Supplementary Information for:

Calcium-mediated Intramolecular Hydroamination Catalysis

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Experimental Details

General Considerations

All manipulations were carried out using a standard Schlenk line or within a glovebox (operating at < 2 ppm O_2) containing an inert dinitrogen atmosphere. All hydrocarbon solvents were dried with standard drying agents before use. C_6D_6 was dried with molten potassium and vacuum transferred to a Youngs storage ampoule prior to use. All organic reagents were purchased from Aldrich Chemical Co. and used as received. All aminoalkenes and alkynes were synthesised by standard Gabriel methodology or using literature techniques.¹ Amine substrates were dried over KOH, vacuum transferred and freeze-thaw degassed prior to use. 1H NMR data were accumulated at 270 MHz on a JEOL GX 270 NMR spectrometer and referenced internally using residual protio resonances relative to tetramethyl silane. Compound **1** was synthesised by a literature procedure.²

General procedure for NMR-scale experiments

Standard NMR experiments were conducted using Youngs tap NMR tubes. Samples were prepared under a nitrogen atmosphere in the glovebox. Typically the alkaline earth compound (40mg) was dissolved in pre-dried deuterated solvent (C_6D_6 or d_8 -toluene) and the substrate added using a calibrated micro litre pipette. For **III**, **IV** and **V** the reaction was effectively complete before insertion of the sample into the spectrometer for catalyst loadings > 2 mol% of **1**. Percentage conversion was determined by comparison of product peaks to an internal tetrakis(trimethylsilyl)silane standard (0.31 ppm in C_6D_6). The cyclisation of substrate **VI** was accomplished by insertion of the NMR tube into a oilbath preheated to $60^\circ C$ and controlled by a digital contact thermometer.

Preparative scale procedures for Hydroamination/Cyclisation Reactions

Stoichiometric synthesis of 2-ethylpyrroline, **Ia**

To a stirred solution of **1** (0.25g, 0.36 mmol) in hexane was added an equimolar quantity of 6-aminohept-2-yne **I** (45 μ l, 0.36 mmol) as a solution in hexane. The resultant mixture was stirred for at room temperature then evaporated to dryness. The resultant solid was extracted with a 50:50 mixture of ether:water. The ether layer was separated and dried over magnesium sulphate. Passage through a silica column and evaporation to dryness gave the product 2-ethylpyrroline, **Ia**, (11 μ l, 0.11 mmol, 40 %) as an orange oil.

1H NMR ($CDCl_3$, $25^\circ C$): 3.80 (m, 2H), 2.47 (t, 2H), 2.34 (t, 2H), 1.86 (m, 3H) [Lit³ 1H NMR ($CDCl_3$): 3.83-3.77, 2.47, 2.35, 1.92-1.80 and 1.16]. Mass Spec (70 eV EI): m/z 98 (M+H), 69 (M+H- CH_2CH_3). [Lit³ m/z = 97 (M⁺), 96, 69, 56, 54, 42, 41].

a) Volatile products **IIIa**,⁴ and **Va,b**.⁵

Approximately 250 mg of the appropriate substrate was dissolved in 10 mL of dry C_6H_6 in a Schlenk tube fitted with a Youngs tap. An aliquot of a 0.1 M solution (5 or 10 mol%) of **1** in C_6H_6

was added at room temperature and the resulting pale yellow solution stirred for 10 minutes. The reaction was then quenched by exposure of the solution to the ambient atmosphere for 10 minutes. All volatiles were vacuum transferred and treated with HCl (1-2 mL of a 1.0 M solution in diethyl ether), prior to evaporation to dryness to produce the heterocyclic products as the corresponding hydrochloride salts, isolated as colorless solids, which were characterised by ^1H NMR in D_2O .

The free pyrrolidine heterocycles were isolated by treatment of the hydrochlorides in CH_2Cl_2 with an aqueous saturated sodium carbonate solution. The CH_2Cl_2 layer was then separated and dried over magnesium sulfate. Filtration and removal of CH_2Cl_2 produced the target heterocycles as colorless oils that were characterised by ^1H NMR in C_6D_6 .

2,4,4-trimethylpyrrolidine hydrochloride, IIIa.HCl.

Yield: 76%. ^1H NMR (D_2O , 25°C): δ 1.13 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.17 (s, 3H, $\text{C}(\text{CH}_3)_2$), ca. 1.36 (dd, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)$, partially obscured by other signal) 1.39 (d, 3H, $^3J_{\text{HH}} = 6.4$ Hz, $\text{CH}(\text{CH}_3)$), 1.53 (d, 1H, $^2J_{\text{HH}} = 10.6$ Hz, CH_2NH), 1.58 (d, 1H, $^2J_{\text{HH}} = 10.6$ Hz, CH_2NH), 2.06 (dd, 1H, $^2J_{\text{HH}} = 13.1$ Hz., $^3J_{\text{HH}} = 6.0$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 3.87 (m, 1H, $\text{CH}(\text{CH}_3)$).

2,4,4-trimethylpyrrolidine, IIIa.

^1H NMR (C_6D_6 , 25°C): δ 0.97 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.02 (s, 3H, $\text{C}(\text{CH}_3)_2$), ca. 1.03 (dd, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)$, partially obscured by other signal), 1.52 (dd, 1H, $^2J_{\text{HH}} = 12.3$ Hz., $^3J_{\text{HH}} = 6.8$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 2.49 (d, 1H, $^3J_{\text{HH}} = 10.9$ Hz, CH_2NH), 2.66 (d, 1H, $^2J_{\text{HH}} = 10.9$ Hz, CH_2NH), 3.09 (m, 1H, $\text{CH}(\text{CH}_3)$).

4-Allyl-2,4-dimethylpyrrolidine hydrochloride, mixture of diastereomers Va.HCl and Vb.HCl.

Yield: 65%. ^1H NMR (D_2O , 25°C): δ 1.12 (s, 3H, $\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}=\text{CH}_2)$), 1.27 (s, 3H, $\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}=\text{CH}_2)$), 1.32 (d, 6H, $^3J_{\text{HH}} = 6.7$ Hz., coincident $\text{CH}(\text{CH}_3)$), 1.39 (dd, 1H, $^3J_{\text{HH}} = 6.5$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 1.62 (dd, 1H, $^2J_{\text{HH}} = 11.3$ Hz., Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 1.98 (d, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.02 (d, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$) ca. 2.20 (dd, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)$), 2.23 (d, 2H, $^2J_{\text{HH}} = 7.4$ Hz., coincident CH_2NH), 2.99 – 3.20 (m, 4H, coincident CH_2NH , $\text{CH}_2\text{CH}(\text{CH}_3)$), 3.66 (m, 2H, coincident $\text{CH}(\text{CH}_3)$), 5.18 (m, 4H, coincident $=\text{CH}_2$), 5.81 – 5.92 (m, 2H, coincident $\text{CH}=\text{CH}_2$).

4-Allyl-2,4-dimethylpyrrolidine, mixture of diastereomers Va and Vb.

^1H NMR (C_6D_6 , 25°C): δ 0.89 (s, 3H, $\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}=\text{CH}_2)$), 0.96 (s, 3H, $\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}=\text{CH}_2)$), 1.04 (d, 6H, $^3J_{\text{HH}} = 6.2$ Hz., coincident $\text{CH}(\text{CH}_3)$), 1.39 (dd, 1H, $^2J_{\text{HH}} = 12.1$ Hz., $^3J_{\text{HH}} = 6.4$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 1.62 (dd, 1H, $^2J_{\text{HH}} = 12.1$ Hz., $^3J_{\text{HH}} = 6.4$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 1.96 (d, 2H, $^3J_{\text{HH}} = 7.4$ Hz., $\text{CH}_2\text{CH}=\text{CH}_2$), 2.01 (d, 2H, $^3J_{\text{HH}} = 7.4$ Hz., $\text{CH}_2\text{CH}=\text{CH}_2$), 2.42 (dd, 1H, $^2J_{\text{HH}} = 10.4$ Hz., $^3J_{\text{HH}} = 7.6$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 2.56 (d, 2H, $^2J_{\text{HH}} = 6.4$ Hz., coincident CH_2NH), 2.74 (dd, 1H, $^2J_{\text{HH}} = 10.4$ Hz., $^3J_{\text{HH}} = 7.6$ Hz., $\text{CH}_2\text{CH}(\text{CH}_3)$), 3.04 (m, 1H, coincident $\text{CH}(\text{CH}_3)$), 4.99 (m, 4H, coincident $=\text{CH}_2$), 5.65 – 5.82 (m, 2H, coincident $\text{CH}=\text{CH}_2$).

b) Volatile product, VIa.

Approximately 250 mg of **VI** was dissolved in 10 mL of dry C_6H_6 in a Schlenk tube fitted with a Youngs tap. An aliquot of a 0.1 M solution of **1** in C_6H_6 was added at room temperature and the resulting pale yellow solution stirred at 60°C for 14 hours. The reaction was then quenched by exposure of the solution to the ambient atmosphere for 10 minutes. All volatiles were vacuum transferred and treated with HCl (ca. 1 mL of a 1.0 M solution in diethyl ether), prior to evaporation to dryness to produce the heterocyclic product as the hydrochloride salt, isolated as a colorless solid, which was characterised by ^1H NMR in D_2O .

The free piperidine, **VIa**, was isolated by treatment of **VI.HCl** in CH_2Cl_2 with an aqueous saturated sodium carbonate solution. The CH_2Cl_2 layer was then separated and dried over

magnesium sulfate. Filtration and removal of CH_2Cl_2 produced the target heterocycle as a colorless oil that was characterised by ^1H NMR in C_6D_6 .

2,5,5-trimethylpiperidine hydrochloride, VIa.HCl.

Yield = 65%. ^1H NMR (D_2O , 25°C): δ 0.98 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.03 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.30 (d, 3H, $^3J_{\text{HH}} = 6.4$ Hz., $\text{CH}(\text{CH}_3)$), 1.49 – 1.60 (m, 3H, CH_2), 1.78 – 1.85 (m, 1H, CH_2), 2.78 (d, 1H, $^2J_{\text{HH}} = 12.6$ Hz., CH_2NH), 3.00 (d, 1H, $^2J_{\text{HH}} = 12.6$ Hz., CH_2NH), 3.07 – 3.15 (m, 1H, $\text{CH}(\text{CH}_3)\text{NH}$).

2,5,5-trimethylpiperidine, VIa

^1H NMR (C_6D_6 , 25°C): δ 0.85 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.30 (d, 3H, $^3J_{\text{HH}} = 6.4$ Hz., $\text{CH}(\text{CH}_3)$), 1.08 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.16 – 1.42 (m, 3H, CH_2), 1.45 – 1.50 (m, 1H, CH_2), 2.34 (m, 2H, CH_2NH), 2.48 (m, 1H, $\text{CH}(\text{CH}_3)\text{NH}$).

c) Involatile product, IVa.⁶

Approximately 250 mg of **IV** was dissolved in 10 mL of dry C_6H_6 in a Schlenk tube fitted with a Youngs tap. An aliquot of a 0.1 M solution of **1** in C_6H_6 was added at room temperature and the resulting pale yellow solution stirred for 10 minutes. The reaction was then quenched by exposure of the solution to the ambient atmosphere for 10 minutes. All volatiles were removed *in vacuo* and the product, **IVa** was isolated as a viscous, colorless oil by distillation on a Kugelrohr apparatus (155°C @ 0.03 mbar).

2-methyl-4,4-diphenylpyrrolidine, IVa.

Yield: 80%. ^1H NMR (CDCl_3 , 25°C): 1.23 (d, 3H, $^3J_{\text{HH}} = 6.2$ Hz., $\text{CH}(\text{CH}_3)$), 2.06 (dd, 1H, $^2J_{\text{HH}} = 12.6$ Hz., $^3J_{\text{HH}} = 8.9$ Hz., $\text{CH}_2(\text{CH}(\text{CH}_3))$), 2.78 (dd, 1H, $^2J_{\text{HH}} = 12.6$ Hz., $^3J_{\text{HH}} = 6.5$ Hz., $\text{CH}_2(\text{CH}(\text{CH}_3))$), 3.37 (m, 1H, $\text{CH}(\text{CH}_3)$), 3.49 (d, 1H, $^2J_{\text{HH}} = 11.4$ Hz., CH_2NH), 3.69 (d, 1H, $^2J_{\text{HH}} = 11.4$ Hz., CH_2NH), 7.14 – 7.33 (m, 10H, C_6H_5).

Spectra Key

P – Product

S – Substrate

* - impurity present in starting material

C0 – Original catalyst

C1 – Primary amide intermediate

C2 – Adducted heterocycle

Figure S1

Figure S2

Figure S3

Figure S4

References

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