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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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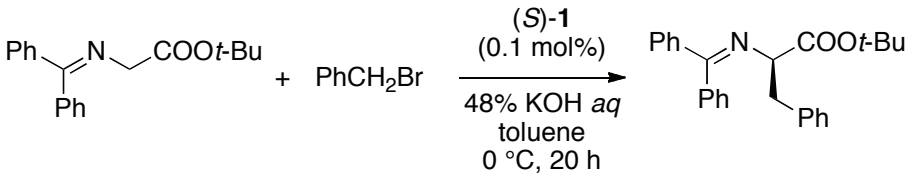
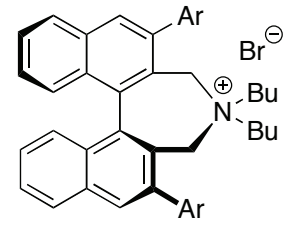
Enantioselective Alkylation of *N*-(Diphenylmethylene)glycinate *tert*-Butyl Ester: Synthesis of (*R*)-2-(Benzhydrylidenamino)-3-Phenylpropanoic Acid *tert*-Butyl Ester





(*S*)-**1** (Ar = 3,4,5-F_3-C_6H_2)

Submitted by Seiji Shirakawa, Kenichiro Yamamoto, Kun Liu, and Keiji Maruoka.[1]
Checked by Spencer Eggen and Scott E. Denmark.

1. Procedure

(R)-2-(Benzhydrylidenamino)-3-phenylpropanoic acid tert-butyl ester. An oven-dried, 300-mL, four-necked, round-bottomed flask, equipped with an overhead mechanical stirrer, a 125-mL pressure-equalizing dropping funnel capped with an argon inlet, and two rubber septa (Note 1) is charged with *N*-(diphenylmethylene)glycine *tert*-butyl ester (5.00 g, 16.9 mmol, 1.0 equiv) (Note 2), (*S*)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepinium bromide [(*S*)-**1**] (12.7 mg, 17.0 μmol, 0.001 equiv) (Note 3), benzyl bromide (2.41 mL, 3.47 g, 20.3 mmol, 1.20 equiv) (Note 4), and toluene (56.4 mL) (Note 5). The stirring mixture is cooled to ~0 °C in a 2-propanol bath (Note 6), and aqueous 48% potassium hydroxide solution (56.4 mL) (Note 7) is added dropwise over 33 min through the dropping funnel (Note 8). The mixture is stirred for 20 h at ~0 °C at a constant stirring speed (300 rpm) under an argon atmosphere (Note 9). The reaction mixture is diluted by the addition of water (113 mL) and the 2-propanol bath is removed. After being stirred for 15 min at ambient temperature, the reaction mixture is transferred to a 1-L separatory

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funnel, and toluene (100 mL) is added. The aqueous layer is separated and extracted twice with toluene (100 mL). The combined organic layers are washed with brine (100 mL) and dried over anhydrous magnesium sulfate (15 g). The resulting suspension is filtered and concentrated on a rotary evaporator (Note 10). The residue is loaded onto a column (diameter: 6 cm) wet-packed with silica gel (150 g) and hexanes/*tert*-butyl methyl ether (*t*-BuOMe), 15:1 containing 1% of triethylamine (Note 11). The crude product is purified by gradient elution with hexanes/*t*-BuOMe (15:1 to 10:1) to afford product (7.87 g) (Note 12). After extensive drying, the product (6.40 g, 98% yield) is obtained as a colorless, viscous oil (Notes 13, 14, 15, 16, and 17).

2. Notes

1. The oven temperature is ~205 °C. The round-bottomed flask has three 24-40 necks and one 9-30 neck. The addition funnel, mechanical stirrer adapter, and septum are fitted on the 24-40 necks, while the 9-30 neck is fitted with a small rubber septum. The Teflon paddle of the mechanical stirrer is 4.65 cm in length and 1.9 cm in height. The internal temperature was monitored with an Omega Type K microprocessor digital thermometer with 0.2 cm-width probe.

2. *N*-(Diphenylmethylene)glycine *tert*-butyl ester (99%) was purchased from Alfa Aesar and used as received. The submitters used *N*-(diphenylmethylene)glycine *tert*-butyl ester (>98%) purchased from Tokyo Chemical Industry Co., Ltd. (TCI) and used as received.

3. (*S*)-4,4-Dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho-[2,1-c:1',2'-e]azepinium bromide [(*S*)-**1**] (99%) was purchased from Strem Chemicals, Inc. and used as received. The submitters used [(*S*)-**1**] (> 90%) from Kanto Chemical Co., Inc. as received. The checkers found that an increase in catalyst loading from 0.05 (recommended by the submitters) to 0.10% was essential to obtain enantiomeric ratios greater than 96:4 er.

4. Benzyl bromide (98%) was purchased from Sigma-Aldrich Co. and was freshly distilled over $MgSO_4$ (10 mmHg, 73–75 °C) under a nitrogen atmosphere. The submitters used benzyl bromide (98%) purchased from Sigma-Aldrich Co. as received.

5. Toluene (Certified ACS grade) was purchased from Thermo Fisher Scientific, Inc. and used as received.

6. The 2-propanol bath temperature (0 ± 2 °C) was maintained by a Thermo Scientific Neslab CC-100 Immersion Cooler with Cryotrol dial controller. As the solution cools, some of the starting material precipitates, forming a whitish, cloudy suspension.

7. The submitters used 48% potassium hydroxide solution from Kanto Chemical Co., Inc. without purification. The checkers prepared a 48% potassium hydroxide solution from solid pellets (Sigma-Aldrich Co., puriss. p.a., ≥86% (T) pellets) in water purified by a Millipore Milli-Q Integral Water Purification System.

8. The solution is stirred at 300 rpm until the internal temperature equilibrated to 1 °C. At this time, the addition of the base solution is begun. During the addition of the potassium hydroxide solution, the internal temperature is kept under 3 °C. Upon completion of the addition of base, the addition funnel is replaced by an argon inlet and the large septum is replaced with a glass stopper.

9. TLC analysis of the reaction mixture indicates the consumption of the starting materials after 10 h. The TLC analysis was performed on EMD Millipore Merck silica gel 60 F_{254} plates [*N*-(diphenylmethylene)glycine *tert*-butyl ester (starting material): R_f = 0.31, product: R_f = 0.41, 15:1 hexanes/*t*-BuOMe, visualized with 254 nm UV lamp].

10. The suspension is filtered through a Pyrex 150 mL course fritted glass funnel (packed with 7.0 g of Celite) into a 1-L suction filtration flask. The filtrate is then transferred with toluene to a 1-L teardrop-shape flask. Toluene is removed by rotary evaporation (16.5–38 °C, 18–20 mmHg) to yield 8.20 g (>100%) of crude product.

11. Neutralization of the silica gel with hexanes/*t*-BuOMe, 15:1 containing 1% triethylamine is necessary to minimize hydrolysis of the product on the column. The neutralized silica was rinsed with 20 column volumes of 15:1 hexanes/*t*-BuOMe (~5 L total) to achieve an eluate pH near 7. The checkers used silica gel purchased from Sigma-Aldrich Co. (Merck, grade 9385, 230-400 mesh, 60 Å). The submitters used silica gel purchased from Daiso Co., Ltd. (Daisogel IR-60–40/63). The hexanes used were Optima grade (Sigma-Aldrich Co.). The *t*-BuOMe used was Reagent Grade (98%) from Sigma-Aldrich Co. The triethylamine was 99% grade from Alfa-Aesar and freshly distilled over calcium hydride under a nitrogen atmosphere.

12. The column was eluted with hexanes/ *t*-BuOMe with a ratio of 15:1 (500 mL) followed by 10:1 (1000 mL) (172 fractions, 8 mL fraction size).

TLC indicates the presence of the desired alkylation product and benzophenone (R_f= 0.29, hexanes/*t*-BuOMe, 15:1, visualized with a 254 nm UV lamp). Fractions 47-164 were combined and concentrated (11.5–20 °C, 18–20 mmHg). ^{1}H NMR analysis indicates the presence of ~136 mole % of hexanes.

13. The checkers obtained a 92% yield on a ½- scale run (e.r. 98:2).

14. Hexanes were reduced to ~2.7 mole % by using a Büchi GKR-51 Kugelrohr distillation apparatus with continuous turning under vacuum (0.04–0.05 mmHg) at ambient temperature. The amount of hexanes present was determined by ^{1}H NMR spectroscopic analysis of aliquots at 0, 36, 96, and 186 hours. NMR analysis also indicates the presence of ~2.7 mole % benzophenone.

15. *(R)*-2-(Benzhydrylidenamino)-3-phenylpropanoic acid *t*-butyl ester has the following physical and spectroscopic data: e.r. = 98.5:1.5; $[\alpha]^{24}_D$ = 190.9 (*c* = 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44 (s, 9 H), 3.16 (dd, *J* = 9.4, 13.4 Hz, 1 H), 3.23 (dd, *J* = 4.2, 13.4 Hz, 1 H), 4.11 (dd, *J* = 4.2, 9.3 Hz, 1 H), 6.60 (br d, *J* = 5.4 Hz, 2 H), 7.03–7.08 (m, 2 H), 7.13–7.21 (m, 3 H), 7.24–7.39 (m, 6 H), 7.55–7.59 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 28.03, 39.58, 67.92, 81.09, 126.13, 127.64, 127.90, 128.01, 128.05, 128.16, 128.69, 128.85, 130.04, 136.35, 138.35, 139.55, 170.24, 170.80; IR 3060 (m), 3027 (m), 2977 (m), 2929 (m), 1731 (s), 1623 (m), 1446 (m), 1367 (s), 1285 (s), 1148 (s), 697 (s) cm^{-1}. MS (EI) *m/z* (relative intensity): 294.2 (12.7), 285.1 (11.0), 284.1 (47.7), 244.1 (32.8), 243.1 (17.9), 242.1 (100.0), 238.1 (29.9), 227.0 (16.2), 207.1 (14.6), 206.1 (11.8), 193.1 (27.1), 192.1 (70.7), 165.1 (21.6), 117.1 (10.5), 115.1 (25.3), 91.1 (14.0), 77.1 (11.1). HRMS (ESI-TOF) calcd for $C_{26}H_{28}NO_2^+$: 386.2120 ([M + H]$^+$). Found: 386.2112. The enantioselectivity was determined by chiral stationary phase HPLC analysis [Daicel Chiralcel OD-H column, 1% 2-propanol/hexane, 0.50 mL/min, 18 bar, λ = 251 nm, retention times: (*R*)-enantiomer (major): 14.19 min, (*S*)-enantiomer (minor): 25.91 min]. Chiral HPLC analysis was calibrated using a 77:23 ratio of the two enantiomers.

16. Some hydrolysis of the product to the free amine and benzophenone is observed during large-scale chromatographic separation. On the basis of ^{1}H NMR integration, there is 2.3 mole % benzophenone relative to product. A pure sample was prepared as follows. A small portion of the product (150 mg) contaminated with benzophenone from the first chromatographic separation can be further purified by a second chromatographic separation at reduced temperature. The product is loaded onto a jacketed column

(diameter: 2 cm) wet-packed with silica gel (29 g) and hexanes/*t*-BuOMe, 49:1. The product is purified by gradient elution (hexanes/*t*-BuOMe, 49:1 to 9:1) to yield 0.145 g of product (Note 16), which required extensive drying to remove solvent (Note 17).

17. A portion of silica gel (150 g) was neutralized by stirring with 5 mL of triethylamine, 10 mL of *t*-BuOMe, and 485 mL of hexanes in a 1-L round-bottom flask. The suspension was filtered through a 150-mL coarse fritted funnel and the silica gel was dried by rotary evaporation (17–22 °C, 18–20 mm Hg). The neutralized silica gel was rinsed with 750 mL *t*-BuOMe then with 1.0 L of hexanes/*t*-BuOMe, 49:1 prior to loading. Poly(vinyl) tubing is attached to the jacketed column is run through a water/ice slush. Gradient elution proceeds with 100 mL of each solution (49:1 through 9:1) in increments of 49:1, 24:1, etc. (146 fractions, 2.5 mL fraction size). The solutions were pre-chilled in a water/ice slush. Fractions 79-130 were combined and concentrated (15.5–22 °C, 18–20 mmHg). TLC conditions were the same as those in Note 12, except that the TLC plates were first neutralized with 4% triethylamine in dichloromethane.

18. The product was transferred to a one-piece medium Kugelrohr distillation bulb and attached to a diffusion pump apparatus. The apparatus consists of a Büchi GKR-50 heating chamber connected to an Edwards SI100 Diffusion Pump with 90 V AC pump heater electrical supply. The product was heated between 50–70 °C at a pressure range of $2.9–3.0\times10^{-5}$ mm Hg. The viscosity of the product oil dramatically decreases as temperature is increased, but the oil does not distill under these conditions.

Handling and Disposal of Hazardous Chemicals

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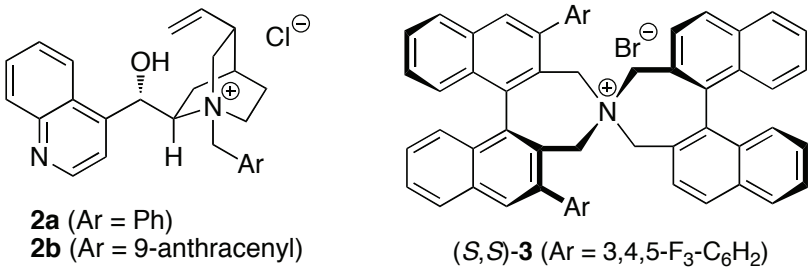
disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

3. Discussion

α-Amino acids are a biologically significant class of compounds, since they are the basic building blocks for peptides and proteins, and they are the biopolymers responsible for both the structure and function of most living things. Accordingly, the development of truly efficient methods for the preparation of α-alkyl-α-amino acid, especially in an enantiomerically pure form, has become of great importance. Asymmetric synthesis of α-amino acids by phase-transfer alkylation using a chiral catalyst and a prochiral protected glycine derivative would provide a particularly attractive method for the preparation of optically active α-alkyl-α-amino acids.[2] First catalytic asymmetric alkylation of a glycine derivative under phase-transfer conditions was achieved by using a cinchona alkaloid derived chiral phase-transfer catalyst **2a** with moderate enantioselectivity.[3] The *N*-9-anthracenylmethyl group substituted catalyst **2b** was developed to improve the enantioselectivity.[4,5] After these reports, many types of cinchona-derived chiral phase-transfer catalysts were developed for the reaction.[2] Purely synthetic binaphthyl-modified new *N*-spiro-type chiral phase-transfer catalyst (*S*,*S*)-**3** was also developed for the reaction.[6] Compared to other phase-transfer catalysts, such as cinchona-derived catalysts, binaphthyl-modified *N*-spiro-type catalysts of type **3** generally require lower catalyst loading (1 mol%) and provide alkylated products in higher enantiomeric excesses. Based on the design of binaphthyl-modified *N*-spiro-type catalysts of type **3**, very reactive high-performance catalyst (*S*)-**1** was developed.[7] Most notably, the reaction proceeded smoothly under mild phase-transfer conditions in the presence of only 0.05~0.1 mol% of (*S*)-**1** to afford the corresponding alkylation products with excellent enantioselectivities (Table 1).

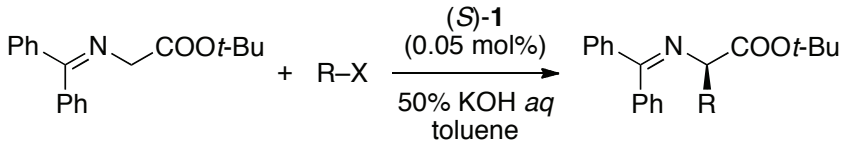


2a (Ar = Ph)
2b (Ar = 9-anthracenyl)

(*S*,*S*)-**3** (Ar = 3,4,5-F_3-C_6H_2)

Figure 2. Chiral Phase-Transfer Catalysts

Table 1. Enantioselective Alkylation of Glycine Derivative



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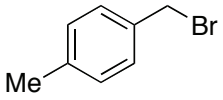
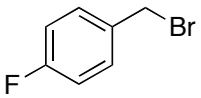
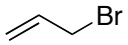
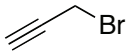
1		0 °C, 4 h	99	98
2		0 °C, 5 h	99	98
3		0 °C, 3 h	87	98
4		0 °C, 4 h	88	98
5[a]		–20 °C, 1 h	67	99

[a] Use of 0.1 mol% of (*S*)-**1** and $CsOH{\cdot}H_2O$

1. Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto, 606-8502, Japan. E-mail: maruoka@kuchem.kyoto-u.ac.jp

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(R)-2-(Benzhydrylidenamino)-3-phenylpropanoic acid tert-butyl ester; (119272-91-2)

N-(Diphenylmethylene)glycine *tert*-butyl ester; (81477-94-3)

(*S*)-4,4-Dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5- dihydro-3*H*-dinaphtho [2,1-c:1',2'-e]azepinim bromide; (851942-89-7)

Benzyl bromide; (100-39-0)

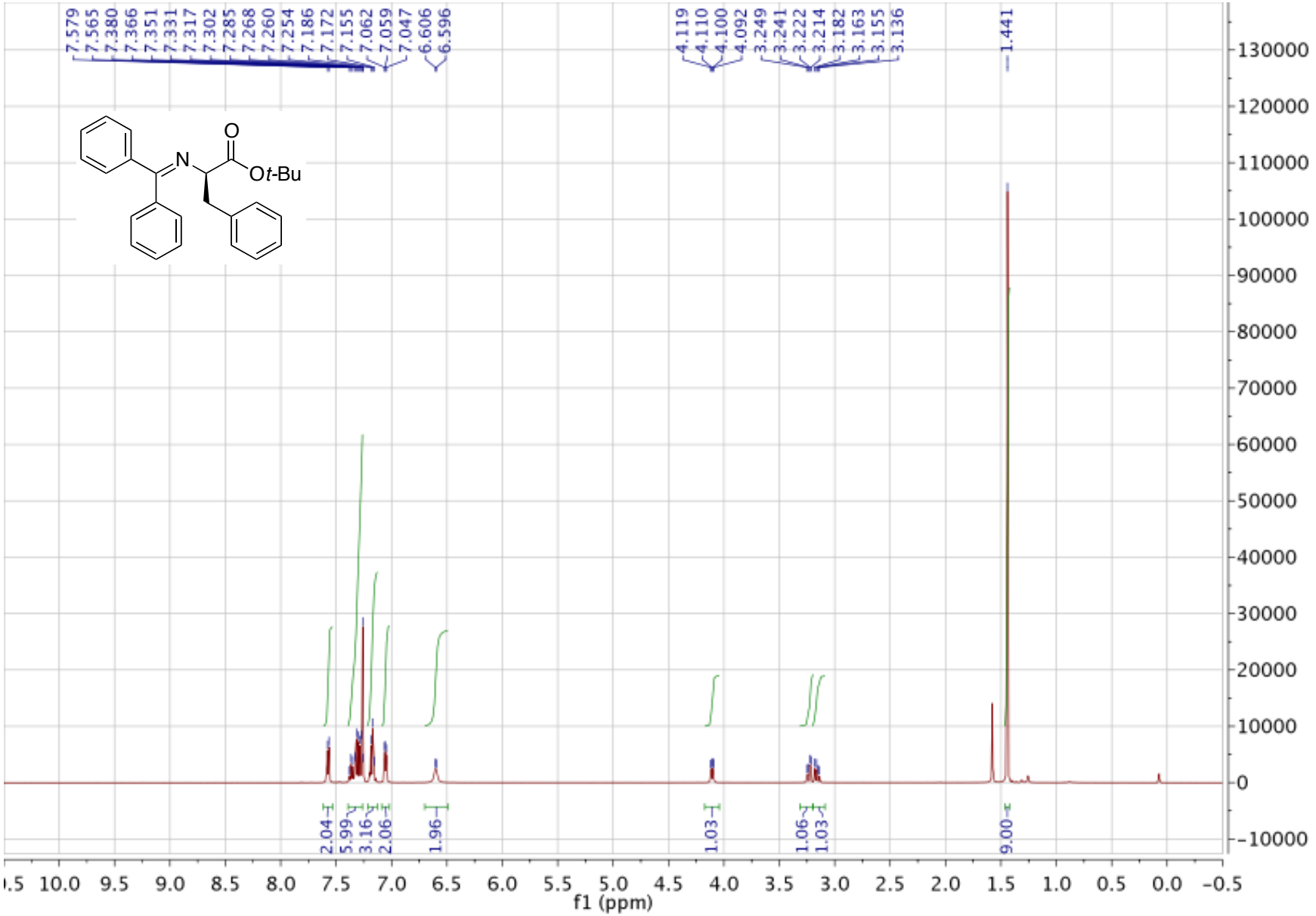
Keiji Maruoka was born in 1953 in Mie, Japan. He graduated from Kyoto University (1976) and received his Ph.D. (1980) from University of Hawaii (Thesis Director: Professor Hisashi Yamamoto). He became an assistant professor of Nagoya University (1980) and was promoted to a lecturer (1985) and an associate professor (1990) there. He moved to Hokkaido University as a full professor (1995−2001), and he currently is a professor of chemistry in Kyoto University since 2000. His research interests are the design of high-performance organocatalysts and bidentate Lewis acid chemistry.

Seiji Shirakawa was born in 1974 in Ehime, Japan. He graduated from Nihon University (1997) and received his Ph.D. (2004) from Kyoto University (Thesis Director: Professor Keiji Maruoka). He worked with Professor James L. Leighton at Columbia University (2004–2005) and Professor Shu Kobayashi at University of Tokyo (2005–2007) as a postdoctoral fellow. He was appointed as an assistant professor at Nihon University in 2007, and he currently is an associate professor in Kyoto University since 2009.

Kenichiro Yamamoto was born in Madison, Wisconsin, USA, in 1978 and raised in Yamaguchi, Japan. He obtained his M.S. degree from Kyoto University in 2004 under the direction of Professor Keiji Maruoka. Since 2004, he has been working as process chemist in the Research & Development Center of NAGASE & CO., LTD. (Kobe, Japan). From 2009, he has been doing postgraduate studies in Kyoto University under the direction of Professor Keiji Maruoka.

Kun Liu was born in 1984 in Shandong Province, China. He graduated from Tianjin University (2006) and received his Master degree from the same university under supervision of Professor Jun-An Ma (2008). Currently he is a doctor-course student at Kyoto University under the supervision of Professor Keiji Maruoka.

Spencer Eggen received his B.S. degree in Chemistry with highest honors in 2011 from Texas Christian University. During his years as an undergraduate, he worked in the laboratories of Dr. Onofrio Annunziata, studying polymer-porphyrin interactions. In 2011, he joined Scott Denmark's research group at the University of Illinois, Urbana-Champaign. His research interests include the development of new Phase Transfer-catalyzed reactions.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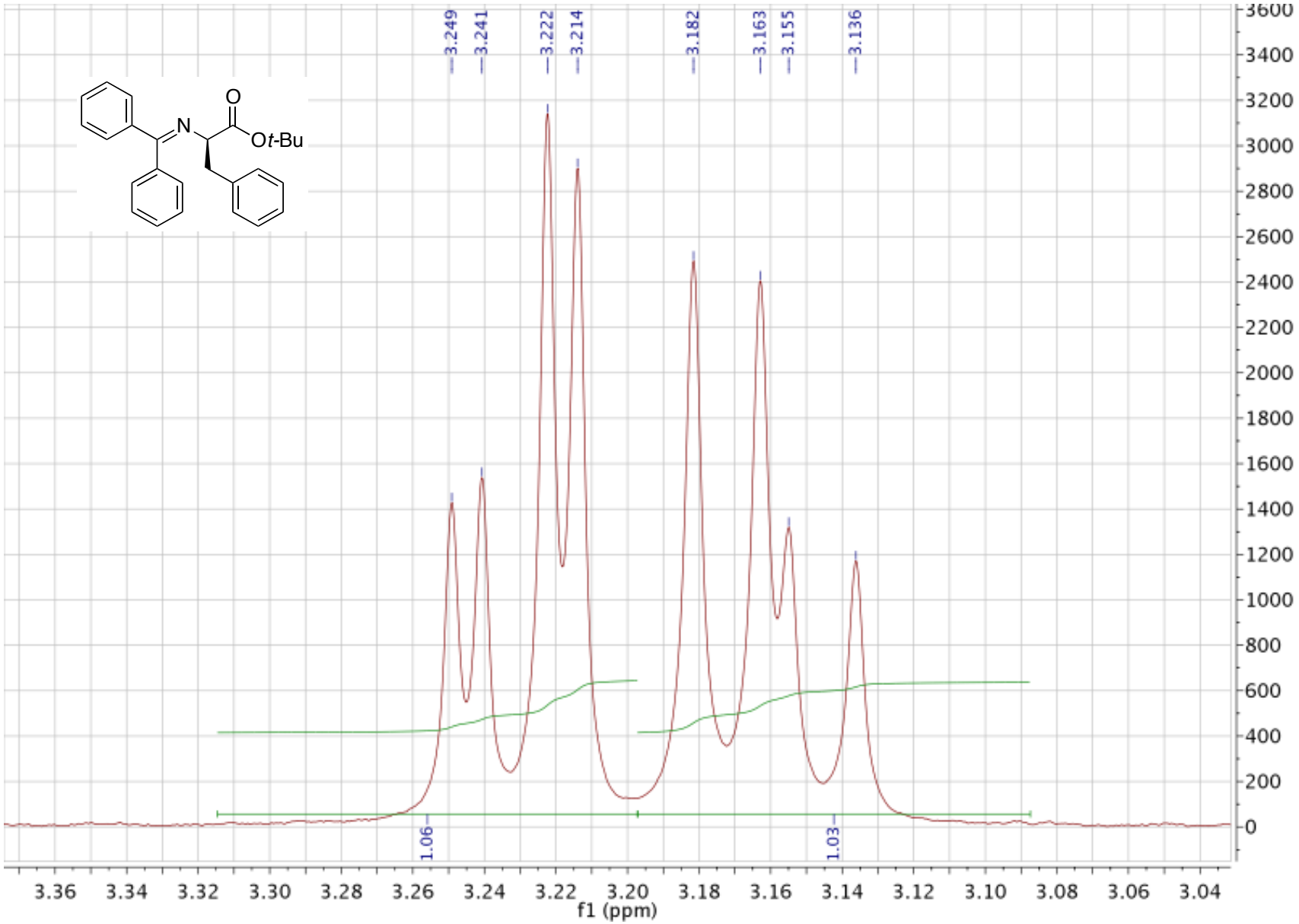
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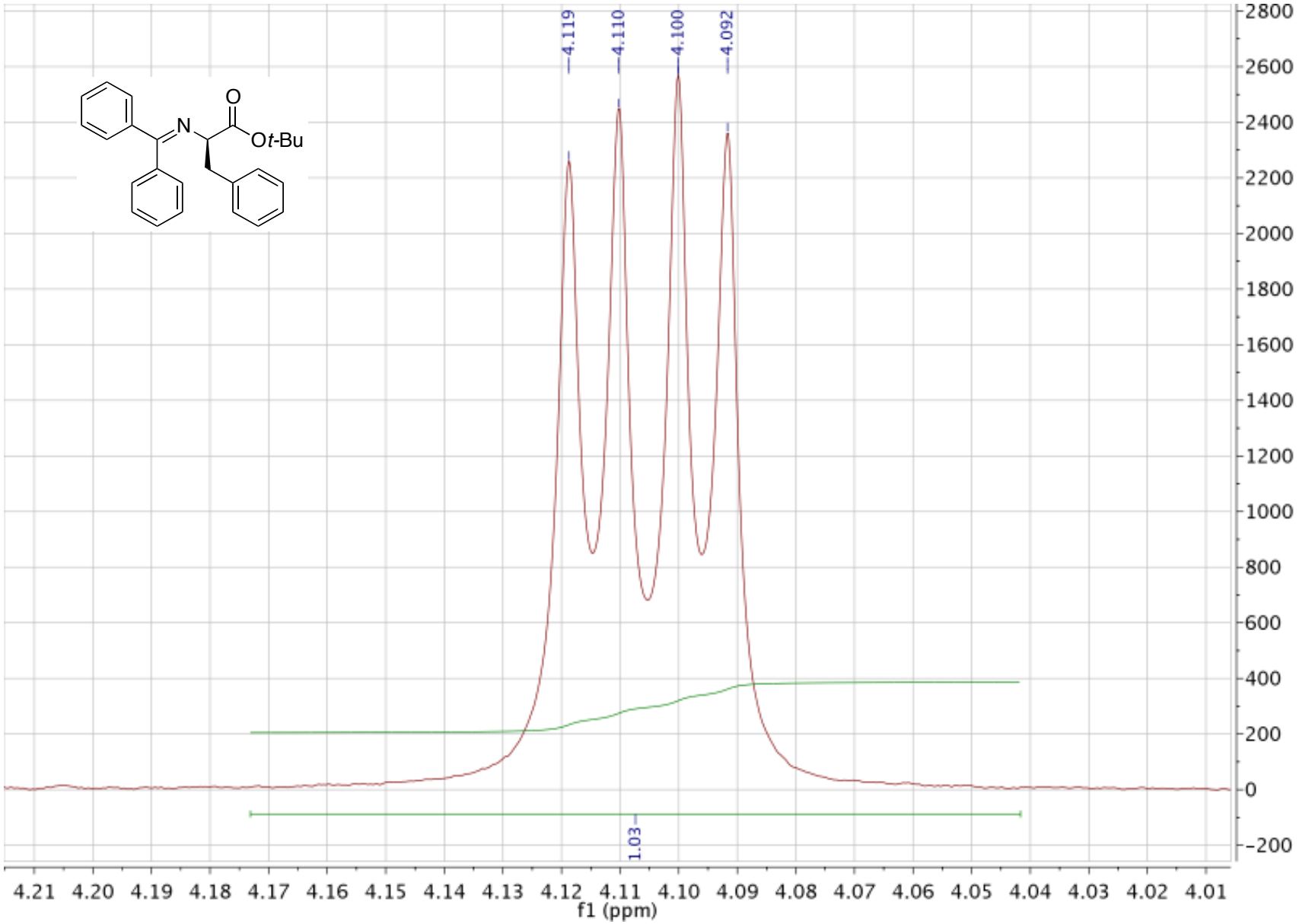
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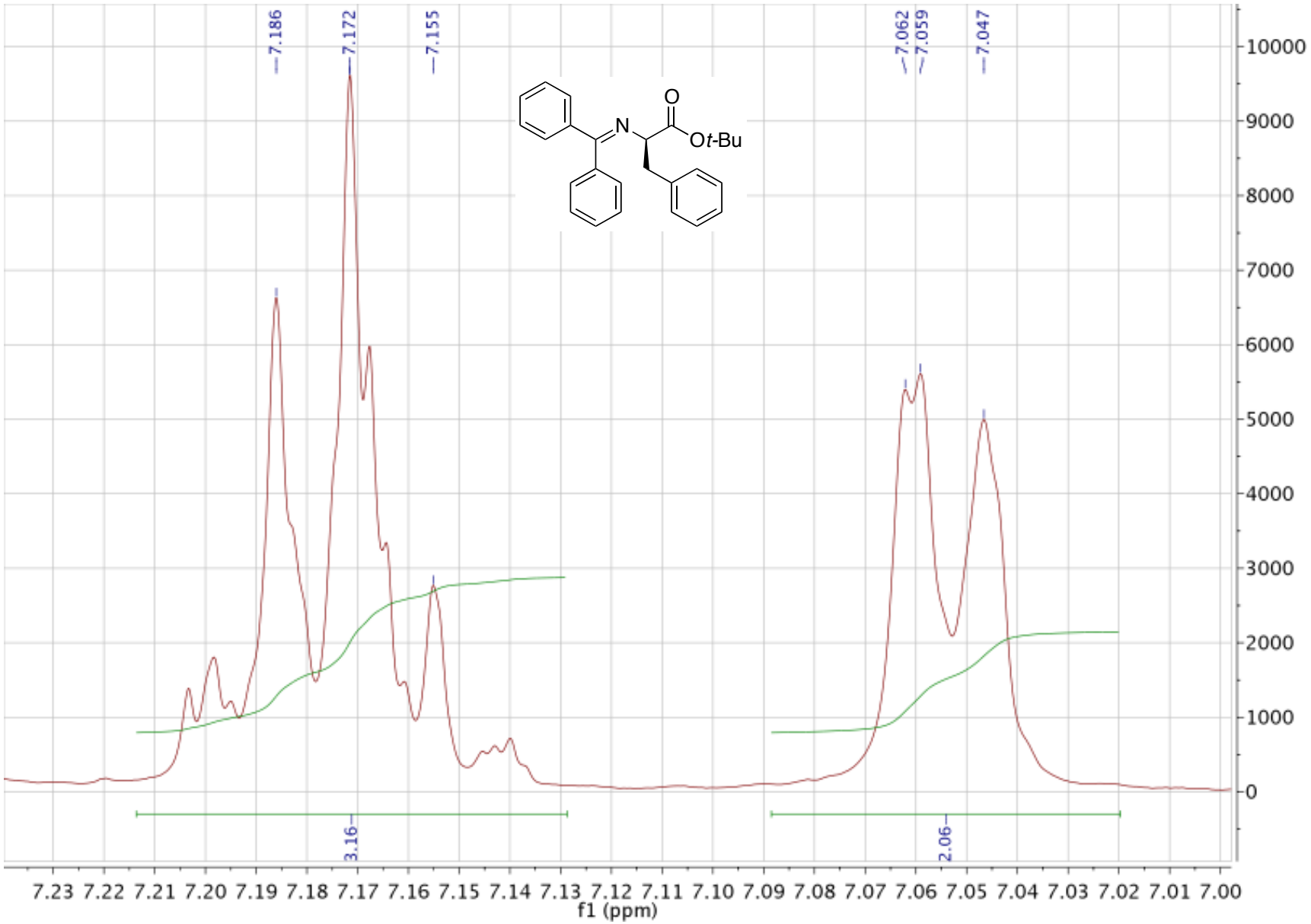
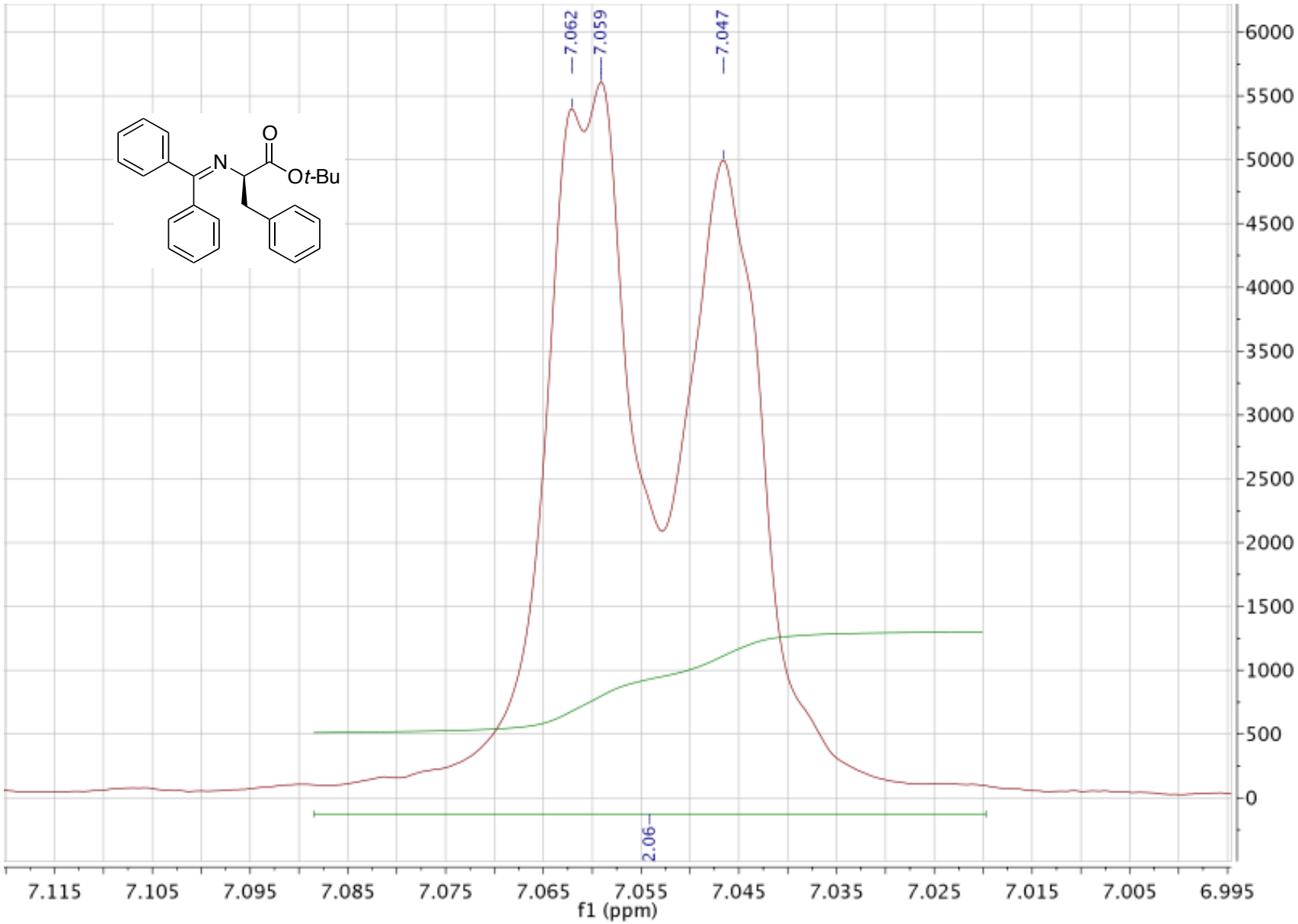
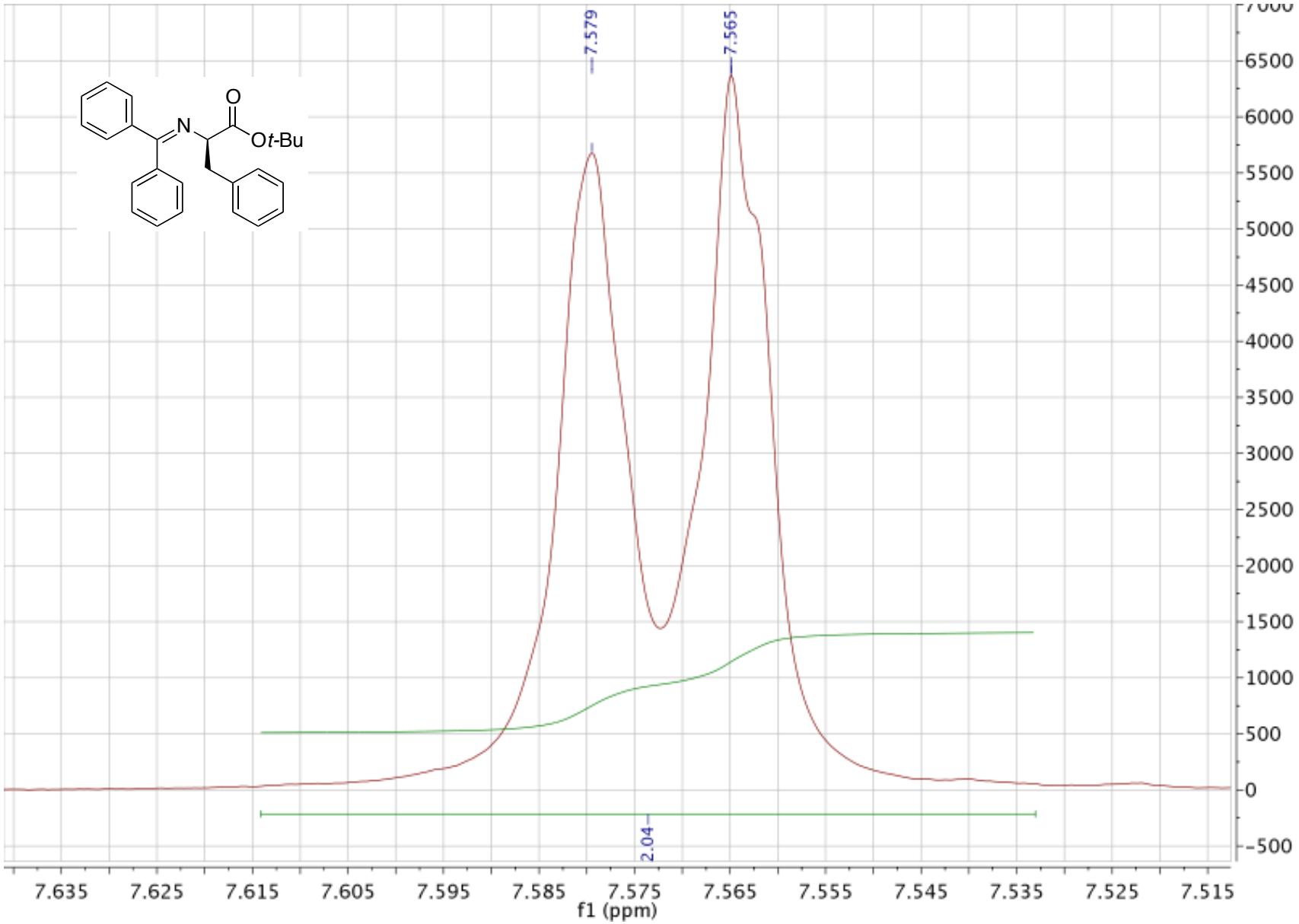
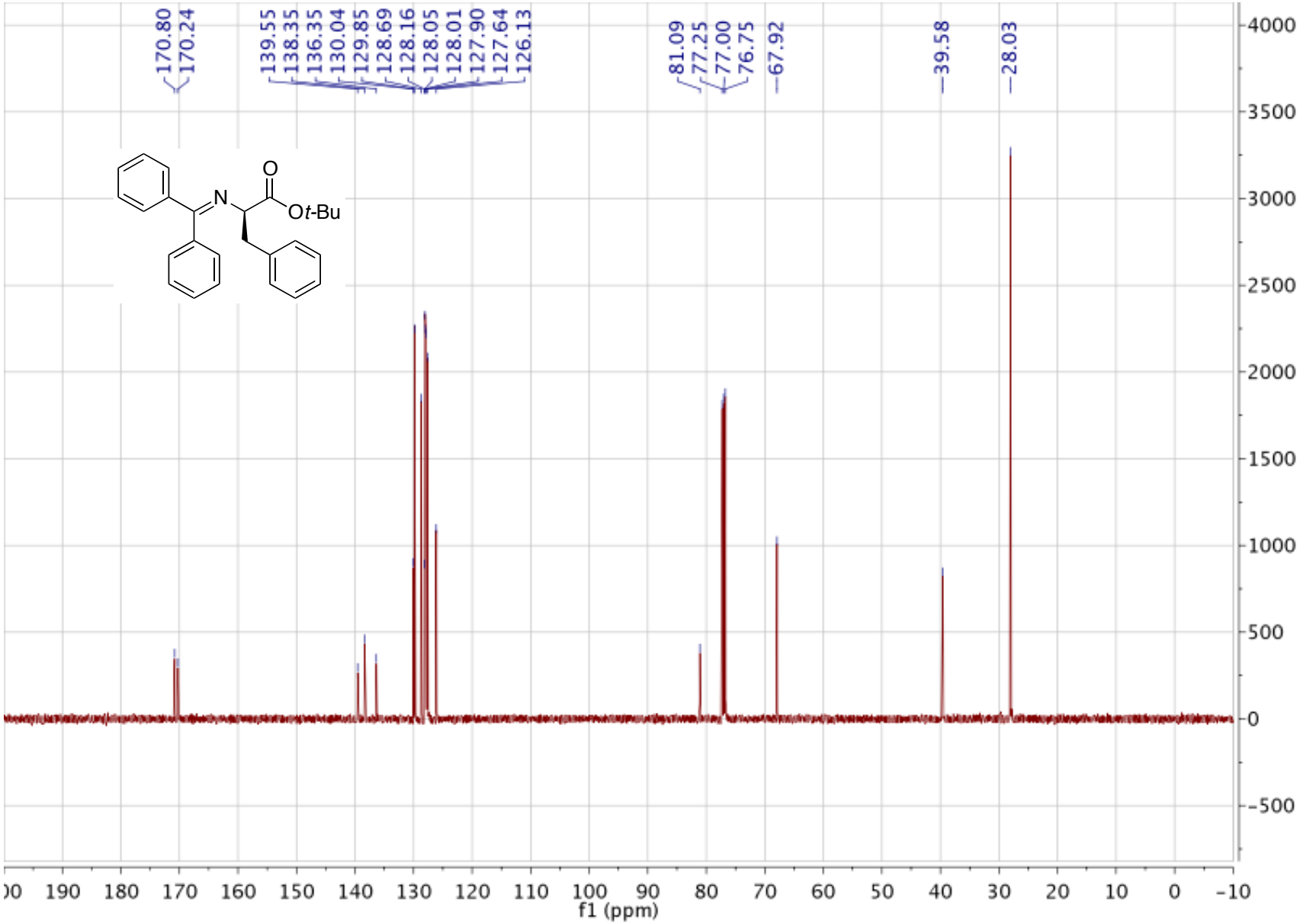
N
O*t*-Bu
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
4.21 4.20 4.19 4.18 4.17 4.16 4.15 4.14 4.13 4.12 4.11 4.10 4.09 4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01
f1 (ppm)


7.186
7.172
7.155
7.062
7.059
7.047
N
O
Ot-Bu
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3.16
2.06
7.23 7.22 7.21 7.20 7.19 7.18 7.17 7.16 7.15 7.14 7.13 7.12 7.11 7.10 7.09 7.08 7.07 7.06 7.05 7.04 7.03 7.02 7.01 7.00
f1 (ppm)


7.062
7.059
7.047
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2.06
7.115
7.105
7.095
7.085
7.075
7.065
7.055
7.045
7.035
7.025
7.015
7.005
6.995
f1 (ppm)
O
N
O*t*-Bu


7.579
7.565
O
N
Ot-Bu
2.04
7.635
7.625
7.615
7.605
7.595
7.585
7.575
7.565
7.555
7.545
7.535
7.525
7.515
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500


170.80
170.24
139.55
138.35
136.35
130.04
129.85
128.69
128.16
128.05
128.01
127.90
127.64
126.13
81.09
77.25
77.00
76.75
67.92
39.58
28.03
O
N
Ot-Bu
4000
3500
3000
2500
2000
1500
1000
500
0
-500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)