Supplementary Information for

Anti-Markovnikov Intermolecular Hydroamination: A Bis(amidate)-Titanium Precatalyst for the Preparation of Aldimines

Zhe Zhang, and Laurel L. Schafer*

Department of Chemistry, the University of British Columbia, Vancouver, British Columbia, Canada. E-mail: schafer@chem.ubc.ca

Experimental Procedures.

General. All reactions were carried out using standard Schlenk line and glovebox techniques, under an atmosphere of nitrogen, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under inert atmosphere. Hexanes and toluene were purified by passage through a column of activated alumina and degassed with nitrogen. C_6D_6 was degassed and dried over molecular sieves. Benzoyl chloride was purchased from Aldrich and used as received. Amines were distilled from CaH_2 under nitrogen. Alkynes were purchased from Aldrich and purified by distillation prior to use. $Ti(NEt_2)_4$ was purchased from Strem and used as received. Amide proligands were prepared from appropriate amines and benzoyl chloride according to literature procedures.[1] ^{1}H, and ^{13}C spectra were recorded on either a Bruker 300 MHz or 400 MHz Avance spectrometer at ambient temperature and chemical shifts are given relative to residual solvent. IR samples were either neat or were prepared as Nujol mulls on NaCl disks or KBr pellets and recorded on a BOMEM Michelson Series MB-100 FTIR spectrophotometer. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source. GCMS spectra were recorded on an Agilent series 6890 GC system with a 5973 Mass Selective Detector. Elemental analyses and single-crystal X-ray structure determinations were performed at the Department of Chemistry, University of British Columbia.

General procedure for the preparation of bis(amidate)titanium-bis(amido) complexes.

Example: the synthesis of bis(*N*-2′,6′-di*iso*propylphenyl(phenyl)amidate)titanium-bis(diethylamido), 1. In a 100 mL round-bottomed Schlenk flask equipped with stir bar, a suspension of *N*-2′,6′-di*iso*propylphenyl(phenyl)amide (295 mg, 1.05 mmol) in 20 mL anhydrous ether was added a solution of $Ti(NEt_2)_4$ (168 mg, 0.500 mmol) in 20mL anhydrous ether at –78 °C under N_2. The reaction solution was allowed to stir at room temperature for three hours. Removal of the solvent under reduced pressure and extraction with anhydrous hexane followed by filtration in the glove box gave a dark red solution. The solvent was removed *in vacuo* to afford a red solid, which was used as the crude catalyst without further purification. Yield: 82%. The crude product was recrystalized in hexane/benzene to afford red microcrystals. ^{1}H NMR (C_6D_6, 300 MHz): δ 0.83 (12H, br t, J=6.7 Hz, N-($CH_2CH_3)_2$), 0.91 (12H, br d, J=6.5 Hz, CH($CH_3)_2$), 1.37

(12H, br d, J=6.5 Hz, $\mathrm{CH(C}\mathit{H}_3\mathrm{)_2}$), 3.77-3.80 (4H, m, $\mathrm{C}\mathit{H}\mathrm{(CH_3)_2}$), 3.95 (8H, br q, J=6.4 Hz, $\mathrm{N\text{-}(C}\mathit{H}_2\mathrm{CH_3)_2}$), 6.85-7.65 (16H, m, Ar-*H*); MS(EI): *m/z* 752 (M^+), 680 ($M\text{-}NEt_2$), 608 ($M\text{-}NEt_2 \times 2$); Anal. Calcd. For $C_{46}H_{64}N_4O_2Ti \bullet ½C_6H_6$: C, 74.31; H, 8.53; N, 7.07. Found: C, 74.30; H, 8.80; N, 7.11.

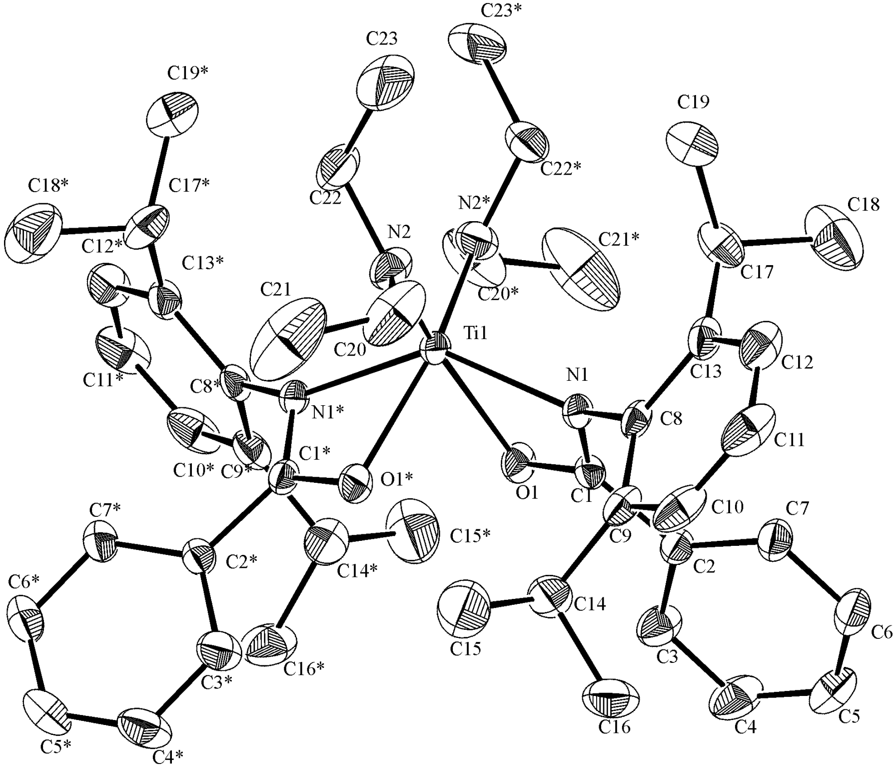

Figure 1. ORTEP plot of the structure of bis(amidate)titanium-bis(amido) complex **1** at 50% ellipsoids and with selected bond lengths (Å), bond and torsion angles (deg): Ti-O(1) 2.146(1), Ti-N(1) 2.156(1), Ti-N(2) 1.899(2), O(1)-Ti-O(1*) 81.92(7), O(1)-Ti-N(1) 61.21(5), O(1)-Ti-N(1*) 88.30(5), O(1)-Ti-N(2) 159.30(5), O(1)-Ti-N(2*) 91.39(7), N(1)-Ti-N(1*) 140.42(8), N(1)-Ti-N(2) 99.21(6), N(1)-Ti-N(2*) 105.68(6), N(2)-Ti-N(2*) 101.1(1).[2]

General procedure for the intermolecular hydroamination catalyzed by bis(amidate)titanium-bis(amido) complexes of Table 1

Example: complex 1 as the catalyst. A sealed-NMR tube was loaded with 1 equiv. (**1**) (20 mg, 0.027 mmol), 10 equiv. 1-hexyne (22 mg, 0.27 mmol), 20 equiv. t-butylamine (39 mg, 0.54 mmol), 10 equiv. 1,3,5-trimethoxybenzene (45 mg, 0.27 mmol) as an internal standard and approximately 1 mL C_6D_6 in the glove box. The tube was heated at 65 ^oC until all the alkyne was consumed. The conversion and yield were determined by comparison of the integration of the internal standard and a well-resolved signal for the product imine. When all the alkyne had been consumed, the reaction solution was treated with CH_2Cl_2 (5 mL) and silica gel (0.50 g). The mixture was stirred for 10 hours at room temperature and then filtered. The filtrate was used as a sample for the GC-MS. The ratio of the Anti-M and M was calculated by the integration of the resulting hexanal and 2-hexanone to verify the ratios determined by ^1H NMR spectroscopy.

General procedure for the intermolecular hydroamination catalyzed by complex 1 of Table 2

Example: 1-hexyne reacted with benzylamine. A 25 mL Schlenk tube was loaded with complex **1** (10 mg, 0.013 mmol), 1-hexyne (20 equiv., 22 mg, 0.27 mmol), benzylamine (20 equiv., 29 mg, 0.27 mmol) and approximately 1.5 mL benzene in the glove box. The tube was heated at 65 ^{o}C for 24 hours. Then the mixture was cooled to room temperature and diluted with 10 mL anhydrous ether. $LiAlH_4$ (24 equiv., 12 mg, 0.31 mmol) was added and the reaction mixture was stirred for 24 hours at room temperature. Then, 0.1 mL sat. NH_4Cl was added to quench the reaction. The mixture was filtered and concentrated under reduced pressure. Flash chromatography on silica gel (eluted with ether/Et_3N=10:1) afforded the pure *N*-benzylhexylamine as the single product. Yield: 88%

***N-t*-butylhexylamine**[3] Yield: 82%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (3H, t, J=6.8 Hz, CH$_2$C*H*3), 1.06 (9H, s, C(C*H*$_3$)$_3$), 1.26-1.44 (8H, m, C*H*$_2$), 2.50 (2H, t, J=7.1 Hz, C*H*$_2$NH); MS(EI): *m/z* 157(M$^+$), 142(M$^+$-CH$_3$).

***N-iso*propylhexylamine**[4] Yield: 88%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (3H, t, J=7.1 Hz, CH$_2$C*H*3), 1.02 (6H, d, J=6.2 Hz, CH(C*H*$_3$)$_2$), 1.26-1.43 (8H, m, C*H*$_2$), 2.54 (2H, t, J=7.3 Hz, C*H*$_2$NH), 2.70-2.78 (1H, m, C*H*(CH$_3$)$_2$); MS(EI): *m/z* 143(M$^+$), 128(M$^+$-CH$_3$).

***N*-benzylhexylamine**[5] Yield: 88%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (3H, t, J=6.2 Hz, CH$_2$C*H*3), 1.24-1.54 (8H, m, C*H*$_2$), 2.62 (2H, t, J=7.2 Hz, C*H*$_2$NH), 3.79 (2H, s, Ar-C*H*$_2$NH), 7.22-7.37 (5H, m, Ar-*H*); MS(EI): *m/z* 191(M$^+$), 190(M$^+$-H), 176(M$^+$-CH$_3$).

***N-t*-butyl(2-cyclohexyl)ethylamine** Yield: 72%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84-0.90 (3H, m, C*H*$_2$), 1.07 (9H, s, C(C*H*$_3$)$_3$), 1.13-1.68 (11H, m, C*H*$_2$), 2.53 (2H, t, J=7.3 Hz, C*H*$_2$NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.33, 26.63, 29.07, 33.47, 35.96, 38.78, 40.11, 50.19; MS(EI): *m/z* 183(M$^+$), 168(M$^+$-CH$_3$); IR (NaCl/neat, cm^{-1}): 3300 (vw, NH), 2922 (s), 1448 (m), 1232 (m), 740 (m); HRMS *m/z* Calc'd for $C_{12}H_{25}N$ [M$^+$]: 183.19870; Found: 183.19886.

***N-iso*propyl(2-cyclohexyl)ethylamine** Yield: 89%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84-0.93 (3H, m, C*H*$_2$), 1.02 (6H, d, J=6.3, CH(C*H*$_3$)$_2$), 1.15-1.68 (11H, m, C*H*$_2$), 2.57 (2H, t, J=7.3 Hz, C*H*$_2$NH), 2.75 (1H, m, C*H*(CH$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.05, 26.32, 26.62, 33.47, 35.89, 38.17, 45.25, 48.82; MS(EI): *m/z* 169(M$^+$), 154(M$^+$-CH$_3$); IR (NaCl/neat, cm^{-1}): 3435 (w, NH), 2966 (s), 2922 (s), 1448 (m), 1174 (m), 734 (w); HRMS *m/z* Calc'd for $C_{11}H_{23}N$ [M$^+$]: 169.18305 Found: 169.18343.

***N*-benzyl(2-cyclohexyl)ethylamine** Yield: 87%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86-1.68 (14H, m), 2.63 (2H, t, J=7.3 Hz, C*H*$_2$NH), 3.77 (2H, s, ArC*H*$_2$NH), 7.22-7.31 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.31, 26.61, 33.44, 35.74, 37.80, 47.15, 54.19, 126.81, 128.02, 128.34, 140.63; MS(EI): *m/z* 217(M$^+$), 91($C_7H_7^+$); IR (NaCl/neat, cm^{-1}): 3300 (vw, NH), 2922 (s), 2850 (s), 1450 (m), 1120 (w), 732 (m); HRMS *m/z* Calc'd for $C_{15}H_{23}N$ [M$^+$]: 217.18305 Found: 217.18293.

***N*-benzyl(3,3-dimethyl)butylamine** Yield: 95%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (9H, s, C(C*H*$_3$)$_3$), 1.42 (2H, t, J=7.0 Hz, C*H*$_2$C(CH$_3$)$_3$), 2.58 (2H, m, C*H*$_2$NH), 3.78 (2H, s, C*H*$_2$-Ar), 7.28-7.33 (5H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.61, 30.31, 44.14, 45.75, 54.31, 126.82, 128.06, 128.34, 140.56; MS(EI): *m/z* 191(M$^+$), 120(M$^+$-C_5H_{11}), 106((M$^+$-C_6H_{13}), 91($C_7H_7^+$); IR (NaCl/neat, cm^{-1}): 3200 (vw, NH), 2955 (s), 2912 (m), 2864 (m), 1454 (m), 1118 (w), 734 (m), 698 (m); HRMS *m/z* Calc'd for $C_{15}H_{23}N$ [M^+]: 191.16740 Found: 191.16747.

4-Triphenylsiloxybut-1-yne 2 reacted with *iso*propylamine, (eq. 1). A 10 mL Schlenk tube was loaded with complex **1** (10 mg, 0.013 mmol), 4-triphenylsiloxylbut-1-yne (20 equiv., 87 mg, 0.26 mmol), *iso*propylamine (40 equiv, 32 mg, 0.52 mmol) and approximately 1.5 mL benzene in the glove box. The tube was heated at 65 °C for 24 hours. Then the mixture was cooled to room temperature and treated with CH_2Cl_2 (10 mL) and silica gel (0.50 g). The mixture was stirred for 10 hours at room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel (eluted with Hexane/Ether=10:1) to afford the pure 4-triphenylsiloxylbutanal. Yield: 85% (76 mg); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89-1.93 (2H, m, C*H*$_2$), 2.64 (3H, t, J=7.2, C*H*$_2$CHO), 3.84 (2H, t, J=6.0 Hz, C*H*$_2$O), 7.39-7.62 (15H, m, Ar-*H*), 9.74 (1H, s, C*H*O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.09, 40.59, 62.78, 127.90, 130.09, 133.95, 135.31, 202.33; IR (KBr/Nujol, cm^{-1}): 1724 (s, CO), 1427 (m), 699 (s); MS (EI): *m/z* 346(M^+), 345(M^+-H); Anal. Calcd. For $C_{22}H_{22}O_2Si$: C, 76.26; H, 6.40. Found: C, 76.29; H, 6.46.

5-*t*-butyldimethylsiloxypent-1-yne 3 reacted with *iso*propylamine, (eq. 1). Same experimental procedure as above. 5-(*t*-butyldimethylsiloxy)pentanal[6] Yield: 94% (53 mg); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.02 (6H, s, Si(C*H*$_3$)$_2$), 0.86 (9H, s, C(C*H*$_3$)$_3$), 1.50-1.55 (2H, m, C*H*$_2$), 1.64-1.69 (2H, m, C*H*$_2$), 2.43 (2H, dt, J=7.2, 1.7, C*H*$_2$CHO), 3.58 (2H, t, J=12.4, C*H*$_2$O), 9.74 (1H, t, J=1.7,C*H*O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -5.36, 18.30, 18.61, 25.91, 32.09, 43.60, 62.57, 202.67; MS(EI): *m/z* 216(M^+), 215(M^+-H); IR (NaCl/neat, cm^{-1}): 2957 (s), 1712 (s, CO), 1265 (s), 740 (s); HRMS *m/z* Calc'd for $C_{15}H_{23}O_2Si$ [M^+-1]: 215.14673. Found: 215.14654.

Benzophenone protected propargylamine reacted with *iso*propylamine (eq. 2). The experiment was carried out in sealed NMR tube as described in the procedure for Table 1. The conversion and yield were determined by comparison of the integration of the internal standard and a well-resolved signal for the product imine at 7.67 ppm. Yield: 92%.

Trimethylsilylacetylene reacted with *iso*propylamine (eq. 3). The experiment was carried out in sealed NMR tube as described in the procedure for Table 1. The conversion and yield were determined by comparison of the integration of the internal standard and a well-resolved signal for the product imine at 7.52 ppm. Yield: 90%.

Synthesis of (±)-6,7-dimethoxy-2-pentyl-1,2,3,4-tetrahydroisoquinoline, 6.[7] A 25 mL Schlenk tube was loaded with complex **1** (30 mg, 0.040 mmol), 3,4-dimethoxylphenethylamine **4** (20 equiv., 145 mg, 0.80 mmol), 1-hexyne (20 equiv., 66 mg, 0.80 mmol) and approximately 2 mL benzene in glove box. The tube was heated at 65 °C for 24 hours. Then the mixture was cooled to room temperature and trifluoroacetic acid (4 mL) was added. After heating to reflux for 12 hours, the reaction mixture was treated with sat. $NaHCO_3$ (100 mL). The resulting mixture was extracted with ether and dried ($MgSO_4$). The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (eluted with CH_2Cl_2/MeOH=10:1). Yield:

92% (193 mg); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (3H, t, J=6.9 Hz, CH_3), 1.25-1.82 (9H, m, $(CH_2)_4CH_3$, N*H*), 2.65-3.22 (4H, m, CH_2CH_2NH), 3.82 (6H, s, CH_3O), 3.87 (1H, t, J=7.0 Hz, Ar-C*H*NH), 6.54 (1H, s, Ar-*H*), 6.59 (1H, s, Ar-*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.08, 22.67, 25.90, 29.58, 32.07, 36.58, 41.17, 55.51, 55.81, 56.00, 109.23, 111.76, 127.19, 131.79, 147.12, 147.17. MS(EI): *m/z* 263 (M^+).

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