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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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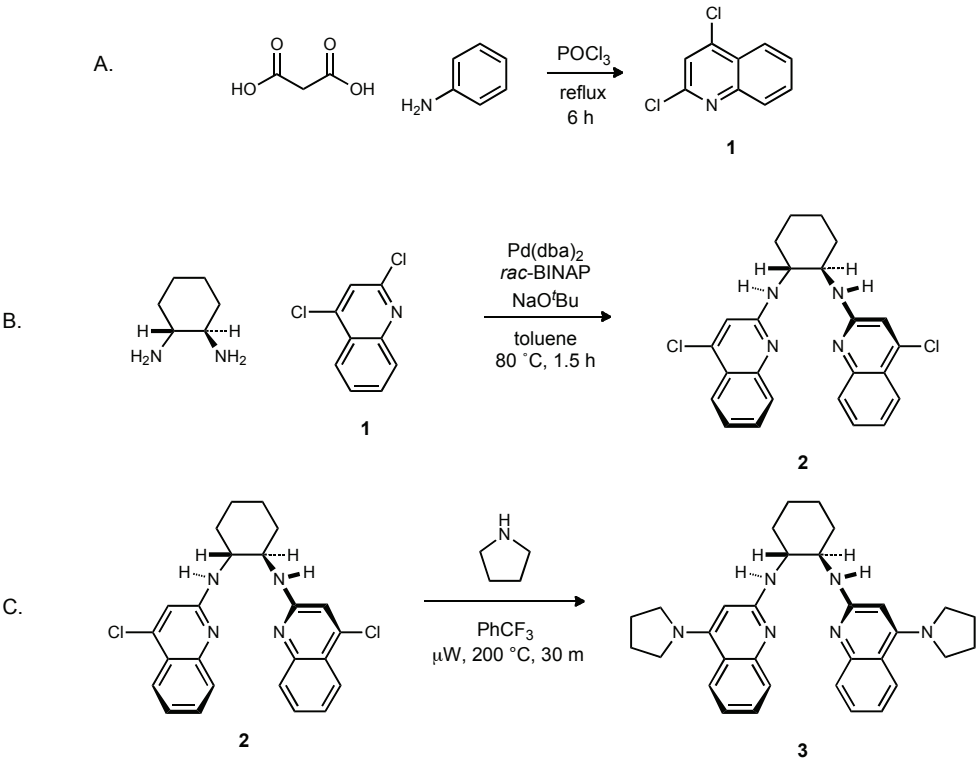
Preparation of H,[4] PyrrolidineQuin-BAM (PBAM)



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Checked by Alexander F. G. Goldberg and Brian M. Stoltz.

1. Procedure

Caution! Part A of this procedure must be carried out in a well-ventilated hood and the apparatus must be equipped with a hydrogen chloride (HCl) trap to avoid exposure to HCl gas.

A. 2,4-Dichloroquinoline (**1**). A 250-mL, 3-necked, round-bottomed flask was equipped with a teflon-coated, oval-shaped stir bar (41 x 20 mm) and charged with malonic acid (26.0 g, 250 mmol, 1 equiv, Note 1).[2] A rubber septum was connected to one of the side necks and a condenser is attached to the middle neck. That condenser was equipped with a line that runs to an HCl trap (Note 2). The flask was lowered into an ice water bath and $POCl_3$ (100 mL) was poured into the open neck. The open neck was sealed with a rubber septum. A slight flow of nitrogen gas was introduced

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into the system through a needle (16 gauge) inserted into one of the side neck septa (Note 3). Stirring was initiated at 300 rpm. Aniline (22.8 mL, 250 mmol, 1 equiv) was added slowly to the stirring mixture by syringe through a side neck septum over a period of 20 min (Note 4). The flask was then removed from the ice water bath, allowed to stir for 10 min, placed into an oil bath (~110 °C) and the mixture was stirred for 6 h (Note 5). The flask was removed from the oil bath and allowed to cool for 5 min without stirring (Note 6). The mixture was slowly and carefully poured onto crushed ice (~ 1 L) in a 2 L beaker while intermittently stirring with a spatula. The residual material in the 3-neck round-bottomed flask was removed by carefully adding water (100 mL) to the flask and scraping out with a spatula. The aqueous mixture was triturated by vigorous stirring with the spatula (Note 7). The 2 L quench beaker was placed into a bucket of ice. Aqueous NaOH (6 M, 475 mL) was added slowly (over a period of 25 min, maintaining the temperature ≤ 50 °C) while intermittently stirring (Note 8). The beaker was removed from the ice bath and the suspension was allowed to warm to ambient temperature and age with stirring (77 x 13 mm stir bar, ~100 rpm) for 12 h (Note 9). The pH of the supernatant was ~7. The suspension was then vacuum filtered through a Büchner funnel (12.5 cm diameter). Water (150 mL) was used to rinse the residual material from the beaker. The filtered orange-red solid was rinsed with water (150 mL) on the filter. After thoroughly air-drying on the filter (> 1 h), the solid was transferred into 2 cellulose thimbles (43 mm x 123 mm, int. diam. x ext. length). The contents of each thimble were subjected to a Soxhlet extraction with hexanes (300 mL, Note 10) for 16 h. The combined extracts were concentrated (Note 10) by rotary evaporation (30 °C, 13 mmHg) and further dried under vacuum (1–2 mmHg) to leave a yellow solid (13.9–14.6 g, 28–29%, Notes 11 and 12) that was used in step B without further purification (Note 13).

B. *H,*^{4}*ClQuin-BAM* (**2**). A 100 mL, round-bottomed flask (24/40 joint) equipped with a teflon-coated oval stir bar (32 x 15 mm), rubber septum and an inlet needle connected to an argon/vacuum manifold (Note 16) was first charged with (*R,R*)-1,2-diaminocyclohexane (1.63 g, 14.3 mmol, 1 equiv, Notes 17 and 18). Then, $Pd(dba)_2$ (164 mg, 285 μmol, 0.02 equiv), *rac*-BINAP (356 mg, 572 μmol, 0.04 equiv), 2,4-dichloroquinoline (**1**) (5.66 g, 28.6 mmol, 2 equiv) and sodium *tert*-butoxide (4.12 g, 42.9 mmol, 3 equiv, Note 19) were added. The reaction vessel was evacuated and backfilled with argon three times, then left under a positive pressure of argon.[3] Toluene

(35 mL) was dispensed into the flask, and the resulting red-brown solution was placed into an oil bath heated to 80 °C with stirring (Notes 20 and 21, *Caution: possible exotherm!*). The reaction was monitored by TLC (Note 22); after 1.5 h, nearly complete conversion was observed. The reaction was cooled to 25 °C, and saturated NH_4Cl (10 mL) and water (10 mL) were added to the flask. The suspension was stirred for 5 min and cooled to 0 °C for 10 min. The reaction mixture was filtered through a Büchner funnel (9 cm diameter) and washed with water (50 mL) and hexanes (150 mL) to afford a light yellow solid. This crude solid was transferred to a pre-weighed 100 mL round-bottomed flask with a 24/40 joint and dried under vacuum (1–2 mmHg) for at least 10 h to leave 4.57–4.80 g of a light beige-yellow solid (73–77%) (Note 23), which was used in step C without further purification.

C. H,^{4}PyrrolidineQuin-BAM (PBAM) (**3**). A 10–20 mL microwave vial equipped with an oval stir bar (12 x 8 mm) was charged with H,^{4}ClQuin-BAM (**2**) (4.30 g, 9.83 mmol, 1 equiv, Note 24), pyrrolidine (3.23 mL, 39.3 mmol, 4 equiv), and trifluorotoluene (3.3 mL) (Note 25). The vial was sealed, and this suspension was heated with stirring in the microwave at 170 °C for 3 min, then at 200 °C for 30 min (Notes 26 and 27, *Caution: exothermic!*). The reaction mixture was diluted and transferred with 20 mL of dichloromethane to a 500-mL round-bottomed flask for evaporation (Note 28). The reaction was then concentrated by rotary evaporation (80 °C, 13 mmHg), redissolved in dichloromethane (50 mL), transferred to a 125 mL separatory funnel, and washed with aqueous NaOH (3 M, 50 mL) and water (4 x 50 mL). The resulting organic layer was dispensed into a 125 mL Erlenmeyer flask and dried ($MgSO_4$, 2 g). The solution was filtered (flask and filter were rinsed with an extra 25 mL of dichloromethane) into a 250 mL round-bottomed flask and concentrated by rotary evaporation (30 °C, 13 mmHg) and high vacuum (0.2 mmHg, 1 h) to provide a light brown powder (Note 29).

As much of the material as possible was transferred as a solid from the round-bottomed flask to a pre-weighed 250 mL Erlenmeyer flask. The remaining solid was dissolved and transferred into a 25-mL pear-shaped flask with 10 mL of dichloromethane and concentrated by rotary evaporation (30 °C, 13 mmHg) and high vacuum (0.2 mmHg, 1 h). This material was then added to the 250 mL Erlenmeyer flask. The material was dissolved in a 90:10 mixture of acetone and toluene (20 mL/g crude product) with heating in a water bath (70 °C) (Note 30). The solution was removed from heat and

placed on the bench for 1 hour to cool to room temperature. The flask was placed in an ice bath for 3 h or until no further crystallization was observed. The mother liquor was carefully decanted, leaving crystals that were washed with ice-cold acetone (2 x 10 mL). Residual solvent was removed from the crystals by placing the flask under vacuum (1–2 mmHg) for a period of 5–10 min (Note 31). The crystalline material was transferred to a pre-weighed 20 mL glass scintillation vial and dried for ~14 h in a drying pistol (0.2 mmHg) over refluxing toluene. The vial was temporarily removed from the drying pistol, and the material was thoroughly pulverized with a spatula and returned to the drying pistol for an additional 6 h. The dried material was a cream colored powder (3.08–3.54 g, 62–71% yield) (Notes 32 and 33).

2. Notes

1. Malonic acid (99%), phosphorous oxychloride (99%) and hexanes (mixture of isomers, ACS Grade, >98.5%) were purchased from Sigma-Aldrich and used as received. Aniline (99.9%) and toluene (ACS grade) were purchased from Fisher Scientific Company and used as received.

2. The reflux condenser is fitted with an outlet that is connected with Tygon tubing to two 250 mL bubblers, the first empty, and the second filled with water to serve as the HCl trap.

3. The gas flow should be monitored by constantly checking the bubbler during the aniline addition to prevent the development of negative pressure in the system.

4. A creamy, yellow heterogeneous mixture is observed after completion of the aniline addition. Some solids may aggregate near the surface and will slowly dissolve in the next stage of the reaction.

5. Within the first 10 minutes of heating, vigorous gas evolution is observed as the mixture becomes homogeneous. Within 20 min, the color of the solution transitions from yellow to red to dark brown/black. Over approximately 90 min, the gas evolution subsides, and a gentle reflux is observed.

6. If the solution is cooled for longer than 5 minutes, the reaction mixture may thicken to an extent that renders it difficult to transfer the entire contents of the flask to the quench beaker.

7. This served to break up the largest fragments of material and to increase the surface area of the solid for efficient quenching in the following step.

8. This workup procedure should fully hydrolyze all P-Cl bonds leaving sodium phosphate as the byproduct of $POCl_3$ quenching.[4]

9. This served to fully quench the suspension and to produce a finer crude solid with fewer chunks. This facilitated transfer into the Soxhlet thimble and allowed for a more efficient extraction due to increased surface area of the solid.

10. It may be necessary to filter the hexanes extract if red solid precipitates from the solution: The combined extracts were filtered through Celite® (21 g) in a coarse sintered glass funnel (46 mm diameter). The filter cake was washed with hexanes (2 x 50 mL)

11. The crude 2,4-dichloroquinoline (**1**) exhibited the following: mp 62.0–64.2 (uncorrected); R_f = 0.42 (10% EtOAc/hexanes); IR (film) 3062, 1572, 1553 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (s, 1 H), 7.67 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1 H), 7.81 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1 H), 8.05 (d, *J* = 8.5 Hz, 1 H), 8.21 (dd, *J* = 8.4, 1.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 122.2, 124.4, 125.4, 128.1, 129.2, 131.8, 144.6, 148.3, 150.0; HRMS (APCI-ESI) calcd for $C_9H_6Cl_2N$ $[M+H]^+$ 197.9872; found 197.9870. This data matched the values given in the literature.[2] The checkers observed the development of a brown discoloration during prolonged storage at ambient temperature in air. This does not affect its use in subsequent reactions.

12. The submitters obtained yields between 33–36% using a smaller Soxhlet apparatus, which may have contributed to a greater extraction efficiency, with thimble dimensions: 33 mm x 94 mm (int. diam. x ext. length).

13. The crude material can be further purified by recrystallization. The crude solid (5.0 g) was dispensed into a 50 mL Erlenmeyer flask and dissolved in 20 mL of a 3:1 mixture of hexanes and toluene with heating in a ~70 °C water bath. The solution was allowed to slowly cool to room temperature (Note 14) before it was placed in an ice-water bath. After 2 hours, the mother liquor was decanted. The recrystallization flask was kept in the ice-water bath while the crystals were rinsed with ice-cold hexanes (5 mL). The hexanes were decanted and residual solvent was removed by vacuum (0.2 mmHg) to leave a yellow crystalline solid (2.99–3.17 g, 60–63% recovery, Note 15).

14. The submitters note that if a precipitate forms when the solution is cooled to room temperature, then the solution should be filtered before cooling in an ice-water bath.

15. The melting point range of the recrystallized 2,4-dichloroquinoline (**1**) was 64.1–65.0 °C (uncorrected). The submitters note that material that was purified by column chromatography (0–4% EtOAc in hexanes) exhibited a melting point of 64.0–64.5 °C (uncorrected).

16. The apparatus was flame-dried under reduced pressure (1–2 mmHg) and then maintained under a positive pressure of argon during the course of reaction.

17. (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene (97%) was purchased from Sigma-Aldrich and was used as received. Sodium *tert*-butoxide (97%) was purchased from Sigma-Aldrich, stored in a glovebox under a nitrogen atmosphere, and otherwise used as received. Toluene (ACS grade) was purchased from Fisher and was dried by passage through a column of activated alumina as described by Grubbs.[5] The checkers used bis(dibenzylideneacetone)palladium as received from Sigma Aldrich and (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (99%) as received from Strem Chemicals. The submitters prepared bis(dibenzylideneacetone)palladium according to the procedure of Rettig and Maitlis.[6] The submitters used (1*R*,2*R*)-(−)-1,2-diaminocyclohexane resolved from a *trans*/*cis* mixture (60/40) using the protocol of Jacobsen[7] with L-(+)-tartaric acid; the salt was then dissolved in 10 M NaOH and continuously extracted using benzene in a liquid/liquid extractor for 5 days. This diamine is stored in a freezer.

18. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane is a white solid but becomes a viscous oil as it warms to room temperature. To avoid difficulties in transfer, the diamine is weighed directly into the reaction vessel without allowing the diamine to warm to room temperature.

19. Sodium *tert*-butoxide was dispensed into an oven-dried vial in a glovebox under a nitrogen atmosphere. This vial was sealed and removed from the glovebox and its contents were then quickly transferred into the round-bottomed flask.

20. The reaction should be monitored very carefully for the first 10 minutes; the checkers consistently observed an exotherm within the first 5 minutes of heating. When probed, the internal temperature gradually increased to 80 °C over 4 minutes of heating, then quickly rose to its boiling point within 30 seconds. When the solution began to boil, the flask was removed from the oil bath and allowed to cool at ambient temperature until a precipitate formed (See Note 21).

21. After 5–10 minutes a solid formed and was manually dispersed after removal of the flask from the oil bath by vigorously swirling the flask by hand. The flask was then returned to the oil bath.

22. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm). UV light was used to visualize the product. With 20% ethyl acetate in hexanes, the starting material has R_f = 0.40 and the product has R_f = 0.07. Upon reaction completion, there may still be a relatively faint spot visible of the same R_f as the starting material.

23. This material is of sufficient purity for use as a reactant to make compound **3**. The submitters note that it can be further purified by column chromatography (10% ethyl acetate in hexanes); the melting point of material purified by column chromatography is 236.0–237.0 °C. The submitters note that the crude material exhibited some variation from batch to batch in terms of melting point; a range of 235–245 °C was observed, but individual samples exhibited a routinely narrow (≤ 2 °C) melting point range. H,^{4}ClQuin-BAM (**2**) exhibited the following: mp 240.7–243.0; $[\alpha]_D^{25}$ +568 (*c* 1.02, DMSO); R_f = 0.31 (20% EtOAc in hexanes); IR (KBr) 3250, 2942, 1614 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 1.29–1.45 (m, 4 H), 1.71–1.79 (m, 2 H), 2.18–2.26 (m, 2 H), 4.05 (br s, 2 H), 6.84 (s, 2 H), 7.22–7.29 (m, 4 H), 7.53–7.62 (m, 4 H), 7.82 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 24.3, 31.8, 53.6, 112.6, 120.3, 122.1, 123.4, 126.0, 130.4, 140.2, 148.5, 156.5; HRMS (APCI-ESI) calcd for $C_{24}H_{23}Cl_2N_4$ $[M+H]^+$ 437.1300; found 437.1295. The submitters have found H,^{4}ClQuin-BAM to be a bench stable solid: no decomposition of this compound has been observed after years of storage on the benchtop in a screw cap vial.

24. Pyrrolidine (99%) was purchased from Alfa Aesar. α,α,α-trifluorotoluene (99+%) was purchased from Acros. Dichloromethane (ACS grade) and acetone (ACS grade) were purchased from Sigma-Aldrich. All reagents were used as received.

25. Care should be taken to wash solids on the vial wall below the solvent level to prevent localized heating.

26. The reaction was performed in a Biotage Initiator EXP US 355302 microwave reactor in a sealed vial, at the "Normal" absorption level. This microwave system monitors the pressure and heat inside the sealed vial and shuts off for safety purposes when 20 bar or 250 °C is reached. A two-stage heating protocol was found by the checkers to prevent an exotherm which exceeds the safety parameters of the microwave system; this was sometimes

observed by the submitters when the reaction was heated immediately to 200 °C. Using the described protocol, the checkers observed a temperature peak at approximately 185 °C during the initial heating stage. During the second stage, the temperature was observed to peak at approximately 210 °C and the pressure at 11 bar; the temperature then stabilized at 200 °C, and the pressure at approximately 9.5 bar. Different microwave reactors may have different safety parameters and vial headspaces: *caution is strongly recommended if different microwave instrumentation is employed*.

27. Confirmation of consumption of starting material can be made by TLC with UV visualization (10% methanol/0.5% acetic acid/89.5% dichloromethane, starting material R_f = 0.49 (checkers) (R_f = 0.79 reported by submitters); product R_f = 0.35).

28. The contents of the microwave vial will congeal upon cooling, but the use of 20 mL of dichloromethane will sufficiently dissolve and transfer the mixture. It might be necessary to stir the contents of the vial with the added dichloromethane for several minutes to get this congealed mixture to dissolve for transfer. The use of an abnormally large flask (500 mL for less than 30 mL of solution) is necessary because this viscous mixture foams upon concentration by rotavap. The extra headspace is needed to prevent the crude product from foaming out of the flask and into the rotavap bump trap.

29. The submitters note that the material at this stage can be dried by subjecting the material to a drying pistol heated by refluxing toluene for 24–48 h and have found this dried material without further purification to give the same performance (stereoselection) as a catalyst as material further purified (column chromatography or recrystallization).

30. The crude material might fully dissolve and crystallize in a matter of seconds upon addition of the solvent mixture at room temperature. These crystals may not fully redissolve upon heating and swirling, but the recrystallization will still work when the solution is cooled.

31. Vacuum was applied with a needle through a septum secured to the top of the flask. The goal of this manipulation is merely to obtain a free-flowing solid.

32. The submitters note that the mother liquor and crystal washings can be concentrated and subjected to the same recrystallization procedure to obtain an additional 800 mg of product. The submitters note that during the determination of the melting point, the material gradually turns from white to slightly brown between 200 °C and the melting point. Despite this appearance change, the melting point observed by the submitters is

consistent at 243–245 °C. The submitters have noticed some variation in the melting point range (241–246 °C), but individual samples exhibit a routinely narrow (≤ 2 °C) melting point. PBAM (**3**) exhibited the following: $[\alpha]_D^{25}$ +398 (*c* 1.02, $CHCl_3$); R_f = 0.35 (10% MeOH/CH_2Cl_2 with 0.5% acetic acid); IR (film) 3241, 3047, 2933, 2848, 1592, 1525 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.36–1.55 (m, 4 H), 1.75–1.89 (m, 10 H), 2.26–2.34 (m, 2 H), 3.05–3.16 (m, 4 H), 3.24–3.35 (m, 4 H), 4.10 (br m, 2 H), 5.28 (s, 2 H), 5.68 (br s, 2 H), 7.01 (dd, *J* = 8.3, 6.8, 1.3 Hz, 2 H), 7.40 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 2 H), 7.65 (d, *J* = 7.9 Hz, 2 H), 7.87 (dd, *J* = 8.4, 1.3 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.3, 25.7, 33.5, 51.7, 56.4, 93.0, 118.8, 119.3, 124.8, 126.5, 128.5, 150.0, 153.3, 158.5; HRMS (APCI-ESI) calc'd for $C_{32}H_{39}N_6$ $[M+H]^+$ 507.3236; found 507.3245; Anal. calcd for $C_{32}H_{38}N_6$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.93; H, 7.44; N, 16.65. The submitters note that PBAM purified by column chromatography has been stable upon storage in a screw cap vial on the benchtop for several years without sign of decomposition.

33. The checkers observed a ~3% acetone impurity in the ^1H NMR, along with a depressed melting point (135–163 °C); the submitters used a vacuum pump which reached 0.1 mmHg during the drying pistol stage. The checkers employed this material in an enantioselective aza-Henry reaction of the Boc-protected imine of *o*-tolualdehyde with nitroethane, as previously reported by the submitters, and obtained the same level of enantioselectivity as reported.[8]

Safety and Waste Disposal Information

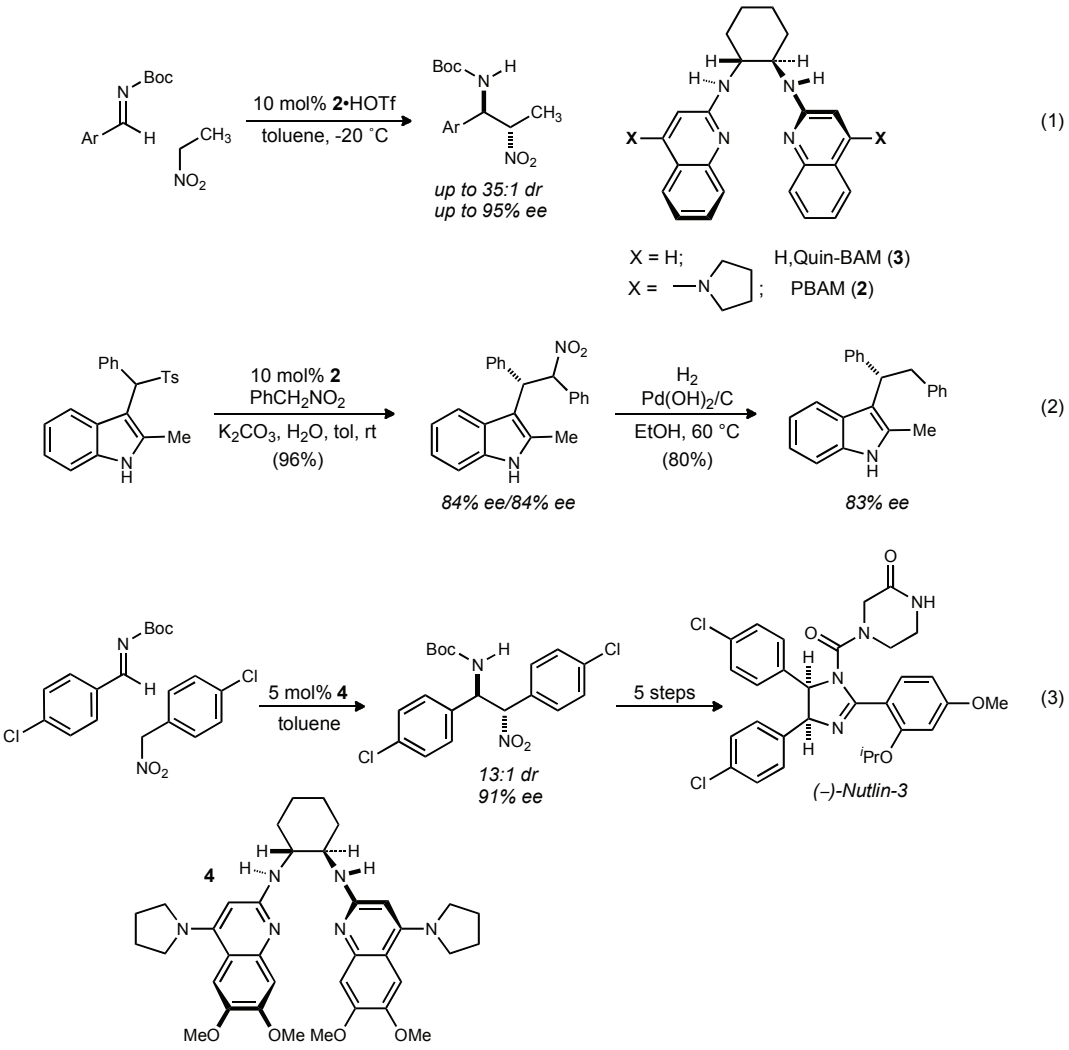
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

BisAMidine ('BAM') ligands were first described in 2004 and discovered to be effective catalysts – as their protic acid complexes (e.g. **3**·HOTf, eq 1) – for the diastereo- and enantioselective aza-Henry reaction (eq 1). The nitroalkane adducts are readily reduced, delivering *vic*-diamines in a two step sequence and differentially protected at the amine nitrogens. This class of catalysts, often referred to as chiral proton catalysts to

emphasize the importance of the polar ionic hydrogen bond responsible for activation and orientation of the substrate, has since emerged as an increasingly general solution to reagent control of aza-Henry reactions. The title compound (H,^{4}PyrrolidineQuin-BAM, 'PBAM')[8] was recently reported as a substantially more reactive and equally selective catalyst for the aza-Henry addition of nitroalkanes to aryl aldimines (eq 1).[9] This reagent, again as its triflic acid salt, expands the scope of the nitroalkane component, facilitating the stereocontrolled addition of a broad range of primary nitroalkanes and secondary nitroalkanes (e.g. nitropropane). This catalyst was discovered to be effective as a chiral Brønsted base in the alkylation of nitroalkanes using indolenine electrophiles (eq 2).[10] More recently, the addition of aryl nitromethane pronucleophiles were investigated, as these are notoriously difficult donors in the aza-Henry reaction.[11,12] In an interesting twist, the protonation state of the BAM ligand no longer affected the stereoselection in many cases.[13] Regardless, further modification of the fundamental PBAM backbone by installation of methoxy substituents (**4**) furnished the addition products with high diastereo- and enantioselection (eq 3). This development enabled the first enantioselective synthesis of (–)-Nutlin-3[13] (eq 3), the first potent small molecule inhibitor of p53/MDM2 discovered by Hoffmann-La Roche.[14]

The synthesis of PBAM described here is a significant improvement upon our previously reported procedure.[8] The initial procedure relied upon similar reaction conditions but flash column chromatography was used to purify after each step. The chromatographic purification for the final compound was particularly troublesome as large volumes of solvent (dichloromethane, methanol, and acetic acid) were required for the compound to fully elute from the column. The products of these two reactions are now purified by straightforward washings, filtrations, and a recrystallization after the last step. The scale of this procedure is nearly an order of magnitude greater than previously reported.



Appendix
Chemical Abstracts Nomenclature; (Registry Number)

2,4-Dichloroquinoline; (703-61-7)
Malonic acid; (141-82-2)
Phosphorus oxychloride; (10025-87-3)
Aniline; (62-53-3)
Bis(dibenzylideneacetone)palladium; (32005-36-0)
2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene; (98327-87-8)
Sodium-*tert*-butoxide; (865-48-5)
(1*R*,2*R*)-(−)-1,2-Diaminocyclohexane; (20439-47-8)
Pyrrolidine; (123-75-1)
Trifluoromethyl benzene; (98-08-8)

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Jeffrey N. Johnston completed his B.S. Chemistry degree at Xavier University in 1992, and a Ph.D. in organic chemistry at The Ohio State University in 1997 with Prof. Leo A. Paquette. He then worked as an NIH postdoctoral fellow with Prof. David A. Evans at Harvard University. He began his independent career at Indiana University, where he was promoted to Professor of Chemistry in 2005. In 2006, his research program moved to Vanderbilt University. His group has developed a range of new reactions and reagents that are used to streamline the total synthesis of complex alkaloid natural products. The development of new Brønsted acid-catalyzed reactions, as well as chiral proton catalysts, are ongoing investigational themes.

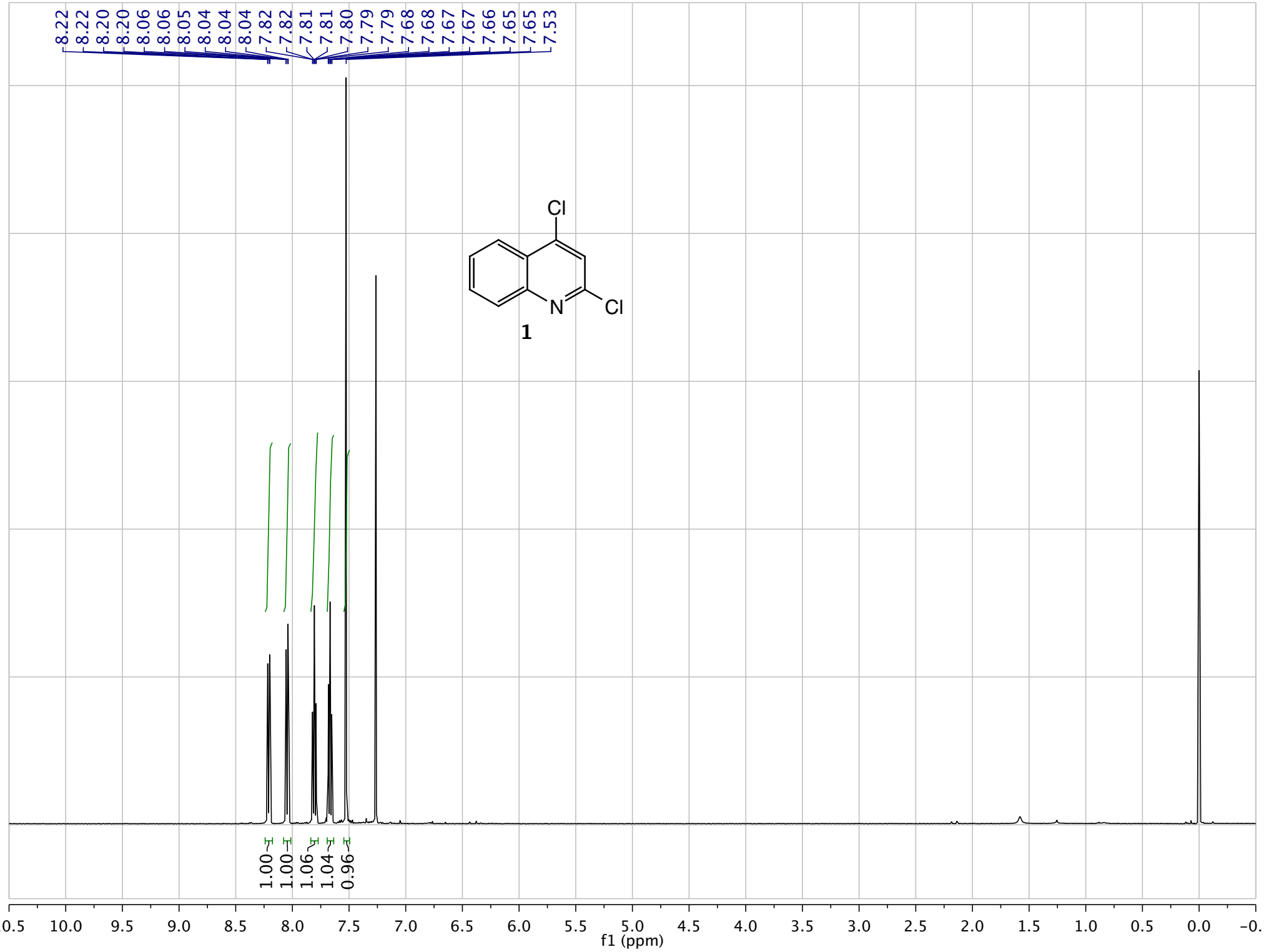
Tyler A. Davis was born in 1983 in Nashville, TN. In the summer of 2004, he conducted research in the lab of Prof. S. Bruce King at Wake Forest University. He graduated *magna cum laude* from Lipscomb University with his B.S. degree in biochemistry in 2005. He completed his Ph. D. in the laboratory of Professor Jeffrey Johnston at Vanderbilt in 2011. His studies focused on the synthesis and application of chiral BisAMidine (BAM) organocatalysts with increased Brønsted basicity. Tyler is currently a postdoctoral scholar in the laboratory of Prof. Tomislav Rovis at Colorado State University.

Mark C. Dobish, a native of New Wilmington, PA, received his B.S. degree in chemistry from Allegheny College in 2007, where he investigated boron-mediated transfers under the tutelage of Prof. P. J. Persichini. He then began graduate studies with Prof. Johnston at Vanderbilt University as a Vanderbilt Institute of Chemical Biology Fellow. Mark's graduate research focuses on enantioselective transformations using the BisAMidine (BAM) library of catalysts as it applies to new reactions and small molecule drug targets.

Kenneth E. Schwieter was born and raised in Cincinnati, OH. He received his B.S. degree in chemistry from Xavier University in 2011 under the direction of Prof. Rick Mullins. He was a 2010 NSF-REU student in the Johnston lab, and matriculated at Vanderbilt in 2011 to continue his work.

Aspen Chun is a native of California (Los Angeles) and received her B.S. Chemistry degree from Vanderbilt in 2011. She was an undergraduate researcher in the Johnston laboratory, and is currently a staff scientist in the Vanderbilt Program in Drug Discovery.

Alex Goldberg was born in Longbranch, New Jersey in 1986 and was raised in Toronto, Canada. He received his B.ScH. degree from Queen's University in Kingston in 2008 under the supervision of Prof. Cathleen M. Crudden. During this time, he also worked in the research groups of Prof. Mark Lautens at the University of Toronto, and Prof. Ilan Marek at the Technion – Israel Institute of Technology. He began his doctoral studies at the California Institute of Technology in the fall of 2008 under the direction of Prof. Brian M. Stoltz as an NSERC Postgraduate scholar. His graduate research has focused on the total synthesis of Scandine and the Melodinus Alkaloids.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7.67
7.67
7.66
7.65
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7.53
Cl
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Cl
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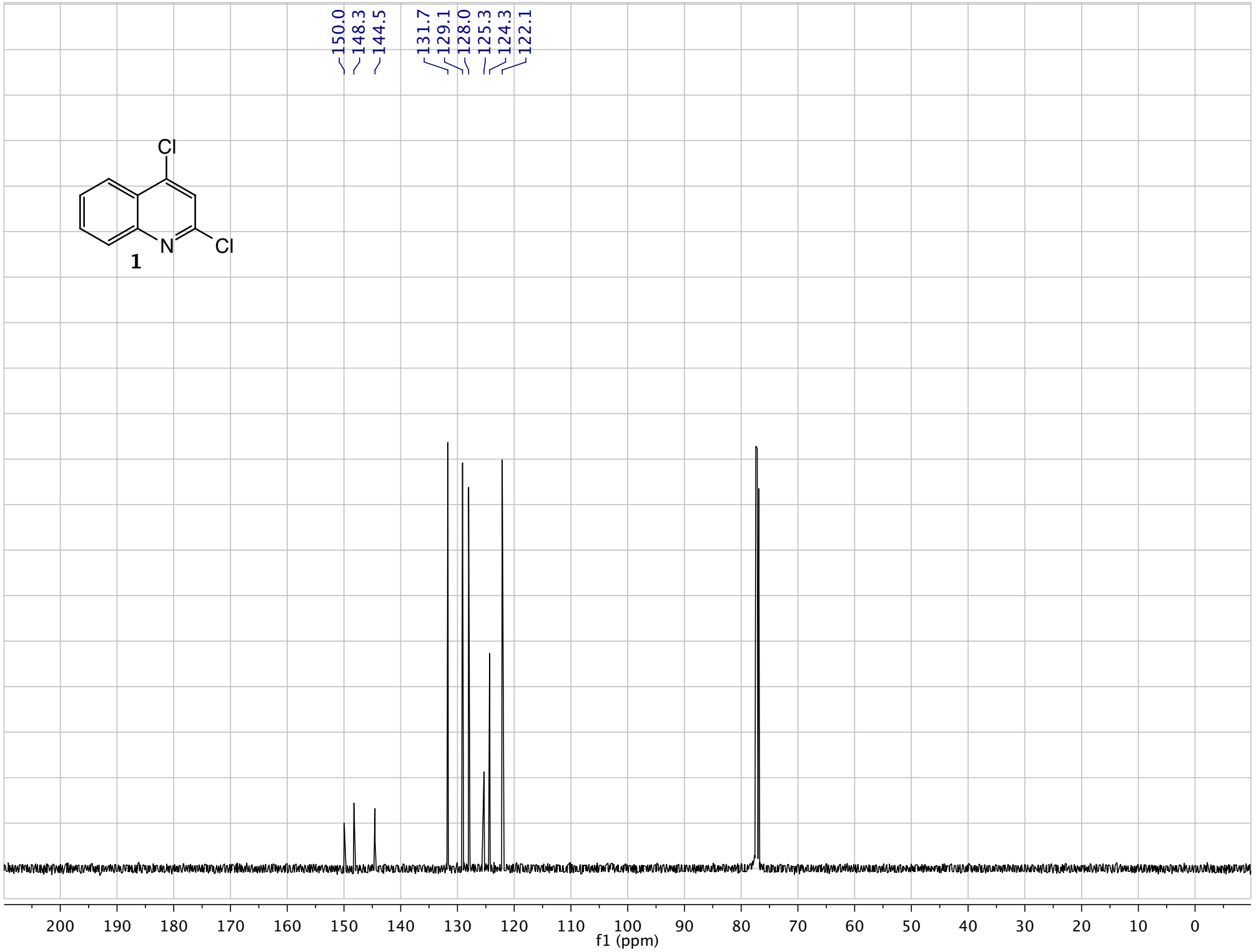
0.96
f1 (ppm)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Cl
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180
170
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150
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110
100
90
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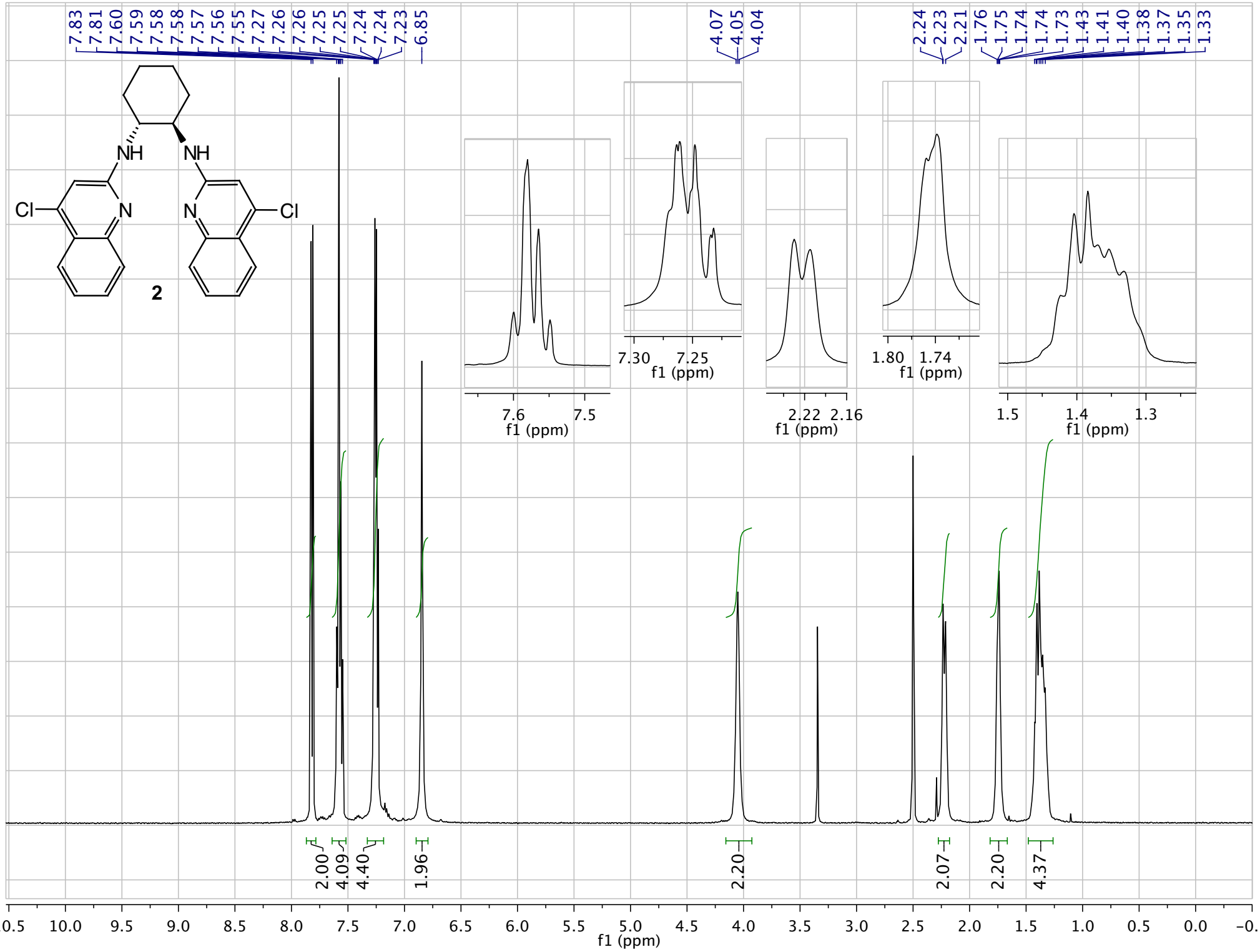
70
60
50
40
30
20
10
0
f1 (ppm)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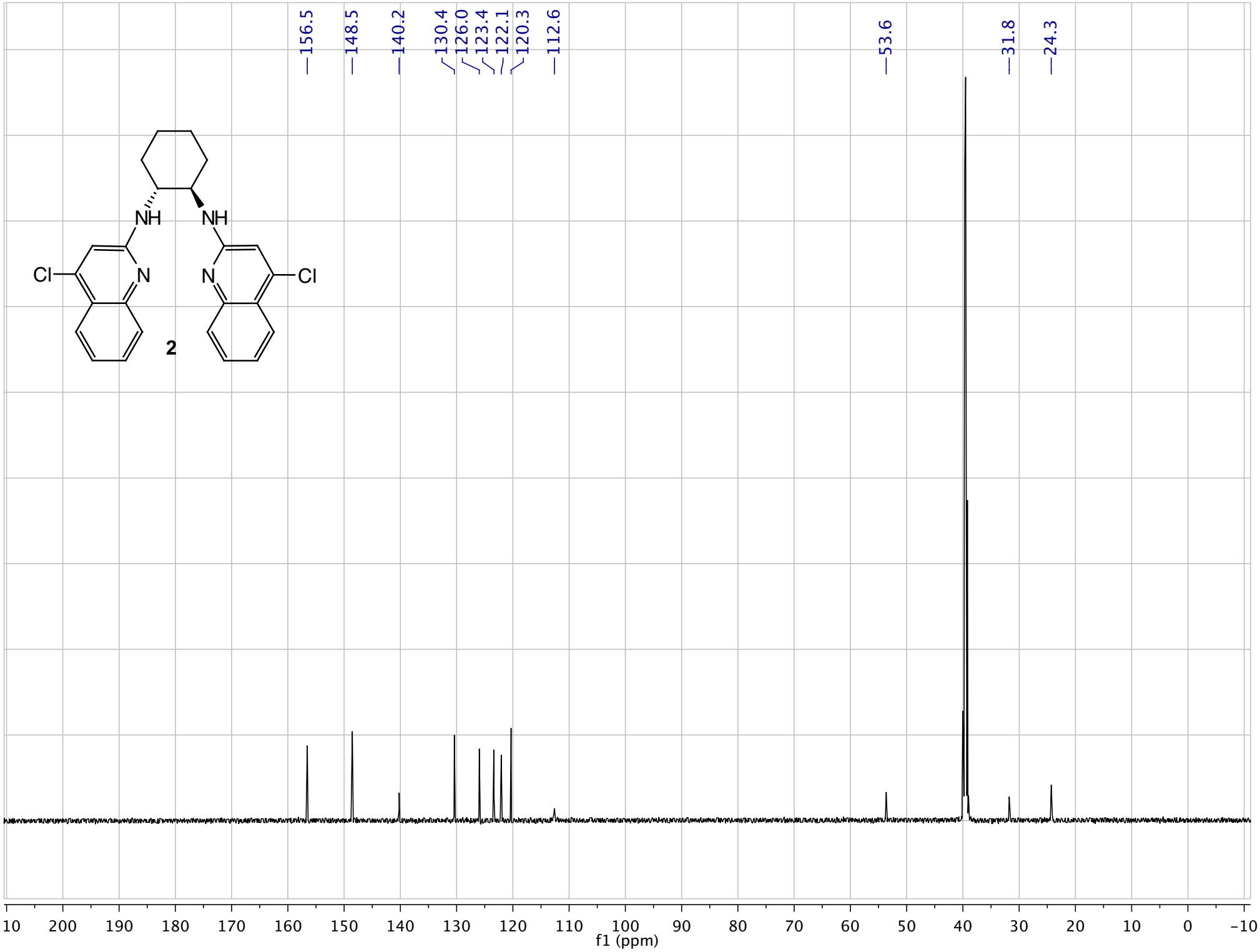
4.07 4.05 4.04
2.24 2.23 2.21 1.76 1.75 1.74 1.74 1.73 1.43 1.41 1.40 1.38 1.37 1.35 1.33
NH NH
Cl N N Cl
2
7.6 7.5 f1 (ppm)
7.30 7.25 f1 (ppm)
2.22 2.16 f1 (ppm)
1.80 1.74 f1 (ppm)
1.5 1.4 1.3 f1 (ppm)
2.00 4.09 4.40 1.96 2.20 2.07 2.20 4.37
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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NH
Cl
N
N
Cl
2
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200
190
180
170
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30
20
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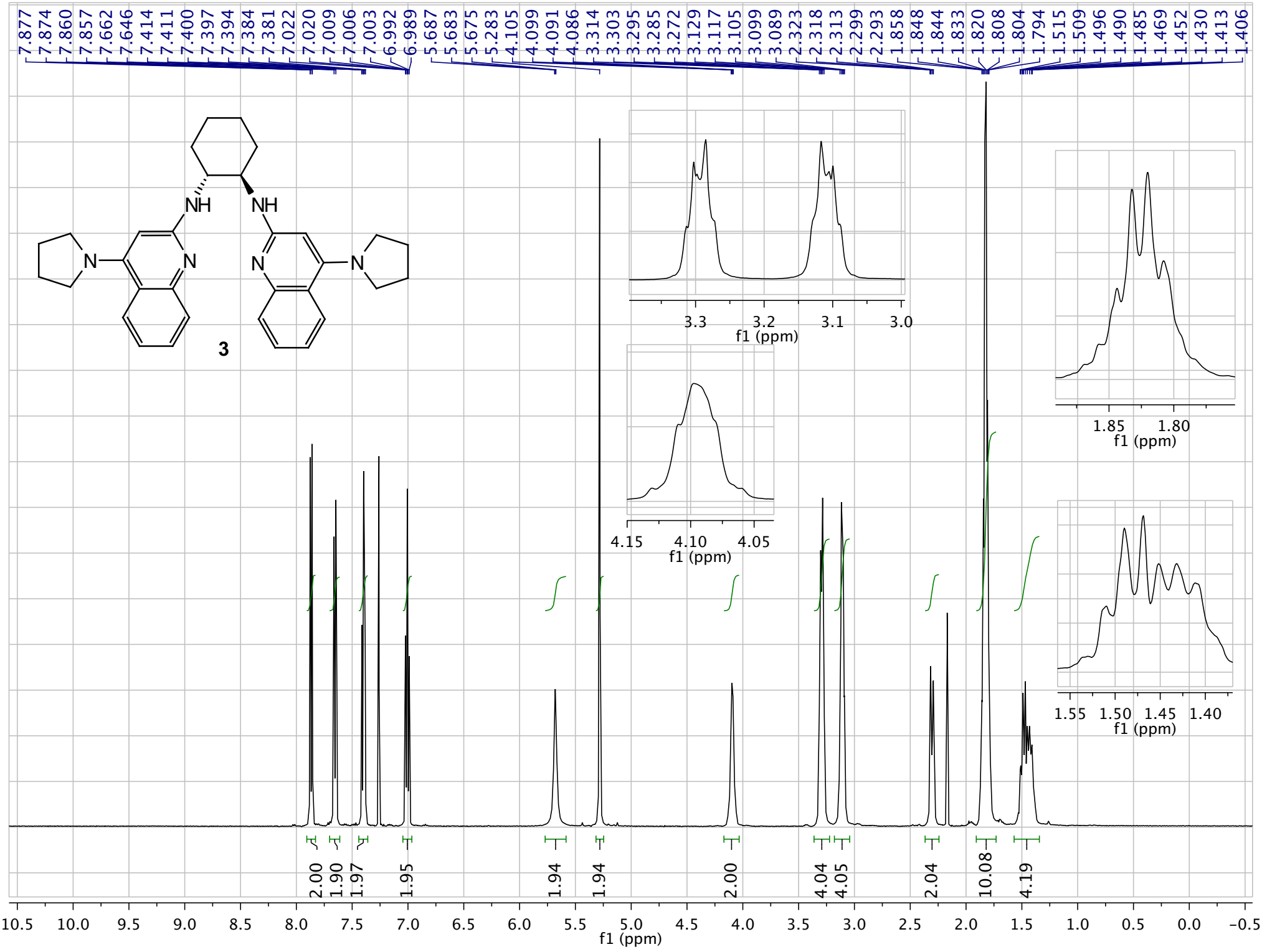
0
−10
f1 (ppm)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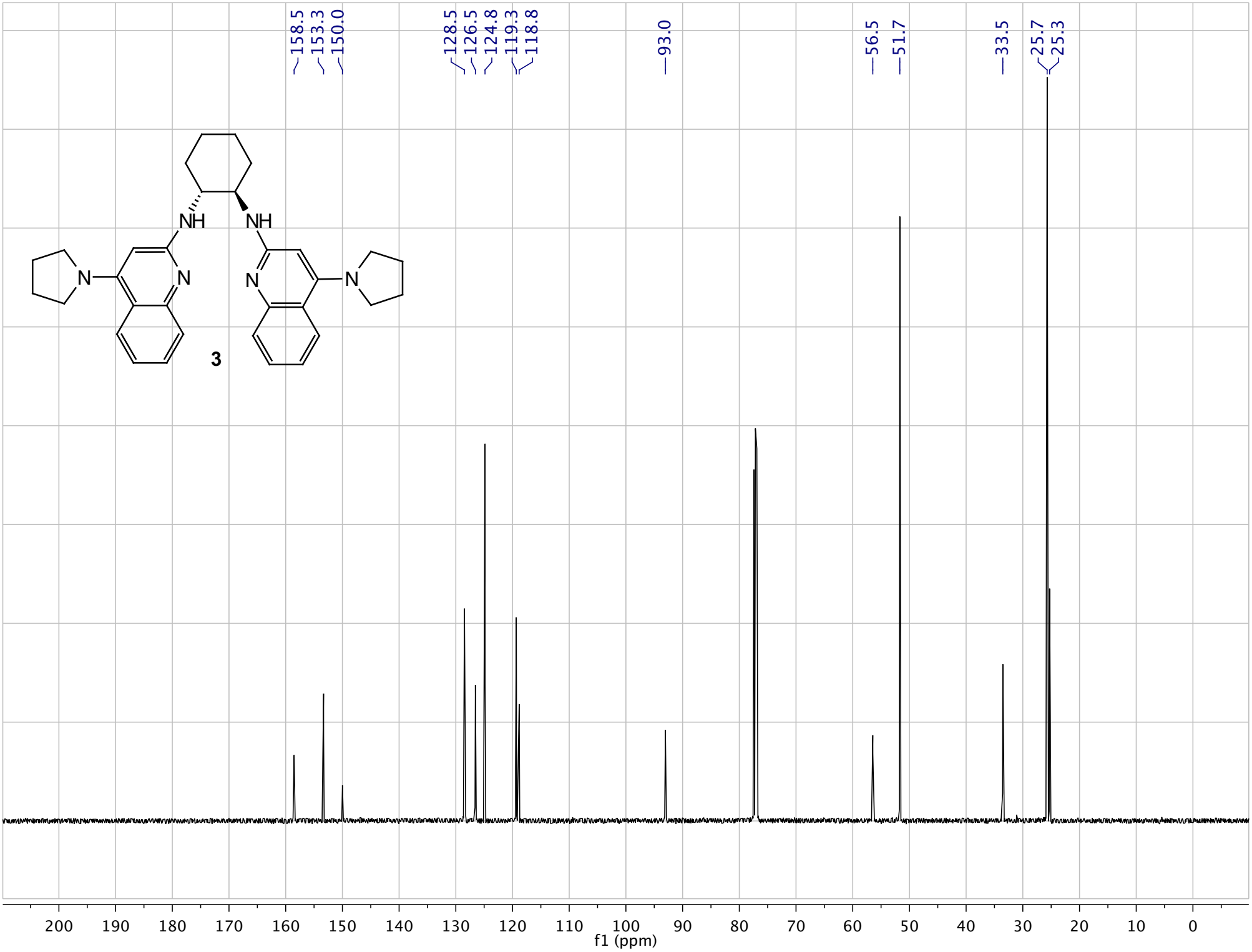
NH
NH
N
N
N
N
3
3.3 3.2 3.1 3.0
f1 (ppm)
4.15 4.10 4.05
f1 (ppm)
1.85 1.80
f1 (ppm)
1.55 1.50 1.45 1.40
f1 (ppm)
2.00 1.90 1.97 1.95 1.94 1.94 2.00 4.04 4.05 2.04 10.08 4.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)