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Supporting Information

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Metallophosphite-Induced Nucleophilic Acylation of α,β-Unsaturated Amides: Facilitated Catalysis via a Diastereoselective Retro-[1,4]-Brook Rearrangement

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Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on the following instruments: Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Combustion analyses were preformed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and aqueous ceric ammonium nitrate molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Reagents were massed out in the glovebox. Yield refers to isolated yield o analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Diethyl ether was dried by passage through a column of neutral alumina under nitrogen prior to use.[1] Acylsilanes were prepared by the literature methods.[2] (±)-TADDOL-phosphite was synthesized via the method reported in a previous communication.[3]

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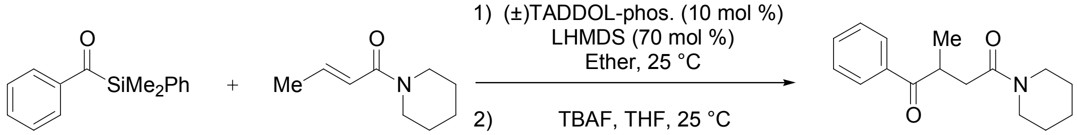
[1] P. J. Alaimo, D. W. Peters, J. Arnold, R. G. Bergman, *J. Chem. Ed.* **2001**, *78*, 64.

[2] (a) Acyl triethylsilanes were prepared through three steps from the corresponding aldehydes. For detailed information, see: X. Linghu, D. A. Nicewicz, J. S. Johnson, *Org. Lett.* **2002**, *4*, 2957-2960.. (b) Acyl trimethylsilanes were prepared by reductive silylation of methylbenzoate. For detailed information, see: E. C. Tongco, Q. Wang, G. K. S. Prakash, *Synth. Commun.* **1997**, *27*, 2117-2123. (c) Acyl dimethylphenylsilanes were prepared by reductive lithiation of chlorodimethylphenyl silane, transmetallation and addition to acid chlorides. For detailed information, see: B. F. Bonini, M. Comesfranchini, G. Mazzanti, U. Passamonti, A. Ricci, P. Zani, *Synthesis* **1995**, 92-96**.**

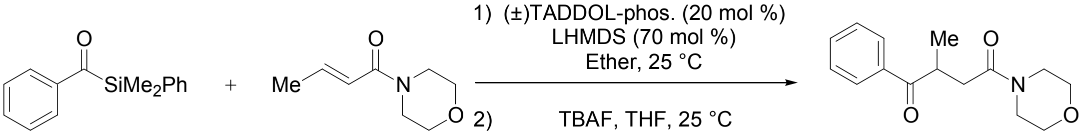
[3] Linghu, X.; Potnick, J. R.; Johnson, J. S., *J. Am. Chem. Soc.* **2004**, *126*, 3070-3071.

General procedure (A) for the reaction of acylsilanes with β-alkyl substituted unsaturated amides. In the glovebox, 0.42 mmol of acylsilane and 0.46 mmol (1.1 equiv) of amide were added to a dry pear-shaped flask, while 0.083 mmol (0.2 equiv) of the TADDOL-phosphite and 0.29 mmol (0.7 equiv) of lithium hexamethyldisilazide (LHMDS) were added to a dry round-bottom flask with magnetic stir bar. The flasks were removed from the glovebox and 3.0 mL of Et_2O was added to the metallophosphite and stirred under N_2. The acylsilane/amide mixture was added to the metallophosphite via cannula and the delivery flask was rinsed using 7 mL of Et_2O. The resulting mixture was stirred under N_2 at room temperature until starting material was consumed (TLC analysis). The solvent was removed *in vacuo* and an aliquot was taken to determine diastereoselectivity by ^{1}H NMR spectroscopy comparing the integrations of the isolated signals assigned for the protons *ortho* to the ketone carbonyl present at ~8.00 and ~7.80 ppm. The residue was redissolved in THF. The reaction mixture was treated with 0.84 mmol (2.0 equiv) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF and immediately quenched with several milliliters of a saturated aqueous solution of NH_4Cl. The product was then extracted with Et_2O, washed with water (2x), and a saturated aqueous solution of $NaHCO_3$ (2x). The organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated. The product then was purified by flash chromatography, eluting with the indicated solvent system to afford the pure 1,4-dicarbonyl compound.

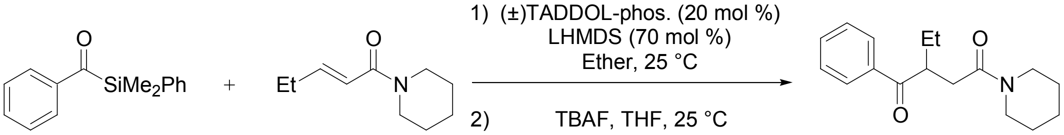
General procedure (B) for the reaction of acylsilanes with β-aryl substituted unsaturated amides. In the glovebox, 0.42 mmol of acylsilane was added to a dry pear-shaped flask, while 0.083 mmol (0.2 equiv) of the TADDOL-phosphite, 0.29 mmol (0.7 equiv) of LHMDS, and 0.63 mmol (1.5 equiv) of the amide were added to a dry round-bottom flask with magnetic stir bar. The flasks were removed from the glovebox and 3.0 mL of Et_2O was added to the metallophosphite mixture and the resulting solution was stirred under N_2. The acylsilane in 5 mL of Et_2O was added very slowly (1 drop/ 2 sec) to the metallophosphite via cannula and the delivery flask was rinsed using 2 mL of Et_2O. The resulting mixture was stirred under N_2 at room temperature until starting material was consumed (TLC analysis). The solvent was removed *in vacuo* and an aliquot was taken to determine diastereoselectivity by ^{1}H NMR spectroscopy comparing the integrations of the isolated signals assigned for the proton alpha to the ketone carbonyl present at ~5.40 and ~5.20 ppm. The residue was re-dissolved in THF. The reaction mixture was treated with 0.84 mmol (2.0 equiv) of a 1 M solution of TBAF in THF was added and immediately quenched with several milliliters of a saturated aqueous solution of NH_4Cl. The product was then extracted with Et_2O, washed with water (2x), and a saturated aqueous solution of $NaHCO_3$ (2x). The organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated. The product then was purified by flash chromatography, eluting with the indicated solvent system to afford the pure 1,4-dicarbonyl compound.



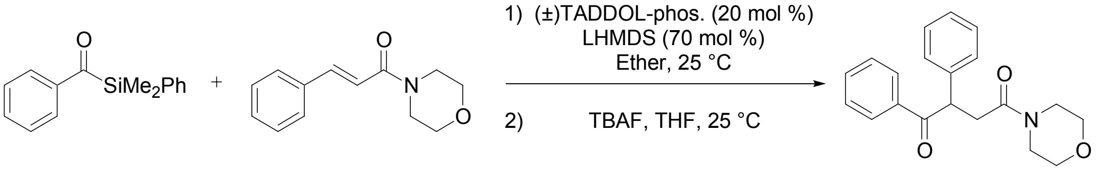
2-Methyl-1-phenyl-4-piperidin-1-yl-butane-1,4-dione (7a, entry 1). The title compound was prepared according to General Procedure **A** using 95 mg of acylsilane, 73 mg of amide, 20 mg of phosphite, 46 mg of LHMDS, and 10 mL of Et_2O. After 2 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4a** = 7:1; δ 7.92 (minor) and δ 7.72 (major). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 30% EtOAc in hexanes to afford 78 mg (76%) of the product as a clear, pale yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3061, 2933, 2856, 1684, 1639, 1444, 1369, 1223, 1196, 1122, 1016, 978, 706; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07-7.98 (m, 2H), 7.54-7.47 (m, 1H), 7.47-7.39 (m, 2H), 4.10-4.00 (m, 1H), 3.53-3.36 (m, 4H), 3.02 (dd, *J* = 16.0, 8.8 Hz, 1H), 2.40 (dd, *J* = 16.4, 4.8 Hz, 1H), 1.66-1.49 (m, 6H), 1.17 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.9, 169.3, 136.1, 132.6, 128.41, 128.40, 46.4, 42.6, 37.0, 36.9, 26.2, 25.4, 24.4, 17.8; TLC (40% EtOAc in hexanes) R_f 0.32; **Anal.** Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.21; H, 8.27; N, 5.29.



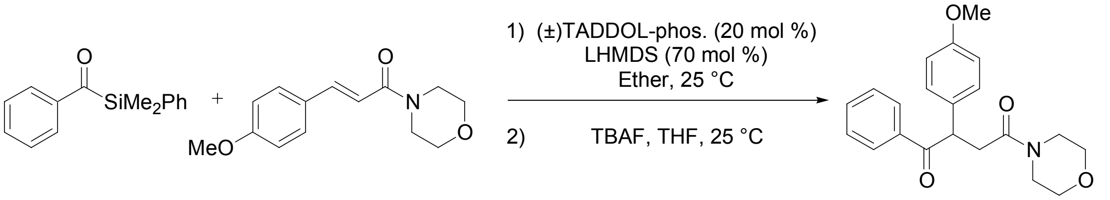
2-Methyl-4-morpholin-4-yl-1-phenyl-butane-1,4-dione (7b, entry 2). The title compound was prepared according to General Procedure **A** using 80.0 mg of acylsilane, 52.0 mg of amide, 34.0 mg of phosphite, 39.0 mg of LHMDS, and 10 mL of Et_2O. After 0.5 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4b** = 4:1; δ 7.93 (minor) and δ 7.82 (major). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 1:1 EtOAc/hexanes to afford 87.0 mg (82%) of the product as a clear, pale yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2974, 2922, 2862, 1670, 1651, 1597, 1579, 1446, 1410, 1279, 1228, 1194, 1113, 1036, 982, 845, 712, 580; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09-7.95 (m, 2H), 7.57-7.38 (m, 3H), 4.13-4.00 (m, 1H), 3.80-3.30 (m, 8H), 3.05 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.39 (dd, *J* = 16.4, 4.4 Hz, 1H), 1.20 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.7, 169.9, 136.0, 132.9, 128.5, 128.4, 66.8, 66.5, 45.8, 41.9, 37.0, 36.6, 18.0; TLC (40% EtOAc in hexanes) R_f 0.14; **Anal.** Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.84; H, 7.32; N, 5.17.



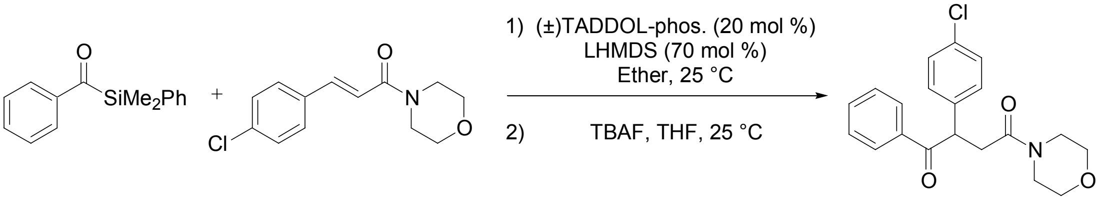
2-Ethyl-1-phenyl-4-piperidin-1-yl-butane-1,4-dione (7c, entry 3). The title compound was prepared according to General Procedure **A** using 99.0 mg of acylsilane, 76.5 mg of amide, 42.6 mg of phosphite, 48.7 mg of LHMDS, and 10 mL of Et_2O. After 0.75 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4c** = 1.3:1; δ 7.92 (major) and δ 7.74 (minor). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 30% EtOAc in hexanes to afford 82.7 mg (74%) of the product as a clear, pale yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3055, 2966, 2941, 2858, 1678, 1632, 1446, 1265, 1227, 1007, 739, 702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10-8.03 (m, 2H), 7.59-7.50 (m, 1H), 7.50-7.43 (m, 2H), 4.03-3.95 (m, 1H), 3.55-3.41 (m, 4H), 3.03 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.47 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.79-1.44 (m, 10H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.0, 169.6, 137.2, 132.7, 128.5, 46.5, 43.6, 42.8, 34.9, 26.4, 25.6, 25.5, 24.5, 11.8 (two coincident aromatic resonances); TLC (40% EtOAc in hexanes) R_f 0.33; **Anal.** Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.39; H, 8.55; N, 5.04.



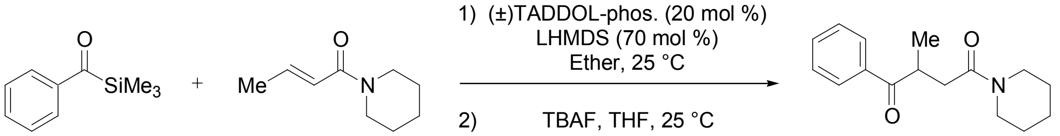
4-Morpholin-4-yl-1,2-diphenyl-butane-1,4-dione (7d, entry 4). The title compound was prepared according to General Procedure **B** using 85 mg of acylsilane, 115 mg of amide, 36 mg of phosphite, 44 mg of LHMDS, and 10 mL of Et_2O. After 5 min at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4d** = 10:1; δ 5.40 (minor) and δ 5.20 (major). The silylated intermediate (**4d**) was run through a silica gel plug with 40% EtOAc in hexanes, concentrated, and re-dissolved in THF. Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 30% EtOAc in hexanes to afford 92 mg (81%) of the product as a white, foamy solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3061, 2966, 2901, 2858, 2247, 1772, 1687, 1639, 1442, 1273, 1117, 1036, 953, 910, 735, 702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05-7.95 (m, 2H), 7.50-7.46 (m, 1H), 7.42-7.19 (m, 7H), 5.26 (dd, J = 10.0, 4.0 Hz, 1H), 3.76-3.38 (m, 9H), 2.66 (dd, J = 16.0, 4.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.1, 169.6, 138.3,136.2, 132.8, 129.0, 128.8, 128.4, 128.1, 127.3, 66.6, 66.3, 49.3, 45.7, 41.9, 37.9; TLC (40% EtOAc in hexanes) R_f 0.19; **Anal.** Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.21; H, 6.65; N, 4.27.



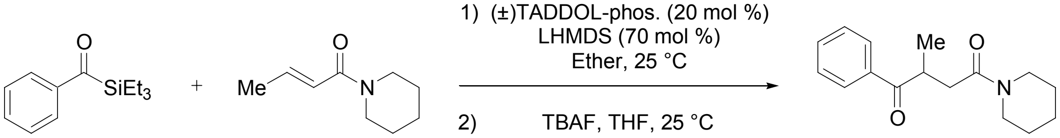
2-(4-Methoxyphenyl)-4-morpholin-4-yl-1-phenyl-butane-1,4-dione (7e, entry 5). The title compound was prepared according to General Procedure **B** using 100.0 mg of acylsilane, 154.0 mg of amide, 43.0 mg of phosphite, 49.0 mg of LHMDS, and 10 mL of Et_2O. After 0.5 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4e** = 11:1; δ 5.32 (minor) and δ 5.12 (major). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 50% EtOAc in hexanes to afford 86.2 mg (59%) of the product as a white solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3481, 3057, 2964, 2924, 2856, 1684, 1643, 1512, 1444, 1362, 1302, 1250, 1180, 1115, 1036, 955, 835, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99-7.96 (m, 2H), 7.46-7.41 (m, 1H), 7.37-7.32 (m, 2H), 7.22-7.19 (m, 2H), 6.81-6.78 (m, 2H), 5.16 (dd, J = 10.0, 4.1 Hz, 1H), 3.72 (s, 3H), 3.70-3.37 (m, 9H), 2.59 (dd, J = 16.0, 4.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.38, 169.84, 158.90, 136.49, 132.72, 130.38, 129.24, 128.84, 128.42, 114.56, 66.79, 66.48, 55.19, 48.69, 45.90, 42.06, 37.92; TLC (40% EtOAc in hexanes) R_f 0.14; mp 63-66 °C; **Anal.** Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.53; H, 6.78; N, 3.80.



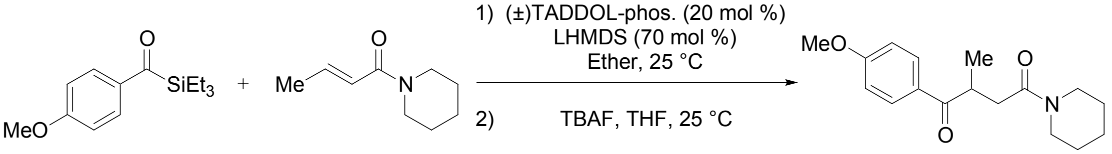
2-(4-Chlorophenyl)-4-morpholin-4-yl-1-phenyl-butane-1,4-dione (7f, entry 6). The title compound was prepared according to General Procedure **B** using 85 mg of acylsilane, 134 mg of amide, 27 mg of phosphite, 48 mg of LHMDS, and 10 mL of Et_2O. After 2 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4f** = 8:1; δ 5.38 (minor) and δ 5.18 (major). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 50% EtOAc in hexanes to afford 99 mg (79%) of the product as a white, foamy solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3062, 2964, 2922, 2858, 2249, 1716, 1682, 1645, 1446, 1362, 1234, 1115, 912, 723; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05-7.93 (m, 2H), 7.52-7.47 (m, 1H), 7.44-7.47 (m, 2H), 7.28-7.27 (s, 1H), 5.23 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.75-3.40 (m, 9H), 2.61 (dd, *J* = 16.0, 4.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.0, 169.4, 137.1, 136.3, 133.4, 133.0, 129.6, 129.3, 128.9, 128.6, 66.8, 66.5, 48.8, 45.9, 42.2, 37.9; TLC (40% EtOAc in hexanes) R_f 0.28; For ^{1}H NMR spectrum, see the Appendix.



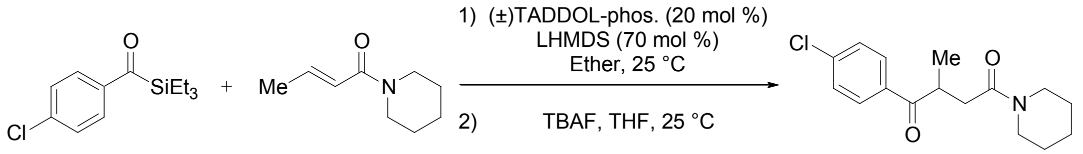
2-Methyl-1-phenyl-4-piperidin-1-yl-butane-1,4-dione (7a, entry 7). The title compound was prepared according to General Procedure **A** using 65.0 mg of acylsilane, 56.0 mg of amide, 37.0 mg of phosphite, 42.0 mg of LHMDS, and 10 mL of Et_2O. After 3 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4g** = 10:1; δ 8.04 (major) and δ 7.97 (minor). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 30% EtOAc in hexanes to afford 76.3 mg (81%) of the product as clear, pale yellow oil. Analytical data for title compound is identical to **7a**.



2-Methyl-1-phenyl-4-piperidin-1-yl-butane-1,4-dione (7a, entry 8). The title compound was prepared according to General Procedure **A** using 80.0 mg of acylsilane, 56.0 mg of amide, 37.0 mg of phosphite, 42.0 mg of LHMDS, and 10 mL of Et_2O. After 2.5 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4h** = 4:1; δ 8.02 (major) and δ 7.95 (minor). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 30% EtOAc in hexanes to afford 86.3 mg (92%) of the product as a clear, pale yellow oil. Analytical data for title compound is identical to **7a**.

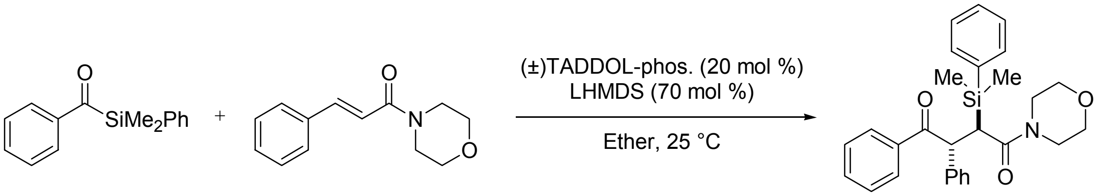


1-(4-Methoxyphenyl)-2-methyl-4-piperidin-1-yl-butane-1,4-dione (7i, entry 9). The title compound was prepared according to General Procedure **A** using 101 mg of acylsilane, 68.4 mg of amide, 40.9 mg of phosphite, 46.5 mg of LHMDS, and 10 mL of Et_2O. After 1 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4i** = 3.5:1; δ 8.01 (major) and δ 7.95 (minor). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 40% EtOAc in hexanes to afford 101 mg (87%) of the product as a white solid. Analytical data for title compound: **IR** (Nujol, cm^{-1}) 3442, 2942, 2922, 2865, 1672, 1633, 1601, 1574, 1508, 1450, 1417, 1244, 1196, 1178, 1028, 976, 850; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 11.6 Hz, 2H), 6.90 (d, *J* = 11.6 Hz, 2H), 4.06-3.97 (m, 1H), 3.82 (s, 3H), 3.52-3.41 (m, 4H), 2.98 (dd, *J* = 16.4, 8.8 Hz, 1H), 2.37 (dd, *J* = 16.4, 5.2 Hz, 1H), 1.62-1.41 (m, 6H), 1.16 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.3, 169.4, 163.2, 130.7, 129.2, 113.6, 55.3, 46.4, 42.6, 36.8, 36.7, 26.3, 25.4, 24.4, 18.0; TLC (40% EtOAc in hexanes) R_f 0.21; mp 87-90 °C; **Anal.** Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.56; H, 8.06; N, 4.64.

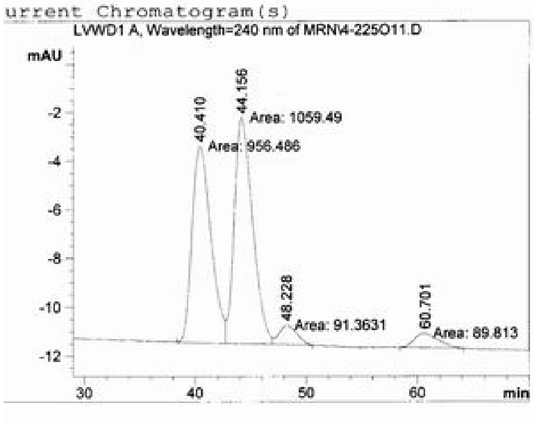


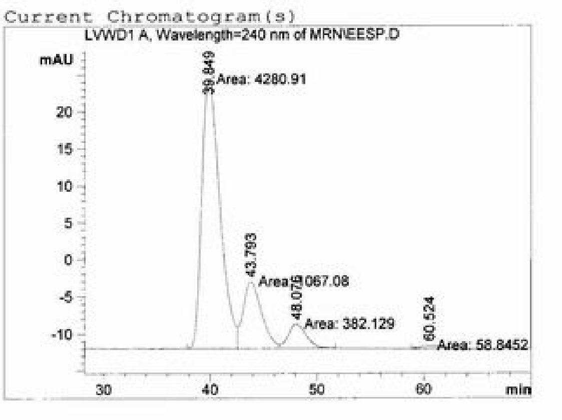
1-(4-Chlorophenyl)-2-methyl-4-piperidin-1-yl-butane-1,4-dione (7j, entry 10). The title compound was prepared according to General Procedure **A** using 92.5 mg of acylsilane, 56.0 mg of amide, 37.0 mg of phosphite, 42.0 mg of LHMDS, and 10 mL of Et_2O. After 2 h at 25 °C, the reaction was complete and the product was analyzed: *d.r.* of **4j** = 3:1; δ 7.96 (major) and δ 7.90 (minor). Following TBAF deprotection and aqueous workup, the product was purified by flash chromatography with 30% EtOAc in hexanes to afford 71.8 mg (67%) of the product as a thick, clear, orange oil. Analytical data for title compound: **IR** (Nujol, cm^{-1}) 3448, 2937, 2922, 2858, 1678, 1632, 1589, 1570, 1458, 1443, 1244, 1221, 1194, 1090, 1016, 980, 843, 748, 517, 480; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.03-3.94 (m, 1H), 3.52-3.37 (m, 4H), 3.03 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.40 (dd, *J* = 16.4, 4.4 Hz, 1H), 1.70-1.40 (m, 6H), 1.15 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.8, 169.2, 139.0, 134.7, 129.9, 128.7, 46.4, 42.7, 37.1, 37.0, 26.3, 25.4, 24.4, 17.7; TLC (40% EtOAc in hexanes) R_i 0.34; **Anal.** Calcd for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.89; N, 4.77. Found: C, 65.38; H, 6.91; N, 4.72.

General procedure (C) for preparation and isolation of 4. In the glovebox, 0.42 mmol of acylsilane was added to a dry pear-shaped flask, while 0.083 mmol (0.2 equiv) of the TADDOL-phosphite, 0.29 mmol (0.7 equiv) of LHMDS, and 0.63 mmol (1.5 equiv) of the amide were added to a dry round-bottom flask with magnetic stir bar. The flasks were removed from the glovebox and 3.0 mL of Et_2O was added to the metallophosphite mixture and the resulting solution was stirred under N_2. The acylsilane in 5 mL of Et_2O was added very slowly (1 drop/2 sec) to the metallophosphite via cannula and the delivery flask was rinsed using 2 mL of Et_2O. The resulting mixture was stirred under N_2 at room temperature until starting material was consumed (TLC analysis). The solvent was removed *in vacuo* and the product was purified by flash chromatography, eluting with the indicated solvent system to afford the pure α-silylated product (**4**).

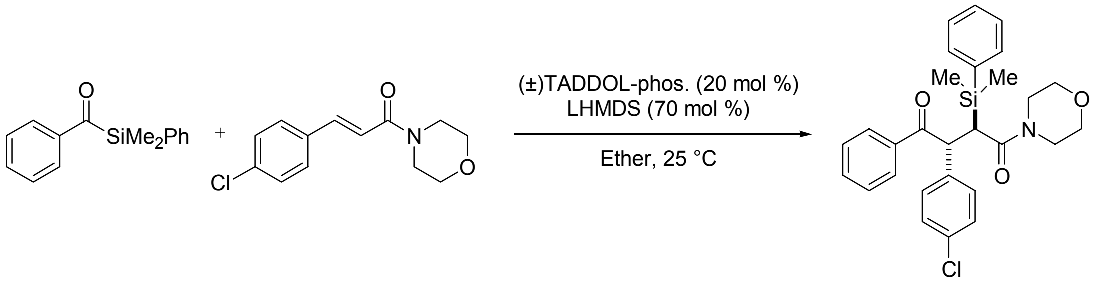


2-(Dimethylphenylsilanyl)-1-morpholin-4-yl-3,4-diphenyl-butane-1,4-dione (4d). The title compound was prepared according to General Procedure **C** using 85 mg of acylsilane, 115 mg of amide, 36 mg of phosphite, 44 mg of LHMDS, and 10 mL of Et_2O. After 5 min at 25 °C, the reaction was complete. The product was purified by flash chromatography with 30% EtOAc in hexanes to afford 131 mg (81%) of the product as a white solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3066, 2960, 2854, 1676, 1614, 1448, 1427, 1281, 1254, 1184, 1115, 1032, 877, 833, 698; **^{1}H NMR** of major anti diastereomer (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2H), 7.58-7.48 (m, 2H), 7.45-7.40 (m, 1H), 7.34-7.14 (m, 9H), 7.13-7.06 (m, 1H), 5.20 (d, J = 11.2 Hz, 1H), 3.58 (d, J = 11.2 Hz), 3.50-3.39 (m, 1H), 3.35-3.26 (m, 1H), 3.26-3.12 (m, 2H), 3.09-2.95 (m, 2H), 2.95-2.80 (m, 2 H), 0.49 (s, 3H), 0.33 (s, 3H); **^{13}C NMR** of major anti diastereomer (100 MHz, $CDCl_3$) δ 198.9, 171.6, 139.0, 136.6, 136.1, 134.4, 132.7, 129.2, 128.4, 128.2, 127.4, 127.0, 66.6, 66.1, 53.5, 46.4, 41.3, 38.2, -1.9, -3.2 (two sets of coincident aromatic resonances); TLC (40% EtOAc in hexanes) major R_f 0.46, minor R_f 0.35; mp 137-139 °C; **Anal.** Calcd for $C_{28}H_{31}NO_3Si$: C, 73.49; H, 6.83; N, 3.06. Found: C, 73.41; H, 6.92; N, 2.96. The major *anti* diastereomer was obtained in 60% ee as determined by chiral CSP-SFC analysis (Chiralcel OD-H, 2.0% MeOH, 2.0 mL/min, 125 bar, 40 °C, 240 nm, $t_{\text{r-major}}$ 39.9 min, $t_{\text{r-minor}}$ 43.8 min) and the minor *syn* diastereomer in 74% ee (Chiralcel OD-H, 2.0% MeOH, 2.0 mL/min, 125 bar, 40 °C, 240 nm, $t_{\text{r-major}}$ 48.1 min, $t_{\text{r-minor}}$ 60.5 min). CSP-SFC chromatograms for both racemic and enantioenriched samples (Scheme 3) are shown below:



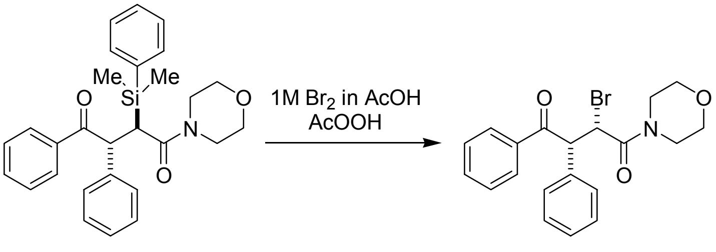


Procedure for the recrystallization of 4d. The product was dissolved in hot ethanol and allowed to cool to room temperature. White, needle-like crystals formed and were taken for X-ray crystallographic analysis.



2-(4-Chlorophenyl)-3-(dimethylphenylsilanyl)-4-morpholin-4-yl-1-phenyl-butane-1,4-dione (4f). The title compound was prepared according to General Procedure **C** using 85 mg of acylsilane, 134 mg of amide, 27 mg of phosphite, 48 mg of LHMDS, and 10 mL of Et_2O. After 5 min at 25 °C, the reaction was complete. The product was purified by flash chromatography with 30% EtOAc in hexanes to afford 153 mg (88%) of the product (dr = 8:1) as a white, foamy solid. Analytical data for title compound: **IR** (thin film, cm^{-1}); 3068, 2962, 2922, 2856, 2247, 1714, 1678, 1620, 1427, 1281, 1115, 1034, 837, 736; ^{1}**H NMR** of major anti diastereomer (400 MHz, $CDCl_3$) δ; 7.78-7.72 (m, 2H), 7.55-7.41 (m, 3H), 7.36-7.28 (m, 2H), 7.27-7.19 (m, 5H), 7.18-7.13 (m, 2H), 5.18 (d, J = 11.4 Hz, 1H), 3.56 (d, J = 11.4 Hz), 3.45-2.93 (m, 8H), 0.48 (s, 3H), 0.32 (s, 3H); ^{13}**C NMR** of major anti diastereomer (100 MHz, $CDCl_3$) δ 198.8, 171.5, 137.6, 136.1, 136.0, 134.4, 133.0, 129.9, 129.4, 128.6, 128.43, 128.37, 127.6, 66.7, 66.2, 52.8, 46.4, 41.4, 38.2, -1.9, -3.2 (two coincident aromatic resonances); TLC (40% EtOAc in hexanes) major R_f, 0.35 minor; R_f, 0.25; **Anal.** Calcd for $C_{28}H_{30}ClNO_3Si$: C, 68.34; H, 6.14; N, 2.85. Found: C, 68.08; H, 6.14; N, 2.68.

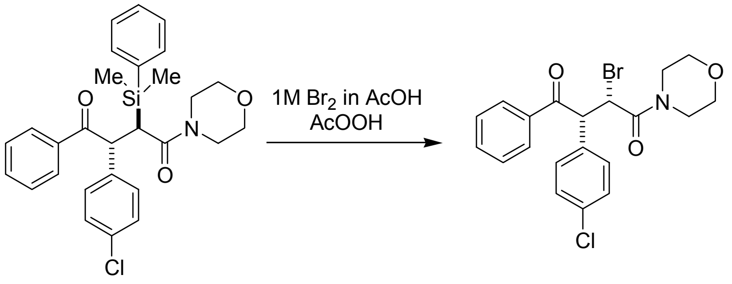
General procedure (D) for the bromination of 4. To a round-bottom flask with magnetic stir bar, 0.55 mmol of **4** was dissolved in 1.7 mmol of AcOOH (32 wt % in AcOH, 3 equiv). Via pipet, 1.7 mmol (3 equiv) of a 1 M Br_2 solution in AcOH was added and the reaction was stirred overnight at room temperature. After 12 h, the starting material had been consumed (TLC analysis). The reaction mixture was diluted with EtOAc and a saturated aqueous solution of $Na_2S_2O_3$ was added drop wise until orange color had dispersed. The product was then washed with water (2x), and a saturated aqueous solution of $NaHCO_3$ (2x). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The product then was purified by flash chromatography, eluting with the indicated solvent system to afford pure **8**.



4d

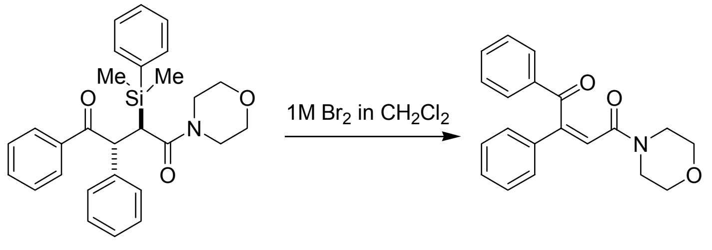
2-Bromo-1-morpholin-4-yl-3,4-diphenyl-butane-1,4-dione (8d). The title compound was prepared according to General Procedure **D** using 253 mg of **4d**, 0.35 mL of AcOOH (32 wt % in AcOH), and 1.7 mL of a 1 M Br_2 solution in AcOH. The product then was purified by flash chromatography, eluting with 30% EtOAc in hexanes to afford 221 mg (76%) of the product (dr 3:1) as a white solid. Analytical data for title compound: **IR** (Nujol, cm^{-1}) 2958, 2927, 2850, 1732, 1662, 1597, 1491, 1458, 1377, 696; **^{1}H NMR** of major syn diastereomer (400 MHz, $CDCl_3$) δ 8.00-7.9 (m, 2H), 7.51-7.43 (m, 1H), 7.42-7.25 (m, 7H), 5.38 (d, *J* = 10.8 Hz, 1H),5.10 (d, *J* = 10.4 Hz, 1H), 3.89-3.52 (m, 8H); **^{13}C NMR** of major syn diastereomer (100 MHz, $CDCl_3$) δ 198.6, 167.3, 135.4, 135.0, 133.3, 129.1, 129.0, 128.8, 128.5, 128.1, 66.6, 66.3, 57.3, 47.0, 46.6, 42.8; TLC (40% EtOAc in hexanes) major R_f 0.47, minor R_f 0.33; mp 135 °C (decomp.); **Anal.** Calcd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01; N, 3.48. Found: C, 59.37; H, 5.08; N, 3.42.

Procedure for the re-crystallization of 8d. The product was dissolved in hot ethyl acetate and allowed to cool to room temperature. White, cubic crystals formed and were taken for X-ray crystallographic analysis.



4f

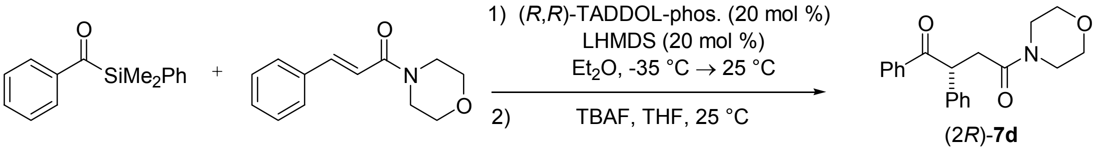
2-Bromo-3-(4-chloro-phenyl)-1-morpholin-4-yl-4-phenyl-butane-1,4-dione (8f). The title compound was prepared according to General Procedure **D** using 120 mg of **4f**, 2 mL of AcOOH (32 wt % in AcOH), and 2 mL of a 1 M Br_2 solution in AcOH. The product then was purified by flash chromatography, eluting with 33% EtOAc in hexanes to afford 92 mg (87 %) of the product (dr 3:1) as a white, foamy solid. Analytical data for title compound: **IR** (Nujol mull, cm^{-1}) 2954, 2872, 2723, 2669, 1716, 1651, 1595, 1462, 1377, 1286, 1269, 1220, 1171, 1115, 1093, 1034, 721; **^{1}H NMR** of major syn diastereomer (400 MHz, $CDCl_3$) δ 8.00-7.91 (m, 2H), 7.51-7.43 (m, 1H), 7.40-7.35 (m, 2H), 7.33 (s, 4H), 5.37 (d, *J* = 10.4 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 3.85-3.53 (m, 8H); **^{13}C NMR** of major syn diastereomer (100 MHz, $CDCl_3$) δ 198.4, 167.1, 135.2, 134.3, 133.6, 130.5, 129.2, 128.8, 128.7 (two coincident resonances) 66.6, 66.3, 56.6, 46.7, 42.8 (two coincident resonances); TLC (33% EtOAc in hexanes) R_f 0.22 (the diastereomers coelute); **LRMS** (ES): 438.1, 436.2 $[M+H]^+$ (2 major isotopomers). For ^{1}H NMR spectrum, see the Appendix.



4a **9**

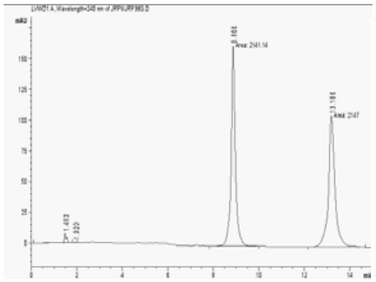
Procedure for synthesis of (*Z*)-4-Morpholin-4-yl-1,2-diphenyl-but-2-ene-1,4-dione (9) from 4a. To a 20-mL scintillation vial with magnetic stir bar was added 80.0 mg of **4a** and 1.5 mL CH_2Cl_2. To this solution was added 0.53 mL of a 1 M Br_2 solution in CH_2Cl_2 (3 eq) via pipet and the reaction mixture was stirred at room temperature overnight. After 12 h, the starting material had been consumed (TLC analysis). The reaction mixture was diluted with Et_2O and a saturated aqueous solution of $Na_2S_2O_3$ was added drop wise until the orange color disappeared. The organic layer was separated and washed with water (2x), and a saturated aqueous solution of $NaHCO_3$ (2x). The organic extracts were dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography (gradient elution EtOAc in hexanes 40% - 70%) to afford 56 mg (100%) of a single isomer of the product (**9**) as a white solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3467, 3060, 2968, 2922, 2858, 1672, 1635, 1597, 1456, 1437, 1275, 1228, 1115, 1047, 916, 850, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2H), 7.45-7.41 (m, 2H), 7.04-6.97 (m, 6H), 6.37 (s, 1H), 3.37-2.70 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.33, 164.49, 153.63, 136.78, 135.45, 133.56, 130.25, 129.49, 129.47, 129.06, 127.16, 118.83, 67.12; TLC (40% EtOAc in hexanes) R_f 0.16; mp 128-129 °C; **Anal.** Calcd for

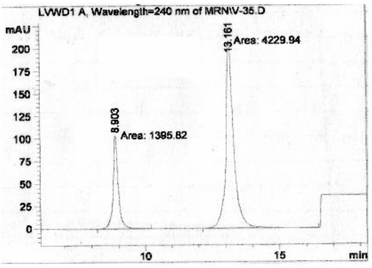
$C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.85; H, 6.08; N, 4.46. The relative stereochemistry was determined by NOESY analysis. (See Appendix for NOESY spectrum).

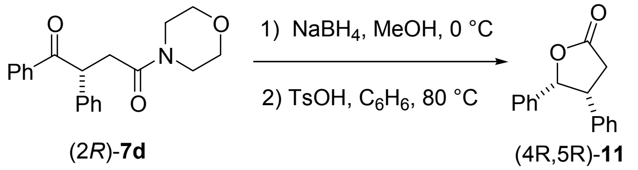


(2*R*)-**7d**

Procedure for the enantioselective reaction of benzoyl dimethylphenylsilane with morpholine cinnamamide. In the glovebox, 100 mg (0.42 mmol, 1.0 equiv) of acylsilane were added to a dry, 20-mL scintillation vial, while 42.6 mg (0.083 mmol, 0.2 equiv) of the (*R*,*R*)-TADDOL-phosphite, 13.9 mg (0.083 mmol, 0.2 equiv) of LHMDS, and 136 mg (0.63 mmol, 1.5 equiv) of the amide were added to a second dry 20-mL scintillation vial. Four mL of Et_2O were added to the metallophosphite mixture in order to dissolve all of the contents of the vial, 2 mL of Et_2O were added to the acylsilane, and both vials were placed in the freezer at -35 °C. After 0.5 hr, the vials were removed from the freezer and the acylsilane solution was added to the metallophosphite mixture slowly (1 drop/sec) via pipette and allowed to warm to room temperature. After the starting material was consumed (TLC analysis), the solvent was removed *in vacuo*. The silylated intermediate was passed through a silica gel plug using 40% EtOAc in hexanes, concentrated, and re-dissolved in THF. The reaction mixture was treated with .32 mL (0.84 mmol, 2.0 equiv) of a 1 M solution of TBAF in THF and was immediately quenched with several milliliters of a saturated aqueous solution of NH_4Cl. The product was then extracted with Et_2O and washed with water (2x). The organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated. The product then was purified by flash chromatography, eluting with 50% EtOAc/hexanes to afford 83.1 mg (68%) of the product as a white, foamy solid in 50% ee as determined by chiral CSP-SFC analysis ((*S,S*)-Whelk-O1, 10.0% MeOH, 2.0 mL/min, 200 bar, 40 °C, 240 nm, $t_{\text{r-major}}$ 13.2 min, $t_{\text{r-minor}}$ 8.9 min); $[\alpha]_D^{25}$ +126 (c = 0.5, CH_2Cl_2); CSP-SFC chromatograms for both racemic and 50% ee samples are shown below:







Assignment of absolute configuration for enantioenriched 7d. To a solution of 72 mg (0.23 mmol, 1.0 equiv) of ketone **7d** in MeOH (6 mL) at 0 °C was added 10 mg (0.28 mmol, 1.2 equiv) of $NaBH_4$ with stirring. After 30 min, the excess borohydride was destroyed by careful addition of 1 M HCl and then 10 ml of H_2O. The resulting mixture was extracted with ether (2x). The organic extracts were combined and washed with water (2 x 10 mL), a saturated aqueous solution of $NaHCO_3$ (2 x 10 mL) and brine. The organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford the crude secondary alcohol (dr >10:1) which was used without further purifications.

p-Toluenesulfonic acid (21 mg, 0.11 mmol, 0.5 equiv) was added to a solution of the crude secondary alcohol in C_6H_6 (15 mL). The resulting mixture was stirred at 25 °C for 12 h and refluxed for 4 h. After the reaction was cooled to 25 °C, 15 mL of H_2O was added. The resulting mixture was extracted with ether (2x). The organic extracts were combined and washed with a saturated aqueous solution of $NaHCO_3$ (2 x 10 mL), 10 mL of H_2O, and brine. The organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford the crude lactone product that was purified by flash chromatography (3.5:1 hexanes:EtOAc) to afford 30 mg (58%, two steps) of the pure *cis*-diastereomer of **11** (according to reported ^{1}H NMR and mp)[4] as a white solid. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3470, 3064, 3032, 2929, 1778, 1604, 1635, 1498, 1456, 1415, 1319, 1304, 1288, 1174, 1144, 1029, 980, 881, 723, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20-7.05 (m, 6H), 6.95-6.77 (m, 4H), 5.82 (d, *J* = 6.4 Hz, 1H), 4.06 (ddd, *J* = 8.0, 6.4, 6.4 Hz, 1H), 3.05 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.94 (dd, *J* = 17.2, 6.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.5, 136.6, 135.5, 128.2, 127.93, 127.86, 127.8, 127.3, 125.7, 84.6, 46.9, 34.9; TLC (3:1 hexanes:EtOAc) R_f 0.33; mp 91.5-93.5 °C (Lit.:[4] mp 90-92 °C for cis-isomer, 100-102 °C for trans-isomer); $[\alpha]_D^{25}$ +54 (c = 0.35, $CHCl_3$) (Lit.:[4] $[\alpha]_D^{25}$ +48 (c = 1.0, $CHCl_3$) for (4*R*,5*R*)-cis-isomer). (See Appendix for ^{1}H NMR spectrum).

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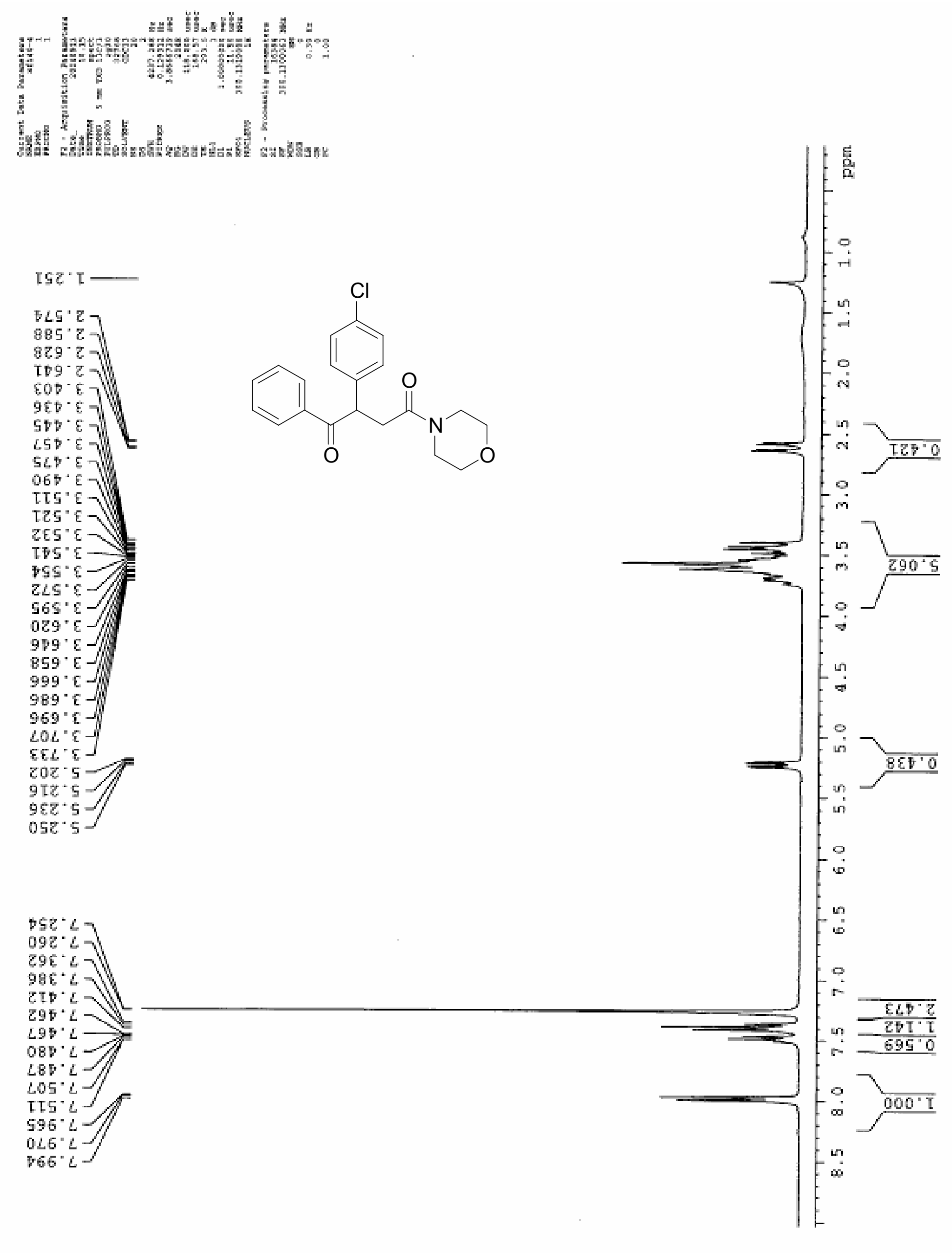
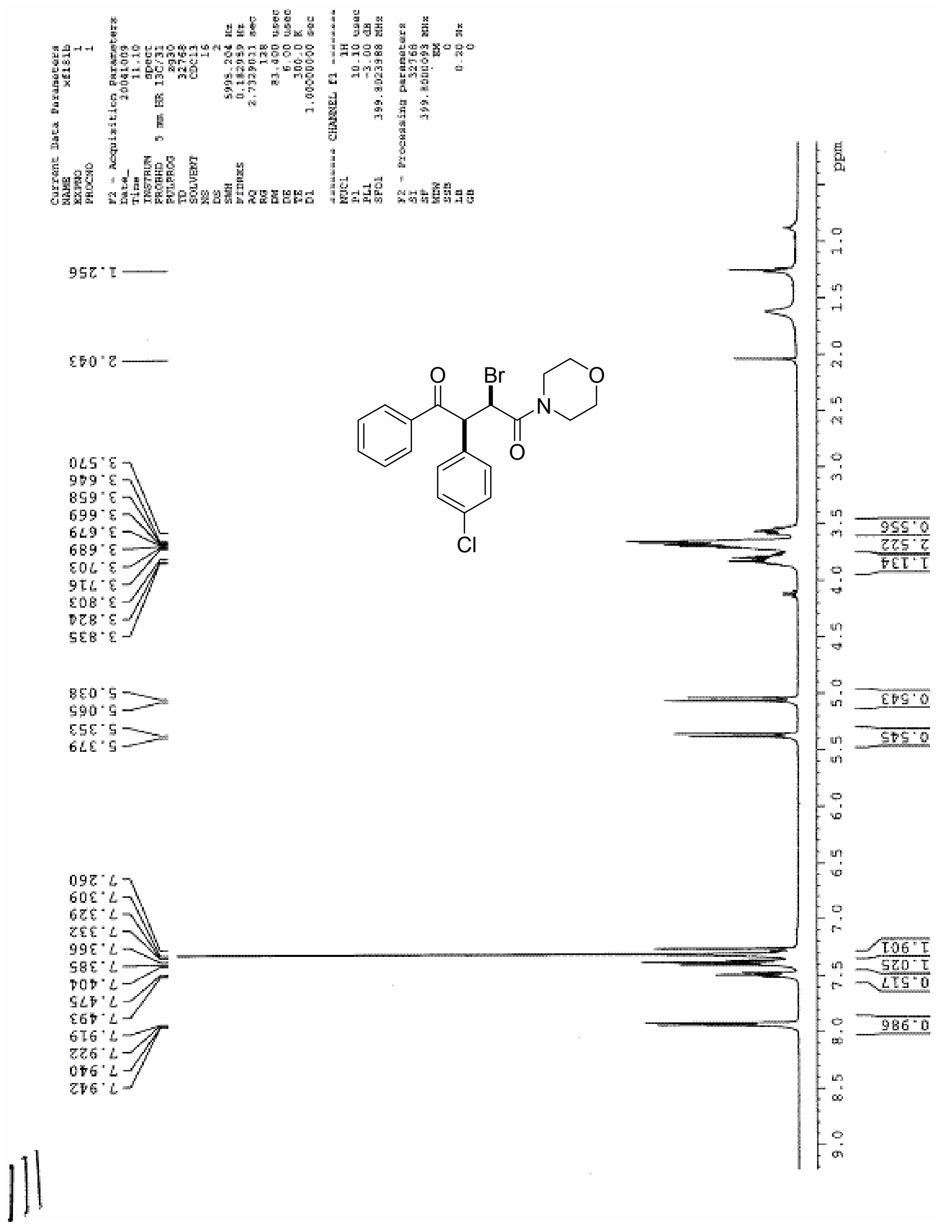
[4] C. J. Chang, J. M. Fang, L. F. Liao, *J. Org. Chem.* **1993**, *58*, 1754-1761.

Appendix

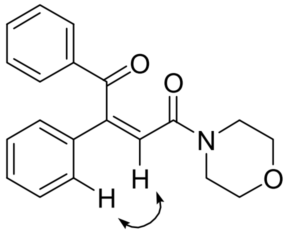
^{1}H NMR in $CDCl_3$ for (**7f**, **entry 6**)



^{1}H NMR in $CDCl_3$ for (**10f**)

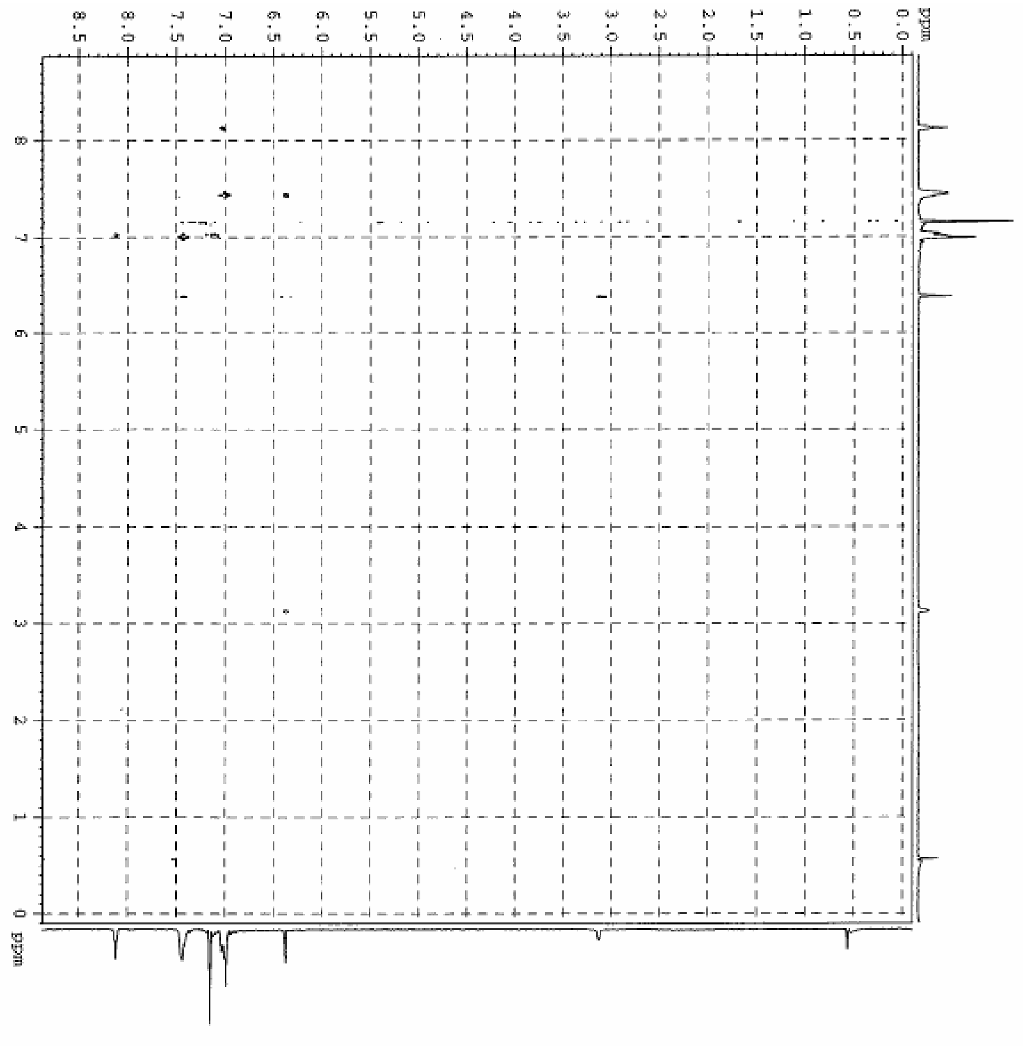


NOESY Spectrum for **9**



9

NOE
present



^{1}H NMR in $CDCl_3$ for (**11**)