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The Generation of Ketenes from Acid Chlorides Using NaH/Crown Ether Shuttle-Deprotonation for Use in Asymmetric Catalysis

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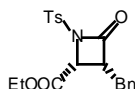
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Supporting Information

General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used were commercially available from Aldrich and Acros. All solvents and acid chlorides were dried and distilled by standard methods. Catalysts **2**,¹ Imine **3**,² and 2,3,4,5,6,6-Hexachloro-2,4-cyclohexadien-1-one **5**³ were prepared according to literature procedure. ¹H and ¹³C NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in CDCl₃. The ¹H (400 MHz) and ¹³C (101 MHz) chemical shifts are given in parts per million () with respect to internal TMS standard or residual solvent peaks. FTIR spectra were recorded on a Bruker Vector 22 spectrometer and optical rotations were recorded on a Perkin Elmer 120 polarimeter at room temperature. Enantiomeric ratios were obtained using a Waters Millipore Model 510 head unit, a Waters Millipore Lambda-Max Model 481LC spectrophotometer, and a Hewlett Packard integrator with a Regis Technologies (*R,R*)-Whelk-01 Chiral analytical HPLC column for **4** or a Chiracel AD analytical column for **6**.

Representative synthesis of β -lactams **4.** To a suspension of NaH (0.062 g, 2.58 mmol), benzoylquinine (0.055 g, 0.13 mmol) and 15-crown-5 (0.028 g, 0.13 mmol) in toluene (5 mL) at -78° C⁴ was added hydrocinnamoyl chloride **1** (0.479 g, 2.83 mmol) in toluene (1 mL) over 3 min. The mixture was then stirred vigorously for 7 h. A solution of **3** (0.330 g, 1.29 mmol) in toluene (9 mL) was then added through a syringe pump over 1 h (0.16 mL/min) and the reaction was warmed to room temperature over 6 h. The reaction was then quenched with 1M HCl (3 mL) and washed three times with 10% Na₂CO₃ (10 mL). The combined aqueous layers were back extracted twice with Et₂O (10 mL) and the combined organic layers were then dried over MgSO₄, filtered and concentrated. The crude product was purified on a short plug of silica (15% EtOAc/hexanes) to yield **4** (0.290 g, 60%).



Cis-(3*R*,4*R*)-1-*p*-toluenesulfonyl-3-benzyl-4-ethoxycarbonylazetidinone (4a**).**⁵ White crystalline solid recrystallized from Et₂O/hexanes (major diastereomer): mp = 93° C; [α]_D = +14.2° (c = 0.0123, CHCl₃); ¹H NMR (CDCl₃) 7.94 (d, 2H), 7.38 (d, 2H), 7.2- 7.3 (m, 3H), 7.11 (d, 2H), 4.73 (d, 1H), 4.17 (m, 1H), 3.99 (m, 1H), 3.89 (m, 1H), 3.08 (dd, 1H), 2.83 (dd, 1H), 2.47 (s, 3H), 1.12 (t, 3H) ppm; ¹³C NMR (CDCl₃) 167.5, 164.2, 145.7, 136.3, 135.5, 129.9, 128.8, 128.5, 128.1, 127.1, 62.3, 56.8, 53.3, 30.6, 21.9, 13.9 ppm; IR (CHCl₃) 3020, 1802, 1746, 1523, 1476, 1425, 1372, 1217. Anal Calcd for C₂₀H₂₁NO₅S C, 62.0; H, 5.46; N, 3.62. Found C, 61.9; H, 5.45; N, 3.62.

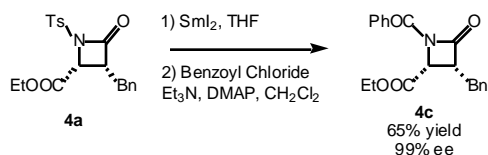
¹ Pracejus, H.; Maetje, H. *J. Prakt. Chem.* **1964**, 24, 195-205.

² Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, 49, 5058-5064.

³ Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, 123, 1531-1532.

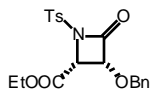
⁴ The optimal procedure for the formation of the corresponding ketene from acid chloride **1b** was 0° C for 1h. The reaction was then cooled to -78° C and the general procedure followed without any additional modifications.

⁵ The absolute configuration is assumed to be consistent with prior results; Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, 122, 7831-7832.



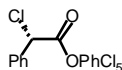
Determination of the enantiopurity of 4a. Due to difficulties with the separation of **4a** on chiral HPLC, it was converted to the N-benzoyl derivative **4c** to determine enantiopurity.⁶ A solution of SmI₂ (1.0 g, 2.58 mmol) in THF (0.04 M) was added to **4** at room temperature and stirred for 6 h. The reaction was quenched with brine and extracted four times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated. Into a flask containing the crude residue were added *N,N*-dimethylaminopyridine (DMAP, 0.0063 g, 0.052 mmol) and CH₂Cl₂ (10 mL). To this solution cooled to 0° C were added Et₃N (0.157 g, 1.55 mmol) and benzoyl chloride (0.145 g, 1.03 mmol). The reaction was stirred overnight, then washed three times with 10% Na₂CO₃ and the combined organic layers were dried over MgSO₄, filtered and concentrated. The crude residue was subjected to column chromatography (7% EtOAc/hexane) to yield **4c** (0.113 g, 65% yield).

Cis-(3*R*,4*R*)-1-benzoyl-3-benzyl-4-ethoxycarbonylazetidinone (4c). White crystalline solid recrystallized from Et₂O/hexanes (major diastereomer): mp = 129-130° C; [α]_D = +7.2° (c = 0.008, CHCl₃); ¹H NMR (CDCl₃) 8.06 (d, 2H), 7.59 (m, 2H), 7.47 (m, 4H), 7.24 (m, 2H), 4.76 (d, 1H), 4.42 (m, 2H), 3.91 (m, 1H), 3.23 (m, 1H), 3.10 (m, 1H), 1.18 (t, 3H) ppm; ¹³C NMR (CDCl₃) 168.7, 167.5, 164.2, 133.5, 129.9, 128.9, 128.6, 128.5, 128.3, 127.2, 126.4, 61.9, 54.0, 53.3, 51.0, 13.9 ppm; IR (CHCl₃) 3030, 2963, 2929, 1799, 1745, 1680, 1262, 1098, 1016; HPLC (10% CH₂Cl₂/1% HOAc/hexanes, 1.0 mL/min) (*R,R*) = 57.2, (*R,S*) = 41.0, (*S,R*) = 68.8, (*S,S*) = 52.2 min. Anal Calcd for C₂₀H₁₉NO₄ C, 71.2; H, 5.68; N, 4.15. Found C, 71.1; H, 5.67; N, 4.16.

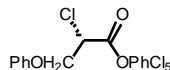


Cis-(3*R*,4*R*)-1-p-toluenesulfonyl-3-benzyloxy-4-ethoxycarbonylazetidinone (4b). White crystalline solid recrystallized from Et₂O/hexanes. All other data consistent with published report.⁶

Representative synthesis of α-haloesters 6. To a suspension of NaH (0.068 g, 2.7 mmol), benzoyl quinine (0.55 g, 0.13 mmol) and 15-crown-5 (0.028 g, 0.013 mmol) in THF (20 mL) at -78° C was added phenylacetyl chloride **1a** (0.5 g, 2.7 mmol) in THF (1mL). A solution of **5** (0.407 g, 1.35 mmol) in THF (20mL) was then added through a syringe pump over 3 h and the reaction was allowed to warm to room temperature. The reaction was then quenched with 150 mL H₂O. The aqueous layer was extracted twice with 25 mL of diethylether and once with 20 mL of CH₂Cl₂. The combined organic layers were then dried over MgSO₄, filtered and concentrated. The crude product was purified on a short plug of silica (hexanes) to yield **6a** (0.357 g, 63%).



(S)-2-Chloro-2-phenyl-acetic acid pentachlorophenyl ester (5a). White crystalline solid recrystallized from Et₂O/hexanes. All other data consistent with published report.³



(S)-2-Chloro-3-phenoxypropionic acid pentachlorophenyl ester (5b). White crystalline solid recrystallized from Et₂O/hexanes. All other data consistent with published report.³

⁶ Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831-7832.