An unusual dianion equivalent from acylsilanes for the synthesis of substituted **β**-keto esters

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Supporting Information

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General Information

All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. THF, Et₂O, CH₂Cl₂ and toluene were purified by passage through a bed of activated alumina.¹ Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.² Purification of reaction products was carried out by flash chromatography using EM Reagent 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 anisaldehyde, ceric ammonium nitrate stain, or phosphomolybic acid followed by heating. Melting points were obtained on a Melt-temp 3 instrument and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) or Mercury 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Protondecoupled ¹³C-NMR spectra were recorded on a Varian Inova 500 (125 MHz) or Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). Mass spectra data were obtained on either a Thermo-Finnigan MAT900 high resolution mass spectrometer, a VG 70-250SE HRMS or Thermo-Finnigan LCQ Advantage HPLC-MS in the Northwestern University Analytical Services Laboratory.

Aryl acylsilanes were prepared according to the method of Yamamoto and co-workers,³ commercially available acetyl trimethylsilane was purchased and used without further purification. Reactions were carried out using either a freshly prepared solution of lithium diisopropylamide in THF or a commercial solution of LDA (1.8 M) in heptane and THF. These solutions were titrated immediately prior to use. Silyl enol ether **16** was prepared according to the method of Fleming and co-workers.⁴

General Procedure for **β**-Ketoesters 3-10

To a flame-dried round bottom flask fitted containing a magnetic stirring bar was added diazoester **1a-c** and acylsilane **2a-d** in THF (2 mL). The mixture was cooled to -78 °C using a dry ice-acetone bath and a solution of LDA was added by cannula. After complete addition, the mixture was stirred for a further 30 minutes. At this point the first electrophile (MeOH or alkyl halide) was added and the mixture warmed to 0 °C and stirred until the reaction was judged to be complete by thin layer chromatography. The reaction mixture was partitioned between EtOAc and saturated ammonium chloride, and the aqueous layer extracted with EtOAc (3 × 10 mL).

¹ A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics* 1996, **15**, 1518-1520.

² D. D. Perrin and W. L. Armarego, *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

³ K. Yamamoto, A. Hayashi, S. Suzuki and J. Tsuji, *Organometallics* 1987, **6**, 974-979.

⁴ I. Fleming, J. Iqbal and E. P. Krebs, *Tetrahedron* 1983, **39**, 6, 841-846.

The combined organic fractions were then dried (Na_2SO_4) , filtered and evaporated. Purification by flash chromatography on silica gel provided the title compounds as described below.

General Procedure for Disubstituted β-Ketoesters 11-15

To a flame-dried round bottom flask fitted containing a magnetic stirring bar was added diazoester **1a-c** and acylsilane **2a-d** in THF (2 mL). The mixture was cooled to -78 °C using a dry ice-acetone bath a solution of LDA was added by cannula. After complete addition, the mixture was stirred for a further 30 minutes. At this point the first electrophile was added and the mixture warmed to 0 °C and stirred until the reaction was judged to be complete by thin layer chromatography (5-10 h). At this point, an excess of the second reagent was added and the mixture heated to the indicated temperature for 16 h. The reaction mixture was partitioned between EtOAc and saturated ammonium chloride, and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic fractions were then dried (Na₂SO₄), filtered and evaporated. Purification by flash chromatography on silica gel provided the title compounds as described below.



Ethyl benzoylacetate (3a): Prepared according to general procedure using acylsilane 1a (71 mg, 0.4 mmol), ethyl diazoacetate 2a (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution). Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (6-12%) afforded 76 mg (99%) of 3 as a colorless oil.

Analytical data for **3a**: $R_f 0.41$ (10:1 hexanes/EtOAc); IR (film) 1732, 1684, 1655, 1635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93-7.91 (m, 2H), 7.76-7.74 (m, 2H *enol tautomer*), 7.59-7.55 (m, 1H), 7.48-7.39 (m, 5H + *enol tautomer*), 5.64 (s, 1H *enol tautomer*), 4.25-4.16 (s, 3H + *enol tautomer*), 3.97 (s, 2H), 1.33-1.29 (m, 3H *enol tautomer*), 1.24-1.21 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 192.8, 167.7, 136.2, 134.0, 131.4, 129.0, 128.7, 126.2, 87.6, 61.7, 60.5, 46.2, 14.3; LRMS (electrospray): Exact mass calcd for C₁₁H₁₂O₃ [M]⁺, 220.26. Found [M+H], 221.1.



tert-Butyl benzoylacetate (4): Prepared according to general procedure using acylsilane 1a (71 mg, 0.4 mmol), *tert*-butyl diazoacetate 2b (57 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution). The reaction mixture Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (2-10%) afforded 87 mg (98%) of 4 as a

colorless oil. Analytical data for **4**: $R_f 0.43$ (10:1 hexanes/EtOAc); IR (film) 1733, 1684 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96-7.91 (m, 2H), 7.62-7.59 (m, 1H), 7.59-7.55 (m, 1H), 7.51-7.48 (m, 2H), 5.60 (s, 1H *enol tautomer*), 4.25-4.16 (s, 3H + *enol tautomer*), 3.91 (s, 2H), 1.45 (s, 9H), 1.36 (s, 9H *enol tautomer*); ¹³C NMR (100 MHz, CDCl₃) δ 192.8, 167.7, 136.2, 134.0, 131.4, 129.0, 128.7, 126.2, 87.6, 61.7, 60.5, 46.2, 14.3; LRMS (electrospray): Exact mass calcd for C₁₃H₁₆O₃ [M]⁺, 220.26. Found [M+H], 221.2.



Ethyl 4-methylbenzoylacetate (5): Prepared according to general procedure using acylsilane **1b** (77 mg, 0.4 mmol), ethyl diazoacetate **2a** (46 mg, 0.4 mmol), and a solution of LDA in heptane-THF, (222 μ L of a 1.8 M solution). Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 82 mg (98%) of **5** as a colorless oil. Analytical data for **5**: R_f 0.40 (10:1 hexanes/EtOAc); IR 1742, 1684 (film) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.86-7.84 (m, 2H), 7.74-7.72 (m, 2H *enol tautomer*), 7.29-7.21 (m, 4H *including enol tautomer*), 5.61 (s, 1H *enol tautomer*), 4.23-4.19 (s, 3H + *enol tautomer*), 3.98 (s, 2H), 2.43 (s, 3H), 1.33-1.29 (m, 3H *enol tautomer*), 1.24-1.21 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 192.4, 167.4, 133.8, 129.8, 129.7, 128.9, 61.7, 46.2, 21.9, 14.3; LRMS (electrospray): Exact mass calcd for C₁₂H₁₄O₃ [M]⁺, 206.24. Found [M], 206.1.

Ethyl acetoacetate (6): Prepared according to general procedure using acylsilane **1c** (58 mg, 0.5 mmol), ethyl diazoacetate **2a** (58 mg, 0.5 mmol), and a solution of LDA in heptane-THF, (222 μ L of a 1.8 M solution). Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (4-8%) afforded 51 mg (79%) of **6** as a colorless oil. Analytical data for **6**: R_f 0.35 (8:1 hexanes/EtOAc); IR (film) 1733, 1717 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.99 (m, 2H *enol tautomer*), 4.24-4.20 (m, 4H *including enol tautomer*), 3.46 (s, 2H), 3.41 (s, 2H *enol tautomer*), 4.23-4.19 (s, 4H *including enol tautomer*), 2.28 (s, 3H), 2.23 (s, 3H *enol tautomer*), 1.33-1.29 (m, 3H), 1.28-1.27 (m, 3H *enol tautomer*); ¹³C NMR (125 MHz, CDCl₃) δ 200.9, 61.6, 50.4, 30.4, 14.3; LRMS (electrospray): Exact mass calcd for C₆H₁₀O₃ [M]⁺, 130.14. Found [M+H], 131.5.



Me

trans-Cinnamyl benzoylacetate (7): Prepared according to general procedure using acylsilane 1a (71 mg, 0.4 mmol), cinammyl diazoacetate 2d (80 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution). Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 106

mg (95%) of 7 as a colorless oil. Analytical data for 7: $R_f 0.27$ (9:1 EtOAc/hexanes); IR (film) 1737, 1683 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97-7.21 (m, 6H), 7.74-7.40 (m, 6H), 7.38-7.21 (m, 8H), 6.64-6.58 (m, 2H *including enol tautomer*), 6.24-6.11 (m, 2H *including enol tautomer*), 5.68 (s, 2H *including enol tautomer*), 4.86-4.76 (m, 4H *including enol tautomer*), 4.03 (s, 2H), ¹³C NMR (125 MHz, CDCl₃) δ 192.4, 175.4, 135.7, 134.8, 134.5, 134.0, 129.4, 128.8, 128.7, , 126.8, 67.8, 66.2, 46.4, 46.2; LRMS (electrospray): Exact mass calcd for C₁₈H₁₇O₃ [M]⁺, 280.11. Found [M], 280.3.

Ethyl 2-methyl-3-oxo-3-phenylpropanoate (8): Prepared according to general procedure using acylsilane **1a** (71 mg, 0.4 mmol), ethyl diazoacetate **2a** (46 mg, 0.4 mmol), followed by MeI (1.2 equiv). Flash column chromatography using gradient elution mixtures of EtOAc/hexanes

(4-10%) afforded 77 mg (93%) of **8** as a colorless oil. Analytical data for **8**: $R_f 0.27$ (9:1 hexanes/EtOAc); IR (film) 1733, 1688 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.99-7.98 (m, 2H), 7.62-7.59 (m, 1H), 7.51-7.48 (m, 2H), 4.41-4.37 (m, 1H), 4.19-4.14 (m, 3H), 1.57-1.54 (m, 3H), 1.20-1.16 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 196.1, 171.1, 136.0, 133.7, 128.9, 128.8, 61.6,

48.5, 14.2, 13.9; LRMS (electrospray): Exact mass calcd for $C_{12}H_{14}O_3$ [M]⁺, 206.24. Found [M+H], 206.2.



Ethyl 2-benzyl-3-oxo-3-phenylpropanoate (9): Prepared according to general procedure using acylsilane **1a** (71 mg, 0.4 mmol), ethyl diazoacetate **2a** (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution), followed by addition of BnBr (0.65 mmol) was added, the reaction mixture was stirred at 23 °C for a further 16 h. Flash column

chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 107 mg (95%) of **9** as a colorless oil. Analytical data for **9**: $R_f 0.54$ (7:1 EtOAc/hexanes); IR (film) 1737, 1717 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.98-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.41 (m, 2H), 7.27-7.19 (m, 5H), 4.63-4.61 (m 1H), 4.25-4.15 (m, 2H), 3.39-3.33 (s, 2H), 1.15-1.12 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 194.7, 169.5, 138.6, 136.4, 133.8, 129.2, 128.9, 128.7, 126.9, 61.7, 56.2, 35.0, 14.2; LRMS (electrospray): Exact mass calcd for C₁₈H₁₈O₃ [M]⁺, 282.13. Found [M+H], 283.4.



Ethyl 2-benzyl-3-oxobutanoate (10): Prepared according to general procedure using acylsilane 1c (46 mg, 0.4 mmol), ethyl diazoacetate 2a (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution). after stirring at -78 °C for 30 minutes followed by addition of BnBr (0.65 mmol) was added, the reaction mixture was stirred at 23 °C for a further 16 h. Flash

column chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 67 mg (76%) of **10** as a colorless oil. Analytical data for **10**: $R_f 0.35$ (9:1 EtOAc/hexanes); IR (film) 1730, 1702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.08 (m, 5H), 4.12-4.07 (m, 2H), 7.3.77-3.33 (m, m, 1H), 3.16-3.13 (m, 2H), 2.18 (s, 3H), 1.20-1.14 (m, 3H; ¹³C NMR (125 MHz, CDCl₃) δ 202.7, 169.3, 138.3, 128.9, 128.8, 126.9, 61.7, 61.5, 34.2, 29.9, 14.2; LRMS (electrospray): Exact mass calcd for C₁₁H₁₂O₃ [M]⁺, 220.11. Found [M], 220.1.

Ph OEt g (4

Ethyl 2,2-diallyl-3-oxo-3-phenylpropanoate (11): Prepared according to general procedure using acylsilane 1a (71 mg, 0.4 mmol), ethyl diazoacetate 2a (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution) at -78 °C for 30 minutes. Allyl iodide, (2.0 mmol) was added in a single portion and the mixture stirred overnight at room temperature. Flash

column chromatography using gradient elution mixtures of EtOAc/hexanes (2-6%) afforded 99 mg (91%) of **11** as a colorless oil. Analytical data for **11**: R_f 0.41 (9:1 EtOAc/hexanes); IR (film) 1733, 1684 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.85 (m, 2H), 7.54-7.45 (m, 1H), 7.29-7.21 (m, 2H), 5.61-5.59 (m, 2H), 5.10-5.02 (m, 4H), 4.15-4.14 (m, 2H), 2.83-2.81 (m, 4H), 1.11-1.08 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 196.1, 172.8, 136.2, 132.3, 128.4, 119.7, 61.8, 60.9, 46.2, 37.2, 14.3; LRMS (electrospray): Exact mass calcd for $C_{17}H_{20}O_3$ [M]⁺, 272.14. Found [M], 272.1.



Cyclopentanecarboxylic acid, 1-benzoyl- ethyl ester (12): Prepared according to general procedure using acylsilane **1a** (71 mg, 0.4 mmol), ethyl diazoacetate **2a** (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 μ L of a 1.7 M solution). 1,4-diiodobutane, (0.7 mmol) was added in a single portion and the mixture heated at 50 °C for 24 h. Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 82 mg (84%) of 12 as a colorless oil. Analytical data for 12: R_f 0.24 (9:1 EtOAc/hexanes); IR (film) 1735, 1685 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.88-7.87 (m, 2H), 7.74-7.72 (m, 1H), 7.53-7.44 (m, 1H), 7.44-7.41 (m, 2H), 4.07-4.04 (m, 2H),

2.40-2.32 (m, 4H), 1.78-1.69 (m, 4H), 1.00-0.97 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 196.4, 175.0, 135.6, 133.0, 129.0, 128.7, 63.8, 61.5, 35.3, 26.5, 14.0; LRMS (electrospray): Exact mass calcd for C₁₅H₁₈O₃ [M]⁺, 246.13. Found [M], 246.0.



1H-Indene-2-carboxylic acid, 2-benzoyl-2,3- ethyl ester (13): Prepared according to general procedure using acylsilane 1a (71 mg, 0.4 mmol), ethyl diazoacetate 2a (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 µL of a 1.7 M solution). After 30 minutes at -78 °C, α , α '-Dibromo-o-xylene (1.0 mmol) was added in a single portion and the mixture heated at 50 °C for 24 h. Flash column chromatography using gradient elution mixtures of

EtOAc/hexanes (2-10%) afforded 90 mg (77%) of 13 as a colorless oil. Analytical data for 13: R_f 0.50 (6:1 EtOAc/hexanes); IR (film) 1733, 1683 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.94-7.92 (m, 2H), 7.56-7.55 (m, 1H), 7.48-7.44 (m, 2H), 7.21-7.16 (m, 4H), 4.15-4.11 (m, 2H), 3.86-3.72 (m, 4H), 1.05-1.03 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 194.8, 173.9, 140.0, 134.9, 133.2, 129.1, 128.8, 127.2, 124.4, 63.7, 62.0, 41.1, 14.0; LRMS (electrospray): Exact mass calcd for C₁₉H₁₈O₃ [M]⁺, 294.13. Found [M], 294.1.



Ethyl 2-methyl-2-allyl-3-oxo-3-phenylpropanoate (14): Prepared according to general procedure using acylsilane 1a (71 mg, 0.4 mmol), ethyl diazoacetate OEt 2a (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 µL of a 1.64 M solution). Methyl iodide (1.0 mmol) was added in a single portion and reaction mixture stirred at 23 °C for 6 h. allyl iodide was then added (3.0 mmol), and the

mixture heated at 40 °C for 16 h. Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 80 mg (81%) of 14 as a colorless oil. Analytical data for 14: R_f 0.24 (12:1 EtOAc/hexanes); IR (film) 1737, 1715 cm⁻¹ ¹H NMR (500 MHz, CDCl₃) δ 7.92 (m, 2H), 7.58-7.41 (m, 3H), 5.77-5.62 (m, 1H), 5.18-5.04 (m, 2H), 5.61 (s, 1H), 4.19-4.14 (m, 2H), 2.81-2.75 (m, 2H), 1.51 (s, 3H), 1.14-1.29 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.1, 174.0. 136.1, 134.1, 129.8, 129.6, 118.9, 61.8, 58.1, 41.2, 21.9, 14.3; LRMS (electrospray): Exact mass calcd for $C_{15}H_{18}O_3$ [M]⁺, 246.30. Found [M+H], 246.4.

Ethyl 2-benzyl-2-methyl-3-oxobutanoate (15): Prepared according to general procedure using acylsilane 1c (46 mg, 0.4 mmol), ethyl diazoacetate 2a (46 mg, 0.4 mmol), and a solution of LDA in THF, (235 µL of a 1.64 M solution). benzyl bromide (0.65 mmol) was added in a single portion and reaction mixture stirred at 23 °C for 12 h. Methyl iodide (3.0 mmol) was then added, and the mixture heated at 50

°C for 16 h. Flash column chromatography using gradient elution mixtures of EtOAc/hexanes (4-10%) afforded 65 mg (69%) of **15** as a colorless oil. Analytical data for **15**: $R_f 0.38$ (9:1 EtOAc/hexanes); IR (film) 1733, 1713 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.23 (m, 3H), 7.11-7.09 (m, 2H), 4.24-4.16 (2, 1H), 3.30-3.05 (m, 2H), 2.19 (s, 3H), 1.30 (s, 3H), 1.29-1.26 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.6, 172.6, 136.7, 130.4, 128.4, 127.0, 61.6, 61.1. 40.7, 26.7, 19.3, 14.2; LRMS (electrospray): Exact mass calcd for $C_{15}H_{18}O_3$ [M]⁺, 234.13. Found [M+H], 234.2.

Alkylation of silyl enol ether 17

A solution of silyl enol ether **17** (132 mg/0.5 mmol) in THF at -78 °C was treated with LDA (0.6 mmol). After stirring for 1 h at -78 °C, MeI (1.5 mmol) was added and the mixture was warmed to 23 °C. After stirring for 16 h, the reaction mixture was partitioned between EtOAc and aqueous saturated ammonium chloride, the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic fractions were then dried (Na₂SO₄), filtered and evaporated. Purification by flash chromatography on silica gel provided 67 mg (65%) of compound **8**.

Selected ¹H and ¹³C NMR Spectra













*S*15

BHT Addition experiment

A solution of acylsilane **1b** (0.4 mmol) and EDA **2a** (0.4 mmol) in C_6D_6 was cooled to 5 °C and a commercial solution of LDA (0.4 mmol) in THF-heptane stabilized by ethylbenzene was added. The mixture was stirred for 30 minutes, and BHT (0.4 mmol) was added. The reaction mixture was then examined directly by ¹H NMR spectroscopy (500 MHz).

