Catalytic Enantioselective Michael Additions to Unsaturated Ester Derivatives Using Chiral Copper(II) Lewis Acid Complexes

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General Information. Unless noted, all reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Dichloromethane, hexanes, and benzene were distilled from calcium hydride under nitrogen. Toluene was distilled from potassium under nitrogen. Methanol was distilled from magnesium under nitrogen, and the remaining alcohols were distilled from CaO under nitrogen. Tetrahydrofuran and ether were distilled from benzophenone ketyl under nitrogen. $CuCl_2$ and $AgSbF_6$ were purchased from Cerac and used without further purification. $Cu(OTf)_2$ was purchased from Aldrich Chemical Co. and used without further purification. Purification of reaction products was carried out by flash chromatography using EM Reagents silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating.

Melting points were measured with a Büchi SMP-20 melting point apparatus equipped with an Omega Model 450 AET thermocouple and are uncorrected. Infrared spectra were recorded on a Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. In situ IR spectra were recorded on a ReactIR 1000 from ASI Applied Systems (Millersville, MD; www.asirxn.com) fitted with an immersible DiComp ATR probe. The spectra were acquired using 128 scans per spectrum at a resolution of 8 using ReactIR 2.1 software. Graphs were constructed by exporting raw data points (A vs. t) to Microsoft Excel 98 for further manipulation.

^1H NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a Bruker AM-400 (100 MHz) spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm and d_6-benzene at 128.5 ppm). Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Electrospray mass spectra were obtained using a LCT mass spectrometer (Micromass Instruments, Beverly, MA). Exact mass measurements were obtained by internal calibration with an appropriate lock mass compound. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1050 Series HPLC equipped with a variable wavelength detector using a Chiralcel AD, OD-H or OJ column (0.46 cm x 25 cm) from Daicel. X-Ray crystallographic data was collected using a Siemens SMART CCD (charge coupled device) based diffractometer equipped with an LT-2 low-temperature apparatus operating at 213 K.

General procedure for the preparation of ketene acetals. The thioester[2] (1 eq) was added to a cold (-78 °C) 0.4 M solution of lithium diisopropylamide (1.2 eq) in THF and stirred for 1 h before the addition of chlorotrimethylsilane (1.1 eq). The reaction mixture was warmed to ambient temperature over a four

(1) Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pregamon Press, Oxford, 1988.

(2) We have noted that thioesters can be prone to the production of a white precipitate. This precipitate persists during the distillation process, sometimes forming more rapidly as a result of the distillation. Filtering of the enolsilane through a silica gel plug using 10% ether in hexanes effectively removes the solids, providing after concentration a clear distillable liquid free of this contaminant.

hour period of time, diluted with pentane, washed with phosphate buffer (pH=7) and 0.5 M aq $CuSO_4$, and dried (Na_2SO_4). Removal of the solvent and distillation of the crude liquid under reduced pressure afforded the desired ketene thioacetal.[3] Isomerization of the enolsilane olefin can occur if the pot temperature exceeds 110 °C.

General procedure for the preparation of (Z)-ketene thioacetals. *In most cases, it was necessary to use freshly dried/distilled reagents immediately prior to use in order to attain the highest levels of stereoselectivity (>95:5).* The Collum procedure[4] was followed: A chilled (0 °C) slurry of TMP•HBr (1.3 eq, 0.09 M in THF) was treated with *n*-BuLi (2.4 eq, 1.6 M in hexanes), stirred for 5 min, and cooled to –78 °C. A solution of the thioester (1.0 eq, 0.5 M in THF) was cannulated into the light yellow solution and stirred an additional 30 m. Chlorotrimethylsilane (2 eq) and triethylamine (0.5 eq) were added, and the solution was warmed to 0 °C over a 4 h period before diluting with pentane, washing with phosphate buffer (pH=7) and 0.5M aq $CuSO_4$. The organic layer was dried (Na_2SO_4) and concentrated to furnish a liquid that was distilled under reduced pressure.

General procedure for the preparation of (*E*)-ketene thioacetals. *In most cases, it was necessary to use freshly dried/distilled reagents immediately prior to use in order to attain the highest levels of stereoselectivity (>95:5).* The Ireland[5] procedure was adapted: A solution of LDA (1 eq) and HMPA (23% v/v)was stirred for 10 m prior to cooling (-78 °C) and treatment with the thioester (1.1 eq). The solution was stirred for 15 m, treated with chlorotrimethylsilane (1 eq), and warmed slowly to 0 °C. The crude mixture was diluted with pentane, washed with phosphate buffer (pH=7) and 0.5 M $CuSO_4$, and dried (Na_2SO_4) prior to concentration under reduced pressure. The crude liquid was distilled under vacuum to furnish the title compound as a colorless liquid.

General procedure for the catalyzed reaction of enolsilanes with Michael acceptors 1 using complex 2. A dry 1-dram vial with magnetic stirrer was charged with (*S*,*S*)-*tert*-Bu-box copper(II) chloride complex[6] (0.1 eq, 12.8 mg, 25 μmol) and silver hexafluoroantimonate (0.2 equiv, 17.2 mg, 50 μmol) in an inert atmosphere (N_2) glove box. The flask was fitted with a septum, brought out of the glove box, and CH_2Cl_2 (0.5 mL) was added by syringe. The mixture was stirred in the dark for 1 h to produce a cloudy green mixture that was filtered through a plug of dry Celite directly into a flask containing the substrate in CH_2Cl_2 (0.2 mL) precooled to the desired reaction temperature. In experiments using an alcohol additive, the neat alcohol (1 equiv) was added at this time. The resulting blue solution was then treated with the enolsilane. After the indicated time, the reaction mixture was quenched with 2:1 (v/v) 3 M NH_4OH/saturated aqueous NaCl (1 mL). After warming to ambient temperature, the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography on silica gel with the indicated solvent system afforded the pure products which were then assayed for stereochemical composition using the indicated instrumental technique. Authentic racemic samples were prepared under similar conditions using tin(IV) chloride (1.5 eq) at -78 °C.

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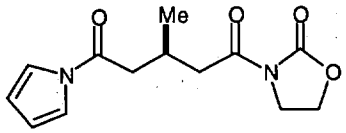
(3) Enolsilane analytical data: Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, in press. *tert*-Butyl thioester enolsilane: Gerlach, H.; Kunzler, P. *Helv. Chim. Acta* **1978**, *61*, 2503-2509.

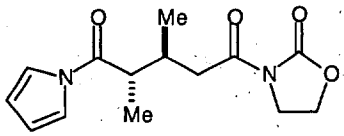
(4) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571-9574.

(5) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877. We have also occasionally used the Fukuzumi-Otera protocol: Otera, J.; Fujita, Y.; Fukuzumi, S. *Synlett* **1994**, 213-214.

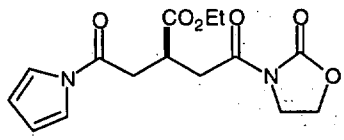
(6) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541-4544. The ligand is also available from Aldrich Chemical.



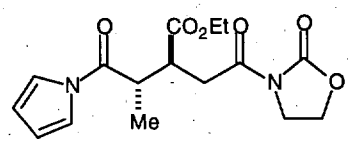
According to the general procedure, a solution of crotonylimide (19.3 mg, 0.125 mmol) was treated with the catalyst (5 mol%) and hexafluoroisopropanol (13 μL, 0.125 mmol), followed by the addition of acetyl pyrrole enolsilane (47 μL, 0.25 mmol). After 15 min at -20 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (29.4 mg, 90%). HPLC analysis (Chiralcel AD, 10% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (minor) = 10.7, t_r (major) = 12.9 gave the isomeric composition of the product: 91% ee. IR (film) 1779, 1716 (br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (br s, 2H), 6.28 (d, *J* = 2.3 Hz, 2H), 4.40 (td, *J* = 8.0, 1.4 Hz, 2H), 4.00 (t, *J* = 8.0 Hz, 2H), 3.03 (dd, *J* = 15.2, 5.3 Hz, 1H), 2.99 (d, *J* = 6.8 Hz, 2H), 2.74 (m, 1H), 2.66 (dd, *J* = 15.2, 7.8 Hz, 1H), 1.11 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.9, 169.4, 153.5, 119.0, 113.0, 62.0, 42.4, 41.5, 41.0, 26.6, 20.2; TLC (30% EtOAc/hexanes) R_f 0.083; HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O_4$ [M]$^+$, 264.1110. Found 264.1101; Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10. Found: C, 58.90; H, 6.10.



According to the general procedure, a solution of crotonylimide (19.3 mg, 0.125 mmol) was treated with the catalyst (5 mol%) and hexafluoroisopropanol (13 μL, 0.125 mmol), followed by the addition of propionyl pyrrole enolsilane (52 μL, 0.25 mmol, *Z*:*E* = >98:2). After 1 hour at -20 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (30.4 mg, 88%). HPLC analysis (Chiralcel AD, 10% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (d1, major) = 26.9, t_r (d2, major) = 30.1, t_r (d2, minor) = 32.8, t_r (d1, minor) = 36.2 gave the isomeric composition of the product: dr = >99:1, 98% ee. IR (film) 1779, 1707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (br d, 2H), 6.30 (dd, *J* = 2.4, 2.4 Hz, 2H), 4.40 (dd, *J* = 8.0, 8.0 Hz, 2H), 4.00 (ddd, *J* = 9.0, 8.0, 1.6 Hz, 2H), 3.22-3.16 (m, 1H), 3.16 (dd, *J* = 17.0, 4.6 Hz, 1H), 2.82 (dd, *J* = 17.0, 8.4 Hz, 1H), 2.63-2.53 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.6, 172.1, 153.4, 119.1, 113.2, 62.0, 42.49, 42.45, 37.9, 32.4, 18.4, 14.4; TLC (30% EtOAc/hexanes) R_f 0.10; HRMS (electrospray): Exact mass calcd for $C_{14}H_{18}N_2NaO_4$ [M+Na]$^+$, 301.1164. Found 301.1169; Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52. Found: C, 60.70; H, 6.54.

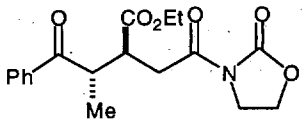


According to the general procedure, a solution of fumaroylimide (26.6 mg, 0.125 mmol) was treated with the catalyst (5 mol%) and hexafluoroisopropanol (13 μL, 0.125 mmol), followed by the addition of acetyl pyrrole enolsilane (47 μL, 0.25 mmol). After 2 hours at -20 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (36.9 mg, 92%). HPLC analysis (Chiralcel AD, 30% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (d1, minor) = 20.5, t_r (d2, major) = 23.8, gave the isomeric composition of the product: 95% ee. IR (film) 1778, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (br s, 2H), 6.27 (d, *J* = 2.4 Hz, 2H), 4.41 (t, *J* = 8.2 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.99 (t, *J* = 8.2 Hz, 2H), 3.53 (ddd, *J* = 12.6, 6.3, 6.3 Hz, 1H), 3.44 (dd, *J* = 18.1, 6.6 Hz, 1H), 3.63 (dd, *J* = 17.2, 6.1 Hz, 1H), 3.27 (dd, *J* = 18.1, 5.7 Hz, 1H), 3.09 (dd, *J* = 17.2, 6.8 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.1, 171.0, 168.3, 153.4, 118.9, 113.3, 62.2, 61.2, 42.3, 36.3, 36.2, 35.4, 13.9; TLC (30% EtOAc/hexanes) R_f 0.061; HRMS (electrospray): Exact mass calcd for $C_{15}H_{19}N_2O_6$ [M+H]$^+$, 323.1243. Found 323.1228; Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.63. Found: C, 55.91; H, 5.66.

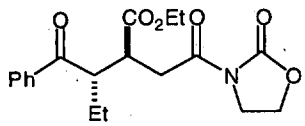


According to the general procedure, a solution of fumaroylimide (26.6 mg, 0.125 mmol) was treated with the catalyst (5 mol%) and hexafluoroisopropanol (13 μL, 0.125 mmol), followed by the addition of propionyl pyrrole enolsilane (52 μL, 0.25 mmol, *Z*:*E* = >98:2). After 1 hour at -20 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (38.2 mg, 91%). HPLC analysis (Chiralcel AD, 10%

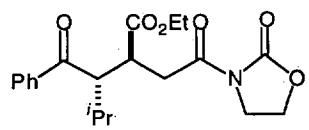
^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (d1, major) = 39.4, t_r (d2, major) = 42.6, t_r (d2, minor) = 44.6, t_r (d1, minor) = 56.9 gave the isomeric composition of the product: dr = 97:3, 94% ee. IR (film) 1780, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 2H), 6.30 (br d, *J* = 2.7 Hz, 2H), 4.42 (t, *J* = 8.3 Hz, 2H), 4.12-4.04 (m, 2H), 4.03-3.94 (m, 2H), 3.69 (ddd, *J* = 13.9, 7.0 Hz, 1H), 3.50-3.43 (m, 2H), 3.29 (ddd, *J* = 16.2, 7.0, 7.0 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.7 (2C), 171.3, 153.4, 119.1, 113.4, 62.2, 61.3, 42.7, 42.4, 38.5, 33.0, 14.5, 13.7; TLC (30% EtOAc/hexanes) R_f 0.081; HRMS (electrospray): Exact mass calcd for $C_{16}H_{20}N_2NaO_6$ $[M+Na]^+$, 359.1219. Found 359.1203; Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99. Found: C, 57.06; H, 6.09.



According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (19 μL, 0.18 mmol), followed by the addition of propiophenone enolsilane (58 μL, 0.25 mmol, *Z*:*E* = >98:2). After 20 hours at 0 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (43.0 mg, 99%). HPLC analysis (Chiralcel AD, 40% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (d1, major) = 23.1, t_r (d2, major) = 25.0, t_r (d1, minor) = 28.8, t_r (d2, minor) = 31.7 gave the isomeric composition of the product: dr = 95:5, 92% ee. IR (film) 1781, 1729, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.55 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.46 (dd, *J* = 7.9, 7.9 Hz, 2H), 4.40 (dd, *J* = 8.1, 8.1 Hz, 2H), 4.12-3.92 (series of m, 5H), 3.49-3.39 (m, 2H), 3.20 (d, *J* = 14.4 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.9, 173.4, 171.5, 153.4, 135.8, 133.0, 128.6, 128.3, 62.1, 61.0, 42.4, 42.4, 40.6, 33.1, 14.0, 13.9; TLC (40% EtOAc/hexanes) R_f 0.12; HRMS (EI): Exact mass calcd for $C_{18}H_{21}NO_6$ $[M]^+$, 347.1369. Found 347.1355; Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09. Found: C, 62.01; H, 6.22.

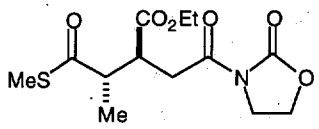


According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (19 μL, 0.18 mmol), followed by the addition of butyrophenone enolsilane (58 μL, 0.25 mmol, *Z*:*E* = >98:2). After 20 hours at 0 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil that slowly crystallized (43.4 mg, quant), mp, 79-81 °C. HPLC analysis (Chiralcel AD, 20% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (d1, major) = 20.0, t_r (d2, minor) = 21.8, t_r (d2, minor) = 23.5, t_r (d1, major) = 25.5 gave the isomeric composition of the product: dr = 100:1, 94% ee. IR (film) 1780, 1729, 1692, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.57 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.47 (dd, *J* = 7.7, 7.7 Hz, 2H), 4.40 (dd, *J* = 8.1, 8.1, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.98 (dd, *J* = 7.8, 7.8 Hz, 2H), 3.95-3.91 (m, 1H), 3.46 (d, *J* = 14.8 Hz, 1H), 3.46-3.41 (m, 1H), 3.14 (d, *J* = 14.8 Hz, 1H), 1.91-1.80 (m, 1H), 1.63-1.53 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.6, 173.4, 171.6, 153.4, 136.9, 133.1, 128.7, 128.4, 62.1, 61.1, 47.2, 42.4, 41.8, 33.2, 21.7, 13.9, 11.7; TLC (30% EtOAc/hexanes) R_f 0.10; HRMS (CI, NH_3): Exact mass calcd for $C_{19}H_{27}N_2O_6$ $[M+NH_4]^+$, 379.1869. Found 379.1856; Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41. Found: C, 62.98; H, 6.40.



According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (19 μL, 0.18 mmol), followed by the addition of isovalerophenone enolsilane (64 μL, 0.25 mmol, Z:E = >98:2). After 20 hours at 0 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (45.0 mg, 99%). HPLC analysis (Chiralcel OJ, 10% EtOH/hexanes, 0.5 mL/min, 254 nm; t_r (d1, major) = 21.9, t_r (d1, minor) = 31.3 (minor diastereomer not observed) gave the isomeric composition of the product: dr = >99:1, 94% ee. IR (film) 1781, 1728, 1692, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.2,

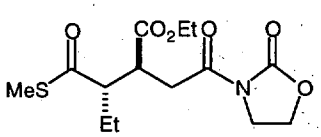
1.4 Hz, 2H), 7.58-7.54 (m, 1H), 7.47 (dd, *J* = 7.8, 7.8, 2H), 4.41 (dd, *J* = 8.1, 8.1 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 4.04-3.98 (m, 1H), 3.97-3.93 (m, 2H), 3.54 (dd, *J* = 17.5, 9.3 Hz, 1H), 3.49-3.44 (m, 1H), 3.21 (dd, *J* = 17.5, 2.8 Hz, 1H), 2.21 (dq, *J* = 13.8, 6.9 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 202.1, 175.5, 173.6, 171.7, 138.0, 133.0, 128.6, 128.4, 62.1, 61.1, 51.2, 42.4, 41.0, 33.2, 28.0, 21.1, 19.6, 13.9; TLC (30% EtOAc/hexanes) R_f 0.10; HRMS (CI, NH_3): Exact mass calcd for $C_{20}H_{29}N_2O_6$ $[M+NH_4]^+$, 393.2026. Found 393.2020; Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 63.73; H, 6.70.



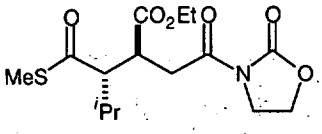
According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (13 μL, 0.12 mmol), followed by the addition of methylthio propionate enolsilane (47 μL, 0.25 mmol, *Z*:*E* = >98:2). After 10 hours at -78 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (35.2 mg, 93%). HPLC analysis (Chiralcel AD, 15% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, major) = 21.0, t_r (*anti*, minor) = 24.3, t_r (*syn*, major) = 26.4, t_r (*syn*, minor) = 30.9 gave the isomeric composition of the product: dr = 90:10, 83% ee. IR (film) 1783, 1730, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, *J* = 8.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.04-3.96 (m, 2H), 3.49-3.41 (m, 2H), 3.15 (qd, *J* = 7.1, 4.6 Hz, 1H), 3.01 (ddd, *J* = 16.4, 7.6, 7.6 Hz, 1H), 2.29 (s, 3H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.4, 172.7, 171.3, 153.4, 62.1, 61.0, 48.1, 42.4, 42.3, 33.0, 14.0, 13.7, 11.5; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{13}H_{19}NaNO_6S$ $[M+Na]^+$, 340.0831. Found 340.0826. Anal. Calcd for $C_{13}H_{19}NO_6S$: C, 49.20; H, 6.03. Found: C, 49.30; H, 6.12.

In the absence of HFIP, the product was obtained in 97% yield and as a 95:5 mixture of diastereomers, the major isomer in 89% ee.

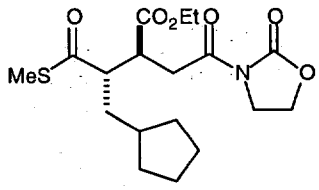
Using TMS-X (47 μL, 0.25 mmol, *E*:*Z* = >98:2), the *syn* diastereomer predominated. HPLC analysis (Chiralcel AD, 15% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, major) = 21.0, t_r (*anti*, minor) = 24.3, t_r (*syn*, major) = 26.4, t_r (*syn*, minor) = 30.9 gave the isomeric composition of the product: dr = 63:37, 75% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, *J* = 8.1 Hz, 2H), 4.23-4.11 (m, 2H), 3.98 (td, *J* = 7.7, 2.3 Hz, 2H), 3.42 (dd, *J* = 18.2, 10.8 Hz, 1H), 3.25 (ddd, *J* = 11.1, 8.0, 3.1 Hz, 1H), 3.03 (dd, *J* = 18.2, 3.2 hz, 1H), 2.96 (ddd, *J* = 14.7, 7.1, 7.1 Hz, 1H), 2.30 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.4, 173.1, 171.3, 153.4, 62.2, 60.9, 49.3, 43.6, 42.4, 35.6, 15.8, 14.1, 11.6.



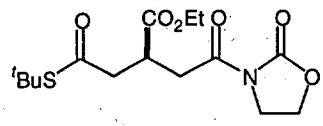
According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (13 μL, 0.12 mmol), followed by the addition of methylthio butyrate enolsilane (55 μL, 0.25 mmol, *Z*:*E* = 97:3). After 2 hours at -78 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (35.5 mg, 89%). HPLC analysis (Chiralcel AD, 15% EtOH/hexanes, 1 mL/min, 254 nm; t_r (*syn*, major) = 33.7, t_r (*syn*, minor) = 36.0, t_r (*anti*, minor) = 39.3, t_r (*anti*, major) = 43.3 gave the isomeric composition of the product: dr = 95:5, 90% ee. IR (film) 1785, 1727, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, *J* = 8.2 Hz, 2H), 4.13 (dq, *J* = 7.1, 7.1 Hz, 1H), 4.12 (dq, *J* = 7.1, 7.1 Hz, 1H), 4.03-3.92 (m, 2H), 3.46 (dd, *J* = 18.1, 10.5 Hz, 1H), 3.31 (ddd, *J* = 10.5, 4.8, 3.2 Hz, 1H), 3.06 (dd, *J* = 18.1, 3.2 hz, 1H), 2.95 (ddd, *J* = 9.7, 4.8, 4.8 Hz, 1H), 2.29 (s, 3H), 1.83-1.74 (m, 1H), 1.57-1.47 (m, 1H), 1.24 (t, *J* = 7.1 hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 200.9, 172.7, 171.5, 153.4, 62.1, 61.0, 55.7, 42.3, 42.3, 33.6, 22.2, 14.0, 11.7, 11.4; HRMS (CI, NH_3): Exact mass calcd for $C_{14}H_{25}N_2O_6S$ $[M+NH_4]^+$, 349.1433. Found 349.1440. Anal. Calcd for $C_{14}H_{21}NO_6S$: C, 50.74; H, 6.39. Found: C, 50.91; H, 6.45.



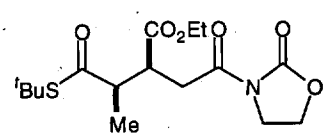
According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (13 μL, 0.12 mmol), followed by the addition of methylthio isovaleryl enolsilane (57 μL, 0.24 mmol, *Z*:*E* = 93:7). After 4.5 hours at -78 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (38.0 mg, 93%). HPLC analysis (Chiralcel ODH, 15% EtOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, minor) = 12.2, t_r (*anti*, major) = 13.9, t_r (*syn*, major) = 20.8, t_r (*syn*, minor) = 29.2 gave the isomeric composition of the product: dr = 100:1, 98% ee. IR (film) 1783, 1733, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (t, *J* = 8.5 Hz, 2H), 4.24-4.11 (m, 2H), 4.09-3.97 (m, 2H), 3.59 (dd, *J* = 18.2, 10.7 Hz, 1H), 3.38 (ddd, *J* = 10.7, 4.8, 3.4 Hz, 1H), 3.10 (dd, *J* = 18.2, 3.4 Hz, 1H), 2.78 (dd, *J* = 8.6, 4.8 Hz, 1H), 2.32 (s, 3H), 2.23-2.14 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 200.5, 172.8, 171.5, 153.4, 62.1, 61.2, 61.0, 42.4, 40.7, 34.3, 28.2, 20.8, 20.2, 14.0, 11.8; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{15}H_{23}NaNO_6S$ $[M+Na]^+$, 368.1144. Found 368.1146. Anal. Calcd for $C_{15}H_{23}NO_6S$: C, 52.16; H, 6.71. Found: C, 52.27; H, 6.82.



According to the general procedure, a solution of fumaroylimide (107 mg, 0.50 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (106 μL, 1.0 mmol), followed by the addition of the cyclopentylmethyl substituted methyl thioester enolsilane (0.261 μL, 1.0 mmol, *Z*:*E* = 96:4). After 24 hours at -78 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (193 mg, quant) that crystallized upon standing. HPLC analysis (Chiralcel AD, 15% EtOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, minor) = 24.0, t_r (*syn*, major) = 26.0, t_r (*syn*, minor) = 31.4, t_r (*anti*, major) = 36.0 gave the isomeric composition of the product: dr = 98:2, 98% ee. IR (film) 1783, 1729, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (t, *J* = 8.2 Hz, 2H), 4.19-4.08 (m, 2H), 4.02-3.91 (m, 2H), 3.48 (dd, *J* = 18.3, 10.8 Hz, 1H), 3.31 (ddd, *J* = 10.8, 4.2, 3.0 Hz, 1H), 3.09 (ddd, *J* = 10.8, 4.2, 4.2 Hz, 1H), 3.02 (dd, *J* = 18.3, 3.0 Hz, 1H), 2.28 (s, 3H), 1.99-1.91 (m, 1H), 1.81-1.74 (m, 1H), 1.72-1.66 (m, 2H), 1.56-1.52 (m, 2H), 1.51-1.46 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.22-1.19 (m, 1H), 1.05-0.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.0, 172.5, 170.4, 153.4, 62.1, 61.1, 53.4, 42.9, 42.4, 37.9, 34.8, 33.2, 32.0, 25.0, 14.1, 11.7; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{18}H_{27}NaNO_6S$ $[M+Na]^+$, 408.1457. Found 408.1454. Anal. Calcd for $C_{18}H_{27}NO_6S$: C, 56.09; H, 7.06. Found: C, 56.23; H, 7.00.



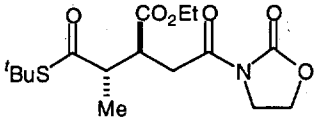
According to the general procedure, a solution of fumaroylimide (107 mg, 0.50 mmol) was treated with the catalyst (10 mol%), followed by the addition of *tert*-butyl thioacetate enolsilane (0.255 μL, 1.0 mmol). After 36 hours at -78 °C, the solution was quenched and purified in the predescribed manner to give the product as a colorless oil (148 mg, 86%). HPLC analysis (Chiralcel ODH, 15% ^{i}PrOH/hexanes, 0.9 mL/min, 254 nm; t_r (minor) = 20.3, t_r (major) = 28.6 gave the isomeric composition of the product: 89% ee. IR (film) 1782, 1733, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, *J* = 8.1 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.96 (td, *J* = 8.1, 2.0 Hz, 2H), 3.37-3.29 (m, 2H), 3.07 (ddd, *J* = 17.5, 7.7, 7.7 Hz, 1H), 2.89 (dd, *J* = 16.1, 5.8 Hz, 1H), 2.67 (dd, *J* = 16.1, 7.2 Hz, 1H), 1.40 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 197.4, 173.1, 171.0, 153.4, 62.1, 60.9, 48.3, 44.7, 42.3, 36.8, 36.0, 29.7, 14.0; HRMS (CI, NH_3): Exact mass calcd for $C_{15}H_{27}N_2O_6S[M+NH_4]^+$, 363.1590. Found 363.1580; Anal. Calcd for $C_{15}H_{23}NO_6S$: C, 52.16; H, 6.71. Found: C, 52.33; H, 6.76.



According to the general procedure, a solution of fumaroylimide (25.6 mg, 0.12 mmol) was treated with the catalyst (10 mol%) and hexafluoroisopropanol (13 μL, 0.12 mmol), followed by the addition of *tert*-butyl thiopriopionate enolsilane (61 μL, 0.24 mmol, *E*:*Z* = 95:5). After 36 hours at -78 °C, the solution was quenched and purified in the predescribed manner to give the

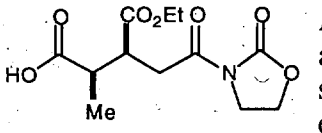
product as a colorless oil (40.5 mg, 94%). HPLC analysis (Chiralcel ODH, 10% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, major) = 26.4, t_r (*syn*, major) = 28.6, t_r (*anti*, minor) = 45.7, t_r (*syn*, minor) = 51.3 gave the isomeric composition of the product: dr = >99:1, >99% ee. IR (film) 1784, 1729, 1703, 1676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, *J* = 8.1 Hz, 2H), 4.18-4.09 (m, 2H), 3.95 (td, *J* = 8.1, 1.7 Hz, 2H), 3.37 (dd, *J* = 18.2, 10.8 Hz, 1H), 3.14 (ddd, *J* = 10.8, 8.2, 3.3 Hz, 1H), 3.04 (dd, *J* = 18.2, 3.3 Hz, 1H), 2.78 (dq, *J* = 7.1 Hz, 1H), 1.43 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.6, 173.0, 171.3, 153.3, 62.1, 60.8, 49.6, 48.3, 43.6, 42.3, 35.6, 29.7, 15.5, 14.1; HRMS (CI, NH_3): Exact mass calcd for $C_{16}H_{26}NO_6S[M+H]^+$, 360.1481. Found 360.1484; Anal. Calcd for $C_{16}H_{25}NO_6S$: C, 53.47; H, 7.01. Found: C, 53.39; H, 7.01.

When conducted in the absence of HFIP, the reaction delivered the product in 61% yield after 3 days.

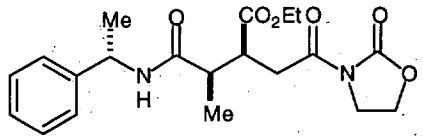


^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (t, *J* = 8.1 Hz, 2H), 4.16-4.06 (m, 2H), 4.00-3.92 (m, 2H), 3.43 -3.33 (m, 2H), 3.01-2.95 (m, 2H), 1.41 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.8, 173.0, 171.5, 153.4, 62.1, 60.9, 48.6, 42.5, 42.3, 33.1, 29.7, 29.6, 14.0, 13.9.

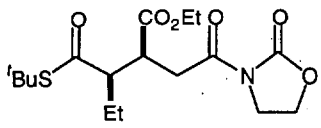
General procedure for the hydrolysis of thioesters using bromine. Bromine (3 drops) was added to a solution of thioester (80 μmol) in THF-H_2O (5:1, 2 mL) at ambient temperature. The solution was stirred for 1 h, poured into aq sodium thiosulfate (0.2 M, 3 mL) and extracted with EtOAc. The combined organic extracts were dried and concentrated to give the desired analytically pure acid.



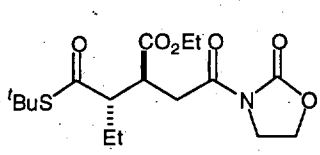
A solution of the above thioester (200 mg, 0.56 mmol) in THF-H_2O (5 mL, 5:1) at 25 °C was treated with NBS (149 mg, 0.84 mmol). The orange solution was stirred for 45 min, poured into aq sodium thiosulfate (0.2 M, 50 mL), and extracted with ethyl acetate (3x). The combined organic layers were washed with water and brine, dried, and concentrated to a tan solid (153 mg, 96%) which was analytically pure. IR (film) 3330, 1781, 1730, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, *J* = 8.1 Hz, 2H), 4.18-4.08 (m, 2H), 3.98 (td, *J* = 7.6, 2.0 Hz, 2H), 4.50 (dd, *J* = 18.1, 10.5 Hz, 1H), 3.36-3.31 (m, 1H), 2.96 (dd, *J* = 18.1, 3.5 Hz, 1H), 2.84 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 179.4, 172.7, 171.3, 153.5, 62.2, 61.0, 42.7, 42.4, 40.6, 35.1, 14.0, 13.8; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{12}H_{17}NaNO_7$ $[M+Na]^+$, 310.0903. Found 310.0898.



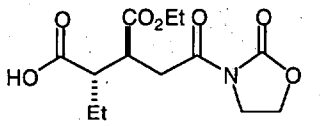
To a cold (-10 °C) solution of the above acid (24 mg, 84 μmol) in ethyl acetate (1 mL) was added N-methylmorpholine (10 μL) and isobutyl chloroformate (11 μL, 88 μmol). After 30 min, (S)-α-methylbenzylamine (12 μL, 92 μmol) was added and stirring continued for 2 hours. The solution was poured into brine (5 mL) and extracted with ethyl acetate (3x). The organic layers were dried and concentrated to give an oil that was subjected to silica gel chromatography (70% EtOAc in hexanes) to furnish the product as a white solid (26 mg, 79%). IR (film) 3308, 1778, 1730, 1692, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 6.01 (d, *J* = 7.9 Hz, 1H), 5.14-5.07 (m, 1H), 4.40 (t, *J* = 8.0 Hz, 2H), 4.20-4.12 (m, 2H), 4.04-3.96 (m, 2H), 3.3 (dd, *J* = 18.0, 10.3 Hz, 1H), 3.20-3.08 (m, 2H), 2.50-2.42 (m, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.5, 171.3, 171.3, 153.5, 143.0, 128.7, 127.4, 126.2, 62.2, 60.9, 48.8, 44.1, 42.9, 42.3, 35.9, 21.6, 16.0, 14.2; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{20}H_{26}NaN_2O_6$ $[M+Na]^+$, 413.1689. Found 413.1637.



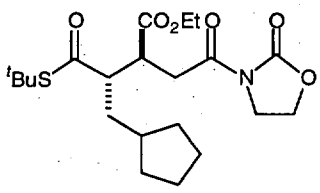
According to the general procedure, a solution of fumaroylimide (107 mg, 0.50 mmol) was treated with the catalyst (10 mol%), followed by the addition of *tert*-butyl thiobutyrate enolsilane (390 μL, 1.5 mmol, *Z*:*E* = 95:5). After 4 days at -78 °C, the solution was quenched and purified in the predescribed manner to give the product as a waxy solid (125 mg, 67%). HPLC analysis (Chiralcel AD, 15% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, major) = 12.1, t_r (*anti*, minor) = 13.1, t_r (*syn*, minor) = 15.7, t_r (*syn*, major) = 18.3 gave the isomeric composition of the product: dr = 91:9, 90% ee. IR (film) 1783, 1730, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, *J* = 8.1 Hz, 2H), 4.19-4.13 (m, 2H), 4.04-3.94 (m, 2H), 3.47 (dd, *J* = 18.1, 10.5 Hz, 1H), 3.30 (ddd, *J* = 10.5, 7.1, 5.0 Hz, 1H), 3.10 (dd, *J* = 18.1, 3.3 Hz, 1H), 2.81 (ddd, *J* = 9.8, 5.0, 5.0 Hz, 1H), 1.81-1.72 (m, 1H), 1.55-1.48 (m, 1H), 1.45 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.2, 172.8, 171.5, 153.4, 62.1, 60.9, 55.9, 48.3, 42.35, 42.27, 33.7, 29.6, 22.3, 14.0, 11.7; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{17}H_{27}NaNO_6S$ $[M+Na]^+$, 396.1457. Found 396.1473. Anal. Calcd for $C_{17}H_{27}NO_6S$: C, 54.67; H, 7.29.



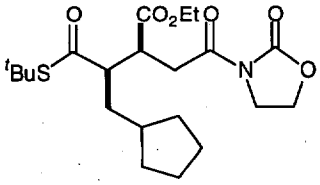
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, *J* = 8.0 Hz, 2H), 4.21-4.11 (m, 2H), 3.97 (t, *J* = 7.3 Hz, 2H), 3.39 (dd, *J* = 18.8, 11.6 Hz, 1H), 3.15-3.14 (m, 1H), 3.11 (ddd, *J* = 8.6, 8.6, 5.5 Hz, 1H), 2.69 (ddd, *J* = 9.4, 9.4, 4.3 Hz, 1H), 1.78-1.68 (m, 1H), 1.62-1.49 (m, 1H), 1.46 (s, 9H, 1.28 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.2, 173.5, 171.1, 153.3, 62.1, 60.8, 56.5, 48.6, 43.0, 42.3, 35.5, 29.6, 23.9, 14.1, 11.4.



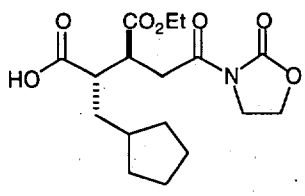
Bromine (3 drops) was added to a room temperature THF-H_2O (5:1, 2 mL) solution of the thioester (30 mg, 80 μmol), and the mixture was stirred for 1 hour prior to pouring into aq sodium thiosulfate (0.2 M, 3 mL). The mixture was extracted with ethyl acetate (3x), and the organic layers were dried and concentrated to provide the acid as a colorless gum (16 mg, 66%). IR (film) 3230, 1781, 1732, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, *J* = 8.1 Hz, 2H), 4.19-4.08 (m, 2H), 4.00 (td, *J* = 7.7, 2.4 Hz, 2H), 3.48 (dd, *J* = 17.9, 9.8 Hz, 1H), 3.35 (ddd, *J* = 9.4, 5.7, 3.5 Hz, 1H), 3.10 (dd, *J* = 17.9, 3.5 Hz, 1H), 2.80 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 1H), 1.79-1.68 (m, 1H), 1.61-1.51 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 179.3, 172.9, 171.4, 153.5, 62.2, 61.2, 47.4, 42.4, 41.7, 33.8, 21.8, 14.1, 11.9; HRMS (CI, NH_3): Exact mass calcd for $C_{13}H_{23}N_2O_7[M+NH_4]^+$, 319.1508. Found 319.1499.



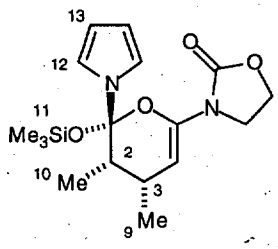
According to the general procedure (no additive), a solution of fumaroylimide (107 mg, 0.50 mmol) was treated with the catalyst (10 mol%), followed by the addition of the cyclopentyl methyl-substituted *tert*-butyl thioester enolsilane (383 μL, 1.5 mmol, *E*:*Z* = 95:5). After 2 days at -50 °C, the solution was quenched and purified in the predescribed manner to give the product as a white solid (109 mg, 51%), mp 79-83 °C. HPLC analysis (Chiralcel AD, 10% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, minor) = 12.7, t_r (*anti*, major) = 15.4, t_r (*syn*, minor) = 18.8, t_r (*syn*, major) = 20.8 gave the isomeric composition of the product: dr = 90:10, >99% ee. IR (film) 1784, 1731, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (t, *J* = 8.2 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.00-3.93 (m, 2H), 3.48 (dd, *J* = 18.2, 10.7, 1H), 3.28 (ddd, *J* = 10.7, 4.3, 3.1 Hz, 1H), 3.04 (dd, *J* = 18.2, 3.1 Hz, 1H), 2.94 (ddd, *J* = 10.7, 4.3, 3.8 Hz, 1H), 1.94-1.86 (m, 1H), 1.83-1.77 (m, 1H), 1.75-1.70 (m, 2H), 1.57-1.52 (m, 2H), 1.50-1.43 (m, 2H), 1.43 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.05-0.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.3, 172.7, 171.7, 153.3, 62.1, 61.0, 48.3, 42.8, 42.3, 37.9, 34.8, 33.3, 33.1, 32.0, 29.5, 25.0, 14.1; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{21}H_{33}NaNO_6S$ $[M+Na]^+$, 450.1926. Found 450.1939. Anal. Calcd for $C_{21}H_{33}NO_6S$: C, 58.99; H, 7.78. Found: C, 59.20; H, 7.83.



According to the general procedure, a solution of fumaroylimide (53.5 mg, 0.25 mmol) was treated with the catalyst (10 mol%) and HFIP (26 μL, 0.25 mmol), followed by the addition of the cyclopentyl methyl-substituted *tert*-butyl thioester enolsilane (115 μL, 0.38 mmol, *Z*:*E* = 88:12). After 2 days at -20 °C, the solution was quenched and purified in the predescribed manner to give the product as a white solid (98.2 mg, 92%). HPLC analysis (Chiralcel AD, 10% ^{i}PrOH/hexanes, 1 mL/min, 254 nm; t_r (*anti*, minor) = 12.7, t_r (*anti*, major) = 15.4, t_r (*syn*, minor) = 18.8, t_r (*syn*, major) = 20.8 gave the isomeric composition of the product: dr = 73:27, 99% ee. Recrystallization from hot hexanes provides the *syn* adduct (60.3 mg, 56% overall) in dr = 98:2, 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (t, *J* = 8.1 Hz, 2H), 4.20-4.12 (m, 2H), 3.97 (td, *J* = 8.1, 2.2 Hz, 2H), 3.41 (dd, *J* = 18.7, 11.4 Hz, 1H), 3.13-3.03 (series of m, 2H), 2.84-2.78 (m, 1H), 1.90-1.81 (m, 2H), 1.79-1.71 (m, 2H), 1.61-1.40 (series of m, 5H), 1.45 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.05-1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 201.5, 173.3, 171.5, 153.3, 62.1, 60.8, 54.3, 43.7, 42.3, 37.6, 37.0, 35.3, 33.2, 32.3, 29.6, 25.1, 14.2.



Bromine (3 drops) was added to a room temperature THF-water (5:1, 2 mL) solution of the thioester (50 mg, 118 μmol), and the mixture was stirred for 2 hours prior to pouring into aq sodium thiosulfate (0.2 M, 4 mL). The mixture was extracted with ethyl acetate (3x), and the organic layers were dried and concentrated to provide the acid as a white gum (25.3 mg, 61%). IR (film) 3309, 1783, 1732, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (br s, 1H), 4.40 (t, *J* = 8.2 Hz, 2H), 4.18-4.08 (m, 2H), 3.98 (td, *J* = 7.9, 3.4 Hz, 2H), 3.48 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.35 (ddd, *J* = 10.1, 4.8, 3.4 Hz, 1H), 3.04 (dd, *J* = 18.0, 3.4 Hz, 1H), 2.90 (ddd, *J* = 12.3, 4.8, 4.8 Hz, 1H), 1.89-1.64 (m, 4H), 1.60-1.46 (m, 5H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.08-1.02 (m, 1H), 0.98-0.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 179.8, 172.8, 171.5, 153.5, 62.2, 61.2, 45.0, 42.4, 42.1, 38.0, 33.5, 32.9, 31.8, 24.9, 14.0; HRMS (FAB, MNBA, NaI added): Exact mass calcd for $C_{17}H_{25}NaNO_7$ $[M+Na]^+$, 378.1529. Found 378.1526.



According to the general procedure (no alcohol additive), a solution of crotonyl oxazolidinone (18.6 mg, 0.50 μmol) was treated with the catalyst (5 mol%), followed by the addition of (*Z*) propionyl pyrrole enolsilane (51 μL, 24 μmol, *Z*:*E* = >98:2). After 1.5 h at -20 °C, the solution was quenched and purified in the predescribed manner to give the Michael adduct as a colorless oil (26.4 mg, 79%) the dihydropyran as a colorless oil (2.5 mg, 6%). IR (film) 1178, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 2.2 Hz, 2H), 6.08 (dd, *J* = 2.2 Hz, 2H), 4.55 (d, *J* = 3.8 Hz, 1H), 4.31-4.27 (m, 2H), 3.89-3.82 (m, 1H), 3.57-3.49 (m, 2H), 2.69-2.60 (m, 1H), 1.18 (d, *J* = 7.3 Hz, 3H), 1.12 (d, *J* = 7.2 Hz, 3H), -0.037 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.3, 153.5, 171.0, 118.2, 108.5, 57.9, 42.8, 40.3, 28.6, 14.2, 9.5, 0.93; TLC (40% EtOAc/hexanes) R_f 0.47; HRMS (ES): Exact mass calcd for $C_{17}H_{30}N_3O_4S$ $[M+NH_4]^+$, 368.2006. Found 368.1990.

The relative stereochemistry of the dihydropyran was elucidated on a degassed (freeze-pump-thaw) solution (2.5 mg in $CDCl_3$) using a GOESY pulse program[7] on a DMX 500 MHz NMR equipped with field gradients. Using a 700 msec mixing time, irradiation of H_{12} resulted in enhancements to H_{13} (3.0%), H_2 (5.3%), H_{11} (4.8%). Similarly, a 1 s mixing time and irradiation of H_{11} resulted in enhancements of H_{12} (8.4%), H_9 (1.7%), and H_{10} (3.1%).

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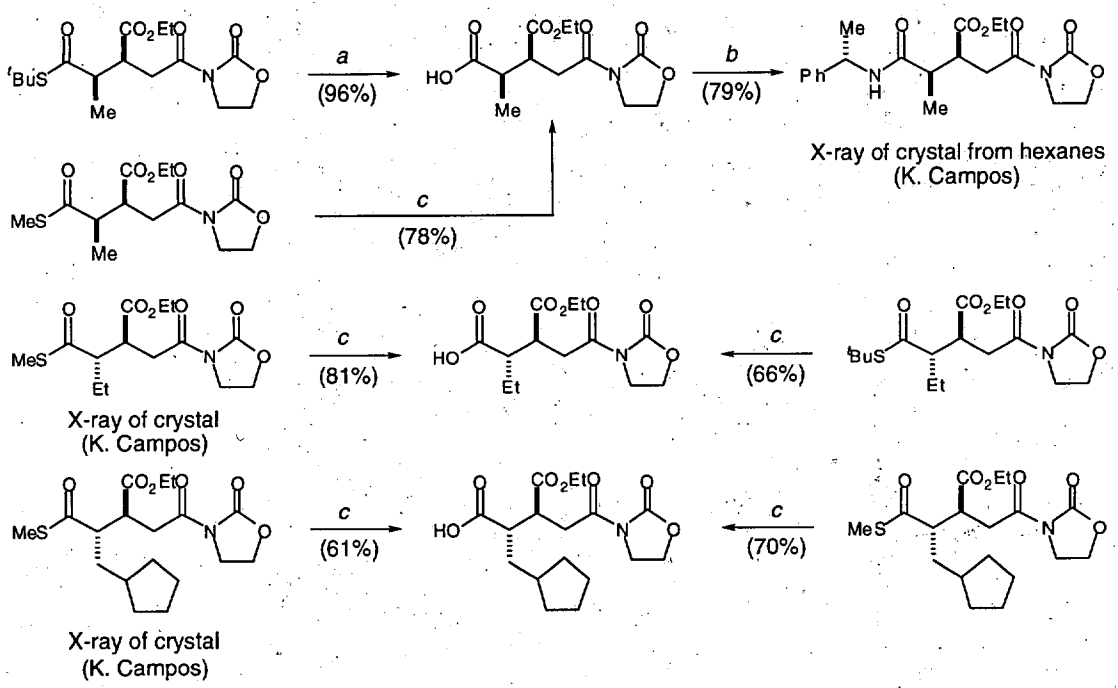
[7] (a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199-4200. (b) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. *J. J. Am. Chem. Soc.* **1994**, *116*, 6037-6038.

Table 1. Elucidation of Michael Addition Product Relative and Absolute Stereochemistry[a]



[a]Reagents and conditions: (a) NBS, 5:1 THF-H_2O, 25 °C; (b) *i*-butylchloroformate, (*S*)-α-methyl benzylamine, NMM, EtOAc, 0 °C; (c) Br_2, THF-H_2O.