

PRACTICAL SYNTHESIS OF 4-PYRIDYL PHOSPHONATES

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A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE
GRADUATE PROGRAM IN CHEMISTRY
YORK UNIVERSITY
TORONTO, ONTARIO

MARCH 2026

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Abstract

Pyridyl phosphonates are valuable motifs in medicinal chemistry, catalysis, and materials science. Common routes for their synthesis often rely on prefunctionalized pyridines, transition-metal-catalyzed cross-coupling reactions, special free radical conditions or photochemical reactions. Herein, we report a mild, one-pot, and regioselective method to access 4-pyridyl phosphonates from simple pyridines via chloroformate-mediated pyridine activation, nucleophilic phosphite addition, and oxidative rearomatization using molecular oxygen. The method shows broad tolerance toward 3-substituted pyridines, while challenges associated with 2-substitution were addressed through a complementary post-functionalization strategy enabling access to 2-substituted pyridyl phosphonate scaffolds.

Acknowledgements

I would like to express my sincere gratitude to my supervisor, Dr. Arturo Orellana, for his mentorship, guidance, and unwavering support throughout my research. His scientific insight, patience, and encouragement were instrumental in shaping both this project and my personal development. Beyond his expertise in chemistry, I am deeply grateful for his mentorship outside the laboratory. His advice and perspective have had a profound influence on me, and I will carry these lessons forward as I move into the next stage of my life. I am truly appreciative of the opportunities and experiences he has provided me during my time in his group.

I would also like to thank my supervisory committee members, Dr. Christine Le and Dr. Ryan Hili, for their feedback, constructive criticism, and valuable discussions throughout my graduate studies. Their perspectives and guidance have greatly strengthened this work.

I am grateful to the members of the Orellana Lab for their support and collaboration. In particular, I would like to acknowledge Tomas Tjew and Natasha Gupta for their contributions and work related to this thesis. I also thank Micheal Petosa, Seyed Masoumi, Asal Samnejad, and Karan Mehta for their help and friendship, which made the lab a positive and engaging place to work. I extend special thanks to Dr. Andrei Nikolaev and Dr. Faizan Rasheed for their patience, advice, and assistance. Without their support, this work would not have been possible.

I would also like to thank the NMR specialists, Dr. Howard Hunter and Dr. Dmitry Pichugin, for their technical expertise, assistance, and guidance with NMR experiments throughout this work.

I acknowledge the Department of Chemistry at York University for providing the facilities and resources that made this research possible. I am also grateful to the many wonderful people in the department whom I have had the privilege of working with and befriending during my time here. Your support and friendship have made this experience truly memorable, and I wish you all the best in the future.

I would also like to express my deepest gratitude to Madeleine Agostino, for her support, patience, and encouragement throughout this journey. I am grateful for her understanding and for being a calming presence during both the challenging and rewarding moments of this process.

Finally, I would like to thank my mother, father, and sister for their unwavering love, encouragement, and support. Their belief in me has been a constant source of strength throughout my academic and personal journey, and my appreciation for everything they have done for me extends beyond what words can express.

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List of Abbreviations

ADHP	Alkylidene dihydropyridine
Alloc-Cl	Allyl chloroformate
Ar	Argon
Bipy	2,2'-Bipyridine
DHP	Dihydropyridine
DHPP	Dihydropyridine phosphonate
EDA	Electron donor–acceptor
equiv.	equivalent
ESI	Electrospray ionization
FDA	Food and Drug Administration
FPPS	Farnesyl pyrophosphate synthase
HRMS	High-resolution mass spectrometry
HSAB	Hard and soft acids and bases
Hz	hertz
IR	Infrared spectroscopy
<i>J</i>	coupling constant
mGlu4	Metabotropic glutamate receptor 4
mol	moles

NMR	Nuclear magnetic resonance
NMDA	N-methyl-D-aspartate
O ₂	Molecular oxygen
ppm	parts per million
R _f	Retention factor
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TOF	Time-of-flight
UV	Ultraviolet light

Chapter I: Introduction

1.1 Importance of Pyridines in Pharmaceuticals

A structural analysis of small-molecule drugs approved by the U.S. Food and Drug Administration (FDA) found that nitrogen-containing heterocycles are the most prevalent structural motifs across all approved pharmaceuticals, appearing in approximately 82% of all approved small-molecule drugs.¹ Among these, pyridine was identified as the most prevalent nitrogen heterocycle, underscoring its importance in medicinal chemistry (Figure 1.1).¹

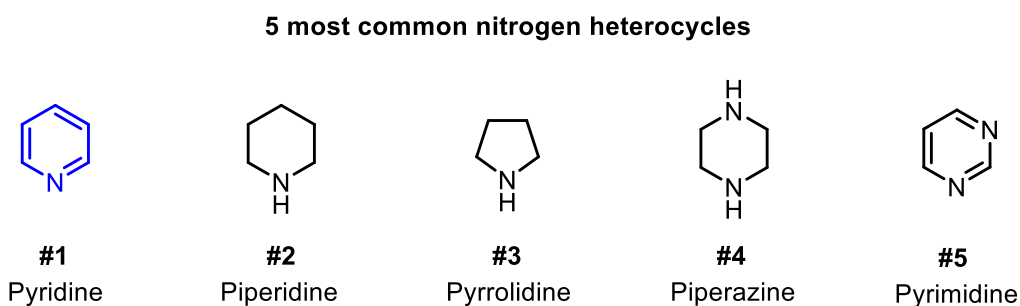


Figure 1.1: Frequency of nitrogen heterocycles in U.S. FDA-approved small molecule drugs.

The prominence of pyridine frameworks extends beyond pharmaceuticals to natural products and agrochemicals, where they serve as key structural elements in biologically active molecules.² Pyridine rings are widely employed in drug design because they allow modulation of physicochemical properties, including basicity, polarity, lipophilicity, and hydrogen-bonding capacity, while also serving as a versatile bioisostere for phenyl rings.³ As a result, substitution of a phenyl ring with a pyridine can substantially influence the pharmacological profile of a drug candidate, affecting parameters including aqueous solubility, metabolic stability, permeability, and target-binding efficiency.⁴ In several

cases, incorporation of a pyridine motif in a drug candidate has led to improvements in biological potency, metabolic stability, and permeability.⁴ For example, Hong *et al.* demonstrated that incorporation of a pyridine ring in place of a phenyl group within a tricyclic thiazolopyrazole metabotropic glutamate receptor 4 (mGlu4) positive allosteric inhibitor resulted in a 190-fold increase in cellular permeability (**Figure 1.2**).⁵

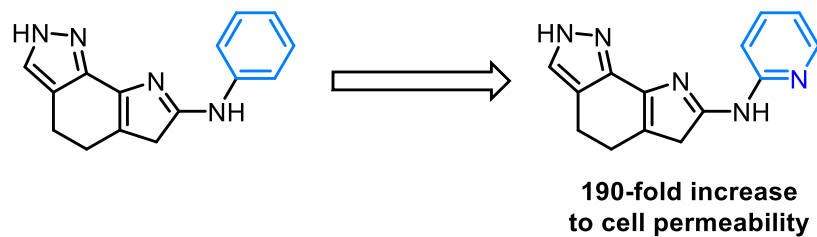


Figure 1.2: Bioisosteric effect of pyridine on the cell permeability of an mGlu4 positive allosteric inhibitor.

In response to the salient value of the pyridine motif in medicinal chemistry, together with the continued reliance of pharmaceutical discovery on synthetic methodologies developed in academic research,⁶ the central aim of our work is to develop strategies for the selective functionalization of pyridines. We prioritize the use of inexpensive and readily available reagents to achieve broad functional group tolerance and high selectivity to produce decorated heterocycles. These principles enable the development of practical and general synthetic tools for the preparation of valuable small molecules, thereby contributing meaningfully to the acceleration of drug discovery efforts.

1.2 Pyridyl Phosphonates in Medicinal Chemistry

Among the many privileged functionalizations of pyridines, pyridyl phosphonates - molecules containing a pyridine ring bearing a phosphonate substituent (**Figure 1.3**) - have attracted interest in medicinal chemistry due to their unique combination of

physicochemical and biological properties. Phosphonates are characterized by a pentavalent phosphorus center bearing a direct carbon-phosphorus bond and three oxygen substituents, this class broadly encompasses both dialkyl phosphonates and their corresponding phosphonic acids. Incorporation of a phosphonate group onto a pyridine scaffold combines the electronic properties of the motif with the strong polarity, anionic character, and metal-coordinating ability of phosphonates. As a result, pyridyl phosphonates often display enhanced potency and selectivity alongside improved solubility and metabolic stability, arising from the complementary contributions of the phosphonate and pyridine functionalities.

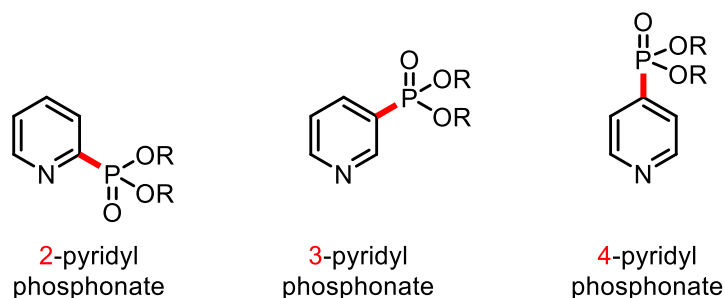


Figure 1.3: General structural motifs of 2-, 3-, and 4-pyridyl dialkylphosphonates, illustrating the positional relationship between the pyridine ring and the phosphonate substituent.

Risedronate, a drug used to treat osteoporosis, provides a clear illustration of how incorporating a pyridine ring onto a phosphorus-containing scaffold motif can enhance biological potency and selectivity. Risedronate, a 3-pyridyl bisphosphonate, potently inhibits farnesyl pyrophosphate synthase (FPPS) in osteoclasts and exhibits approximately 1,000-fold greater potency than the first-generation bisphosphonate etidronate, as well as several-fold higher potency than earlier amino-bisphosphonates such as pamidronate (**Figure 1.4**).⁷ This enhanced activity arises from the

complementary contributions of the pyridine ring, which improves binding interactions within the FPPS active site, and the geminal phosphonate groups, which strongly chelate Mg^{2+} cofactors and bone mineral, collectively conferring high potency and selectivity for bone-targeted enzyme inhibition.^{7,8}

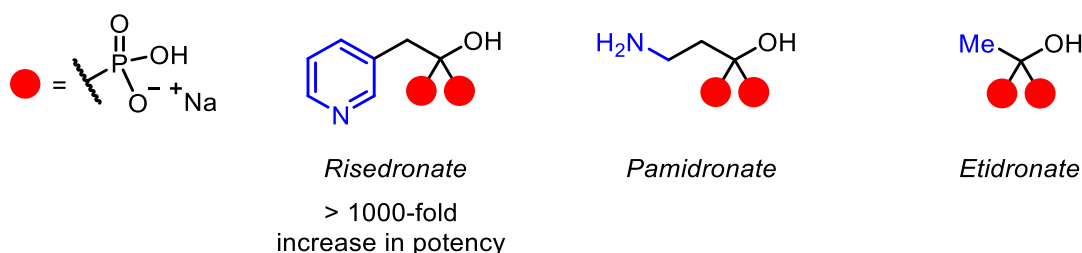


Figure 1.4: Chemical structures of bisphosphonate drugs used in osteoporosis therapy: risedronate, etidronate, and pamidronate.

In drug design, phosphonate groups are frequently employed as bioisosteric replacements for phosphate esters, where substitution of a labile P–O bond with a robust C–P linkage confers resistance to enzymatic hydrolysis and metabolic degradation, thereby addressing stability challenges.^{9,10} The polarity of phosphonate groups, typically mean that they are deprotonated at physiological pH. This can be exploited by appending the phosphonate moiety onto poorly soluble prodrugs and the ionized phosphonate group maintained solubility through the gut pH range, enabling good absorption and bioavailability.¹¹ Pyridyl phosphonates have also been exploited in a variety of biologically important applications. 4-pyridyl phosphonates act as a class of stable nucleotide analogue that mimic natural substrates while resisting enzymatic breakdown.¹² These analogues have been widely used as antiviral and antiproliferative agents by interfering with polymerase and kinase activities (**Figure 1.5**).¹³

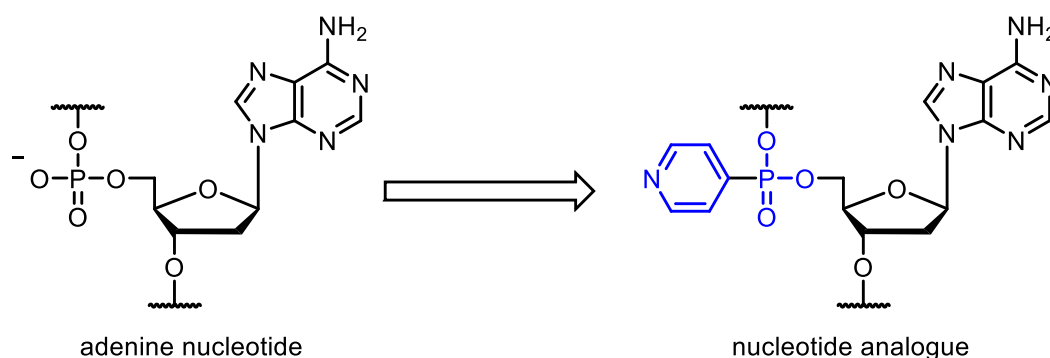


Figure 1.5: Comparison of a natural nucleotide and a representative 4-pyridyl phosphonate nucleotide analogue.

The utility of pyridyl phosphonate groups in modulating biological function extends beyond enzymes involved in phosphoryl transfer and nucleotide metabolism.¹⁰ 9-Phosphoryl acridine derivatives exhibit low-micromolar inhibition of butyrylcholinesterase together with activity against β -amyloid aggregation and oxidative stress (**Figure 1.6a**).¹⁴ These processes are closely associated with neurotransmitter imbalance, protein aggregation, and neuronal damage in neurodegenerative disease.¹⁴ In a related context, pyridyl phosphonates also serve as valuable synthetic intermediates, as reduction of the pyridine ring affords the corresponding piperidine phosphonates. These piperidine phosphonate derivatives have been developed as structural analogues of the N-methyl-D-aspartate (NMDA) receptor antagonist selfotel, demonstrating how pyridyl phosphonate scaffolds can provide access to motifs relevant for receptor modulation (**Figure 1.6b**).¹⁵ NMDA receptors play a central role in the development and function of the central nervous system, being involved in cognition, learning, memory, and the regulation of essential physiological rhythms.¹⁵ Dysregulation of NMDA receptor signaling is associated with cognitive impairment and neurodegeneration, and has been implicated in numerous

central nervous system disorders, including stroke, ischemia, Huntington's and Parkinson's diseases, Alzheimer's disease, epilepsy, neuropathic pain, schizophrenia, and mood disorders.¹⁵ Consequently, NMDA receptor antagonists represent an important therapeutic strategy for the treatment of these conditions. Collectively, these examples highlight pyridyl phosphonates as privileged structures in medicinal chemistry, capable of either directly targeting biological relevant receptors or serving as versatile precursors to pharmacologically relevant motifs that are represented in drug discovery.

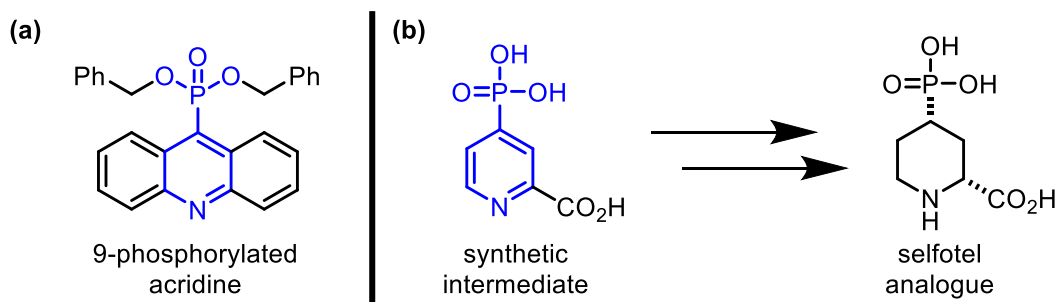


Figure 1.6: (a) 9-phosphoryl acridine derivatives reported to exhibit low-micromolar butyrylcholinesterase inhibition. (b) Structural analogues of the NMDA receptor antagonist selfotel, obtained via reduction of pyridyl phosphonate intermediate.

In addition to their medicinal applications, pyridyl phosphonates exhibit broad utility across other areas of chemistry, particularly in catalysis and materials science. In catalytic systems, the pyridine nitrogen can function as a classical neutral N-donor ligand by coordinating to a transition-metal center, while the phosphonate group binds strongly to metal surfaces (**Figure 1.7a**).^{16–18} This bifunctional binding capability has been exploited to immobilize molecular catalysts on conductive or semiconducting metal oxide surfaces, enabling robust catalytic systems for transformations such as photoelectrochemical water oxidation.^{17,18} Less frequently, pyridyl phosphonates act as chelating ligands in which

both the pyridine nitrogen and the phosphonate oxygen atoms simultaneously coordinate to a single metal center (**Figure. 1.7b**).¹⁹ These cooperative binding modes can influence the electronic structure of the metal complex, leading to improved catalyst stability and altered reactivity.¹⁹

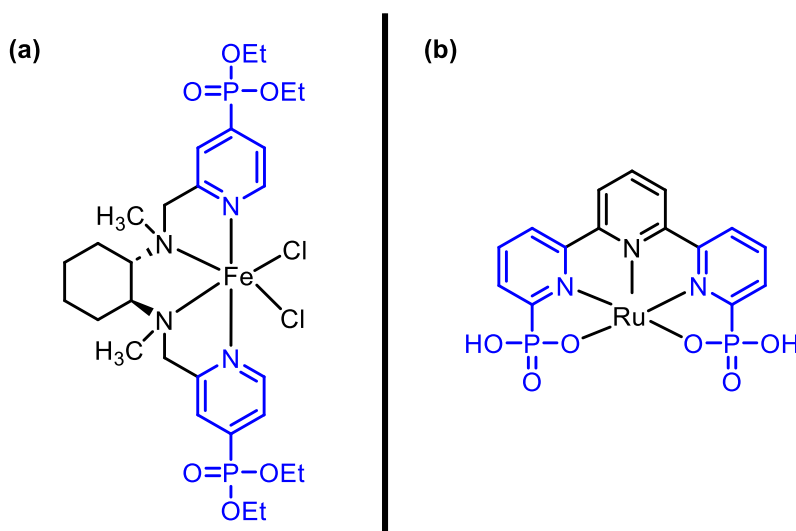
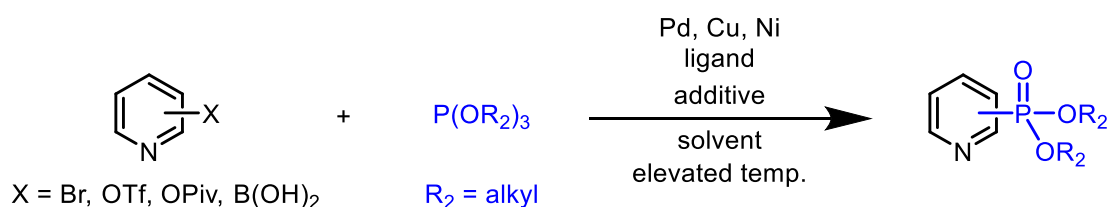


Figure 1.7: (a) Illustrating the dual functionality of pyridyl diethylphosphonate derivatives as metal-coordinating ligands and surface-anchoring groups. Reproduced from Klepser and Bartlett.¹⁷ (b) Pyridyl phosphonic acid ligands, in which the pyridine nitrogen and phosphonate oxygen atoms coordinate simultaneously to a single ruthenium center. Reproduced from Llobet et al.¹⁹

Collectively, these examples underscore the importance of pyridyl phosphonates as multifunctional motifs within medicinal and catalysis chemistry. Their broad utility and growing prominence highlight the need for efficient and general synthetic access to these compounds.

1.3 Existing Strategies for the Synthesis of Pyridyl Phosphonates

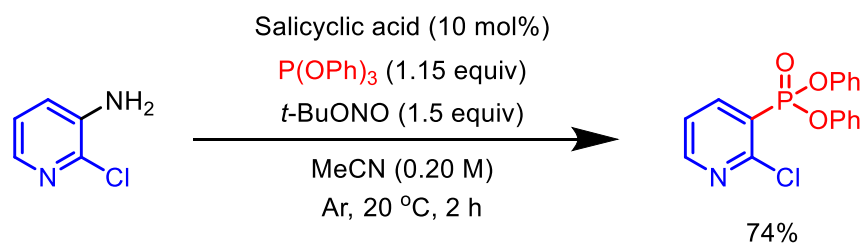
Given their utility, various approaches for the synthesis of pyridyl dialkylphosphonates have been developed.²⁰ Many reported approaches rely on transition-metal-catalyzed substitution of pre-functionalized pyridine substrates, including halides,^{21–23} sulfonates,^{24–26} pivalates,²⁷ or boronic acid derivatives (**Scheme 1.1**).²⁸ These cross-coupling strategies enable installation of the phosphonate group at the C-3 position of the pyridine, which is difficult to access due to the intrinsically non-electrophilic nature of this position. These methods require pre-functionalization, which can increase overall step count and reduce step economy. In addition, the reliance on transition-metal catalysts such as palladium, nickel, or copper can present challenges in pharmaceutical synthesis, where catalyst cost, sustainability, and downstream purification are important considerations.²⁹ The harsh conditions required for efficient cross coupling can reduce the functional group tolerance of the methods.



Scheme 1.1: General transition-metal-catalyzed strategies for the synthesis of pyridyl dialkylphosphonates via substitution of pre-functionalized pyridine substrates.

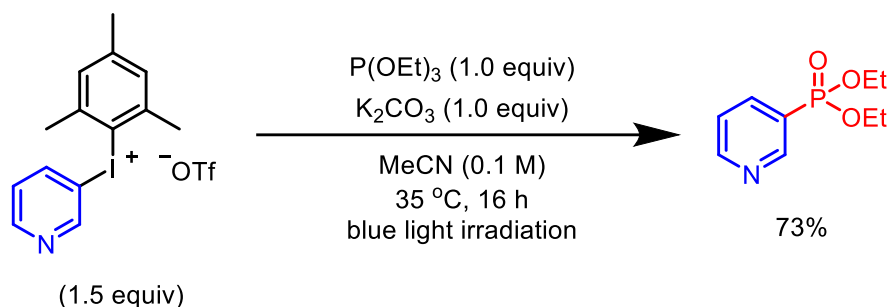
Phosphonylation of diazonium-substituted pyridines represents an alternative, metal-free strategy for C-P bond formation that proceeds through a radical mechanism (**Scheme 1.2**).^{30,31} In these reactions, aminopyridines are first converted into the corresponding diazonium salts, which undergo homolytic cleavage to generate nitrogen gas and the

pyridyl radicals. These radicals can then be intercepted by phosphorus nucleophiles, such as trialkyl phosphites, leading to formation of the corresponding pyridyl phosphonates.³⁰ Importantly, these reactions proceed without the need for transition-metal catalysts and can often be conducted under relatively mild conditions. The requirement for the formation of diazonium salts introduces additional synthetic steps and may present safety and scalability concerns due to the instability of diazonium intermediates.



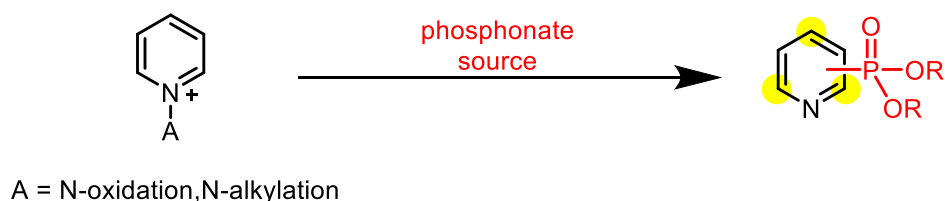
Scheme 1.2: Optimized conditions for radical phosphonylation of diazonium-substituted pyridines using trialkyl phosphites, forming pyridyl phosphonates. Adapted from Gonzalez-Gomez et al.³⁰

Alternatively, pyridyl dialkylphosphonates can be synthesized through photochemical strategies, including photoredox catalysis and irradiation of electron donor-acceptor (EDA) complexes (**Scheme 1.3**).^{32–36} In these methods, visible-light excitation promotes single-electron transfer to generate reactive radical intermediates, enabling C-P bond formation under comparatively mild and metal-free conditions. This approach expands access to a variety of pyridyl phosphonates by circumventing the need for bases or high temperatures typically associated with cross-coupling reactions. However, these transformations often rely on specialized photocatalysts or carefully tuned EDA complexes, which may limit generality and scalability.



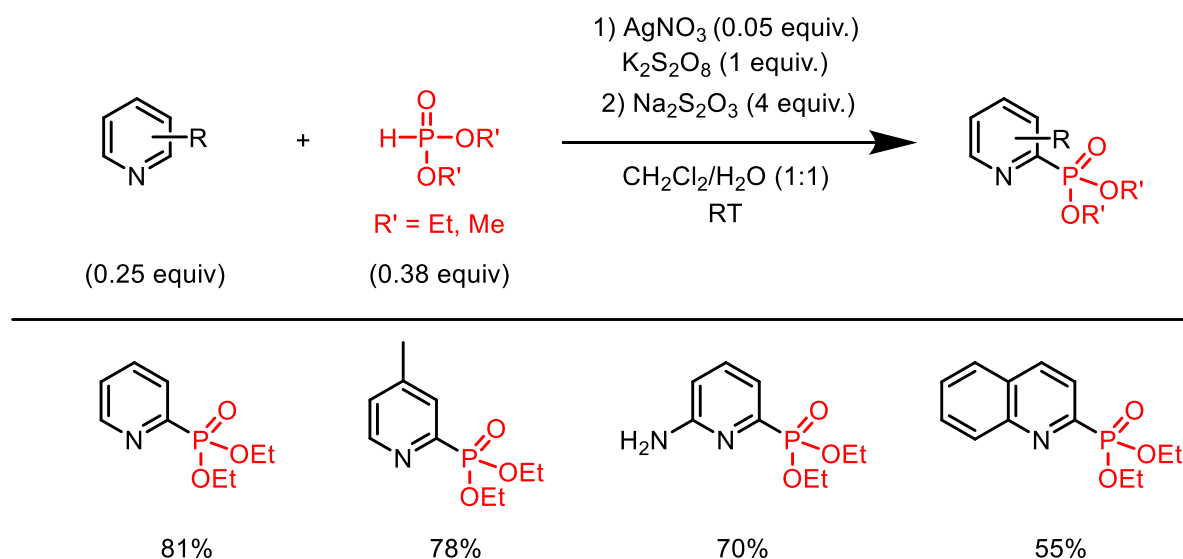
Scheme 1.3: Visible-light-mediated, metal-free phosphonylation of heteroaryl substrates via excitation of EDA complexes, generating radical intermediates that enable C–P bond formation. Adapted from Lakhdar et al.³²

An alternative strategy for the synthesis of pyridyl phosphonates involves temporary activation of the pyridine nitrogen, either through oxidation to the corresponding N-oxide³⁷ or through N-alkylation³⁸ to form a pyridinium intermediate (**Scheme 1.4**). In these approaches, activation of the pyridine ring increases the electrophilicity of the pyridine ring, enabling nucleophilic addition of phosphorus reagents such as trialkyl phosphites, followed by elimination to furnish the pyridyl phosphonate. As a consequence of the electronic effects introduced by N-activation, phosphonylation typically occurs at the C-2, C-4, or C-6 positions of the pyridine, where positive charge density is most effectively stabilized in the activated pyridine system. While these methods provide metal-free access to phosphonylated pyridines under relatively mild conditions, they generally require additional steps to install and subsequently remove the activating group.



Scheme 1.4: Strategies for pyridine activation via formation of pyridine N-oxides or N-alkyl pyridinium intermediates, enabling subsequent nucleophilic phosphonylation.

Phosphonylation of unactivated pyridines can be achieved through Minsci-type radical reactions, which enable direct C–H functionalization without pre-functionalization or N-activation of the pyridine (**Scheme 1.5**).³⁹ A suggested mechanism involves the oxidation of Ag(I) to Ag(II) via potassium persulfate, which in turn promotes single-electron oxidation of trialkyl phosphite to generate an cationic phosphonyl radical.³⁹ The resulting phosphonyl then undergoes electrophilic addition to the pyridine substrate, forming a cation radical intermediate.³⁹ This intermediate lose a hydrogen, an electron, and another hydrogen to afford the phosphonylated pyridine product.³⁹ The need for stoichiometric oxidants, an expensive silver catalyst and acidic, radical-generating conditions can limit functional-group tolerance and scalability of the method.



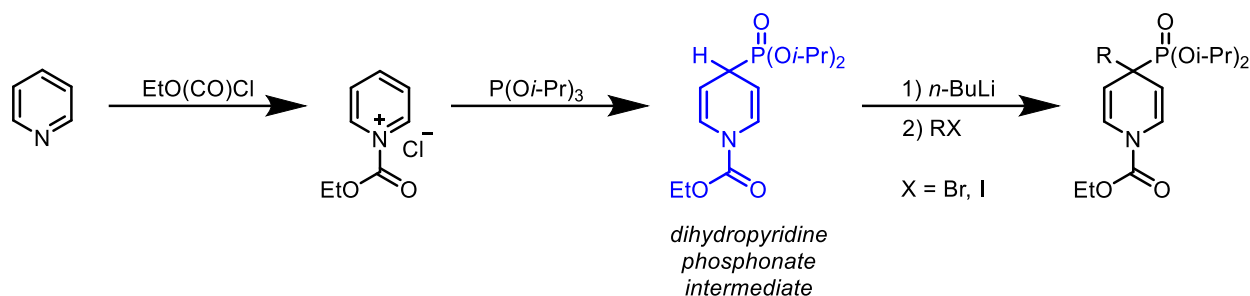
Scheme 1.5: Select examples of Minisci-type radical phosphonylation of unactivated pyridines under silver catalysis, enabling C–P bond formation by Huang.³⁹

Collectively, these existing synthetic strategies to accessing pyridyl phosphonates are constrained by a variety of limitations. Transition-metal-catalyzed cross-coupling strategies require pre-functionalized substrates, precious or toxic metal catalysts, and

reaction conditions that can reduce functional-group tolerance. Metal-free alternatives, including diazonium-based radical phosphonylation and photochemical methods, alleviate some sustainability concerns but often rely on unstable intermediates, specialized catalysts and finely tuned reaction parameters that limit scalability and generality. N-activation strategies provide mild access to phosphonylated pyridines but introduce additional steps to install and remove activating groups. Minisci-type phosphonylation enables direct C–H functionalization of unactivated pyridines depended on stoichiometric oxidants and expensive silver catalysts. These limitations highlight the need for synthetic methods that combine mild conditions, broad functional-group tolerance, and while avoiding pre-functionalization or reliance on precious metals.

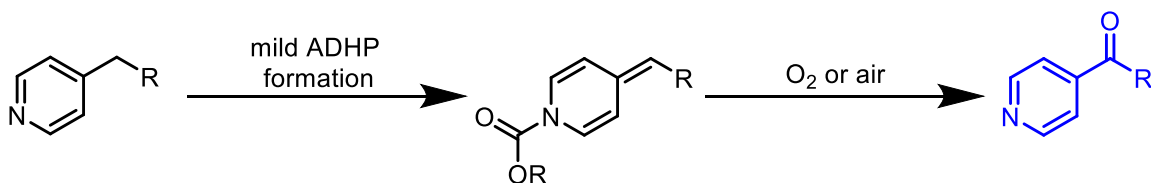
1.4 A New Approach to Pyridyl Phosphonates

Guided by our group's emphasis on sustainability and practicality, we identified a clear unmet need for a practical synthetic methodology to access pyridyl phosphonates. In Stevens' review of *Direct Phosphonylation of Aromatic Azaheterocycles*, a key opportunity was highlighted.²⁰ In 1981, Akiba and co-workers reported the regioselective synthesis of 4-alkylpyridines via alkylation of diisopropyl 1-ethoxycarbonyl-1,4-dihydropyridine-4-phosphonate.⁴⁰ This phosphonate intermediate is generated through reaction of pyridine with a chloroformate reagent, followed by addition of a trialkyl phosphite (**Scheme 1.6**).⁴⁰



Scheme 1.6: Akiba's chloroformate-mediated formation of dihydropyridine diisopropylphosphonate intermediates from pyridine.⁴⁰

Stevens' notes, that no attempt was made to rearomatize the resulting dihydropyridine phosphonate (DHPP), and its potential as a direct precursor to pyridyl phosphonates was not explored.²⁰ In our work exploring the reactivity of alkylidene dihydropyridines (ADHPs) we noted that they undergo rearomatization upon exposure to air or molecular oxygen to form 4-acyl pyridines (**Scheme 1.7**).⁴¹



Scheme 1.7: ADHP oxidation to form 4-acyl pyridines.

We therefore reasoned that analogous dihydropyridine phosphonate intermediates, when exposed to aerobic conditions, should undergo similar rearomatization to directly affording pyridyl phosphonates. If successful, this approach would represent an exceptionally mild, selective, practical, and sustainable route to pyridyl phosphonates. This synthetic strategy relies on the use of inexpensive reagents while avoiding harsh conditions or precious-metal catalysts. The central aim of this work is to develop a

sustainable, and practical methodology for the functionalization of pyridines, with a emphasis on the efficient synthesis of pyridyl phosphonates.

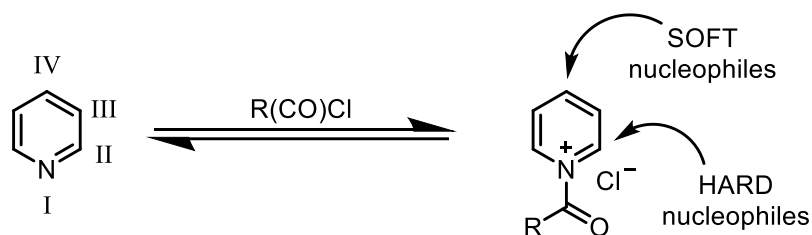
Chapter II: Synthesis of Pyridyl Phosphonates

2.1 Proposed Strategy

Despite the variety of methods to access pyridyl phosphonates, general and sustainable synthetic strategies remain limited. These limitations underscore the need for new synthetic approaches that are operationally simple, cost-effective, and broadly applicable to diverse pyridine scaffolds. We aimed to access DHPP intermediates that could be readily oxidized to the corresponding rearomatized pyridyl phosphonates. Prior work from our group, regarding the stability and reactivity of ADHPs provided valuable guidance. Notably, this study demonstrated that ADHPs generated from ethyl chloroformate were the most prone to decomposition to the corresponding acyl-pyridine like products, consistent with enhanced susceptibility toward oxidation and rearomatization.⁴² By analogy, we anticipated that DHPPs formed via ethyl chloroformate (or chloroformates of similar electronic properties) activation would exhibit the greatest propensity for oxidation, thereby increasing the likelihood of efficient rearomatization to the desired pyridyl phosphonates. Additionally, N-acyl pyridinium salts are also more electrophilic than N-alkyl pyridinium salts due to increased activation of the π -system making it suitable for the following nucleophilic addition step.⁴³

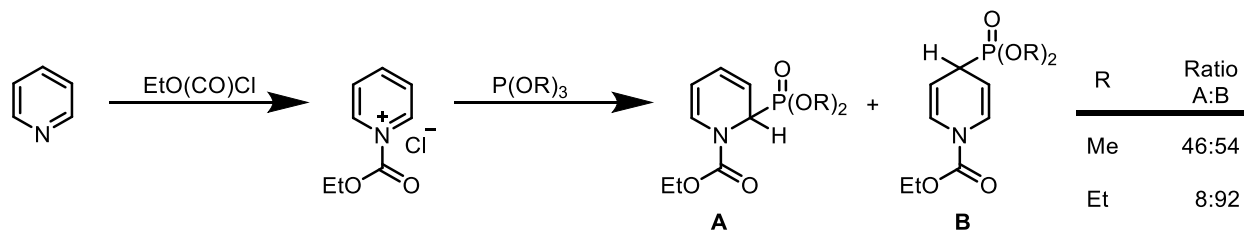
N-activation of pyridines generates a pyridinium-like electrophile in which the ring becomes susceptible to nucleophilic addition, with the largest electrophilic character expressed at the C-2 and C-4 positions. In such systems, regioselectivity is often governed by a nucleophile “hardness”, hard nucleophiles preferentially undergo 1,2-addition, whereas softer nucleophiles favor 1,4-addition (**Scheme 2.1**).⁴³ Trialkyl phosphites are classified as soft nucleophiles according to hard/soft acid/base (HSAB)

theory due to the large, polarizable phosphorus-centered lone pair of electrons. Consistent with this classification, phosphites react preferentially with soft electrophiles such as alkyl iodides and bromides in the Michaelis–Arbuzov reaction, with reactivity decreasing for harder electrophiles ($R-I > R-Br > R-Cl > R-F$).⁴⁴ Accordingly, we anticipated that using a trialkyl phosphite would preferentially add to the 4-position, providing a basis for the observed regioselective formation of 4-substituted dihydropyridine phosphonate intermediates.



Scheme 2.1: General reactivity trends of hard and soft nucleophiles toward acyl-activated pyridines.

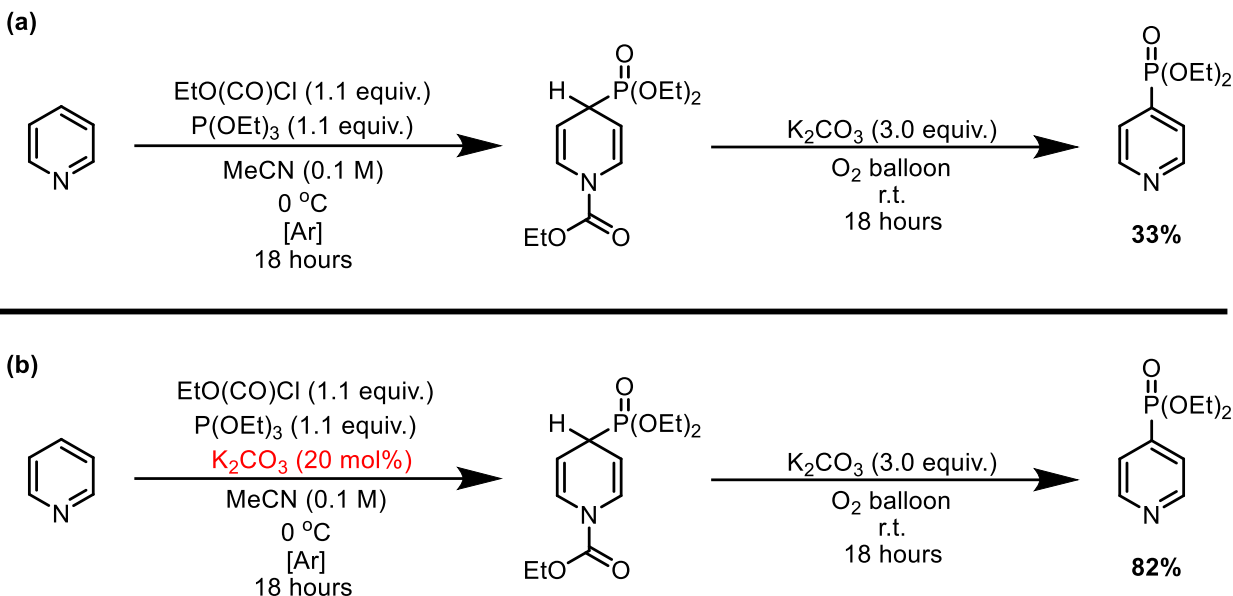
Additionally, the alkyl substituent on the trialkyl phosphite was expected to influence regioselectivity, as reported by Akiba and co-workers.⁴⁰ They observed that activation with ethyl chloroformate followed by reaction with trimethyl phosphite afforded a 1:1 mixture of 2-pyridyl and 4-pyridyl phosphonates, whereas the use of triethyl phosphite resulted in near exclusive formation of the 4-pyridyl phosphonate (**Scheme 2.2**).⁴⁰ On this basis, triethyl phosphite was selected as the phosphorus source in this study to maximize regioselective C-4 functionalization.



Scheme 2.2: Influence of trialkyl phosphite nucleophile sterics on regioselectivity on chloroformate-activated pyridine phosphonylation. Adapted from Akiba et al.⁴⁰

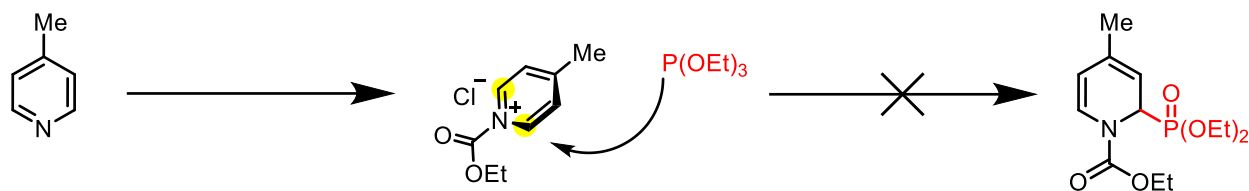
2.2 Reaction Development

Reaction development began by treating pyridine with ethyl chloroformate followed by triethyl phosphite in MeCN at 0 °C under an inert atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight, affording the corresponding dihydropyridine phosphonate intermediate. In a one-pot fashion, potassium carbonate was added, followed by sparging the reaction mixture with an oxygen-filled balloon and allowing the reaction to proceed overnight, affording the corresponding 4-pyridyl phosphonate in 33% yield (**Scheme 2.3a**). We hypothesized that the low yield resulted from hydrolysis of ethyl chloroformate under humid laboratory conditions, leading to formation of hydrochloric acid. To mitigate this, 20 mol % potassium carbonate was incorporated into the reaction mixture prior to activation with our chloroformate to neutralize adventitious acid. Under otherwise identical one-pot oxidation conditions, this adjustment significantly improved the yield of the desired product to 82% (**Scheme 2.3b**). Additionally, exclusive formation of the 4-pyridyl phosphonate was observed, with no detectable 2-pyridyl phosphonate regioisomer, demonstrating that the developed protocol is regioselective for simple pyridine.



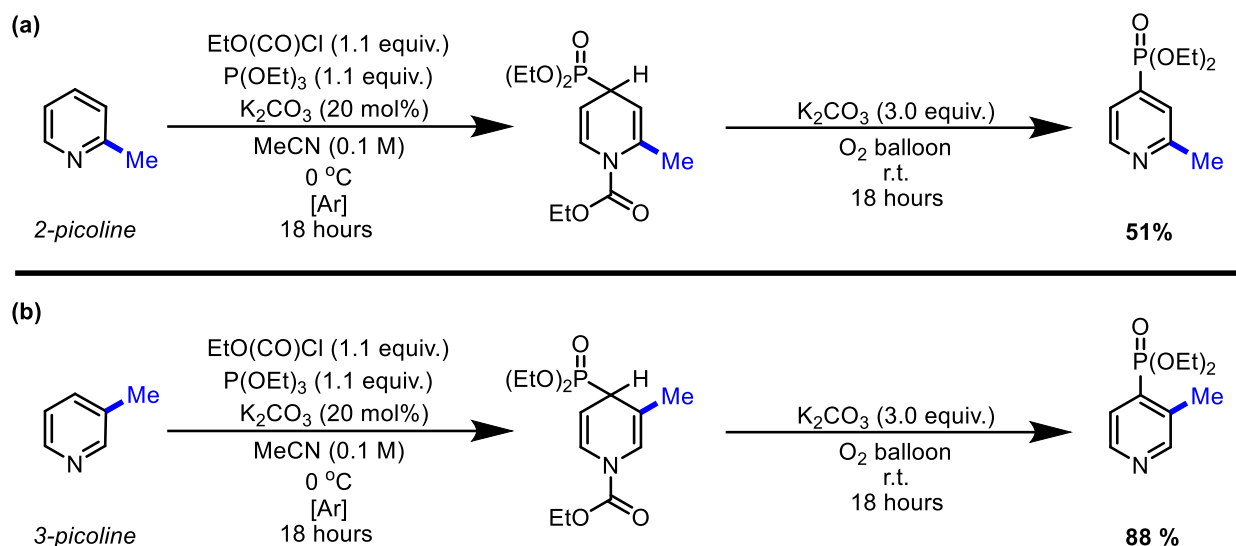
Scheme 2.3: Development of a one-pot chloroformate-mediated pyridine phosphonylation and oxidative rearomatization protocol. **(a)** Initial conditions afforded 4-pyridyl diethylphosphonate in isolated yield of 33%. **(b)** Addition of potassium carbonate prior to activation significantly improved the isolated yield to 82%.

Encouraged by the successful application of our method to unsubstituted pyridine, we sought to evaluate its generality across a range of substituted pyridines. To assess the applicability of the optimized conditions, we examined 2-picoline, 3-picoline, and 4-picoline as substrates. For 4-picoline, we hypothesized that nucleophilic addition would occur preferentially at the C-2 position, as the C-4 position is blocked by the methyl substituent. However, upon subjecting 4-picoline to the optimized DHPP formation conditions, we were unable to observe formation of the corresponding DHPP intermediate. We attribute this outcome to steric hindrance imposed by the chloroformate activating group, which increases congestion at the C-2 position of the pyridinium intermediate (**Scheme 2.4**). This steric encumbrance likely prevents the phosphite nucleophile from accessing the C-2 position, thereby inhibiting dihydropyridine formation.



Scheme 2.4: Steric inhibition of DHPP formation from 4-picoline under chloroformate activation conditions.

When treating 2-picoline under our optimized reaction conditions, we anticipated nucleophilic addition at the C-4 position, as the C-2 electrophilic site is blocked by the methyl substituent. Under these conditions, full conversion to the corresponding dihydropyridine phosphonate (DHPP) intermediate was not achieved. Nevertheless, the crude reaction mixture was carried forward to the oxidative rearomatization step, affording the corresponding 4-pyridyl phosphonate in 51% isolated yield (**Scheme 2.5a**). The incomplete conversion to the DHPP intermediate can be rationalized by steric hindrance from the C-2 methyl substituent, which can impede efficient N-activation of the pyridine ring, thereby reducing the extent of nucleophilic addition.⁴⁵ In contrast, 3-picoline showed complete conversion to the DHPP intermediate and performed efficiently under the oxidative rearomatization conditions, affording the corresponding 4-pyridyl diethylphosphonate in 88% isolated yield (**Scheme 2.5b**). Encouraged by these results and confident in our optimized conditions, we proceeded to conduct a substrate scope study on a variety of 2- and 3-substituted pyridines.

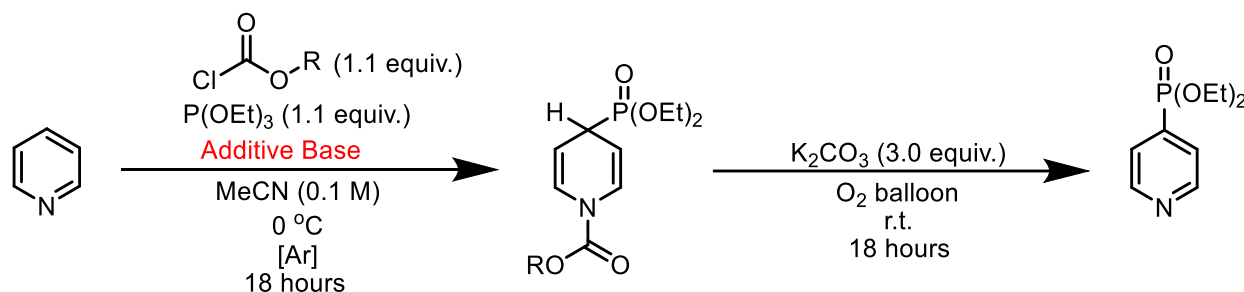


Scheme 2.5: Evaluation of substituted pyridine substrates under the optimized chloroformate-mediated phosphonylation and oxidative rearomatization conditions. **(a)** 2-Picoline afforded isolated yield of 51%. **(b)** 3-Picoline afforded isolated yield of 88%.

During the course of our study, we encountered supply issues with ethyl chloroformate, which prompted its substitution with isobutyl chloroformate, selected for its similar structural and electronic properties. This substitution was made under the assumption that it would exhibit similar reactivity and, comparable yields to those observed for previously tested pyridine substrates. Additionally, we reasoned that the use of potassium carbonate to neutralize adventitious acid would no longer be necessary for this step, as the freshly opened chloroformate reagent was unlikely to contain acidic impurities arising from hydrolysis. Accordingly, a brief optimization study was conducted using pyridine (**Table 2.1**). In the first experiment, ethyl chloroformate was replaced with isobutyl chloroformate while potassium carbonate was retained during DHPP formation (**Table 2.1** - **Entry 3**), affording an isolated yield of 74%. This result indicated that isobutyl chloroformate is a suitable replacement for ethyl chloroformate. Subsequently, the

necessity of the base additive was evaluated by repeating the experiment in the absence of potassium carbonate (**Table 2.1 - Entry 4**), which resulted in an improved isolated yield of 80%. On the basis of these results, isobutyl chloroformate was adopted for subsequent substrate scope studies without the addition of potassium carbonate.

Table 2.1. Optimization of reaction conditions

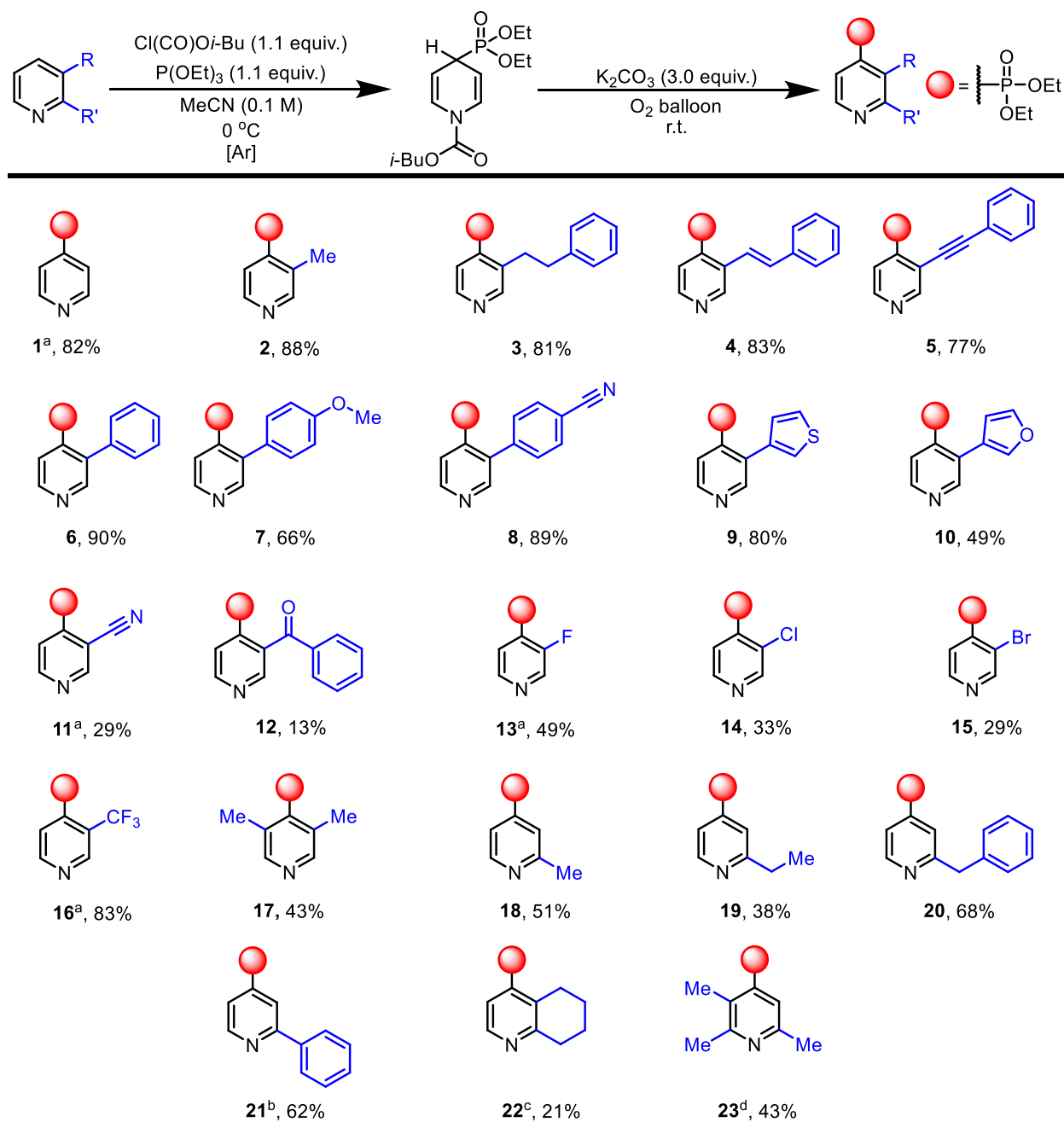


Entry	Chloroformate	Additive Base Present	Pyridyl Phosphonate
		K ₂ CO ₃ (20 mol %)	Isolated % Yield
1	R = Ethyl	NO	33%
2	R = Ethyl	YES	82%
3	R = Isobutyl	YES	74%
4	R = Isobutyl	NO	80%

2.3 Substrate Scope Study

With optimized conditions in hand, we conducted substrate scope studies. A range of 2- and 3-substituted pyridines bearing alkyl, electron-withdrawing, electron-donating, aromatic, and heteroaromatic substituents were subjected to the optimized reaction conditions (**Figure 2.1**). The parent compound (**1**) was prepared in 82% isolated yield. Substitution at the 3-position of the pyridine was tolerated with a wide range of groups. Methyl- (**2**), phenethyl- (**3**), styryl- (**4**) and alkynyl-substituted (**5**) pyridines all provided the desired products in good to excellent yields (77-88%). Aryl substitution at the three-

position of the pyridine was also tolerated. 3-phenyl pyridine provided the corresponding phosphonate (**6**) in 90% yield, and substitution of the phenyl ring with a para-methoxy group (**7**) and with a para-nitrile group (**8**) gave the desired products with isolated yields of 66% and 89% respectively. Pyridines bearing thiophene (**9**) and furan (**10**) rings gave isolated yields of 80% and 49%. These heteroaromatic scaffolds are of particular interest due to the incorporation of thiophene and furan motifs in bioactive small molecules and FDA-approved pharmaceuticals.^{46–48} Thiophene-containing compounds have been reported across diverse therapeutic areas, including anticancer, anti-inflammatory, and anticonvulsant agents.⁴⁶ Similarly, furan-containing heterocycles are frequently employed as phenyl bioisosteres and appear in numerous natural products and drug candidates.^{47,48} The incorporation of thiophene and furan substituents into pyridyl phosphonate frameworks therefore provides access to structurally complex and medically relevant scaffolds for potential downstream biological study. Notably, the pyridines bearing electron-rich aromatic substituents (**7** and **10**) gave slightly diminished yields.

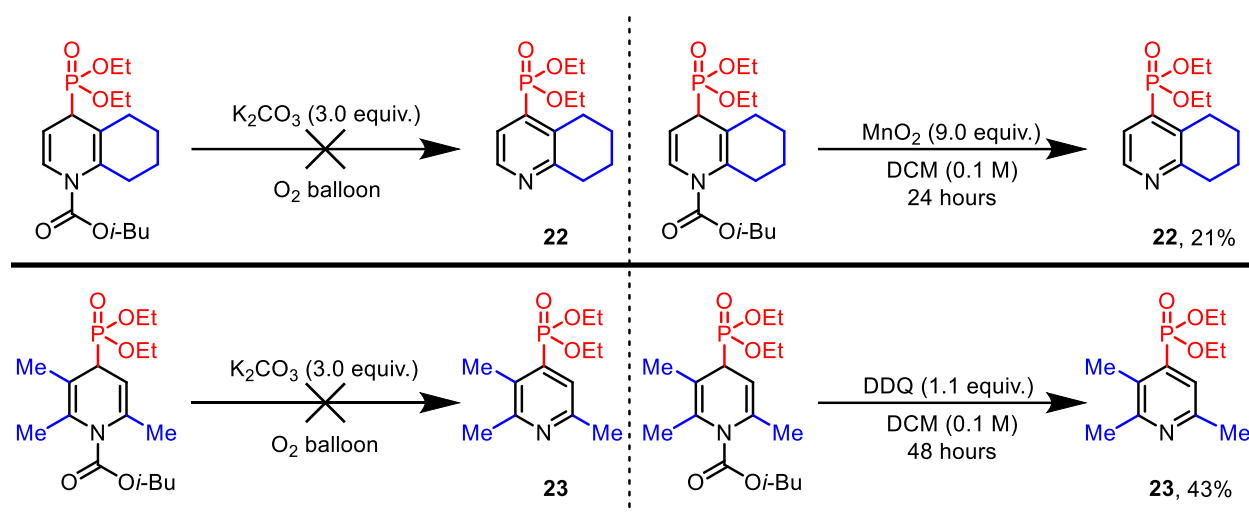


^a reaction completed using ethyl chloroformate, ^b product **21** is formed via alternative methods (see Section 3.3), ^c product **22** is oxidized using MnO_2 (9.0 equiv.) in DCM (0.1 M) over 24 hours (see Section 3.3) ^d product **23** is oxidized using DDQ (1.1 equiv.) in DCM (0.1 M) over 48 hours (see Section 3.3)

Figure 2.1: Substrate scope – 4-pyridyl diethylphosphonates.

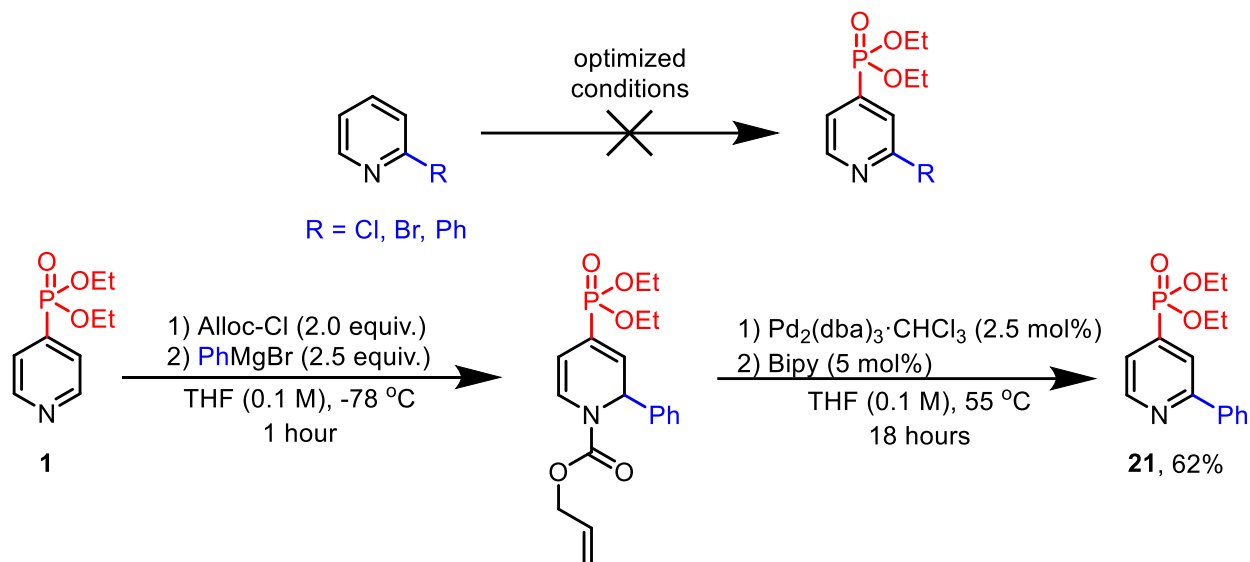
Pyridines bearing strongly electron-withdrawing substituents, such as nitrile (**11**) and benzoyl (**12**) groups at the 3-position, afforded the expected products in considerably lower yields (29% and 13%, respectively). This trend is consistent with attenuation of pyridine nitrogen nucleophilicity and basicity, which disfavors efficient N-activation. 3-substituted halopyridines, including 3-fluoro- (**13**), 3-chloro- (**14**), and 3-bromopyridine (**15**), provided the desired phosphonates in modest yields of 49%, 33%, and 29%, respectively. 3-trifluoromethylpyridine (**16**) and 3,5-dimethylpyridine afforded the corresponding phosphonates (**17**) in good and modest yields of 83% and 43%, respectively.

In contrast, dearomatization of 2-substituted pyridines using N-activating groups such as chloroformates is generally challenging and often requires forcing conditions.⁴⁹ We therefore evaluated the performance of our mild conditions on this class of substrates. Pyridine phosphonates derived from 2-methyl- (**18**), 2-ethyl- (**19**), and 2-benzylpyridine (**20**) were obtained, albeit in modest yields, consistent with steric and electronic deactivation adjacent to the pyridine nitrogen. The synthesis of pyridine phosphonates from tetrahydroquinoline (**22**) and 2,3,5-trimethylpyridine (**23**) proved challenging because the corresponding dihydropyridine phosphonate intermediates were resistant to oxidative rearomatization under our standard conditions and required stoichiometric oxidants to afford the desired products (**Scheme 2.6**).



Scheme 2.6: Oxidatively resistant dihydropyridine diethylphosphonate intermediates derived from tetrahydroquinoline and 2,3,5-trimethylpyridine.

Notably, 2-chloro-, 2-bromo-, and 2-phenylpyridine were unreactive under the optimized conditions, as we were unable to form the corresponding DHPP intermediates. This lack of reactivity is consistent with steric congestion at the 2-position, which hinders effective N-activation.⁴⁹ Additionally, this trend aligns with attenuation of pyridine nitrogen nucleophilicity and basicity in these substrates, which further disfavors efficient N-activation, particularly in the case of the chloro- and bromo-substituted pyridines.⁴⁹ However, we observed that we could overcome this challenge through a post - dearomatization modification strategy where functionalization at the 2-position occurs after installing the phosphonate group on the pyridine substrate.⁵⁰ Activation of the parent phosphonate (**1**) with allyl chloroformate followed by treatment with a hard nucleophile, such as phenylmagnesium bromide, enabled selective C-2 functionalization, and subsequent oxidation afforded product (**20**) in 62% isolated yield. This strategy provides a general approach to access 2-substituted 4-pyridyl phosphonates from the parent compound intermediate (**Scheme 2.7**).



Scheme 2.7: Post-functionalization strategy for C-2 substitution of 4-pyridyl phosphonates via allyl chloroformate activation, Grignard addition, followed by oxidative rearomatization to afford 2-substituted pyridyl phosphonates. Application of this protocol to parent compound (**1**) furnished product (**21**) in 62% isolated yield.

2.4 Conclusion

Given the established utility of pyridyl phosphonates, the development of mild and regioselective methods to access these value-added scaffolds presents significant opportunities for further synthetic and medicinal chemistry applications. Building on our previous work in pyridine functionalization, we report a practical one-pot strategy for the synthesis of 4-pyridyl phosphonates from simple pyridines. This approach exploits the inherent electrophilicity of the C-4 position in chloroformate-activated pyridinium intermediates, which undergo nucleophilic addition by trialkyl phosphites followed by oxidative rearomatization. Notably, this transformation proceeds under mild, metal-free conditions and does not require photoredox catalysis or prefunctionalized substrates. The methodology demonstrates broad functional-group tolerance, accommodating alkyl, aryl,

heteroaryl, and halogen substituents at the C-3 position in good yields. Although 2-substituted pyridines exhibited reduced reactivity to our optimized conditions, several examples were successfully synthesized. In addition, a complementary post-functionalization strategy enabled selective C-2 substitution of 4-pyridyl phosphonates, providing access to 2-substituted pyridyl phosphonate scaffolds. Overall, the methodology offers operational simplicity, high regioselectivity, and broad functional-group tolerance, and provides a versatile foundation for the synthesis of pyridyl diethylphosphonates with potential applications in medicinal chemistry, catalysis, and materials science.

Chapter III: Experimental Protocols and Compound Data

3.1 General Experimental

All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon. Triethylamine (Et_3N) and diisopropylamine ($i\text{-Pr}_2\text{NH}$) were distilled from CaH_2 prior to use. Tetrahydrofuran (THF), acetonitrile (CH_3CN) and diethyl ether (Et_2O) were dispensed from an Inert PureSolv solvent purification system. Commercial reagents were used as received. Thinlayer chromatography (TLC) was performed on SiliCycle® silica gel 60 F₂₅₄ plates. Visualization was carried out using UV light (254 nm) and/or KMnO_4 , $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, vanillin, or anisaldehyde solutions. Hexanes (ACS grade), acetone (ACS grade) and ethyl acetate (ACS grade) were used as received. Flash column chromatography⁵¹ was carried out using a glass column packed with SiliCycle® SiliaFlash® silica gel (230-400 mesh, 40- 63 μ , 60 Å pore size) or Buchi® Pure C810 flash chromatography system. ^1H -NMR, ^{19}F -NMR, ^{31}P -NMR and ^{13}C -NMR spectra were recorded on a Bruker 300 AV, Bruker 400 AV, Bruker 600 or Bruker 700 AV spectrometer in chloroform- d (99.8 % deuterated), benzene- d_6 (99.6 % deuterated), dichloromethane- d_2 (99.5 % deuterated) or acetonitrile- d_3 (99.8 % deuterated). All ^{31}P -NMR spectra were externally referenced to a capillary of 85% phosphoric acid in CDCl_3 . NMR data acquisition and processing was carried out using TopSpin 4.2. Chemical shifts (δ) are reported in ppm and calibrated using the chemical shift of the residual nondeuterated solvent (**^1H -NMR:** CDCl_3 : δ 7.26, CD_2Cl_2 : δ 5.30, C_6D_6 : δ 7.16, CD_3CN : δ 1.94 **^{13}C -NMR:** CDCl_3 : δ 77.16, CD_2Cl_2 : δ 53.84, C_6D_6 : δ 128.06, CD_3CN : δ 1.32). Coupling constants J are reported in Hertz (Hz) and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dq (doublet of quartet), td (triplet of doublets), tt (triplet of triplet), dd (doublet of doublets), dddd (doublet of doublet of doublet of doublets), m (multiplet), br (broad)⁵². Infrared (IR) spectra were recorded as thin films (neat) using AlphaPlatinum ATR, Bruker, diamond crystal FTIR instrument. High-resolution mass spectra were collected on Agilent 6230 ESI TOF instrument at York University.

General Procedure (A): Preparation of Dihydropyridine Phosphonates (DHPP)

The pyridine substrate was dissolved in acetonitrile (0.1 M) in an oven-dried round-bottom flask equipped with a stir bar. The flask was placed under an inert atmosphere using an argon filled balloon and cooled to 0 °C using an ice water bath. Isobutyl or ethyl chloroformate (1.1 equiv.) was added dropwise, and the mixture was stirred at 0 °C for 1 h. Triethyl phosphite (1.1 equiv.) was then added dropwise at 0 °C, and the reaction was allowed to warm to room temperature while stirring. Formation of the dihydropyridine phosphonate (DHPP) intermediate was monitored by TLC (visualized via 254 nm UV light and KMnO_4 staining). If conversion was incomplete, the mixture was heated to 50 °C until full consumption of the pyridine substrate or until the reaction stalled. The reaction mixture was then subjected to **General Procedure B** to afford the corresponding 4-pyridyl phosphonate.

General Procedure (B): Synthesis of 4-Pyridyl Phosphonates via DHPPs

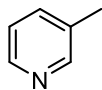
Procedure B was carried out sequentially in a one-pot fashion without isolation of the dihydropyridine phosphonate intermediate. Oven-dried K_2CO_3 (3 equiv.) was added to the reaction mixture containing the DHPP intermediate. The reaction mixture was sparged using an O_2 balloon to establish an oxygenated atmosphere. The mixture was stirred at room temperature for 18 hours while monitoring the consumption of the intermediate by TLC (visualized via 254 nm UV light and KMnO_4 staining). If the oxidation stalled, the mixture was heated to 50 °C. Upon completion or stalling, the mixture was extracted with EtOAc, filtered through a cotton plug to remove residual K_2CO_3 , and the filtrate was washed with brine. The organic layer was dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography using a gradient of 0→100% EtOAc/hexanes.

3.2 NMR Spectra of Substrates

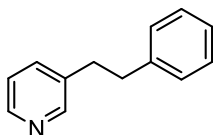
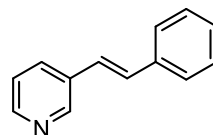
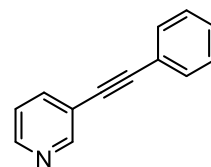
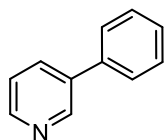
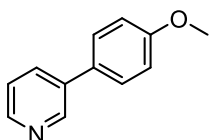
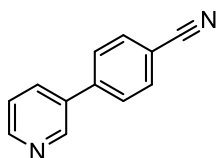
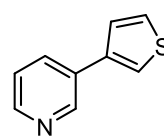
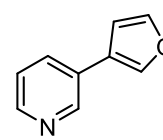
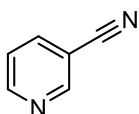
Summary of Substrates

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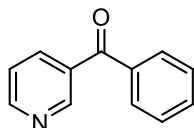
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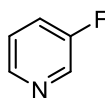
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**S3****S4****S5****S6****S7****S8****S9****S10****S11**

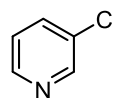
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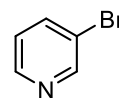
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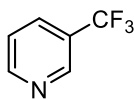
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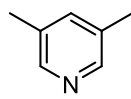
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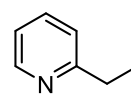
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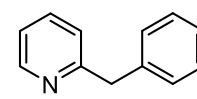
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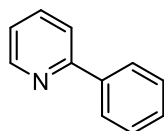
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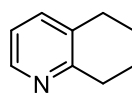
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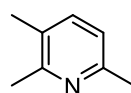
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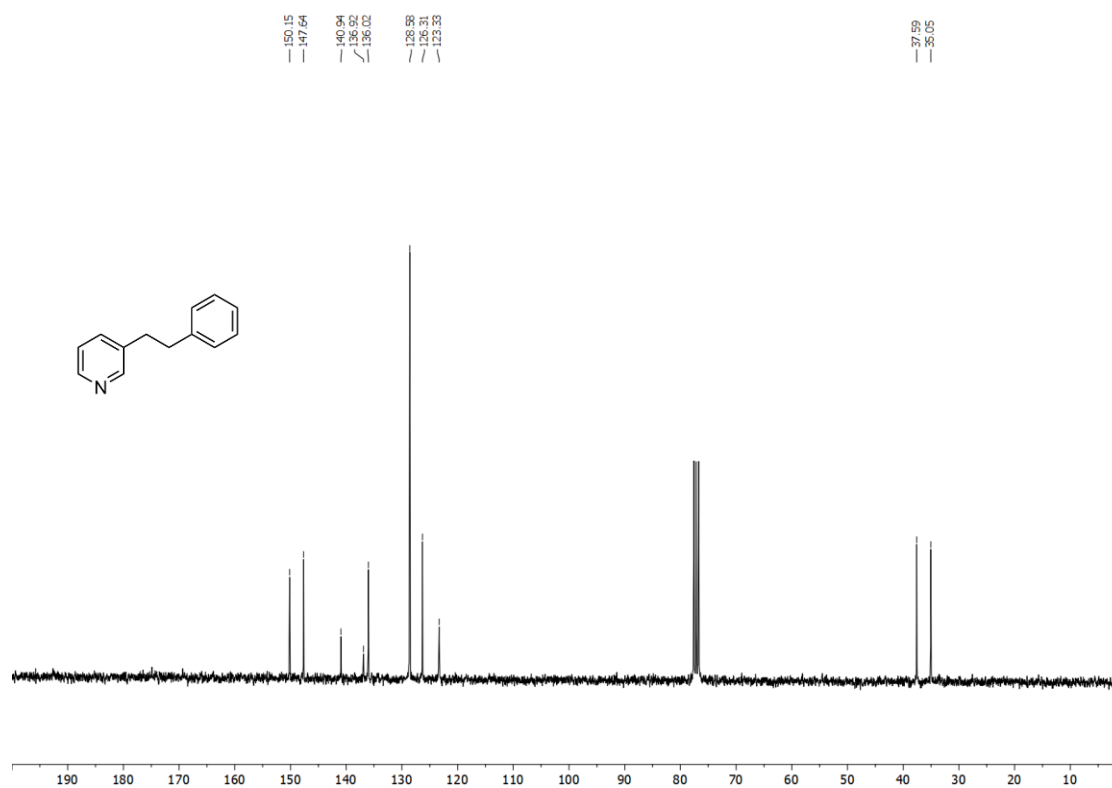
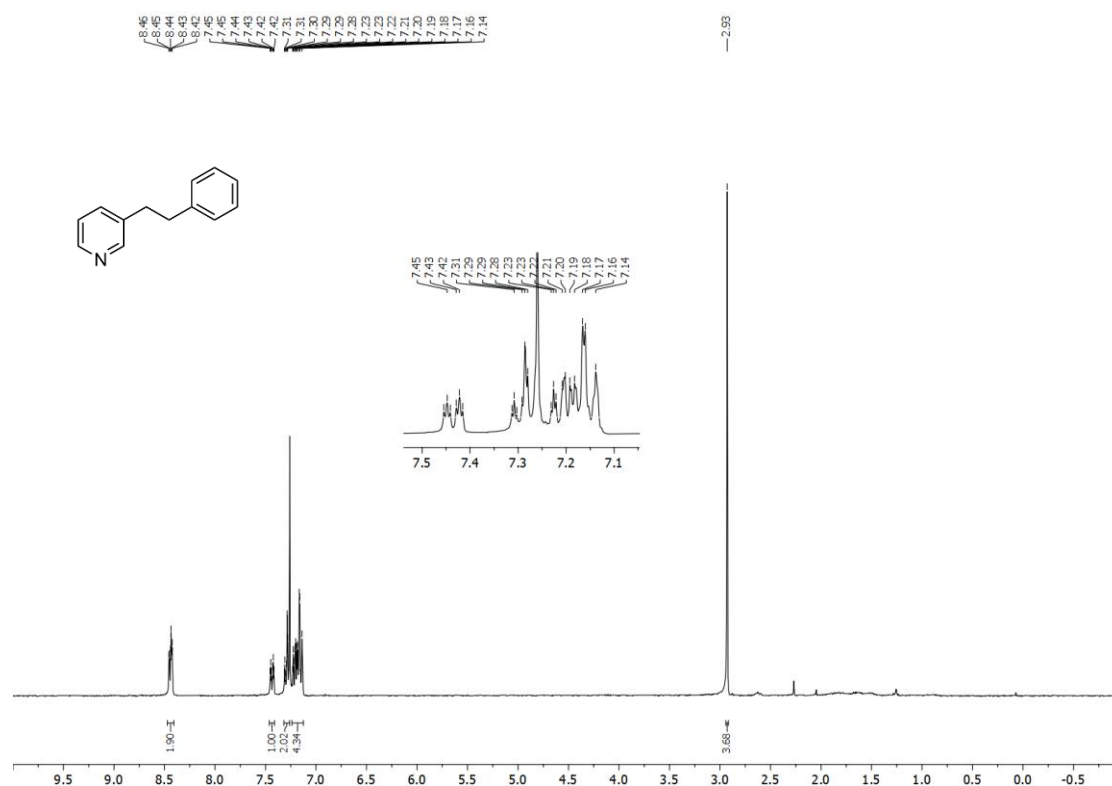
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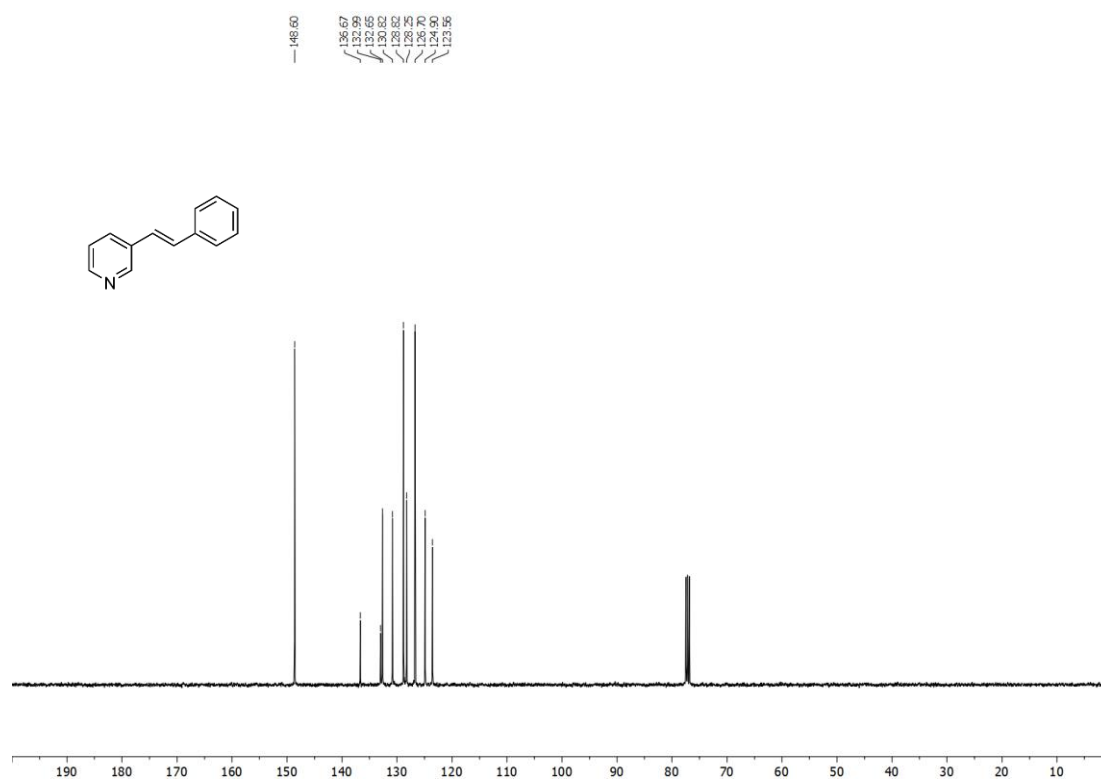
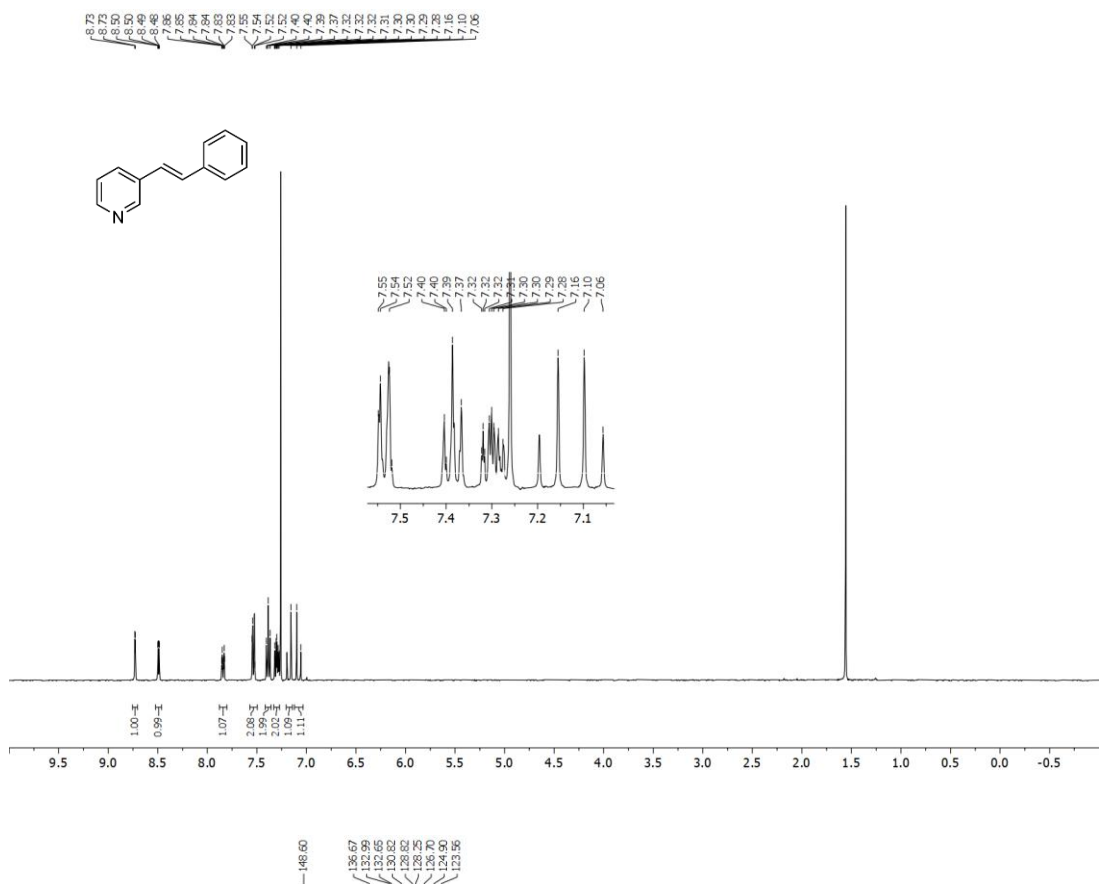
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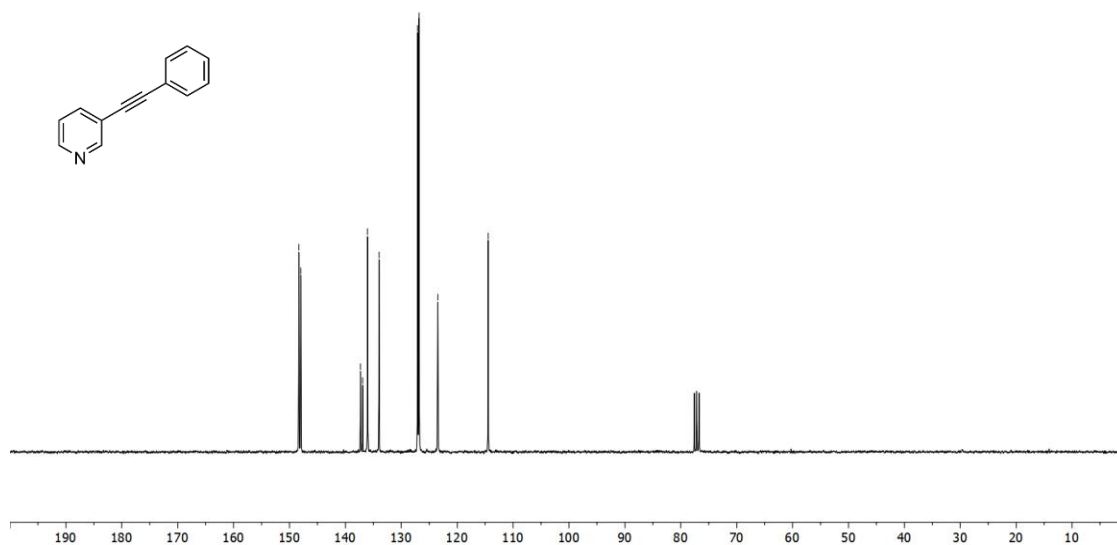
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^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **S3**⁵³

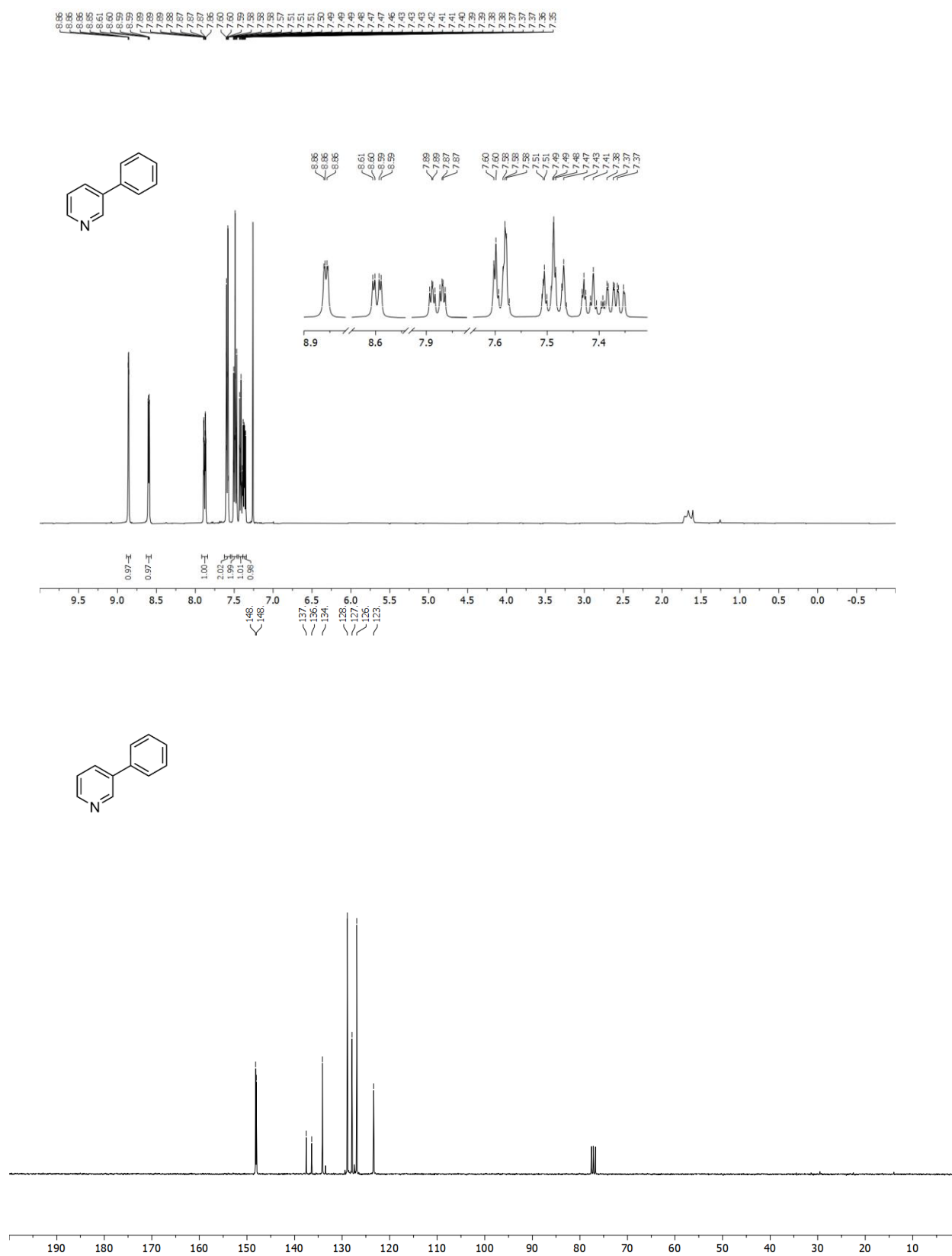


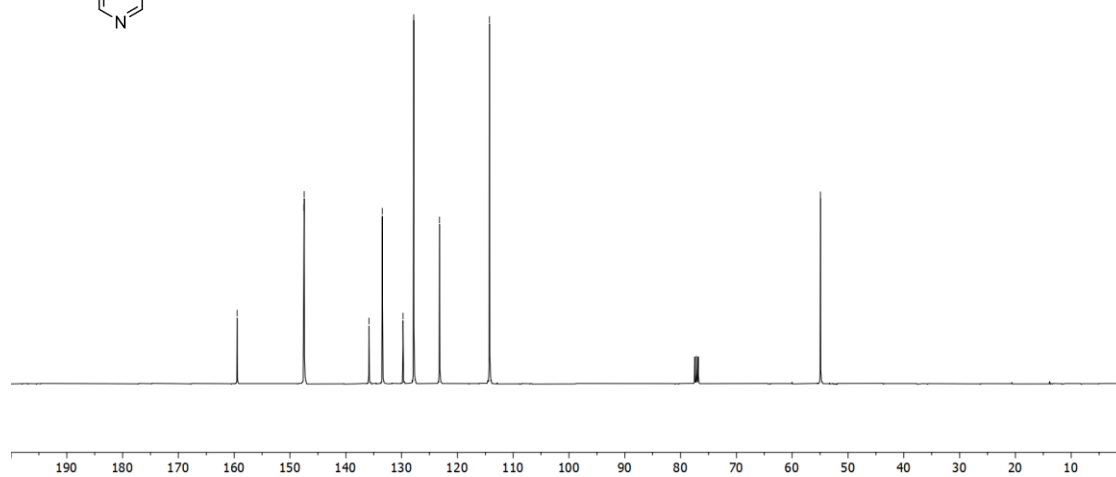
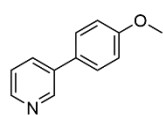
^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **S4**⁵⁴

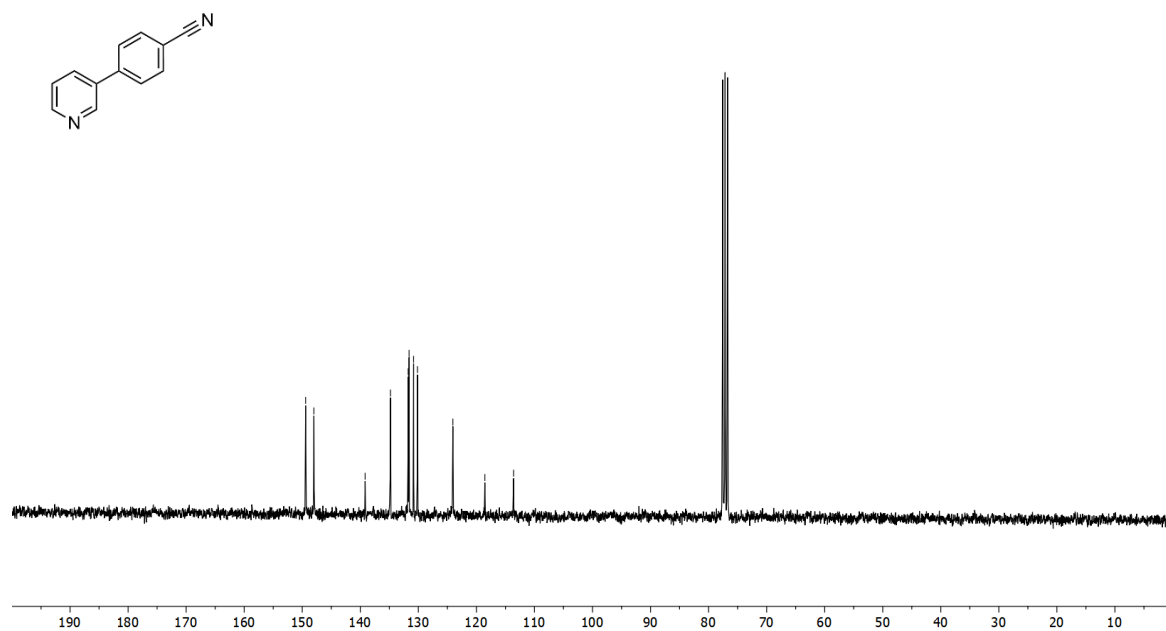




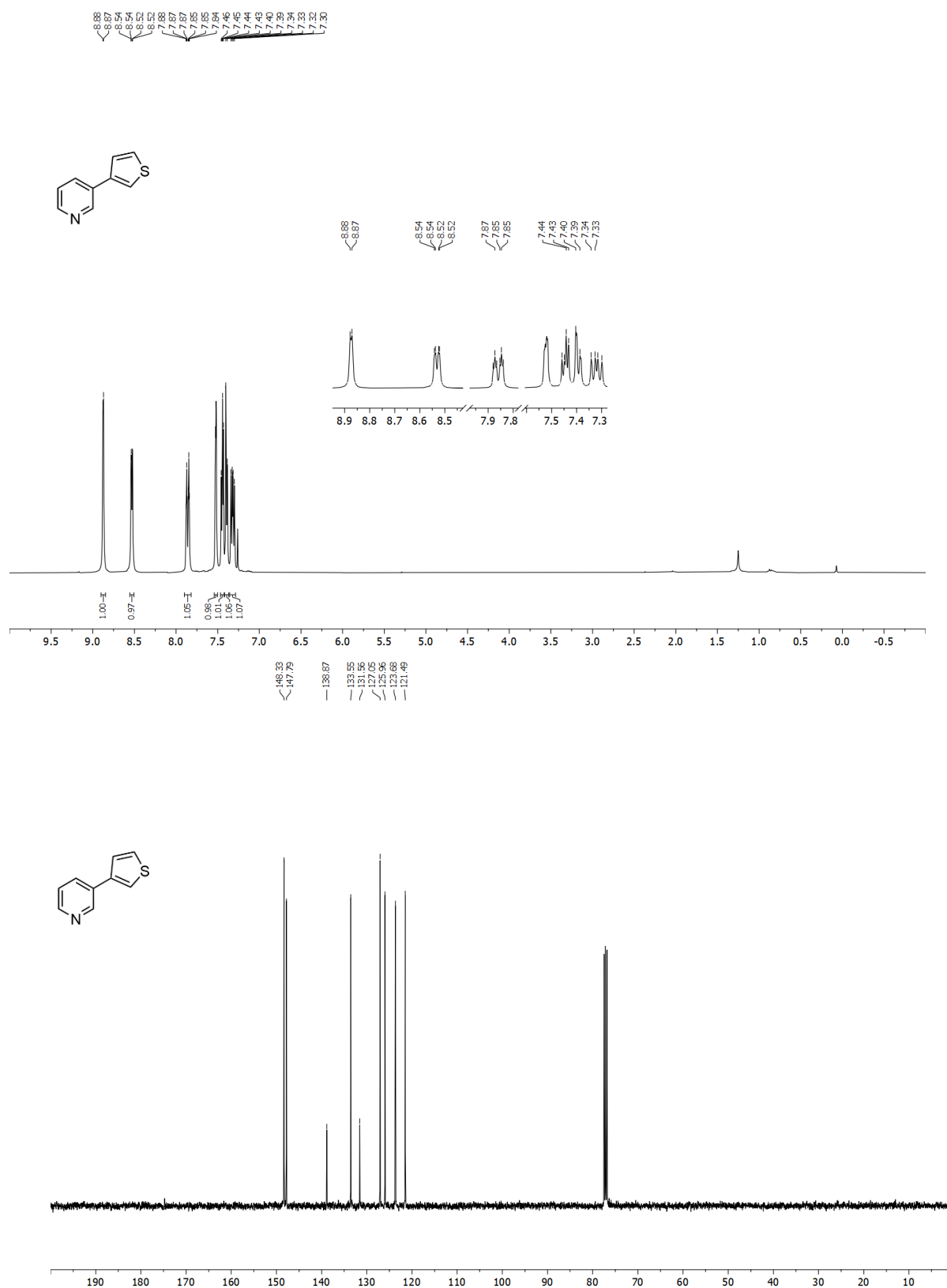
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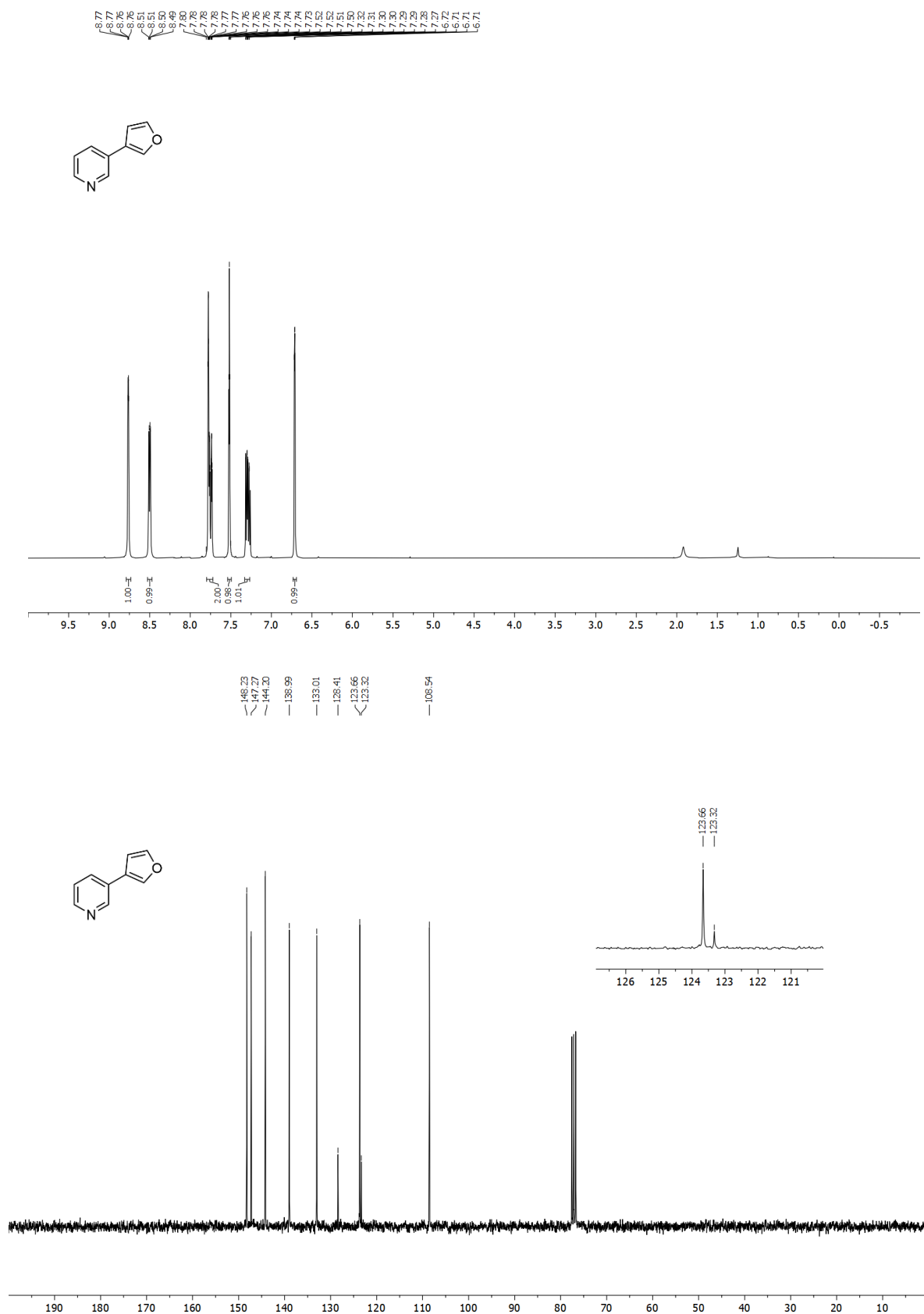




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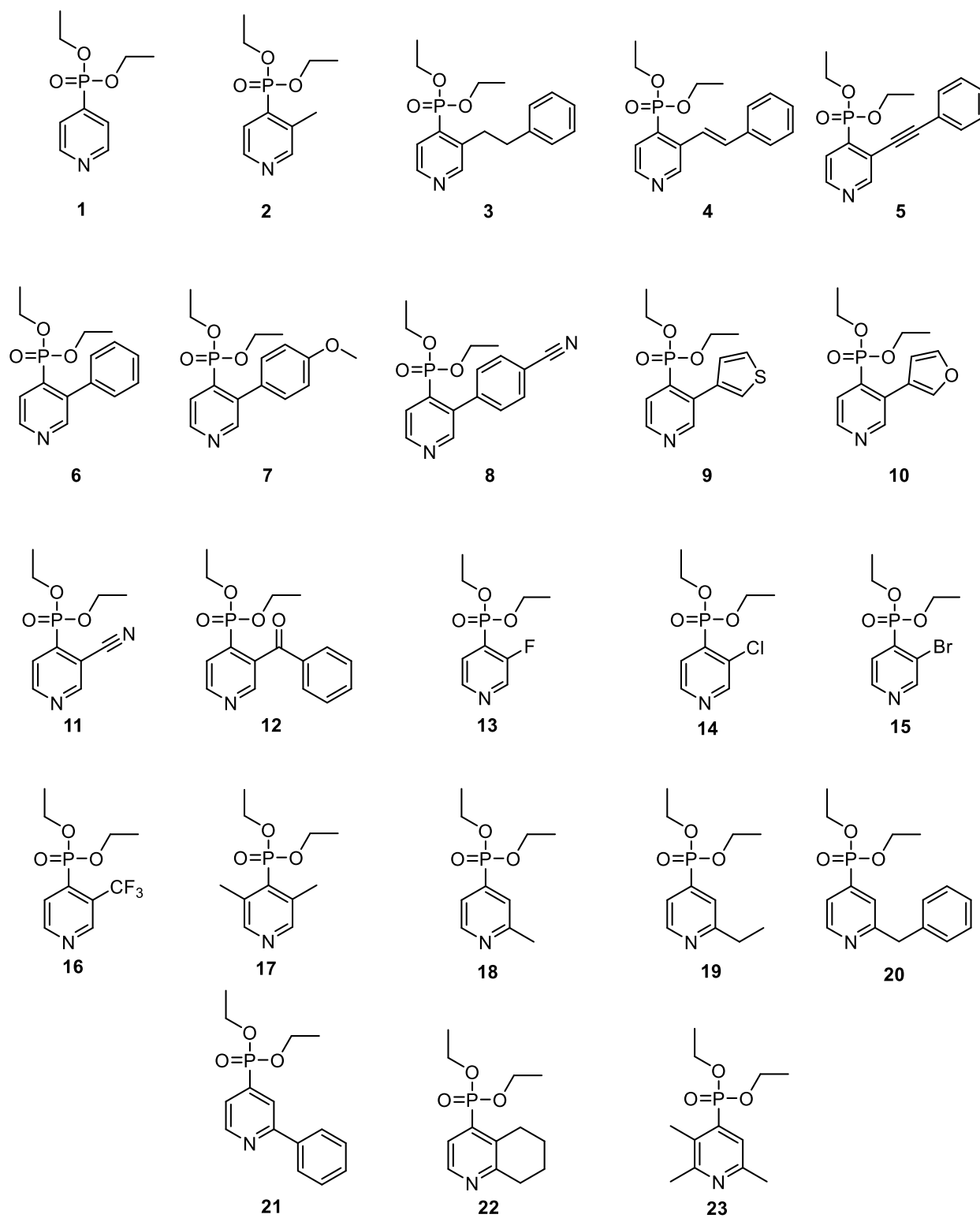


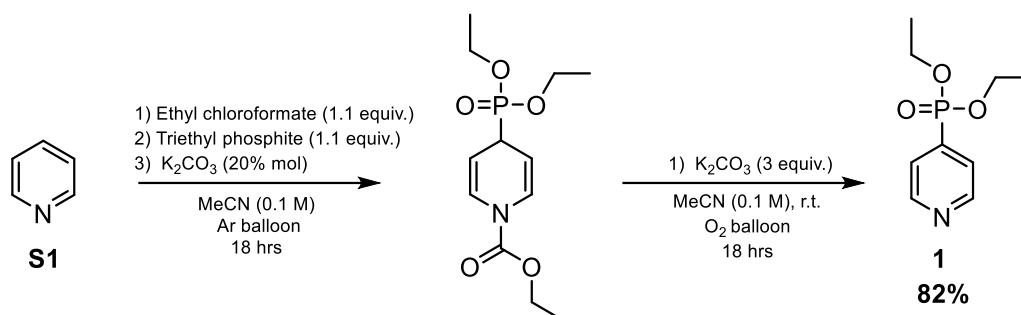
^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **S10**⁵⁹



3.3 Preparation, Structural Data and NMR Spectra of 4-Pyridylic Phosphonates

Summary of 4-Pyridylic Phosphonates





Pyridine (200 mg, 2.53 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (70 mg, 0.51 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (1049 mg, 7.59 mmol, 3.0 equiv.) according to **procedure B**, provided product **1** (446 mg, 2.07 mmol, 82% yield) as a yellow oil.

Rf = 0.35 in 60% EtOAc/hexanes.

1H -NMR (300 MHz, $CDCl_3$)
 δ 8.77 (t, J = 5.6 Hz, 2H), 7.66 (dd, J = 13.4, 5.9 Hz, 2H),
 4.29 – 4.03 (m, 4H), 1.34 (t, J = 7.1 Hz, 6H)

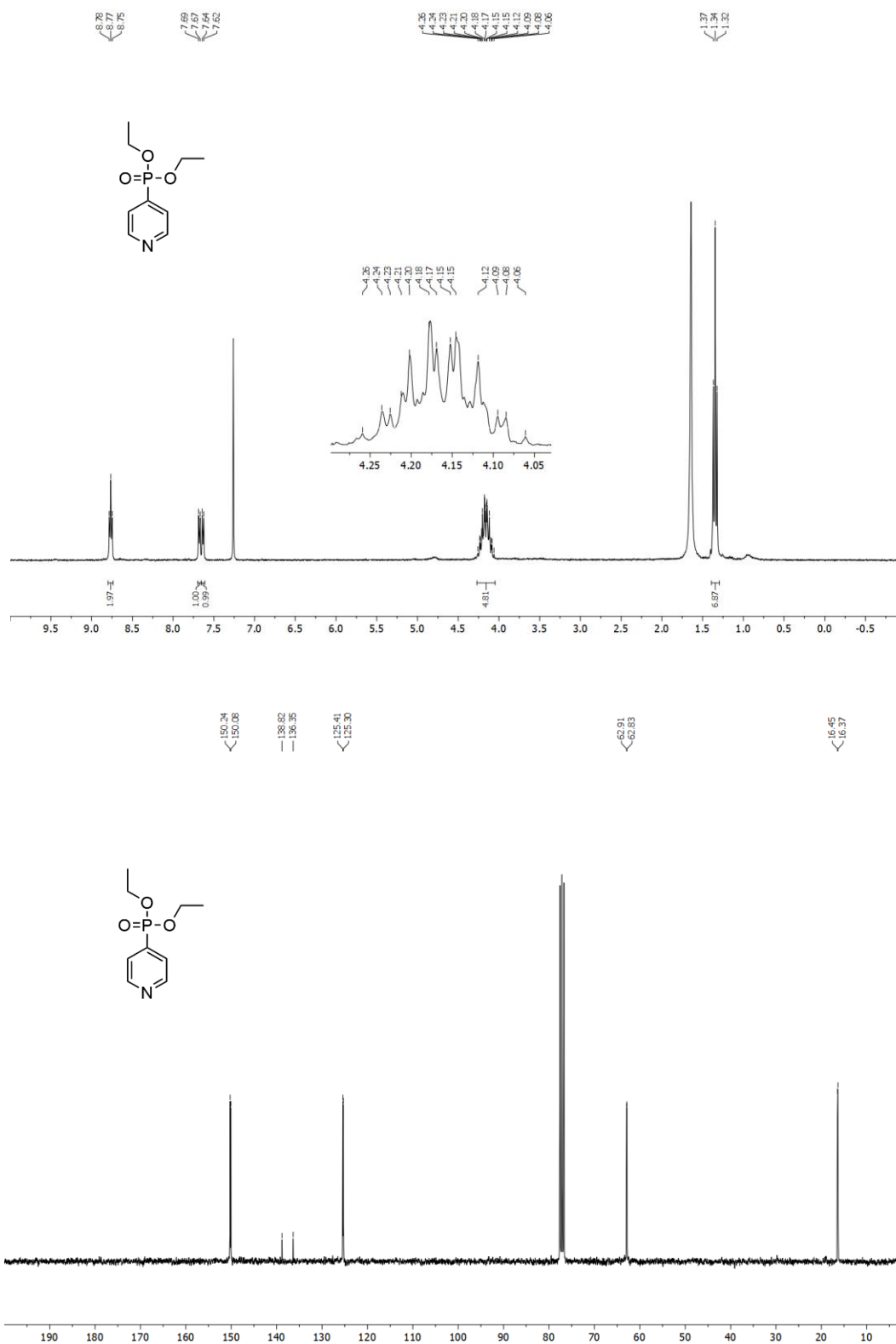
$^{13}C\{^1H\}$ -NMR (75 MHz, $CDCl_3$)
 δ 150.2 (d, $^3J_{C-P}$ = 12.3 Hz), 137.6 (d, $^1J_{C-P}$ = 185.8 Hz),
 125.4 (d, $^2J_{C-P}$ = 8.2 Hz), 62.9 (d, $^2J_{C-P}$ = 5.7 Hz),
 16.4 (d, $^3J_{C-P}$ = 6.3 Hz)

$^{31}P\{^1H\}$ -NMR (121 MHz, $CDCl_3$)
 δ 15.3

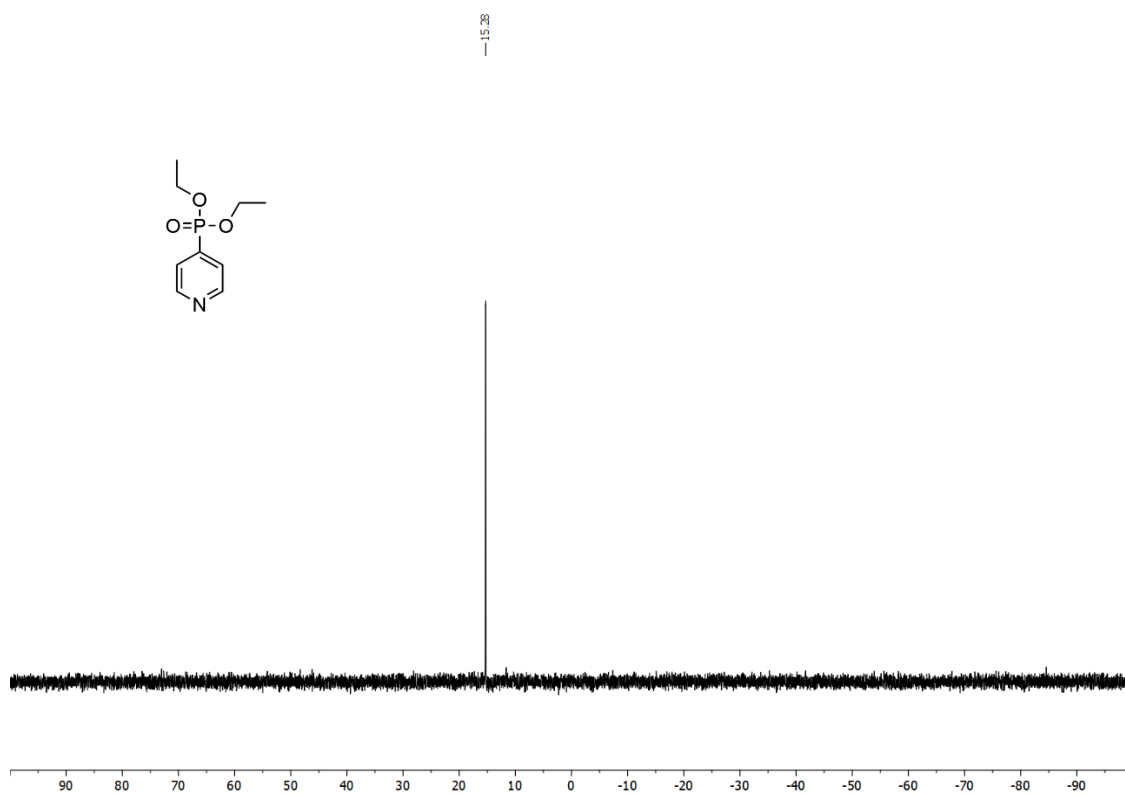
IR Alpha-Platinum ATR, Bruker, diamond crystal
 $\tilde{\nu}$ = 3010, 1400, 1260, 1150, 1005, 992, 630, 520 cm^{-1}

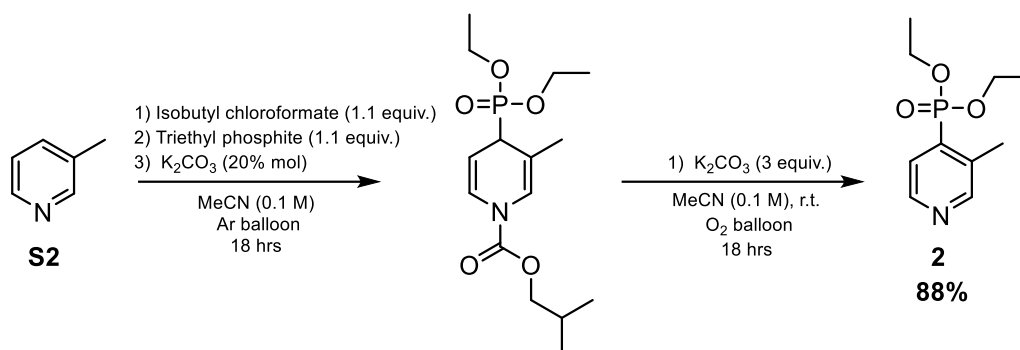
HRMS ESI+ TOF
 m/z $[M+H]^+$ calcd for $C_9H_{15}NO_3P$. 216.0784; Found 216.0783.

^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **1**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **1**





3-Methylpyridine (200 mg, 2.15 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (59 mg, 0.43 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (891 mg, 6.45 mmol, 3.0 equiv.) according to **procedure B**, provided product **2** (433 mg, 1.89 mmol, 88% yield) as a yellow oil.

R_f = 0.35 in 60% EtOAc/hexanes.

¹H-NMR

(300 MHz, $CDCl_3$)

δ 8.54 (d, J = 6.3 Hz, 2H), 7.69 (dd, J = 14.4, 4.9 Hz, 1H),
4.27 – 4.02 (m, 4H), 2.53 (s, 3H), 1.33 (t, J = 7.1 Hz, 6H)

¹³C{¹H}-NMR

(75 MHz, $CDCl_3$)

δ 151.9 (d, $^3J_{C-P}$ = 12.3 Hz), 147.3 (d, $^3J_{C-P}$ = 12.3 Hz),
135.8 (d, $^1J_{C-P}$ = 182.0 Hz), 135.5 (d, $^2J_{C-P}$ = 8.0 Hz),
126.4 (d, $^2J_{C-P}$ = 7.8 Hz), 62.5 (d, $^2J_{C-P}$ = 5.7 Hz),
18.1 (d, $^3J_{C-P}$ = 3.5 Hz), 16.3 (d, $^3J_{C-P}$ = 6.3 Hz)

³¹P{¹H}-NMR

(121 MHz, $CDCl_3$)

δ 16.0

IR

Alpha-Platinum ATR, Bruker, diamond crystal

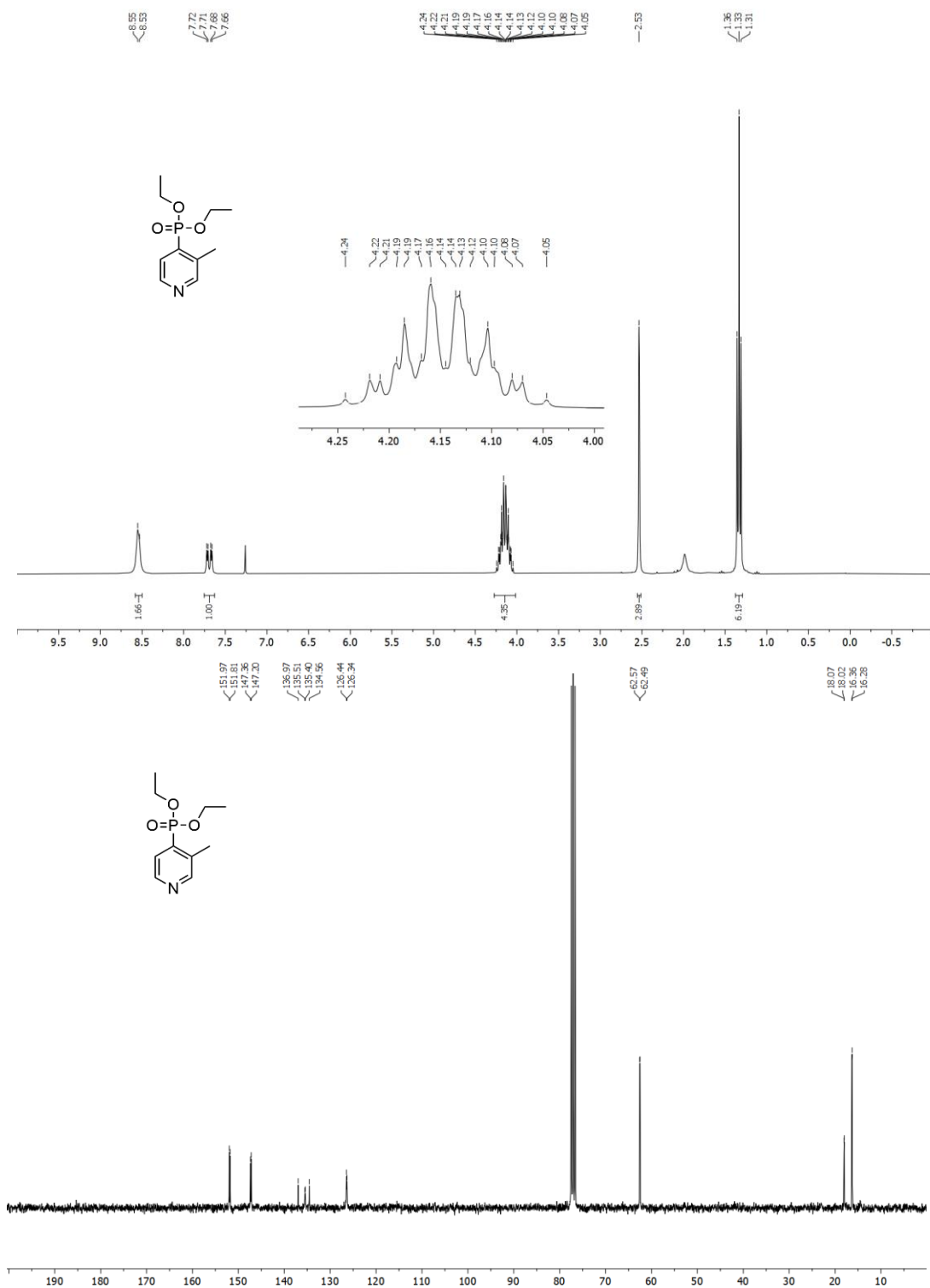
$\tilde{\nu}$ = 3020, 1420, 1290, 1170, 1002, 990, 650, 540 cm^{-1}

HRMS

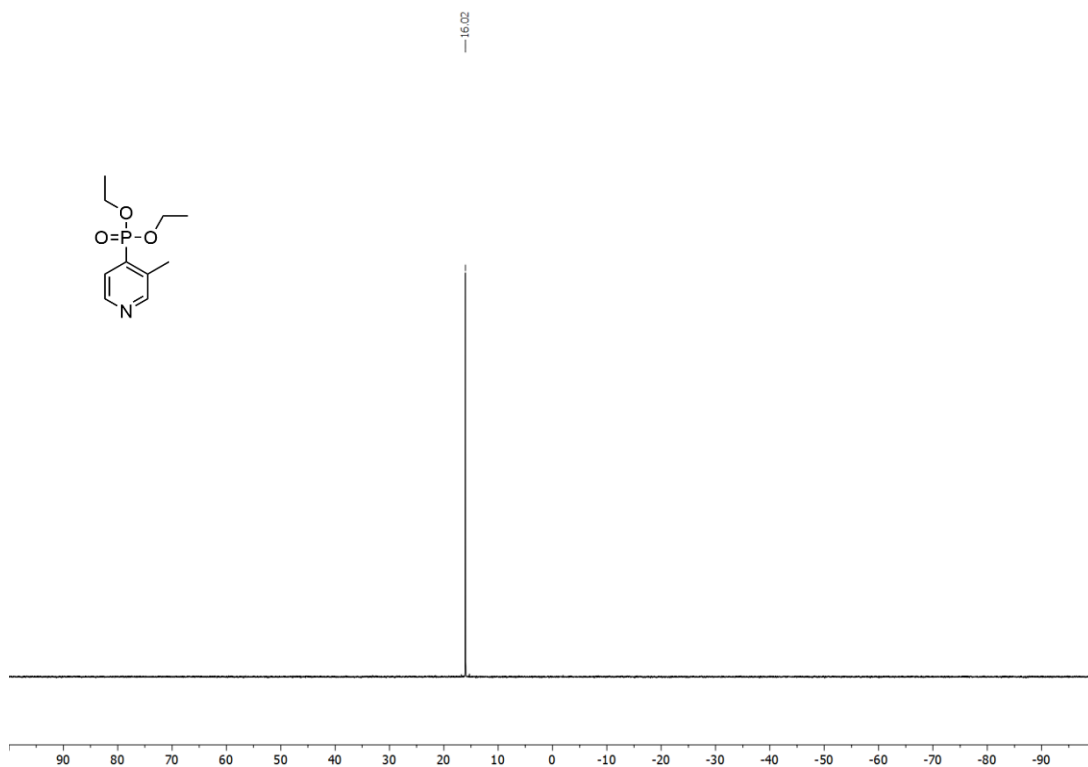
ESI+ TOF

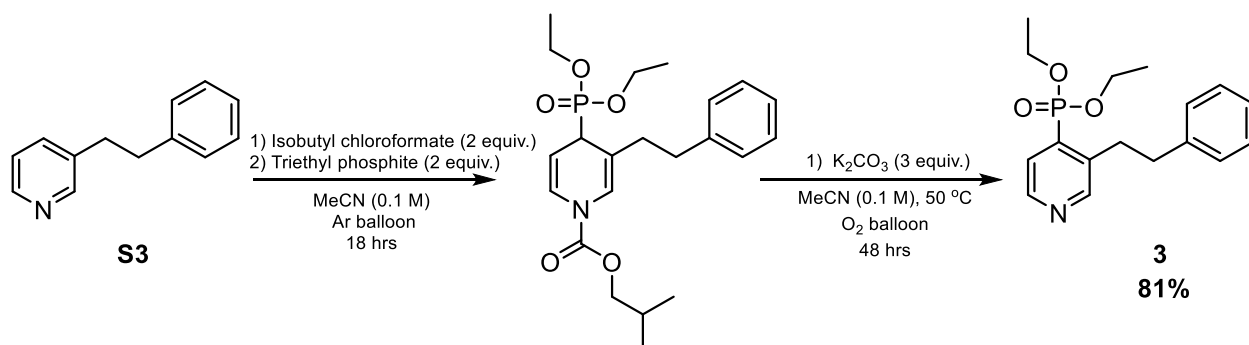
m/z $[M+H]^+$ calcd for $C_{10}H_{17}NO_3P$. 230.0868; Found 230.0943.

^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **2**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **2**





3-(2-Phenylethyl)pyridine (40 mg, 0.22 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (60 mg, 0.44 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (73 mg, 0.44 mmol, 2 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (92 mg, 0.66 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C for 48 hours, affording product **3** (56 mg, 0.18 mmol, 81%) as a yellow oil.

R_f = 0.25 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, $CDCl_3$)

δ 8.58 (t, J = 4.7 Hz, 1H), 8.53 (d, J = 7.1 Hz, 1H),
7.72 (dd, J = 14.3, 5.1 Hz, 1H), 7.35 – 7.18 (m, 5H),
4.29 – 4.09 (m, 4H), 3.24 (t, J = 10.98 Hz, 2H),
2.96 (t, J = 8.23 Hz, 2H), 1.36 (t, J = 7.0 Hz, 6H)

¹³C{¹H}-NMR

(101 MHz, $CDCl_3$)

δ 152.2 (d, $^3J_{C-P}$ = 12.3 Hz), 147.6 (d, $^3J_{C-P}$ = 12.2 Hz), 141.3,
139.3 (d, $^2J_{C-P}$ = 8.6 Hz), 135.6 (d, $^1J_{C-P}$ = 182.2 Hz), 128.7,
128.6, 126.7 (d, $^2J_{C-P}$ = 8.0 Hz), 126.4, 62.8 (d, $^3J_{C-P}$ = 5.8 Hz),
37.9, 34.3 (d, $^3J_{C-P}$ = 3.5 Hz), 16.5 (d, $^3J_{C-P}$ = 6.3 Hz)

³¹P{¹H}-NMR

³¹P NMR (121 MHz, $CDCl_3$)

δ 16.2

IR

Alpha-Platinum ATR, Bruker, diamond crystal

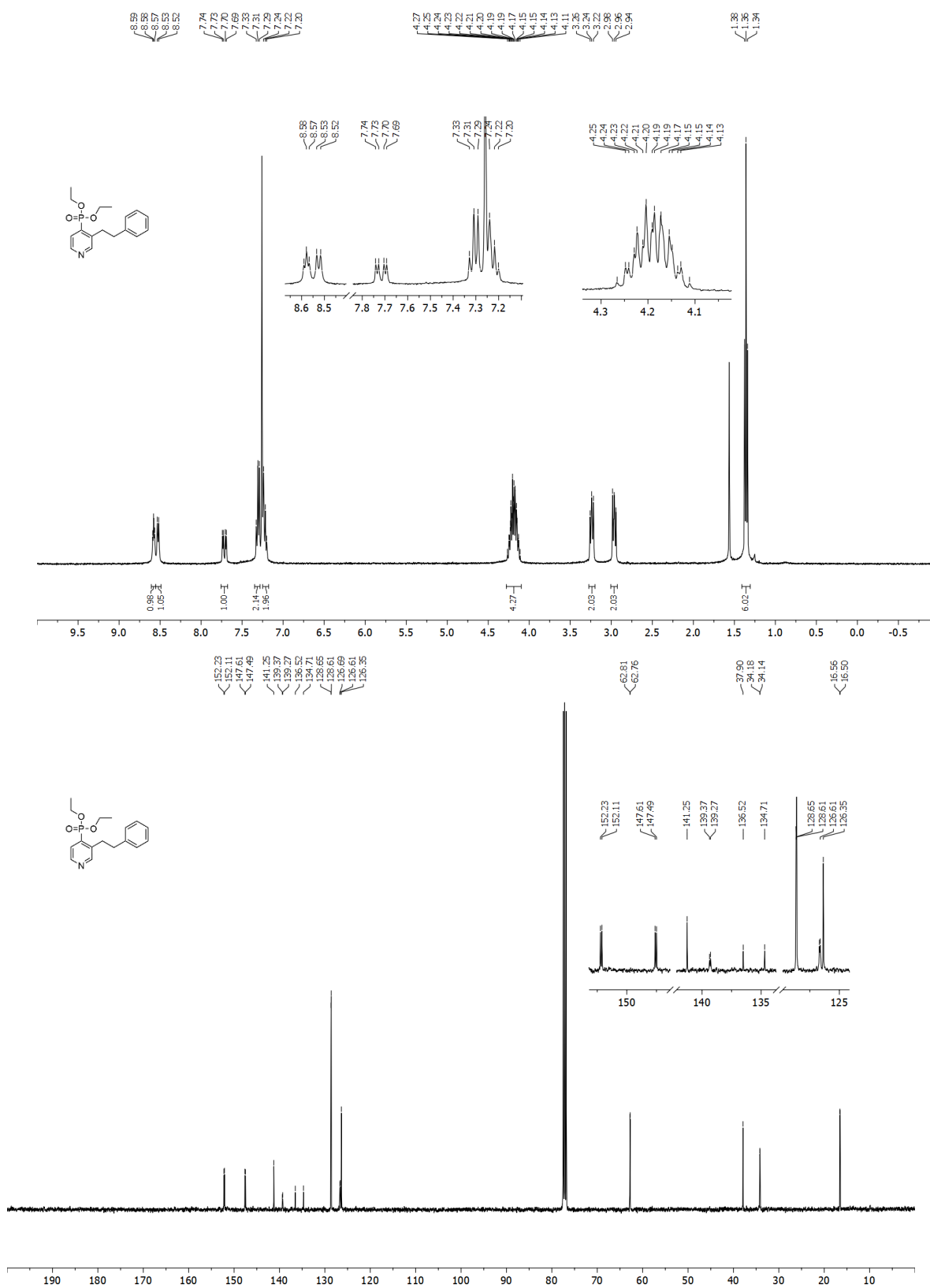
$\tilde{\nu}$ = 3010, 1425, 1260, 1110, 1005, 985, 720, 610 cm^{-1}

HRMS

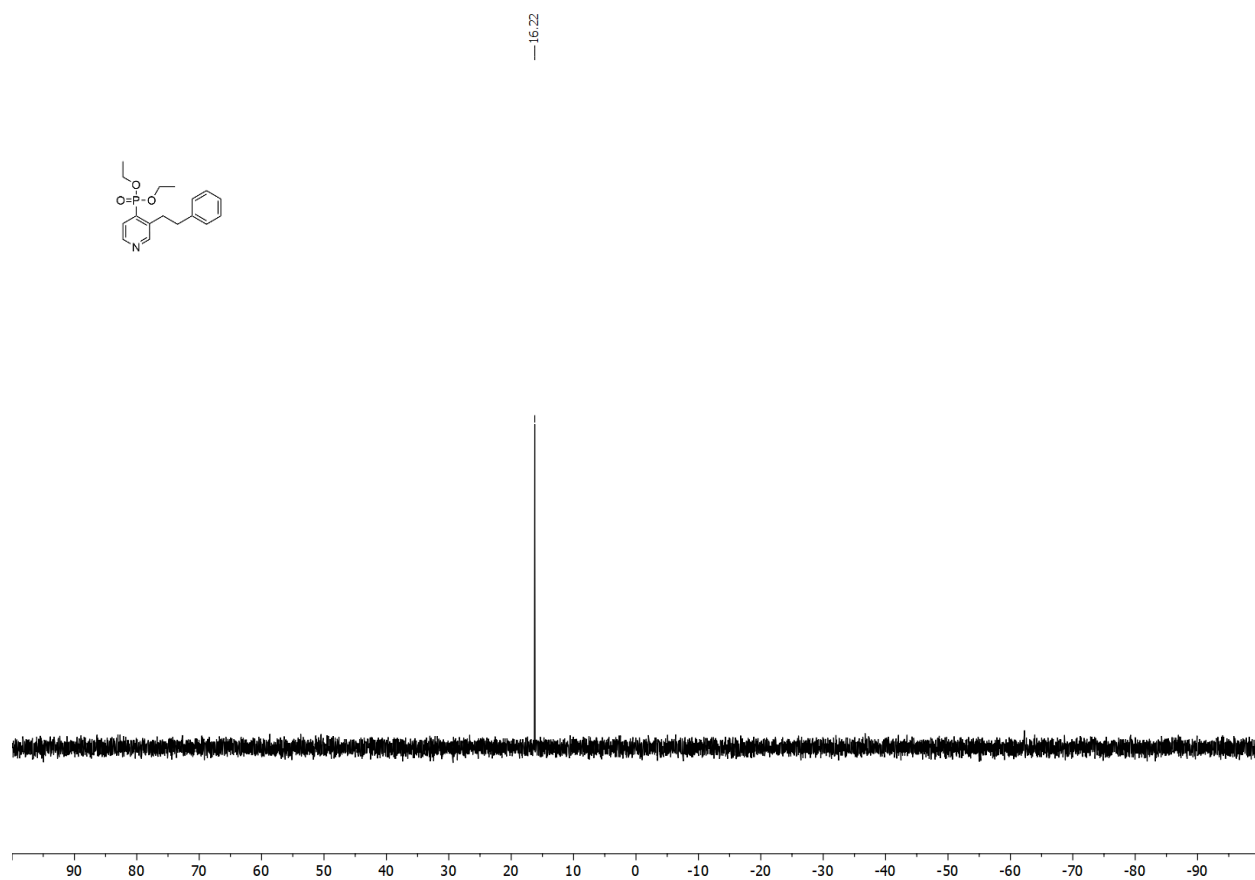
ESI+ TOF

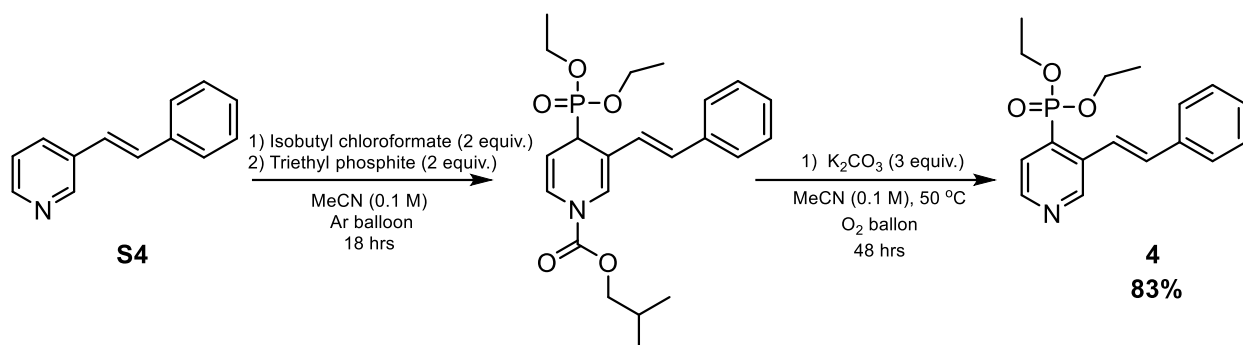
m/z [M+H]⁺ calcd for $C_{17}H_{22}NO_3P$. 320.1410; Found 320.1412.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **3**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **3**





3-Styrylpyridine (50 mg, 0.28 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (76 mg, 0.56 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (93 mg, 0.56 mmol, 2.0 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (116 mg, 0.84 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C for 48 hours, affording product **4** (73 mg, 0.23 mmol, 83%) as a yellow oil.

R_f = 0.25 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, $CDCl_3$)

δ 9.04 (d, J = 6.7 Hz, 1H), 8.61 (t, J = 4.8 Hz, 1H),
 7.79 (d, J = 4.7 Hz, 1H), 7.75 (d, J = 6.9 Hz, 1H),
 7.56 (d, J = 7.4 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H),
 7.32 (tt, 7.3, 2.1 Hz), 7.15 (d, J = 16.3 Hz, 1H),
 4.28 – 4.05 (m, 4H), 1.33 (t, J = 7.1 Hz, 6H)

¹³C{¹H}-NMR

(176 MHz, $CDCl_3$)

δ 148.0 (d, $^3J_{C-P}$ = 12.1 Hz), 147.8 (d, $^3J_{C-P}$ = 11.4 Hz), 136.6,
 135.1 (d, $^2J_{C-P}$ = 8.1 Hz), 134.0 (d, $^1J_{C-P}$ = 180.3 Hz), 133.1,
 128.9, 128.6, 127.0, 126.6 (d, $^2J_{C-P}$ = 7.9 Hz),
 124.0 (d, $^3J_{C-P}$ = 4.7 Hz), 62.7 (d, $^2J_{C-P}$ = 5.7 Hz),
 16.3 (d, $^3J_{C-P}$ = 6.3 Hz)

³¹P{¹H}-NMR

³¹P NMR (121 MHz, $CDCl_3$)

δ 15.8

IR

Alpha-Platinum ATR, Bruker, diamond crystal

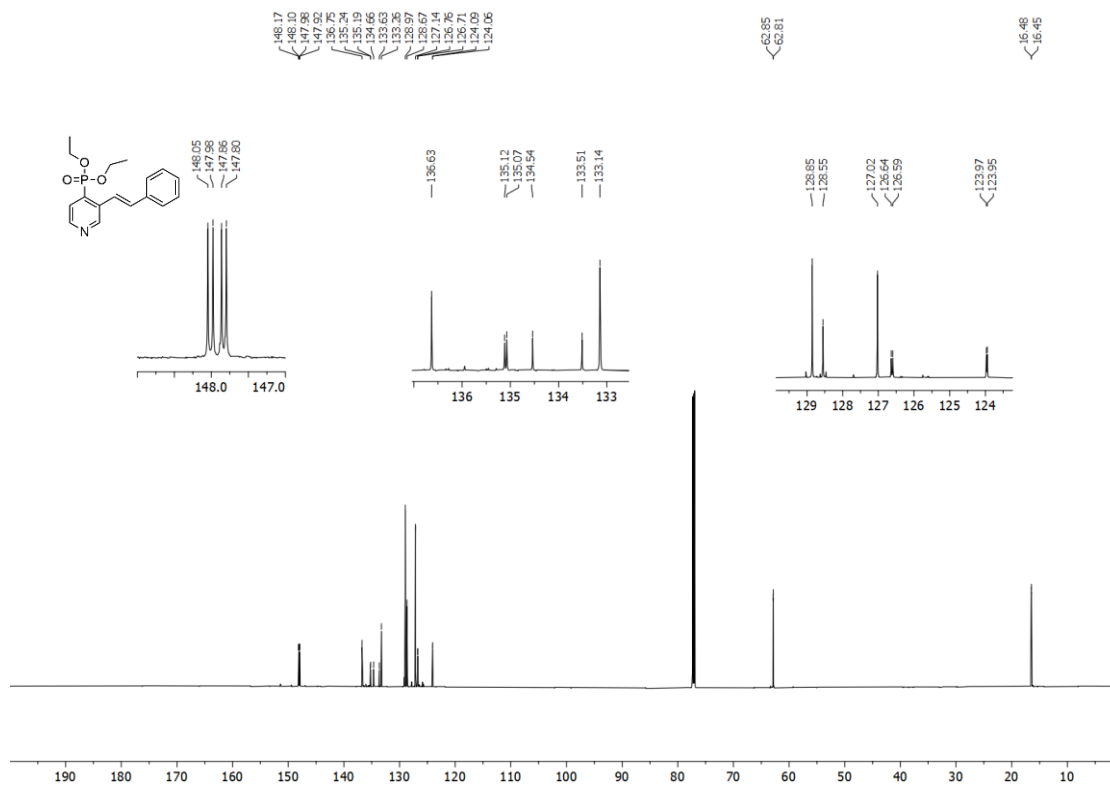
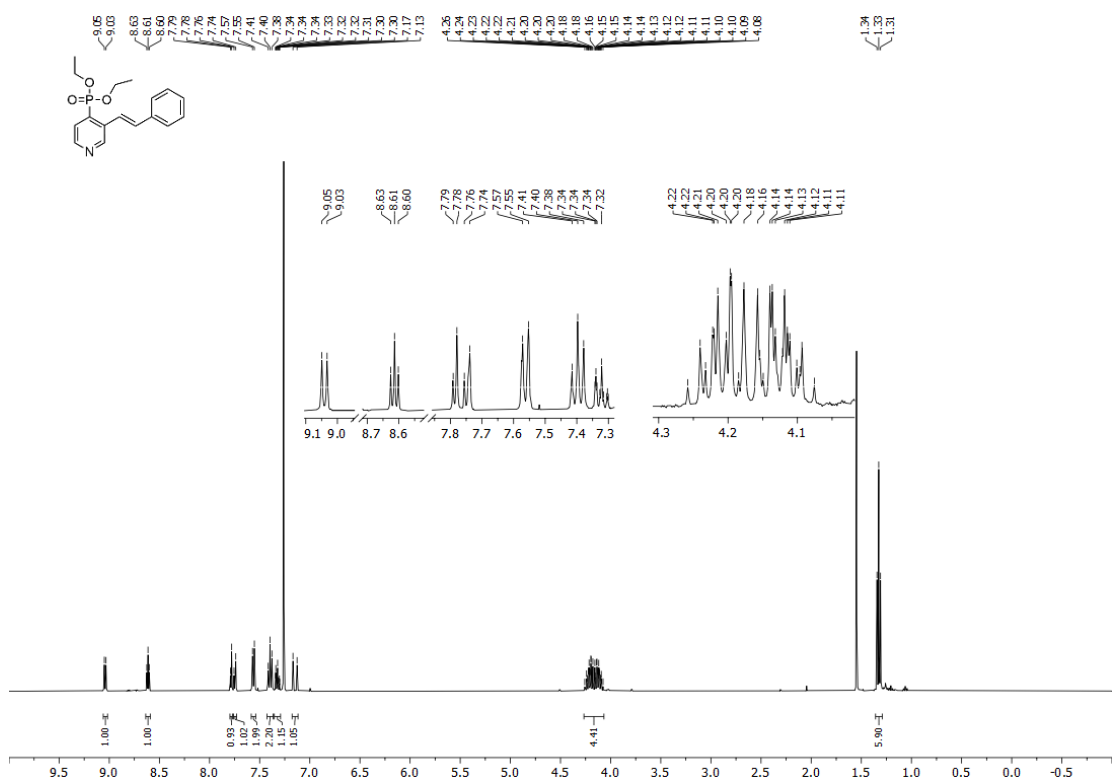
$\tilde{\nu}$ = 2997, 1256, 1002, 993, 771, 764, 587 cm^{-1}

HRMS

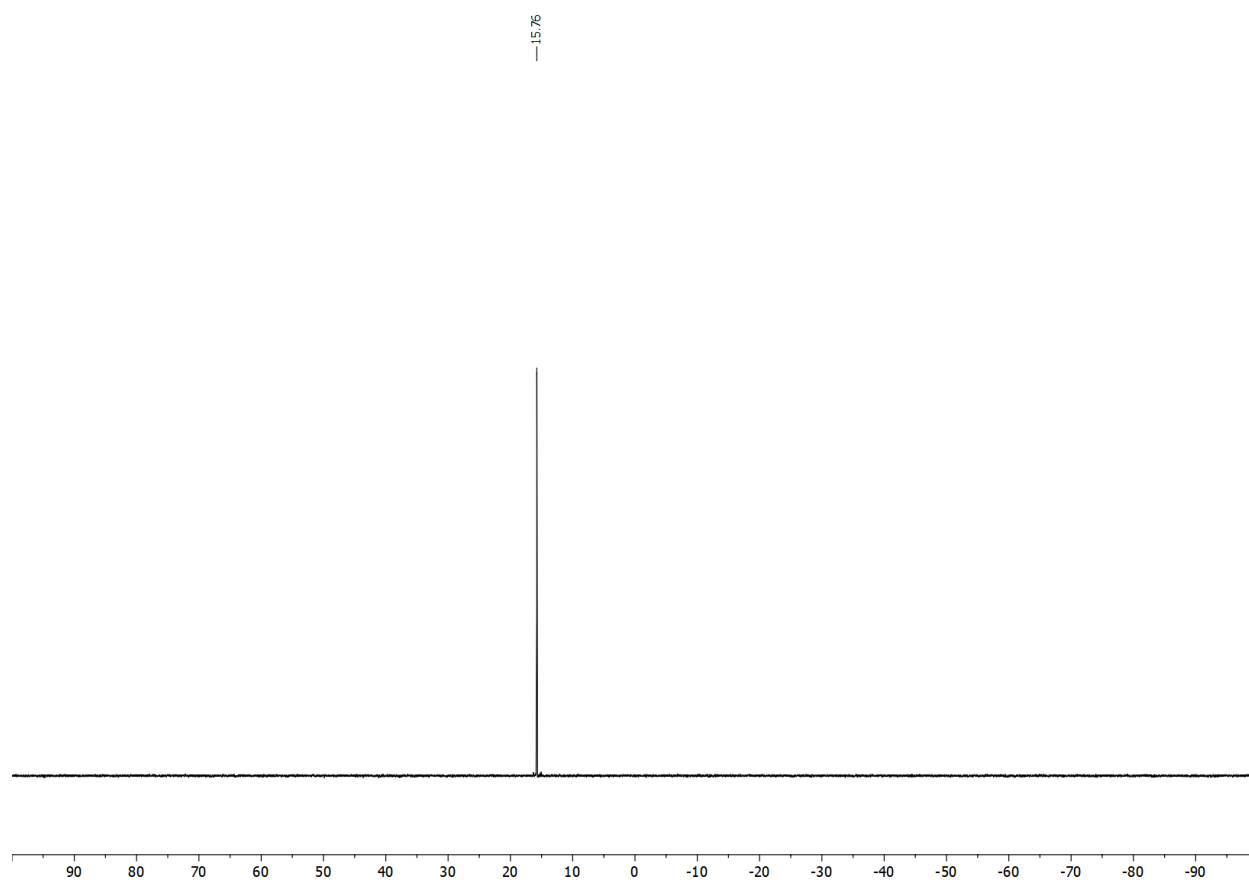
ESI+ TOF

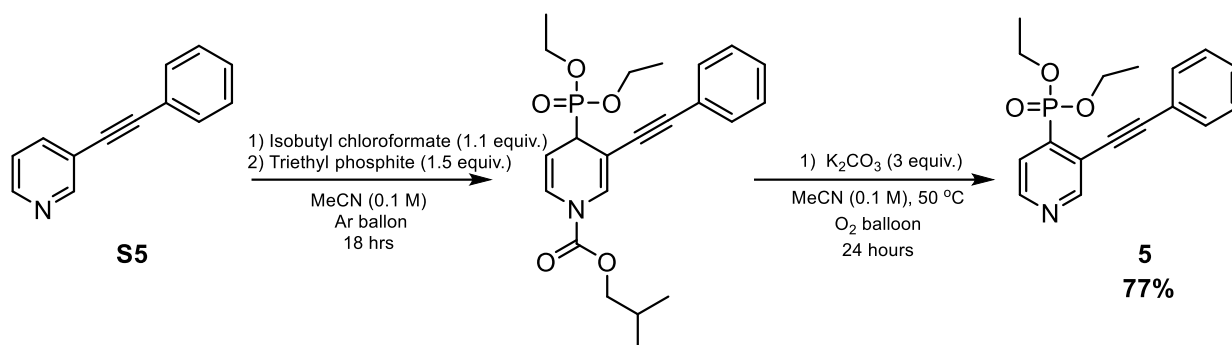
m/z [M+H]⁺ calcd for $C_{17}H_{21}NO_3P$. 318.1254; Found 318.1254.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(176 MHz, CDCl_3) spectra of **4**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **4**





3-(2-Phenylethynyl)pyridine (100 mg, 0.56 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (84 mg, 0.62 mmol, 1.1 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (140 mg, 0.84 mmol, 1.5 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (232 mg, 1.68 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C for 24 hours, affording product **5** (136 mg, 0.43 mmol, 77%) as a yellow oil.

R_f = 0.25 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, CDCl₃)

δ 8.88 (dd, J = 6.0, 0.9 Hz, 1H), 8.66 (t, J = 4.8 Hz, 1H),
7.84 (ddd, J = 14.1, 4.9, 0.9 Hz, 1H), 7.63 – 7.56 (m, 2H),
7.43 – 7.35 (m, 3H), 4.33 – 4.11 (m, 4H), 1.35 (td, J = 7.1, 0.6 Hz, 6H)

¹³C{¹H}-NMR

(101 MHz, CDCl₃)

δ 153.6 (d, $^3J_{C-P}$ = 9.9 Hz), 148.4 (d, $^3J_{C-P}$ = 12.2 Hz),
138.4 (d, $^1J_{C-P}$ = 183.8 Hz), 131.8, 129.3, 128.6,
126.8 (d, $^2J_{C-P}$ = 7.4 Hz), 122.5, 121.6 (d, $^3J_{C-P}$ = 4.9 Hz),
97.7, 85.1 (d, $^2J_{C-P}$ = 6.4 Hz), 63.0 (d, $^2J_{C-P}$ = 5.8 Hz),
16.5 (d, $^3J_{C-P}$ = 6.5 Hz)

³¹P{¹H}-NMR

³¹P NMR (162 MHz, CDCl₃)

δ 13.4

IR

Alpha-Platinum ATR, Bruker, diamond crystal

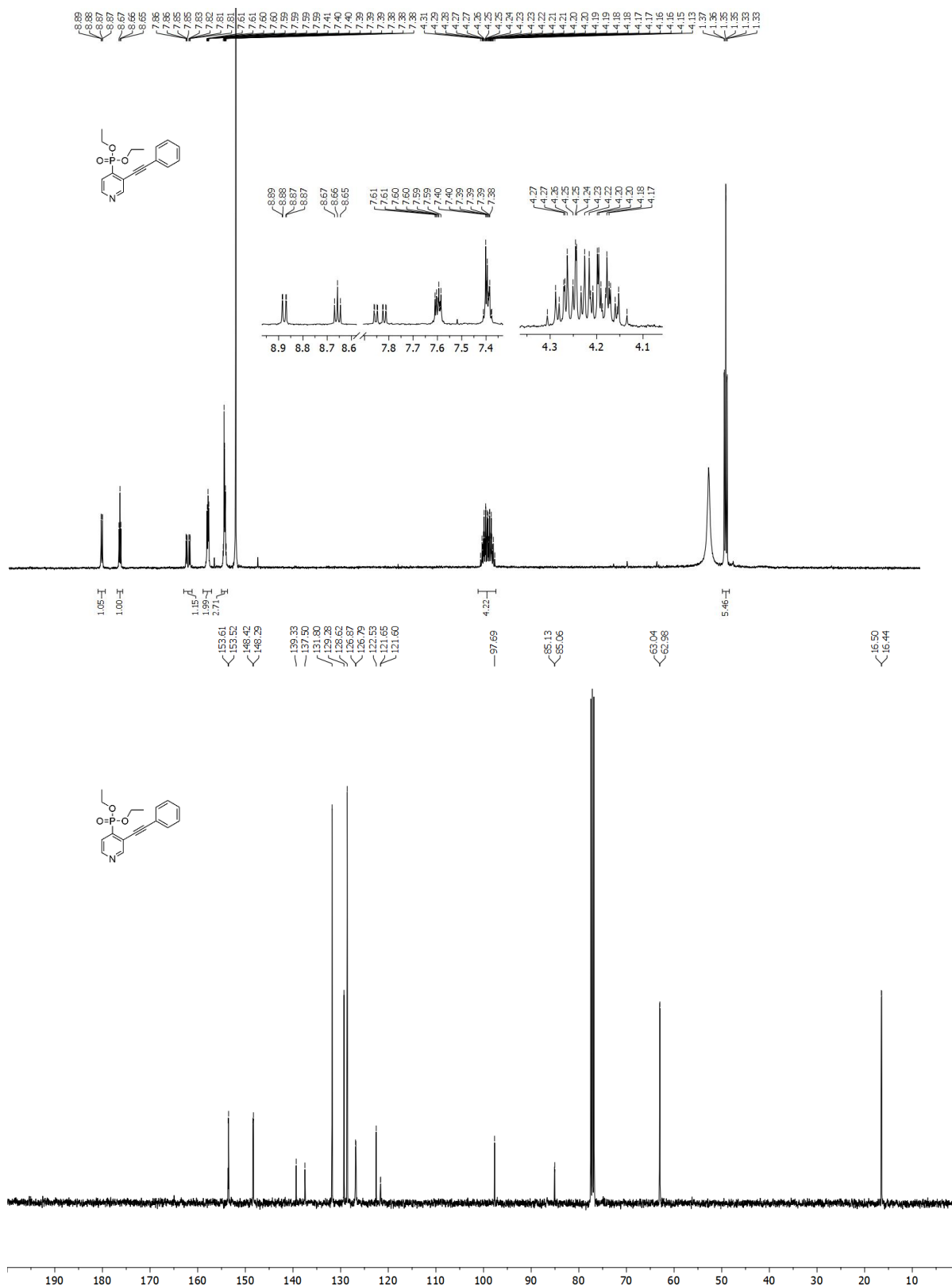
$\tilde{\nu}$ = 3000, 2210, 1615, 1450, 1115, 1005, 992, 770, 565 cm⁻¹

HRMS

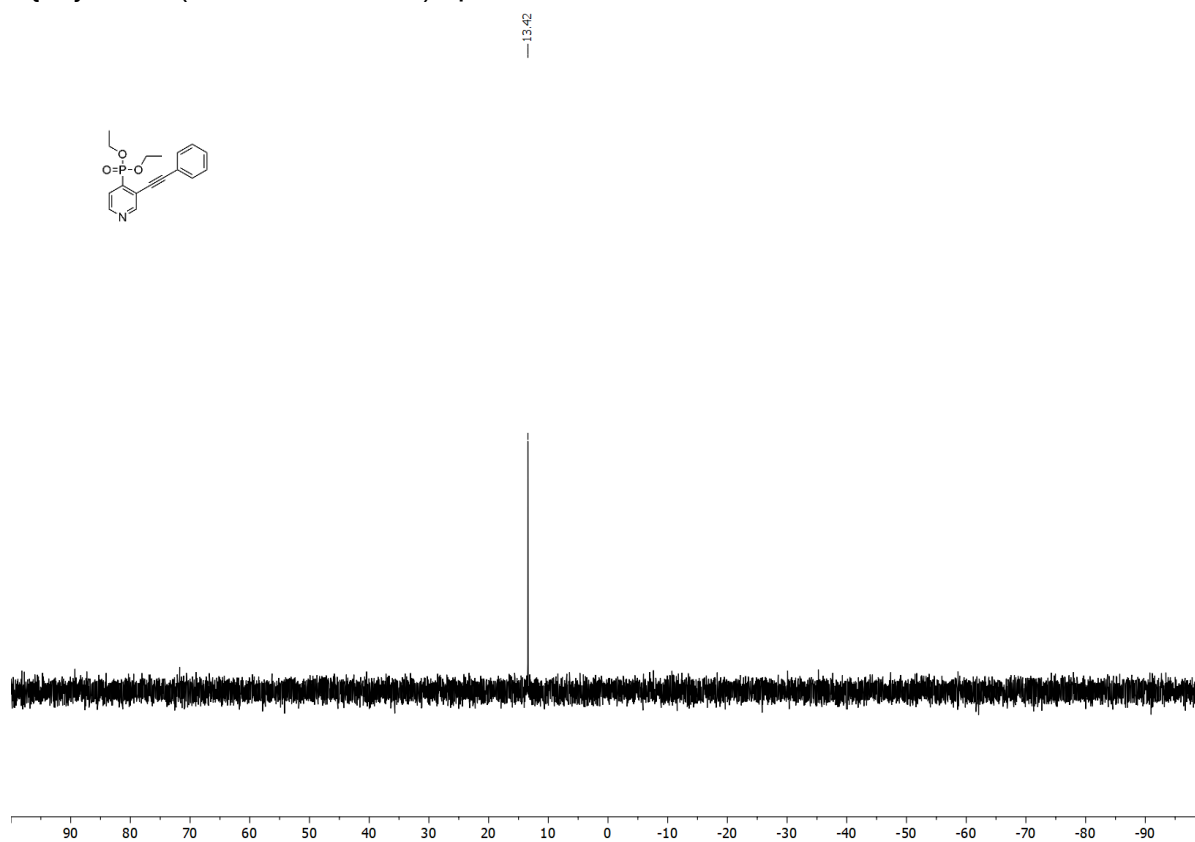
ESI+ TOF

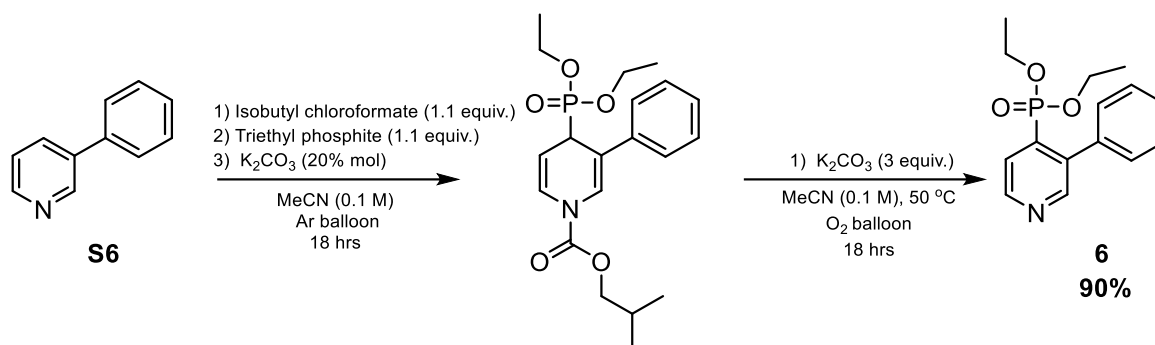
m/z [M+H]⁺ calcd for C₁₇H₁₉NO₃P. 316.1097; Found 316.1098.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **5**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **5**





3-Phenylpyridine (150 mg, 0.97 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (27 mg, 0.19 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (402 mg, 2.91 mmol, 3.0 equiv.) according to **procedure B**, except the reaction mixture was stirred at 50 °C, providing product **6** (278 mg, 0.87 mmol, 90% yield) as a yellow oil.

R_f = 0.35 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, $CDCl_3$)

δ 8.72 (t, J = 4.9 Hz, 1H), 8.63 (d, J = 6.6 Hz, 1H),
7.85 (dd, J = 14.3, 5.0 Hz, 1H), 7.45 – 7.43 (m, 5H),
4.03 – 3.79 (m, 4H), 1.14 (t, J = 7.1 Hz, 6H)

¹³C{¹H}-NMR

(75 MHz, $CDCl_3$)

δ 151.3 (d, $^3J_{C-P}$ = 11.5 Hz), 148.2 (d, $^3J_{C-P}$ = 12.2 Hz),
139.4 (d, $^2J_{C-P}$ = 8.0 Hz), 137.4 (d, $^3J_{C-P}$ = 4.3 Hz),
135.5 (d, $^1J_{C-P}$ = 184.8 Hz), 129.4, 128.0, 127.7,
126.2 (d, $^2J_{C-P}$ = 7.9 Hz), 62.2 (d, $^2J_{C-P}$ = 6.2 Hz),
15.9 (d, $^3J_{C-P}$ = 6.6 Hz)

³¹P{¹H}-NMR

(121 MHz, $CDCl_3$)

δ 12.9

IR

Alpha-Platinum ATR, Bruker, diamond crystal

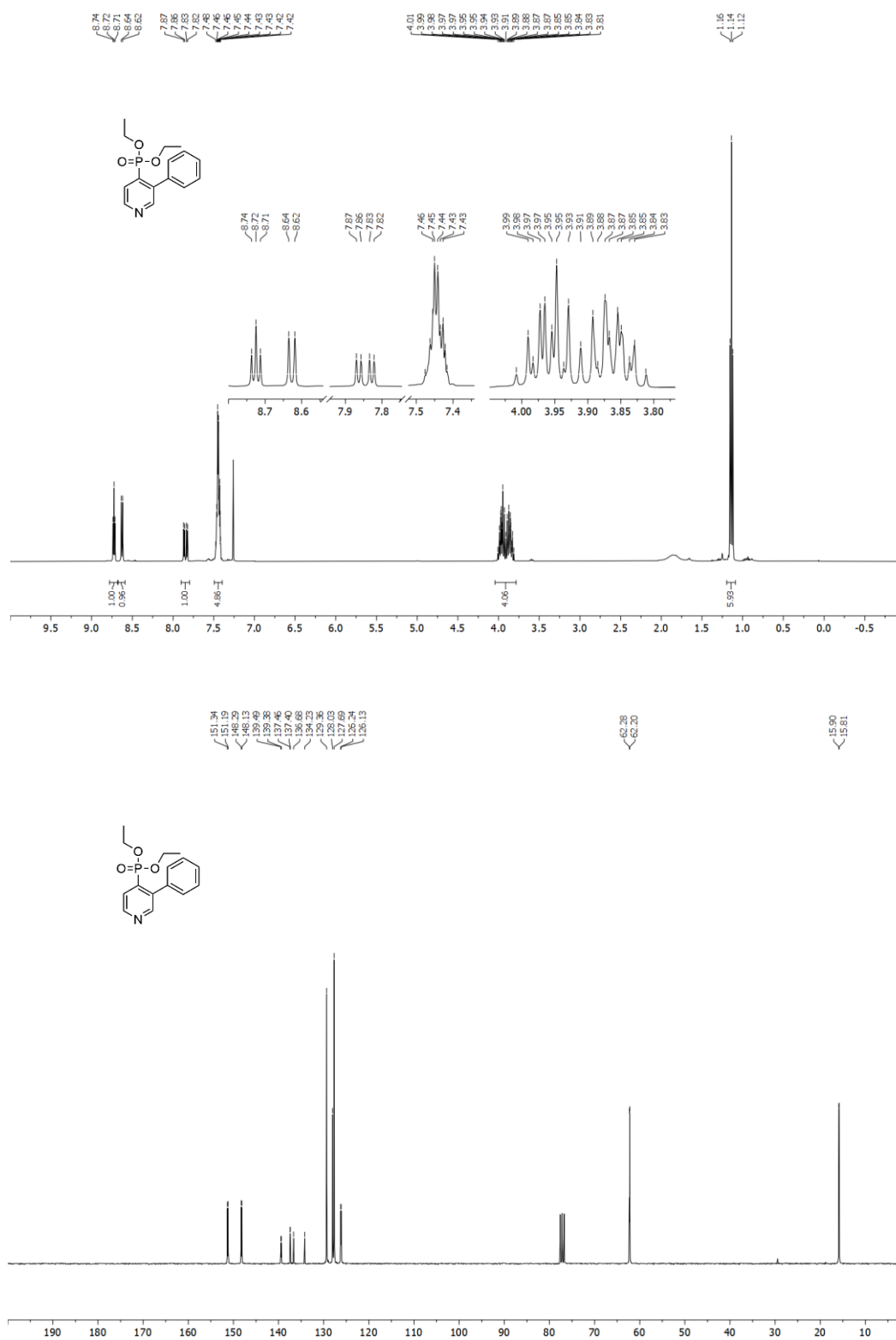
$\tilde{\nu}$ = 2950, 1420, 1220, 1140, 1005, 992, 650 cm^{-1}

HRMS

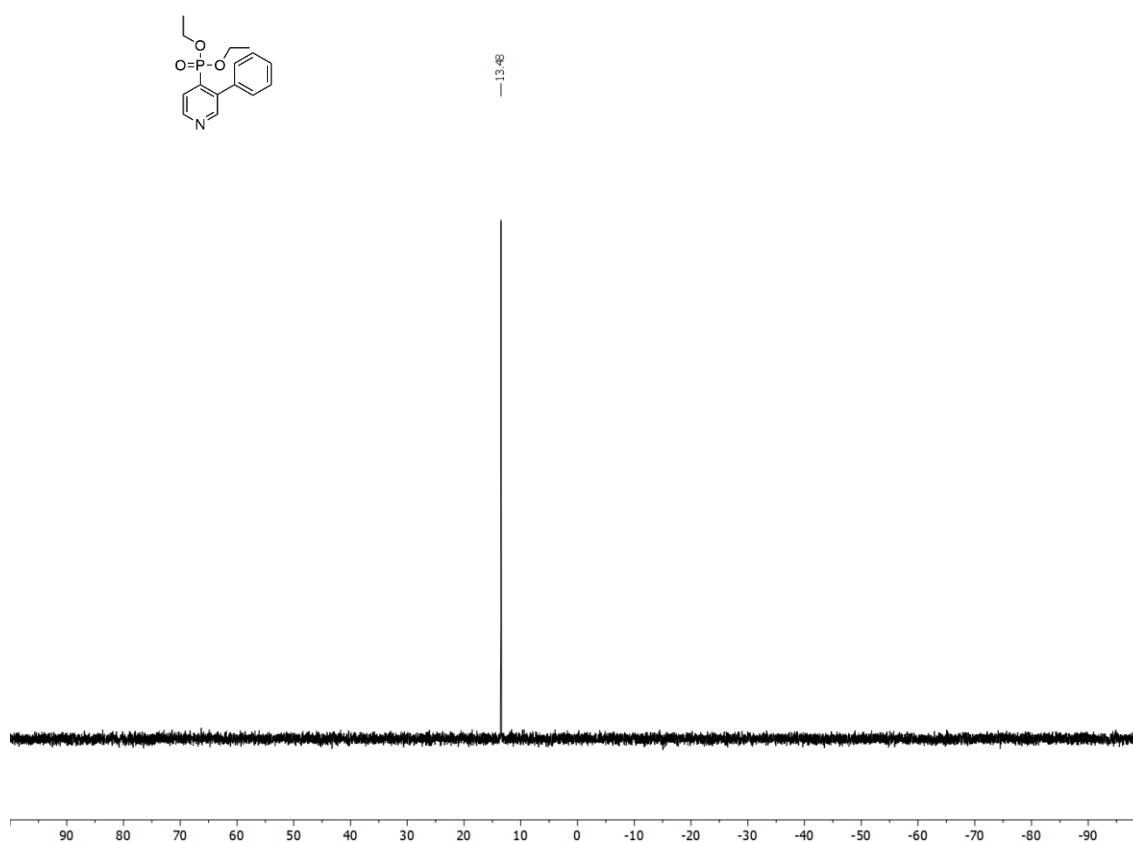
ESI+ TOF

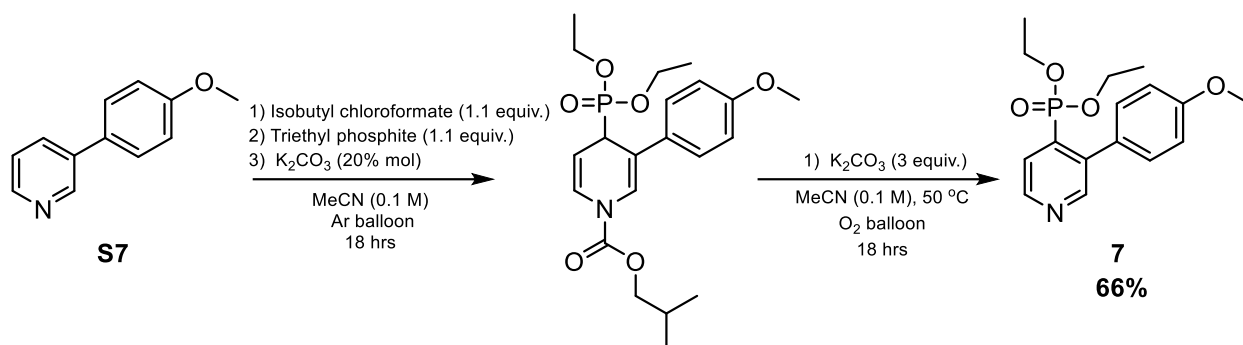
m/z [M+H]⁺ calcd for $C_{15}H_{19}NO_3P$ 292.1097; Found 292.1097.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **6**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **6**





3-(4-Methoxyphenyl)pyridine (188 mg, 1.01 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (28 mg, 0.20 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (419 mg, 3.03 mmol, 3.0 equiv.) according to **procedure B**, except the reaction mixture was stirred at 50 °C, providing product **7** (213 mg, 0.67 mmol, 66% yield) as a yellow oil.

R_f = 0.35 in 60% EtOAc/hexanes.

1H -NMR

(400 MHz, $CDCl_3$)

δ 8.70 (t, J = 4.8 Hz, 1H), 8.63 (d, J = 6.3 Hz, 1H),
 7.95 (dd, J = 14.1, 5.1 Hz, 1H), 7.50 – 7.35 (m, 2H),
 7.03 – 6.95 (m, 2H), 4.08 – 3.88 (m, 4H), 3.87 (s, 3H),
 1.18 (t, J = 7.1 Hz, 6H)

$^{13}C\{^1H\}$ -NMR

(101MHz, $CDCl_3$)

δ 159.7, 151.6 (d, $^3J_{C-P}$ = 11.6 Hz), 147.9 (d, $^3J_{C-P}$ = 12.1 Hz),
 139.6 (d, $^2J_{C-P}$ = 7.3 Hz), 135.7 (d, $^1J_{C-P}$ = 184.3 Hz),
 129.8 (d, $^3J_{C-P}$ = 4.4 Hz), 126.5 (d, $^2J_{C-P}$ = 8.2 Hz),
 62.5 (d, $^2J_{C-P}$ = 6.1 Hz), 55.3, 16.1 (d, $^3J_{C-P}$ = 6.5 Hz)

$^{31}P\{^1H\}$ -NMR

(162 MHz, $CDCl_3$)

δ 13.5

IR

Alpha-Platinum ATR, Bruker, diamond crystal

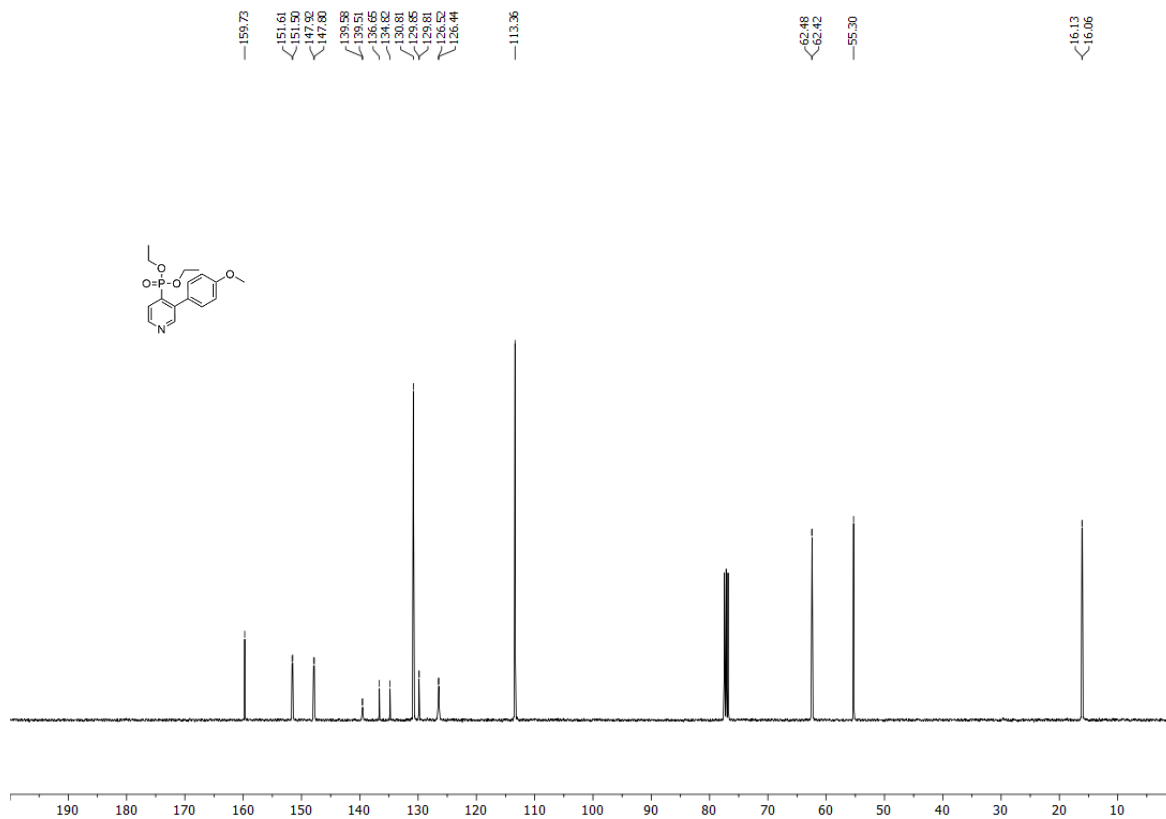
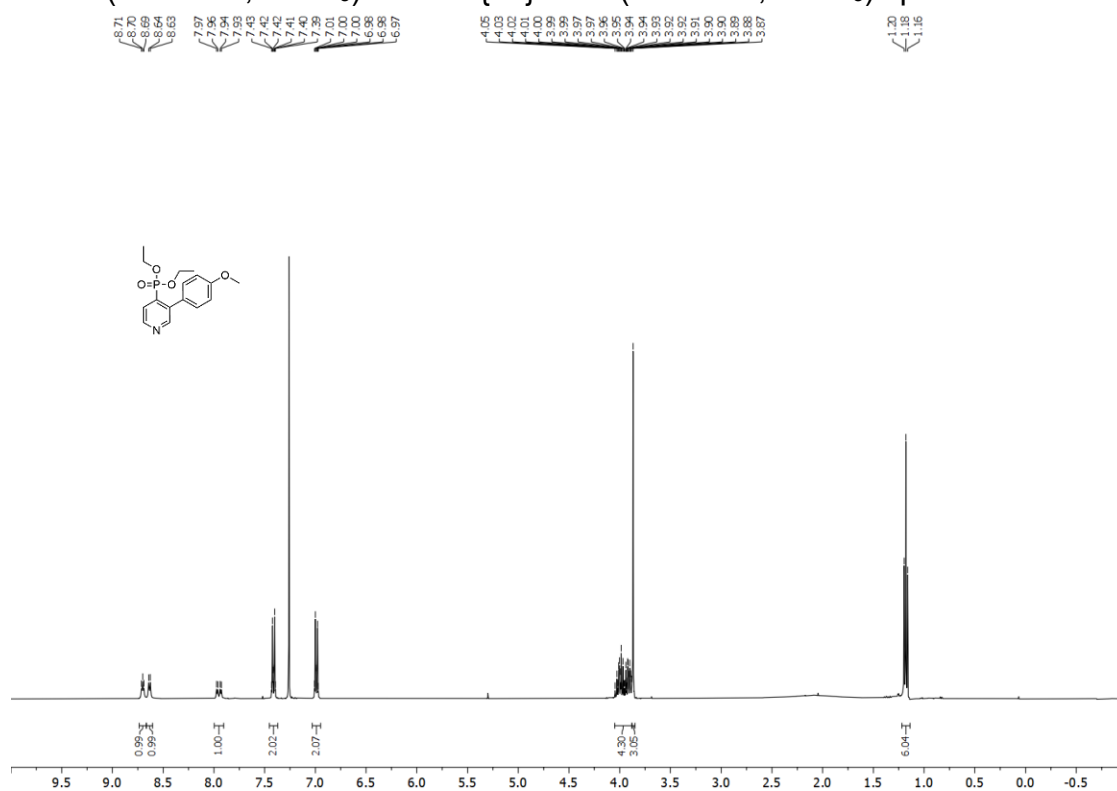
$\tilde{\nu}$ = 2900, 1610, 1240, 1010, 990, 735, 572 cm^{-1}

HRMS

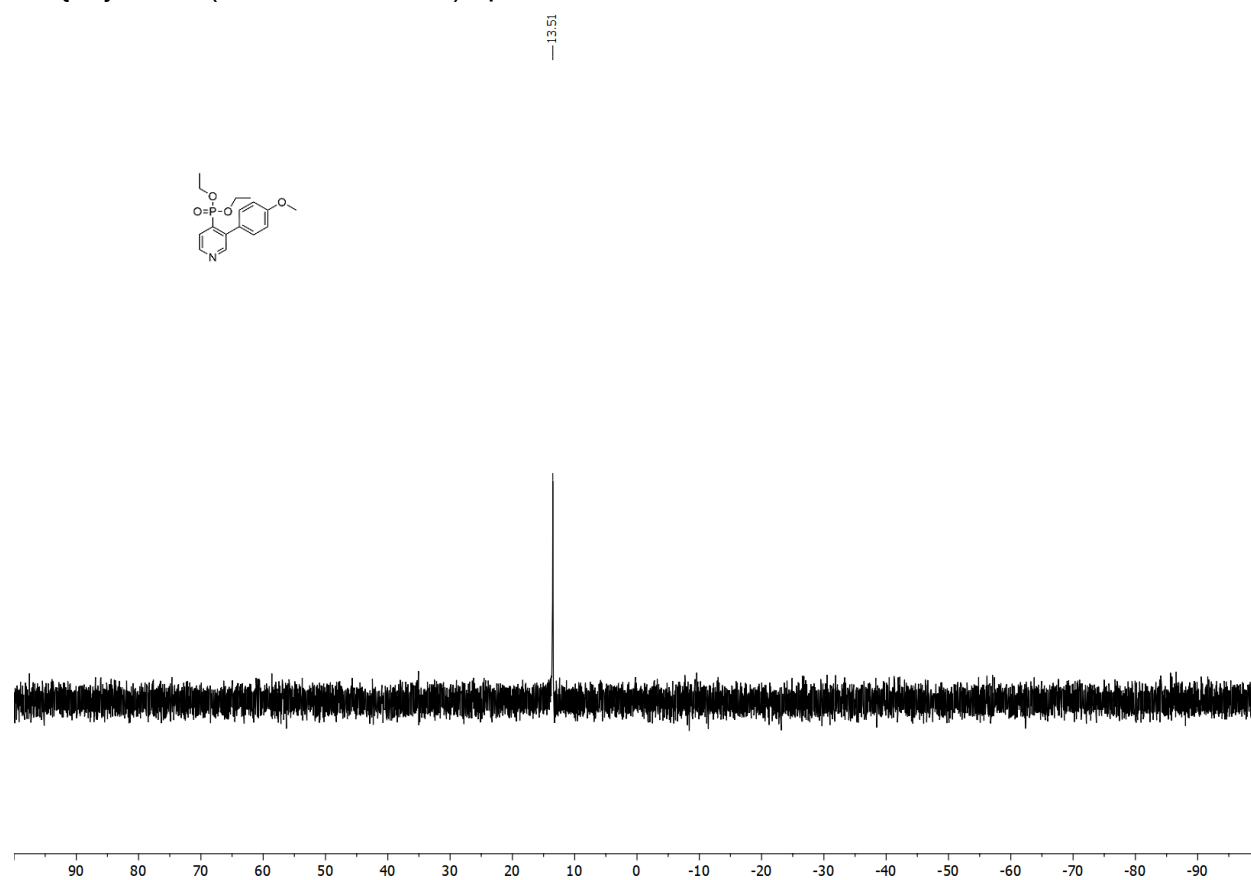
ESI+ TOF

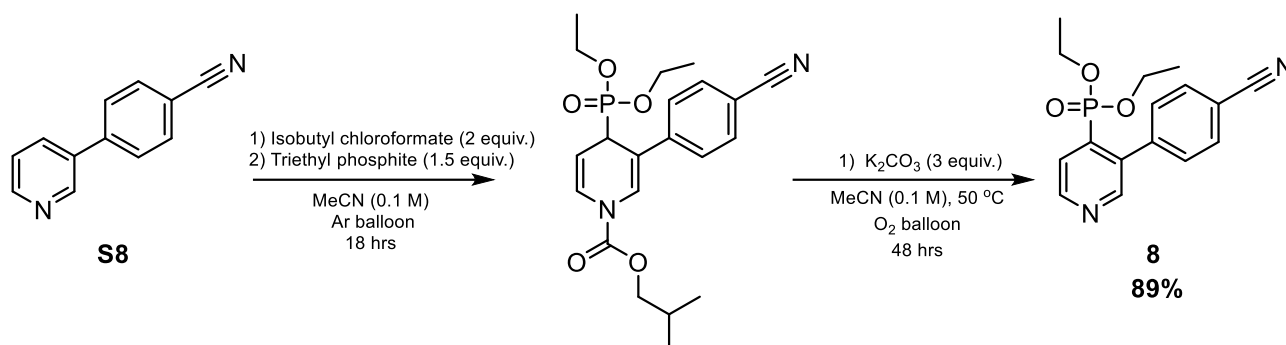
m/z $[M+H]^+$ calcd for $C_{16}H_{21}NO_4P$ 322.1203; Found 322.1203.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **7**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **7**





4-(3-Pyridinyl)benzonitrile (50 mg, 0.28 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (76 mg, 0.56 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (70 mg, 0.42 mmol, 1.5 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (116 mg, 0.84 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C for 48 hours, affording product **8** (79 mg, 0.25 mmol, 89%) as a yellow oil.

R_f=0.25 in 60% EtOAc/hexanes.

¹H-NMR

(300 MHz, CDCl₃)

δ 8.80 (t, J = 4.8 Hz, 1H), 8.60 (d, J = 6.5 Hz, 1H),
7.86 (dd, J = 14.7, 5.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H),
7.59 (d, J = 8.4 Hz, 2H), 4.10 – 3.84 (m, 4H),
1.17 (t, J = 7.0 Hz, 6H)

¹³C{¹H}-NMR

(101 MHz, CDCl₃)

δ 151.0 (d, $^3J_{C-P}$ = 11.2 Hz), 149.7 (d, $^3J_{C-P}$ = 12.0 Hz),
142.6 (d, $^3J_{C-P}$ = 4.2 Hz), 137.8 (d, $^2J_{C-P}$ = 7.6 Hz),
136.0 (d, $^1J_{C-P}$ = 185.0 Hz), 131.8, 130.6,
126.5 (d, $^2J_{C-P}$ = 7.6 Hz), 118.7, 112.4, 62.9 (d, $^2J_{C-P}$ = 6.2 Hz),
16.3 (d, $^3J_{C-P}$ = 6.4 Hz)

³¹P{¹H}-NMR

³¹P NMR (121 MHz, CDCl₃)

δ 14.1

IR

Alpha-Platinum ATR, Bruker, diamond crystal

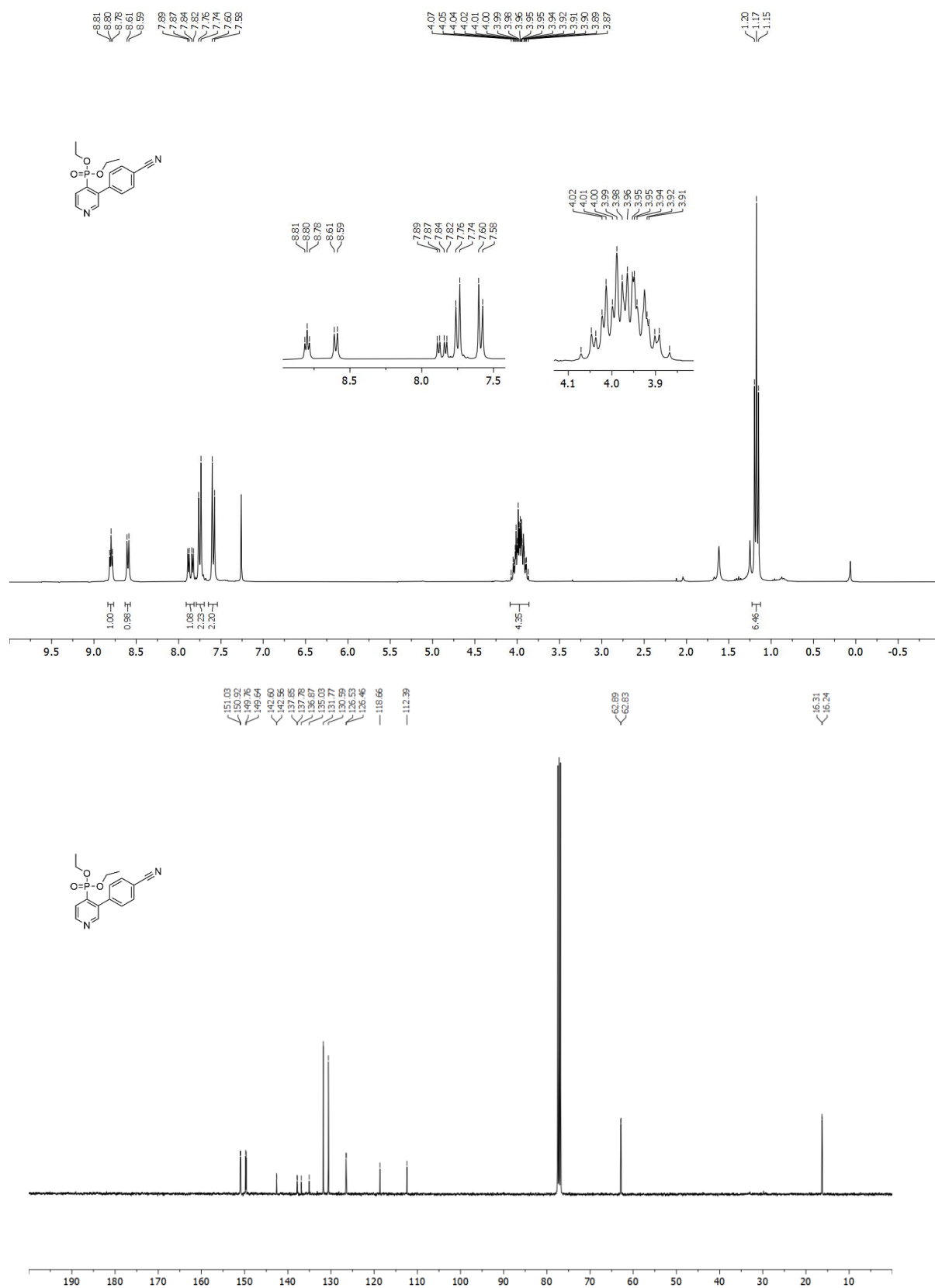
$\tilde{\nu}$ = 2962, 2273, 1771, 1009, 989, 781, 736, 588 cm⁻¹

HRMS

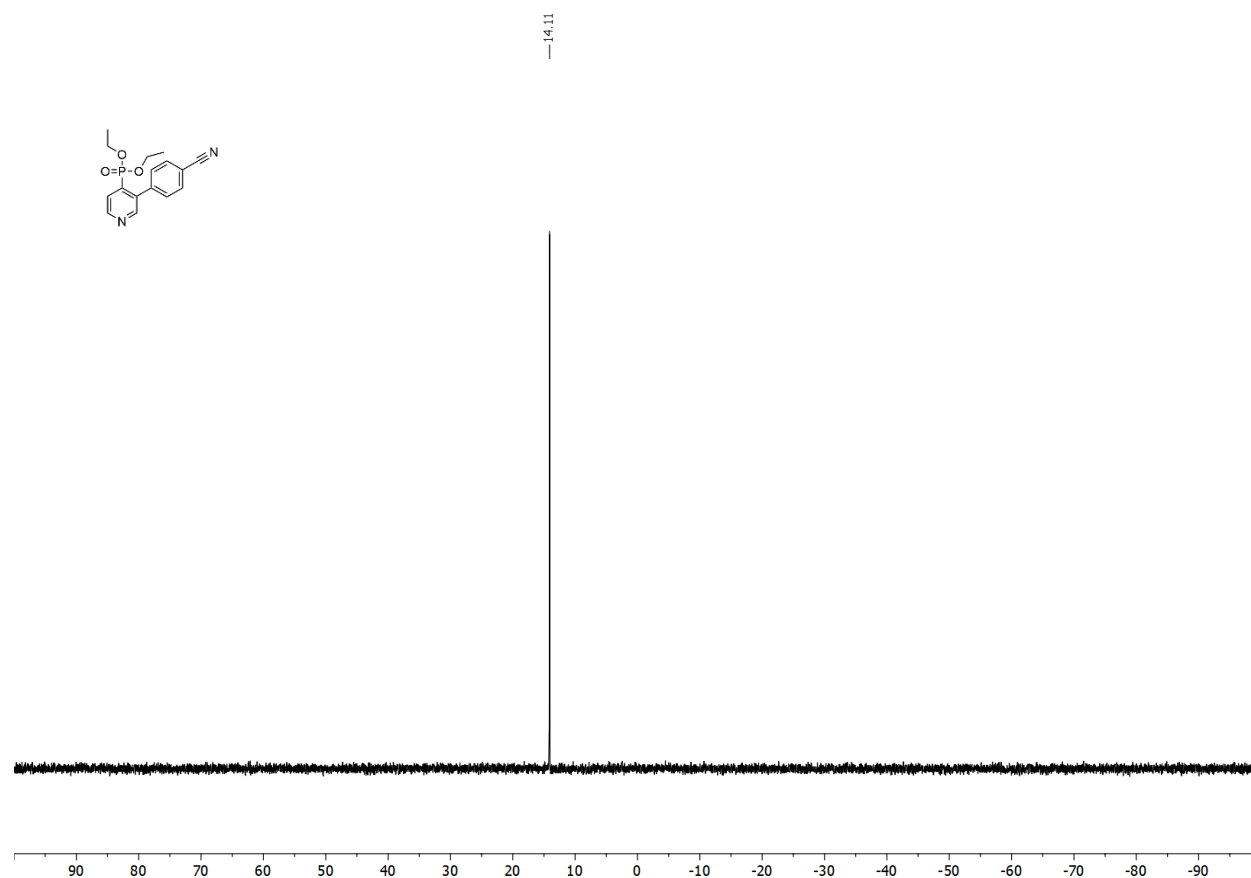
ESI+ TOF

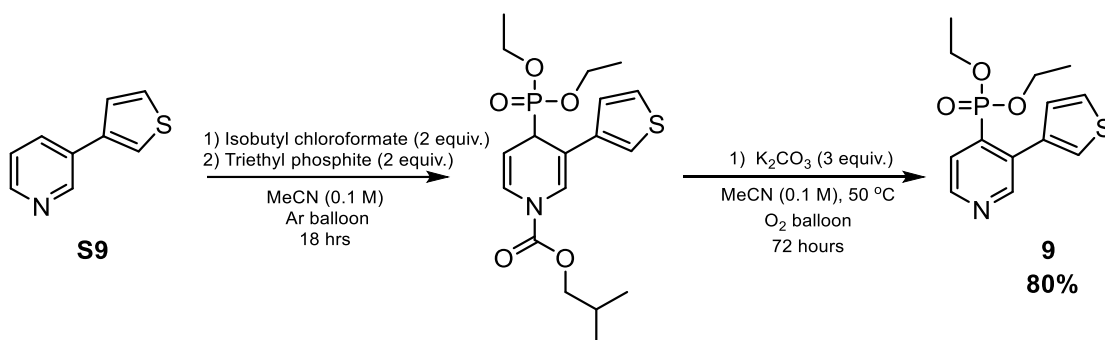
m/z [M+H]⁺ calcd for C₁₆H₁₈N₂O₃P. 317.1050; Found 317.1051.

^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **8**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **8**





3-(3-Thienyl)pyridine (120 mg, 0.74 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (202 mg, 1.48 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (246 mg, 1.48 mmol, 2.0 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (306 mg, 2.22 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C for 72 hours, affording product **9** (177 mg, 0.60 mmol, 80%) as a yellow oil.

R_f = 0.35 in 70% EtOAc/hexanes.

¹H-NMR

(300 MHz, CDCl₃)

δ 8.74 – 8.64 (m, 2H), 7.83 (ddd, J = 14.2, 5.0, 0.7 Hz, 1H),
 7.55 (dd, J = 3.0, 1.3 Hz, 1H), 7.39 (dd, J = 5.0, 3.0 Hz, 1H),
 7.31 (dd, J = 4.9, 1.3 Hz, 1H), 4.12 – 3.84 (m, 4H),
 1.19 (td, J = 7.1, 0.6 Hz, 6H)

¹³C{¹H}-NMR

(75 MHz, CDCl₃)

δ 151.6 (d, $^3J_{C-P}$ = 11.3 Hz), 148.5 (d, $^3J_{C-P}$ = 12.2 Hz),
 137.7 (d, $^3J_{C-P}$ = 4.6 Hz), 135.6 (d, $^1J_{C-P}$ = 184.7 Hz),
 134.7 (d, $^2J_{C-P}$ = 7.9 Hz), 129.3, 126.7 (d, $^2J_{C-P}$ = 7.8 Hz), 125.5,
 125.3, 62.7 (d, $^2J_{C-P}$ = 6.2 Hz), 16.2 (d, $^3J_{C-P}$ = 6.6 Hz)

³¹P{¹H}-NMR

³¹P NMR (121 MHz, CDCl₃)

δ 15.0

IR

Alpha-Platinum ATR, Bruker, diamond crystal

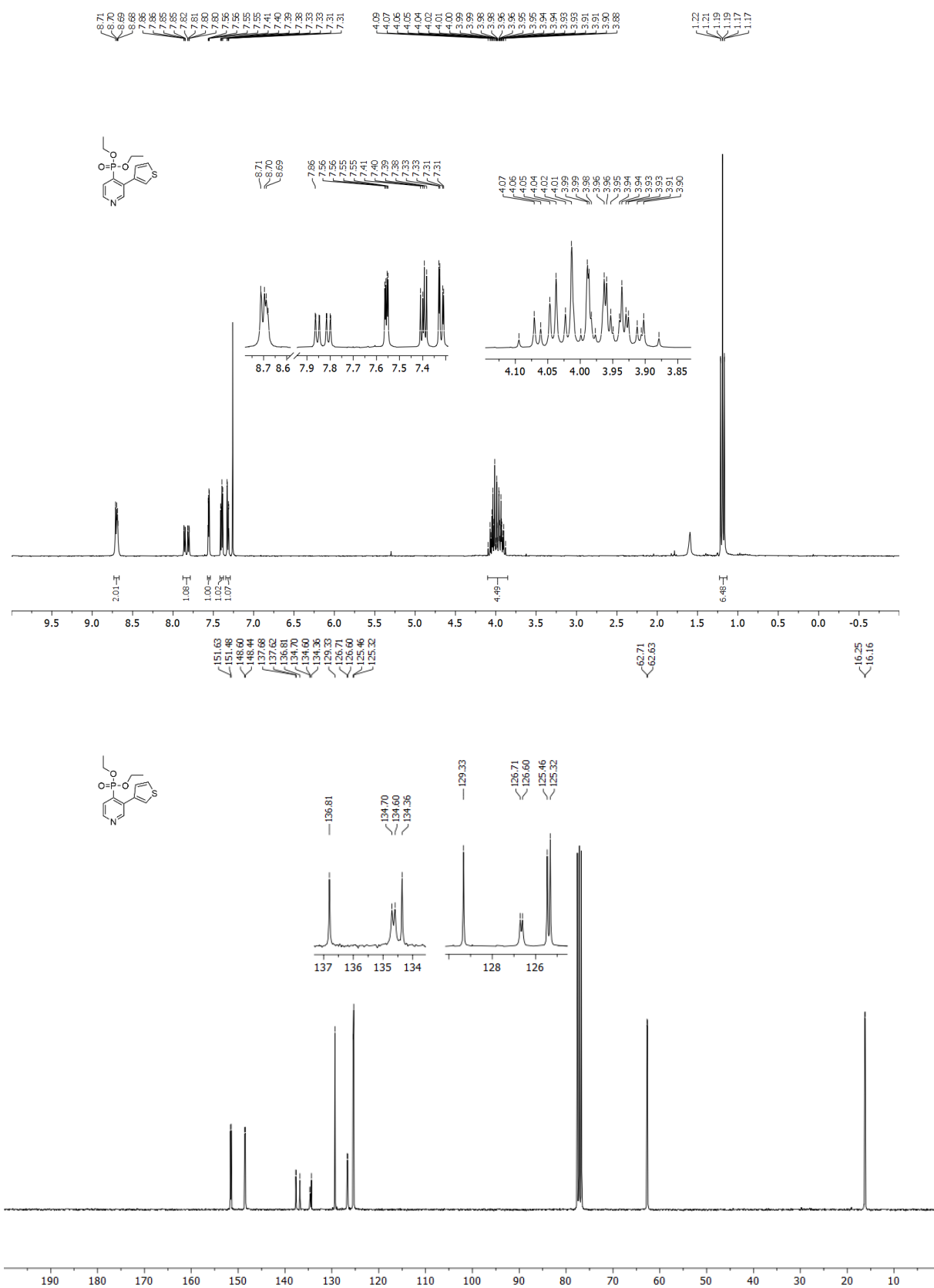
$\tilde{\nu}$ = 3100, 2995, 1220, 1005, 996, 792, 557 cm⁻¹,

HRMS

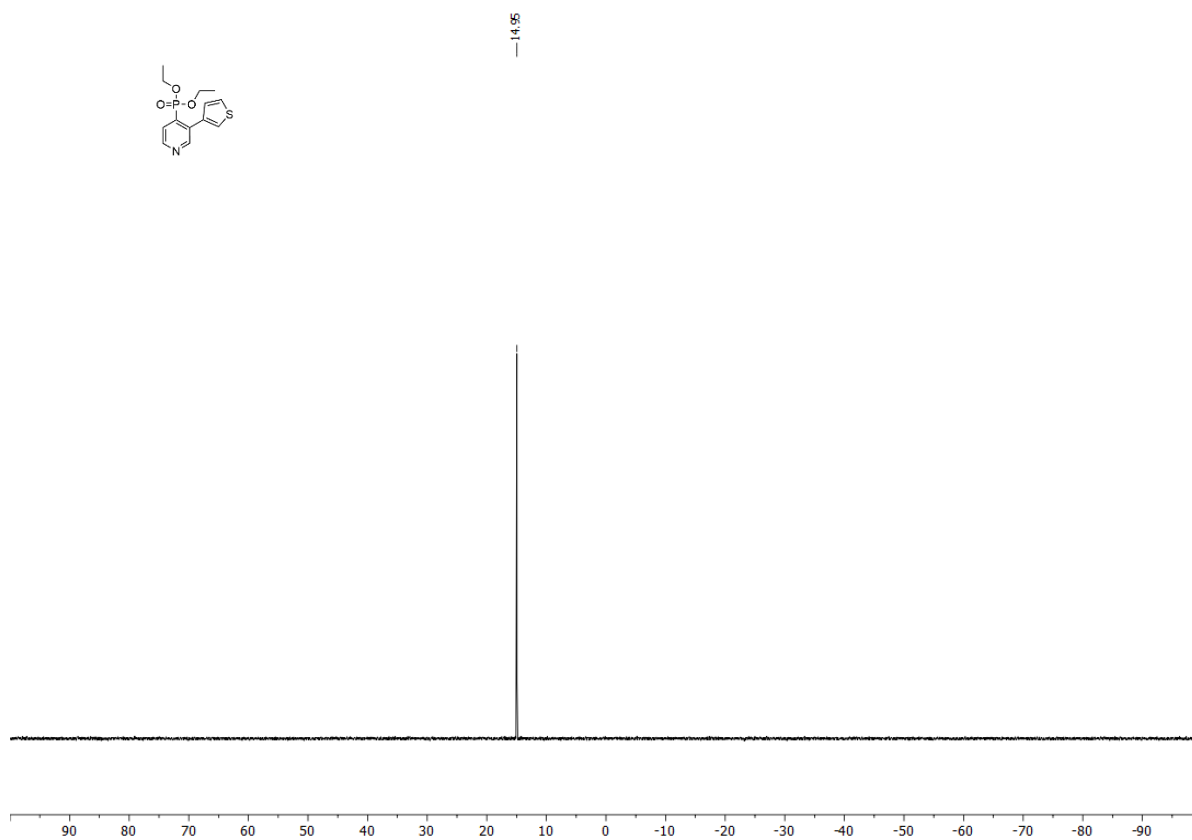
ESI+ TOF

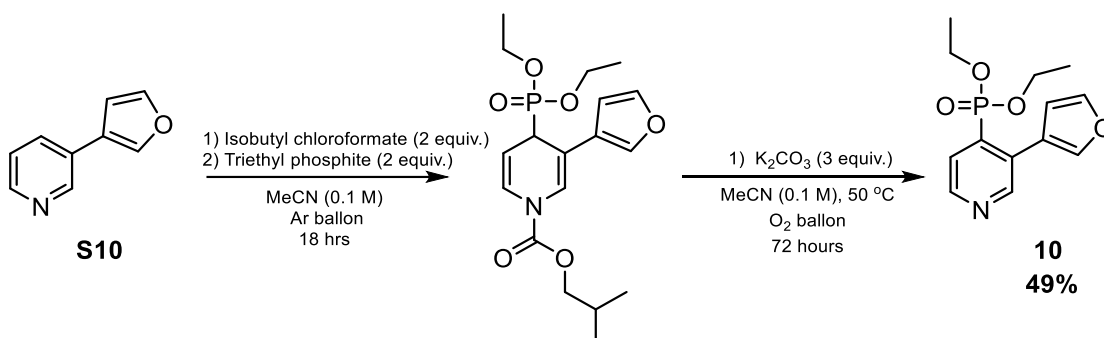
m/z [M+H]⁺ calcd for C₁₃H₁₇NO₃PS. 298.0661; Found 298.0661.

^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **9**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **9**





3-(3-Furanyl)pyridine (120 mg, 0.83 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (226 mg, 1.66 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (275 mg, 1.66 mmol, 2.0 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (343 mg, 2.49 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C for 72 hours, affording product **10** (114 mg, 0.41 mmol, 49%) as a yellow oil.

R_f = 0.35 in 70% EtOAc/hexanes.

¹H-NMR

(600 MHz, $CDCl_3$)

δ 8.70 (d, J = 6.6 Hz, 1H), 8.67 (t, J = 4.8 Hz, 1H),
7.83 (dd, J = 14.4, 5.0 Hz, 1H), 7.79 (s, 1H), 7.50 (s, 1H),
6.74 (s, 1H), 4.15 – 3.98 (m, 1H), 1.25 (t, J = 7.1 Hz, 6H)

¹³C{¹H}-NMR

(151 MHz, $CDCl_3$)

δ 151.6 (d, $^3J_{C-P}$ = 11.3 Hz), 148.6 (d, $^3J_{C-P}$ = 12.1 Hz), 142.9,
142.0, 135.6 (d, $^1J_{C-P}$ = 184.2 Hz), 130.9 (d, $^2J_{C-P}$ = 7.1 Hz),
126.9 (d, $^2J_{C-P}$ = 7.4 Hz), 122.0 (d, $^3J_{C-P}$ = 4.9 Hz), 112.2,
62.8 (d, $^2J_{C-P}$ = 6.1 Hz), 16.3 (d, $^3J_{C-P}$ = 6.4 Hz)

³¹P{¹H}-NMR

³¹P NMR (162 MHz, $CDCl_3$)

δ 15.0

IR

Alpha-Platinum ATR, Bruker, diamond crystal

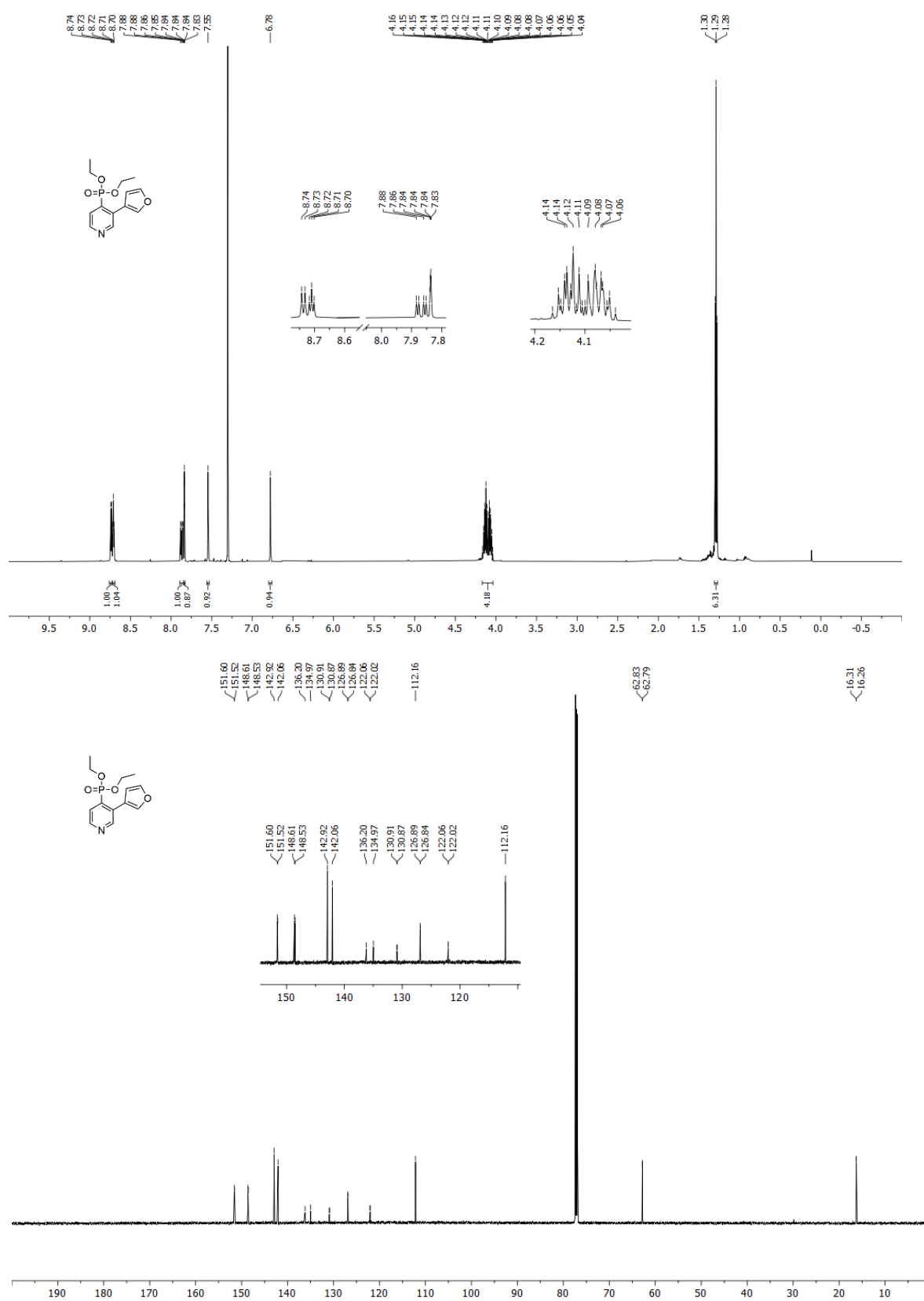
$\tilde{\nu}$ = 3002, 1443, 1252, 1004, 987, 777, 590 cm^{-1}

HRMS

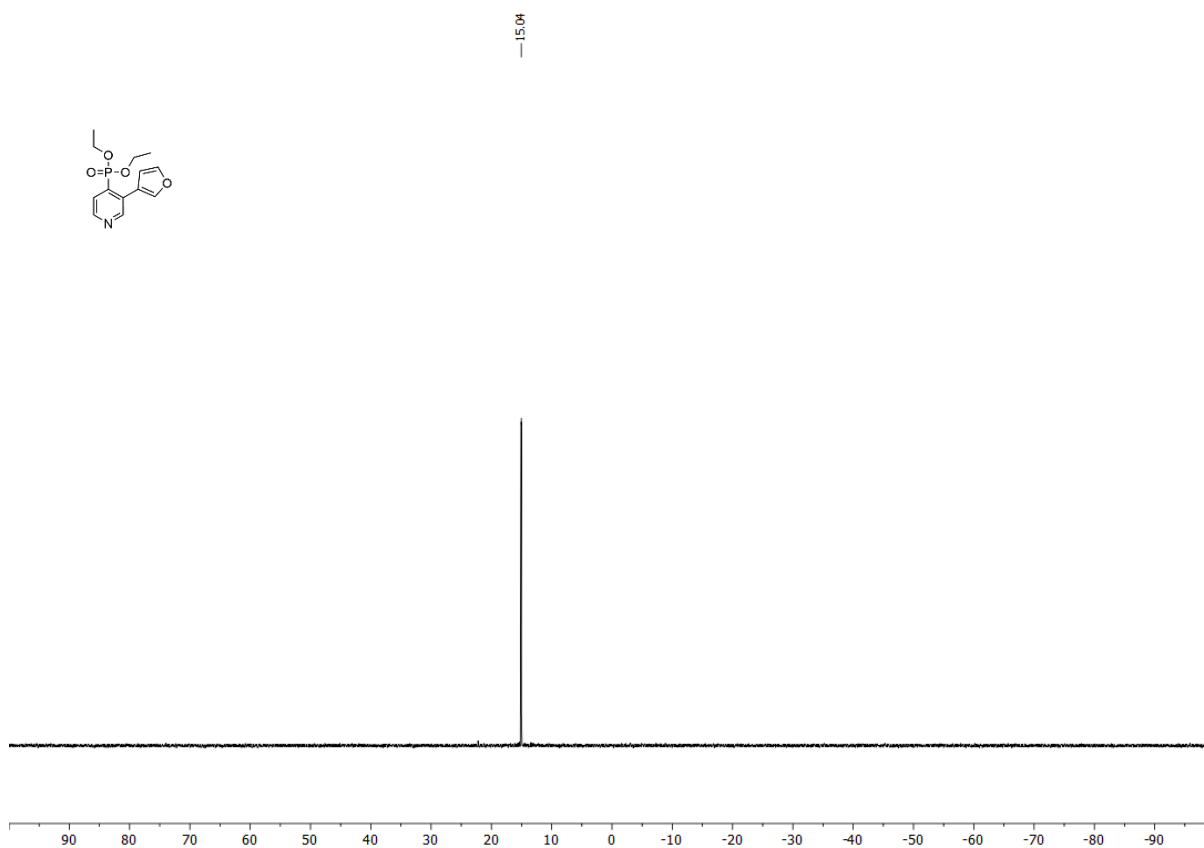
ESI+ TOF

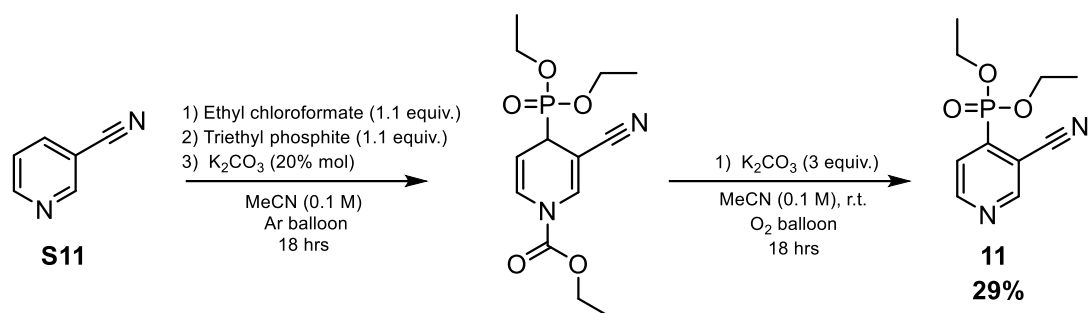
m/z $[M+H]^+$ calcd for $C_{13}H_{17}NO_4P$. 282.0890; Found 282.0891.

^1H -NMR (600 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(151 MHz, CDCl_3) spectra of **10**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **10**





3-Cyanopyridine (200 mg, 1.92 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (53 mg, 0.38 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (796 mg, 5.76 mmol, 3.0 equiv.) according to **procedure B**, provided product **11** (134 mg, 0.56 mmol, 29% yield) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

1H -NMR

(300 MHz, $CDCl_3$)

δ 9.01 (d, J = 5.6 Hz, 1H), 8.93 (t, J = 5.1 Hz, 1H),
7.94 (dd, J = 14.1, 4.9 Hz, 1H), 4.39 – 4.16 (m, 4H),
1.40 (t, J = 7.0 Hz, 6H)

$^{13}C\{^1H\}$ -NMR

(101 MHz, $CDCl_3$)

δ 154.0 (d, $^3J_{C-P}$ = 8.5 Hz), 153.1 (d, $^3J_{C-P}$ = 11.7 Hz),
141.1 (d, $^1J_{C-P}$ = 184.9 Hz), 127.1 (d, $^2J_{C-P}$ = 7.0 Hz),
115.3 (d, $^2J_{C-P}$ = 6.0 Hz), 110.9 (d, $^3J_{C-P}$ = 3.2 Hz),
64.0 (d, $^2J_{C-P}$ = 6.2 Hz), 16.4 (d, $^3J_{C-P}$ = 6.2 Hz)

$^{31}P\{^1H\}$ -NMR

(121 MHz, $CDCl_3$)

δ 9.7

IR

Alpha-Platinum ATR, Bruker, diamond crystal

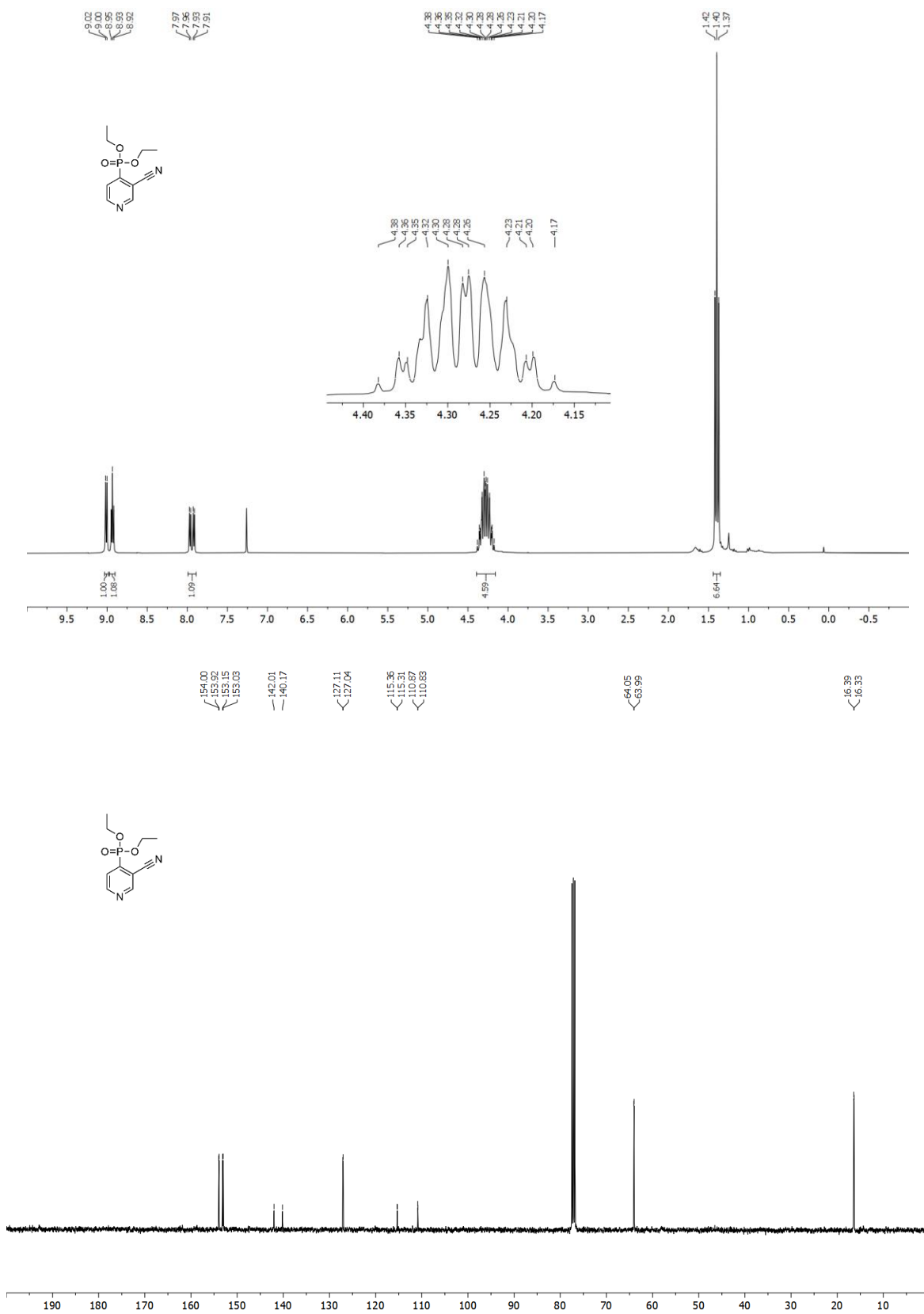
$\tilde{\nu}$ = 3010, 2250, 1260, 1100, 1005, 610 cm^{-1}

HRMS

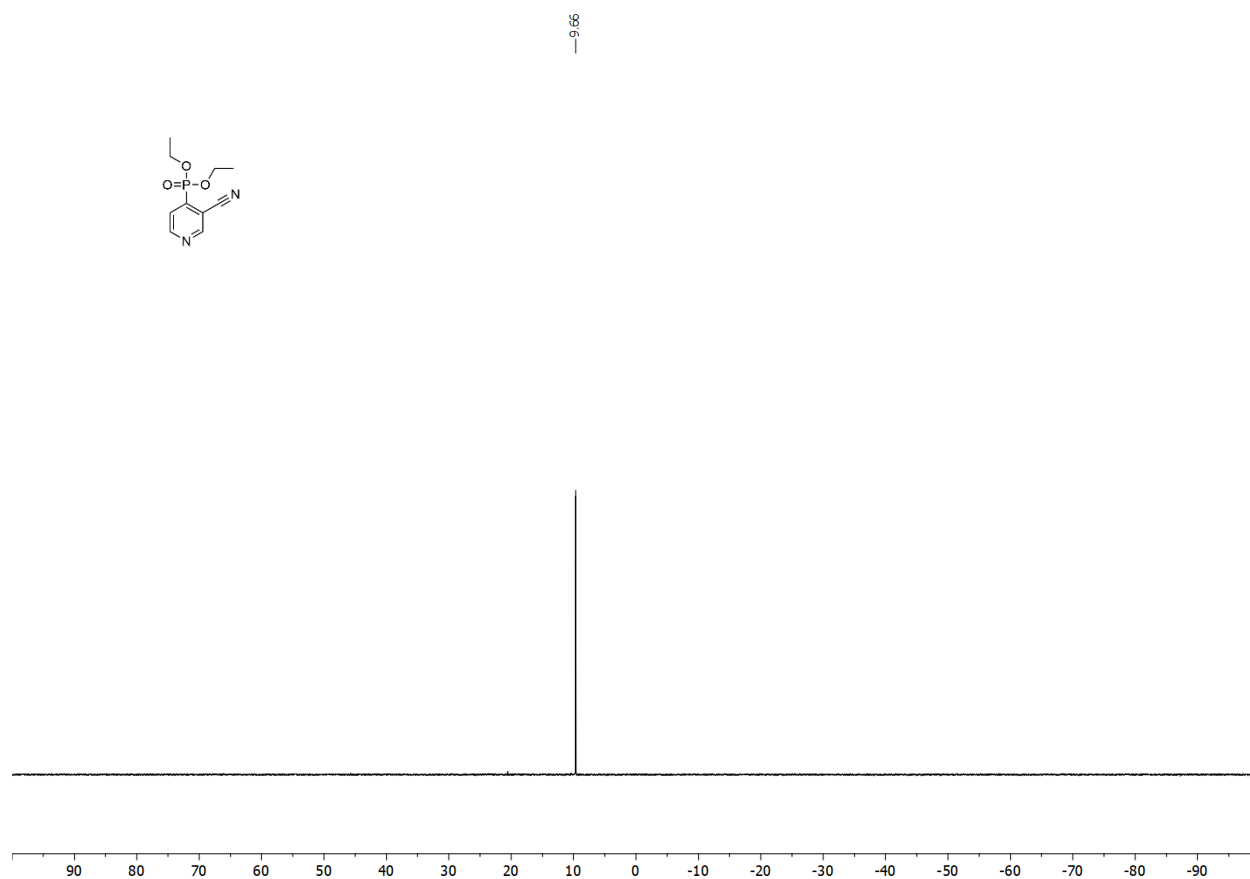
ESI+ TOF

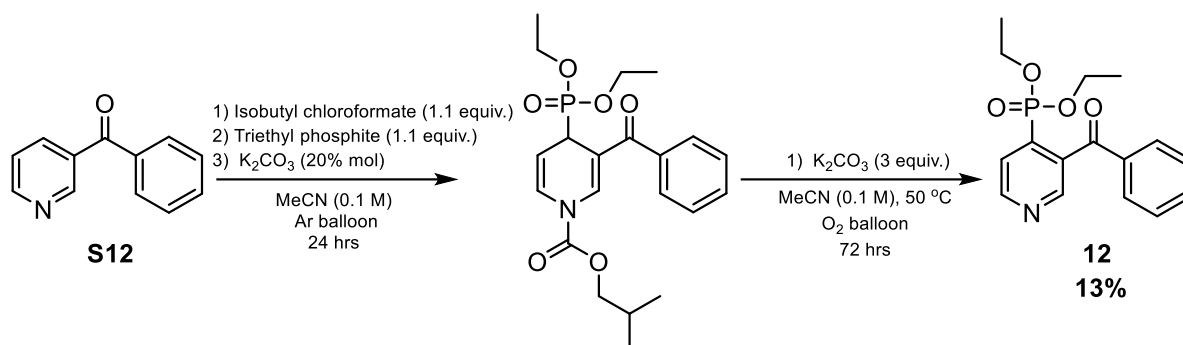
m/z $[M+H]^+$ calcd for $C_{10}H_{14}N_2O_3P$. 241.0737; Found 241.0741.

^1H -NMR (300 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **11**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) spectra of **11**





3-Benzoylpyridine (250 mg, 1.36 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**. Treatment of the crude intermediate with K_2CO_3 (564mg, 4.08mmol, 3.0 equiv.) according to **procedure B**, except the reaction mixture was stirred for 72 hours at 50 °C, providing product **12** (57 mg, 0.177 mmol, 13% yield) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, $CDCl_3$)

δ 8.85 (t, J = 4.8 Hz, 1H), 8.64 (d, J = 6.0 Hz, 1H),
 7.86 (dd, J = 13.8, 4.8 Hz, 1H), 7.76 (dd, J = 8.4, 1.3 Hz, 2H),
 7.64 – 7.55 (m, 1H), 7.45 (t, J = 7.8 Hz, 1H), 4.12 – 3.90 (m, 4H),
 1.14 (t, J = 7.1 Hz, 6H)

¹³C{¹H}-NMR

(101 MHz, $CDCl_3$)

δ 194.9 (d, $^3J_{C-P}$ = 3.8 Hz), 150.7 (d, $^3J_{C-P}$ = 11.6 Hz),
 148.1 (d, $^3J_{C-P}$ = 10.8 Hz), 137.5 (d, $^2J_{C-P}$ = 8.7 Hz), 136.7,
 136.3 (d, $^1J_{C-P}$ = 185.8 Hz), 134.0, 130.3, 128.7,
 126.8 (d, $^2J_{C-P}$ = 7.8 Hz), 63.1 (d, $^2J_{C-P}$ = 6.1 Hz),
 16.1 (d, $^3J_{C-P}$ = 6.5 Hz)

³¹P{¹H}-NMR

³¹P NMR (162 MHz, $CDCl_3$)

δ 12.9

IR

Alpha-Platinum ATR, Bruker, diamond crystal

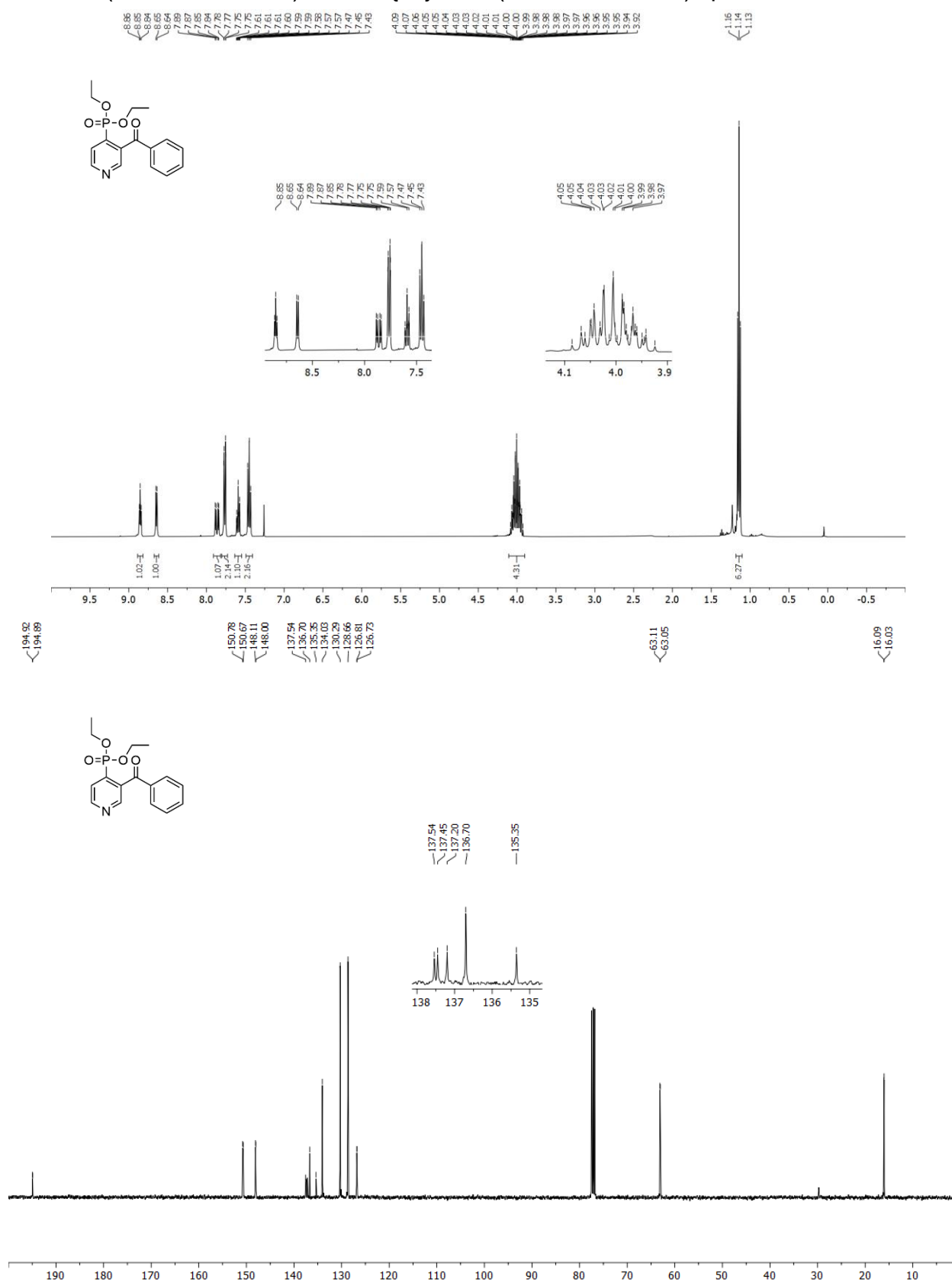
$\tilde{\nu}$ = 2950, 1710, 1240, 1100, 1010, 980, 730, 610 cm^{-1}

HRMS

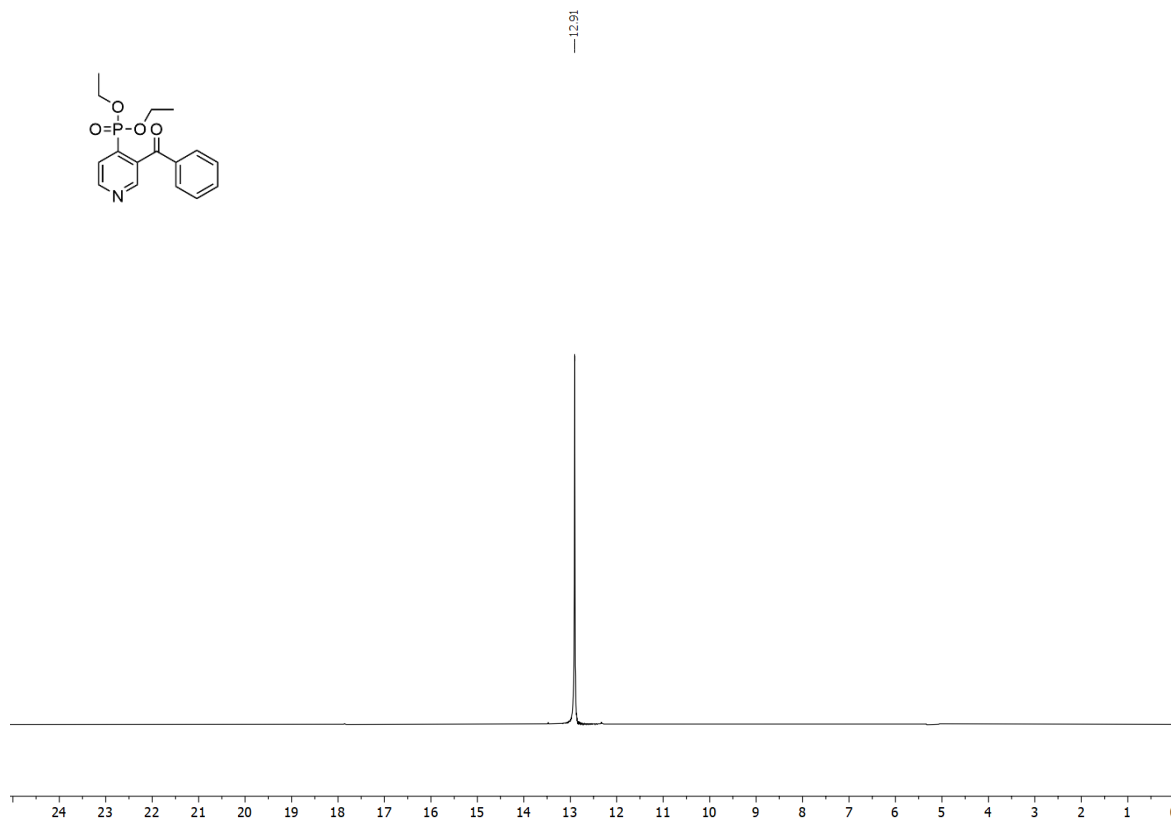
ESI+ TOF

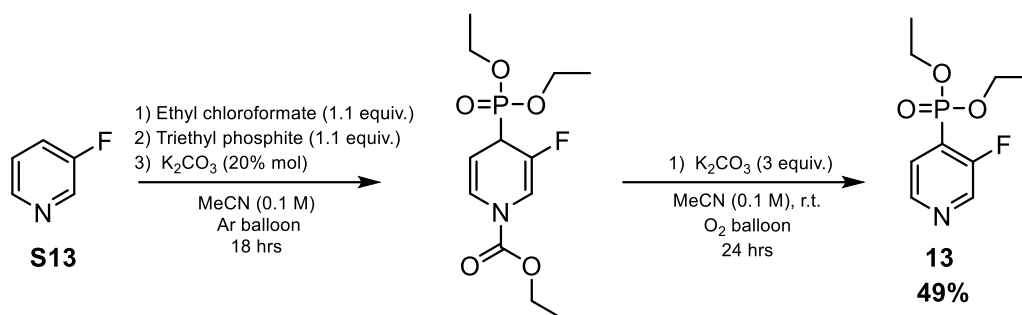
m/z $[M+H]^+$ calcd for $C_{16}H_{19}NO_4P$. 320.1046; Found 320.1047.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **12**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **12**





3-Fluoropyridine (150 mg, 1.54 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (43 mg, 0.31 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (640 mg, 4.62 mmol, 3.0 equiv.) according to **procedure B**, provided product **13** (176 mg, 0.75 mmol, 49% yield) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

¹H-NMR (700 MHz, $CDCl_3$)
 δ 8.54 (t, J = 11.5 Hz, 2H), 7.69 (dt, J = 14.5, 5.0 Hz, 1H),
 4.26 – 4.11 (m, 4H), 1.33 (t, J = 7.1 Hz, 6H)

¹³C{¹H}-NMR (176 MHz, $CDCl_3$)
 δ 159.0 (d, $^1J_{C-P}$ = 263.1 Hz),
 145.9 (dd, $^3J_{C-P}$ = 11.9 Hz, $^4J_{C-F}$ = 5.1 Hz),
 139.2 (dd, $^2J_{C-F}$ = 25.3 Hz, $^3J_{C-P}$ = 6.2 Hz), 127.4 (d, $^2J_{C-P}$ = 4.8 Hz),
 125.0 (dd, $^1J_{C-F}$ = 184.0, $^2J_{C-P}$ = 16.1 Hz), 63.3 (d, 2J = 5.8 Hz),
 16.4 (d, 3J = 6.3 Hz)

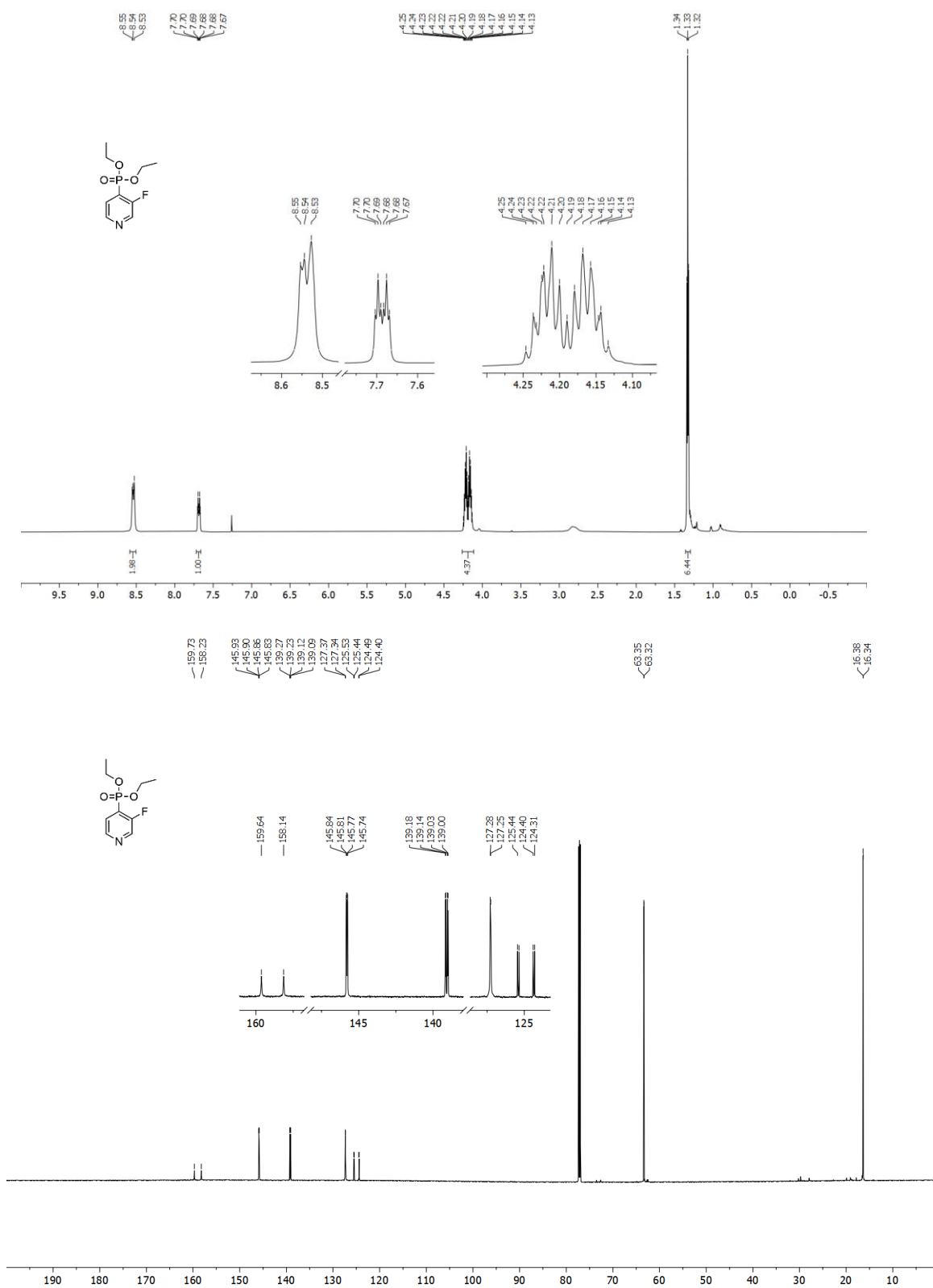
³¹P{¹H}-NMR (121 MHz, $CDCl_3$)
 δ 10.3

¹⁹F{¹H}-NMR (282 MHz, $CDCl_3$)
 δ -118.6

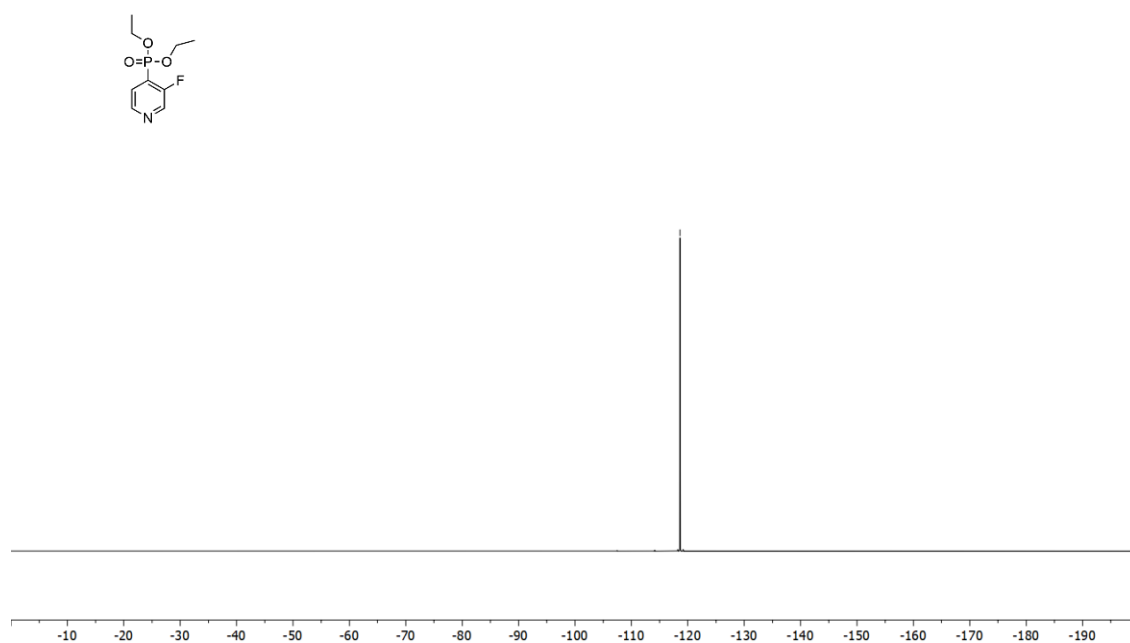
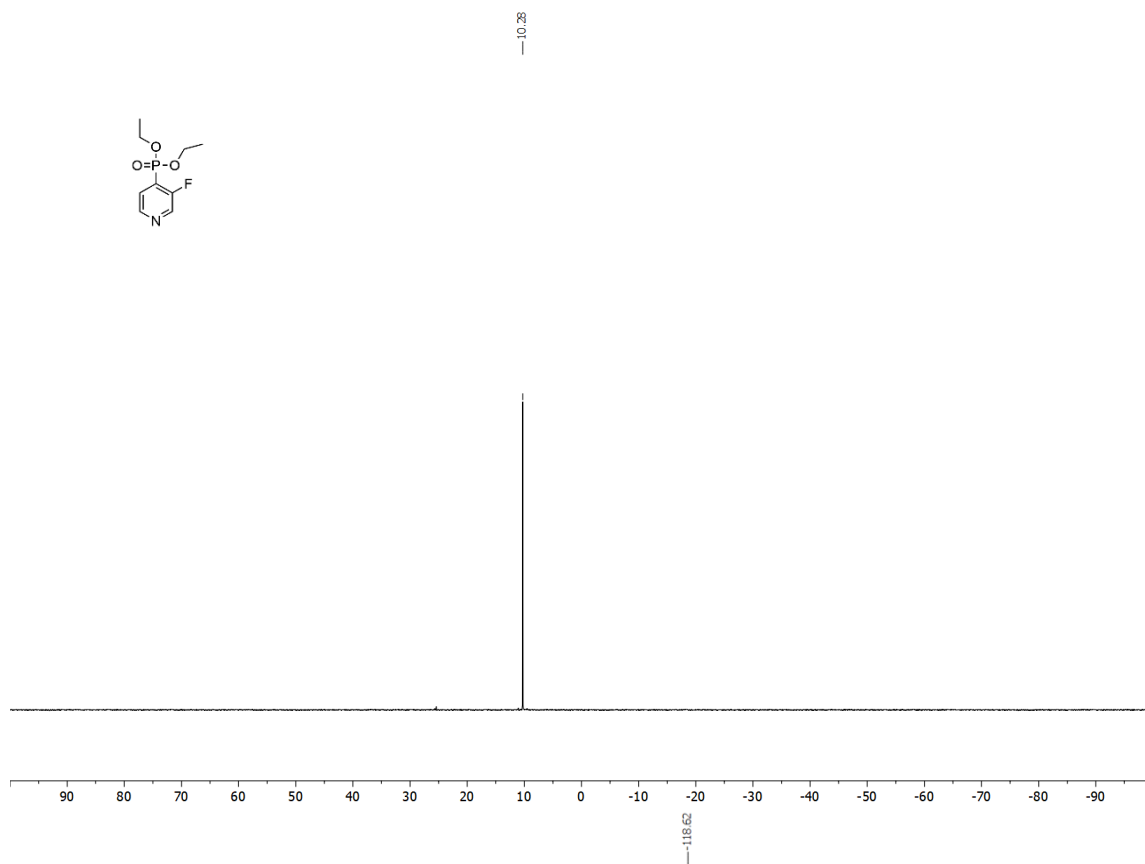
IR Alpha-Platinum ATR, Bruker, diamond crystal
 $\tilde{\nu}$ = 2998, 1477, 1243, 1005, 992, 770, 591 cm^{-1}

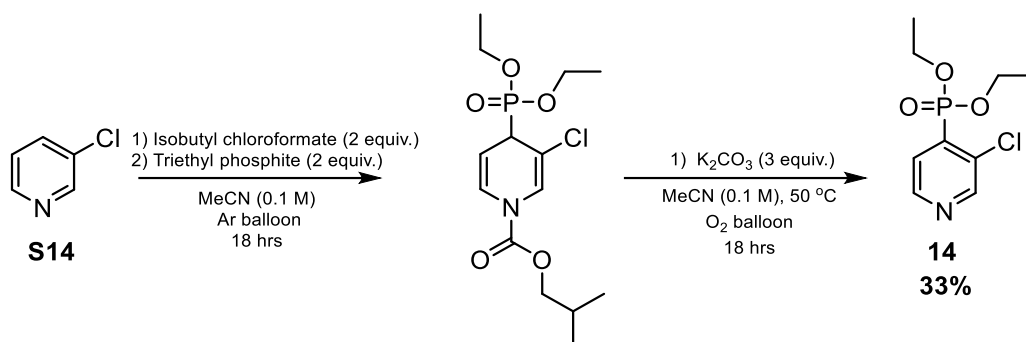
HRMS ESI+ TOF
 m/z $[M+H]^+$ calcd for $C_9H_{14}FNO_3P$. 234.0693; Found 234.1790.

^1H -NMR (700 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(176 MHz, CDCl_3) spectra of **13**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) and $^{19}\text{F}\{^1\text{H}\}$ -NMR (282 MHz, CDCl_3) spectra of **13**





3-Chloropyridine (150 mg, 1.32 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that isobutyl chloroformate (180 mg, 2.64 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (220 mg, 2.64 mmol, 2.0 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (548 mg, 3.96 mmol, 3.0 equiv.) according to **procedure B**, except that the reaction mixture was stirred at 50 °C, provided product **14** (110 mg, 0.44 mmol, 33%) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, $CDCl_3$)

δ 8.70 (d, J = 6.2 Hz, 1H), 8.62 (t, J = 4.5 Hz, 1H),
7.82 (dd, J = 14.2, 4.8 Hz, 1H),
4.32 – 4.07 (m, 4H), 1.37 (t, J = 7.0 Hz, 6H).

¹³C{¹H}-NMR

(101 MHz, $CDCl_3$)

δ 150.7 (d, $^3J_{C-P}$ = 8.2 Hz), 147.8 (d, $^3J_{C-P}$ = 11.6 Hz),
136.1 (d, $^1J_{C-P}$ = 186.9 Hz), 133.4, 128.26 (d, $^2J_{C-P}$ = 6.5 Hz),
63.3 (d, $^2J_{C-P}$ = 5.9 Hz), 16.3 (d, $^3J_{C-P}$ = 6.4 Hz)

³¹P{¹H}-NMR

³¹P NMR (162 MHz, $CDCl_3$)

δ 10.0

IR

Alpha-Platinum ATR, Bruker, diamond crystal

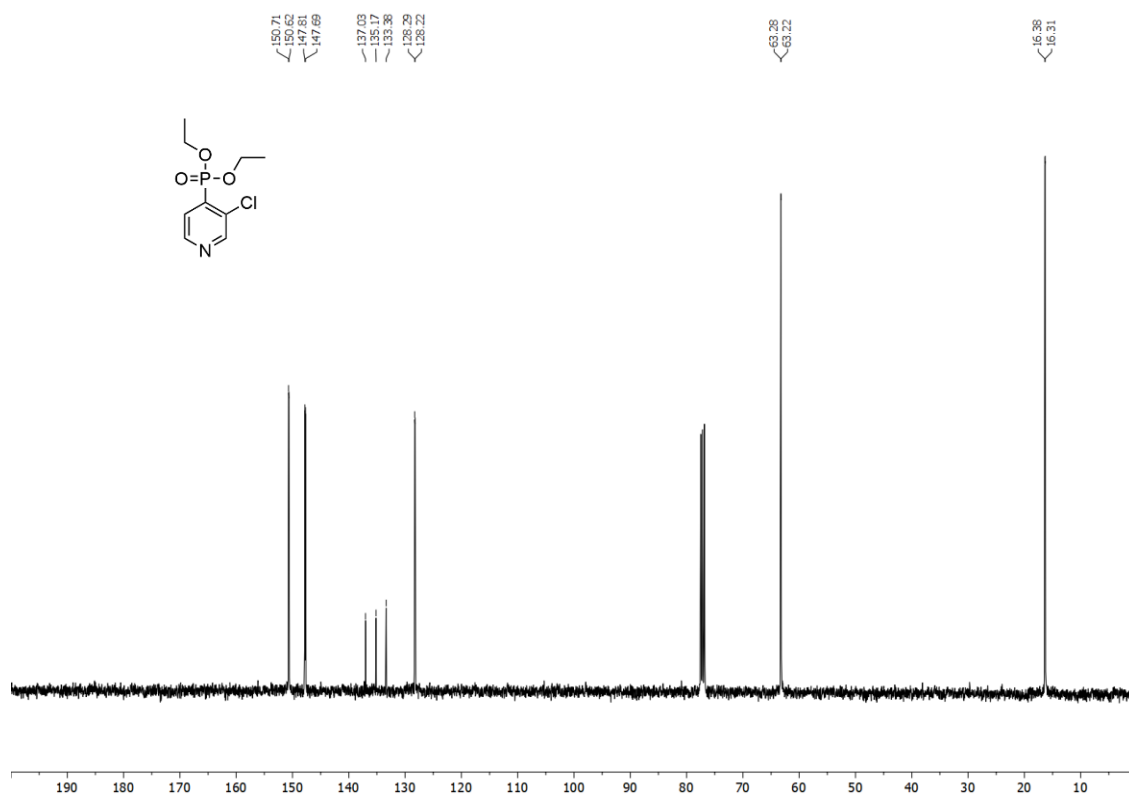
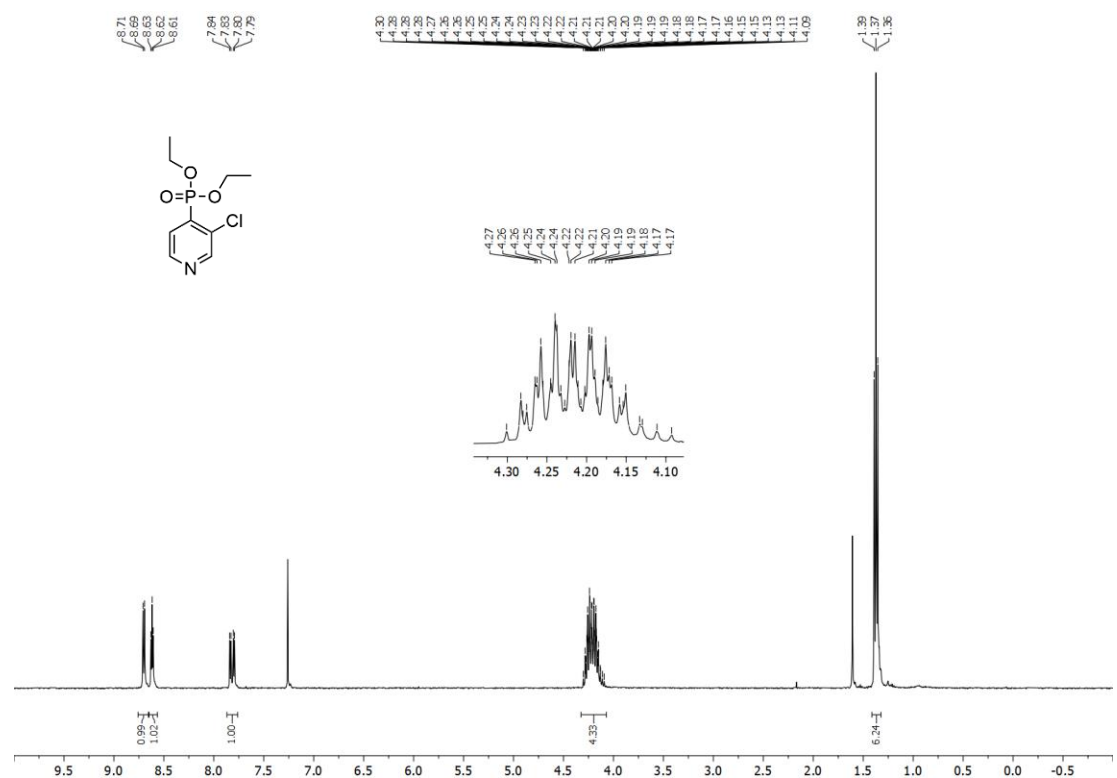
$\tilde{\nu}$ = 3006, 1398, 1270, 1005, 990, 792, 562 cm^{-1}

HRMS

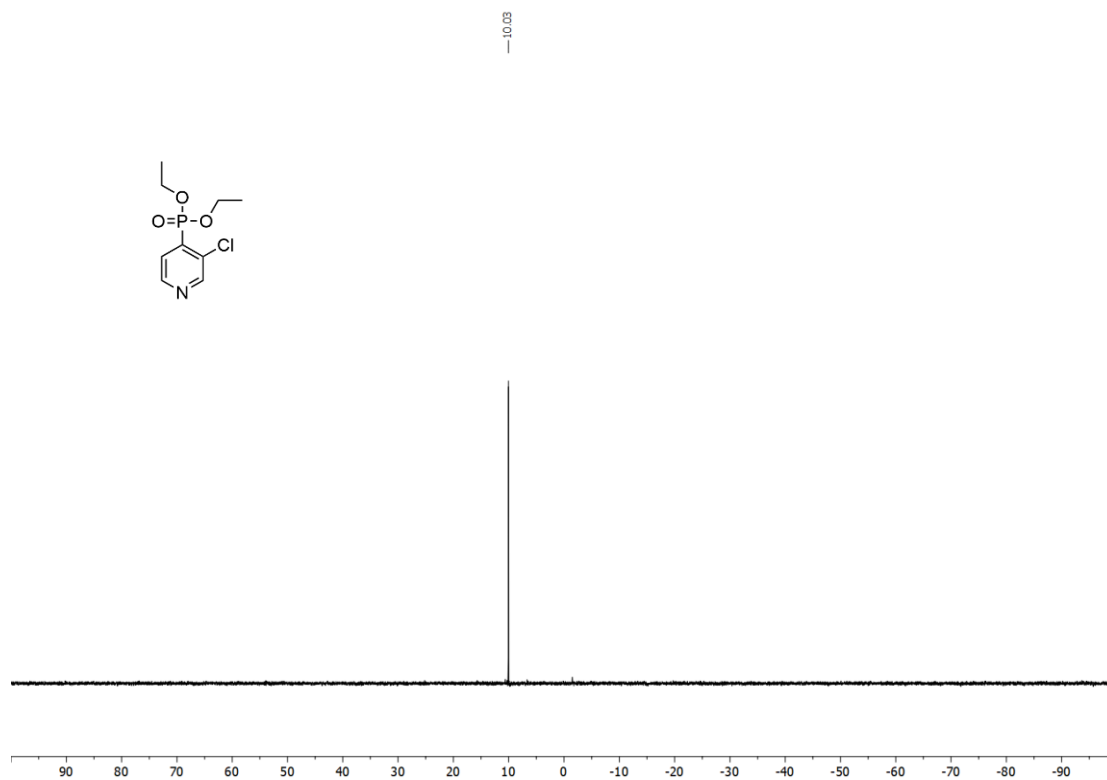
ESI+ TOF

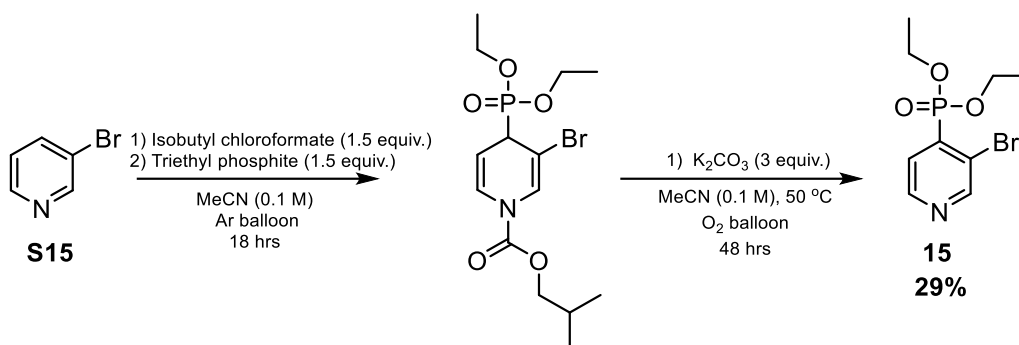
m/z $[M+H]^+$ calcd for $C_9H_{14}ClNO_3P$. 250.0394, Found 250.0395.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **14**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **14**





3-Bromopyridine (100 mg, 0.63 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that isobutyl chloroformate (130 mg, 0.95 mmol, 1.5 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (158 mg, 0.95 mmol, 1.5 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (261 mg, 1.89 mmol, 3.0 equiv.) according to **procedure B**, except that the reaction mixture was stirred at 50 °C for 48 hours, provided product **15** (53 mg, 0.18 mmol, 29%) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

1H -NMR

(400 MHz, $CDCl_3$)

δ 8.85 (d, J = 6.1 Hz, 1H), 8.66 (t, J = 4.4 Hz, 1H),
7.84 (dd, J = 14.1, 4.7 Hz, 1H), 4.32 – 4.11 (m, 4H),
1.38 (t, J = 7.1 Hz, 6H)

$^{13}C\{^1H\}$ -NMR

(101 MHz, $CDCl_3$)

δ 153.3 (d, $^3J_{C-P}$ = 9.1 Hz), 148.2 (d, $^3J_{C-P}$ = 11.5 Hz),
138.3 (d, $^1J_{C-P}$ = 188.1 Hz), 129.0 (d, $^2J_{C-P}$ = 6.9 Hz),
122.6 (d, $^2J_{C-P}$ = 2.4 Hz), 63.3 (d, $^2J_{C-P}$ = 5.8 Hz),
16.4 (d, $^3J_{C-P}$ = 6.2 Hz)

$^{31}P\{^1H\}$ -NMR

^{31}P NMR (162 MHz, $CDCl_3$)

δ 11.6

IR

Alpha-Platinum ATR, Bruker, diamond crystal

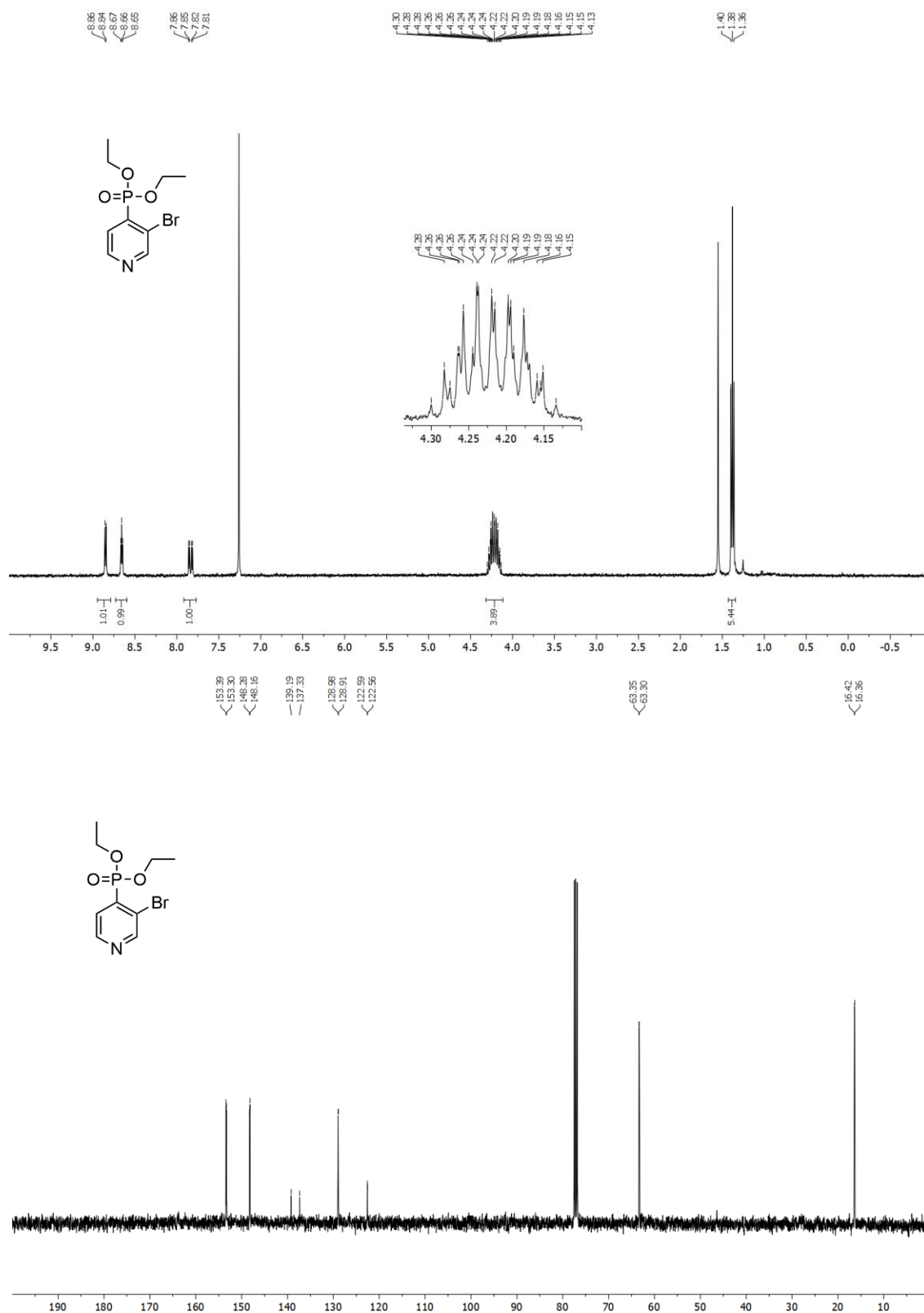
$\tilde{\nu}$ = 3010, 1482, 1272, 1006, 992, 780, 568 cm^{-1}

HRMS

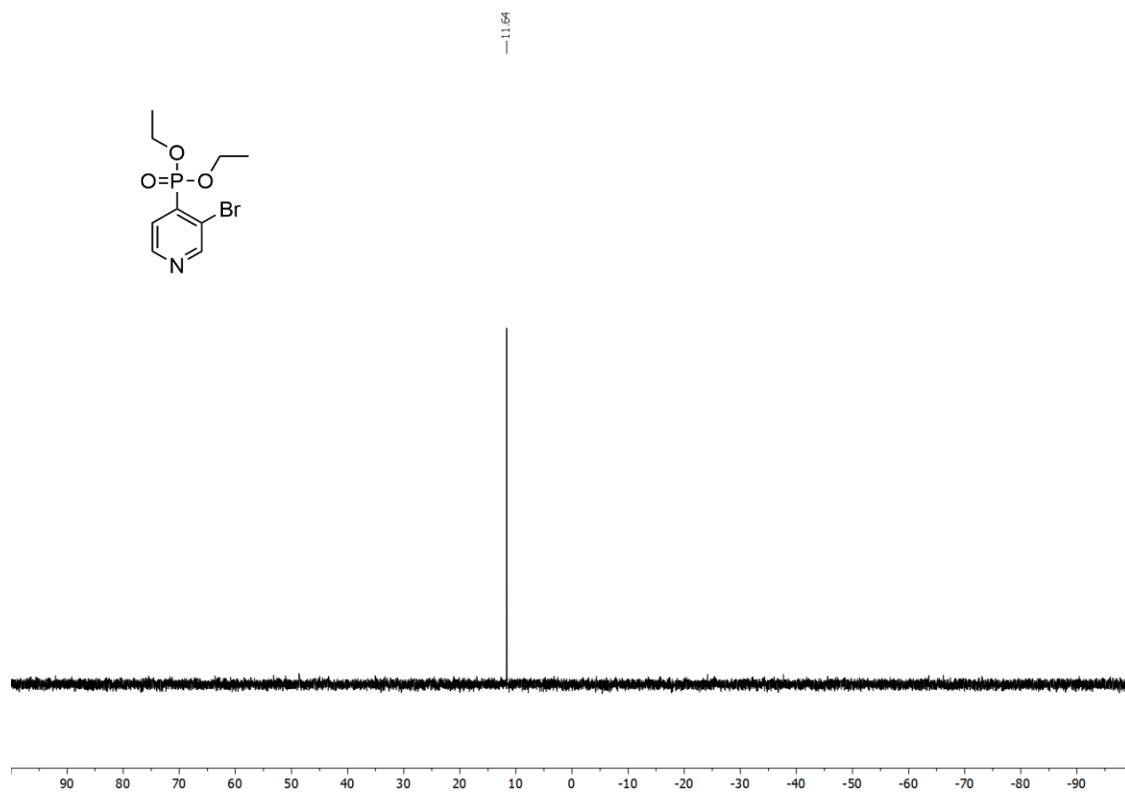
ESI+ TOF

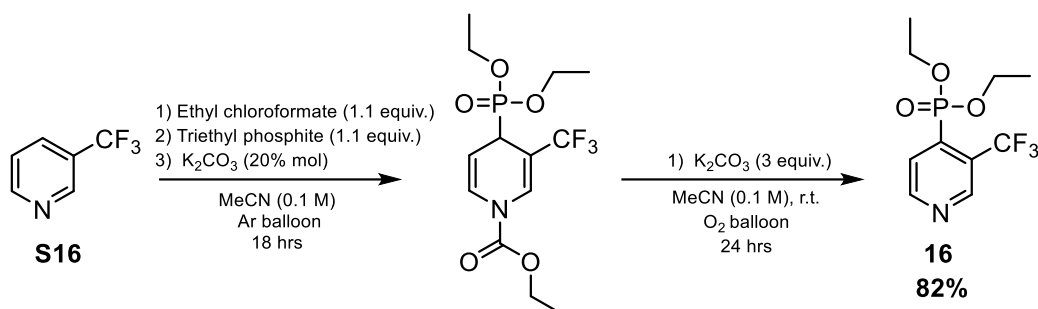
m/z $[M+H]^+$ calcd for $C_9H_{14}BrNO_3P$. 293.9890, Found 293.9890.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **15**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **15**





3-(Trifluoromethyl)pyridine (100 mg, 0.68 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that K_2CO_3 (19 mg, 0.14 mmol, 20 mol%) was added prior to the dropwise addition of the chloroformate. Treatment of the crude intermediate with K_2CO_3 (283 mg, 2.04 mmol, 3.0 equiv.) according to **procedure B** afforded product **16** (158 mg, 0.56 mmol, 82%) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

1H -NMR

(700 MHz, $CDCl_3$)

δ 8.57 (d, J = 6.7 Hz, 1H), 8.55 (t, J = 4.0 Hz, 1H),
7.71 (dt, J = 14.2, 5.0 Hz, 1H), 4.30 – 4.14 (m, 4H),
1.36 (t, J = 7.1 Hz, 6H)

$^{13}C\{^1H\}$ -NMR

(176 MHz, $CDCl_3$)

δ 156.2 (d, $^1J_{C-P}$ = 226.0 Hz),
147.2 (dq, $^3J_{C-P}$ = 23.4, $^3J_{C-F}$ = 3.9 Hz),
133.4 (dq, $^2J_{C-P}$ = 11.9, $4J_{C-F}$ = 3.7 Hz),
128.5 (qd, $^2J_{C-F}$ = 33.5, $^2J_{C-P}$ = 4.1 Hz), 127.7 (d, $^3J_{C-P}$ = 25.2 Hz),
123.1 (q, $^1J_{C-F}$ = 273.2 Hz), 63.6 (d, $^2J_{C-P}$ = 6.0 Hz),
16.4 (d, $^3J_{C-P}$ = 6.1 Hz)

$^{31}P\{^1H\}$ -NMR

(121 MHz, $CDCl_3$)

δ 10.3

$^{19}F\{^1H\}$ -NMR

(282 MHz, $CDCl_3$)

δ -118.5

IR

Alpha-Platinum ATR, Bruker, diamond crystal

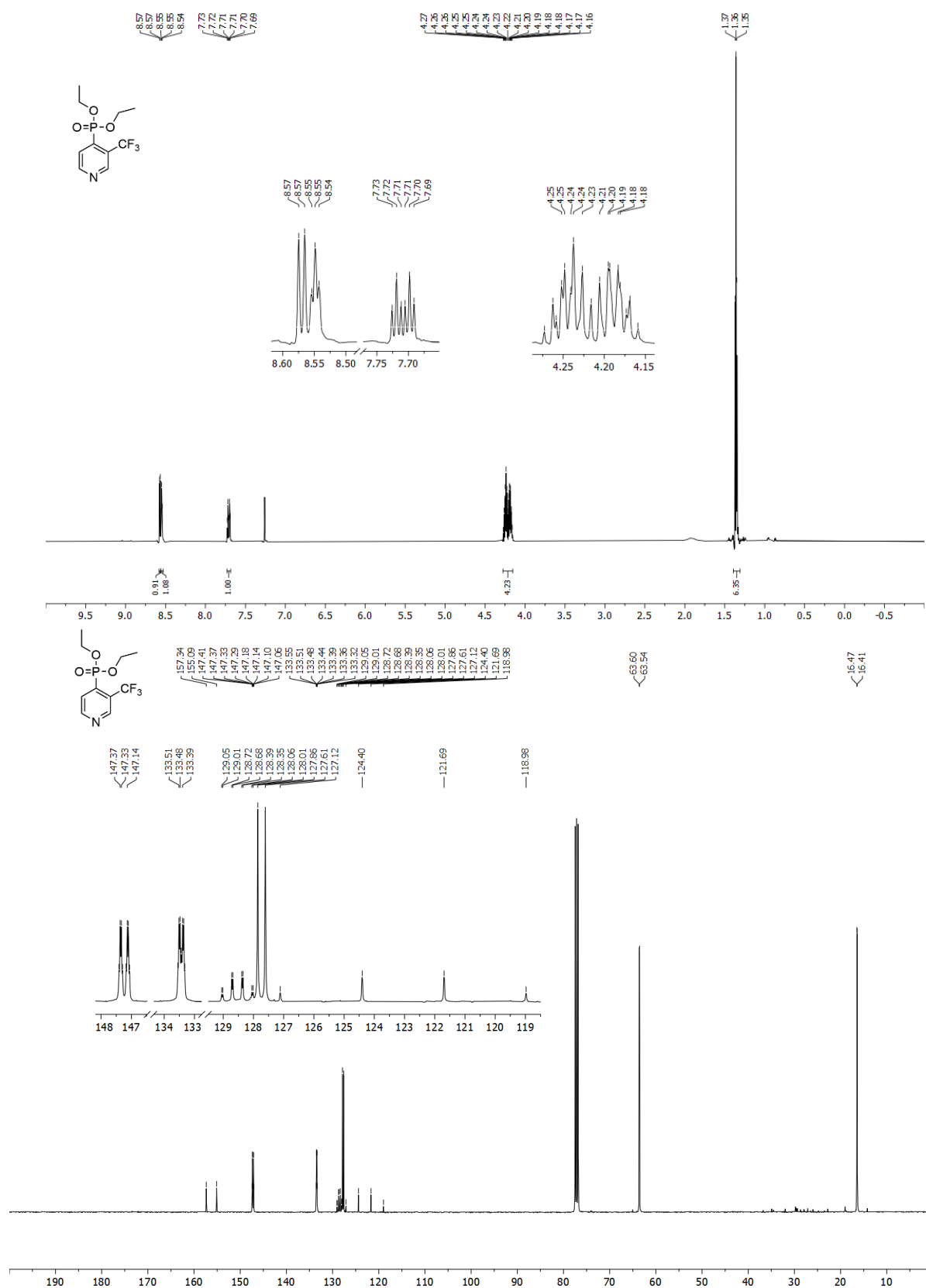
$\tilde{\nu}$ = 3001, 1434, 1277, 1005, 991, 846, 560 cm^{-1}

HRMS

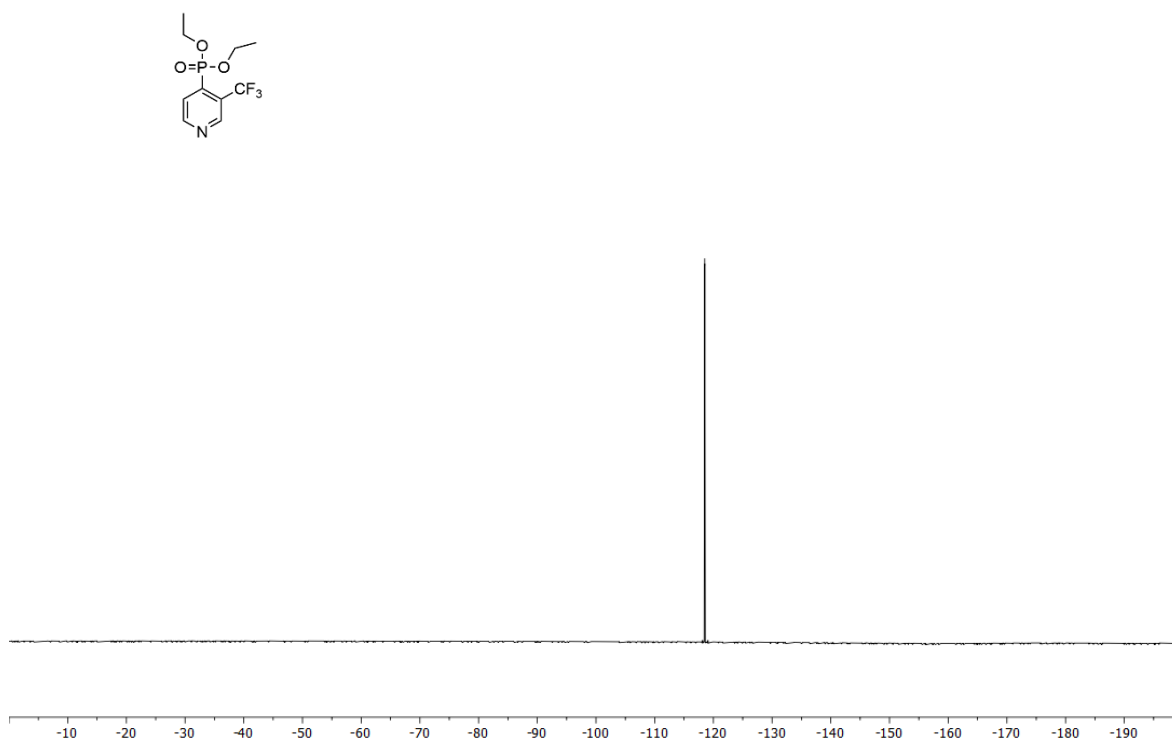
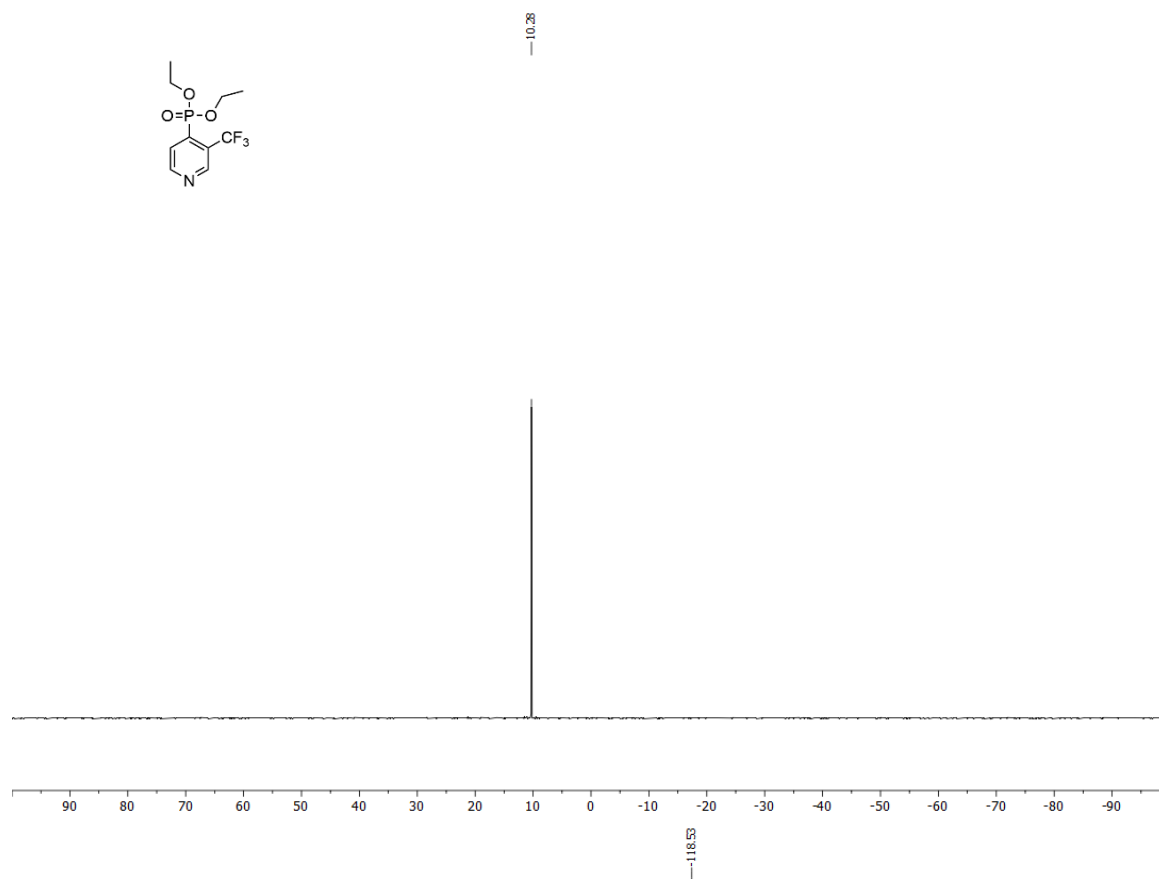
ESI+ TOF

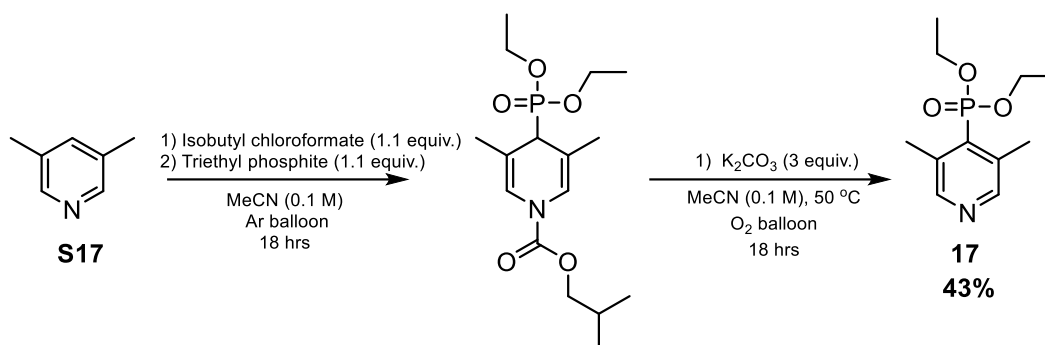
m/z $[M+H]^+$ calcd for $C_{10}H_{14}F_3NO_3P$. 284.0658; Found 284.0660.

^1H -NMR (700 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(176 MHz, CDCl_3) spectra of **16**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (121 MHz, CDCl_3) and $^{19}\text{F}\{^1\text{H}\}$ -NMR (282 MHz, CDCl_3) spectra of **16**





3,5-Lutidine (100 mg, 0.93 mmol, 1.0 equiv.) was transformed to the corresponding dihydropyridine phosphonate according to **procedure A**, except that isobutyl chloroformate (140 mg, 1.02 mmol, 1.1 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (170 mg, 1.02 mmol, 1.1 equiv.) at 0 °C. Treatment of the crude intermediate with K₂CO₃ (386 mg, 2.79 mmol, 3.0 equiv.) following **procedure B**, except that the reaction mixture was stirred at 50 °C, affording product **17** (97 mg, 0.40 mmol, 43%) as a yellow oil.

R_f = 0.35 in 60% EtOAc/hexanes.

¹H-NMR

(400 MHz, CDCl₃)

δ 8.34 (d, *J* = 6.3 Hz, 2H), 4.24 – 4.00 (m, 4H),

2.57 (d, *J* = 1.9 Hz, 6H), 1.31 (t, *J* = 7.1 Hz, 6H)

¹³C{¹H}-NMR

(101 MHz, CDCl₃)

δ 150.2 (d, ³*J*_{C-P} = 12.9 Hz), 136.3 (d, ²*J*_{C-P} = 9.7 Hz),

134.1 (d, ¹*J*_{C-P} = 177.2 Hz), 62.0 (d, ²*J*_{C-P} = 5.5 Hz),

19.7 (d, ³*J*_{C-P} = 2.9 Hz), 16.4 (d, ³*J*_{C-P} = 6.5 Hz)

³¹P{¹H}-NMR

³¹P NMR (162 MHz, CDCl₃)

δ 16.8

IR

Alpha-Platinum ATR, Bruker, diamond crystal

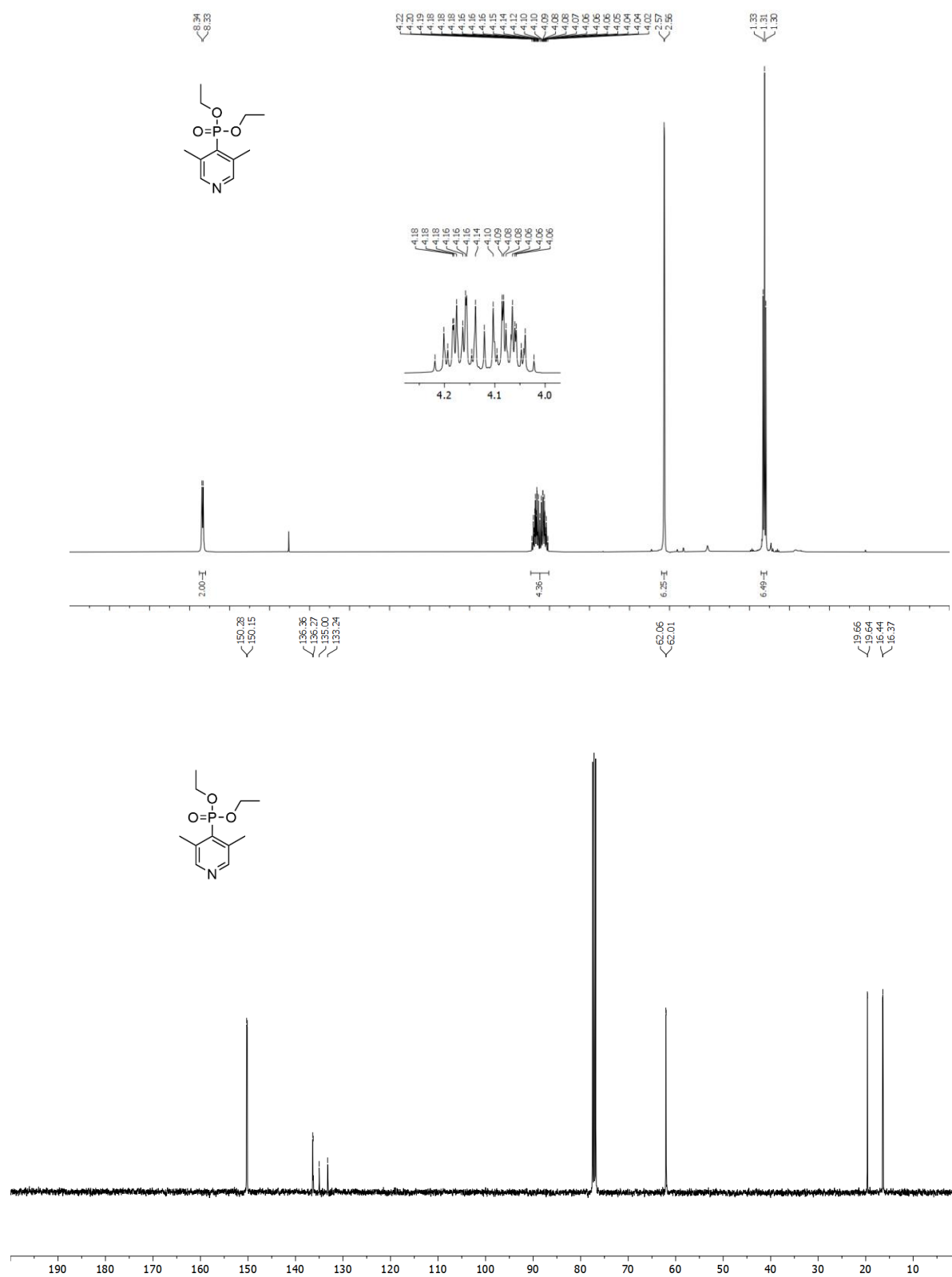
$\tilde{\nu}$ = 3010, 1460, 1260, 1120, 1005, 992, 670, 545 cm⁻¹

HRMS

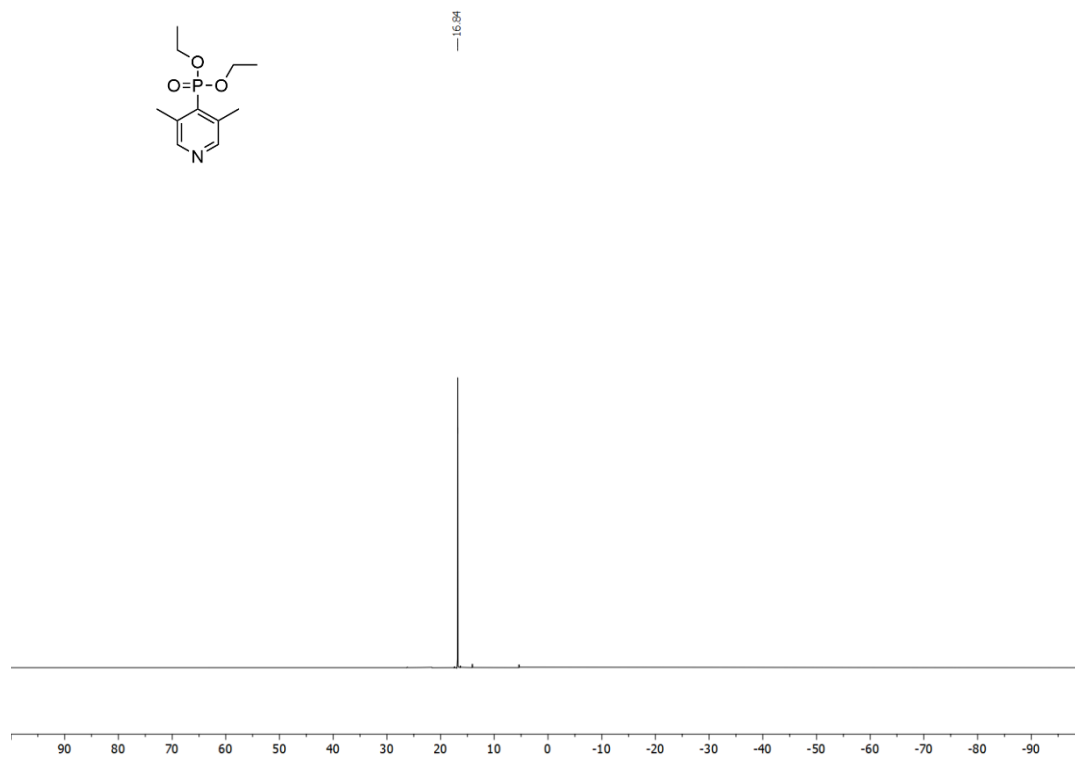
ESI+ TOF

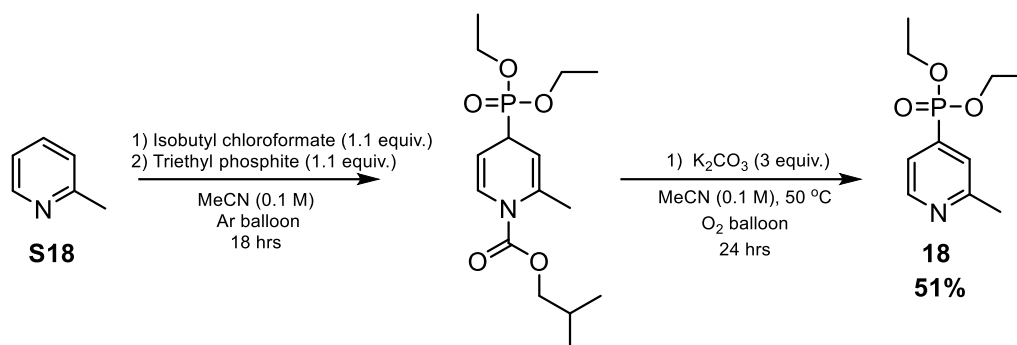
m/z [M+H]⁺ calcd for C₁₁H₁₉NO₃P. 244.1097; Found 244.1098.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **17**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **17**





2-Methylpyridine (100 mg, 1.07 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that isobutyl chloroformate (161 mg, 1.18 mmol, 1.1 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (196 mg, 1.18 mmol, 1.1 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (444 mg, 3.21 mmol, 3.0 equiv.) according to **procedure B**, except that the reaction mixture was stirred at 50 °C for 24 hours, provided product **18** (126 mg, 0.55 mmol, 51%) as a yellow oil.

R_f = 0.35 in 60% EtOAc/hexanes.

¹H-NMR (400 MHz, $CDCl_3$)
 δ 8.64 (t, J = 5.3 Hz, 1H), 7.54 (d, J = 14.0 Hz, 1H),
 7.44 (dd, J = 13.1, 5.0 Hz, 1H), 4.25 – 4.04 (m, 4H), 2.62 (s, 3H),
 1.34 (t, J = 7.1 Hz, 6H)

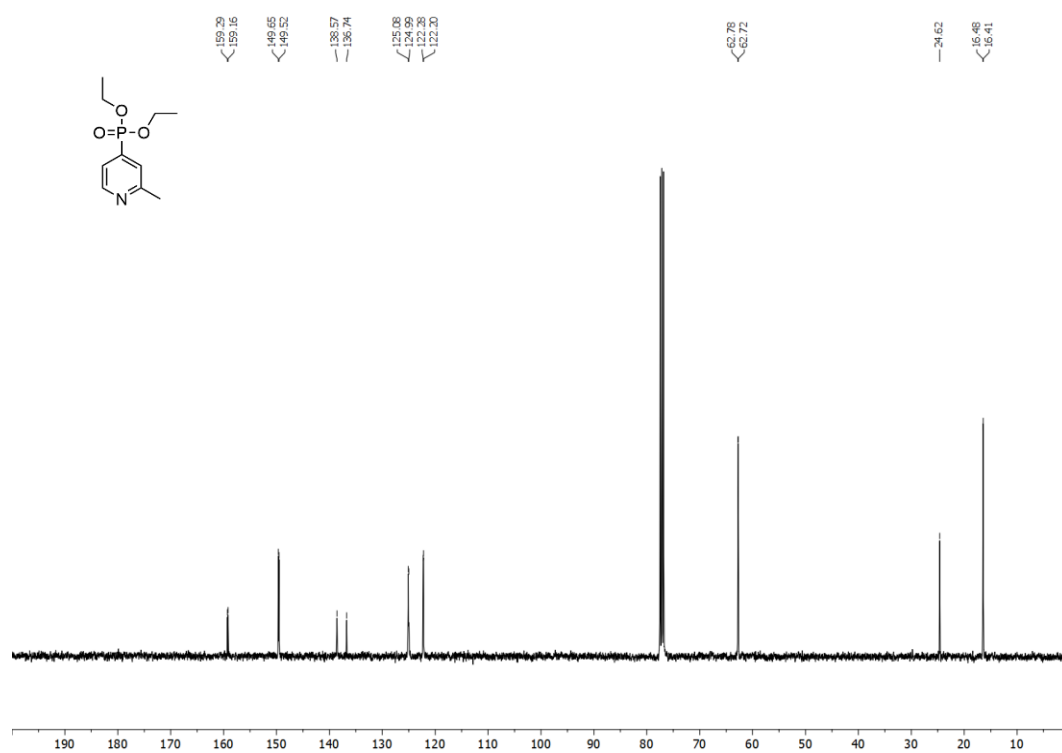
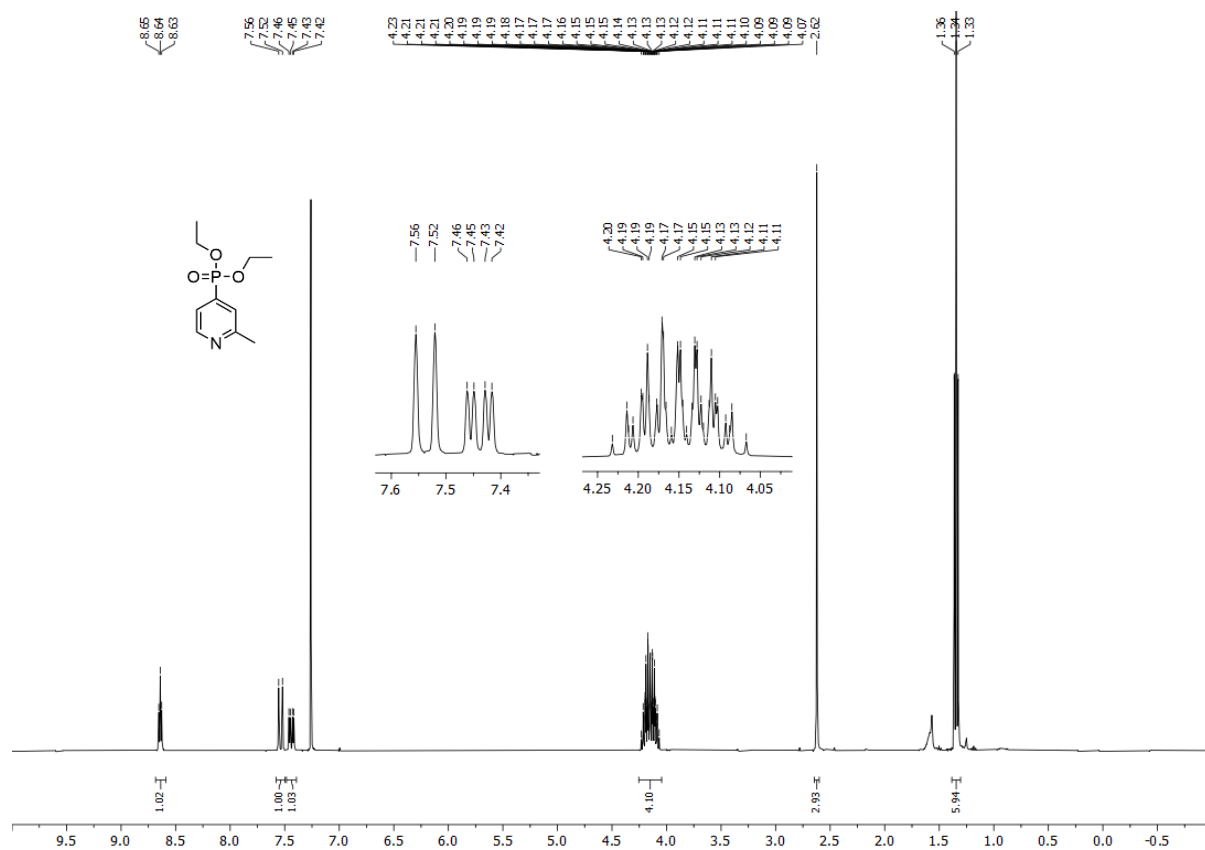
¹³C{¹H}-NMR (101 MHz, $CDCl_3$)
 δ 159.2 (d, $^3J_{C-P}$ = 12.6 Hz), 149.6 (d, $^3J_{C-P}$ = 13.0 Hz),
 137.7 (d, $^1J_{C-P}$ = 184.7 Hz), 125.0 (d, $^2J_{C-P}$ = 8.4 Hz),
 122.2 (d, $^2J_{C-P}$ = 8.0 Hz), 62.8 (d, $^2J_{C-P}$ = 5.7 Hz), 24.6,
 16.5 (d, $^3J_{C-P}$ = 6.4 Hz)

³¹P{¹H}-NMR ³¹P NMR (162 MHz, $CDCl_3$)
 δ 15.9

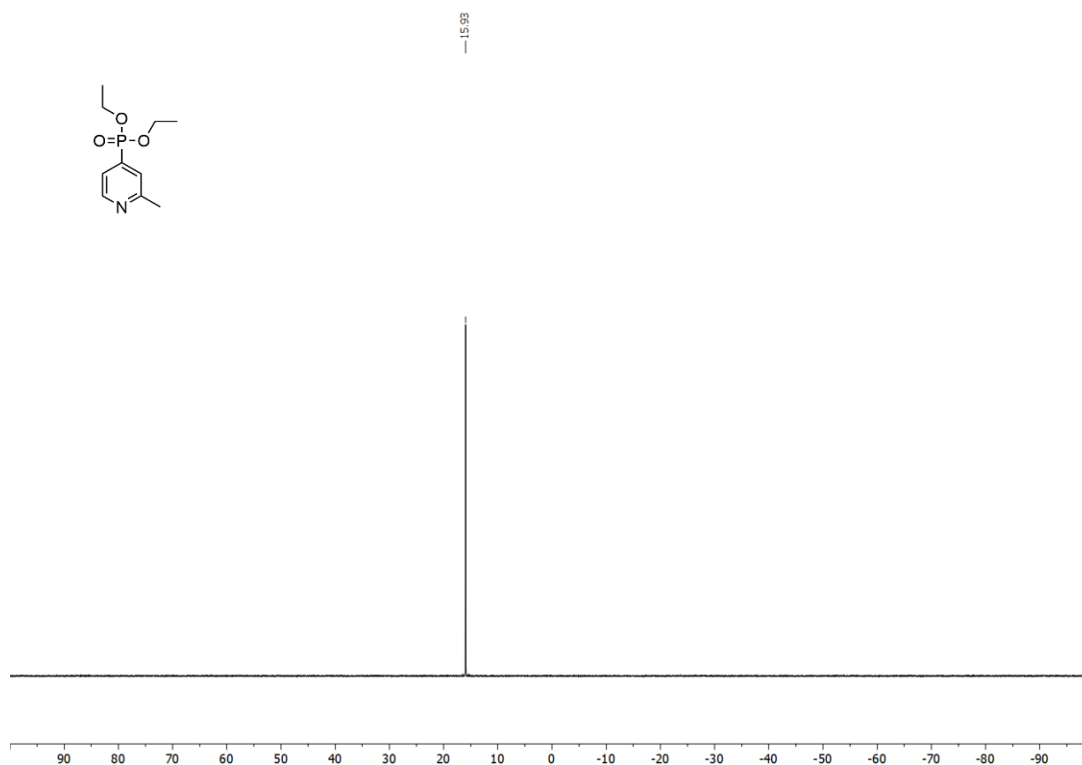
IR Alpha-Platinum ATR, Bruker, diamond crystal
 $\tilde{\nu}$ = 2987, 1522, 1247, 1006, 993, 812, 568 cm^{-1}

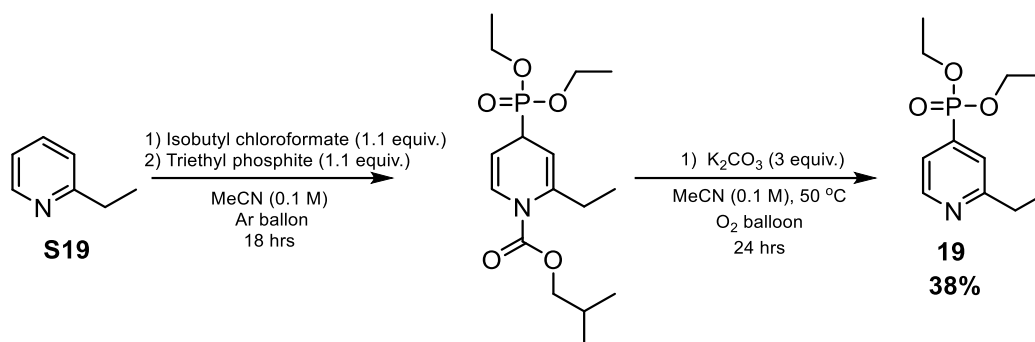
HRMS ESI+ TOF
 m/z [M+H]⁺ calcd for $C_{10}H_{17}NO_3P$. 230.0941; Found 230.0949.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **18**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **18**





2-Ethylpyridine (100 mg, 0.93 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that isobutyl chloroformate (140 mg, 1.02 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (170 mg, 1.02 mmol, 2.0 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (444 mg, 3.21 mmol, 3.0 equiv.) according to **procedure B**, except that the reaction mixture was stirred at 50 °C for 24 hours, provided product **19** (86 mg, 0.35 mmol, 38%) as a yellow oil.

R_f = 0.35 in 60% EtOAc/hexanes.

1H -NMR

(400 MHz, $CDCl_3$)

δ 8.67 (t, J = 5.3 Hz, 1H), 7.55 (d, J = 14.0 Hz, 1H),
7.44 (dd, J = 13.1, 5.0 Hz, 1H), 4.26 – 4.05 (m, 4H),
2.89 (q, J = 7.6 Hz, 2H), 1.34 (td, J = 7.1, 5.3 Hz, 9H)

$^{13}C\{^1H\}$ -NMR

(101 MHz, $CDCl_3$)

δ 164.3 (d, $^3J_{C-P}$ = 12.2 Hz), 149.6 (d, $^3J_{C-P}$ = 13.0 Hz),
137.7 (d, $^1J_{C-P}$ = 184.6 Hz), 124.0 (d, $^2J_{C-P}$ = 8.5 Hz),
122.5 (d, $^2J_{C-P}$ = 8.2 Hz), 62.8 (d, $^2J_{C-P}$ = 5.6 Hz),
31.6 (d, $^4J_{C-P}$ = 1.7 Hz), 16.5 (d, $^3J_{C-P}$ = 6.4 Hz), 13.8

$^{31}P\{^1H\}$ -NMR

^{31}P NMR (162 MHz, $CDCl_3$)

δ 16.1

IR

Alpha-Platinum ATR, Bruker, diamond crystal

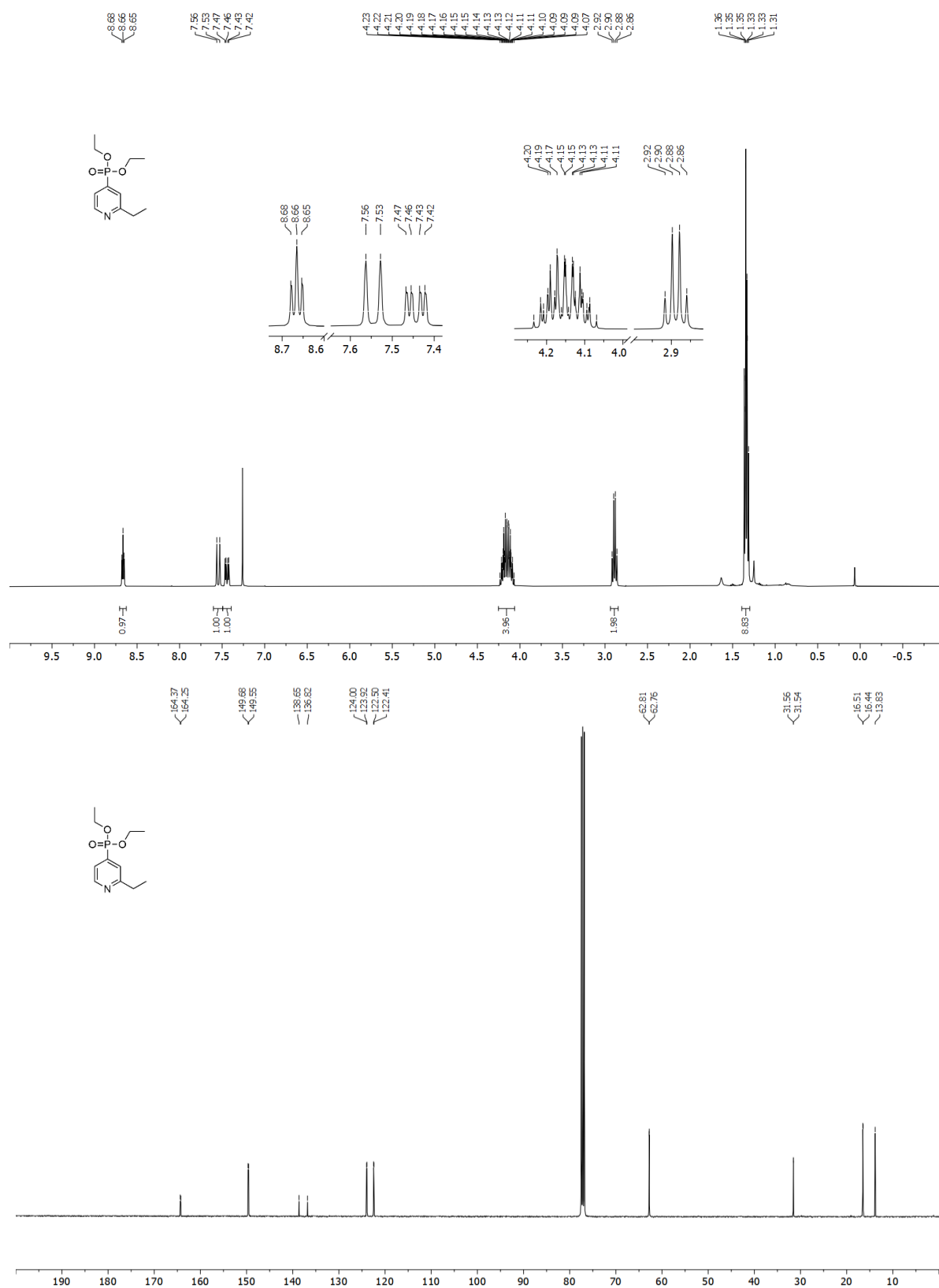
$\tilde{\nu}$ = 2991, 1563, 1257, 1003, 991, 777, 564 cm^{-1}

HRMS

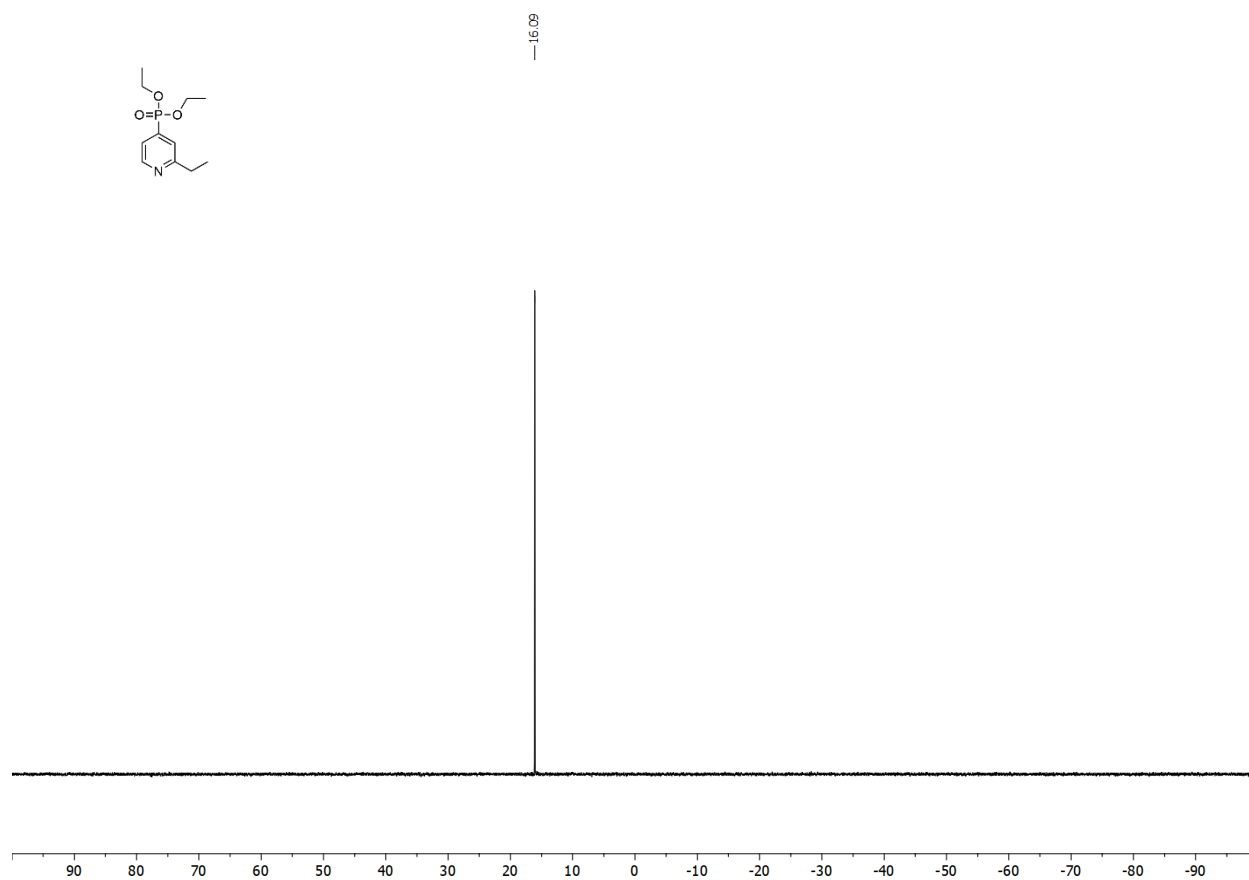
ESI+ TOF

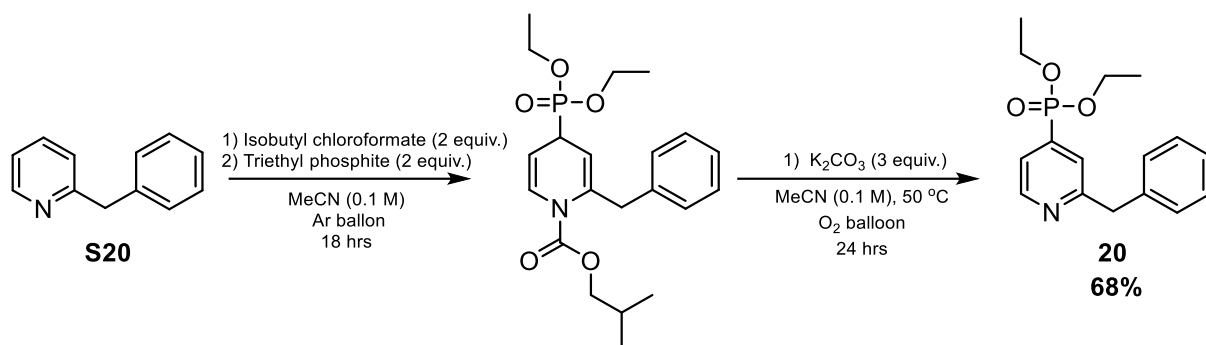
m/z $[M+H]^+$ calcd for $C_{11}H_{18}NO_3P$. 244.1097; Found 244.1099.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **19**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **19**





2-Benzylpyridine (150 mg, 0.89 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**, except that isobutyl chloroformate (243 mg, 1.78 mmol, 2.0 equiv.) was added at 50 °C and the reaction was stirred for 2 hours before dropwise addition of triethyl phosphite (296 mg, 1.78 mmol, 2.0 equiv.) at 0 °C. Treatment of the crude intermediate with K_2CO_3 (369 mg, 2.67 mmol, 3.0 equiv.) according to **procedure B**, except that the reaction mixture was stirred at 50 °C for 24 hours, providing product **20** (184 mg, 0.61 mmol, 68%) as a yellow oil.

R_f = 0.30 in 60% EtOAc/hexanes.

1H -NMR

(400 MHz, $CDCl_3$)

δ 8.69 (t, J = 5.2 Hz, 1H), 7.51 (d, J = 14.1 Hz, 1H),
7.46 (dd, J = 13.1, 4.9 Hz, 1H), 7.35 – 7.18 (m, 5H), 4.20 (s, 2H),
4.19 – 3.99 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H)

$^{13}C\{^1H\}$ -NMR

(101 MHz, $CDCl_3$)

δ 161.7 (d, $^3J_{C-P}$ = 12.5 Hz), 149.7 (d, $^3J_{C-P}$ = 12.9 Hz),
138.8, 138.0 (d, $^1J_{C-P}$ = 185.2 Hz) 129.1, 128.7, 126.6,
124.8 (d, $^2J_{C-P}$ = 8.7 Hz), 122.7 (d, $^2J_{C-P}$ = 8.0 Hz),
62.7 (d, $^2J_{C-P}$ = 5.6 Hz), 44.7, 16.3 (d, $^3J_{C-P}$ = 6.2 Hz)

$^{31}P\{^1H\}$ -NMR

^{31}P NMR (162 MHz, $CDCl_3$)

δ 15.7

IR

Alpha-Platinum ATR, Bruker, diamond crystal

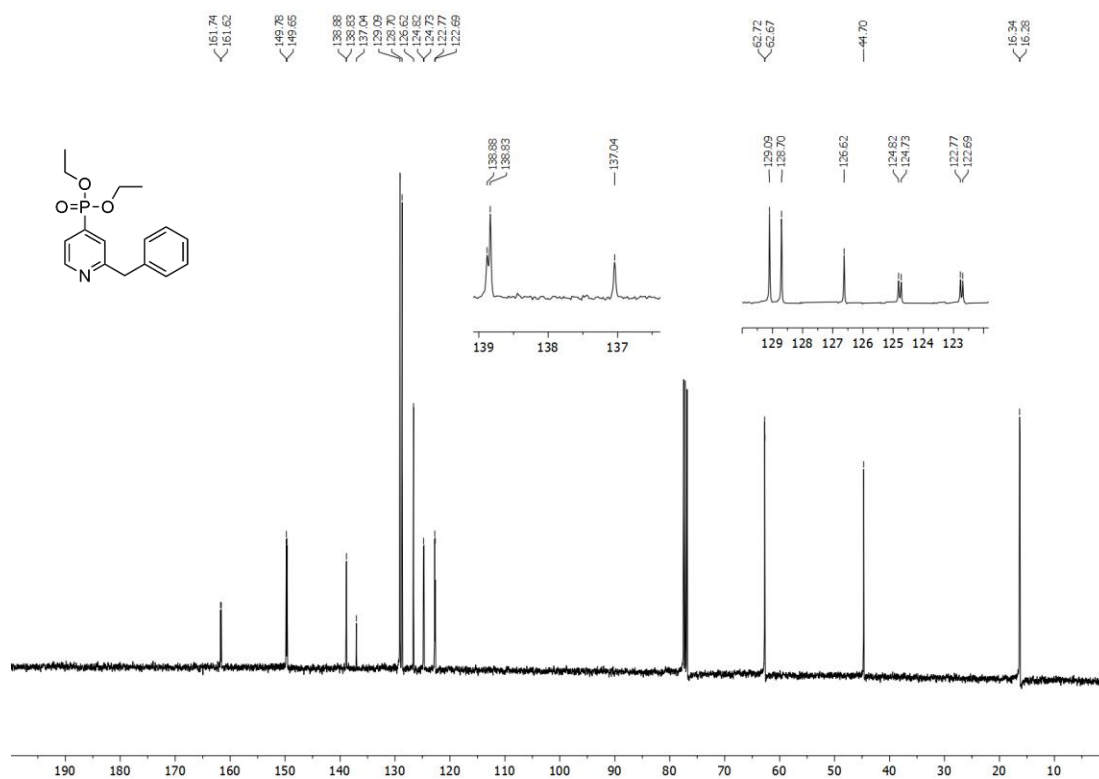
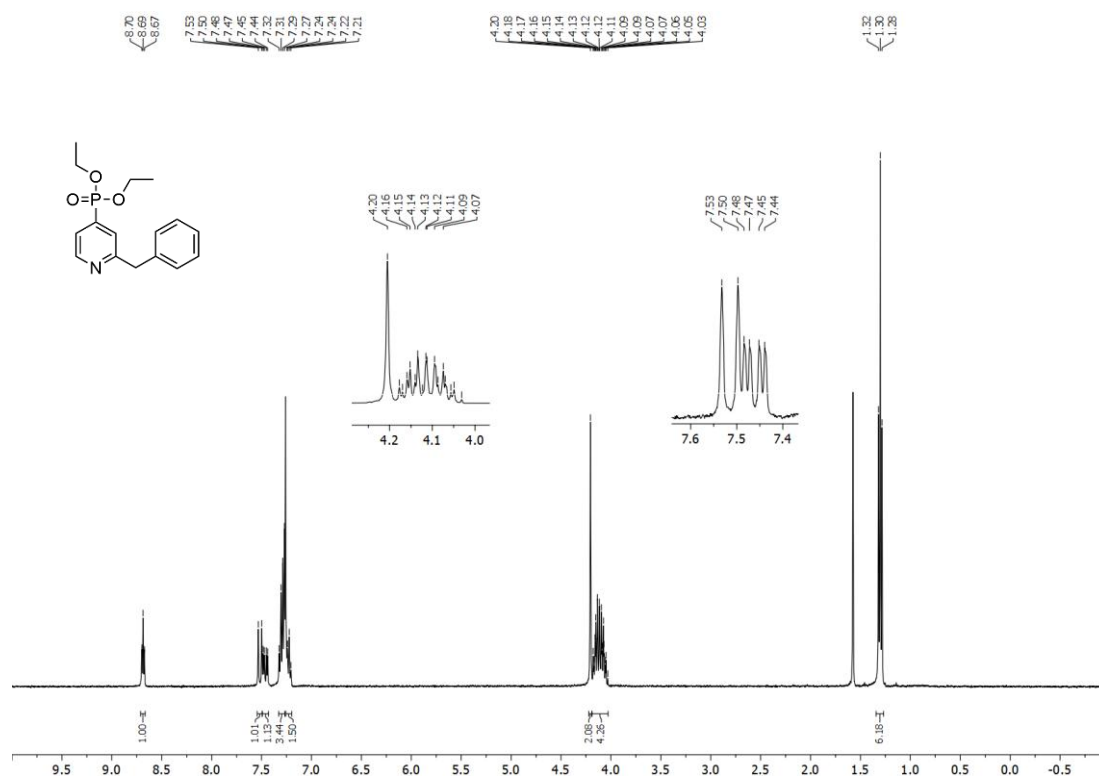
$\tilde{\nu}$ = 2997, 1512, 1263, 1004, 991, 720, 576 cm^{-1}

HRMS

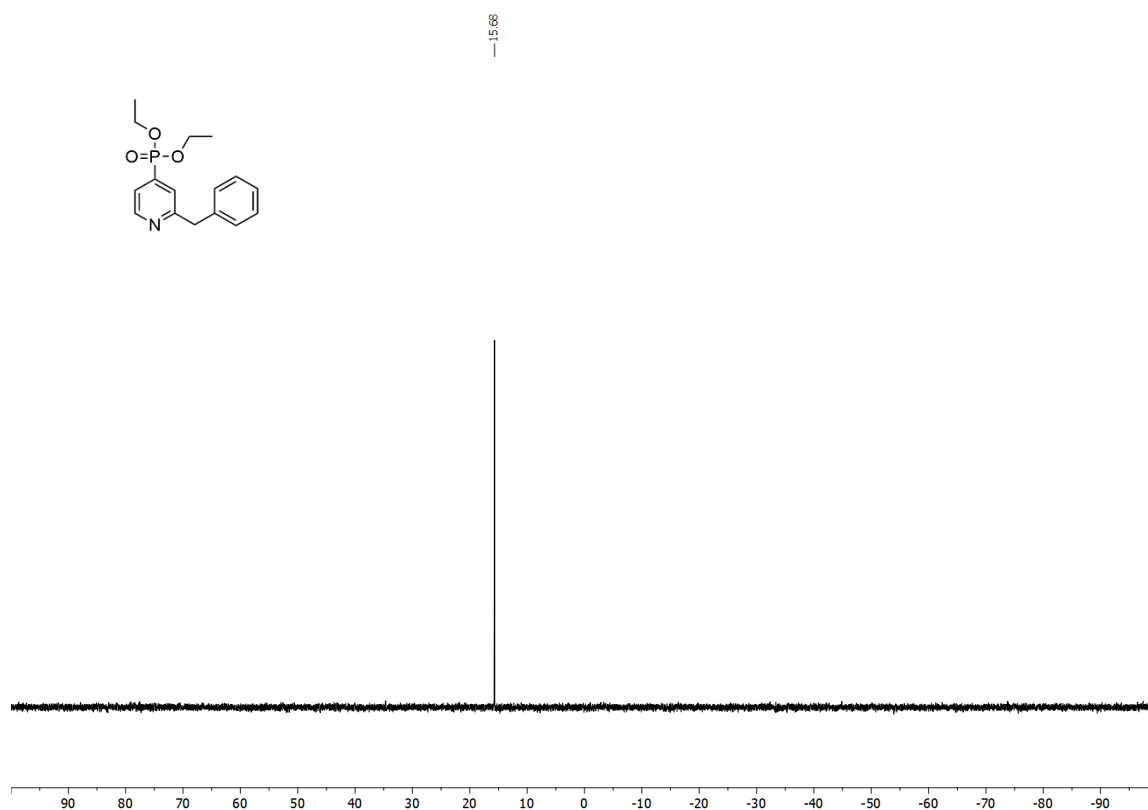
ESI+ TOF

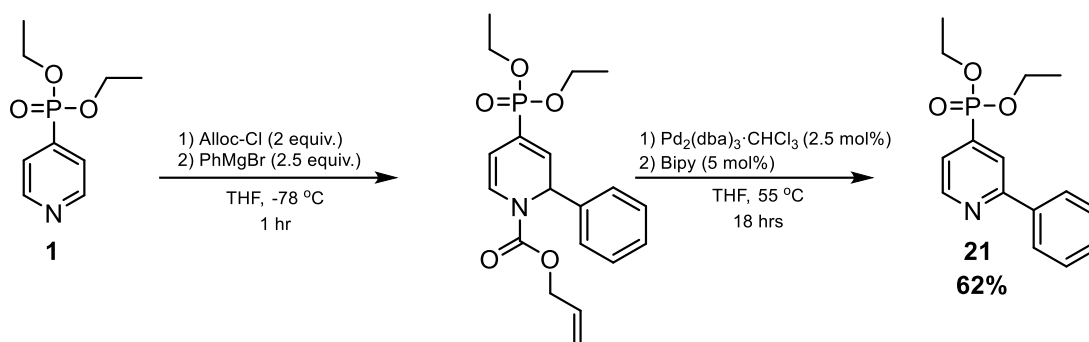
m/z $[M+H]^+$ calcd for $C_{16}H_{21}NO_3P$. 306.1254; Found 306.1254.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **20**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **20**





An oven dried round bottomed flask equipped with a stir bar was charged with a 0.1 M solution of pyridyl phosphonate **1** (50 mg, 0.23mmol, 1.0 equiv.) in anhydrous THF. The solution was cooled to -78 °C. Allyl chloroformate (56 mg, 0.47 mmol, 2.0 equiv.) was added in a dropwise manner, and the resulting solution was stirred for 1 hour at -78 °C. Phenylmagnesium bromide (0.58 mL, 0.58 mmol, 2.5 equiv., 1.0 M in THF) was added to the mixture in a dropwise manner. The resulting mixture was stirred for 1 hour at -78 °C. The mixture was allowed to warm to ambient temperature while stirring for 1 hour. The reaction was quenched by dropwise addition of ice-cold water (20 mL). After stirring for 15 minutes, the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried with MgSO₄, filtered through a cotton plug, and concentrated using a rotary evaporator. The crude dihydropyridine intermediate was obtained and used for next step without further purification.

A dry round-bottomed flask equipped with a stir bar was charged with Pd₂(dba)₃·CHCl₃ (6 mg, 0.0058 mmol, 2.5 mol%), 2,2'-bipyridine (2 mg, 0.012 mmol, 5 mol%) and 1 mL of anhydrous THF. The resulting mixture was stirred for 30 minutes at ambient temperature. The dihydropyridine intermediate was dissolved in 1 mL of anhydrous THF and added slowly to the palladium catalyst solution. The resulting mixture was placed in an oil bath, stirred and heated to 55 °C overnight. The mixture was cooled to ambient temperature and concentrated using a rotary evaporator. The crude product was purified by flash column chromatography, providing product **21** (42 mg, 0.14 mmol, 62% yield) as a yellow oil.

R_f = 0.35 in 60% EtOAc in hexanes.

¹H-NMR (400 MHz, CDCl₃)
δ 8.83 (t, J = 5.1 Hz, 1H), 8.11 (d, J = 14.2 Hz, 1H),
8.04 (d, J = 6.9 Hz, 2H), 7.58 (dd, J = 13.2, 4.7 Hz, 1H),
7.53 – 7.19 (m, 3H), 4.28 – 4.10 (m, 4H), 1.37 (t, J = 7.1 Hz, 6H)

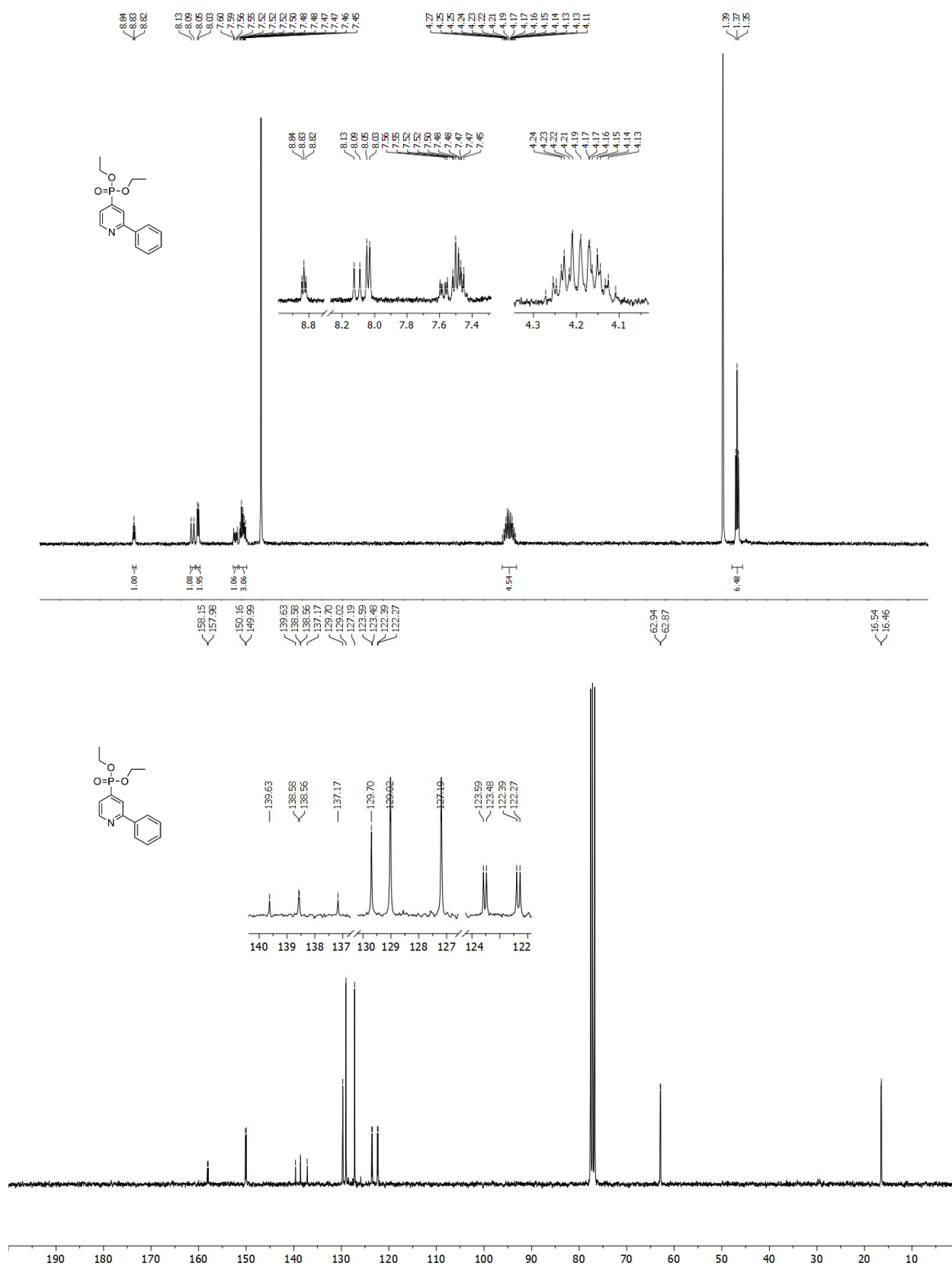
¹³C{¹H}-NMR (75 MHz, CDCl₃)
δ 158.1 (d, $^3J_{C-P}$ = 12.7 Hz), 150.1 (d, $^3J_{C-P}$ = 13.0 Hz),
138.6 (d, $^4J_{C-P}$ = 5.9 Hz), 138.4 (d, $^1J_{C-P}$ = 185.3 Hz), 129.7,
129.0, 127.2, 123.5 (d, $^2J_{C-P}$ = 8.0 Hz), 122.3 (d, $^2J_{C-P}$ = 9.1 Hz),
62.9 (d, $^2J_{C-P}$ = 5.6 Hz), 16.5 (d, $^3J_{C-P}$ = 6.3 Hz)

³¹P{¹H}-NMR ³¹P NMR (162 MHz, CDCl₃)
δ 15.8

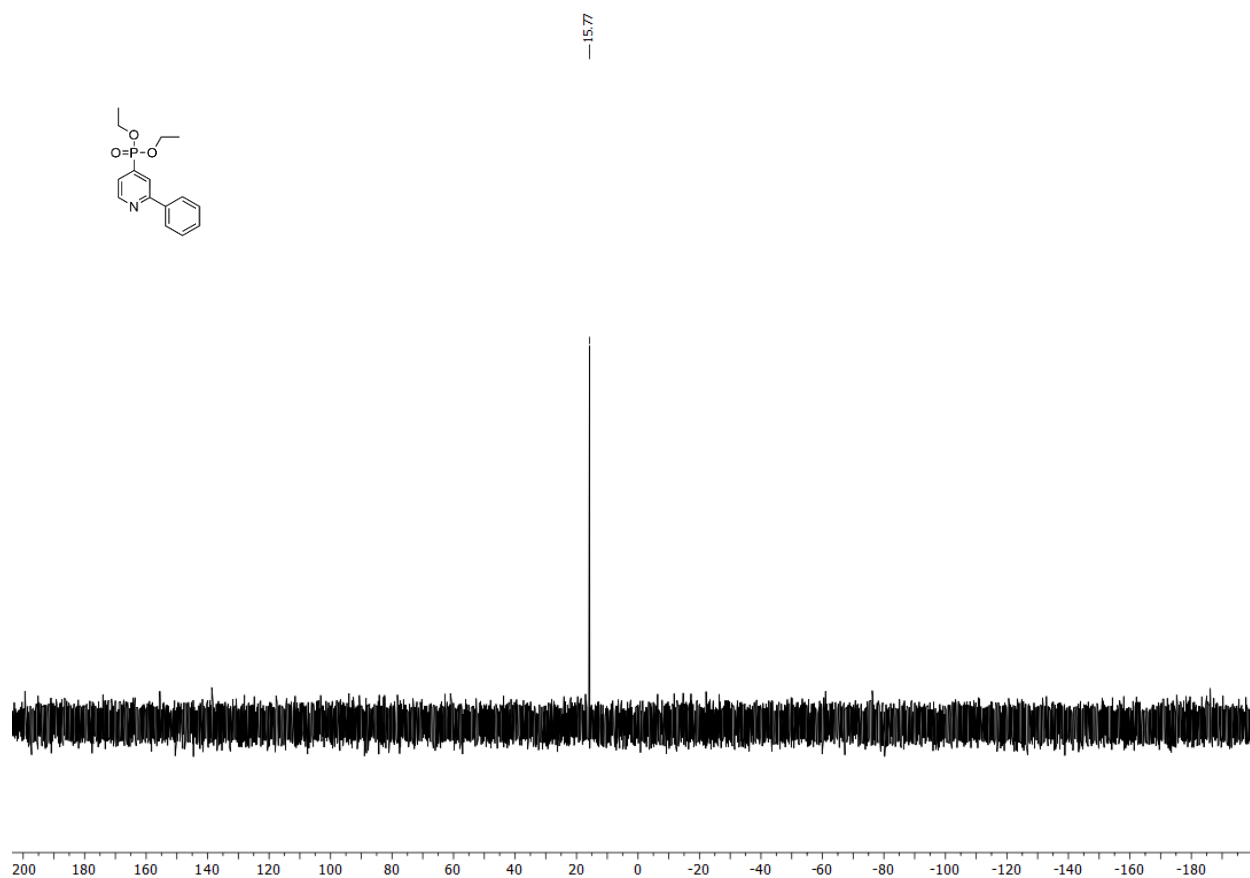
IR Alpha-Platinum ATR, Bruker, diamond crystal
 $\tilde{\nu}$ = 2980, 1394, 1250, 1140, 1012, 960, 538 cm⁻¹

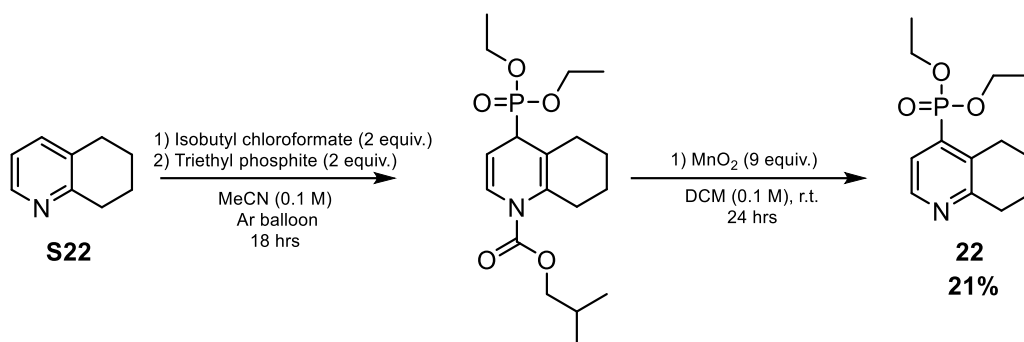
HRMS ESI+ TOF
 m/z [M+H]⁺ calcd for C₁₅H₁₉NO₃P. 292.1097, Found 292.1099.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(75 MHz, CDCl_3) spectra of **21**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **21**





S22 (100 mg, 0.75 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**. The crude was concentrated using a rotary evaporator and dissolved in anhydrous DCM forming a 0.1 M solution. Manganese (IV) oxide (587 mg, 6.75 mmol, 9 equiv.) was added to the reaction mixture, the round bottom flask was sealed with a rubber septum and allowed to stir for 24 hours. The mixture was extracted with EtOAc, filtered through a cotton plug to remove residual manganese (IV) oxide, and the filtrate was washed with brine. The organic layer was dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography, providing product **22** (43 mg, 0.16 mmol, 21% yield) as a yellow oil.

$R_f = 0.30$ in 60% EtOAc/hexanes.

$^1\text{H-NMR}$

(400 MHz, CDCl_3)

δ 8.47 (t, $J = 5.1$ Hz, 1H), 7.53 (dd, $J = 14.4, 4.8$ Hz, 1H),
4.25 – 4.06 (m, 4H), 3.06 (t, $J = 4.4$ Hz, 2H), 2.99 (t, $J = 6.6$ Hz, 2H),
2.02 – 1.78 (m, 4H), 1.35 (t, $J = 7.1$ Hz, 6H)

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$

(101 MHz, CDCl_3)

δ 158.7 (d, $^3J_{\text{C-P}} = 12.2$ Hz), 146.6 (d, $^3J_{\text{C-P}} = 13.4$ Hz),
135.8 (d, $^1J_{\text{C-P}} = 180.5$ Hz), 134.7 (d, $^2J_{\text{C-P}} = 9.8$ Hz),
124.5 (d, $^2J = 8.4$ Hz), 62.5 (d, $^2J = 5.9$ Hz),
33.3 (d, $^3J = 2.8$ Hz), 27.4 (d, $^3J = 4.1$ Hz), 22.6, 22.5,
16.4 (d, $^3J = 6.3$ Hz)

$^{31}\text{P}\{^1\text{H}\}\text{-NMR}$

^{31}P NMR (162 MHz, CDCl_3)

δ 16.8

IR

Alpha-Platinum ATR, Bruker, diamond crystal

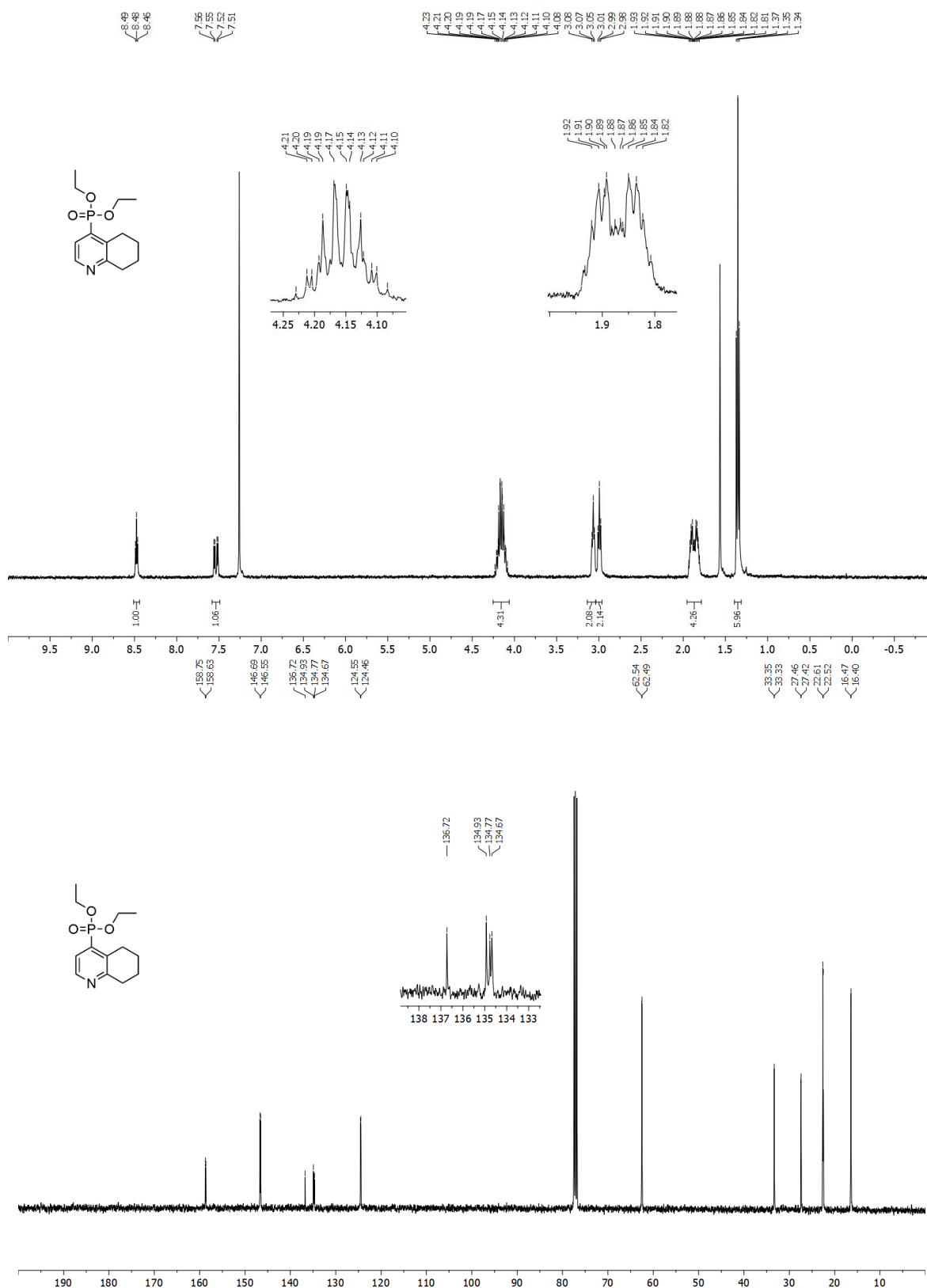
$\tilde{\nu} = 2982, 1758, 1432, 1268, 1005, 986, 642 \text{ cm}^{-1}$

HRMS

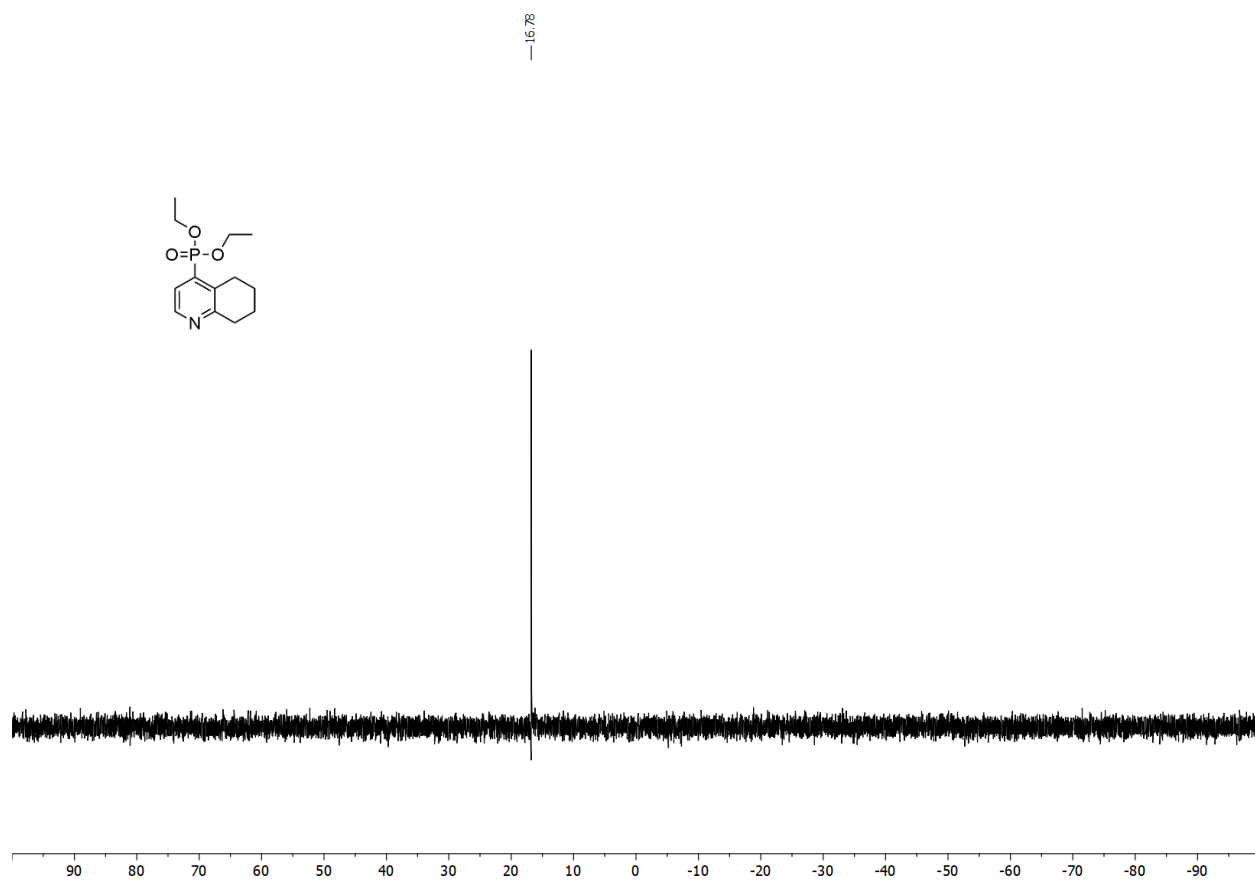
ESI+ TOF

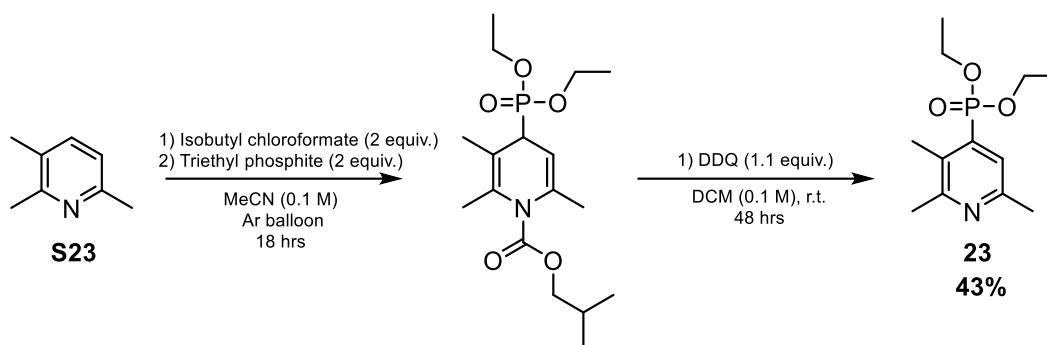
m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{P}$. 270.1254, Found 270.1255.

^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR(101 MHz, CDCl_3) spectra of **22**



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **22**





S23 (100 mg, 0.83 mmol, 1.0 equiv.) was transformed into the corresponding dihydropyridine phosphonate using **procedure A**. The crude was concentrated using a rotary evaporator and dissolved in anhydrous DCM forming a 0.1 M solution. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (207 mg, 0.91 mmol, 1.1 equiv.) was added to the reaction mixture, the round bottom flask was sealed with a rubber septum and allowed to stir for 48 hours. The mixture was extracted with EtOAc, filtered through a cotton plug, and the filtrate was washed with brine. The organic layer was dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography, providing product **23** (92 mg, 0.36 mmol, 43% yield) as a yellow oil.

$R_f = 0.35$ in 60% EtOAc/hexanes.

$^1\text{H-NMR}$

(400 MHz, CDCl_3)

δ 8.23 (d, $J = 6.4$ Hz, 1H), 4.24 – 4.00 (m, 4H), 2.55 (s, 6H),
2.52 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 6H)

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$

(101 MHz, CDCl_3)

δ 156.1 (d, $^3J_{\text{C-P}} = 13.0$ Hz), 148.7 (d, $^3J_{\text{C-P}} = 14.2$ Hz),
134.8 (d, $^2J_{\text{C-P}} = 10.0$ Hz), 134.2 (d, $^1J_{\text{C-P}} = 176.2$ Hz),
134.2 (d, $^2J_{\text{C-P}} = 9.7$ Hz), 61.9 (d, $^2J_{\text{C-P}} = 5.7$ Hz),
23.5 (d, $^4J_{\text{C-P}} = 2.5$ Hz), 19.8 (d, $^4J_{\text{C-P}} = 2.6$ Hz),
17.8 (d, $^3J_{\text{C-P}} = 3.6$ Hz), 16.4 (d, $^3J_{\text{C-P}} = 6.4$ Hz)

$^{31}\text{P}\{^1\text{H}\}\text{-NMR}$

^{31}P NMR (162 MHz, CDCl_3)

δ 17.8

IR

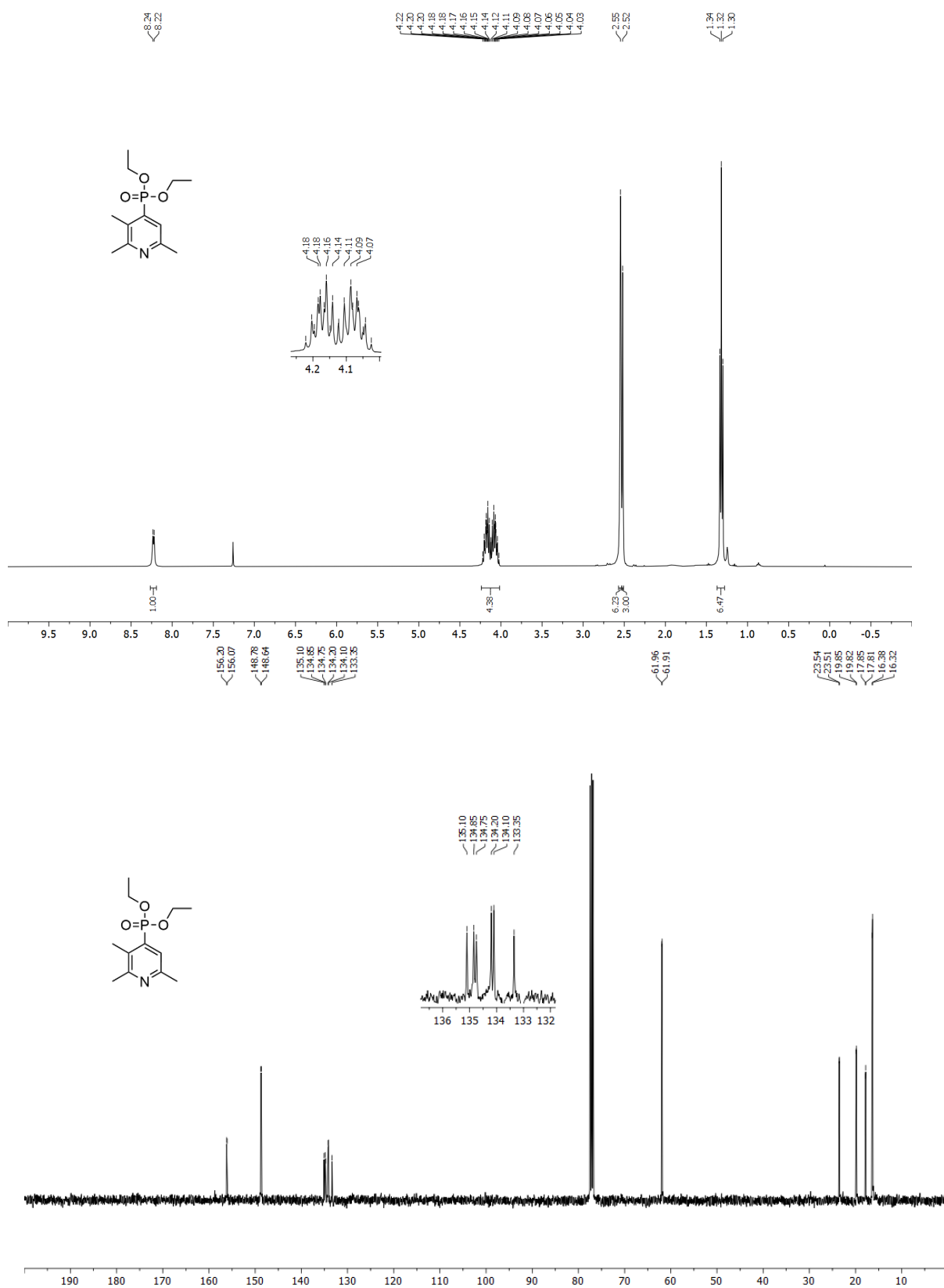
Alpha-Platinum ATR, Bruker, diamond crystal

$\tilde{\nu} = 2980, 1362, 1250, 1012, 958, 608, 542 \text{ cm}^{-1}$

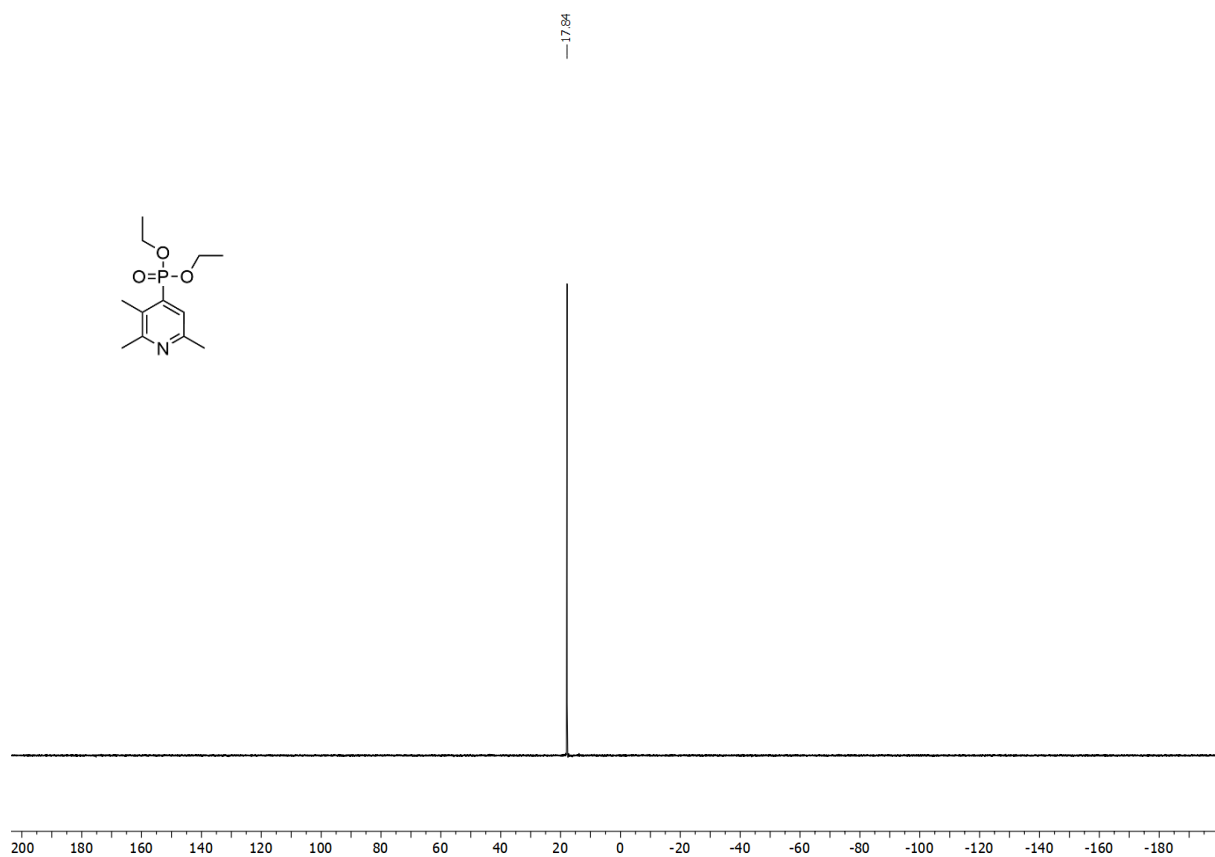
HRMS

ESI+ TOF

m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_3\text{P}$. 258.1254, Found 258.1255.



$^{31}\text{P}\{^1\text{H}\}$ -NMR (162 MHz, CDCl_3) spectra of **23**



Chapter IV: References

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