

Supporting Information for

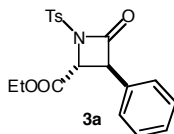
An Anionic Nucleophilic Catalyst System for the Diastereoselective
Synthesis of *trans*- β -Lactams

Anthony Weatherwax, Ciby J. Abraham, and Thomas Lectka *

Department of Chemistry, Johns Hopkins University, 3400 North Charles Street,
Baltimore, Maryland, 21218

General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used were commercially available from Aldrich, Fluka and Acros Chemicals. All solvents and acid chlorides were dried and distilled by standard methods. ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 MHz instrument in CDCl_3 . The ^1H (400 MHz) and ^{13}C (101 MHz) chemical shifts are given in parts per million (δ) with respect to internal TMS standard or residual solvent peaks. FTIR spectra were recorded on a Bruker Vector 22. The α -imino ester **2** was synthesized from ethyl glyoxylate and *N*-*p*-toluenesulfonyl isocyanate by Weinreb's procedure.¹ Catalyst **4a** has been previously characterized.²

General Procedure for the Synthesis of β -Lactams. To a solution of imidazoline derivative **4b** (23 mg, 0.031 mmol) and proton sponge **5** (76 mg, 0.312 mmol) in toluene (5 mL) at 0 °C was added phenylacetyl chloride **1a** (48 mg, 0.312 mmol) in toluene (1 mL) followed by imino ester **2** (240 mg, 0.936 mmol) in toluene (3 mL). The reaction was maintained at 0 °C overnight before it was quenched with 1M HCl (5 mL) at 0 °C. The aqueous layer was then extracted three times with CH_2Cl_2 and the combined organic layers were dried over MgSO_4 and filtered through Celite. Absorption onto silica gel followed by column chromatography (10% ethyl acetate/hexanes) afforded product **3a** in 50% yield (58 mg) and 37:1 dr [trans:cis].

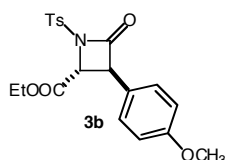


Trans-1-*p*-toluenesulfonyl-3-phenyl-4-ethoxycarbonylazetidione (3a). White crystalline solid recrystallized from Et_2O /hexanes: ^1H NMR (CDCl_3); δ 7.98 (d, 2H), 7.35

¹ Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

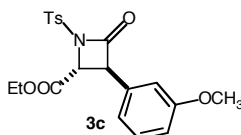
² Matura, T.; Ito, Y.; Saito, I. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3805-3809.

(d, 4H), 7.22 (m, 2H), 7.11 (m, 1H), 4.62 (d, 1H), 4.39 (d, 1H), 4.30 (m, 2H), 2.48 (s, 3H), 1.31 (t, 3H) ppm; ^{13}C NMR (CDCl_3) δ 168.2, 163.0, 145.9, 135.5, 131.9, 130.0, 129.5, 129.0, 128.2, 127.3, 62.5, 60.1, 59.1, 21.9, 14.4, ppm; IR (CH_2Cl_2): 1803, 1750, 1516, 1370, 1254, 1172, 1089, 1032 cm^{-1} . Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_5\text{S}$: C, 61.11; H, 5.13; N, 3.75. Found C, 61.23; H, 5.17; N, 3.76.



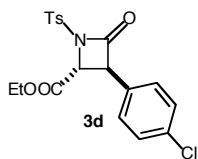
***Trans*-1-*p*-toluenesulfonyl-3-(4-methoxyphenyl)-4-ethoxycarbonylazetidinone**

(3b). White crystalline solid recrystallized from Et_2O /hexanes: ^1H NMR (CDCl_3); δ 7.97 (d, 2H), 7.39 (d, 2H), 7.12 (d, 2H), 6.87 (d, 2H), 4.54 (d, 1H), 4.32 (d, 1H), 4.28 (m, 2H), 3.79 (s, 3H), 2.47 (s, 3H), 1.30 (t, 3H) ppm; ^{13}C NMR (CDCl_3) δ 167.8, 163.0, 159.2, 145.1, 134.8, 129.2, 128.0, 127.5, 123.3, 114.2, 61.7, 60.0, 58.3, 55.3, 21.1, 13.6 ppm; IR (CH_2Cl_2): 1804, 1751, 1516, 1370, 1254, 1172, 1089, 1033 cm^{-1} . Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_6\text{S}$: C, 59.54; H, 5.25; N, 3.47. Found C, 59.65; H, 5.28; N, 3.49.



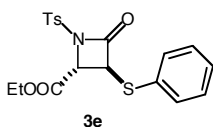
***Trans*-1-*p*-toluenesulfonyl-3-(3-methoxyphenyl)-4-ethoxycarbonylazetidinone**

(3c). Yellowish oil, would not crystallize from Et_2O /hexanes: ^1H NMR (CDCl_3); δ 7.98 (d, 2H), 7.39 (d, 2H), 7.26 (t, 1H), 6.86 (d, 1H), 6.79 (d, 1H), 6.72 (s, 1H), 4.60 (d, 1H), 4.36 (d, 1H), 4.29 (m, 2H), 3.78 (s, 3H), 2.47 (s, 3H), 1.31 (t, 3H) ppm; ^{13}C NMR (CDCl_3) δ 167.8, 162.5, 159.8, 145.5, 135.2, 132.7, 129.9, 127.8, 119.1, 114.0, 112.5, 62.3, 59.7, 58.6, 55.1, 21.5, 13.8 ppm; IR (CH_2Cl_2): 1802, 1749, 1373, 1173, 1088 cm^{-1} . Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_6\text{S}$: C, 59.54; H, 5.25; N, 3.47. Found C, 59.90; H, 5.59; N, 3.31.



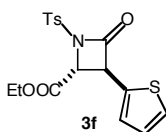
***Trans*-1-*p*-toluenesulfonyl-3-(4-chlorophenyl)-4-ethoxycarbonylazetidinone (3d).**

White crystalline solid recrystallized from Et₂O/hexanes: ¹H NMR (CDCl₃); δ 7.96 (d, 2H), 7.39 (d, 2H), 7.33 (d, 2H), 7.15 (d, 2H), 4.57 (d, 1H), 4.35 (d, 1H), 4.29 (m, 2H), 2.47 (s, 3H), 1.31 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 168.3, 162.7, 146.1, 135.6, 130.4, 129.9, 128.9, 127.4, 63.0, 60.3, 58.5, 22.1, 14.4 ppm; IR (CH₂Cl₂): 1805, 1751, 1372, 1189, 1091, 1016 cm⁻¹. Anal. Calcd. for C₁₉H₁₉ClNO₅S: C, 55.95; H, 4.45; N, 3.43. Found C, 56.17; H, 4.48; N, 3.44.



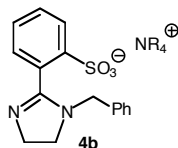
***Trans*-1-*p*-toluenesulfonyl-3-thiophenyl-4-ethoxycarbonylazetidinone (3e).**

White crystalline solid recrystallized from Et₂O/hexanes: ¹H NMR (CDCl₃); δ 7.76 (d, 2H), 7.48 (d, 2H), 7.30 (d, 3H), 7.26 (d, 2H), 4.32 (d, 1H), 4.28 (d, 1H), 4.25 (m, 2H), 2.46 (s, 3H), 1.29 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 169.8, 167.2, 161.0, 146.0, 145.3, 134.4, 129.6, 129.4, 129.3, 127.5, 62.3, 58.8, 57.1, 21.5, 14.7 ppm; IR (CH₂Cl₂): 1806, 1748, 1373, 1174, 1090, 1026 cm⁻¹. Anal. Calcd. for C₁₉H₁₉NO₅S₂: C, 56.28; H, 4.72; N, 3.45. Found C, 56.01; H, 4.75; N, 3.45.



***Trans*-1-*p*-toluenesulfonyl-3-thiophenyl-4-ethoxycarbonylazetidinone (3f).**

White crystalline solid recrystallized from Et₂O/hexanes: ¹H NMR (CDCl₃); δ 7.96 (d, 2H), 7.39 (d, 2H), 7.30 (dd, 1H), 6.98 (m, 2H), 4.58 (d, 1H), 4.56 (d, 1H), 4.29 (m, 2H), 2.48 (s, 3H), 1.32 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 165.6, 161.8, 145.8, 135.1, 132.5, 129.1, 128.0, 127.4, 126.8, 126.4, 62.7, 61.9, 54.6, 21.7, 14.0 ppm; IR (CH₂Cl₂): 1806, 1752, 1372, 1172, 1089, 1024 cm⁻¹. Anal. Calcd. for C₁₇H₁₇NO₅S₂: C, 53.81; H, 4.52; N, 3.69. Found C, 53.73; H, 4.44; N, 3.70.



3-benzyl-2-(phenyl-2-sulfonate)-2-imidazoline tetraheptylammonium salt (**4b**).³

Sulfobenzoic anhydride (1.000 g, 5.050 mmol), N-benzyl ethylenediamine (0.782 g, 5.050 mmol), and 20 mL of toluene were combined in a sealed tube and heated to 220 °C for 30 h, then allowed to cool to RT. The reaction mixture was filtered and the solids washed thoroughly with toluene, and then recrystallized from MeOH/CH₂Cl₂ to obtain 3-benzyl-2-(phenyl-2-sulfonic acid)-2-imidazoline as a white powder (1.170 g, 3.698 mmol, 73% yield). Tetraheptylammonium chloride (1.485 g, 3.161 mmol) was dissolved in 20 mL CH₂Cl₂, to which was added 20 mL water. The previously prepared imidazoline derivative (1.000 g, 3.161 mmol) was added to this solution as a solid and allowed to stir for 5 min. With vigorous stirring, 6.3 mL of a 1M NaOH solution was then added dropwise, and the reaction was stirred overnight. The solution is observed to go from cloudy to clear. Upon completion, the organics were drawn off and the aqueous extracted 5X with 10 mL portions of CH₂Cl₂. Combined all organics, dried briefly over MgSO₄, filtered through Celite, then concentrated *in vacuo* to obtain the desired product (1.9 g, 2.62 mmol, 83% yield) as a viscous yellow-orange oil: ¹H NMR (DMSO-d₆): δ 7.83 (dd, 1H), 7.71 (dd, 1H), 7.51 (m, 2H), 7.37 (d, 2H), 7.32 (t, 2H), 7.24 (t, 1H), 3.73 (s, 2H), 3.17 (m, 12H), 2.88 (t, 2H), 2.73 (t, 2H), 1.57 (s, 9), 1.29 (s, 40), 0.88 (t, 15H) ppm; ¹³C NMR (DMSO-d₆): δ 168.3, 144.2, 139.9, 131.5, 131.0, 130.7, 129.8, 128.4, 127.0, 126.8, 57.9, 52.3, 48.8, 45.6, 38.5, 31.1, 28.2, 25.9, 22.1, 21.1, 14.1 ppm; IR (CH₂Cl₂): 2959, 2930, 2860, 1457, 1277, 1256, 1175 cm⁻¹. (m/z): 410.7 (positive ion), 333.6 (n+18, negative ion). Anal. Calcd. for C₁₆H₁₉N₂O₄S:⁴ C, 57.47; H, 5.43; N, 8.38. Found C, 57.16; H, 5.36; N, 8.34.

Epimerization Studies

General Procedure for Epimerization Studies. To *cis*-**3a** (20 mg, 0.054 mmol) in 4 mL toluene at 0 °C was added proton sponge (11 mg, 0.054 mmol) and catalyst **4b** (4 mg, 0.005 mmol) together in 1 mL toluene. Let stir overnight, maintaining temperature at 0 °C. Quenched with 1M HCl (5 mL) at 0 °C. The aqueous layer was then extracted three times with CH₂Cl₂ and the combined organic layers were dried over MgSO₄ and filtered

³ Synthesis adapted from Moehrke, H.; Koch, H.; von Freyberg, H. Verfahren zur Herstellung Heterocyclischer Verbindungen. Eur. Pat. Appl. DE865305, 1953.

⁴ Microanalysis was conducted on the 3-benzyl-2-(phenyl-2-sulfonic acid)-2-imidazoline component of the catalytic system only and includes one mol equiv of water which was found to be irremovable even when drying under high vacuum over P₂O₅. The tetraheptylammonium portion was purchased from Acros and used as is. Due to a slight excess of the cation present, a ¹H NMR spectrum (see attached) is provided in lieu of microanalysis on the final, ion paired catalyst system.

through Celite, then concentrated *in vacuo*. This crude reaction mixture was analyzed by NMR to determine the final dr of the β -lactam product.

The table below summarizes the results of these studies. Excluding trial 2, all tests were conducted at 0 °C and allowed to run overnight to mimic the conditions under which the lactams are formed, as discussed in our general β -lactam procedure above. Trial 2 was allowed to run at RT for 3 days to ascertain the equilibrium ratio of *trans* to *cis* diastereomers. Trial 4 suggests that PS by itself produces little epimerization, while catalyst **4b** by itself (trial 3) causes the substrate to undergo only modest epimerization. When **4b** and PS are combined (trials 1 and 2), a more significant shift in the dr is noted. However, the final observed dr, even at equilibrium, does not approach the level of selectivity observed in the products of our reactions (37:1 for lactam **3a**), suggesting that the dr obtained in our experiments is not primarily due to epimerization of initially formed *cis*- β -lactam products. This evidence is further bolstered by trial 5 wherein a product mixture (**3b**) with an excess of the *trans* diastereomer was observed to lose selectivity upon further interaction with the catalyst and PS.

Trial #	Reagents	Rxn Time	Rxn Temp	Starting dr (t:c)	Final dr (t:c)
1	<i>cis</i> - 3a , 4b , PS	overnight	0° C	1 : 17	1.4 : 1
2	<i>cis</i> - 3a , 4b , PS	3 days	RT	1 : 17	1.6 : 1
3	<i>cis</i> - 3a , 4b	overnight	0° C	1 : 17	1 : 1.7
4	<i>cis</i> - 3a , PS	overnight	0° C	1 : 17	1 : 11
5	3b , 4b , PS	overnight	0° C	8.4 : 1	7.9 : 1

3-benzyl-2-(phenyl-2-sulfonate)-2-imidazolone tetraheptylammonium salt (4b)

Current Data Parameters
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 PROCNO 1
 F2 - Acquisition Parameters

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 SWH 0.126314 Hz
 FIDRES 3.958464 sec
 AQ 60.400 usec
 DM 10.00 usec
 DE 296.4 K
 TE 1.00000000 sec
 DI 1
 TD 1

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 PL 0.00 dB
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 PC 1.00

