

Bifunctional Asymmetric Catalysis: A Tandem Nucleophile/Lewis Acid Promoted Synthesis of β -Lactams

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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 **5a-b**,¹ and imine **3**,² 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.

General Procedure for the Tandem Nucleophile/Lewis Acid Promoted Synthesis of β -Lactams. To a suspension of In(OTf)₃ (3 mg, 0.013 mmol), benzoylquinine **5a** (5.6 mg, 0.013 mmol) and proton sponge (28 mg, 0.13 mmol) in toluene (7.5 mL) at -78° C was added dropwise phenylacetyl chloride **1a** (20 mg, 0.13 mmol) in toluene (0.5 mL).³ A solution of imine **3** (32 mg, 0.13 mmol) in toluene (1 mL) was then added via syringe pump over 1 h. The reaction was allowed to warm to room temperature over 6 h, before it was quenched with 1M HCl (3 mL). The aqueous layer was extracted twice with CH₂Cl₂ and the combined organic layers were dried over MgSO₄ and filtered through Celite. Absorption onto silica gel followed by column chromatography (25% Et₂O/hexanes) afforded product **4a** in 95% yield (46 mg) and 98% ee (dr 60:1).

Preparation of quinine derivative 5c. A solution of 2-benzyloxy-4-methyl-benzoylchloride⁴ (1.8 mmol) in 2 mL of THF was added slowly to a solution of quinine (533 mg, 1.64 mmol), and 0.26 mL of Et₃N (1.97 mmol) in 10 mL THF at 0° C. It was allowed to warm to RT overnight and worked up according to literature procedure.¹ The crude product was redissolved in 20 mL EtOH and hydrogenated under standard conditions (~40 psi, 10 mol% Pd/C) for 3h. It was then filtered through a plug of celite, and concentrated. Absorption onto silica gel followed by column chromatography (5% EtOH, EtOAc) afforded product **5c** in a combined 90% yield (678 mg). Off-white crystalline solid recrystallized from Et₂O/CH₂Cl₂: mp = 74-75° C; [α]₂₅ = -54.2° (c = 0.01, CHCl₃); ¹H NMR (CDCl₃) 8.65 (d, 1H), 7.95 (d, 1H), 7.71 (s, 1H), 7.42 (d, 1H), 7.35 (dd, 1H), 7.19 (d, 1H), 7.12 (dd, 1H), 6.81 (d, 1H), 4.22 (d, 1H), 3.9 (s, 3H), 3.56-3.72 (m, 4H), 3.2-3.3 (m, 1H), 2.8-3.05 (m, 2H), 2.29 (s, 3H), 1.70-2.00 (m, 4H), 1.26-1.54 (m, 3H), 0.84 (t, 3H) ppm; ¹³C NMR (CDCl₃) 175.6, 159.4,

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 For **4d** and **4f**, the acid chloride was added to a solution of proton sponge and BQ in 7.5 mL of toluene and stirred at 0° C for 30 min and then cooled to -78° C. A suspension of In(OTf)₃ and the imine (1 mL of toluene) was added via syringe pump over 1h.

⁴ Rewcastle, G. W.; Atwell, G. J.; Zhung, L.; Baguley, B. C.; Denny, W. A.; *J. Med. Chem.* **1991**, *34*, 217-222.

158.6, 146.8, 144.3, 139.6, 133.8, 131.5, 130.4, 128.1, 126.7, 122.7, 122.5, 117.5, 116.2, 101.01, 56.0, 55.4, 54.9, 40.2, 36.0, 26.5, 25.7, 25.0, 24.6, 20.3, 11.4 ppm; IR (CHCl₃) 2964, 2360, 2341, 1752, 1623 cm⁻¹. Anal Calcd for C₂₈H₃₂N₂O₄ C, 73.02; H, 7.00; N, 6.08. Found C, 73.05; H, 6.98; N, 6.10.

Preparation of catalyst 6b. To the quinine derivative **5c** (29 mg, 0.0065 mmol) and 1.6 mg NaH (0.0065 mmol) was added minimal amount of THF (< 0.5mL). The solution was stirred for 15 min. In most cases the slightly heterogeneous solution (excess NaH) was filtered through disposable syringe filters to yield a clear and colorless solution. This was combined with neat In(OTf)₃ (36 mg, 0.0065 mmol) and the homogeneous yellow mixture was added according to the general reaction protocol.