

Continuous Synthesis and use of N-Heterocyclic Carbene Copper (I) Complexes from Insoluble Cu₂O

Suzanne M. Opalka^{a,b}, Jin Kyoon Park^{a,c}, Ashley R. Longstreet^a, and D. Tyler McQuade^{a*}

^aDepartment of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306 (USA) and ^bDepartment of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14853 (USA) and ^cDepartment of Chemistry and Chemical Institute for Functional Materials Pusan National University, Busan, 609-735 (Korea)

*mcquade@chem.fsu.edu

Contents	Page
1. General Information	2
2. Reactant Synthesis	2-4
3. General Reactor Setup	
3a: Preparation of copper oxide column	4-5
3b: Reactor configuration	5
4. Experiments to assess the Influence of Column Temperature	5
5. Substrate Scope and Product Characterization	6-7
6. General Reactor Setup Using Ion Exchange Resin	
6a: Preparation of ion exchange resin	8
6b: Reactor configuration	8
7. Substrate Scope and Product Characterization with Ion Exchange Resin	8-9
8. Long Term Stability Experiments	9
9. β -borylation Reaction – Large Scale	
9a: Reactor setup	9-10
9b: Borylation of acrylate 6a	10-11
10. β -borylation Reaction – Using Ion Exchange	
9a: Reactor setup	11-12
9b: Borylation of acrylate 6b	12-13
9c: Chromatograms of Racemic and Enantiomerically Enriched Product 7b	14
11. References	15
12. ¹ H and ¹³ C NMR Spectra of Chemical Compounds	16-41

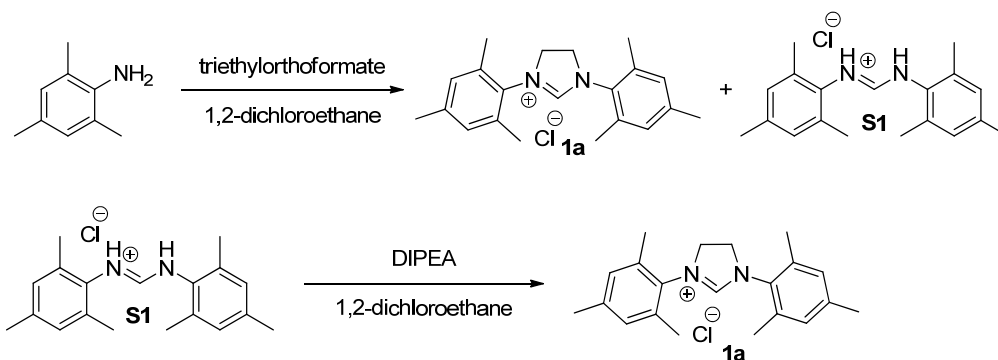
1. General Information

Flash chromatography was performed using silica gel (230-400 mesh). For analytical thin layer chromatography (TLC), silica gel 60 F₂₅₄ plates were used. All commercial reagents were used without further purification. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on 600 or 700 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), coupling constants in Hertz (Hz), integration.

Reactions were performed with a commercially available Vapourtec R series reactor controlled by FlowCommander™ software. Mixtures of solid copper(I) oxide and filler material were packed into a glass Omnifit column (6.6 mm diameter) fitted with Vapourtec end caps and PTFE frits. All tubing and fittings were supplied with the reactor, but the tubing was standard 1.00 mm bore PFA and standard PTFE fittings.

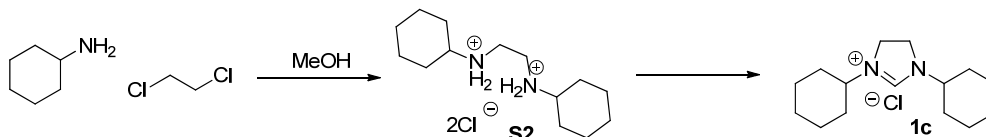
The following starting materials were purchased: 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (**1b**), 1,3-Dicyclohexylbenzimidazolium chloride (**1d**), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (**4**). We previously reported the synthesis of 6-membered ring NHC Imidazoquinazolium salt (**5**)¹ and (E)-isobutyl 3-(o-tolyl)acrylate (**6b**).¹

2. Reactant Synthesis



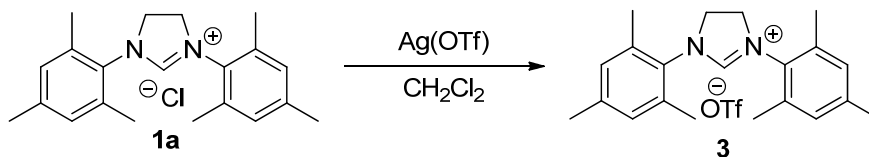
1,3-dicyclohexyl-4,5-dihydro-1H-imidazol-3-ium chloride (1a).² Triethyl orthoformate (6.2 mL, 37 mmol, 1 equiv), 2,4,6-trimethylaniline (10.4 mL, 74 mmol, 2 equiv), and 1,2-dichloroethane (20.4 mL, 259 mmol, 7 equiv) were charged into a Schlenk flask. The flask was sealed under static vacuum and heated to 120 °C. After 25 h, the mixture was cooled and excess reagents were removed *in vacuo*. The viscous liquid was dissolved in a minimal amount of dichloromethane, and the solution was added dropwise into boiling toluene. The white solid was collected by vacuum filtration and rinsed with portions of hot toluene to yield **1a** (3.95 g, 31%). A mixture of remaining **1a** and **S1** was recrystallized from the toluene filtrate as it cooled and was collected as a yellow solid by vacuum filtration (4.60 g). N,N-diisopropylethylamine (5.6 mL, 31.9 mmol, 2.2 equiv) was charged to a Schlenk flask containing a solution of the **1a** and **S1** mixture in 1,2-dichloroethane (11.4 mL, 145 mmol, 10 equiv). The flask sealed under static vacuum and heated to 120 °C. After 48 h the flask was cooled and excess reagents

were removed *in vacuo*. The viscous liquid was dissolved in a minimal amount of dichloromethane, and the solution was added dropwise to boiling toluene. The white solid was collected by vacuum filtration and rinsed with portions of hot toluene to yield compound **1a** (3.75 g, 30%). ¹H NMR: (600 MHz, CDCl₃) δ 9.67 (s, 1H), 6.87 (s, 4H), 4.48 (s, 4H), 2.32 (s, 12H), 2.25 (s, 6H) ppm. ¹³C NMR: (151 MHz, CDCl₃) δ 160.1, 139.9, 134.8, 130.2, 129.6, 51.7, 20.8, 17.8 ppm. The ¹H NMR and ¹³C NMR data were in accordance with those described in the literature.²



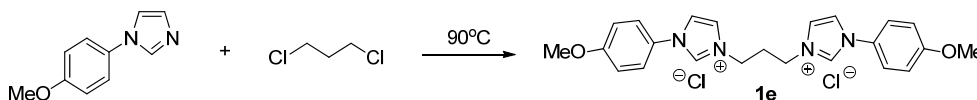
1,3-dicyclohexyl-4,5-dihydro-1H-imidazol-3-ium chloride (1c).³ To a solution of cyclohexylamine (8.5 mL, 74 mmol, 2.2 eq) in methanol (6.7 mL) was added 1,2-dichloroethane (2.7 mL, 33.6 mmol, 1 eq). The solution was refluxed for 48 h. The cooled reaction mixture was poured into 150 mL of vigorously stirring acetone. The white solid was collected by vacuum filtration and recrystallized in ethanol/H₂O to give **S2** (3.47 g, 35%) as a white solid. ¹H NMR: (600 MHz, D₂O) δ 3.40 (s, 4H), 3.16 (m, 2H), 2.06 (br d, *J*=10.6 Hz, 4H), 1.81 (br d, *J*=12.9 Hz, 4H), 1.63 (m, 2H), 1.31 (m, 8H), 1.15 (m, 2H) ppm. ¹³C NMR (151 MHz, D₂O) δ 58.1, 40.2, 28.8, 24.4, 23.9 ppm. The ¹H NMR and ¹³C NMR data were in accordance with those described in the literature.⁴

To a 10 mL pressurized microwave vessel equipped with a stir bar was added **S2** (1.0 g, 3.4 mmol, 1 eq) and triethylorthoformate (2.5 mL, 15 mmol, 4.46 eq). The vessel was capped and irradiated for 6 min at a temperature set to 145 °C at 75 W microwave power (no ramp was applied). The mixture was poured into diethyl ether (20 mL), and **1c** (0.72 g, 79%) was collected as a white solid by vacuum filtration. ¹H NMR: (600 MHz, CDCl₃) δ 9.72 (s, 1H), 3.99 (s, 4H), 3.82 (tt, *J*=5.83 Hz, 2H), 2.02 (br d, *J*=11.29 Hz, 4H), 1.84 (br d, *J*=13.93 Hz, 4H), 1.66 (br d, *J*=13.55 Hz, 2H), 1.49 (dq, *J*=4.08 Hz, 4H), 1.35 (tq, *J*=4.33 Hz, 4H), 1.15 (tq, *J*=13.05 Hz, 2H) ppm. ¹³C NMR: (151 MHz, CDCl₃) δ 154.2, 57.3, 45.3, 31.0, 24.7 ppm. The ¹H NMR and ¹³C NMR data were in accordance with those described in the literature.³



1,3-Bis(2,4,6-trimethylphenyl)imidazolium triflate (3). Silver trifluoromethanesulfonate (2.25 g, 8.75 mmol, 2.0 eq) was dissolved in CH₂Cl₂ (18 mL) and MeOH (10mL). Then 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride **1a** (1.5 g, 4.37 mmol, 1.0 eq) was added. The reaction was stirred at room temperature for 1.25 hours. The resulting suspension was filtered through celite, and rinsed with CH₂Cl₂. The resulting solution was concentrated, re-dissolved in dichloromethane, filtered through a 0.2μm PTFE membrane and washed with water 3 times. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to yield the desired triflate salt **3** (1.0236 g, 51% yield). ¹H NMR: (600 MHz, CDCl₃) δ 8.27 (s, 1H), 6.94 (s, 4H), 4.46 (s, 4H), 2.32 (s, 12H), 2.29 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 159.4, 140.7, 134.9, 130.04, 130.01, 120.6 (q, *J*=320.6), 51.7, 21.0, 17.57. The ¹H NMR and ¹³C NMR data were in

accordance with those described in the literature.⁵



3,3'-(propane-1,3-diyl)bis(1-(4-methoxyphenyl)-1H-imidazol-3-ium) chloride (1e): 1-(4-methoxyphenyl)-1H-imidazole (598.4 mg, 3.44 mmol, 2.5 eq) and 1,3-dichloropropane (130 μ L, 1.374 mmol, 1.0 eq) were added to a vial equipped with a stir bar. Upon heating to 90 $^{\circ}$ C overnight a hard substance formed. The reaction was cooled to room temperature, dissolved in methanol and dichloromethane and the product was precipitated with methyl *tert*-butyl ether. The resulting solid was rinsed with methyl *tert*-butyl ether to yield an off-white powder (538.6 mg, 96% pure with residual solvent as impurity, 82% yield). ^1H NMR: (600 MHz, CD_3OH) δ 9.68 (br m, 2H), 8.08 (t, $J=1.74$ Hz, 2H), 7.99 (t, $J=1.71$ Hz, 2H), 7.72 (m, 4H), 7.18 (m, 4H), 4.59 (t, $J=7.32$ Hz, 4H), 3.91 (s, 6H), 2.77 (p, $J=7.34$ Hz, 2H) ppm. ^{13}C NMR (151 MHz, CD_3OH) δ 162.5, 136.7, 129.4, 125.0, 124.5, 123.5, 116.5, 56.4, 48.2, 31.3 ppm. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{Cl}_2\text{N}_4\text{O}_2$: C: 59.87; H: 5.68; N: 12.14. Found: C: 55.82; H: 5.98; N: 11.36. Discrepancy between calculated and actual elemental analysis likely due to residual solvent.

3. Reactor Setup

A) Preparation of copper(I) oxide column

A vial containing 2.0 g of activated 4 \AA molecular sieves and 2.0 g of copper (I) oxide powder (<5 μm particle size) was mixed using a vortex mixer for 2*30s. The resulting powder was gently mixed with a spatula prior to use to ensure a uniform sample. To a glass Omnifit column (6.6 mm diameter) 440 mg of activated 4 \AA molecular sieves were added to the column and packed tightly with a glass rod. Then 1.65 g of the copper (I) oxide/4 \AA molecular sieve mixture was gently packed into the column. An additional 275 mg of 4 \AA molecular sieves was packed on top of the column and the cap secured. To determine the void volume of the column toluene was flushed through the system at 1.00 mL/min for ~30 min. The void volume was measured to be 1.6 mL and was assumed for all experiments. The column was then flushed with 80% CH_2Cl_2 /toluene for ~30 minutes at 1.00 mL/min. Upon packing a void appeared at the top of the column, but the cap was left in place.

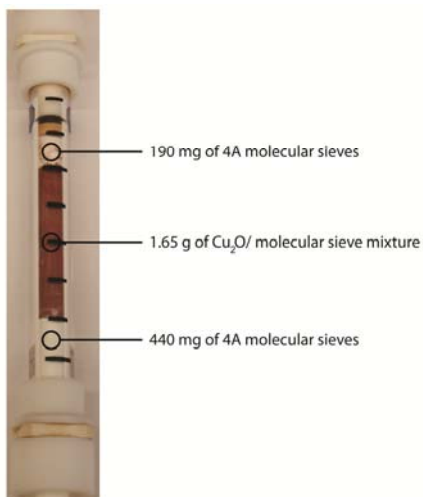
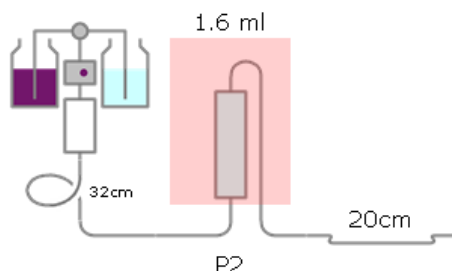


Figure S1: Column after packing the molecular sieves and copper(I) oxide into an Omnifit column.

B) Reactor Configuration



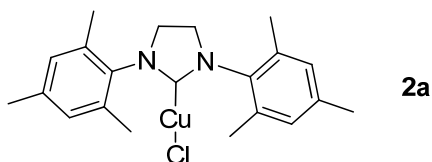
Description of reactor from left to right: One pump was connected with 32 cm of drop tubing to the bottom⁶ of a glass Omnifit column (6.6 mm diameter) containing 1.65 g of the copper(I) oxide/4 Å molecular sieve plus the molecular sieve endcaps (as outlined above) with a void volume ~1.6 mL. An additional 20 cm of tubing connected the top outlet of the column to a 100 psi backpressure regulator (not shown) and extra tubing to reach a fraction collector.

4. Experiments to assess the influence of column temperature

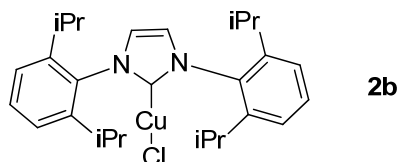
The column and reactor were assembled as described above. The setup was first flushed with toluene to determine the void volume of the column and then an 80% CH₂Cl₂/ 20% toluene solution. A stock solution of **1a** (0.020M) was prepared in an 80% CH₂Cl₂/ 20% toluene solution. A series of experiments were performed to assess the conversion of the reaction to product at a given column temperature using a flow rate of 800 µL/min corresponding to ~2 minute residence time. After the system reached equilibrium 6.5 mL of product stream was collected with a theoretical maximum of 130 µmol of product. The vials were concentrated, dried under nitrogen for 15 minutes, and further dried under vacuum. Conversion to product was assessed by ¹H NMR by integrating the product and starting material peaks in relationship to each other. Three trials were performed on the same column and an average was plotted.

5. Substrate Scope and Product Characterization

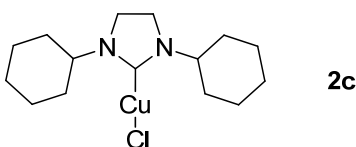
The general reactor setup was used as described above. The same copper oxide/molecular sieve column was reused for multiple substrates with only washing of solvent in between uses (substrates requiring MeOH were done last or separately). Stock solutions containing 0.020M substrates (generally prepared using 80% CH₂Cl₂/ 20% toluene) were passed through the Cu₂O/molecular sieve column set to 110 °C at a rate of 0.800 mL/min. 10 mL of product was collected with a theoretical maximum of 0.200 mmoles expected. The resulting solutions were concentrated, dried, and yield determined upon weighing. Purity was assessed by ¹H NMR.



(1,3-dimesitylimidazolidin-2-yl)copper(I) chloride 2a: Prepared according to general reactor setup. The solution was concentrated and dried to yield **2a** (75.3 mg, 93% yield). ¹H NMR (600 MHz, CDCl₃) δ 6.95 (s, 4H), 3.95 (s, 4H), 2.31 (s, 12H), 2.29 (s, 6H) ppm. ¹³C NMR (150 MHz, CDCl₃) δ 202.6, 138.6, 135.5, 135.0, 129.8, 51.0, 21.1, 18.1 ppm. The ¹H NMR and ¹³C NMR data were in accordance with those described in the literature.⁷

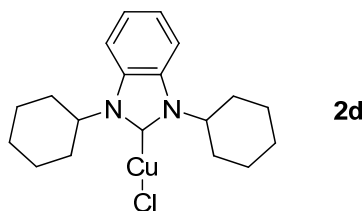


(1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-imidazol-2-yl)copper(I) chloride 2b: Prepared according to general reactor setup except a 5% MeOH/ 80% CH₂Cl₂/ 15% toluene stock solution was used due to solubility of starting material. The solution was concentrated and dried to yield **2b** (92 mg, 94% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.49 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 7.8 Hz, 4H), 7.13 (s, 2H), 2.56 (hept, J = 6.9 Hz, 4H), 1.30 (d, J = 6.9 Hz, 12H), 1.23 (d, J = 7.0 Hz, 12H) ppm. ¹³C NMR (150 MHz, CDCl₃) δ 180.6, 145.6, 134.4, 130.6, 124.2, 123.2, 28.7, 24.8, 23.9 ppm. The ¹H NMR and ¹³C NMR data were in accordance with those described in the literature.⁸

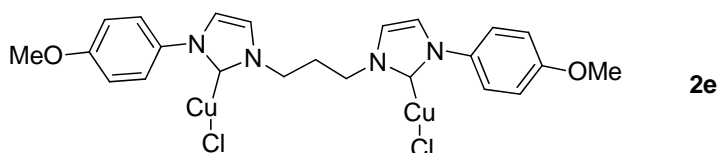


(1,3-dicyclohexylimidazolidin-2-yl)copper(I) chloride 2c: General reactor setup was used, however, a fresh column was prepared and the flow rate was decreased to 0.400 mL/min (~4 min residence time). Additionally, the fraction collector was disconnected and the product was collected under argon and further dried under nitrogen. It was filtered through silica gel with CH₂Cl₂ under nitrogen to obtain a white solid that upon standing in a capped vial degrades to a green gel. (58 mg, 86% yield, 99% purity with

CH₂Cl₂ as main contaminant, purity decreases over time to give ¹H NMR peaks assumed to be cyclic urea). ¹H NMR (600 MHz, CDCl₃) δ 3.89-3.80 (m, 2H), 3.51 (s, 4H), 1.86-1.75 (bs, 8H), 1.67 (m, 2H), 1.49 (m, 4H), 1.37 (m, 4H), 1.09 (m, 2H) ppm. ¹³C NMR (150 MHz, CDCl₃) δ 197.5, 59.7, 44.2, 32.0, 25.3, 25.2 ppm.



(1,3-dicyclohexyl-2,3-dihydro-1H-benzo[d]imidazol-2-yl)copper(I) chloride 2d: Prepared according to general reactor setup. The solution was concentrated and dried to yield **2d** (69.3 mg, 91% yield). Solvent can be more readily removed by drying under vacuum while heating. ¹H NMR (600 MHz, CDCl₃) δ 7.57 – 7.54 (m, 2H), 7.36 – 7.33 (m, 2H), 4.50 (tt, *J* = 12.3, 3.8 Hz, 2H), 2.43 (qd, *J* = 12.6, 3.6 Hz, 4H), 2.09 (d, *J* = 12.3 Hz, 4H), 2.00 (d, *J* = 14.0 Hz, 4H), 1.80 (d, *J* = 12.9 Hz, 2H), 1.54-1.46 (m, 4H), 1.41 (qt, *J* = 12.9, 3.2 Hz, 2H) ppm. ¹³C NMR (150 MHz, CDCl₃) δ 180.3, 133.2, 123.5, 111.8, 59.7, 33.9, 26.1, 25.2 ppm. Anal. Calcd. for C₁₉H₂₆ClCuN₂: C: 59.83; H: 6.87; N: 7.34. Found: C: 59.82; H: 6.92; N: 7.26.



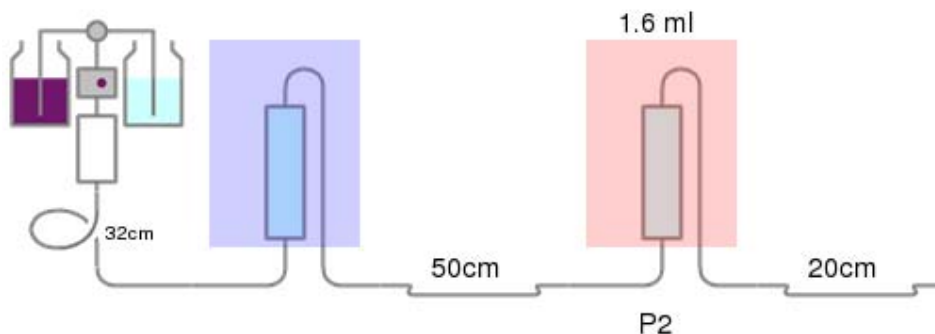
1,3-bis(3-(4-methoxyphenyl)-2,3-dihydro-1H-imidazol-1-yl)propyl copper(I) chloride (2e). Prepared according to general reactor setup except a 5% MeOH/ 80% CH₂Cl₂/ 15% toluene stock solution was used due to solubility of starting material. (111.1 mg, 98% purity with CH₂Cl₂ as contaminant, 93% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.55 – 7.49 (m, 4H), 7.26 – 7.21 (m, 4H), 7.02 – 6.96 (m, 4H), 4.34 (t, *J* = 7.1 Hz, 4H), 3.85 (s, 6H), 2.69 (p, *J* = 7.1 Hz, 2H) ppm. ¹³C NMR (176 MHz, CDCl₃) δ 175.4, 160.2, 132.6, 125.2, 122.3, 121.3, 114.9, 55.7, 48.6, 32.5. Anal. Calcd. for C₂₃H₂₄Cl₂Cu₂N₄O₂: C: 47.10; H: 4.12; N: 9.55. Found: C: 46.63; H: 4.10; N: 9.27. Discrepancy between calculated and actual elemental analysis likely due to residual solvent.

6. General Reactor Setup Using Ion Exchange Resin

A) Preparation of ion exchange column

A glass Omnifit column (6.6 mm diameter) was packed to a height of ~6 cm with Dowex 1x4, 200-400 mesh ion exchange resin by first suspending the resin in MeOH and packing by vacuum filtration and lightly packing with a glass rod. The end-cap was secured and the water was removed by running MeOH and acetone sequentially through the column for ~20 minutes at 1.00 mL/min. Then 80% CH₂Cl₂/5% MeOH/15% toluene was run through the column for ~20 minutes at 1.00 mL/min, the top was cinched down, and additional solvent was passed through the column.

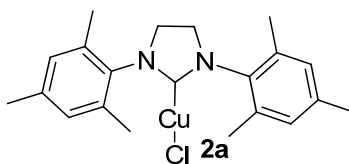
B) Reactor Configuration



Description of reactor from left to right: One pump was connected with 32 cm of drop tubing to the bottom of a glass Omnifit column (6.6 mm diameter) containing ion exchange resin packed as described above with an assumed void volume of 1.6 mL. An additional 50 cm of tubing connected the top outlet of the ion exchange column to the bottom of a glass Omnifit column (6.6 mm diameter) containing 1.65 g of the copper(I) oxide/4 Å molecular sieve (as outlined above) with a void volume ~1.6 mL. An additional 20 cm of tubing connected the top outlet of the column to a 100 psi backpressure regulator (not shown) and extra tubing to reach a fraction collector.

7. Substrate Scope and Product Characterization with Ion Exchange Resin

The general reactor setup as described in section 6b was used. The same ion exchange column and copper(I) oxide/4 Å molecular sieve column was reused for multiple substrates with only washing of solvent in between uses. Stock solutions containing 0.020M of substrate in 80% CH₂Cl₂/5% MeOH/15% toluene were passed through the ion exchange (set 22 °C) and copper (I) oxide (set 110 °C) columns at a rate of 0.800 mL/min and 10 mL of product was collected with a theoretical maximum of 0.200 mmoles expected.



From triflate salt **3** (77.2 mg, 95% yield). The ^1H NMR data matched those obtained for substrate **2a**. (see above)

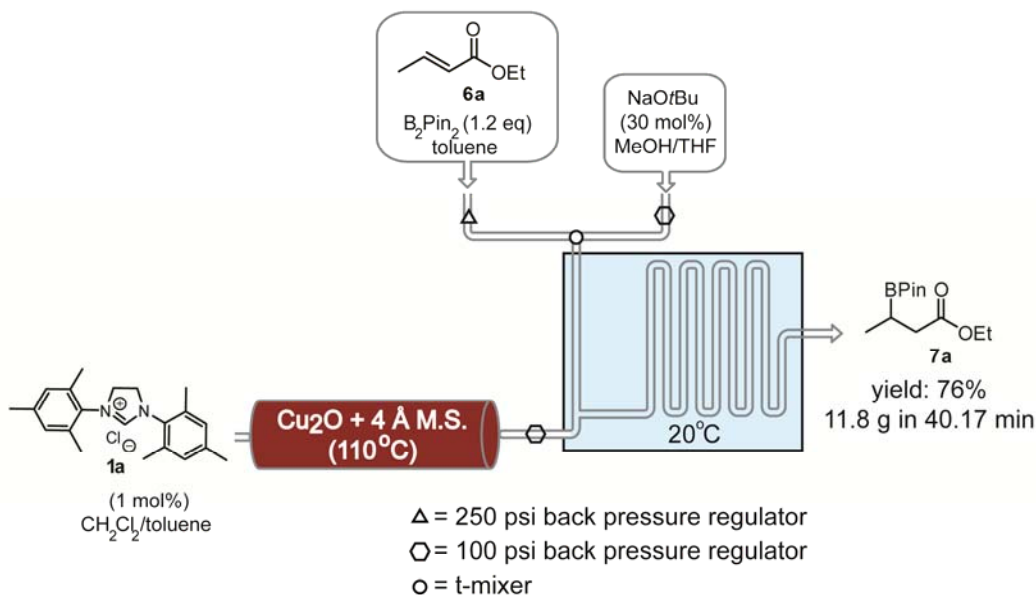
From tetrafluoroborate salt **4** (77.6 mg, 95% yield). The ^1H NMR data matched those obtained for substrate **2a**. (see above)

8. Long Term Stability Experiments

A glass Omnifit column (6.6 mm diameter) containing 1.65 g of the copper (I) oxide/4Å molecular sieve (prepared as described above) with a void volume ~ 1.6 mL was setup in the microreactor according to section 3A/3B. A stock solution of **1a** (0.2M) or (0.02M) was prepared in 80% CH_2Cl_2 / 20% toluene. The reactor was programmed to continuously run **1a** through the reactor and periodically collect 1.5 mL or 10 mL fractions. The fractions were immediately concentrated or placed under a nitrogen atmosphere before concentration and then placed under vacuum. Purity was assessed by NMR and conversion was calculated. Time was plotted as a function of the mid-point of the collection period.

9. β -borylation Reaction – Large Scale

A) Reactor Configuration – Reactor view



Description of Reactor from left to right: The first pump (used to introduce the NHC-catalyst) was connected with 32 cm of drop tubing to the **bottom** of a glass Omnifit column (6.6 mm diameter) packed with Cu₂O/4Å molecular sieve column (as outlined above) with a void volume ~ 1.6 mL. An additional 32 cm of tubing connected the **top** outlet of the column to a 100 psi backpressure regulator which was connected to one inlet on a 10.0 mL tube cooled reactor (no quench used – see Figure S2). A second pump (with a 250 psi back pressure regulator placed in-line after the pump – used to introduce the acrylate and B₂Pin₂)

was connected with 50 cm of drop tubing to a t-mixer where a third pump (with 56 cm of drop tubing and a 100 psi back pressure regulator placed in-line after the pump was used to introduce the NaOtBu). This combined reagent stream was connected to the second inlet of the 10 mL tube cooled reactor. Finally, upon exiting the coil an additional ~47 cm of tubing was used to reach a collection vessel.

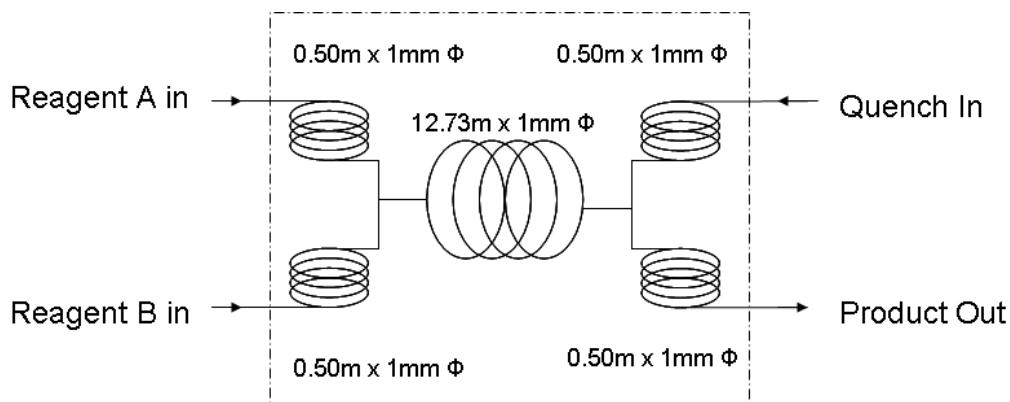


Figure S2: Detailed schematic of the 10.0 mL coil reactor – note no quench is used in these experiments therefore the reaction can continue outside the reactor.

B) Borylation of acrylate **6a**

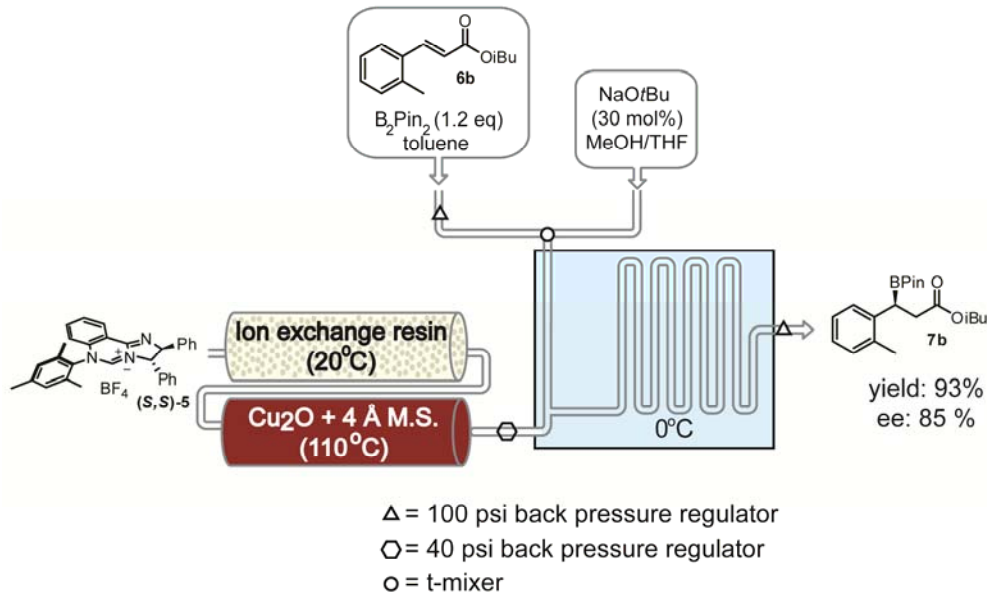


Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (7a**):** A reactor was assembled as outlined above. A solution of imidazolium salt **1a** (0.02 M, 0.01 eq) in 80% CH₂Cl₂/ 20% toluene was prepared and pumped through a Cu₂O/4Å molecular sieve column (set at 110 °C) at a rate of 0.800 mL/min (~2 minute residence time in the copper oxide column). Upon exiting the resulting solution entered the coil reactor and was pre-cooled to 20°C. A single stock solution of α,β-unsaturated ester **6a** (0.4 M, 1 eq) and bis(pinacolato) diboron (0.48 M, 1.2 eq) was prepared in dry toluene (pumped at a rate of 4 mL/min) and combined with a separate solution of NaOtBu (0.192 M, 0.30 eq, pumped at a rate of 2.5 mL/min) in a 70% anhydrous MeOH/30% dry THF solution prior to entering the coil reactor. The reagent and catalyst streams reacted at 20 °C and upon reaching equilibrium (~10 min) product was collected for 40.167 min (theoretical 64.3 mmol), filtered through silica gel, washed with Et₂O, and concentrated. Hexanes was added to precipitate pinacol. After filtration and concentration the product was distilled under reduced pressure and further purified by column chromatography using 5% EtOAc/95% hexanes to provide an oil (11.79 g, 76% yield) after drying under vacuum. ¹H NMR (600 MHz, CDCl₃) δ 4.12 (q, J=7.12 Hz, 2H), 2.43 (dd, J=16.4, 7.7, 1H), 2.36 (dd, J=16.4, 6.7 Hz, 1H), 1.37 (m, J=6.29 Hz, 1H), 1.26-1.22 (m, 16 H), 1.00 (d, J=7.50 Hz, 3H) ppm. ¹³C NMR (150 MHz, CDCl₃) δ 173.9, 83.1, 60.1, 37.7, 24.72, 24.67, 15.1, 14.3

ppm. The ^1H NMR and ^{13}C NMR data were in accordance with those described in the literature.¹

10. β -borylation Reaction – Using Ion Exchange

A) Reactor Configuration – Reactor view



Preparing ion exchange resin: Dowex 1x4, 200-400 mesh ion exchange resin was suspended in a saturated NaCl/water solution and shaken overnight. The resin was filtered, washed with water and ethanol and dried at 60 °C under vacuum. Then 1 g of the dried ion exchange resin was measured out into the column and packed by vacuum filtration using 25% dry CH_2Cl_2 / 75% dry toluene.

Description of Reactor from left to right (see figure S3 below for picture): The first pump (used to introduce the NHC-catalyst) was connected with 32 cm of drop tubing to the **bottom** of a glass Omnifit column (6.6 mm diameter) containing ion exchange resin (prepared as described above), followed by 50 cm of tubing to reach the bottom of a $\text{Cu}_2\text{O}/4\text{\AA}$ molecular sieve column (packed as outlined above) with a void volume ~ 1.6 mL. An additional 32 cm of tubing connected the **top** outlet of the column to a 40 psi backpressure regulator which was connected to one inlet on a 5.0 mL tube cooled reactor (effective reaction space in cooled region 5.44 mL, no quench used – see Figure S4). A second pump (with a 100 psi back pressure regulator placed in-line after the pump – used to introduce the acrylate and B_2Pin_2) was connected with 50 cm of drop tubing to a t-mixer where a third pump (used to introduce the NaOtBu with 50 cm of drop tubing was also connected. This combined reagent stream was connected to the second inlet of the 5 mL tube cooled reactor. Finally, an additional 20 cm of tubing connected the outlet of the coil to a 100 psi backpressure regulator and extra tubing to reach a fraction collector.

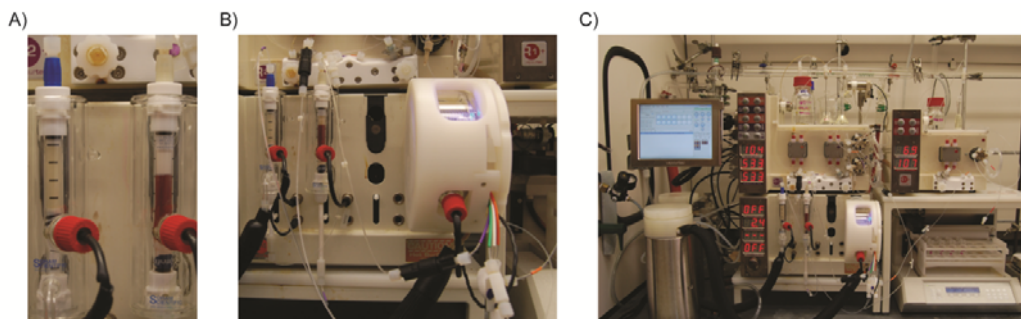


Figure S3: Representative composite reactor setup for performing copper carbene catalyzed β -borylation reaction. **A)** Glass Omnifit columns are packed with ion exchange resin and Cu_2O /molecular sieves (1:1 by weight). **B)** The columns are placed in-line with a cooled 5 mL PFA coil tube reactor. **C)** The components are connected to HPLC pumps for solvent and reagent inputs. A computer is programmed to control the timing of reagent/solvent inputs and fraction collection.

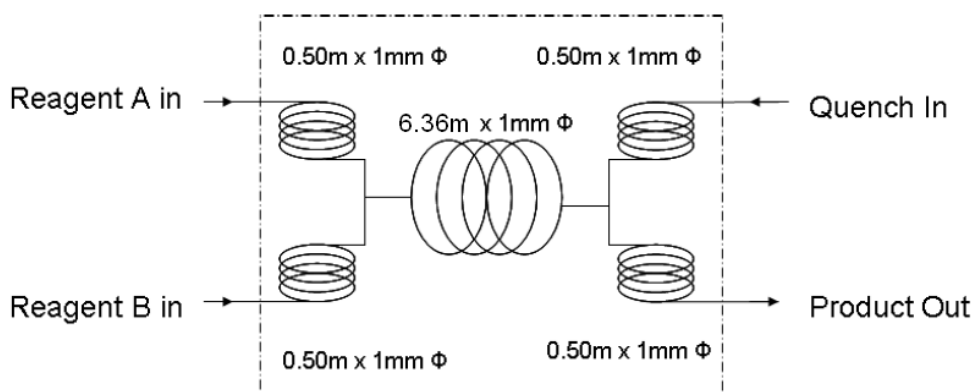
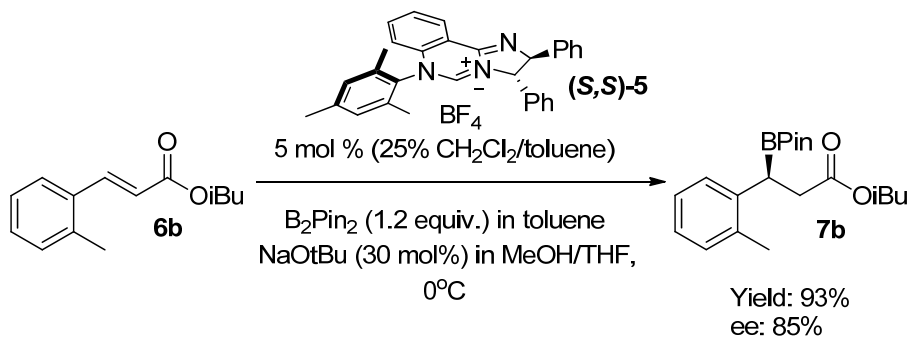


Figure S4: Detailed schematic of the 5.0 mL coil reactor – note no quench is used in these experiments therefore there is an effective 5.44 mL of reaction space in cooled region.

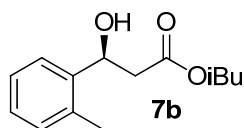
B) Borylation of acrylate 6b



Isobutyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(o-tolyl)propanoate (7b):

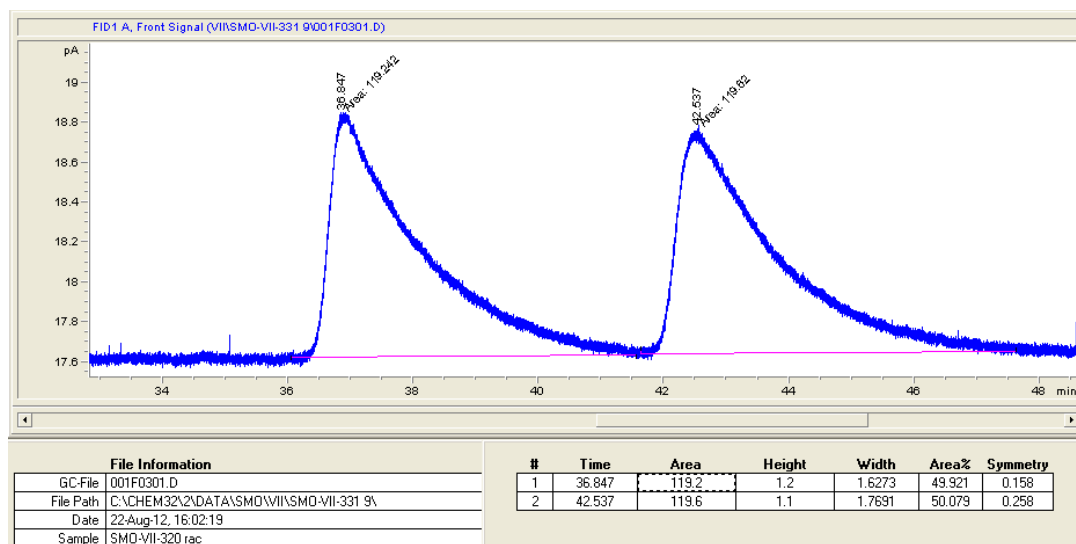
A reactor was assembled as outlined above. A solution of 6-NHC imidazoquinazolium salt **5** (0.02 M, 0.05 eq) in 25% dry CH₂Cl₂/ 75% dry toluene was prepared (filtered to remove any fine particulates) and pumped through a column of ion exchange resin (set to 20 °C) followed by a Cu₂O/4Å molecular sieve column (set at 110 °C) at a rate of 1.6 mL/min (~1 minute residence time in the copper oxide column). Upon exiting the resulting solution entered the coil reactor and was pre-cooled to 0°C. A single stock solution of α,β -unsaturated ester **6b** (0.4M, 1 eq) and bis(pinacolato) diboron (0.48 M, 1.2 eq) was prepared in dry toluene (pumped at a rate of 1.6 mL/min) and combined with a separate solution of NaOtBu (0.6 M, 0.30 eq, pumped at a rate of 0.320 mL/min) in a 70% anhydrous MeOH/30% dry THF solution prior to entering the coil reactor. The reagent and catalyst streams reacted at 0 °C and upon reaching equilibrium (note: an extended equilibration period is required ~30 mL total of catalyst **5** to obtain high enantioselectivity) 15 mL (theoretical 2.73 mmol) were collected, filtered through silica gel, washed with Et₂O, concentrated, and chromatographed with 10% EtOAc/ 95% hexanes to yield a colorless oil, 880.9 mg, 93% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.20 – 7.02 (m, 4H), 3.86 (dd, J = 10.5, 6.8 Hz, 1H), 3.79 (dd, J = 10.6, 6.7 Hz, 1H), 2.95 (dd, J = 10.0, 6.1 Hz, 1H), 2.88 (dd, J = 16.5, 10.0 Hz, 1H), 2.63 (dd, J = 16.5, 6.1 Hz, 1H), 2.36 (s, 3H), 1.96 – 1.82 (m, 1H), 1.21 (s, 6H), 1.17 (s, 6H), 0.89 (d, J = 6.7 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 173.7, 139.9, 136.2, 130.4, 127.6, 126.0, 125.5, 83.5, 70.5, 36.7, 27.7, 24.6, 24.5, 20.0, 19.07, 19.10. The ¹H NMR and ¹³C NMR data were in accordance with those reported in the literature.¹ To determine the enantioselectivity the boronate was dissolved in ethyl acetate and treated with excess 1M NaOH and peroxide. The organic layer was separated, water layer washed with ethyl acetate. The combined organic layers were dried and concentrated. This crude product was subjected to chiral GC analysis using an Astex CHIRALDEX β -DM column to determine the enantioselectivity.

C) Chromatograms of Racemic and Enantiomerically Enriched Product 7b

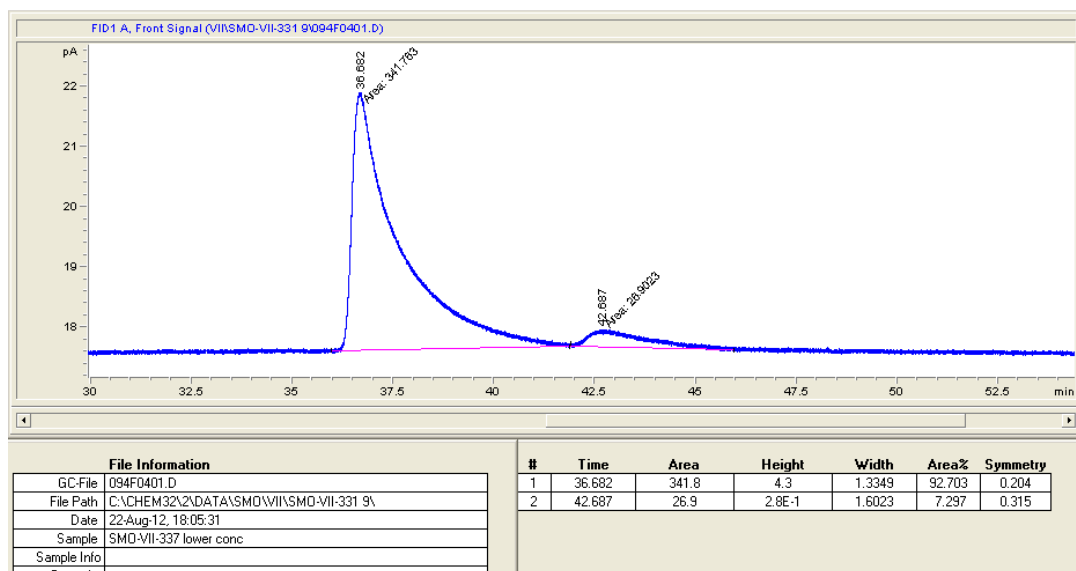


Method: Astex CHIRALDEX B-DM 30 m x 0.25 mm, 0.12 μ m film thickness 130 °C hold 60 min flow 5 ml/min.

Racemic:



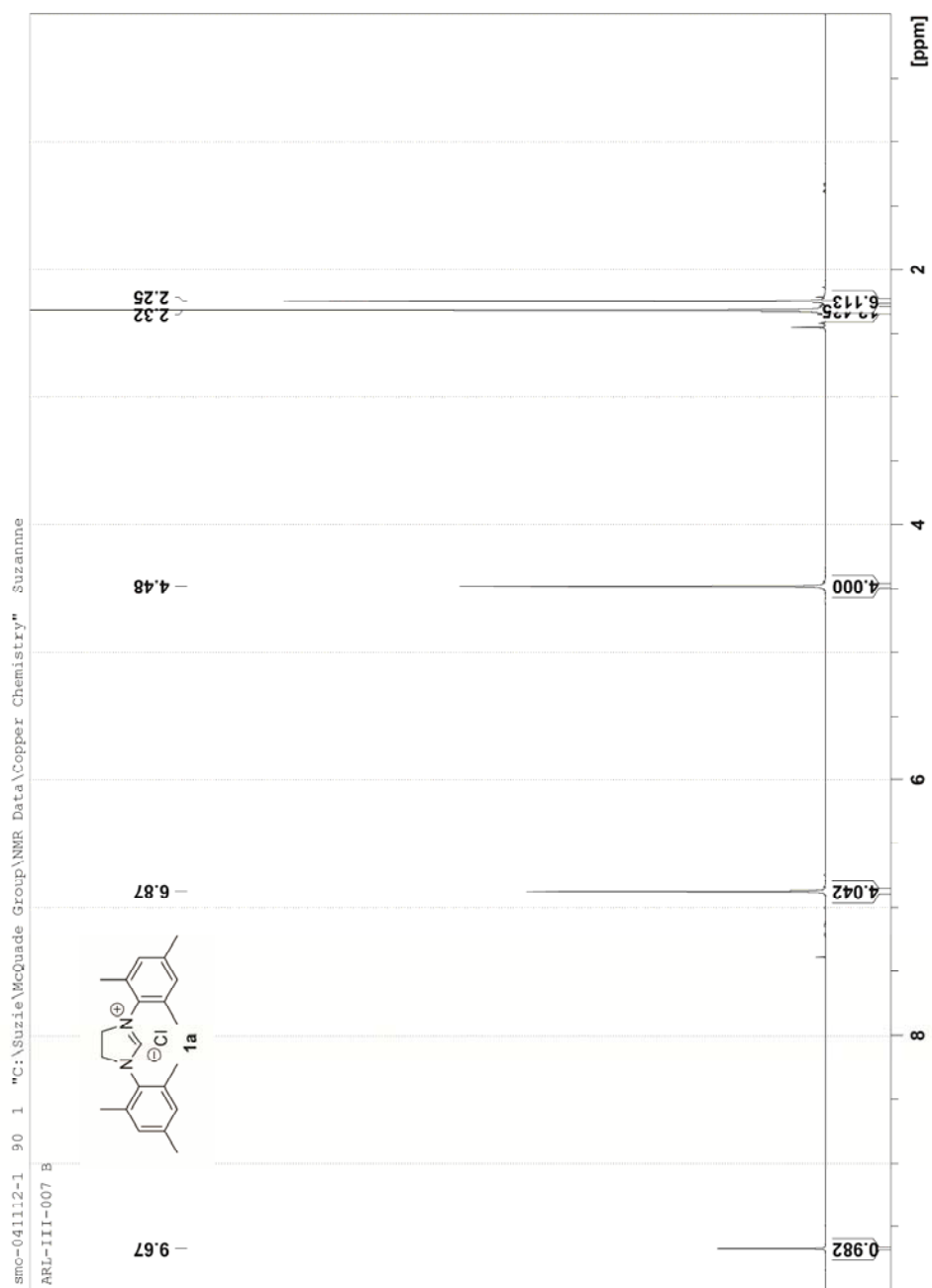
Enantioenriched: 85% ee



11. References

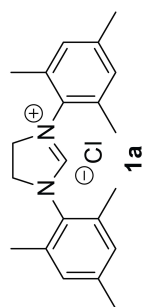
- (1) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008.
- (2) Kuhn, K. M.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2075.
- (3) Aidouni, A.; Bendahou, S.; Demonceau, A.; Delaude, L. *J. Comb. Chem.* **2008**, *10*, 886.
- (4) Lechner, B.-D.; Merzweiler, K. *Acta Crystallographica Section E* **2010**, *66*, o122.
- (5) McGarrigle, E. M.; Fritz, S. P.; Favereau, L.; Yar, M.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3060.
- (6) We noticed a dependence on the direction of flow and yield. We found the best results with flow from the bottom of the column to the top.
- (7) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784.
- (8) Liu, J.; Zhang, R.; Wang, S.; Sun, W.; Xia, C. *Org. Lett.* **2009**, *11*, 1321.

12. ^1H and ^{13}C NMR Spectra of Chemical Compounds



smo-041112-1 91 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

ARL-III-007 B



160.10

139.87
134.80
130.24
129.63

77.37
77.16
76.95

51.70

20.81
17.77

[ppm]

50

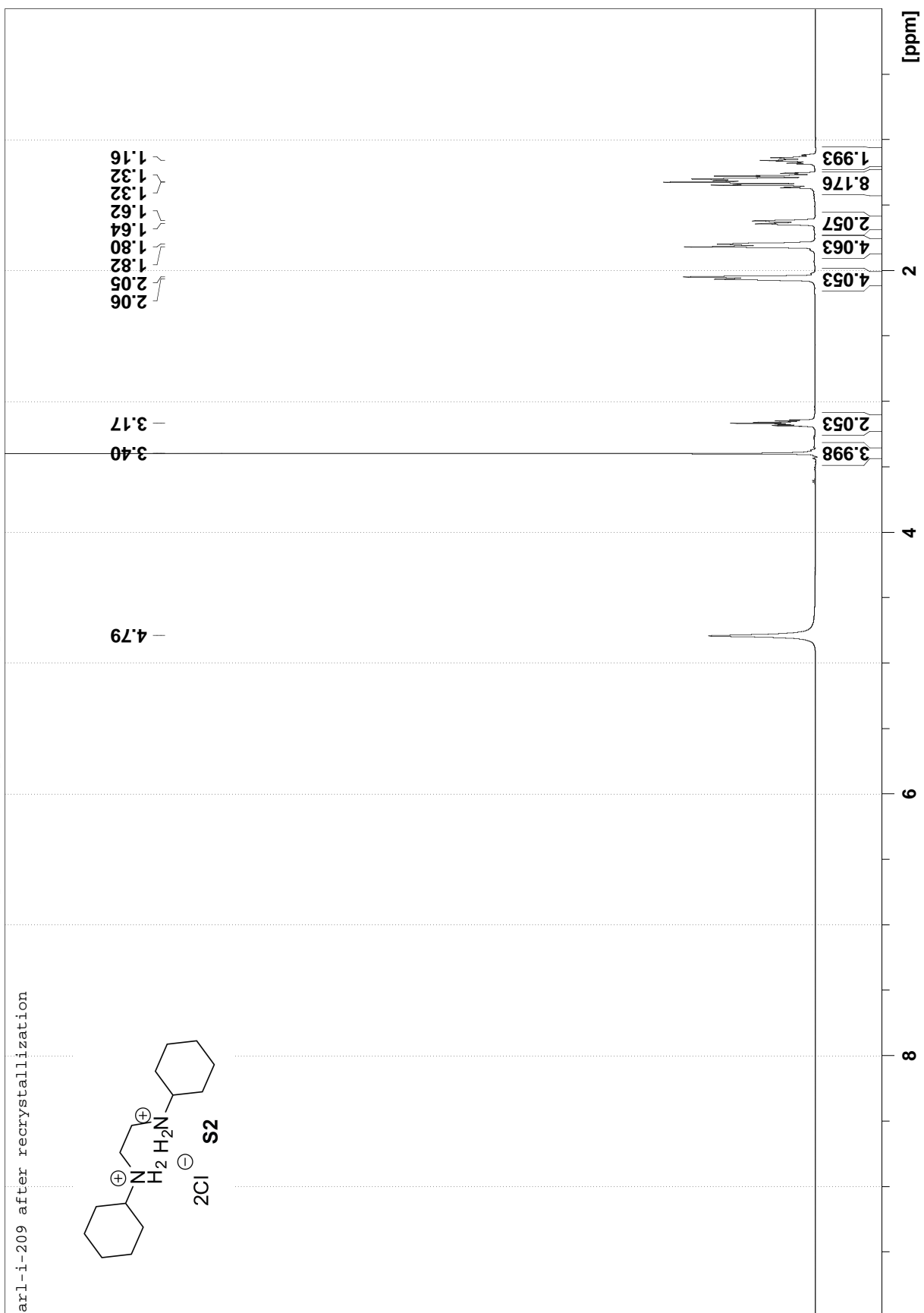
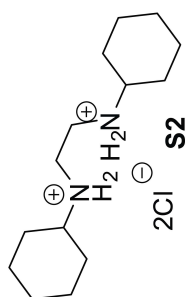
100

150

200

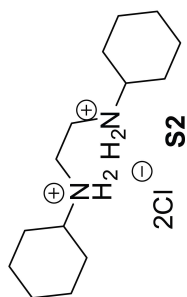
arl-021112-1 40 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

arl-i-209 after recrystallization



smo-041112-1 122 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

cyclohexyl diamine dihydrochloride



28.78
24.42
23.86

40.16

58.07

[ppm]

50

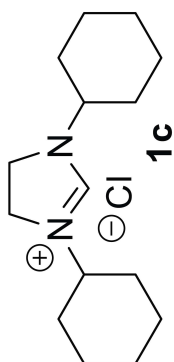
100

150

200

smo-041112-1 50 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

ARL-III-001



9.72

3.99
3.85
3.84
3.83
3.83
3.81
2.72
2.03
2.02
2.01
2.00
1.85
1.85
1.83
1.68
1.66
1.65
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.41
1.39
1.38
1.38
1.37
1.36
1.36
1.34
1.19
1.17
1.16
1.16
1.15

1.008

4.000
2.049
1.090
4.017
4.074
2.133
4.048
4.059
2.036

[ppm]

2

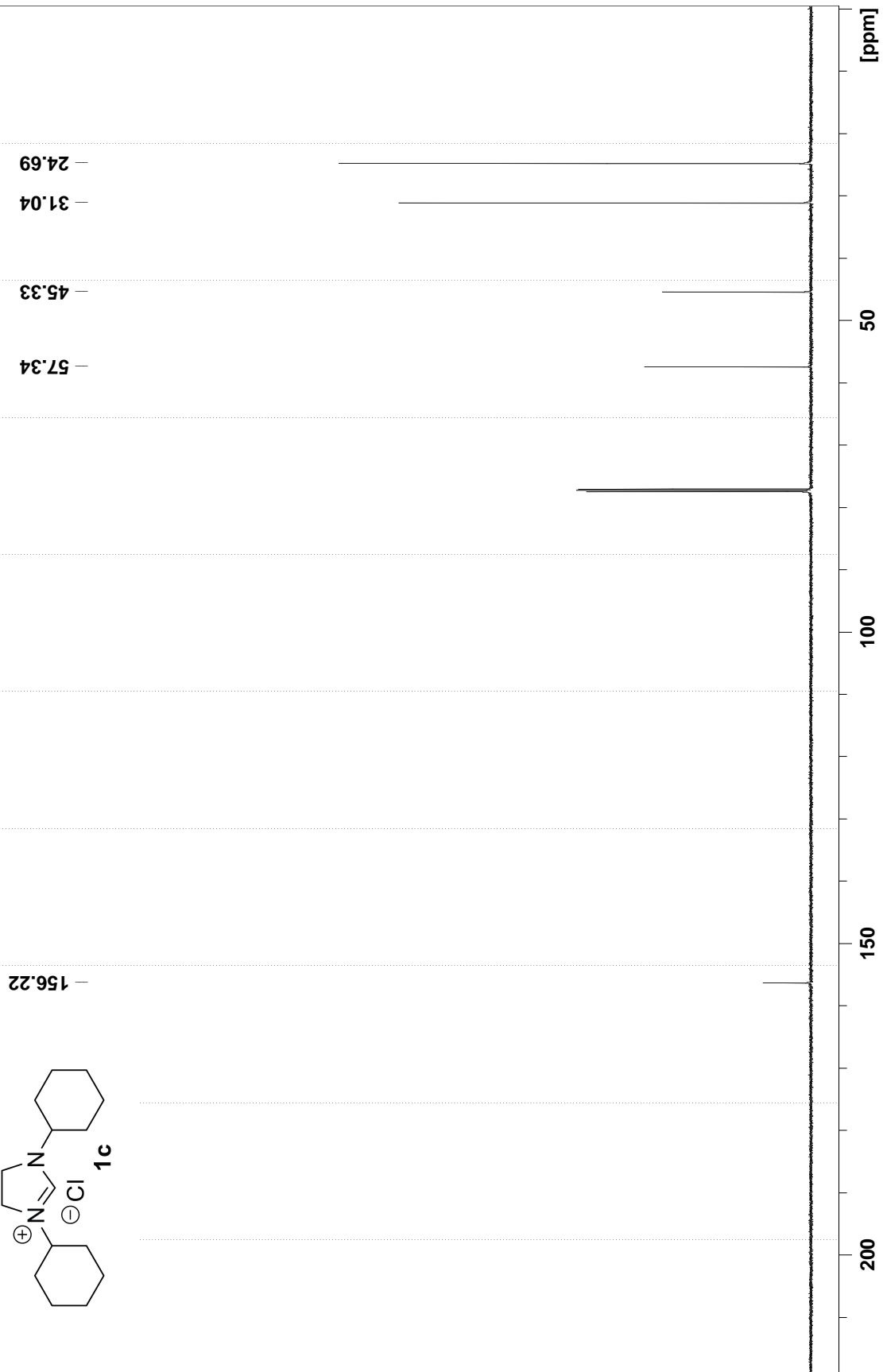
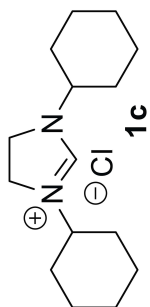
4

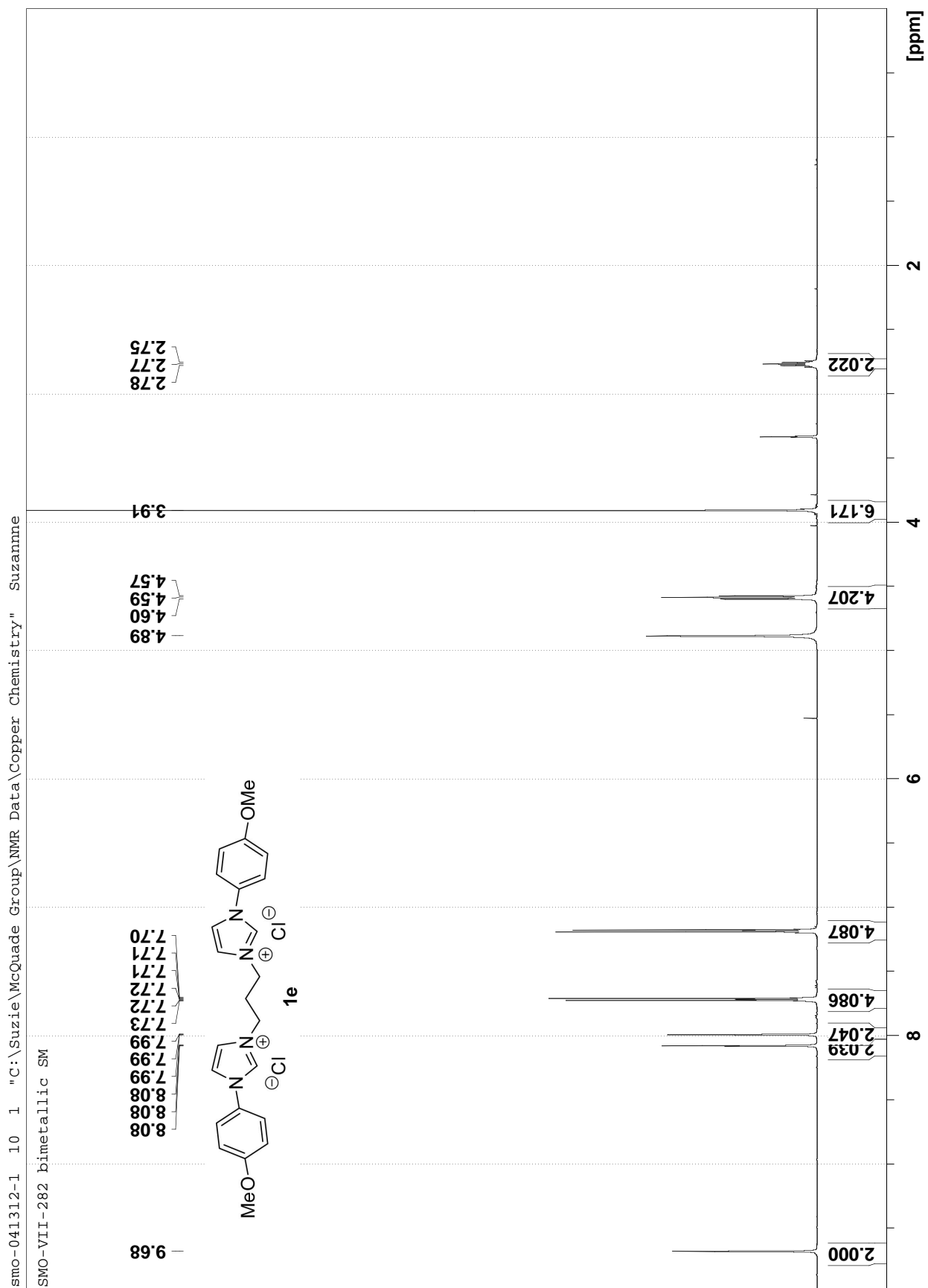
6

8

smo-041112-1 51 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

ARL-III-001



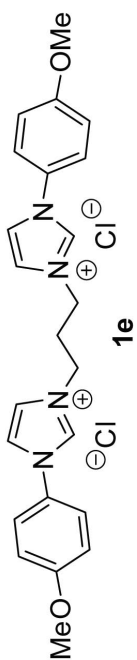


smo-041312-1 12 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SMO-VII-282 bimetallic SM

162.49
136.70
129.36
125.00
124.50
123.45
116.49

56.39
48.18
31.33



[ppm]

50

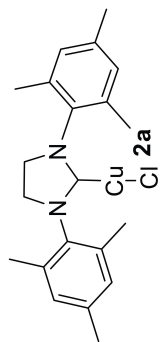
100

150

200

smo-031412-1 70 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannme

SMO-VII-274 E



6.95

3.95

2.31
2.29

3.903

4.000

17.633

[ppm]

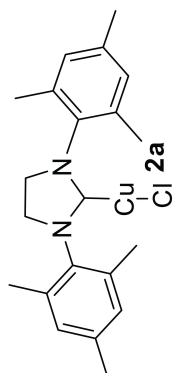
2

4

6

8

SMO-VII-287C



202.62

138.62
135.46
135.04
129.77

51.01

21.05
18.05

[ppm]

50

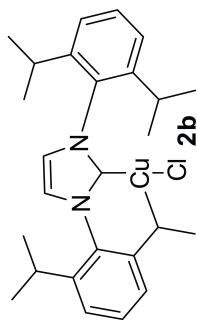
100

150

200

smo-031412-1 30 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SMO-VII-274 C



7.50
7.49
7.47
7.30
7.29
7.13

2.58
2.57
2.56
2.55
2.54

1.31
1.30
1.23
1.22

1.950
3.942
1.937

4.082

12.298
12.298

[ppm]

2

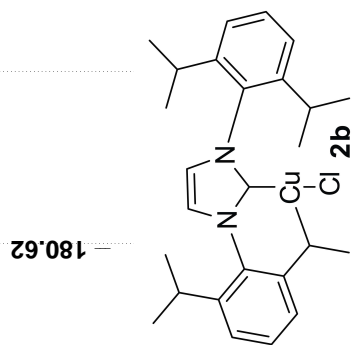
4

6

8

smo-031412-1 32 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SMO-VII-274 C



[ppm]

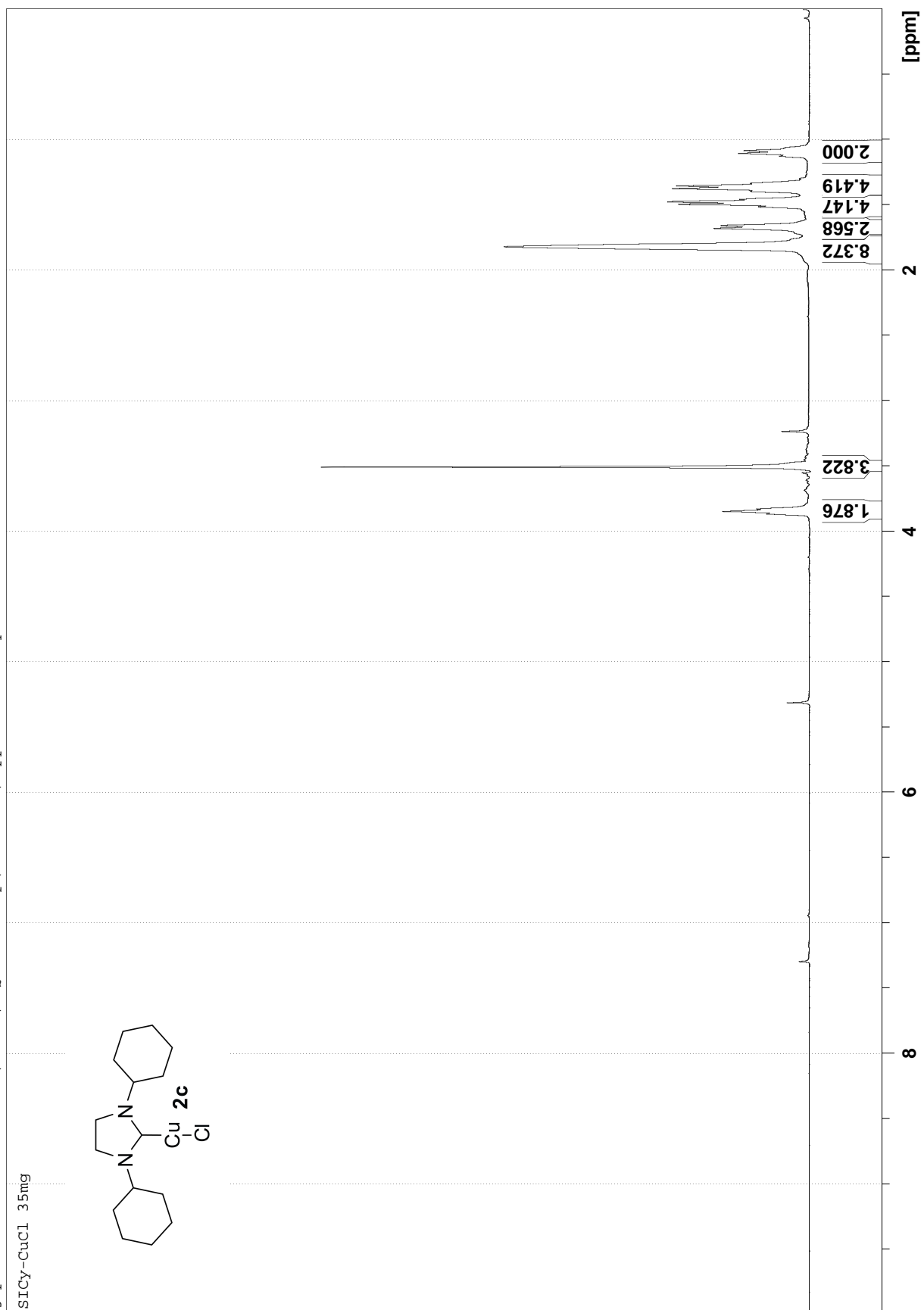
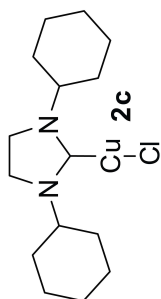
50

100

150

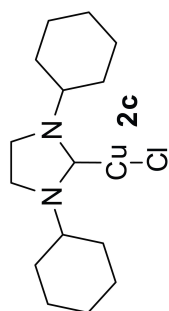
j\kp-032912-1 10 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzannme

SICy-CuCl 35mg



j\kp-032912-1 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SICy-CuCl 35mg



197.50

59.65

44.17

31.99

25.31
25.19

[ppm]

50

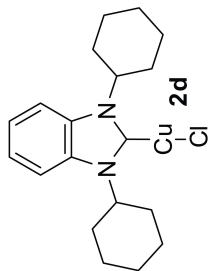
100

150

200

smo-032412-2 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SMO-VII-278 A



4.48
4.49
4.50
4.51
4.52

2.46
2.45
2.44
2.43
2.42
2.40
2.40
2.10
2.08
2.01
1.99
1.82
1.79
1.52
1.52
1.50
1.49
1.49
1.48
1.47
1.44
1.43
1.42
1.41
1.40

7.56
7.56
7.55
7.55
7.35
7.35
7.34
7.34

1.989
1.942

2.00

3.932

1.005
3.983

1.992

2.062

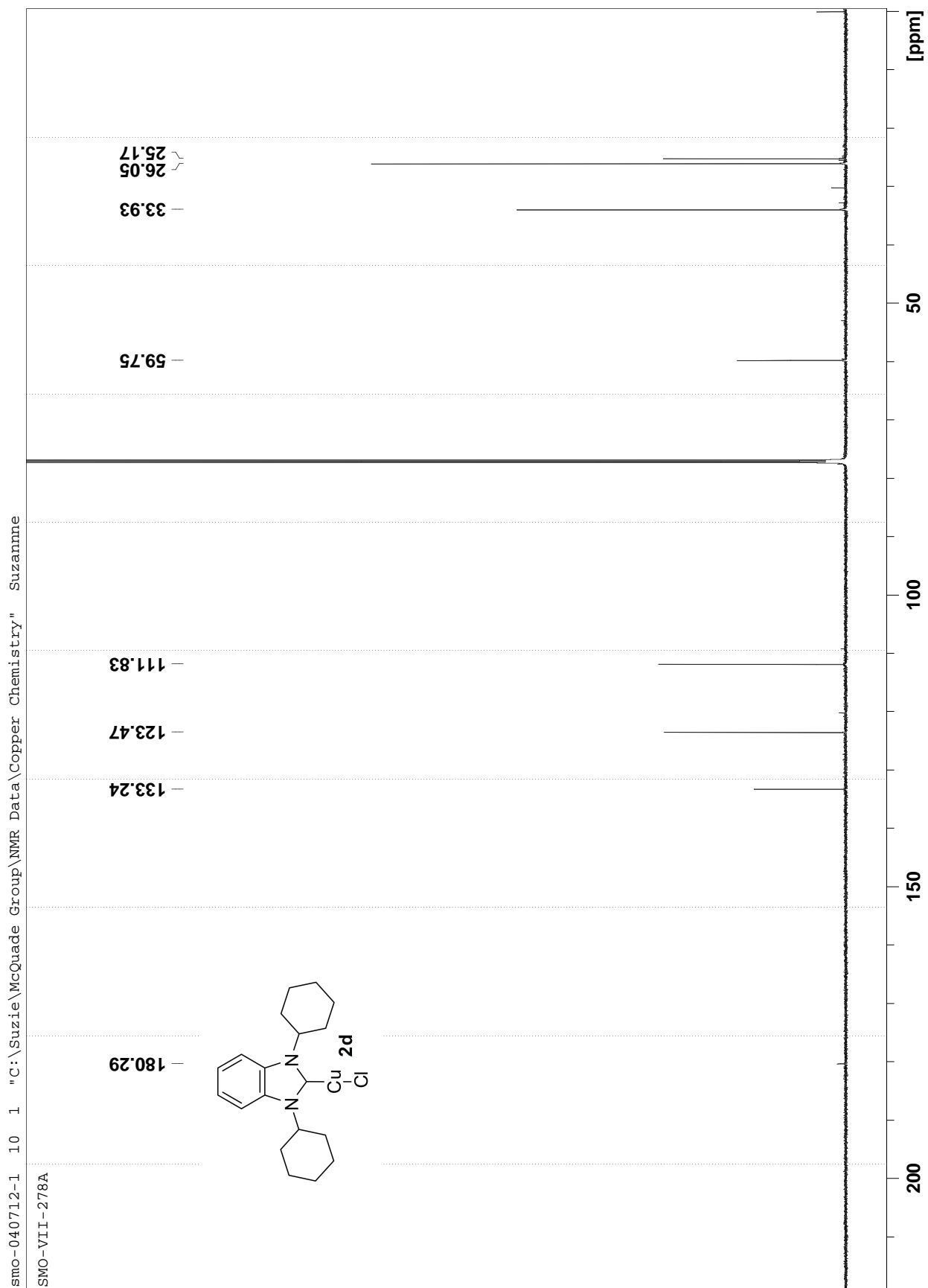
[ppm]

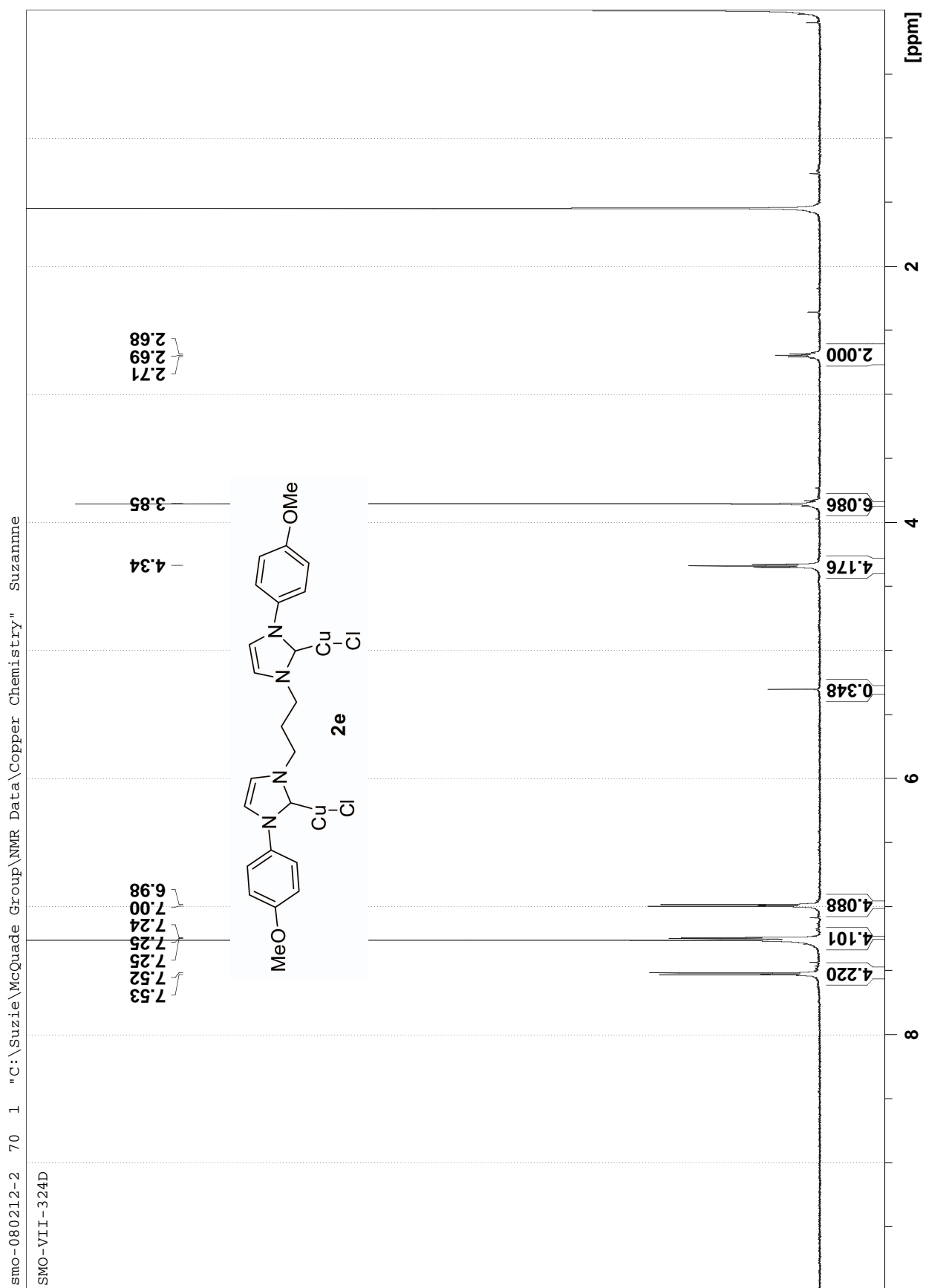
2

4

6

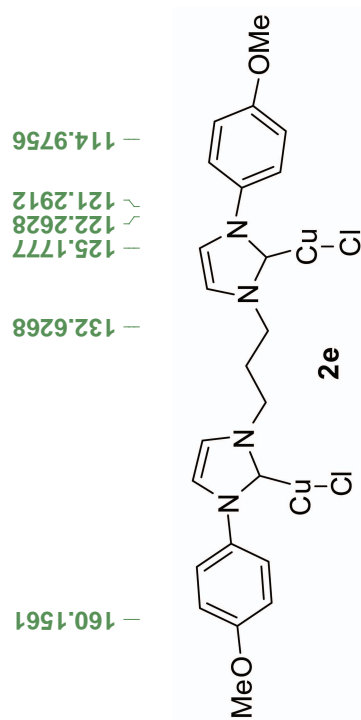
8





bhc-test-080612 3 1 C:\Bruker\TOPSPIN chen

1H/13C CPD Test b. chen
for Suzie



175.3783

160.1561

132.6268

125.1777

122.2628

121.2912

114.9756

77.0822

55.7065

48.5812

32.5494

0.0000

[rel]

0.3

0.2

0.1

0.0

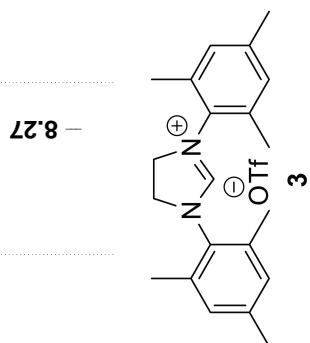
150

100

50

[ppm]

SMO-VII-276



8.27

6.94

4.46

2.32
2.29

0.942

3.852

4.000

17.559

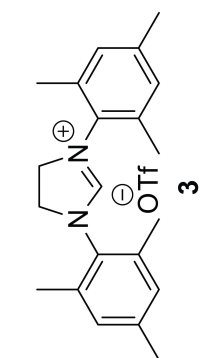
[ppm]

2

4

6

8



159.40

140.67

134.94

130.04

130.02

123.74

121.62

119.49

117.37

51.67

21.04

17.57

[ppm]

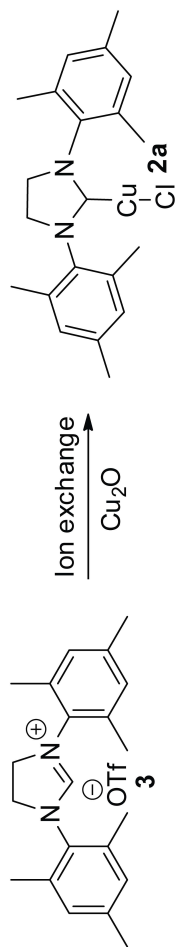
50

100

150

200

SMO-VII-289 A

6.95
2.32
2.30

3.96

6.078
6.072

4.000

3.886

[ppm]

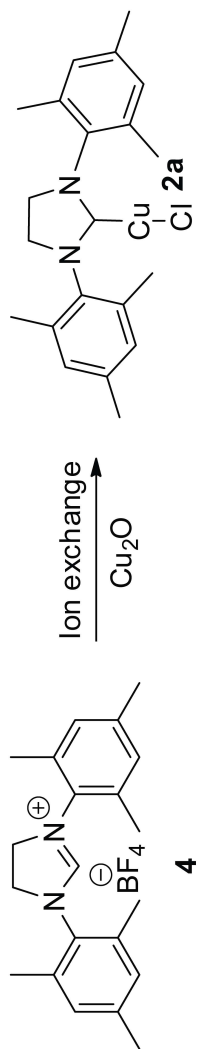
2

4

6

8

SMO-VII-289 B



6.95
2.32
1.55

3.96

17.778

4.000

3.787

[ppm]

2

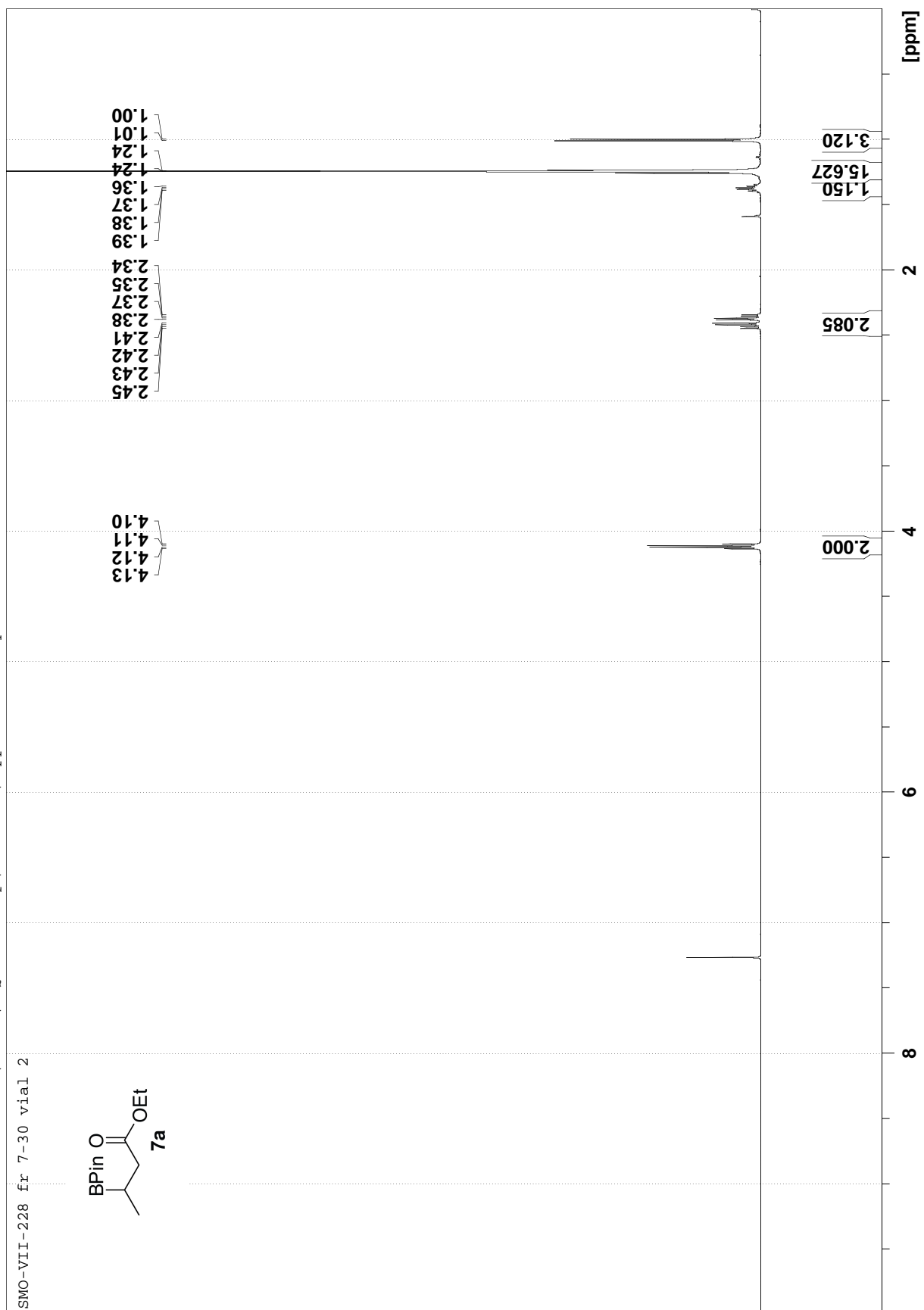
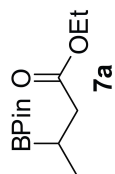
4

6

8

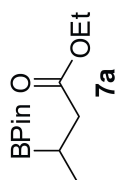
smo-112912-1 20 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SMO-VII-228 fr 7-30 vial 2



smo-112912-1 54 1 "C:\Suzie\McQuade Group\NMR Data\Copper Chemistry" Suzanne

SMO-VII-228 fr 7-30 vial 2



173.88

83.13
77.22
77.01
76.80

60.11

37.71

24.72
24.67

15.06
14.30

-0.01

200

150

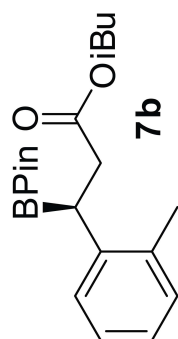
100

50

0

[ppm]

smo-vii-337



7.19
7.18
7.17
7.12
7.11
7.11
7.09
7.06
7.06
7.05
7.04
7.03
7.03

3.87
3.86
3.86
3.85
3.81
3.80
3.79
3.78
2.97
2.96
2.95
2.94
2.90
2.88
2.87
2.85
2.64
2.63
2.62
2.61
2.36
1.91
1.90
1.88
1.87
1.86
1.21
1.17
0.89
0.88

0.998

1.035

1.037

1.060

3.012

1.006

6.165

6.263

8

6

4

2

[ppm]

smo-vii-337

173.66

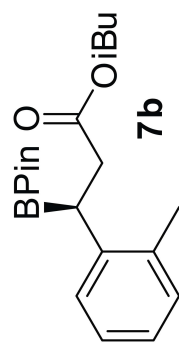
139.87
136.18
130.37
127.58
126.00
125.51

83.47

70.50

36.67

27.73
24.62
24.53
20.02
19.10
19.07



[ppm]

50

100

150

200