Organic Syntheses

Preparation of *O*-Pivaloyl Hydroxylamine Triflic Acid

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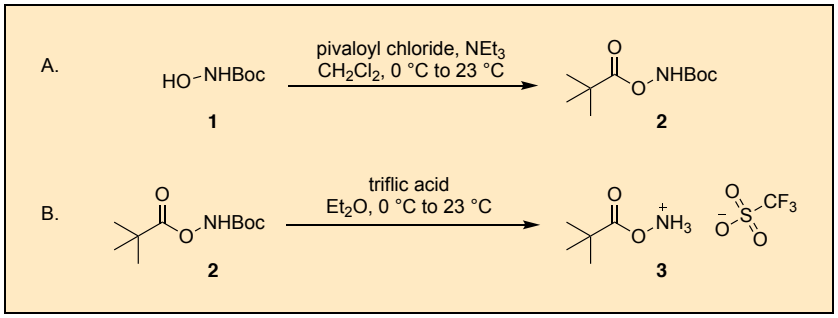

Procedure (Note 1)

A. *tert-Butyl pivaloyloxy carbamate* (**2**). In air, a 1-L round-bottomed flask (29/32) equipped with a Teflon-coated egg-shaped magnetic stirbar (40 x 20 mm) is consecutively charged with *N*-Boc hydroxylamine (30.0 g, 0.225 mol) (Note 2), dichloromethane (CH_2Cl_2, 0.4 L, 0.6 M) (Note 2) and triethylamine (31.3 mL, 22.8 g, 0.225 mol, 1.0 equiv) (Note 2). The reaction vessel is then placed in an ice/water bath and stirred until all solids have dissolved (Note 3). The round-bottomed flask is equipped with a 50-mL dropping funnel (14/23, Teflon stopcock, pressure compensation) (Note 4) which is filled with pivaloyl chloride (PivCl, 28.0 mL, 27.5 g, 0.228 mol, 1.0 equiv) (Note 2). The dropping funnel is sealed with a rubber septum attached to a balloon (Note 5). PivCl is added dropwise to the stirring solution over 30 min (Note 6) and left for a further 30 min before the ice/water bath is removed. After an additional 2 hours of stirring at room temperature (Note 7), the resulting suspension is vacuum-filtered

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(Notes 8 and 9) and the filter cake is washed with CH_2Cl_2 (2 x 20 mL). The colorless filtrate is transferred to a 1-L separatory funnel (NS 29, Teflon stopcock) and washed subsequently with distilled water (0.20 L), a saturated aqueous solution of $NaHCO_3$ (0.20 L) and a saturated aqueous solution of NaCl (0.10 L). The final organic layer is dried by stirring over anhydrous Na_2SO_4 (15 g) for 15 min in a 1-L beaker and subsequent vacuum filtration. The filter residue is washed with CH_2Cl_2 (2 x 10 mL). Final removal of the solvent on a rotary evaporator (Note 10) affords 46.8 g (96%) of *tert*-butyl pivaloyloxy carbamate **2** as a colorless solid (Notes 11 and 12).

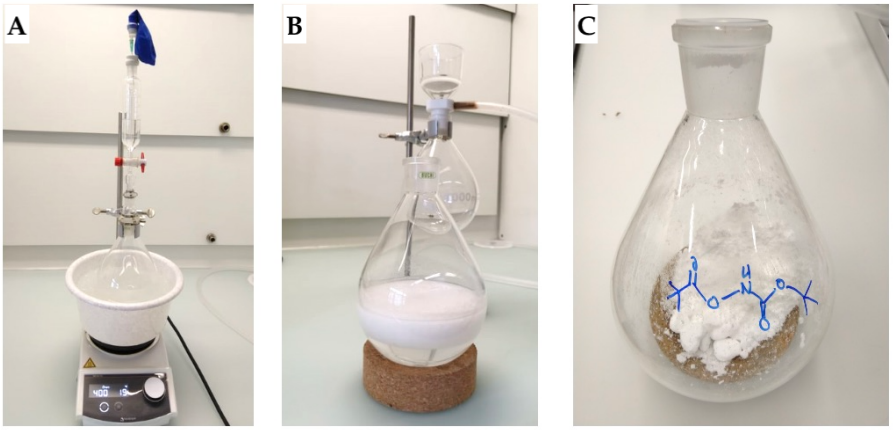


Figure 1. A) Reaction set-up, B) Filtration of the reaction mixture, and C) Product of pivaloylation step

B. *O-Pivaloyl hydroxylamine triflic acid (**3**)*. In air, a 1-L two-necked, round-bottomed flask (29/32 in central position, 14/23 in side position) equipped with a Teflon-coated egg-shaped magnetic stirbar (40 x 20 mm) is charged with 45 g *tert*-butyl pivaloyloxy carbamate *(**2**)* (0.21 mmol, 1.0 equiv) followed by 0.4 L of Et_2O (0.6 M) (Note 2). The reaction vessel is placed in an ice/water bath and stirred until all solids have dissolved (Note 3). Then, the two-necked, round-bottomed flask is equipped with a 50-mL dropping funnel (14/23, Teflon stopcock, pressure compensation) (Note 4) which is filled with triflic acid (18 mL, 31 g, 0.20 mmol, 1.0 equiv) (Note 2). The acid is added over 30 min (Note 13) and left for further 30 min before the ice/water bath is removed. During additional 3 hours of stirring at room temperature (Note 7), a white precipitate is formed. Additional colorless precipitate crashes out upon addition of *n*-pentane (0.15 L) (Note 2). Subsequently, the suspension is

vacuum filtered (Note 9), the reaction vessel rinsed with *n*-pentane (3 x 50 mL) and the filter cake carefully washed with ice-cold CH_2Cl_2 (3 x 50 mL) (Note 14). Upon drying under high vacuum for 16 h (Note 15), 45.6 g of *O*-pivaloyl hydroxylamine triflic acid **3** is obtained as a colorless, crystalline, free flowing solid in 83% yield (Notes 16 and 17).

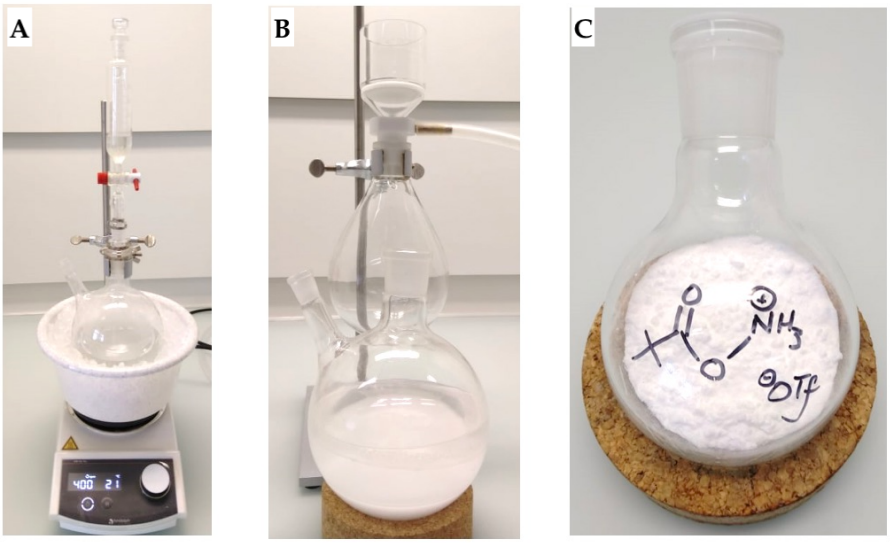


Figure 2. A) Reaction set-up, B) Filtration of the reaction mixture, and C) Product of deprotection step

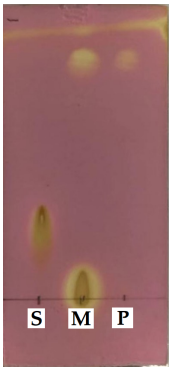
Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories"

(American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with *N*-Boc-hydroxylamine, dichloromethane, triethylamine, pivaloyl chloride, sodium hydrogen carbonate, diethyl ether, triflic acid, *n*-pentane as well as the proper procedures for setting up experimental operations. Provide additional caution with regard to highly corrosive triflic acid, the use of diethyl ether which is prone to form peroxides and gaseous by-products generated upon *N*-Boc-deprotection.

2. *N*-Boc hydroxylamine (99%) was obtained from Fluorochem Ltd (The checkers purchased *N*-Boc hydroxylamine (>98%) from Tokyo Chemical Industry Co., Ltd.). Dichloromethane (HPLC grade, unstabilized) was obtained from VWR International GmbH (The checkers purchased dichloromethane (99.8%) from Acros Organics). Triethylamine (99%) was obtained from Acros Organics (The checkers purchased triethylamine (99%) from Alfa Aesar). Pivaloyl chloride (99%) was obtained from Sigma Aldrich (The checkers purchased pivaloyl chloride (99%) from Acros Organics). Diethyl ether (≥ 99.7%) was obtained from VWR International GmbH (The checkers purchased diethyl ether (≥ 99.5%) from Tansoole). Triflic acid (97%) was obtained from Fluorochem Ltd (The checkers purchased triflic acid (98%) from Alfa Aesar). *n*-Pentane (≥ 99.0%) was obtained from VWR International GmbH (The checkers purchased *n*-Pentane (≥ 99%) from Tansoole). All chemicals were used as received.
3. A MR Hei-Tec stirring plate obtained from Heidolph Instruments GmbH & Co. KG was used throughout this manuscript. Unless reported otherwise, a stir rate of 400 rpm was used.
4. The graduated dropping funnel was connected to the wide neck *via* a glass adapter (29/32 male to 14/23 female).
5. The rubber septum was attached to a balloon *via* a needle adapter to prevent over-pressure. The reaction was carried out under air. Reactions performed under nitrogen gave a comparable result.
6. Even before complete addition of PivCl, the stirred reaction mixture became cloudy.
7. The room temperature throughout this manuscript refers to temperature between 20 and 25 °C.

8. The reaction can be monitored by TLC (SiO_2, CH_2Cl_2/Et_2O 15/1, starting material **1**: R_f 0.24, product **2**: R_f 0.87; $KMnO_4$) to observe complete consumption of starting material (S refers to starting material **1**. M refers to reaction mixture. P refers to product **2**.).



Scheme 3. TLC monitoring of Step A

9. Glass fritted funnels obtained from ROBU-GLAS ® with porosity Por.4, 60 mm diameter and 125 mL capacity were used. For the filtration a vacuum pump supplied by Vacuubrand GmbH & Co. KG was used to establish reduced pressure. To wash the filter cake effectively, vacuum was turned off between separate washing cycles, washing solvent was added and the resulted mixture was stirred thoroughly with a stainless steel spatula before the washing solvent was removed by vacuum suction.
10. Rotary evaporator R-300 purchased from BÜCHI Labortechnik AG was used and rotation rate was 200 rpm, the temperature of the water bath was set to 40 °C. To remove the solvent, the following drying method was used: 30 min at 450 mmHg, 20 min at 300 mmHg, 10 min at 75 mmHg.
11. The white solid has the following characteristics, which matches those reported in the literature.[2]: mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (s, 9H), 1.49 (s, 9H), 7.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 27.0, 28.1, 38.2, 83.1, 155.8, 177.8; HRMS (ESI) *m*/*z* calcd. for $C_{10}H_{19}NO_4Na^+$ $[M+Na]^+$: 240.1206. Found: 240.1205; IR (film): 3270, 2981, 1777, 1720, 1473, 1395, 1369, 1280, 1255, 1164, 1101, 1075, 1022, 859, 772, 754, 601 cm^{-1}. Purity of the compound was checked by elemental analysis for which the product from the rotary evaporator was broken up with a spatula and dried under high vacuum over 16 h (see Note 15): Anal. Calc.

for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.27; H, 8.92; N, 6.44. Drying the product under high vacuum is not necessary for the next step.

12. A second run on the same scale yielded 46.6 g (95%) of product with the same purity.
13. The addition of triflic acid should be done with great care and attention during execution. First, the deprotection reaction creates significant amounts of gaseous by-products. Second, due to its high density, a steady dropping rate is difficult to achieve and the dropping might cease.
    Et_2O was chosen as solvent due to the fact that product **3** crashes out of the solvent and readily forms a white precipitate. When compared to experiments using THF or CH_2Cl_2 as solvent, the use of Et_2O resulted in a simplified work-up.
    The reaction is determined to be finished when no further significant gas evolution is observed. Further, TLC analysis as described in Note 8 can be used to monitor complete consumption of starting material **1**.
14. The wash step with CH_2Cl_2 is necessary to remove an impurity from the reaction mixture with following spectroscopic characteristics: ^{1}H NMR (400 MHz, CD_3CN) δ: 1.44 (s, *n*H), 1.32 (s, *n*H).
15. High vacuum was established with a vacuum oil pump provided by Vacuubrand GmbH & Co. KG. For drying, a pressure lower than 0.08 mmHg was maintained.
16. The white, free flowing solid has the following characteristics: mp 139–141 °C; ^{1}H NMR (400 MHz, CD_3CN) δ: 1.29 (s, 9H), 9.94 (br s, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ: 26.8, 39.1, 121.4 (q, J = 317 Hz), 175.2; ^{19}F NMR (376 MHz, CD_3CN) δ: –79.36 (referenced against C_6F_6.[3]) IR (film): 2982, 2728, 1786, 1540, 1482, 1222, 1180, 1081, 1022, 856, 796, 756, 634, 585, 516, 490 cm^{-1}.Purity of the dried compound was checked by elemental analysis: Anal. Calc. for $C_6H_{12}NO_5SF_3$: C, 26.97; H, 4.53; N, 5.24. Found: C, 26.91; H, 4.64; N, 5.38.
17. A second run on the same scale yielded 46.1 g (84%) of product with the same purity.
18. Further recrystallization from *n*BuOAc (1 mL solvent / g solid) at 90 °C can be performed, but does not enhance the purity of the product. DSC data reported by *Legnani et al.* shows that the first exothermic event with compound **3** occurs at 164.5 °C (ΔH = 20.86 J/g), before the compound decomposes at 191.9 °C (ΔH = 296.97 J/g).[4] The compound is stable at room temperature and can be stored under air for several weeks.

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

O-Pivaloyl hydroxylamine triflic acid **3** was first reported by the Fagnou group[5] and used to install an *O*-pivaloyl hydroxylamine motif by reaction with benzoyl chlorides. Equipped this way, these molecules could undergo a rhodium-catalyzed annulation reaction without the use of an external oxidant. Subsequently, other groups have demonstrated the use of this moiety as an internal oxidant for the synthesis of various N-heterocycles.[6]

The facile synthesis and stability of *O*-pivaloyl hydroxylamine triflic acid (**3**) has also driven the use of this reagent in intermolecular amination reactions. The first use of **3** as direct aminating reagent was reported by Glorius and co-workers in a directed amination of arenes.[2] Its reactivity with alkenes in iron-catalyzed reactions was demonstrated by the Morandi group to obtain primary, unprotected aminoalcohols[7] and aminochlorinated[4] compounds.

Earlier protocols to synthesize triflate salt **3** all started from *N*-Boc-protected hydroxylamine and used pivalic anhydride for the pivaloylation step.[5,6e] However, it turned out that the removal of unreacted anhydride (boiling point 193 °C) is cumbersome on larger scale. Replacing it with pivaloyl chloride, as described in this manuscript, delivers a cleaner product without the need for further purification. Milder reaction conditions can also be applied using this new protocol.

The subsequent *N*-Boc deprotection reaction with the highly reactive triflic acid forms the corresponding ammonium salt. Performing the reaction on a larger scale results in the formation of a by-product, which can be removed by an additional washing step.

In conclusion, a two-step procedure for the multi-decagram synthesis of *O*-pivaloyl hydroxylamine triflic acid (**3**) is disclosed herein. The new procedure should find broad application in synthesis due to its low cost (≈ 1 US$/g), simplicity of execution, and utility in subsequent amination reactions.

References

1. Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland, E-mail: bill.morandi@org.chem.ethz.ch; ORCID: 0000-0003-3968-1424. We kindly acknowledge ETH Zürich and SNSF (184658) for financial support. We kindly thank E. M. Carreira for sharing analytical equipment, as well as MoBiAS (ETH) for elemental analysis (P. Kälin, ETH) and HRMS measurements. Further, we would like to thank G. Toupalas, E. Denton and V. Gasser for carefully proof-reading the manuscript and M. Lutz for the portrait pictures.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

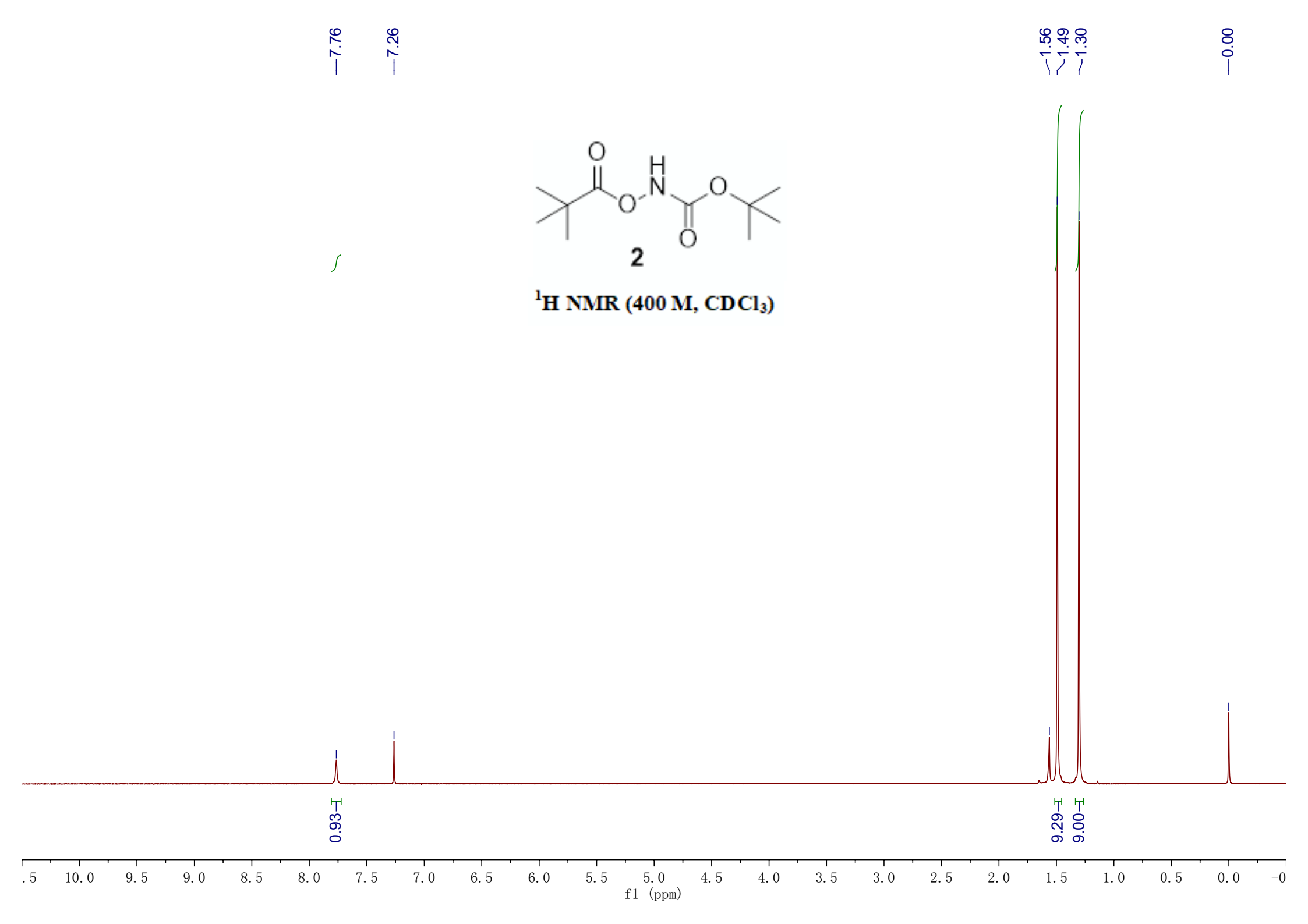
O-Pivaloyl hydroxylamine triflic acid: *O*-Pivaloylhydroxylammonium trifluoromethanesulfonate; (1293990-73-4)
Pivaloyl chloride: 2,2-Dimethylpropanoyl chloride; (3282-30-2)

Szabolcs Makai studied at the Ludwig-Maximilians University in Munich, Germany (2012–2018), where he obtained his M. Sc. degree in Chemistry. After conducting his Bachelor thesis in the labs of Prof. D. Trauner, he visited during his Master studies the group of Prof. S. V. Ley at the University of Cambridge, UK. After an industrial placement at Novartis in Basel, CH, he joined the Morandi group for his Master's thesis at the Max-Planck-Institut für Kohlenforschung in Mülheim a. d. Ruhr, Germany. He continued as doctoral candidate within the same group at the Laboratorium für Organische Chemie of the ETH Zurich.

Eric Falk studied at the ETH Zürich from 2013 to 2018 earning a BSc and MSc in chemistry. During his studies, he conducted research projects in the research groups of Prof. Antonio Togni and Prof. Jeffrey W. Bode and his master thesis under the supervision of Prof. Erick M. Carreira. In August 2018, he joined the group of Prof. Bill Morandi as a doctoral candidate at the Laboratorium für Organische Chemie of the ETH Zürich.

Bill Morandi studied at the ETH Zurich (2003–2008), earning a BSc in Biology and an MSc in Chemical Biology as an Oskar-Jeger Scholar. After a Ph.D. with Prof. Erick M. Carreira, he moved in 2012 to CalTech to work with Prof. Robert H. Grubbs as a Swiss National Science Foundation postdoctoral fellow. In 2014, he was awarded an independent Max Planck Research Group Leader position by the Max Planck Society to start independent research at the Max-Planck-Institut für Kohlenforschung. Since July 2018, he has been a professor at the Laboratorium für Organische Chemie of the ETH Zurich.

Dr. Zhaobin Han received his B.S. degree in chemistry from Nanjing University in 2003. He received his Ph.D. degree from Shanghai Institute of Organic Chemistry under the supervision of Prof. Kuiling Ding and Prof. Xumu Zhang in 2009, working on development of novel chiral ligands for asymmetric catalysis. Now he is an associate professor in the same institute and his current research interests focus on the development of efficient catalytic methods based on homogeneous catalysis.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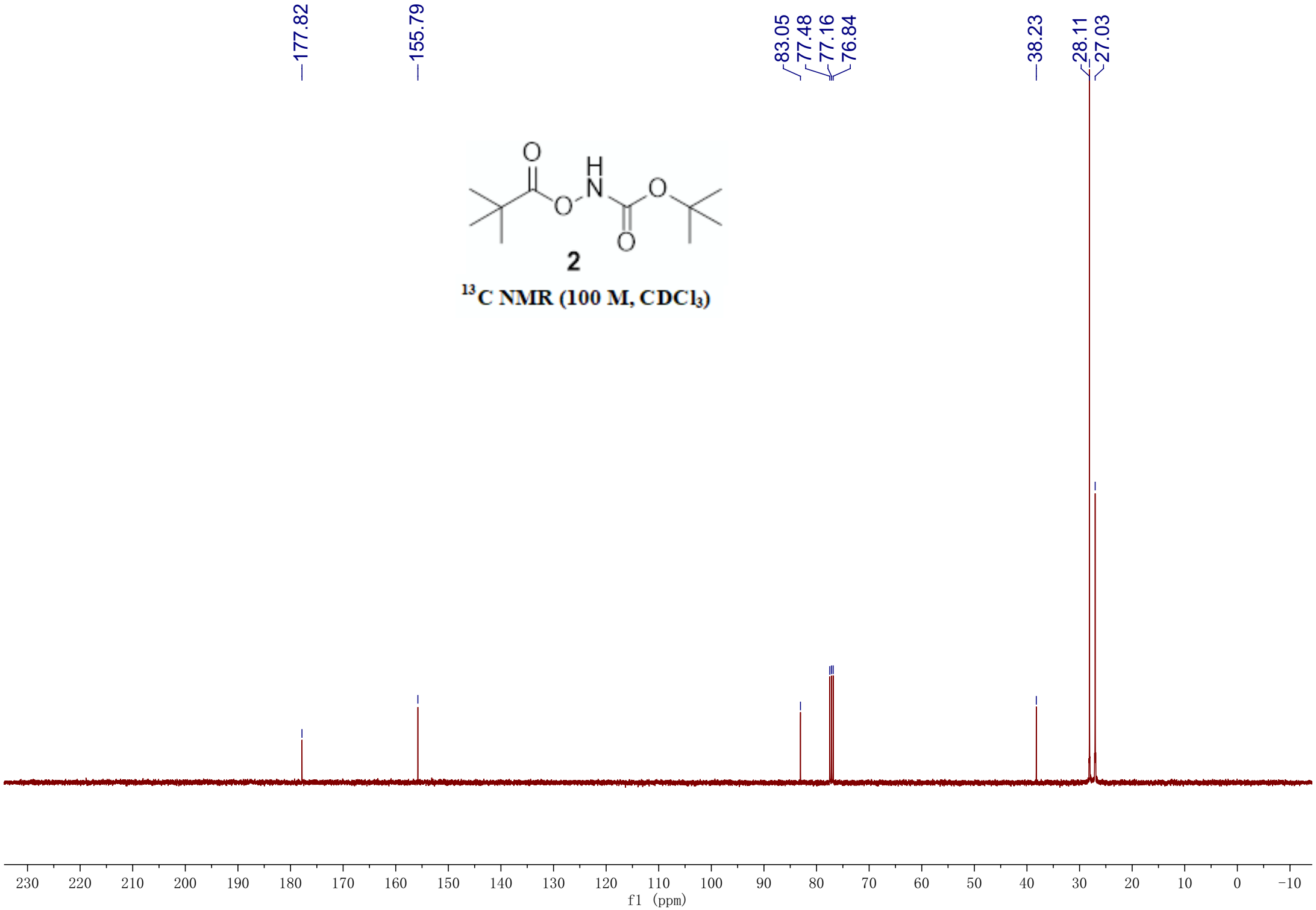
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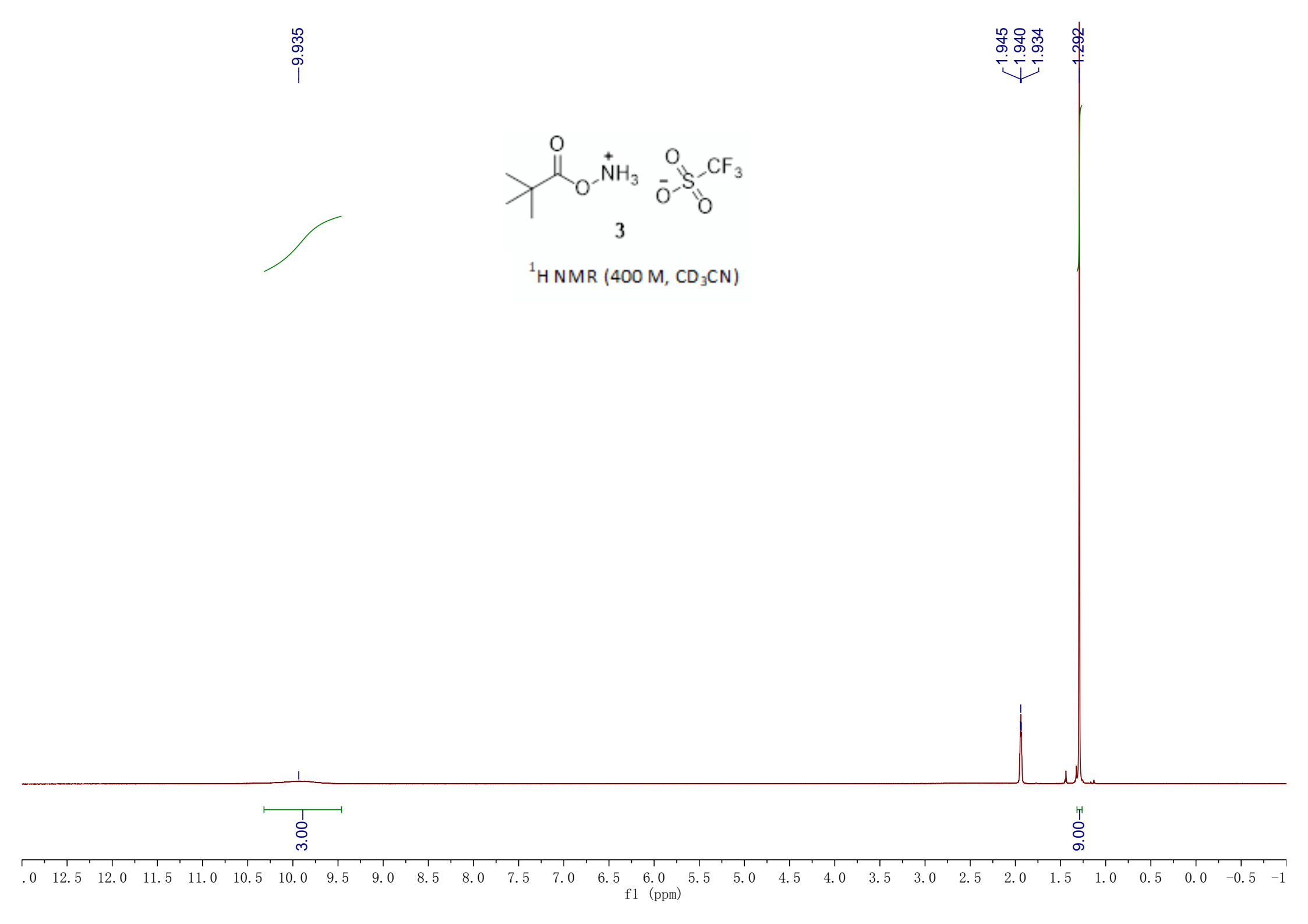
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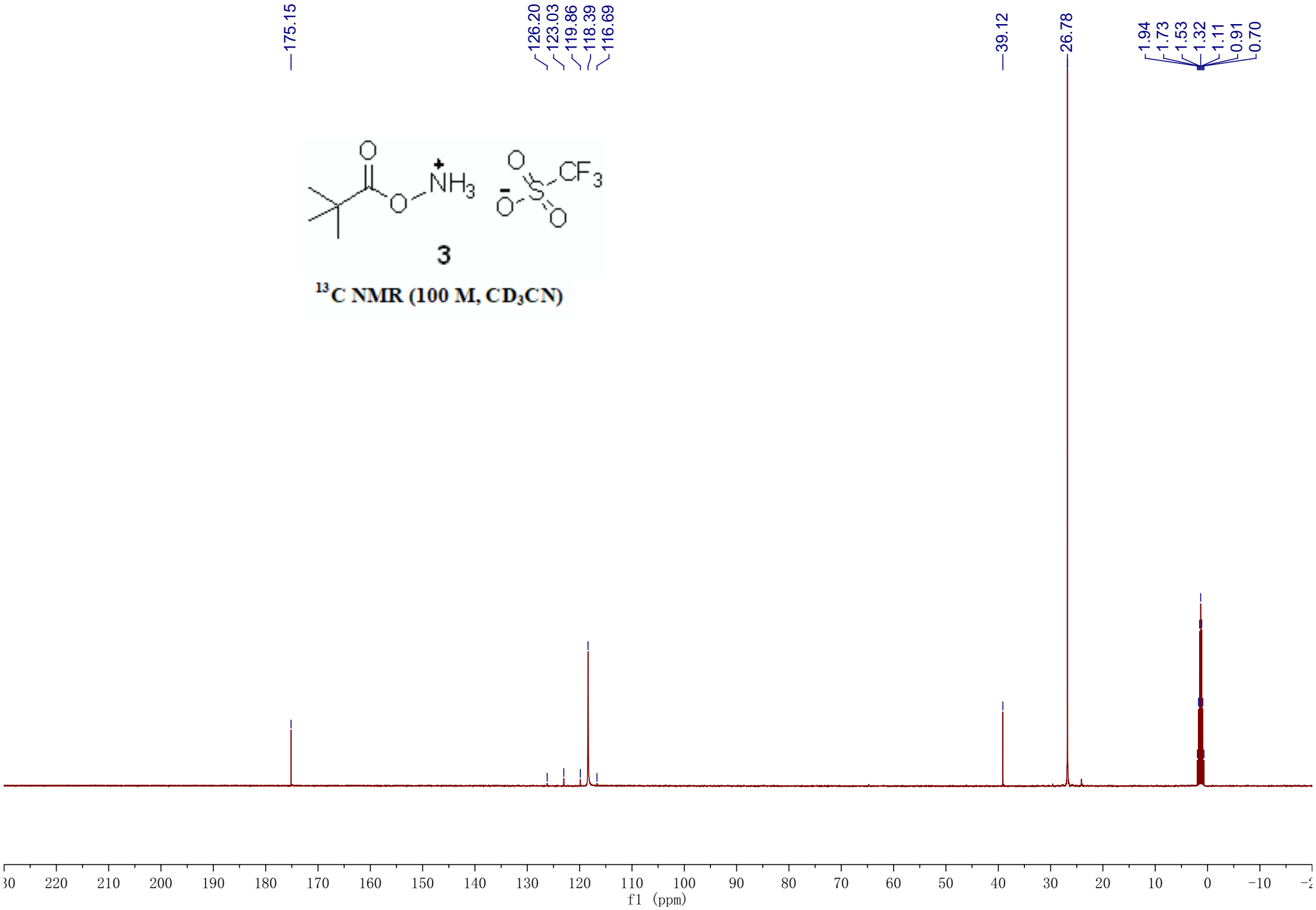

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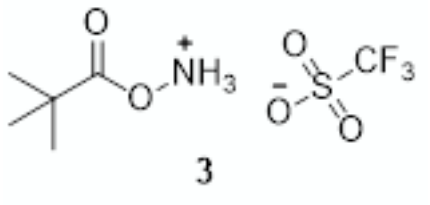

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^{19}F NMR (376 M, CD_3CN)