: T_{ret} *R*-**2k** = 11.61 min; T_{ret} *S*-**2k** = 13.12 min = 98% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as a thick colorless oil (665mg, 80%). A duplicate experiment afforded **2k** in 79% isolated yield with an average yield of 80%. Analytical data for **2k**: $[\alpha]^{25}_{D}$ = -111.1 ° (c = 2.0 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.96 - 8.02 (m, 2 H), 7.73 (dd, *J*=6.65, 2.15 Hz, 1 H), 7.53 - 7.61 (m, 2 H), 7.46 (t, *J*=7.63 Hz, 2 H), 7.22 (t, *J*=9.00 Hz, 1 H), 4.93 (dd, *J*=10.27, 3.23 Hz, 1 H), 4.08 - 4.19 (m, 1 H), 3.62 - 3.81 (m, 5 H), 3.52 - 3.60 (m, 1 H), 3.38 - 3.46 (m, 1 H), 3.30 - 3.38 (m, 1 H), 3.10 (dd, *J*=17.80, 3.33 Hz, 1 H) ; ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 197.6, 169.7, 136.2, 133.4, 128.6, 128.2, 127.1, 126.8, 126.6, 116.5, 116.3, 66.8, 66.5, 46.2, 42.9, 42.6, 35.2; HRMS calcd for $C_{21}H_{19}F_4NO_3$ $[M+H]^+$ 410.1374 found 410.1395**;** IR (neat) 1683, 1644, 1505, 1437, 1328, 1229, 1161, 1112, 1028, 991, 905, 830, 746, 689, 617, 578 cm^{-1}.



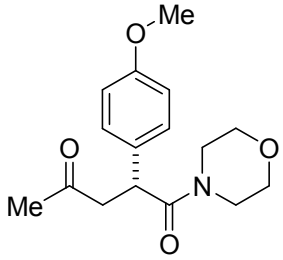
2-(2-chlorophenyl)-1-morpholino-4-phenylbutane-1,4-dione (2l): According to the general procedure for the rhodium-catalyzed

conjugate addition reaction, (*E*)-1-morpholino-4-phenylbut-2-ene-1,4-dione (500 mg, 2.04 mmol) was reacted with 2-chlorophenylboronic acid (478 mg, 3.06 mmol), Rh catalyst **5** (21 mg, 0.031 mmol), triethylamine (0.28 mL, 2.04 mmol), in tetrahydrofuran:water (19:1, 7.5 mL). The crude material was analyzed by HLPC (Method A: T_{ret} **2l** = 4.17 min; T_{ret} **3l** = 3.60 min; >99:1; Method O: T_{ret} *R*-**2l** = 4.34 min; T_{ret} *S*-**2l** = 5.14 min = 97% ee) and then purified by flash column chromatography (50 % ethyl acetate in hexanes) to afford the product as a thick yellow oil (482 mg, 66 %). A duplicate experiment afforded **2l** in 68% isolated yield with an average yield of 67%. Analytical data for **2l**: $[\alpha]^{25}_{D}$ = -107.8 ° (c = 2.0 in ethyl acetate); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.87 - 7.93 (m, 9 H) 7.43 - 7.49 (m, 5 H) 7.29 - 7.38 (m, 18 H) 7.12 - 7.22 (m, 10 H) 4.87 (dd, *J*=10.76, 2.74 Hz, 5 H) 3.93 (dd, *J*=17.61, 10.76 Hz, 5 H) 3.40 - 3.67 (m, 28 H) 3.14 - 3.22 (m, 5 H) 3.06 - 3.13 (m, 5 H) 2.92 (dd, *J*=17.61, 2.74 Hz, 5 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.0, 170.6, 136.7, 136.4, 133.2, 132.7, 130.0, 128.9, 128.8, 128.5, 128.2, 127.7, 126.7, 66.8, 66.4, 46.0, 42.7, 42.2, 40.56; HRMS calcd for $C_{20}H_{20}ClNO_3$ $[M+H]^+$ 358.1204 found 358.1207; IR (neat) 3309, 1630, 1591, 1428, 1334, 1111, 1025, 749, 688, 592, 467, 435 cm^{-1}.



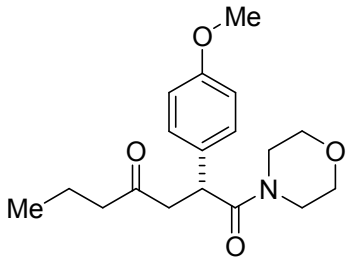
(*R*)-2,4-bis(4-methoxyphenyl)-1-morpholinobutane-1,4-dione (6b). According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (*E*)-1-(4-methoxyphenyl)-4-morpholinobut-2-ene-1,4-dione (0.55 g, 2.0 mmol) was reacted with 4-methoxyphenylboronic acid (456 mg, 3.0 mmol), Rh catalyst **5**(27 mg, 0.04 mmol), triethyamine (0.42 mL, 3.0 mmol), in

tetrahydrofuran:water (19:1, 5 mL). The crude reaction mixture was analyzed by HPLC (Method C: T_{ret} *R*-**6b** = 3.7 min; T_{ret} *S*-**6b** = 4.4 min = >99% ee; T_{ret} *enantiomer 1*-**7b** = 4.1min; T_{ret} *enantiomer 2*-**7b** = 5.2 min; >99:1 **6b**:**7b**). The crude material was purified by flash column chromatography (30 % to 100 % ethyl acetate in hexanes) to afford the product as a colorless solid (755 mg, 96% yield). A duplicate experiment afforded **6b** in 97% isolated yield with an average yield of 96%. Analytical data for **6b:** mp (115-117 °C); $[\alpha]^{25}_{D}$ = - 144.9 ° (c = 1.3 in dichloromethane). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.95 (d, *J*=8.53 Hz, 2 H), 7.23 (d, *J*=8.53 Hz, 2 H), 6.90 (d, *J*=9.03 Hz, 2 H), 6.87 (d, *J*=8.53 Hz, 2 H), 4.47 (dd, *J*=9.79, 3.76 Hz, 1 H), 4.04 (dd, *J*=17.82, 9.79 Hz, 2 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.76 - 3.33 (m, 7 H), 3.27 - 3.09 (m, 1 H), 3.01 (dd, *J*=17.57, 3.51 Hz, 1 H); ^{13}C NMR (101 MHz, *CHLOROFORM-d*) δ 197.2, 171.2, 163.5, 158.7, 131.4, 130.4, 129.8, 128.7, 114.5, 113.6, 66.8, 66.4, 55.4, 55.3, 46.2, 43.9, 43.1, 42.6; HRMS (ESI) calcd for $C_{21}H_{24}NO_4$ [M+H] 384.1811 found 384.1802, IR (neat) 2910, 2853, 1671, 1631, 1597, 1513, 1458, 1257, 1185, 1028, 856 cm^{-1}.



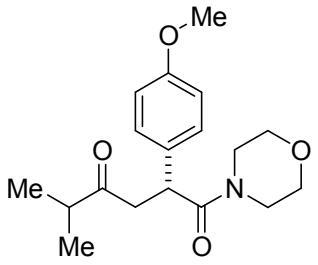
(*R*)-2-(4-methoxyphenyl)-1-morpholinopentane-1,4-dione (6c): According to the general procedure for the rhodium-catalyzed conjugate addition reaction (*E*)-1-morpholinopent-2-ene-1,4-dione (366 mg, 2.0 mmol) was reacted with 4-methoxyphenylboronic acid (456 mg, 3.0 mmol), Rh catalyst **5** (27 mg, 0.04 mmol), triethylamine (0.42 mL, 3.0 mmol), in tetrahydrofuran:water (19:1, 5 mL). The crude material was purified by flash column chromatography (60 % to 100 % ethyl acetate in hexanes) to afford the product as a colorless oil (525 mg, 90 %). A duplicate experiment

afforded **6c** in 89% isolated yield with an average yield of 90%. HPLC analysis (Method C: Tr *R*-**6b** = 2.4 min; Tr *S*-**6b** = 2.7 min = 97% ee; Tr *enantiomer 1*-**7b** = 3.6min; Tr *enantiomer 2*-**7b** = 4.4 min; 97:3 **6b**:**7b**). $[\alpha]_D^{25}$ -124.6° (*c* = 1.28, methanol); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.1 (d, *J*=8.6 Hz, 2 H), 6.8 (d, *J*=8.8 Hz, 2 H), 4.3 (dd, *J*=10.1, 4.0 Hz, 1 H), 3.8 (s, 3 H), 3.7 (m, 2 H), 3.5 (m, 5 H), 3.3 (m, 1 H), 3.1 (m, 1 H), 2.5 (dd, *J*=17.7, 4.0 Hz, 1 H), 2.2 (s, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ 207.5, 171.0, 158.7, 131.0, 128.5, 114.5, 66.7, 66.3, 55.2, 48.6, 46.1, 43.2, 42.5, 30.2; HRMS calcd for $C_{16}H_{21}NO_4$ $[M+H]^+$, 292.1550. Found 292.1564. IR (neat) 1712, 1636, 1511, 1243, 1111, 1026 837, 786 cm^{-1};

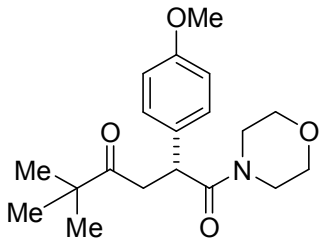


2-(4-methoxyphenyl)-1-morpholinoheptane-1,4-dione (6d): According to the general procedure for the rhodium-catalyzed conjugate addition reaction (*E*)-1-morpholinohept-2-ene-1,4-dione (150 mg, 0.71 mmol) was reacted with 4-methoxyphenylboronic acid (163 mg, 1.07 mmol), Rh catalyst **5**(9.4 mg, 0.014 mmol), triethylamine (0.15 mL, 1.07 mmol) in tetrahydrofuran:water (19:1, 1.8 mL). The crude material was purified by flash column chromatography (60 % to 100 % ethyl acetate in hexanes) to afford the product as a colorless oil (209 mg, 92 %). A duplicate experiment afforded **6d** in 89% isolated yield with an average yield of 90%. HPLC analysis (Method E: T_{ret} *R*-**6d** = 10.2 min; T_{ret} *S*-**6d** = 7.9 min = 99% ee). $[\alpha]_D^{25}$ -115.2 ° (*c* = 1.55, methanol); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.1 (d, *J*=8.6 Hz, 2 H), 6.8 (d, *J*=8.6 Hz, 2 H), 4.3 (dd, *J*=10.0, 4.1 Hz, 1 H), 3.8 (s, 3 H), 3.7 (m, 2 H), 3.5 (m, 4 H), 3.4 (dd, *J*=17.5, 10.1 Hz, 1 H), 3.3 (ddd, *J*=13.3, 5.6, 2.6 Hz, 1 H), 3.1

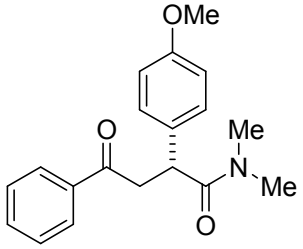
(ddd, *J*=10.8, 7.4, 2.7 Hz, 1 H), 2.5 (dd, *J*=17.7, 4.0 Hz, 1 H), 2.4 (m, 2 H), 1.6 (td, *J*=15.0, 7.0 Hz, 3 H), 0.9 (t, *J*=7.3 Hz, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 209.8, 171.0, 158.6, 131.1, 128.5, 114.4, 66.7, 66.3, 55.2, 47.8, 46.0, 44.9, 42.9, 42.5, 17.0, 13.6. HRMS calcd for $C_{18}H_{25}NO_4$ $[M+H]^+$, 320.1856. Found 320.1876. IR (neat) 1710, 1639, 1511, 1245, 1112, 1031, 835, 790 cm^{-1}



(*R*)-2-(4-methoxyphenyl)-5-methyl-1-morpholinohexane-1,4-dione(6e): According to the general procedure for the rhodium-catalyzed conjugate addition reaction (*E*)-5-methyl-1-morpholinohex-2-ene-1,4-dione (100 mg, 0.47 mmol) was reacted with 4-methoxyphenylboronic acid (108 mg, 0.71 mmol), Rh catalyst **5** (31 mg, 0.047 mmol), triethylamine (0.10 mL, 0.71 mmol) in tetrahydrofuran:water (19:1, 1.2 mL). The crude material was purified by flash column chromatography (60 % to 100 % ethyl acetate in hexanes) to afford the product as a yellow oil (123 mg, 81 %). A duplicate experiment afforded **6e** in 82% isolated yield with an average yield of 82%. HPLC analysis (Method F: T_{ret} *R*-**6e** = 14.8 min; T_{ret} *S*-**6e** = 12.8 min = 99% ee). $[\alpha]_D^{25}$ -123.6 ° (*c* = 1.30, methanol); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.1 (d, *J*=8.6 Hz, 2 H), 6.8 (d, *J*=8.8 Hz, 2 H), 4.3 (dd, *J*=9.8, 4.1 Hz, 1 H), 3.8 (s, 3 H), 3.7 (m, 2 H), 3.5 (m, 5 H), 3.3 (m, 1 H), 3.1 (td, *J*=7.2, 3.9 Hz, 1 H), 2.6 (dt, *J*=13.9, 7.0 Hz, 1 H), 2.6 (dd, *J*=17.7, 4.1 Hz, 1 H), 1.1 (dd, *J*=14.4, 6.9 Hz, 6 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 213.3, 171.0, 158.7, 131.2, 128.6, 114.4, 66.7, 66.4, 55.3, 46.1, 45.7, 43.0, 42.5, 41.0, 18.1, 18.0; HRMS calcd for $C_{18}H_{25}NO_4$ $[M+H]^+$, 320.1856. Found 320.1861. IR (neat) 1707, 1639, 1511, 1242, 1112, 1033, 834 cm^{-1}.

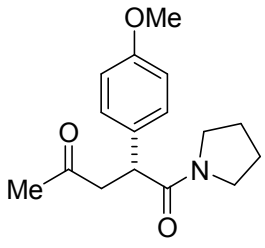


2-(4-methoxyphenyl)-5,5-dimethyl-1-morpholinohexane-1,4-dione (6f): According to the general procedure for the rhodium-catalyzed conjugate addition reaction (*E*)-5,5-dimethyl-1-morpholinohex-2-ene-1,4-dione (68 mg, 0.30 mmol) was reacted with 4-methoxyphenylboronic acid (68 mg, 0.45 mmol), Rh catalyst **5** (20 mg, 0.030 mmol), potassium hydroxide (25 mg, 0.45 mmol), and tetrahydrofuran:water (19:1, 0.75 mL). The crude material was purified by flash column chromatography (60 % to 100 % ethyl acetate in hexanes) to afford the product as a yellow solid (79 mg, 79 %) (Method G: T_{ret} *R*-**6e** = 1.6 min; T_{ret} *S*-**6e** = 3.3 min = 99% ee). A duplicate experiment afforded **6f** in 78% isolated yield with an average yield of 78%. mp: 48-52 °C; $[\alpha]_D^{25}$ -135.4 ° (*c* = 1.28, methanol); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.1 (d, *J*=8.6 Hz, 2 H), 6.8 (d, *J*=8.6 Hz, 2 H), 4.2 (dd, *J*=9.7, 4.0 Hz, 1 H), 3.8 (s, 3 H), 3.7 (m, 2 H), 3.5 (m, 5 H), 3.3 (m, 1 H), 3.1 (m, 1 H), 2.6 (dd, *J*=17.8, 4.1 Hz, 1 H), 1.1 (s, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 214.6, 171.0, 158.6, 131.2, 128.6, 114.3, 66.7, 66.3, 55.2, 46.0, 43.8, 42.8, 42.6, 42.5, 26.3; HRMS calcd for $C_{19}H_{27}NO_4$ $[M+H]^+$, 334.2019 . Found 334.2033. IR (neat) 1701, 1640, 1510, 1241, 1112, 1029, 830 cm^{-1}.



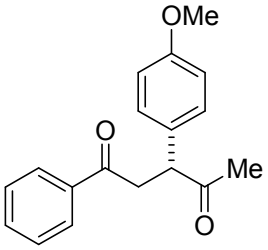
(*R*)-2-(4-methoxyphenyl)-N,N-dimethyl-4-oxo-4-phenylbutanamide (6g): According to the general procedure for the rhodium-catalyzed conjugate addition reaction, (E)-*N,N*-

dimethyl-4-oxo-4-phenylbut-2-enamide (500 mg, 2.46mmol) was reacted with 4-methoxyphenylboronic acid (450 mg, 2.95 mmol), Rh catalyst **5** (33 mg, 0.05 mmol), triethylamine (0.51 mL, 3.69 mmol), in tetrahydrofuran:water (19:1, 10 mL). The reaction mixture was analyzed by HLPC (Method A: T_{ret} **6g** = 4.6 min; T_{ret} **7g** = 4.4 min; >99:1; Method I: T_{ret} *R*-**6g** = 9.0 min; T_{ret} *S*-**7g** = 13.5 min = 98% ee). The crude material was purified by flash column chromatography (20-80 % ethyl acetate in hexanes) to afford the product as a colorless oil (680 mg, 89%), $[\alpha]^{25}_{D}$ = -188.6 ° (c = 9.6 in dichloromethane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.87 - 8.02 (m, 2 H), 7.50 (t, *J*=7.43 Hz, 1 H), 7.39 (t, *J*=7.63 Hz, 2 H), 7.20 - 7.31 (m, 2 H), 6.80 - 6.92 (m, 2 H), 4.50 (dd, *J*=9.98, 3.72 Hz, 1 H), 4.08 (dd, *J*=17.80, 9.98 Hz, 1 H), 3.76 (s, 3 H), 3.05 (d, *J*=3.72 Hz, 1 H), 2.97 - 3.03 (m, 4 H), 2.93 (s, 3 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 198.5, 179.3, 158.4, 136.4, 132.8, 131.1, 128.6, 128.2, 127.9, 114.1, 55.0, 44.3, 43.0, 36.9, 35.7, HRMS calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 321.1600 found 312.1633; IR (neat) 2933, 1682, 1635, 1595, 1580, 1509, 1448, 1395, 1246, 1139, 1031, 992, 746, 723, 687cm^{-1}.



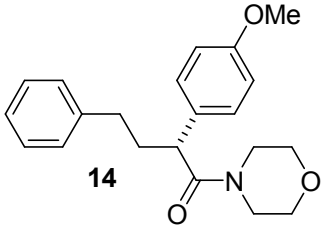
(*R*)-2-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)pentane-1,4-dione (6h): According to the general procedure for the rhodium-catalyzed conjugate addition reaction (*E*)-1-(pyrrolidin-1-yl)pent-2-ene-1,4-dione (334 mg, 2.0 mmol) was reacted with 4-methoxyphenylboronic acid (456 mg, 3.0 mmol), Rh catalyst **5** (27 mg, 0.04 mmol), triethylamine (0.42 mL, 3.0 mmol) in tetrahydrofuran:water (19:1, 5 mL). The crude material was purified by flash column chromatography (60 % to 100 % ethyl acetate in

hexanes) to afford the product as a colorless oil (451 mg, 82 %). A duplicate experiment afforded **6h** in 70% isolated yield with an average yield of 76%. (Method D: T_{ret} *R*-**6h** = 5.3 min; T_{ret} *S*-**6h** = 6.1 min = 99% ee). $[\alpha]_D^{25}$ -133.9 ° (*c* = 1.46, methanol); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.20 (d, *J*=8.67 Hz, 2 H), 6.83 (d, *J*=8.67 Hz, 2 H), 4.10 (dd, *J*=10.17, 3.77 Hz, 1 H), 3.78 (s, 3 H), 3.57 - 3.68 (m, 1 H), 3.42 - 3.56 (m, 2 H), 3.30 - 3.41 (m, 1 H), 3.08 - 3.20 (m, 1 H), 2.52 (dd, *J*=17.71, 3.96 Hz, 1 H), 2.16 (s, 3 H), 1.69 - 1.96 (m, 4 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 207.7, 170.9, 158.6, 131.0, 128.9, 114.2, 55.2, 48.6, 46.1, 46.0, 45.0, 30.2, 26.0, 24.1; HRMS calcd for $C_{16}H_{21}NO_3$ $[M+H]^+$, 276.1594. Found 276.1610. IR (neat) 1711, 1631, 1511, 1249, 1177, 1162, 1031 839, 787 cm^{-1};



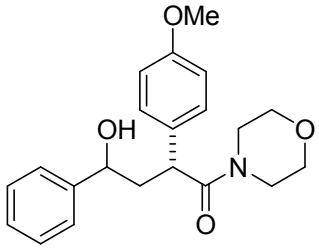
(R)-3-(4-methoxyphenyl)-1-phenylpentane-1,4-dione (12). Anhydrous cerric chloride (750 mg, 3.04 mmol, 3.0 equiv.) was slurried in dry tetrahydrofuran (3.5 mL) at ambient for 24 h. Additional tetrahydrofuran (2.5 mL) was added, the mixture was stirred for 1 h and then cooled to -78 °C. Methylmagnesium bromide (1.00 mL, 3.0 M in tetrahydrofuran, 3.0 mmol, 3.0 equiv.) was added drop-wise via syringe over 1 min. The mixture was aged at – 78 °C for 2 h to provide a pale yellow suspension. A second flask was charged with keto amide **2a** (353 mg, 1.00 mmol, 1.0 equiv.) and dry tetrahydrofuran (2.0 mL) and warmed briefly to 35 °C to dissolve the solids. The resulting solution was cooled to -78 °C and lithium hexamethyldisilazide (970 μL, 1N in tetrahydrofuran, 0.97 mmol, 0.97 equiv.) was added drop-wise via syringe over ~1 min. The resulting homogeneous pale yellow mixture was stirred at -78 °C for 2 h. This mixture was then

transferred via cannula into the first flask at -78 °C, rinsing with 1 mL tetrahydrofuran. The reaction mixture obtained was allowed to warm from -78 °C to ambient over 2h and then aged at ambient for 30 min. The mixture was cooled to 0 °C, saturated aqueous ammonium chloride (1 mL) was added followed by diethyl ether (40 mL) and water (20 mL) . Aqueous hydrochloric acid (1N, 5 mL) was added to dissolve the solids and the layers were separated. The aqueous phase was extracted with diethyl ether (1 x 20 mL). The combined organic extracts were concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 90:10 hexanes:ethyl acetate) to afford, after concentration of the appropriate fractions, diketone **12** (133 mg, 49%, 98 %ee) as a colorless oil. A separate experiment afforded **12** in 56% yield (average yield for both experiments is: 52%). Enantiomeric excess determined by chiral SFC analysis (Method J), T_{ret} **12** major= 2.7 min; T_{ret} minor = 2.3 min = 98% ee. $[\alpha]^{25}_{D}$ = -217.9° (c = 1.08, in acetonitrile). ^{1}H NMR (CHLOROFORM-*d*, 400 MHz): δ ppm 7.94–7.96 (m, 2H), 7.53–7.58 (m, 1H), 7.42-7.46 (m, 2H), 7.19-7.22 (m, 2H), 6.86-6.91 (m, 2H), 4.38 (dd, *J* = 10.0, 3.9 Hz, 1H), 3.97 (dd, *J* = 18.2, 10.0 Hz, 1H), 3.80 (s, 3H), 3.11 (dd, *J* = 18.2, 3.9 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (CHLOROFORM-*d*, 101 MHz): ppm 207.4, 198.2, 159.0, 136.4, 133.1, 129.8, 129.3, 128.5, 128.0, 114.5, 55.2, 52.9, 42.2, 29.0. HRMS calcd. For $C_{18}H_{19}O_3$ $[M+H]^+$: 283.1334 found: 283.1335. IR (neat): 1712, 1681, 1510, 1353, 1178, 1032, 831 cm^{-1}

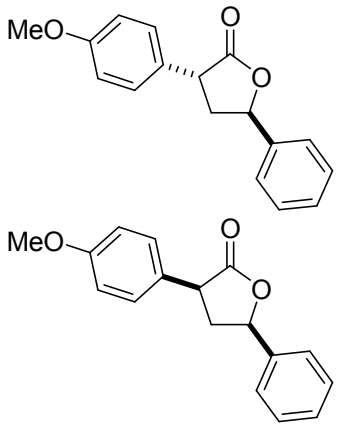


(R)-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutan-1-one (13). To a stirred solution of *(R)*-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutane-1,4-dione (**2a**) (176 mg, 0.500

mmol), palladium II acetate (11 mg, 0.050 mmol) and chlorobenzene (10 μL, 0.10 mmol) in degassed tetrahydrofuran (2.5 mL) was added degassed aqueous KF (1 mL, 232 mg/mL, mmol, 5 equiv.) to afford a biphasic mixture. The reaction flask was immersed in a preheated (50 °C) oil-bath. Neat polymethylhydrosiloxane (PMHS) (150 μL, 250 mmol, 5.0 equiv.) was added drop-wise via syringe over ~5 minutes (CAUTION: vigorous gas evolution) and the mixture immediately turned black. The mixture was heated at 50 °C for 2 h and then cooled to RT. Diethyl ether (25 mL) and water (20 mL) were added and the layers were separated. The aqueous phase was extracted with ethyl ether (1 x 20 mL). The combined organic extracts were washed with brine (1 x 20 mL) dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 65:35 hexanes – ethyl acetate) to afford, after concentration of the appropriate fractions, amide **13** (136 mg, 80%, >99% ee) as a colorless solid (mp 64-65 °C). Enantiomeric excess determined by chiral SFC analysis (Method K), T_{ret} **13** major= 4.8 min; T_{ret} minor = 5.4 min = >99% ee. $[\alpha]^{25}_{D}$ = -32.6 ° (c = 0.85 in acetonitrile) ^{1}H NMR (CHLOROFORM-*d*, 400 MHz): δ ppm 7.26–7.30 (m, 2H), 7.13-7.20 (m, 5H), 6.84-6.86 (m, 2H), 3.79 (s, 3H), 3.71-3.77 (m, 1H), 3.61-3.67 (m, 1H), 3.45-3.59 (m, 4H), 3.25-3.35 (m, 2H), 3.08-3.14 (m, 1H), 2.52-2.67 (m, 2H), 2.39-2.47 (m, 1H), 1.96-2.04 (m, 1H). ^{13}C NMR (CHLOROFORM-*d*, 101 MHz): δ ppm 171.6, 158.5, 141.7, 131.9, 128.8, 128.5, 128.3, 125.9, 114.3, 66.8, 66.3, 55.2, 46.6, 45.9, 42.4, 36.2, 33.5. HRMS calcd. For $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1913 found: 340.1922. IR (neat): 2842, 1628, 1506, 1440, 1231, 1028, 749 cm^{-1}



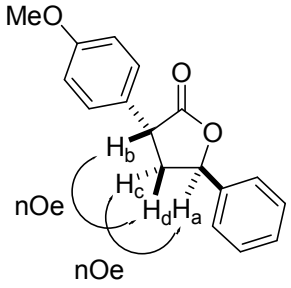
(R)-4-hydroxy-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutan-1-one (14). To a cold (0 °C) stirred solution of *(R)*-2-(4-methoxyphenyl)-1-morpholino-4-phenylbutane-1,4-dione (**2a**) (625 mg, 1.77 mmol, 1.0 equiv.) in dry tetrahydrofuran (6.5 mL) was added lithium triterbutoxyaluminumhydride (2.50 mL, 1.0 M in tetrahdrofuran, 2.50 mmol, 1.4 equiv.) dropwise via syringe over 10 min. The resulting mixture was stirred at 0 °C for 2 h. Saturated, aqueous ammonium chloride (2 mL) was *slowly* added (CAUTION: gas evolution). Water (15 mL) and ethyl acetate (25 mL) were added and the layers were separated. The aqueous phase was extracted with ethyl acetate (1 x 20 mL). The combined organic extracts were washed with brine (1 x 15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. ^{1}H nmr analysis of the crude reaction product (627.5 mg white foam, >99%) indicated the formation of two epimeric alcohols (**14**) in a ratio of 8:1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.35–7.44 (m, 5H), 7.23-7.26 (m, 2H), 6.90-6.93 (m, 2H), 5.68 (dd, *J*= 7.2, 5.2 Hz, 1H). This mixture was used without further purification in the next reaction.



(3R,5R)-3-(4-methoxyphenyl)-5-phenyl-dihydrofuran-2(3H)-one (16); (3R,5S)-3-(4-methoxyphenyl)-5-phenyl-dihydrofuran-2(3H)-one (15). To a stirred solution of alcohols **14** (627 mg, 1.77 mmol, 1.0 equiv.) in dry toluene (12.5 mL) was added solid *p*-toluenesulfonic acid monohydrate (305 mg, 1.77 mmol, 1.0 equiv.) and the resulting mixture was stirred at RT for 12h. Ethyl acetate (30 mL) and water (30 mL)

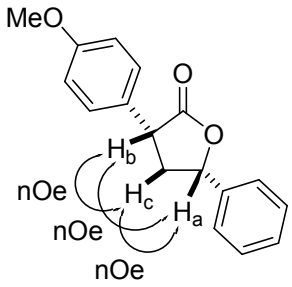
were added and the layers were separated. The aqueous phase was extracted with ethyl acetate (1 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (20 mL), brine (1 x 20 mL) and concentrated under reduced pressure. ^{1}H NMR analysis of the crude reaction mixture showed the formation of two epimeric products in ratio of 8:1. The mixture was purified by flash chromatography (silica gel, 9:1 to 7:3 hexane – ethyl acetate) to afford, after concentration of the appropriate fractions, two products.

The first compound that eluted was the *trans*-lactone **15** (324 mg, 68%, >99 % ee), a colorless oil which slowly crystallized to a colorless solid (mp 59-63 °C). Enantiomeric excess determined by chiral HPLC analysis (Method L), T_{ret} **15** major= 11.3 min; T_{ret} minor = 29.1 min = >99% ee. $[\alpha]^{25}_{D}$ = -83.1 (c = 0.76 in acetonitrile). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.35–7.44 (m, 5H), 7.23-7.26 (m, 2H), 6.90-6.93 (m, 2H), 5.68 (dd, *J*= 7.2, 5.2 Hz, 1H, H_a), 3.89 (dd, *J*= 8.4, 8.4 Hz, 1H, H_b), 3.81 (s, 3H), 2.79-2.86 (m, 1H, H_c), 2.66-2.72 (m, 1H, H_d). ^{13}C NMR ($CDCl_3$, 101 MHz): δ ppm 177.3, 159.0, 139.4, 128.8, 128.4, 128.3, 125.0, 114.4, 78.6, 55.2, 44.2, 39.2., HRMS calc'd. for $C_{17}H_{16}O_3$ $[M+H]^+$: 269.1178 found: 269.1184. IR (neat): 1767, 1611, 1513, 1248, 1156, 1030, 1015, 832 cm^{-1}.



Key NOE correlations from 2D-NOESY

The second compound that eluted was *cis*-lactone **16** (42 mg, 9 %, >99 %ee), a white solid (mp 128-130 °C). Enantiomeric excess determined by chiral HPLC analysis (Method L), T_{ret} **16** major= 11.1 min; T_{ret} minor = 15.4 min = >99% ee. $[\alpha]^{25}_{D}$ = -25.0 (c = 0.74 in acetonitrile). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ ppm 7.35–7.44 (m, 5H), 7.22-7.28 (m, 2H), 6.89-6.93 (m, 2H), 5.50 (dd, *J*=10.8, 5.50 Hz, 1H, H_a), 3.99 (dd, *J*=12.9, 8.50 Hz, 1H, H_b), 3.80 (s, 3H), 3.02-3.08 (m, 1H, H_c), 2.36 (ddd, *J*=12.9, 11.0, 10.8, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ ppm 176.7, 159.1, 138.7, 129.2, 128.8, 128.6, 128.0, 125.5, 114.3, 79.05, 55.3, 46.9, 40.6. HRMS calc'd. For $C_{17}H_{16}O_3$ $[M+H]^+$: 269.1178 found: 269.1186. IR (neat): 1760, 1513, 1332, 1244, 1156, 936, 768 cm^{-1}.



Key NOE correlations from 2D-NOESY

The total yield of lactones **15** and **16** was 366 mg (77 %).