Organic Syntheses

Aminocarbonylation Using Electron-rich Di-*tert*-butylphosphinoferrocene

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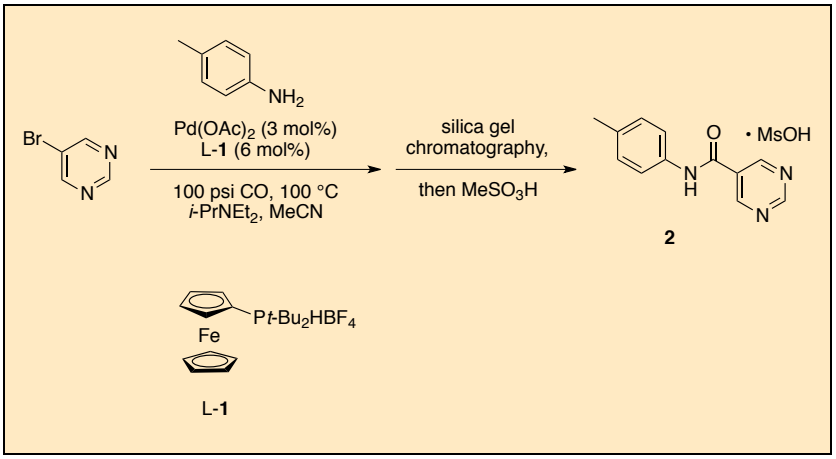

Procedure

A. *Pyrimidine-5-carboxylic acid p-tolylamide methanesulfonate* (**2**). A 475 mL Parr vessel containing a cylindrical Teflon-coated magnetic stir bar (5 cm in length, 1 cm in diameter) is charged with *p*-tolylamine (4.01 g, 37.1 mmol, 1.0 equiv) (Note 1), 5-bromo-pyrimidine (7.34 g, 44.8 mmol, 1.2 equiv) (Note 2), palladium acetate (257 mg, 1.23 mmol, 0.03 equiv) (Note 3), and ligand **1** (970 mg, 2.25 mmol, 0.06 equiv) in open air (Note 4). Acetonitrile (80.0 mL) (Note 5) and *N*,*N*-diisopropylethylamine (26.1 mL,

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149 mmol, 4.0 equiv) (Note 6) are added to the vessel. The vessel is sealed and purged with carbon monoxide three times. The vessel is then pressurized with carbon monoxide to 100 psi, and placed in a room-temperature oil bath. The oil bath is heated to 100 °C. The reaction is stirred at 100 °C (bath temperature) and 100 psi CO for 4 h (Notes 7 and 8). The reaction vessel is removed from the oil bath and cooled to ambient temperature while stirring. After releasing the pressure, HPLC analysis shows that *p*-tolylamine is fully consumed. The reaction mixture is transferred to a 250 mL one-necked round-bottomed flask and concentrated on a rotary evaporator (Note 9) to fully remove acetonitrile and the tertiary amine. To the resulting dark semi-solid is added 2-MeTHF (100 mL) (Note 10) and 1 M aqueous NaOH (50 mL), and the resulting dark mixture is stirred vigorously for 1 h (Note 11). The two-phase mixture is then filtered through a pad of Celite (1 cm) in a 150 mL fritted funnel (medium porosity, Note 12) into a one-necked 500 mL round-bottomed flask using house vacuum. The Celite pad is washed with 2-MeTHF (2 x 100 mL). The combined filtrates are transferred to a 1 L separatory funnel and allowed to stand for 15 min. The lower aqueous layer is discarded. The upper organic layer is washed with water (2 x 100 mL) and then transferred to a one-

necked 500 mL round-bottomed flask (Note 13). Dry silica gel (16 g) is added to the flask, and the resultant mixture is dried on a rotary evaporator until a brown powder is obtained (Note 14). This material is then placed atop a silica gel column (250 g, 8 cm diameter) that had been conditioned with 450 mL 20% EtOAc/hexanes. Sand is added on top of the silica gel. The column is eluted first with 1300 mL 20% EtOAc/hexanes to remove non-polar impurities. Pure EtOAc is then used to elute the product. The fractions are then combined and concentrated in vacuo to give 6.1 g of the crude free base product as a light brown solid (Note 15). A final purification is then carried out (Note 16). The solids are transferred to a three-necked 250 mL flask (the necks contain an inert gas valve and two septa, one containing a thermocouple), followed by addition of 2-MeTHF (85 mL). The mixture is stirred for ca 5 min at 65 °C under N_2 to give a brown solution. Methanesulfonic acid (1.95 mL, 30 mmol, 0.8 equiv) (Notes 17, 18 and 19) is then added at once via syringe, causing the immediate formation of a thick slurry of the MsOH salt. The suspension is stirred at 65 °C for 30 min, then heat is turned off and the mixture is allowed to cool slowly to ambient temperature (approximately three hours). The slurry is then filtered through a medium-fritted filter funnel using house vacuum, washing the cake with 2-MeTHF (1 x 20 mL). After 30 min, the dry solids are collected to give 8.7 g (76%) of the product salt as a tan powder (Notes 20, 21, and 22).

Notes

1. *p*-Tolylamine (99.0%) was purchased from Aldrich and used as received.
2. 5-Bromo-pyrimidine (97%) was purchased from Aldrich and used as received.
3. Palladium (II) acetate (98%) was purchased from Aldrich and used as received.
4. Ligand **L-1** was prepared as described in *Org. Synth.* **2013**, *90*, 316–326.
5. Anhydrous acetonitrile was purchased from Aldrich and used as received.
6. *N*,*N*-Diisopropylethylamine (99.5%) was purchased from Aldrich and used as received.

7. The checkers observed an increase in pressure to 110 psi upon heating, followed by a decrease in pressure to 88 psi after approximately 90 min reaction time. The reaction pressure remained at 88 psi for the remainder of the reaction.
8. The reaction mixture becomes darker at extended reaction times, making visualization of the subsequent phase separation difficult. The reaction is completed in approximately 4 h.
9. Vacuum (25-50 mmHg) and water bath (60 °C) were used. Full removal of the tertiary amine is critical to the success of the salt formation. Successful removal of tertiary amine can be monitored by ^{1}H NMR of the crude in d_6-DMSO.
10. 2-MeTHF (>99%) was purchased from Aldrich and used as received.
11. The carbonylation generates significant amounts (~ 10-20%) of an impurity derived from the desired product: it is the imide in which *two* acyl-pyrimidine fragments are on the aniline nitrogen atom ($C_{17}H_{13}N_5O_2$, HRMS $[M+H]^+$ calc 320.1142, found: 320.1141). Treating the reaction mixture with 1M NaOH converts this material to additional product (plus pyrimidine carboxylic acid), increasing the isolated yield of **2**.
12. The filtration removes dark materials that obscure the phase separation.
13. If an emulsion is observed at this stage, longer periods of settling may be required.
14. If necessary, a spatula can be used to scrape some of the material off the inside wall of the flask.
15. Fractions of 65 mL were collected. The desired free-base intermediate was collected in fractions 11–26. R_f = 0.4 (75% EtOAc in hexanes) visualized by UV irradiation.
16. Some mixed fractions can be included as the product is further purified during salt formation.
17. Methanesulfonic acid (99.5%) was purchased from Aldrich and used as received.
18. The amount of methanesulfonic acid used (0.8 equiv) was determined based on the crude yield of the free-base. A second crop of product was obtained by a subsequent salt formation reaction using 0.2 equiv of MsOH. This process only produced an additional 2% of **2•MsOH** (in decreased purity).
19. The checkers observed an increase in internal temperature to 73 °C upon addition of MsOH.

20. Compound **2•MsOH** exhibits the following analytical data: ^{1}H NMR and ^{13}C NMR spectra are reported relative to d_6-DMSO (δ 2.50 ppm and δ 39.52 ppm, respectively). ^{1}H NMR (20 mg solid in 0.6 mL d_6-DMSO, 500 MHz) δ: 2.28 (s, 3 H), 2.47 (s, 3 H), 7.17 (d, *J* = 8 Hz, 2 H), 7.63 (d, *J* = 8 Hz, 2 H), 9.25 (s, 2 H), 9.34 (s, 1 H), 10.52 (s, 1 H), 10.94 (br s, 1 H); ^{13}C NMR (d_6-DMSO, 126 MHz) δ: 20.6, 39.7, 120.4, 128.7, 129.2, 133.4, 136.1, 156.2, 160.1, 162.0; IR (neat film, NaCl): 3411, 3278, 3111, 3034, 2930, 1648, 1620, 1601, 1540, 1514, 1414, 1191, 1150, 1042, 1023.6, 918, 823, 811, 697 cm^{-1}; mp 209.6–210.1 °C; HRMS (FAB+) for free base $C_{12}H_{12}N_3O$ $[M+H]^+$: calcd, 214.0980; found, 214.0987; Elem. Anal. calcd. for $C_{13}H_{15}N_3O_4S$: C, 50.48; H, 4.89; N, 13.58; found: C, 50.66; H, 4.87; N, 13.44.
21. The checkers observed that the chemical shift of the broad singlet at 10.94 ppm is dependent on the ^{1}H NMR sample concentration (increases with concentration).
22. On a half-scale run, the checkers isolated compound **2•MsOH** in 76% yield.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that

is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

The direct palladium-catalyzed carbonylation of aryl halides in the presence of alcohols or amines is an efficient way to synthesize esters and amides, respectively.[2] The synthesis of esters is relatively well precedented, whereas the amino carbonylation, which is of great importance for the synthesis of pharmaceuticals, remains a bigger challenge. An early report by Heck[3] used triphenylphosphine as ligand with aryl and vinyl bromides and later Milstein[4] introduced di-isopropylphosphinopropane (dippp) for aryl chlorides. Buchwald reported more recently[5] on the use of Xantphos for aryl bromides as well as for two examples of hetero aryl bromides. We demonstrated[6] the amino carbonylation of hetero aryl bromides and iodides using the electron-rich ligand di-*tert*-butyl-phosphinoferrocene. The synthesis of this ligand is the subject of a preceding *Organic Syntheses* procedure.[7] The ligand is isolated as the HBF_4-salt (L-**1**). To our knowledge, this is the first example of gram scale aminocarbonylation that employs base hydrolysis of an imide by-product to increase the isolated yield.

References

1. Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., P. O. Box 368, Ridgefield, CT 06877. E-mail:magnus.eriksson@boehringer-ingelheim.com; bo.qu@boehringer-ingelheim.com
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Di-*tert*-butylphosphinoferrocene: Ferrocene, [bis(1,1-dimethylethyl)phosphino]-; (223655-16-1)
Palladium acetate: Acetic acid, palladium(2+) salt (2:1); (3375-31-3)
p-Tolylamine: Benzenamine, 4-methyl-; (106-49-0)
5-Bromo-pyrimidine: Pyrimidine, 5-bromo-; (4595-59-9)
N,*N*-Diisopropylethylamine: *N*-Ethyl-*N*,*N*-diisopropylamine; (7087-68-5)

Dr. Carl Busacca received his B.S. in Chemistry from North Carolina State University, and did undergraduate research in Raman spectroscopy and ^{60}Co radiolyses. After three years with Union Carbide, he moved to the labs of A.I. Meyers at Colorado State University, earning his Ph.D. in 1989 studying asymmetric cycloadditions. He worked first for Sterling Winthrop before joining Boehringer-Ingelheim in 1994. He has worked extensively with anti-virals, and done research in organopalladium chemistry, ligand design, organophosphorus chemistry, asymmetric catalysis, NMR spectroscopy, and the design of efficient chemical processes. He is deeply interested in the nucleosynthesis of transition metals in supernovae.

Dr. Magnus Eriksson was born in Stockholm, Sweden. He received his undergraduate degree in Chemical Engineering and his Ph.D. in Organic Chemistry from Chalmers University of Technology in Gothenburg in 1995 under the guidance of Professor Martin Nilsson working on copper-promoted 1,4-additions to carbonyl compounds. After post-doctoral work at Boehringer Ingelheim Pharmaceuticals and at MIT with Professor Stephen Buchwald, he joined Boehringer Ingelheim Pharmaceuticals in 2000 where he is currently a Principal Scientist. His research interests include Process Research, catalytic transformations and synthetic methodology.

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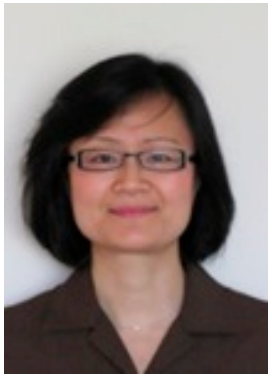

Dr. Bo Qu was born in China, where she received a B.S. degree in chemistry. She then completed her M.S. at University of Science and Technology of China. She obtained her Ph.D. from the University of South Carolina in 2002 under the guidance of Prof. Richard Adams. After 3 years of postdoctoral studies at Cornell University with Prof. David Collum, she joined the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals in Ridgefield, CT, where she is currently a Senior Scientist. Dr. Qu's research interests focus on development of new catalytic transformations for efficient chemical processes, organometallic chemistry, and automated parallel syntheses.

Dr. Heewon Lee obtained her B.S. in Chemistry and MS in Physical Chemistry from Seoul National University in Seoul, South Korea. She earned her Ph.D. in Analytical Chemistry at the University of Michigan in Ann Arbor. After postdoctoral positions, she worked at ArQule for two years, and joined Boehringer Ingelheim Pharmaceuticals in 2000. Currently, she is Senior Associate Director in Chemical Development department and leads Analytical Research Group. She is responsible for analytical method development, in-process control for Process R&D, and quality control of outsourced materials. She is also involved in the Genotoxic Impurity Council and Process Analytical Technology (PAT).

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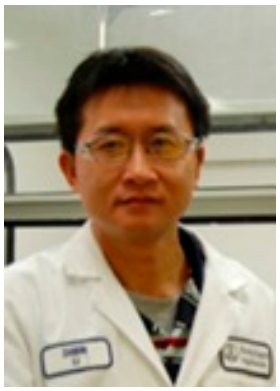
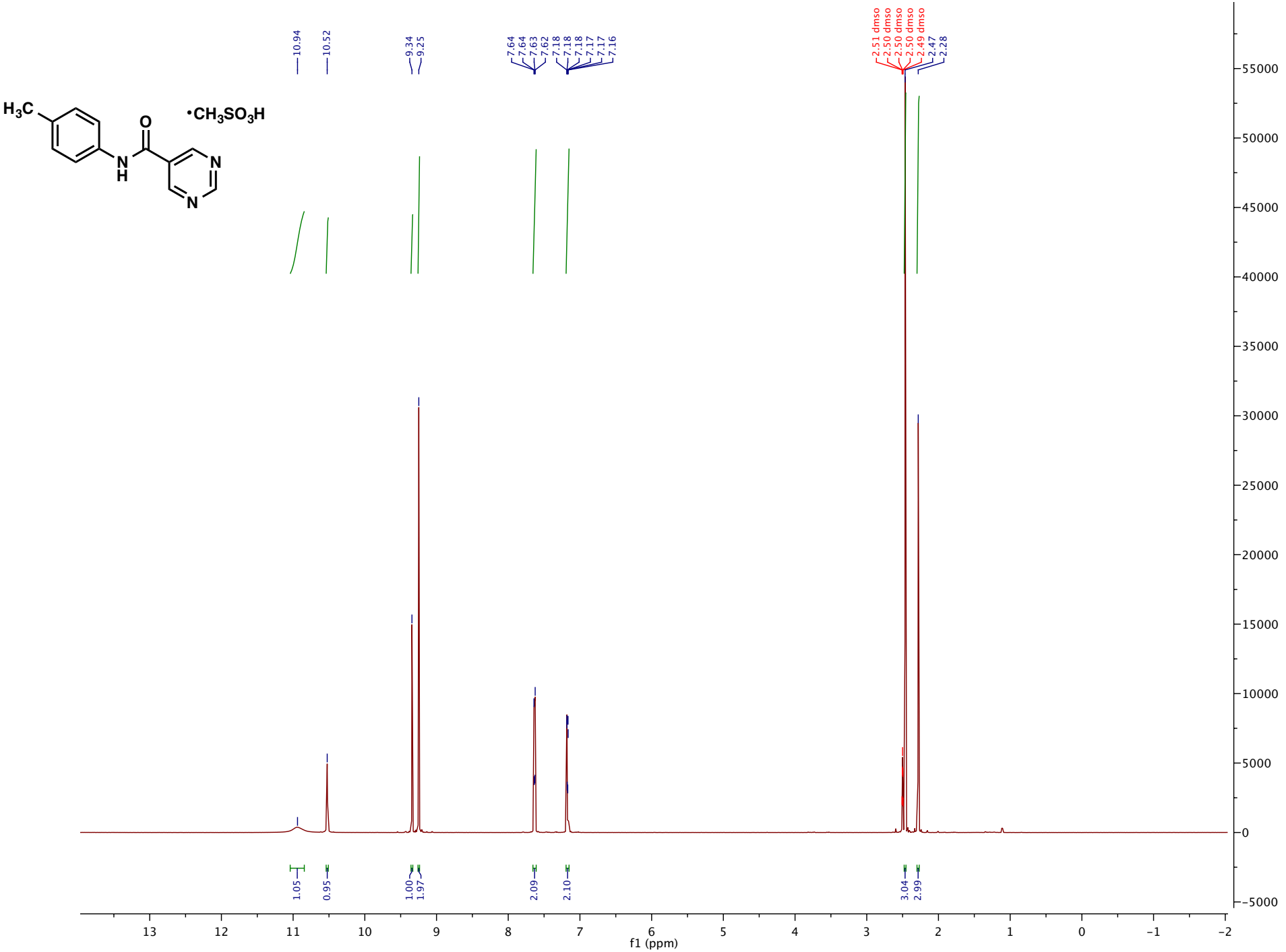


Zhibin Li joined Boehringer-Ingelheim Pharmaceutical (Ridgefield, US) in 2006, where he has been working in the areas of manual and high through-put polymorph / salt / cocrystal screen, physical form characterization, chiral separation by crystallization, and crystallization development of active pharmaceutical ingredients. Zhibin has a Ph.D. in Chemistry.

Dr. Chris H. Senanayake obtained his Ph.D. with Professor James H. Rigby at Wayne State University followed by postdoctoral fellow with Professor Carl R. Johnson. In 1989, he joined Process Development at Dow Chemical Co. In 1990, he joined the Merck Process Research Group. After Merck, he accepted a position at Sepracor, Inc. in 1996 where he was appointed to Executive Director of Chemical Process Research. In 2002, he joined Boehringer Ingelheim Pharmaceuticals. Currently, he is the Vice President of Chemical Development. He is the co-author more than 340 papers and patents in many areas of synthetic organic chemistry.

Beau P. Pritchett received his B.S. degree in Chemistry and B.S.E. degree in Chemical Engineering from Tulane University in 2012. In the fall of 2012, he joined the laboratories of Professor Brian M. Stoltz at Caltech where he has pursued his Ph.D. as an NSF predoctoral fellow. His research interests include chemical synthesis, reaction design, and their applications in natural product synthesis and human medicine.

Nicholas R. O'Connor received a B.A. in chemistry from Macalester College in 2011, conducting research with Professor Rebecca C. Hoye. He then moved to the California Institute of Technology and began his doctoral studies under the direction of Professor Brian M. Stoltz. His graduate research focuses on cycloadditions of strained rings and the application of these reactions to natural product synthesis.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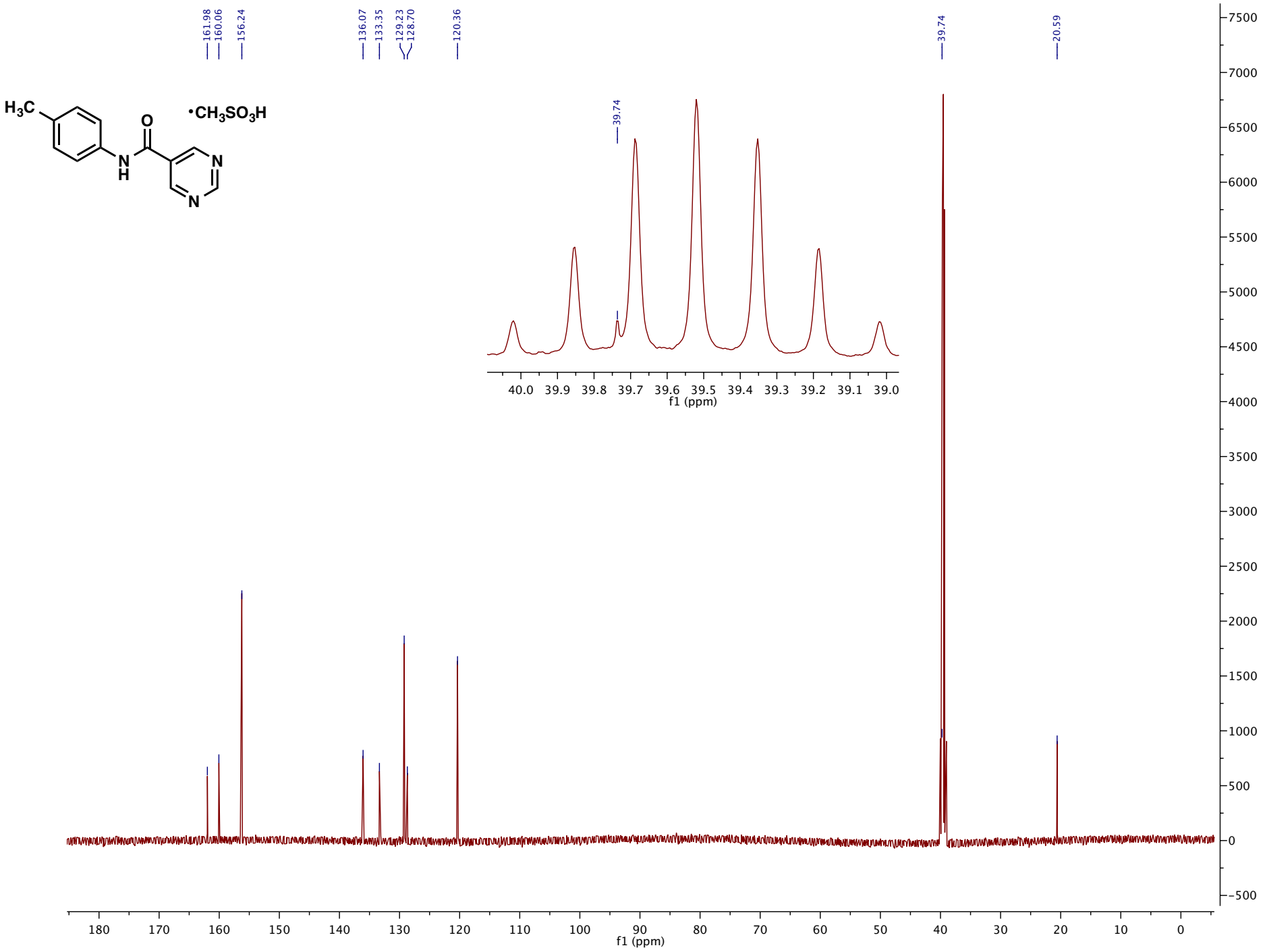
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