Organic Syntheses

Water-promoted, Open-flask Synthesis of Amine-boranes: 2-Methylpyridine-borane (2-Picoline-borane)

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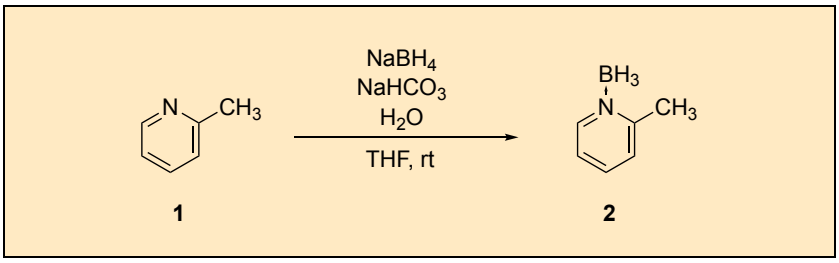
Checked by Hwisoo Ree and Richmond Sarpong



Procedure (Note 1)

A. *2-Methylpyridine-borane (**2**).* A single-necked, air-dried, 500 mL round-bottomed flask is charged with a Teflon-coated, egg-shaped magnetic stir bar (2.6 cm). Sodium borohydride (4.54 g, 120 mmol, 2 equiv) and powdered sodium bicarbonate (20.16 g, 240 mmol, 4 equiv) are weighed and added to the flask via a powder funnel, open to air (Notes 2, 3, and 4). The flask is then charged with 2-methylpyridine (5.93 mL, 60 mmol, 1 equiv) via a syringe, followed by the addition of tetrahydrofuran (100 mL) (Figure 1). The heterogenous mixture is then stirred vigorously at room temperature, followed by the dropwise addition of water (4.3 mL, 240 mmol, 4 equiv) via a syringe over a period of 15 min (Notes 5, 6, 7, and 8). Once the addition of water is complete, tetrahydrofuran (20 mL) is added along the sides of the flask to wash the solids into the reaction mixture (Note 9).

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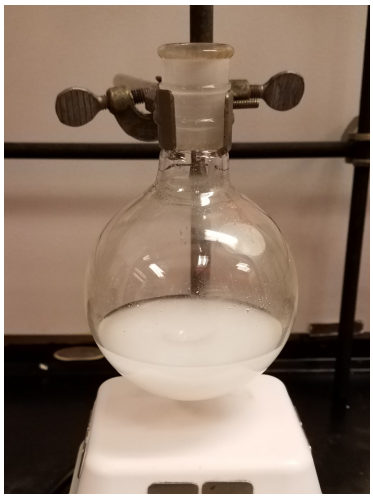


Figure 1. Reaction setup for synthesis of 2

The heterogenous mixture is stirred vigorously for 24 h at room temperature, open to air (Notes 10, 11 and 12) (Figure 2). The contents are filtered under vacuum through a bed of Celite (1-inch-thick) over an 80-mL sintered glass filter of coarse porosity (40-60 μm) (Figure 3).

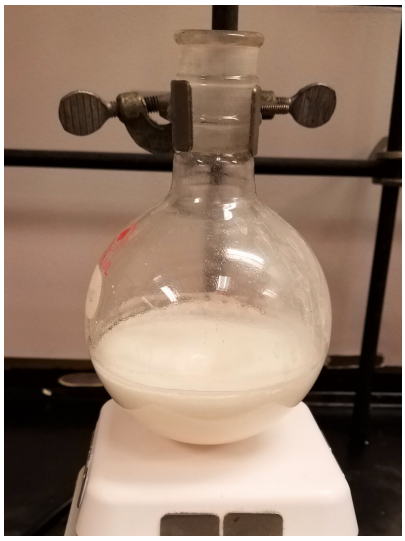


Figure 2. After stirring for 24 h at room temperature

Figure 3. Filtration setup (provided by Checker)

The solid residue on the surface of the reaction flask is dislodged using a spatula and additional tetrahydrofuran (3 x 20 mL) is added to the reaction flask to transfer the residue to the glass filter. The filter cake is then washed with tetrahydrofuran (3 x 20 mL) to extract the product from the filter cake. The tetrahydrofuran extracts are combined in a 500 mL, single-necked, round-bottomed flask and concentrated to dryness by rotary evaporation (Note 13). The product is additionally dried under high vacuum (Note 14) for 12 h to obtain **2** (5.98 g, 93%) (Notes 15, 16, 17, and 18) as a white solid (Figure 4).

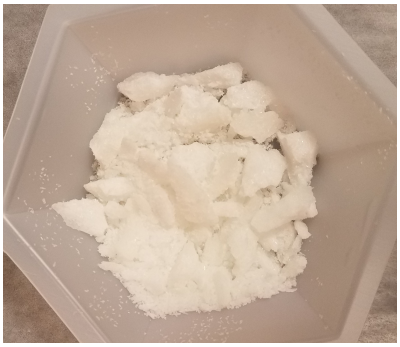


Figure 4. Sample of 2-methylpyridine-borane (2)

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 sodium borohydride, sodium bicarbonate, 2-methylpyridine, tetrahydrofuran, celite and ethyl acetate.
2. The following reagents were purchased from commercial sources and used without further purification: Sodium borohydride (powder, >99%, Sigma-Aldrich) and tetrahydrofuran (ACS reagent, >99%, contains 250 ppm BHT as inhibitor). Deionized water was used for the addition.
3. Sodium bicarbonate (powder, ACS grade, Macron fine chemicals) was finely powdered before use (Figure 5), utilizing a mortar and pestle until no crystalline solid was visible. The Submitters report longer reaction times and decreased (5-10%) yields will result if the sodium bicarbonate is not powdered.

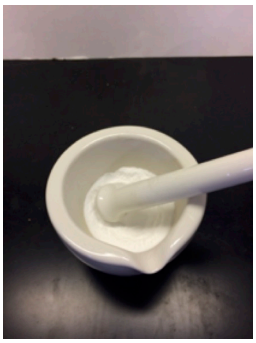


Figure 5. Powdered sodium bicarbonate (provided by Checker)

4. 2-Methylpyridine (98%, Sigma-Aldrich) was distilled under nitrogen over KOH pellets prior to use.
5. The reaction should be carried out in a well-ventilated hood due to the hazards associated with hydrogen gas and carbon dioxide released during the reaction.
6. The reaction is exothermic in nature and a room temperature water bath may be used for reactions conducted on a scale larger than what is described here.
7. The addition of water leads to frothing due to the evolution of hydrogen gas. If there is appreciable froth formation, small portions of water can be added periodically over 15 min rather than continuous dropwise addition.
8. For reactions on a smaller scale (up to 5 mmol of amine), water is added as a solution in tetrahydrofuran.
9. If necessary a spatula can be used to scrape the solids off the sides of the flask.
10. The reaction progress is monitored by TLC analysis (EtOAc 100%, starting material R_f = 0.5, product R_f = 0.85) and ^{11}B NMR spectroscopy. A reaction aliquot is withdrawn using a glass pipette and a drop of DMSO is added to solubilize all of the sodium borohydride prior to ^{11}B NMR spectroscopic analysis. ^{11}B NMR (193 MHz, $CDCl_3$) δ: –12.79 (q, J = 98.8 Hz)
11. Due to the highly heterogenous nature of the reaction, the reaction times can vary. The reaction is run for 24 h to ensure completion. Longer reaction times do not affect the reaction yield or product purity. When performed on a 5 mmol scale (with respect to the amine), the reaction was complete in 4 h.

12. The reaction flask can be closed using a rubber septum attached to a vent through a needle.
13. Pressure: 40 mmHg; Bath temperature: 35 °C.
14. Pressure: 1 mmHg; Temperature: room temperature.
15. A half scale reaction provided 2.82 g (88%) of the product.
16. Characterization data for **2**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.23–2.27 (br q, BH_3), 2.75 (s, 3H), 7.29 (t, *J* = 6.7 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 8.74 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 22.7, 122.6, 126.9, 139.6, 148.9, 158.0, ^{11}B NMR (193 MHz, $CDCl_3$) δ: –13.85 (q, *J* = 97.9 Hz). IR (ATR, thin film): 3081, 2987, 2370, 2304, 2260, 1617, 1480, 1459, 1183, 1152, 938, 764 cm^{-1}. mp 44-46 °C. HRMS (ESI+) *m*/*z* calc'd for C_6H_7BN $[M - 1]^+$: *m*/*z* 106.0823, found: 106.0826. The purity of the compound was determined to be 98.1% by quantitative ^{1}H NMR analysis using 6.5 mg of dimethyl fumarate (purity: 99.3%) as the standard and 14.5 mg of **2**. Two signals for **2** were selected (8.76 and 7.82 ppm) and the average value of their peak integral area was used for calculations.
17. Product **2** contains minor amounts (<0.3%) of 2,6-di-*tert*-butyl-4-methylphenol (BHT) from the solvent THF. Using inhibitor-free THF provides **2** with no BHT contamination.
18. Recommended storage conditions: Recommended storage temperature: 2–8 °C. Keep container tightly closed in a dry and well-ventilated location. Do not allow product to contact water during storage. Store separately from acids or oxidants. Samples of **2** have been stored without exclusion of air over a year without evidence of significant decomposition by ^{11}B NMR spectroscopic analysis. The product should not be added to any waste containing acids or oxidants due to the potential formation of dihydrogen and other gases.

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

Amine-boranes, classic examples of a Lewis base-Lewis acid adduct, were first synthesized eight decades ago.[2,3] Their air and moisture stability has enabled their use as safe borane carriers.[4] An array of organic transformations, such as hydroboration,[5] reduction,[6] reductive amination,[7] borylation,[8] B-H insertion,[9] etc. also utilize amine-boranes as reagents (Figure 6). Their high hydrogen content and energy density has led to their investigation as safe hydrogen storage materials[10] and green hypergolic propellants.[11] Recently, the dehydrocoupling of amine-boranes for the synthesis of polyaminoboranes has garnered considerable attention.[12]

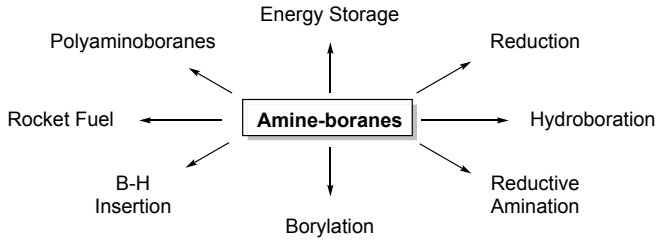
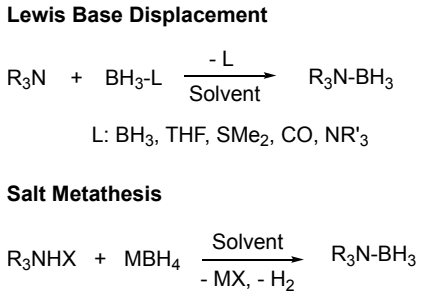


Figure 6. Applications of amine-boranes

2-Methylpyridine-borane, in particular, has been employed as a safe and relatively non-toxic alternative to sodium cyanoborohydride[13] and pyridine-borane[14] for reductive amination of aldehydes and ketones.[15] In addition, reductive amination with aldehyde bisulfites[16] and carbohydrates[17] using **2** has also been reported. Some other applications of **2** include reductive alkoxyamination,[18] reductive alkylation of hydrazine[19] and amino acid derivatives,[20] synthesis of nanoparticles,[21] chemical functionalization of alginates,[22] DNA cross-linking,[23] labeling of oligosaccharides,[24] and protein PEGylation.[25]

The development of synthetic routes to amine-boranes has not kept pace with the progress in their applications (Scheme 1). The most common route to amine-boranes remains the displacement of a Lewis base by an amine from borane complexes, such as borane-tetrahydrofuran or borane-dimethyl sulfide.[2] However, these adducts are pyrophoric and toxic, restricting their large-scale use. On the other hand, the stable borane-ammonia adduct requires refluxing in THF for the trans-amination to occur.[26]



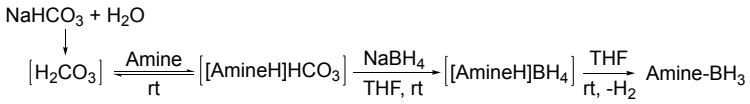
Scheme 1. Routes to synthesize amine-boranes

An alternate route to amine-boranes is via the metathesis of metal borohydrides with alkylammonium salts.[27] However, $LiBH_4$ is a flammable solid necessitating the use of inert reaction conditions, whereas, the air stable $NaBH_4$ is poorly soluble in common ethereal solvents, severely restricting the generality of the reaction. Moreover, several alkylammonium salts are not readily available. To overcome the solubility issue with $NaBH_4$, the relatively expensive dimethoxyethane has been utilized as the solvent[28] or 18-crown-6[29] or benzoic acid[30] have been used as additives.

We recently described a direct synthesis of amine-boranes from $NaBH_4$, $(NH_4)_2SO_4$, and the corresponding amines in THF.[31] Yet, the reaction

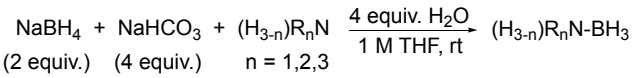
necessitated the use of refluxing conditions due to the synthesis of borane-ammonia as the by-product. Also, none of the above-mentioned methods can be effectively used for the synthesis of amine-boranes bearing borane reactive functionalities. If accessible, these functionalized amine-boranes could not only act as novel reagents for organic synthesis but also function as tailored materials for surface modification, energy storage, and various other applications. Moreover, development of such a reaction methodology could expand the scope of borane as an amine-protecting group.

To bring this methodology to fruition, we had to overcome the two disadvantages of the salt metathesis route; poor solubility of reagents in ethereal solvents and the lack of commercial availability of a number of alkylammonium salts. To address the latter, we envisaged an in-situ preparation of alkylammonium salts from the corresponding amines via treatment with a mild acid, such as carbonic acid prepared from sodium bicarbonate and water (Scheme 2). The alkylammonium salts would then undergo metathesis with $NaBH_4$, followed by dehydrogenation to provide the target amine-boranes. We believed that the added water should also provide a suitable reaction environment to solubilize the inorganic reagents, facilitating salt metathesis. The success of our proposal would rely on the ready capture of the amine by carbonic acid prior to its decomposition and the stability of $NaBH_4$ under the mildly acidic reaction conditions.



Scheme 2. Proposal for amine-borane synthesis

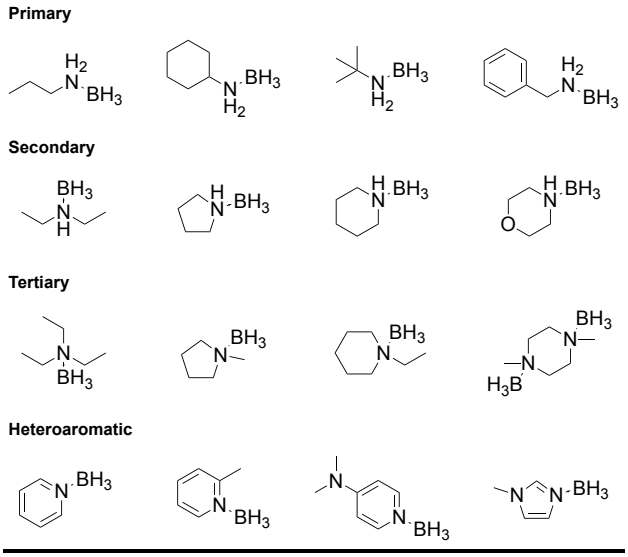
Delightfully, the preliminary reaction using $NaBH_4$, $NaHCO_3$, triethylamine, and water in tetrahydrofuran furnished triethylamine-borane in good yields. Several mono and dibasic mineral acid salts were then screened to improve product yields, but to no avail. Next, we proceeded to examine the effect of the stoichiometry of reagents on the reaction outcome. Near quantitative yields of the amine-borane were obtained with 2 equiv. $NaBH_4$, and 4 equiv. each of $NaHCO_3$, and water for an equiv. of the amine in THF at 1 M concentration (with respect to $NaBH_4$) (Scheme 3). An excess of $NaBH_4$ is required since a portion of it is hydrolyzed by the carbonic acid formed during the reaction.



Scheme 3. Optimized reaction conditions

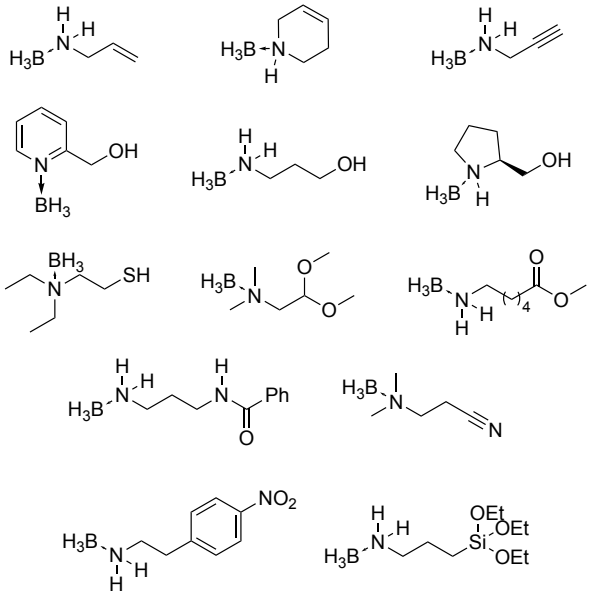
Under the optimized conditions, several primary, secondary, and tertiary alkylamines as well as heteroaromatic amines underwent conversion to the corresponding amine-boranes (Table 1).

Table 1. Substrate scope for alkyl and heteroaromatic amines



Having accomplished a mild synthesis of amine-boranes without the intermediacy of borane-Lewis base adducts, amines bearing borane-reactive functional groups were included as substrates. Pleasantly, amines containing functionalities, such as alkene, alkyne, hydroxyl, thiol, ester, amide, nitrile, and nitro all furnished the corresponding amine-boranes (Table 2). Thus, the above described methodology represents the first general synthesis of unfunctionalized as well as functionalized amine-boranes from $NaBH_4$ and the corresponding amines. [32]

Table 2. Substrate scope for functionalized amines



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Appendix
Chemical Abstracts Nomenclature (Registry Number)

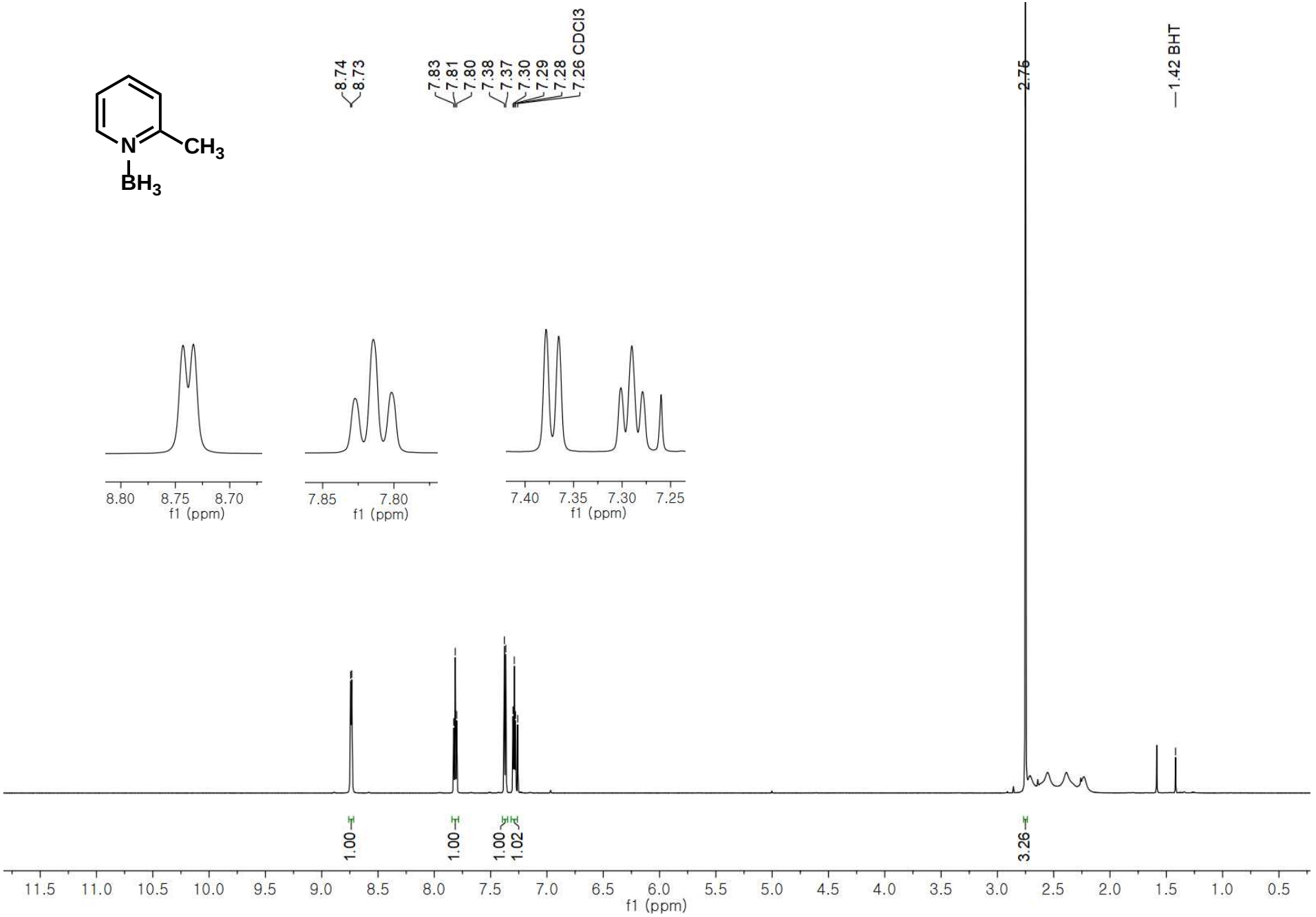
2-Methylpyridine: Pyridine, 2-methyl-; (109-06-8)
Sodium borohydride: Borate(1-), tetrahydro-, sodium (1:1); (16940-66-2)
Sodium bicarbonate: Carbonic acid sodium salt (1:1); (144-55-8)
2-Methylpyridine-borane: Boron, trihydro(2-methylpyridine)-, (T-4)-; (3999-38-0)

Dr. Ameya S. Kulkarni received his B. Tech. in Pharmaceutical Chemistry and Technology from the Institute of Chemical Technology, Mumbai, India in 2012. He received his Ph. D. under the guidance of Professor P. V. Ramachandran at Purdue University in 2017. His research focuses on the chemistry of amine-boranes with an application to organic synthesis and energetic materials.

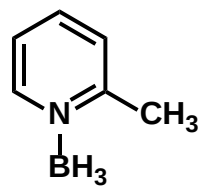
Prof. P. V. Ramachandran received his B. Sc. and M. Sc. from the University of Calicut, India and his Ph. D. from the Indian Institute of Technology, Kanpur under the tutelage of Prof. Subramania Ranganathan. Subsequently he joined the laboratories of Prof. Herbert C. Brown at Purdue University as a postdoctoral fellow. He began his academic career at Purdue in 1997 where he is currently a Professor of Chemistry. His research interests are in the areas of organoborane and fluoroorganic synthetic methodologies.

Hwisoo Ree received her B. S. and M. S. from Korea University with Prof. Hak Joong Kim, and is currently a Ph. D. student in the laboratories of Prof. Richmond Sarpong at UC Berkeley. Her research focuses on natural product synthesis.

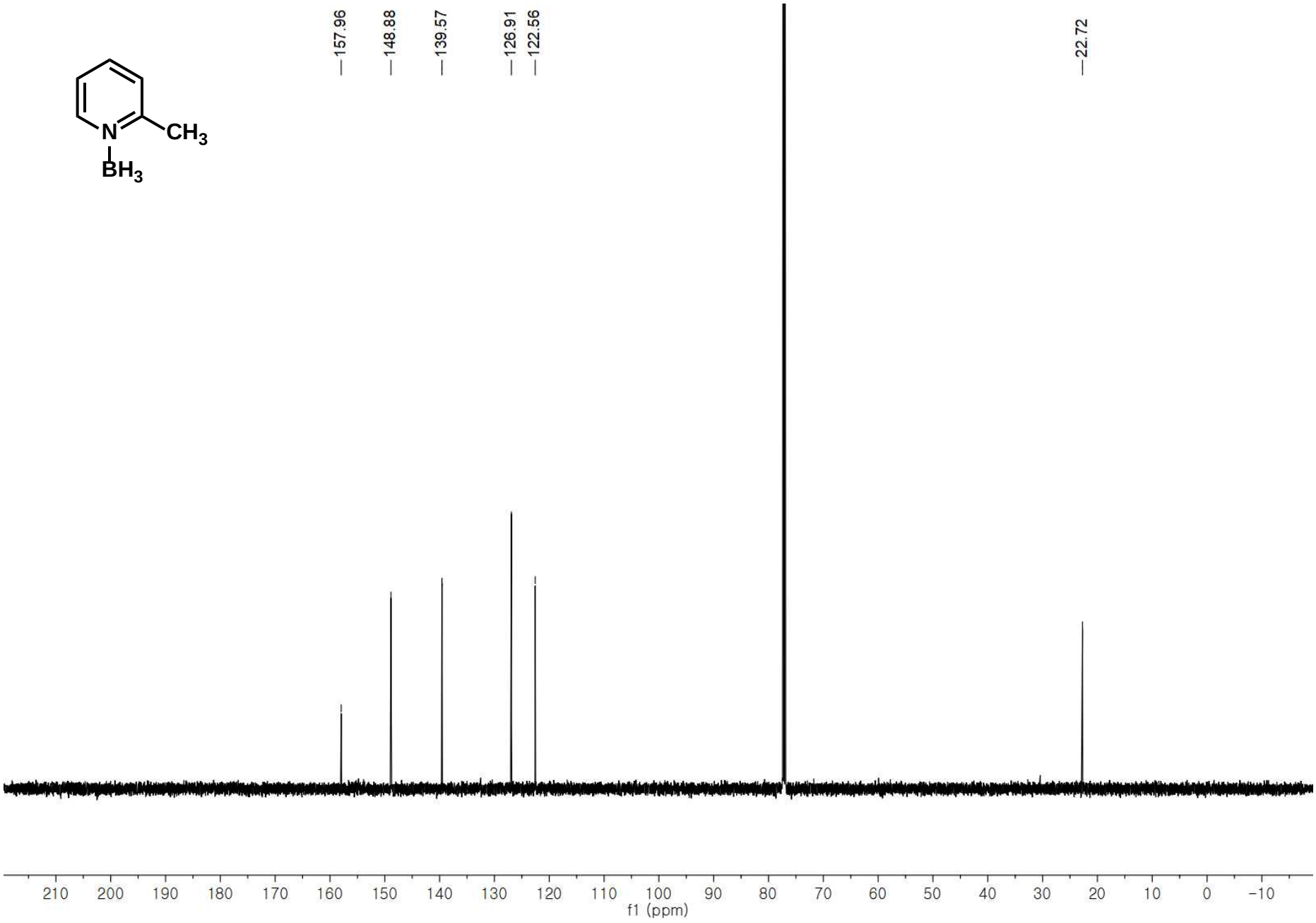
2-Methylpyridine-borane (^{1}H NMR, 600 MHz, $CDCl_3$)



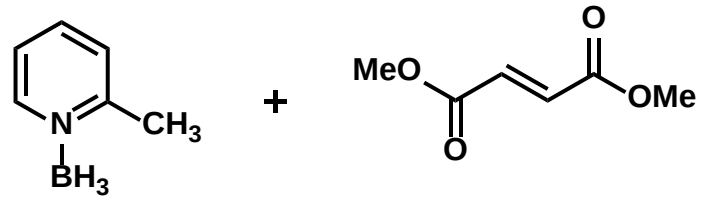
2-Methylpyridine-borane (^{11}B NMR, 193 MHz, $CDCl_3$)



2-Methylpyridine-borane (^{13}C NMR, 150 MHz, $CDCl_3$)



2-Methylpyridine-borane + Dimethylfumarate (^{1}H NMR, 600 MHz, $CDCl_3$)



+

$$\text{Molar ratio} = \frac{1}{\frac{0.673}{2}} = 2.97$$

$$mg_{cpd} = 14.5\ mg$$

$$mg_{std} = 6.5\ mg$$

$$P_{std} = 0.993$$

$$wt\% = \frac{6.5\ mg \times 106.96\ g/mol \times 2.97 \times 0.993}{14.5\ mg \times 144.13\ g/mol} = 98.1\%$$