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# Practical and Regioselective Synthesis of C4-Alkylated Pyridines

Jin Choi<sup>†</sup>, Gabriele Laudadio<sup>†</sup>, Edouard Godineau<sup>††</sup>, Phil S. Baran<sup>\*†</sup>

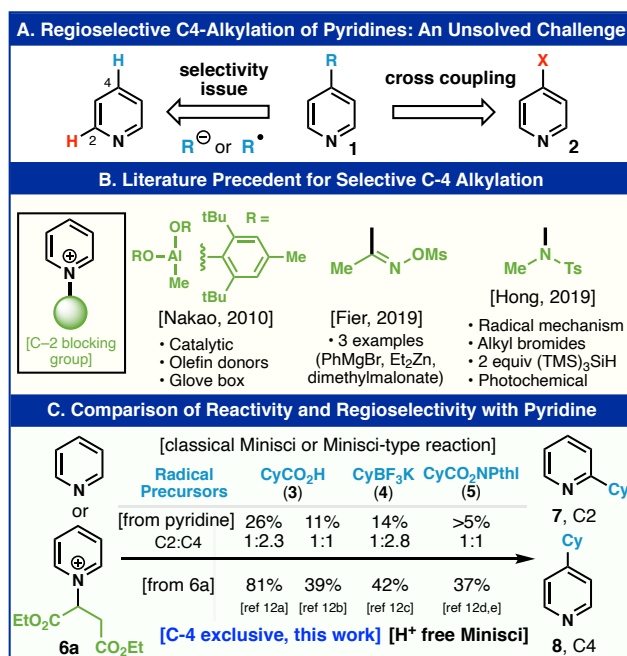
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**ABSTRACT:** The direct position-selective C–4 alkylation of pyridines has been a longstanding challenge in heterocyclic chemistry, particularly from pyridine itself. Historically this has been addressed using pre-functionalized materials to avoid overalkylation and mixtures of regioisomers. This study reports the invention of a simple maleate-derived blocking group for pyridines that enables exquisite control for Minisci-type decarboxylative alkylation at C–4 that allows for inexpensive access to these valuable building blocks. The method is employed on a variety of different pyridines and carboxylic acid alkyl donors, is operationally simple, scalable, and is applied to access known structures in a rapid and inexpensive fashion. Finally, this work points to an interesting strategic departure for the use of Minisci chemistry at the earliest possible stage (native pyridine) rather than current dogma that almost exclusively employs Minisci as a late-stage functionalization technique.

The power of C–H functionalization logic in the context of synthesizing heteroaromatic structures is undeniable.<sup>1</sup> Its increasing utility in discovery and medicinal chemistry contexts is a testament to its utility in late-stage derivatization enabling structure activity relationships to be rapidly explored.<sup>2</sup> In particular, the venerable Minisci reaction and its many variants have long been recognized as a way to bypass pre-functionalized heterocycles.<sup>3</sup> Just as the Friedel-Crafts reaction is commonplace for electron rich arene functionalization via electrophilic substitution, free radicals can react with electron deficient heterocycles by capitalizing on innate reactivity.<sup>4</sup> In cases where a heterocycle has multiple sites to intercept a free radical, mixtures often result which can be useful in a discovery setting but is problematic when a singular regiochemical outcome is desired (e.g. process scale).<sup>5</sup> For example, simple 4-alkylated pyridines (**1**, Figure 1A) are inaccessible using Minisci chemistry if a single regioisomer is desired. In such cases, prefunctionalization is necessary and the logical synthon is halopyridine **2**. This conundrum has rendered the early-stage application of Minisci chemistry on pyridine and mono-substituted pyridines rare in medicinal chemistry and, to our knowledge, non-existent on process scale. A recent collaborative program<sup>6</sup> within the agrochemical industry brought to our attention the need for a simple and inexpensive solution to this unmet challenge in pyridine alkylation for which available methods were not applicable. To be sure, several attempts to solve this problem from unfunctionalized starting materials have appeared over the past decade (Figure 1B) mostly based on blocking competitive C–2 sites using transient or covalently linked species at the pyridine nitrogen.<sup>7</sup> Nakao's pioneering studies using bulky Al-based Lewis-acids in an elegant hydroarylation process is limited to olefin donors and must be performed in a glove box.<sup>8</sup> The Fier group at Merck invented clever oxime-based pyridinium species that could be employed in three examples of C–C bond formation with carbon-based nucleophiles.<sup>9</sup> Finally, the

Hong group reported a radical-type addition using *N*-sulfonamidopyridinium species<sup>10</sup> using alkyl bromide donors requiring photochemical initiation and super stoichiometric amounts of an expensive silane [(TMS)<sub>3</sub>SiH].<sup>11</sup> While this is an important precedent it could not be employed easily on process scale as three steps are needed to install the blocking group (1. *N*-amination using hydroxylamine-*O*-sulfonic acid, 2. tosylation, and 3. methylation with Meerwein's salt along with 1 column purification, 1 recrystallization). The Buchwald group reported a Cu-catalyzed, selective C4 functionalization of pyridine with styrenes without a covalent blocking group, via a novel intramolecular rearrangement mechanism mediated by a pyridine coordinated copper species.<sup>7e,7h</sup> Herein we disclose a highly practical method featuring on a new blocking group based on a simple fumarate backbone (**6a**) enabling classic Minisci decarboxylative alkylations to take place with exquisite selectivity at C–4 (Figure 1C) under acid-free conditions. Emblematic of this advance is the preparation of 4-cyclohexylpyridine (**8**) which cannot be accessed from pyridine in a synthetically useful yield and as a mixture of isomers under four different Minisci-type conditions.

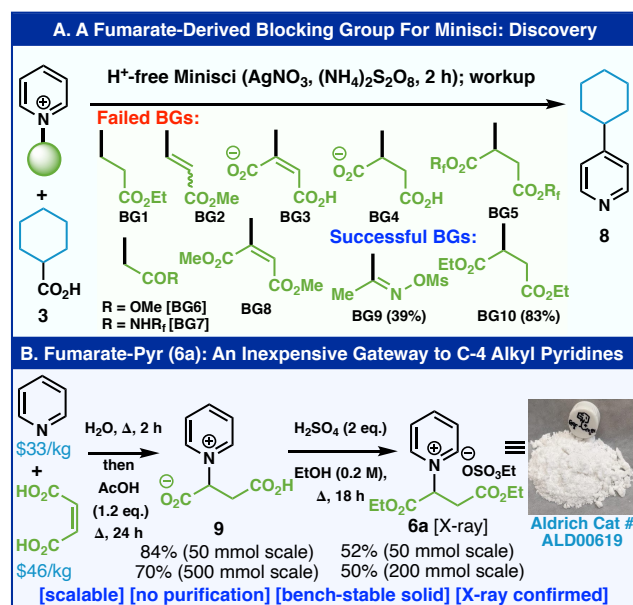


**Figure 1.** (A) An unsolved challenge in the field of Minisci reaction. (B) Literature precedent. (C) Comparison experiment with pyridine

Tactically, scalable access to valuable structures such as **8** (81% isolated yield from **6a**) can now be enabled with a dramatic reduction in cost. From a strategic perspective, this work opens a new

dimension of retrosynthetic logic for use of the Minisci transform at an early rather than late stage.

Guided by colleagues at Syngenta (E.G.) several criteria needed to be met for a practical blocking group (BG) design, such as: (1) derivation from feedstock materials (ca. \$5/mole), (2) simple installation and removal, (3) high stability, ease of handling, and solubility in multiple solvents, and most critically, (4) complete regiochemical control to avoid the need for any chromatography. Towards this end, multiple BGs were explored with most falling into one of two categories (Figure 2A): (1) simple BG installation with either modest or low reactivity under Minisci conditions (**BG1**, **2**, **4**, **6**) or (2) difficulty in forming a stable BG adduct. After extensive exploration, **BG10** emerged as an ideal candidate satisfying all of the criteria laid out above. **BG9** was the only other moderately successful one however it exhibited reduced reactivity towards Minisci addition. The preparation of pyridinium **6a** with **BG10** could be prepared through a simple, chromatography-free, two-step sequence starting from commodity materials (pyridine and maleic acid) followed by esterification. The structure of pyridinium **6a** was confirmed by X-ray crystallography and contained the ethyl sulfonate as a counter-anion. This crystalline salt represents a straightforward gateway to a variety of C-4 alkylated pyridines (*vide infra*) and has been commercialized by Sigma-Aldrich (catalog # ALD00619).



**Figure 2.** (A) Fumarate-derived blocking group for Minisci reaction in discovery stage (B) The pyridinium **6a** as an inexpensive gateway to C4 alkylated pyridine synthesis.

The generalization of this fumarate-based BG approach is illustrated in Table 1 using acid-free Minisci conditions on a range of primary, secondary, and tertiary carboxylic acids. Although these C-4 alkylated pyridines appear simple, it is instructive to comment on the means by which such compounds were previously prepared. In nearly all cases the current method represents a more practical and cost-effective solution. In the case of primary carboxylic acid adducts, pyridine **11** was accessed from prefunctionalized 4-methylpyridine via lithiation-S<sub>N</sub>2 with corresponding alkyl bromide (ca. \$105/g<sup>13b</sup>).<sup>14</sup> Pyridine **12** was obtained through an analogous sequence using an alkyl bromide containing a protected alcohol requiring subsequent deprotection and chlorination (ca. \$945/g<sup>13b</sup>).<sup>15</sup> Pyridine **13**, **14** and **17** were previously prepared via photochemical addition on 4-vinyl pyridine.<sup>16</sup> Pyridine **15** required a Pd-cross coupling on either 4-vinyl or 4-bromopyridine (Heck<sup>17a</sup>

or Sonogashira,<sup>17b</sup> respectively) followed by reduction (ca. \$530/g<sup>13c</sup>). Similarly, pyridine **16** can be accessed via reduction of the Heck product of 4-vinylpyridine and an aryl iodide.<sup>18</sup>

Numerous secondary carboxylic acids were employed to access such pyridines with high simplicity when placed in context. For example, pyridine **8** has been prepared multiple times leading either to mixtures (e.g., Figure 2B) or requiring pre-functionalized pyridines (ca. \$584/g<sup>13d</sup>).<sup>19</sup> Similarly, pyridine **18** has been accessed from 4-bromopyridine through photochemical and electrochemical reductive couplings or by employing Hong's BG (Figure 1B) and a Hantzsch ester radical precursor<sup>10b</sup> (ca. \$150/g<sup>13c</sup>). Pyridine **21** has been accessed either via cross coupling/Hydrogenation<sup>20a</sup> or C4-selective Grignard addition using TBSOTf to generate a transient BG and reoxidation<sup>20b</sup> (ca. \$100/g<sup>13b</sup>). Cyclopropyl containing pyridine **23** was accessed either from 4-bromo or 4-Bpin pyridine via Suzuki or Grignard addition/rearomatization (ca. \$226/g<sup>13a</sup>).<sup>21</sup> The trivial cyclohexanone pyridine **25** has only been accessed in a controlled fashion using multistep routes with protecting groups and FG manipulations (ca. \$871/g<sup>13c</sup>).<sup>22</sup>

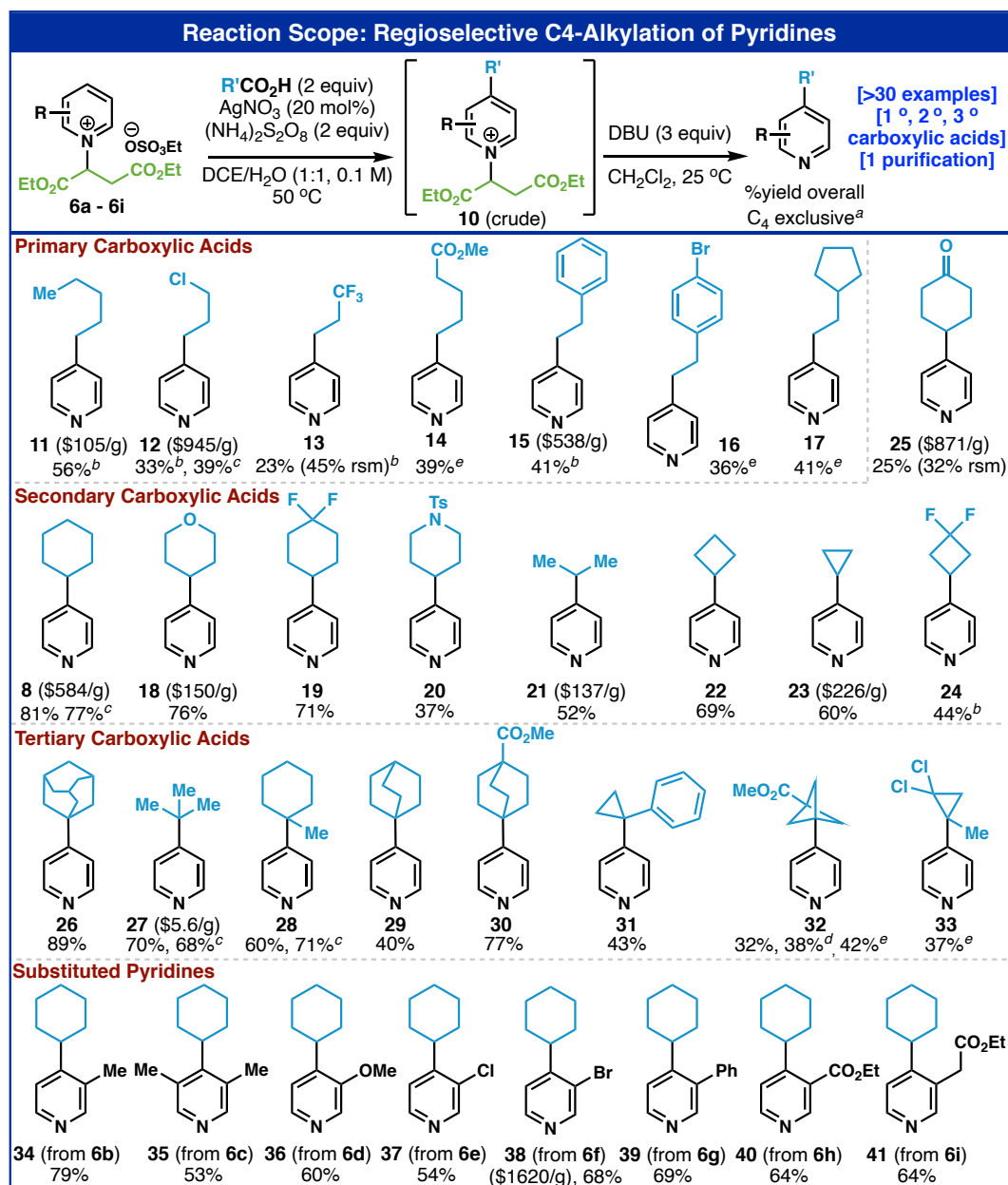
Many of the quaternary center containing C-4 alkylated pyridines (derived from tertiary carboxylic acids) prepared here are new (**29-33**) and are likely desirable starting materials for medicinal chemistry programs. Of the known alkylated pyridines in this series, two were prepared as mixtures of regioisomers using radical chemistry (**26** and **28**)<sup>23,24</sup> or via Minisci addition to 4-cyanopyridine.<sup>25</sup>

The chemistry outlined above is not limited to the parent pyridine **6a** but can also be employed on mono (**6b**, **6d-i**) or bis (**6c**) substituted pyridines. Pyridines **35**, **39**, and **41** are new compounds and might be challenging to access controllably from the parent pyridines in other ways. Pyridines such as **37**, **38** (ca. \$1620/g<sup>13g</sup>), and **40** have previously been synthesized either through Grignard addition/oxidation sequences<sup>7c</sup> or via Hong's HAT-based method<sup>10d</sup> employing BG's similar to that in Figure 1B.

It is worth noting that pyridines **8**, **12**, **27** and **28** have been prepared on a gram-scale with no significant reduction in yield. The limitations of this reaction (see SI for full disclosure) stem from the acidic conditions used to install the BG and a lack of tolerance for preexisting C-2 functionality.

Having facile access to pure C-4 alkylated pyridines open up a new opportunity for early-stage Minisci chemistry to be employed in the synthesis of 2,4-difunctionalized systems. Historically, such heterocycles are prepared by employing Minisci at the end of a sequence in order to obtain more regioselective outcomes. As shown in Figure 3A, a reversal of this traditional choreography is now feasible. Thus, adduct **8** can be submitted to known C-2 selective pyridine functionalizations such as carbamoylation<sup>26</sup>, cyanation<sup>9</sup>, and amidation<sup>27</sup> to afford pyridines **42**, **43**, and **44**, respectively. This sequence of events is general and can be utilized to obtain **46** (Minisci followed by borono-Minisci<sup>28</sup>), **47** and **48** (double Minisci), and **49** (Minisci followed by amidation). Conventional retrosynthesis of such compounds would likely involve pre-functionalized handles for controlling regiochemistry whereas in the present case innate reactivity and the fumarate-BG overcomes this challenge.

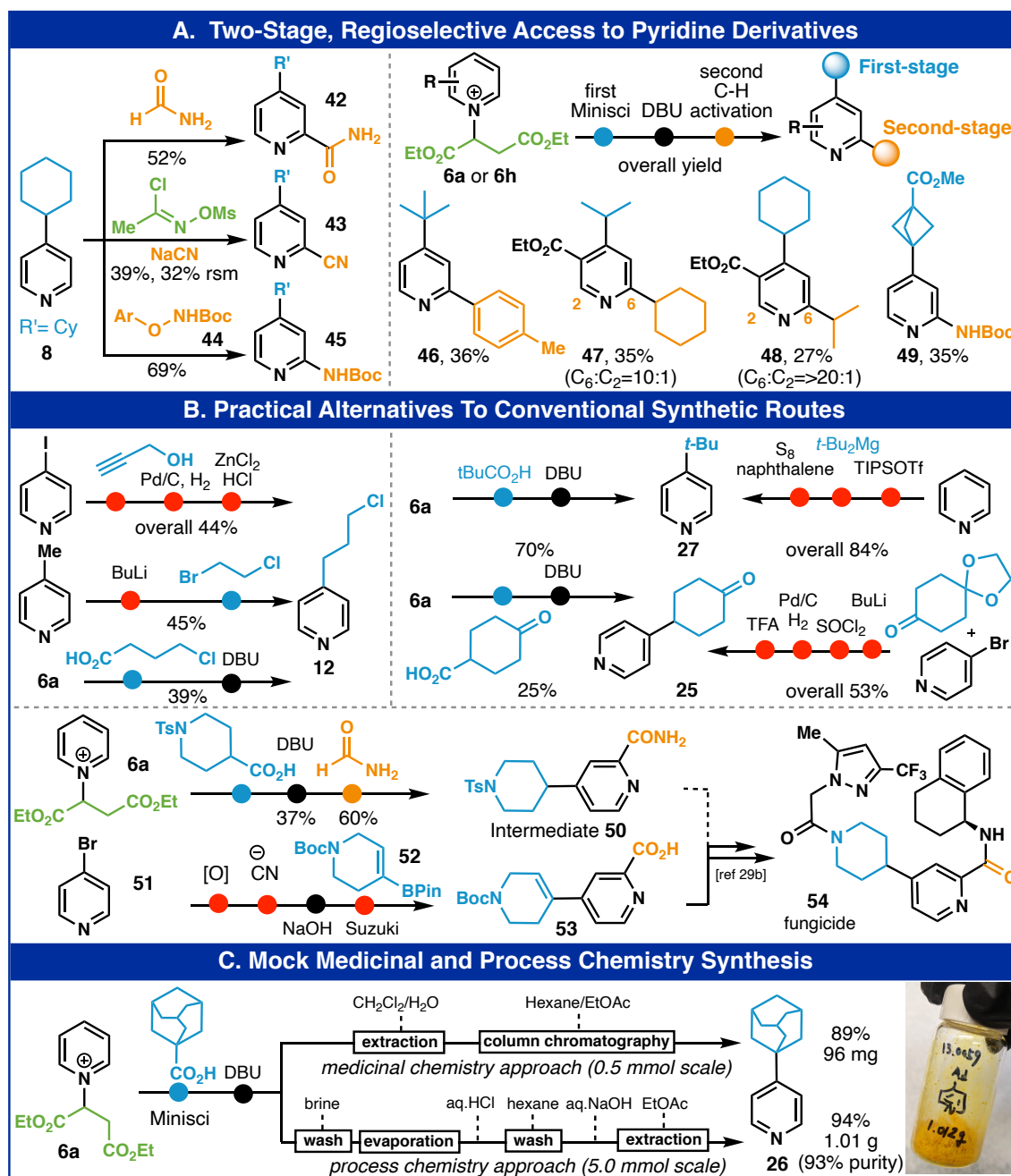
As mentioned above (Table 1), many of the pyridines reported herein have been prepared by less direct pathways and this is graphically depicted for pyridines **12**, **27**, and **25** in Figure 3B. The avoidance of pre-functionalized pyridines, pyrophoric reagents, and expensive transition metals are highlights of this method. Moreover, a proof of concept is shown for how the fungicide (oomycetes) candidate **54** could conceivably be accessed in a far more practical way



**Table 1.** Reaction scope of the regioselective Minisci reaction. a) **6a** (0.5 mmol), carboxylic acid (1.0 mmol), AgNO<sub>3</sub> (20 mol%), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (1.0 mmol), DCE: H<sub>2</sub>O=1:1, 0.1 M, 50 °C, 2 h. The regioselectivity was determined by crude NMR after first step and confirmed again after final purification step. b) using carboxylic acid (2.0 mmol, 4 equiv) on the Minisci reaction step and DBU (3.0 mmol, 6 equiv) on the removal step. c) 5.0 mmol scale reaction. d) carboxylic acid was used as a limiting reagent. e) performed in 0.3 M. See Supporting Information for detailed experimental procedures.

from pyridine. Prior studies employed chemistry that was cost-prohibitive for the agrochemical industry commencing from **51** and employing expensive boronate ester **52**, N-oxide chemistry, toxic TMSCN, and a Pd catalyst to access 1,3-disubstituted **53** which required a subsequent hydrogenation to remove the 3,4-unsaturation.<sup>29</sup> In contrast, the two-stage Minisci approach from **6a** accesses a synthetically equivalent intermediate **50** directly without any of those drawbacks. Finally, as a demonstration of practicality in both medicinal and process scenarios pyridine **26** can be prepared and purified either through column chromatography or through a simple extraction/washing protocol.

To summarize, a simple solution to the longstanding challenge of practical C-4 alkylation of pyridines has been presented using a simple blocking group derived from inexpensive maleic acid. The resulting pyridinium species is stable and, in many instances, crystalline. The resulting functionalization can be accomplished using classic Minisci conditions without the addition of any acid and proceeds to give a singular adduct at C-4. The scope of this reaction is broad and can be strategically used in concert with other functionalizations or as a stand-alone method to provide high value pyridines that despite their trivial appearance, have posed challenges for direct and inexpensive synthesis in a scalable way.



**Figure 3.** (A) Two-stage derivatization. (B) Practical alternatives to conventional synthetic routes. (C) Mock medicinal and process chemistry synthesis. See Supporting Information for detailed experimental procedures.

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### Notes

The authors declare no competing financial interest.

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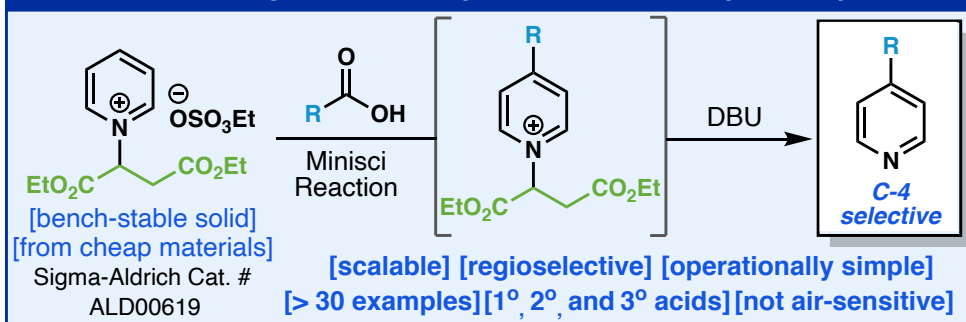
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## Practical and Regioselective Synthesis of C-4 Alkylated Pyridines



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# Supporting Information

## Practical and Regioselective Synthesis of C4-Alkylated Pyridines

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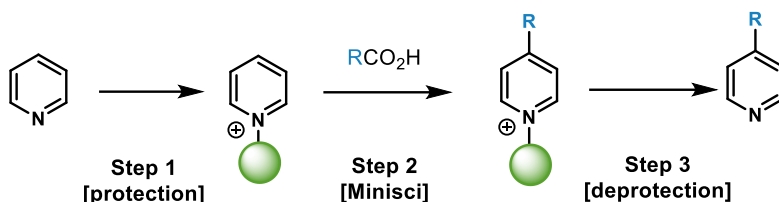
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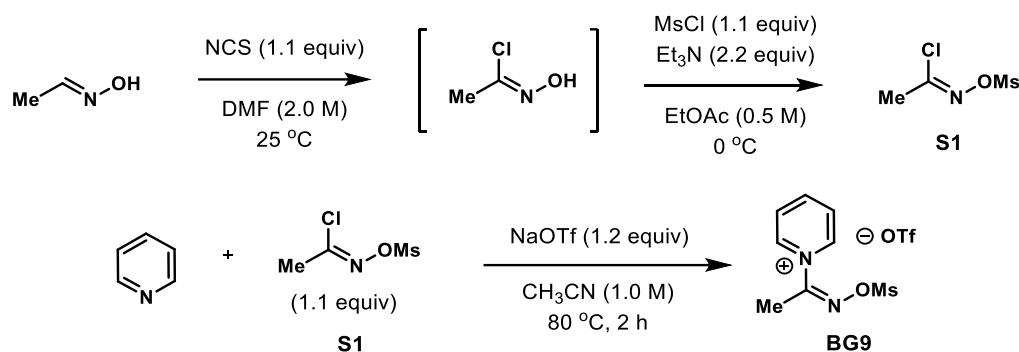
## 1. General Information

Reagents were purchased at Combi-Blocks, Sigma-Aldrich, Acros Organic, Strem and Alfa Aesar and used without further purification unless otherwise stated. Isolated yields refer to chromatographically and NMR yields refer to spectroscopically ( $^1\text{H}$  NMR) homogeneous material, unless otherwise stated. Acetonitrile (MeCN), and diethyl ether were obtained by passing the previously degassed solvents through an activated alumina column. Other solvents for reaction such as dichloroethane (DCE), water and ethanol were used HPLC grade. For determination of  $^1\text{H}$  NMR yields, dimethyl sulfone or 1,3,5-trimethoxybenzene were used as internal standards (automatic baseline correction was applied). All electrochemical reactions were run using a commercial potentiostat, an IKA ElectraSyn 2.0 unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck Milipore Sigma silica plates (60 F<sub>254</sub>), using short-wave, long-wave UV light (254 nm, 365 nm) for visualization, and *p*-anisaldehyde or potassium permanganate as developing agents. Flash column chromatography was performed using Merck Milipore Sigma silica gel (60, particle size 0.043–0.063 mm). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX400 instruments, and chemical shifts for  $^1\text{H}$  and  $^{13}\text{C}$  NMR are reported relative to the solvent peaks (7.26 ppm for  $^1\text{H}$  NMR in  $\text{CDCl}_3$ , 77.16 ppm for  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$ ).  $^{19}\text{F}\{^1\text{H}\}$  NMR data were calibrated using trichlorofluoromethane as an external reference (0.0 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on a Waters LC-TOF (I-Class and G2-XS) mass spectrometer using ESI or APCI ion sources, a Thermo Fisher Scientific LTQ Orbitrap XL mass spectrometer using ESI ion source and an Agilent Technologies 6230 TOF LC/MS with a Dual AJS ESI ion source.

## 2. Initial Screening to C-2 Blocking Groups



**Figure S1.** General scheme for screening pyridine C-2 blocking groups



**Figure S2.** Synthesis of known pyridinium salt, **BD9**<sup>[1]</sup>

Acetaldehyde oxime (2.5 g, 42.3 mmol, 1.00 equiv.) was dissolved in DMF (20 mL) at room temperature. *N*-chlorosuccinimide (5.93 g, 44.4 mmol, 1.05 equiv.) was added as a solid in 5 portions over approximately 1 h. After complete addition, the reaction mixture was stirred for 20 minutes, and then poured into 50 mL of EtOAc. The mixture was washed 2 x 15 mL brine, 2 x 25 mL water, 1 x 15 mL brine. The organic solution was dried over  $\text{MgSO}_4$  and concentrated on a rotavap to approximately 50 mL (Note: extensive concentration was avoided due to the potential loss of the product). The mixture was transferred to a 500 mL round bottom flask with large magnetic stirring bar. The mixture was diluted with EtOAc (total volume 100 mL) and cooled in an ice bath to 0 °C. Triethylamine (13 mL, 93.0 mmol, 2.2 equiv.) was added dropwise over 5 minutes. During this time, a thick slurry is formed, which cannot be stirred efficiently with a stir bar. Methanesulfonyl chloride (3.6 mL, 47.0 mmol, 1.1 equiv.) is added dropwise over 10 minutes, the white solid ( $\text{Et}_3\text{N}\cdot\text{HCl}$ ) is filtered away and rinsed with EtOAc. The filtrate is transferred to a separatory funnel and washed 2 x 40 mL water, 1 x 15 mL brine. The organic solution is dried over  $\text{MgSO}_4$  and concentrated to dryness. The residue is mixed well with heptane (300 mL) to afford a solid suspension. The solid is collected and washed twice with heptane and dried to afford a white crystalline solid **S1** (3.829 g, 53% overall yield).

**<sup>1</sup>H NMR** (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  3.24 (s, 3H), 2.44 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  148.80, 36.34, 22.92.

To a screw-cap 5 mL culture tube was added pyridine (161  $\mu\text{L}$ , 2.0 mmol, 1.0 equiv.), *N*-((methanesulfonyl)oxy)acetimidoyl chloride (**S1**, 377.5 mg, 2.2 mmol, 1.1 equiv.), sodium trifluoromethanesulfonate ( $\text{NaOTf}$ , 413 mg, 2.4 mmol, 1.2 equiv.), and acetonitrile (2 mL, 1.0 M). The vial was sealed and heated at 80 °C with rapid stirring for 2 h (>80% conversion). The reaction mixture was cooled to room temperature and then the reaction mixture was diluted with ethyl acetate, observed pale yellow precipitate. This solid was washed twice with ethyl acetate. The resulting solid was dried

<sup>1</sup> Pier, P. S. *J. Am. Chem. Soc.* **2017**, 139, 9499–9502.

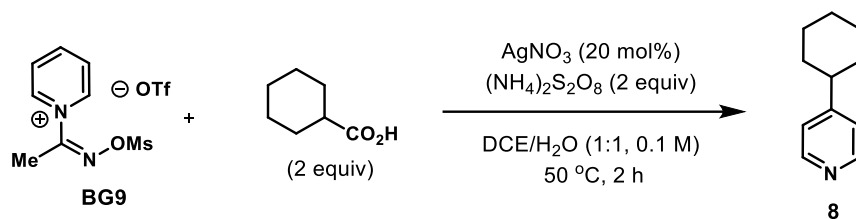
under reduced pressure, obtained desired product **BG9** as a pale yellowish solid (426 mg, 55% yield). This solid was used further step without further purification.

**<sup>1</sup>H NMR** (500 MHz, CD<sub>3</sub>CN) δ 8.90 – 8.86 (m, 2H), 8.80 (tt, *J* = 7.9, 1.4 Hz, 1H), 8.30 (dd, *J* = 8.0, 6.7 Hz, 2H), 3.34 (s, 3H), 2.71 (s, 3H).

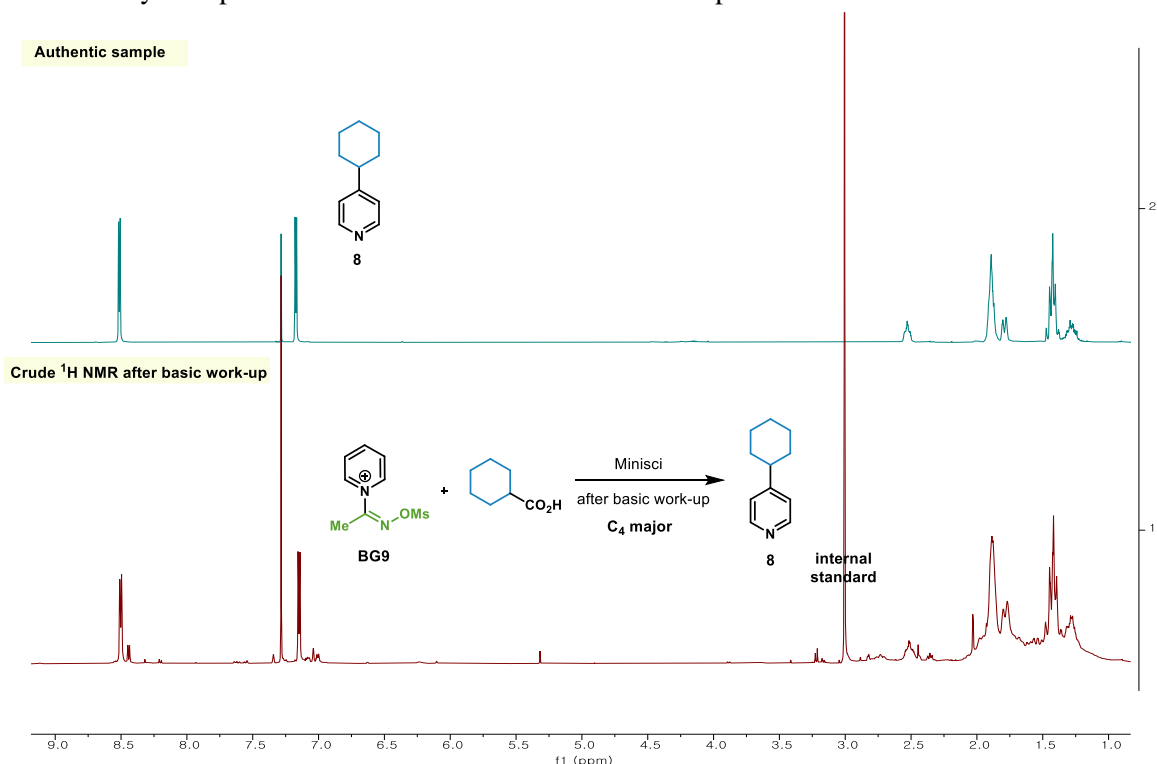
**<sup>13</sup>C NMR** (126 MHz, CD<sub>3</sub>CN) δ 151.70, 149.95, 142.89, 128.88, 36.82, 19.42

**HRMS** [M]<sup>+</sup> = C<sub>8</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup>: calculated for 215.0490, found 215.0490

## 2.1 Reaction with Pyridinium Salt BG9

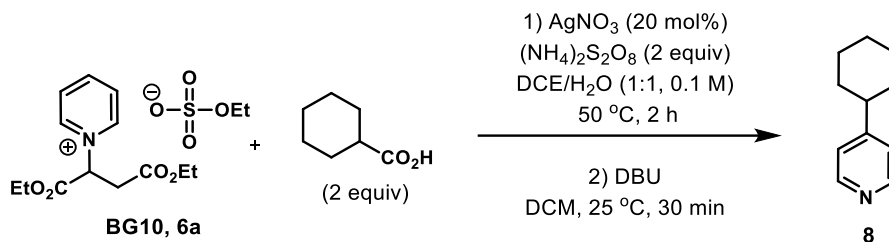


The 15 mL culture tube were with Teflon septa and screw cap. To this vial containing a stir bar was added pyridinium **BG9** (0.5 mmol, 182 mg, 1 equiv), cyclohexane carboxylic acid (128 mg, 1.0 mmol, 2 equiv), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (228 mg, 1.0 mmol, 2 equiv) and AgNO<sub>3</sub> (17 mg, 0.1 mmol, 20 mol%) and dichloroethane (2.5 mL) and H<sub>2</sub>O (2.5 mL) were then added and stirred for at 50 °C for 2 h. The reaction was monitored by crude NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL) and saturated aqueous NaHCO<sub>3</sub> (3 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was analyzed by NMR dissolved in CDCl<sub>3</sub>. Dimethyl sulfone (0.5 mmol) was used as an internal standard. The desired product **8** was observed in 39% NMR yield. The C-2 alkylated product was not observed in crude NMR spectrum.

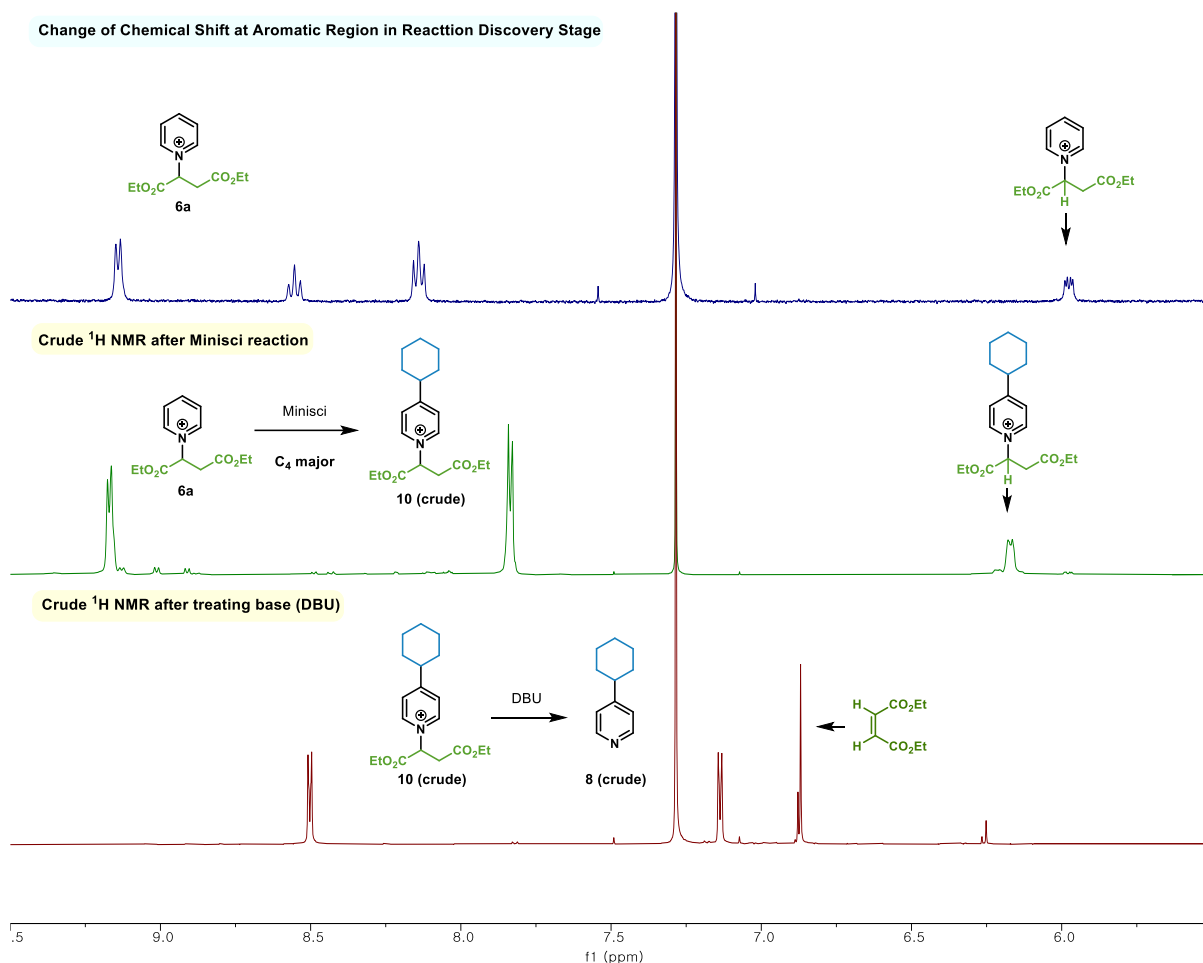


**Figure S3.** Crude NMR after Minisci reaction using the **BG9**

## 2.2 Reaction Discovery Using Fumarate-derived Pyridinium 6a



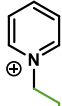
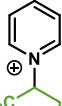
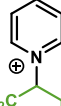
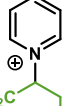
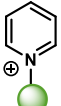
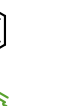
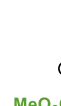
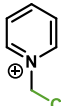
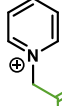
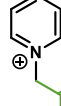
The 15 mL culture tube were with Teflon septa and screw cap. To this vial containing a stir bar was added pyridinium **BG10, 6a** (0.5 mmol, 188 mg, 1 equiv), cyclohexane carboxylic acid (128 mg, 1.0 mmol, 2 equiv),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (228 mg, 1.0 mmol, 2 equiv) and  $\text{AgNO}_3$  (17 mg, 0.1 mmol, 20 mol%) and dichloroethane (2.5 mL) and  $\text{H}_2\text{O}$  (2.5 mL) were then added and stirred for at  $50^\circ\text{C}$  for 2 h. The reaction was monitored by crude NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The crude material was re-dissolved in DCM (5 mL), treated with DBU (3 equiv, 225  $\mu\text{L}$ ) at  $25^\circ\text{C}$  for 30 min. The reaction mixture was analyzed by NMR dissolved in  $\text{CDCl}_3$ . Dimethyl sulfone (0.5 mmol) was used as an internal standard. The desired product **8** was observed in 83% NMR yield. The C-2 alkylated product was not observed in crude NMR spectrum.



**Figure S4.** Reaction discovery: change chemical shift after Minisci reaction using the **BG10 (6a)**

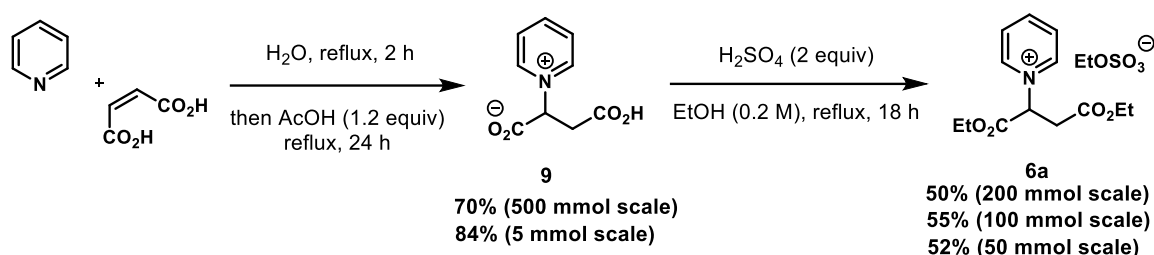
## 2.3 Summary of Experimental Results Using Blocking Groups

We successfully synthesized various **BGs** using known procedure. In some cases pure products could not be obtained (**BG2**, **BG5**, **BG8**) due to their instability at room temperature. When Minisci reaction was carried out, low conversion (**BG1**, **BG2**, **BG4**, **BG6**) and/or decomposition (**BG5**, **BG 3**, **BG7**) were observed.

			
<b>BG1</b>	<b>BG4, 9</b>	<b>BG10, 6a</b>	<b>BG5</b>
<b>Step 1 (protection)</b>	<ul style="list-style-type: none"> <li>• react with alkyl halide</li> <li>• scalable</li> </ul>	<ul style="list-style-type: none"> <li>• react with maleic acid</li> <li>• scalable</li> </ul>	<ul style="list-style-type: none"> <li>• esterification from 9</li> </ul>
<b>Step 2 (Minisci)</b>	<ul style="list-style-type: none"> <li>• low conversion at standard condition</li> <li>• high regioselectivity</li> </ul>	<ul style="list-style-type: none"> <li>• moderate conversion (50%)</li> <li>• high regioselectivity</li> </ul>	<ul style="list-style-type: none"> <li>• full conversion</li> <li>• high regioselectivity</li> </ul>
<b>Step 3 (deprotection)</b>	not tested	not tested	clean, very fast (DBU, 25 °C)
			
<b>BG2</b>	<b>BG3</b>	<b>BG8</b>	
<b>Step 1 (protection)</b>	<ul style="list-style-type: none"> <li>• react with alkyne</li> <li>• <i>E/Z</i> mixture</li> </ul>	<ul style="list-style-type: none"> <li>• react with alkynyl diacid</li> <li>• scalable</li> </ul>	<ul style="list-style-type: none"> <li>• react with alkyne</li> <li>• unstable at r.t.</li> </ul>
<b>Step 2 (Minisci)</b>	<ul style="list-style-type: none"> <li>• low conversion</li> <li>• high regioselectivity</li> </ul>	<ul style="list-style-type: none"> <li>• no conversion</li> <li>• decomposition</li> </ul>	not tested
			
<b>BG6</b>		<b>BG7</b>	
<b>Step 1 (protection)</b>	<ul style="list-style-type: none"> <li>• react with alkyl halide</li> </ul>	<ul style="list-style-type: none"> <li>• commercially available</li> </ul>	<ul style="list-style-type: none"> <li>• react with alkyl halide</li> </ul>
<b>Step 2 (Minisci)</b>	<ul style="list-style-type: none"> <li>• low conversion</li> <li>• high regioselectivity</li> </ul>	<ul style="list-style-type: none"> <li>• no conversion</li> <li>• decomposition</li> </ul>	<ul style="list-style-type: none"> <li>• no conversion</li> <li>• decomposition</li> </ul>

**Figure S5.** Synthetic trial and Minisci reaction screening to blocking groups

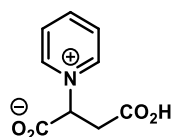
### 3. Practical Synthesis of Feedstock 6a



The procedure was developed and modified based on known literature.<sup>[2]</sup>

#### 3.1 Step 1: Synthesis of pyridinium 9

A solution of maleic acid (58.05 g, 500 mmol) and pyridine (1 equiv., 40.26 mL, 500 mmol) in  $\text{H}_2\text{O}$  (250 mL) was stirred at 90 °C for 2 h. After crystalline appeared in reaction mixture, acetic acid (34.3 mL, 1.2 equiv., 600 mmol) was added. The solution was kept in suspension with stirring at the same temperature for 24 h. The crude reaction mixture was cooled down to room temperature, filtered, washed with MeOH and EtOAc. The resulting white solid was dried under reduced pressure by rotary evaporator and high vacuum for overnight. The product **9** (68.3 g, 70% yield) was obtained as a white solid. The resulting product was used for next step without further purification.



#### 3-carboxy-2-(pyridin-1-ium-1-yl)propanoate (**9**)

<sup>1</sup>H NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.87 – 8.84 (m, 2H), 8.53 – 8.49 (m, 1H), 8.02 (t,  $J$  = 6.8 Hz, 2H), 5.59 (ddd,  $J$  = 9.7, 3.8, 2.1 Hz, 1H), 3.60 – 3.42 (m, 1H), 3.43 – 3.24 (m, 1H).

HRMS  $[M] = \text{C}_9\text{H}_9\text{NO}_4$ : calculated for 196.0610, found 196.0612

#### 3.2 Step 2: Esterification; Synthesis of pyridinium feedstock 6a

A solution of pyridinium carboxylate inner salt **9** (50 mmol, 9.758 g) and concentrated sulfuric acid (2 equiv., 100 mmol, 5.25 mL) in EtOH (250 mL, 0.2 M) was stirred at 90 °C for 18 h. The reaction was monitored by TLC and LCMS (30% conversion, 15 min, 70% conversion, 1 h, 95% conversion after 18 h). After the reaction was done, solvent (EtOH) was evaporated by reduced pressure at least 15 min. The concentrated crude mixture was diluted in  $\text{CH}_2\text{Cl}_2$  (200 mL) and  $\text{H}_2\text{O}$  (50 mL) and extracted by  $\text{CH}_2\text{Cl}_2$  with monitoring TLC both aqueous and organic phase. (approximately 50 mL x 10 times, total organic phase volume = 750 mL). [Note: when lowering use of water (below 10 mL), the yield was higher above 90%. However, the crude material was obtained as sticky oil that containing the mono-

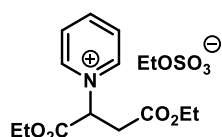
<sup>2</sup> Uemura, K.; Sano, K.; Matsumoto, A.; Yoshida, Y.; Mino, T.; Sakamoto, M. *Chem. Asian J.* **2019**, *14*, 4150–4153.

esterification product (below 5%) and residual  $\text{CH}_2\text{Cl}_2$ .] The combined organic phase was dried by  $\text{Na}_2\text{SO}_4$ , filtered, concentrated under reduced pressure. The resulting colorless liquid was added anhydrous diethyl ether (30 mL) and dried by reduced pressure. After the residual solvent was totally evaporated by reduced pressure, the product was obtained as a white solid (9.76 g, 52% yield). The resulting product was used for next step without further purification.

For 100 mmol scale reaction, a solution of pyridinium carboxylate inner salt **9** (100 mmol, 19.517 g) and concentrated sulfuric acid (2 equiv., 200 mmol, 10.5 mL) in EtOH (500 mL, 0.2 M) was stirred at 90 °C for 18 h. After the work-up, the product was obtained as a white solid (20.87 g, 55 % yield).



For 200 mmol scale reaction, a solution of pyridinium carboxylate inner salt **9** (200 mmol, 39.03 g) and concentrated sulfuric acid (2 equiv., 400 mmol, 21.0 mL) in EtOH (1000 mL, 0.2 M) was stirred at 90 °C for 18 h. After the work-up, the product was obtained as a white solid (37.65 g, 50 % yield).



### Pyridinium Feedstock (**6a**)

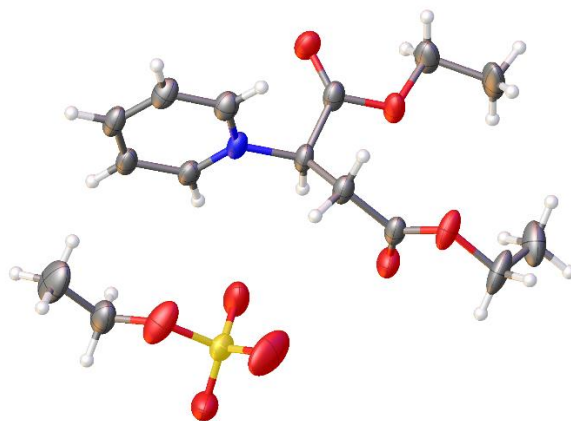
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.37 (d,  $J = 5.6$  Hz, 2H), 8.58 – 8.53 (m, 1H), 8.09 (dd,  $J = 7.9, 6.7$  Hz, 2H), 6.30 – 6.24 (m, 1H), 4.43 – 4.24 (m, 2H), 4.22 – 4.09 (m, 5H), 3.78 (dd,  $J = 18.9, 8.0$  Hz, 1H), 3.52 (dd,  $J = 18.9, 3.2$  Hz, 1H), 1.28 (td,  $J = 7.1, 5.5$  Hz, 6H), 1.23 (t,  $J = 7.1$  Hz, 3H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 166.3, 146.5, 128.1, 68.6, 63.8, 63.7, 62.1, 37.2, 15.2, 14.0, 13.9.

**LRMS**  $[\text{M}]^+ = \text{C}_{13}\text{H}_{18}\text{NO}_4^+$ : calculated for 252.12, found 252.16.

**HRMS**  $[\text{M}]^+ = \text{C}_{13}\text{H}_{18}\text{NO}_4^+$ : calculated for 252.1236, found 252.1236

### 3.3. X-ray Structure of Pyridinium **6a**



## Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker APEX II diffractometer equipped with Cu K $_{\alpha}$  radiation ( $\lambda=1.54178$  Å).

Crystals of the subject compound were used as received (grow from DCM).

A 0.200 x 0.200 x 0.180 mm colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using  $\phi$  and  $\omega$  scans. Crystal-to-detector distance was 40 mm and exposure time was 1.0, 2.0, 3.0 and 4.0 seconds (depending on the  $2\theta$  range) per frame using a scan width of  $1.50^\circ$ . Data collection was 97.8% complete to  $67.500^\circ$  in  $\theta$ . A total of 26320 reflections were collected covering the indices,  $-10 \leq h \leq 10$ ,  $-10 \leq k \leq 10$ ,  $-15 \leq l \leq 15$ . 3309 reflections were found to be symmetry independent, with a  $R_{\text{int}}$  of 0.0413. Indexing and unit cell refinement indicated a **Primitive, Triclinic** lattice. The space group was found to be ***P*-1**. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Good data and refinement, minor disorder on CH<sub>2</sub>-CH<sub>3</sub> atoms

P-1 “Racemic” space group

SI-Table 1. Crystal data and structure refinement for Baran785 (**6a**).

Report date	2021-04-30	
Identification code	baran785 ( <b>6a</b> )	
Empirical formula	C <sub>15</sub> H <sub>23</sub> N O <sub>8</sub> S	
Molecular formula	C <sub>13</sub> H <sub>18</sub> N O <sub>4</sub> , C <sub>2</sub> H <sub>5</sub> O <sub>4</sub> S	
Formula weight	377.40	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	$a = 8.7948(2)$ Å	$\alpha = 88.7630(10)^\circ$ .
	$b = 8.8282(2)$ Å	$\beta = 75.8870(10)^\circ$ .
	$c = 12.7065(3)$ Å	$\gamma = 75.0200(10)^\circ$ .
Volume	$923.36(4)$ Å <sup>3</sup>	
Z	2	
Density (calculated)	1.357 Mg/m <sup>3</sup>	
Absorption coefficient	1.936 mm <sup>-1</sup>	
F(000)	400	
Crystal size	0.2 x 0.2 x 0.18 mm <sup>3</sup>	
Crystal color, habit	colorless block	
Theta range for data collection	3.590 to 68.241°.	
Index ranges	$-10 \leq h \leq 10$ , $-10 \leq k \leq 10$ , $-15 \leq l \leq 15$	
Reflections collected	26320	
Independent reflections	3309 [ $R_{\text{int}} = 0.0413$ ]	
Completeness to $\theta = 67.500^\circ$	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.5841	

Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3309 / 1 / 249
Goodness-of-fit on F <sup>2</sup>	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0483, wR2 = 0.1230
R indices (all data)	R1 = 0.0586, wR2 = 0.1321
Largest diff. peak and hole	0.786 and -0.319 e.Å <sup>-3</sup>

SI-Table 2. Atomic coordinates (x 10<sup>4</sup>) and equivalent isotropic displacement parameters (Å<sup>2</sup>x 10<sup>3</sup>) for Baran785. U(eq) is defined as one third of the trace of the orthogonalized U<sup>ij</sup> tensor.

	x	y	z	U(eq)
C(1)	5680(3)	2083(3)	6301(2)	31(1)
N(1)	7184(2)	1889(2)	5419(2)	31(1)
O(1)	1688(2)	4679(2)	7176(2)	46(1)
C(2)	4387(3)	3588(3)	6208(2)	33(1)
O(2)	2341(2)	2171(2)	6598(2)	46(1)
C(3)	2711(3)	3377(3)	6686(2)	34(1)
O(3)	4751(2)	2226(2)	8173(1)	39(1)
C(4)	6115(3)	2009(3)	7394(2)	34(1)
O(4)	7459(2)	1803(2)	7523(1)	40(1)
C(5)	6(3)	4595(4)	7598(3)	56(1)
C(6)	-193(4)	3792(4)	8642(3)	63(1)
C(9)	7677(3)	620(3)	4739(2)	31(1)
C(10)	9080(3)	423(3)	3916(2)	35(1)
C(11)	9962(3)	1519(3)	3810(2)	38(1)
C(12)	9428(3)	2810(3)	4527(2)	39(1)
C(13)	8026(3)	2992(3)	5329(2)	36(1)
C(7)	4950(20)	1899(15)	9275(9)	47(3)
C(8)	3274(7)	2301(9)	9984(4)	72(2)
C(7A)	4920(30)	2436(15)	9288(11)	41(3)
C(8A)	4859(9)	4069(8)	9659(5)	54(2)
S(1)	4179(1)	2384(1)	3083(1)	36(1)
O(5)	5765(2)	2645(3)	2289(2)	63(1)
O(6)	4693(2)	1606(3)	3994(2)	62(1)
O(7)	3159(3)	3921(3)	3353(3)	84(1)
O(8)	3562(2)	1403(3)	2514(2)	58(1)
C(14)	6984(3)	1278(4)	1801(2)	53(1)
C(15)	8505(4)	1750(5)	1240(3)	74(1)

SI-Table 3. Bond lengths [Å] and angles [°] for Baran785 (**6a**).

C(1)-H(1)	1.0000
C(1)-N(1)	1.484(3)
C(1)-C(2)	1.533(3)
C(1)-C(4)	1.523(3)
N(1)-C(9)	1.342(3)
N(1)-C(13)	1.355(3)
O(1)-C(3)	1.320(3)
O(1)-C(5)	1.466(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(2)-C(3)	1.509(3)
O(2)-C(3)	1.205(3)
O(3)-C(4)	1.329(3)
O(3)-C(7)	1.467(9)
O(3)-C(7A)	1.481(11)
C(4)-O(4)	1.200(3)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(5)-C(6)	1.484(4)
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(9)-H(9)	0.9500
C(9)-C(10)	1.383(3)
C(10)-H(10)	0.9500
C(10)-C(11)	1.374(4)
C(11)-H(11)	0.9500
C(11)-C(12)	1.381(4)
C(12)-H(12)	0.9500
C(12)-C(13)	1.371(3)
C(13)-H(13)	0.9500
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(7)-C(8)	1.49(2)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(7A)-H(7AA)	0.9900
C(7A)-H(7AB)	0.9900
C(7A)-C(8A)	1.510(15)
C(8A)-H(8AA)	0.9800
C(8A)-H(8AB)	0.9800
C(8A)-H(8AC)	0.9800
S(1)-O(5)	1.577(2)
S(1)-O(6)	1.440(2)
S(1)-O(7)	1.416(2)
S(1)-O(8)	1.424(2)
O(5)-C(14)	1.425(4)
C(14)-H(14A)	0.9900

C(14)-H(14B)	0.9900
C(14)-C(15)	1.511(4)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
N(1)-C(1)-H(1)	107.7
N(1)-C(1)-C(2)	112.04(18)
N(1)-C(1)-C(4)	109.06(18)
C(2)-C(1)-H(1)	107.7
C(4)-C(1)-H(1)	107.7
C(4)-C(1)-C(2)	112.43(19)
C(9)-N(1)-C(1)	119.0(2)
C(9)-N(1)-C(13)	121.9(2)
C(13)-N(1)-C(1)	119.1(2)
C(3)-O(1)-C(5)	115.3(2)
C(1)-C(2)-H(2A)	109.6
C(1)-C(2)-H(2B)	109.6
H(2A)-C(2)-H(2B)	108.1
C(3)-C(2)-C(1)	110.2(2)
C(3)-C(2)-H(2A)	109.6
C(3)-C(2)-H(2B)	109.6
O(1)-C(3)-C(2)	112.2(2)
O(2)-C(3)-O(1)	124.1(2)
O(2)-C(3)-C(2)	123.7(2)
C(4)-O(3)-C(7)	115.8(8)
C(4)-O(3)-C(7A)	115.3(10)
O(3)-C(4)-C(1)	108.25(19)
O(4)-C(4)-C(1)	125.6(2)
O(4)-C(4)-O(3)	126.2(2)
O(1)-C(5)-H(5A)	109.4
O(1)-C(5)-H(5B)	109.4
O(1)-C(5)-C(6)	111.1(3)
H(5A)-C(5)-H(5B)	108.0
C(6)-C(5)-H(5A)	109.4
C(6)-C(5)-H(5B)	109.4
C(5)-C(6)-H(6A)	109.5
C(5)-C(6)-H(6B)	109.5
C(5)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
N(1)-C(9)-H(9)	120.2
N(1)-C(9)-C(10)	119.5(2)
C(10)-C(9)-H(9)	120.2
C(9)-C(10)-H(10)	120.1
C(11)-C(10)-C(9)	119.8(2)
C(11)-C(10)-H(10)	120.1
C(10)-C(11)-H(11)	120.3
C(10)-C(11)-C(12)	119.3(2)
C(12)-C(11)-H(11)	120.3
C(11)-C(12)-H(12)	120.0

C(13)-C(12)-C(11)	120.0(2)
C(13)-C(12)-H(12)	120.0
N(1)-C(13)-C(12)	119.4(2)
N(1)-C(13)-H(13)	120.3
C(12)-C(13)-H(13)	120.3
O(3)-C(7)-H(7A)	110.8
O(3)-C(7)-H(7B)	110.8
O(3)-C(7)-C(8)	104.9(10)
H(7A)-C(7)-H(7B)	108.8
C(8)-C(7)-H(7A)	110.8
C(8)-C(7)-H(7B)	110.8
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
O(3)-C(7A)-H(7AA)	108.0
O(3)-C(7A)-H(7AB)	108.0
O(3)-C(7A)-C(8A)	117.2(8)
H(7AA)-C(7A)-H(7AB)	107.2
C(8A)-C(7A)-H(7AA)	108.0
C(8A)-C(7A)-H(7AB)	108.0
C(7A)-C(8A)-H(8AA)	109.5
C(7A)-C(8A)-H(8AB)	109.5
C(7A)-C(8A)-H(8AC)	109.5
H(8AA)-C(8A)-H(8AB)	109.5
H(8AA)-C(8A)-H(8AC)	109.5
H(8AB)-C(8A)-H(8AC)	109.5
O(6)-S(1)-O(5)	105.64(12)
O(7)-S(1)-O(5)	103.98(14)
O(7)-S(1)-O(6)	113.41(17)
O(7)-S(1)-O(8)	114.61(15)
O(8)-S(1)-O(5)	107.30(13)
O(8)-S(1)-O(6)	111.04(15)
C(14)-O(5)-S(1)	117.02(19)
O(5)-C(14)-H(14A)	109.9
O(5)-C(14)-H(14B)	109.9
O(5)-C(14)-C(15)	108.9(3)
H(14A)-C(14)-H(14B)	108.3
C(15)-C(14)-H(14A)	109.9
C(15)-C(14)-H(14B)	109.9
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

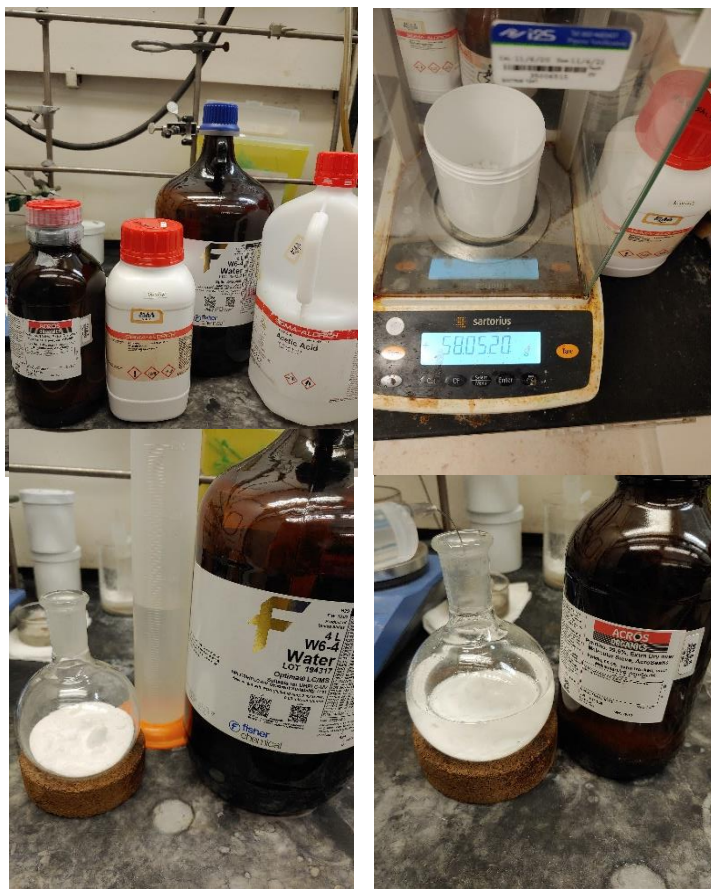
SI-Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for Baran785 (**6a**). The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
C(1)	21(1)	37(1)	25(1)	4(1)	2(1)	0(1)
N(1)	21(1)	38(1)	27(1)	6(1)	-2(1)	1(1)
O(1)	26(1)	36(1)	60(1)	12(1)	9(1)	5(1)
C(2)	24(1)	38(1)	29(1)	7(1)	-1(1)	1(1)
O(2)	30(1)	59(1)	43(1)	-12(1)	3(1)	-10(1)
C(3)	25(1)	43(1)	26(1)	6(1)	-2(1)	2(1)
O(3)	30(1)	54(1)	24(1)	5(1)	-1(1)	3(1)
C(4)	27(1)	34(1)	30(1)	4(1)	-1(1)	4(1)
O(4)	29(1)	50(1)	36(1)	6(1)	-8(1)	1(1)
C(5)	25(1)	47(2)	73(2)	14(2)	14(1)	6(1)
C(6)	58(2)	60(2)	50(2)	-4(2)	22(1)	-12(2)
C(9)	22(1)	39(1)	28(1)	3(1)	-6(1)	0(1)
C(10)	23(1)	48(2)	26(1)	3(1)	-4(1)	4(1)
C(11)	23(1)	53(2)	30(1)	12(1)	-1(1)	0(1)
C(12)	28(1)	44(2)	41(1)	12(1)	-4(1)	-6(1)
C(13)	30(1)	37(1)	34(1)	7(1)	-5(1)	-2(1)
C(7)	41(4)	62(8)	25(3)	7(4)	-5(3)	5(7)
C(8)	48(3)	124(6)	19(2)	-1(3)	-2(2)	15(3)
C(7A)	41(4)	46(8)	24(4)	16(4)	-7(3)	7(7)
C(8A)	59(4)	58(4)	31(3)	-6(3)	-7(3)	5(3)
S(1)	24(1)	37(1)	40(1)	-4(1)	-6(1)	2(1)
O(5)	36(1)	59(1)	83(2)	30(1)	-2(1)	-7(1)
O(6)	38(1)	96(2)	36(1)	2(1)	-3(1)	4(1)
O(7)	45(1)	41(1)	152(3)	-17(1)	-18(2)	10(1)
O(8)	36(1)	81(2)	53(1)	-24(1)	-3(1)	-14(1)
C(14)	36(1)	79(2)	34(1)	6(1)	-1(1)	-5(1)
C(15)	46(2)	112(3)	54(2)	30(2)	6(2)	-19(2)

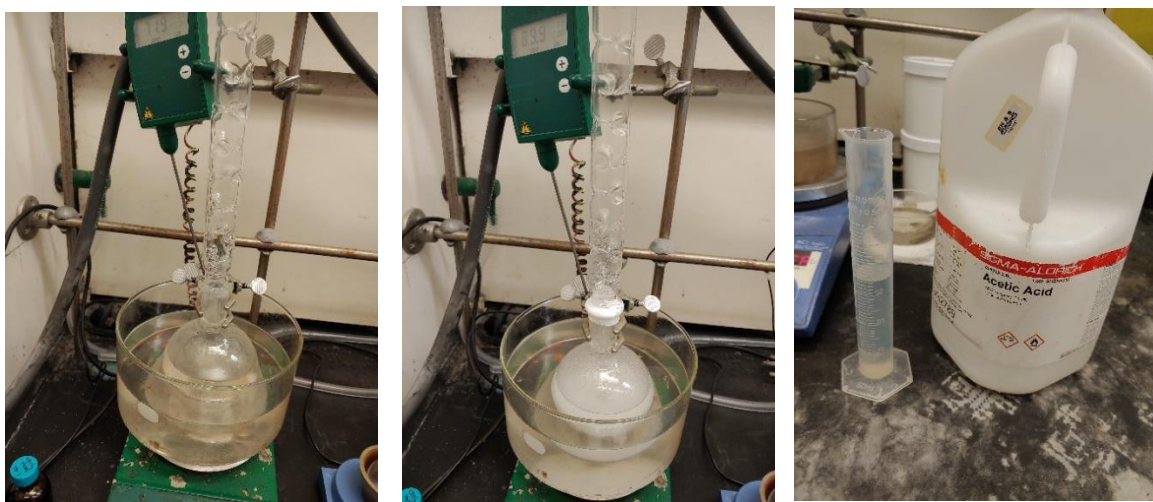
SI-Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^{-3}$ ) for Baran785 (**6a**).

	x	y	z	U(eq)
H(1)	5224	1174	6232	37
H(2A)	4545	4472	6598	39
H(2B)	4501	3842	5435	39
H(5A)	-305	4017	7060	67
H(5B)	-726	5669	7708	67
H(6A)	479	2707	8525	94
H(6B)	-1335	3796	8923	94
H(6C)	146	4345	9168	94
H(9)	7068	-139	4821	38
H(10)	9432	-466	3426	42
H(11)	10930	1391	3249	46
H(12)	10034	3571	4464	47
H(13)	7647	3885	5819	43
H(7A)	5601	2553	9486	56
H(7B)	5503	779	9325	56
H(8A)	2722	3389	9878	108
H(8B)	3317	2185	10745	108
H(8C)	2676	1596	9794	108
H(7AA)	5967	1728	9349	49
H(7AB)	4047	2085	9800	49
H(8AA)	5764	4412	9195	80
H(8AB)	4945	4063	10413	80
H(8AC)	3829	4792	9607	80
H(14A)	6600	768	1267	64
H(14B)	7216	520	2363	64
H(15A)	8809	2358	1754	111
H(15B)	8305	2391	624	111
H(15C)	9390	807	977	111

#### 4. Graphical Procedure for Pyridinium Feedstock 6a Synthesis



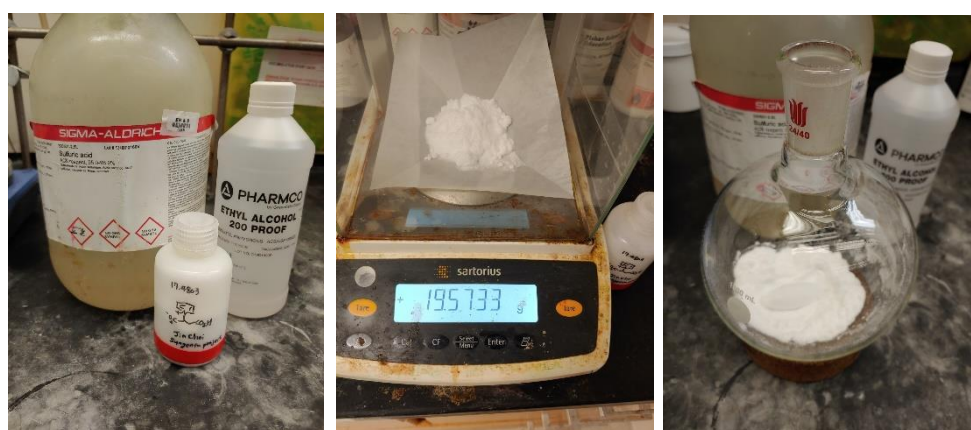
**Fig. S6. Reaction set-up to 1<sup>st</sup> step of feedstock synthesis.** Reagents and solvent (upper left), weigh mass of 500 mmol maleic acid (upper right), maleic acid and stirring bar in 500 mL RBF (bottom left), added 250 mL water and 500 mmol pyridine (bottom right).



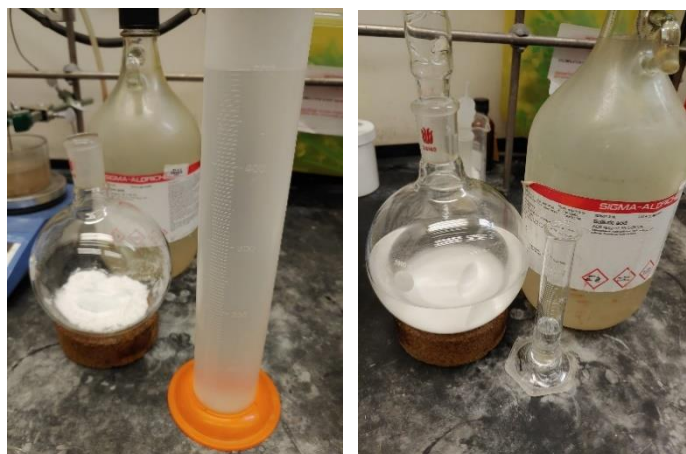
**Fig. S7. Reaction set-up to 1<sup>st</sup> step of feedstock synthesis (continued).** Observed homogeneous solution to start heating with Vigreux condenser (left), reaction mixture was turned to be heterogeneous solution with white solid was precipitated after 2 h (center), adding 600 mmol of AcOH (right).



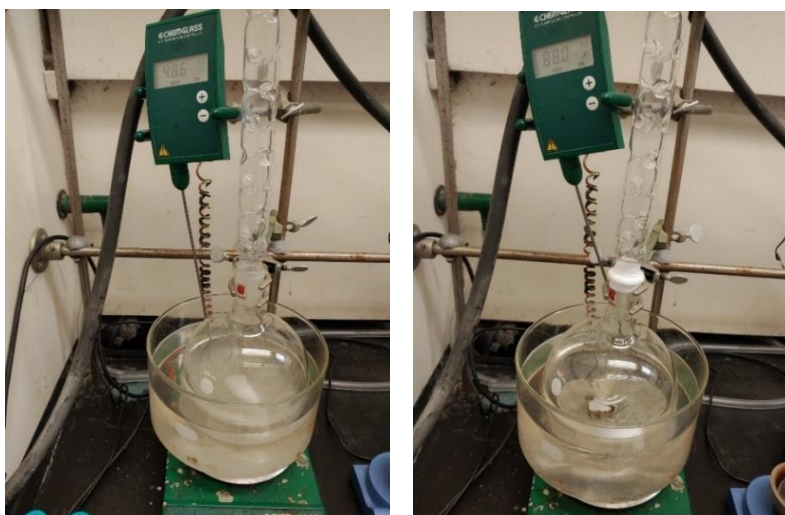
**Fig. S8. Work-up procedure for 1<sup>st</sup> step of feedstock synthesis.** Precipitated solid was obtained by filtering using Büchner funnel, washed EtOAc, MeOH (upper left, center). The resulting solid was dried by rotary evaporator and high vac. (upper right), The pyridinium **9** was stored in 100 mL Nalgene bottle, stable in ambient temperature (bottom).



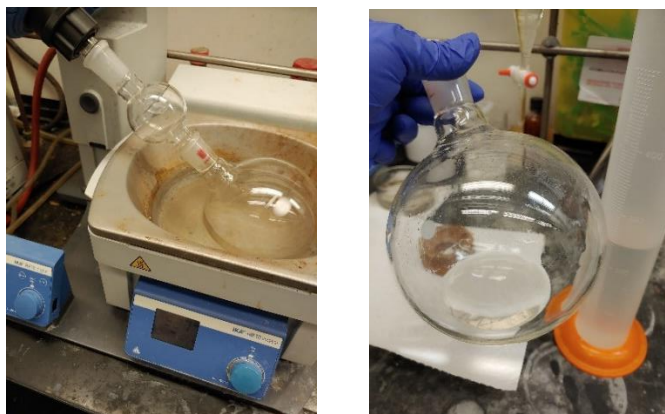
**Fig. S9. Reaction set-up to 2<sup>nd</sup> step of feedstock synthesis.** Reagents and solvent (left), weigh mass of 100 mmol pyridinium **9** (center), pyridinium **9** and stirring bar in 1000 mL RBF (right)



**Fig S10. Reaction set-up to 2<sup>nd</sup> step of feedstock synthesis (continued).** 500 mL EtOH (left), 10.5 mL concentrated H<sub>2</sub>SO<sub>4</sub> (right)



**Fig. S11. Reaction set-up to 2<sup>nd</sup> step of feedstock synthesis (continued).** Observed heterogeneous solution to start heating with Vigreux condenser (left), Reaction mixture was turned to be homogeneous solution during heating condition (right)



**Fig. S12. Work-up procedure for 2<sup>nd</sup> step of feedstock synthesis.** solvent evaporation using rotatory evaporator after completed reaction (left), crude liquid after evaporating solvent (right).



**Fig. S13. Work-up procedure for to 2<sup>nd</sup> step of feedstock synthesis (continued).** diluted with  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$  (left), extracted with  $\text{CH}_2\text{Cl}_2$ , dried by  $\text{Na}_2\text{SO}_4$  (center), filtered, evaporated residual solvent by rotatory evaporator (right).

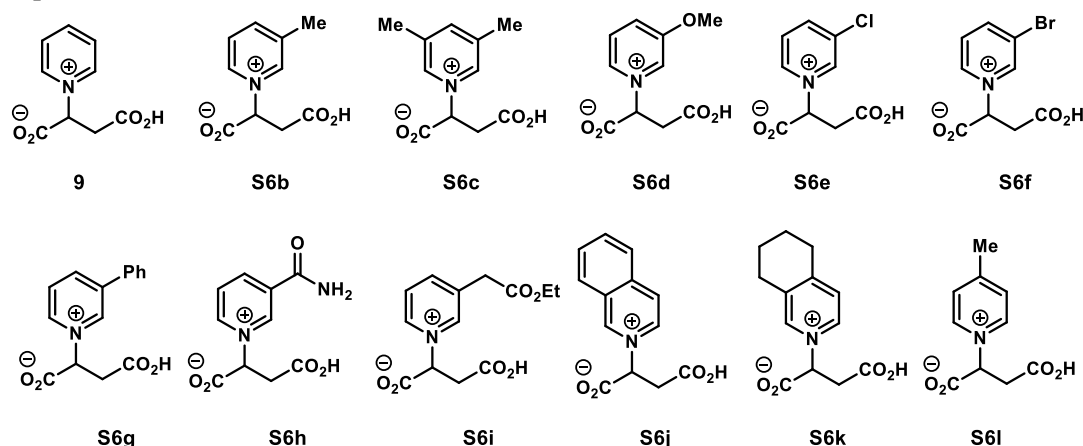


**Fig. S14. Resulting pyridine feedstock.** The resulting liquid after work-up was added anhydrous  $\text{Et}_2\text{O}$  for removing the residual solvent (left), dried product as a white solid (center), The resulting feedstock **6a** was stored in 20 mL vial, stable in ambient temperature (right).

## 5. General Procedure for Pyridinium Feedstock (6b – 6i) Synthesis

### General Procedure A

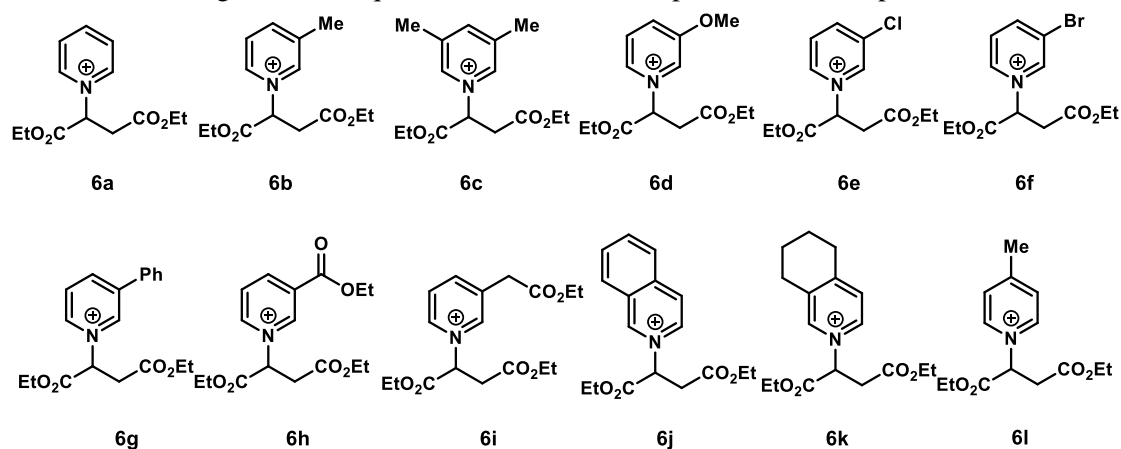
A solution of maleic acid (1.16 g, 10 mmol) and substituted pyridine (1 equiv., 10 mmol) in H<sub>2</sub>O (5 mL) was stirred at 90 °C for 2 h. After crystalline appeared in reaction mixture, acetic acid (686  $\mu$ L, 1.2 equiv. 12 mmol) was added. The solution was kept in suspension with stirring at the same temperature for 24 h. The crude reaction mixture was cooled down to room temperature, filtered, washed with small amount of MeOH and EtOAc. The resulting white solid was dried under reduced pressure by rotary evaporator and high vacuum for overnight. The product was obtained and used for next step without further purification.



**Figure S15.** Synthesized pyridinium salts followed by general procedure A

### General Procedure B

A solution of pyridinium carboxylate inner salt (2.5 mmol, 1 equiv.) and concentrated sulfuric acid (2 equiv., 5 mmol, 260  $\mu$ L) in EtOH (12.5 mL, 0.2 M) was stirred at 90 °C for 18 h. After the reaction was done, solvent (EtOH) was evaporated by reduced pressure. The concentrated crude mixture was diluted in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and H<sub>2</sub>O (2 mL) and extracted by CH<sub>2</sub>Cl<sub>2</sub> with monitoring TLC both aqueous and organic phase. The combined organic phase was dried by Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure. The resulting colorless liquid was used for next step without further purification.



**Figure S16.** Synthesized pyridinium feedstocks followed by general procedure B  
Counter-anion = ethyl sulfonate (EtOSO<sub>3</sub><sup>-</sup>)

## 6. General Procedure for Minisci (type) and Deprotection Reactions

### General Procedure C: Classic Minisci Reaction

To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar pyridinium, **6a** (0.5 mmol, 188 mg, 1 equiv), carboxylic acid (1.0 mmol, 2 equiv), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (228 mg, 1.0 mmol, 2 equiv) and AgNO<sub>3</sub> (16.7 mg, 0.1 mmol, 20 mol%) were added, together with dichloroethane (2.5 mL) and H<sub>2</sub>O (2.5 mL). The biphasic mixture was stirred at 50 °C for 2 hours. The reaction was monitored and regioselectivity was analyzed by crude NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in *vacuo*. The crude material was used next step without further purification.

### General Procedure D: Base-promoted Deprotection Reaction

The crude alkylated product was added DBU (225 µL, 1.5 mmol, 3 equiv) in dichloromethane (5 mL, 0.1 M). and the reaction mixture was stirred at room temperature for 30 min. Upon the reaction completion, the reaction mixture was transferred to a separatory funnel containing 1 N NaOH (3 mL) for adjusting pH >10 [Note: In case of base sensitive substrate, aq. NaOH could be changed by aq. NaHCO<sub>3</sub>]. The aqueous phase was extracted with dichloromethane (3 x 3 mL) and combined organic phase was washed with brine. The resulting combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in *vacuo*. The crude material was purified by silica gel chromatography to yield the desired product.

### General Procedure E: Minisci-type Reaction Reported by Baxter Group <sup>[3]</sup>

To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium **6a** (0.5 mmol, 188 mg, 1 equiv), carboxylic acid (1.0 mmol, 2 equiv), Selectfluor (177 mg, 1.0 mmol, 2 equiv) and AgNO<sub>3</sub> (16.7 mg, 0.1 mmol, 20 mol%) were added, together with dichloroethane (2.5 mL) and H<sub>2</sub>O (2.5 mL). The biphasic mixture was stirred at 50 °C. The reaction was monitored and regioselectivity was analyzed by crude NMR or LCMS. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in *vacuo*. The crude material was used next step without further purification.

### General Procedure F: Minisci-type Reaction Reported by Molander Group <sup>[4]</sup>

To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium **6a** (0.5 mmol, 188 mg, 1 equiv), potassium alkyltrifluoroborate (0.5 mmol, 1 equiv), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (337 mg, 1.5 mmol, 3 equiv) and AgNO<sub>3</sub> (16.7 mg, 0.1 mmol, 20 mol%) were added, together with dichloroethane (2.5 mL) and H<sub>2</sub>O (2.5 mL). The biphasic mixture was stirred at room temperature for 24 h. Upon completion, the reaction was diluted with dichloromethane (1 mL). The aqueous phase was

<sup>3</sup> Galloway, J. D.; Mai, D. N.; Baxter, R. D. *Org. Lett.* **2017**, *19*, 5772–5775.

<sup>4</sup> Presset, M.; Fleury-Brégeot, N.; Oehrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 4615–4619.

extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was used next step without further purification.

### General Procedure G: Minisci-type Reaction Reported by Lei & Wang Group (e-chem)<sup>[5], [6]</sup>

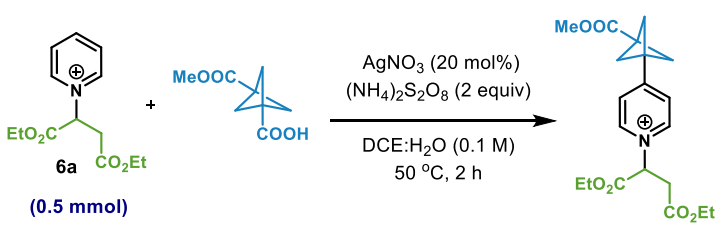
To an oven-dried 5 mL ElectraSyn vial, equipped with two graphite electrodes and a magnetic stirbar, the corresponding pyridinium **6a** (188 mg, 0.5 mmol, 1.0 equiv.), the *N*-hydroxyphthalimide ester (0.6 mmol, 1.2 equiv.) and *n*-Bu<sub>4</sub>NBF<sub>4</sub> (82.3 mg, 0.05 M, 0.25 mmol) were added, together with DMA (5 mL) was added. The reaction mixture was stirred and electrolyzed at a constant current of 5.0 mA under room temperature for 5.5 h (approximately 2.5 F). The reaction was quenched with saturated sodium bicarbonate aqueous solution (10 mL) and extracted with EtOAc (3 × 10 mL). Then the combined organic layers were filtered, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude material was used next step without further purification.

### General Procedure H: Minisci-type Reaction using Unactivated Ether<sup>[7]</sup>

To a 15 mL culture tube equipped with Teflon septum screw cap and containing a stir bar, pyridinium **6a** (0.5 mmol, 188 mg, 1 equiv), ether (1.0 mmol, 2 equiv) and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (228 mg, 1.0 mmol, 2 equiv) were added, together with acetone (1.7mL) and H<sub>2</sub>O (0.8 mL). The reaction mixture was stirred for at 90 °C for 2-4 h. Upon completion, the reaction was evaporated by reduced pressure, diluted with dichloromethane (1 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was used next step without further purification.

## 7. Optimization Screening for Expensive Carboxylic Acids

The pyridinium **6a** could be prepared from inexpensive materials, therefore the reaction with precious carboxylic acid containing substrates was reoptimized. As a result, similar yields with the radical precursor as limiting reagent were observed.

	Variations	%NMR yield (isolated)
	None	34% (32%)
	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	16%
	AgNO <sub>3</sub> two additions	28%
	<b>Acid limiting reagent</b>	<b>40% (38%)</b>
	80 °C	Trace
	80 °C, Acid limiting reagent	Trace
	80 °C, 30 min	9%
	80 °C, Acid lim. reagent, 30 min	14%
	0.05 M	33%
	0.2 M	35%
	<b>0.3 M</b>	<b>44% (42%)</b>
	0.4 M	44%

**Figure S17.** Reaction screening for low yield example using expensive carboxylic acid

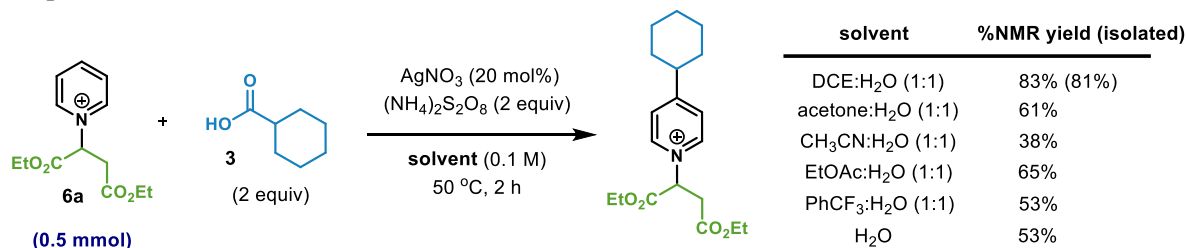
<sup>5</sup> Liu, Y.; Xue, L.; Shi, B.; Bu, F.; Wang, D.; Lu, L.; Shi, R.; Lei, A. *Chem. Commun.*, **2019**, 55, 14922–14925.

<sup>6</sup> Niu, K.; Song, L.; Hao, Y.; Liu, Y.; Wang, Q. *Chem. Commun.*, **2020**, 56, 11673–11676.

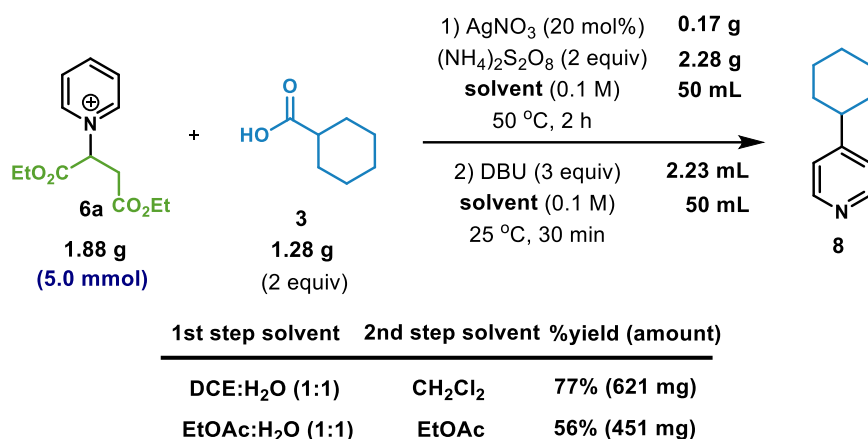
<sup>7</sup> McCallum, T.; Jouanno, L.-A.; Cannilo, A.; Barriault, L. *Synlett* **2016**, 27, 1282–1286.

## 8. Green Solvent Screening for Process Chemistry

For a potential application in process chemistry setting, alternative, non halogenated solvents were investigated. Many of the green solvent tested (EtOAc, CH<sub>3</sub>CN, H<sub>2</sub>O) provided similar results compared to the benchmark reaction.



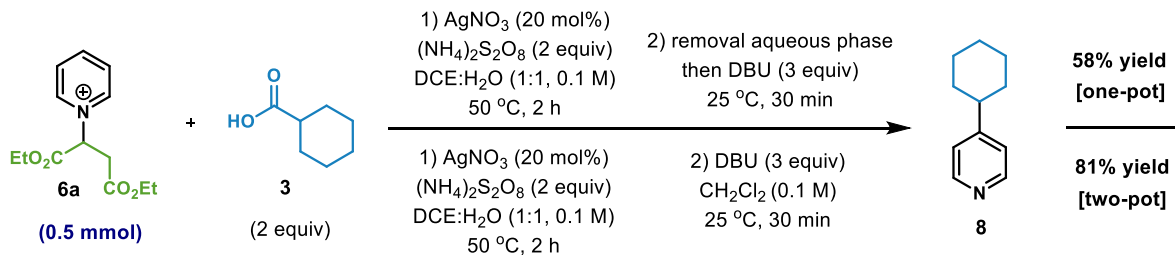
**Figure S18.** Green solvent screening



**Figure S19.** Comparison of scale-up result between standard and green solvent

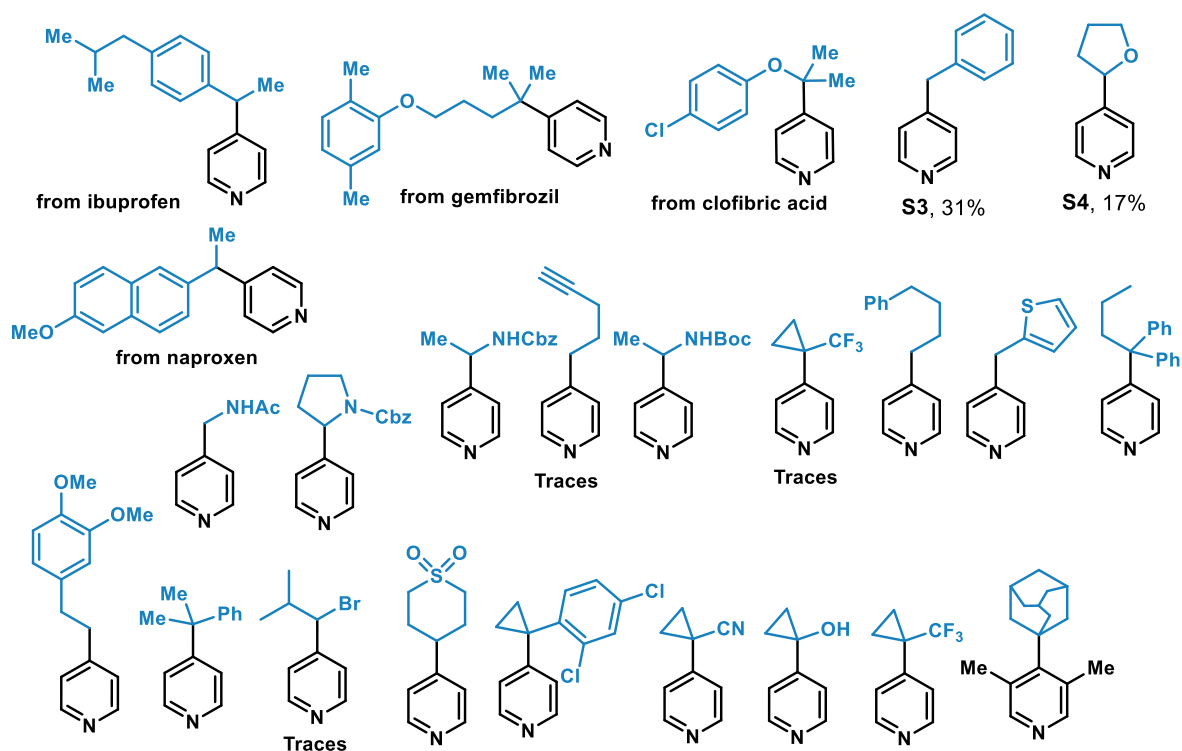
## 9. Comparison with One-pot Protocol

In order to minimize the loss of product during extraction step before the basic deprotection, a one-pot procedure was tested. However, a drop in the isolated yield of the desired product was observed.



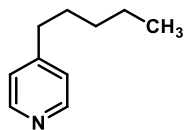
**Figure S20.** Trial and result for one-pot protocol

## 10. Unsuccessful or Challenging Substrates in Minisci Reaction



**Figure S21.** Unsuccessful or challenging substrates in Minisci reaction

## 11. Characterization of Products in Table 1



### 4-pentylpyridine (11)

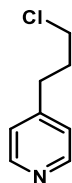
Following the modified general procedure C and D, *n*-hexanoic acid (232 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu$ L, 3.0 mmol, 6 equiv) was used in procedure D [Table 1, footnote b]. The compound **11** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as an orange liquid (42.1 mg, 56% yield).

$R_f$  = 0.42 (*n*-hexane:EtOAc = 1:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (d,  $J$  = 6.0 Hz, 2H), 7.12 (d,  $J$  = 6.0 Hz, 2H), 2.66 – 2.58 (t,  $J$  = 7.7 Hz, 3H), 1.65 (p,  $J$  = 7.5 Hz, 2H), 1.40 – 1.29 (m, 4H), 0.91 (t,  $J$  = 7.0 Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  151.80, 149.60, 123.92, 35.22, 31.35, 29.98, 22.45, 13.96.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{10}\text{H}_{16}\text{N}^+$ : calculated for 150.1283, found 150.1284



### 4-(3-chloropropyl)pyridine (12)

Following the modified general procedure C and D, 4-chlorobutyric acid (197  $\mu$ L, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu$ L, 3.0 mmol, 6 equiv) was used in procedure D [Table 1, footnote b]. The compound **12** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a yellow liquid (25.4 mg, 33% yield).

#### For scale-up reaction (5.0 mmol scale)

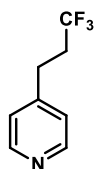
Following the modified general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), 4-chlorobutyric acid (1.97 mL, 20.0 mmol, 4 equiv),  $\text{AgNO}_3$  (167 mg, 1.0 mmol, 20 mol%),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and  $\text{H}_2\text{O}$  (25 mL) in procedure C and DBU (4.5 mL, 30.0 mmol, 6 equiv) was used in procedure D [Table 1, footnote b]. The compound **12** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as pale brown liquid (302.3 mg, 39% yield).

$R_f$  = 0.45 (*n*-hexane: EtOAc = 1:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (d,  $J$  = 6.1 Hz, 2H), 7.16 (d,  $J$  = 6.0 Hz, 2H), 3.56 (t,  $J$  = 6.3 Hz, 2H), 2.85 – 2.79 (m, 2H), 2.23 – 2.03 (m, 2H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  149.86, 149.73, 123.97, 43.80, 32.81, 32.09.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_8\text{H}_{11}\text{ClN}^+$ : calculated for 156.0580, found 156.0582



**4-(3,3,3-trifluoropropyl)pyridine (13)**

Following the modified general procedure C and D, carboxylic acid (284 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu\text{L}$ , 3.0 mmol, 6 equiv) was used in procedure D [**Table 1, footnote b**]. The compound **13** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 3:2), obtained as a yellow liquid (20.3 mg, 23% yield). [*Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar*]

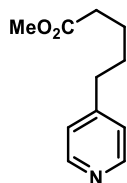
$R_f$  = 0.25 (*n*-hexane: EtOAc = 1:1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (d,  $J$  = 5.4 Hz, 2H), 7.16 (d,  $J$  = 5.3 Hz, 2H), 2.94 – 2.84 (m, 2H), 2.44 (ddd,  $J$  = 10.5, 8.2, 5.7 Hz, 2H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  150.10, 147.81, 126.38 (q,  $J$  = 276.6 Hz), 123.56, 34.38 (q,  $J$  = 29.1 Hz), 27.58 (q,  $J$  = 3.4 Hz).

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -69.24.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_8\text{H}_9\text{F}_3\text{N}^+$ : calculated for 176.0687, found 176.0688



**methyl 5-(pyridin-4-yl)pentanoate (14)**

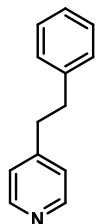
Following the modified general procedure C and D (0.3 M, DCE:H<sub>2</sub>O 1:1), adipic acid monomethyl ester (160 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225  $\mu\text{L}$ , 1.5 mmol, 3 equiv) was used in procedure D [**Table 1, footnote e**]. The compound **14** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow solid (37.7 mg, 39% yield).

$R_f$  = 0.15 (*n*-hexane: EtOAc = 1:1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.56 – 8.39 (m, 2H), 7.09 (d,  $J$  = 5.3 Hz, 2H), 3.66 (s, 3H), 2.65 – 2.59 (m, 2H), 2.34 (h,  $J$  = 3.6, 3.0 Hz, 2H), 1.66 (p,  $J$  = 3.6 Hz, 4H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.81, 150.92, 149.75, 123.84, 51.56, 34.86, 33.75, 29.65, 24.43.

**HRMS**  $[M+H]^+ = C_{11}H_{16}NO_2^+$ : calculated for 194.1181, found 194.1182



**4-phenethylpyridine (15)**

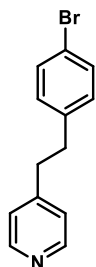
Following the general procedure C and D, hydrocinnamic acid (300 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu$ L, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1, footnote b**]. The compound **15** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (36.0 mg, 39% yield).

$R_f$  = 0.40 (*n*-hexane: EtOAc = 1:1)

**$^1H$  NMR** (500 MHz,  $CDCl_3$ )  $\delta$  8.56 – 8.39 (m, 2H), 7.28 (t,  $J$  = 7.6 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.16 – 7.12 (m, 2H), 7.11 – 7.08 (m, 2H), 2.93 (s, 4H).

**$^{13}C$  NMR** (126 MHz,  $CDCl_3$ )  $\delta$  151.14, 149.32, 140.64, 128.58, 128.49, 126.38, 124.18, 37.17, 36.60.

**HRMS**  $[M+H]^+ = C_{13}H_{14}N^+$ : calculated for 184.1126, found 184.1126



**4-(4-bromophenylethyl)pyridine (16)**

Following the general procedure C and D, 3-(4-bromophenyl)-propanoic acid (458 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu$ L, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1, footnote b**]. The compound **16** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (34.1 mg, 26% yield).

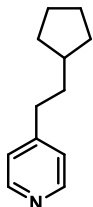
Following the modified general procedure C and D (0.3 M, DCE:H<sub>2</sub>O= 1:1), 3-(4-bromophenyl)-propanoic acid (458 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu$ L, 3.0 mmol, 6 equiv) was used in procedure D [**Table 1, footnote e**]. The compound **16** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (47.2 mg, 36% yield).

$R_f$  = 0.20 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.57 – 8.41 (m, 2H), 7.44 – 7.33 (m, 1H), 7.18 – 7.05 (m, 1H), 7.00 (d, J = 8.3 Hz, 1H), 2.91 (tt, J = 8.1, 4.0 Hz, 2H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 148.9, 139.4, 131.7, 130.3, 124.4, 120.3, 37.0, 36.0.

**HRMS** [M+H]<sup>+</sup> = C<sub>13</sub>H<sub>13</sub>BrN<sup>+</sup>: calculated for 262.0231, found 262.0240



**4-(2-cyclopentylethyl)pyridine (17)**

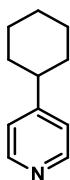
Following the modified general procedure C and D (0.3 M, DCE:H<sub>2</sub>O = 1:1), 3-cyclopentyl propanoic acid (142 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225 μL, 1.5 mmol, 3 equiv) was used in procedure D [Table 1, footnote e]. The compound **17** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1), obtained as a yellow solid (36.2 mg, 41% yield).

**R<sub>f</sub>** = 0.55 (*n*-hexane: EtOAc = 2:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.51 – 8.42 (m, 2H), 7.15 – 7.03 (m, 2H), 2.67 – 2.52 (m, 2H), 1.84 – 1.72 (m, 3H), 1.67 – 1.58 (m, 4H), 1.55 – 1.48 (m, 2H), 1.18 – 1.06 (m, 2H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 152.11, 149.67, 124.01, 39.71, 36.97, 34.59, 32.71, 25.31.

**HRMS** [M+H]<sup>+</sup> = C<sub>12</sub>H<sub>18</sub>N<sup>+</sup>: calculated for 176.1439, found 176.1443



**4-cyclohexylpyridine (8)**

Following the general procedure C and D, cyclohexane carboxylic acid (128 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 2:1), obtained as an orange liquid (65.1 mg, 81% yield).

**For scale-up reaction (5.0 mmol scale)**

Following the general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), cyclohexane carboxylic acid **3** (1.28 g, 10.0 mmol, 2 equiv), AgNO<sub>3</sub> (167 mg, 1.0 mmol, 20 mol%), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and H<sub>2</sub>O (25 mL) in procedure C and DBU (2.25 mL, 15.0 mmol, 3 equiv) was used in procedure D. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a yellow liquid (621 mg, 77% yield).

#### For scale-up reaction using green solvent (5.0 mmol scale)

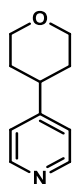
Following the general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), cyclohexane carboxylic acid **3** (1.28 g, 10.0 mmol, 2 equiv), AgNO<sub>3</sub> (167 mg, 1.0 mmol, 20 mol%), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (2.28 g, 10.0 mmol, 2 equiv) was added in ethyl acetate (25 mL) and H<sub>2</sub>O (25 mL) in procedure C and DBU (2.25 mL, 15.0 mmol, 3 equiv) was used in procedure D. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1), obtained as a yellow liquid (452 mg, 56% yield).

**R<sub>f</sub>** = 0.43 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.49 (d, *J* = 6.2 Hz, 2H), 7.15 (d, *J* = 6.2 Hz, 2H), 2.54 – 2.47 (m, 1H), 1.87 (tq, *J* = 6.6, 3.8 Hz, 4H), 1.79 – 1.73 (m, 1H), 1.40 (td, *J* = 9.5, 2.5 Hz, 4H), 1.30 – 1.21 (m, 1H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.35, 149.32, 122.65, 44.02, 33.63, 26.64, 26.05.

**HRMS** [M+H]<sup>+</sup> = C<sub>11</sub>H<sub>16</sub>N<sup>+</sup>: calculated for 162.1283, found 162.1288



#### 4-(tetrahydro-2H-pyran-4-yl)pyridine (**18**)

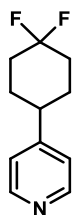
Following the general procedure C and D, tetrahydro-2H-pyran-4-carboxylic acid (130 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **18** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:2), obtained as a pale yellow liquid (61.8 mg, 76% yield).

**R<sub>f</sub>** = 0.13 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.56 (d, *J* = 6.1 Hz, 2H), 7.19 (d, *J* = 6.1 Hz, 2H), 4.15 – 4.08 (m, 2H), 3.62 – 3.51 (m, 2H), 2.80 (dt, *J* = 10.8, 5.2 Hz, 1H), 1.81 (dt, *J* = 6.0, 3.7 Hz, 4H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 154.90, 149.55, 122.32, 67.98, 40.90, 32.91.

**HRMS** [M+H]<sup>+</sup> = C<sub>10</sub>H<sub>14</sub>NO<sup>+</sup>: calculated for 164.1075, found 164.1078



#### 4-(4,4-difluorocyclohexyl)pyridine (**19**)

Following the general procedure C and D, 4,4-difluorocyclohexane-1-carboxylic acid (164  $\mu$ L, 1.0 mmol, 2 equiv) was used in procedure C. The compound **19** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 1:1), obtained as a yellow liquid (70.1 mg, 71% yield).

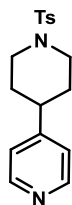
$R_f$  = 0.20 (*n*-hexane: EtOAc = 1:1)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (d,  $J$  = 6.2 Hz, 2H), 7.16 (d,  $J$  = 6.1 Hz, 2H), 2.62 (td,  $J$  = 9.8, 8.1, 5.6 Hz, 1H), 2.30 – 2.19 (m, 2H), 1.97 – 1.78 (m, 6H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.84 (d,  $J$  = 2.5 Hz), 149.99, 122.73 (dd,  $J$  = 243.0, 239.4 Hz), 122.21, 41.76, 33.77 (dd,  $J$  = 25.7, 23.0 Hz), 29.44 (d,  $J$  = 10.1 Hz).

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -94.31, -94.94, -104.75, -105.38.

HRMS  $[\text{M}+\text{H}]^+ = \text{C}_{11}\text{H}_{14}\text{F}_2\text{N}^+$ : calculated for 198.1094, found 198.1100



#### 4-(1-tosylpiperidin-4-yl)pyridine (**20**)

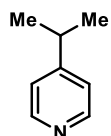
Following the general procedure C and D, 1-tosylpiperidine-4-carboxylic acid (283 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **20** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 1:3), obtained as a yellow liquid (58.0 mg, 37% yield).

$R_f$  = 0.10 (*n*-hexane: EtOAc = 1:1)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (d,  $J$  = 6.1 Hz, 2H), 7.70 (d,  $J$  = 8.3 Hz, 2H), 7.37 (d,  $J$  = 8.0 Hz, 2H), 7.10 (d,  $J$  = 6.1 Hz, 2H), 3.97 (d,  $J$  = 11.7 Hz, 1H), 2.48 (s, 3H), 2.38 (td,  $J$  = 11.9, 2.9 Hz, 4H), 1.94 – 1.78 (m, 4H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.72, 149.88, 143.67, 133.10, 129.71, 127.77, 122.17, 46.47, 41.17, 31.71, 21.56.

HRMS  $[\text{M}+\text{H}]^+ = \text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2\text{S}^+$ : calculated for 317.1324, found 317.1332



#### 4-isopropylpyridine (**21**)

Following the general procedure C and D, isobutyric acid (92  $\mu$ L, 1.0 mmol, 2 equiv) was used in procedure C. The compound **21** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate =

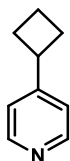
5:1 to 3:1), obtained as a yellow liquid (31.7 mg, 52% yield). [*Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar*]

$R_f$  = 0.35 (*n*-hexane: EtOAc = 1:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.56 (d,  $J$  = 6.1 Hz, 2H), 7.17 (d,  $J$  = 6.1 Hz, 2H), 2.91 (hept,  $J$  = 7.0 Hz, 1H), 1.28 (d,  $J$  = 7.0 Hz, 6H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.50, 149.78, 121.99, 33.56, 23.10.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_8\text{H}_{12}\text{N}^+$ : calculated for 122.0964, found 122.0964



#### 4-cyclobutylpyridine (22)

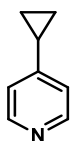
Following the general procedure C and D, cyclobutane carboxylic acid (100 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **22** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a pale yellow liquid (46.1 mg, 69% yield).

$R_f$  = 0.35 (*n*-hexane: EtOAc = 1:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (d,  $J$  = 6.1 Hz, 2H), 7.13 (d,  $J$  = 5.9 Hz, 2H), 3.55 (p,  $J$  = 8.5 Hz, 1H), 2.43 – 2.34 (m, 2H), 2.21 – 2.12 (m, 2H), 2.13 – 2.04 (m, 1H), 1.95 – 1.87 (m, 1H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  154.90, 149.62, 121.70, 39.33, 28.93, 18.36.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_9\text{H}_{12}\text{N}^+$ : calculated for 134.0964, found 134.0963



#### 4-cyclopropylpyridine (23)

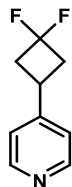
Following the general procedure C and D, cyclopropane carboxylic acid (86 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **23** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 1:1), obtained as an orange liquid (36.0 mg, 60% yield). [*Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar*]

$R_f$  = 0.35 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.43 (d, *J* = 6.1 Hz, 2H), 6.97 (d, *J* = 6.1 Hz, 2H), 1.87 (tt, *J* = 8.3, 4.9 Hz, 1H), 1.15 – 1.05 (m, 2H), 0.81 (dt, *J* = 7.0, 4.8 Hz, 2H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 153.76, 149.43, 120.73, 14.95, 10.53.

**HRMS** [M+H]<sup>+</sup> = C<sub>8</sub>H<sub>10</sub>N<sup>+</sup>: calculated for 120.0808, found 120.0812



#### 4-(3,3-difluorocyclobutyl)pyridine (**24**)

Following the general procedure C and D, 3,3-difluoro cyclopropane carboxylic acid (272 mg, 2.0 mmol, 4 equiv) was used in procedure C (4 equiv, 450 μL). [Table 1, footnote b]. The compound **24** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as an orange liquid (37.0 mg, 44% yield).

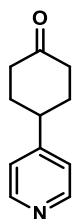
**R<sub>f</sub>** = 0.25 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.61 – 8.54 (m, 2H), 7.22 – 7.12 (m, 2H), 3.38 (pt, *J* = 6.8, 3.5 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.75 – 2.62 (m, 2H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 152.5, 149.6, 122.1, 121.7 – 116.1 (m), 42.0 (dd, *J* = 23.9, 22.7 Hz), 27.4 (dd, *J* = 14.7, 4.7 Hz).

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -85.24 (d, *J* = 195.0 Hz), -100.98 (d, *J* = 194.3 Hz).

**HRMS** [M+H]<sup>+</sup> = C<sub>9</sub>H<sub>10</sub>F<sub>2</sub>N<sup>+</sup>: calculated for 170.0781, found 170.0781



#### 4-(pyridin-4-yl)cyclohexan-1-one (**25**)

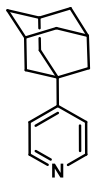
Following the general procedure C and D, 4-oxocyclohexane-1-carboxylic acid (142 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **25** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:2), obtained as an orange liquid (22.2 mg, 25% yield).

**R<sub>f</sub>** = 0.18 (ethyl acetate only)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.57 (d, *J* = 6.2 Hz, 2H), 7.20 (d, *J* = 6.2 Hz, 2H), 3.09 – 2.99 (m, 1H), 2.55 (dd, *J* = 7.6, 3.1 Hz, 4H), 2.31 – 2.21 (m, 2H), 2.04 – 1.89 (m, 2H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  210.00, 153.55, 150.03, 122.16, 41.98, 40.97, 33.04.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{11}\text{H}_{14}\text{NO}^+$ : calculated for 176.1075, found 176.1077



**4-(adamantan-1-yl)pyridine (26)**

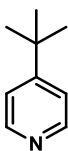
Following the general procedure C and D, 1-adamantyl carboxylic acid (180 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **26** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a pale yellow solid (95.9 mg, 89% yield).

$R_f$  = 0.55 (*n*-hexane: EtOAc = 1:1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (d,  $J$  = 6.3 Hz, 2H), 7.27 (d,  $J$  = 6.3 Hz, 2H), 2.17 – 2.11 (m, 3H), 1.91 (d,  $J$  = 2.9 Hz, 6H), 1.85 – 1.74 (m, 6H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.91, 149.68, 120.37, 42.36, 36.58, 36.24, 28.63.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{15}\text{H}_{20}\text{N}^+$ : calculated for 214.1596, found 214.1602



**4-(tert-butyl)pyridine (27)**

Following the general procedure C and D, pivalic acid (102 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **27** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 2:1), obtained as a pale yellow liquid (47.0 mg, 70% yield). [*Caution: this compound was quite volatile, all of the solvent evaporating step was performed below 40 °C, above 100 mbar*]

**For scale-up reaction (5.0 mmol scale)**

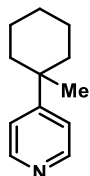
Following the modified general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), pivalic acid (1.02 mL, 10.0 mmol, 2 equiv),  $\text{AgNO}_3$  (167 mg, 1.0 mmol, 20 mol%),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and  $\text{H}_2\text{O}$  (25 mL) in procedure C and DBU (2.3 mL, 15.0 mmol, 3 equiv) was used in procedure D. The compound **27** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a pale yellow liquid (452 mg, 67% yield).

$R_f$  = 0.35 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.53 (d, *J* = 6.3 Hz, 2H), 7.31 (d, *J* = 6.3 Hz, 2H), 1.34 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 160.26, 149.42, 120.81, 34.70, 30.50

**HRMS** [M+H]<sup>+</sup> = C<sub>9</sub>H<sub>14</sub>N<sup>+</sup>: calculated for 136.1126 found 136.1122



**4-(1-methylcyclohexyl)pyridine (28)**

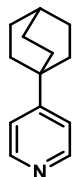
Following the general procedure C and D, 1-methylcyclohexane-1-carboxylic acid (142 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **28** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as an orange liquid (52.3 mg, 60% yield).

**R<sub>f</sub>** = 0.55 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.53 (d, *J* = 6.1 Hz, 2H), 7.28 (d, *J* = 6.1 Hz, 2H), 1.99 (dq, *J* = 8.6, 4.3, 3.1 Hz, 2H), 1.65 – 1.54 (m, 4H), 1.49 – 1.36 (m, 4H), 1.19 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 159.06, 149.81, 121.42, 38.06, 37.17, 30.00, 26.13, 22.48.

**HRMS** [M+H]<sup>+</sup> = C<sub>12</sub>H<sub>18</sub>N<sup>+</sup>: calculated for 176.1439, found 176.1445



**4-(bicyclo[2.2.2]octan-1-yl)pyridine (29)**

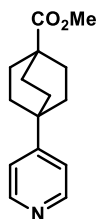
Following the general procedure C and D, bicyclo[2.2.2]octane-1-carboxylic acid (154 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **29** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as an orange liquid (37 mg, 40% yield).

**R<sub>f</sub>** = 0.30 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.51 – 8.44 (m, 2H), 7.23 – 7.18 (m, 2H), 1.79 – 1.73 (m, 6H), 1.72 – 1.65 (m, 7H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 159.8, 149.5, 121.3, 34.5, 31.6, 26.3, 24.4.

**HRMS** [M+H]<sup>+</sup> = C<sub>13</sub>H<sub>18</sub>N<sup>+</sup>: calculated for 188.1439, found 188.1441



**methyl 4-(pyridin-4-yl)bicyclo[2.2.2]octane-1-carboxylate (30)**

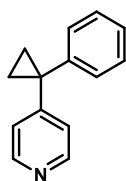
Following the general procedure C and D, 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (212 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **30** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 1:1), obtained as an orange liquid (94.5 mg, 77% yield).

$R_f$  = 0.20 (*n*-hexane: EtOAc = 1:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (d,  $J$  = 6.3 Hz, 2H), 7.22 (d,  $J$  = 6.3 Hz, 2H), 3.69 (s, 3H), 1.95 (dd,  $J$  = 10.4, 5.2 Hz, 6H), 1.86 (dd,  $J$  = 10.4, 5.2 Hz, 6H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.99, 158.11, 149.59, 120.97, 51.80, 39.04, 34.75, 31.09, 28.46.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{15}\text{H}_{20}\text{NO}_2^+$ : calculated for 246.1494, found 246.1502



**4-(1-phenylcyclopropyl)pyridine (31)**

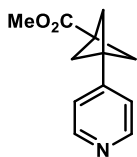
Following the general procedure C and D, 1-phenylcyclopropane-1-carboxylic acid (162 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **31** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a pale brown liquid (41.8 mg, 43% yield).

$R_f$  = 0.35 (*n*-hexane: EtOAc = 1:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (d,  $J$  = 6.3 Hz, 1H), 7.39 – 7.29 (m, 3H), 6.96 – 6.94 (m, 2H), 1.45 (d,  $J$  = 2.1 Hz, 1H), 1.38 (d,  $J$  = 2.1 Hz, 1H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.53, 149.47, 143.03, 129.80, 128.63, 126.96, 121.79, 29.13, 17.71.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{14}\text{H}_{14}\text{N}^+$ : calculated for 196.1126, found 196.1133



### Methyl 3-(pyridine-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (**32**)

Following the general procedure C and D, 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (170 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **32** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow liquid (32.0 mg, 32% yield).

#### For reaction with carboxylic acid as limiting reagent

Following the modified general procedure C and D, using 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid as limiting reagent (85 mg, 0.5 mmol) and 2 equiv of the pyridinium salt (376 mg, 1.0 mmol, 2 equiv) was used in procedure C [Table 1, Footnote d]. The compound **32** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow liquid (38.0 mg, 38% yield).

#### For reaction on concentrated solution (0.3 M)

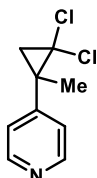
Following the modified general procedure C and D (0.3 M, DCE:H<sub>2</sub>O=1:1), 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (170 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225  $\mu$ L, 1.5 mmol, 3 equiv) was used in procedure D [Table 1, footnote e]. The compound **32** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow solid (42.3 mg, 42% yield).

$R_f$  = 0.30 (*n*-hexane: EtOAc = 1:1)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.54 (d, *J* = 4.9 Hz, 2H), 7.13 (d, *J* = 4.2 Hz, 2H), 3.71 (s, 3H), 2.35 (s, 6H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.2, 149.5, 148.6, 121.6, 53.3, 51.9, 40.9, 37.4.

HRMS [M+H]<sup>+</sup> = C<sub>12</sub>H<sub>14</sub>NO<sub>2</sub><sup>+</sup>: calculated for 204.1025, found 204.1031



### 4-(2,2-dichloro-1-methylcyclopropyl)pyridine. (**33**)

Following the modified general procedure C and D (0.3 M, DCE:H<sub>2</sub>O=1:1), 2,2-dichloro-1-methylcyclopropane-1-carboxylic acid (169 mg, 1.0 mmol, 2 equiv) was used in procedure C and DBU (225  $\mu$ L, 1.5 mmol, 3 equiv) was used in procedure D [Table 1, footnote e]. The compound **33** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a yellow solid (37.0 mg, 37% yield).

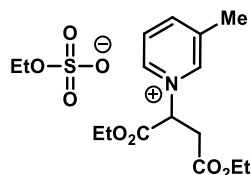
**R<sub>f</sub>** = 0.45 (*n*-hexane: EtOAc = 1:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.61 (d, *J* = 5.1 Hz, 2H), 7.25 – 7.23 (m, 2H), 1.99 (d, *J* = 7.5 Hz, 1H), 1.68 (s, 3H), 1.65 (d, *J* = 7.5 Hz, 1H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 150.1, 149.9, 123.8, 35.7, 31.6, 24.6.

**HRMS** [M+H]<sup>+</sup> = C<sub>9</sub>H<sub>10</sub>Cl<sub>2</sub>N<sup>+</sup>: calculated for 202.0190, found 202.0195

## 12. Characterization of Substituted Pyridinium Salts



### Pyridinium Feedstock **6b**

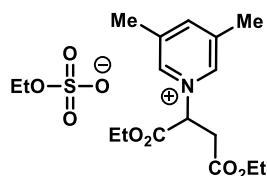
Following the general procedure B, the starting pyridinium **S6b** (523 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6b** was obtained as a colorless liquid (919 mg, 94% yield).

$R_f = 0.25$  (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.24 (d,  $J = 1.8$  Hz, 1H), 9.17 (d,  $J = 6.0$  Hz, 1H), 8.33 (dt,  $J = 8.0, 0.9$  Hz, 1H), 7.99 (dd,  $J = 8.0, 6.2$  Hz, 1H), 6.25 (dd,  $J = 7.8, 3.2$  Hz, 1H), 4.38 – 4.25 (m, 2H), 4.13 (dd,  $J = 24.8, 7.1$  Hz, 4H), 3.80 (dd,  $J = 19.0, 7.8$  Hz, 1H), 3.52 (dd,  $J = 19.0, 3.2$  Hz, 1H), 2.65 (s, 3H), 1.30 (dt,  $J = 8.6, 7.1$  Hz, 6H), 1.25 (t,  $J = 7.1$  Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.25, 166.39, 147.00, 146.10, 143.45, 139.59, 127.40, 68.33, 63.68, 63.38, 61.93, 37.17, 18.76, 15.18, 14.00, 13.91.

**HRMS** [M]<sup>+</sup> = C<sub>14</sub>H<sub>20</sub>NO<sub>4</sub><sup>+</sup>: calculated for 266.1392, found 266.1396



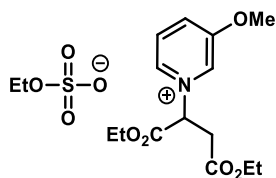
### Pyridinium Feedstock **6c**

Following the general procedure B, the starting pyridinium **S6c** (558 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6c** was obtained as a colorless liquid (1.01 g, >99% yield).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.01 (s, 2H), 8.09 (s, 1H), 6.20 (dd,  $J = 7.5, 3.2$  Hz, 1H), 4.32 (ddd,  $J = 35.2, 10.7, 7.1$  Hz, 2H), 4.21 – 4.06 (m, 4H), 3.79 (dd,  $J = 19.0, 7.6$  Hz, 1H), 3.50 (dd,  $J = 19.0, 3.2$  Hz, 1H), 2.59 (s, 6H), 1.29 (m, 6H, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.43, 166.50, 147.49, 143.15, 138.74, 68.14, 63.70, 63.58, 61.89, 37.24, 18.61, 15.13, 14.01, 13.91.

**HRMS** [M]<sup>+</sup> = C<sub>15</sub>H<sub>22</sub>NO<sub>4</sub><sup>+</sup>: calculated for 280.1549, found 280.1558



### Pyridinium Feedstock **6d**

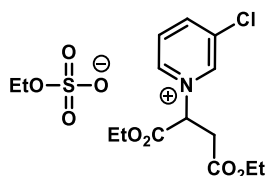
Following the general procedure B, the starting pyridinium **S6d** (564 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6d** was obtained as a colorless liquid (895 mg, 88% yield).

$R_f$  = 0.20 (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.08 (d,  $J$  = 1.2 Hz, 1H), 8.91 (d,  $J$  = 6.1 Hz, 1H), 8.10 – 8.07 (m, 1H), 7.99 (dd,  $J$  = 8.8, 6.0 Hz, 1H), 6.27 (dd,  $J$  = 7.8, 3.2 Hz, 1H), 4.31 (dd,  $J$  = 21.1, 7.1 Hz, 2H), 4.15 (d,  $J$  = 7.2 Hz, 2H), 4.10 (s, 3H), 4.10 – 4.06 (m, 2H), 3.77 (dd,  $J$  = 18.9, 7.8 Hz, 1H), 3.50 (dd,  $J$  = 18.9, 3.2 Hz, 1H), 1.32 – 1.22 (m, 9H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.17, 166.25, 158.67, 138.55, 132.95, 132.80, 128.28, 68.68, 63.74, 63.64, 61.93, 57.90, 37.18, 15.09, 13.99, 13.89.

**HRMS** [M]<sup>+</sup> = C<sub>14</sub>H<sub>20</sub>NO<sub>5</sub><sup>+</sup>: calculated for 282.1341, found 282.1349



### Pyridinium Feedstock **6e**

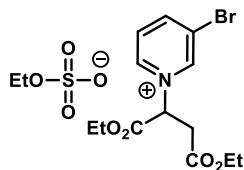
Following the general procedure B, the starting pyridinium **S6e** (574 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6e** was obtained as a yellow liquid containing of diethyl maleate as a impurity (752 mg, 73% yield).

$R_f$  = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.40 (d,  $J$  = 6.3 Hz, 1H), 9.36 (s, 1H), 8.58 – 8.52 (m, 1H), 8.23 (dd,  $J$  = 8.5, 6.2 Hz, 1H), 6.31 (dd,  $J$  = 7.8, 3.1 Hz, 1H), 4.35 (d,  $J$  = 7.1 Hz, 2H), 4.29 (dd,  $J$  = 20.2, 7.2 Hz, 2H), 4.20 – 4.13 (m, 2H), 3.77 (dd,  $J$  = 19.0, 7.8 Hz, 1H), 3.59 (dd,  $J$  = 19.0, 3.1 Hz, 1H), 1.44 – 1.21 (m, 9H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.24, 166.06, 146.65, 145.59, 145.09, 135.48, 129.18, 68.94, 63.91, 63.89, 62.08, 36.90, 15.07, 13.99, 13.89.

**HRMS** [M]<sup>+</sup> = C<sub>13</sub>H<sub>17</sub>ClNO<sub>4</sub><sup>+</sup>: calculated for 286.0846, found 286.0848



### Pyridinium Feedstock **6f**

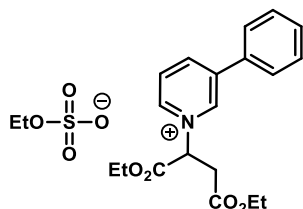
Following the general procedure B, the starting pyridinium **S6f** (2.74 mg, 10 mmol) was reacted with sulfuric acid (1.05 mL, 20 mmol) in EtOH (50 mL) at 90 °C for 24 h. The title compound **6f** was obtained as a yellow liquid after a filtration over a silica plug (first EtOAc, then CH<sub>2</sub>Cl<sub>2</sub>:MeOH=8:2) (3.07 g, 67% yield).

**R<sub>f</sub>** = 0.50 (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 4: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.48 (dt, *J* = 6.2, 1.3 Hz, 1H), 9.44 (t, *J* = 1.6 Hz, 1H), 8.67 (ddd, *J* = 8.3, 1.9, 1.0 Hz, 1H), 8.14 (dd, *J* = 8.4, 6.2 Hz, 1H), 6.33 (dd, *J* = 7.9, 3.0 Hz, 1H), 4.38 – 4.22 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.77 (dd, *J* = 19.0, 7.9 Hz, 1H), 3.55 (dd, *J* = 19.0, 3.0 Hz, 1H), 1.31 – 1.21 (m, 9H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 170.3, 166.2, 149.5, 147.2, 146.1, 129.4, 122.6, 69.0, 64.0, 63.5, 62.2, 37.1, 15.3, 14.1, 14.0.

**HRMS** [M]<sup>+</sup> = C<sub>13</sub>H<sub>17</sub>BrNO<sub>4</sub><sup>+</sup>: calculated for 330.0341, found 330.0343



### Pyridinium Feedstock **6g**

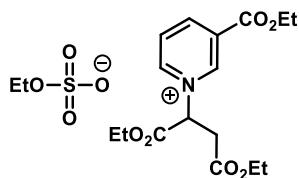
Following the general procedure B, the starting pyridinium **S6g** (678 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6g** was obtained as a colorless liquid (1.105 g, 98% yield).

**R<sub>f</sub>** = 0.45 (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.50 (s, 1H), 9.28 (d, *J* = 6.3 Hz, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 8.19 (dd, *J* = 8.2, 6.2 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.55 – 7.45 (m, 3H), 6.40 (dd, *J* = 8.0, 3.1 Hz, 2H), 4.31 (dd, *J* = 21.0, 7.1 Hz, 2H), 4.16 – 4.02 (m, 4H), 3.81 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.55 (dd, *J* = 18.9, 3.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 (dt, *J* = 9.9, 7.1 Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 170.23, 166.45, 144.17, 144.10, 144.06, 141.12, 132.80, 130.48, 129.81, 129.79, 128.46, 127.55, 68.58, 63.69 (2 carbon), 61.92, 37.14, 15.09, 13.98, 13.91.

**HRMS** [M]<sup>+</sup> = C<sub>19</sub>H<sub>22</sub>NO<sub>4</sub><sup>+</sup>: calculated for 328.1549, found 328.1558



### Pyridinium Feedstock **6h**

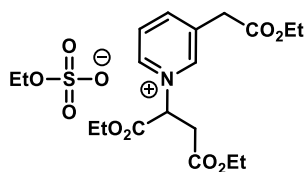
Following the general procedure B, the starting pyridinium **S6h** (595 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6h** was obtained as a yellow liquid (1.049 g, 93% yield).

$R_f = 0.35$  (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.68 (s, 1H), 9.63 (d,  $J = 6.3$  Hz, 1H), 9.04 (d,  $J = 8.1$  Hz, 1H), 8.37 (dd,  $J = 8.1, 6.2$  Hz, 1H), 6.35 (dd,  $J = 7.7, 3.2$  Hz, 1H), 4.51 (qd,  $J = 7.2, 1.5$  Hz, 2H), 4.40 – 4.27 (m, 2H), 4.16 (t,  $J = 7.1$  Hz, 2H), 4.03 (q,  $J = 7.1$  Hz, 4H), 3.79 (dd,  $J = 18.9, 7.7$  Hz, 1H), 3.64 (dd,  $J = 18.9, 3.2$  Hz, 1H), 1.45 (t,  $J = 7.2$  Hz, 3H), 1.31 (t,  $J = 7.2$  Hz, 3H), 1.25 (td,  $J = 7.1, 4.7$  Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.22, 166.27, 161.14, 150.21, 146.80, 146.54, 130.59, 128.92, 68.96, 63.91, 63.62, 63.46, 62.09, 36.84, 15.06, 14.07, 13.98, 13.89.

**HRMS** [M]<sup>+</sup> = C<sub>16</sub>H<sub>22</sub>NO<sub>6</sub><sup>+</sup>: calculated for 324.1447, found 324.1455



### Pyridinium Feedstock **6i**

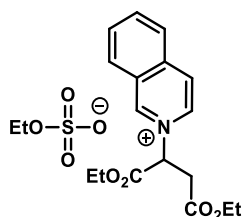
Following the general procedure B, the starting pyridinium **S6i** (706 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6i** was obtained as a colorless liquid (804.6 mg, 70% yield, >80% purity).

$R_f = 0.50$  (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.31 (s, 1H), 9.21 (d,  $J = 6.3$  Hz, 1H), 8.50 (d,  $J = 8.1$  Hz, 1H), 8.05 (dd,  $J = 8.1, 6.2$  Hz, 2H), 6.20 (dd,  $J = 7.8, 3.4$  Hz, 1H), 4.38 – 4.24 (m, 2H), 4.21 (m, 2H), 4.15 (m, 2H), 4.11 (m, 2H), 4.02 (s, 2H), 3.75 (dd,  $J = 18.8, 7.8$  Hz, 1H), 3.53 (dd,  $J = 18.8, 3.4$  Hz, 1H), 1.32 – 1.27 (m, 12H), 1.25 (t,  $J = 7.2$  Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.05, 169.15, 166.24, 147.83, 146.78, 144.56, 135.92, 127.46, 68.51, 63.95, 63.75, 61.96, 37.23, 37.07, 15.07, 14.07, 13.97, 13.88.

**HRMS** [M]<sup>+</sup> = C<sub>17</sub>H<sub>24</sub>NO<sub>6</sub><sup>+</sup>: calculated for 338.1604, found 338.1613



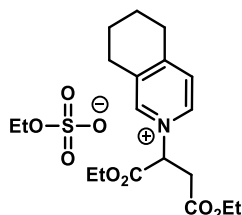
### Pyridinium Feedstock **6j**

Following the general procedure B, the starting pyridinium **S6j** (613 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6j** was obtained as a colorless liquid (948 mg, 89% yield).

$R_f$  = 0.54 (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  10.47 (s, 1H), 8.87 (dd,  $J$  = 6.9, 1.6 Hz, 1H), 8.65 – 8.62 (m, 1H), 8.35 (d,  $J$  = 6.9 Hz, 1H), 8.10 (dd,  $J$  = 5.7, 1.4 Hz, 2H), 7.87 (s, 1H), 6.42 – 6.37 (m, 1H), 4.30 (dd,  $J$  = 14.9, 7.3 Hz, 2H), 4.12 (q,  $J$  = 7.1 Hz, 2H), 4.06 (dd,  $J$  = 7.1, 5.3 Hz, 2H), 3.84 (dd,  $J$  = 18.7, 8.9 Hz, 1H), 3.57 (dd,  $J$  = 18.7, 3.5 Hz, 1H), 1.26 (dt,  $J$  = 10.2, 7.1 Hz, 6H), 1.15 (t,  $J$  = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  169.70, 166.47, 152.42, 137.88, 137.84, 134.96, 132.00, 131.22, 127.67, 127.03, 125.87, 68.29, 63.68, 63.53, 61.76, 36.82, 15.14, 13.93, 13.88.

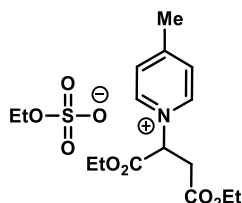


### Pyridinium Feedstock **6k**

Following the general procedure B, the starting pyridinium **S6k** (623 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 24 h. The title compound **6k** was obtained as a yellow liquid (820 mg, 76% yield).

$R_f$  = 0.58 (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.04 (s, 1H), 8.90 (dd,  $J$  = 6.5, 1.7 Hz, 1H), 7.67 (d,  $J$  = 6.5 Hz, 1H), 6.13 (dd,  $J$  = 7.4, 3.2 Hz, 1H), 4.35 – 4.23 (m, 3H), 4.18 – 4.08 (m, 3H), 3.77 (dd,  $J$  = 19.0, 7.4 Hz, 1H), 3.49 (dd,  $J$  = 18.9, 3.2 Hz, 1H), 3.02 (t,  $J$  = 6.3 Hz, 4H), 1.91 (t,  $J$  = 3.3 Hz, 4H), 1.34 – 1.22 (m, 9H).



### Pyridinium Feedstock **6l**

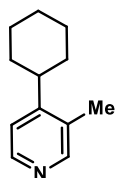
Following the general procedure B, the starting pyridinium **56l** (523 mg, 2.5 mmol) was reacted with sulfuric acid (0.26 mL, 5.0 mmol) in EtOH (12.5 mL) at 90 °C for 18 h. The title compound **6l** was obtained as a colorless liquid (1.16 g, 84% yield).

$R_f = 0.55$  (CH<sub>2</sub>Cl<sub>2</sub>: MeOH= 5: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.19 (d,  $J = 6.9$  Hz, 2H), 7.86 (d,  $J = 6.4$  Hz, 2H), 6.18 (dd,  $J = 7.9, 3.2$  Hz, 1H), 4.32 (dd,  $J = 18.7, 7.2$  Hz, 2H), 4.13 (dd,  $J = 16.9, 7.1$  Hz, 4H), 3.76 (dd,  $J = 18.9, 7.8$  Hz, 1H), 3.51 (dd,  $J = 18.9, 3.2$  Hz, 1H), 2.70 (s, 3H), 1.30 (td,  $J = 7.1, 3.5$  Hz, 6H), 1.25 (t,  $J = 7.1$  Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.23, 166.46, 160.61, 145.41, 128.47, 67.70, 63.68, 63.63, 61.93, 37.09, 22.38, 15.15, 14.00, 13.91.

### 13. Characterization of Products in Table 1 [3,4-Substituted Pyridines]



#### 4-cyclohexyl-3-methylpyridine (**34**)

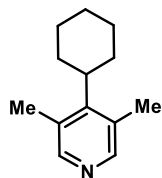
Following the general procedure C and D, the pyridinium **6b** (196 mg, 0.5 mmol) was reacted. The alkylated product **34** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a yellow liquid (69.4 mg, 79% yield, 2 steps).

$R_f = 0.30$  (*n*-hexane:EtOAc = 1: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.37 (d,  $J = 5.1$  Hz, 1H), 8.34 (s, 1H), 7.10 (d,  $J = 5.2$  Hz, 1H), 2.69 (dd,  $J = 7.4, 4.1$  Hz, 1H), 2.31 (s, 3H), 1.92 – 1.74 (m, 4H), 1.48 – 1.37 (m, 4H), 1.30 (dt,  $J = 12.6, 3.6$  Hz, 2H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  154.38, 150.73, 147.82, 130.68, 120.32, 39.79, 32.75, 26.78, 26.11, 16.02.

**HRMS** [M+H]<sup>+</sup> = C<sub>12</sub>H<sub>18</sub>N<sup>+</sup>: calculated for 176.1439, found 176.1445



#### 4-cyclohexyl-3,5-dimethylpyridine (35)

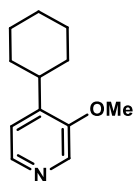
Following the procedure C and D, the pyridinium **6c** (203 mg, 0.5 mmol) was reacted. The alkylated product **35** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 3:1), obtained as a pale yellowish liquid (49.8 mg, 53% yield, 2 steps).

$R_f = 0.30$  (*n*-hexane:EtOAc = 1: 1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.17 (s, 2H), 3.00 – 2.89 (m, 1H), 2.37 (s, 6H), 1.91 – 1.76 (m, 4H), 1.71 – 1.64 (m, 2H), 1.43 – 1.25 (m, 4H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  151.47, 147.43 (suppressed broad peak), 130.79, 41.61, 29.73, 27.29, 26.21, 18.39 (suppressed broad peak)

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{13}\text{H}_{20}\text{N}^+$ : calculated for 190.1596, found 190.1601



#### 4-cyclohexyl-3-methoxypyridine (36)

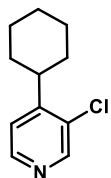
Following the procedure C and D, the pyridinium **6d** (204 mg, 0.5 mmol) was reacted. The alkylated product **36** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 5:1 to 2:1), obtained as a pale yellowish liquid (57.8 mg, 60% yield, 2 steps).

$R_f = 0.25$  (*n*-hexane:EtOAc = 1: 1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (d,  $J = 4.8$  Hz, 1H), 8.20 (s, 1H), 7.11 (d,  $J = 4.9$  Hz, 1H), 3.93 (s, 3H), 3.02 – 2.78 (m, 1H), 1.88 – 1.75 (m, 4H), 1.48 – 1.22 (m, 6H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.21, 144.50, 142.93, 132.88, 121.17, 55.98, 36.40, 32.34, 26.72, 26.20.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{12}\text{H}_{18}\text{NO}^+$ : calculated for 192.1388, found 192.1394



### 3-chloro-4-cyclohexylpyridine (37)

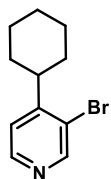
Following the procedure C and D, the pyridinium **6e** (206 mg, 0.5 mmol) was reacted. The alkylated product **37** was isolated by silica gel chromatography (*n*-hexane: diethyl ether = 4:1 to 3:1), obtained as a pale yellowish liquid (53.2 mg, 54% yield, 2 steps).

$R_f$  = 0.20 (*n*-hexane: diethyl ether = 3: 1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (s, 1H), 8.41 (d,  $J$  = 5.1 Hz, 1H), 7.19 (d,  $J$  = 5.1 Hz, 1H), 3.04 – 2.96 (m, 1H), 1.93 – 1.86 (m, 4H), 1.83 – 1.78 (m, 1H), 1.52 – 1.22 (m, 5H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.32, 149.29, 147.91, 131.63, 121.96, 40.13, 32.17, 26.49, 25.98.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{11}\text{H}_{15}\text{ClN}^+$ : calculated for 196.0893, found 196.0900



### 3-bromo-4-cyclohexylpyridine (38)

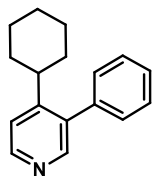
Following the procedure C and D, the pyridinium **6f** (228 mg, 0.5 mmol) was reacted. The alkylated product **38** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1), obtained as a pale yellow liquid (82 mg, 68% yield, 2 steps).

$R_f$  = 0.40 (*n*-hexane:EtOAc = 7:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.63 (s, 1H), 8.40 (d,  $J$  = 5.1 Hz, 1H), 7.15 (d,  $J$  = 5.2 Hz, 1H), 2.98 – 2.84 (m, 1H), 1.87 (t,  $J$  = 11.1 Hz, 5H), 1.78 (d,  $J$  = 13.5 Hz, 1H), 1.49 – 1.19 (m, 5H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.0, 152.0, 148.6, 123.1, 122.5, 43.0, 32.4, 26.6, 26.1.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{11}\text{H}_{15}\text{BrN}^+$ : calculated for 240.0388, found 240.0394



#### 4-cyclohexyl-3-phenylpyridine (**39**)

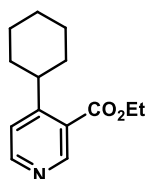
Following the general procedure C and D, the pyridinium **6g** (227 mg, 0.5 mmol) was reacted. The alkylated product **39** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1 to 5:1), obtained as a pale yellowish liquid (82.3 mg, 69% yield, 2 steps).

$R_f$  = 0.24 (*n*-hexane:EtOAc = 4: 1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.53 (d,  $J$  = 5.3 Hz, 1H), 8.42 (s, 1H), 7.51 – 7.41 (m, 3H), 7.34 – 7.25 (m, 2H, 1H), 2.76 – 2.64 (m, 1H), 1.82 – 1.67 (m, 5H), 1.44 (dd,  $J$  = 12.3, 3.3 Hz, 2H), 1.31 – 1.15 (m, 3H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.89, 150.38, 148.70, 138.09, 136.95, 129.44, 128.34, 127.50, 121.20, 39.63, 33.79, 26.40, 25.93.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{17}\text{H}_{20}\text{N}^+$ : calculated for 238.1596, found 238.1603



#### Ethyl 4-cyclohexylnicotinate (**40**)

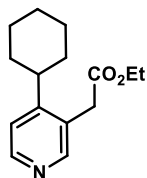
Following the procedure C and D, the pyridinium **6h** (225 mg, 0.5 mmol) was reacted. The alkylated product **40** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1 to 5:1), obtained as a pale yellowish liquid (74.3 mg, 64% yield, 2 steps).

$R_f$  = 0.35 (*n*-hexane:EtOAc = 4: 1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.95 (s, 1H), 8.61 (d,  $J$  = 5.3 Hz, 1H), 7.30 (d,  $J$  = 5.3 Hz, 1H), 4.41 (q,  $J$  = 7.1 Hz, 2H), 3.62 – 3.22 (m, 1H), 1.93 – 1.76 (m, 5H), 1.43 (t,  $J$  = 7.1 Hz, 3H), 1.50-1.28 (m, 5H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.69, 157.53, 152.15, 151.10, 126.12, 121.54, 61.29, 39.77, 33.54, 26.63, 26.05, 14.26.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{14}\text{H}_{20}\text{NO}_2^+$ : calculated for 234.1494, found 234.1502



**Ethyl 2-(4-cyclohexylpyridin-3-yl)acetate (41)**

Following the general procedure C and D, the pyridinium **6i** (232 mg, 0.5 mmol) was reacted. The alkylated product **41** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 4:1 to 2:1), obtained as a pale yellowish liquid (79.0 mg, 64% yield, 2 steps).

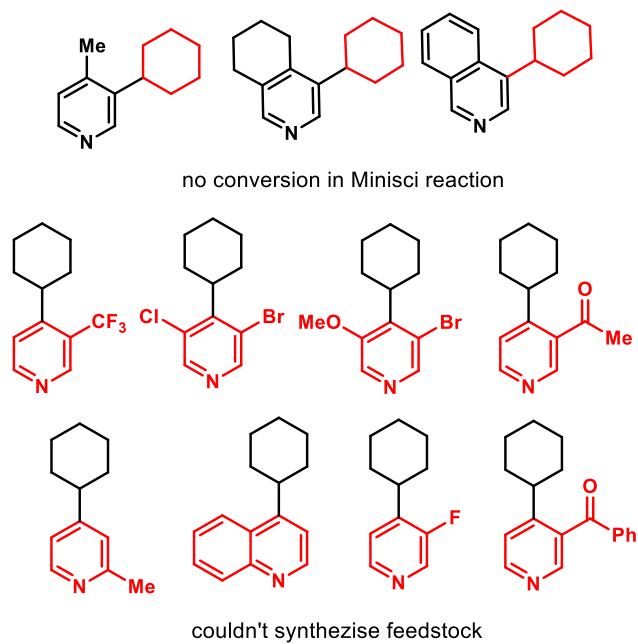
**R<sub>f</sub>** = 0.22 (*n*-hexane:EtOAc = 1: 1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.46 (d, *J* = 5.2 Hz, 1H), 8.40 (s, 1H), 7.19 (d, *J* = 5.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 2.72 – 2.66 (m, 1H), 1.90 – 1.84 (m, 2H), 1.84 – 1.74 (m, 3H), 1.49 – 1.35 (m, 5H), 1.27 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 170.97, 155.15, 151.29, 148.94, 127.68, 121.23, 61.15, 39.90, 36.16, 33.28, 26.66, 25.99, 14.16.

**HRMS** [M+H]<sup>+</sup> = C<sub>15</sub>H<sub>22</sub>NO<sub>2</sub><sup>+</sup>: calculated for 248.1651, found 248.1658

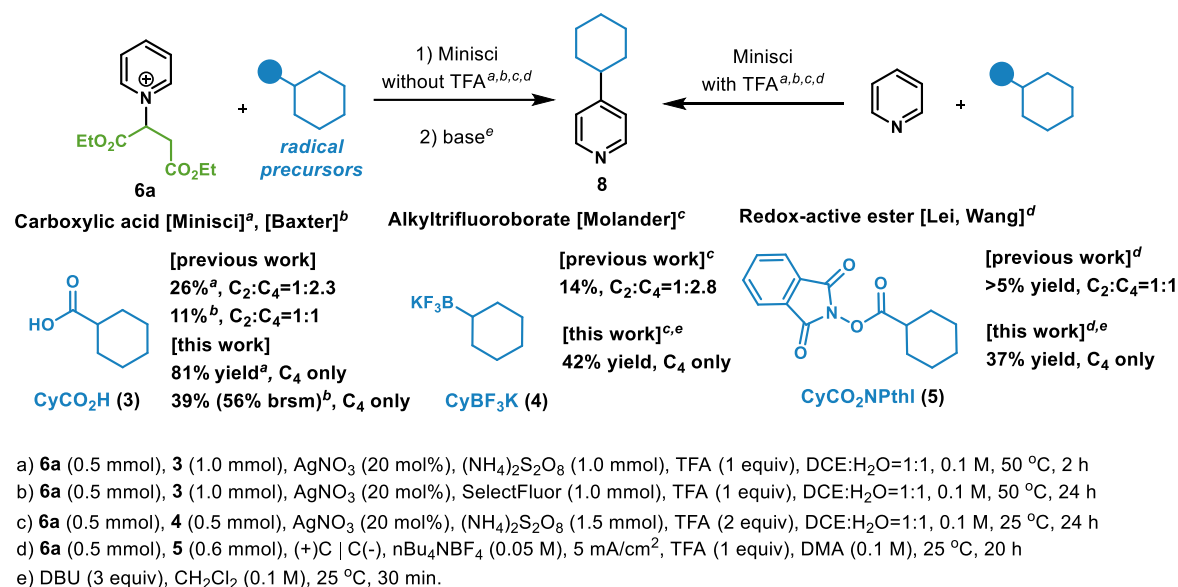
## 14. Unsuccessful or Challenging Substrates in Substituted Pyridine Examples



**Figure S22.** Unsuccessful or challenging substrates in substituted pyridine examples

## 15. Experimental Procedure and Characterization of Compounds in Applications

### 15.1 Comparison with Simple Pyridine Substrate in Figure 1C



**Figure S23.** Comparison experiments between **6a** and simple pyridine

#### Using **6a**

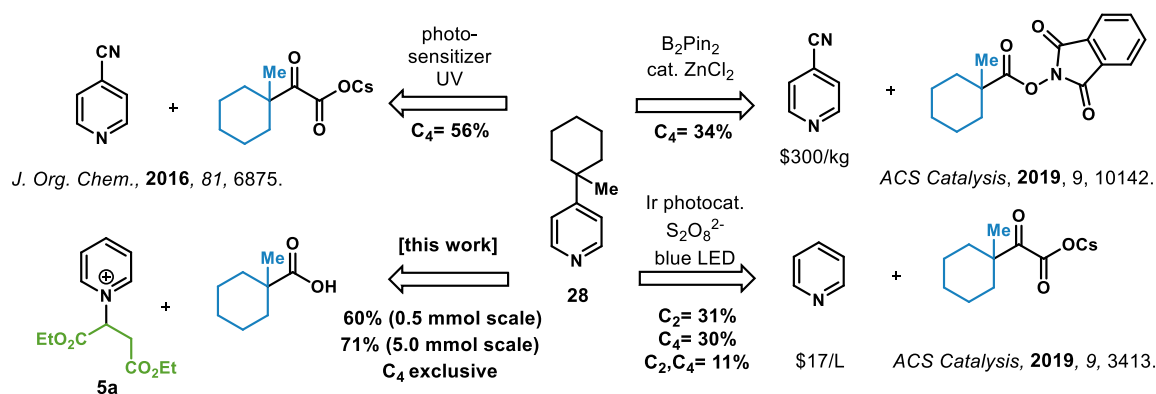
Following the general procedures written above (from C to H) followed by the procedure D, the alkyl precursor radical partners were used accordingly. The compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 2:1), obtained as an orange liquid.

#### Using pyridine

Following the general procedures written above (from C to H), pyridine (40.2 μL, 0.5 mmol, 1 equiv), TFA (19 μL, 0.5 mmol, 1 equiv) the alkyl precursor radical partners were used accordingly. The regioselectivity was determined by crude <sup>1</sup>H NMR using CDCl<sub>3</sub> or CD<sub>3</sub>OD. When possible, the compound **8** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 3:1 to 2:1), obtained as an orange liquid.

### 15.2 Comparison with Literature Examples

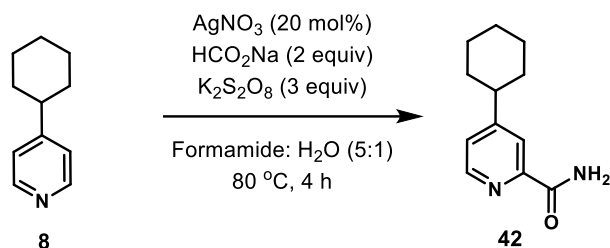
#### Alternative Regioselective Synthetic Approaches for Tertiary-alkyl Substituted Pyridine



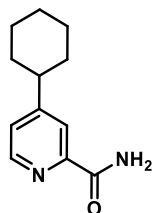
**Figure S24.** Alternative regioselective synthetic route

## 15.3 Two-Stage Derivatization

### 15.3.1. C-2 Carbamoylation



Following the literature procedure <sup>[8]</sup>, to a 5 mL culture tube equipped with screw cap and magnetic stirbar, AgNO<sub>3</sub> (8.7 mg, 0.05 mmol, 20 mol%), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (202 mg, 0.75 mmol, 3 equiv), HCOONa (34 mg, 0.5 mmol, 2 equiv) and corresponding pyridine **8** (40.3 mg, 0.25 mmol) were added, together with formamide (1 mL), and H<sub>2</sub>O (0.2 mL). The resulting mixture was stirred at 80 °C for 4 h. At the end of the reaction, the reaction mixture was cooled to room temperature, poured into a sat. aq NaCl solution (7 mL), and extracted with EtOAc (3 × 7 mL). The organic phases were combined, evaporated in a rotary evaporator. The residue was purified by flash column chromatography on silica gel (*n*-hexane: EtOAc = 5:1 to 2:1) to afford the corresponding product **42** as colorless liquid (26.4 mg, 52% yield).



#### 4-cyclohexylpicolinamide (**42**)

**R<sub>f</sub>** = 0.12 (*n*-hexane:EtOAc = 2: 1)

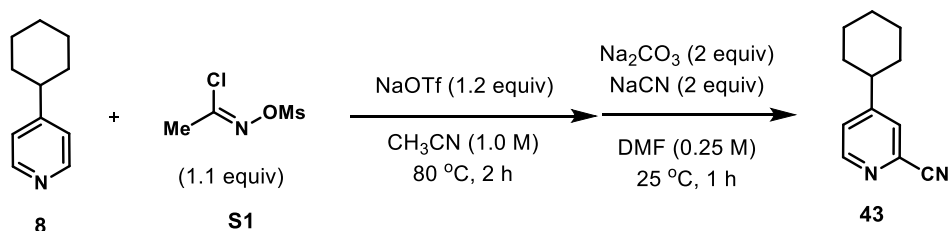
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.44 (d, *J* = 5.0 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.86 (br, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 5.77 (br, 1H), 2.63 – 2.52 (m, 1H), 1.92 – 1.82 (m, 4H), 1.80 – 1.72 (m, 1H), 1.50 – 1.37 (m, 4H), 1.35 – 1.19 (m, 1H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 167.31, 158.45, 149.61, 148.44, 125.30, 121.24, 44.10, 33.55, 26.59, 25.99.

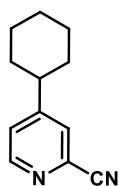
**HRMS** [M+H]<sup>+</sup> = C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O<sup>+</sup>: calculated for 205.1341, found 205.1348

<sup>8</sup> Han, W.; Jin, F.; Zhao, Q.; Du, H.; Yao, L. *Synlett* **2016**, 27, 1854.

### 15.3.2. C-2 Cyanation



Following the literature procedure<sup>[1]</sup>, to a 5 mL culture tube equipped with screw cap and magnetic stirbar, 4-cyclohexyl pyridine (40.3 mg, 0.25 mmol, 1.0 equiv), *N*-((methylsulfonyl)oxy)acetimidoyl chloride (**S1**, 47.2 mg, 0.275 mmol, 1.1 equiv) and sodium trifluoromethanesulfonate (NaOTf, 51.6 mg, 0.30 mmol, 1.2 equiv) were added, together with MeCN (0.25 mL, 1.0 M). Subsequently, the vial was sealed and heated at 80 °C with rapid stirring for 2 h. The reaction mixture was cooled to room temperature and diluted with DMF (1 mL), followed by the addition of Na<sub>2</sub>CO<sub>3</sub> (53 mg, 0.50 mmol, 2.0 equiv) and NaCN (24.5 mg, 0.50 mmol, 2.0 equiv). The vial was sealed and stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, and washed twice with water and once with brine. The organic solution was dried over MgSO<sub>4</sub>, and the product was purified on silica gel (hexane: ethyl acetate = 10:1 to 4:1). The resulting product **43** was obtained as a colorless liquid (18.3 mg, 39% yield) and starting material **8** was recovered (12.9 mg, 32%)



#### 4-cyclohexylpicolinonitrile (**43**)

$R_f = 0.52$  (*n*-hexane:EtOAc = 4:1)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.61 (d, *J* = 5.1 Hz, 1H), 7.57 (s, 1H), 7.39 – 7.34 (m, 1H), 2.59 (s, 1H), 1.91 (d, *J* = 8.0 Hz, 3H), 1.81 (d, *J* = 13.3 Hz, 1H), 1.43 (dt, *J* = 11.5, 6.6 Hz, 4H), 1.35 – 1.20 (m, 1H).

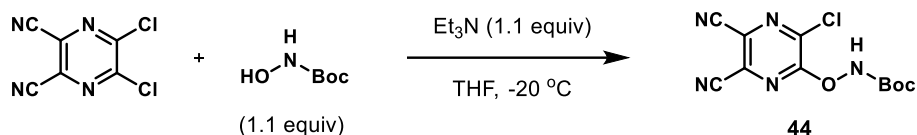
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 158.15, 150.98, 133.96, 127.38, 125.59, 117.54, 43.58, 33.31, 26.29, 25.69.

HRMS [M+H]<sup>+</sup> = C<sub>12</sub>H<sub>15</sub>N<sub>2</sub><sup>+</sup>: calculated for 187.1235, found 187.1237

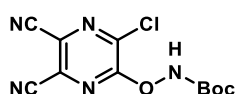
### 15.3.3. C-2 Amidation

Following the literature procedure<sup>[9]</sup>, Compound **45** was synthesized from the aminating reagent **44**.

<sup>9</sup> Fier, P. S.; Kim, S.; Cohen, R. D. *J. Am. Chem. Soc.* **2020**, *142*, 8614–8618.



Into a 100 mL round-bottom flask, 5,6-dichloropyrazine-2,3-dicarbonitrile (1.989 g, 10 mmol, 1.00 equiv), BocNHOH (1.414 g, 11 mmol, 1.10 equiv), and THF (20 mL) were added. The mixture was cooled to -20 °C and Et<sub>3</sub>N (1.53 mL, 11 mmol, 1.10 equiv) was added dropwise over 5 min. The resulting solution was stirred for 20 min at -20 °C, the solids were filtered off, and the filtrate concentrated. The residue was purified on silica gel chromatography (*n*-hexane:ethyl acetate = 100:0 to 4:1). The desired product **44** was obtained as a pale yellow solid (1.64 g, 55% yield).



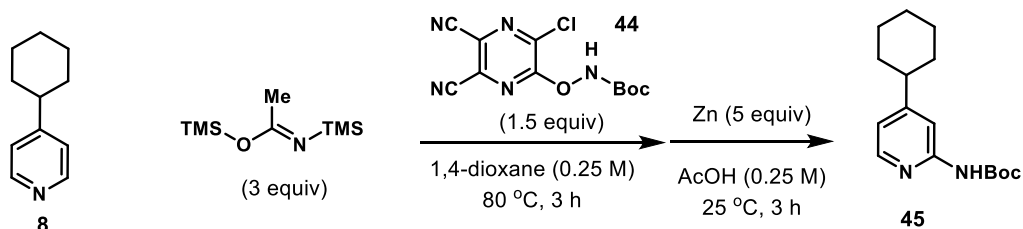
**tert-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate (**44**)**

**R<sub>f</sub>** = 0.35 (*n*-hexane:EtOAc = 4:1)

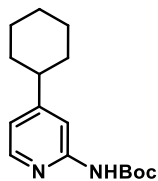
**<sup>1</sup>H NMR** (500 MHz, CD<sub>3</sub>CN) δ 9.35 (s, 1H), 1.50 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, CD<sub>3</sub>CN) δ 157.8, 154.9, 140.5, 129.1, 126.5, 112.7, 112.6, 83.7, 27.2.

**HRMS** [M-H]<sup>-</sup> = C<sub>11</sub>H<sub>9</sub>ClN<sub>5</sub>O<sub>3</sub>: calculated for 294.0394, found 294.0392



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, pyridine substrate (40.3 mg, 0.25 mmol, 1.0 equiv), *N,O*-bis(trimethylsilyl)acetamide (183 μL, 0.75 mmol, 3.0 equiv), and anhydrous 1,4-dioxane (1 mL, 0.25 M) were added, followed by *tert*-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate (**44**, 111 mg, 1.5 equiv). Subsequently, the vial was sealed and heated at 80 °C for 3 h. The reaction mixture was then cooled to ambient temperature, diluted with glacial AcOH (1 mL), and Zn powder (81.7 mg, 1.25 mmol, 5.0 equiv) was added at once. The resulting slurry was stirred vigorously for 3 h at ambient temperature. The mixture was concentrated to dryness, and the product was purified on silica gel (*n*-hexane: ethyl acetate = 10:1 to 1:1). The resulting product **45** was obtained as a white solid (47.8 mg, 69% yield).



**tert-butyl (4-cyclohexylpyridin-2-yl)carbamate (45)**

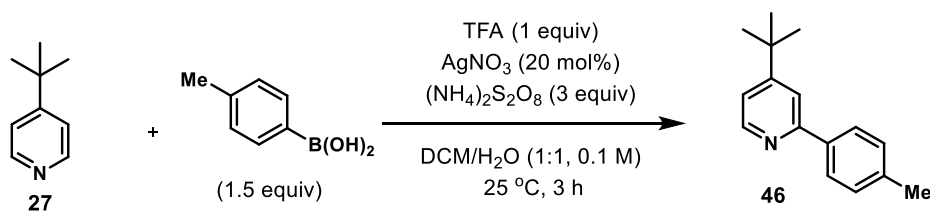
$R_f = 0.58$  (*n*-hexane:EtOAc = 4:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.11 (br, 1H), 8.22 (d,  $J = 5.3$  Hz, 1H), 7.88 (s, 1H), 6.82 (dd,  $J = 5.3$ , 1.6 Hz, 1H), 2.58 – 2.49 (m, 1H), 1.88 (dd,  $J = 19.9$ , 13.8 Hz, 4H), 1.82 – 1.74 (m, 1H), 1.57 (s, 9H), 1.48 – 1.35 (m, 4H), 1.35 – 1.24 (m, 1H).

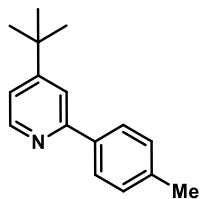
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.30, 152.90, 152.68, 147.46, 117.02, 110.90, 80.56, 44.38, 33.48, 28.41, 26.57, 25.94.

**HRMS**  $[\text{M-Boc}+2\text{H}]^+ = \text{C}_{11}\text{H}_{16}\text{N}_2^+$ : calculated for 177.1392, found 177.1394

**15.3.4. C-2 Arylation**



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, 4-*tert*-butylpyridine (**27**, 0.35 mmol, 47 mg, 1 equiv), 4-methylphenyl boronic acid (0.525 mmol, 1.5 equiv, 71 mg),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (239 mg, 1.05 mmol, 3 equiv),  $\text{AgNO}_3$  (11.7 mg, 0.07 mmol, 20 mol%) and TFA (27  $\mu\text{L}$ , 0.35 mmol, 1 equiv) were added, together with dichloromethane (1.75 mL) and  $\text{H}_2\text{O}$  (1.75 mL). The resulting biphasic mixture was stirred at room temperature for 3 h. The reaction was monitored by TLC or LCMS. Upon completion, the reaction was neutralized with aqueous  $\text{NaHCO}_3$  (5 mL) for adjusting basic pH. (pH >8). The crude mixture was diluted by dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude material was purified on silica gel chromatography (*n*-Hex:EtOAc = 40:1 to 25:1). The desired product **46** was obtained as a colorless oil (41.1 mg, 52% yield). [Overall yield from **6a**, 36% yield]



**4-(tert-butyl)-2-(p-tolyl)pyridine (46)**

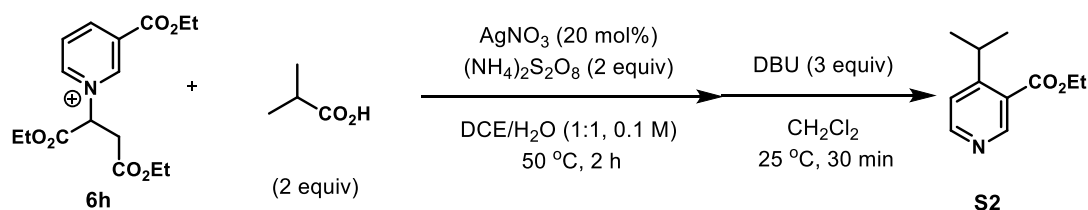
$R_f = 0.35$  (*n*-hexane:EtOAc = 10:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (d,  $J = 5.2$  Hz, 1H), 7.90 (d,  $J = 8.2$  Hz, 2H), 7.71 (s, 1H), 7.31 (d,  $J = 8.2$  Hz, 2H), 7.23 (dd,  $J = 5.3, 1.8$  Hz, 1H), 2.44 (s, 3H), 1.39 (s, 9H).

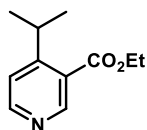
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.64, 157.53, 149.46, 138.68, 137.23, 129.42, 126.91, 119.07, 117.45, 34.86, 30.62, 21.27.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{16}\text{H}_{20}\text{N}^+$ : calculated for 226.1596, found 226.1599

### 15.3.5. Sequential C-2 Functionalization



Following the general procedure C and D, **6h** (228 mg, 0.5 mmol, 1 equiv) and isobutyric acid (92  $\mu\text{L}$ , 1.0 mmol, 2 equiv) was used in procedure C. The compound **S2** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 10:1 to 6:1), obtained as a yellow liquid (52.5 mg, 54% yield).



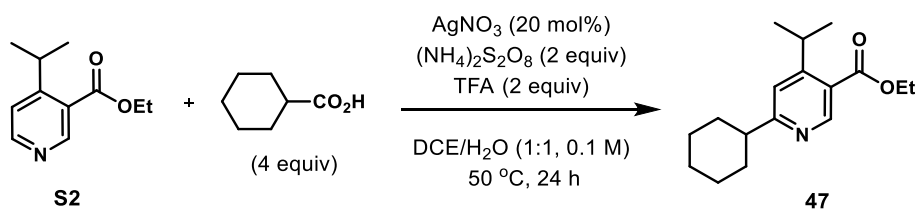
### ethyl 4-isopropylnicotinate (**S2**)

$R_f = 0.30$  (*n*-hexane:EtOAc = 4:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.96 (s, 1H), 8.64 (d,  $J = 5.3$  Hz, 1H), 7.34 (d,  $J = 5.3$  Hz, 1H), 4.42 (q,  $J = 7.1$  Hz, 2H), 3.82 (hept,  $J = 6.8$  Hz, 1H), 1.43 (t,  $J = 7.1$  Hz, 3H), 1.29 (d,  $J = 6.9$  Hz, 6H).

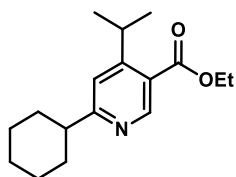
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.60, 158.82, 152.21, 150.97, 126.03, 121.01, 61.34, 29.26, 23.12, 14.23.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{11}\text{H}_{16}\text{NO}_2^+$ : calculated for 194.1181, found 194.1187



To a 8 mL culture tube equipped with screw cap and magnetic stirbar, compound **S2** (0.25 mmol, 48.3 mg, 1 equiv), cyclohexanecarboxylic acid (128 mg, 1.0 mmol, 4 equiv), TFA (38  $\mu\text{L}$ , 0.5 mmol, 2

equiv), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (114 mg, 0.5 mmol, 2 equiv) and AgNO<sub>3</sub> (8.3 mg, 0.05 mmol, 20 mol%) were added, together with dichloroethane (1.25 mL) and H<sub>2</sub>O (1.25 mL). The resulting biphasic mixture was then stirred at 50 °C for 24 h. Upon completion, the reaction was diluted with dichloromethane (2 mL), saturated aq. NaHCO<sub>3</sub> (2 mL) and checked the pH above 7. The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was purified using silica column chromatography (n-hexane: EtOAc = 30:1 to 10:1). The resulting product **47** was obtained as a colorless liquid (44.6 mg, 65% yield) [Overall yield from **6h**, 35% yield] The minor C-2 regioisomer was determined by crude NMR, but couldn't characterize pure product (C6:C2 =10:1)



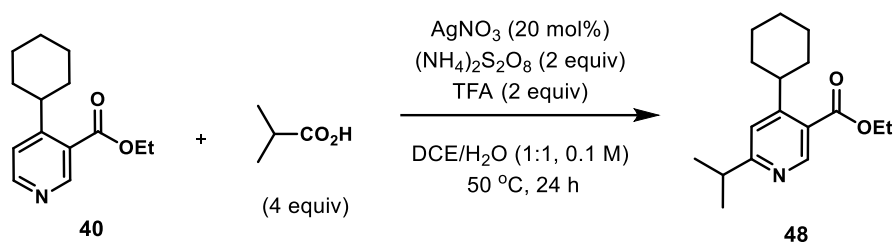
#### ethyl 6-cyclohexyl-4-isopropylpyridine-3-carboxylate (**47**)

**R<sub>f</sub>** = 0.60 (*n*-hexane:EtOAc = 4:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.91 (s, 1H), 7.17 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.83 (hept, *J* = 6.9 Hz, 1H), 2.74 (tt, *J* = 11.9, 3.4 Hz, 1H), 2.00 – 1.84 (m, 4H), 1.78 (dt, *J* = 12.8, 3.3, 1.5 Hz, 1H), 1.57 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.50 – 1.38 (m, 5H), 1.33 (tt, *J* = 12.6, 3.4 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 6H).

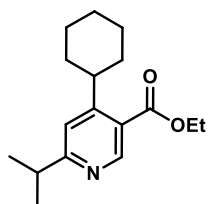
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 169.61, 166.76, 159.28, 150.70, 123.38, 118.19, 61.04, 46.72, 32.71, 29.22, 26.49, 25.99, 23.17, 14.24.

**HRMS** [M+H]<sup>+</sup> = C<sub>17</sub>H<sub>26</sub>NO<sub>2</sub><sup>+</sup>: calculated for 276.1964, found 276.1971



To a 8 mL culture tube equipped with screw cap and magnetic stirbar, compound **40** (0.25 mmol, 58.3 mg, 1 equiv), isobutyric acid (88 mg, 1.0 mmol, 4 equiv), TFA (38 μL, 0.5 mmol, 2 equiv), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (114 mg, 0.5 mmol, 2 equiv) and AgNO<sub>3</sub> (8.3 mg, 0.05 mmol, 20 mol%) were added, together with dichloroethane (1.25 mL) and H<sub>2</sub>O (1.25 mL). The resulting biphasic mixture was stirred at 50 °C for 24 h. Upon completion, the reaction was diluted with dichloromethane (2 mL), saturated aq. NaHCO<sub>3</sub> (2 mL) and checked the pH above 7. The aqueous phase was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was purified using silica column chromatography (*n*-hexane: EtOAc = 30:1 to 10:1). The resulting product **48** was obtained as a colorless liquid (28.2 mg, 41% yield) and the starting material **40** was recovered (23.3 mg, 40% yield). [Overall yield from **6h**, 27% yield]

The minor C-2 regioisomer was detected trace amount in crude NMR, but couldn't characterize pure product (C6:C2 =>20:1)



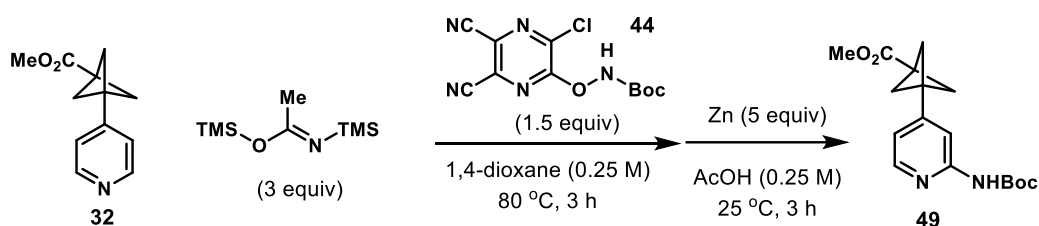
**ethyl 4-cyclohexyl-6-isopropyl-3-pyridinecarboxylate (48)**

$R_f = 0.55$  (*n*-hexane:EtOAc = 4:1)

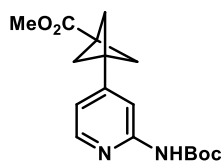
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.91 (s, 1H), 7.16 (s, 1H), 4.39 (q,  $J = 7.1$  Hz, 2H), 3.49 – 3.39 (m, 1H), 3.14 – 3.02 (m, 1H), 1.94 – 1.84 (m, 5H), 1.80 (d,  $J = 12.8$  Hz, 1H), 1.53 – 1.36 (m, 6H), 1.32 (d,  $J = 6.9$  Hz, 7H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.37, 166.86, 158.06, 150.90, 123.48, 118.38, 61.01, 39.78, 36.51, 33.61, 26.71, 26.12, 22.41, 14.26.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{17}\text{H}_{26}\text{NO}_2^+$ : calculated for 276.1964, found 276.1973



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, the pyridine substrate **32** (50.1 mg, 0.25 mmol, 1.0 equiv), *N,O*-bis(trimethylsilyl)acetamide (183  $\mu\text{L}$ , 0.75 mmol, 3.0 equiv), and anhydrous 1,4-dioxane (1 mL, 0.25 M) were added, followed by the addition of *tert*-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate (**44**, 111 mg, 1.5 equiv). Subsequently, the vial was sealed and heated at 80  $^{\circ}\text{C}$  for 3 h. The reaction mixture was cooled to ambient temperature, diluted with glacial AcOH (1 mL), and Zn powder (81.7 mg, 1.25 mmol, 5.0 equiv) was added at once. The resulting slurry was stirred vigorously for 3 h at ambient temperature. The mixture was concentrated to dryness, and the product was purified on silica gel (*n*-hexane: ethyl acetate = 2:1 to 1:1). The resulting product **49** was obtained as a white solid (66.3 mg, 83% yield) [Overall yield from **6a**, 35% yield]



**methyl 3-(2-((tert-butoxycarbonyl)amino)pyridin-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (49)**

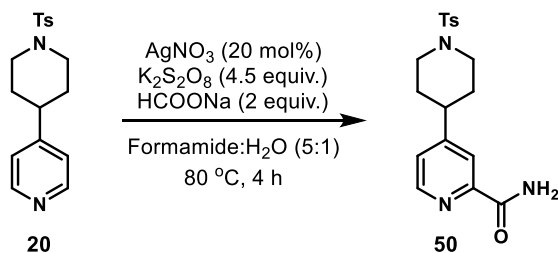
$R_f = 0.55$  (*n*-hexane:EtOAc = 2:1)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.78 (s, 1H), 8.22 (dd,  $J = 5.2, 0.9$  Hz, 1H), 7.79 (s, 1H), 6.78 (dd,  $J = 5.1, 1.5$  Hz, 1H), 3.71 (s, 3H), 2.35 (s, 6H), 1.54 (s, 9H).

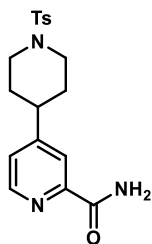
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.40, 152.79, 152.74, 150.73, 147.72, 116.16, 109.91, 81.04, 53.40, 51.91, 41.29, 37.29, 28.51, 28.36.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_4^+$ : calculated for 319.1658, found 319.1655

**15.3.6. Intermediate Synthesis For Oomycetes Fungicide Candidate**



Following a modified literature procedure <sup>[8]</sup>, to a 5 mL culture tube equipped with screw cap and magnetic stirbar,  $\text{AgNO}_3$  (9.0 mg, 0.05 mmol, 20 mol%),  $\text{K}_2\text{S}_2\text{O}_8$  (101 mg, 0.375 mmol, 1.5 equiv),  $\text{HCOONa}$  (34 mg, 0.5 mmol, 2 equiv) and corresponding pyridine **20** (40.3 mg, 0.25 mmol) were added, together with formamide (1 mL), and  $\text{H}_2\text{O}$  (0.2 mL). While the resulting mixture was stirred at 80 °C other 2 portions of  $\text{K}_2\text{S}_2\text{O}_8$  (2x101 mg, 0.375 mmol, 1.5 equiv) were added after 1 hour and 2 hours. The mixture was then stirred at the same temperature for other 2 hours. At the end of the reaction, the reaction mixture was cooled to room temperature, poured into a sat. aq NaCl solution (7 mL), and extracted with EtOAc ( $3 \times 7$  mL). The organic phases were combined, evaporated in a rotary evaporator. The residue was purified by flash column chromatography on silica gel (EtOAc) to afford the corresponding product **50** as white solid (53.9 mg, 60% yield).



**4-(1-tosylpiperidin-4-yl)picolinamide (50)**

$R_f = 0.60$  (EtOAc)

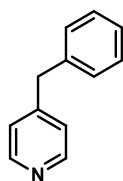
**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 – 8.46 (m, 1H), 8.01 (d,  $J$  = 1.8 Hz, 1H), 7.86 (br, 1H), 7.71 – 7.65 (m, 2H), 7.35 (d,  $J$  = 8.0 Hz, 2H), 7.24 (dd,  $J$  = 5.1, 1.9 Hz, 1H), 5.73 (br, 1H), 3.95 (dp,  $J$  = 11.7, 1.9 Hz, 2H), 2.52 (tt,  $J$  = 12.0, 3.9 Hz, 1H), 2.45 (s, 3H), 2.37 (td,  $J$  = 12.0, 2.8 Hz, 2H), 1.97 – 1.78 (m, 5H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.73, 155.48, 149.82, 148.71, 143.86, 133.26, 129.88, 127.87, 124.68, 121.39, 46.49, 41.33, 31.72, 21.69.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_3\text{S}^+$ : calculated for 360.1382, found 360.1391

## 15.4 Low Yield Examples

### 15.4.1. Minisci Reaction



#### 4-benzylpyridine (S3)

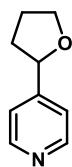
Following the general procedure C and D, phenylacetic acid (272 mg, 2.0 mmol, 4 equiv) was used in procedure C and DBU (450  $\mu\text{L}$ , 3.0 mmol, 6 equiv) was used in procedure D [**Table 1, footnote b**]. The compound **S3** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:1), obtained as a brown solid (25.9 mg, 26% yield).

$R_f$  = 0.25 (*n*-hexane:EtOAc = 1:1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J$  = 5.2 Hz, 4H), 7.32 (t,  $J$  = 7.4 Hz, 4H), 7.24 (t,  $J$  = 7.0 Hz, 1H), 7.18 (d,  $J$  = 7.5 Hz, 4H), 7.12 (d,  $J$  = 5.2 Hz, 4H), 3.98 (s, 3H).

**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  150.6, 149.6, 138.9, 129.2, 128.9, 126.9, 124.4, 41.4.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{12}\text{H}_{12}\text{N}^+$ : calculated for 170.0970, found 170.0974



#### 4-(tetrahydrofuran-2-yl)pyridine (S4)

For reaction with the tetrahydrofuran-2-carboxylic acid as a radical precursor

Following the general procedure C and D, tetrahydrofuran-2-carboxylic acid (116 mg, 1.0 mmol, 2 equiv) was used in procedure C. The compound **S4** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:3), obtained as an orange liquid (12.5 mg, 17% yield).

#### For reaction with the THF as a radical precursor

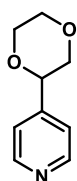
Following the general procedure H and D, tetrahydrofuran (81  $\mu$ L, 1.0 mmol, 2 equiv) was used in procedure H. The compound **S4** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 2:1 to 1:3), obtained as a pale yellow solid (25.4 mg, 34% yield).

$R_f$  = 0.15 (*n*-hexane:EtOAc = 1:2)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (d,  $J$  = 5.1 Hz, 2H), 7.28 (d,  $J$  = 5.5 Hz, 2H), 4.93 (t,  $J$  = 7.2 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.99 (q,  $J$  = 7.4 Hz, 1H), 2.41 (dq,  $J$  = 13.2, 6.9 Hz, 1H), 2.03 (tt,  $J$  = 13.8, 5.8 Hz, 2H), 1.79 (dq,  $J$  = 12.4, 7.6 Hz, 1H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.94, 149.61, 120.53, 79.08, 68.97, 34.32, 25.83.

**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_9\text{H}_{12}\text{NO}^+$ : calculated for 150.0919, found 150.0919



#### 4-(1,4-dioxan-2-yl)pyridine (**S5**)

Following the general procedure H and D, 1,4-dioxane (85  $\mu$ L, 1.0 mmol, 2 equiv) was used in procedure H. The compound **S5** was isolated by silica gel chromatography (*n*-hexane: ethyl acetate = 1:2), obtained as a pale yellow solid (37.1 mg, 45% yield).

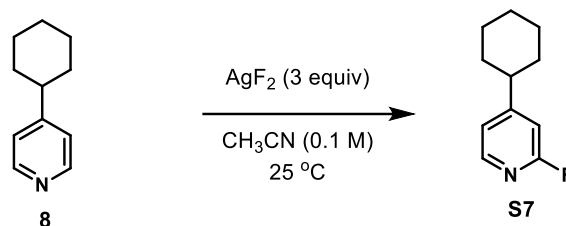
$R_f$  = 0.35 (*n*-hexane:EtOAc = 1:2)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (d,  $J$  = 6.1 Hz, 2H), 7.31 – 7.26 (m, 2H), 4.65 (dd,  $J$  = 10.1, 2.9 Hz, 1H), 3.93 (ddd,  $J$  = 22.6, 12.3, 2.8 Hz, 3H), 3.85 – 3.70 (m, 2H), 3.40 (dd,  $J$  = 11.7, 10.1 Hz, 1H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  149.91, 146.97, 120.88, 76.27, 71.84, 66.86, 66.35.

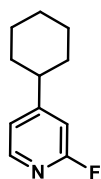
**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_9\text{H}_{12}\text{NO}_2^+$ : calculated for 166.0868, found 166.0873

### 15.4.2. C2-Fluorination



The reaction was performed followed by Fier & Hartwig procedure<sup>[10]</sup>

To an oven-dried 5 mL culture tube, 4-cyclohexylpyridine **8** (40.3 mg, 0.25 mmol, 1 equiv) and anhydrous acetonitrile (2.5 mL) were added. While the solution was stirring rapidly,  $\text{AgF}_2$  (109 mg, 0.75 mmol, 3 equiv) was added at once. The reaction vial was sealed with a Teflon-lined cap with Ar balloon and stirred at room temperature for 2 h. The reaction was completed, poured into a separatory funnel containing 10 mL of saturated aqueous  $\text{NaHCO}_3$ , and extracted with EtOAc. The organic layer was washed once with 10 mL of brine, dried over anhydrous  $\text{MgSO}_4$ , and concentrated. The crude product was purified by silica gel chromatography (*n*-Hex:EtOAc = 50:1 to 30:1) to obtained the title compound **S7** as a colorless liquid (4.9 mg, 11% yield, 85% starting material (**8**) was remained)



#### 4-cyclohexyl-2-fluoropyridine (**S7**)

$R_f = 0.42$  (*n*-hexane:EtOAc = 10:1)

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (d,  $J = 5.2$  Hz, 1H), 7.03 (d,  $J = 4.8$  Hz, 1H), 6.77 (s, 1H), 2.62 – 2.52 (m, 1H), 1.90 (t,  $J = 6.1$  Hz, 4H), 1.83 – 1.75 (m, 1H), 1.42 (dd,  $J = 11.7, 8.8$  Hz, 4H), 1.34 – 1.22 (m, 1H).

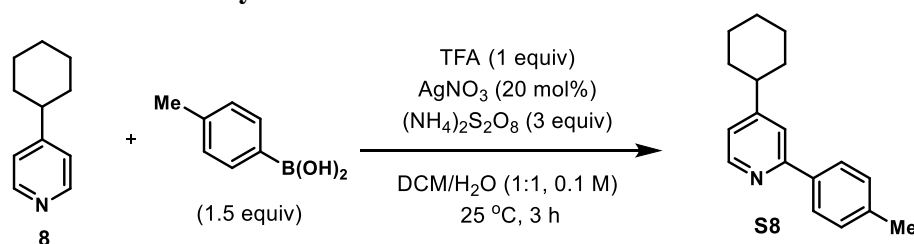
**$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ )  $\delta$  164.21 (d,  $J = 237.5$  Hz), 162.76 (d,  $J = 7.4$  Hz), 147.28 (d,  $J = 15.3$  Hz), 120.21 (d,  $J = 3.9$  Hz), 107.47 (d,  $J = 36.6$  Hz), 43.80 (d,  $J = 2.7$  Hz), 33.41, 26.40, 25.84.

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -71.78.

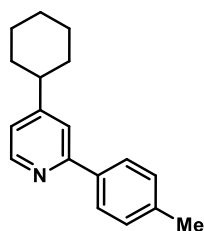
**HRMS**  $[\text{M}+\text{H}]^+ = \text{C}_{11}\text{H}_{15}\text{FN}^+$ : calculated for 180.1189, found 180.1193

<sup>10</sup> Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10139–10147.

### 15.4.3. C-2 Borono Minisci Arylation



To a 5 mL culture tube equipped with screw cap and magnetic stirbar, 4-cyclohexylpyridine **8** (0.25 mmol, 40.3 mg, 1 equiv), 4-methylphenyl boronic acid (0.375 mmol, 1.5 equiv, 51 mg), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (171 mg, 0.75 mmol, 3 equiv), AgNO<sub>3</sub> (8 mg, 0.05 mmol, 20 mol%) and TFA (19 μL, 0.25 mmol, 1 equiv) were added, together with dichloromethane (1.25 mL) and H<sub>2</sub>O (1.25 mL). The resulting biphasic mixture was stirred at room temperature for 3 h. The reaction was monitored by TLC or LCMS. Upon completion, the reaction was neutralized with aqueous NaHCO<sub>3</sub> (5 mL) for adjusting basic pH above 8. The crude mixture was diluted by dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The crude material was purified on silica gel chromatography (*n*-Hex:EtOAc = 30:1 to 15:1). The desired product **S8** was obtained as a colorless oil (8.9 mg, 14% yield).



#### 4-cyclohexyl-2-(p-tolyl)pyridine (**S8**)

**R<sub>f</sub>** = 0.24 (*n*-hexane:EtOAc = 15:1)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.58 (d, *J* = 5.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.56 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.07 (dd, *J* = 5.1, 1.7 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.43 (s, 3H), 1.98 – 1.85 (m, 4H), 1.81 (dt, *J* = 13.1, 1.6 Hz, 1H), 1.53 – 1.24 (m, 5H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 157.50, 157.29, 149.50, 138.69, 136.98, 129.41, 126.84, 120.61, 119.10, 44.16, 33.62, 26.60, 25.99, 21.27.

**HRMS** [M+H]<sup>+</sup> = C<sub>18</sub>H<sub>22</sub>N<sup>+</sup>: calculated for 252.1752, found 252.1757

## 15.5 Mock Medicinal Chemistry and Process Chemistry [Figure 3C]

Following the general procedure C and D, pyridinium **6a** (1.88 g, 5.0 mmol, 1 equiv), 1-adamantyl carboxylic acid (1.80 g, 10.0 mmol, 2 equiv), AgNO<sub>3</sub> (167 mg, 1.0 mmol, 20 mol%), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (2.28 g, 10.0 mmol, 2 equiv) was added in dichloroethane (25 mL) and H<sub>2</sub>O (25 mL) in procedure C and DBU (2.25 mL, 15.0 mmol, 3 equiv) was used in procedure D. After the deprotection step, the crude mixture was washed by brine (20 mL x 3 times), dried using anhydrous sodium sulfate, filtered and concentrated by rotavap. The crude mixture was dissolved in hexane (100 mL) and aq. 1 N HCl (50 mL) to adjust pH below 1. These two phase mixture was poured into separatory funnel, washed hexane

(50 mL x 3 times). The aqueous layer was treated by aq. 1 *N* NaOH to adjust pH above 10, extracted by ethyl acetate (25 mL x 3 times). The combined organic layer was dried by anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The desired product **26** was obtained as a yellow crystalline solid (1.012 g, 94% yield, 93% NMR purity, the purity of resulting solid was analyzed by crude NMR based on integration in aromatic region).

## 16. Troubleshooting: Frequently Asked Questions

### **Question 1: Are there any precautions that need to be taken for running this reaction?**

**Answer:** We used all the reagents without any special handling. The reaction was performed under air without degassing. All of the solvent were used in HPLC grade.

### **Question 2: Is stirring crucial for this reaction?**

**Answer:** Because this classical Minisci reaction is two phase reaction, stirring is important the reaction conversion. Our preferred stirring rate is above 1000 rpm which was enough to mix organic and aqueous phase.

### **Question 3: What is the byproduct of this reaction?**

**Answer:** We observed that most of crude NMR in the Minisci reaction was very clean. An excess of carboxylic acid and unreactive starting material were remained in organic layer and we couldn't trace any byproduct in aqueous phase. In deprotection step using DBU, we observed that stoichiometric diethyl maleate was formed during monitoring on TLC and NMR. This nonpolar product could be isolated, recovered by column chromatography. We also observed yellow color byproduct in low yield examples which was containing aliphatic compound forming in deprotection step.

### **Question 4: What can I do if I observe poor conversion in the Minisci reaction?**

**Answer:** You can increase the reaction time. Alternatively, using more carboxylic acid such as 4 equiv. usually helps to get a better yield. We also found concentrated reaction condition (0.3 M) would be helpful for improving conversion. We would not recommend increasing the temperature based on experimental result (see, **Figure S17**, page S22).

### **Question 5: How do I monitor the reaction?**

**Answer:** We have evaluated the reaction time on the standard substrate, which indicates 1.5 h is enough for full conversion in 0.5 mmol scale. So we chose to leave the reaction for each substrate for 2 h without monitoring. But if you observed partial conversion of the reaction, you can use TLC analysis with UV visualization (254 nm) to see the starting material if it is UV active and KMnO<sub>4</sub> stain for non-UV active substrates. Also, we frequently analyzed aliquot of organic phase using <sup>1</sup>H NMR in CDCl<sub>3</sub> for checking conversion and regioselectivity.

### **Question 6: Does longer reaction time cause decrease of yield?**

**Answer:** We left the reaction running for 48 h in case of compound **19** and a yield drop was observed (71% to 38%). However, we did not observe any loss in yield within 12 h.

### **Question 7: Are alkylated products volatile?**

**Answer:** Some alkylated products with low molecular weight or without functional groups are volatile. All the information regarding the volatile products obtained in this manuscript were mentioned in characterization section of each compound. You can keep the temperature of rotavap water bath below 40 °C and the pressure of rotavap higher than 100 mbar.

### **Question 8: The Minisci reaction is two-phase reaction. Does the yield drop in a larger scale?**

**Answer:** We obtained similar yield when scaling up the reaction to gram scale. Larger scale was not tested.

**Question 9: What's the limitation of current regioselective Minisci reaction?**

**Answer:** “Polar carboxylic acid” (we define “polar” carboxylic acids to be some acid substrates bearing polar group such as N, O heteroatom) are generally not compatible probably because the alkylated product in Minisci reaction is water soluble, we could not extract the Minisci product from aqueous to organic layer. Primary carboxylic acid gave low yield when they used standard condition, so we changed equivalent of carboxylic acid (from 2 equiv to 4 equiv), observing improved yields. Please see “Unsuccessful or Challenging Substrates in This Study” section (see **Figure S21.**, page S24) for the problematic substrates we have tried.

**Question 10: What's the limitation of current preparation of pyridinium feedstocks?**

**Answer:** Please see “Unsuccessful or Challenging Substrates in Substituted Pyridine Examples” section (see **Figure S22.**, page S48) for the problematic substrates we have tried. Most of observed byproduct in unsuccessful cases is the salt formed by the maleic acid and 3-substituted pyridine. All of the 2-substituted pyridine and quinoline were recovered without any conversion.

**Question 11: How do we choose an appropriate conditions for using of expensive carboxylic acid?**

**Answer:** The criteria for how to choose conditions depend on the value of the substrates. More specifically, if the carboxylic acid is more precious such as compound **32**, you should choose carboxylic acid is used as a limiting reagent in General procedure C.

**Question 12: How can we scale-up these Minisci reactions?**

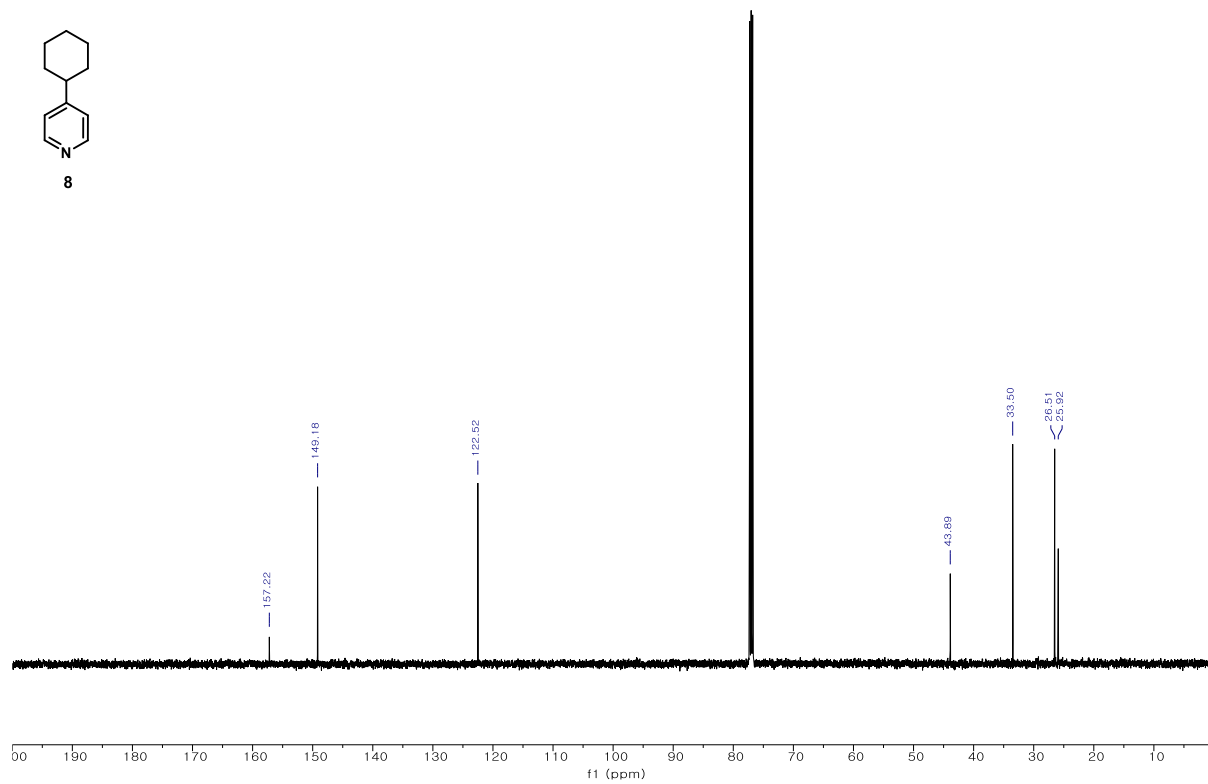
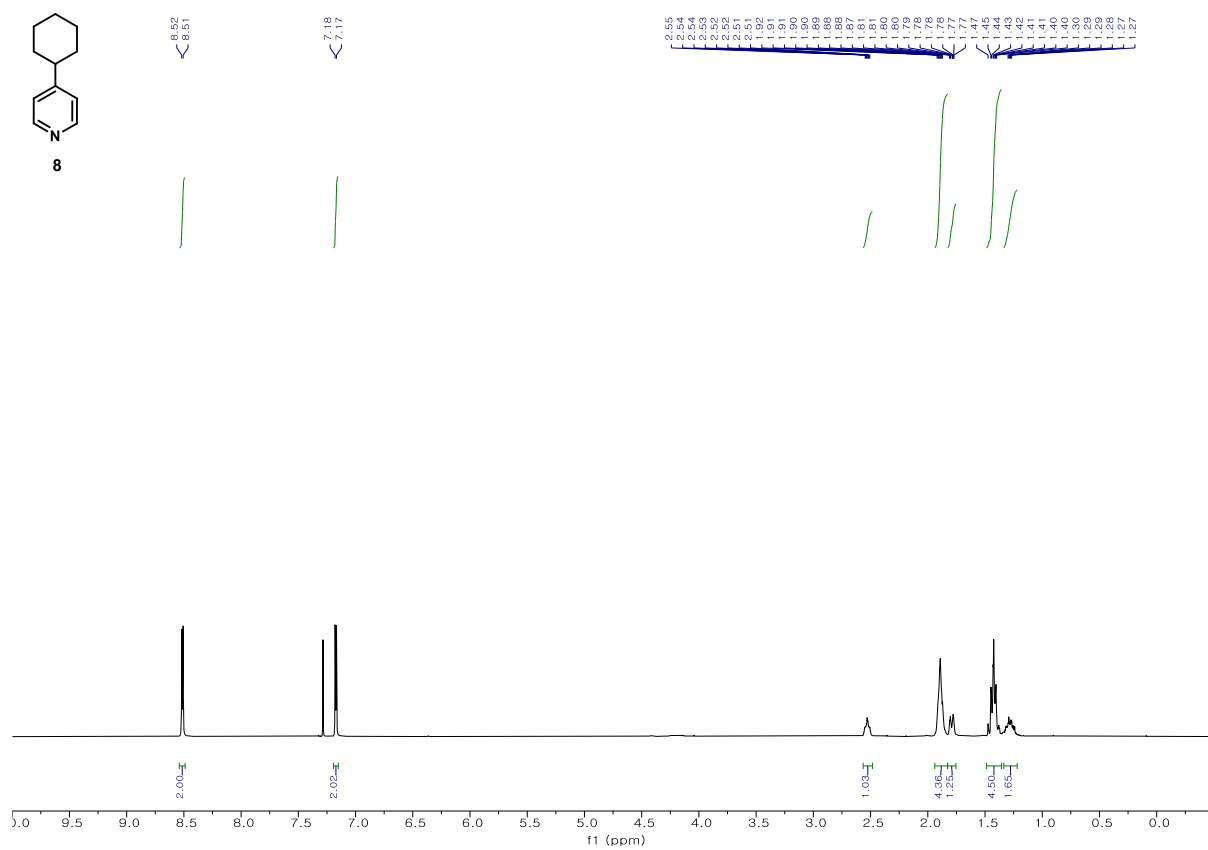
**Answer:** You can scale up to gram-scale for both of the Minisci reaction and deprotection reaction according to the procedure we provided (see **Figure S19.**, page S23). Larger scale reactions than what reported in the manuscript have not been tested. For 5 mmol scale reaction, the deprotection step using DBU is slightly exothermic, so we recommend to keep the vessel temperature below 30 °C using water bath.

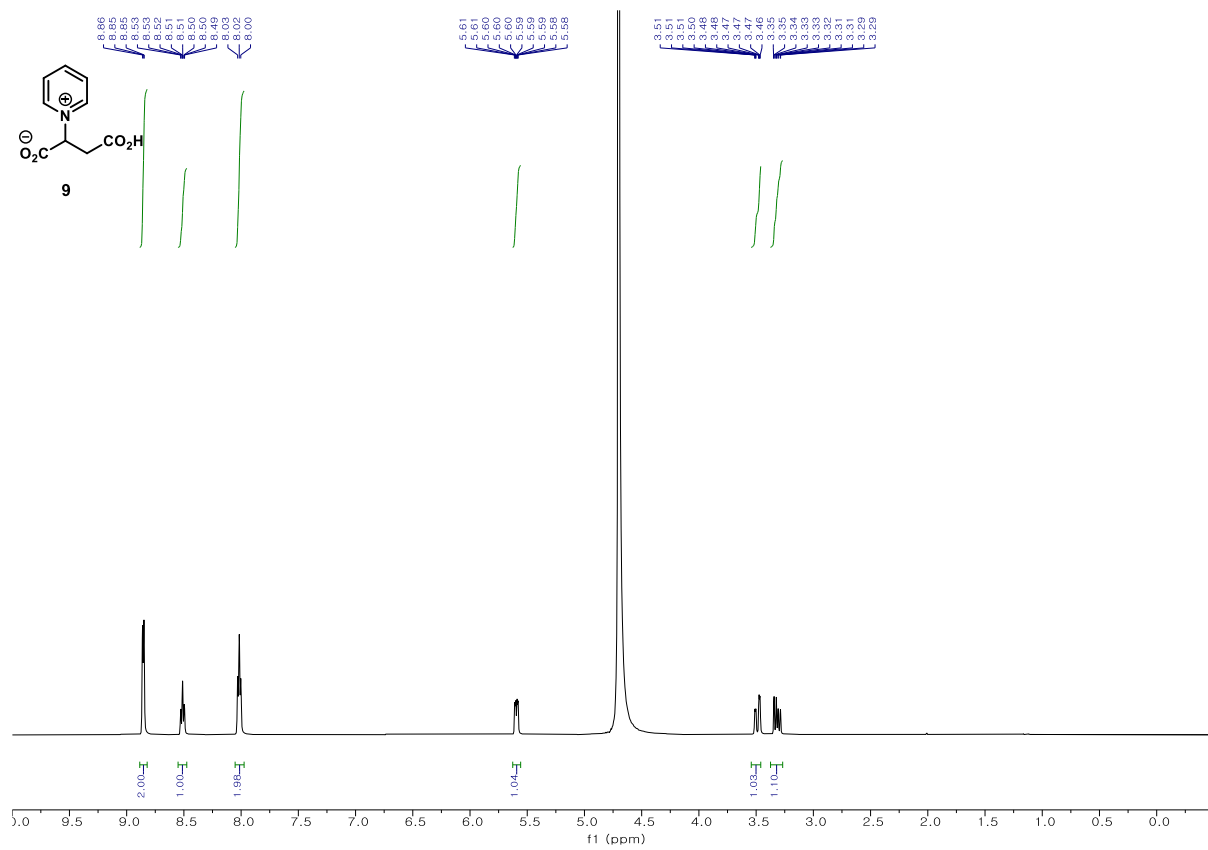
**Question 13: Why do we need an extraction for both the steps?**

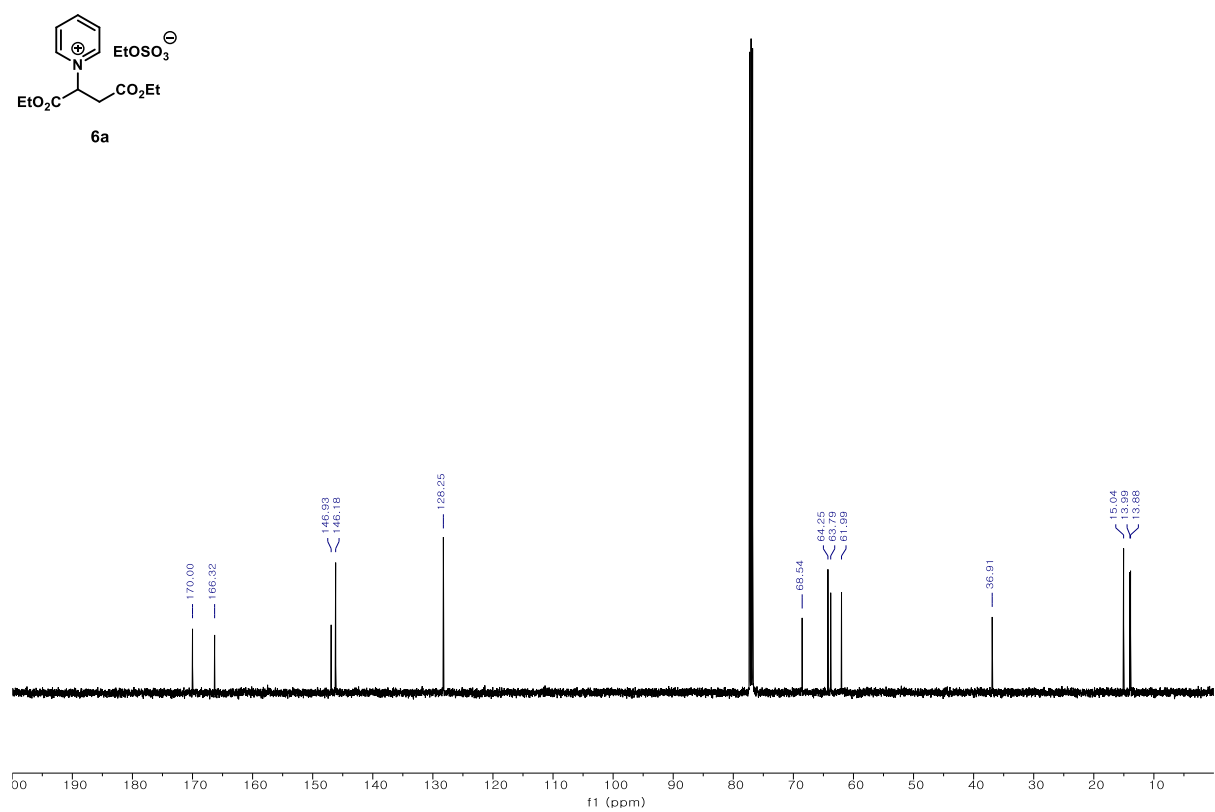
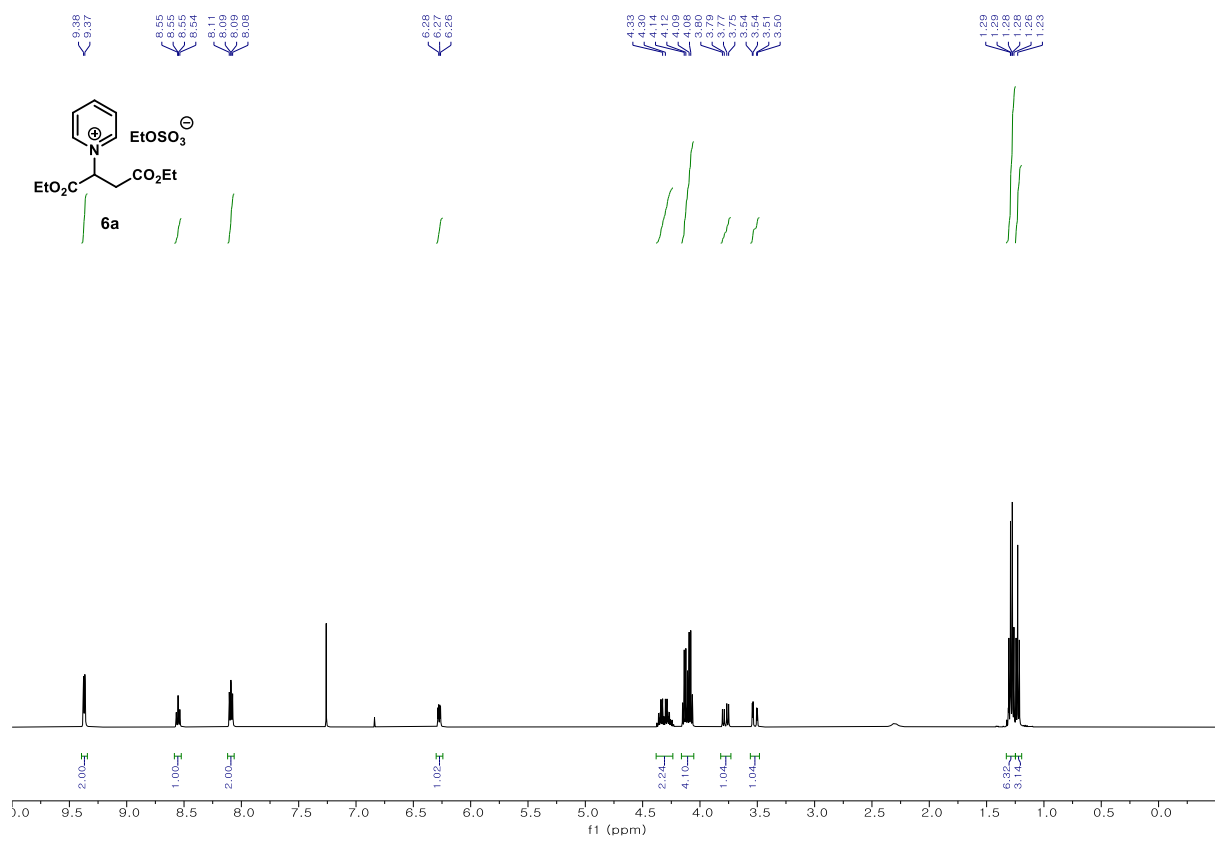
**Answer:** We tried to develop the one-pot reaction without an intermediate extraction step, however all our attempts led to less efficient processes. We think that the role of extraction step in Minisci reaction is eliminating water soluble sulfate, persulfate and silver salt. Furthermore, the role of extraction step in the deprotection reaction is to remove excess of carboxylic acid and DBU.

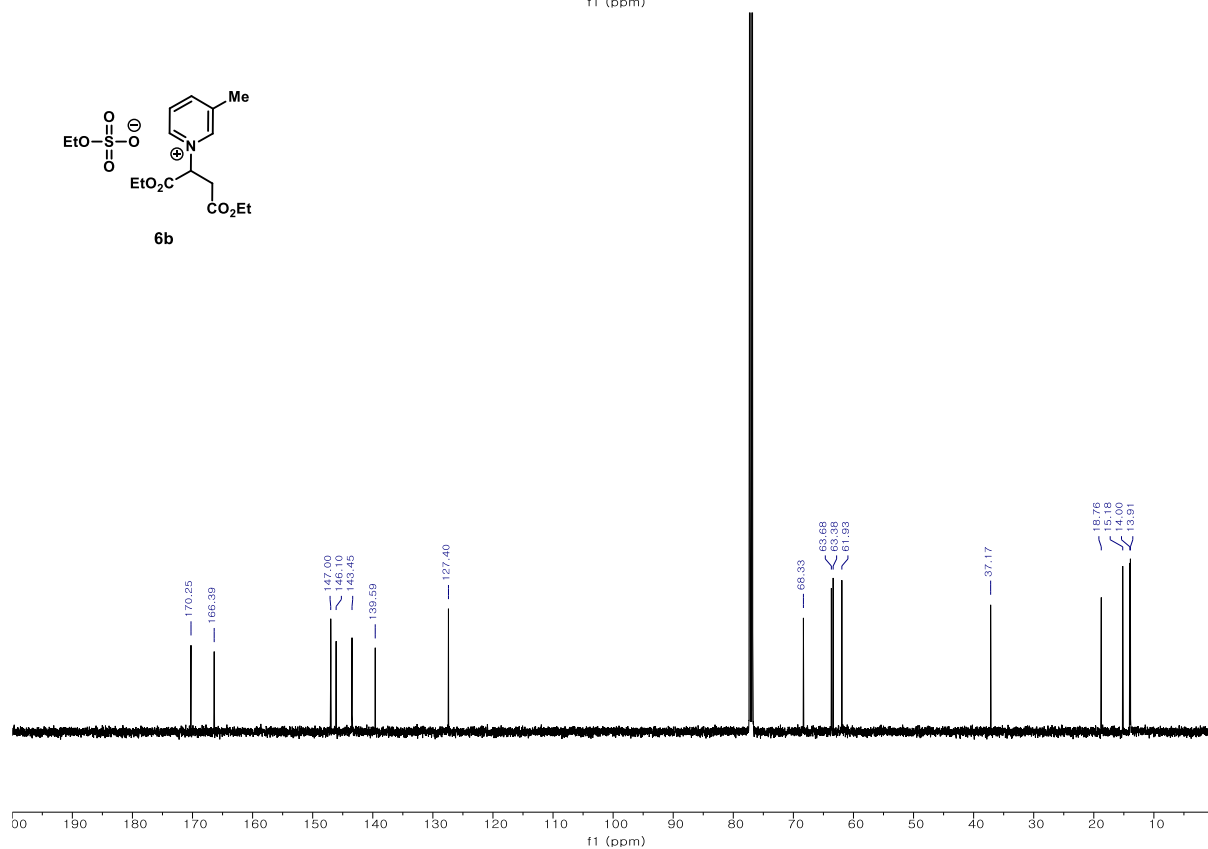
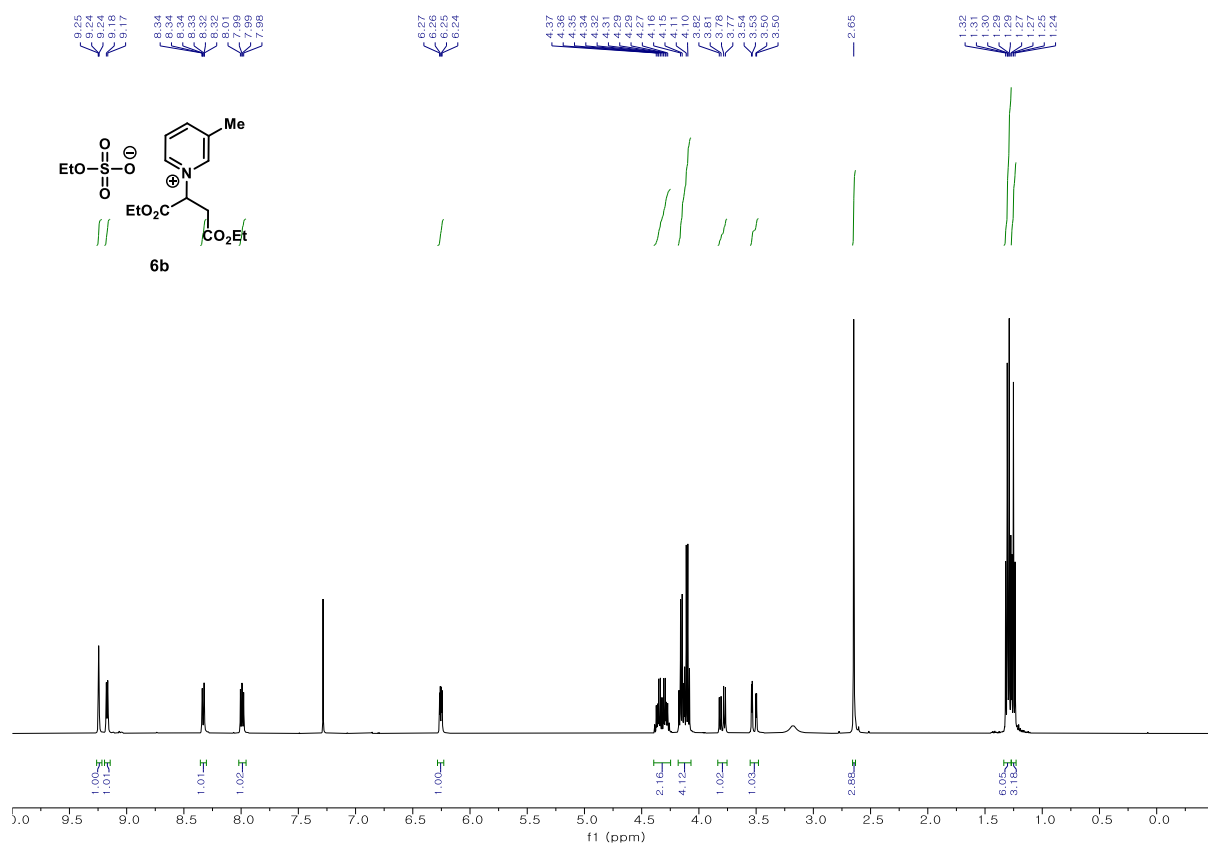
## **Appendix**

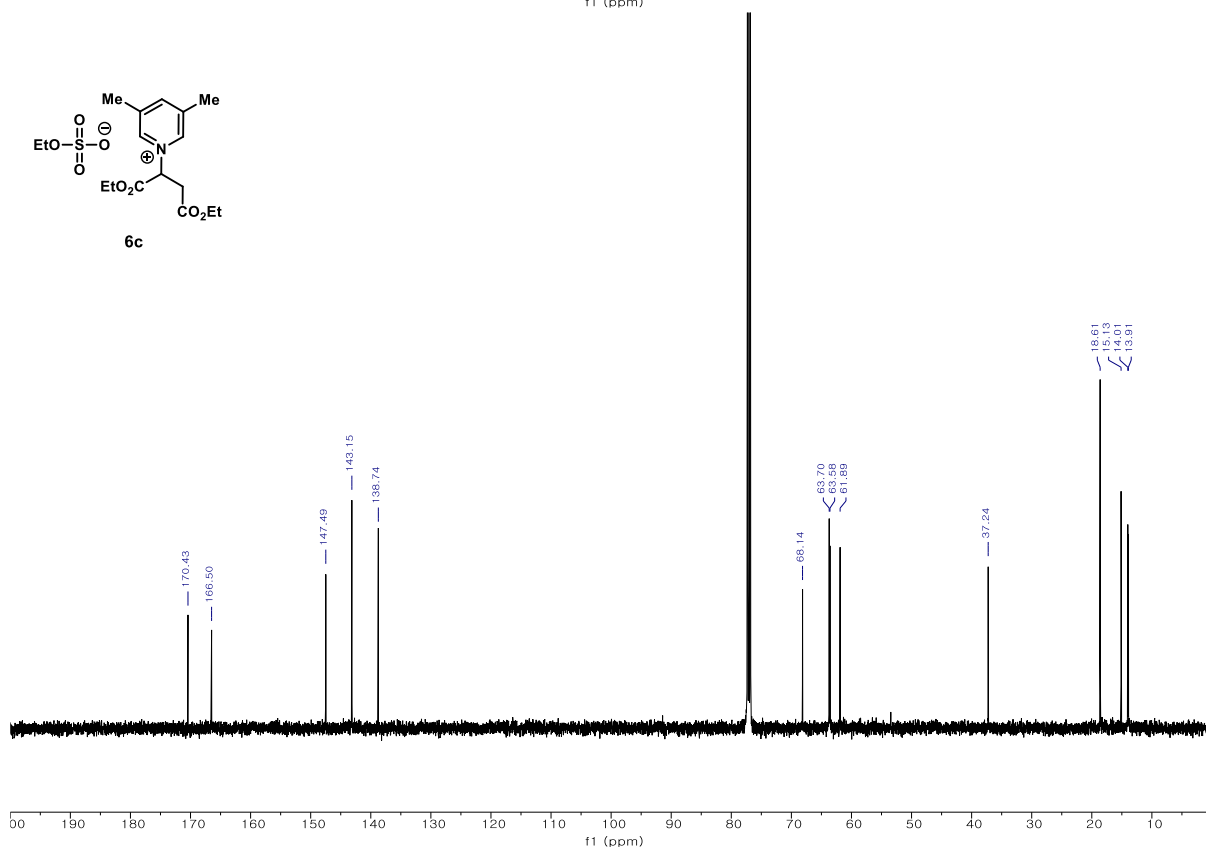
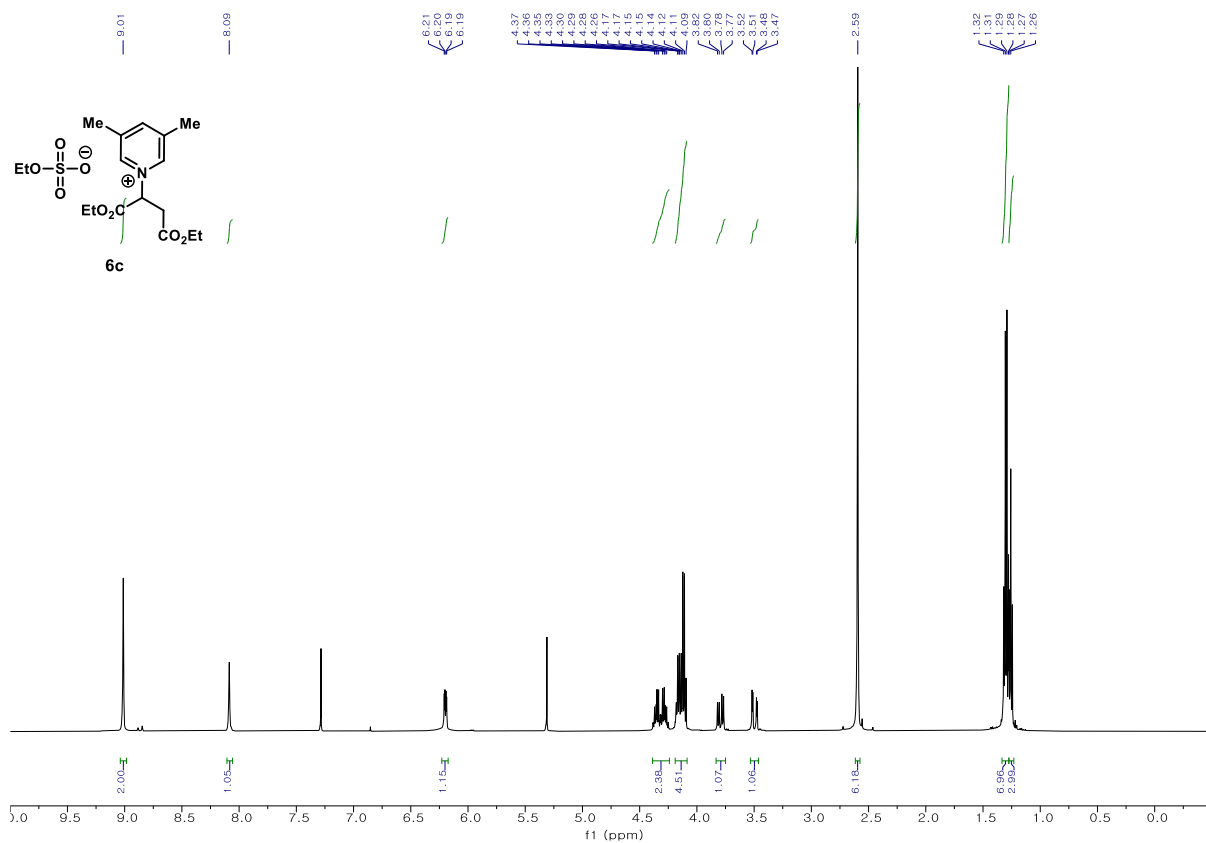
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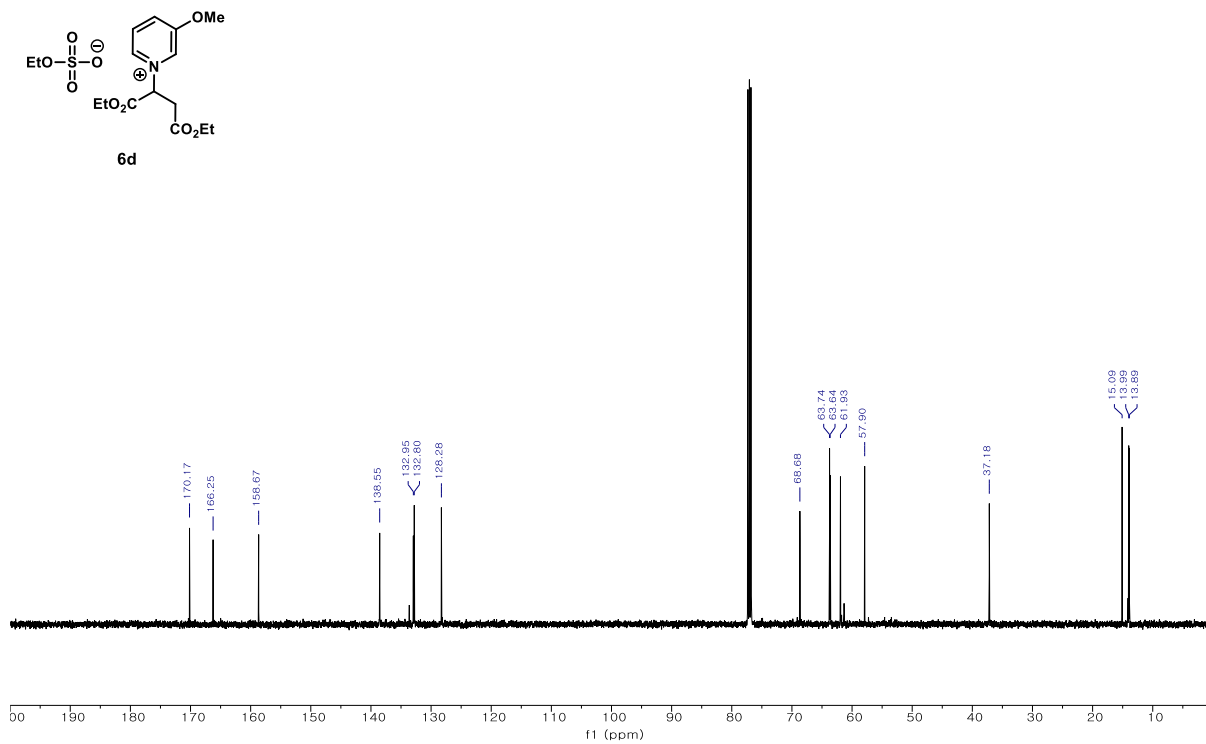
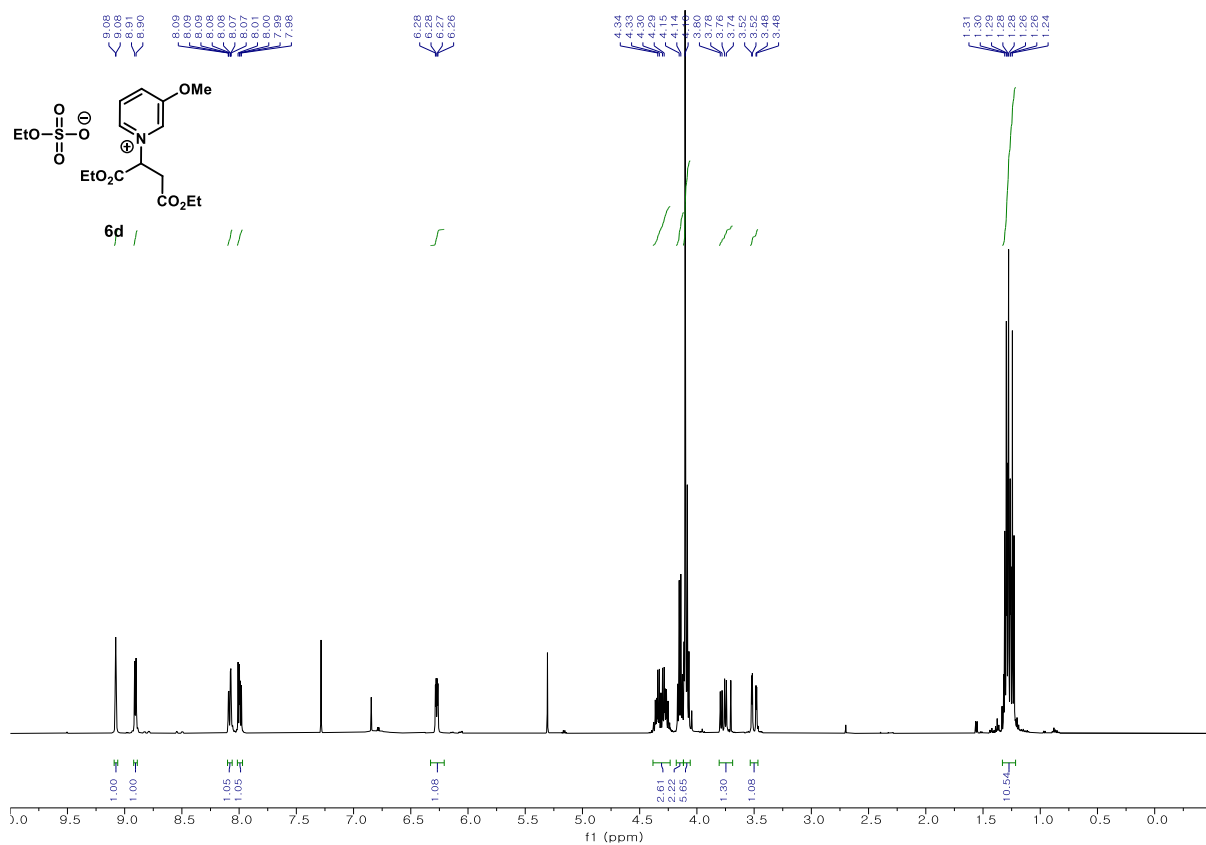


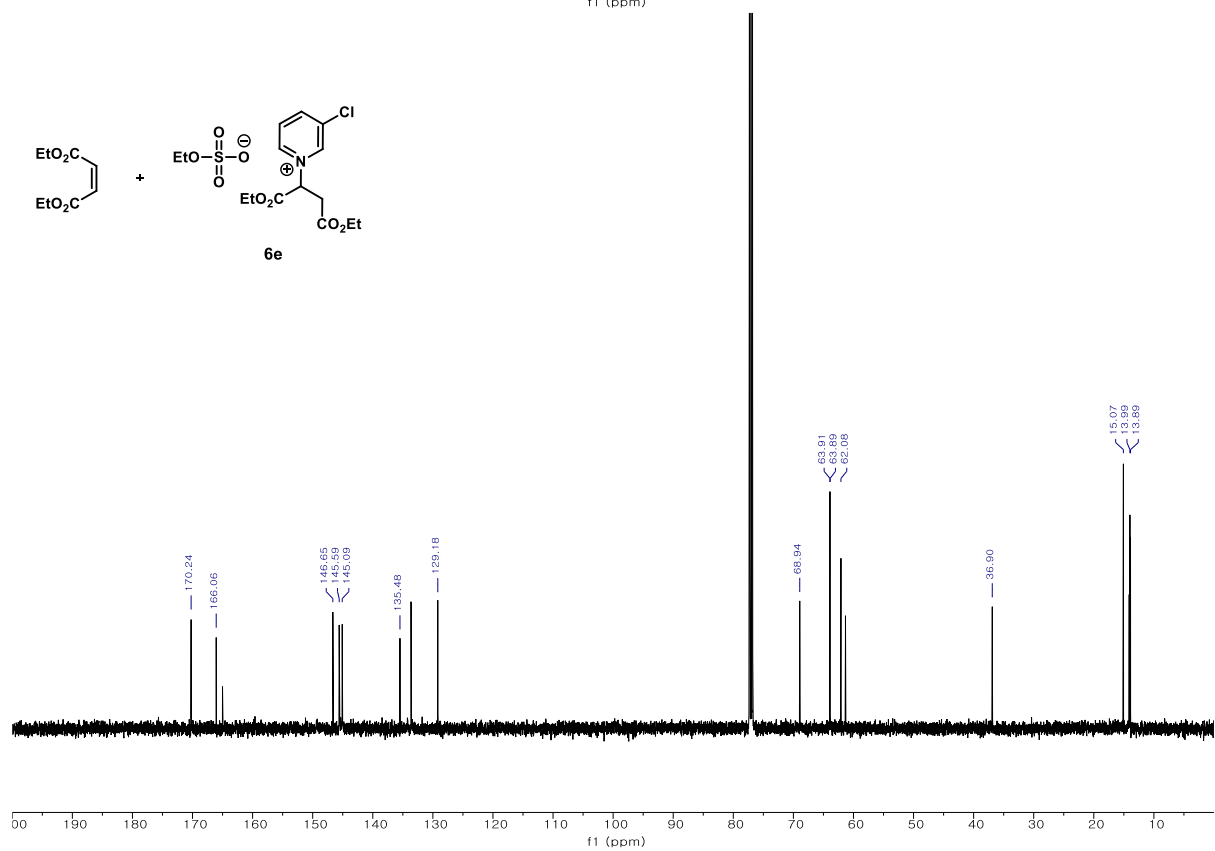
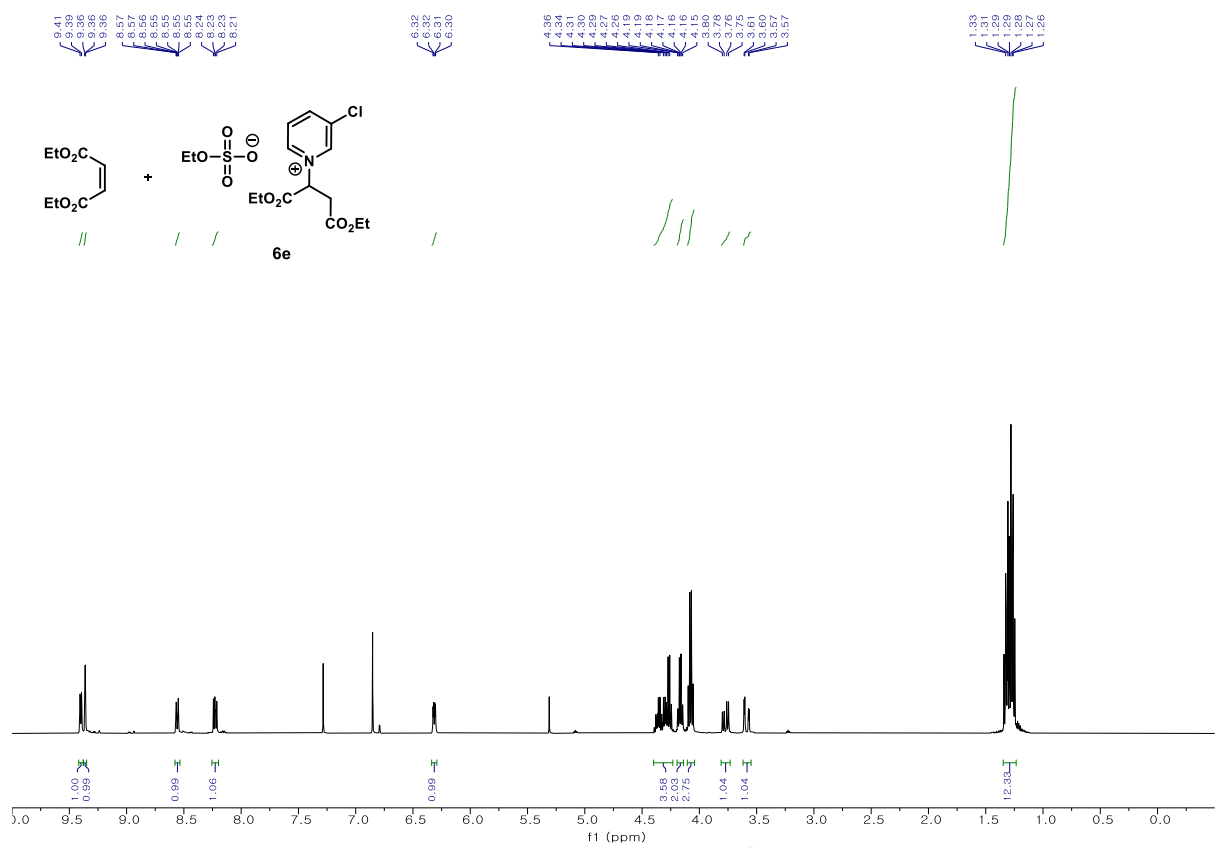


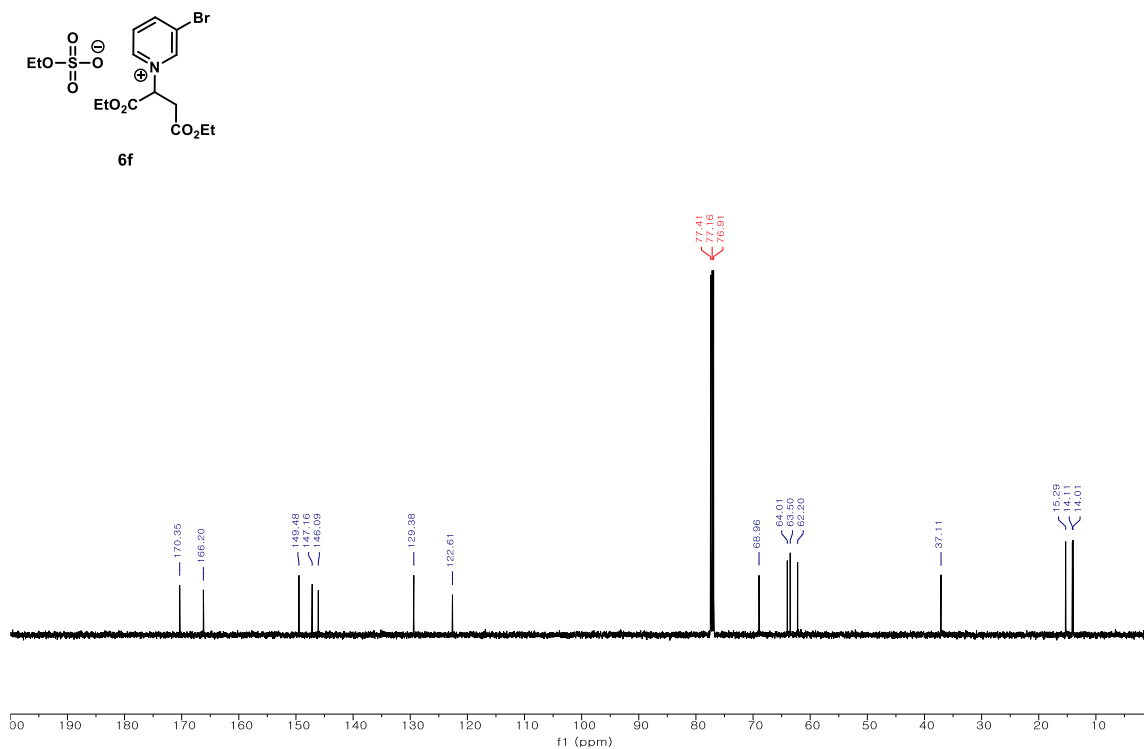
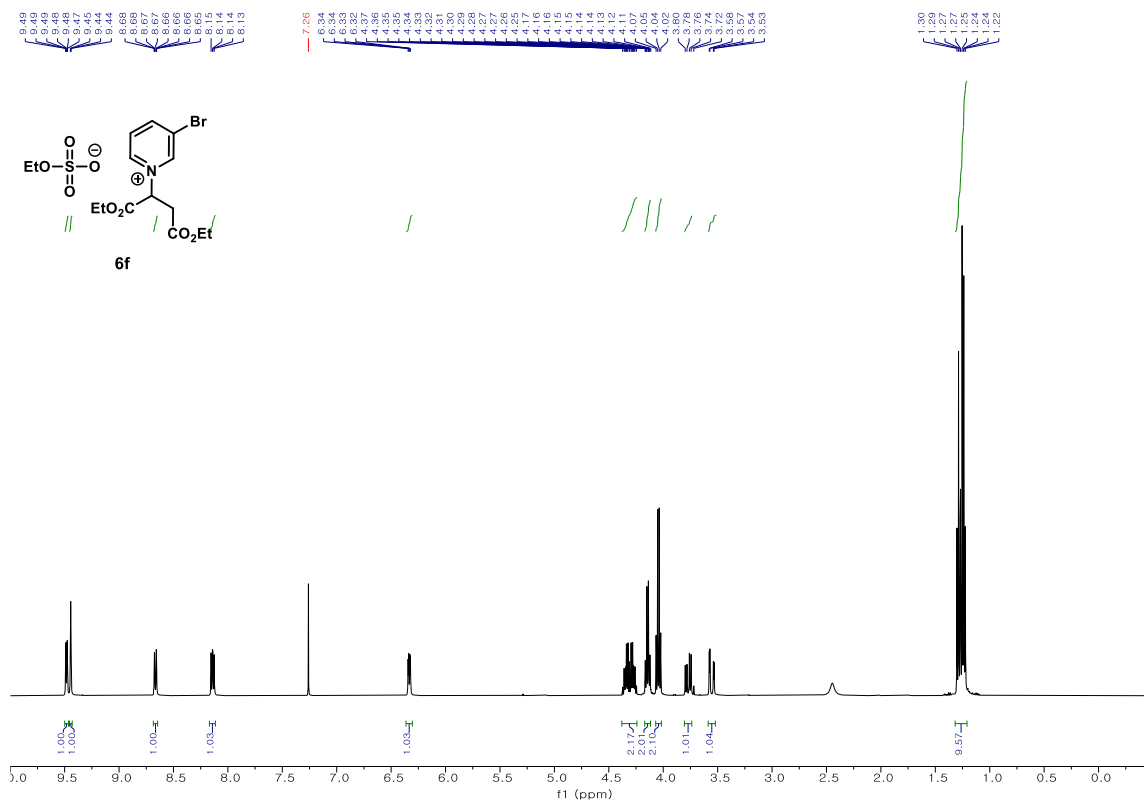


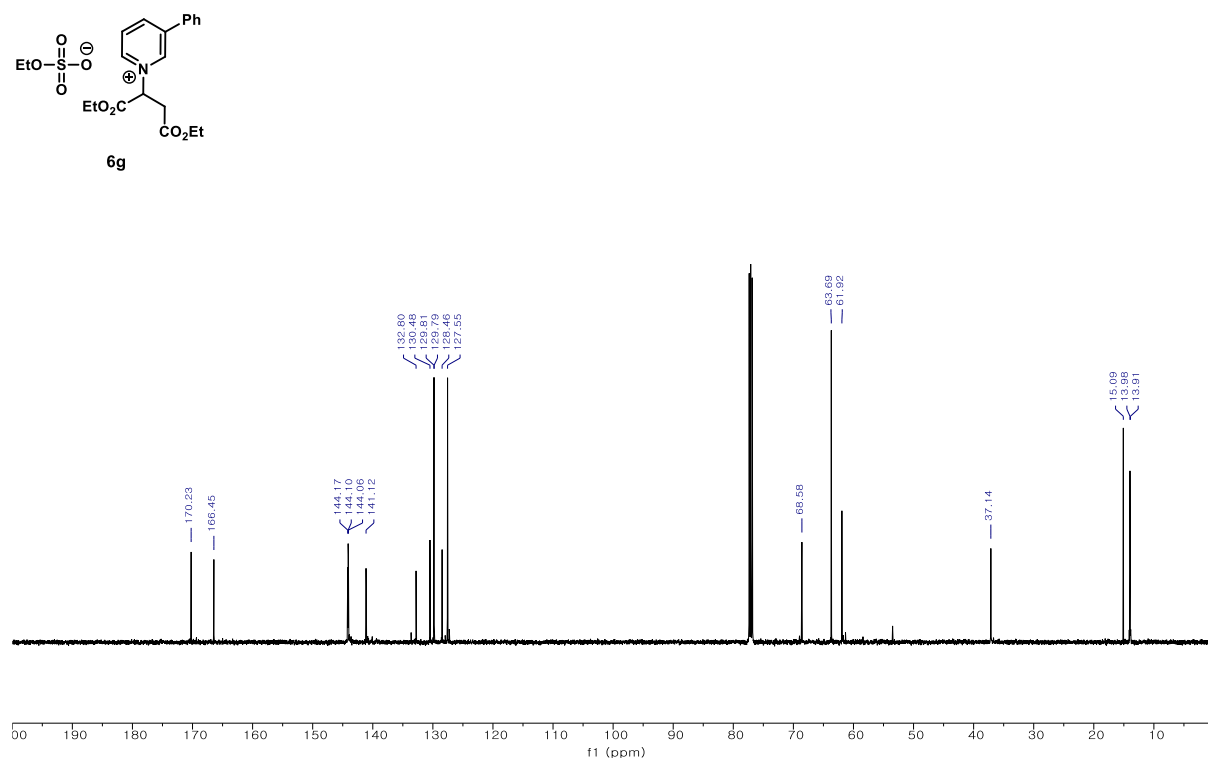
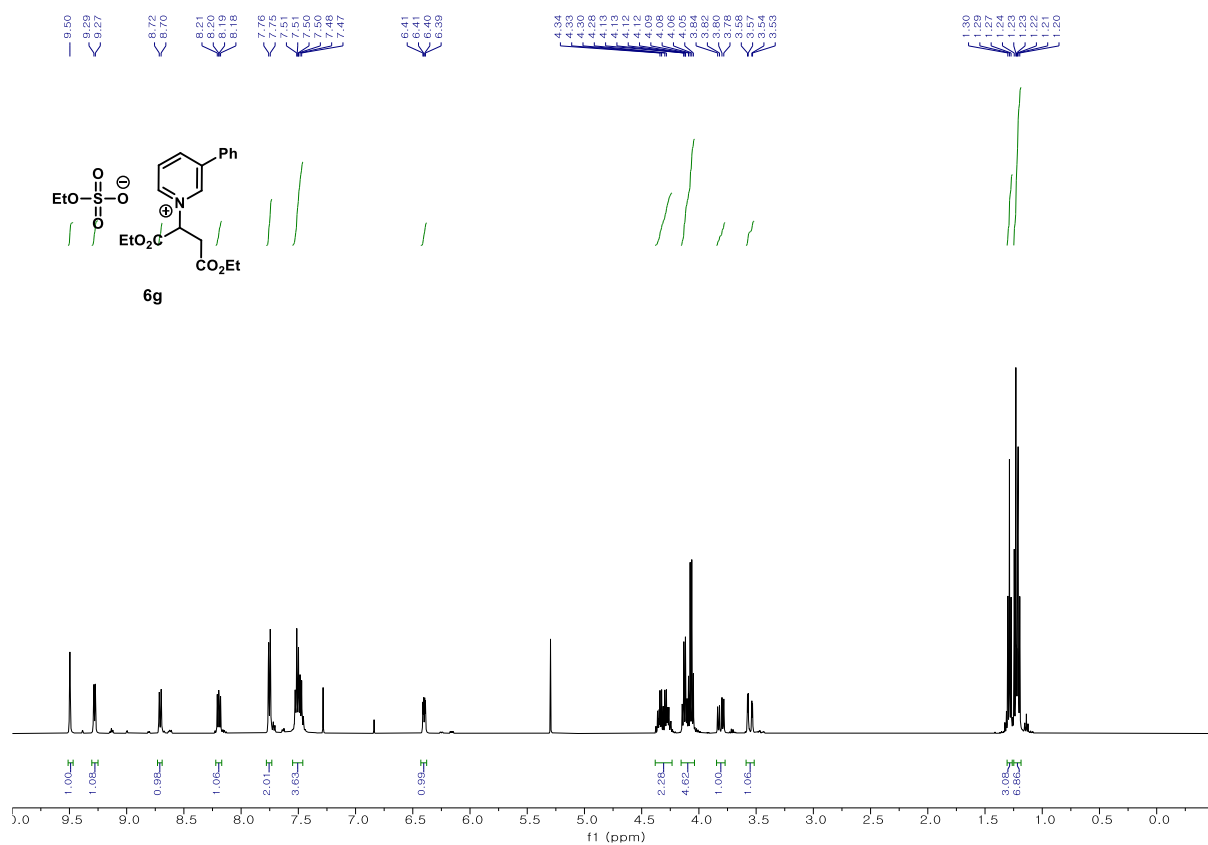


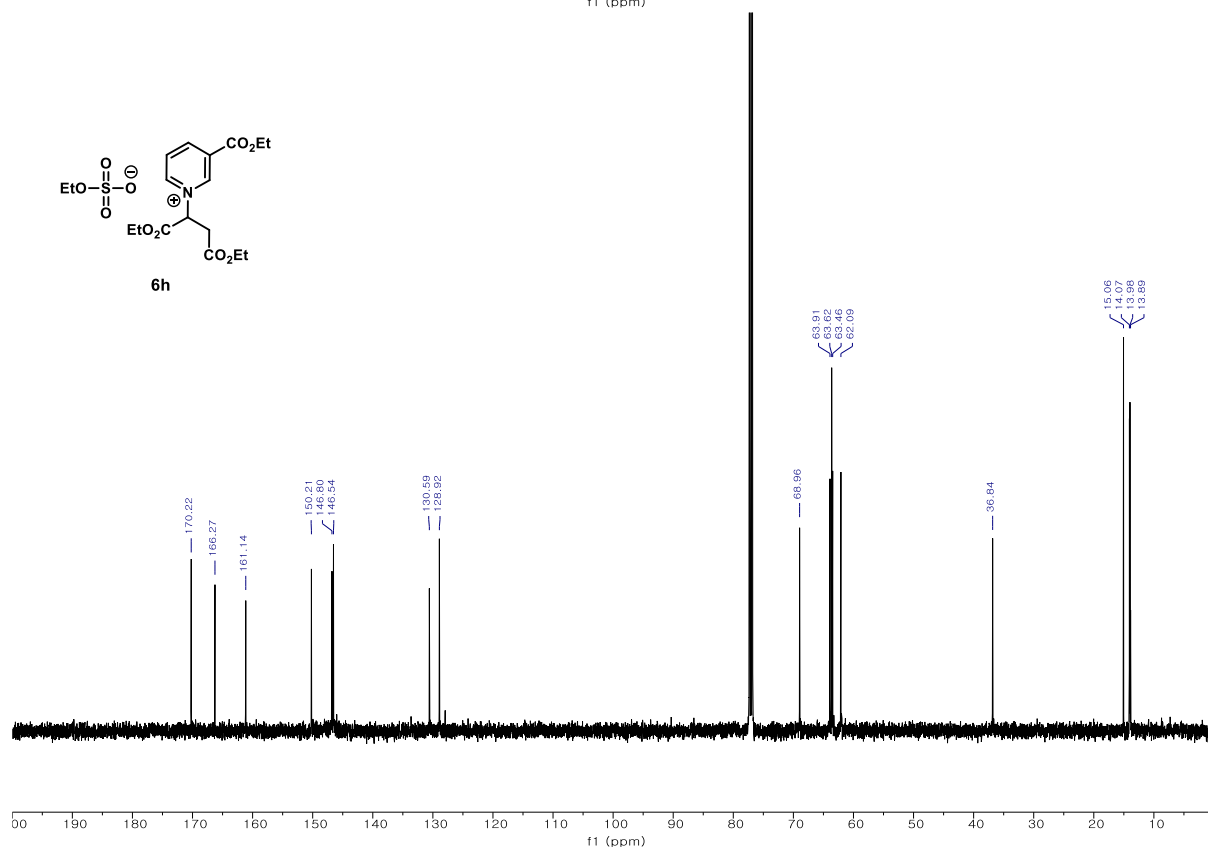
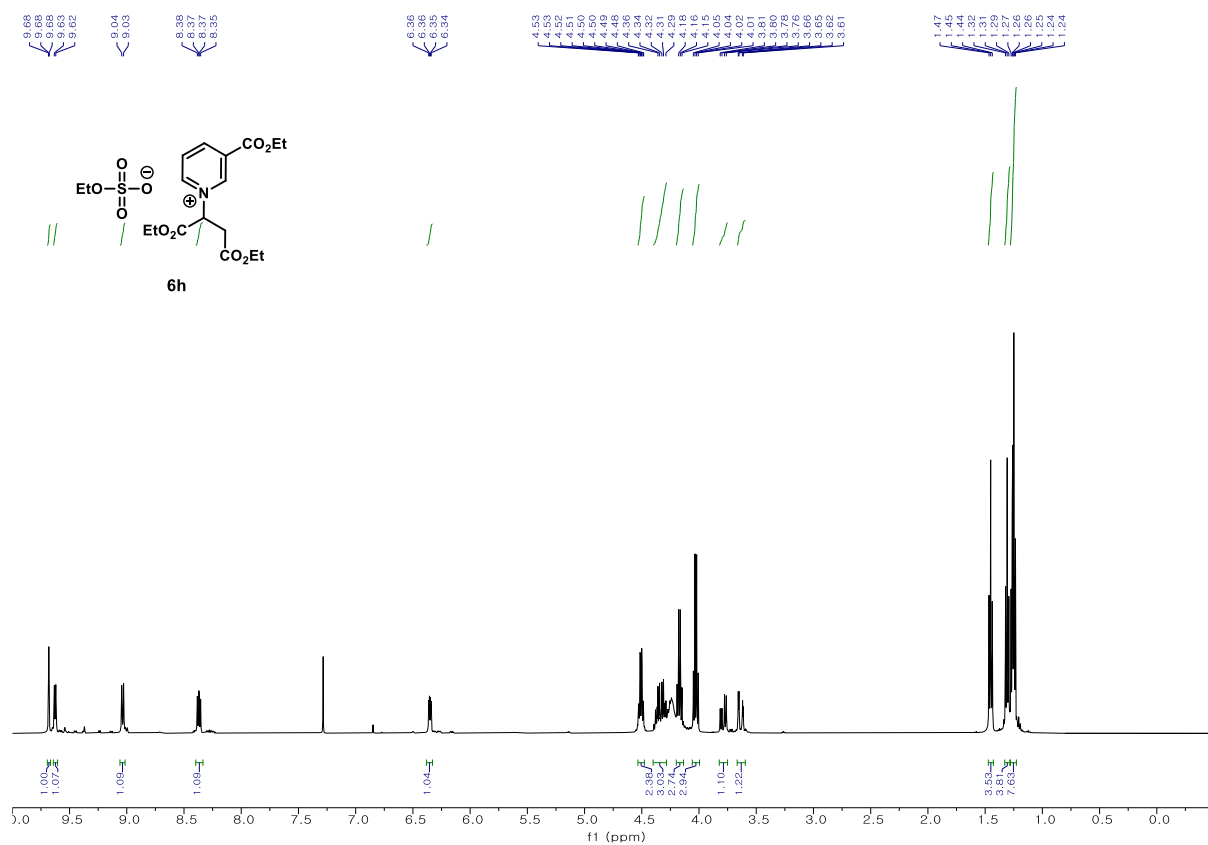


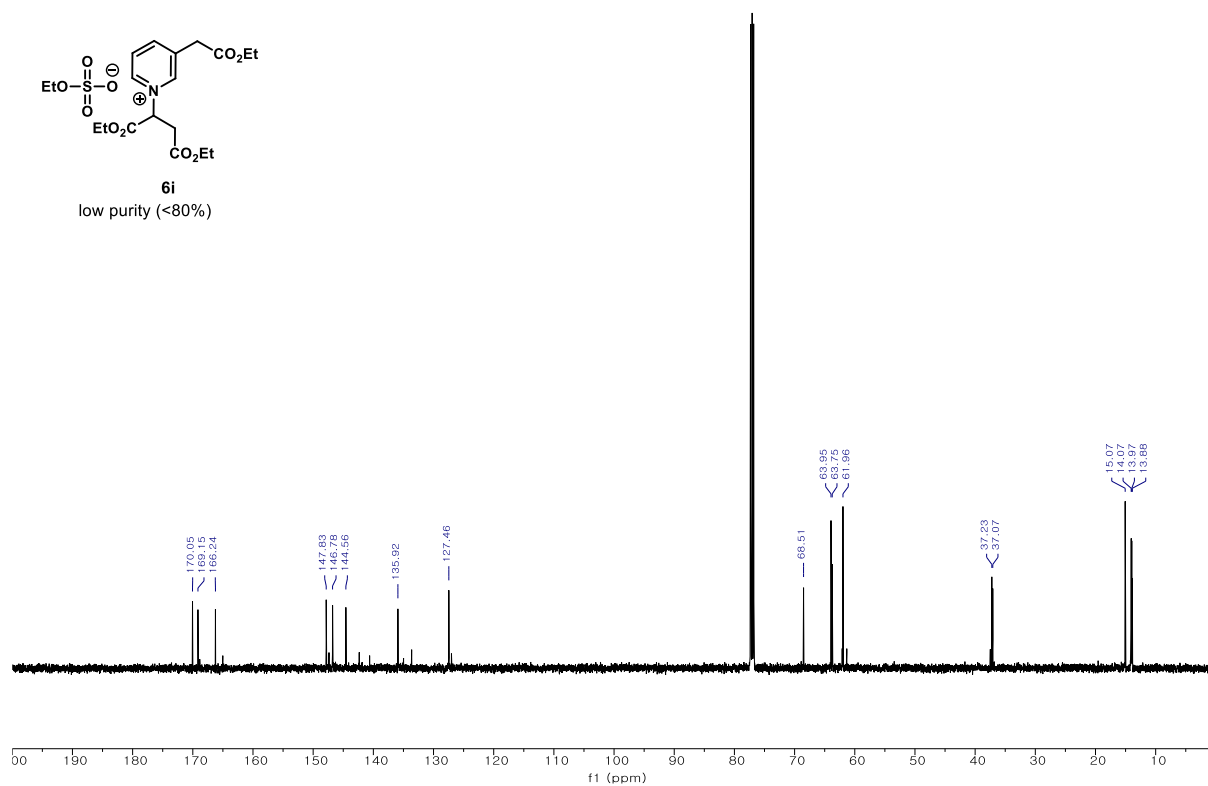
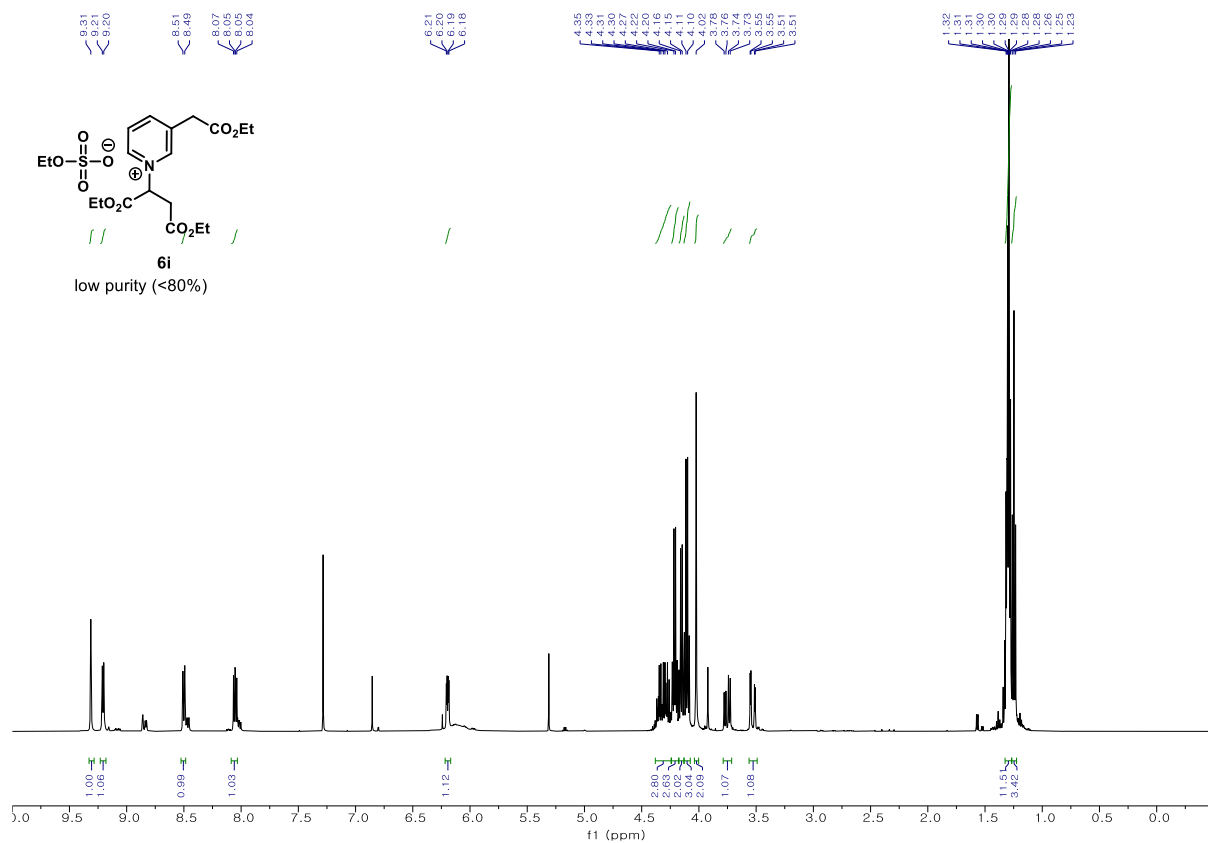


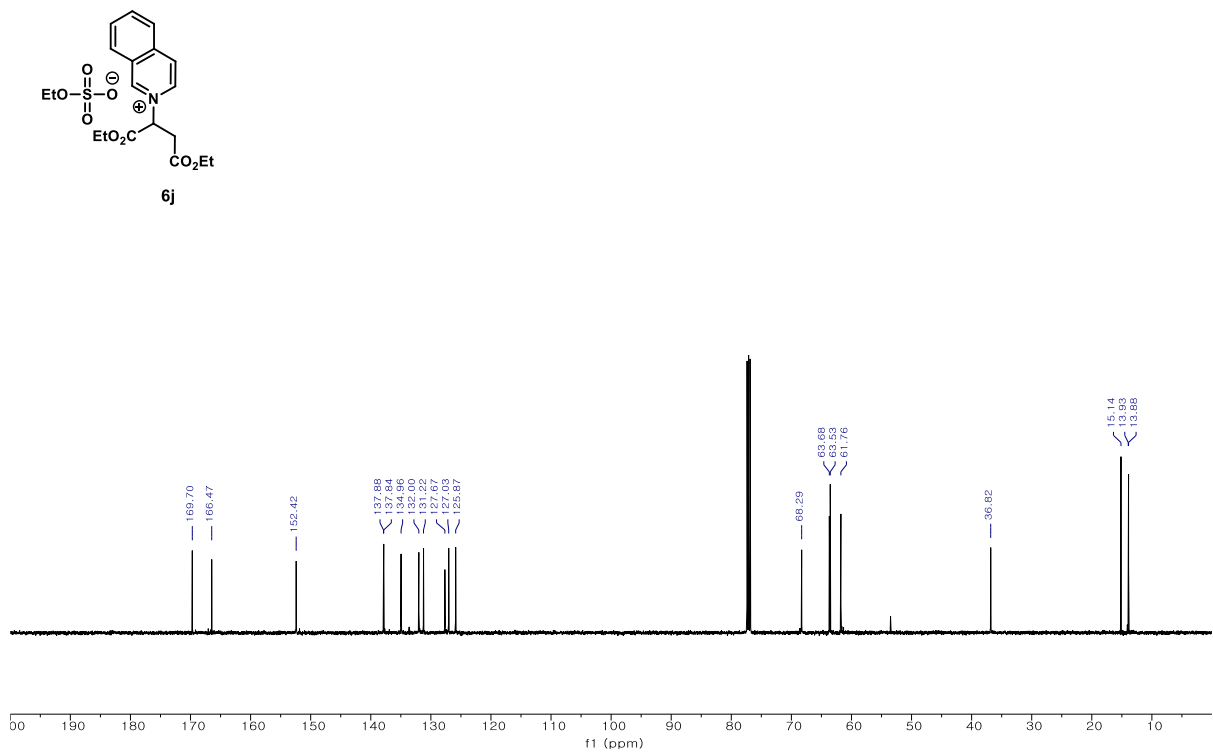
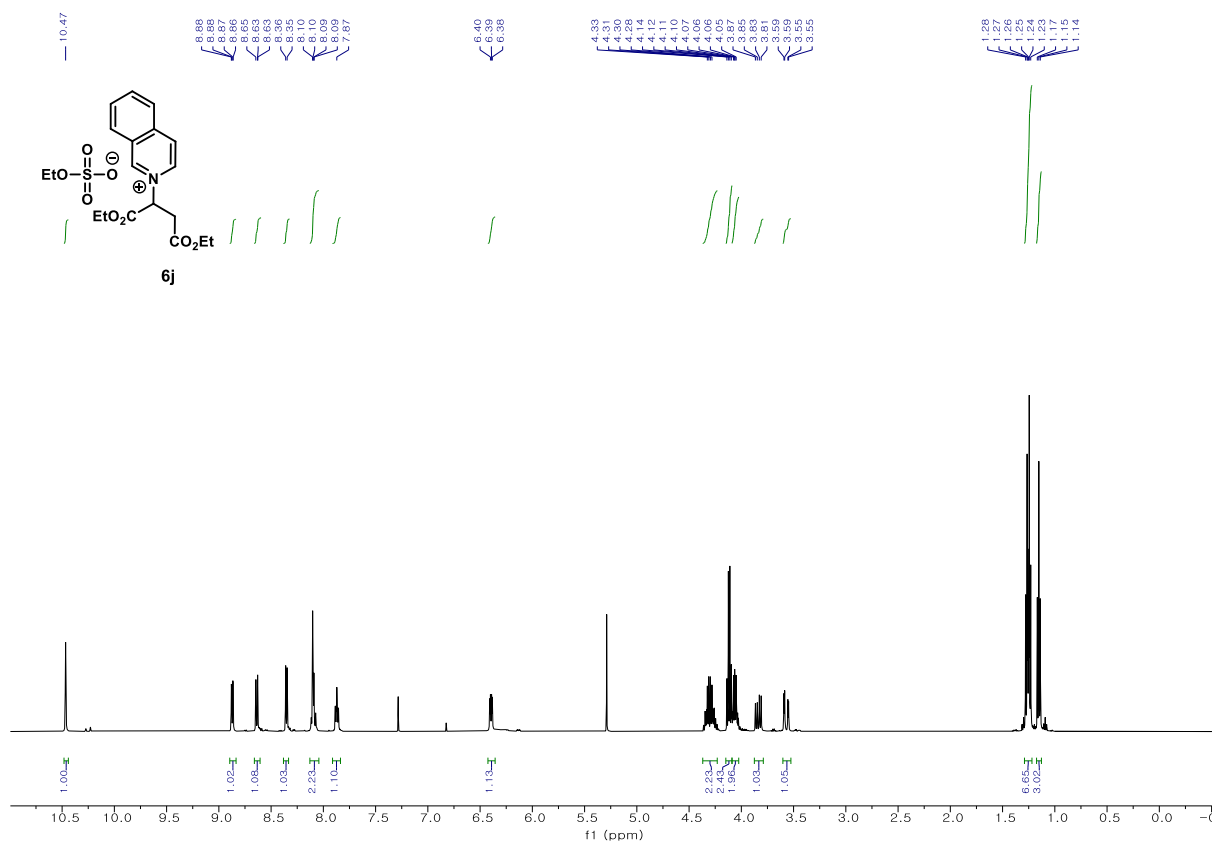




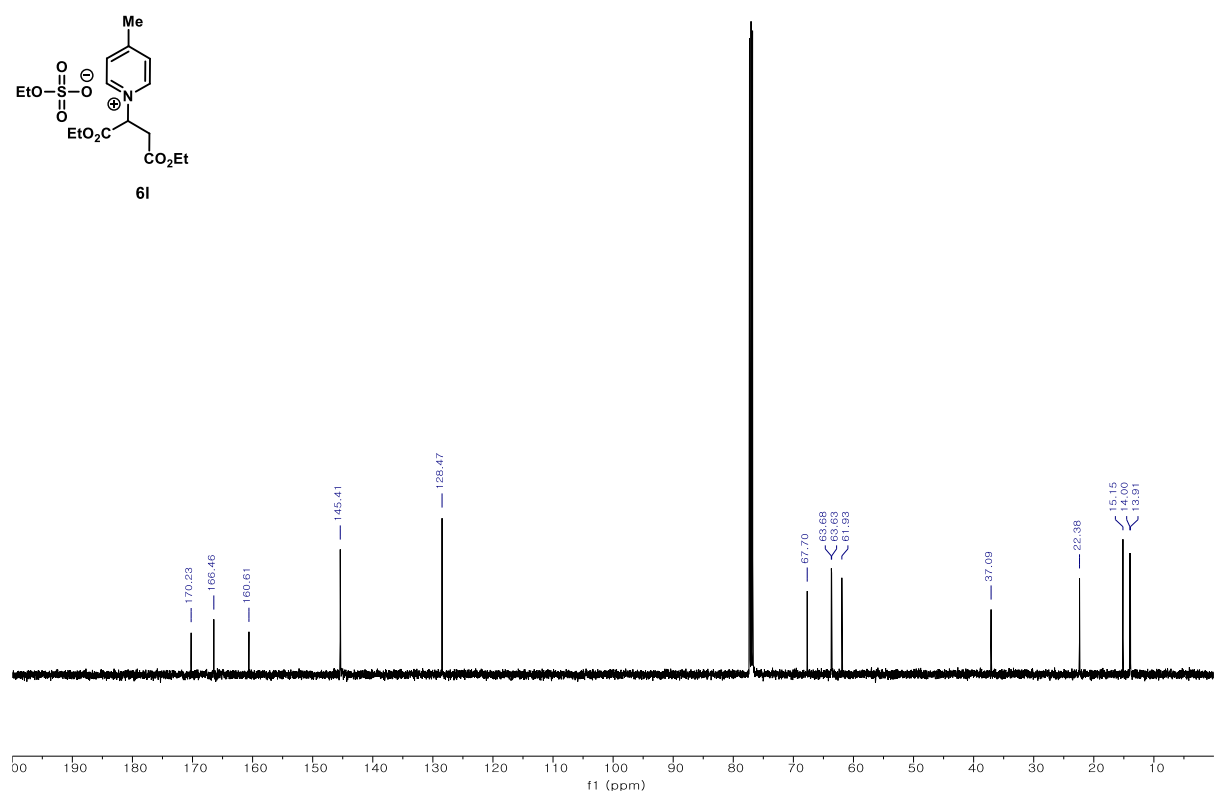
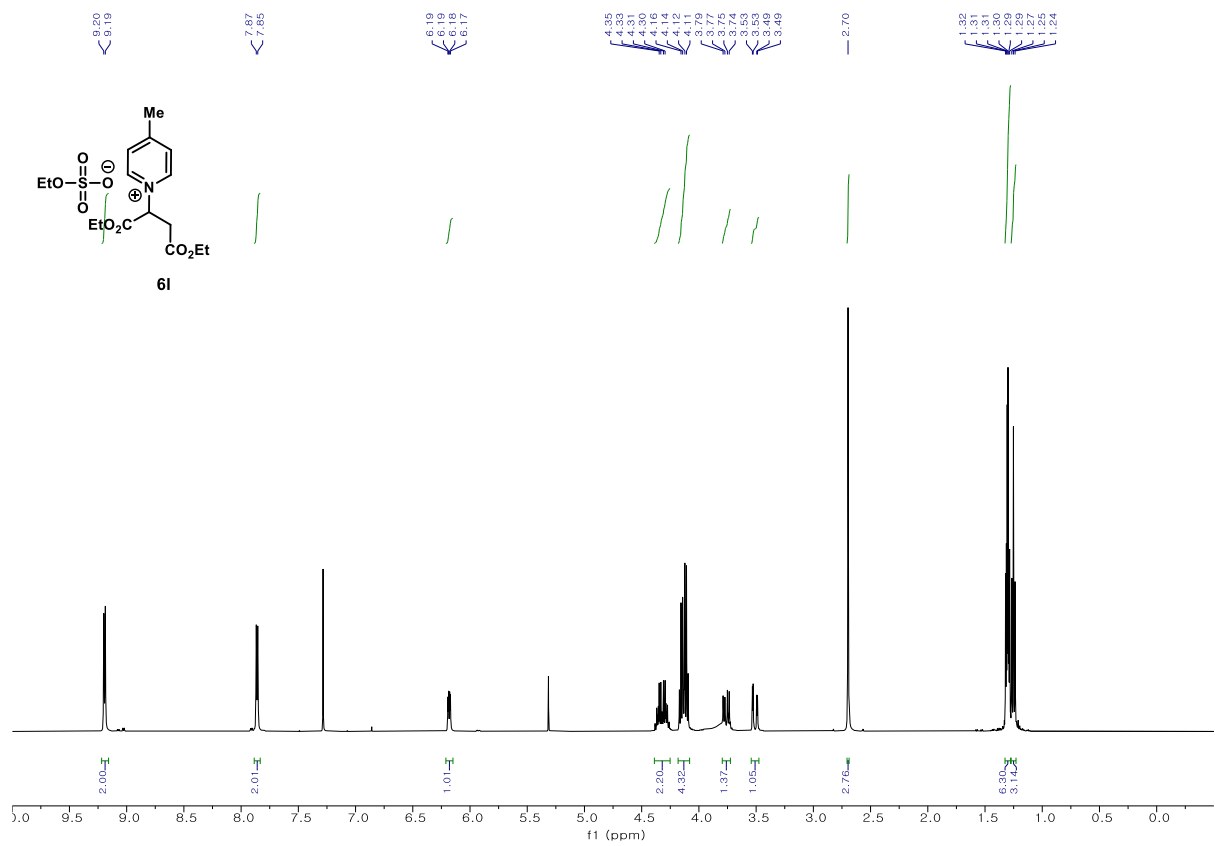


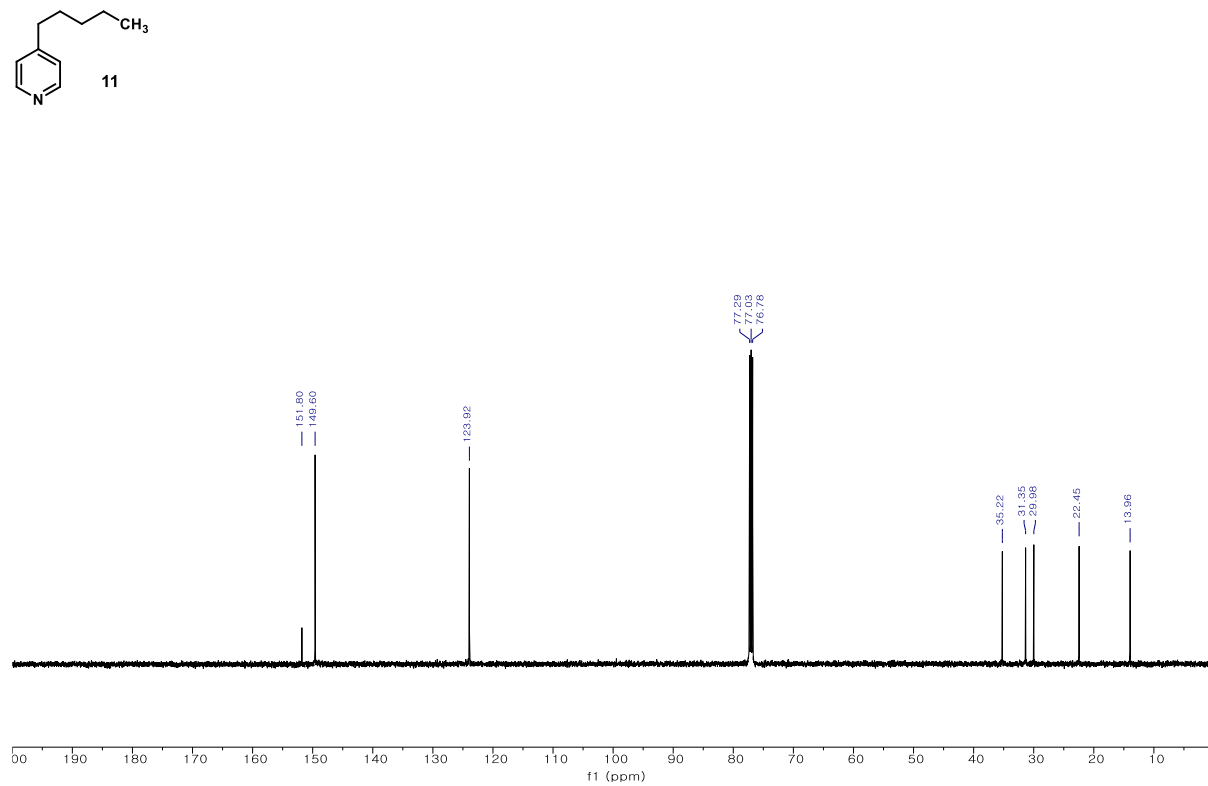
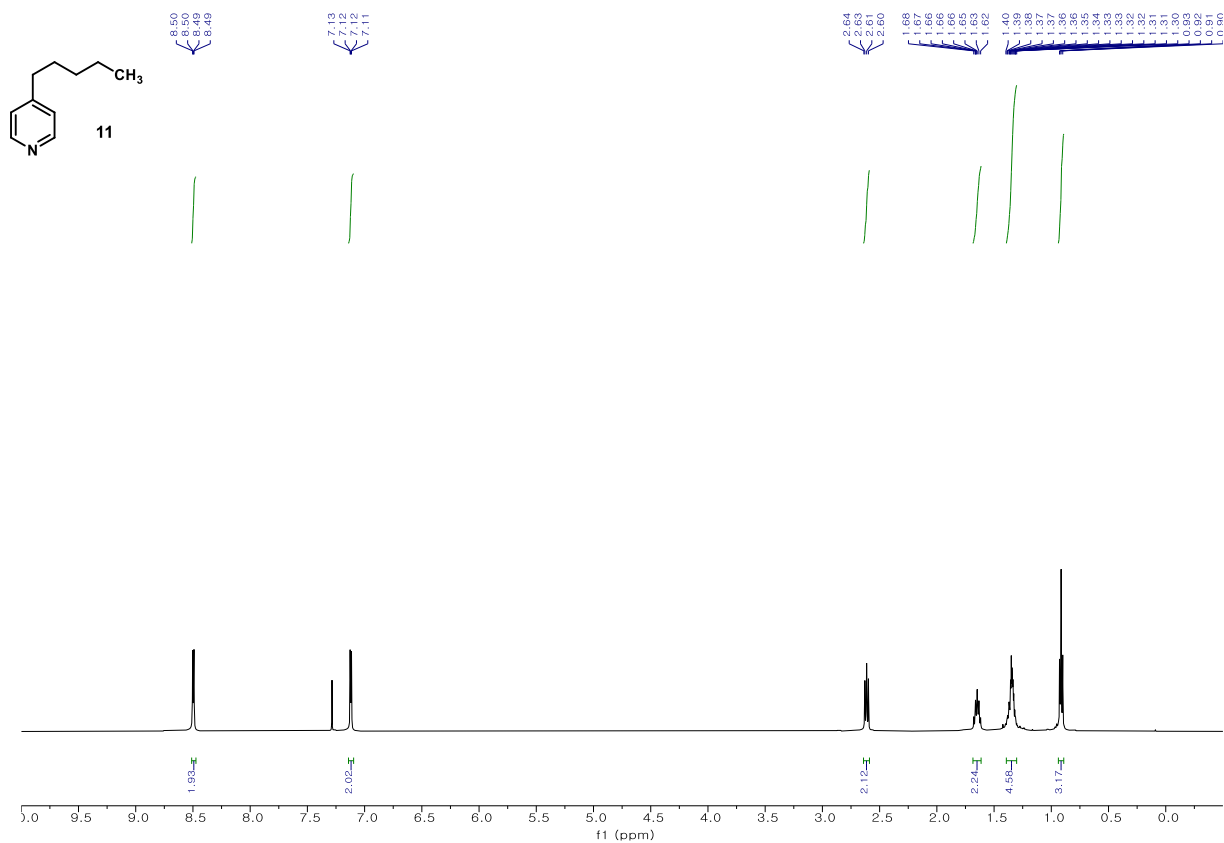


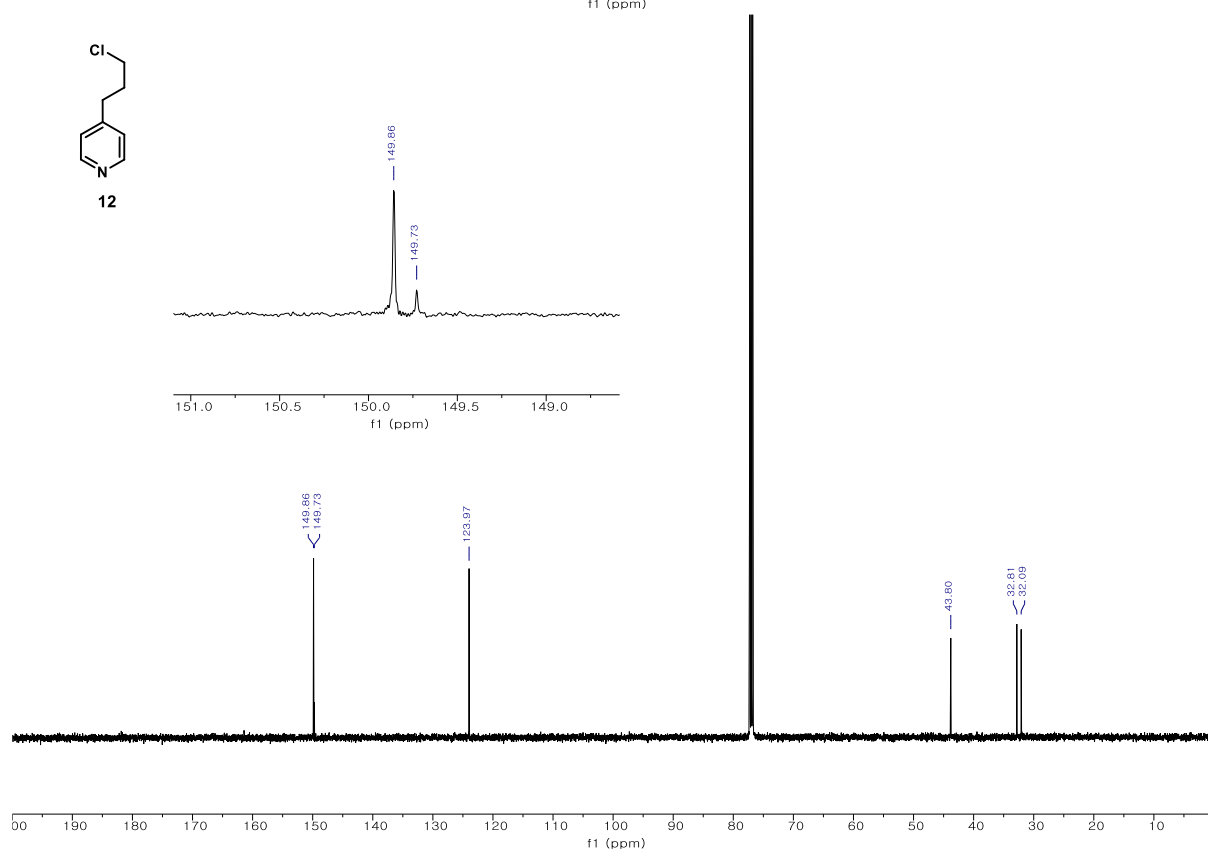
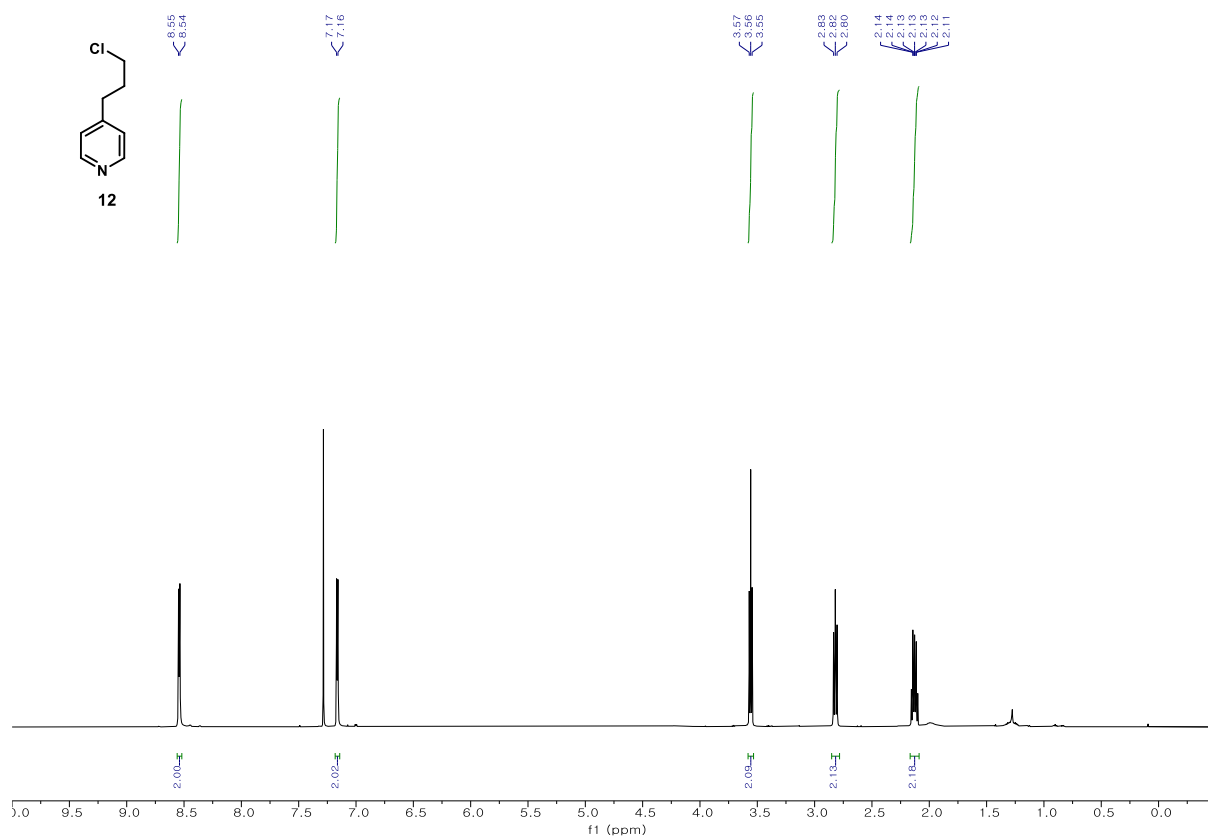


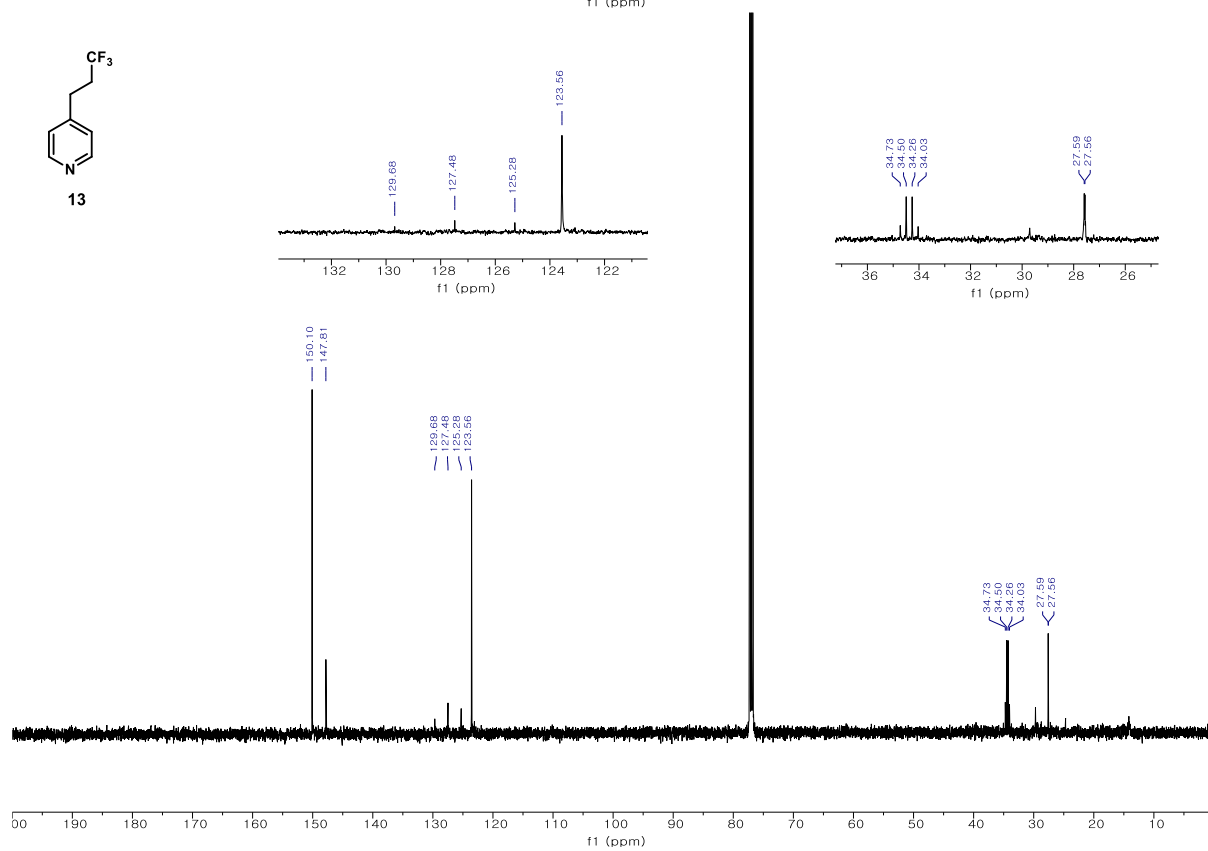
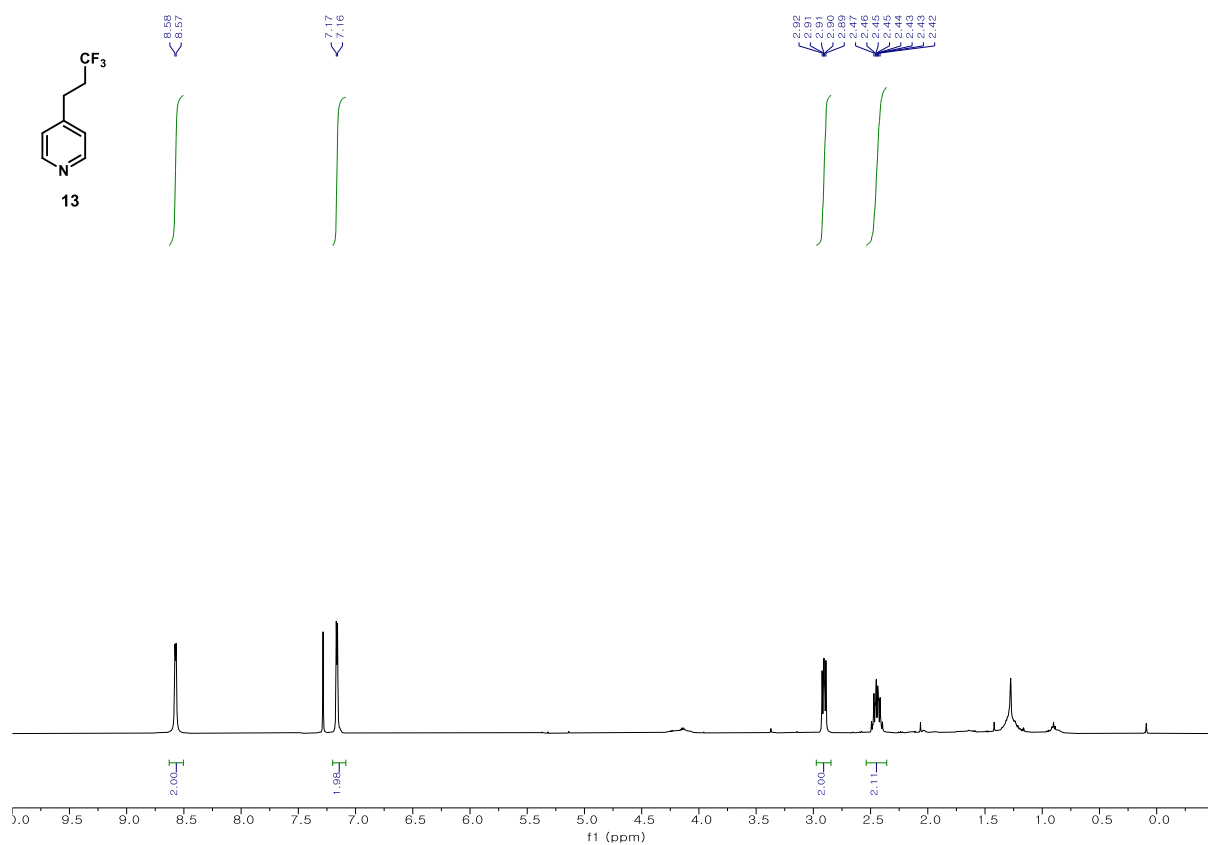


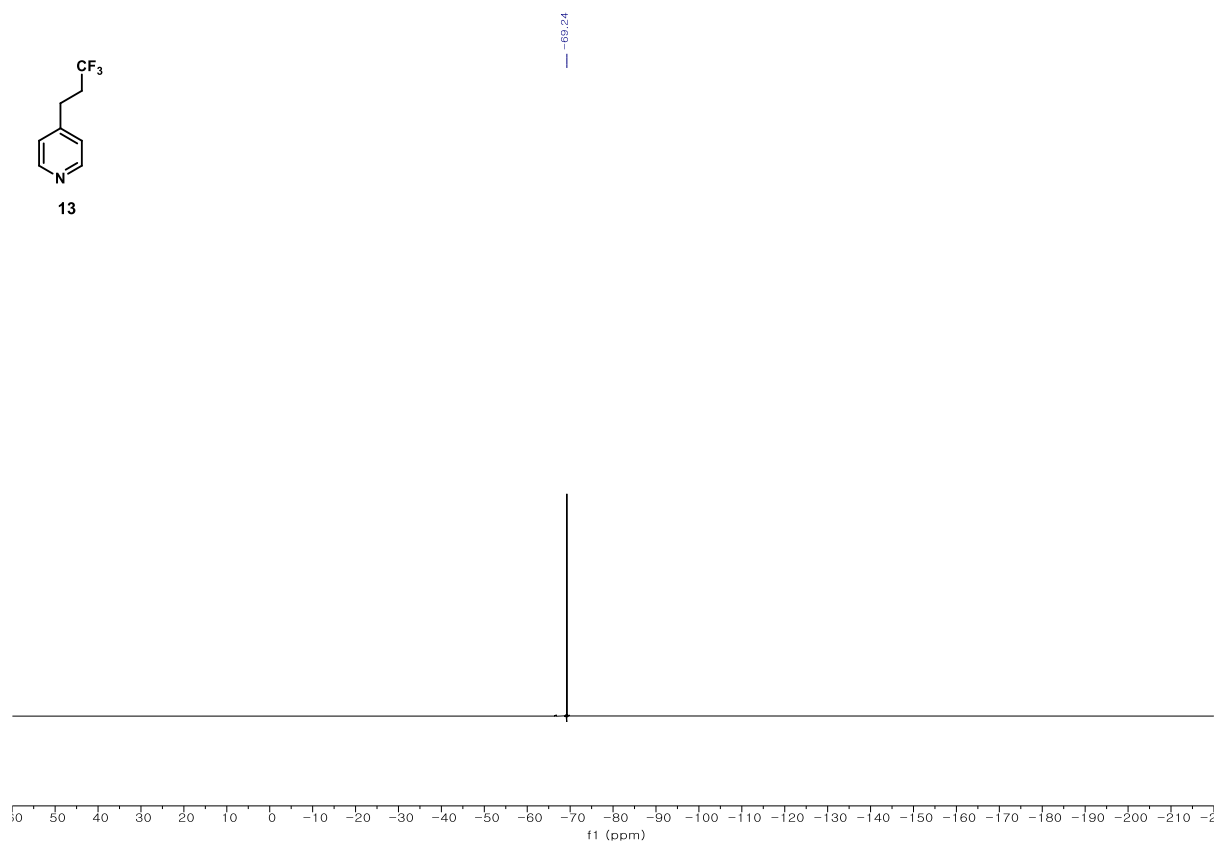
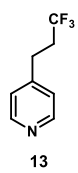


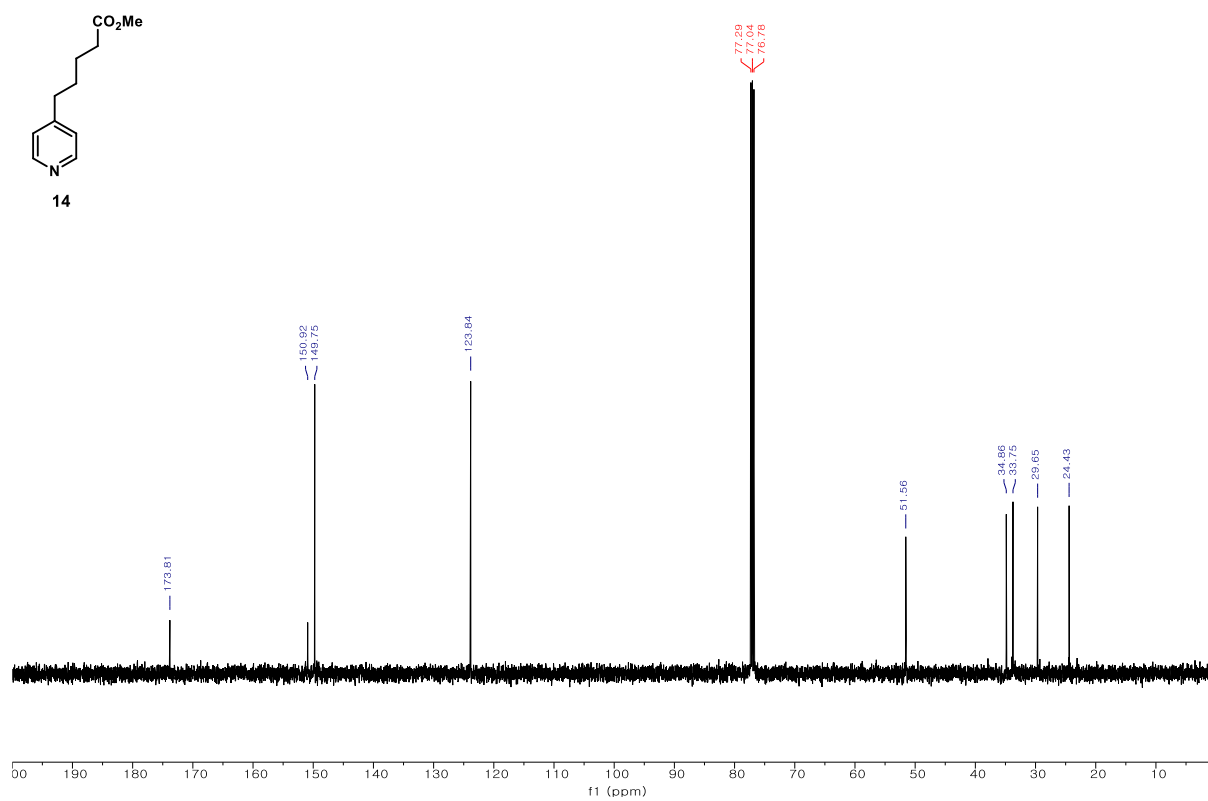
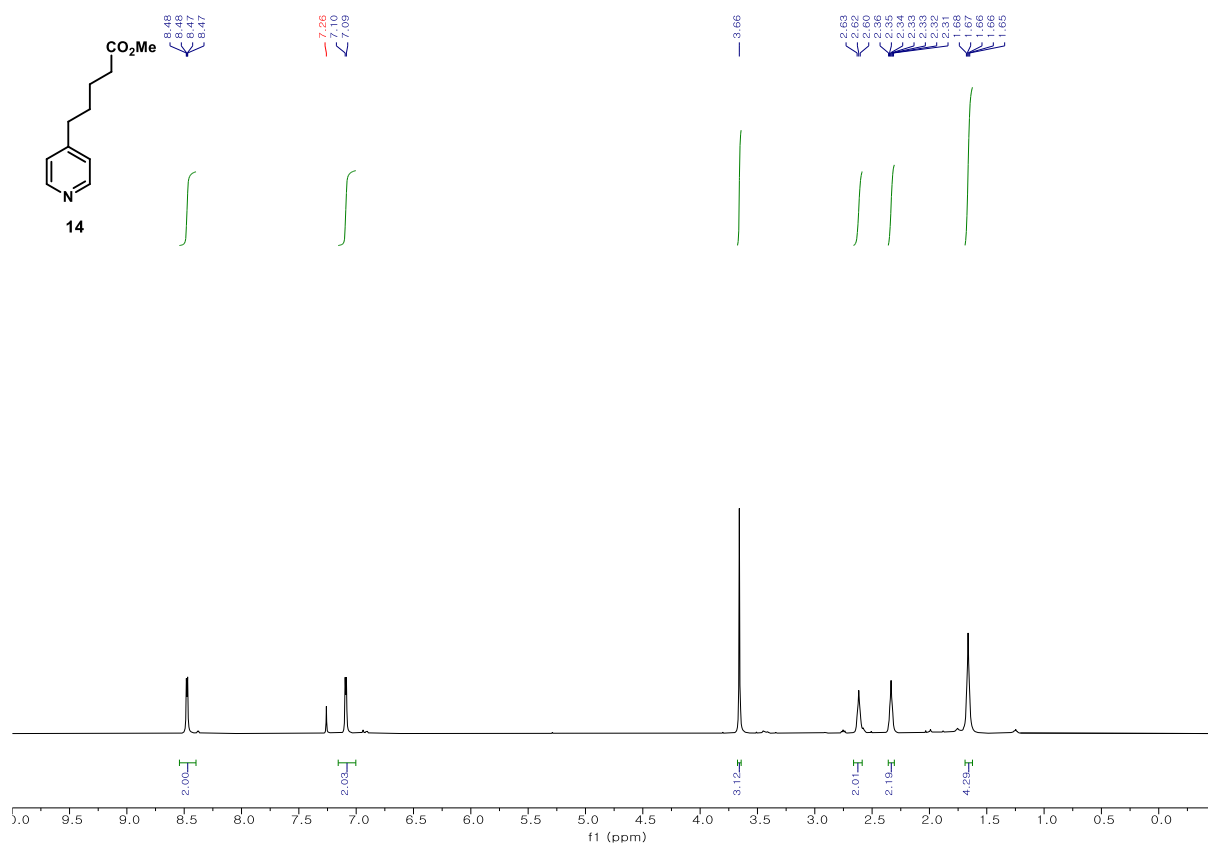


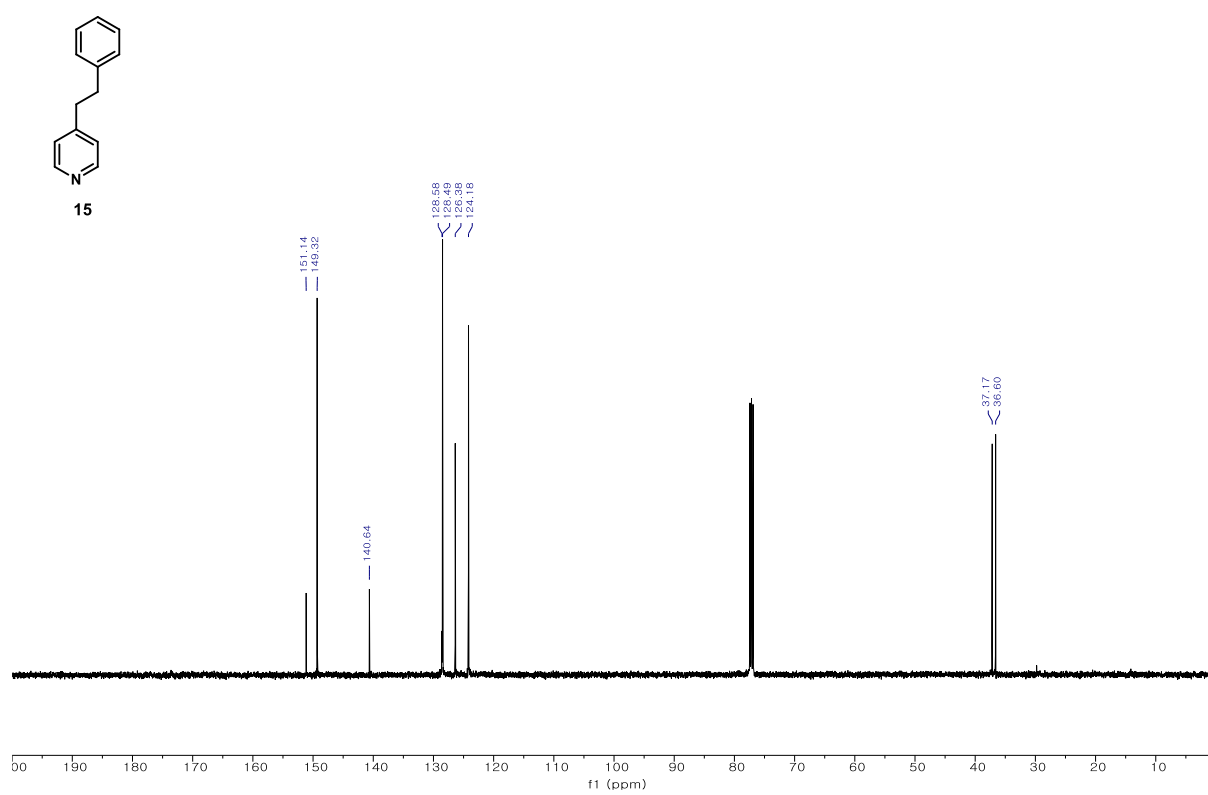
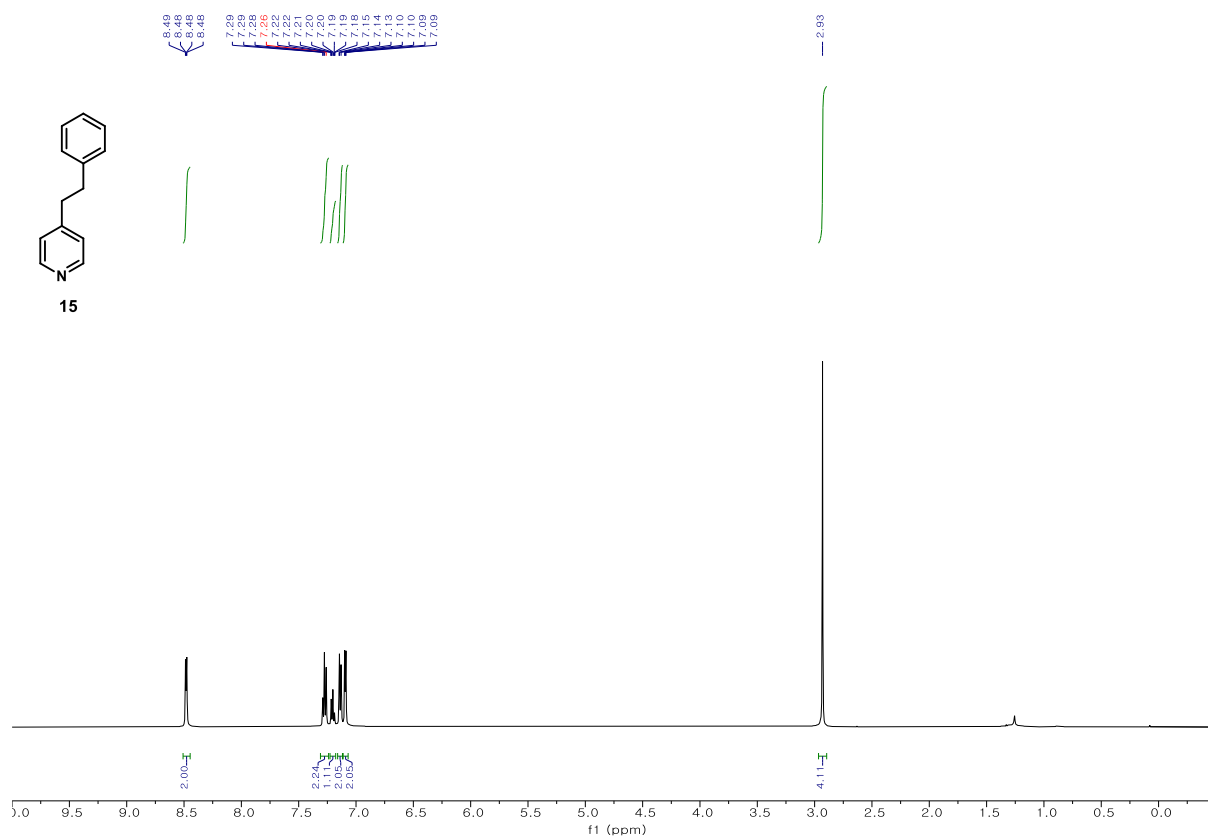


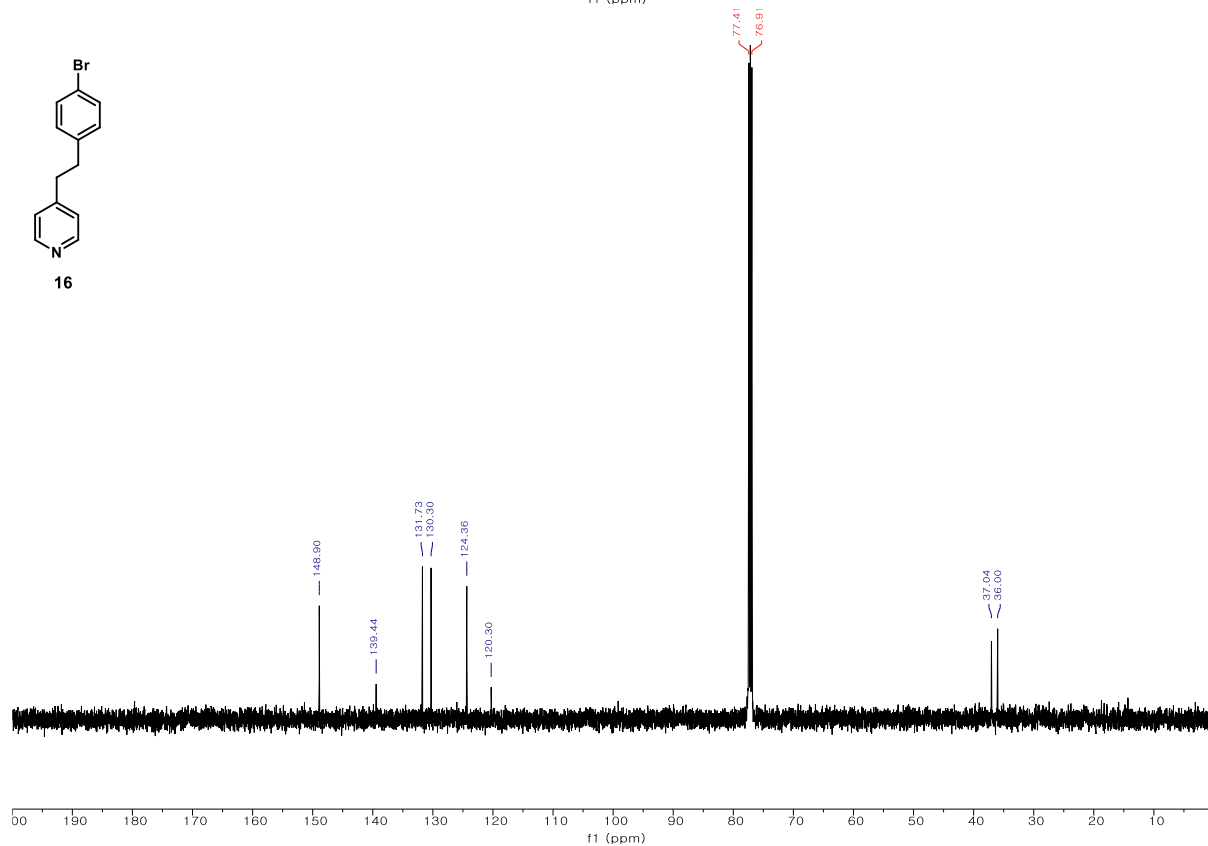
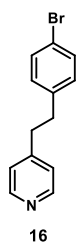
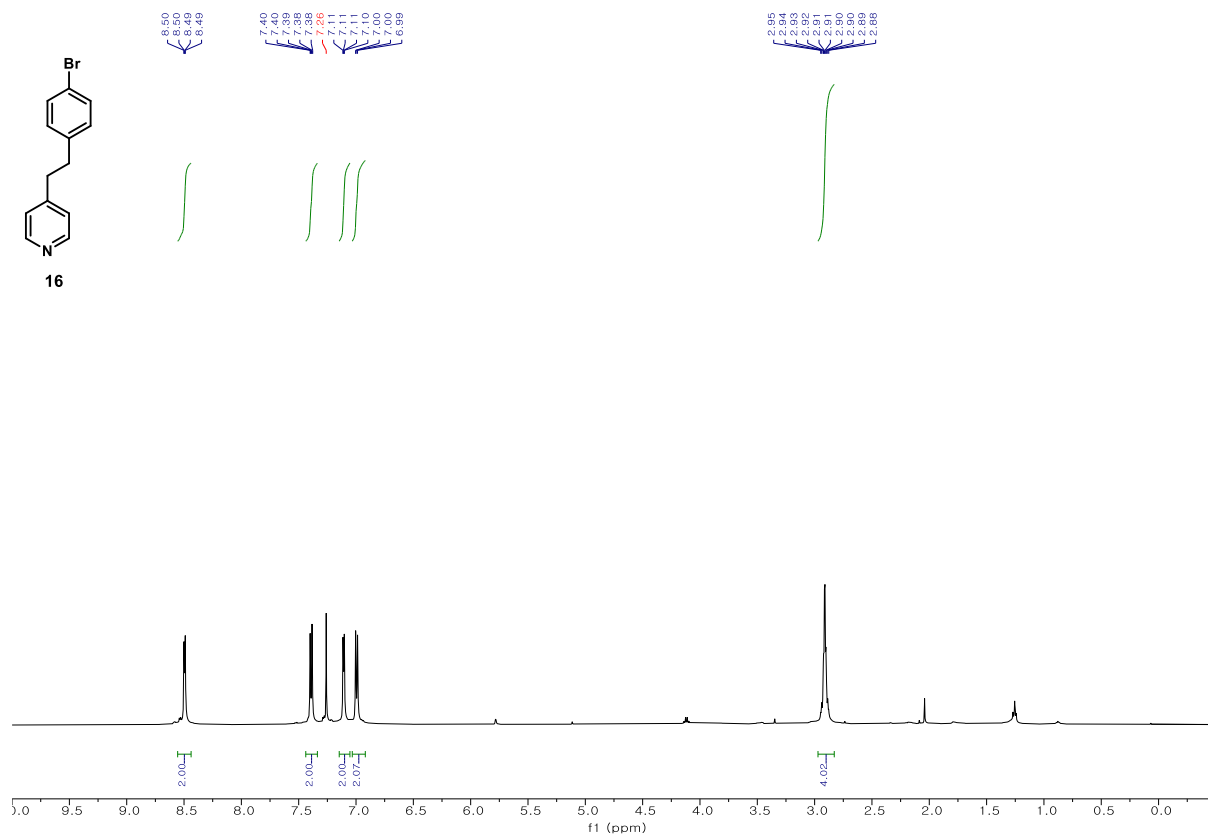
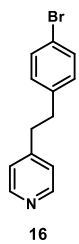


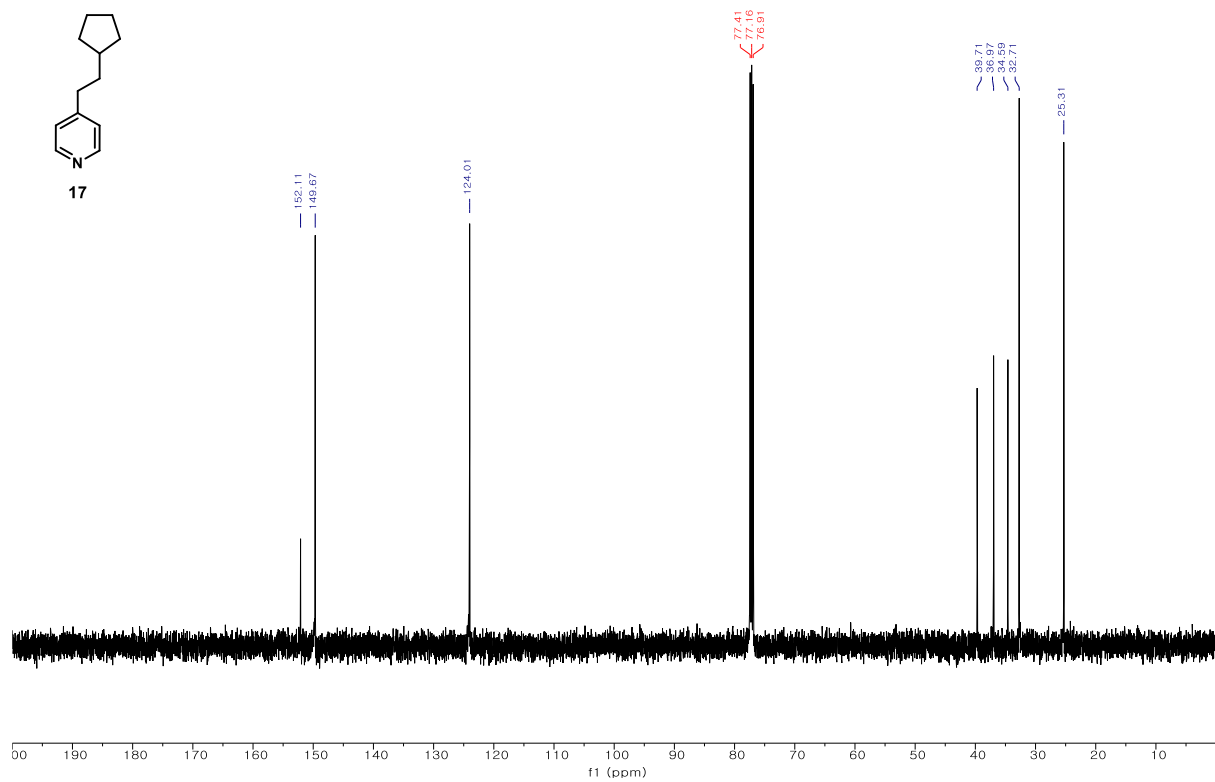
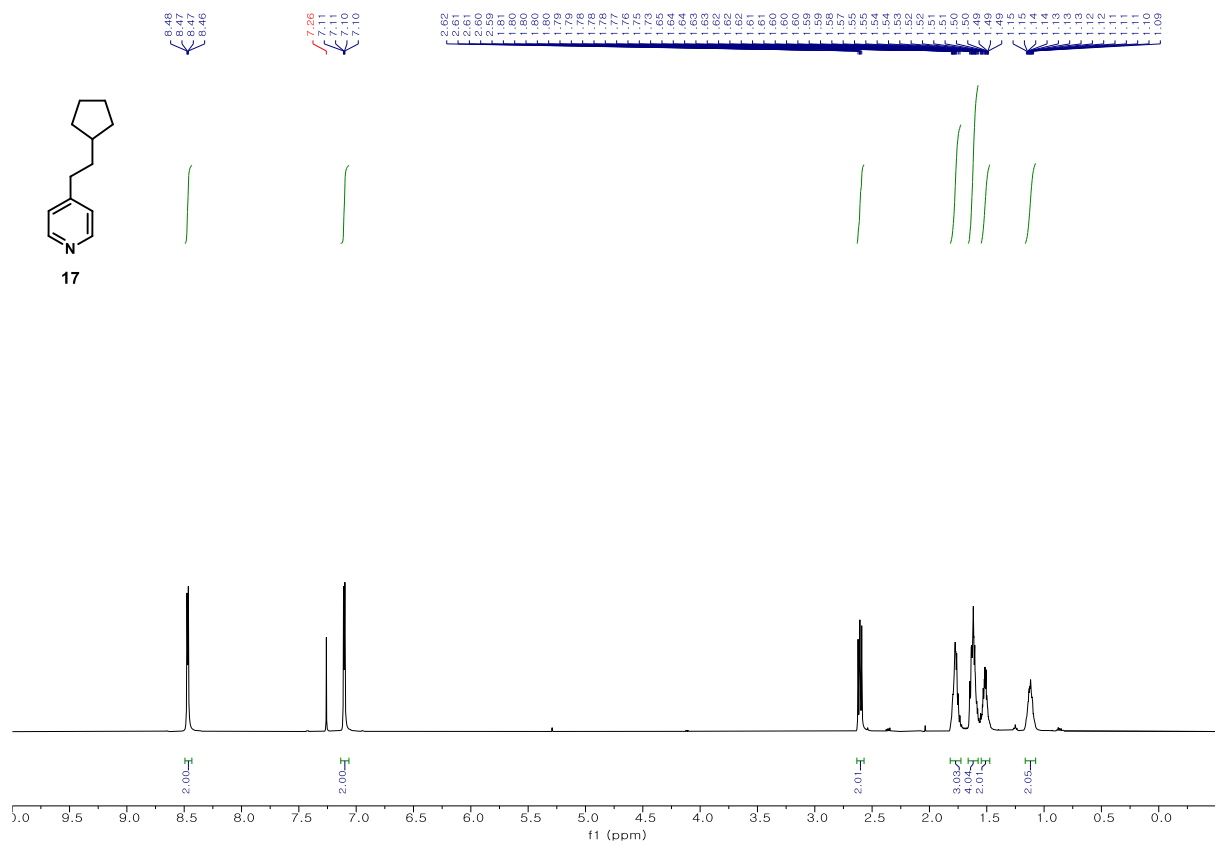


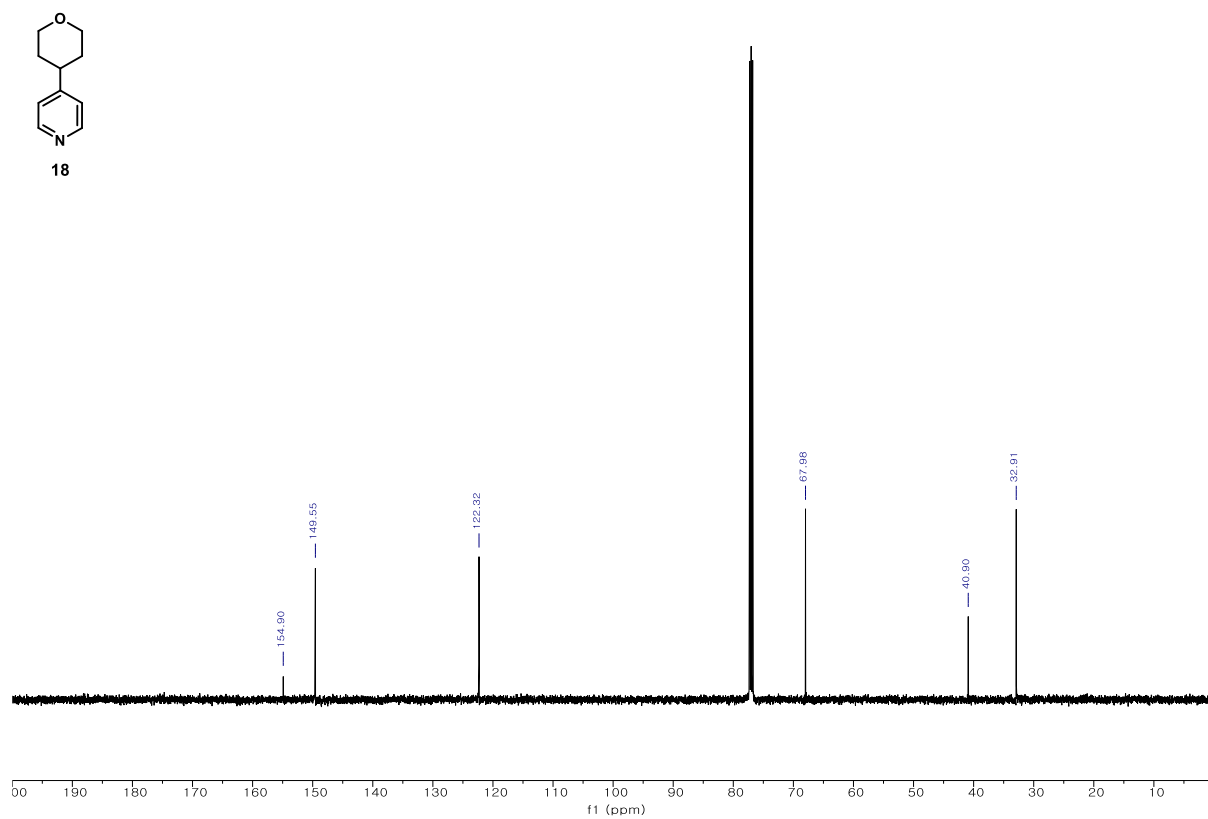
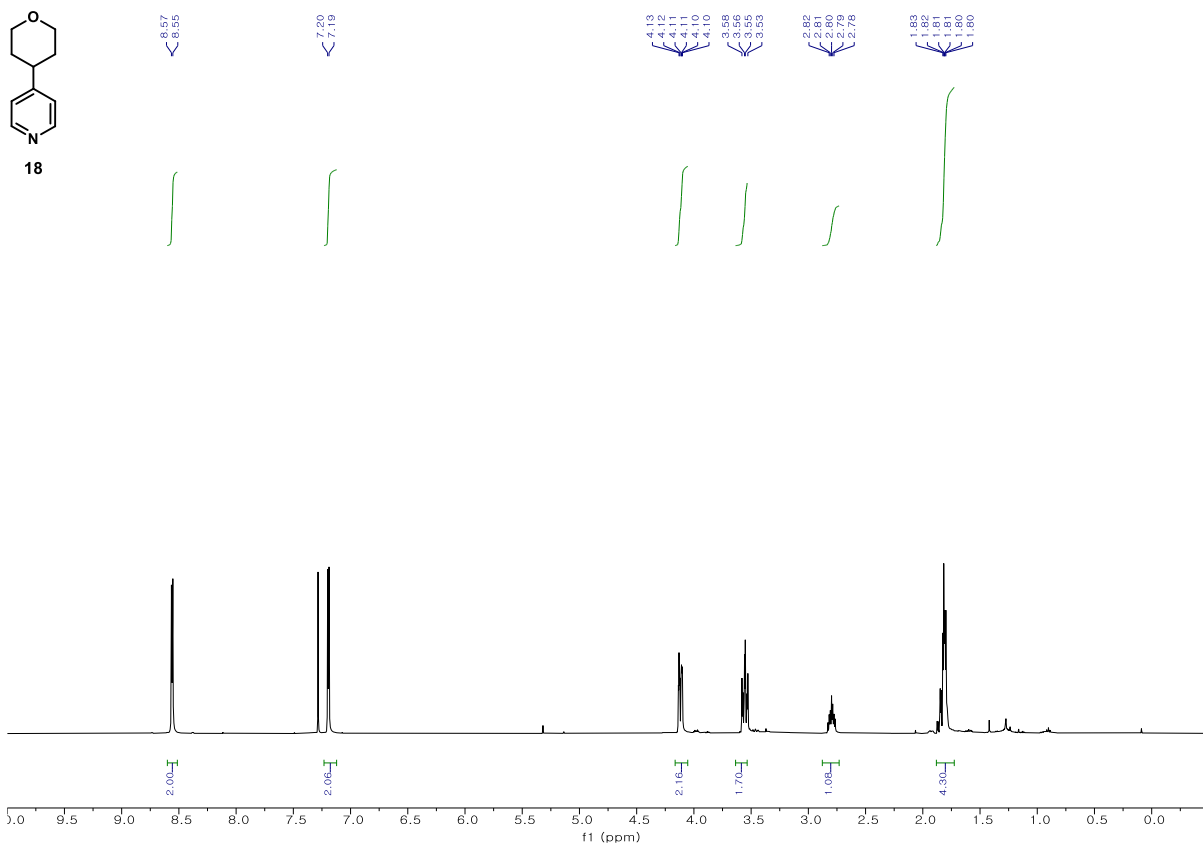


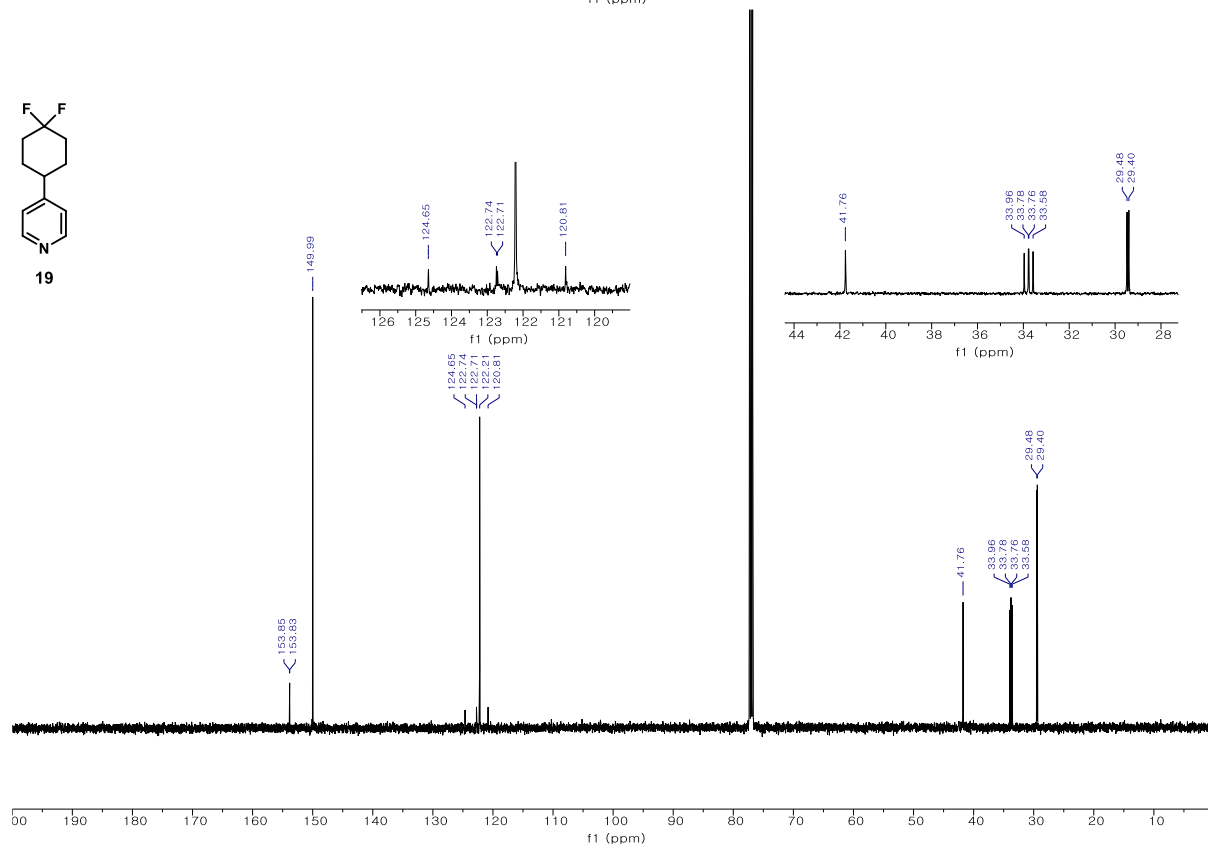


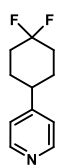






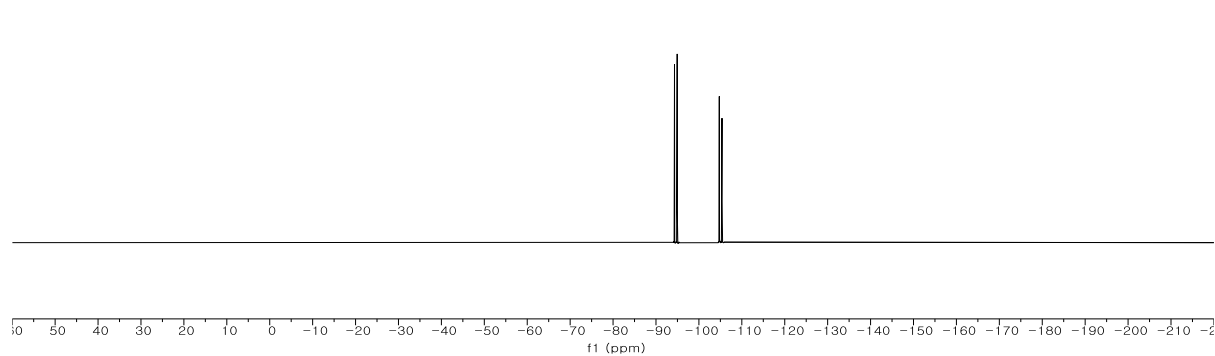


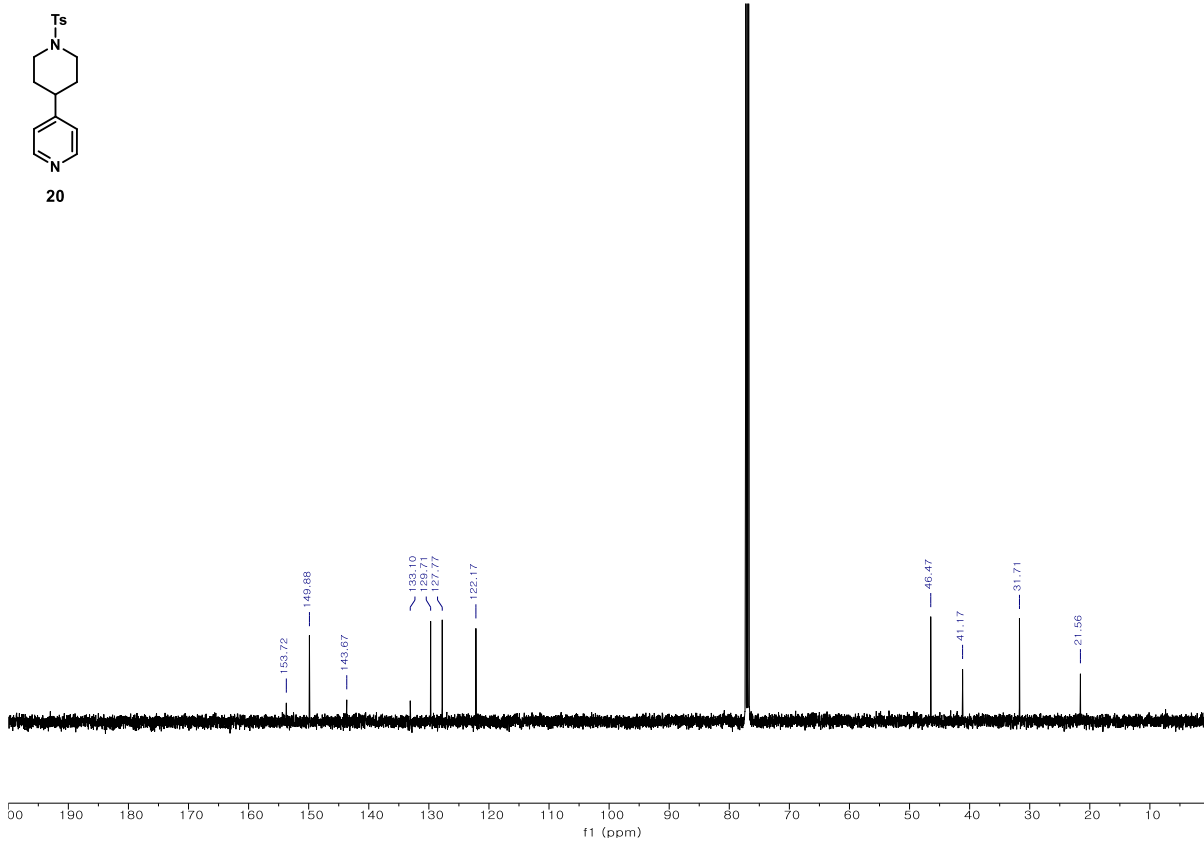
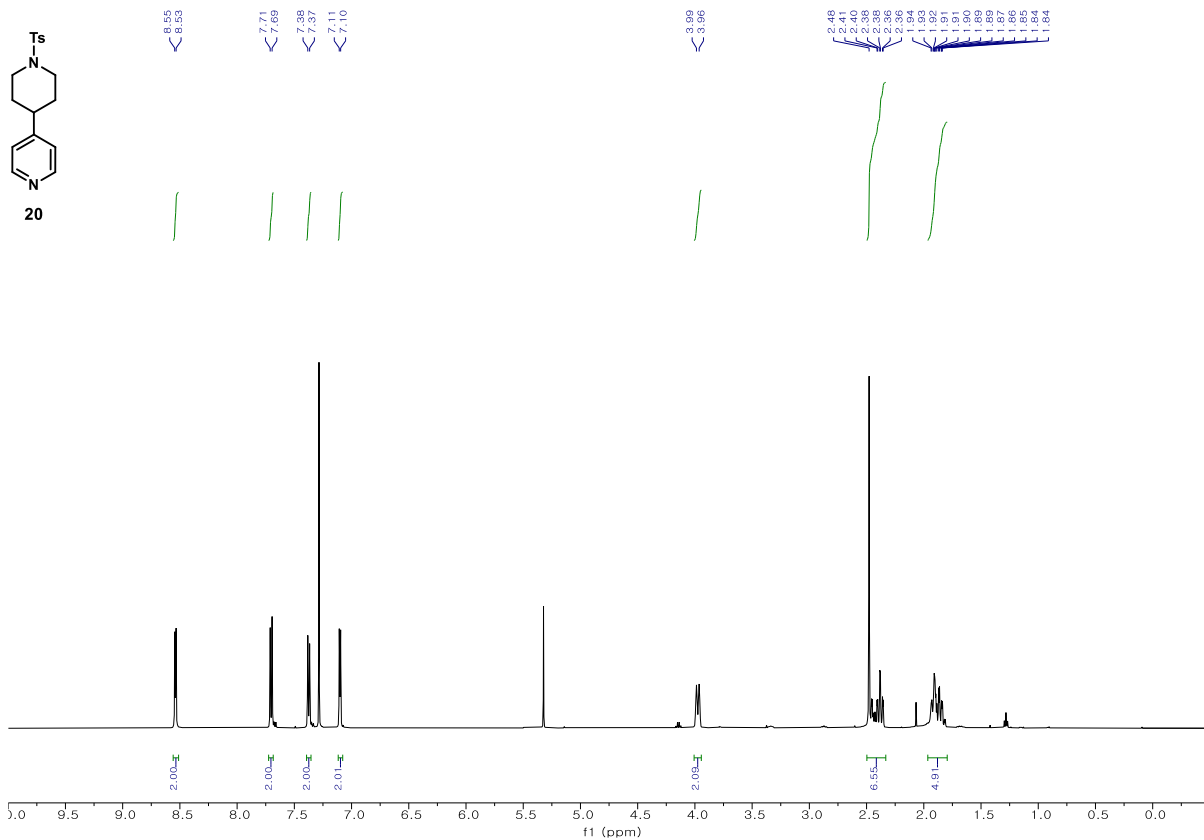


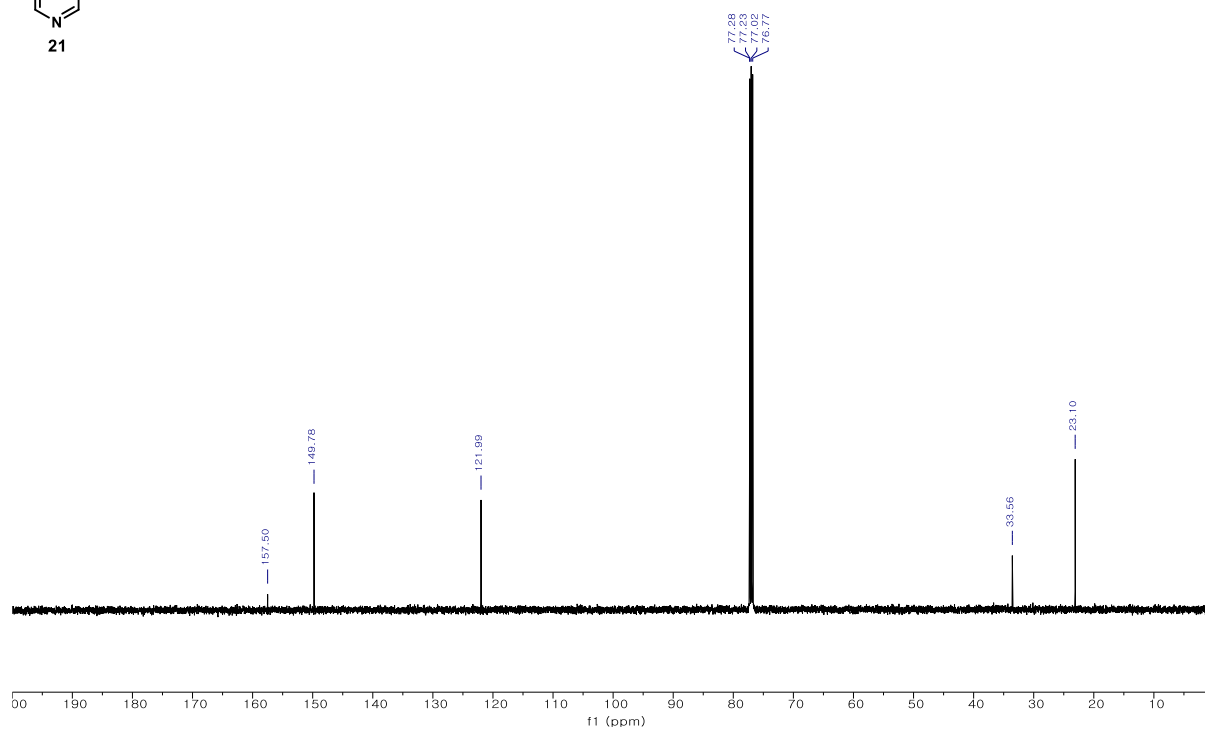
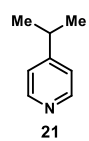
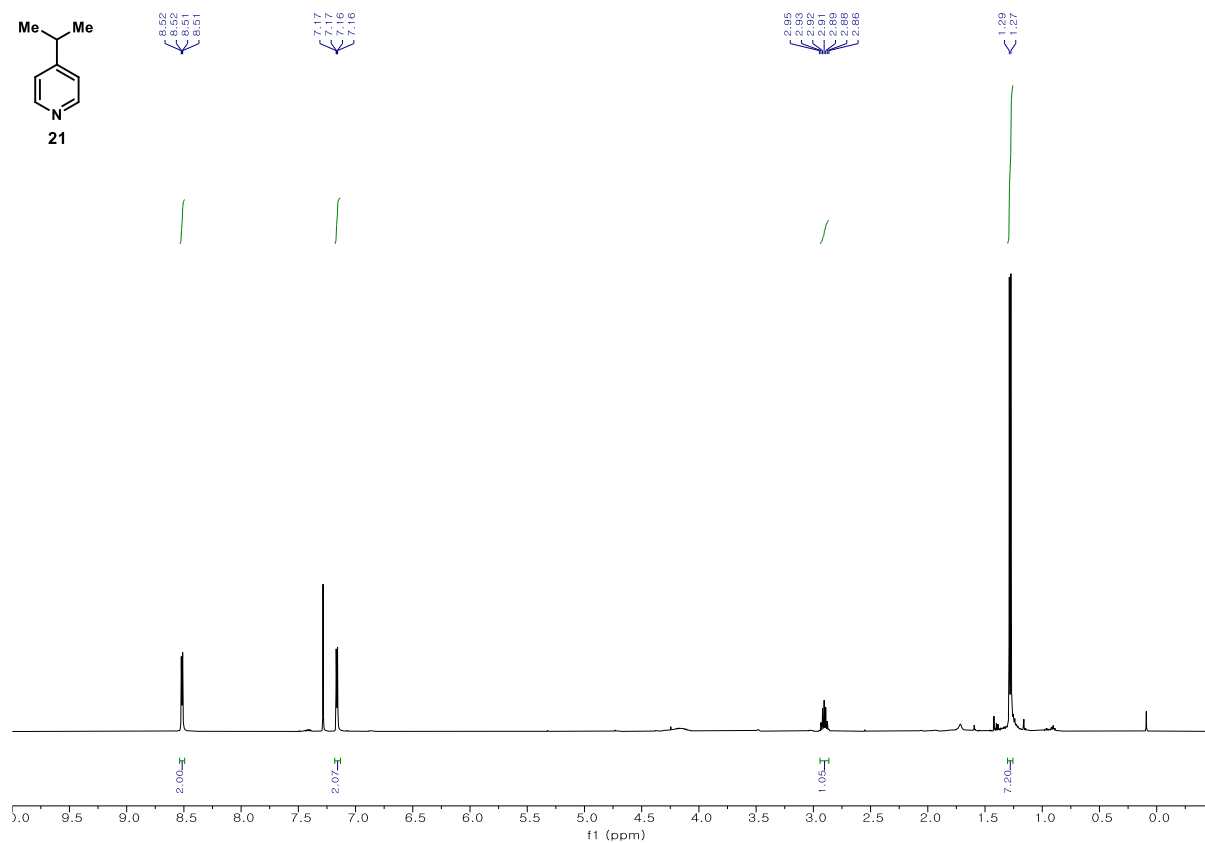
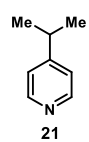


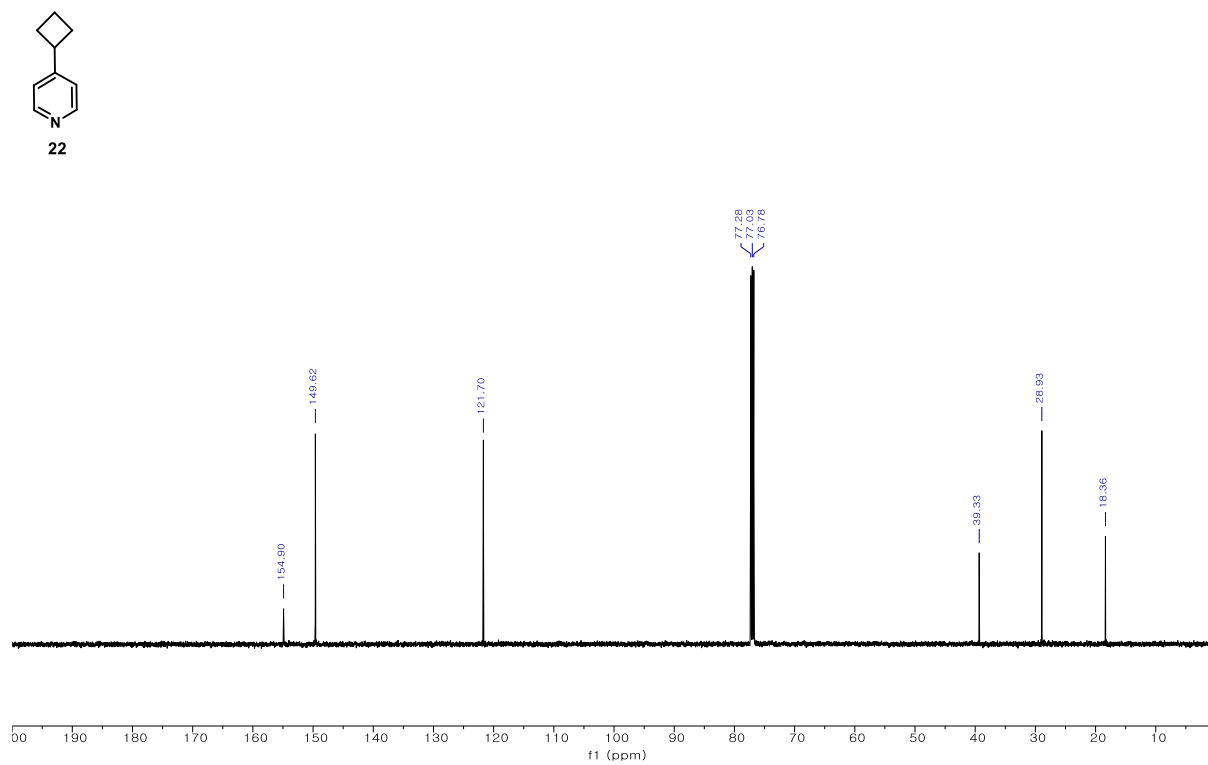
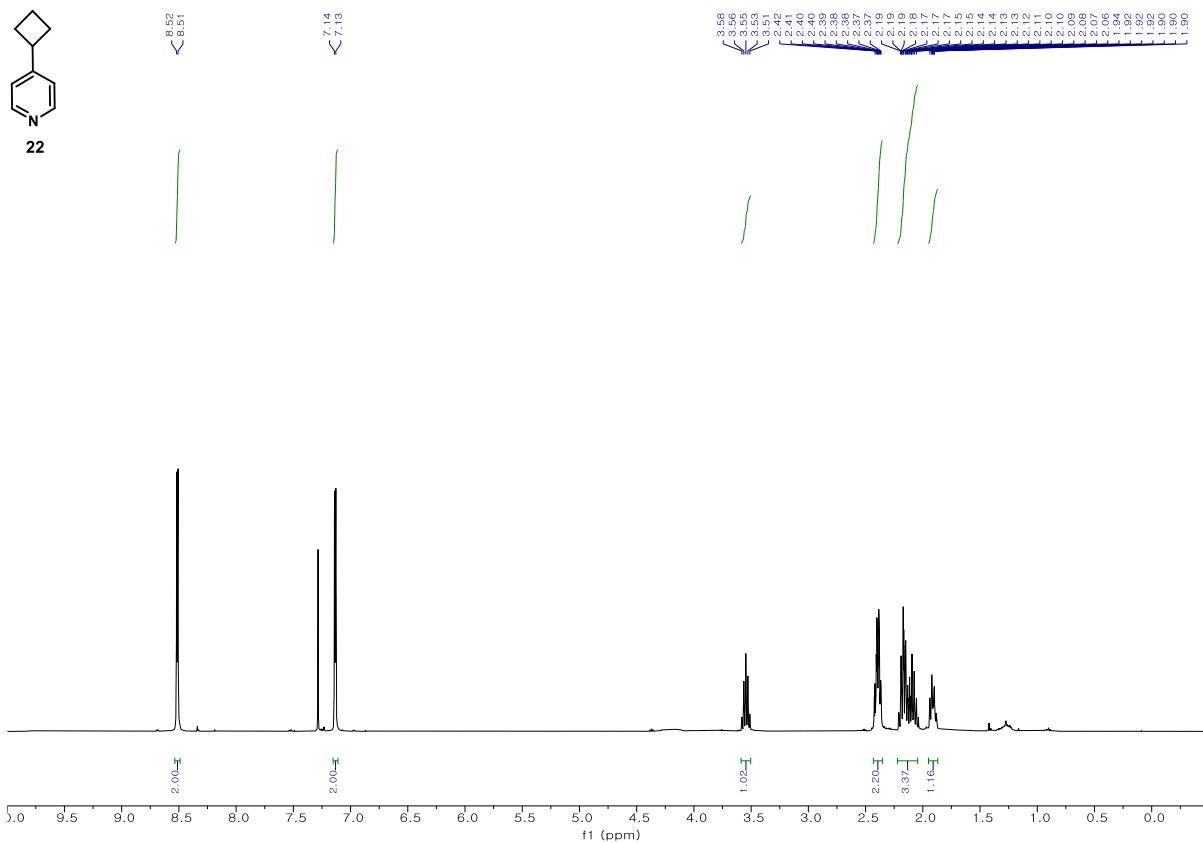
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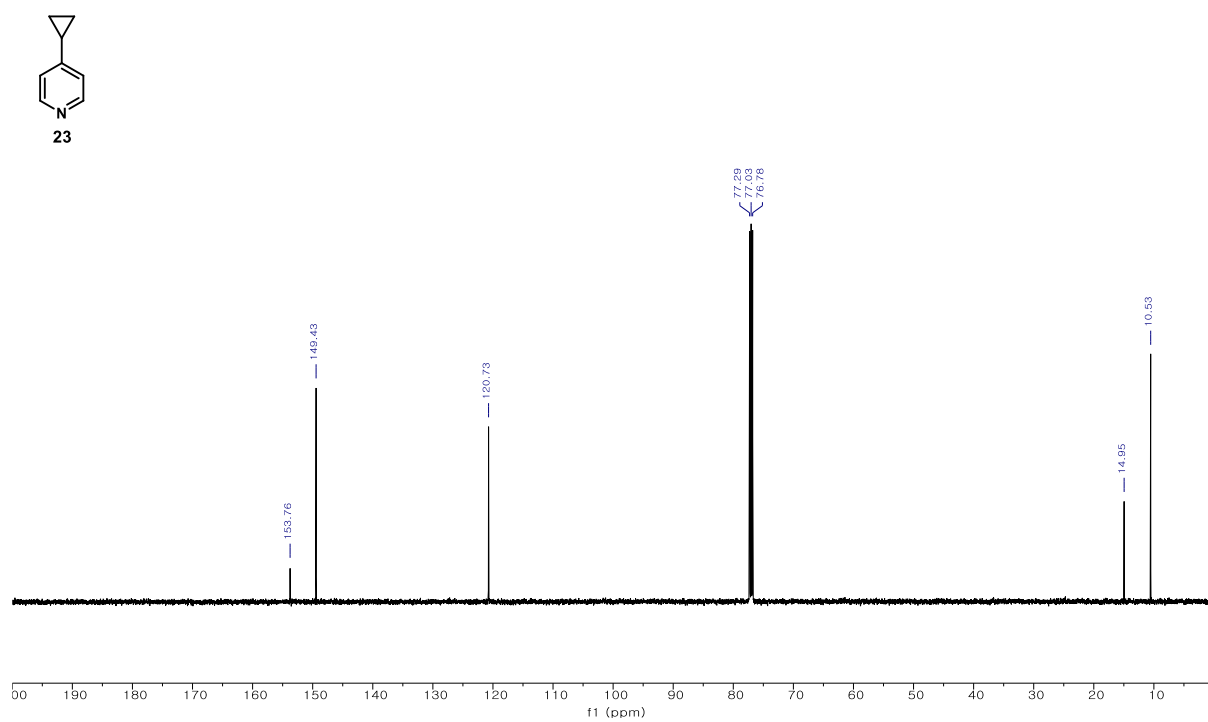
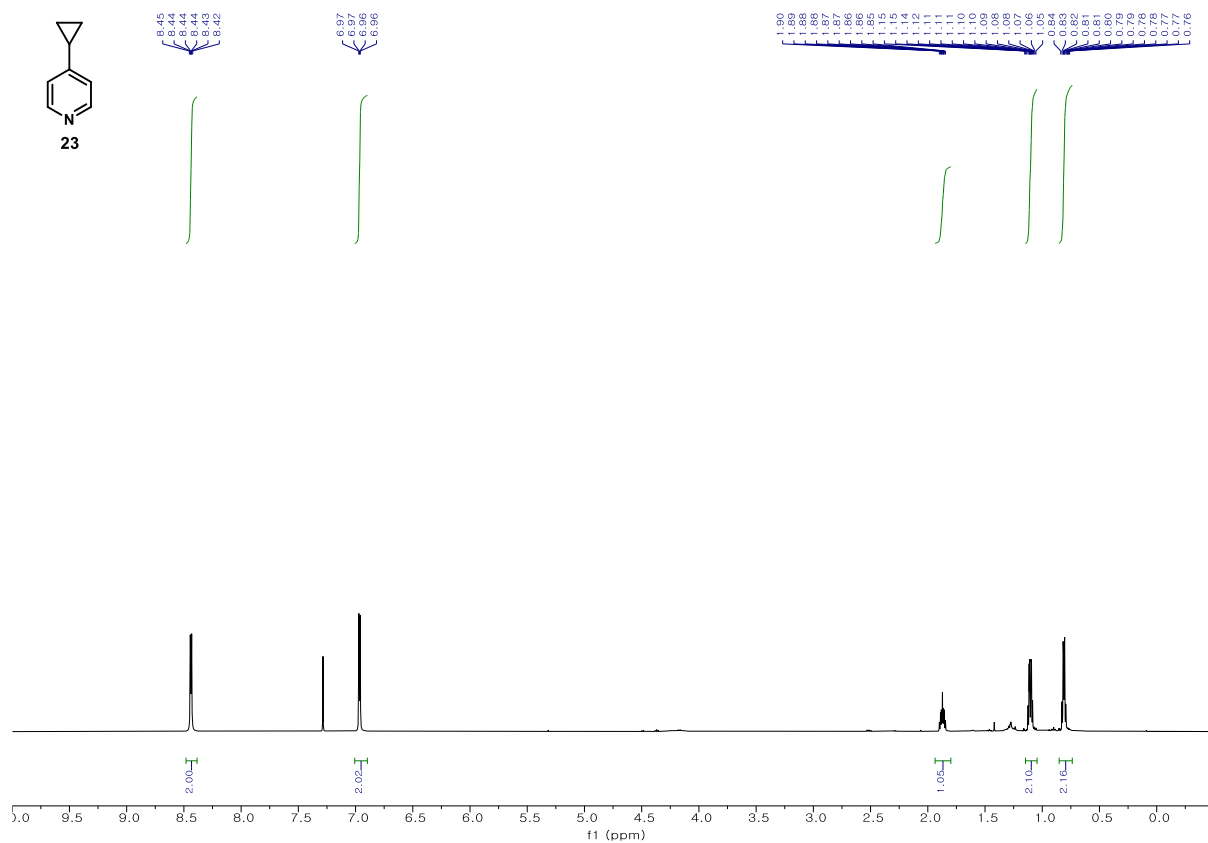
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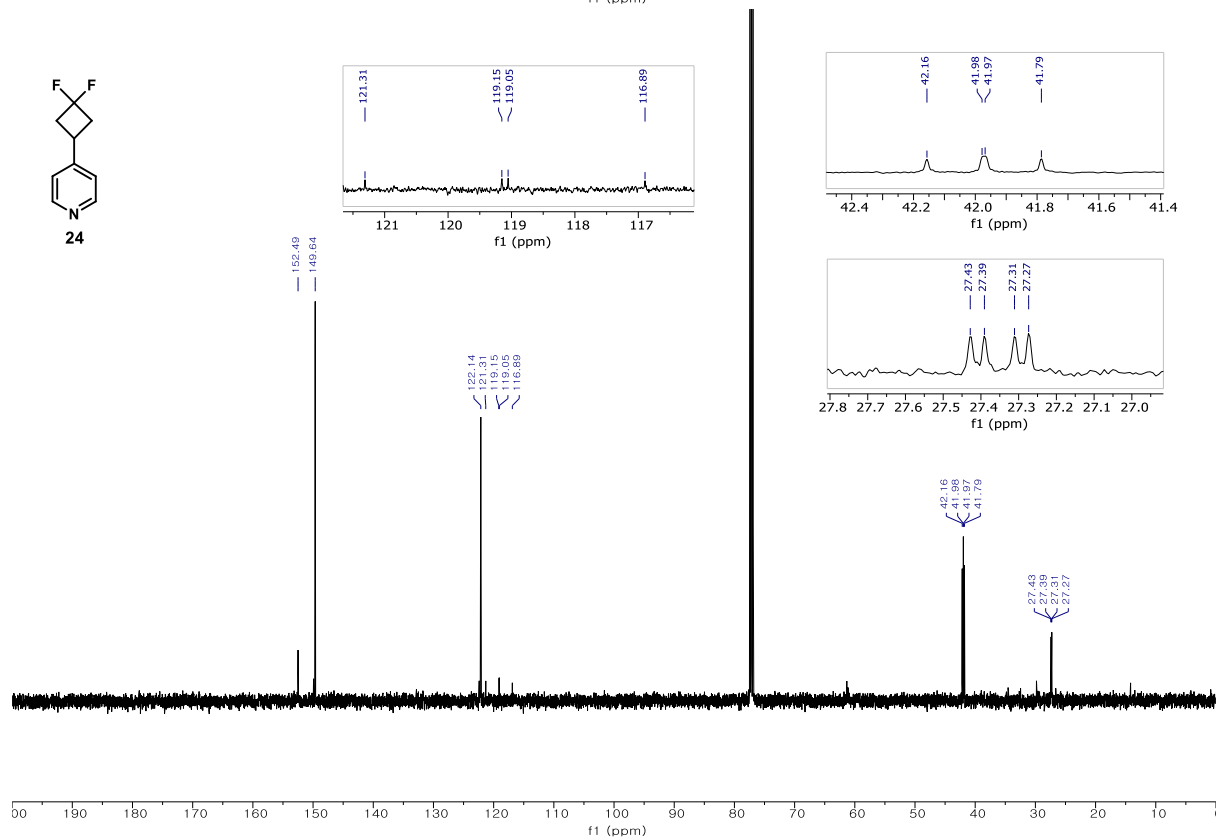
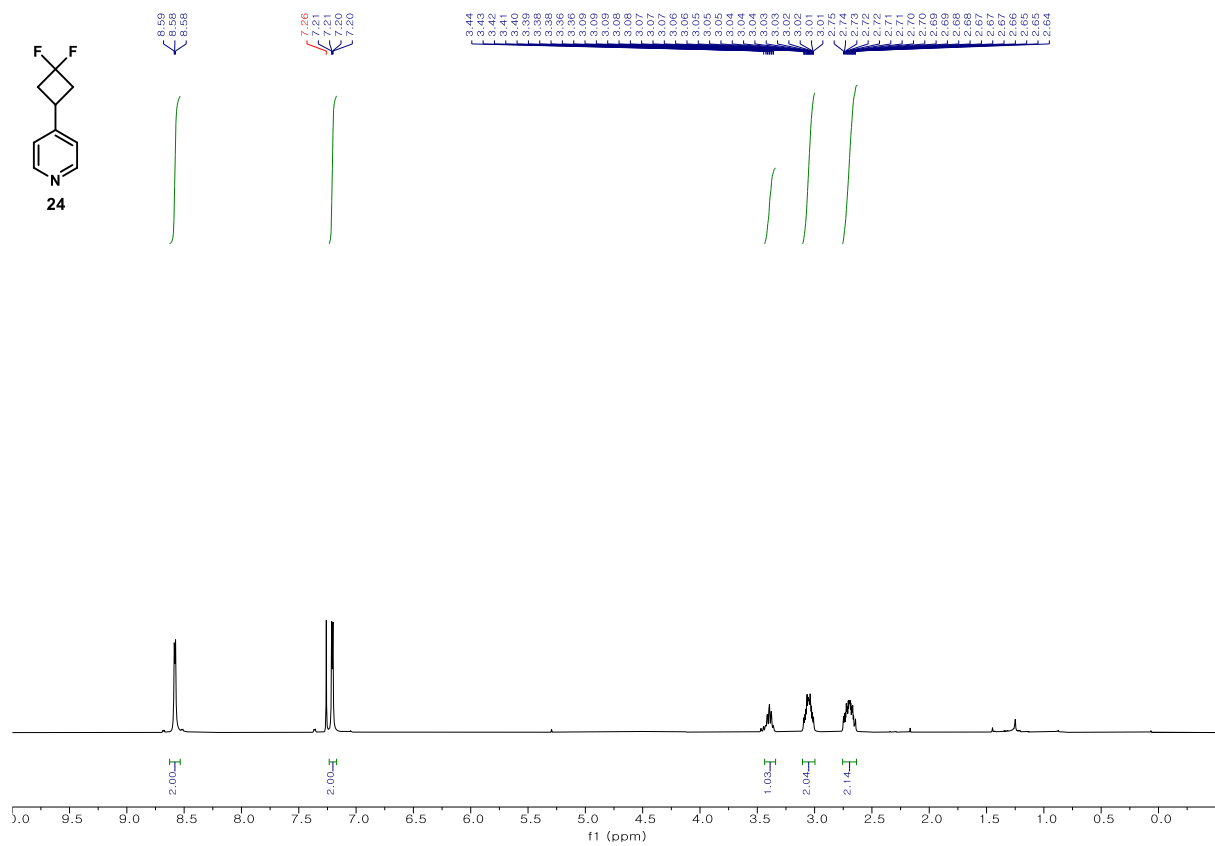


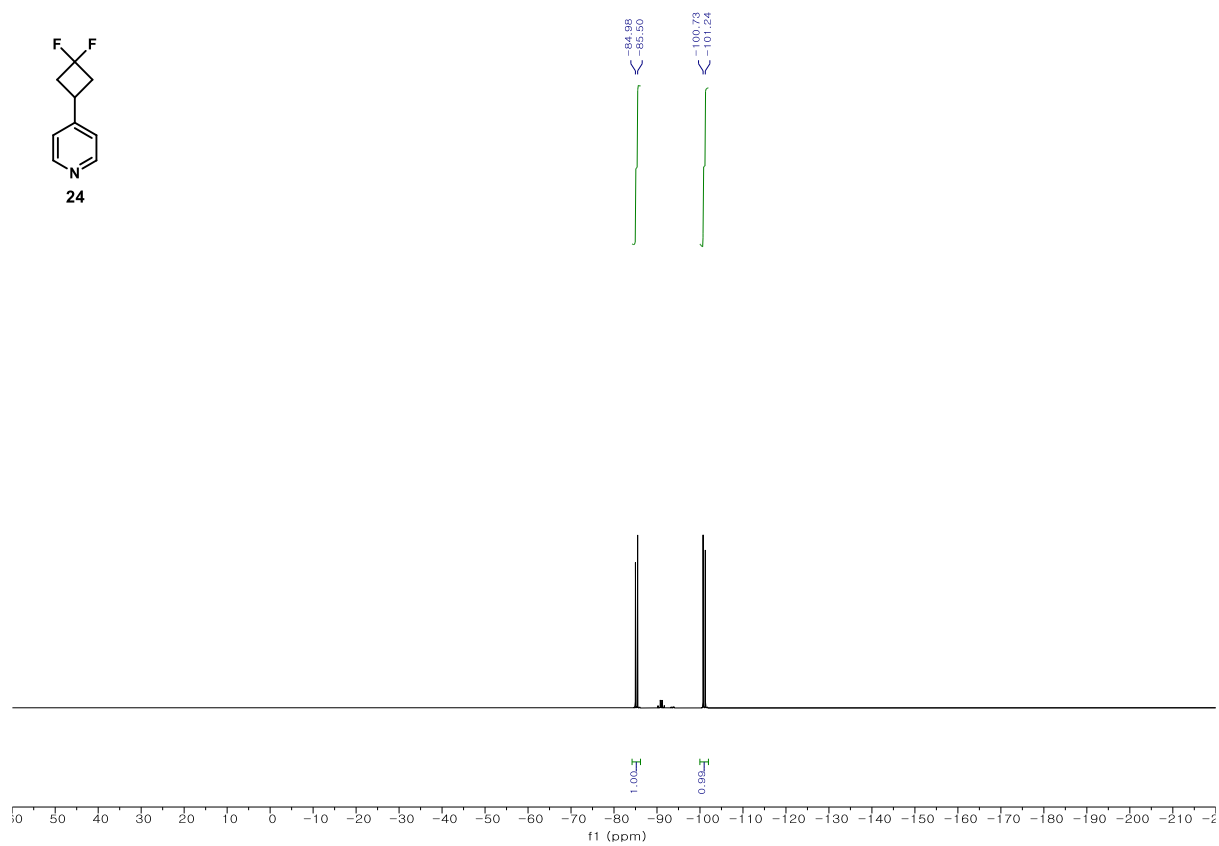
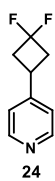


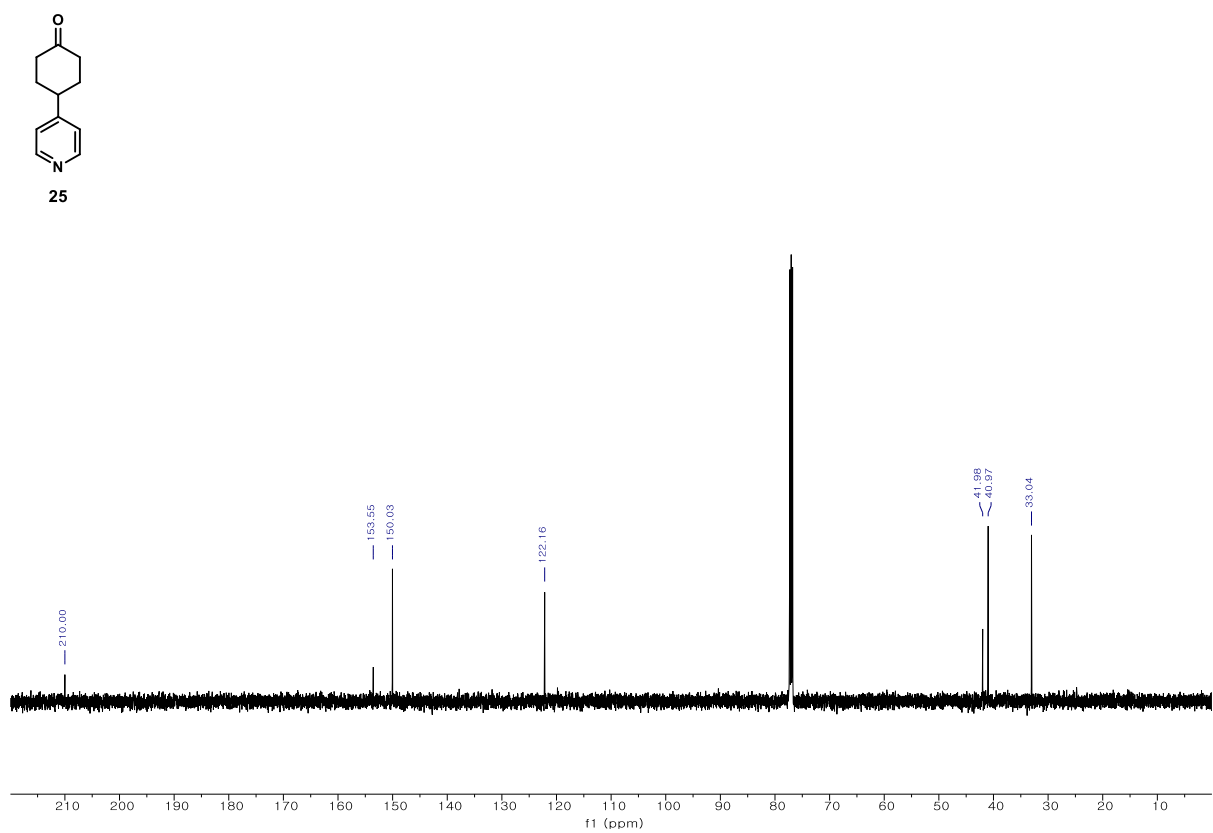
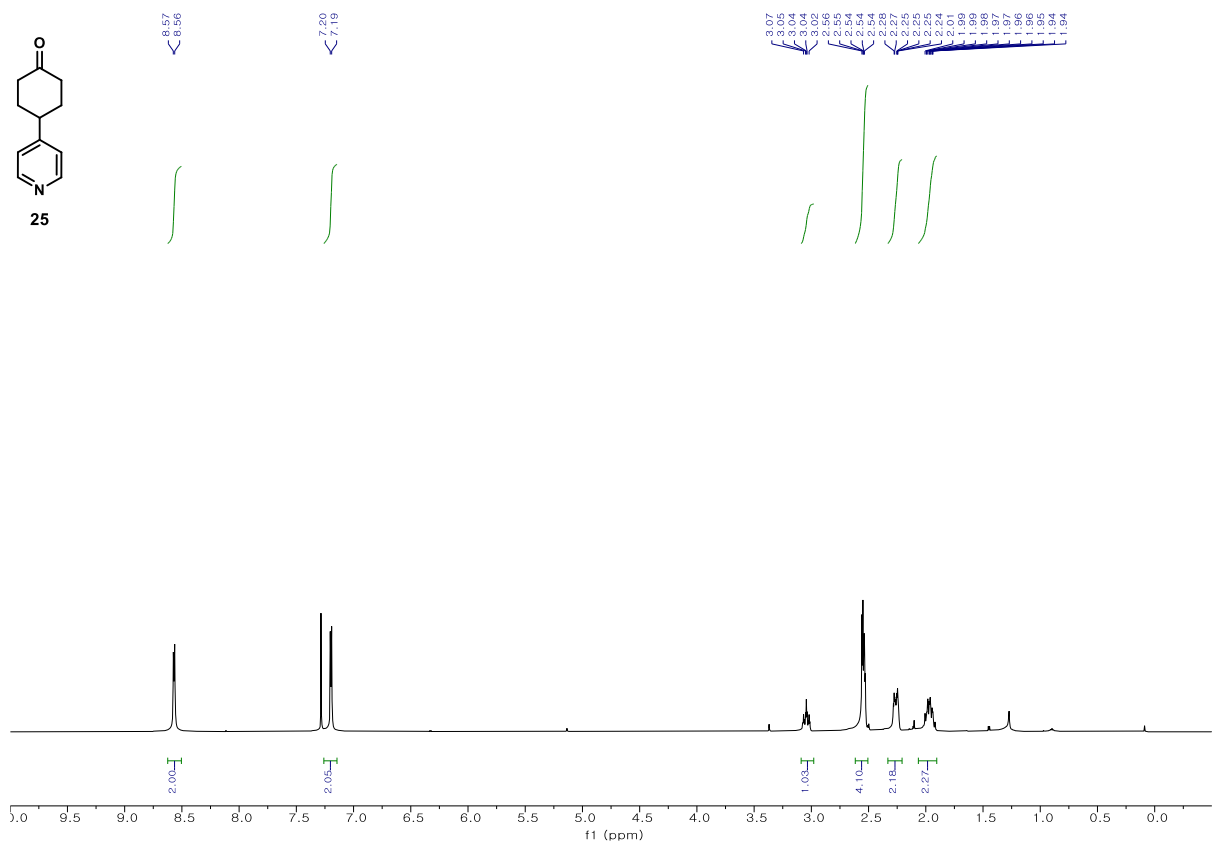


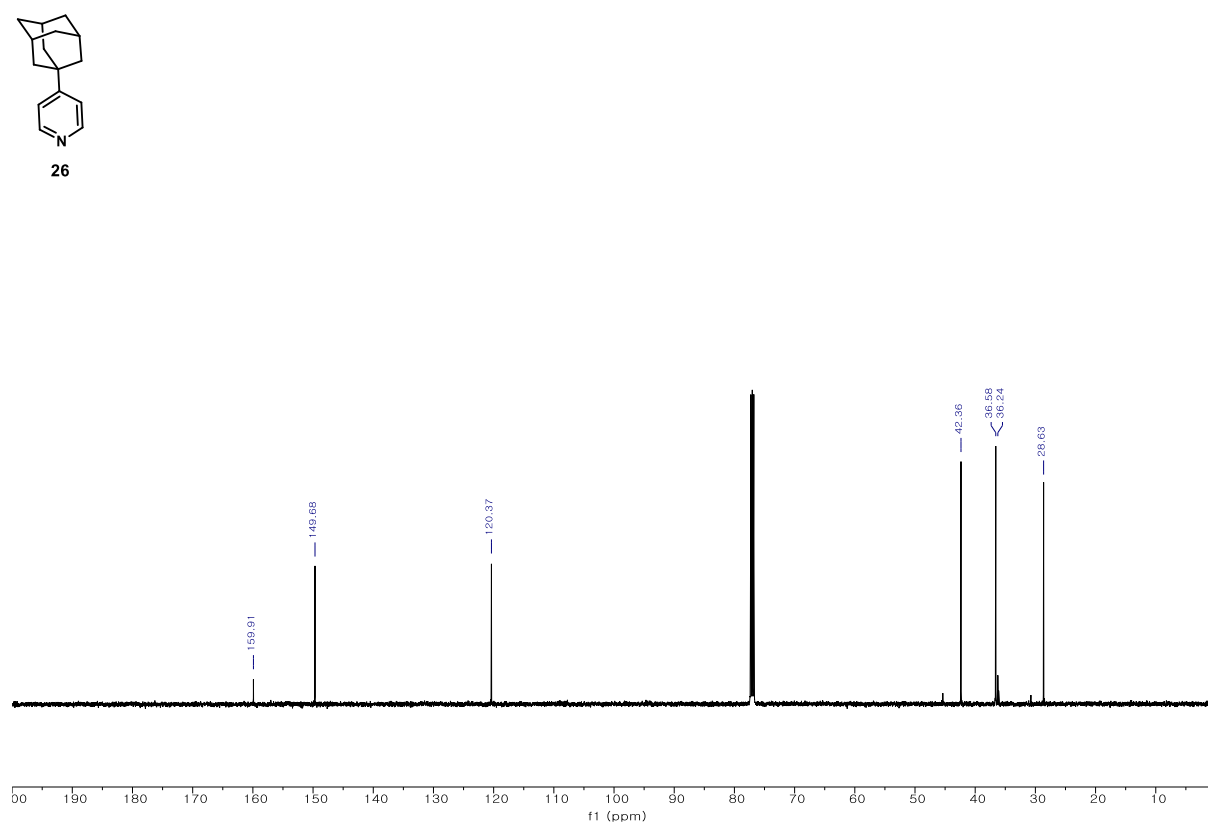
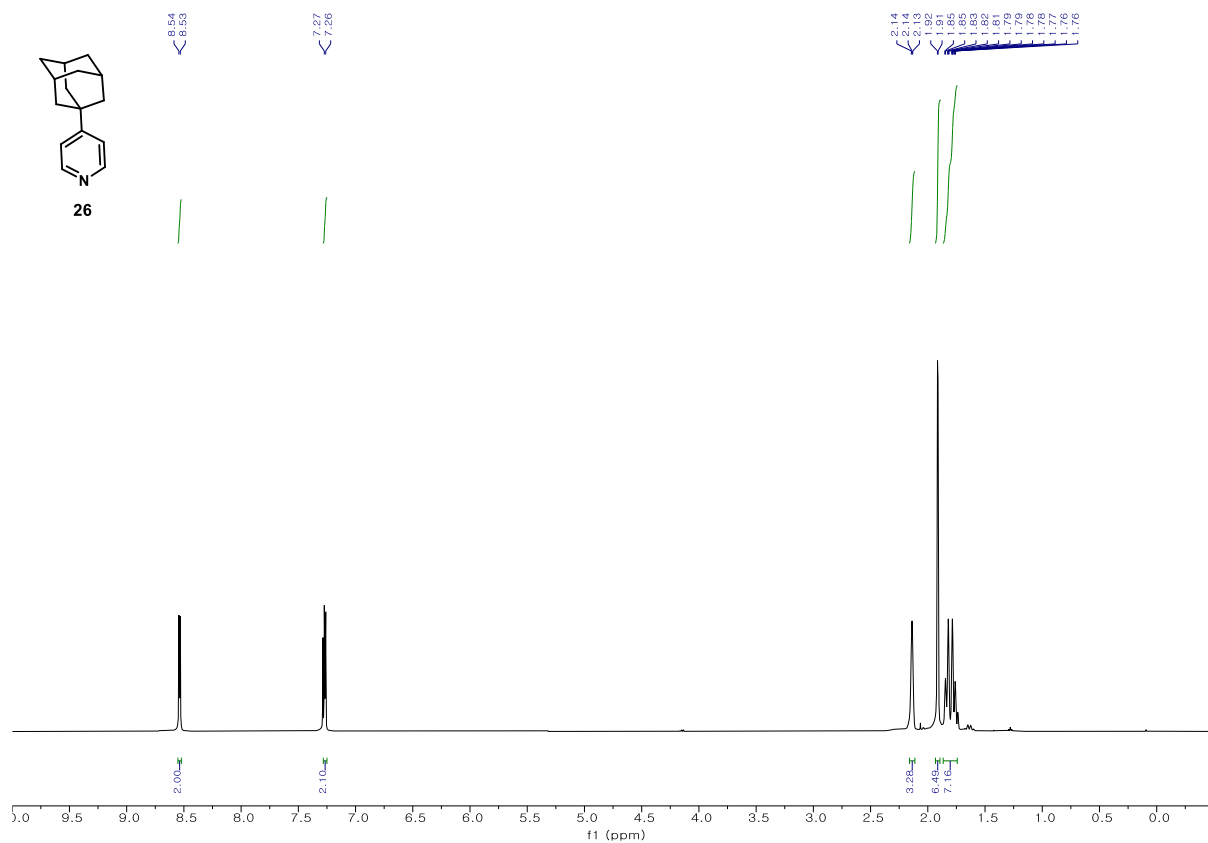


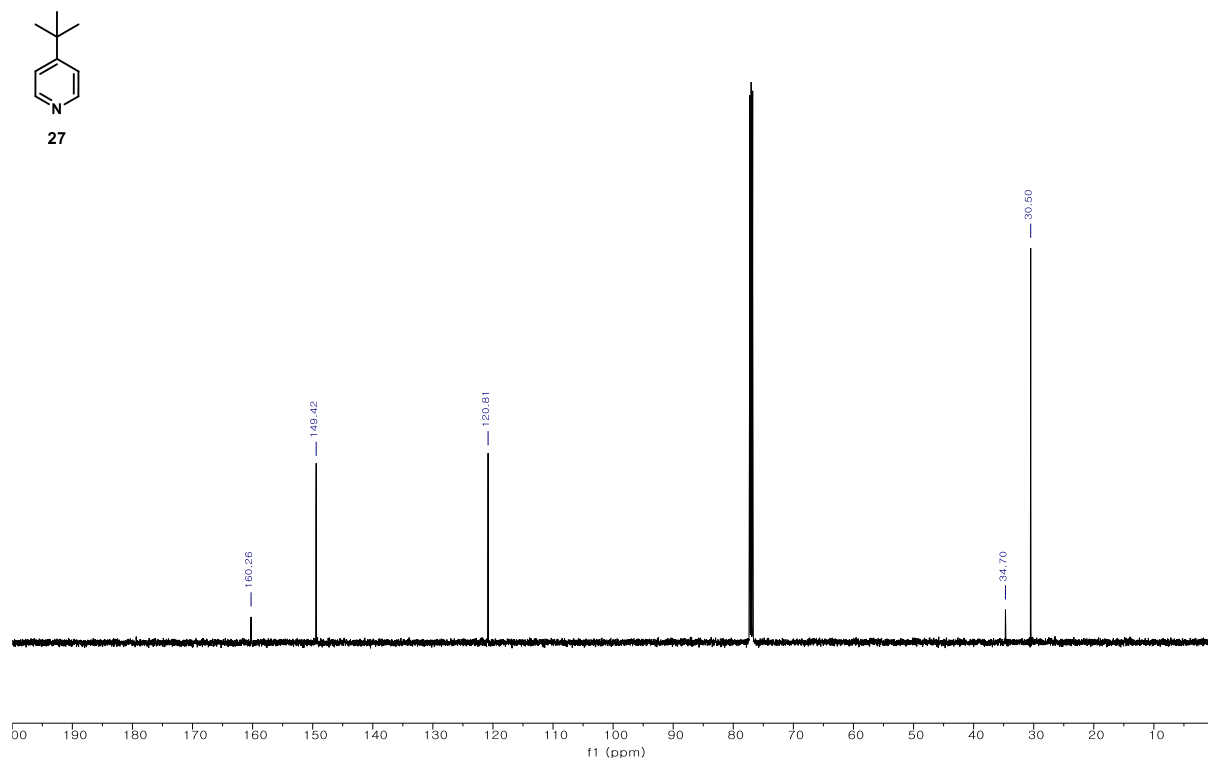
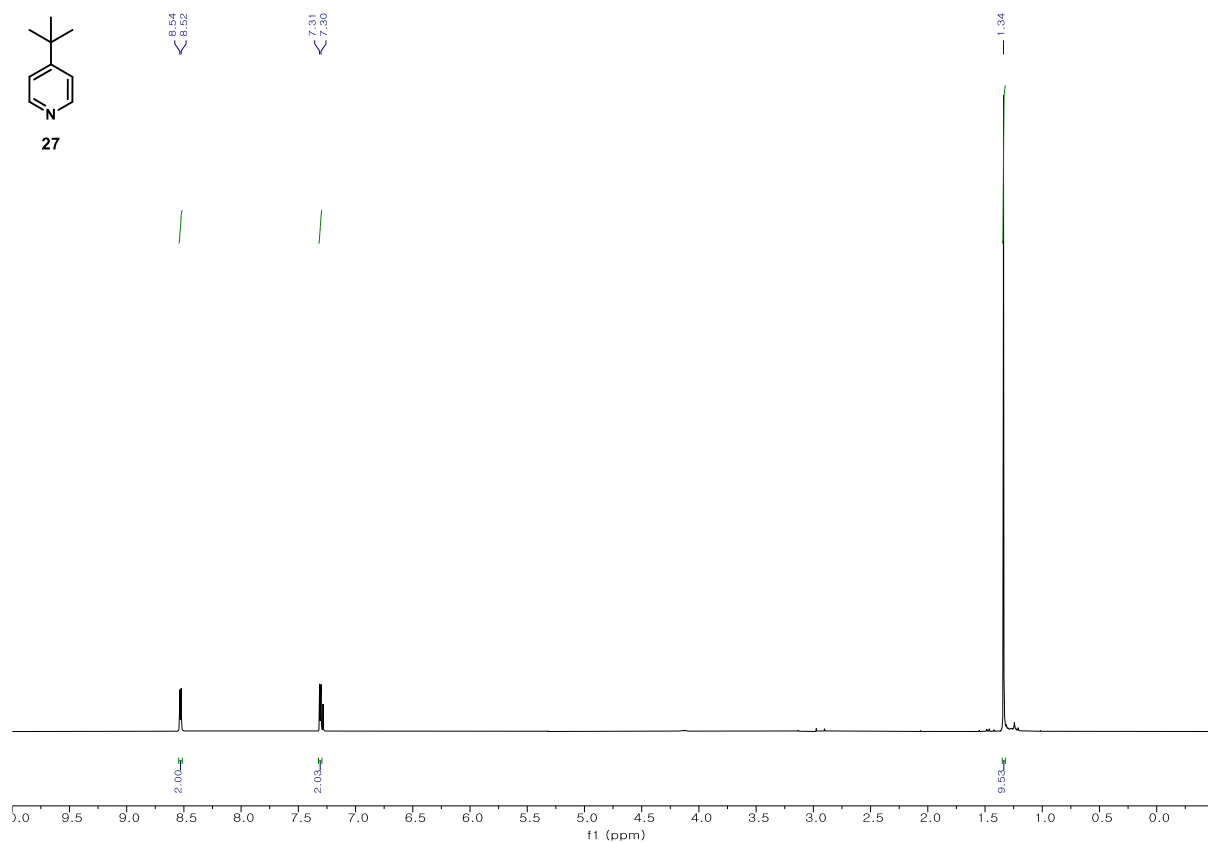


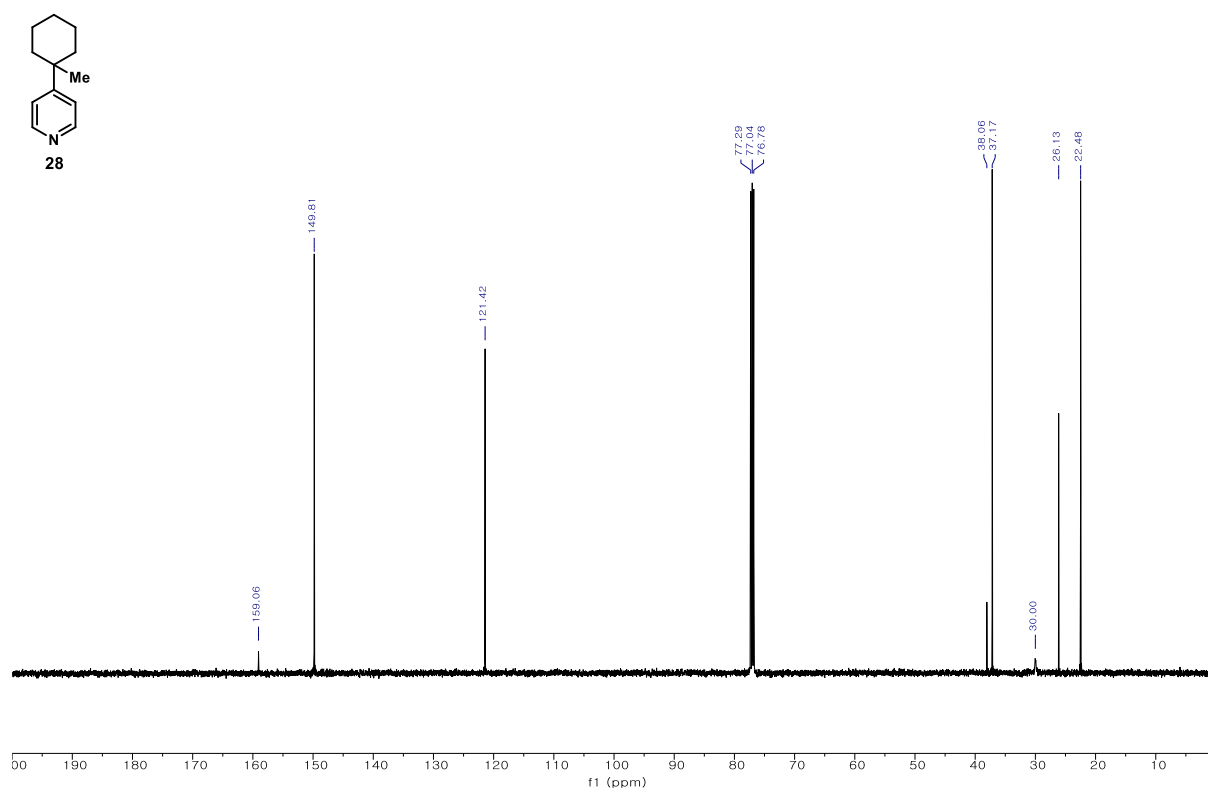
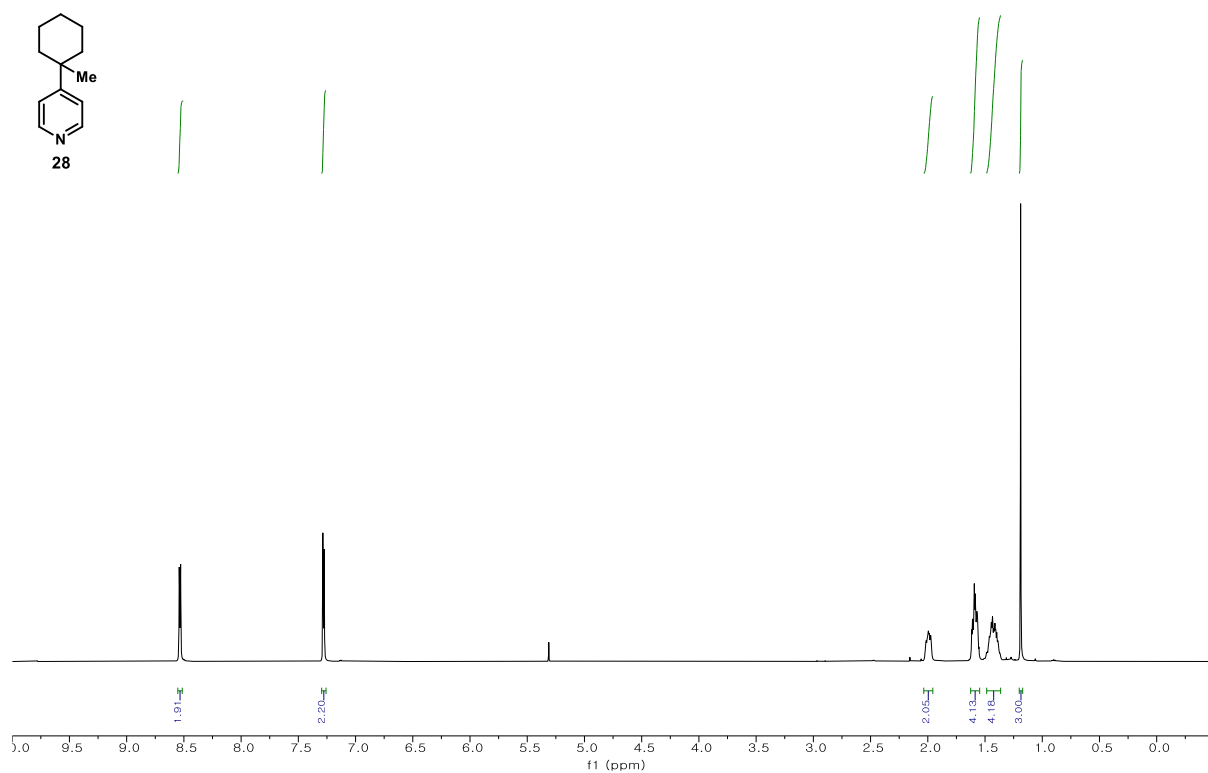


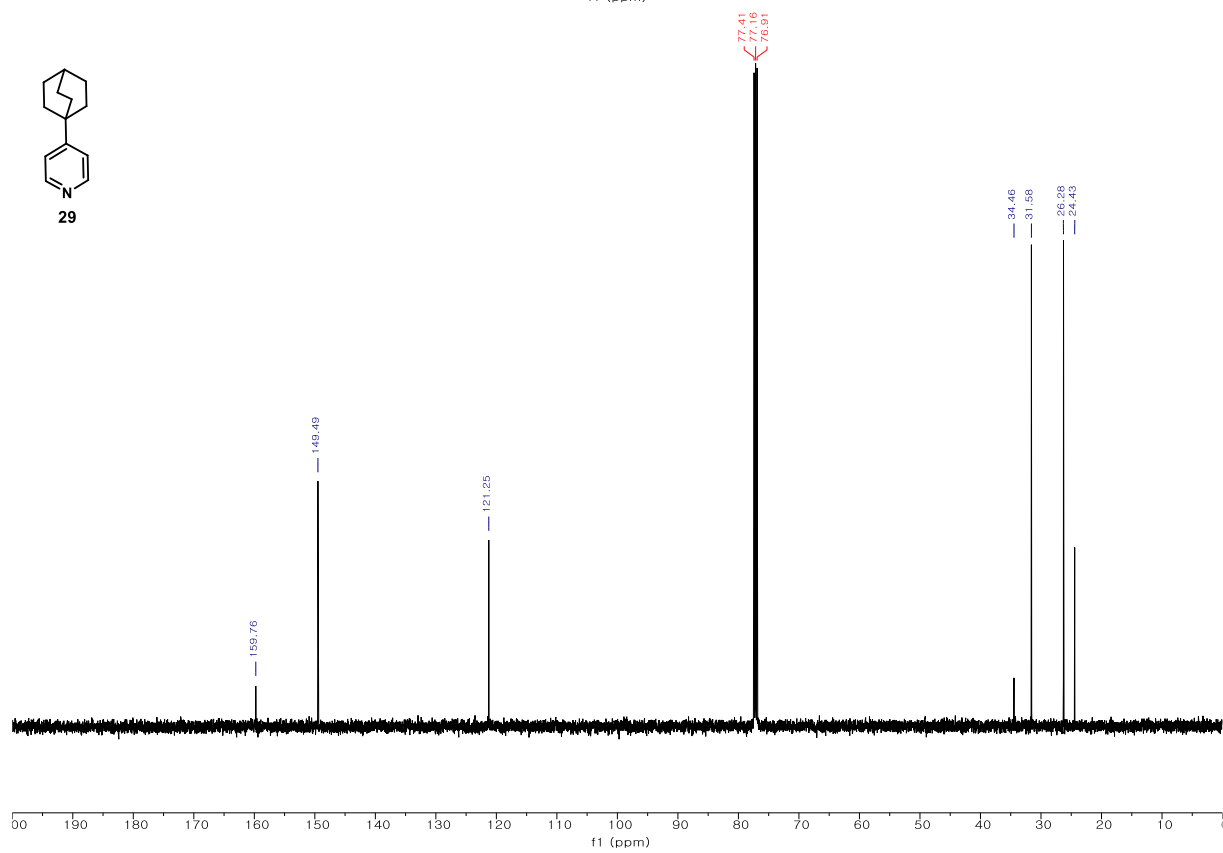
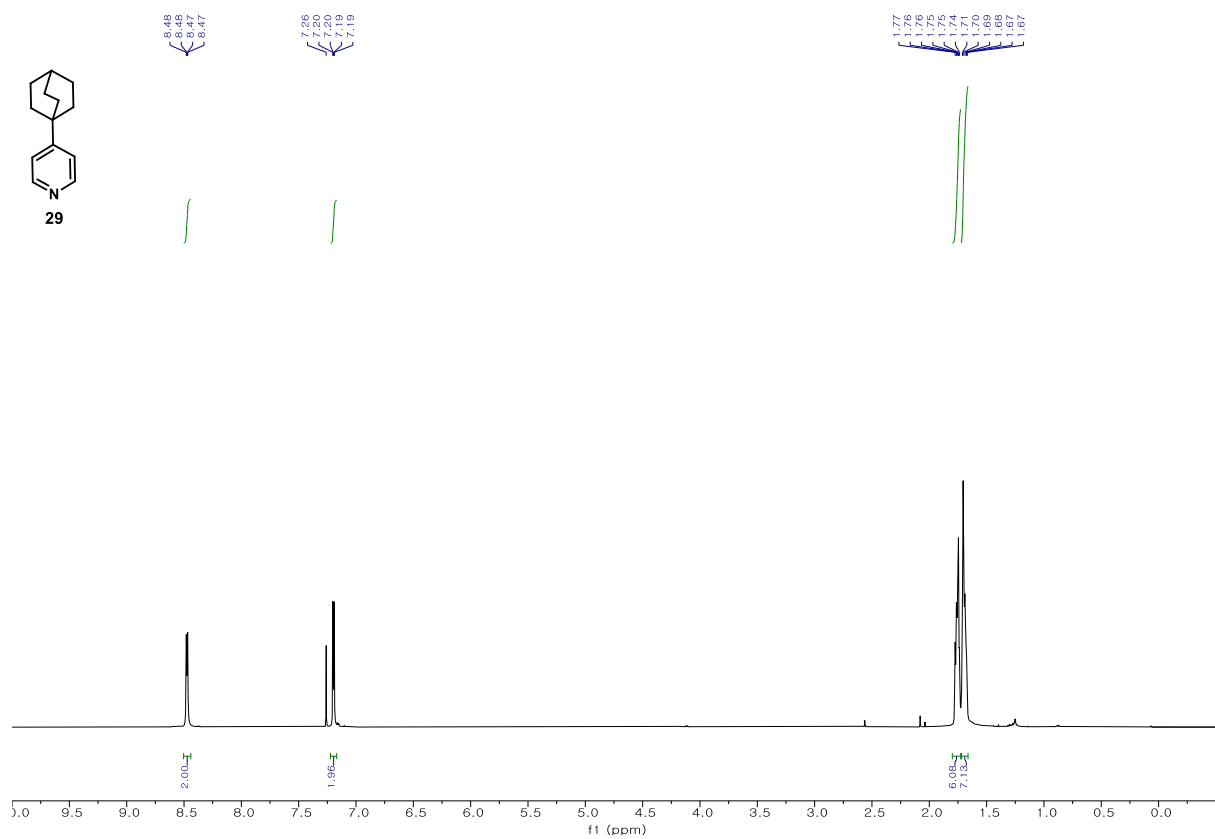


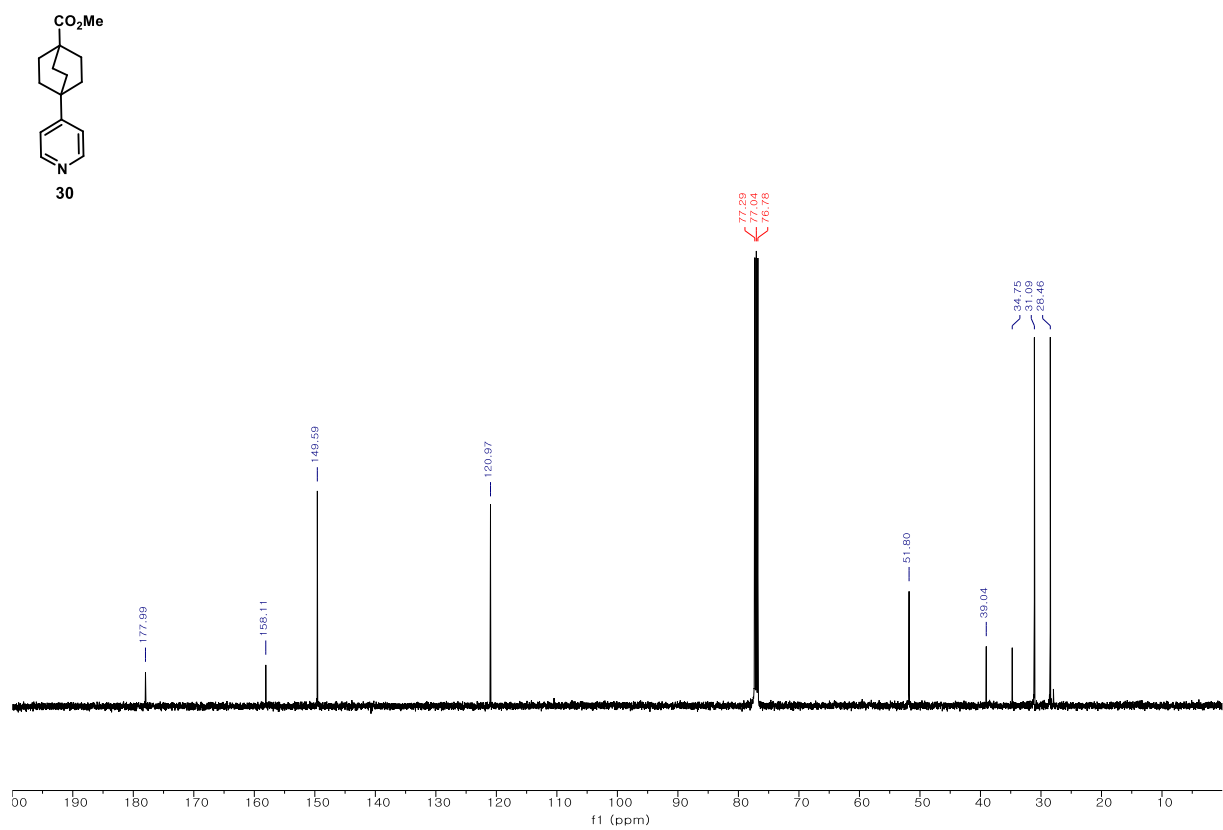
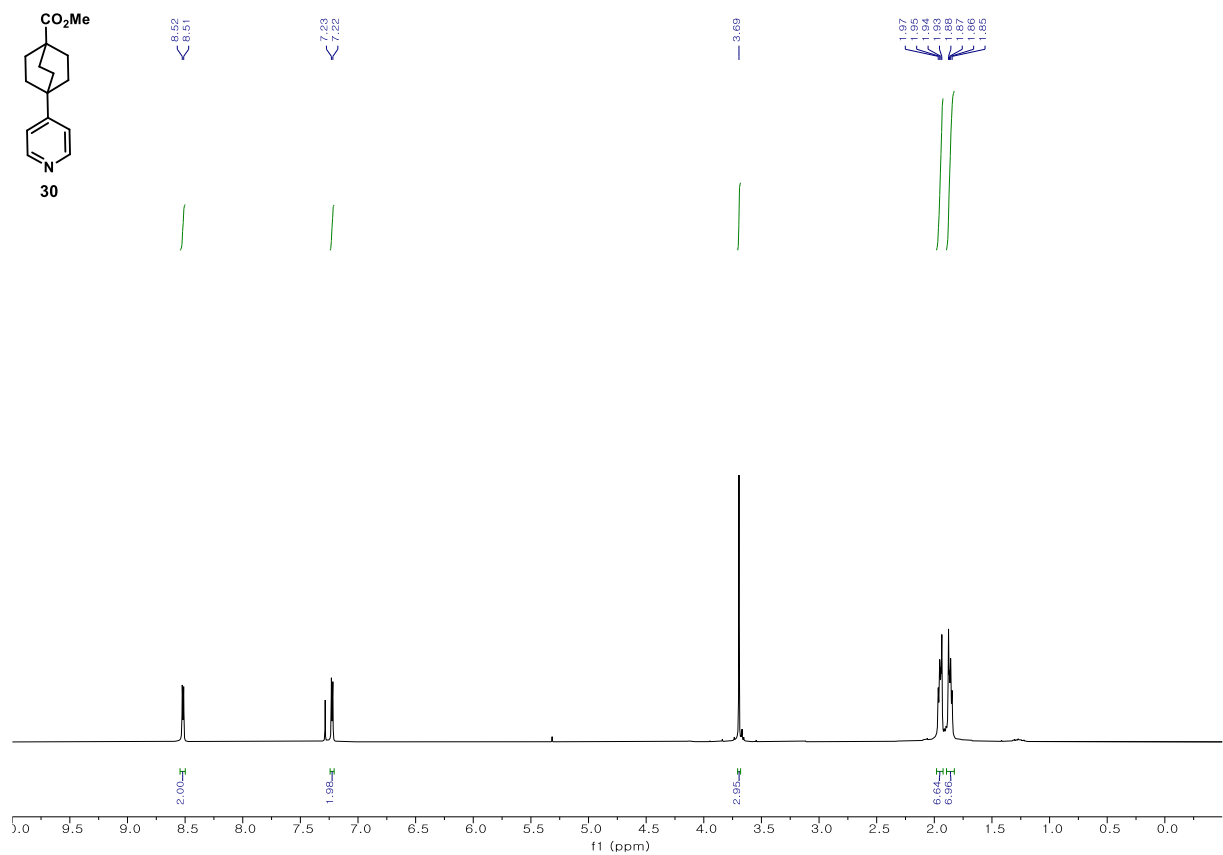


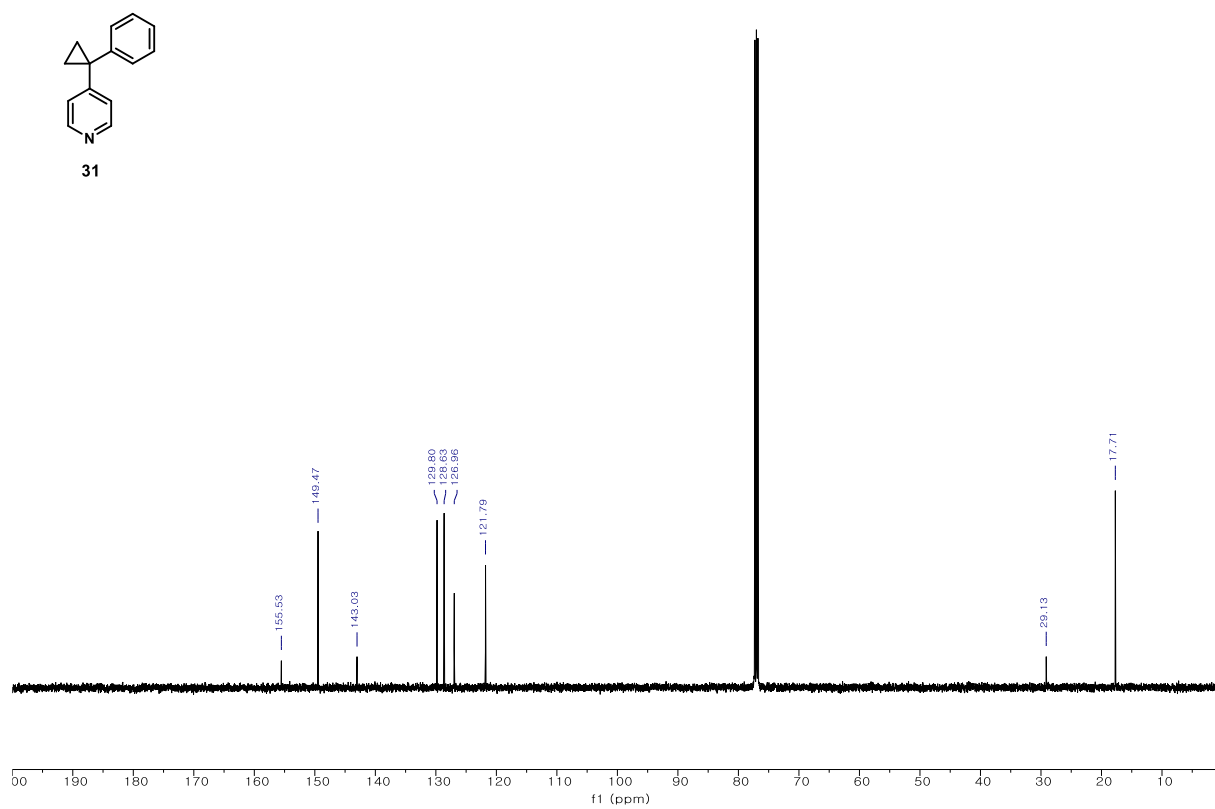
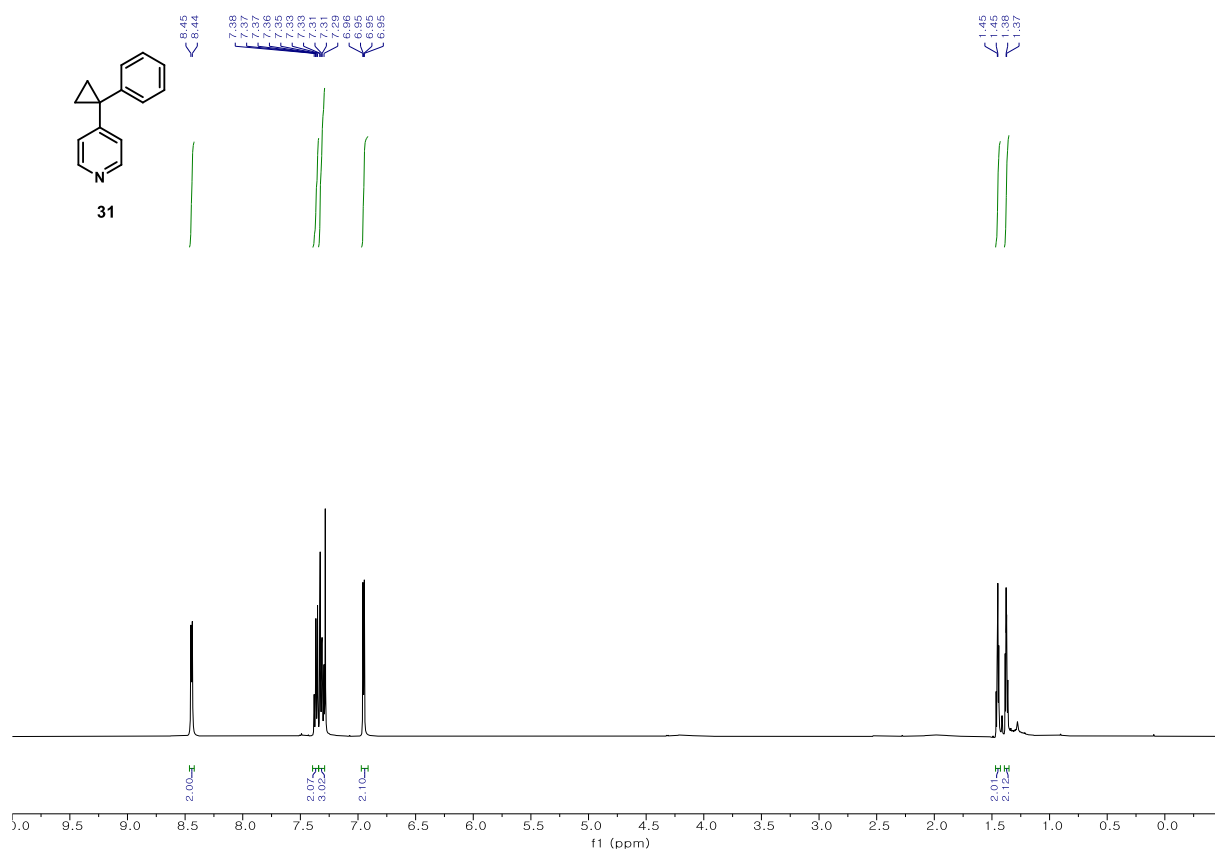


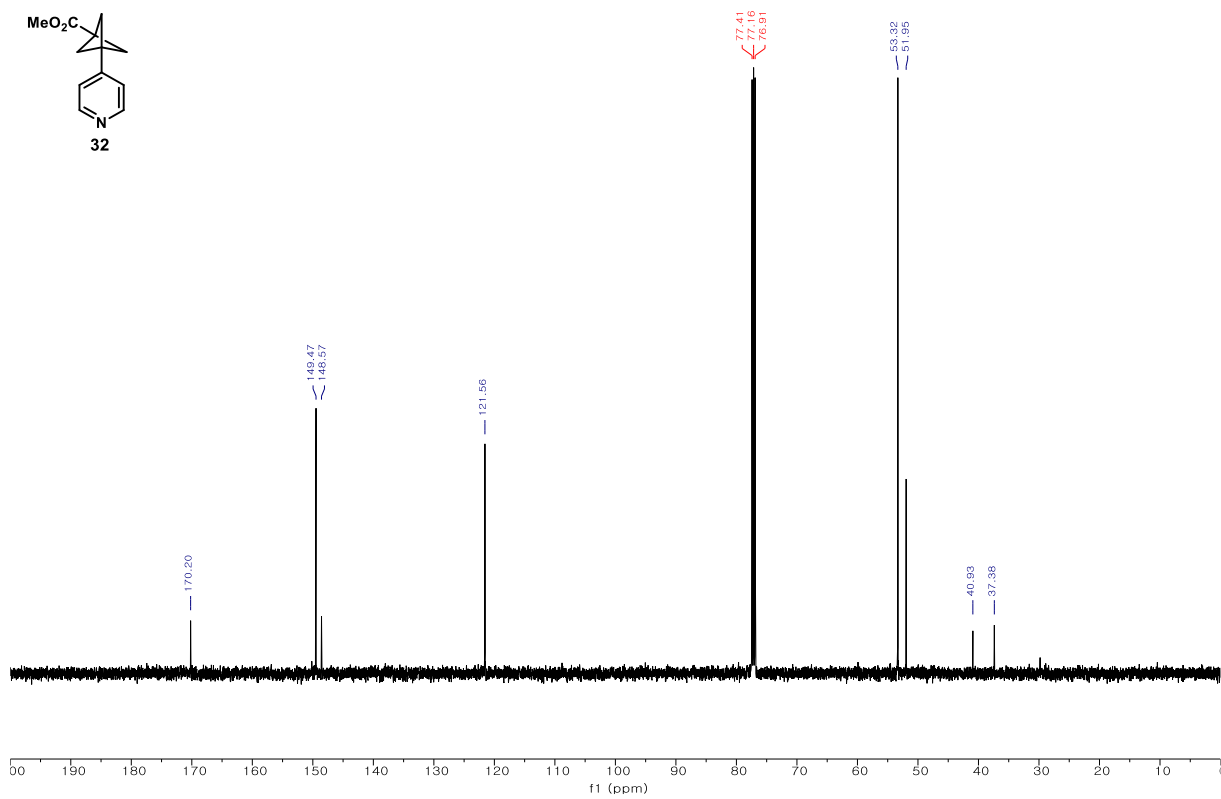
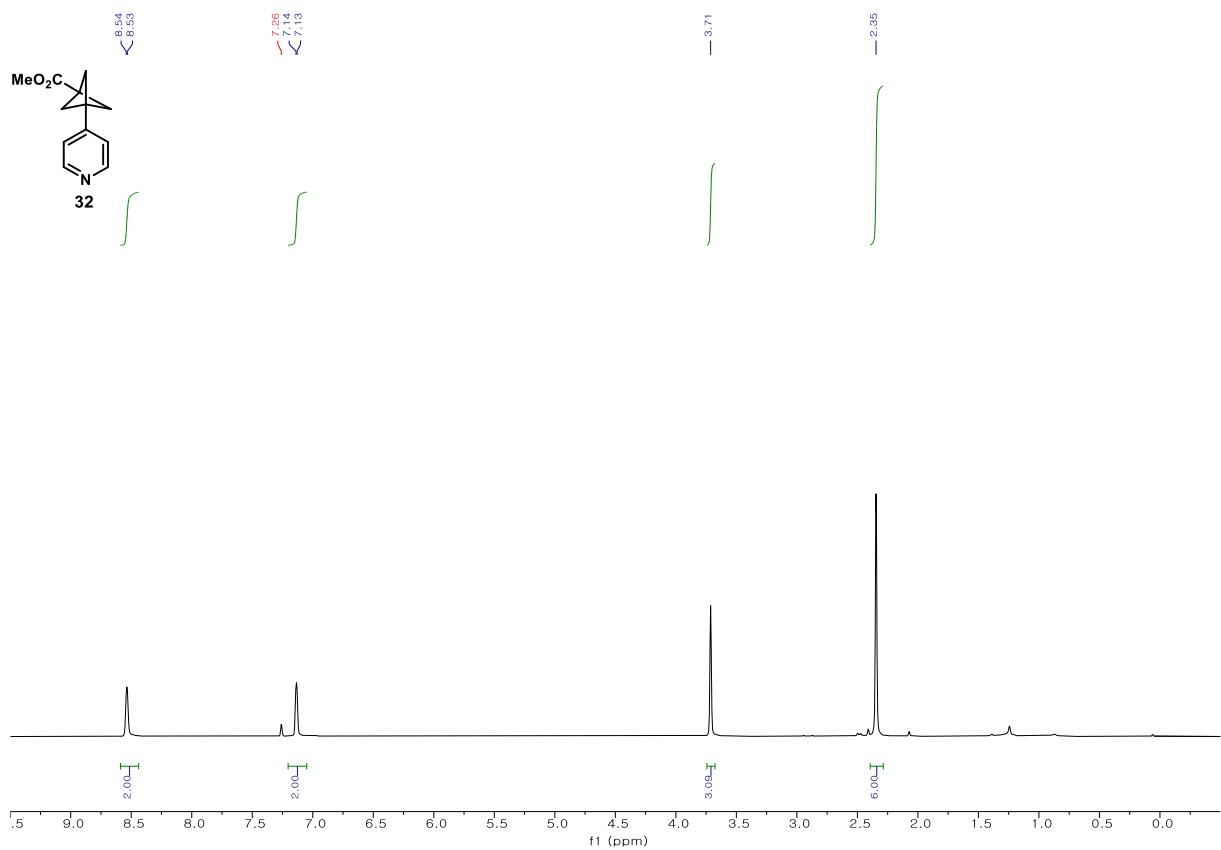


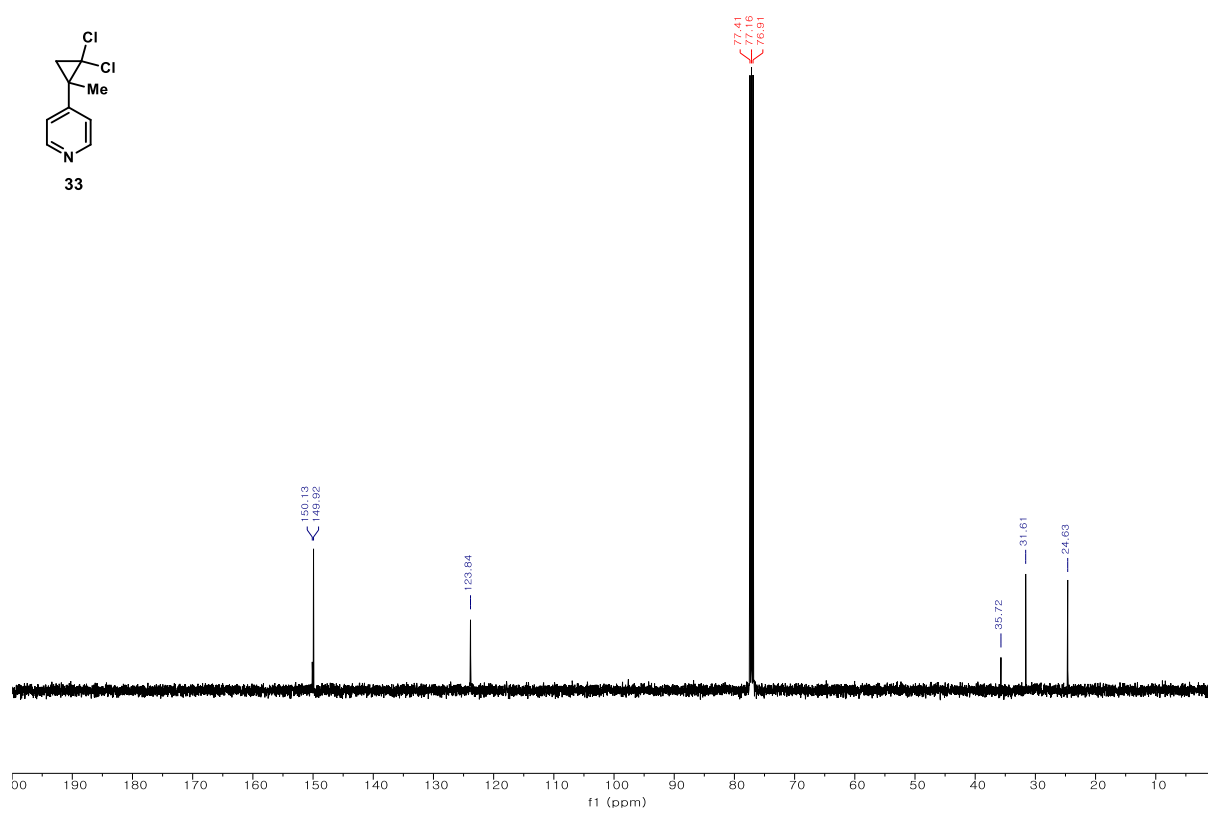
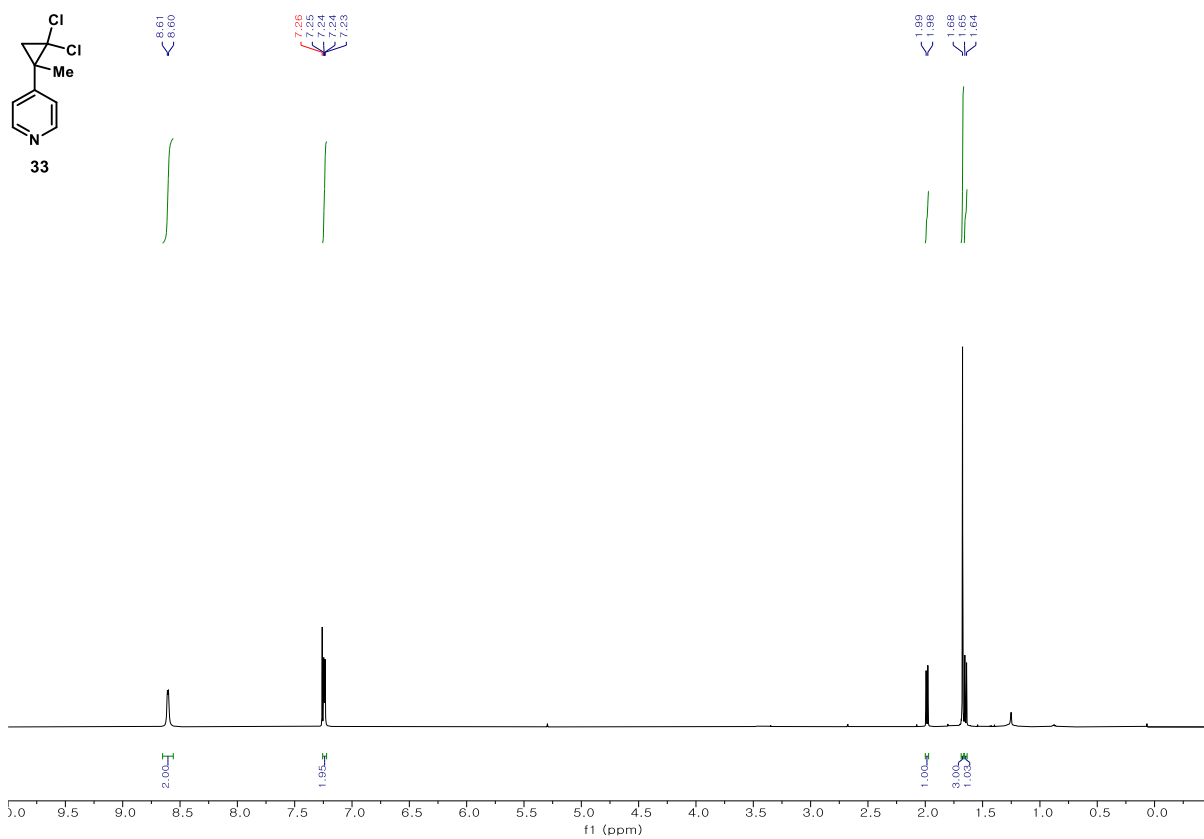


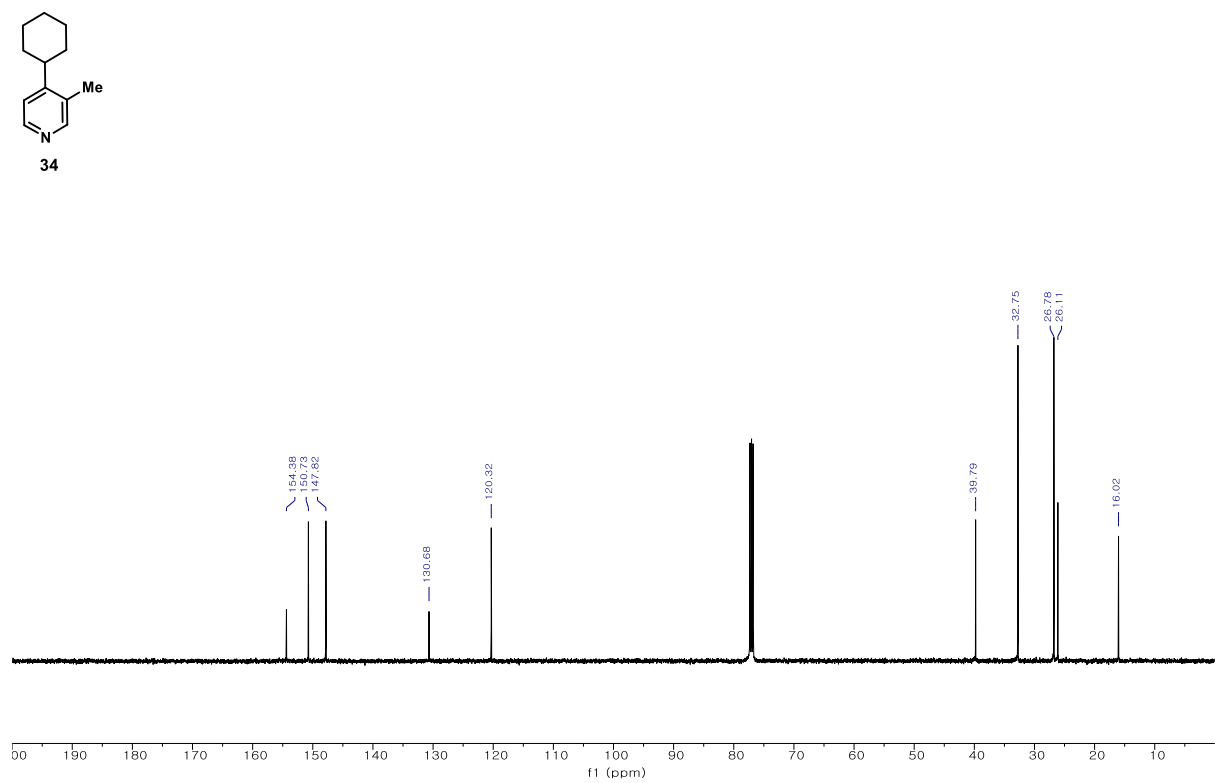
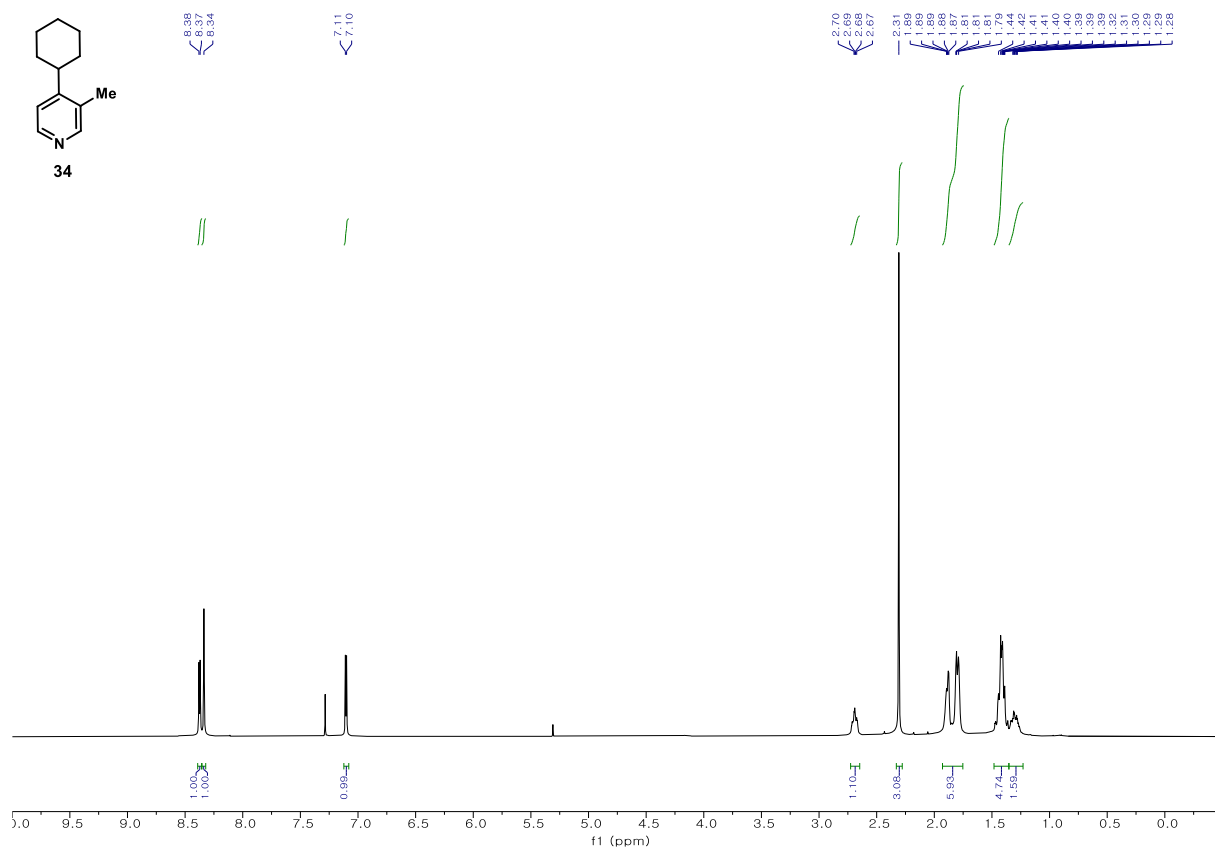


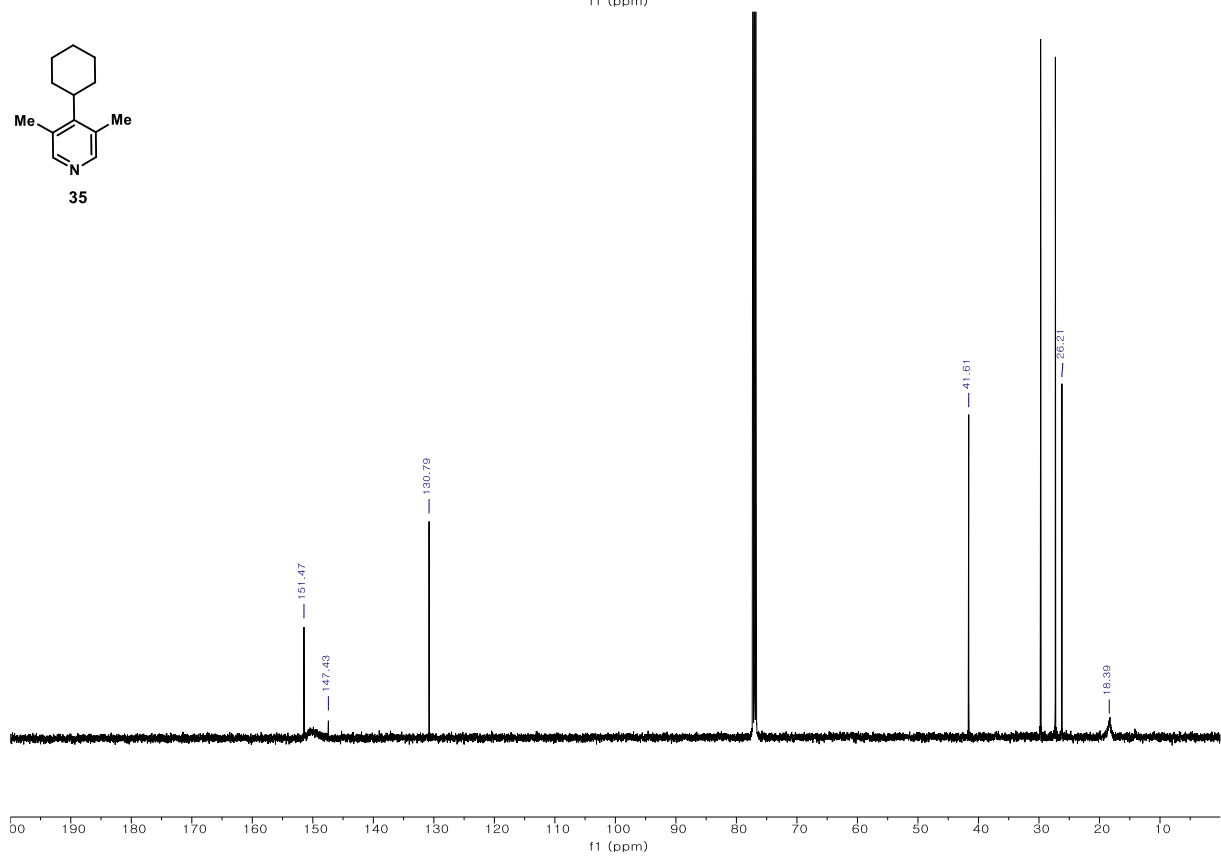
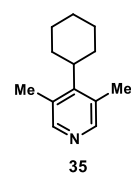
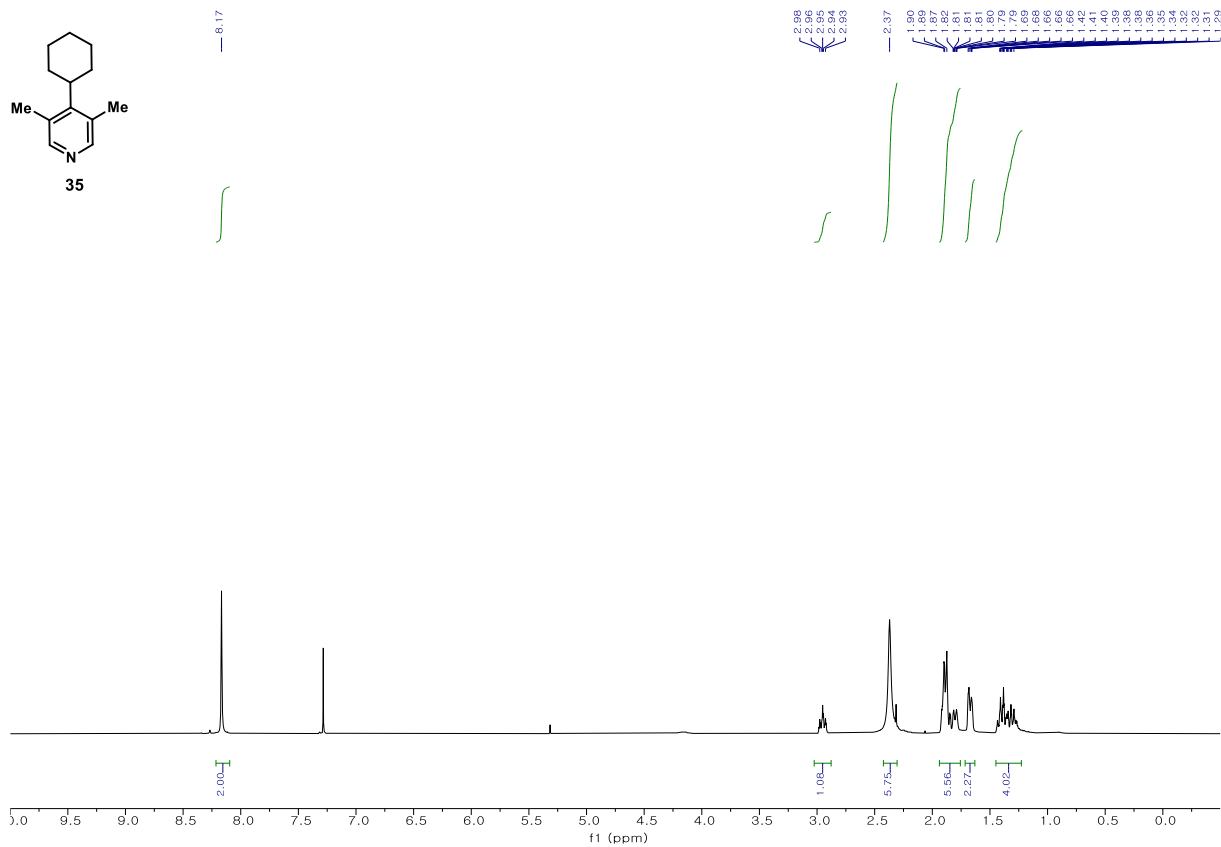
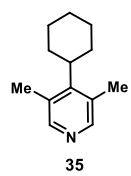


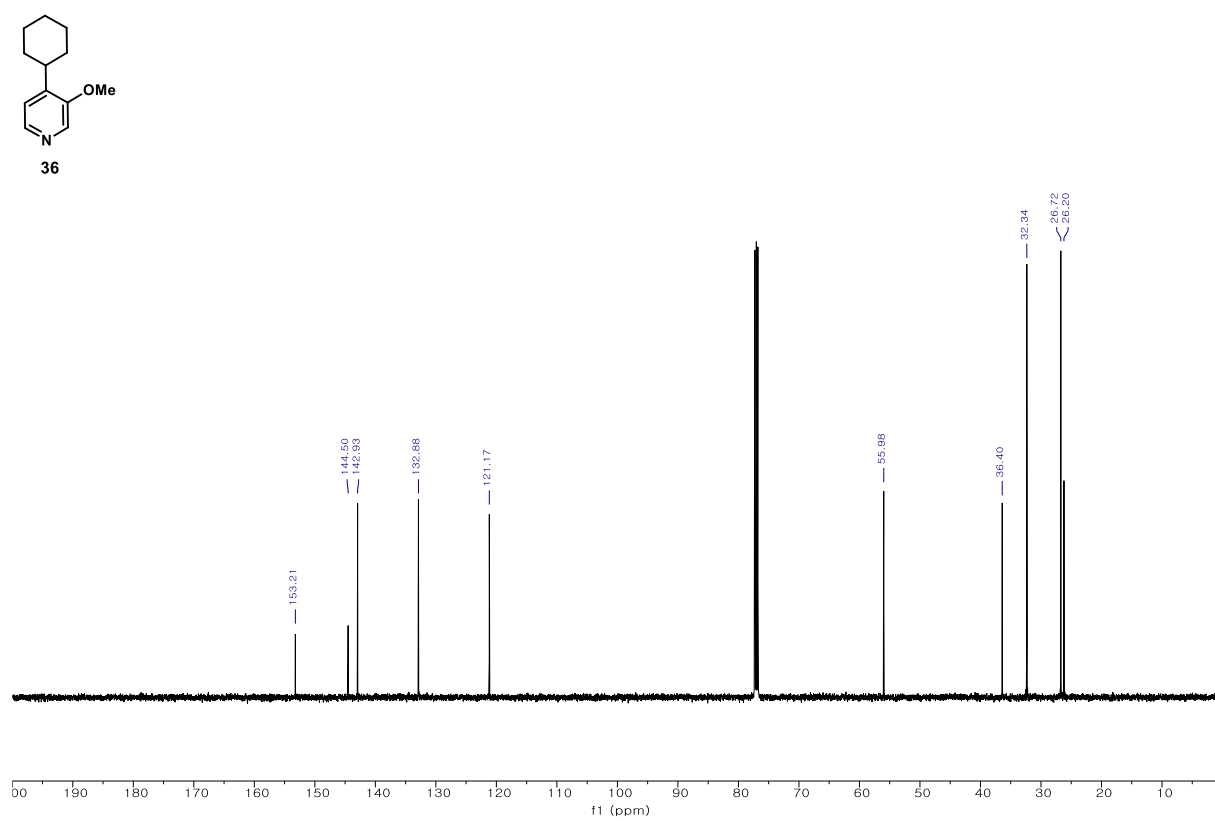
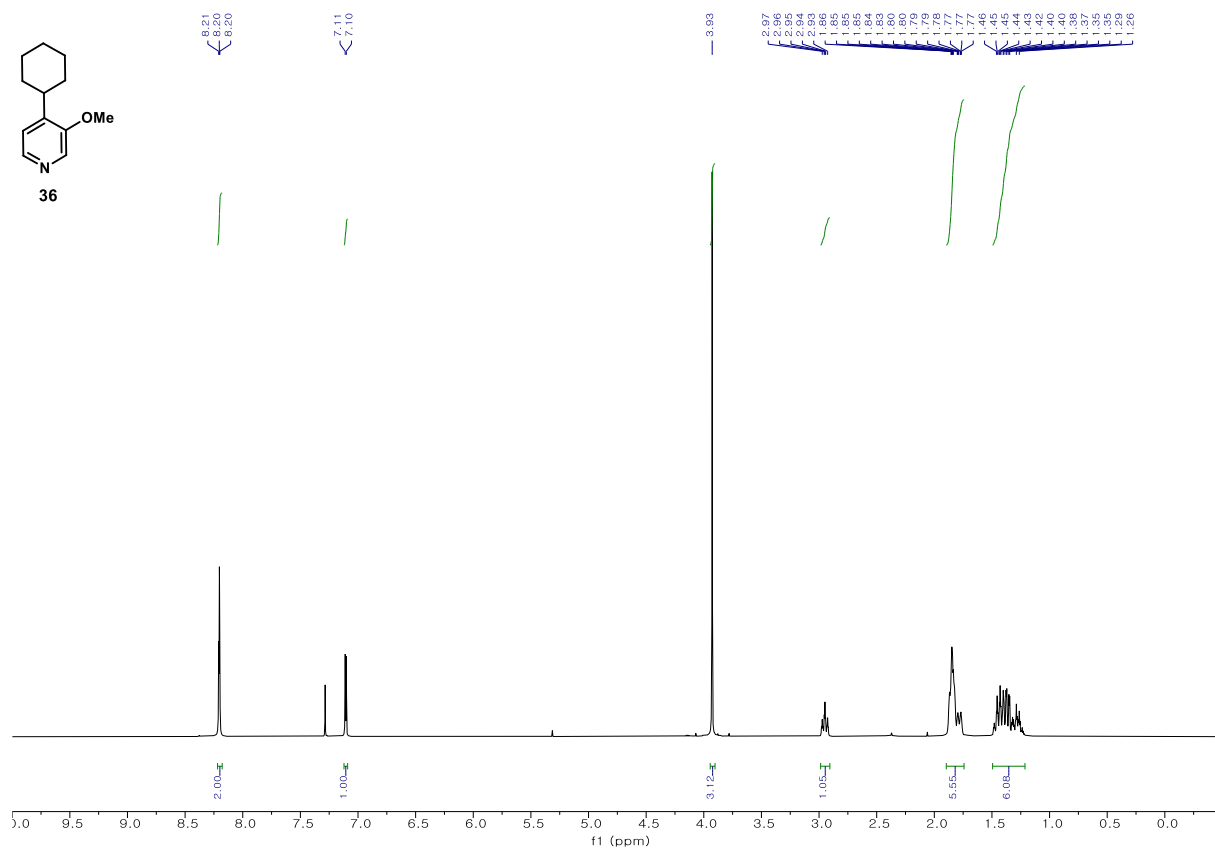


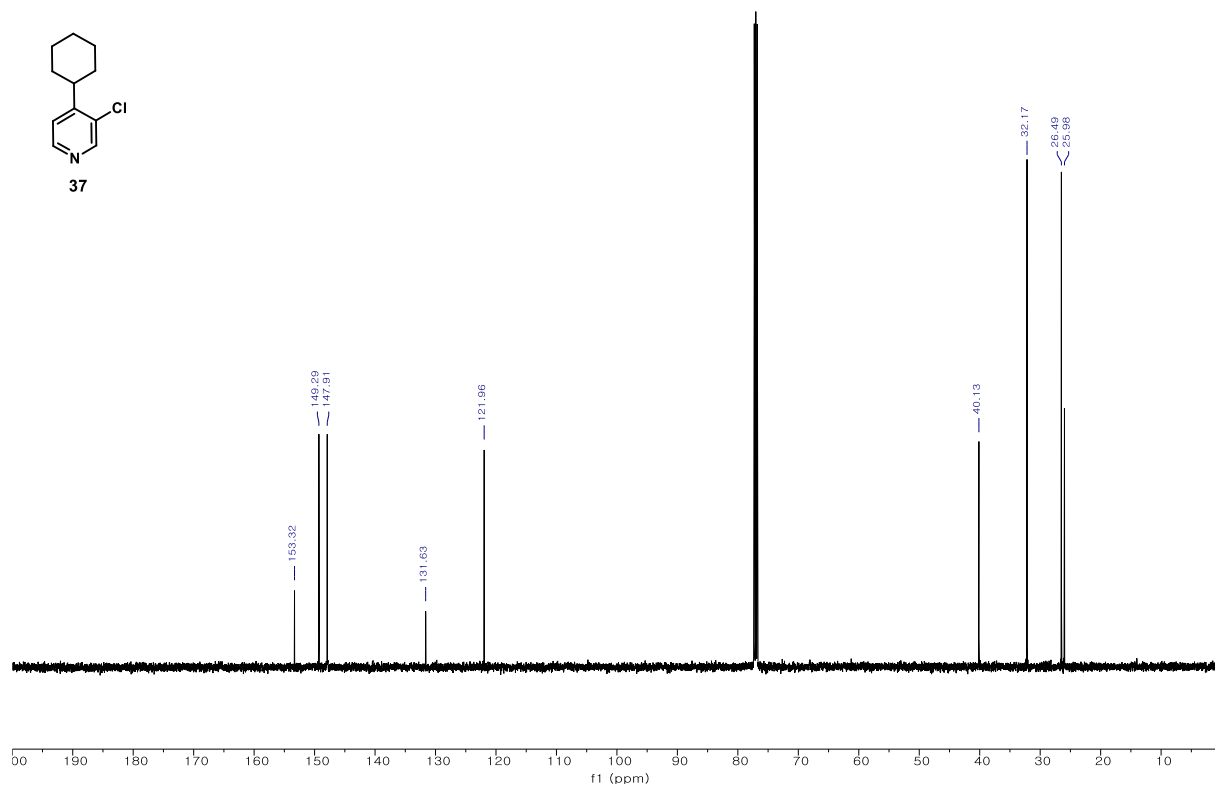
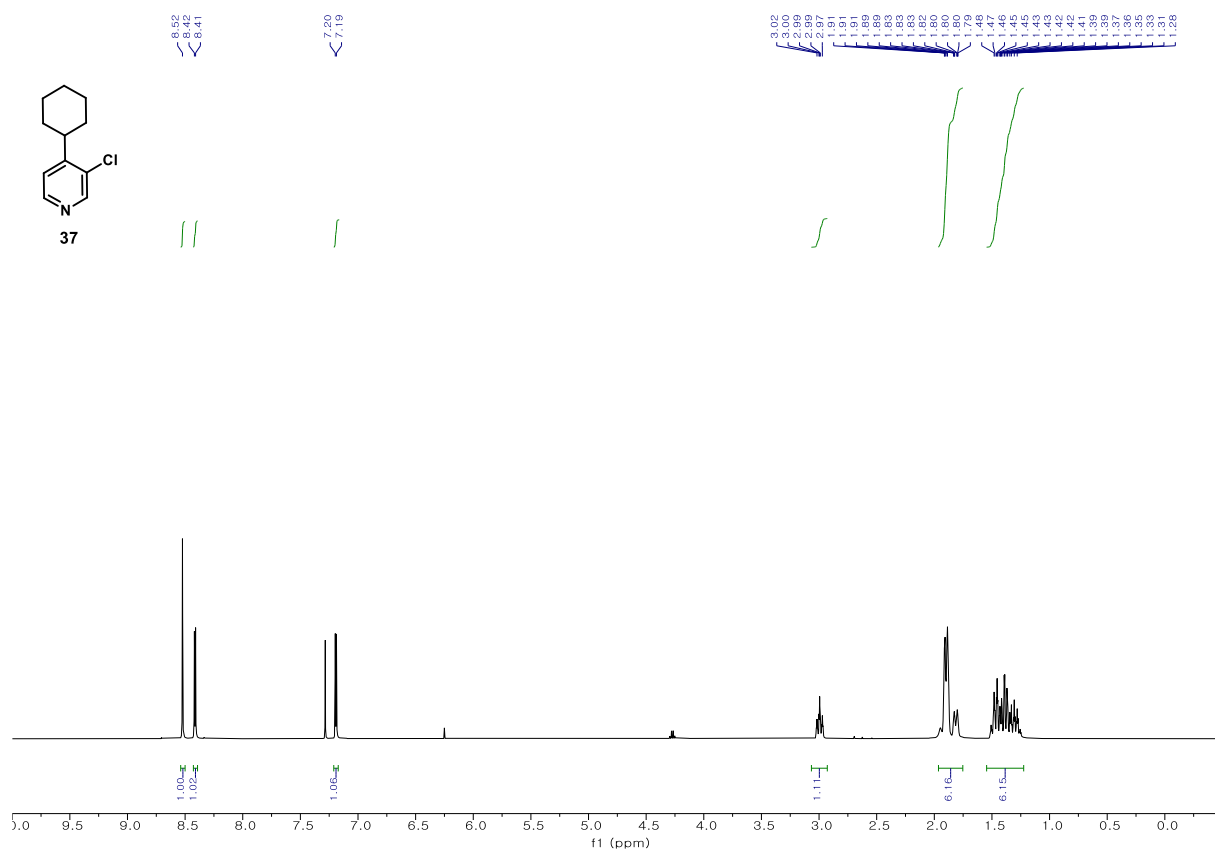


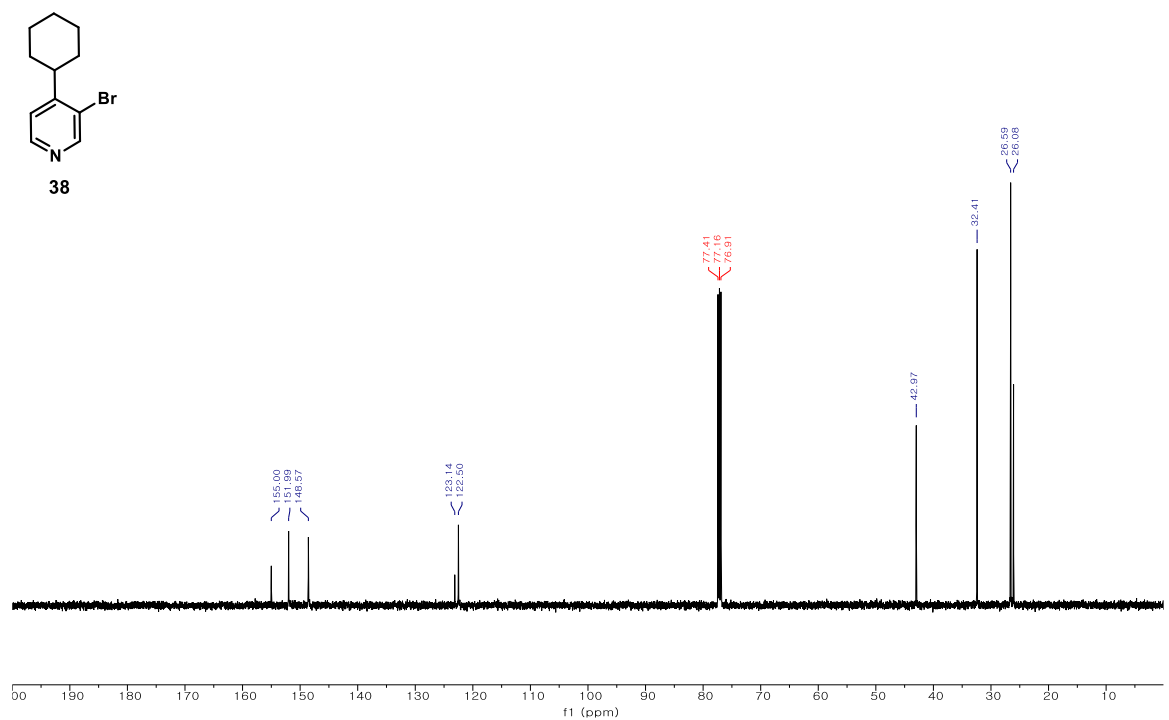
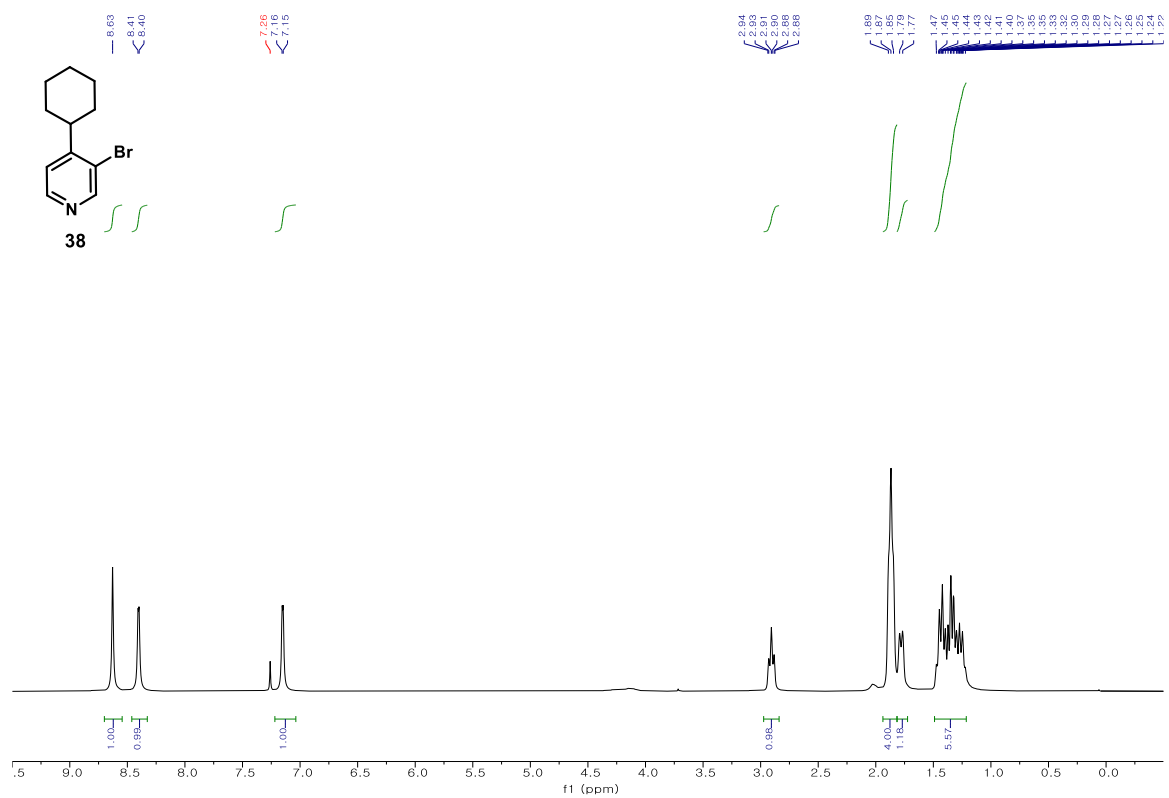


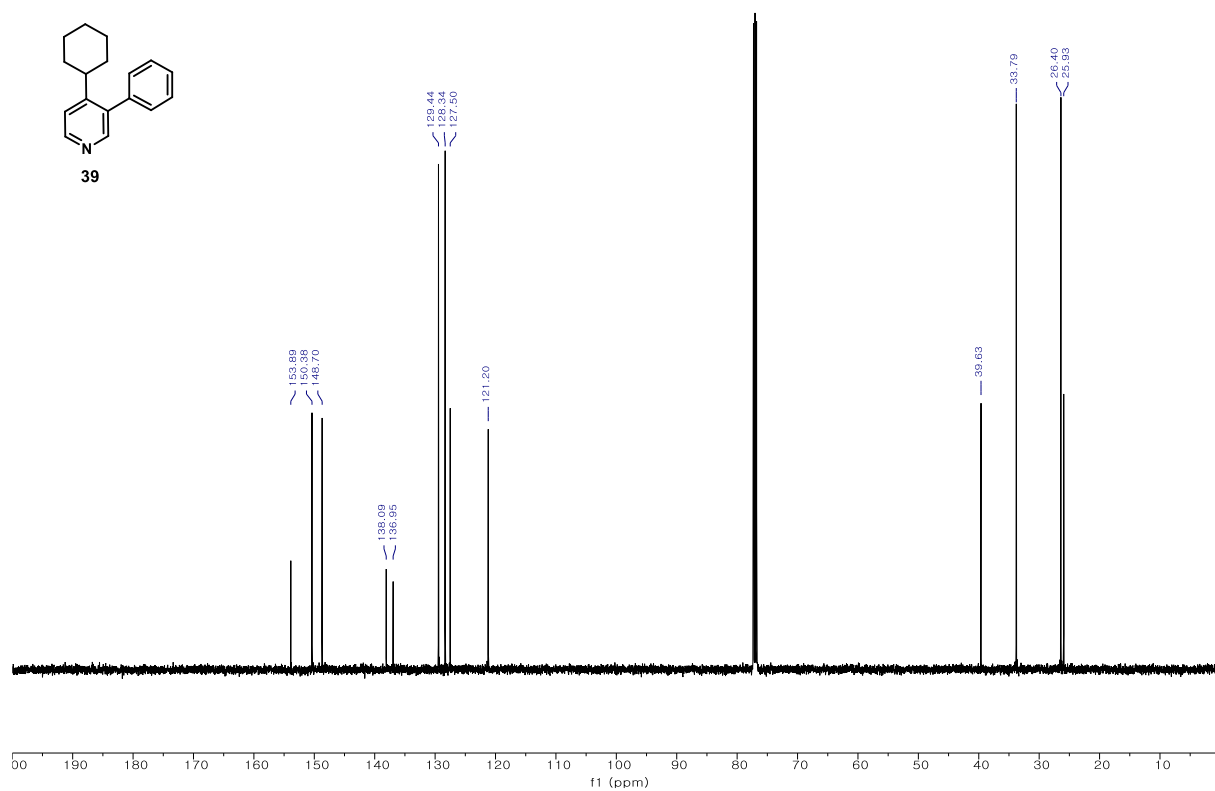
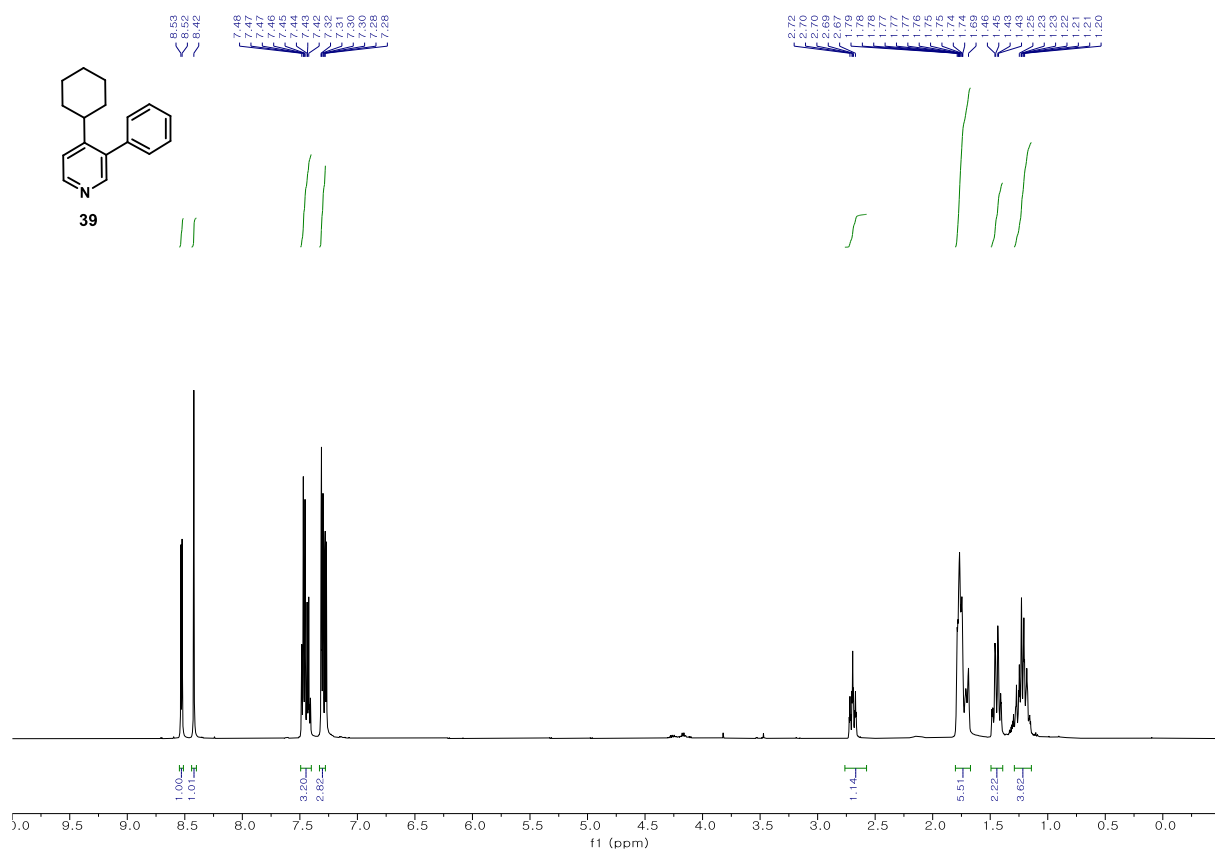


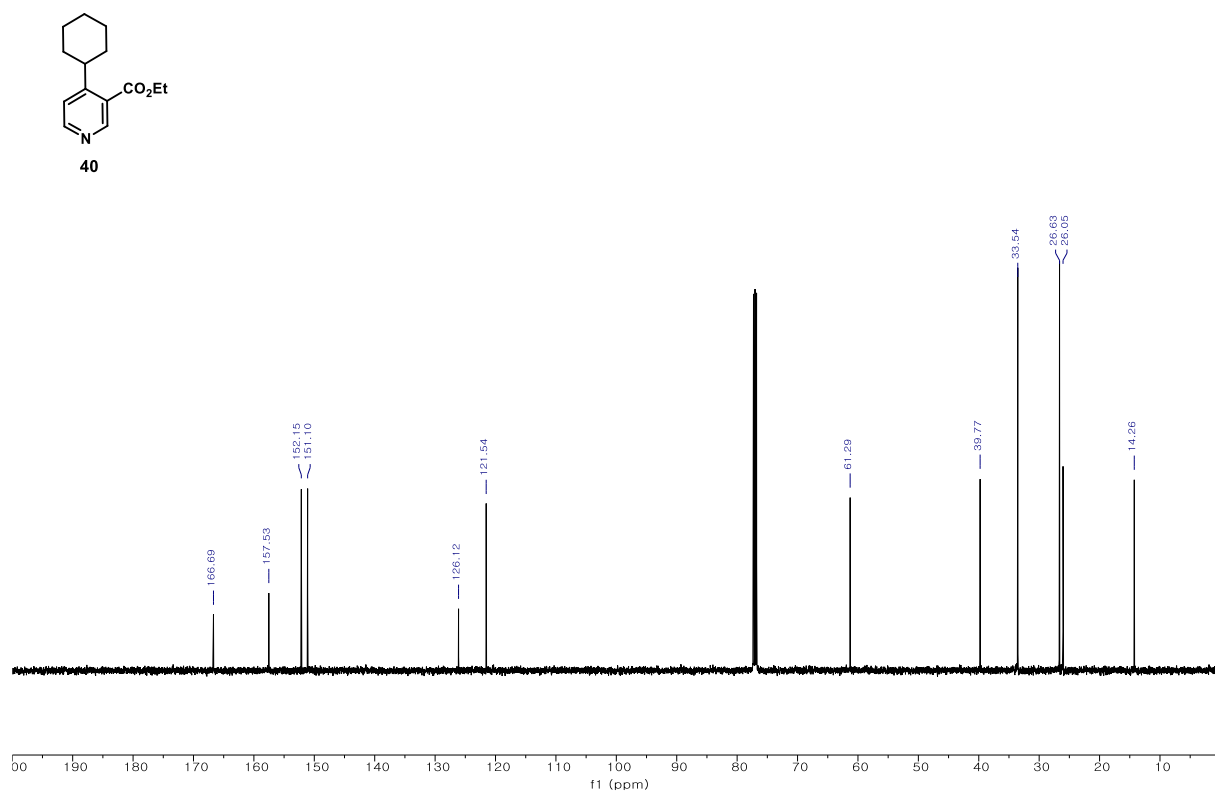
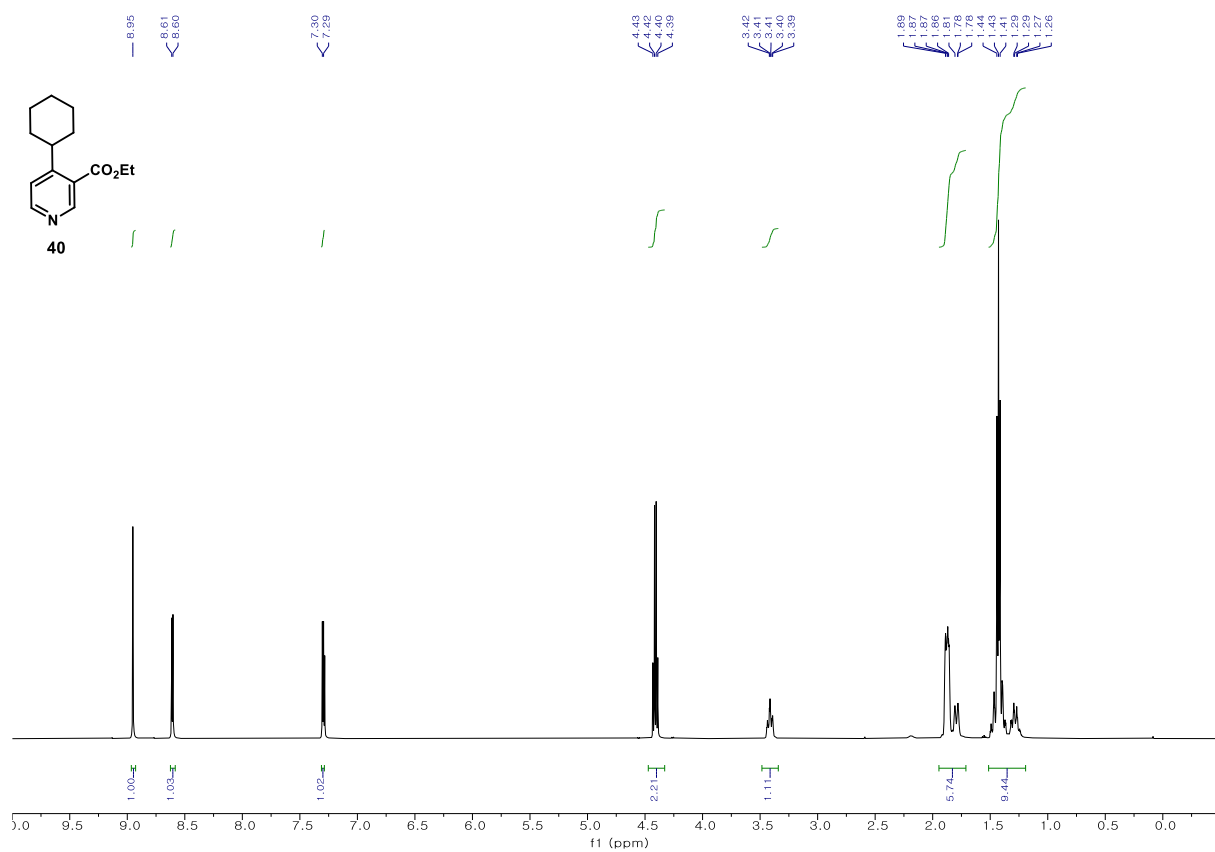


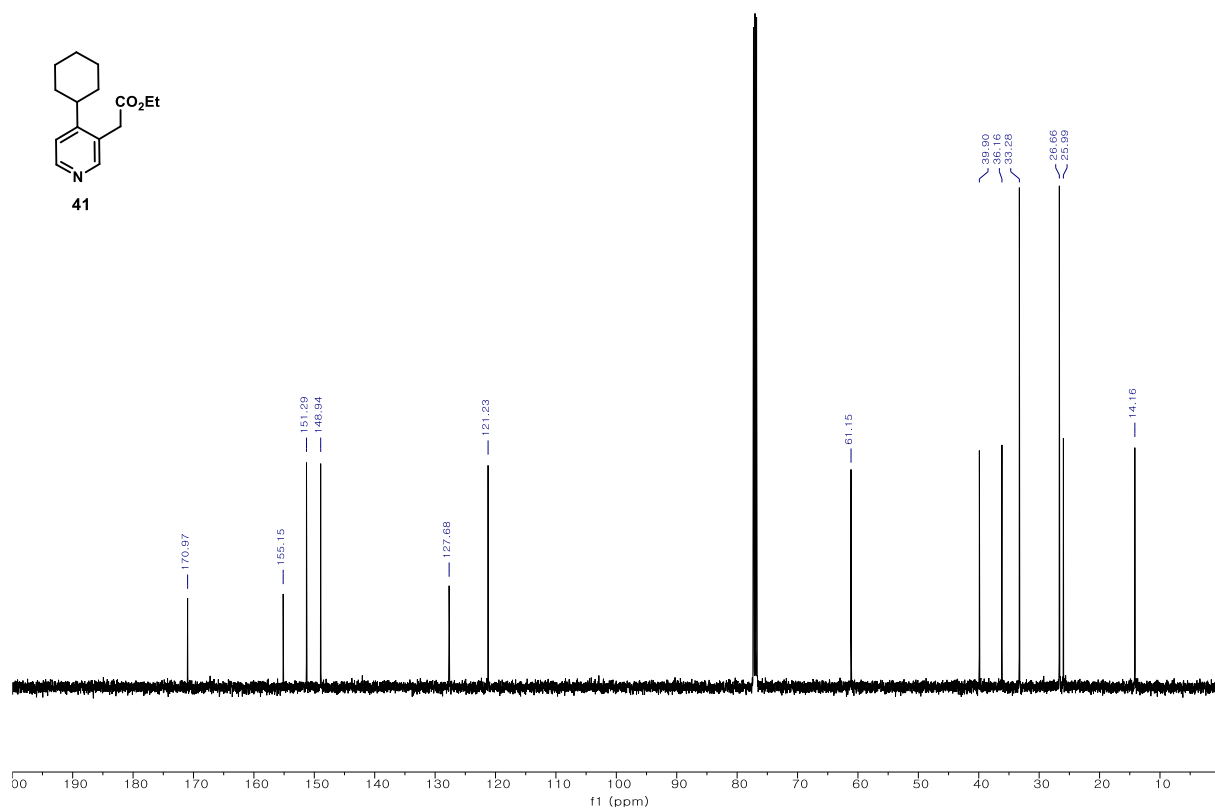
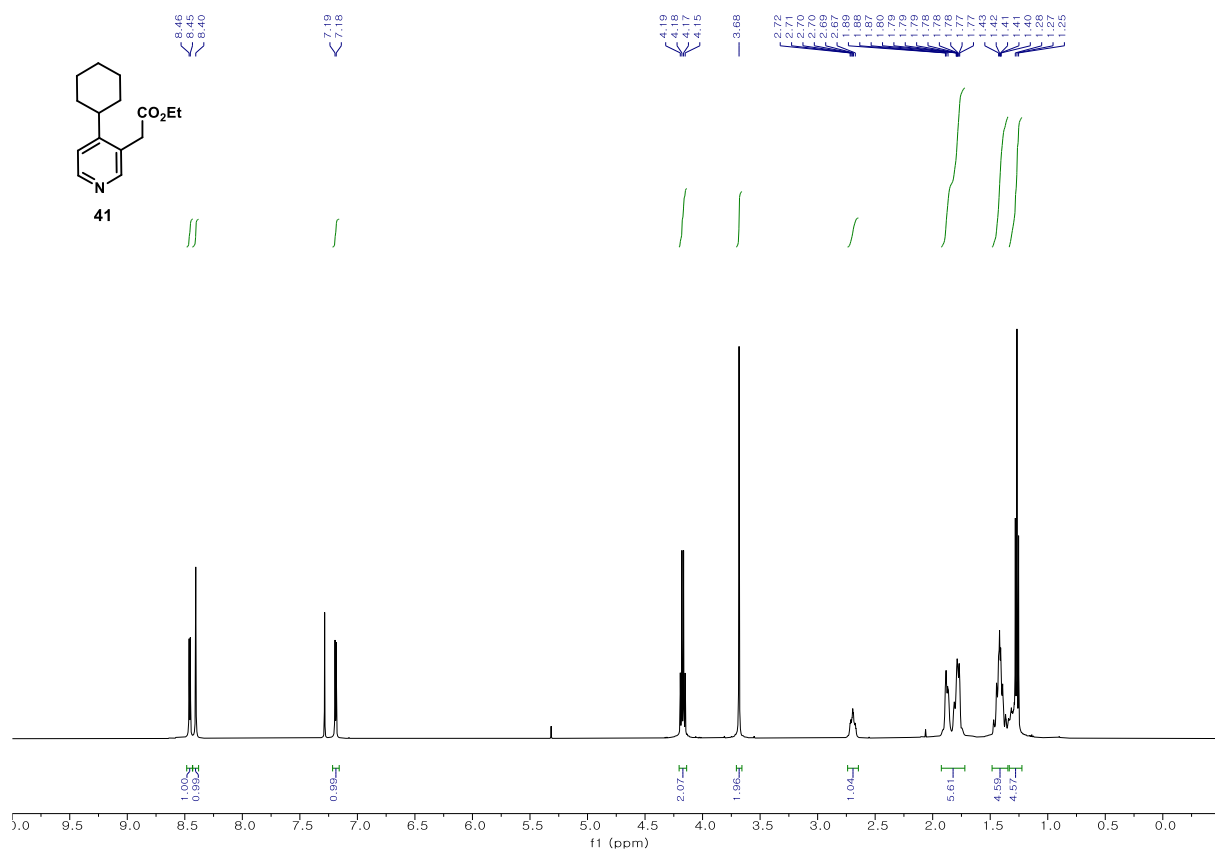


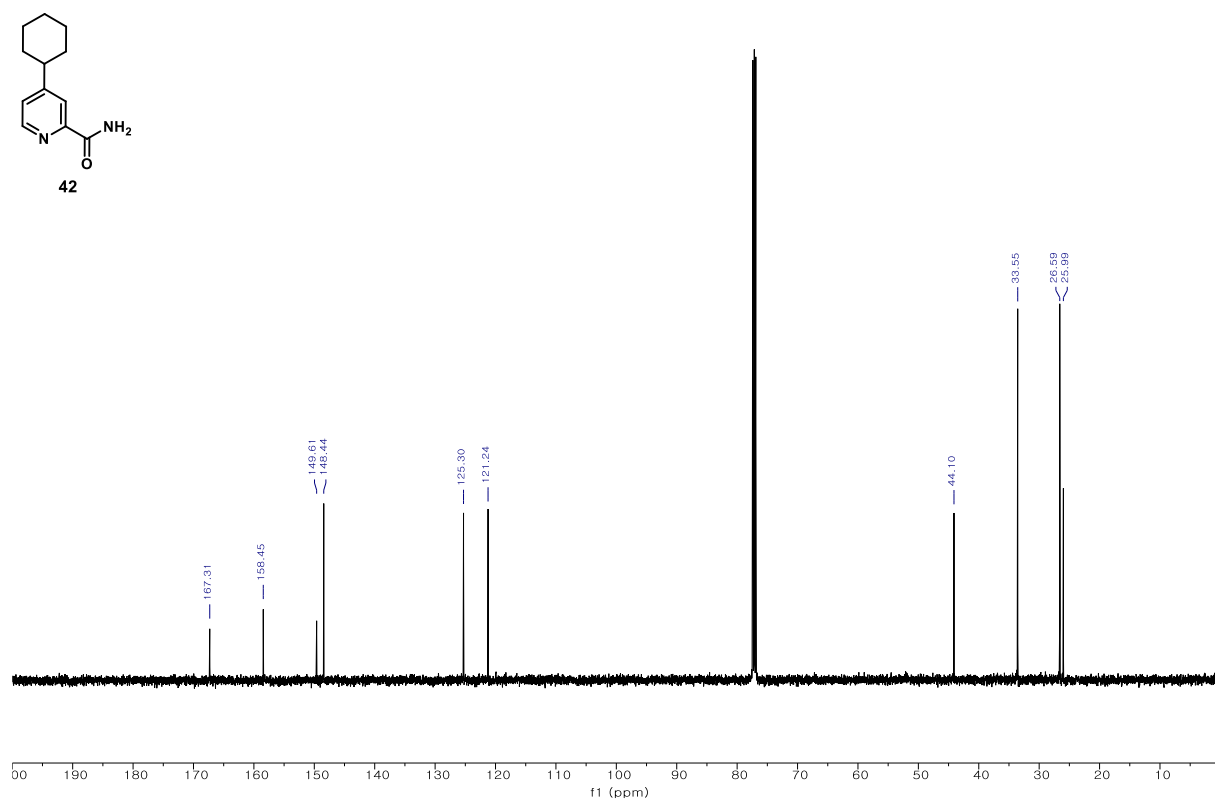
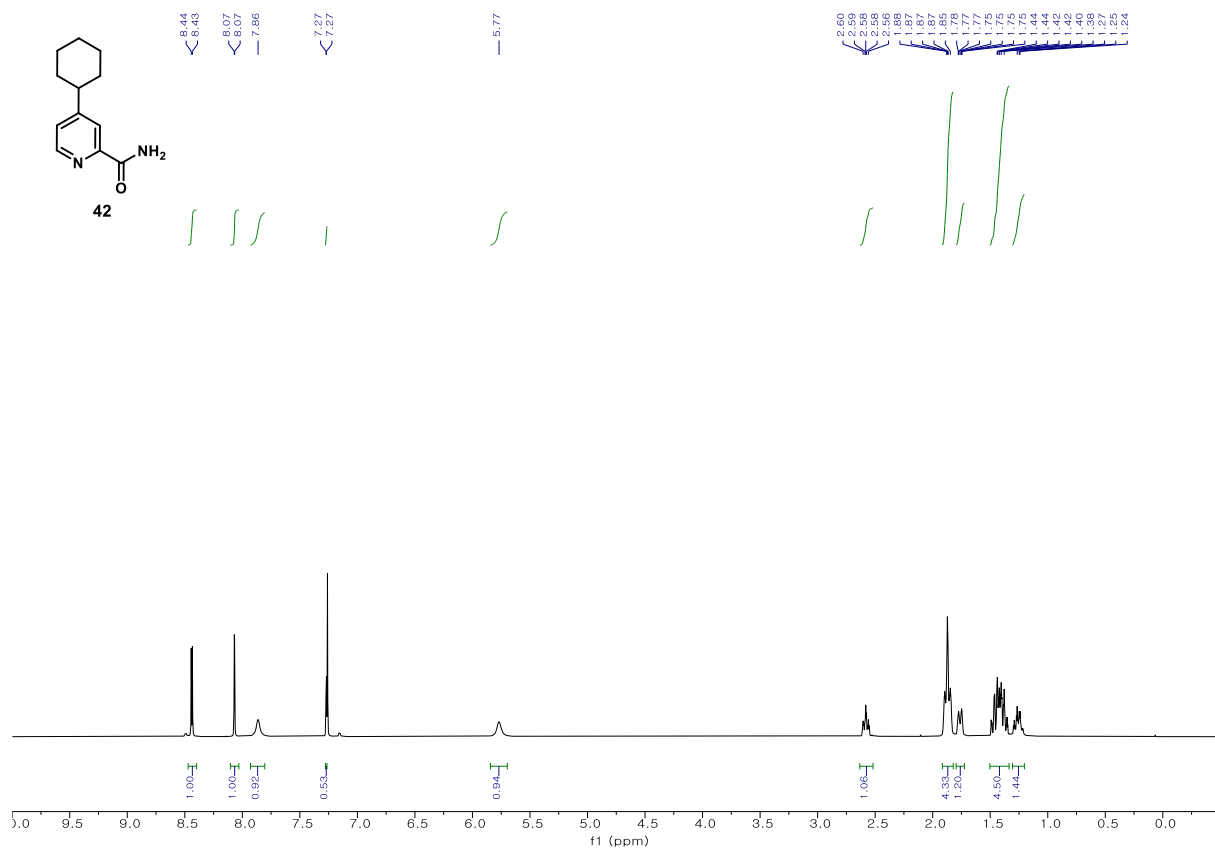


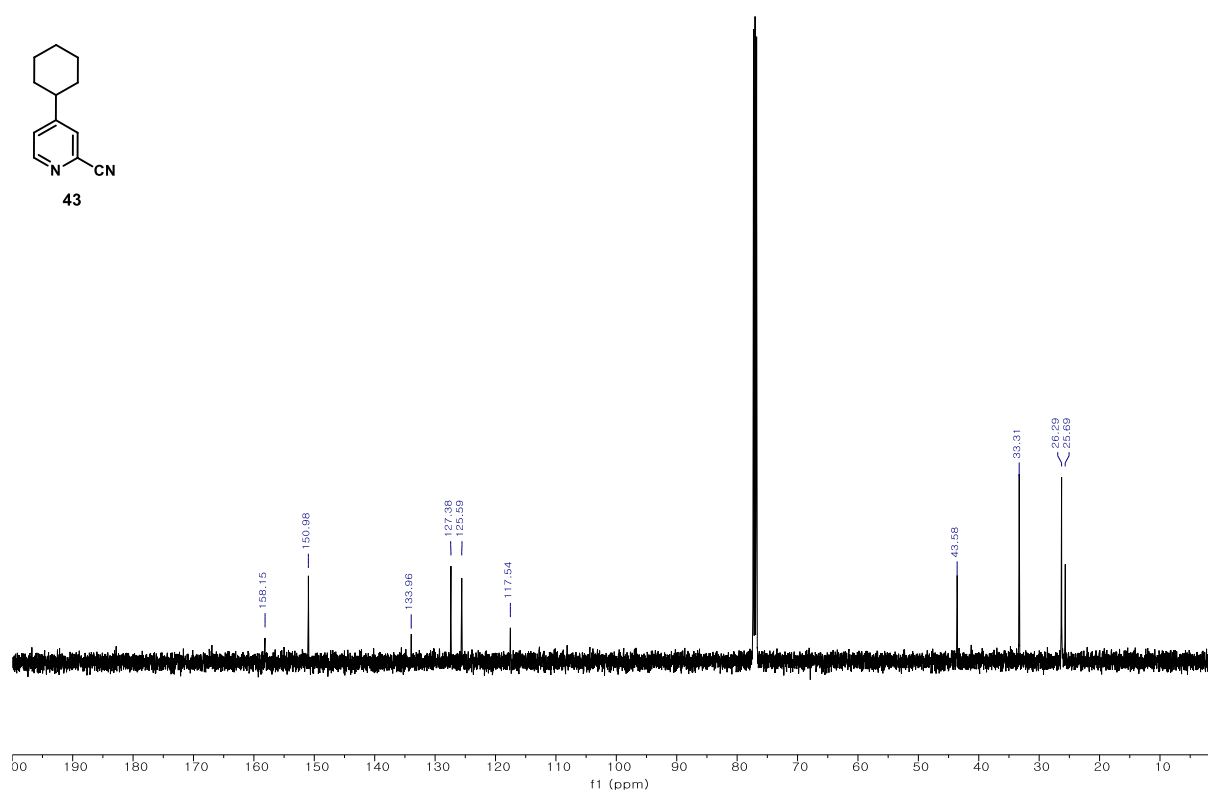
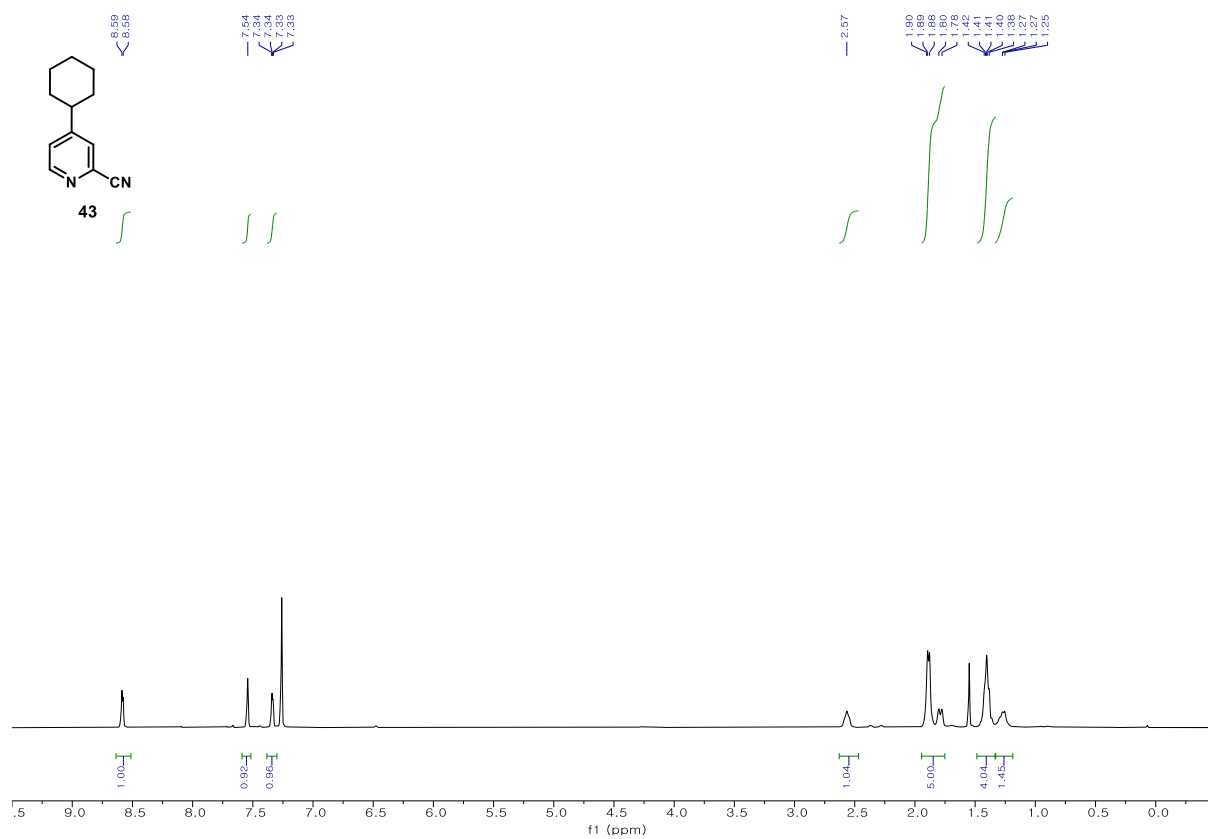


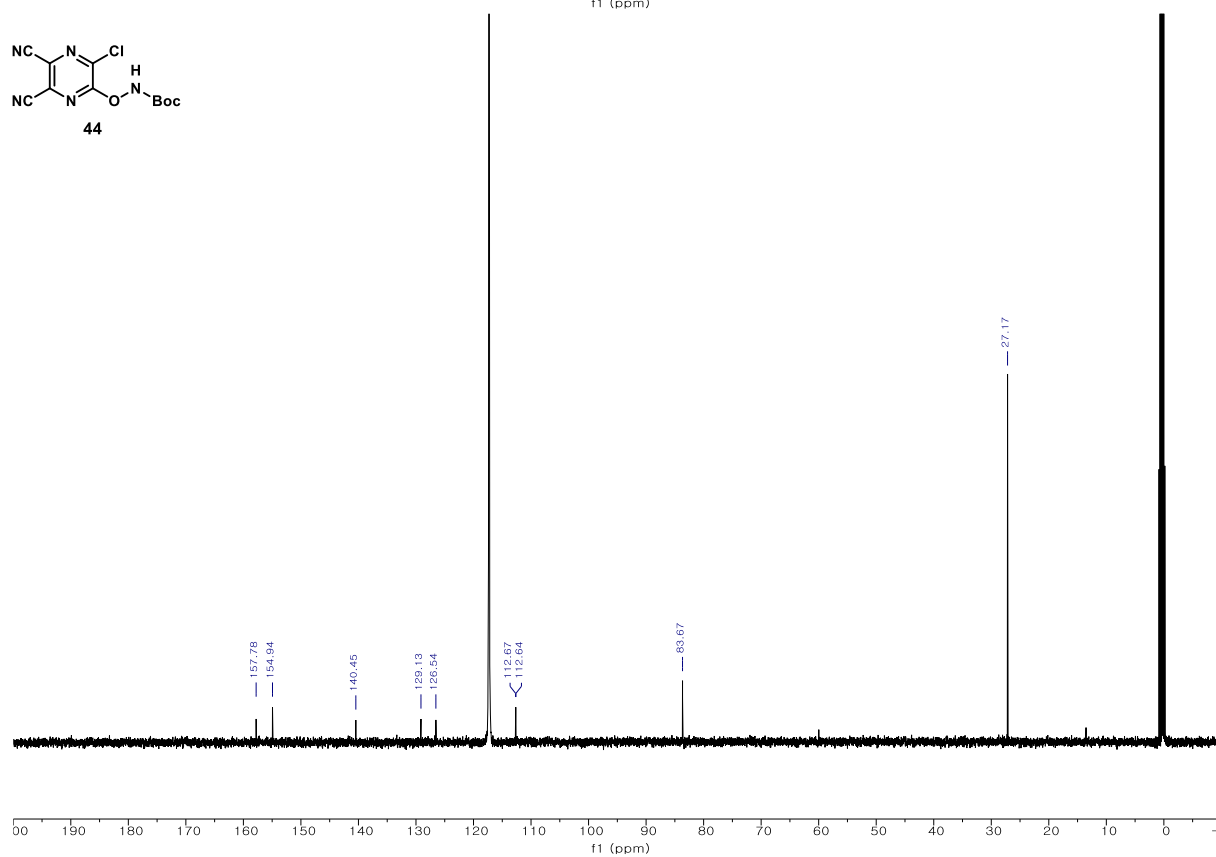
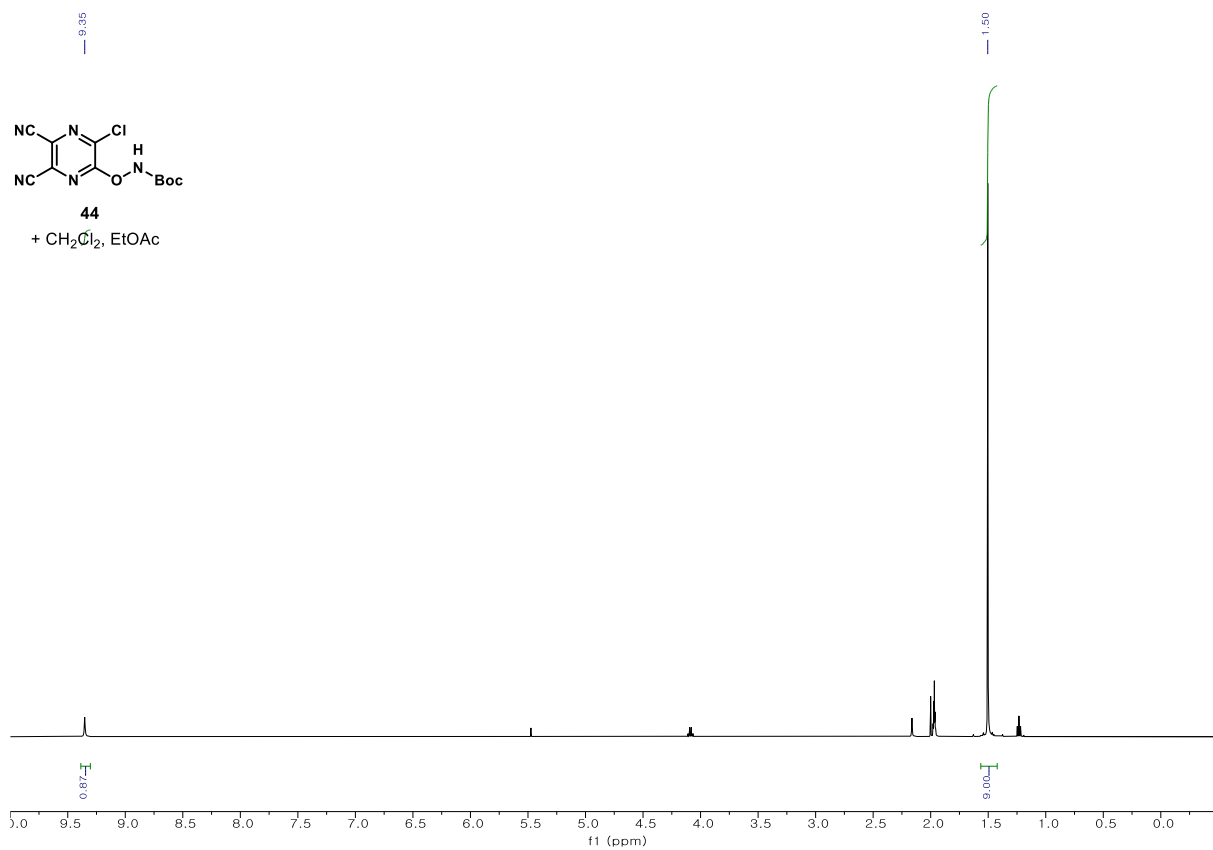


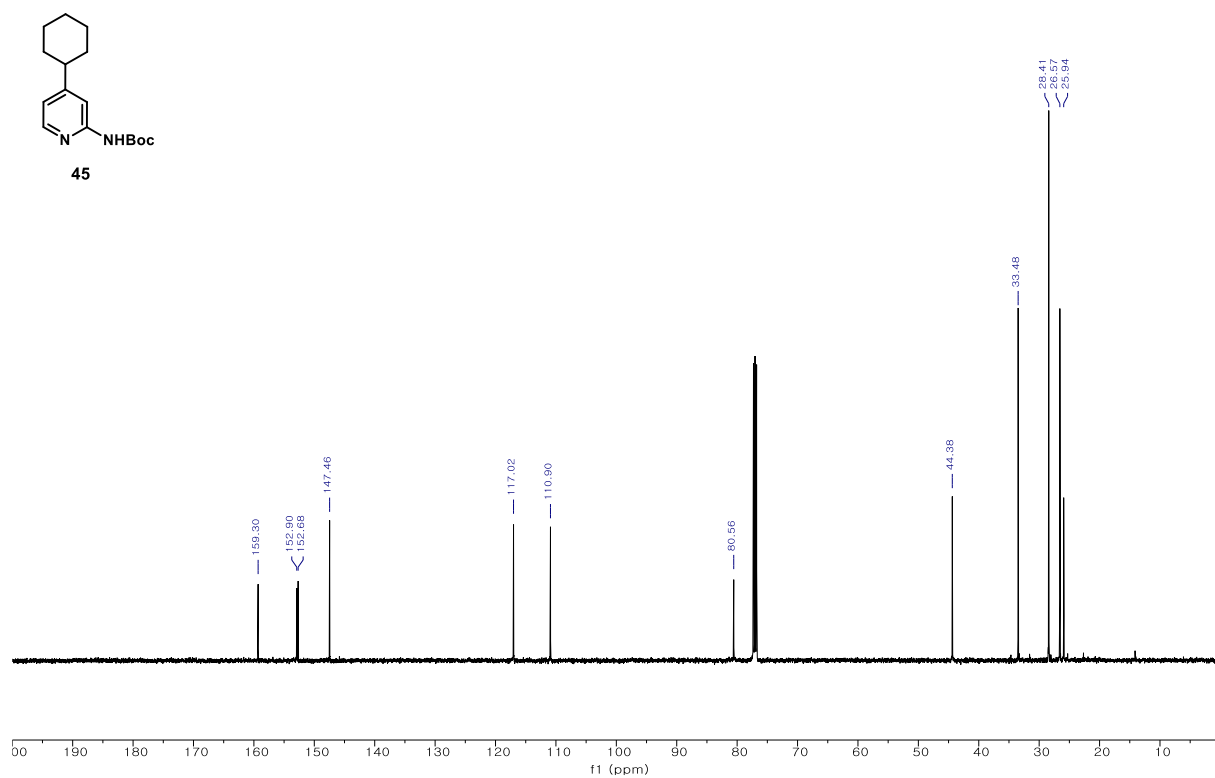
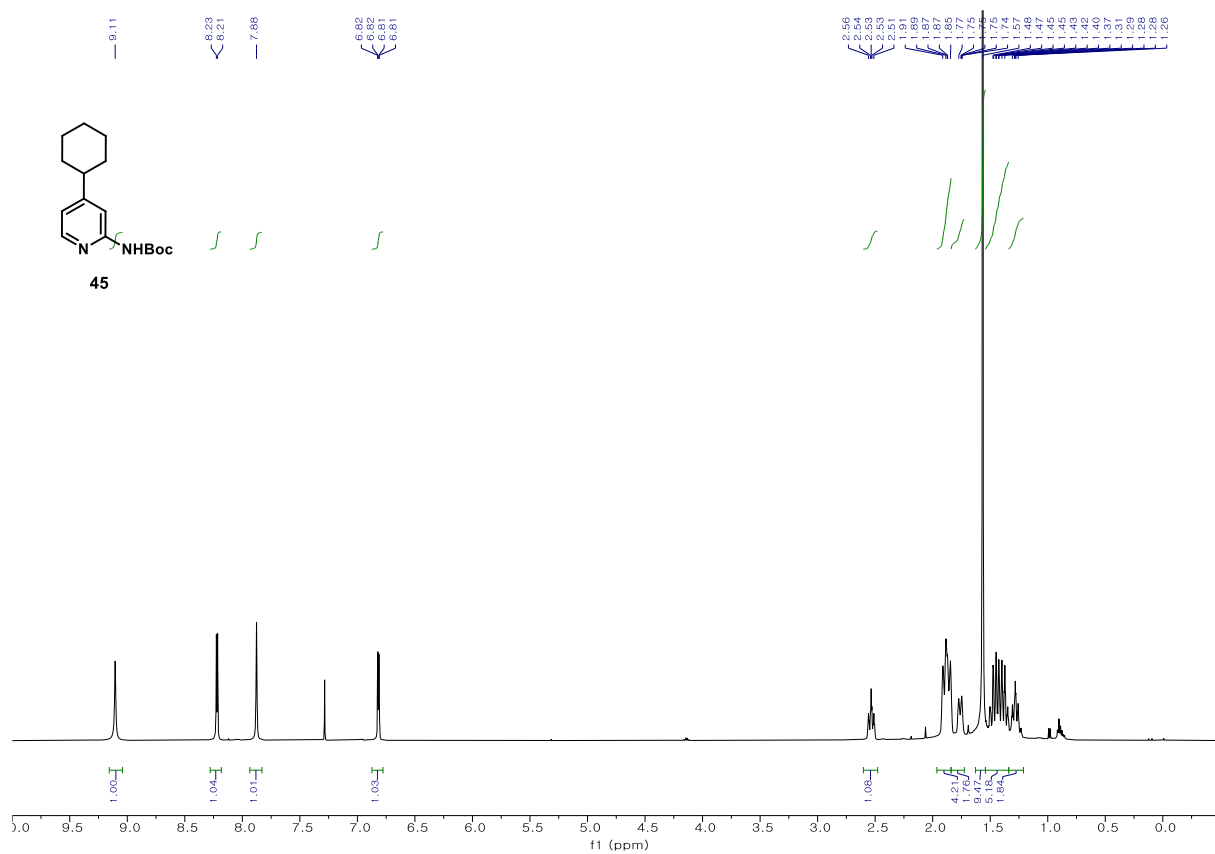


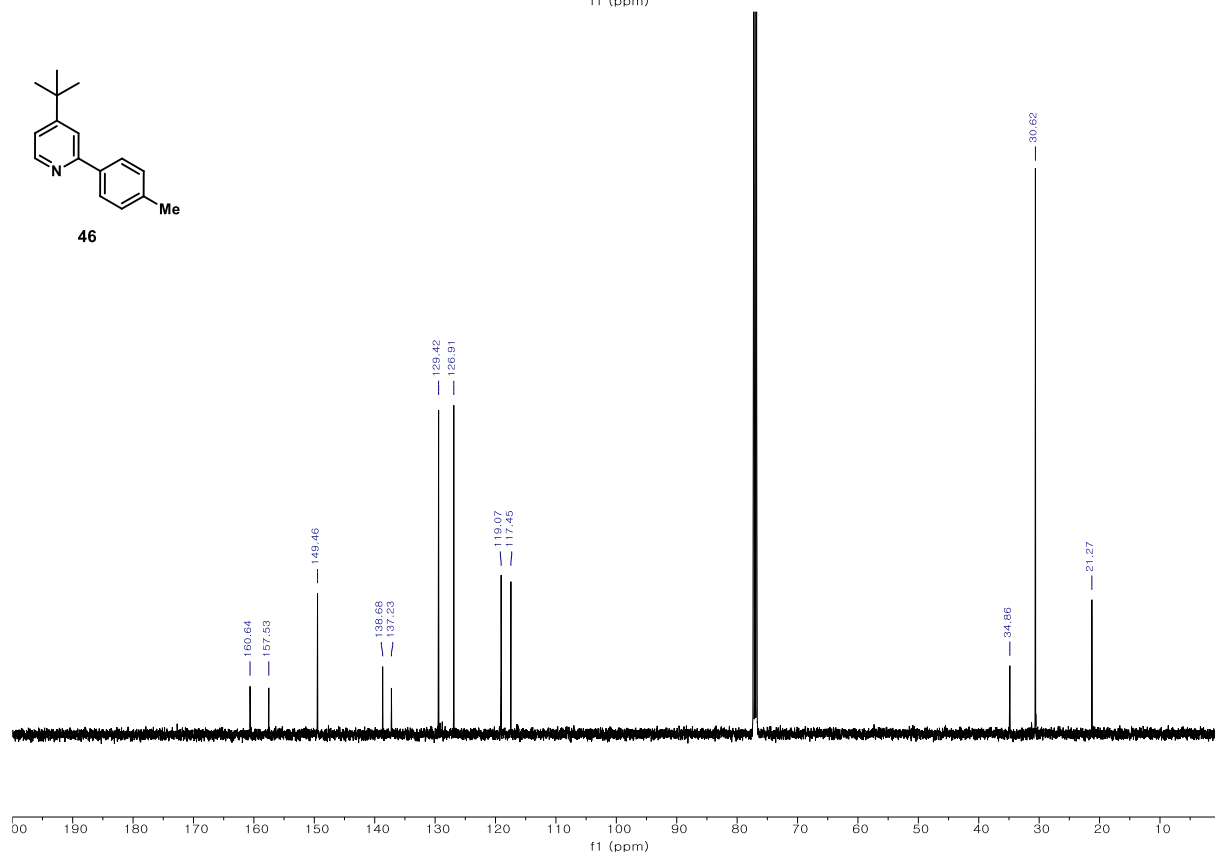
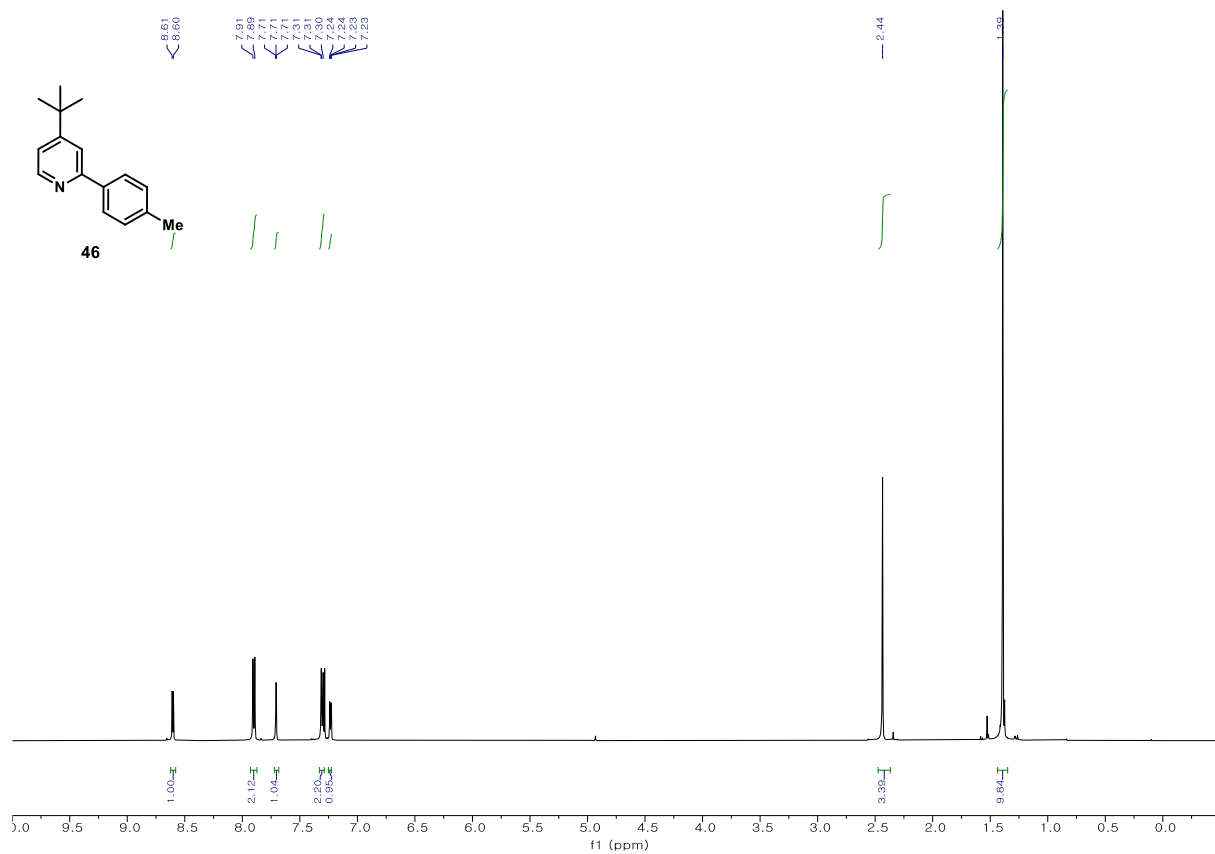


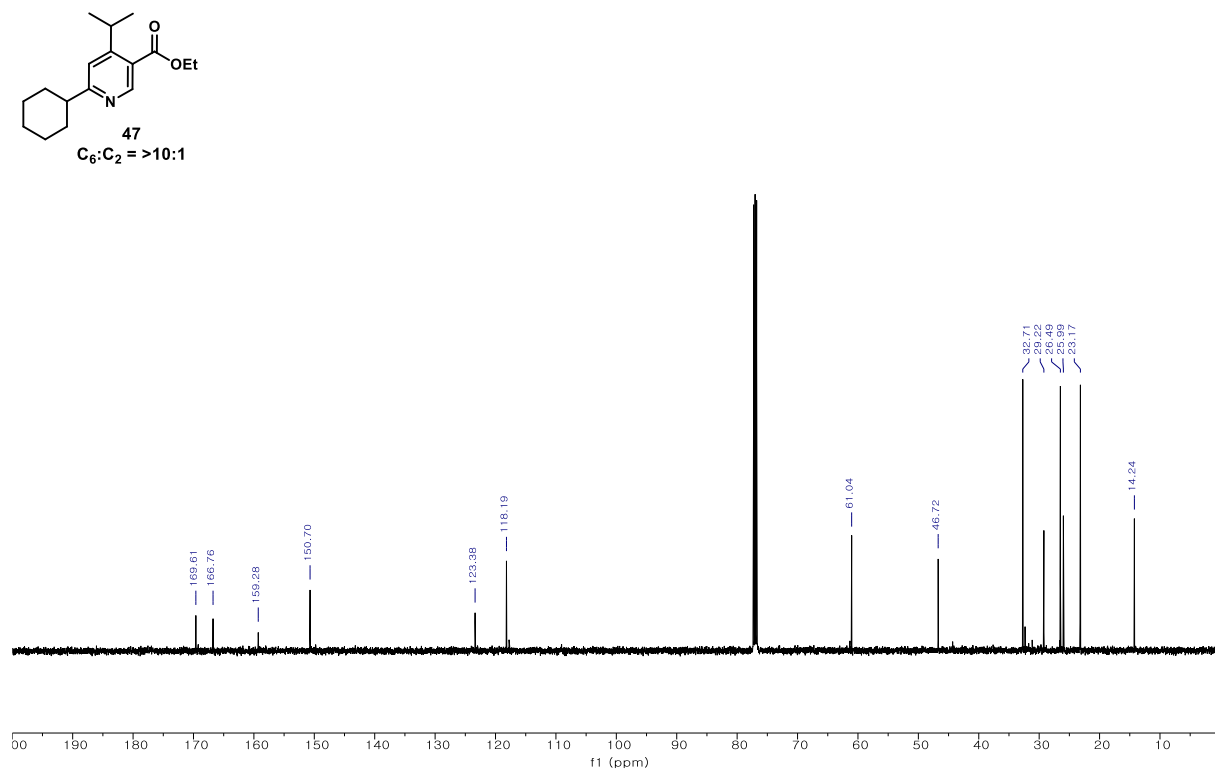
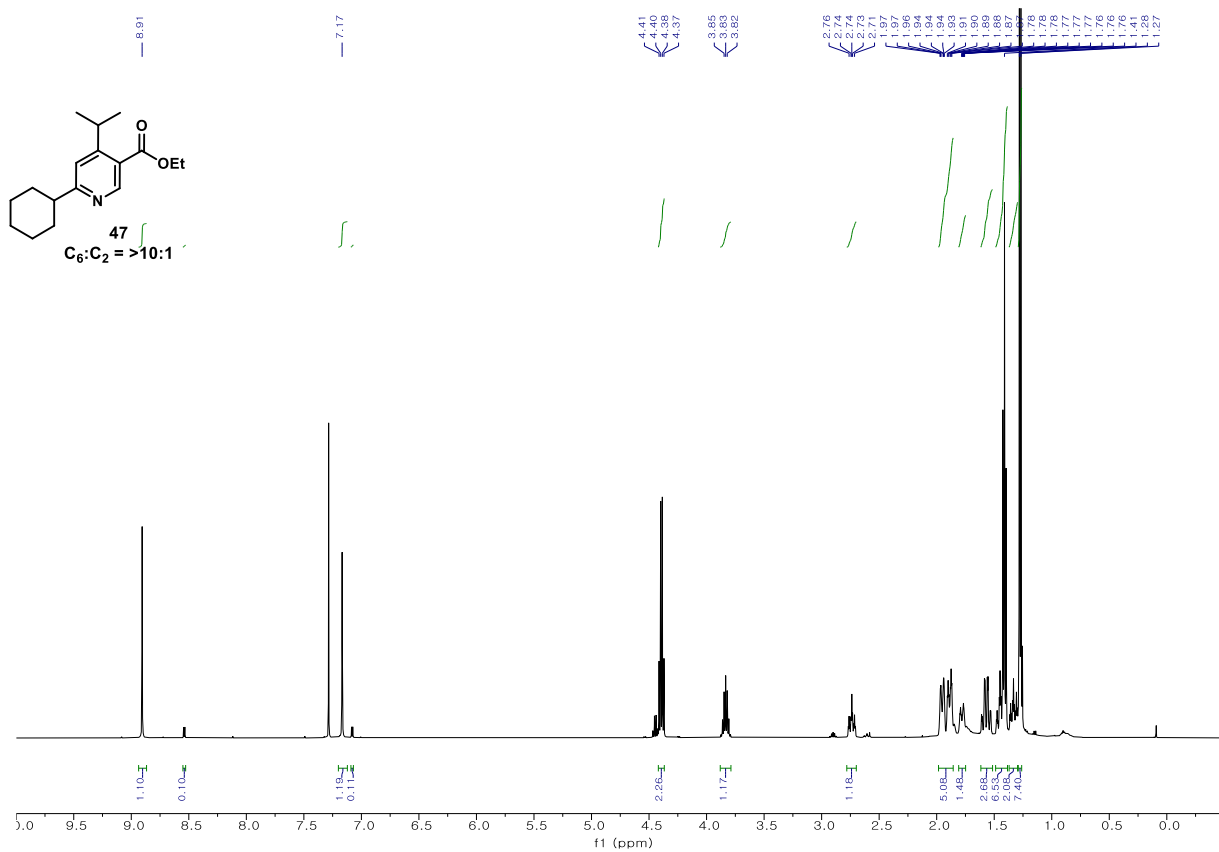


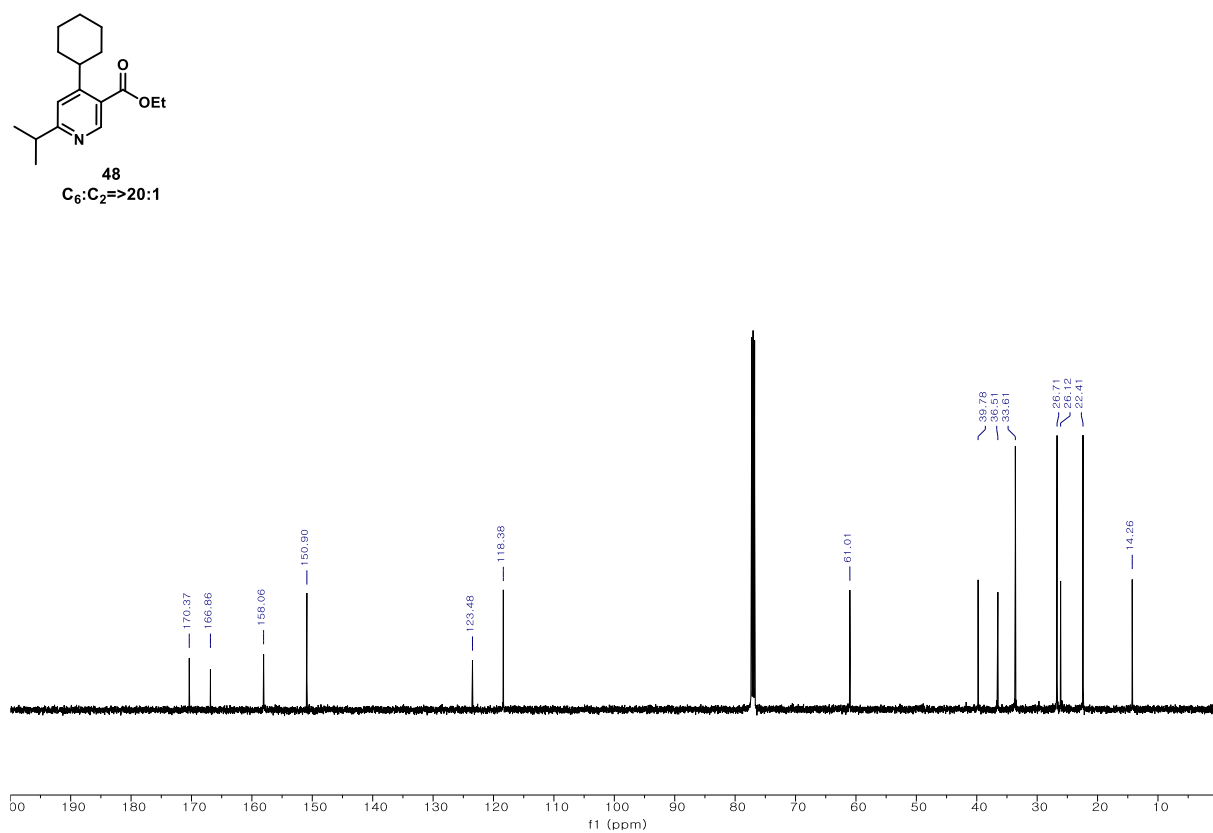
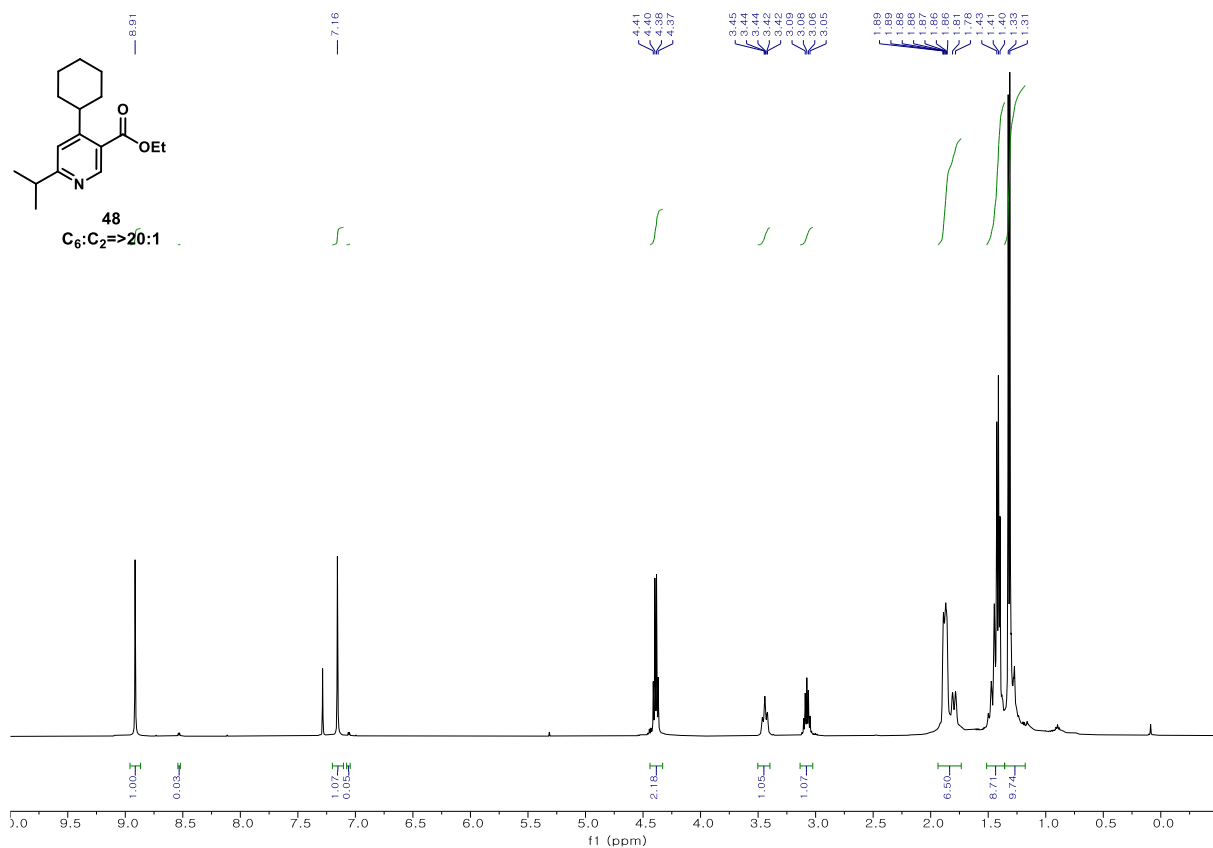


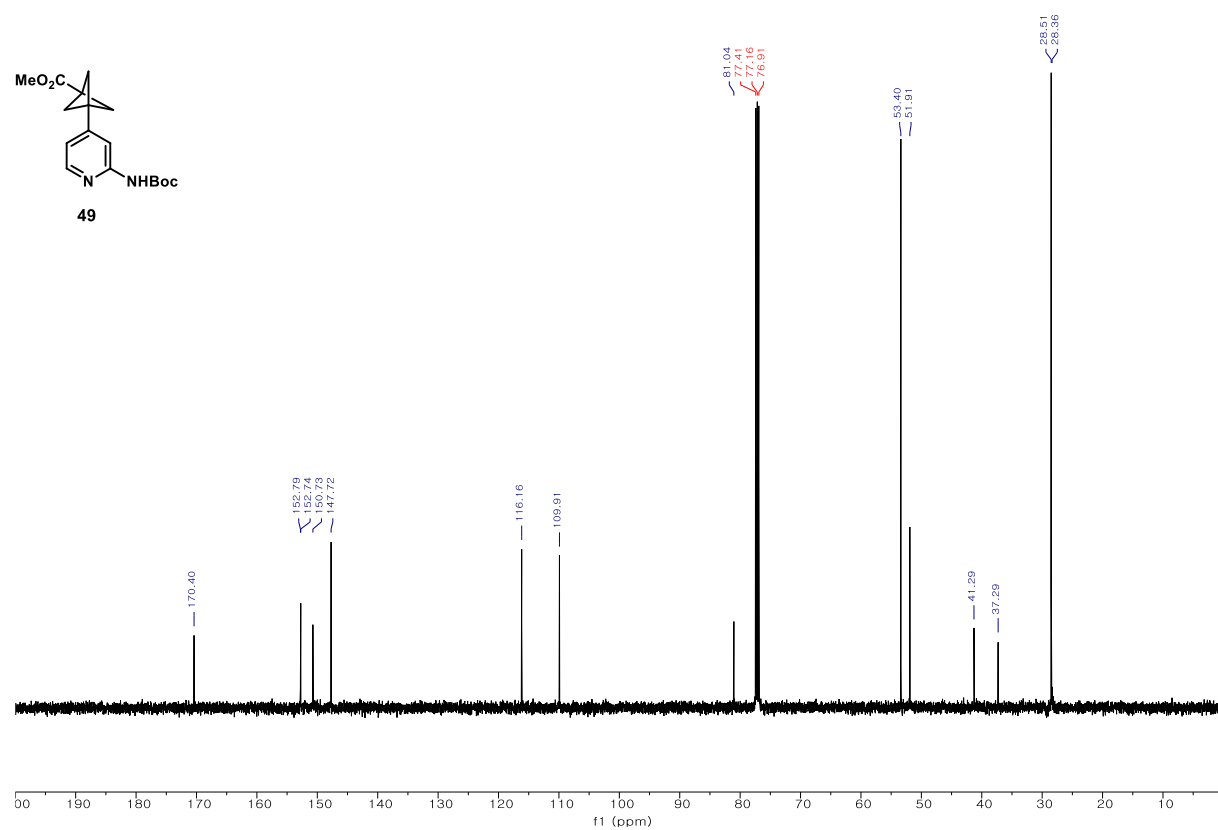
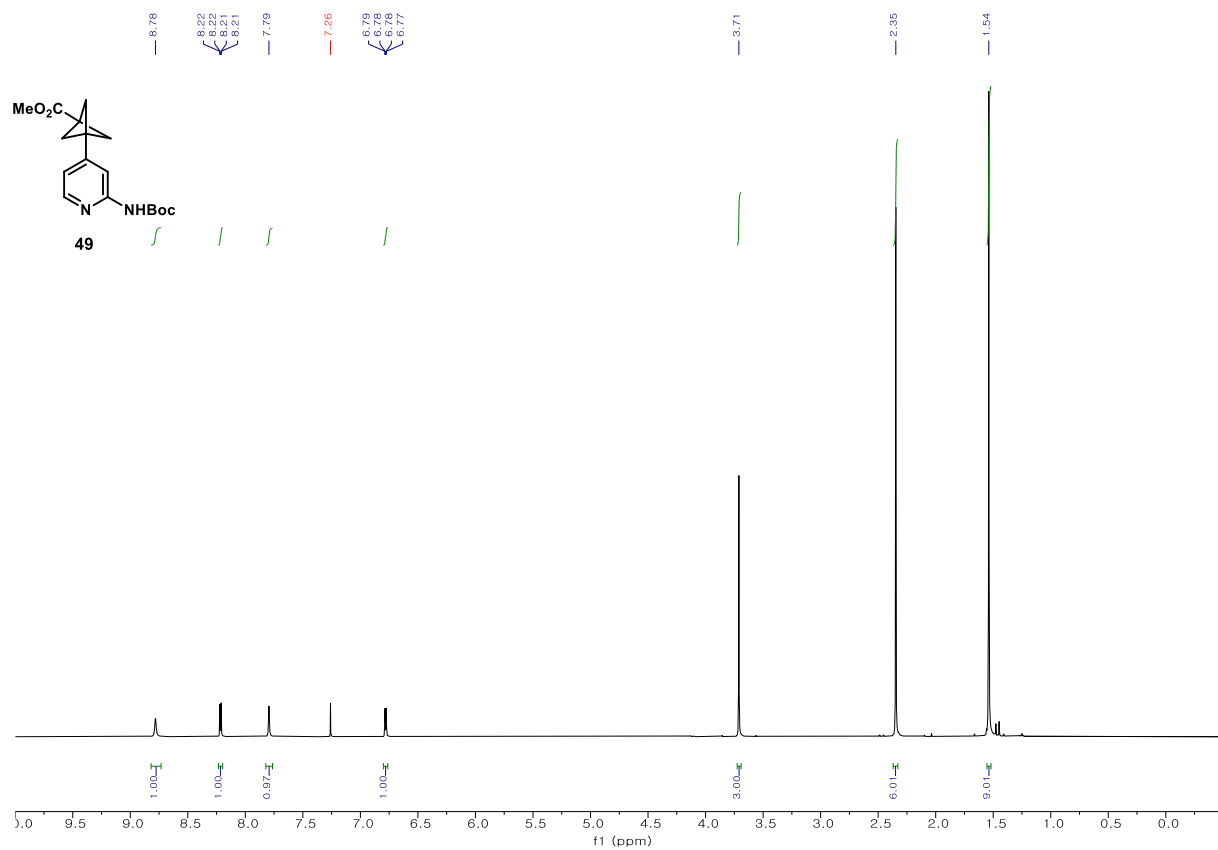


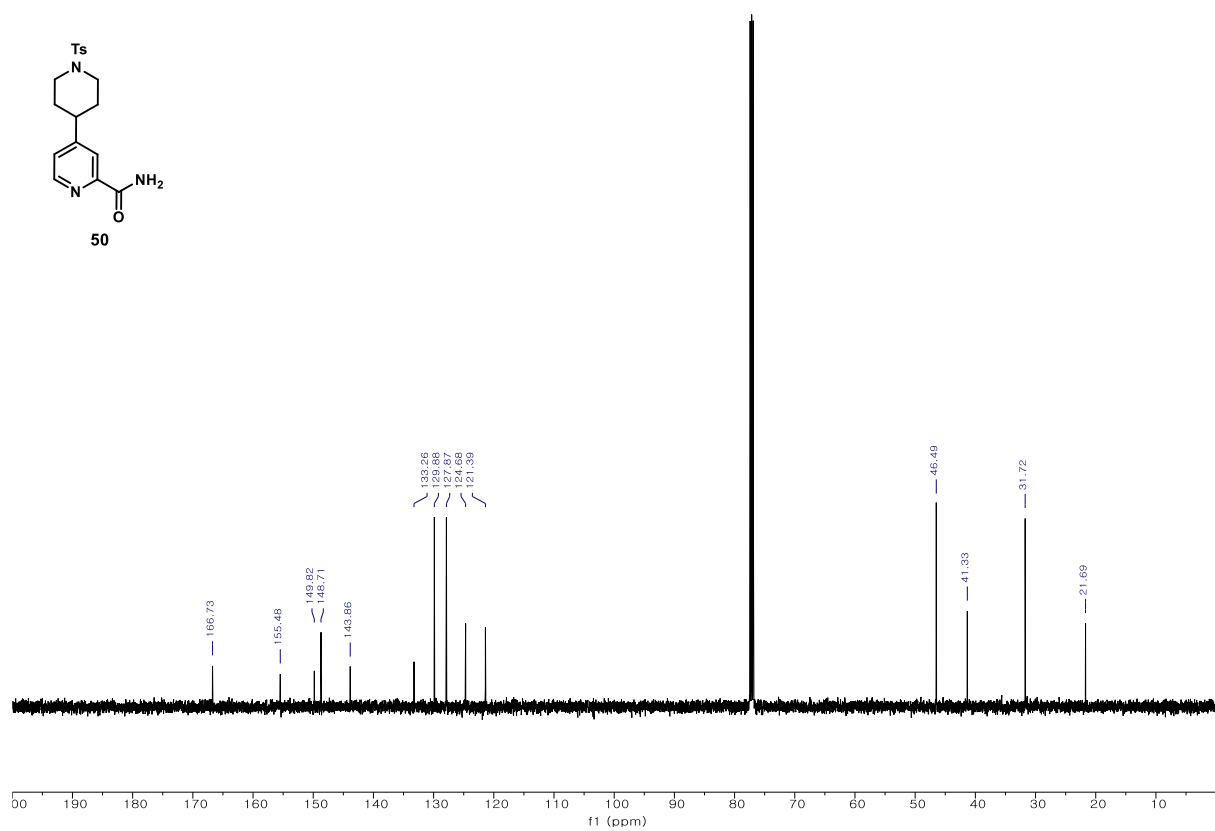


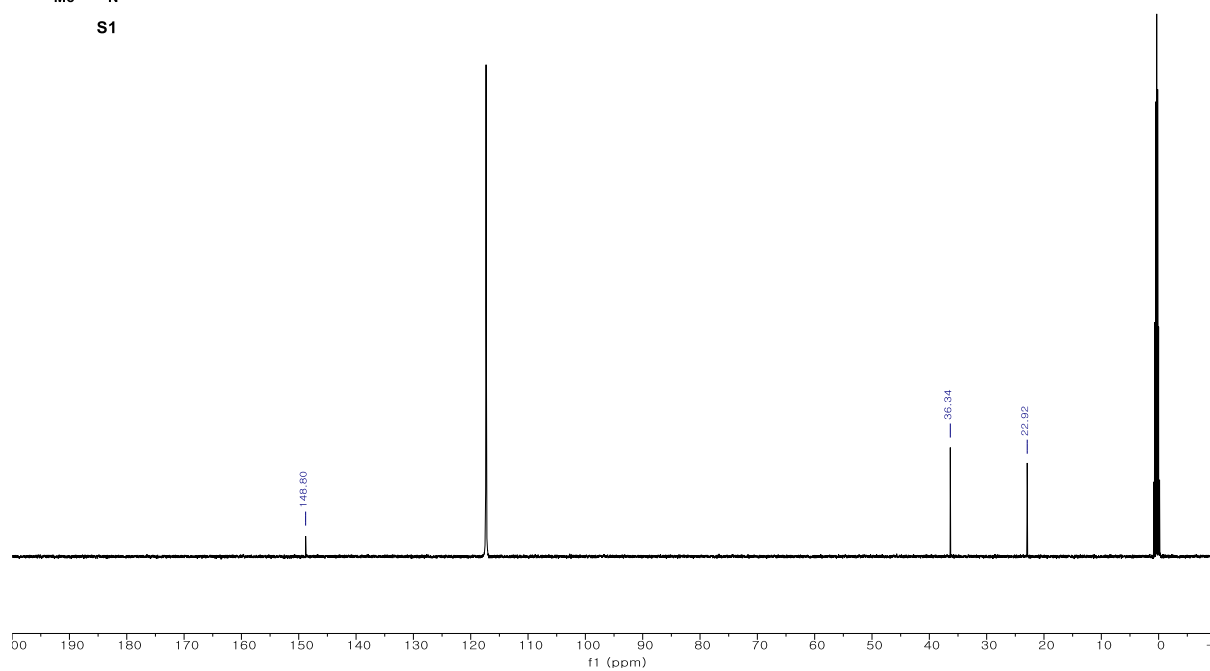
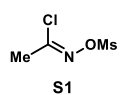
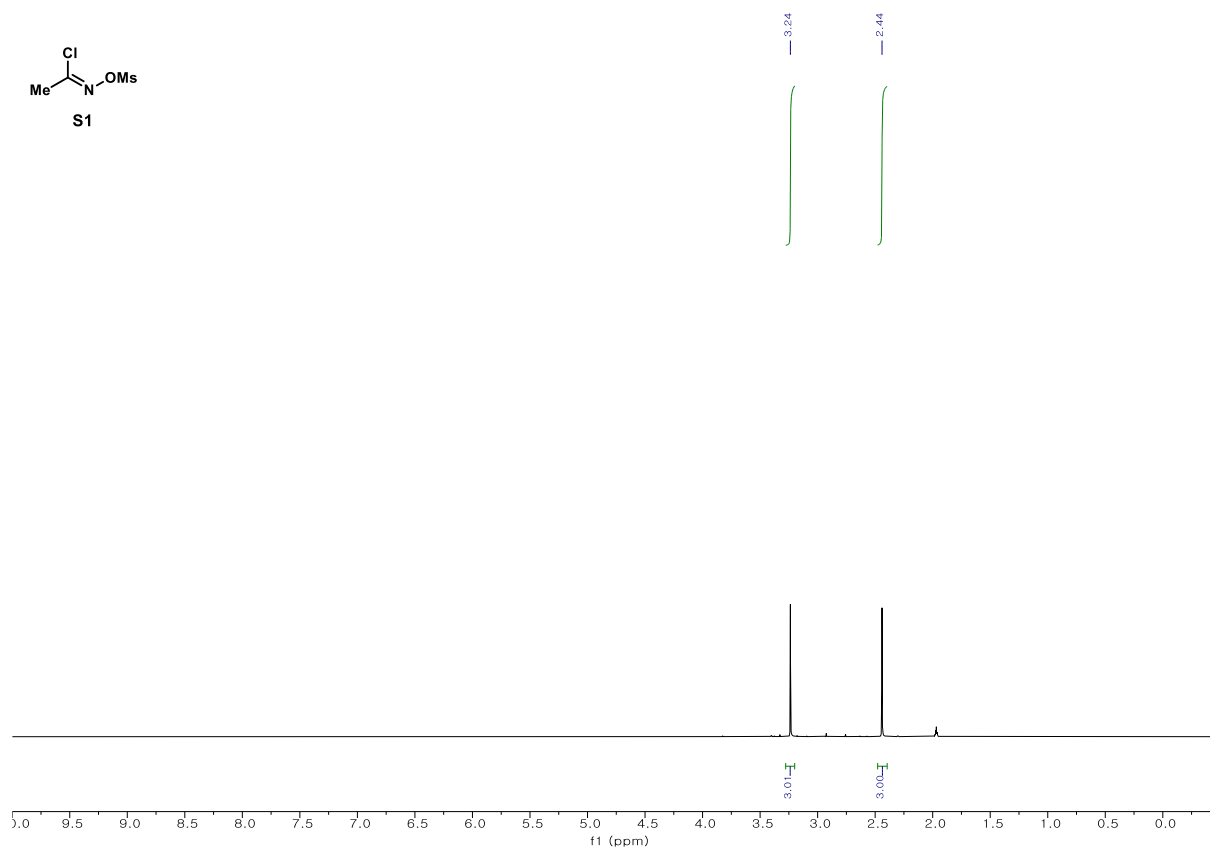
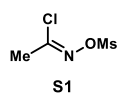


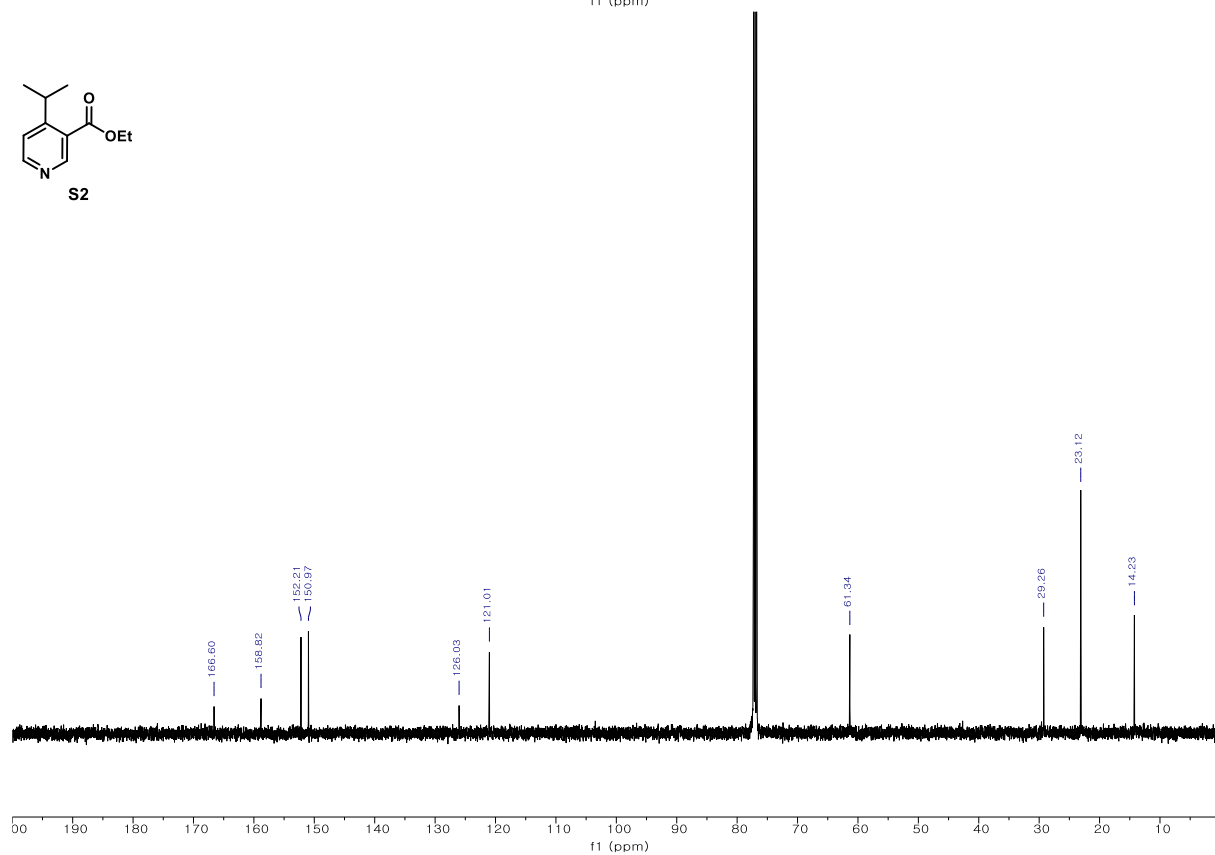
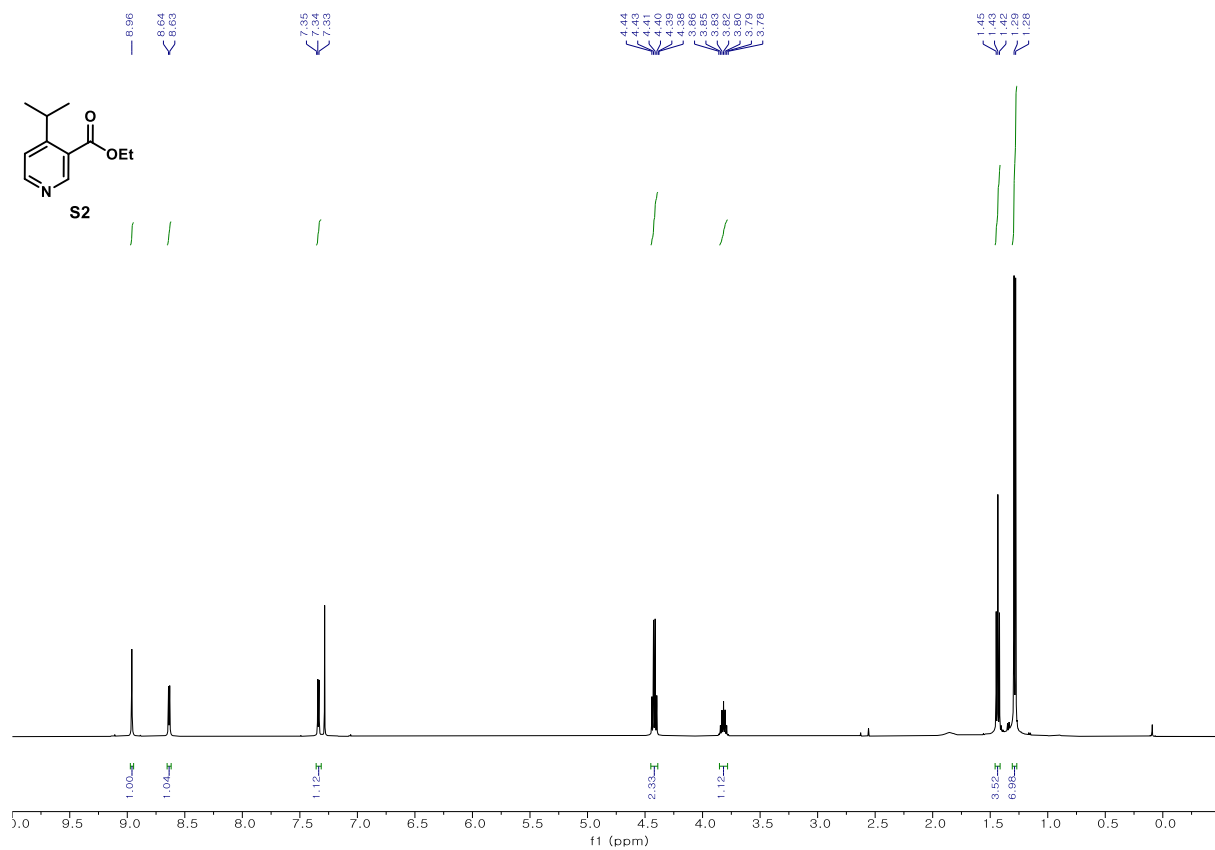


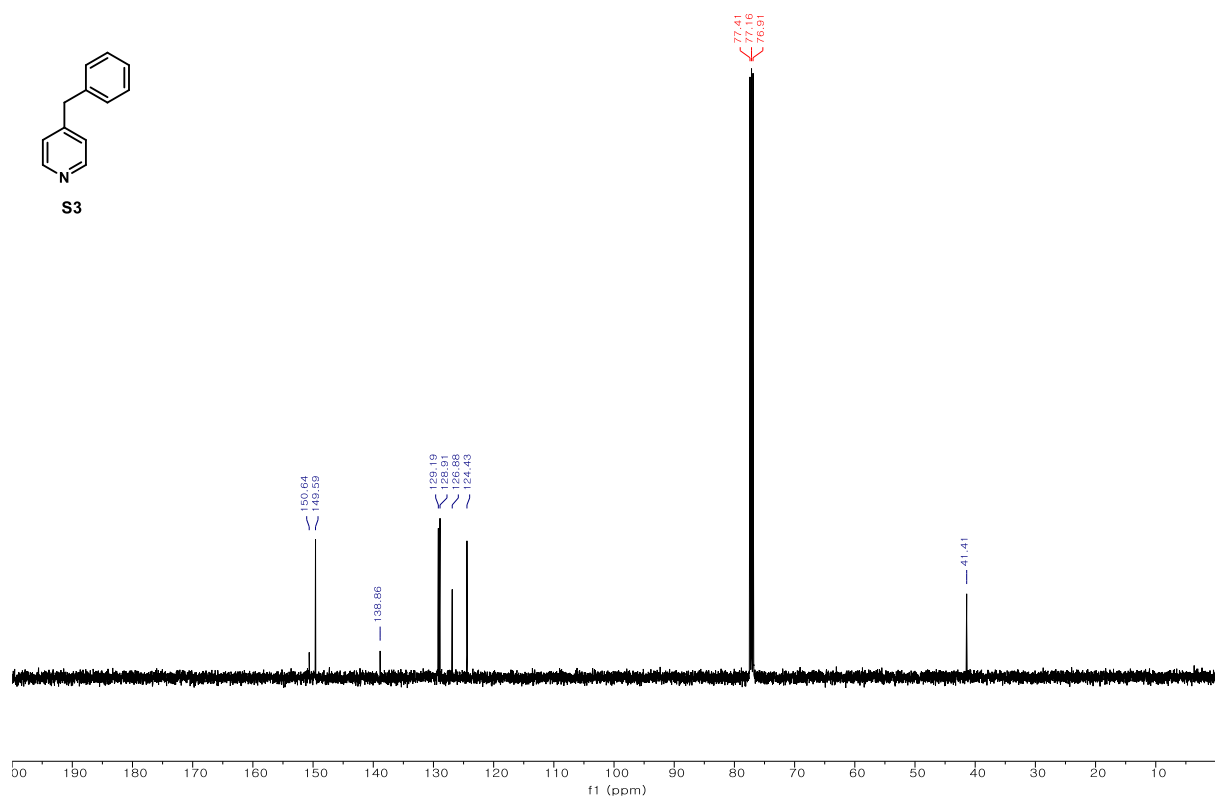
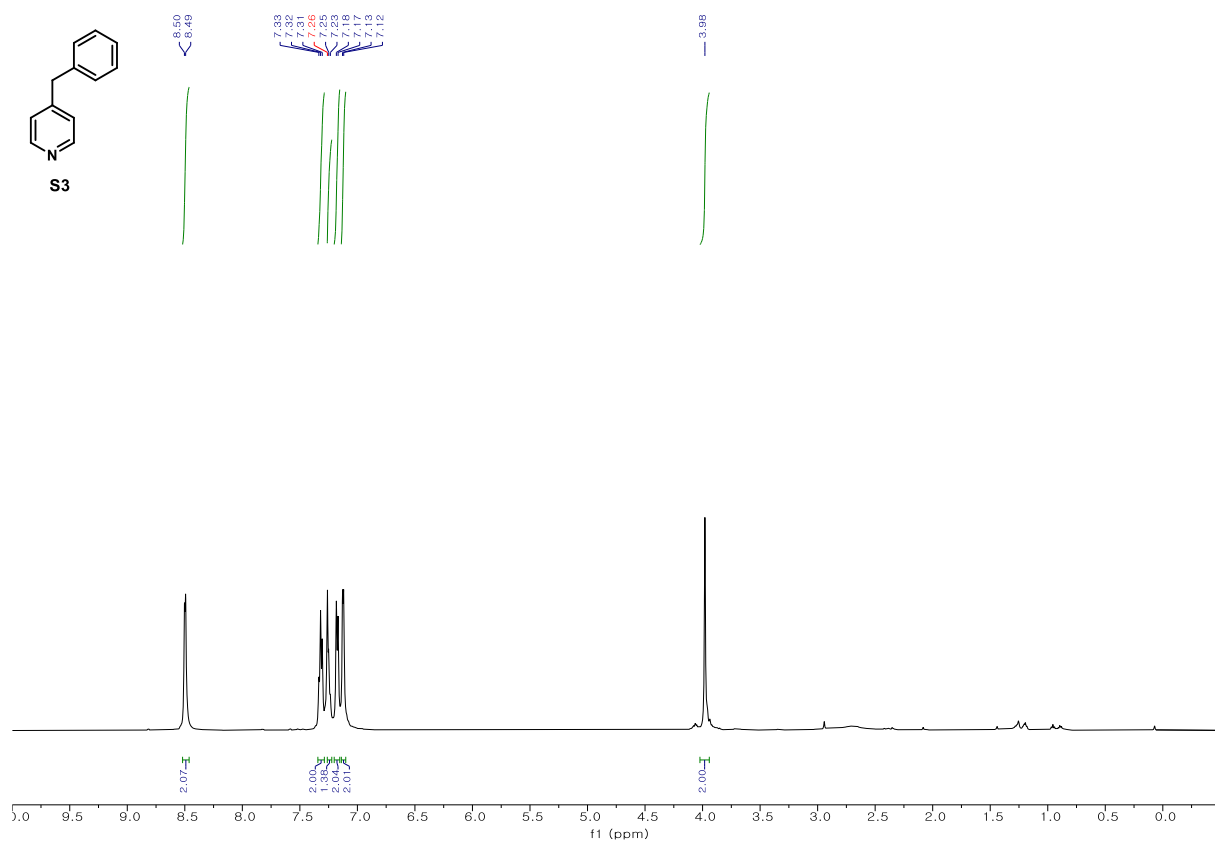


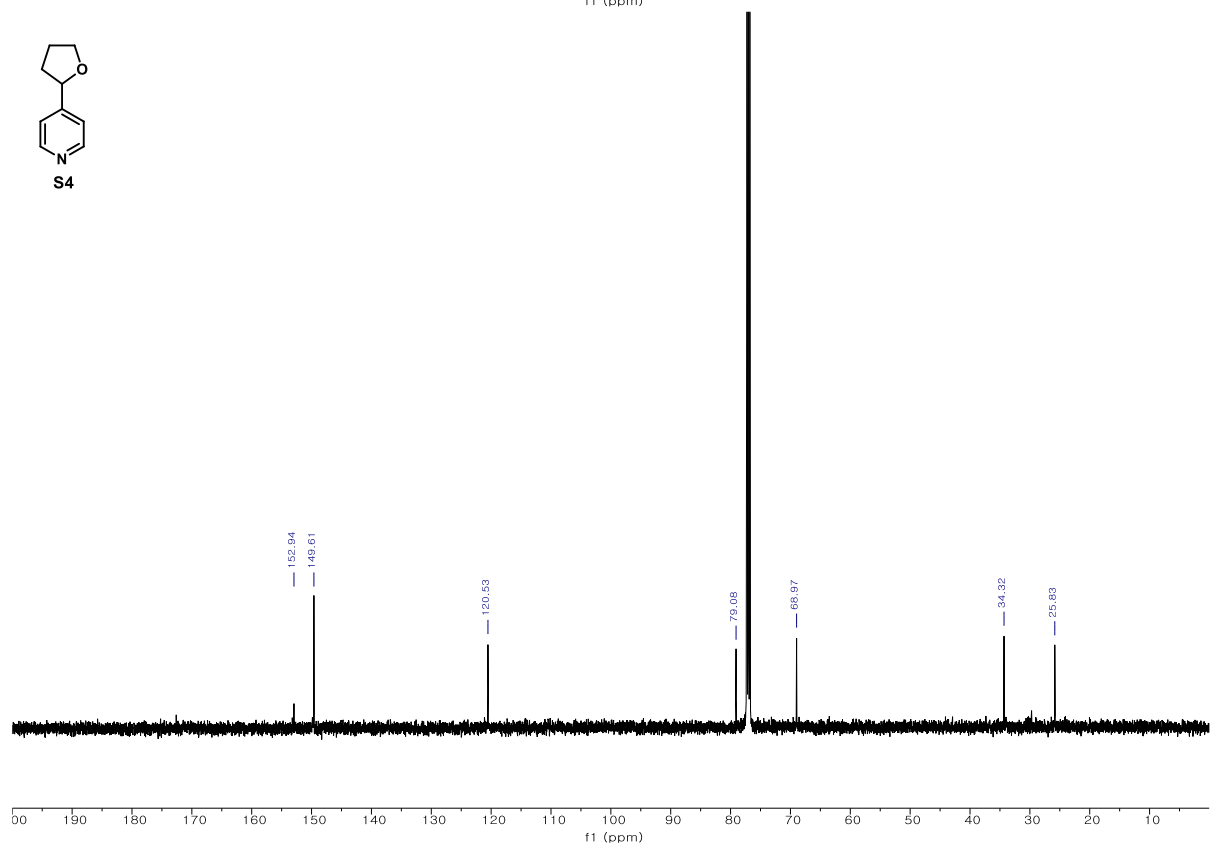
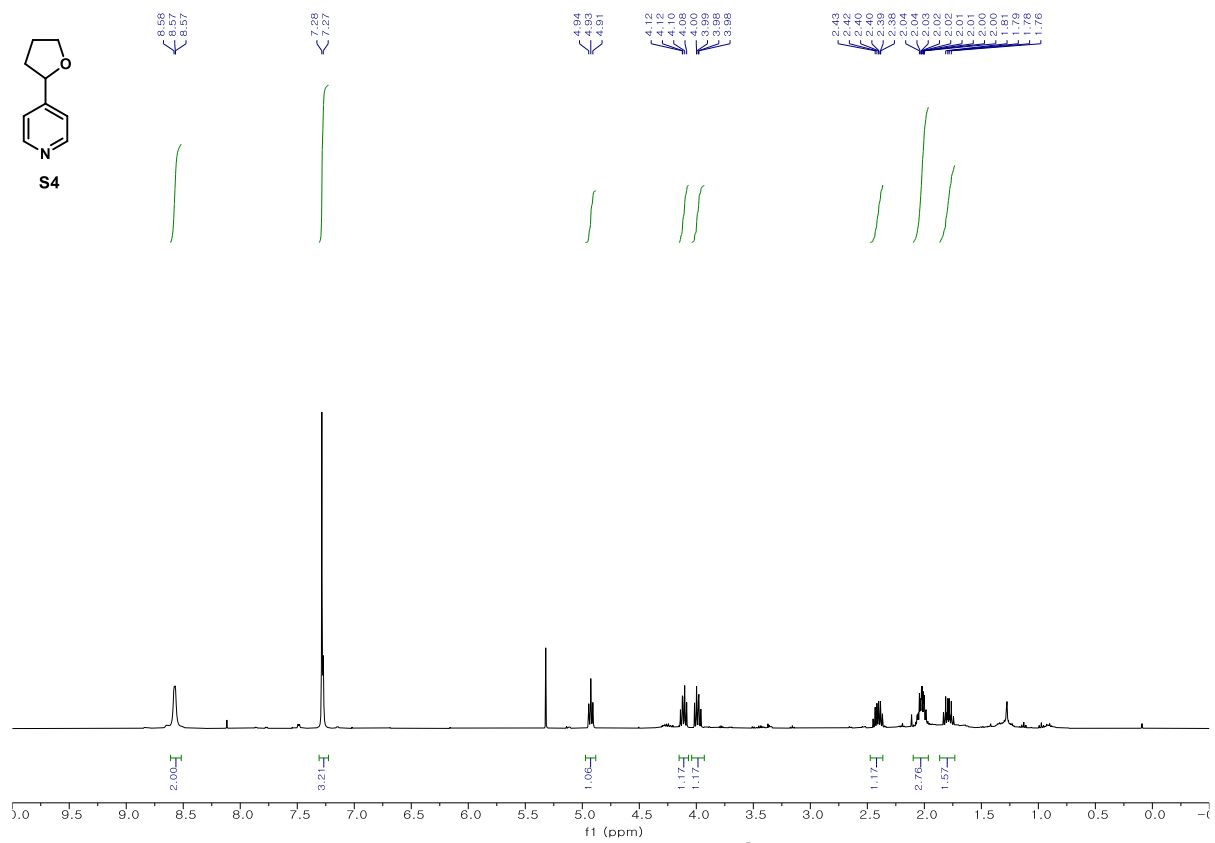


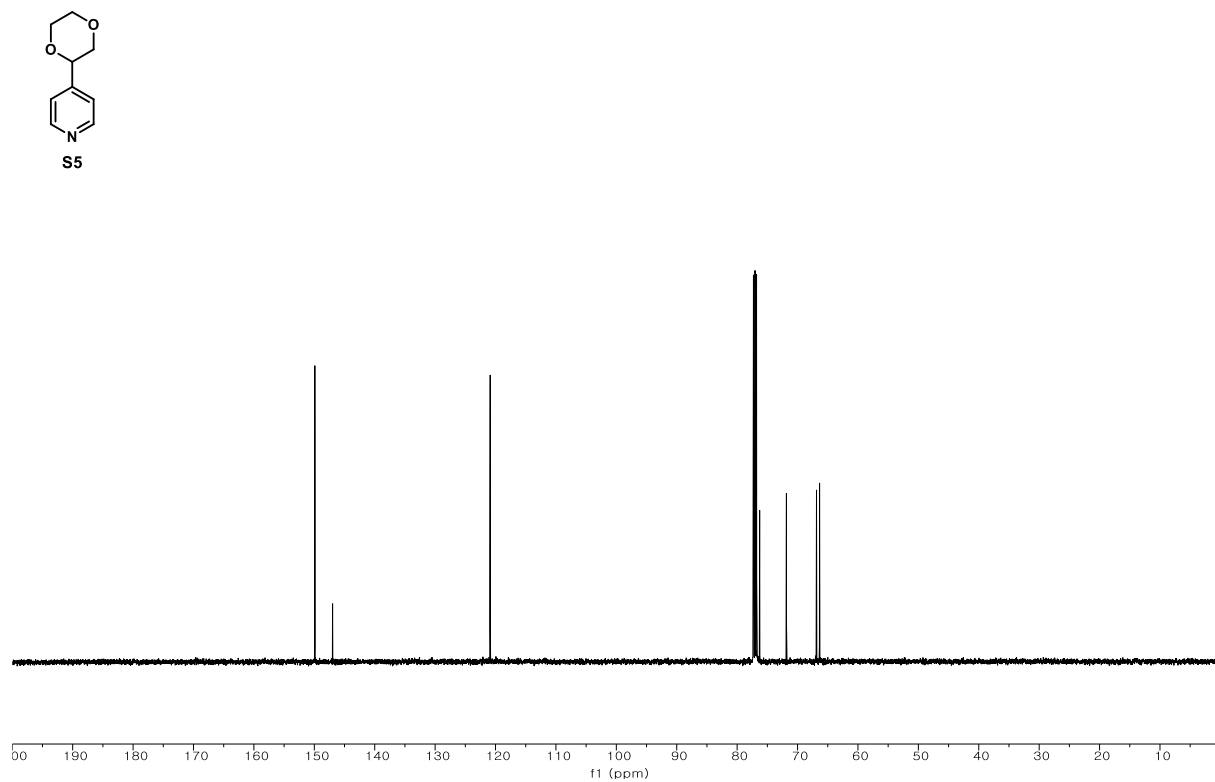
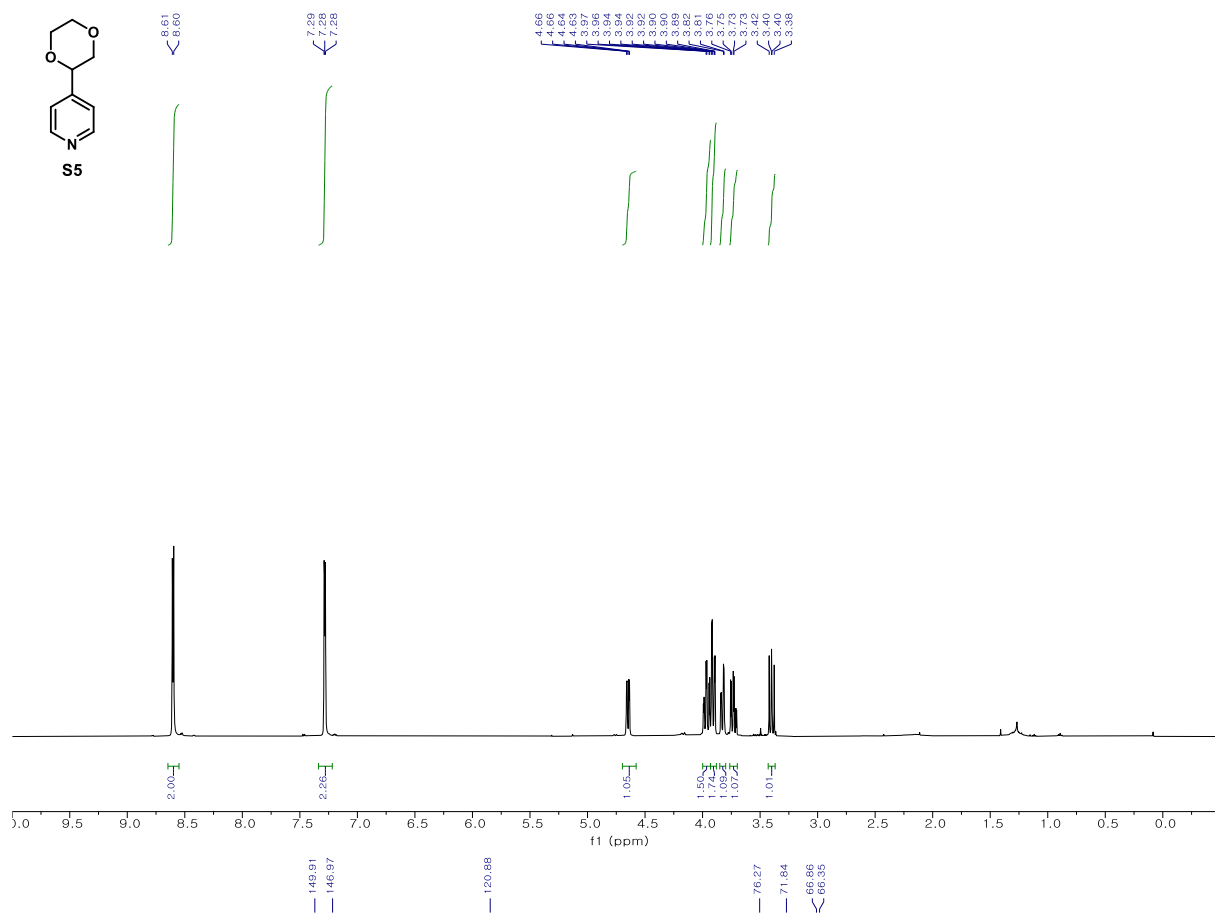


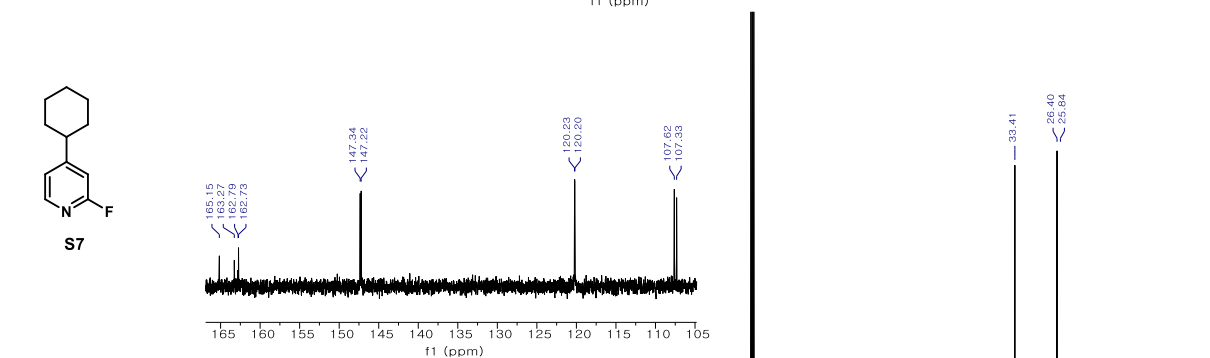


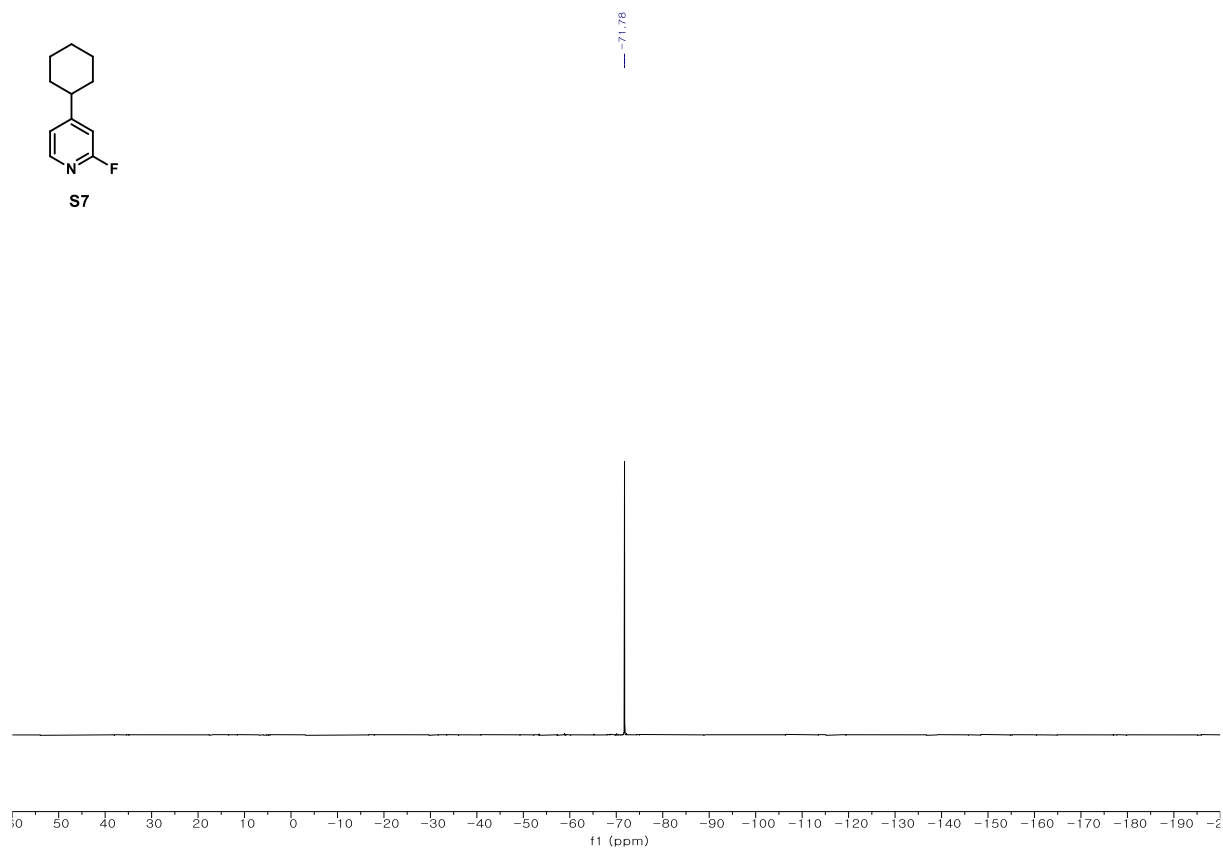
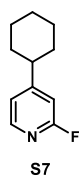


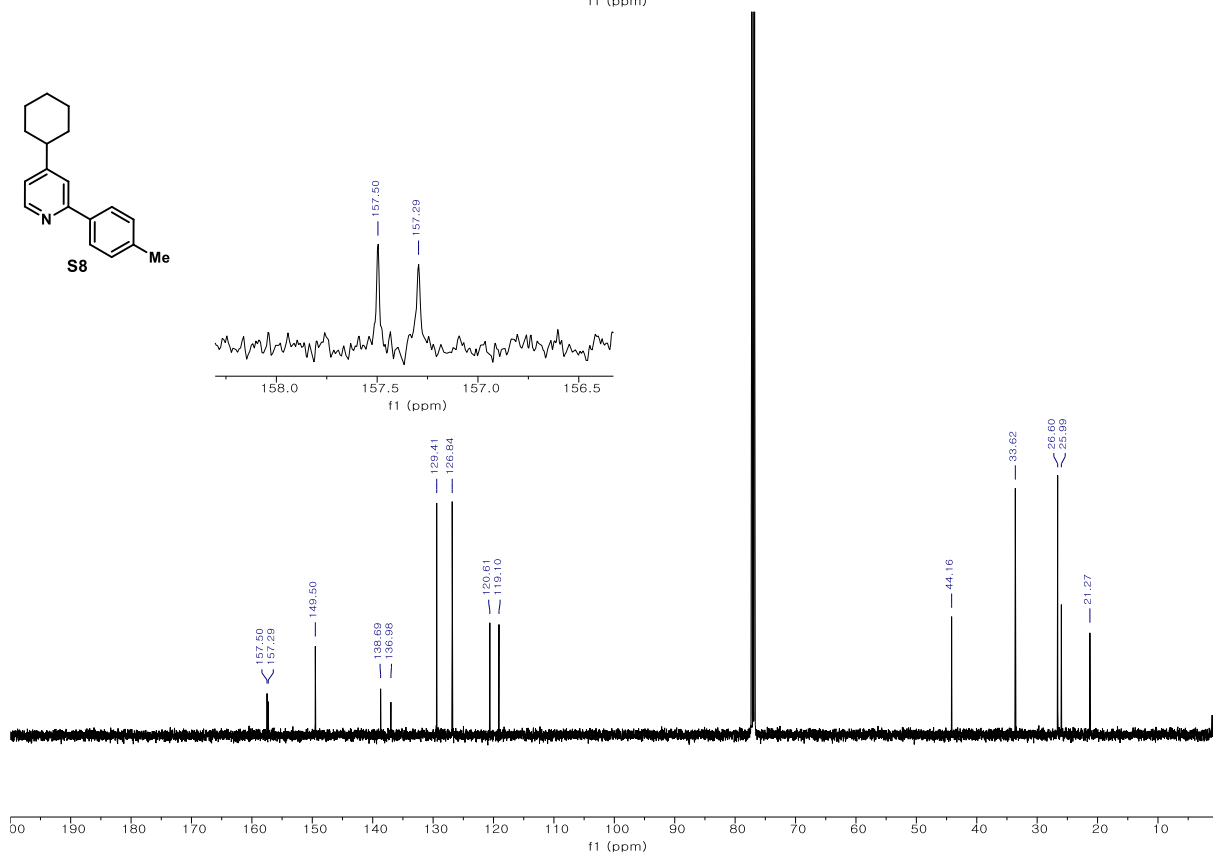
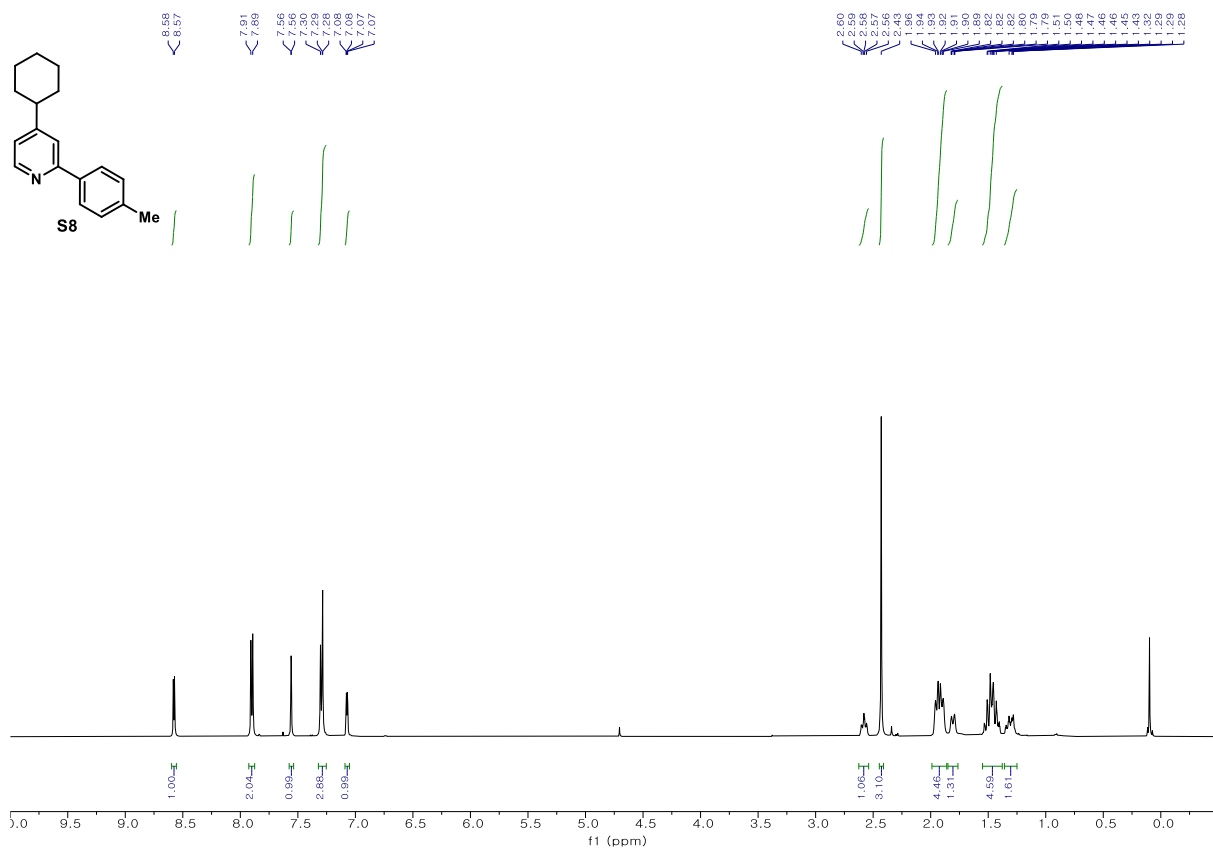












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