Supporting Information for

Bifunctional Lewis Acid-Nucleophile Based Asymmetric Catalysis: Mechanistic Evidence for Imine Activation Working in Tandem with Chiral Enolate Formation in the Synthesis of β-Lactams

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General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All solvents were dried and distilled by standard procedures. The ^{1}H, ^{13}C and ^{19}F NMR spectra were acquired on a Varian Unity 400 MHz Spectrometer. The ^{1}H (400 MHz) and ^{13}C chemical shifts (101 MHz) are given in parts per million (δ) with respect to internal TMS standards or residual solvent peaks. Enantiomeric ratios were obtained using a Regis Technologies (*R*,*R*)-Whelk-01 chiral analytical HPLC column for β-lactams. All reagents used were commercially available and used as received. Catalyst **3a**[1] and imines **5a**[2] and **5b**[3] were prepared according to literature procedures. β-Lactams **6a**-**6h**,[4] and catalyst **3c**[5] were previously characterized.

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 **3a** (5.6 mg, 0.013 mmol) and proton sponge **4** (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).[6] A solution of imine **5a** (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 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 (15% Et_2O/hexanes) afforded product **6a** in 95% yield (46 mg) and 98% ee[7] (dr 60:1 [cis:trans]).

Quinine-Triphenylborate Ether-In(OTf)$_2$ Complex (3b). To a solution of NaH (136 mg, 3.39 mmol, 60% dispersion in mineral oil) in 20 mL THF, a solution of quinine (1.0 g, 3.08 mmol) in 10 mL THF was added. The reaction was allowed to stir for 2 h. Triphenylborane (746 mg, 3.08 mmol) in 3 mL THF was added and the solution was stirred for 18 h. $In(OTf)_3$ was then added and the solution was stirred for another 18 h. The complex was used without further purification to give β-lactam **6a** in 70% yield with 98% ee.

In(BArF)$_3$ Salt (8). $InCl_3$ (400 mg, 0.56 mmol) and Na(BArF)[8] (4.2 mg, 0.188 mmol) were stirred in 3 mL CH_3CN at room temperature until completely homogeneous. The solution was cooled to 0°C until a precipitate appeared, then filtered through a filter needle. The catalyst solution was used directly but can be concentrated to yield a white solid. β-Lactam **6a** is formed in 80% yield and 95% ee.

5-Fluorosalicylic Acid Benzyl Ether. To a solution of 5-fluorosalicylic acid (0.5 g, 3.2 mmol) in 5 mL of DMF was added 1.3 mL of benzyl chloride (11.2 mmol) and 2.2 g of powdered K_2CO_3 (16 mmol). The reaction was left to reflux for 1 h and diluted with water after it had cooled to RT. The organic layer was separated and used without purification. The yellow oil was dissolved in 3 mL of MeOH and treated with 40% aq. NaOH solution (1.5 mL). This solution was allowed to reflux for 2 h and then diluted with 5 mL of water. The reaction was acidified with conc. HCl at which point a precipitate crashed out. The ppt. was recovered and recrystallized ($MeOH/H_2O$) to yield 0.8 g of 2-benzyloxy-5-fluorobenzoic acid. The product was characterized by NMR. ^{1}H NMR ($CDCl_3$) δ 10.82 (bs, 1H); 7.81 (m, 1H); 7.44 (m, 4H); 7.18 (m, 2H); 7.10 (m, 1H); 5.29 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 172.0, 159.2, 154.3, 140.9, 128.7, 127.4, 127.3, 121.7, 118.1, 117.8, 115.6, 77.8 ppm. Anal Calcd for $C_{14}H_{11}O_3$ C, 68.05; H, 4.50. Found C, 68.01; H, 4.53.

***O*-(5-Fluorosalicyloyl) Quinine (3e)**. The 2-benzyloxy-5-fluoro-benzoic acid (0.8 g, 3.2 mmol) was dissolved in 10 mL of CH_2Cl_2 and then treated with 0.3 mL of oxalyl chloride (3.5 mmol) at 0°C. The reaction was left to warm to RT over 3 h at which point the solvent was removed *in vacuo*. A solution of the crude 2-benzyloxy-5-fluoro-benzoylchloride (3.2 mmol) in 5 mL of THF was added slowly to a solution of quinine (930 mg, 2.9 mmol), and 0.5 mL of Et_3N (3.5 mmol) in 10 mL THF at 0° C. It was allowed to warm to RT overnight. The solution was washed twice with a 10 M aqueous KOH solution, washed once with brine, then the aqueous phase was extracted with EtOAc. Organics were combined, dried with $MgSO_4$, filtered and concentrated. The product was purified by column chromatography (99.5% EtOAc/0.5% Et_3N). The purified 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 **3e** in a combined 90% yield (1.3 g). Off-white crystalline solid recrystallized from Et_2O/CH_2Cl_2: ^{1}H NMR ($CDCl_3$) δ 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), 1.70-2.00 (m, 4H), 1.26-1.54 (m, 3H), 0.84 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 175.6, 159.4, 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 ($CHCl_3$) 2962, 2363, 2341, 1750, 1623 cm^{-1}. Anal Calcd for $C_{27}H_{29}N_2O_4$ C, 69.08; H, 6.29; N, 6.03. Found C, 69.05; H, 6.31; N, 6.07.

Preparation of catalyst In(III)-3c. To the quinine derivative **3c** (29 mg, 0.0065 mmol) and NaH (1.6 mg, 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.

***O*-(2-Carboxyphenanthroloyl) Quinine (3g).** To a solution of 2-carboxyphenanthroline[9] (336 mg, 1.5 mmol) and DMF (0.01 mL, 0.15 mmol) in 15 mL CH_2Cl_2, oxalyl chloride (0.2 mL, 2.25 mmol) was added dropwise. The reaction mixture was allowed to stir until gas evolution ceased (~6 h). The solution was concentrated, dissolved in 15 mL THF and fitted with a reflux condenser. Quinine (162 mg, 0.5 mmol) and Et_3N (101 mg, 1 mmol) in 10 mL THF was added and the solution was allowed to reflux for 7 days. The mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated and purified by column chromatography (10% MeOH/CH_2Cl_2 with 1% Et_3N) and recrystallized three times from Et_2O/hexanes. ^1H NMR ($CDCl_3$) δ 9.10 (dd, 1H), 8.68 (d, 1H), 8.42 (q, 2H), 8.33 (dd, 1H), 8.06 (d, 1H), 7.88-7.90 (m, 3H), 7.72 (m, 2H), 7.46 (m, 2H), 5.72 (m, 1H), 5.16 (d, 1H), 5.12 (d, 1H), 4.80 (m, 1H), 4.24 (s, 3H), 3.50-3.72 (m, 4H), 3.32 (m, 1H), 3.24 (m, 1H), 2.85 (m, 1H), 2.78 (m, 1H), 2.38 (m, 1H), 2.10 (m, 1H), 1.8 (m, IH) ppm; ^{13}C ($CDCl_3$) δ 167.0, 158.2, 151.8, 150.0, 148.1, 147.2, 143.8, 142.7, 140.6, 135.9, 135.7, 131.2, 129.2, 128.0, 127.6, 126.4, 126.3, 121.6, 120.8, 120.3, 114.4, 78.5, 60.1, 56.0, 54.5, 50.5, 38.6, 33.2, 28.4 ppm.

Preparation of catalyst Zn-3g. To a stirring solution of **3g** (34 mg, 0.065 mmol) in 5 mL ethanol:triethyl orthoformate (4:1, v/v), $ZnBr_2$ (15 mg, 0.065 mmol) was added and the reaction mixture was stirred for 30 min. The resulting solids were collected, washed with cold ethanol and dried under vacuum. The complex was used without further purification according to the general reaction procedure.

N-(Ethoxycarbonylmethylidine)-2-methoxyaniline (5c). Freshly distilled *o*-methoxy aniline (1.5 mL, 13.3 mmol) was dissolved in 25 mL of toluene. Ethyl glyoxylate (2.7 mL, 13.3 mmol) was added to the solution followed by a gross excess of anhydrous sodium sulfate. The reaction was left to stir at room temperature for 2h. The Na_2SO_4 was filtered off and the filtrate was concentrated down to yield a yellow oil. The oil was stored at –30˚C and showed no degradation. ^1H NMR ($CDCl_3$) δ 7.94 (s, 1H); 7.36 (d, 2H); 6.92 (d, 2H); 4.42 (q, 2H); 3.85 (s, 3H); 1.41 (t, 3H) ppm; ^{13}C ($CDCl_3$) δ 165.1, 161.3, 152.9, 135.6, 128.4, 123.1, 122.5, 115.3, 61.1, 55.9, 14.2 ppm. Anal Calcd for $C_{11}H_{13}NO_3$ C, 63.76; H, 6.32; N, 6.76. Found C, 63.72; H, 6.31; N, 6.78.

1-*p*-Methoxyphenyl-3-phenyl-4-ethoxycarbonylazetidinone. ^1H NMR ($CDCl_3$) δ 7.32 (m, 7H); 6.89 (d, 2H); 4.9 (d, 1H); 4.84 (d, 1H); 3.82 (q, 2H); 3.79 (s, 3H); 0.8 (t, 3H) ppm; ^{13}C ($CDCl_3$) δ 171.2, 167.1, 155.9, 136.2, 130.2, 129.5, 127.7, 122.1, 114.3, 63.8, 61.2, 56.5, 43.1, 13.9 ppm. Anal Calcd for $C_{19}H_{19}NO_4$ C, 70.14; H, 5.89; N, 4.31. Found C, 70.11; H, 5.92; N, 4.29.

1-*o*-Methoxyphenyl-3-phenyl-4-ethoxycarbonylazetidinone. ^1H NMR ($CDCl_3$) δ 7.35 (m, 7H); 6.92 (d, 2H); 5.85 (d, 2H); 5.72 (d, 2H); 3.74 (s, 3H); 3.6 (q, 2H); 1.2 (t, 3H)

ppm; ^{13}C ($CDCl_3$) δ 171.3, 167.1, 152.3, 136.3, 130.4, 129.1, 128.2, 127.1, 125.1, 122.6, 121.3, 63.2, 61.2, 55.9, 43.2, 14.0 ppm. Anal Calcd for $C_{19}H_{19}NO_4$ C, 70.14; H, 5.89; N, 4.31. Found C, 70.17; H, 5.87; N, 4.28.

Competition Reaction with 5b and 5c. Proton sponge (68.5 mg, 0.32 mmol) was placed into a 25 mL round-bottomed flask along with BQ (13.7 mg, 0.032 mmol) and $In(OTf)_3$ (18 mg, 0.032 mmol). The solids were suspended in 5 mL of freshly distilled toluene and cooled to –78˚C. To this mixture was added 0.04 mL of phenylacetyl chloride (0.32 mmol) in 2 mL of toluene. Equal amounts of **5b** and **5c** were combined (66.2 mg, 0.32 mmol), dissolved in 3 mL of toluene and added to the reaction. After 15 min the reaction was quenched with 3 mL of 1 M HCl. After extraction with dichloromethane (3 x 5 mL), the organics were combined, dried with MgSO4, and filtered through Celite. The filtrate was concentrated down to yield a tan residue. A 1H NMR of the crude residue was taken to determine the ratio of **6b** to **6c.**

Mechanistic Studies of Metal-3c Complexes

NMR Experiment for Salicylate-Metal Binding. 80 mg (0.17 mmol) of the catalyst **3e** was heated with 0.08 mL (0.085 mmol) of diethylzinc (1.1 M/toluene) to 50˚C for 30 min and then concentrated in vacuo. Some of the residue (20 mg) was dissolved in 0.5 mL $CDCl_3$ and to this was added a drop of $CFCl_3$ as an internal standard. A ^{19}F NMR taken at RT showed a peak at 4.8 ppm after which another 0.5 eq. of the catalyst was added to determine if there was rapid exchange. A similar experiment was done using $In(OTf)_3$, but its complex was made according to the procedure for In(III)–**3c** with 0.04 mmol of both the catalyst and $In(OTf)_3$. ^{19}F NMR ($CDCl_3$) δ 5.7 ppm.

Determination of Imine Concentration Effects. Three 10-mL flasks were set up in the following manner: To a suspension of NaH (11.0 mg, 0.28 mmol), **3c** (5.5 mg, 0.013 mmol), and 15-crown-5 (0.013 mmol) in toluene (4.5 mL) at –78˚C was added phenylacetyl chloride **1a** (48.0 mg, 0.31 mmol) in toluene (1.0 mL). The solution was allowed to stir at –78˚C for 6 h. The α-imino ester **5a** (16.5 mg, 0.065 mmol; 33 mg, 0.13 mmol; 66 mg, 0.26 mmol) was then added in toluene (4.0 mL) to each of the reactions and allowed to react for 10 min at which time 3.0 mL of 1.0 M HCl was added to quench the reactions. The reactions were extracted with dichloromethane, dried with $MgSO_4$ and concentrated. The resulting residues were subjected to column chromatography through a small plug of silica gel (10% EtOAc/hexanes). The reactions were repeated with 10 mol% of $In(OTf)_3$ and the reaction time with the imine was reduced to 5 min. For the reactions without $In(OTf)_3$ the product yields were, 19 mg, 26 mg, and 30 mg for 0.5, 1.0, and 2.0 eq. of the α-imino ester, respectively. With $In(OTf)_3$, the reaction yielded 20 mg, 26 mg, and 33 mg for 0.5, 1.0, and 2.0 eq. of **5a**, respectively.

Determination of Isotope Effects. Two 10-mL flasks were set up in the following manner. NaH (11.0 mg, 0.28 mmol), **3c** (5.5 mg, 0.013 mmol), and 15-crown-5 (0.013 mmol) were suspended in 4.5 mL of toluene. The reactions were cooled to –78˚C and

phenylacetyl chloride (48.0 mg, 0.31 mmol) was added to one reaction while α,α-phenylacetyl chloride-d_2 (48.5 mg, 0.31 mmol) was added to the other, each in 1.0 mL of toluene. The reactions were allowed to stir for 6 h at –78°C and then the α-imino ester (33.0 mg, 0.13 mmol) was added to each reaction in 2.0 mL of toluene. After 10 min, 3.0 mL of 1.0 M HCl was added to quench the reactions. The reactions were extracted with dichloromethane, dried with $MgSO_4$ and concentrated. The resulting residues were subjected to column chromatography through a small plug of silica gel (10% EtOAc/hexanes). The reactions were repeated and quenched 10 min after imine addition. The reactions were repeated with 10 mol% $In(OTf)_3$ and the reaction time with the imine was reduced to 5 min. For the reactions with phenylacetyl chloride the product yields were, 25 mg after 15 min, 15 mg after 10 min, and 25 mg after 5 min (with $In(OTf)_3$). Similarly, with phenylacetyl chloride-d_2 the yields of lactam product were, 31 mg after 15 min, 18 mg after 10 min, and 30 mg after 5 min (with $In(OTf)_3$).

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6 For 6d and 6f, 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 toluene) was added via syringe pump over 1h.

7 The ee's reported are for the (R,R) enantiomers unless otherwise stated.

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