Rhodium-Catalyzed Reductive Aldol Reactions Using Aldehydes as the Stoichiometric Reductants.

Michael C. Willis* and Robert L. Woodward

**Department of Chemistry, University of Bath, Bath, BA2 7AY, UK.*

Supporting Information

General Information: IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer, using NaCl discs or as solids on a Perkin-Elmer Spectrum One FT-IR spectrometer operating in Attenuated Total Reflectance mode. ^1H NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz, unless otherwise noted, with tetramethylsilane as an internal standard. J values are given in Hz. ^{13}C NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 75 MHz, unless otherwise noted. All dry solvents were freshly distilled under nitrogen prior to use. Dichloroethane was distilled over calcium hydride, tetrahydrofuran was distilled over sodium wire. Petroleum ether refers to that fraction obtained between 40-60°C. All glassware was dried in an oven and allowed to cool under nitrogen prior to use. All commercial reagents were used as obtained, except for 3-(methylthio)propionaldehyde which was distilled before use.

Mass spectrometry measurements were performed at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea; values are quoted as m/z with relative intensity in parentheses.

Thin layer chromatographic analyses were performed on plates coated with Kieselgel 60F₂₅₄. Visualisation was achieved with a 254 nm ultraviolet lamp, followed by staining with vanillin or potassium permanganate. Column chromatographic separation was carried out using silica gel (35–70 mesh).

Preparation of β -Sulfide-Substituted Aldehydes

Aldehydes were prepared according to the method of Weber,¹ with the following minor modifications: A mixture of the enal (1 mol) and thiol (1.25 mol) were stirred at room temperature before addition of sodium hydride (0.5 mol %) in four portions over 15

minutes. **Care, extremely exothermic reaction ensues.** The resultant reaction mixture was left to stir at room temperature for a further 3-10 hours before removal of the volatile components and distillation at reduced pressure to afford the β -(alkylthio)aldehydes as colourless oils.

General procedure for the reductive aldol reactions (Table 1, Entry 1)

Hydrogen gas was bubbled through a stirred solution of $[\text{Rh}(\text{nbd})\text{dppe}]\text{ClO}_4$ (10 mg, 0.014 mmol)² dissolved in DCE (10 mL) for 2 minutes, during this time a color change from dark orange to yellow was realised, the solution was then purged with argon for a further 0.5 minutes. To this mixture was next added 3-(methylthio)propionaldehyde (14 μL , 15 mg, 0.14 mmol) and acrylonitrile (46 μL , 37 mg, 0.7 mmol). The reaction mixture was then heated to 70 °C for 16 hours. The crude reaction mixture was concentrated in *vacuo* and purified by column chromatography (3:1 hexane: EtOAc) to give the product as a colorless oil (16 mg, 88 %) as a mixture of diastereomers (2.3:1); δ_{H} (300 MHz, CDCl_3) (Major diastereomer) 5.08 (1H, ddd, J 8.0, 4.2, 4.2 OCH), 2.90 (1H, m, CHCN), 2.76-2.70 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.66-2.61 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.07 (3H, s, SCH_3), 1.98-1.83 (2H, m, CH_2CHO), 1.27 (3H, d, J 7.4, CHCH_3); (Minor diastereomer) 4.96 (1H, ddd, J 9.0, 5.0, 3.0, OCH), 2.99 (1H, qd, CHCN), 2.76-2.70 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.66-2.61 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.04 (3H, s, SCH_3), 1.98-1.83 (2H, m, CH_2CHO), 1.27 (3H, d, J 7.4, CHCH_3); δ_{C} (75 MHz, CDCl_3) 170.3, 118.8, 70.9, 33.2, 30.6, 29.3, 28.8, 28.0, 14.5, 13.5; ν_{max} (film) / cm^{-1} 2244, 1732; m/z (CI^+ , NH_3) 279 (100 %, $\text{M}+\text{NH}_4$); found 279.1196 [$\text{M}+\text{NH}_4$]⁺ $\text{C}_{11}\text{H}_{23}\text{N}_2\text{O}_2\text{S}_2$ requires 279.1195.

Table 1, Entry 2

The typical procedure was followed to afford the product as a colorless oil (16 mg, 79 %) as a mixture of diastereomers (3.3:1); δ_{H} (300 MHz, CDCl_3) (Major diastereomer) 5.07 (1H, m OCH), 3.04-2.85 (1H, m, CHCN), 2.79-2.71 (2H, m, CH_2S), 2.66-2.56 (10H, m, CH_2S / $\text{CH}_2\text{C}(\text{O})$), 2.09-1.81 (2H, m, $\text{CH}_2\text{CHOC}(\text{O})$), 1.27 (3H, d, J 7.2 CH_3CHCN), 1.20 (3H, t, J 7.5, SCH_2CH_3), 1.19 (3H, t, J 7.5, SCH_2CH_3); (Minor diastereomer) 4.96 (1H, m OCH), 3.04-2.85 (1H, m, CHCN), 2.79-2.71 (2H, m, CH_2S), 2.66-2.56 (10H, m, CH_2S , $\text{CH}_2\text{C}(\text{O})$), 2.09-1.81 (2H, m, $\text{CH}_2\text{CHOC}(\text{O})$), 1.27 (3H, d, J 7.2 CH_3CHCN), 1.20 (3H, t, J 7.5, SCH_2CH_3), 1.19 (3H, t, J 7.5, SCH_2CH_3); δ_{C} (75 MHz, CDCl_3) 171.72, 171.66, 120.2, 119.9, 72.7, 72.4, 35.1, 32.6, 30.8, 30.7, 27.6, 26.9, 26.40, 26.35, 26.35, 26.32, 15.08, 15.05, 15.0, 14.9, 14.7; ν_{max} (film) / cm^{-1} 2928, 1740, 1452; m/z (CI+) 307 (100 %, $\text{M}+\text{NH}_4$), 290, 245; found $[\text{M}+\text{H}]^+$ 290.1243 $\text{C}_{13}\text{H}_{24}\text{NO}_2\text{S}_2$ requires 290.1243.

Table 1, Entry 3

The typical procedure was followed to afford the product as a colorless oil (21 mg, 78 %) as a mixture of diastereomers (2.5:1); δ_{H} (300 MHz, CDCl_3) (Major diastereomer) 7.40-7.16 (10H, m, $\text{Ph} \times 2$), 5.17 (1H, ddd, J 7.5, 7.5, 7.2, OCH), 3.22-3.13 (2H, m, CH_2SPh), 3.13-2.81 (3H, m, CH_2SPh / CHCN), 2.70 (2H, t, J 7.2, CH_2CO_2), 2.18-1.88 (2H, m, $\text{CH}_2\text{CHOC}(\text{O})$), 1.30 (3H, d, J 7.2 CH_3CHCN); (Minor diastereomer) 7.40-7.16 (10H, m, $\text{Ph} \times 2$), 5.06 (1H, ddd, J 7.5, 7.5, 7.2, OCH), 3.22-3.13 (2H, m, CH_2SPh), 3.13-2.81 (3H, m, CH_2SPh / CHCN), 2.67 (2H, t, J 7.2, CH_2CO_2), 2.18-1.88 (2H, m, $\text{CH}_2\text{CHOC}(\text{O})$), 1.26 (3H, d, J 7.2 CH_3CHCN); δ_{C} (75 MHz, CDCl_3) 171.1, 171.06, 135.1, 134.7, 130.41, 130.37, 129.93, 129.91, 129.14, 129.10, 126.9, 126.6, 119.7, 119.4, 72.1, 71.8, 34.2, 34.19, 32.0, 30.4, 30.2, 29.8, 29.7, 29.2, 14.5, 14.2; ν_{max} (film) / cm^{-1} 2922,

1740, 1439; m/z (EI+) 385 (19 %, M+), 275, 203; found $[M+H]^+$ 386.1247 $C_{21}H_{24}NO_2S_2$ requires 386.1243; (Found C, 65.4; H, 6.0, N 3.6. $C_{21}H_{23}NO_2S_2$ requires C, 65.4; H, 6.0; N, 3.6).

Table 1, Entry 4

The typical procedure was followed to afford the product as a colorless oil (19 mg, 88 %) as a mixture of diastereomers (A:B:C, 6.6:3.6:1.0); δ_H (300 MHz, $CDCl_3$) (Diastereomer A) 5.00 (1H, m, OCH), 3.06-2.90 (1H, m, CHCN), 2.58-2.10 (10H, m, SCH_2CH_3 / $CH_2CHC(O)$), 1.32-1.15 (12H, m, SCH_2CH_3 / CH_2CHCH_3), 1.07 (3H, d, J 6.8, CH_3CHCN); (Diastereomer B) 4.84 (1H, m, OCH), 3.06-2.90 (1H, m, CHCN), 2.58-2.10 (10H, m, SCH_2CH_3 / $CH_2CHC(O)$), 1.32-1.15 (12H, m, SCH_2CH_3 / CH_2CHCH_3), 1.02 (3H, d, J 6.8, CH_3CHCN); (Diastereomer C) 5.19 (1H, m, OCH), 3.06-2.90 (1H, m, CHCN), 2.58-2.10 (10H, m, SCH_2CH_3 / $CH_2CHC(O)$), 1.32-1.15 (12H, m, SCH_2CH_3 / CH_2CHCH_3), 1.09 (3H, d, J 6.8, CH_3CHCN); δ_C (75 MHz, $CDCl_3$) 173.5, 173.3, 118.8, 118.3, 74.3, 74.1, 73.5, 39.41, 39.35, 35.1, 34.9, 34.8, 34.7, 34.5, 34.2, 34.0, 33.7, 33.61, 33.57, 32.6, 27.9, 27.5, 27.3, 25.6, 25.4, 25.3, 25.2, 16.3, 16.2, 16.1, 16.0, 14.5, 14.3, 14.2, 13.6, 13.5; ν_{max} (film) / cm^{-1} 2971, 2929, 2361, 1741, 1458; m/z (CI+) 335 (100 %, $M+NH_4$), 318, 273; found $[M+H]^+$ 318.1558 $C_{15}H_{28}NO_2S_2$ requires 318.1556.

Table 1, Entry 5

The typical procedure was followed to afford the product as a colorless oil (16 mg, 73 %) as a mixture of diastereomers (A:B:C, 7.5:5:1); δ_H (300 MHz, $CDCl_3$) (Diastereomer A) 5.14-5.06 (1H, m, OCH), 3.25-3.09 (1H, m, CHCN), 3.09-2.83 (1H, m, CH_3CHSEt), 2.83-2.65 (1H, m, $CHSEt$), 2.59-2.41 (6H, m, SCH_2CH_3 / CH_2CO_2), 2.17-1.60 (2H, m, $CH_2CHOC(O)$), 1.34-1.12 (12H, m, $CHCH_3$ / SCH_2CH_3); (Diastereomer B)

5.29-5.21 (1H, m, OCH), 3.25-3.09 (1H, m, CHCN), 3.09-2.83 (1H, m, CH₃CHSEt), 2.83-2.65 (1H, m, CHSEt), 2.59-2.41 (6H, m, SCH₂CH₃ / CH₂CO₂), 2.17-1.60 (2H, m, CH₂CHOC(O)), 1.34-1.12 (12H, m, CHCH₃ / SCH₂CH₃); (Diastereomer C) 4.99-4.91 (1H, m, OCH), 3.25-3.09 (1H, m, CHCN), 3.09-2.83 (1H, m, CH₃CHSEt), 2.83-2.65 (1H, m, CHSEt), 2.59-2.41 (6H, m, SCH₂CH₃ / CH₂CO₂), 2.17-1.60 (2H, m, CH₂CHOC(O)), 1.34-1.12 (12H, m, CHCH₃ / SCH₂CH₃); δ_c (75 MHz, CDCl₃) 171.2, 171.1, 120.09, 120.06, 72.2, 71.6, 71.3, 71.2, 42.5, 40.5, 40.4, 39.7, 39.6, 37.6, 36.9, 36.8, 36.2, 35.8, 35.7, 31.4, 31.3, 31.0, 30.7, 30.6, 30.1, 24.9, 24.82, 24.78, 24.7, 24.25, 24.16, 23.23, 23.17, 22.0, 21.8, 21.5, 20.8; $\nu_{\max}$ (film) / cm⁻¹ 2968, 2728, 2244, 1740; m/z (EI+) 317 (13 %, M+), 288, 255; found 317.1476 [M+H]⁺ C₁₅H₂₈NO₂S₂ requires 317.1477.

Table 1, Entry 6

The typical procedure was followed to afford the product as a colorless oil (22 mg, 71 %) as a mixture of diastereomers (1.1:1); δ_H (300 MHz, CDCl₃) (Major Diastereomer) 7.35-7.08 (9H, m, Ph × 2), 7.00-6.88 (1H, m, Ph), 5.12-5.02 (1H, m, OCH), 4.28-4.18 (1H, m SCHPh), 3.77-3.61 (1H, m, CHCN), 2.85-2.52 (2H, m C_{H2}CO₂), 2.36-2.10 (4H, m, SCH₂CH₃), 2.10-1.92 (2H, m, CH₂CHO), 1.23-0.95 (6H, m CH₃CH₂S), 0.90-0.77 (3H, d, *J* 7.2, CH₃CHCN); (Minor Diastereomer) 7.35-7.08 (10H, m, Ph × 2), 4.70-4.60 (1H, m, OCH), 4.18-4.10 (1H, m SCHPh), 3.63-3.50 (1H, m, CHCN), 2.85-2.52 (2H, m C_{H2}CO₂), 2.36-2.10 (4H, m, SCH₂CH₃), 2.10-1.92 (2H, m, CH₂CHO), 1.23-0.95 (6H, m CH₃CH₂S), 0.90-0.77 (3H, d, *J* 7.2, CH₃CHCN); δ_c (75 MHz, CDCl₃) 170.2, 170.1, 141.5, 141.4, 129.11, 129.05, 128.3, 128.22, 128.17, 128.1, 119.8, 71.2, 45.5, 41.8, 30.7, 25.61, 25.55, 25.46, 14.73, 14.70; $\nu_{\max}$ (film) / cm⁻¹ 2963, 2921, 2244, 1742, 1453; m/z (CI+) 459 (25 %, M+NH₄), 442, 399, 249; found 442.1873 [M+H]⁺ C₂₅H₃₂O₂S₂N requires 442.1869.

Table 1, Entry 7

The typical procedure was followed to afford the product as a colorless oil (22 mg, 93 %) as a mixture of diastereomers (1.4:1); δ_{H} (300 MHz, CDCl_3) (Major diastereomer) 5.15-5.02 (1H, m, OCH), 3.20-2.75 (2H, m, CHCN / $\text{CH}_3\text{CHC}(\text{O})$), 2.74-2.42 (3H, m, CH_3CHS / $\text{CH}_3\text{CHOC}(\text{O})$), 1.57-1.51 (3H, m, $\text{CH}_3\text{CHC}(\text{O})$), 1.35-1.20 (15H, m, $\text{CH}_3\text{CH}_2\text{S}$ / CH_3), 0.87-0.74 (3H, m, CH_3CN); (Minor Diastereomer) 5.69-5.57 (1H, m, OCH), 3.20-2.75 (2H, m, CHCN / $\text{CH}_3\text{CHC}(\text{O})$), 2.74-2.42 (3H, m, CH_3CHS / $\text{CH}_3\text{CHOC}(\text{O})$), 1.57-1.51 (3H, m, $\text{CH}_3\text{CHC}(\text{O})$), 1.35-1.20 (15H, m, $\text{CH}_3\text{CH}_2\text{S}$ / CH_3), 0.87-0.74 (3H, m, CH_3CN); δ_{C} (75 MHz, CDCl_3) 175.1, 174.93, 174.91, 120.4, 120.3, 75.95, 75.93, 75.1, 41.02, 40.95, 36.7, 36.2, 36.1, 35.3, 35.2, 29.5, 29.1, 27.2, 27.04, 26.99, 26.91, 26.8, 18.0, 17.8, 16.2, 15.9, 15.8, 15.22, 15.18, 15.1, 14.9; ν_{max} (film) / cm^{-1} 2973, 2921, 2244, 1739, 1452; m/z (CI+) 363 (49 %, $\text{M}+\text{NH}_4$), 301, 284, 201; found 346.1870 [$\text{M}+\text{H}$] $^+$ $\text{C}_{17}\text{H}_{32}\text{NO}_2\text{S}_2$ requires 346.1869.

Table 1, Entry 8

The typical procedure was followed to afford the product as a colorless oil (16 mg, 73 %) as a mixture of diastereomers (1.4:1); δ_{H} (300 MHz, CDCl_3) (Major diastereomer) 5.26-5.17 (1H, m, OCH), 2.80-2.65 (3H, m, CHCN / CH_2CO_2), 2.58-2.38 (6H, m, SCH_2), 2.13, (3H, s, $\text{CH}_3\text{C}(\text{O})$), 1.85-1.70 (2H, m, $\text{CH}_2\text{CHOC}(\text{O})$), 1.25-1.13 (6H, m, $\text{CH}_3\text{CH}_2\text{S}$), 1.05 (3H, d, J 7.2, CH_3CHCN); (Minor Diastereomer) 5.34-5.25 (1H, m, OCH) 2.14 (1H, m, CHCN), 2.80-2.65 (2H, m, CH_2CO_2), 2.58-2.38 (6H, m, SCH_2), 2.14, (3H, s, $\text{CH}_3\text{C}(\text{O})$), 1.85-1.70 (2H, m, $\text{CH}_2\text{CHOC}(\text{O})$), 1.25-1.13 (6H, m, $\text{CH}_3\text{CH}_2\text{S}$), 1.04 (3H, d, J 7.2, CH_3CHCN); δ_{C} (75 MHz, CDCl_3) 209.51, 209.47, 171.9, 171.8, 74.0, 73.6, 50.63, 50.60, 35.3, 35.2, 34.6, 32.5, 31.1, 30.8, 29.7, 28.1, 27.7, 27.0, 26.9, 26.6, 26.4, 36.3, 25.9, 23.1, 15.09, 15.07, 12.0, 11.7; ν_{max} (film) / cm^{-1} 2971, 2928,

2103, 1734, 1714, 1644; ; m/z (CI+) 324 (100 %, $M+NH_4$), 307, 262, 190; found 307.1398 $[M+H]^+$ $C_{14}H_{27}O_3S_2$ requires 307.1396.

Table 1, Entry 9

The typical procedure was followed to afford the product as a colorless oil (19 mg, 74 %) as a mixture of diastereomers (3.3:1); δ_H (300 MHz, $CDCl_3$) (Major diastereomer) 8.01-7.95 (2H, m, Ph), 7.56-7.47 (1H, m, Ph), 7.46-7.37 (2H, m, Ph), 5.37-5.24 (1H, m, OCH), 3.87 (1H, quint, J 6.8, $CHCH_3$), 2.71-2.61 (2H, m, SCH_2CH_3), 2.52-2.31 (8H, m, SCH_2 / CH_2CO_2), 1.88-1.74 (2H, m, $CH_2CHOC(O)$), 1.21-1.08 (9H, m, SCH_2CH_3) / $CHCH_3$); (Minor Diastereomer) 7.87-7.82 (2H, m, Ph), 7.56-7.47 (1H, m, Ph), 7.46-7.37 (2H, m, Ph), 5.37-5.24 (1H, m, OCH), 3.75 (1H, quint, J 6.8, $CHCH_3$), 2.71-2.61 (2H, m, SCH_2CH_3), 2.52-2.31 (8H, m, SCH_2 / CH_2CO_2), 1.88-1.74 (2H, m, $CH_2CHOC(O)$), 1.21-1.08 (9H, m, SCH_2CH_3) / $CHCH_3$); δ_C (75 MHz, $CDCl_3$) 201.9, 201.3, 171.9, 171.8, 137.0, 136.7, 129.2, 129.0, 128.7, 128.5, 75.0, 74.8, 44.3, 44.2, 35.3, 35.2, 32.6, 32.5, 30.5, 28.1, 27.8, 26.91, 26.86, 26.4, 26.29, 26.25, 26.15, 15.1, 14.1, 12.2; ν_{max} (film) / cm^{-1} 2969, 2928, 2103, 1734, 1682, 1448; m/z (CI+) 386 (52 %, $M+NH_4$), 369, 252, 235; found 369.1550 $[M+H]^+$ $C_{19}H_{29}O_3S_2$ requires 369.1553.

Table 1, Entry 10

The typical procedure was followed to afford the product as a colorless oil (18 mg, 67 %) as a mixture of diastereomers (3.3:1); δ_H (300 MHz, $CDCl_3$) (Major diastereomer) 7.35-7.25 (2H, m, Ph), 7.21-7.12 (1H, m, Ph), 7.05-6.96 (2H, m, Ph), 5.44-5.29 (1H, m, OCH), 2.99 (1H, quint, J 7.2, $CHCH_3$), 2.73 (2H, br t, J 7.4, CH_2CO_2), 2.61-2.40 (8H, m, CH_2S), 2.05-1.78 (2H, m, $CH_2CHOC(O)$), 1.29-1.12 (9H, m, SCH_2CH_3) / $CHCH_3$); (Minor Diastereomer) 7.35-7.25 (2H, m, Ph), 7.21-7.12 (1H, m, Ph), 7.05-6.96 (2H, m, Ph), 5.44-5.29 (1H, m, OCH), 2.96-2.85 (1H, m, $CHCH_3$), 2.73 (2H, br t, J 7.4,

CH_2CO_2), 2.61-2.40 (8H, m, CH_2S), 2.05-1.78 (2H, m, $\text{CH}_2\text{CHOC(O)}$), 1.29-1.12 (9H, m, SCH_2CH_3 / CHCH_3); δ_{C} (75 MHz, CDCl_3) 172.4, 172.0, 171.9, 171.7, 150.92, 150.86, 130.0, 129.9, 126.4, 121.9, 121.8, 121.7, 115.7, 74.2, 73.7, 46.7, 43.4, 35.3, 32.5, 31.7, 28.0, 27.7, 26.9, 26.4, 26.3, 15.11, 15.06, 13.1, 12.2; ν_{max} (film) / cm^{-1} 2968, 2816, 1758, 1736, 1493; m/z (CI^+) 402 (100 %, $\text{M}+\text{NH}_4$), 385, 291, 268; found 385.1504 $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{29}\text{O}_4\text{S}_2$ requires 385.1502; (Found C, 59.4; H, 7.4. $\text{C}_{19}\text{H}_{28}\text{O}_4\text{S}_2$ requires C, 59.3; H, 7.3).

Preparation of 2-Methyl-5-methylsulfanyl-1-phenylpentane-1,3-dione (5)

To a stirred solution of diisopropylamine (0.78 mL, 582 mg, 4.5 mmol) dissolved in THF (20 mL) cooled to $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (1.8 mL of a 2.5 M hexanes solution) dropwise over 10 minutes. The reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$ for a then to the reaction mixture was added propiophenone (0.6 mL, 4.5 mmol) over a 10 minute period. The reaction mixture was then warmed to room temperature a left for a further 30 minutes before a solution of methy-3-(methylthio)propionate (0.56 mL, 604 mg, 4.5 mmol) dissolved in THF (10 mL) was added over 10 minutes. The reaction mixture was left overnight at room temperature before it was quenched with water (10 mL) and extracted with ether ($3 \times 30\text{ mL}$), the combined organic phases were dried (MgSO_4) and concentrated in *vacuo* to give a pale yellow oil which was purified further by column chromatography (9:1 hexane: EtOAc) to afford the title compound as a colorless oil (479 mg, 45 %); δ_{H} (300 MHz, CDCl_3) 7.93-7.87 (2H, m, Ph), 7.57-7.50 (1H, m, Ph), 4.46 (1H, q, J 7.2, C(O)CHC(O)), 2.82-2.56 (4H, m, $\text{CH}_2\text{CH}_2\text{C(O)}$), 1.98 (3H, br s, SCH_3), 1.39 (3H, d, J 7.2, CHCH_3); δ_{C} (75 MHz, CDCl_3) 204.4, 196.3, 134.8, 132.8, 127.9, 127.7, 55.2, 39.5, 26.8, 14.7, 12.6; ν_{max} (film) / cm^{-1} 2918, 1719, 1675, 1448.

General procedure for three-component reductive aldol reactions: Preparation of *tert*-Butyl 3-cyano-2-(3-methylsulfanylpropionyloxy)butanoate (8)

Hydrogen gas was bubbled through a stirred solution of [Rh(nbd)dppe]ClO₄ (10 mg, 0.014 mmol) dissolved in DCE (10 mL) for 2 minutes, during this time a color change from dark orange to yellow was realised, the solution was then purged with argon for a further 0.5 minutes. To this mixture was next added 3-(methylthio)propionaldehyde (14 µL, 15 mg, 0.14 mmol) followed by *tert*-butyl glyoxylate³ (18 mg, 0.14 mmol) and acrylonitrile (18 µL, 15 mg, 0.28 mmol). The reaction mixture was then heated to 70 °C for 16 hours. The crude reaction mixture was concentrated in *vacuo* and purified by column chromatography (9:1 Hexanxe: EtOAc) to give the product as a colorless oil (25 mg, 60 %) as a mixture of diastereomers (1.4:1); δ_H(300 MHz, CDCl₃) (Major Diastereomer) 5.07 (1H, d, *J* 4.1, OCH), 3.27-3.13 (1H, m, CHCN), 2.80-2.67 (4H, m, CH₂CH₂S), 2.08 (3H, br s, SCH₃), 1.43 (9H, s, *t*-Bu), 1.34 (3H, d, *J* 7.2, CH₃CH); (Minor Diastereomer) 4.95 (1H, d, *J* 4.1, OCH), 3.27-3.13 (1H, m, CHCN), 2.80-2.67 (4H, m, CH₂CH₂S), 2.08, 2.08 (3H, br s, SCH₃), 1.44 (9H, s, *t*-Bu), 1.34 (3H, d, *J* 7.5, CH₃CH); δ_C(75 MHz, CDCl₃) 171.2, 171.1, 166.0, 165.7, 119.5, 119.0, 84.6, 72.5, 72.0, 34.44, 34.39, 29.14, 29.09, 28.5, 28.3, 28.2, 15.92, 15.87, 15.0, 13.7; ν_{max} (film) / cm⁻¹ 2965, 2922, 1747, 1368; *m/z* (CI⁺) 305 (100 %, M+NH₄), 288, 249, 187; found 305.1528 [M+NH₄]⁺ C₁₃H₂₅O₄N₂S requires 305.1530.

Preparation of *tert*-Butyl 3-methyl-2-(3-methylsulfanylpropionyloxy)-4-oxo-4-phenylbutanoate (9)

The general procedure for three component coupling was employed substituting phenyl vinyl ketone (36 µL, 37 mg, 0.28 mmol) for acrylonitrile to give the product as a

colorless oil (51 mg, 99 %) as a mixture of diastereomers (2.1:1); δ_{H} (300 MHz, CDCl_3) (Major Diastereomer) 7.93-7.85 (2H, m, Ph), 7.58-7.48 (1H, m, Ph), 7.47-7.38 (2H, m, Ph), 5.35 (1H, d, J 5.3, OCH), 3.98 (1H, dt, J 7.2, 6.8, CH_2CHCHO), 2.74-2.45 (4H, m, $\text{CH}_2\text{CH}_2\text{S}$), 2.04 (3H, s, SCH_3), 1.34 (9H, s, $t\text{-Bu}$), 1.21 (3H, d, J 6.8, CH_3CH); (Minor Diastereomer) 7.93-7.85 (2H, m, Ph), 7.58-7.48 (1H, m, Ph), 7.47-7.38 (2H, m, Ph), 5.16 (1H, d, J 5.3, OCH), 3.88 (1H, dt, J 7.2, 6.8, CH_2CHCHO), 2.74-2.45 (4H, m, $\text{CH}_2\text{CH}_2\text{S}$), 1.99 (3H, s, SCH_3), 1.38 (9H, s, $t\text{-Bu}$), 1.19 (3H, d, J 6.8, CH_3CH); δ_{C} (75 MHz, CDCl_3) 198.4, 170.0, 169.9, 166.9, 166.7, 135.1, 134.7, 132.3, 132.3, 127.8, 127.5, 127.42, 127.37, 127.25, 81.90, 81.88, 73.36, 73.32, 42.9, 41.2, 41.0, 33.3, 33.1, 28.1, 27.8, 27.7, 26.9, 26.8, 14.43, 14.37, 11.9, 11.5, 10.8; ν_{max} (film) / cm^{-1} 2979, 2920, 1743, 1687, 1156; m/z (CI+) 384 (100 %, $\text{M}+\text{NH}_4$), 328, 264, 208; found 367.1576 $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{27}\text{O}_5\text{S}$ requires 367.1574; (Found C, 61.6; H, 7.2. $\text{C}_{19}\text{H}_{26}\text{O}_5\text{S}$ requires C, 62.3; H, 7.15).

Preparation of ($\text{C}_1\{^2\text{H}\}$)-3-(methylthio)propionaldehyde

To a stirred suspension of LiAlD_4 (1.56 g, 37.3 mmol) in ether (100 mL) cooled to -20°C was added methy-3-(methylthio)propionate (4.7 mL, 5.00 g, 37.3 mmol) over a 30 minute period. The reaction mixture was warmed to room temperature over a 2 hour period. The reaction was then quenched carefully with D_2O (4 mL) and the resulting suspension was dried over MgSO_4 , the resultant slurry was filtered and washed with ether (2×25 mL). The combined organic washings were concentrated in *vacuo* to afford ($\text{C}_1\{^2\text{H}_2\}$, $\text{O}\{^2\text{H}\}$)-3-(methylthio)propanol as a colourless oil. This material was used immediately without further purification. To a solution of the (D_3)-3-(methylthio)propanol (0.5 g, 4.5 mmol) dissolved in DCM (10 mL) at room temperature was added Dess-Martin periodinane (2.04 g, 4.81 mmol) over a 1 hour period. Careful monitoring of the reaction by TLC ensured no over oxidation. Once the reaction was complete the crude reaction mixture was purified by column chromatography (100 % DCM) to afford the title compound as a colorless oil (330 mg, 67 %). This material was used immediately in further reactions; δ_{H} (300 MHz, CDCl_3) 2.77-2.65 (4H, m,

$\text{CH}_2\text{CH}_2\text{S}$), 2.07 (3H, s, SCH_3); δ_{C} (75 MHz, CDCl_3) 200.7 (t, J 27.2, $\text{C}(\text{O})\text{D}$), 43.6 (t, J 3.8, $\text{CH}_2\text{C}(\text{O})$), 26.8, 16.0; ν_{max} (film) / cm^{-1} 2099, 1641.

Preparation of ($\text{C}_5\{^2\text{H}\}$)-*tert*-Butyl 3-methyl-2-(3-methylsulfanylpropionyloxy)-4-oxo-4-phenylbutanoate (11)

The general procedure for the three-component coupling was employed utilising the ($\text{C}_1\{^2\text{H}\}$)-aldehyde and substituting phenyl vinyl ketone (36 μL , 37 mg, 0.28 mmol) for acrylonitrile, to give the product as a colorless oil (52 mg, 99 %) as a mixture of diastereomers (2.1:1); δ_{H} (300 MHz, CDCl_3) (Major Diastereomer) 7.93-7.85 (2H, m, Ph), 7.58-7.48 (1H, m, Ph), 7.47-7.38 (2H, m, Ph), 5.35 (1H, d, J 5.3, OCH), 3.98 (1H, dt, J 7.2, 6.8, CH_2CHCHO), 2.74-2.45 (4H, m, $\text{CH}_2\text{CH}_2\text{S}$), 2.04 (3H, s, SCH_3), 1.34 (9H, s, *t*-Bu), 1.21 (2H, m, CH_2^2HCH); (Minor Diastereomer) 7.93-7.85 (2H, m, Ph), 7.58-7.48 (1H, m, Ph), 7.47-7.38 (2H, m, Ph), 5.16 (1H, d, J 5.3, OCH), 3.88 (1H, dt, J 7.2, 6.8, CH_2CHCHO), 2.74-2.45 (4H, m, $\text{CH}_2\text{CH}_2\text{S}$), 1.99 (3H, s, SCH_3), 1.38 (9H, s, *t*-Bu), 1.19 (2H, m, CH_2^2HCH); δ_{C} (75 MHz, CDCl_3) 198.4, 170.0, 169.94, 169.88, 166.7, 135.1, 134.7, 132.35, 132.32, 127.8, 127.5, 127.42, 127.37, 81.9, 73.4, 72.3, 44.2, 41.1, 40.9, 33.2, 33.1, 27.8, 27.7, 26.9, 26.8, 14.43, 14.38, 11.9, 11.6, 11.3 (t, J 19.6, CH_2DCH); ν_{max} (film) / cm^{-1} 2979, 2920, 1742, 1688, 1154; (Found C, 61.8; H, 7.1. $\text{C}_{19}\text{H}_{25}\text{DO}_5\text{S}$ requires C, 62.1; H, 7.4).

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Table 1, Entry 1

Table 1, Entry 2

Table 1, Entry 3

Table 1, Entry 4

Table 1, Entry 5

Table 1, Entry 6

Table 1, Entry 7

Table 1, Entry 8

Table 1, Entry 9

Table 1, Entry 10

-Methyl-5-methylsulfanyl-1-phenylpentane-1,3-dione

tert-Butyl 3-cyano-2-(3-methylsulfanylpropionyloxy)butane

tert-Butyl 3-cyano-2-(3-methylsulfanylpropionyloxy)-4-oxo-4-phenylbutanoate

(C₅{²H})-*tert*-Butyl 3-cyano-2-(3-methylsulfanylpropionyloxy)-4-oxo-4-phenylbutanate