

Supporting Information for:

One-Carbon Chain Extension of Esters to α -Chloroketones: A Safer Route Without Diazomethane

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General. NMR spectra were obtained at 25 °C in solvent CDCl₃ unless otherwise indicated at a field strength of 400.1 MHz (¹H NMR) or 100.6 MHz (¹³C NMR). Coupling constants (*J*) are given in Hertz. Flash chromatography was performed on 220-400 mesh silica (E. Merck) following the standard procedure [Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923]. The diastereomer ratios for the β-chlorohydrins were determined using a 250 mm Zorbax EclipseXDB-C18 column (1.5 mL/min, 25 min runs) using a solvent gradient as follows. Solvent 1 = 0.1% trifluoroacetic acid in water, solvent 2 = 0.1% trifluoroacetic acid in acetonitrile; initial ratio water/acetonitrile was 95:5 and this was ramped to 5:95 over the course of 23 min.

Synthesis of Achiral α-Chloroketones

Dimethylsulfoxonium 2-(4-chlorophenyl)-2-oxoethylide, 4b. The general procedure for **4a** was followed except using 5 equiv of methylide and a reaction time of 48 h; the crystalline product was obtained in 53% yield. Anal. Calcd for C₁₀H₁₁ClO₂S: C, 52.06; H, 4.81. Found: C, 52.26; H, 5.03. ¹H NMR: δ 3.52 (s, 6H), 4.94 (s, 1H), 7.33 (d, *J* = 8.5, 2H), 7.71 (d, *J* = 8.5, 2H). ¹³C NMR: δ 42.8, 68.9, 128.4, 128.8, 137.1, 137.7, 181.3.

Dimethylsulfoxonium 2-(2-furanyl)-2-oxoethylide, 4c. The general procedure for **4a** was followed; the crystalline product was obtained in 80% yield. Anal. Calcd for C₈H₁₀O₃S: C, 51.59; H, 5.41. Found: C, 51.84; H, 5.46. ¹H NMR: δ 3.46 (s, 6H), 4.98 (s, 1H), 6.39 (s, 1H), 6.86 (s, 1H), 7.36 (s, 1H). ¹³C NMR: δ 42.5, 67.9, 111.2, 111.5, 143.4, 153.4, 172.2.

Dimethylsulfoxonium 2-oxononylide, 4d. The general procedure for **4a** was followed but using 5 equiv of methylide and a 72 h reaction time; the crystalline product was isolated by flash chromatography in 25% yield. . Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.51; H, 10.15. Found: C, 60.32; H, 10.07. 1H NMR: δ 0.83 (m, 3H), 1.25 (m, 8H), 1.52 (m, 2H), 2.12 (t, $J = 7.6$, 2H), 3.36 (s, 6H), 4.36 (s, 1H). ^{13}C NMR: δ 14.0, 22.5, 26.0, 29.0, 29.3, 31.6, 40.9, 42.0, 69.0, 191.3.

2,4'-Dichloroacetophenone, 5b. The general procedure for **5a** was followed and the crystalline product was obtained in 92% yield. An analytical sample was prepared by recrystallization from 80:20 ethanol/water. . Anal. Calcd for $C_8H_6Cl_2O$: C, 50.81; H, 3.20. Found: C, 50.58; H, 3.16. 1H NMR: δ 4.68 (s, 2H), 7.48 (d, $J = 8.5$, 2H), 7.87 (d, $J = 8.5$, 2H). ^{13}C NMR: δ 46.1, 129.7, 130.4, 132.9, 141.0, 190.4.

Chain Extension of α -Amino Epoxides

Dimethylsulfoxonium (3*S*)-2-oxo-3-(benzyloxycarbonylamino)-4-methylpentylide, 7b. The general procedure for **7a** was followed except that 5 equiv of methylide were employed; the crude product was obtained in 98% yield. 1H NMR: δ 0.87 (d, $J = 6.9$, 3H), 0.94 (d, $J = 6.9$, 3H), 2.30 (m, 1H), 3.32 (s, 3H), 3.36 (s, 3H), 4.00 (m, 1H), 4.53 (s, 1H), 5.08 (s, 2H), 5.76 (d, $J = 8.6$, 1H), 7.35 (m, 5H). Several resonances in the ^{13}C NMR appear to be doubled due to apparent hindered rotation. ^{13}C NMR: δ 17.9, 19.8, 32.1, 41.9, 42.2, 53.7, 62.6, 63.5, 66.8, 70.3, 128.2, 128.2, 128.7, 136.9, 156.6, 187.4, 187.6.

Dimethylsulfoxonium 2-oxo-3-(*tert*-butoxycarbonylamino)-4-phenylbutylide, 7c.

The general procedure for **7a** was followed, except that trimethylsulfoxonium iodide was

substituted for the chloride and N-(BOC)-phenylalanine 4-nitrophenyl ester was utilized as substrate. The crude product was obtained in 99% yield. ^1H NMR: δ 1.41 (s, 9 H), 2.98 (m, 2 H), 3.25 (s, 3 H), 3.35 (s, 3 H), 4.28 (s + m, 2 H total), 5.22 (d, J = 8.8, 1 H), 7.15-7.31 (m, 5 H). ^{13}C NMR: δ 28.0, 39.5, 41.5, 41.8, 57.6, 69.4, 79.0, 126.2, 127.9, 129.2, 137.4, 154.9, 186.4.

(S)-1-Chloro-3-(benzyloxycarbonylamino)-4-methyl-2-pentanone, 8b. The general procedure for **8a** was followed except that **7b** was used as starting material. The enantiomeric excess was determined to be >99% by supercritical fluid chromatography (Chiralpak AD-H, 150 x 4.6 mm, 5 μ particle size, 15% methanol in CO_2 mobile phase, 40 $^\circ\text{C}$, 2 mL/min, 150 bar). Retention times for the enantiomers were assigned using an authentic racemate as 2.24 and 2.79 min. Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{ClNO}_3$: C, 59.26; H, 6.39; N, 4.94. Found: C, 58.90; H, 6.26; N, 5.04. ^1H NMR: δ 0.83 (d, J = 7.1, 3H), 1.02 (d, J = 7.1, 3H), 2.19 (m, 1H), 4.21 (s, 2H), 4.55 (m, 1H), 5.10 (s, 1H), 5.41 (d, J = 8.1, 1H), 7.35 (m, 5H). ^{13}C NMR: δ 17.1, 19.9, 30.4, 47.5, 62.8, 67.5, 128.4, 128.6, 128.8, 136.3, 156.7, 201.6.

(3S)-1-Chloro-3-(tert-butoxycarbonylamino)-4-phenyl-2-butanone, 8c. The general procedure for **8a** was followed except that **7c** was used as starting material. The enantiomeric excess was determined to be >99% by supercritical fluid chromatography (Chiralcel OD-H, 250 x 4.6 mm, 5 μ particle size, 3% methanol in CO_2 mobile phase, 40 $^\circ\text{C}$, 2 mL/min, 150 bar). Retention times for the enantiomers were assigned using an authentic racemate as 6.16 and 6.74 min. The product was crystallized from hot 95:5 hexane/MTBE to afford pure **8c** as an off-white solid. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{ClNO}_3$: C,

60.50; H, 6.77; N, 4.70. Found: C, 60.68; H, 6.76; N, 4.63. ^1H NMR: δ 1.40 (s, 9H), 2.94-3.12 (m, 2H), 4.00 (d, $J = 16.2$, 1H), 4.18 (d, $J = 16.2$, 1H), 4.68 (m, 1H), 5.10 (b, 1H), 7.14-7.47 (m, 5H). ^{13}C NMR: δ 28.4, 37.8, 47.8, 58.7, 80.7, 127.5, 129.1, 129.4, 135.9, 155.5, 201.6.

Anti N-Protected Amino Epoxides

(2S,3S)-1-Chloro-3-(benzyloxycarbonylamino)-4-methyl-2-pentanol, 9b. Sodium borohydride (27 mg, 0.72 mmol) was added in one portion to a solution of chloroketone **8b** (184 mg, 0.65 mmol) in ethanol at 0 °C. After 1 h at this temperature, the mixture was diluted with water (10 mL) and was extracted with dichloromethane. HPLC analysis of the crude reaction mixture indicated the ratio of diastereomers anti/syn = 92:8; the identity of these peaks was confirmed by HPLC/mass spectroscopy. The solvent was removed at reduced pressure and the residue was crystallized from hot 95:5 heptane/ethyl acetate to afford **9b** (155 mg, 84%) as a single diastereomer. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{ClNO}_3$: C, 58.84; H, 7.05; N, 4.90. Found: C, 58.81; H, 7.16; N, 4.82. ^1H NMR: δ 0.88 (d, $J = 6.9$, 3H), 0.96 (d, $J = 6.9$, 3H), 2.19 (m, 1H), 2.83 (m, 1H), 3.59 (m, 1H), 3.62-3.80 (m, 3H), 4.81 (m, 1H), 5.11 (s, 2H), 7.37 (s, 5H). ^{13}C NMR: 16.4, 20.3, 27.8, 48.6, 58.4, 67.2, 72.6, 128.2, 128.3, 128.6, 136.4, 157.1.

(2S,3S)-1-chloro-3-(tert-butoxycarbonylamino)-4-phenyl-2-butanol, 9c. A solution of chloroketone **8c** (5.00 g, 16.8 mmol) in THF (84 mL) and water (9 mL) was treated sodium borohydride (1.50 g, 42 mmol) at 0 °C. The temperature was maintained for 45 min after which the reaction mixture was concentrated to dryness. The residue was stirred in a mixture of ethyl acetate (150 mL) and water (25 mL). Saturated potassium

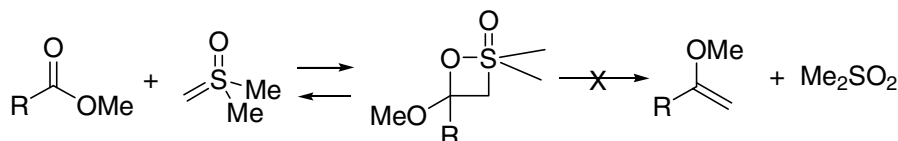
bisulfite solution was carefully added at 0 °C until the pH of the mixture reaches 1.5.

The resulting mixture was diluted with 350 mL of ethyl acetate and the layers were separated. The organic layer was washed with water and brine, dried over magnesium sulfate and concentrated to a white solid. The material was crystallized from hot ethyl acetate to afford **9c** (2.57 g, 50%). Anal. Calcd for C₁₅H₂₂ClNO₃: C, 60.10; H, 7.40; N 4.67. Found: C, 60.17; H, 7.12; N, 4.50. ¹H NMR (DMSO-d₆): δ 1.26 (s, 9H), 2.56 (dd, *J* = 14.2, 12.1, 1H), 2.98 (d, *J* = 14.2, 1 H), 3.44-3.73 (m, 4 H), 5.43 (d, *J* = 7.9, 1H), 6.71 (d, *J* = 12.1, 1H), 7.11-7.30 (m, 5H). ¹³C NMR (DMSO-d₆): δ 28.5, 36.0, 48.3, 54.7, 73.2, 77.9, 126.1, 128.2, 129.7, 139.6, 155.5.

[(1*S*)-1-(2*S*)-Oxiranyl-2-phenylethyl] carbamic acid t-butyl ester, 10. A 10 mL flame-dried flask equipped with a stir bar and an argon inlet was charged with **9c** (200 mg, 0.67 mmol), isopropanol (3.6 mL), and THF (1.0 mL). The solution was cooled to 16 °C and potassium *tert*-butoxide (79 mg, 0.67 mmol) was added in one portion and stirring was continued at this temperature for 30 min. Acetic acid (3 drops) was added and the volatiles were removed at reduced pressure. The residue was taken up in methyl *t*-butyl ether (10 mL) and extracted with aqueous sodium bicarbonate (3 x 1.5 mL). The organic layer was dried with magnesium sulfate, filtered and concentrated to afford epoxide **10** (170 mg, 96%) as a light-yellow oil which solidified at room temperature. . Anal. Calcd for C₁₅H₂₁NO₃: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.77; H, 7.98; N, 5.20. ¹H NMR: δ 1.38 (s, 9H), 2.75 (br m, 1H), 2.80 (m, 1H), 2.87 (m, 1H), 2.95 (m, 2H), 3.69 (m, 1H), 4.46 (br s, 1H), 7.2-7.4 (m, 5H). ¹³C NMR: δ 28.5, 37.8, 47.1, 53.0, 53.4, 79.9, 126.9, 128.7, 129.6, 137.2, 153.4.

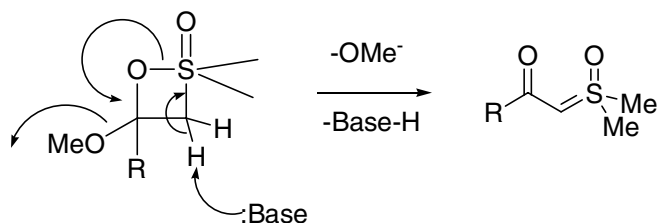
Effect of Excess Base

Mechanistic Rationale. *Excess* dimethylsulfoxonium methylide was invariably required to achieve high conversions in its reaction with esters, raising the possibility of general base catalysis. It is possible that the initial interaction between the neutral sulfur ylide and the carbonyl group will be a reversible 2+2 cycloaddition reaction as shown below.



In fact, Kawashima has structurally characterized a stabilized 1,2- λ^6 -oxathietane and has suggested that related oxathietanes are intermediates in the reaction of oxosulfonium ylides with carbonyl compounds.¹ Moreover, reversible formation of the analogous oxaphosphetane intermediates has been observed spectroscopically during the Wittig reaction.² However, both the relative weakness of the sulfone S=O bond versus the phosphine oxide P=O bond³ and the destabilizing effect of the alkoxy group will disfavor cycloreversion in the opposite sense required to complete the olefination process.

One possible explanation is that the reaction instead proceeds by irreversible deprotonation of the oxathietane intermediate as shown schematically below. Although an equivalent of base (methoxide) is regenerated in this process, such a reaction should be favored by a high concentration of base.



Preliminary Results. Several experiments have failed to provide evidence for this explanation. For example, in otherwise identical reactions methyl 4-chlorobenzoate **3b** was treated with (A) 5 equiv of dimethylsulfoxonium methylide, (B) 3 equiv of dimethylsulfoxonium methylide, or (C) 3 equiv of dimethylsulfoxonium methylide in the presence of an additional 2 equiv of potassium *tert*-butoxide. After 24 h at room temperature, the conversion in A was 73% by HPLC while in B conversion was 26%. In reaction C, the conversion was further diminished (3%) and several unidentified side-products were now present in the HPLC trace. Additional mechanistic studies will be required to understand the requirement for excess sulfur ylide.

During these studies we did note that, when dimethylsulfoxonium methylide was generated from trimethylsulfoxonium chloride and LDA (rather than the usual KO^tBu), the reaction of **4a** was complete in 2 h using as little as 1.5 equiv of reagent. Curiously, applying the same protocol to **4b** did not provide any improvement versus reagent generated with potassium *tert*-butoxide.

An alternative explanation concerning the requirement for excess ylide may simply be that oligomerization of the reagent occurs in competition with the desired attack on the ester functionality. This competitive process would be more severe in the case of the less activated esters. It should be possible to differentiate between these models by kinetic studies; however, these have not been undertaken to date.

References and Notes

1. (a) Ohno, F.; Kawashima, T.; Okazaki, R. *J. Am. Chem. Soc.* **1996**, *118*, 697. (b) Kawashima, T. *Coord. Chem. Rev.* **2003**, *244*, 137.
2. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. However, Vedejs has argued cogently that reversible Wittig reactions are in fact rare and that existing literature examples may represent isolated cases. See: Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1.
3. According to one estimate, the difference in energy between the P=O bond of triphenylphosphine oxide and the S=O bond of dimethylsulphone is 15 kcal/mol. Harlan, E. W.; Berg, J. M.; Holm, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 6992 and especially Table III therein. Moreover, others have assigned a considerably higher strength to the same P=O bond and the 15 kcal/mol value should probably be regarded as a minimum value. Kirklin, D. R.; Domalski, E. S. *J. Chem. Thermodynamics* **1988**, *20*, 743.