Chinese Chemical Letters Metal-free regioselective construction of 2-aryl-2H-tetrazol-5-yl difluoromethylene phosphonates

Dominique Cahard, Shi-Jing Zhai, Fa-Guang Zhang, Jun-An Ma

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Opposed Reviewers:	
Response to Reviewers:	Dear Editor: We thank the editorial office and the reviewers very much for the helpful and constructive comments. Based on these comments, the point-to-point response to all reviewers' comments have been provided in the response letter.

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Communication

Metal-free regioselective construction of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates

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ABSTRACT

Three bench-stable difluoromethylene phosphonate hydrazones were prepared from simple diethyl (difluoromethyl)phosphonate within two steps in good yields. The [3 + 2] cycloaddition reaction of these diazo precursors with aryl diazonium salts has been accomplished under metal-free conditions with exclusive regioselectivity. This transformation provides practical access to a broad panel of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates, including the corresponding derivatives of amino acid (phenylalanine) and drug cores (Pomalidomide and Lapatinib fragment).

Difluoromethylene phosphonates [DFMP, $CF_2PO(OR)_2$] could mimic the naturally occurring phosphates and phosphonates, thus having emerged as a frequently utilized structural motif in the study of various biochemical processes [1,2]. For example, phosphonodifluoromethyl phenylalanine (F_2Pmp) has been developed as one of the most powerful nonhydrolyzable phosphotyrosine mimetics to modulate the corresponding protein-protein interactions and used as protein tyrosine phosphatases (PTPs) inhibitors (Fig. 1) [3–5]. Furthermore, the difluoromethylene phosphonate moiety has also been utilized in the design and development of signal transducer and activator of transcription (STAT) antagonists, fructose-1,6-bisphosphatase (FBPase) inhibitors, $P2Y_1$ receptor antagonists, and cytidine triphosphate synthetase inhibitors (Fig. 1) [6–10]. Therefore, the design and development of new difluoromethylene phosphonate-containing molecular frameworks has emerged as an increasingly important task in synthetic organic chemistry. In this context, while simple aryl-substituted difluoromethylene phosphonates have been extensively studied in the past few decades [11–17], the construction of heterocyclic difluoromethylene phosphonates remains far less explored. More importantly, most previous studies have mainly focused on the use of metalated $CF_2PO(OR)_2$ derivatives to undergo cross-coupling-type transformations, while

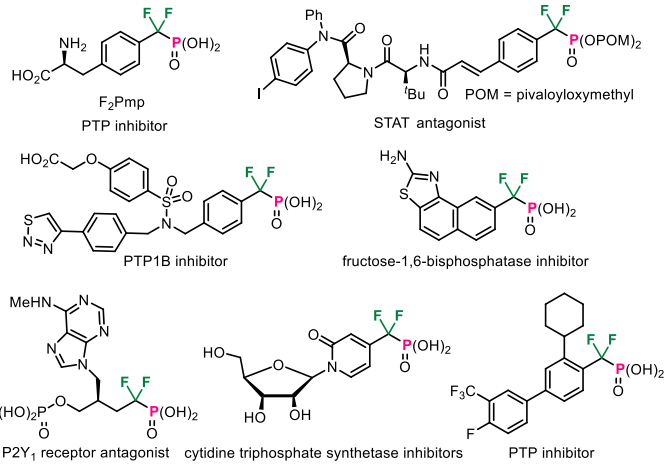
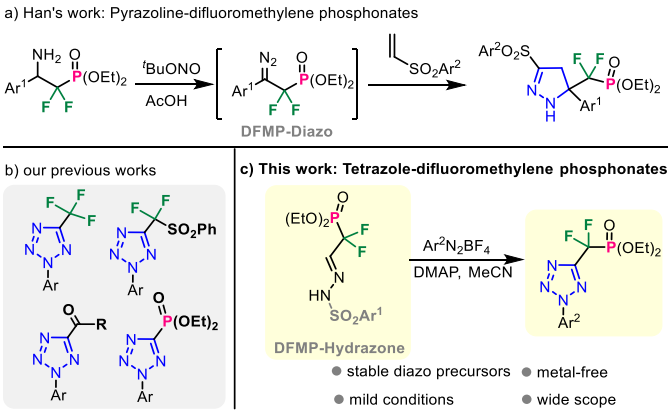


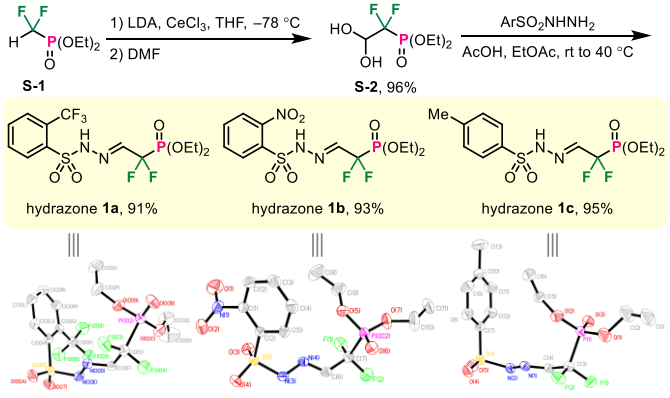
Fig. 1. Selected bio-active difluoromethylene phosphonates.

the development of new reactive DFMP-containing 1,3-dipoles to be used in convergent cycloadditions remains elusive. Very recently, Han, Röschenthaler, and co-workers reported the design of aryl-substituted difluoromethylene phosphonate-containing diazo reagents (DFMP-Diazo, Scheme 1a) [18,19]. The [3 + 2] cycloaddition reaction of DFMP-Diazo with vinyl sulfones enabled the synthesis of difluoromethylene phosphonate-

containing pyrazolines with good efficiency. However, due to the instability of DFMP-containing diazo compounds, the utilization of unsubstituted DFMP-functionalized 1,3-dipolar species to produce aromatic cycloadducts is an unsolved problem. As part of our long interest in fluorinated diazoalkanes [20–28] and the construction of tetrazoles (Scheme 1b) [29–33], herein we report the preparation of three bench-stable DFMP-containing diazo precursors (DFMP-Hydrazones), and their application in the regioselective synthesis of DFMP-tetrazoles via [3 + 2] cycloaddition reactions with aryldiazonium salts (Scheme 1c). Note that this study represents the first example of introducing a difluoromethylene phosphonate motif onto the tetrazole scaffold. These two chemical entities are both metabolically stable to many of the biological transformations and have widespread implications in pharmaceuticals and bioconjugations [34–36].



Scheme 1. Cycloaddition reactions for the preparation of difluoromethylene phosphonate heterocycles.

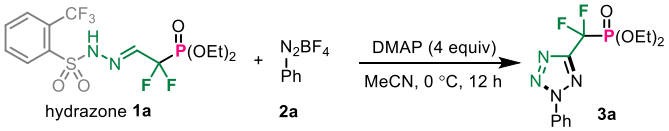


Scheme 2. Preparation of difluoromethylene phosphonate hydrazones.

At the outset, we synthesized three DFMP-hydrazones via the condensation of DFMP-aldehyde precursor **S-2** with the corresponding benzenesulfonyl hydrazides. As outlined in Scheme 2, treating commercially available diethyl (difluoromethyl)-phosphonate **S-1** with LDA in the presence of $CeCl_3$, followed by addition of *N*,*N*-dimethylformamide (DMF) in one-pot, the desired dihydrate **S-2** was smoothly obtained in 96% yield [37,38]. Subsequently, condensation of this masked aldehyde **S-2** with different hydrazides under acidic conditions proved to be viable, thus giving the target DFMP-hydrazones **1a**–**1c** in 91–95% yields [39,40]. Importantly, these diazo precursors were found to be quite stable under bench conditions, and all of them have been successfully crystallized for X-ray diffraction analysis [41].

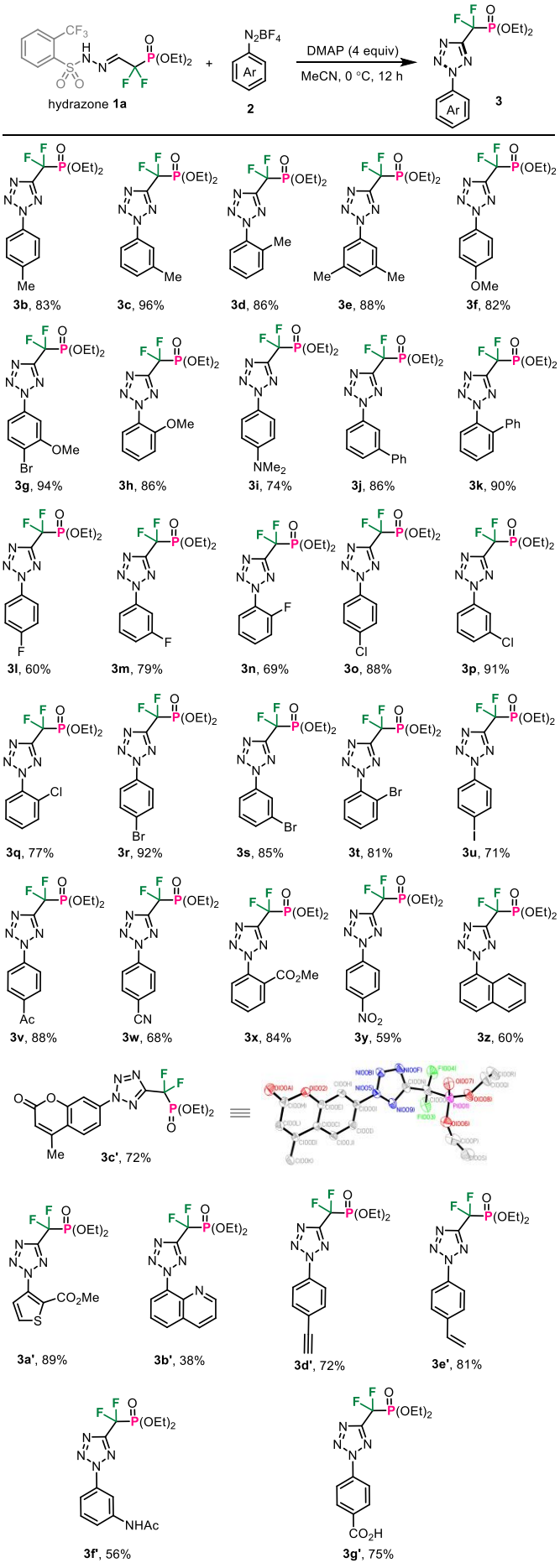
With the three difluoromethylene phosphonate hydrazones in hand, we then proceeded to optimize the [3 + 2] cycloaddition reaction with phenyldiazonium salt **2a** (Table 1) [42]. Pleasingly, by just using 4-dimethylaminopyridine (DMAP) as the base, acetonitrile as the solvent, the desired 2,5-disubstituted tetrazole **3a** was obtained in up to 90% yield from CF_3-hydrazone **1a** without the detection of any regioisomer (entry 1). Employing NO_2-hydrazone **1b** or Me-hydrazone **1c** could also permit the formation of tetrazole **3a**, albeit in decreased yields (entry 2 and 3). The significantly lower yield observed when using Me-hydrazone **1c** could be the result of a lower leaving-group ability of its benzenesulfonyl moiety with respect to **1a** and **1b**. Notably, this reaction does not require the use of an organometallic species and thus should not involve a carbenoid intermediate that is clearly indicative of a different mechanism compared with our previous studies on the silver-catalyzed synthesis of differently decorated tetrazoles [43,44]. Addition of silver acetate to the reaction mixture was not beneficial (entry 4). Changing DMAP to a series of organic and inorganic bases resulted in no obvious improvement (entries 5–10). This cycloaddition transformation was also found to be compatible with different solvents such as THF, CH_2Cl_2, and EtOAc (entries 11–13). Reducing the amount of diazonium salt **2a** to 1 equivalent could still generate **3a** at the expense of a relatively lower yield (entry 14). Using water as a co-solvent was found be viable, albeit in slightly decreased yield (entry 15).

Table 1 Optimization of reaction conditions.[a]



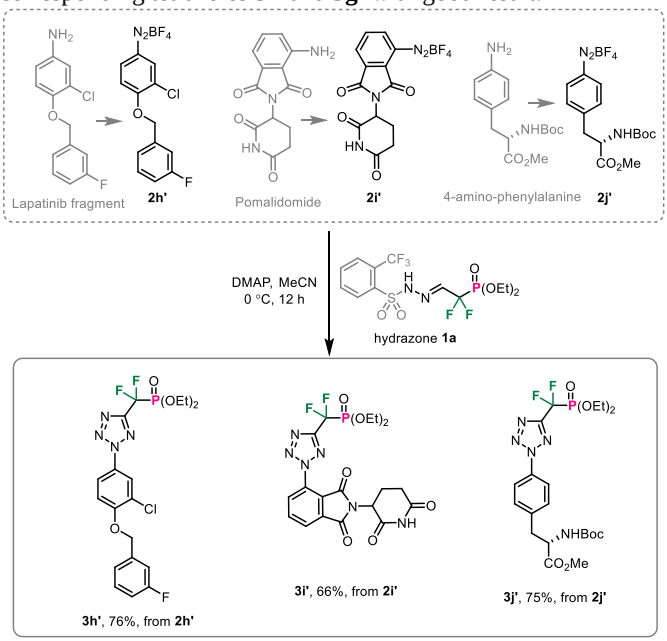
Entry	Variation from the standard conditions	Yield (%) [b]
1	none	90
2	**1b** instead of **1a**	80
3	**1c** instead of **1a**	54
4	AgOAc (5 mol%) was added	85
5	Pyridine instead of DMAP	91
6	DABCO instead of DMAP	80
7	DBU instead of DMAP	77
8	DIPEA instead of DMAP	66
9	Cs_2CO_3 instead of DMAP	80
10	K_3PO_4 instead of DMAP	65
11	THF instead of MeCN	82
12	CH_2Cl_2 instead of MeCN	73
13	EtOAc instead of MeCN	71
14	0.2 mmol of **2a** was employed	68
15	MeCN/H_2O = 1:1 was used as solvent	71

[a] Typical reaction conditions: Hydrazone **1** (0.2 mmol), phenyldiazonium tetrafluoroborate **2a** (0.4 mmol, 77 mg), and the base (0.8 mmol) were mixed in solvent (3 mL) and stirred at 0 °C for 12 hours unless otherwise indicated.
[b] Isolated yield of tetrazole **3a**.

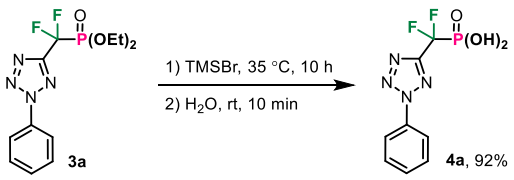


Scheme 3. Substrate scope of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates.

This DMAP-promoted [3 + 2] cycloaddition protocol proved to be quite general with respect to the scope of aryldiazonium salts (Scheme 3). Electron-donating groups substituted at the benzene ring at different positions, including alkyl, alkoxyl, and amino groups, all reacted well with hydrazone **1a** under identical conditions (products **3b**–**3i**). Incorporation of another phenyl group turned out be no problem (products **3j**–**3k**). Fluorine, bromine, and iodine atoms substituted at the *para*, *ortho*, and *meta* locations on the phenyl ring were all well tolerated, and afforded the corresponding tetrazoles **3l**–**3u** in up to 92% yield. Furthermore, strong electron-withdrawing substituents such as -Ac, -CN, -CO_2Me, and -NO_2, had no obvious influence on the reaction performance (products **3v**–**3y**). 1-Naphthyl-, 3-thienyl-, and 8-quinolinyl-derived tetrazol-5-yl difluoromethylene phosphonates **3z**–**3b'** were also obtained with exclusive regioselectivity, albeit with low yield in the case of basic 8-quinolinyl product **3b'**. 7-Coumarin-diazonium salt also underwent the cycloaddition with hydrazone **1a** under standard conditions, thus delivering the coumarin-tetrazole **3c'** in 72% yield (X-ray confirmed) [41]. Importantly, this cycloaddition reaction also tolerates alkynyl and alkenyl moieties as exemplified by the smooth generation of cycloadducts **3d'** and **3e'** in good yields. The presence of protected amino or free carboxylic group in aryldiazonium salts could also be tolerated, giving the corresponding tetrazoles **3f'** and **3g'** with good result.



Scheme 4. Preparation of pharmacophore-derived tetrazolyl difluoromethylene phosphonates.



Scheme 5. Hydrolysis of difluoromethylene phosphonate **3a**.

To further illustrate the utility of this protocol, we conducted cycloaddition reactions with several pharmacophore-derived aryldiazonium salts (Scheme 4). Aniline derivative featuring the Lapatinib's substructure was easily converted to the diazonium salt and cyclized with hydrazone **1a** with good result (product **3h'**).

Despite the presence of free amide group, Pomalidomide-derived diazonium salt was also a feasible substrate for this reaction, and gave access to the corresponding difluoromethylene phosphonate **3i'** in 66% yield. More noteworthy is that phenylalanine-derived diazonium salt **2j'** participated in the cycloaddition process smoothly, thereby providing the noncanonical amino acid **3j'** in good yield with maintained complete regio-control. Finally, the phosphonate group in **3a** was successfully hydrolyzed with the aid of TMSBr, affording the free phosphonic acid **4a** in 92% yield (Scheme 5).

In summary, we have developed a bench-stable difluoromethylene phosphonate hydrazone to serve as the corresponding diazo precursor, and established a metal-free [3 + 2] cycloaddition transformation with aryldiazonium salts. A number of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates were obtained in good yields with single regioselectivity under mild conditions. Future studies will focus on the reaction mechanism and products applications.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgments

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[43] M.-Y. Xiao, M.-M. Zheng, X. Peng, et al., Org. Lett. 22 (2020) 7762−7767.
[44] See the Supporting Information for the proposed mechanism.

Supplementary Material

Supplementary material related to this article can be found, in the online version, at doi.xx

Cover Letter

Dear Editor:

Difluoromethylene phosphonates [DFMP, $CF_2PO(OR)_2$] could mimic the naturally occurring phosphates and phosphonates, thus having emerged as a frequently utilized structural motif in the study of various biochemical processes. In this context, while simple aryl-substituted difluoromethylene phosphonates have been extensively studied in the past few decades, the construction of heterocyclic difluoromethylene phosphonates remains far less explored. More importantly, most previous studies have mainly focused on the use of metalated $CF_2PO(OR)_2$ derivatives to undergo cross-coupling-type transformations, while the development of new reactive DFMP-containing 1,3-dipoles to be used in convergent cycloadditions remains elusive. In this manuscript, we will report the preparation of three bench-stable DFMP-containing diazo precursors (DFMP-Hydrazones), and their application in the regioselective synthesis of DFMP-tetrazoles via [3 + 2] cycloaddition reactions with aryldiazonium salts under metal-free conditions. Note that this study represents the first example of introducing a difluoromethylene phosphonate motif onto the tetrazole scaffold. These two chemical entities are both metabolically stable to many of the biological transformations and have widespread implications in pharmaceuticals and bioconjugations.

Therefore, we are pleased to submit this manuscript to *Chinese Chemical Letters* as an invited contribution in the special collection "*Fluorine Chemistry*". We are convinced that the results of our work described in this manuscript are significantly novel and should be of immediate interest to a wide range of scientists. This work will arguably spark the imagination and further interest of many chemists and would help promote additional research in the fields of synthetic chemistry and fluorine chemistry.

Assurance: We assure that this manuscript is not under consideration for publication elsewhere nor has it been published elsewhere in any medium including electronic journals and computer databases of a public nature.

Thank you very much for your kind consideration.

Best wishes,

Fa-Guang Zhang & Jun-An Ma

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Response Letter

Dear Editor:

We thank the editorial office and the reviewers very much for the helpful and constructive comments. Based on these comments, the point-to-point response to all reviewers' comments are described below:

Reviewer 1:

"...Zhang and Ma have developed a bench-stable difluoromethylene phosphonate hydrazone to serve as the corresponding diazo precursor, and established a metal-free [3 + 2] cycloaddition transformation with aryldiazonium salts. A number of 2-aryl-2H-tetrazol-5-yl difluoromethylene phosphonates were obtained in good yields with single regioselectivity under mild conditions. This article is very innovative, and standard writing. The subject addressed in this article is worthy of investigation, so recommend to accept."

Our response: Thanks a lot for the comment.

Reviewer 2:

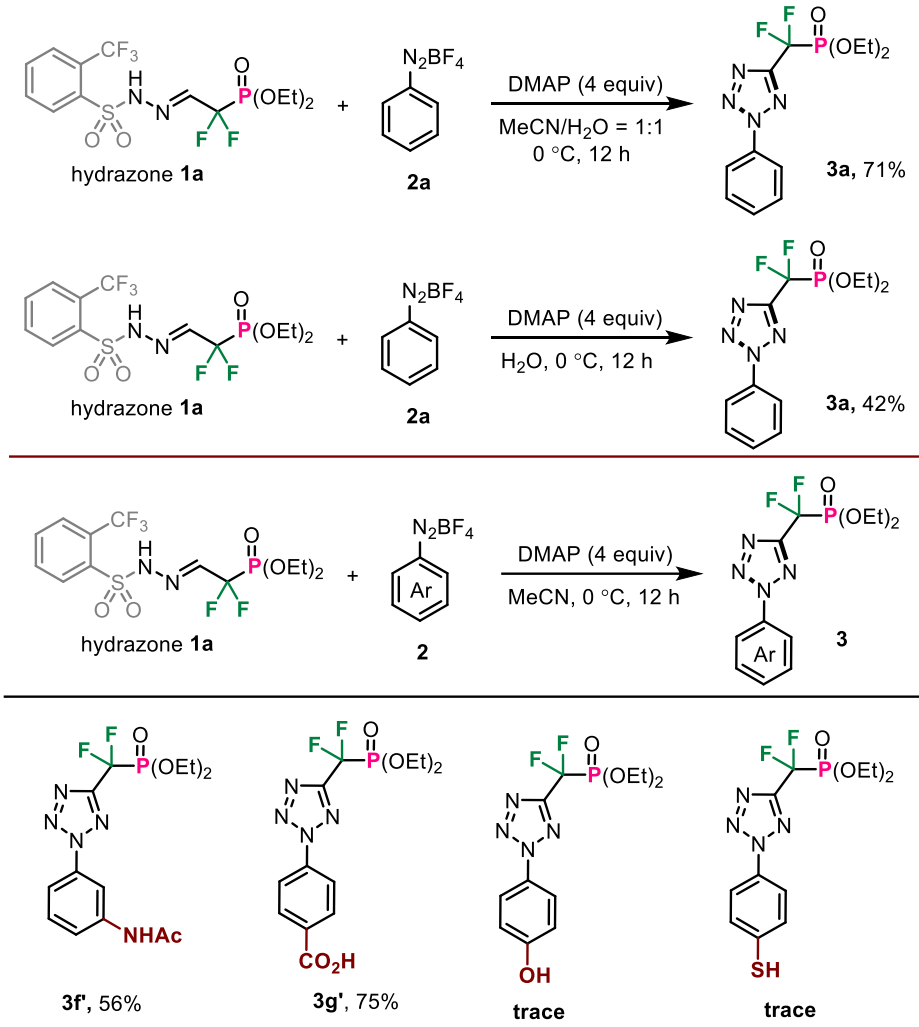
"...The Manuscript by Ma and coworkers reported a facile synthesis of 2-aryl-2H-tetrazol-5-yl difluoromethylene phosphonates from bench-stable difluoromethylene phosphonate hydrazones and aryl diazonium salts. This is an interesting method introducing difluoromethylene phosphonate motif onto the tetrazole scaffold and the chemistry may have potential applications. I thus recommend it be accepted, with the following minor issues:"

"1) The authors describe the reaction as a direct [3+2] cycloaddition reaction. It is true if a diazo intermediate is involved in the reaction pathway. But at this stage, there is no evidence that the diazo intermediate is generated. Therefore, the language should be modified to make sure the distinction is clear."

Our response: We appreciate a lot for this reviewer's comments on our work. We have modified the description of this reaction and removed the "direct" word in the revised manuscript. Furthermore, we have proposed two possible mechanisms in the supporting information.

"2) Since the authors mentioned its potential application of this reaction in bioconjugation, it would be interesting to test if water could be used as (co)solvent and free amino, alcohol, and thiol could be tolerated."

Our response: As shown in the following scheme, we have tried the model reaction by using water as a cosolvent or solvent under otherwise identical conditions. The desired tetrazole **3a** was obtained in 71% and 42%, respectively. Furthermore, we have also tested substrates bearing amino, alcohol, thiol, and carboxylic groups. The presence of protected amino or free carboxylic group in aryldiazonium salts could be tolerated (products **3f'** and **3g'**), whereas only trace amount of the desired products was observed for hydroxyl or thiol-group-substituted diazonium salts. These results have been added in the revised manuscript and supporting information.



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Our response: 我们按照上述要求对GA及摘要进行了进一步修改。

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Communication

Metal-free regioselective construction of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates

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ABSTRACT

Three bench-stable difluoromethylene phosphonate hydrazones were prepared from simple diethyl (difluoromethyl)phosphonate within two steps in good yields. The [3 + 2] cycloaddition reaction of these diazo precursors with aryl diazonium salts has been accomplished under metal-free conditions with exclusive regioselectivity. This transformation provides practical access to a broad panel of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates, including the corresponding derivatives of amino acid (phenylalanine) and drug cores (Pomalidomide and Lapatinib fragment).

Difluoromethylene phosphonates [DFMP, $CF_2PO(OR)_2$] could mimic the naturally occurring phosphates and phosphonates, thus having emerged as a frequently utilized structural motif in the study of various biochemical processes [1,2]. For example, phosphonodifluoromethyl phenylalanine (F_2Pmp) has been developed as one of the most powerful nonhydrolyzable phosphotyrosine mimetics to modulate the corresponding protein-protein interactions and used as protein tyrosine phosphatases (PTPs) inhibitors (Fig. 1) [3–5]. Furthermore, the difluoromethylene phosphonate moiety has also been utilized in the design and development of signal transducer and activator of transcription (STAT) antagonists, fructose-1,6-bisphosphatase (FBPase) inhibitors, $P2Y_1$ receptor antagonists, and cytidine triphosphate synthetase inhibitors (Fig. 1) [6–10]. Therefore, the design and development of new difluoromethylene phosphonate-containing molecular frameworks has emerged as an increasingly important task in synthetic organic chemistry. In this context, while simple aryl-substituted difluoromethylene phosphonates have been extensively studied in the past few decades [11–17], the construction of heterocyclic difluoromethylene phosphonates remains far less explored. More importantly, most previous studies have mainly focused on the use of metalated $CF_2PO(OR)_2$ derivatives to undergo cross-coupling-type transformations, while

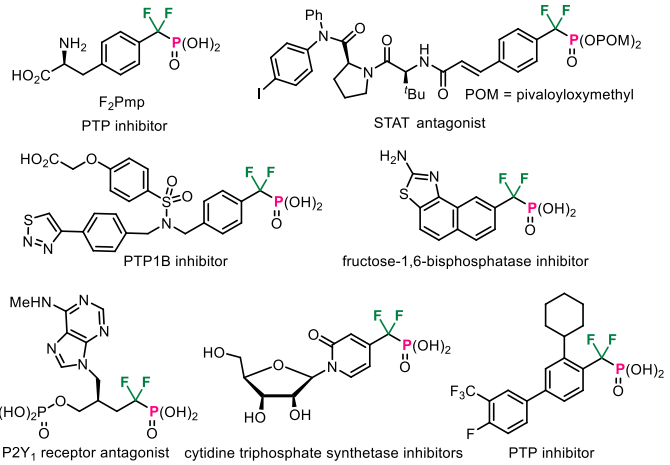
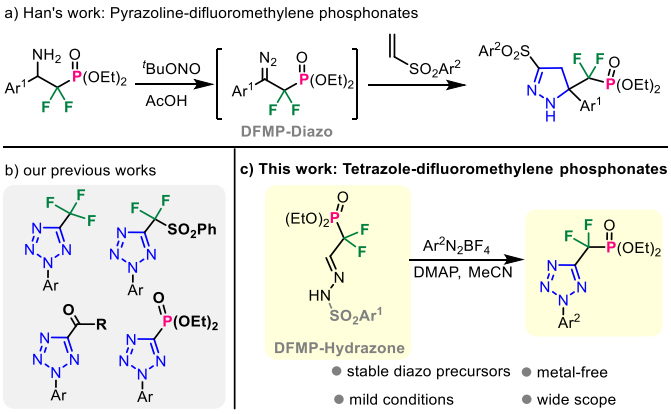


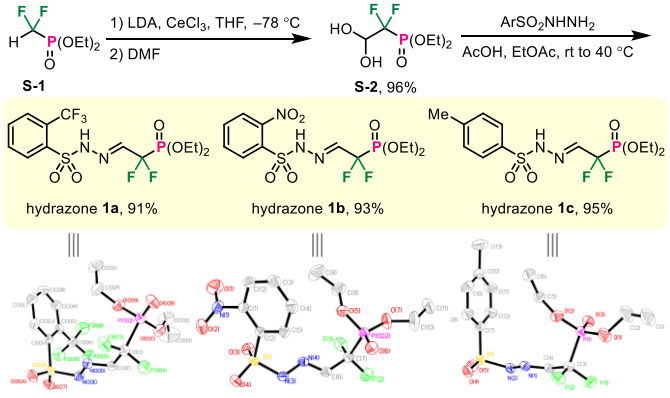
Fig. 1. Selected bio-active difluoromethylene phosphonates.

the development of new reactive DFMP-containing 1,3-dipoles to be used in convergent cycloadditions remains elusive. Very recently, Han, Röschenthaler, and co-workers reported the design of aryl-substituted difluoromethylene phosphonate-containing diazo reagents (DFMP-Diazo, Scheme 1a) [18,19]. The [3 + 2] cycloaddition reaction of DFMP-Diazo with vinyl sulfones enabled the synthesis of difluoromethylene phosphonate-

containing pyrazolines with good efficiency. However, due to the instability of DFMP-containing diazo compounds, the utilization of unsubstituted DFMP-functionalized 1,3-dipolar species to produce aromatic cycloadducts is an unsolved problem. As part of our long interest in fluorinated diazoalkanes [20–28] and the construction of tetrazoles (Scheme 1b) [29–33], herein we report the preparation of three bench-stable DFMP-containing diazo precursors (DFMP-Hydrazones), and their application in the regioselective synthesis of DFMP-tetrazoles via [3 + 2] cycloaddition reactions with aryldiazonium salts (Scheme 1c). Note that this study represents the first example of introducing a difluoromethylene phosphonate motif onto the tetrazole scaffold. These two chemical entities are both metabolically stable to many of the biological transformations and have widespread implications in pharmaceuticals and bioconjugations [34–36].



Scheme 1. Cycloaddition reactions for the preparation of difluoromethylene phosphonate heterocycles.

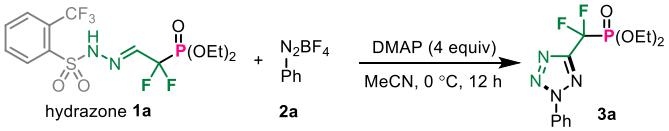


Scheme 2. Preparation of difluoromethylene phosphonate hydrazones.

At the outset, we synthesized three DFMP-hydrazones via the condensation of DFMP-aldehyde precursor **S-2** with the corresponding benzenesulfonyl hydrazides. As outlined in Scheme 2, treating commercially available diethyl (difluoromethyl)-phosphonate **S-1** with LDA in the presence of $CeCl_3$, followed by addition of *N*,*N*-dimethylformamide (DMF) in one-pot, the desired dihydrate **S-2** was smoothly obtained in 96% yield [37,38]. Subsequently, condensation of this masked aldehyde **S-2** with different hydrazides under acidic conditions proved to be viable, thus giving the target DFMP-hydrazones **1a**–**1c** in 91–95% yields [39,40]. Importantly, these diazo precursors were found to be quite stable under bench conditions, and all of them have been successfully crystallized for X-ray diffraction analysis [41].

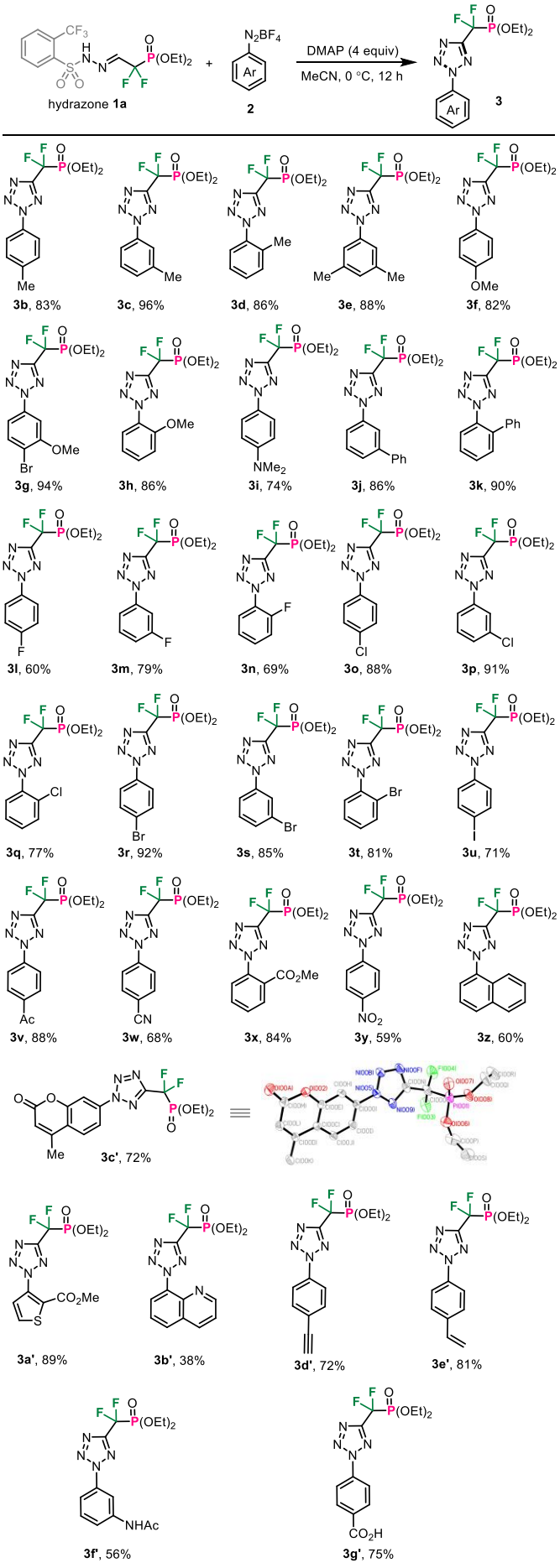
With the three difluoromethylene phosphonate hydrazones in hand, we then proceeded to optimize the [3 + 2] cycloaddition reaction with phenyldiazonium salt **2a** (Table 1) [42]. Pleasingly, by just using 4-dimethylaminopyridine (DMAP) as the base, acetonitrile as the solvent, the desired 2,5-disubstituted tetrazole **3a** was obtained in up to 90% yield from CF_3-hydrazone **1a** without the detection of any regioisomer (entry 1). Employing NO_2-hydrazone **1b** or Me-hydrazone **1c** could also permit the formation of tetrazole **3a**, albeit in decreased yields (entry 2 and 3). The significantly lower yield observed when using Me-hydrazone **1c** could be the result of a lower leaving-group ability of its benzenesulfonyl moiety with respect to **1a** and **1b**. Notably, this reaction does not require the use of an organometallic species and thus should not involve a carbenoid intermediate that is clearly indicative of a different mechanism compared with our previous studies on the silver-catalyzed synthesis of differently decorated tetrazoles [43,44]. Addition of silver acetate to the reaction mixture was not beneficial (entry 4). Changing DMAP to a series of organic and inorganic bases resulted in no obvious improvement (entries 5–10). This cycloaddition transformation was also found to be compatible with different solvents such as THF, CH_2Cl_2, and EtOAc (entries 11–13). Reducing the amount of diazonium salt **2a** to 1 equivalent could still generate **3a** at the expense of a relatively lower yield (entry 14). Using water as a co-solvent was found be viable, albeit in slightly decreased yield (entry 15).

Table 1 Optimization of reaction conditions.[a]



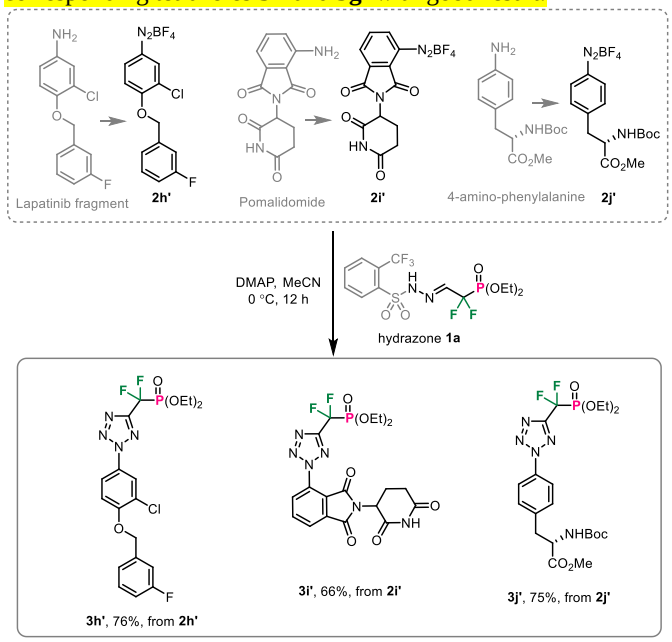
Entry	Variation from the standard conditions	Yield (%) [b]
1	none	90
2	**1b** instead of **1a**	80
3	**1c** instead of **1a**	54
4	AgOAc (5 mol%) was added	85
5	Pyridine instead of DMAP	91
6	DABCO instead of DMAP	80
7	DBU instead of DMAP	77
8	DIPEA instead of DMAP	66
9	Cs_2CO_3 instead of DMAP	80
10	K_3PO_4 instead of DMAP	65
11	THF instead of MeCN	82
12	CH_2Cl_2 instead of MeCN	73
13	EtOAc instead of MeCN	71
14	0.2 mmol of **2a** was employed	68
15	MeCN/H_2O = 1:1 was used as solvent	71

[a] Typical reaction conditions: Hydrazone **1** (0.2 mmol), phenyldiazonium tetrafluoroborate **2a** (0.4 mmol, 77 mg), and the base (0.8 mmol) were mixed in solvent (3 mL) and stirred at 0 °C for 12 hours unless otherwise indicated.
[b] Isolated yield of tetrazole **3a**.

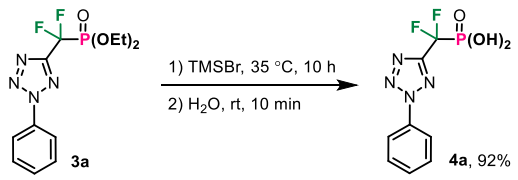


Scheme 3. Substrate scope of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates.

This DMAP-promoted [3 + 2] cycloaddition protocol proved to be quite general with respect to the scope of aryldiazonium salts (Scheme 3). Electron-donating groups substituted at the benzene ring at different positions, including alkyl, alkoxyl, and amino groups, all reacted well with hydrazone **1a** under identical conditions (products **3b**–**3i**). Incorporation of another phenyl group turned out be no problem (products **3j**–**3k**). Fluorine, bromine, and iodine atoms substituted at the *para*, *ortho*, and *meta* locations on the phenyl ring were all well tolerated, and afforded the corresponding tetrazoles **3l**–**3u** in up to 92% yield. Furthermore, strong electron-withdrawing substituents such as -Ac, -CN, -CO_2Me, and -NO_2, had no obvious influence on the reaction performance (products **3v**–**3y**). 1-Naphthyl-, 3-thienyl-, and 8-quinolinyl-derived tetrazol-5-yl difluoromethylene phosphonates **3z**–**3b'** were also obtained with exclusive regioselectivity, albeit with low yield in the case of basic 8-quinolinyl product **3b'**. 7-Coumarin-diazonium salt also underwent the cycloaddition with hydrazone **1a** under standard conditions, thus delivering the coumarin-tetrazole **3c'** in 72% yield (X-ray confirmed) [41]. Importantly, this cycloaddition reaction also tolerates alkynyl and alkenyl moieties as exemplified by the smooth generation of cycloadducts **3d'** and **3e'** in good yields. The presence of protected amino or free carboxylic group in aryldiazonium salts could also be tolerated, giving the corresponding tetrazoles **3f'** and **3g'** with good result.



Scheme 4. Preparation of pharmacophore-derived tetrazolyl difluoromethylene phosphonates.



Scheme 5. Hydrolysis of difluoromethylene phosphonate **3a**.

To further illustrate the utility of this protocol, we conducted cycloaddition reactions with several pharmacophore-derived aryldiazonium salts (Scheme 4). Aniline derivative featuring the Lapatinib's substructure was easily converted to the diazonium salt and cyclized with hydrazone **1a** with good result (product **3h'**).

Despite the presence of free amide group, Pomalidomide-derived diazonium salt was also a feasible substrate for this reaction, and gave access to the corresponding difluoromethylene phosphonate **3i'** in 66% yield. More noteworthy is that phenylalanine-derived diazonium salt **2j'** participated in the cycloaddition process smoothly, thereby providing the noncanonical amino acid **3j'** in good yield with maintained complete regio-control. Finally, the phosphonate group in **3a** was successfully hydrolyzed with the aid of TMSBr, affording the free phosphonic acid **4a** in 92% yield (Scheme 5).

In summary, we have developed a bench-stable difluoromethylene phosphonate hydrazone to serve as the corresponding diazo precursor, and established a metal-free [3 + 2] cycloaddition transformation with aryldiazonium salts. A number of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates were obtained in good yields with single regioselectivity under mild conditions. Future studies will focus on the reaction mechanism and products applications.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgments

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[44] See the Supporting Information for the proposed mechanism.

Supplementary Material

Supplementary material related to this article can be found, in the online version, at doi.xx

Graphical Abstract

Metal-free regioselective construction of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates

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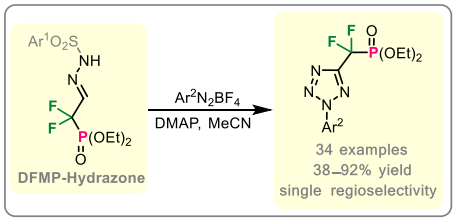

Three bench-stable difluoromethylene phosphonate hydrazones have been developed to function as the corresponding diazo precursor, and cyclized with aryldiazonium salts under metal-free conditions to give the 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates with exclusive regioselectivity.

Supporting Information

Metal-free regioselective construction of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates

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General Information

^{1}H, ^{13}C and ^{31}P were recorded on Bruker AV 400 MHz instrument at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR), 162 MHz (^{31}P NMR), as well as 101 MHz (^{13}C NMR). Chemical shifts were reported in ppm down field from internal Me_4Si and external CCl_3F, respectively. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad). Coupling constants were reported in Hertz (Hz). High resolution mass spectrometry (HRMS) spectra were obtained on a Waters Xevo G2-XS QTof instrument. X-ray structural analysis was conducted on a Bruker APEX-II CCD instrument.

Materials: Toluene was distilled from sodium benzophenone; CH_2Cl_2 (DCM) and *N,N*-dimethylformamide (DMF) were distilled from CaH_2; MeCN was distilled from P_2O_5. All commercially available reagents were used without further purification. The diazonium salts were prepared according to the reported procedures.[1,2]

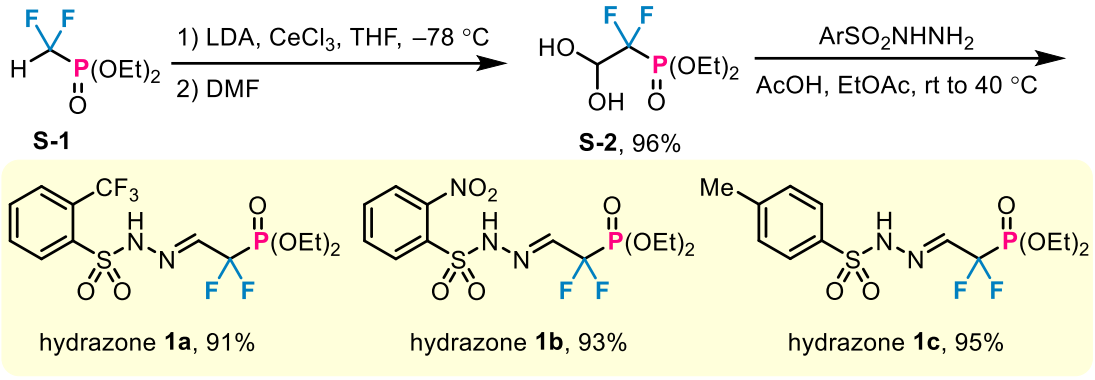
Analytical thin layer chromatography was performed on 0.20 mm silica gel plates. Silica gel (200–300 mesh) was used for flash chromatography. All purchased reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm Qingdao Haiyang silica gel plates. Silica gel (200-300 mesh) (from Qingdao Haiyang Chem. Company, Ltd.) was used for flash chromatography.

Important Safety Note

Handling of diazo compounds and diazonium salts should be done in a well-ventilated fume cupboard. No incidents occurred handling of these reagents during this study, yet the readers should be aware of carcinogenicity and explosiveness of the herein described diazo compounds and diazonium salts. General safety precautions when working with diazo compounds and diazonium salts should be followed. Any reactions described in this manuscript should not be performed without strict risk assessment.[3,4]

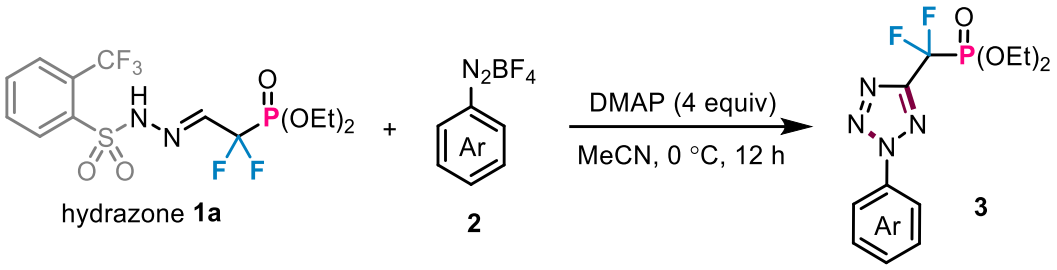
Experimental Procedures

The synthesis of three bench-stable DFMP-containing diazo precursors (DFMP-Hydrazones). (Method A)



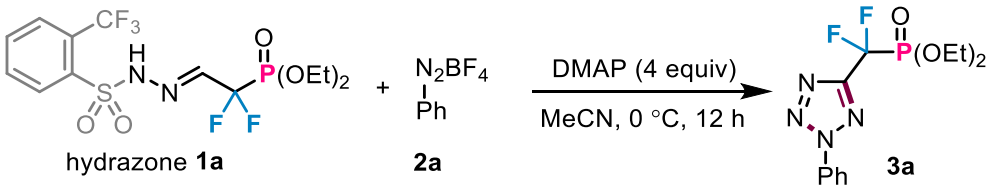
To solution of LDA (41 mL, 2.0 M solution in THF/n-heptane/ethylbenzene) in dry THF at −78 °C was added freshly dried cerium(III) chloride (21 g, 82 mmol) in one portion. The resulting suspension was stirred vigorously at −78 °C for 20 min. Diethyl difluoromethylphosphonate (**S-1**; 15 g, 80 mmol) was added dropwise over 15 min, and the mixture was stirred for 1 h. Freshly distilled *N*, *N*-dimethylformamide (6.2 mL, 6 g, 82 mmol) was slowly added to the pale yellow-orange suspension, and after the mixture was stirred for 1 h further, aqueous hydrochloric acid was added until complete dissolution of cerium salts and the solution was warmed to room temperature. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford diethyl (1,1-difluoro-2,2-dihydroxyethyl)phosphonate (**S-2,** 18.0 g, 96%)[1]. Then a 250 mL bottom flask was charged with **S-2** (60 mmol), $ArSO_2NHNH_2$ (40 mmol) and ethyl acetate (200 mL). Then acetic acid (4 mmol) was added dropwise under Ar atmosphere. Then the mixture was transferred to 40 ºC and stirred overnight, and monitored by TLC (PE:EA=2:1, v/v). After the reaction was complete, the mixture was concentrated under reduced pressure and washed by PE/Et_2O to afford the product **1a** (15.4 g, 91%) as a white solid, **1b** (15.5 g, 93%) as a yellow solid, and **1c** (14.6 g, 95%) as a white solid, respectively.

General procedure for the synthesis of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates. (Method B)



An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with hydrazone **1a** (0.2 mmol), aryl diazonium salts **2** (0.4 mmol), DMAP (0.8 mmol), then MeCN (3 mL) were added under Ar atmosphere. The resulting mixture was allowed to stir at 0 ºC for 12 hours. The resulting organic solution was concentrated under reduced pressure, and the residue was further purified by a silica gel column chromatography to yield the corresponding 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates **3**.

Optimization of Reaction Conditions[a]



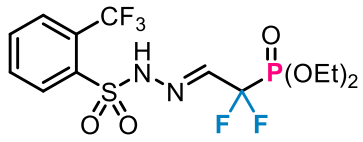
Entry	Variation from the standard conditions	Yield (%) [b]
1	none	90
2	**1b** instead of **1a**	80
3	**1c** instead of **1a**	54
4	AgOAc (5 mol%) was added	85
5	Pyridine instead of DMAP	91
6	DABCO instead of DMAP	80
7	DBU instead of DMAP	77
8	DIPEA instead of DMAP	66
9	Cs_2CO_3 instead of DMAP	80
10	K_3PO_4 instead of DMAP	65
11	K_2HPO_4 instead of DMAP	74
12	K_2CO_3 instead of DMAP	44
13	NaOH instead of DMAP	45
14	THF instead of MeCN	82
15	CH_2Cl_2 instead of MeCN	73
16	EtOAc instead of MeCN	71
17	DMF instead of MeCN	12
18	0.2 mmol of **2a** was employed	68
19	at -10 °C for 12 hours	69

20	at 25 °C for 12 hours	76
21	MeCN/H_2O = 1:1 was used as solvent	71
22	H_2O instead of MeCN	42

[a] Typical reaction conditions: Hydrazone **1** (0.2 mmol), phenyldiazonium tetrafluoroborate **2a** (0.4 mmol, 77 mg), and the base (0.8 mmol) were mixed in solvent (3 mL) and stirred at 0 °C for 12 hours unless otherwise indicated. [b] Isolated yield of tetrazole **3a**.

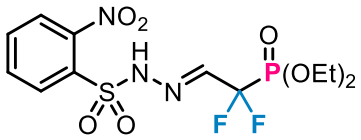
Characterization Data of All New Compounds

Diethyl (*E*)-(1,1-difluoro-2-(2-((2-(trifluoromethyl)phenyl)sulfonyl) hydrazineylidene)ethyl)phosphonate (1a).



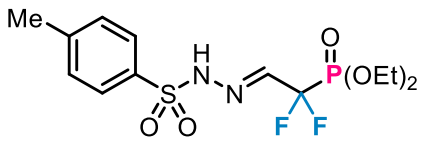
For 40 mmol scale, the standard procedure of method A was followed to provide **1a** as a white solid (15.4 g, 91%). **^{1}H NMR** (400 MHz, DMSO-D_6) δ 8.13 – 8.00 (m, 2H), 7.55 – 7.44 (m, 2H), 4.17 – 3.96 (m, 4H), 1.13 (t, J = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -58.02 (s), -113.08 (d, J = 7.7 Hz), -113.36 (d, J = 7.5 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.14 (t, J = 104.1 Hz). **^{13}C NMR** (101 MHz, DMSO-D_6) δ 137.7 (dd, J = 27.1, 14.5 Hz), 137.3 (d, J = 12.8 Hz), 134.0, 133.4, 131.5, 128.6 (q, J = 6.2 Hz), 126.4 (q, J = 32.9 Hz), 122.7 (d, J = 274.0 Hz), 114.5 (td, J = 260.0, 214.0 Hz), 64.7 (d, J = 6.6 Hz), 16.0 (d, J = 5.3 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{17}N_2O_5F_5PS^+$ $(M+H)^+$: 439.0516, found: *m/z* 439.0506.

Diethyl (*E*)-(1,1-difluoro-2-(2-((2-nitrophenyl)sulfonyl)hydrazineylidene)ethyl) phosphonate (1b).



For 40 mmol scale, the standard procedure of method A was followed to provide **1b** as a yellow solid (15.5 g, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.21 (dd, J = 5.9, 3.4 Hz, 1H), 7.85 – 7.72 (m, 3H), 7.53 – 7.44 (m, 1H), 4.42 – 4.16 (m, 4H), 1.33 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.73 (d, J = 7.0 Hz), -113.00 (d, J = 7.2 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.23 (tq, J = 102.7, 7.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2, 139.2 (td, J = 27.6, 15.8 Hz), 134.6, 132.8, 132.6, 131.7, 125.1, 118.5 – 110.3 (m), 65.9 (d, J = 6.7 Hz), 16.4 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{16}N_3O_7F_2PSNa^+$ $(M+Na)^+$: 438.0312, found: *m/z* 438.0311.

Diethyl (*E*)-(1,1-difluoro-2-(2-tosylhydrazineylidene)ethyl)phosphonate (1c). For



40 mmol scale, the standard procedure of method A was followed to provide **1c** as a white solid (14.6 g, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.21 (q, J = 7.3 Hz, 4H), 2.40 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz,

$CDCl_3$) δ -111.45 (d, J = 7.3 Hz), -111.72 (d, J = 7.1 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.29 (tdt, J = 104.7, 15.7, 7.8 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4, 137.3 (td, J = 27.8, 15.1 Hz), 135.5, 129.7, 127.9, 114.5 (td, J = 261.3, 216.4 Hz), 65.9 (d, J = 6.8 Hz), 21.6, 16.3 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{19}N_2O_5F_2PSNa^+$ $(M+Na)^+$: 407.0618, found: *m/z* 407.0612.

Diethyl (difluoro(2-phenyl-2*H*-tetrazol-5-yl)methyl)phosphonate (3a). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3a** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a yellow oil (59.8 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 – 8.07 (m, 2H), 7.65 – 7.48 (m, 3H), 4.40 (p, J = 7.0 Hz, 4H), 1.41 (t, J = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.52, -109.79. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.94 (tq, J = 100.8, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 – 158.1 (m), 136.5, 130.7, 130.0, 120.3, 113.0 (td, J = 262.9, 217.6 Hz), 65.8 (d, J = 6.5 Hz), 16.5 (d, J = 5.6 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{16}N_4O_3F_2P^+$ $(M+H)^+$: 333.0928, found: *m/z* 333.0926.

Diethyl (difluoro(2-(*p*-tolyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3b). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3b** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red solid (57.5 mg, 83%). M.p.: 31-32 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 4.38 (d, J = 8.0 Hz, 4H), 2.43 (s, 3H), 1.41 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.44, -109.71. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.05 (tp, J = 100.7, 8.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2 – 159.3 (m), 141.1, 134.3 130.4, 120.2 113.0 (td, J = 262.8, 217.4 Hz), 65.8 (d, J = 6.6 Hz), 21.4, 16.5 (d, J = 5.6 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{18}N_4O_3F_2P^+$ $(M+H)^+$: 347.1085, found: *m/z* 347.1089.

Diethyl (difluoro(2-(*m*-tolyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3c). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3c** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a black oil (66.5 mg, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 4.46 – 4.33 (m, 4H), 2.46 (s, 3H), 1.41 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.51, -109.78. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.02 (tp, J = 100.9, 8.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8 (td, J = 27.5, 17.1 Hz), 140.3, 136.4, 131.4, 129.7, 120.8, 117.4, 113.0 (td, J = 262.8, 217.5 Hz), 65.8 (d, J = 6.5 Hz), 21.5, 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{18}N_4O_3F_2P^+$ $(M+H)^+$: 347.1085, found: *m/z* 347.1082.

Diethyl (difluoro(2-(*o*-tolyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3d). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3d** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a yellow oil (59.6 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 14.4, 5.3 Hz, 2H), 4.39 (p, *J* = 7.3 Hz, 4H), 2.37 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.28, -109.55. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.09 (tt, *J* = 101.7, 8.5 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1 – 158.0 (m), 135.9, 133.1, 132.0, 130.9, 127.0, 125.1, 112.9 (td, *J* = 262.5, 217.5 Hz), 65.7 (d, *J* = 6.6 Hz), 18.6, 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{18}N_4O_3F_2P^+$ $(M+H)^+$: 347.1085, found: *m/z* 347.1090.

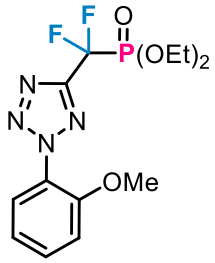
Diethyl ((2-(3,5-dimethylphenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3e). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3e** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red oil (63.4 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.6 Hz, 2H), 7.15 (s, 0H), 4.45 – 4.33 (m, 4H), 2.41 (s, 6H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.49, -109.76. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.05 (tp, *J* = 101.2, 8.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 – 159.1 (m), 140.0, 136.4, 132.3, 118.0, 113.0 (td, *J* = 262.9, 217.6 Hz), 65.8 (d, *J* = 6.6 Hz), 21.4, 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{14}H_{20}N_4O_3F_2P^+$ $(M+H)^+$: 361.1241, found: *m/z* 361.1242.

Diethyl (difluoro(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3f). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3f** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a purple solid (59.5 mg, 82%). M.p.: 38-39 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 2H), 7.04 (d, *J* = 9.1 Hz, 2H), 4.61 – 4.12 (m, 4H), 3.88 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.39, -109.66. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.08 (tt, *J* = 101.7, 8.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 129.8, 121.8, 114.8, 112.9 (td, *J* = 262.8, 217.7 Hz), 65.7 (d, *J* = 6.5 Hz), 55.7, 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{18}N_4O_4F_2P^+$ $(M+H)^+$: 363.1034, found: *m/z* 363.1035.

Diethyl ((2-(4-bromo-3-methoxyphenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3g). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3g** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown solid (80.0 mg, 94%). M.p.: 58-59 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.62 (m, 3H), 4.40 (p, *J* = 7.2 Hz, 4H), 4.02 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.67, -109.94. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.80 (tq, *J* = 100.8,

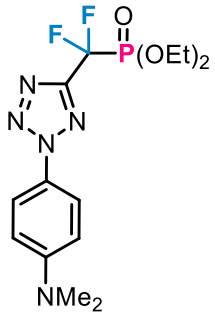
8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0 (td, *J* = 27.6, 17.3 Hz), 157.0, 136.4, 134.3, 114.2, 113.1, 112.9 (td, *J* = 263.2, 217.3 Hz), 103.9, 65.9 (d, *J* = 6.6 Hz), 56.8, 16.4 (d, *J* = 5.6 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{17}N_4O_4BrF_2P^+$ $(M+H)^+$: 441.0139, found: *m/z* 441.0137.

Diethyl (difluoro(2-(2-methoxyphenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3h).



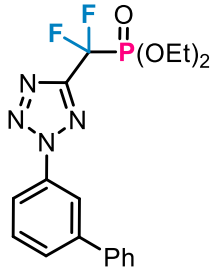
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3h** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a brown oil (62.4 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.8, 6.8 Hz, 2H), 7.16 – 7.07 (m, 2H), 4.45 – 4.34 (m, 4H), 3.84 (s, 3H), 1.39 (t, *J* = 6.7 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.99, -109.26. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.08 (tp, *J* = 100.9, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5 (td, *J* = 27.6, 17.4 Hz), 153.6, 132.8, 127.1, 125.9, 120.8, 113.0 (td, *J* = 262.5, 217.3 Hz), 112.9, 65.8 (d, *J* = 6.6 Hz), 56.3, 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{18}N_4O_4F_2P^+$ $(M+H)^+$: 363.1034, found: *m/z* 363.1028.

Diethyl ((2-(4-(dimethylamino)phenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3i).

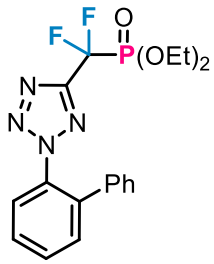


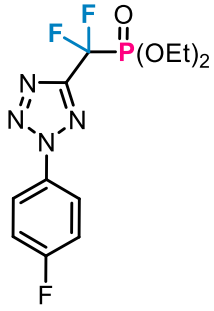
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3i** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a purple solid (55.5 mg, 74%). M.p.: 53-54 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.3 Hz, 2H), 6.76 (d, *J* = 9.3 Hz, 2H), 4.39 (p, *J* = 7.2 Hz, 4H), 3.05 (s, 4H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.17, -109.44. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.25 (tt, *J* = 101.9, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.7 – 157.3 (m), 151.5, 126.0, 121.4, 113.0 (td, *J* = 262.4, 217.5 Hz), 111.8, 65.6 (d, *J* = 6.5 Hz), 40.3, 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{14}H_{21}N_5O_3F_2P^+$ $(M+H)^+$: 376.1350, found: *m/z* 376.1344.

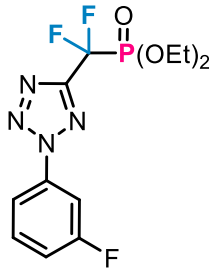
Diethyl ((2-([1,1'-biphenyl]-3-yl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3j).



For 0.2 mmol scale, the standard procedure of method B was followed to provide **3j** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown oil (63.2 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (t, *J* = 2.0 Hz, 1H), 8.13 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.76 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.69 – 7.60 (m, 3H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 6.7 Hz, 1H), 4.56 – 4.30 (m, 4H), 1.43 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.50, -109.77. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.02 (tp, *J* = 101.1, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.9 – 159.3 (m), 143.4, 139.3, 137.0, 130.4, 129.3, 129.2, 128.5, 127.3, 118.9, 118.9, 113.0 (td, *J* = 263.0, 217.5 Hz), 65.9 (d, *J* = 6.5 Hz), 16.5 (d, *J* = 5.6 Hz). **HRMS (ESI)**: calcd. for $C_{18}H_{20}N_4O_3F_2P^+$ $(M+H)^+$: 409.1241, found: *m/z* 409.1238.

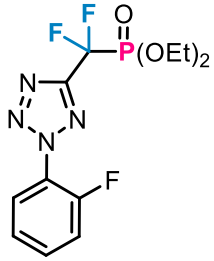
Diethyl ((2-([1,1'-biphenyl]-2-yl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3k). 
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3k** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a brown oil (73.5 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.51 (m, 4H), 7.31 – 7.21 (m, 3H), 7.09 – 6.99 (m, 2H), 4.35 – 4.16 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.28, -109.55. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.93 (tp, *J* = 101.1, 8.5 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6 (td, *J* = 27.7, 17.0 Hz), 138.7, 137.0, 134.7, 131.6, 131.6, 128.7, 128.5, 128.3, 128.1, 126.7, 112.8 (td, *J* = 262.7, 216.9 Hz), 65.7 (d, *J* = 6.5 Hz), 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{18}H_{20}N_4O_3F_2P^+$ $(M+H)^+$: 409.1241, found: *m/z* 409.1243.

Diethyl (difluoro(2-(4-fluorophenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3l). 
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3l** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a brown oil (42.0 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 – 8.12 (m, 2H), 7.33 – 7.22 (m, 2H), 4.40 (p, *J* = 7.1 Hz, 4H), 1.42 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.96 (tt, *J* = 8.9, 4.8 Hz), -109.58, -109.85. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.93 (t, *J* = 100.8 Hz).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6 (d, *J* = 251.9 Hz), 160.0 (td, *J* = 27.5, 17.1 Hz), 132.7 (d, *J* = 3.3 Hz), 122.4 (d, *J* = 8.8 Hz), 117.0 (d, *J* = 23.5 Hz), 112.9 (td, *J* = 263.1, 217.5 Hz), 65.8 (d, *J* = 6.6 Hz), 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3F_3P^+$ $(M+H)^+$: 351.0834, found: *m/z* 351.0834.

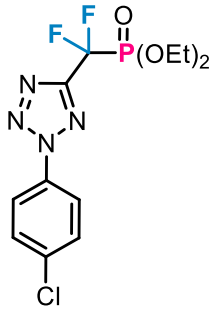
Diethyl (difluoro(2-(3-fluorophenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3m). 
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3m** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown oil (55.3 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 10.7 Hz, 1H), 7.89 (dt, *J* = 8.9, 2.3 Hz, 1H), 7.56 (td, *J* = 8.3, 5.8 Hz, 1H), 7.25 (dt, *J* = 8.3, 4.3 Hz, 1H), 4.47 – 4.32 (m, 4H), 1.41 (t, *J* = 7.2 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.96 (td, *J* = 8.2, 5.5 Hz), -109.72, -109.99. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.83 (tp, *J* = 100.5, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.04 (d, *J* = 249.7 Hz), 160.12 (td, *J* = 27.5, 17.1 Hz), 137.37 (d, *J* = 10.3 Hz), 131.56 (d, *J* = 8.8 Hz), 117.74 (d, *J* = 21.2 Hz), 116.86 – 108.88 (m), 115.91 (d, *J* = 3.4 Hz), 108.22 (d, *J* = 27.4 Hz), 65.88 (d, *J* = 6.6 Hz), 16.46 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3F_3P^+$ $(M+H)^+$: 351.0834, found: *m/z* 351.0831.

Diethyl (difluoro(2-(2-fluorophenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3n). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3n** by column chromatography on silica gel (petroleum ether/EtOAc, 3:1, v/v) as a yellow

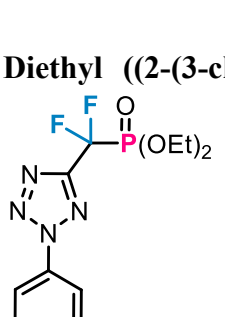
oil (48.3 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 7.7 Hz, 1H), 7.64 – 7.54 (m, 1H), 7.42 – 7.34 (m, 2H), 4.41 (p, *J* = 7.0 Hz, 4H), 1.42 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.37, -109.64, -120.14 (ddd, *J* = 10.9, 7.2, 4.8 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.81 (tq, *J* = 100.3, 8.0 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0 – 159.0 (m), 154.8 (d, *J* = 258.8 Hz), 132.7 (d, *J* = 7.7 Hz), 125.7, 125.1 (d, *J* = 4.1 Hz), 124.8 (d, *J* = 10.4 Hz), 117.9 (d, *J* = 19.2 Hz), 112.9 (td, *J* = 263.1, 217.4 Hz), 65.9 (d, *J* = 6.5 Hz), 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3F_3P^+$ $(M+H)^+$: 351.0834, found: *m/z* 351.0834.



Diethyl ((2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3o). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3o** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a yellow oil (79.6 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 2H), 7.58 – 7.51 (m, 2H), 4.45 – 4.34 (m, 4H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.64, -109.90. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.87 (tp, *J* = 100.5, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1 (td, *J* = 27.6, 17.1 Hz), 136.8, 134.9, 130.2, 121.6, 112.9 (td, *J* = 263.2, 217.3 Hz), 65.9 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3ClF_2P^+$ $(M+H)^+$: 367.0538, found: *m/z* 367.0534.



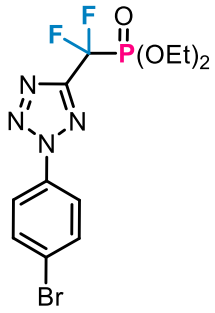
Diethyl ((2-(3-chlorophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3p). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3p** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown solid (66.7 mg, 91%). M.p.: 30-31 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (q, *J* = 1.3 Hz, 1H), 8.11 – 8.02 (m, 1H), 7.57 – 7.47 (m, 2H), 4.45 – 4.33 (m, 4H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.72, -109.98. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.82 (tp, *J* = 100.6, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2 (td, *J* = 27.6, 17.1 Hz), 137.1, 135.9, 131.1, 130.8, 120.6, 118.4, 112.9 (td, *J* = 263.3, 217.4 Hz), 65.9 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3ClF_2P^+$ $(M+H)^+$: 367.0538, found: *m/z* 367.0535.



Diethyl ((2-(2-chlorophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3q). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3q** by column chromatography on silica gel (petroleum ether/EtOAc, 3:1, v/v) as a brown oil (56.4 mg, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (ddd, *J* = 8.0, 3.0, 1.6 Hz, 2H), 7.57 (td, *J* = 7.8, 1.6 Hz, 1H), 7.49 (td, *J* = 7.7, 1.5 Hz, 1H), 4.39 (p, *J* = 7.3 Hz, 4H), 1.40 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.30, -109.56. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.88 (tp, *J* = 100.4, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1 – 159.2 (m), 134.5, 132.5, 131.4, 130.0,

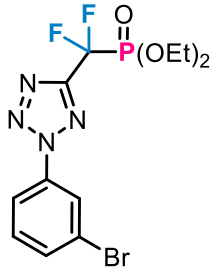
127.9, 112.9 (td, J = 263.0, 217.3 Hz), 65.9 (d, J = 6.6 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3ClF_2P^+$ $(M+H)^+$: 367.0538, found: *m/z* 367.0533.

Diethyl ((2-(4-bromophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3r).



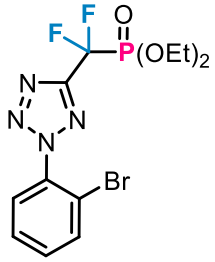
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3r** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a yellow solid (75.6 mg, 92%). M.p.: 49-50 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 2H), 7.73 – 7.69 (m, 2H), 4.44 – 4.35 (m, 4H), 1.41 (t, J = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.64, -109.90. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.86 (tp, J = 100.6, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1 (td, J = 27.6, 17.2 Hz), 135.4, 133.2, 124.8, 121.8, 112.9 (td, J = 263.2, 217.3 Hz), 65.9 (d, J = 6.6 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3BrF_2P^+$ $(M+H)^+$: 411.0033, found: *m/z* 411.0032.

Diethyl ((2-(3-bromophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3s).



For 0.2 mmol scale, the standard procedure of method B was followed to provide **3s** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a brown oil (69.8 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (t, J = 2.0 Hz, 1H), 8.11 (dd, J = 8.2, 1.1 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 7.45 (t, J = 8.2 Hz, 1H), 4.46 – 4.34 (m, 4H), 1.41 (t, J = 7.5 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.70, -109.97. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.83 (tp, J = 100.6, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2 (td, J = 27.6, 17.0 Hz), 137.2, 133.8, 131.3, 123.5, 123.4, 118.9, 112.9 (td, J = 263.2, 217.2 Hz), 65.9 (d, J = 6.6 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3BrF_2P^+$ $(M+H)^+$: 411.0033, found: *m/z* 411.0033.

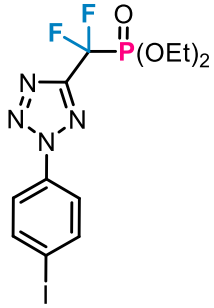
Diethyl ((2-(2-bromophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3t).



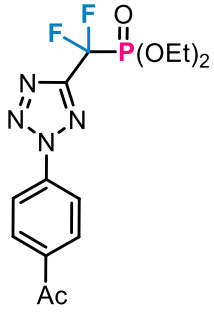
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3t** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown oil (66.6 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.8, 1.6 Hz, 1H), 7.60 (dd, J = 7.7, 2.0 Hz, 1H), 7.57 – 7.45 (m, 2H), 4.38 (p, J = 7.1 Hz, 4H), 1.39 (t, J = 7.5 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.29, -109.55. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.90 (tp, J = 99.8, 7.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9 (td, J = 27.7, 17.0 Hz), 136.2, 134.5, 132.8, 128.5, 128.2, 119.0, 112.9 (td, J = 262.9, 217.2 Hz), 65.8 (d, J = 6.5 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3BrF_2P^+$ $(M+H)^+$: 411.0033, found: *m/z* 411.0033.

Diethyl (difluoro(2-(4-iodophenyl)-2H-tetrazol-5-yl)methyl)phosphonate (3u). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3u** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a yellow

solid (65.0 mg, 71%). M.p.: 64-65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 4H), 4.39 (p, J = 7.2 Hz, 4H), 1.41 (t, J = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.63, -109.90. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.86 (tt, J = 100.6, 8.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1 (td, J = 27.6, 17.2 Hz), 139.2, 136.1, 121.8, 112.9 (td, J = 263.2, 217.3 Hz), 96.4, 65.9 (d, J = 6.6 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_4O_3F_2IP^+$ $(M+H)^+$: 458.9895, found: *m/z* 458.9891.

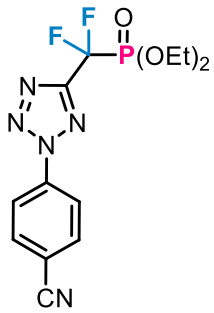


Diethyl ((2-(4-acetylphenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3v).



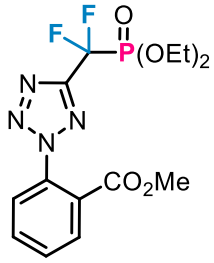
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3v** by column chromatography on silica gel (petroleum ether/EtOAc, 2:1, v/v) as a red-brown solid (65.9 mg, 88%). M.p.: 46-47 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.8 Hz, 2H), 8.19 – 8.12 (m, 2H), 4.70 – 4.19 (m, 4H), 2.66 (s, 3H), 1.41 (t, J = 6.7 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.74, -110.00. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.77 (tp, J = 99.9, 8.0 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.4, 160.3 (td, J = 27.6, 17.3 Hz).139.2, 138.5, 130.1, 120.3, 112.9 (td, J = 263.3, 217.1 Hz), 65.9 (d, J = 6.6 Hz), 26.8, 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{14}H_{18}N_4O_4F_2P^+$ $(M+H)^+$: 375.1034, found: *m/z* 375.1031.

Diethyl ((2-(4-cyanophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3w).



For 0.2 mmol scale, the standard procedure of method B was followed to provide **3w** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a yellow solid (48.6 mg, 68%). M.p.: 44-45 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, J = 11.0 Hz, 2H), 7.91 (d, J = 11.0 Hz, 2H), 4.40 (p, J = 7.1 Hz, 4H), 1.42 (t, J = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.89, -110.15. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.62 (tp, J = 100.0, 8.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (d, J = 17.2 Hz), 138.9, 134.1, 120.9, 117.4, 114.6, 112.8 (td, J = 263.5, 216.9 Hz), 66.0 (d, J = 6.6 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{13}H_{15}N_5O_3F_2P^+$ $(M+H)^+$: 358.0881, found: *m/z* 358.0882.

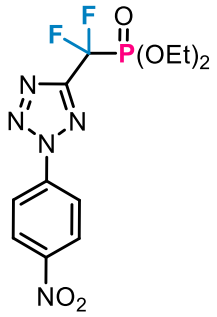
Methyl 2-(5-((diethoxyphosphoryl)difluoromethyl)-2*H*-tetrazol-2-yl)benzoate (3x).



For 0.2 mmol scale, the standard procedure of method B was followed to provide **3x** by column chromatography on silica gel (petroleum ether/EtOAc, 3:1, v/v) as a brown oil (65.6 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 1H), 7.79 – 7.63 (m, 3H), 4.38 (p, J = 7.3 Hz, 4H), 3.68 (s, 3H), 1.39 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.23, -109.49. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.92 (tp, J = 100.7, 8.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.0, 159.8 (td, J = 27.7, 17.3 Hz), 135.2, 132.9, 131.5, 131.4, 127.6, 126.3,

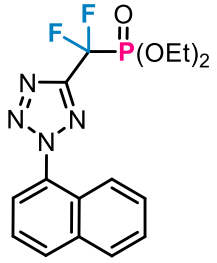
112.9 (td, J = 262.7, 216.9 Hz), 65.9 (d, J = 6.6 Hz), 52.9, 16.4 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{14}H_{18}N_4O_5F_2P^+$ $(M+H)^+$: 391.0983, found: *m/z* 391.0974.

Diethyl (difluoro(2-(4-nitrophenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3y). For



0.2 mmol scale, the standard procedure of method B was followed to provide **3y** by column chromatography on silica gel (petroleum ether/EtOAc, 3:1, v/v) as a yellow solid (44.5 mg, 59%). M.p.: 46-47 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, J = 9.3 Hz, 2H), 8.40 (d, J = 9.2 Hz, 2H), 4.47 – 4.35 (m, 4H), 1.43 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.92, -110.18. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.59 (tp, J = 100.0, 8.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.5 – 158.96 (m), 148.7, 140.1, 125.7, 121.1, 117.1 – 108.7 (m), 66.0 (d, J = 6.7 Hz), 16.5 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{15}N_5O_5F_2P^+$ $(M+H)^+$: 378.0779, found: *m/z* 378.0773.

Diethyl (difluoro(2-(naphthalen-1-yl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3z).



For 0.2 mmol scale, the standard procedure of method B was followed to provide **3z** by column chromatography on silica gel (petroleum ether/EtOAc, 3:1, v/v) as a red oil (45.9 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 1H), 8.01 – 7.94 (m, 2H), 7.88 (d, J = 7.4 Hz, 1H), 7.67 – 7.56 (m, 3H), 4.44 (p, J = 7.0 Hz, 4H), 1.43 (t, J = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.22, -109.49. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.13 (tp, J = 101.3, 8.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0 (td, J = 27.6, 16.9 Hz), 134.4, 133.0, 132.0, 128.6, 127.5, 126.9, 124.9, 123.8, 122.5, 113.1 (td, J = 262.8, 217.3 Hz), 65.9 (d, J = 6.5 Hz), 16.5 (d, J = 5.6 Hz). **HRMS (ESI)**: calcd. for $C_{16}H_{18}N_4O_3F_2P^+$ $(M+H)^+$:383.1085, found: *m/z* 383.1081.

Methyl 3-(5-((diethoxyphosphoryl)difluoromethyl)-2H-tetrazol-2-yl)thiophene-2-carboxylate (3a'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3a'** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown oil (70.6 mg, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, J = 5.3 Hz, 1H), 7.36 (d, J = 5.3 Hz, 1H), 4.46 – 4.30 (m, 4H), 3.75 (s, 3H), 1.39 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.36, -109.62. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.83 (tt, J = 100.4, 8.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7 (td, J = 27.7, 17.2 Hz), 159.7, 135.5, 131.1, 129.0, 126.3, 112.9 (td, J = 263.1, 217.0 Hz), 65.9 (d, J = 6.6 Hz), 52.8, 16.4 (d, J = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{12}H_{16}N_4O_5F_2PS^+$ $(M+H)^+$:397.0547, found: *m/z* 397.0547.

Diethyl (difluoro(2-(quinolin-8-yl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3b'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3b'** by column chromatography on silica gel (petroleum ether/EtOAc, 1:1, v/v) as a brown

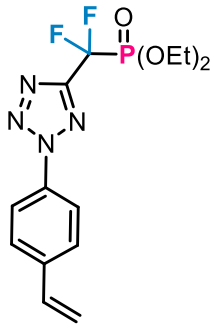
oil (29.1 mg, 38%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 4.3 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 9.8 Hz, 1H), 8.01 (d, *J* = 8.9 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.43 (p, *J* = 7.3 Hz, 4H), 1.42 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.83, -109.10. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 3.04 (tq, *J* = 101.0, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.5 – 159.2 (m), 152.4, 142.4, 136.2, 134.0, 131.9, 129.2, 127.4, 125.7, 122.8, 117.6 – 108.3 (m), 65.9 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.6 Hz). **HRMS (ESI)**: calcd. for $C_{15}H_{16}N_5O_3F_2PNa^+$ $(M+Na)^+$:406.0857, found: *m/z* 406.0858.

Diethyl (difluoro(2-(4-methyl-2-oxo-2*H*-chromen-7-yl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3c'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3c'** by column chromatography on silica gel (petroleum ether/EtOAc, 1:1, v/v) as a red-brown solid (59.7 mg, 72%). M.p.: 86-87 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 2H), 7.81 (d, *J* = 9.2 Hz, 1H), 6.39 (s, 1H), 4.40 (p, *J* = 7.2 Hz, 4H), 2.50 (d, *J* = 1.4 Hz, 3H), 1.42 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.74, -110.01. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.70 (tp, *J* = 100.6, 8.4 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0 – 159.8 (m), 159.6, 154.2, 151.3, 137.9, 126.5, 121.7, 116.7, 115.7, 112.8 (td, *J* = 263.5, 217.1 Hz), 108.9, 66.0 (d, *J* = 6.6 Hz), 18.8, 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{16}H_{18}N_4O_5F_2P^+$ $(M+H)^+$:415.0983, found: *m/z* 415.0984.

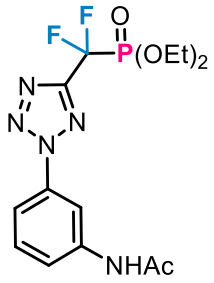
Diethyl ((2-(4-ethynylphenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3d'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3d'** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a red-brown solid (51.1 mg, 72%). M.p.: 60-61 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 4.39 (p, *J* = 7.3 Hz, 4H), 3.24 (s, 1H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.63, -109.90. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.88 (tp, *J* = 100.7, 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0 (dd, *J* = 27.5, 17.1 Hz), 136.1, 133.7, 124.9, 120.2, 112.9 (td, *J* = 263.2, 217.4 Hz), 82.1, 80.7, 65.9 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{14}H_{16}N_4O_3F_2P^+$ $(M+H)^+$:357.0928, found: *m/z* 357.0926.

Diethyl (difluoro(2-(4-vinylphenyl)-2*H*-tetrazol-5-yl)methyl)phosphonate (3e'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3e'** by column chromatography on silica gel (petroleum ether/EtOAc, 4:1, v/v) as a brown

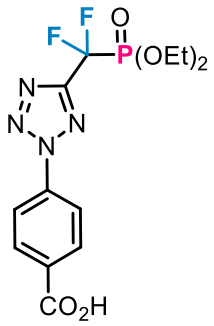
oil (58.1 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.76 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 5.40 (d, *J* = 10.9 Hz, 1H), 4.40 (p, *J* = 7.3 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.49, -109.76. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.99 (tp, *J* = 101.2, 8.3 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9 (td, *J* = 27.6, 17.1 Hz), 140.1, 135.6, 135.3, 127.6, 120.5, 116.6, 115.0 – 109.1 (m), 65.8 (d, *J* = 6.5 Hz), 16.5 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{14}H_{18}N_4O_3F_2P^+$ $(M+H)^+$:359.1085, found: *m/z* 359.1087.

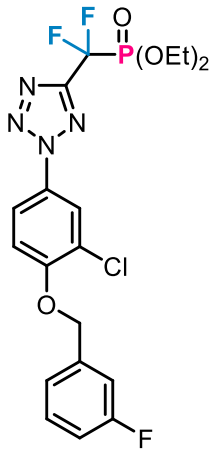


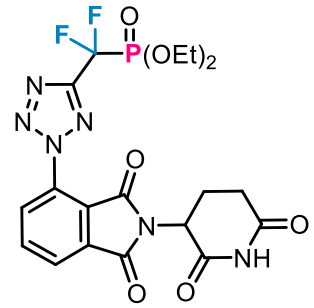
Diethyl ((2-(3-acetamidophenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3f'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3f'** by column chromatography on silica gel (petroleum ether/EtOAc, 1:1, v/v) as a brown oil (43.6 mg, 56%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.22 (s, 1H), 7.66 (dd, *J* = 8.2, 2.2 Hz, 2H), 7.32 (t, *J* = 8.2 Hz, 1H), 4.41 (p, *J* = 7.3 Hz, 4H), 2.20 (s, 3H), 1.42 (t, J = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.43, -109.70. **^{31}P NMR** (162 MHz, $CDCl_3$) 3.18 (t, *J* = 100.8 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7, 159.3 (td, *J* = 27.7, 17.4 Hz), 140.0, 136.2, 130.1, 121.3, 114.8, 112.8 (td, *J* = 263.2, 217.9 Hz), 110.9, 66.2 (d, *J* = 6.8 Hz), 24.4, 16.4 (d, *J* = 5.5 Hz).

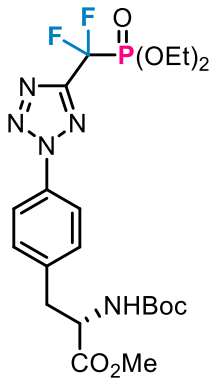


4-(5-((Diethoxyphosphoryl)difluoromethyl)-2*H*-tetrazol-2-yl)benzoic acid (3g'). For 0.2 mmol scale, the standard procedure of method B was followed to provide **3g'** by column chromatography on silica gel (petroleum ether/EtOAc, 1:1, v/v) as a yellow solid (55.7 mg, 74%). M.p.: 98-99 °C. **^{1}H NMR** (400 MHz, DMSO-D_6) δ 8.48 – 7.91 (m, 4H), 4.27 (p, *J* = 7.1 Hz, 4H), 1.27 (t, *J* = 7.0 Hz, 6H). **^{19}F NMR** (376 MHz, DMSO-D_6) -109.04, -109.30. **^{31}P NMR** (162 MHz, DMSO-D_6) δ 3.03 (t, *J* = 97.9 Hz). **^{13}C NMR** (101 MHz, DMSO-D_6) δ 166.1, 161.3 – 156.3 (m), 138.4, 132.9, 131.4, 120.5, 117.7 – 104.9 (m), 65.8 (d, *J* = 6.7 Hz), 16.2 (d, *J* = 5.2 Hz).

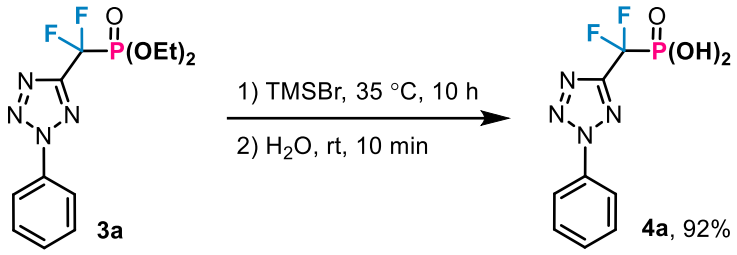


Diethyl ((2-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3h'). 
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3h'** by column chromatography on silica gel (petroleum ether/EtOAc, 2:1, v/v) as a black solid (111.7 mg, 76%). M.p.: 74-75 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.6 Hz, 1H), 7.99 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.28 – 7.15 (m, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 7.03 (t, *J* = 8.4 Hz, 1H), 5.22 (s, 2H), 4.39 (p, *J* = 7.3 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.55, -109.82, -112.23 (td, *J* = 8.9, 5.4 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.89 (tp, *J* = 100.8, 8.0 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.13 (d, *J* = 246.9 Hz), 159.90 (td, *J* = 27.8, 17.3 Hz), 155.64, 138.18 (d, *J* = 7.3 Hz), 130.48 (d, *J* = 8.4 Hz), 130.17, 124.70, 122.60, 122.53 (d, *J* = 2.9 Hz), 119.75, 115.36 (d, *J* = 21.3 Hz), 114.06 (d, *J* = 22.4 Hz), 114.05, 116.89 – 108.83 (m), 70.44 (d, *J* = 2.1 Hz), 65.86 (d, *J* = 6.6 Hz), 16.45 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{19}H_{20}N_4O_4ClF_3P^+$ $(M+H)^+$:491.0863, found: *m/z* 491.0865.

Diethyl ((2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-2*H*-tetrazol-5-yl)difluoromethyl)phosphonate (3i'). 
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3i'** by column chromatography on silica gel (petroleum ether/EtOAc, 1:2, v/v) as a yellow oil (67.6 mg, 66%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.15 (d, *J* = 7.3 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 8.02 (t, *J* = 7.7 Hz, 1H), 5.03 – 4.94 (m, 1H), 4.40 (p, *J* = 7.2 Hz, 4H), 2.93 – 2.66 (m, 3H), 2.21 – 2.11 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.36, -109.63. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.62 (tt, *J* = 99.8, 8.2 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2, 167.9 (d, *J* = 7.0 Hz), 165.4, 163.0, 161.3 – 159.6 (m), 136.1, 133.8, 132.0, 131.1, 126.3, 124.7, 112.8 (td, *J* = 263.5, 216.9 Hz), 66.0 (d, *J* = 6.6 Hz), 49.9, 31.3, 22.4, 16.4 (d, *J* = 5.5 Hz). **HRMS (ESI)**: calcd. for $C_{19}H_{19}N_6O_7F_2PNa^+$ $(M+Na)^+$:535.0919, found: *m/z* 535.0913.

Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(5-((diethoxyphosphoryl)difluoromethyl)-2*H*-tetrazol-2-yl)phenyl)propanoate (3j'). 
For 0.2 mmol scale, the standard procedure of method B was followed to provide **3j'** by column chromatography on silica gel (petroleum ether/EtOAc, 1:1, v/v) as a red-brown oil (80.0 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.09 (d, *J* = 8.1 Hz, 1H), 4.61 (d, *J* = 7.7 Hz, 1H), 4.38 (p, *J* = 7.3 Hz, 4H), 3.71 (s, 3H), 3.30 – 3.18 (m, 1H), 3.16 – 3.01 (m, 1H), 1.44 – 1.36 (m, 15H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.56, -109.82. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 2.96 (tp, *J* = 101.0, 8.0 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 161.0 – 158.4 (m), 155.1, 139.4, 135.4, 130.8, 120.4, 112.9 (td, *J* = 262.9, 217.5 Hz),

80.3, 65.8 (d, J = 6.6 Hz), 54.4, 52.5, 38.2, 28.4, 16.5 (d, J = 5.5 Hz).
HRMS (ESI): calcd. for $C_{21}H_{30}N_5O_7F_2PNa^+$ $(M+Na)^+$:556.1749, found: *m/z* 556.1747.

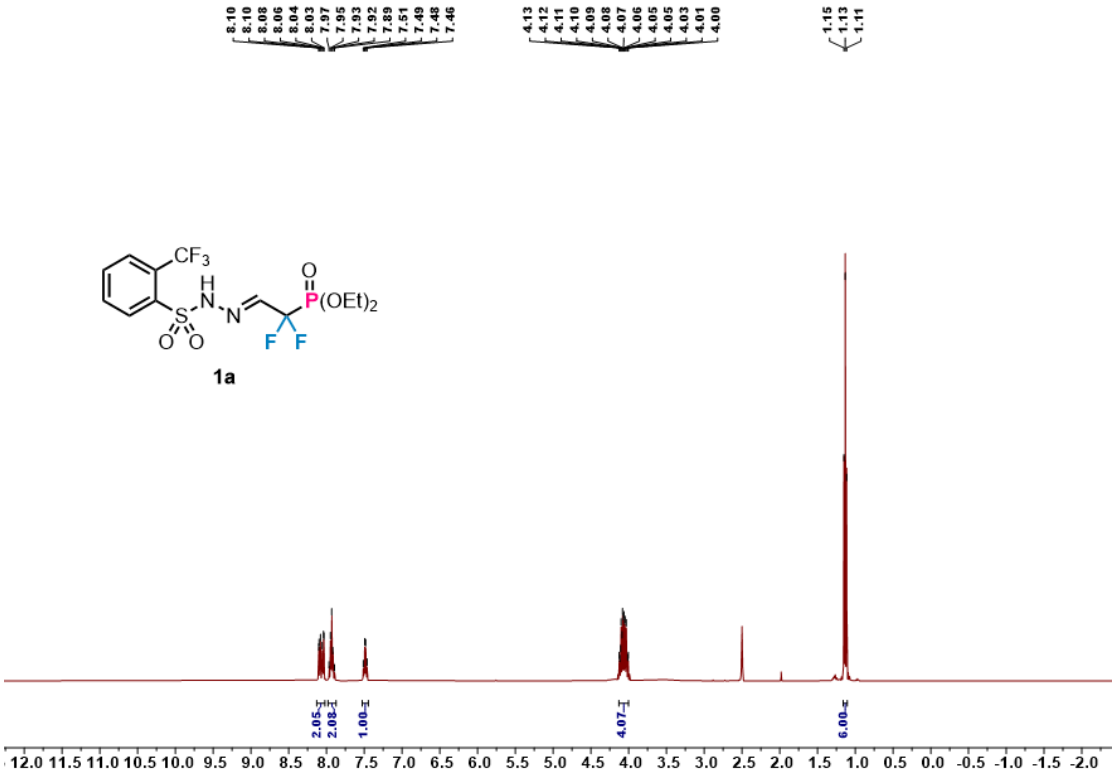


To a solution of compound **3a** (132.9 mg, 0.8 mmol, 1.0 equiv.) in 4 mL of CH_2Cl_2, TMSBr (1.22 g, 8 mmol, 10 equiv.) was added and the reaction was allowed to stir at room temperature for 24 hours. The solution was concentrated under reduced pressure, and the residue was vigorously stirred with 5 mL of water for 1 hour. The aqueous solution was neutralized with ammonium bicarbonate, washed with $CHCl_3$, and concentrated under reduced pressure to give **4a** as white solid, 101.6 mg, 92% yield[2]. M.p.: 173-174 ºC.**^{1}H NMR** (400 MHz, D_2O) δ 7.82 (dd, J = 7.3, 2.6 Hz, 2H), 7.45 – 7.34 (m, 3H). **^{19}F NMR** (376 MHz, D_2O) δ -111.32, -111.56. **^{31}P NMR** (162 MHz, D_2O) δ 0.97 (t, J = 90.0 Hz). **^{13}C NMR** (101 MHz, D_2O) δ 161.2 – 160.0 (m), 135.7, 130.9, 129.8, 120.3, 118.6 – 110.3 (m). **HRMS (ESI)**: calcd. for $C_8H_8N_4O_2F_2P^+$ $(M+H)^+$:277.1470, found: *m/z* 277.1469.

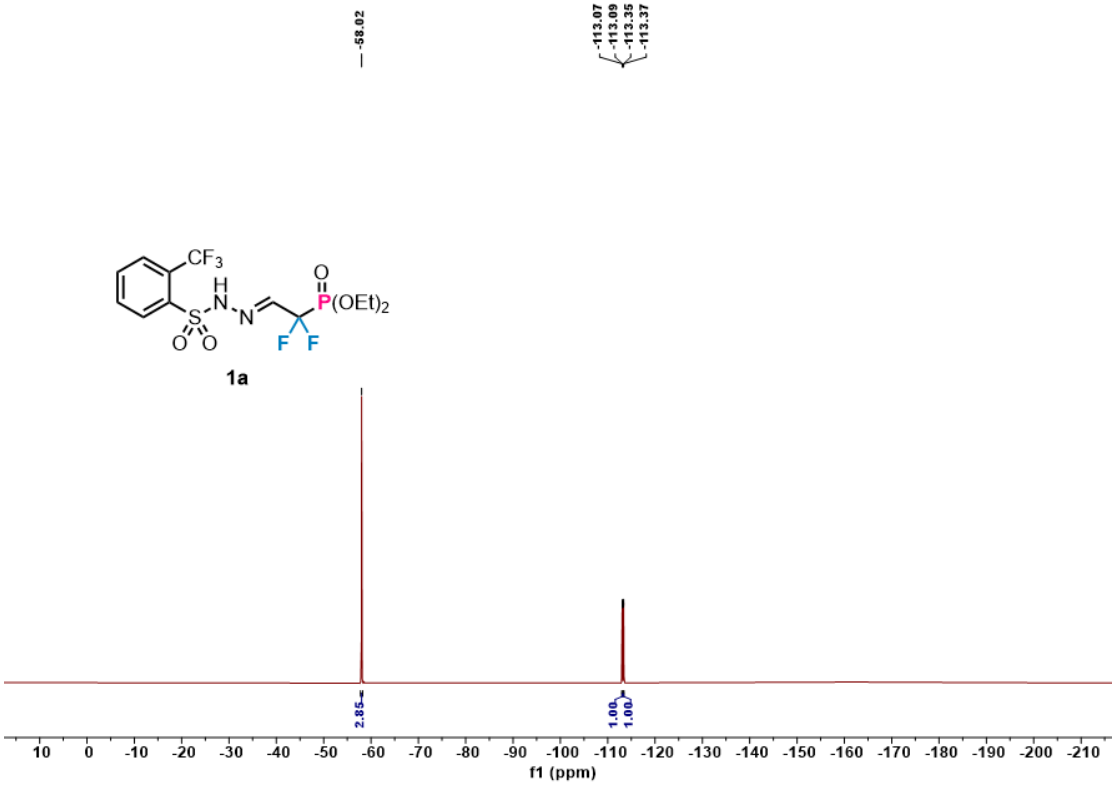
References

[1] R. Pajkert, G.-V. Röschenthaler, J. Org. Chem. 78 (2013) 3697-3708.
[2] S.-J. Zhai, X. Peng, F.-G. Zhang, J.-A. Ma, Org. Lett. 21 (2019) 9884-9888.
[3] J. D. Firth, I. J. S. Fairlamb, Org. Lett. 22 (2020) 7057-7059.
[4] S. P. Green, K. M. Wheelhouse, A. D. Payne, et al., Org. Process Res. Dev. 24 (2020) 67-84.

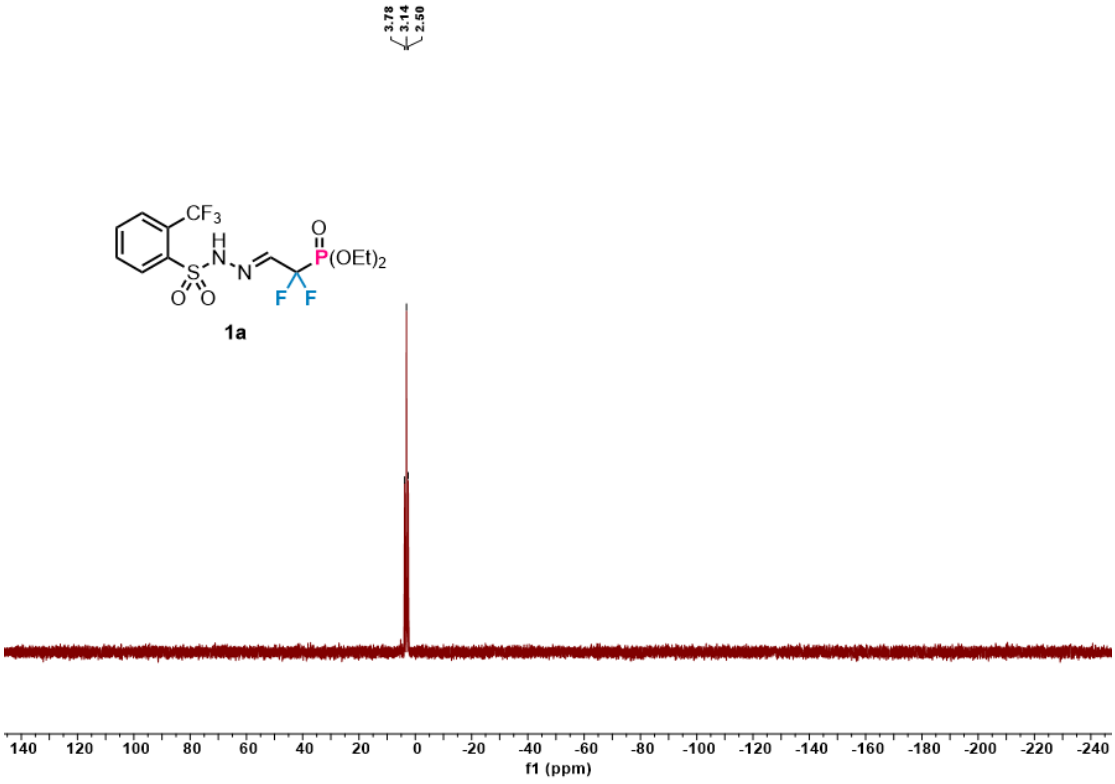
Spectra of All New Compounds



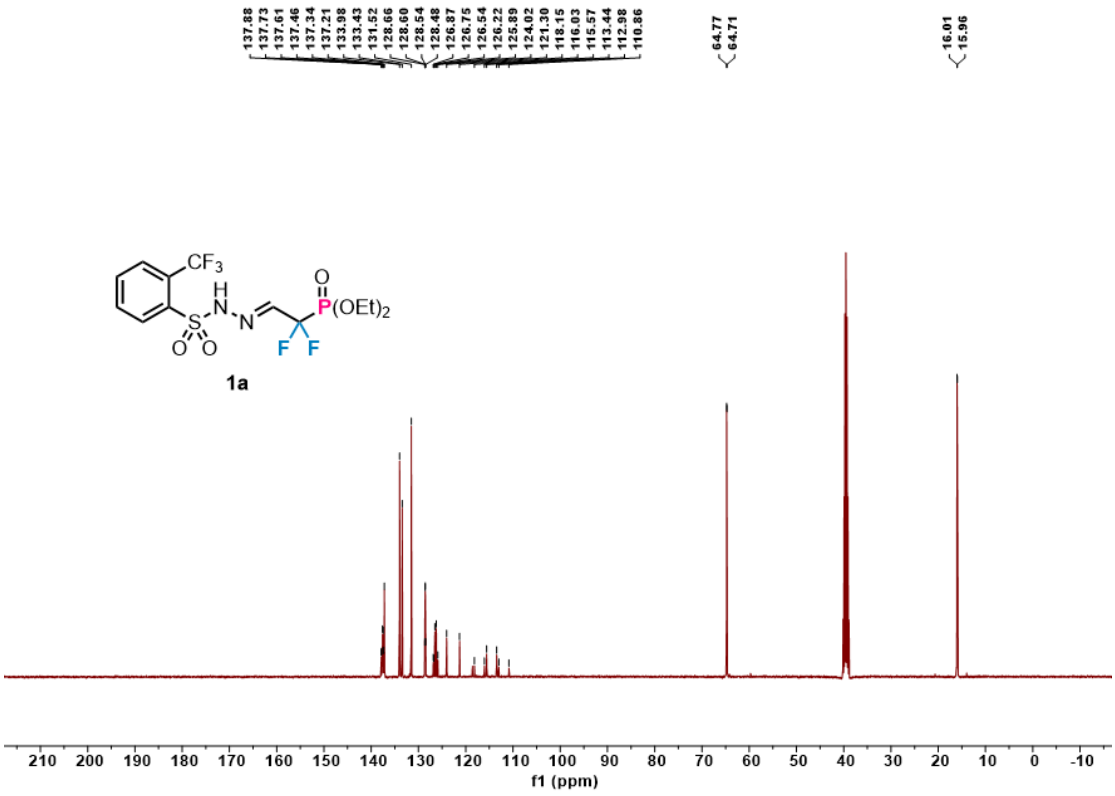
^{1}H-NMR of **1a** (DMSO-d_6, 400 M)



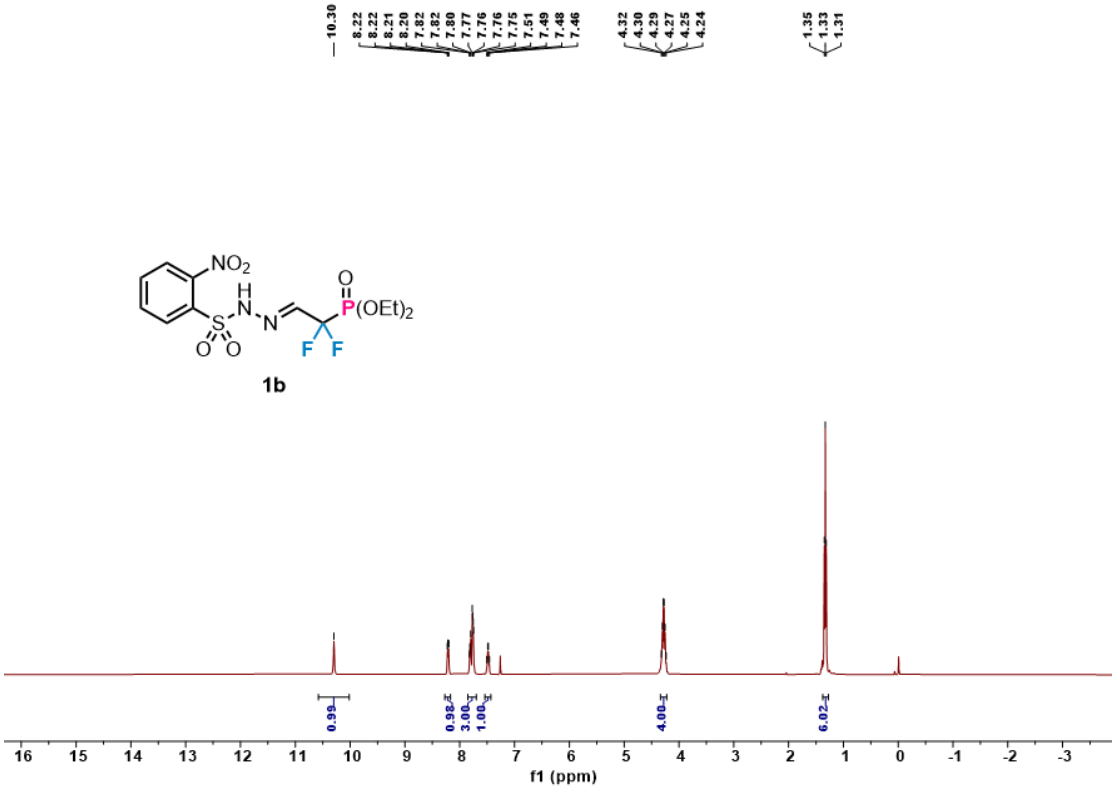
^{19}F-NMR of **1a** ($CDCl_3$, 376 M)



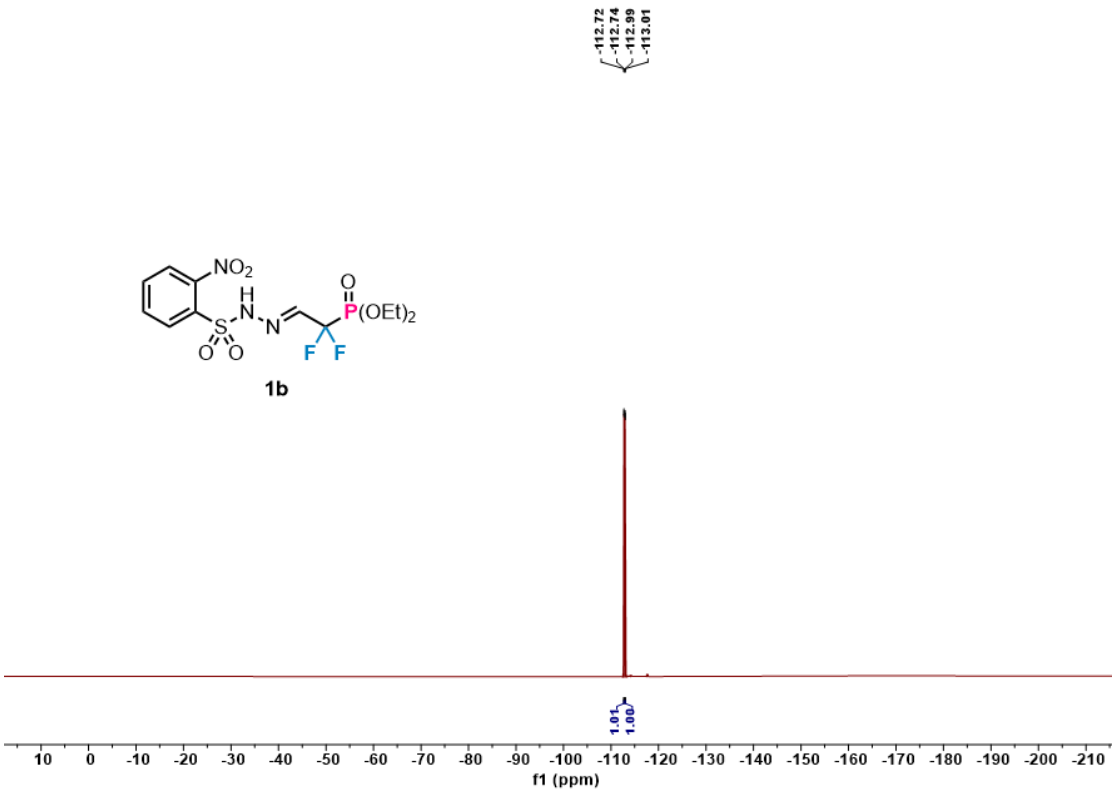
^{31}P-NMR of **1a** ($CDCl_3$, 162 M)



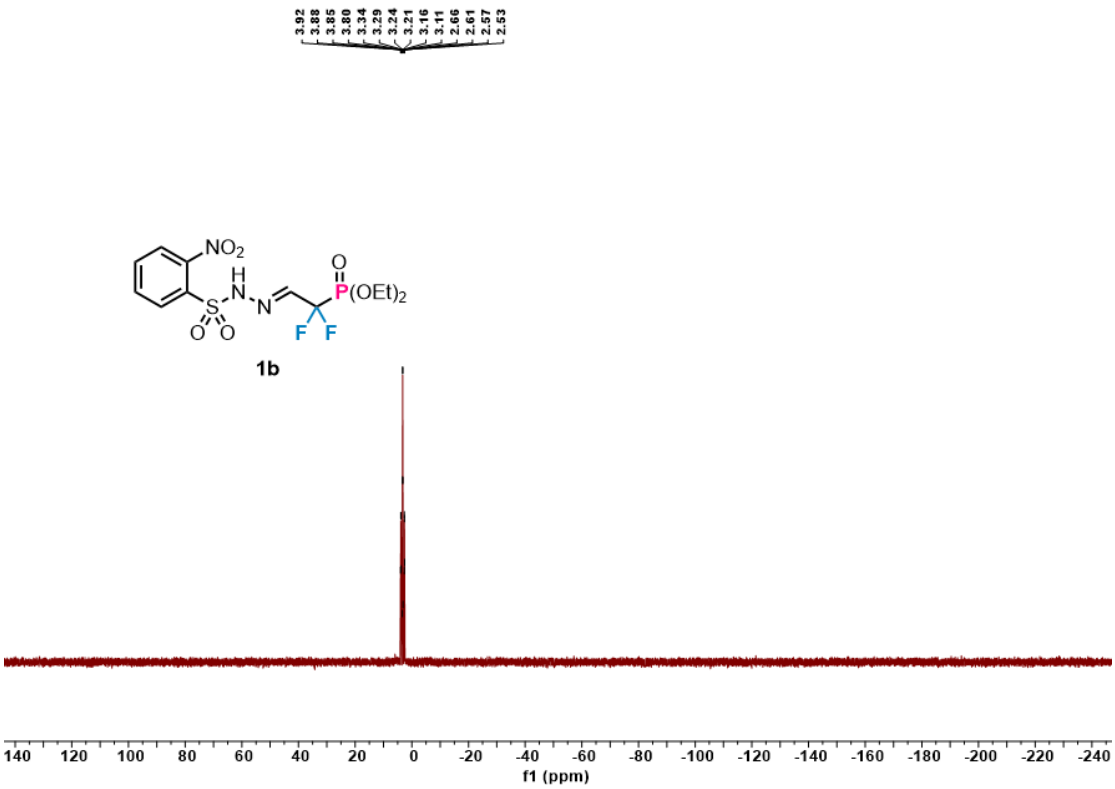
^{13}C-NMR of **1a** (DMSO-d_6, 101 M)



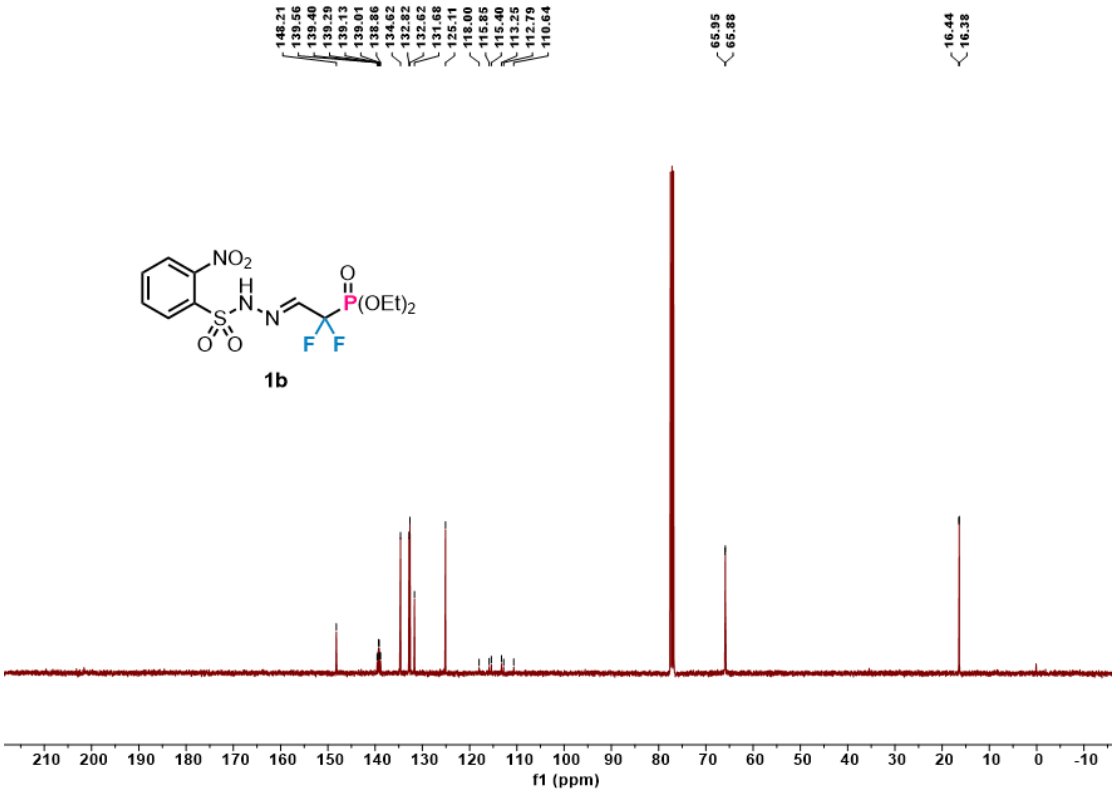
^{1}H-NMR of **1b** ($CDCl_3$, 400 M)



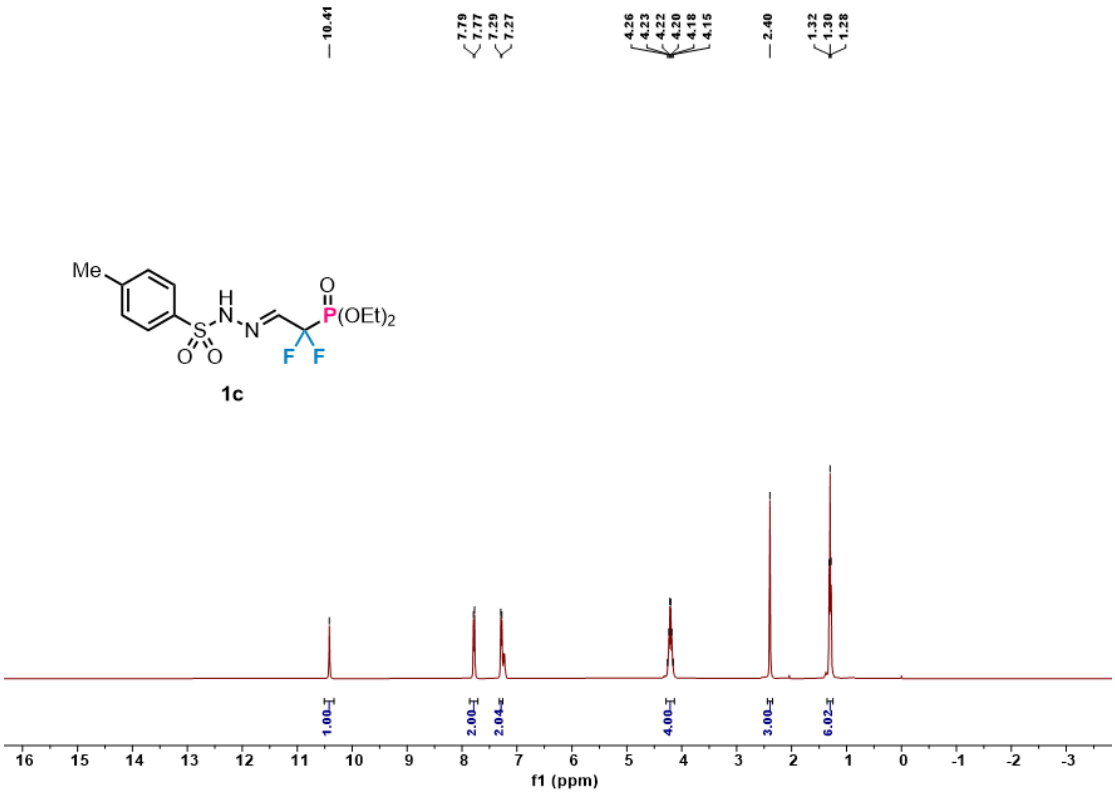
^{19}F-NMR of **1b** ($CDCl_3$, 376 M)



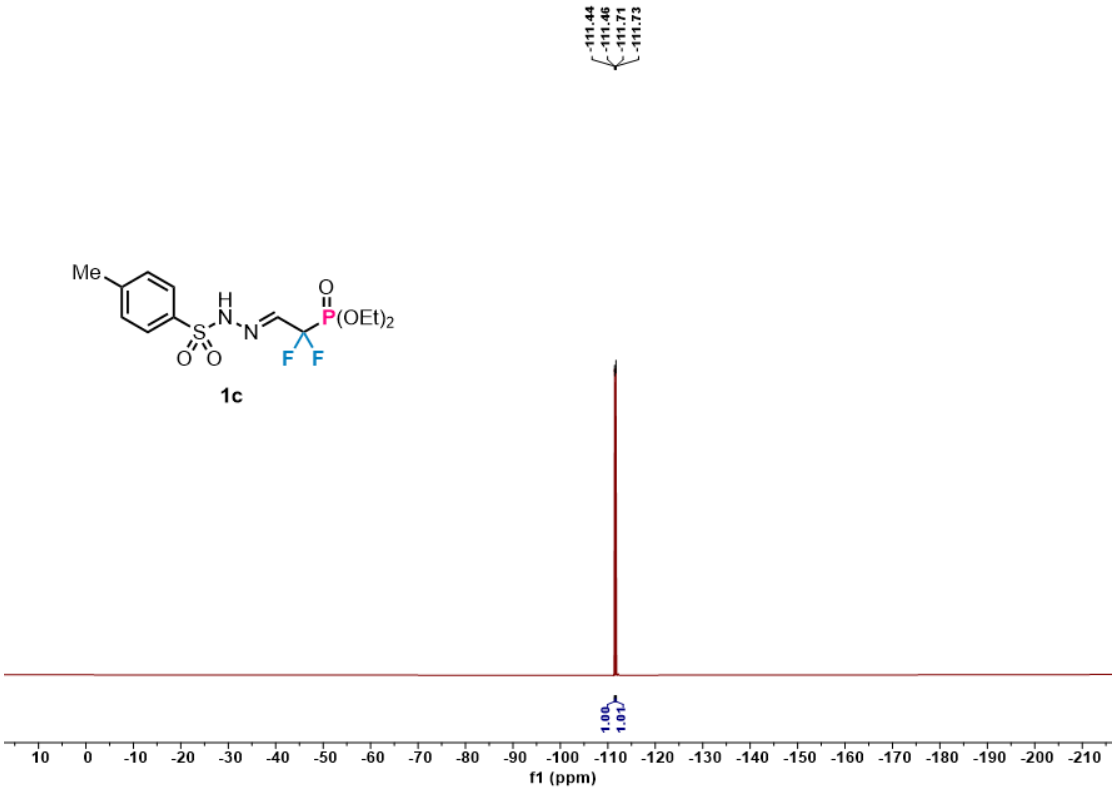
^{31}P-NMR of **1b** ($CDCl_3$, 162 M)



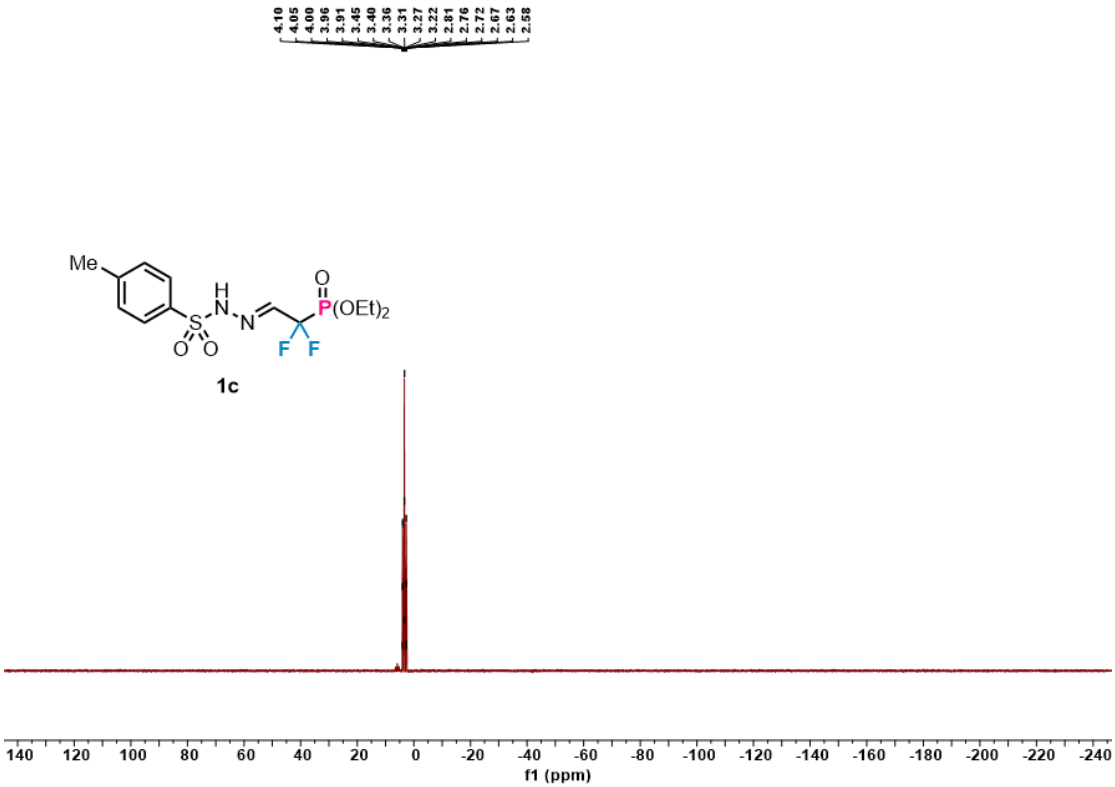
^{13}C-NMR of **1b** ($CDCl_3$, 101 M)



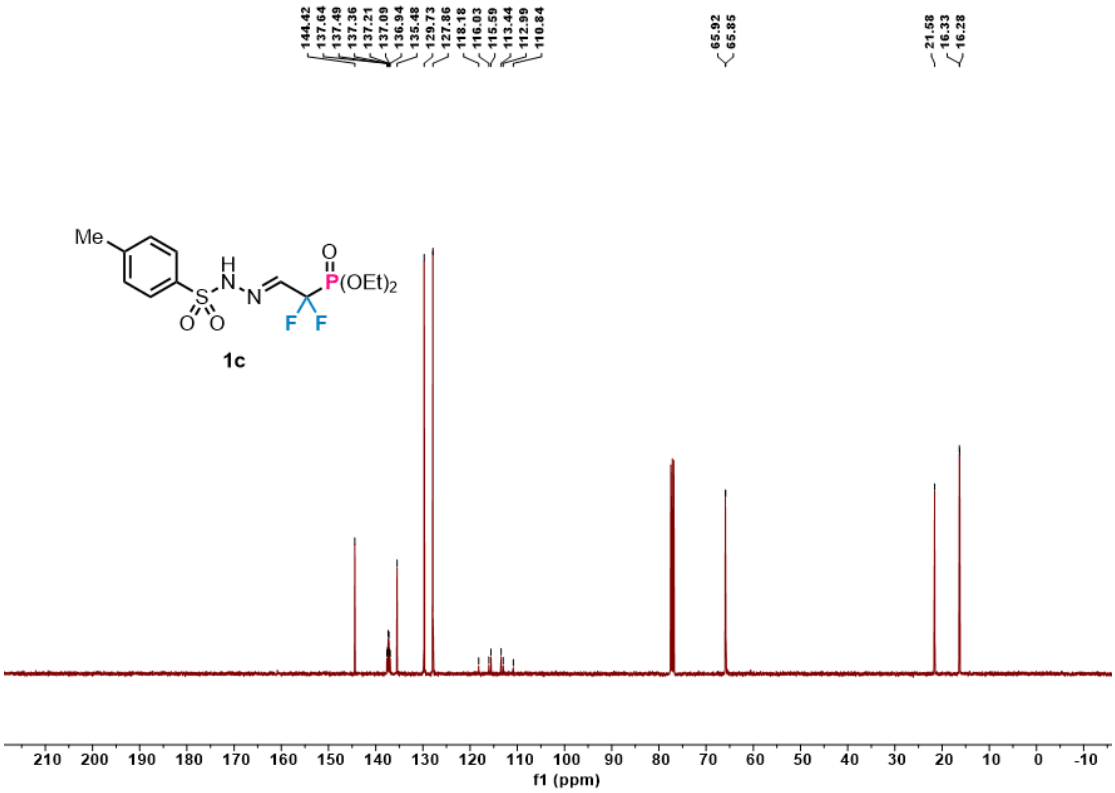
^{1}H-NMR of **1c** ($CDCl_3$, 400 M)



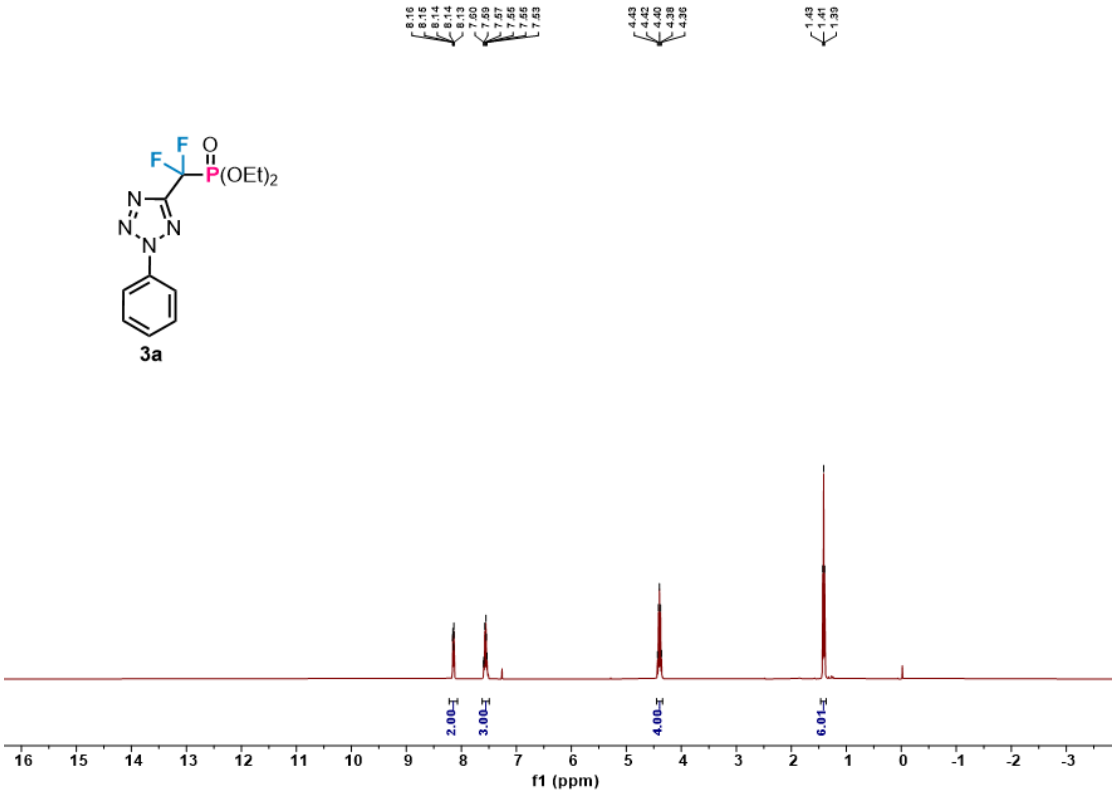
^{19}F-NMR of **1c** ($CDCl_3$, 376 M)



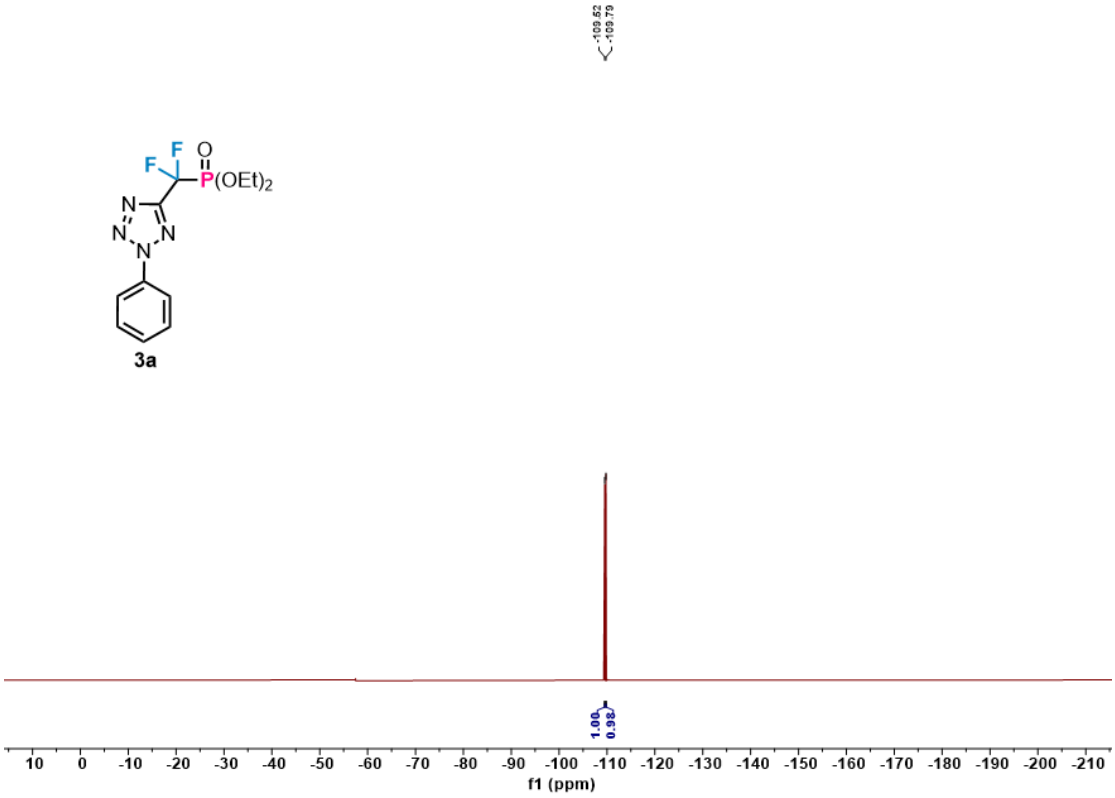
^{31}P-NMR of **1c** ($CDCl_3$, 162 M)



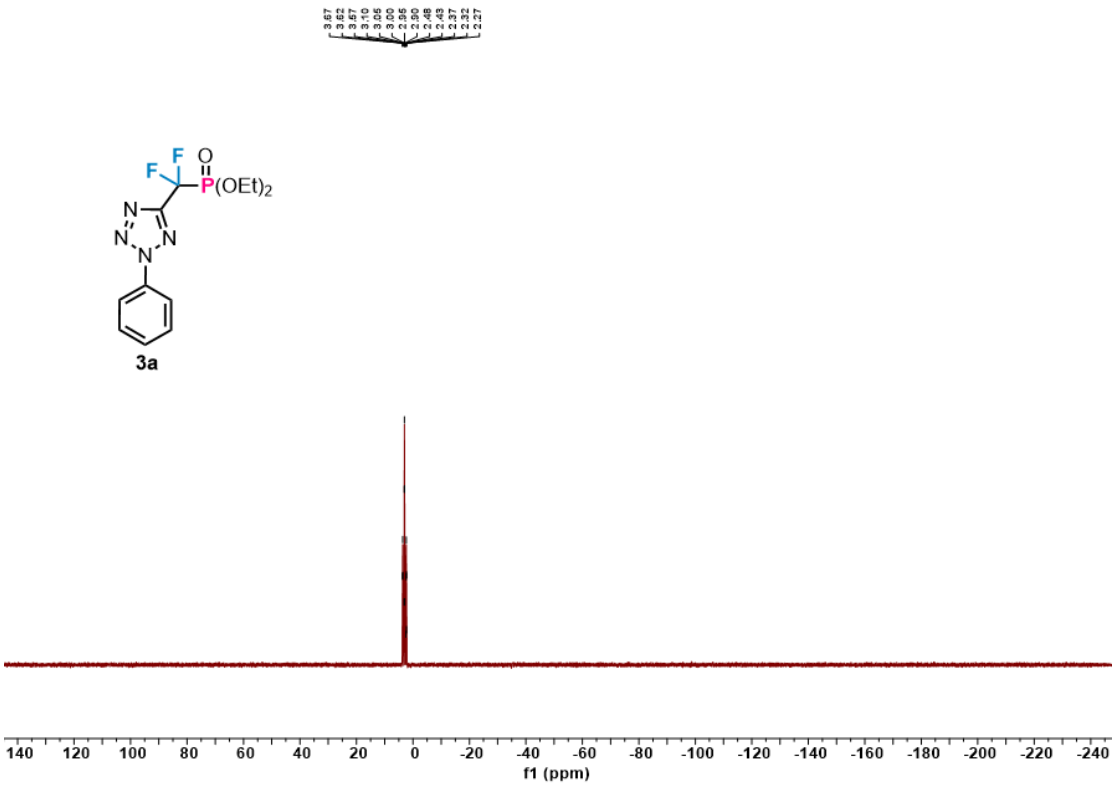
^{13}C-NMR of **1c** ($CDCl_3$, 101 M)



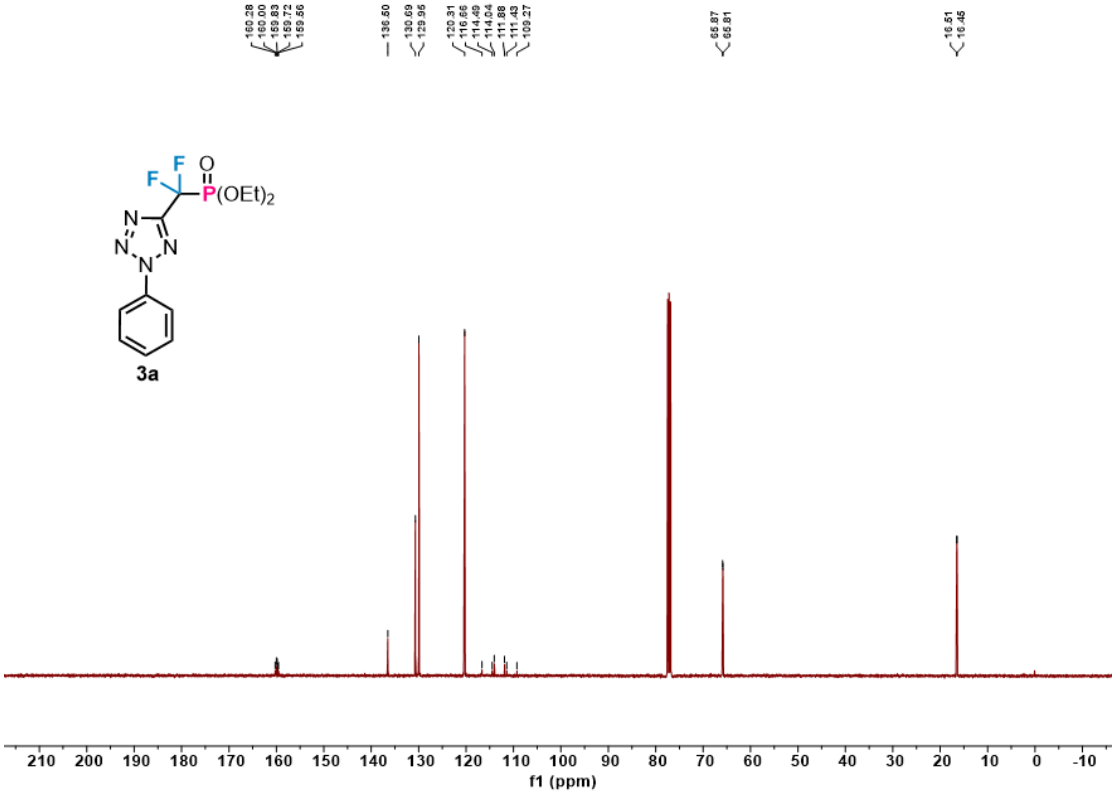
^{1}H-NMR of **3a** ($CDCl_3$, 400 M)



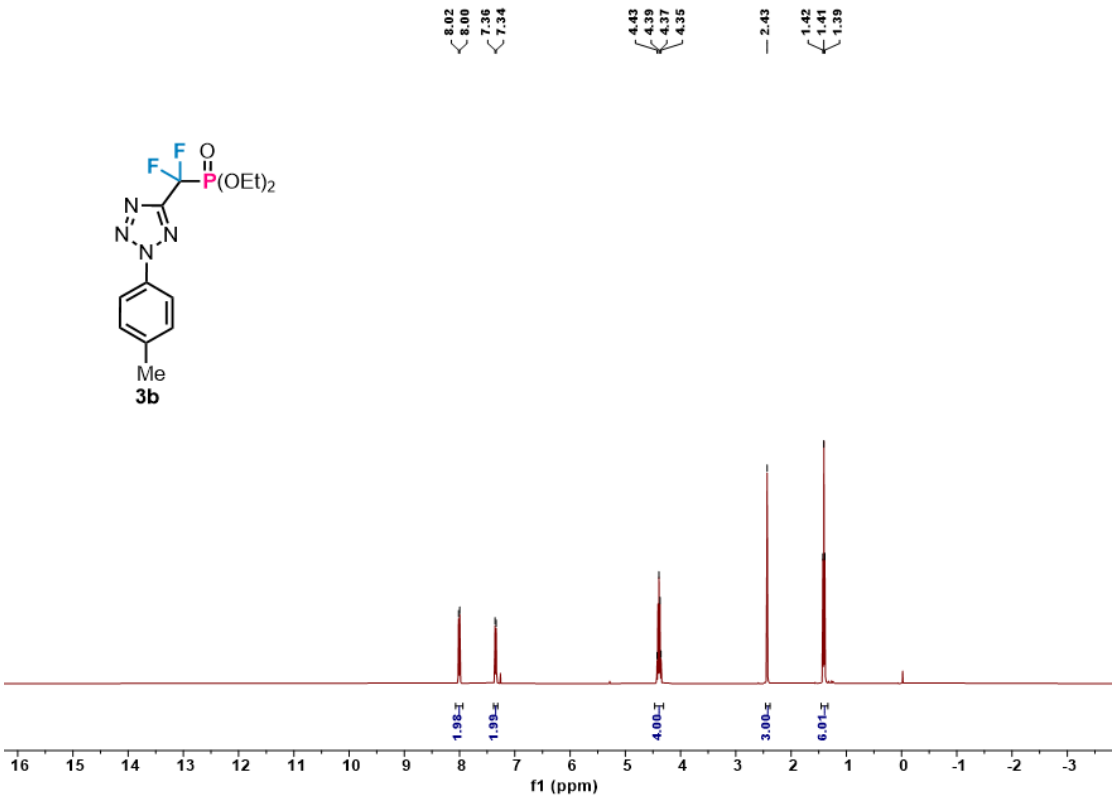
^{19}F-NMR of **3a** ($CDCl_3$, 376 M)



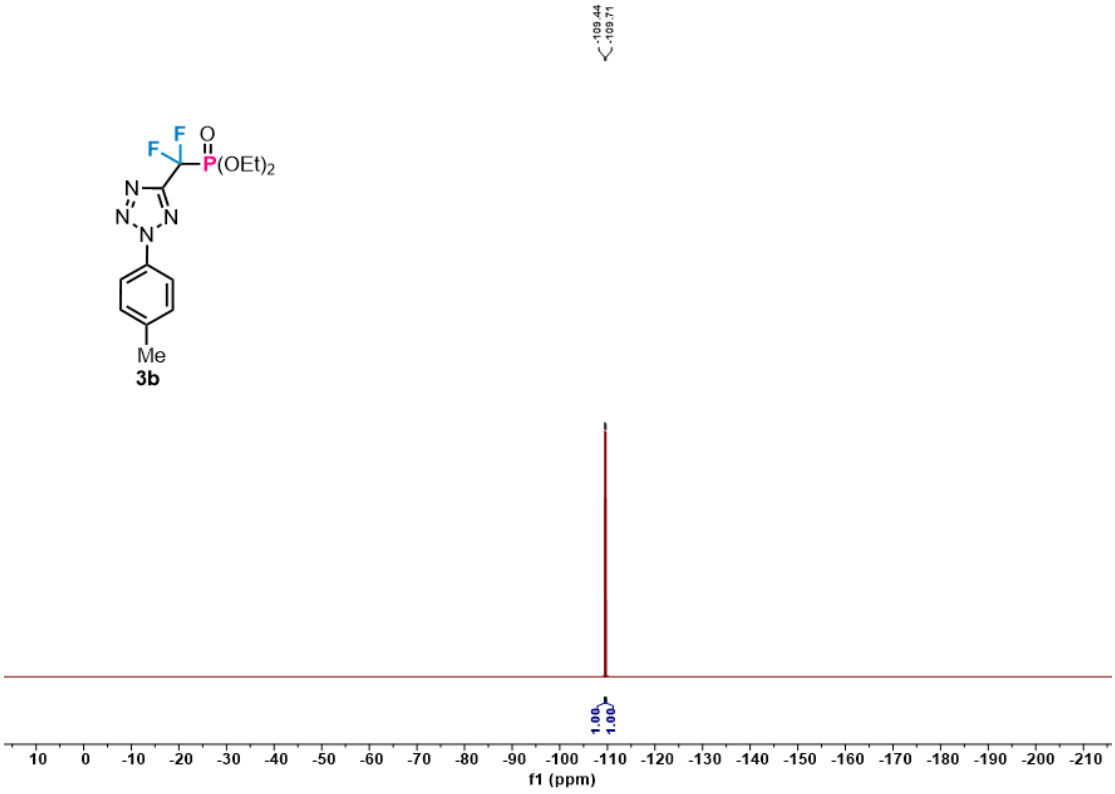
^{31}P-NMR of **3a** ($CDCl_3$, 162 M)



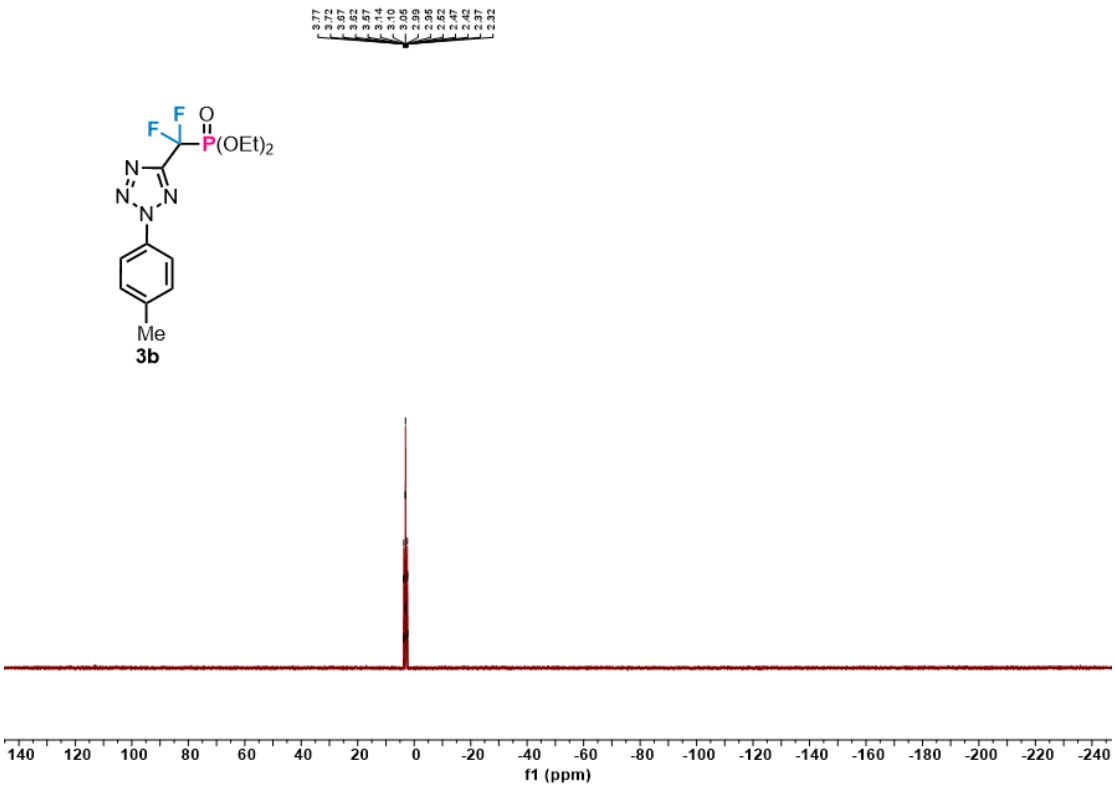
^{13}C-NMR of **3a** ($CDCl_3$, 101 M)



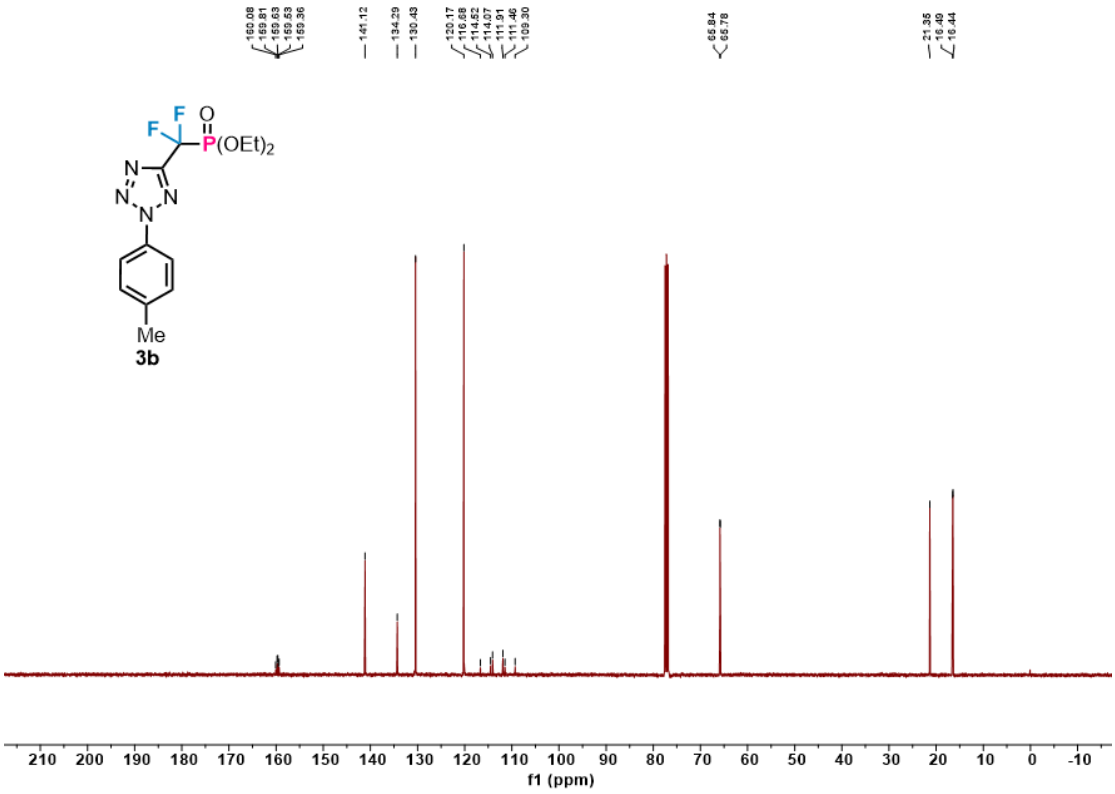
^{1}H-NMR of **3b** ($CDCl_3$, 400 M)



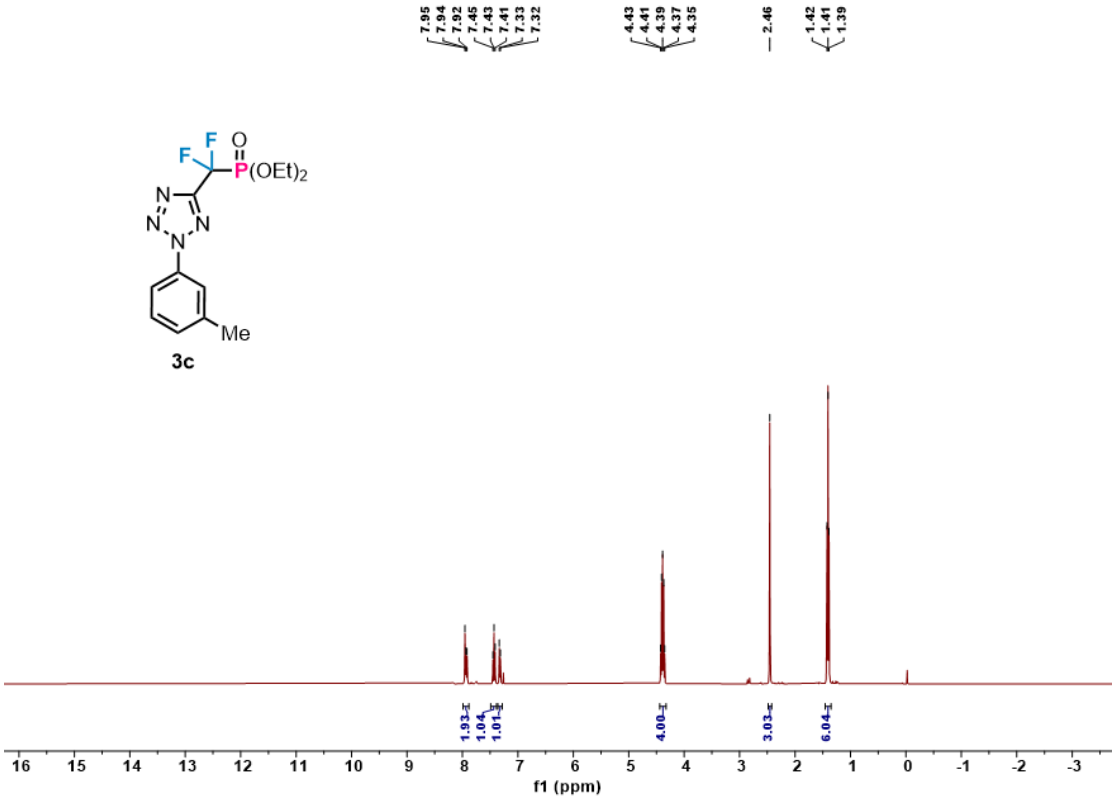
^{19}F-NMR of **3b** ($CDCl_3$, 376 M)



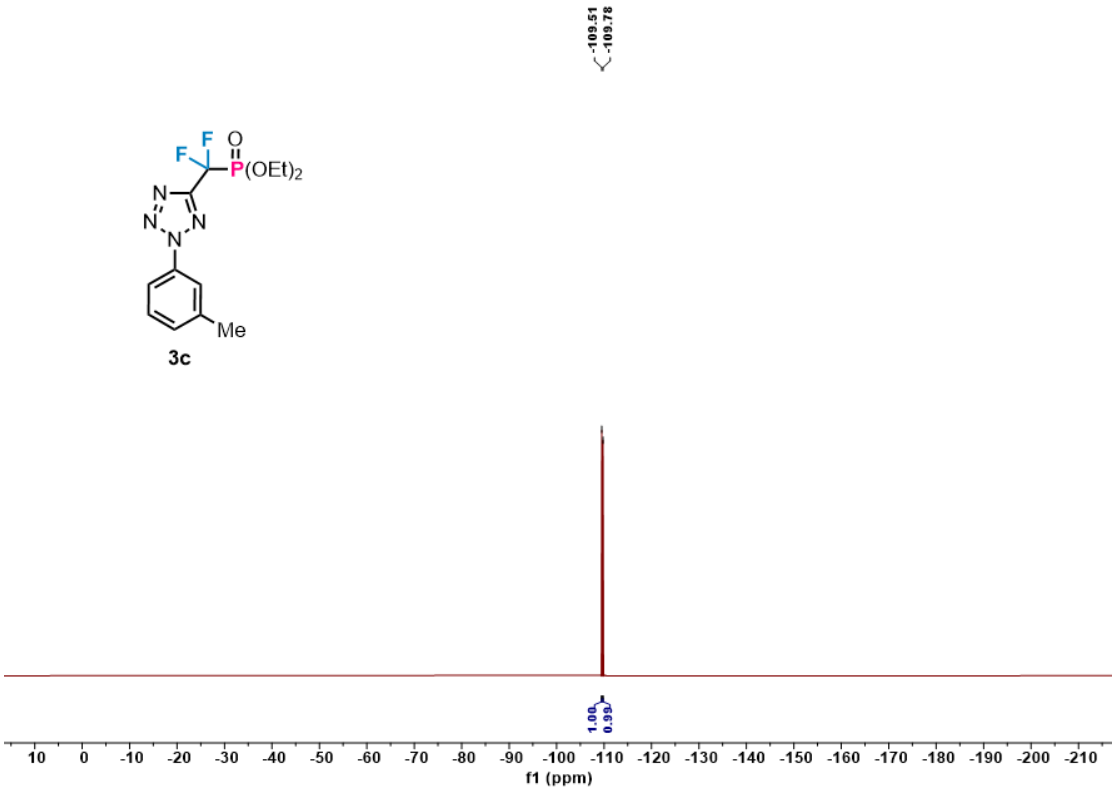
^{31}P-NMR of **3b** ($CDCl_3$, 162 M)



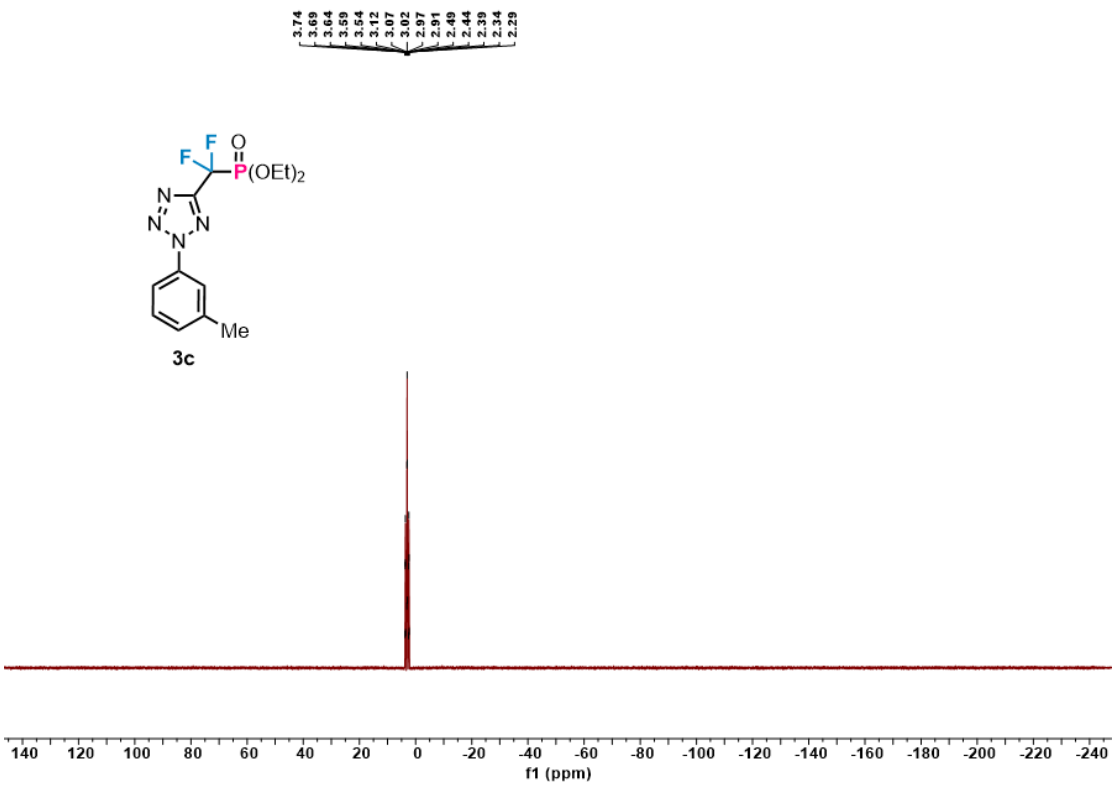
^{13}C-NMR of **3b** ($CDCl_3$, 101 M)



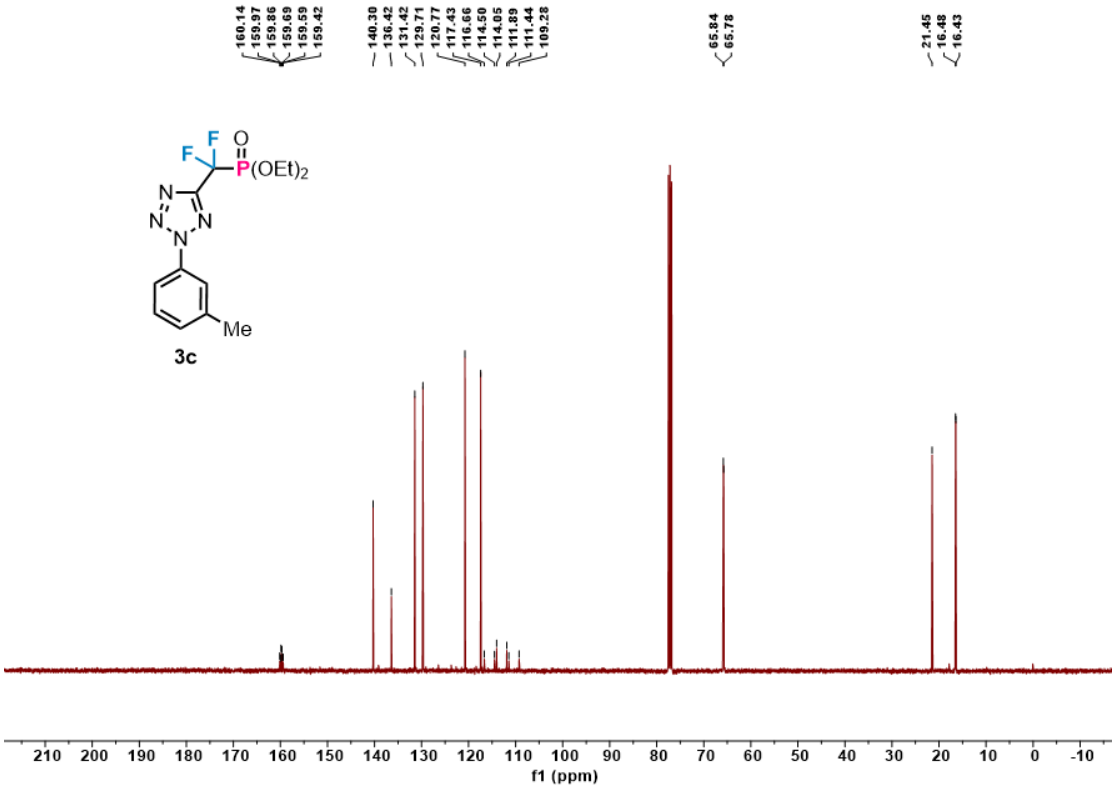
^{1}H-NMR of **3c** ($CDCl_3$, 400 M)



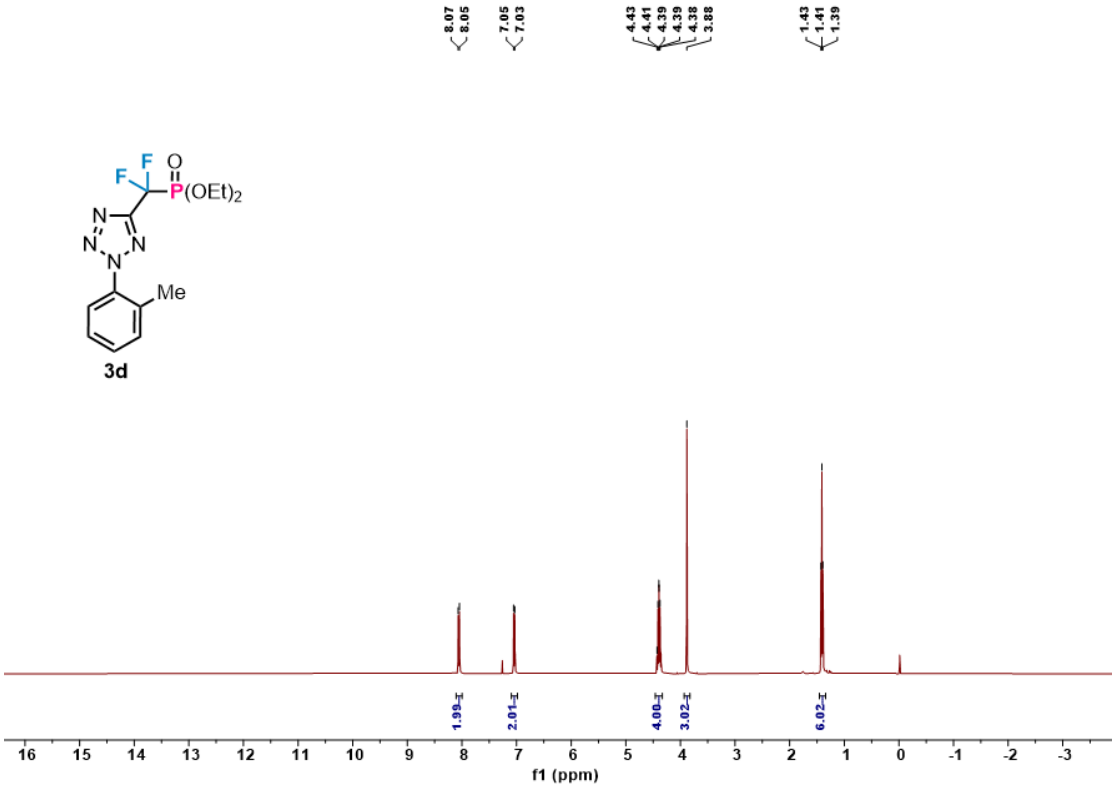
^{19}F-NMR of **3c** ($CDCl_3$, 376 M)



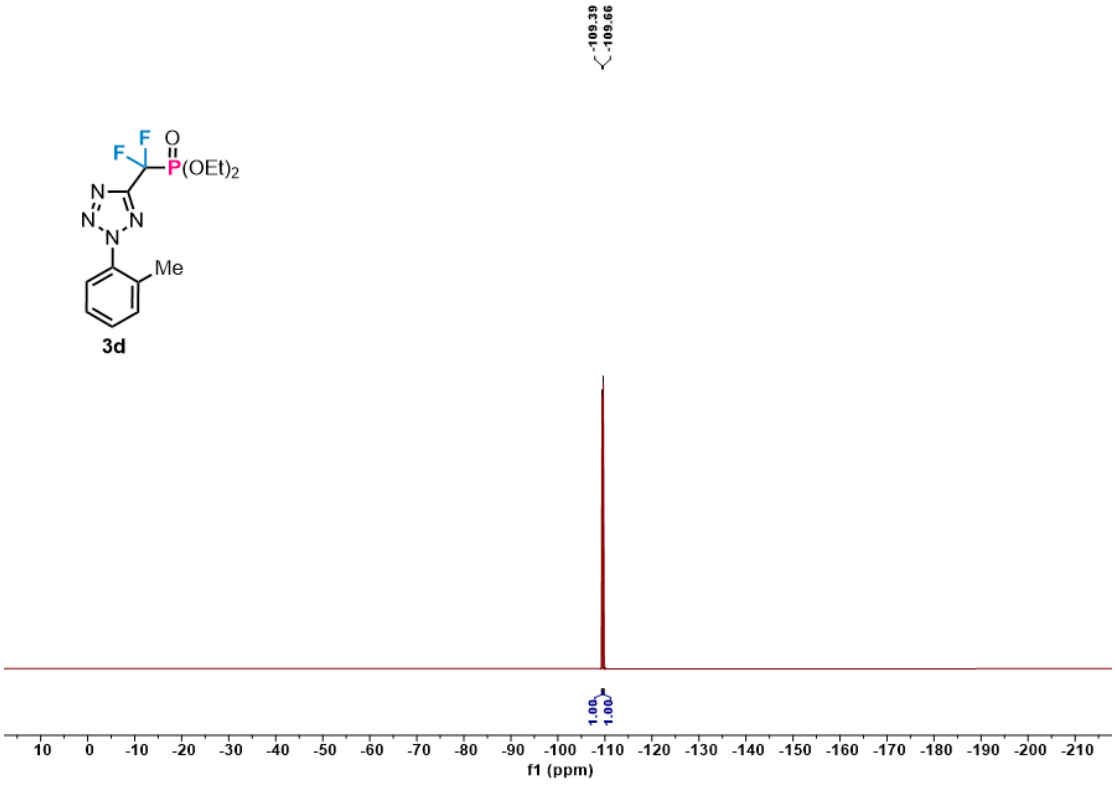
^{31}P-NMR of **3c** ($CDCl_3$, 162 M)



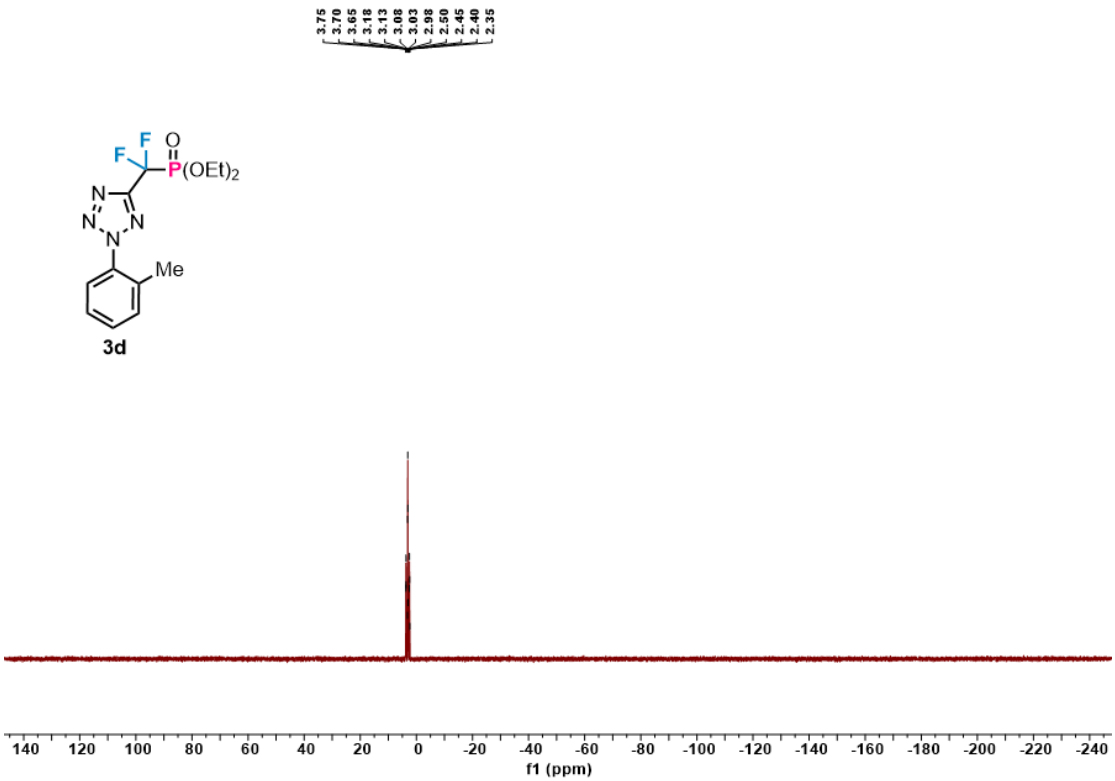
^{13}C-NMR of **3c** ($CDCl_3$, 101 M)



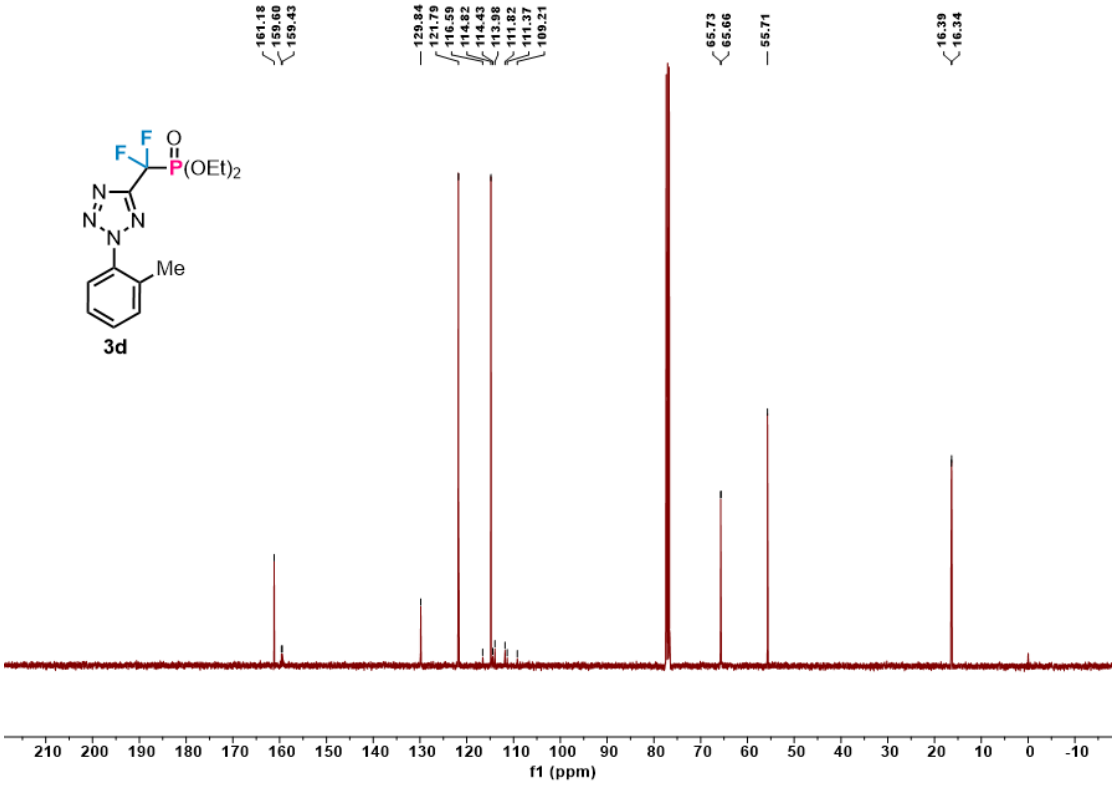
^{1}H-NMR of **3d** ($CDCl_3$, 400 M)



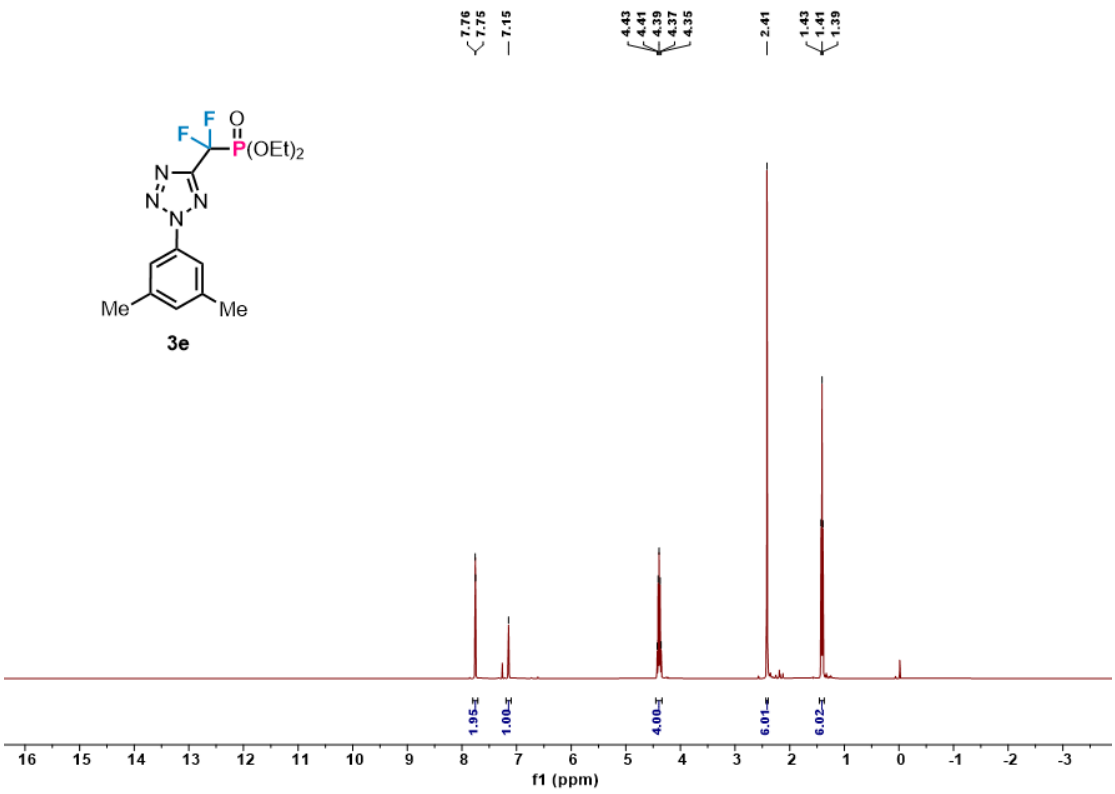
^{19}F-NMR of **3d** ($CDCl_3$, 376 M)



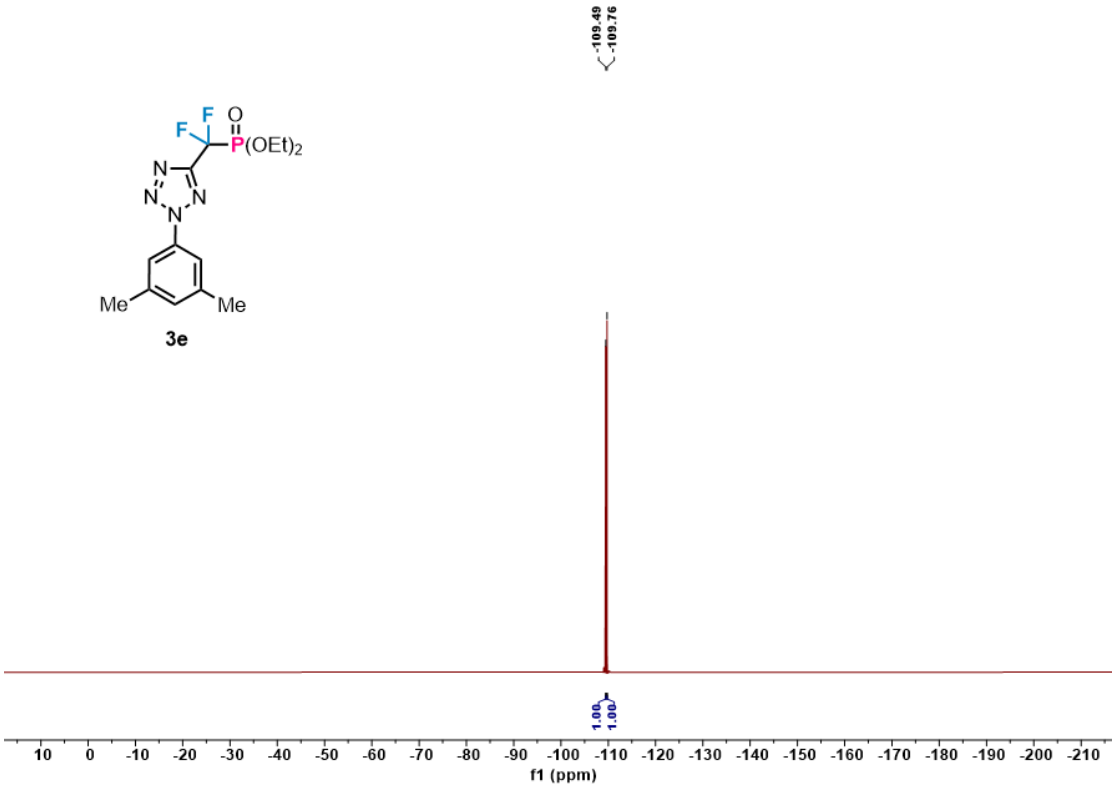
^{31}P-NMR of **3d** ($CDCl_3$, 162 M)



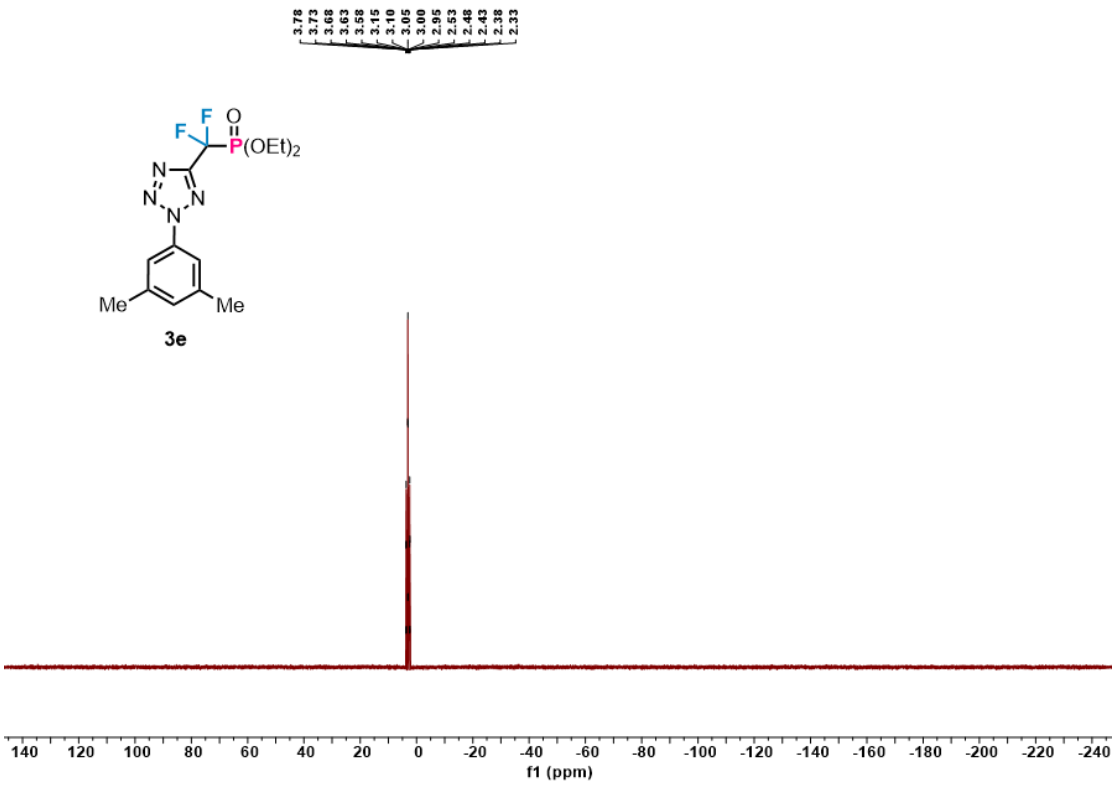
^{13}C-NMR of **3d** ($CDCl_3$, 101 M)



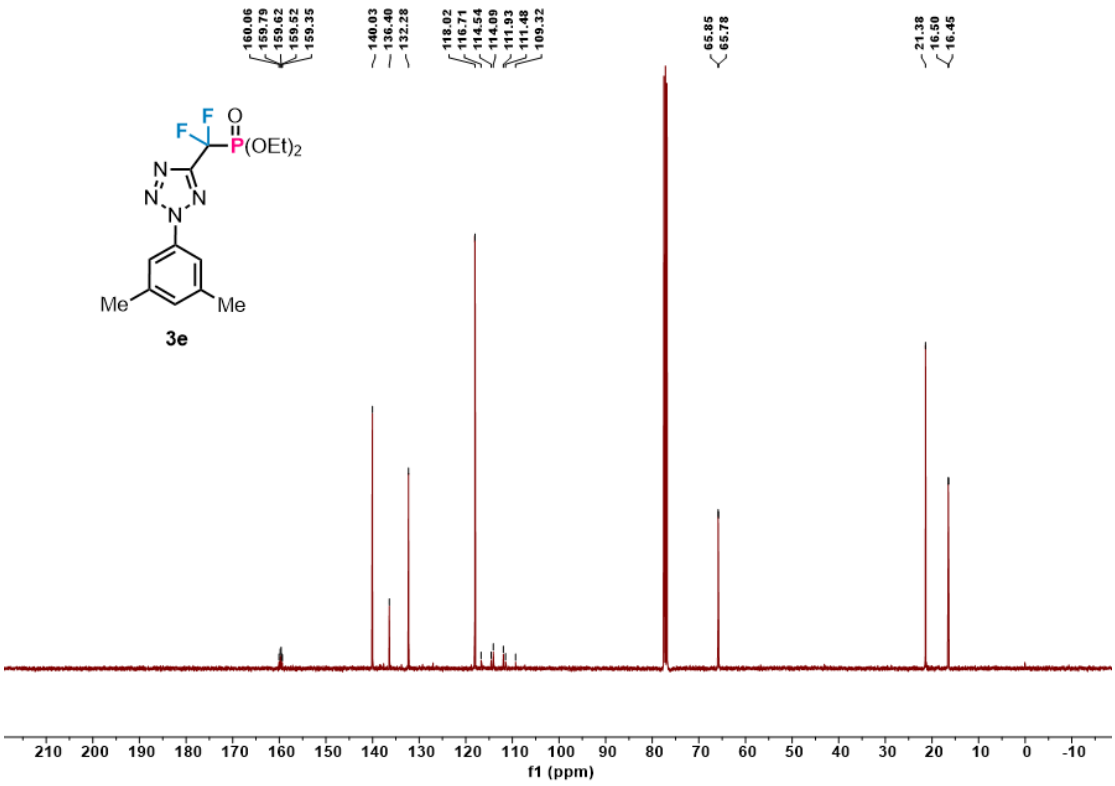
^{1}H-NMR of **3e** ($CDCl_3$, 400 M)



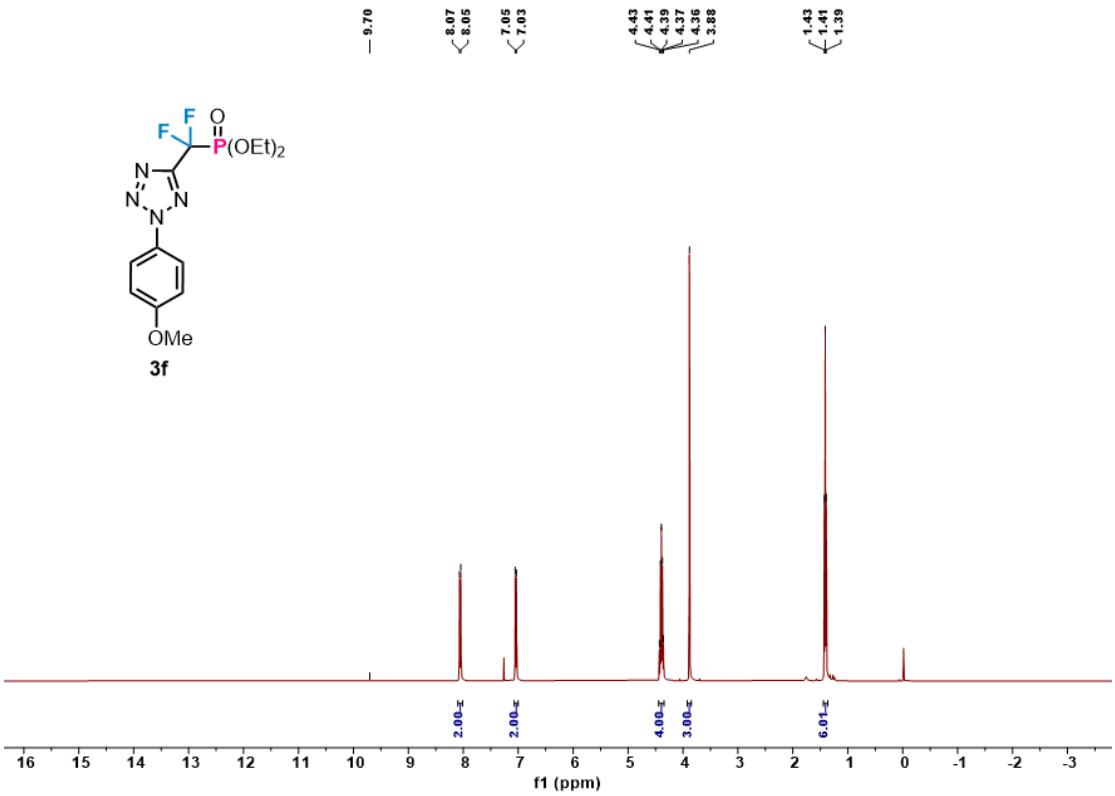
^{19}F-NMR of **3e** ($CDCl_3$, 376 M)



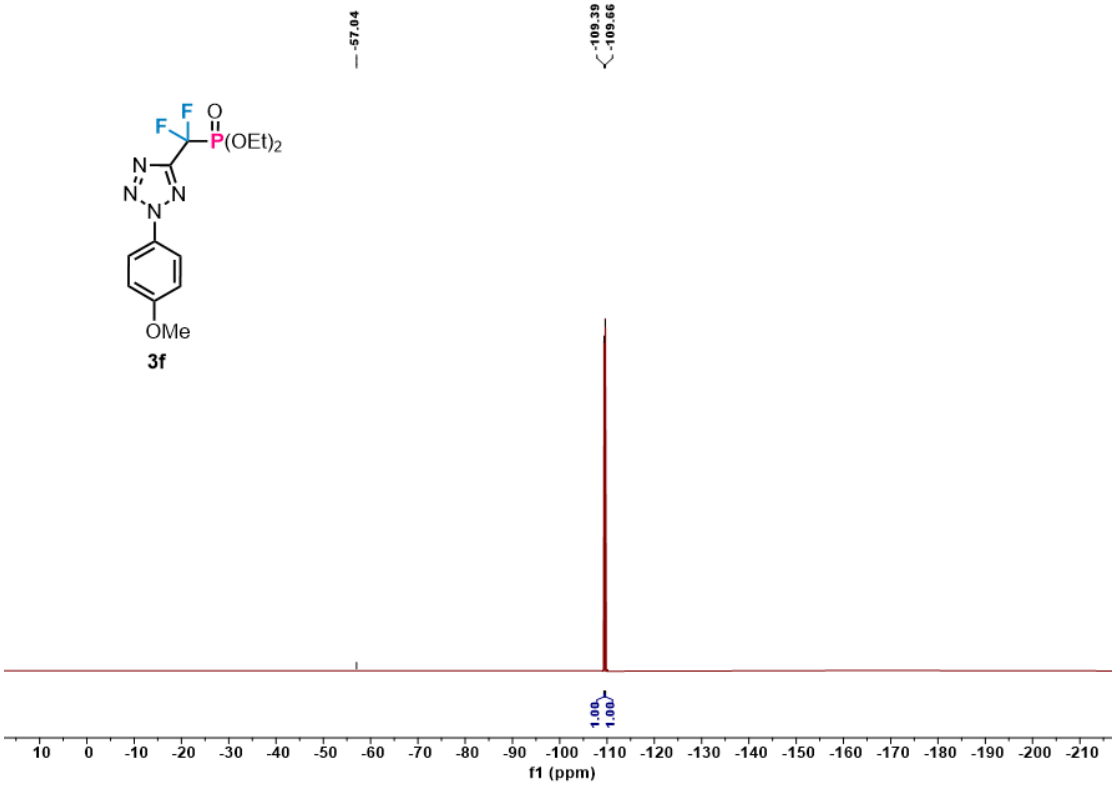
^{31}P-NMR of **3e** ($CDCl_3$, 162 M)



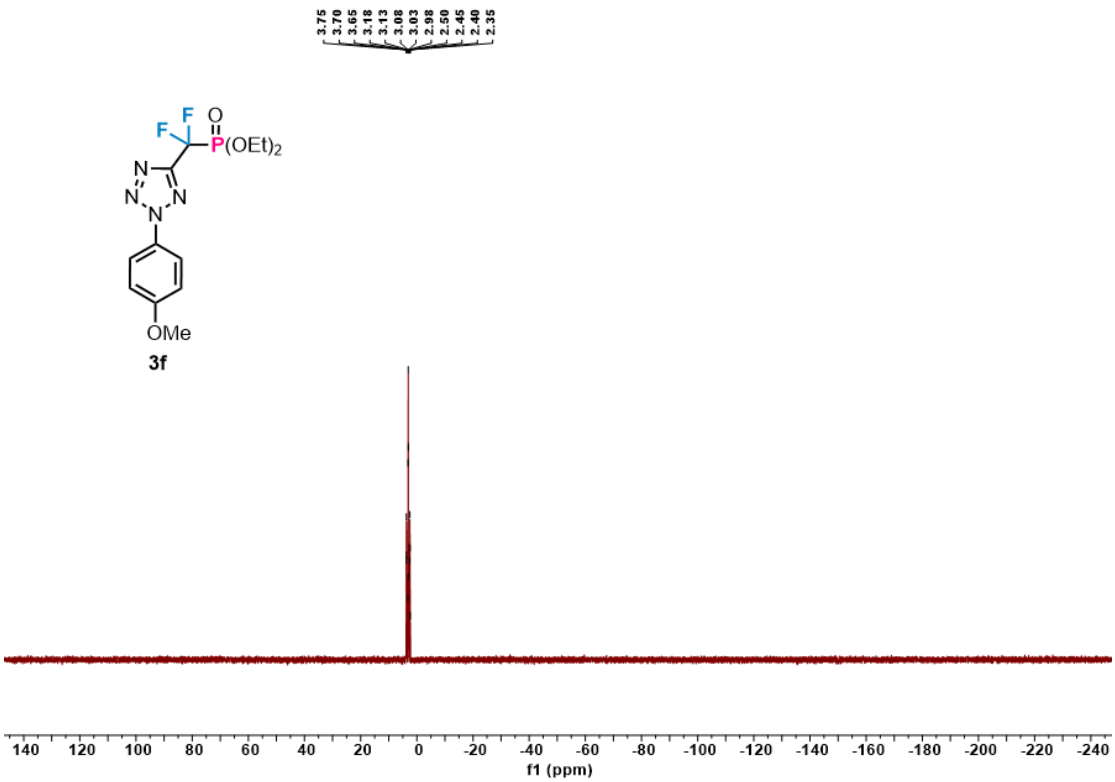
^{13}C-NMR of **3e** ($CDCl_3$, 101 M)



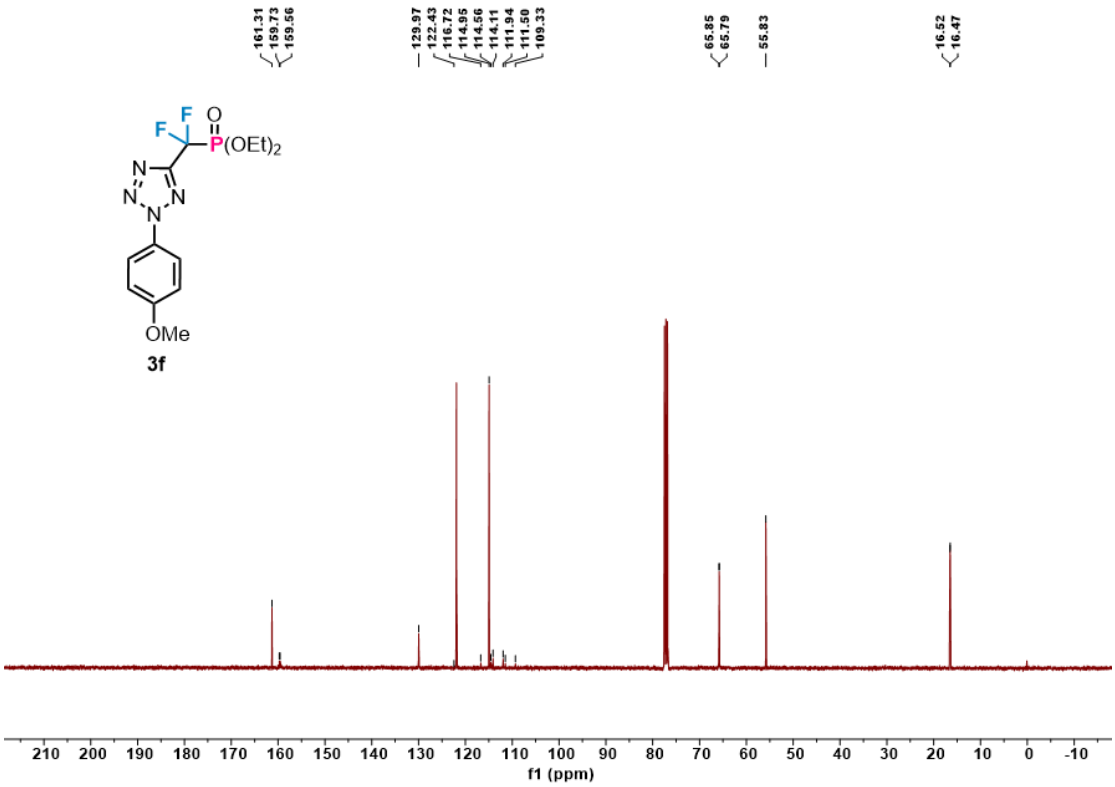
^{1}H-NMR of **3f** ($CDCl_3$, 400 M)



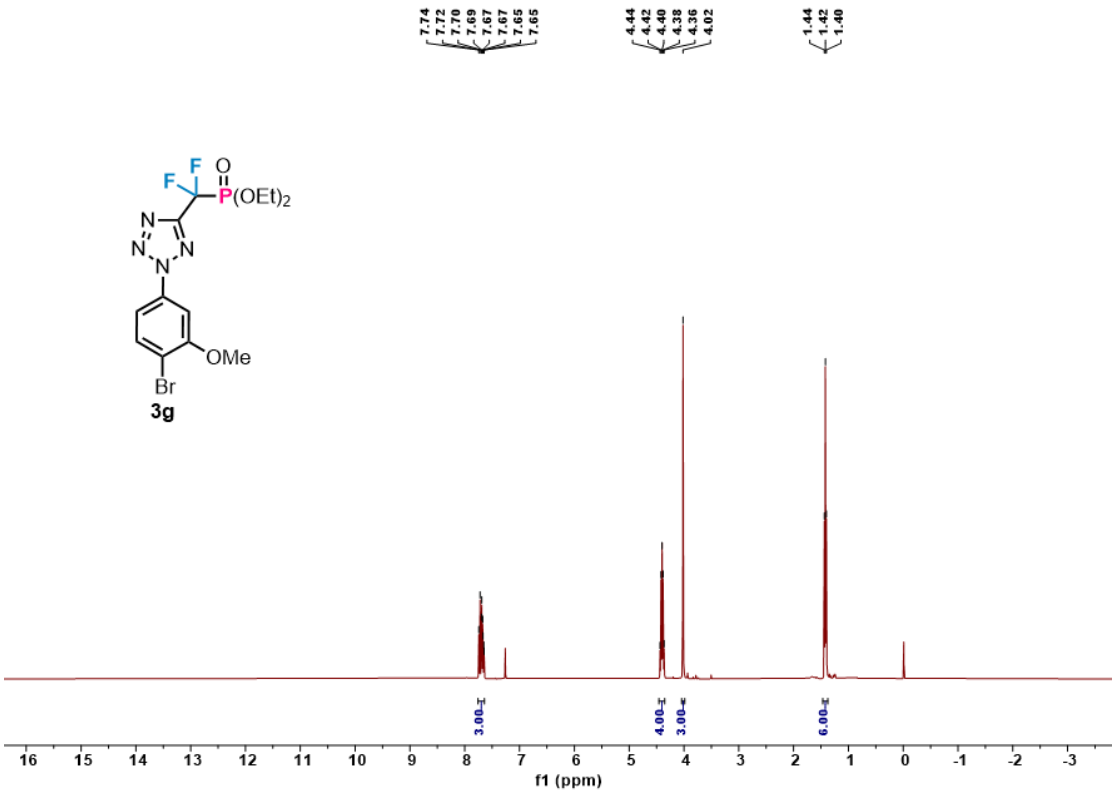
^{19}F-NMR of **3f** ($CDCl_3$, 376 M)



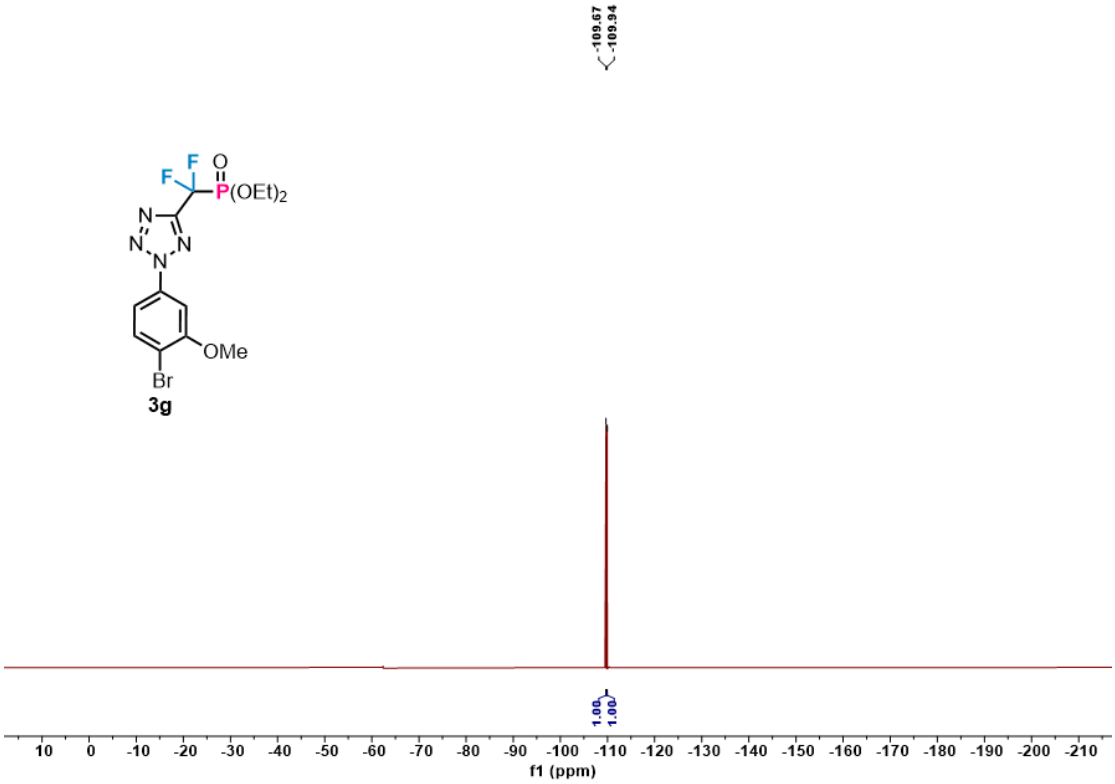
^{31}P-NMR of **3f** ($CDCl_3$, 162 M)



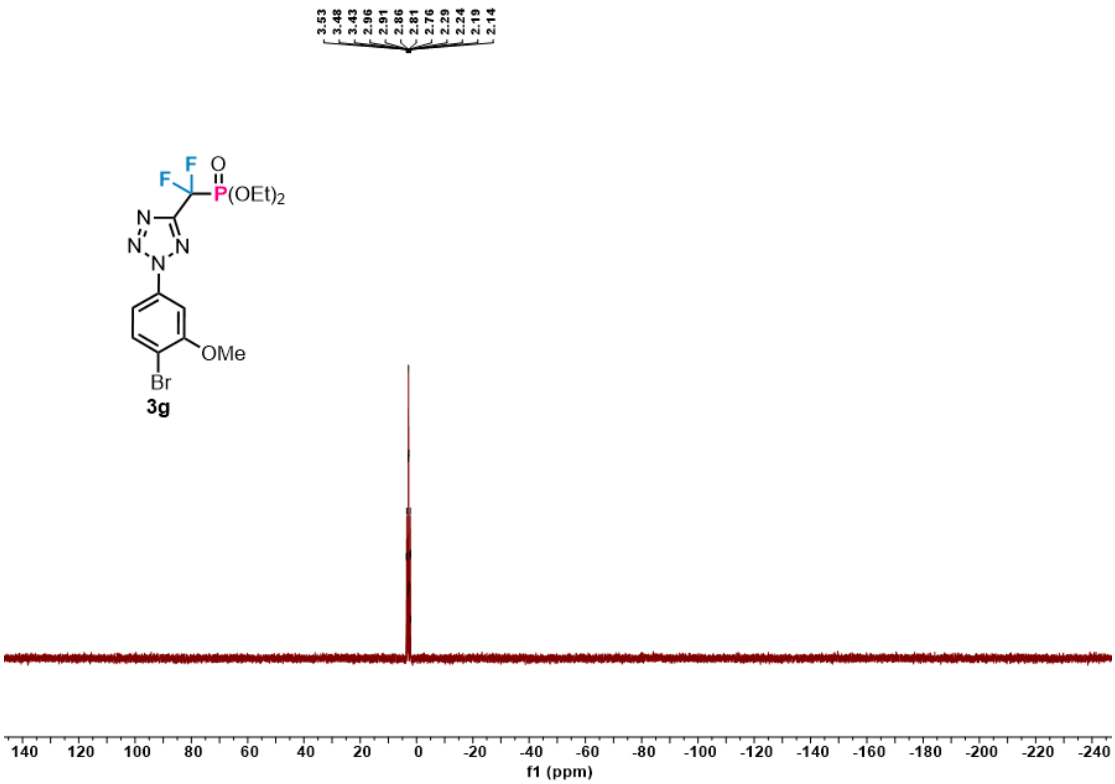
^{13}C-NMR of **3f** ($CDCl_3$, 101 M)



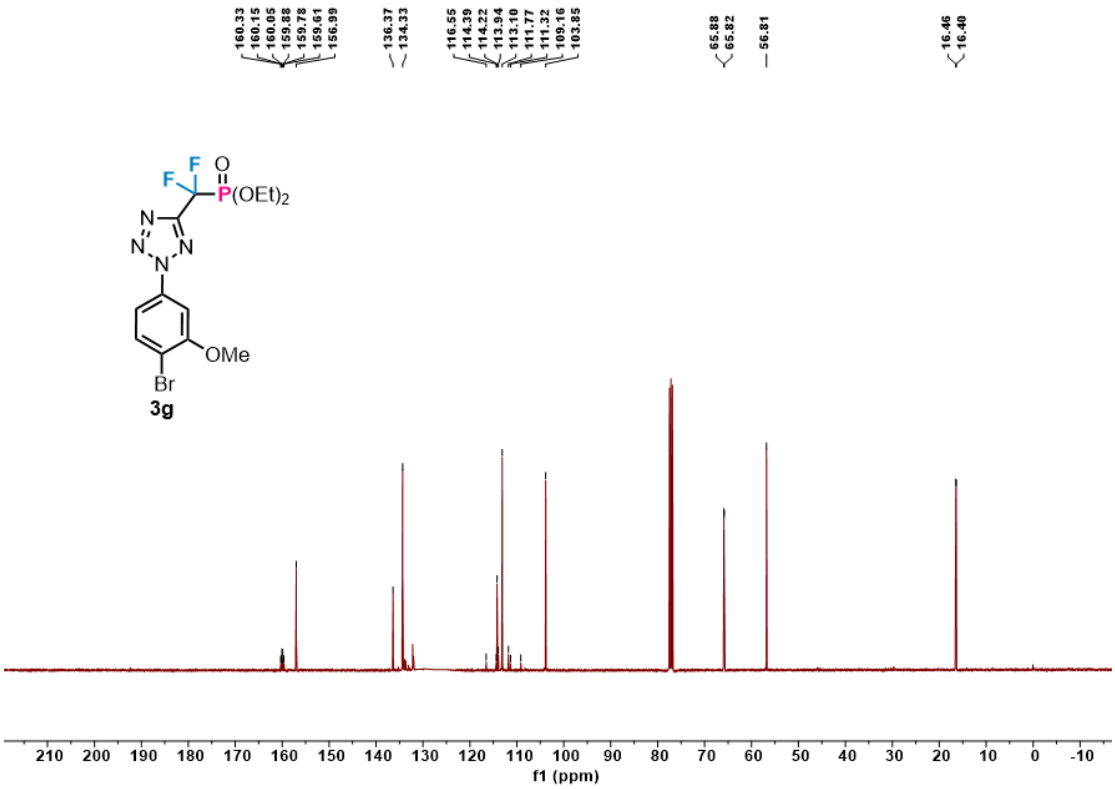
^{1}H-NMR of **3g** ($CDCl_3$, 400 M)



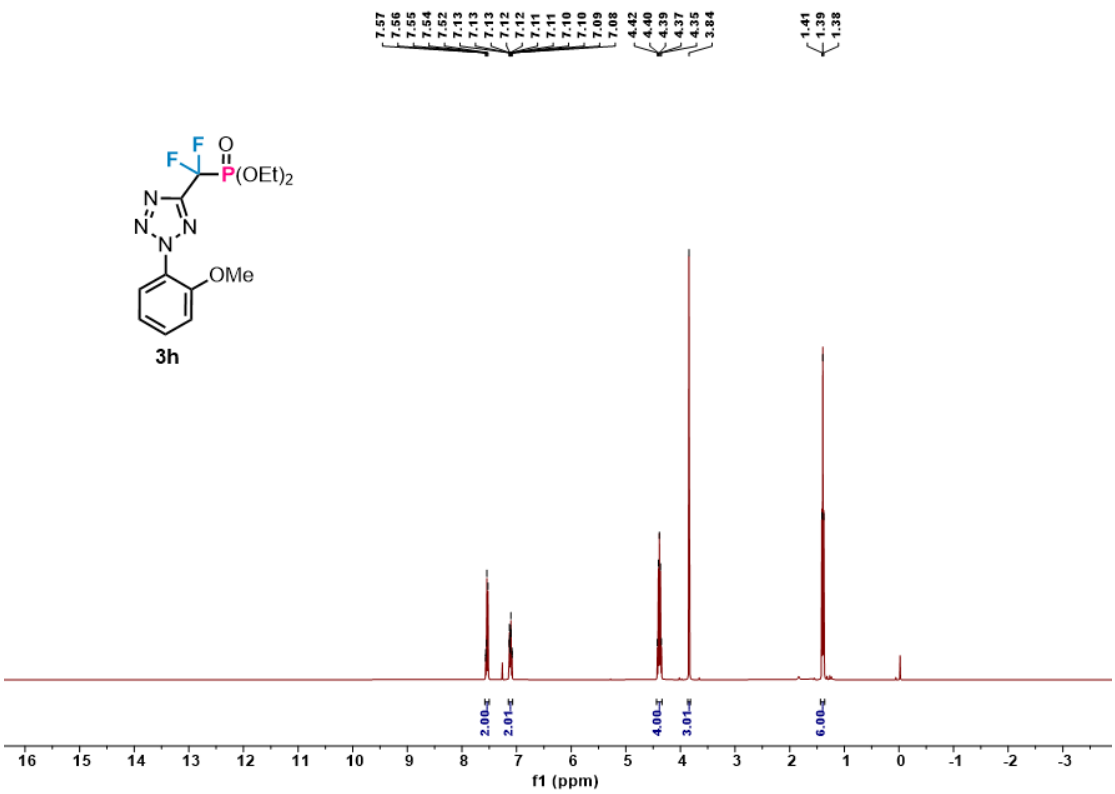
^{19}F-NMR of **3g** ($CDCl_3$, 376 M)



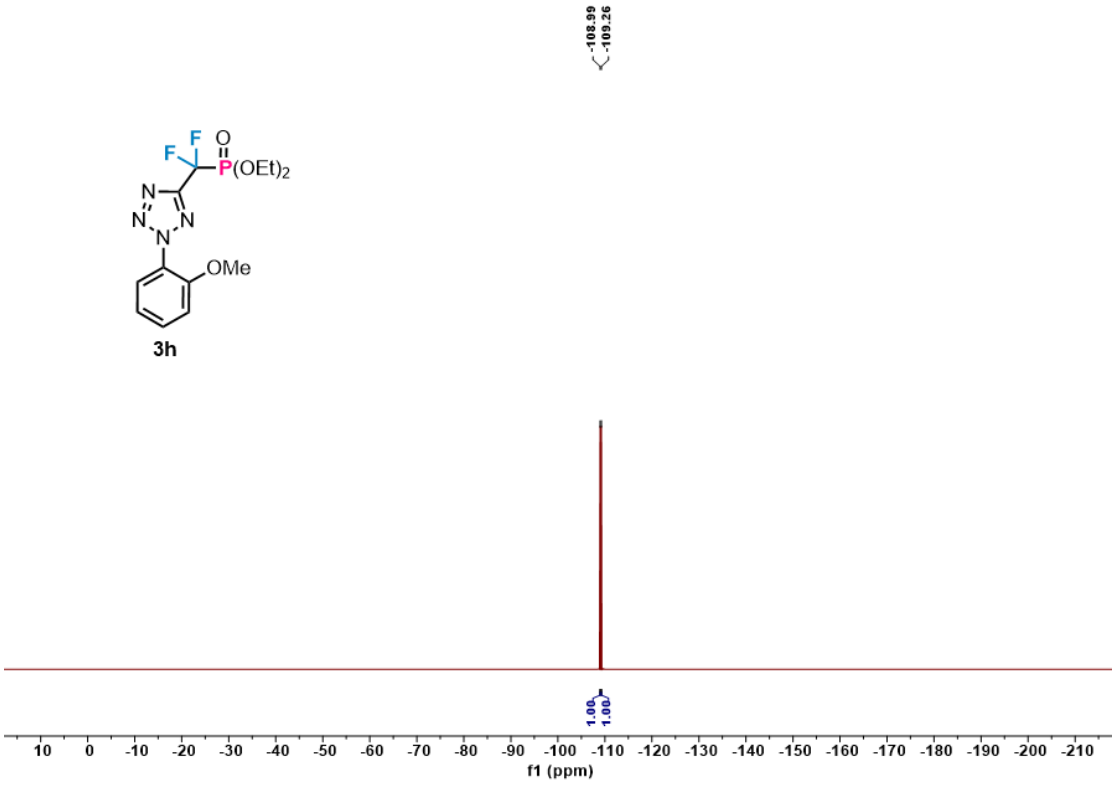
^{31}P-NMR of **3g** ($CDCl_3$, 162 M)



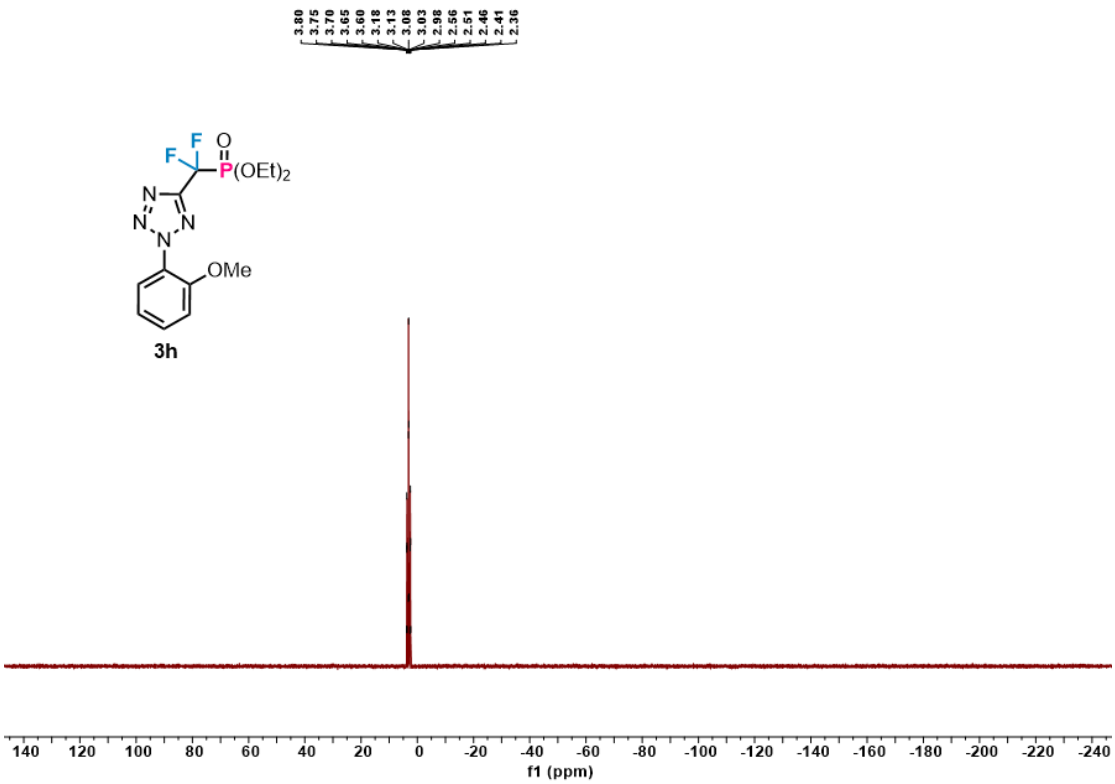
^{13}C-NMR of **3g** ($CDCl_3$, 101 M)



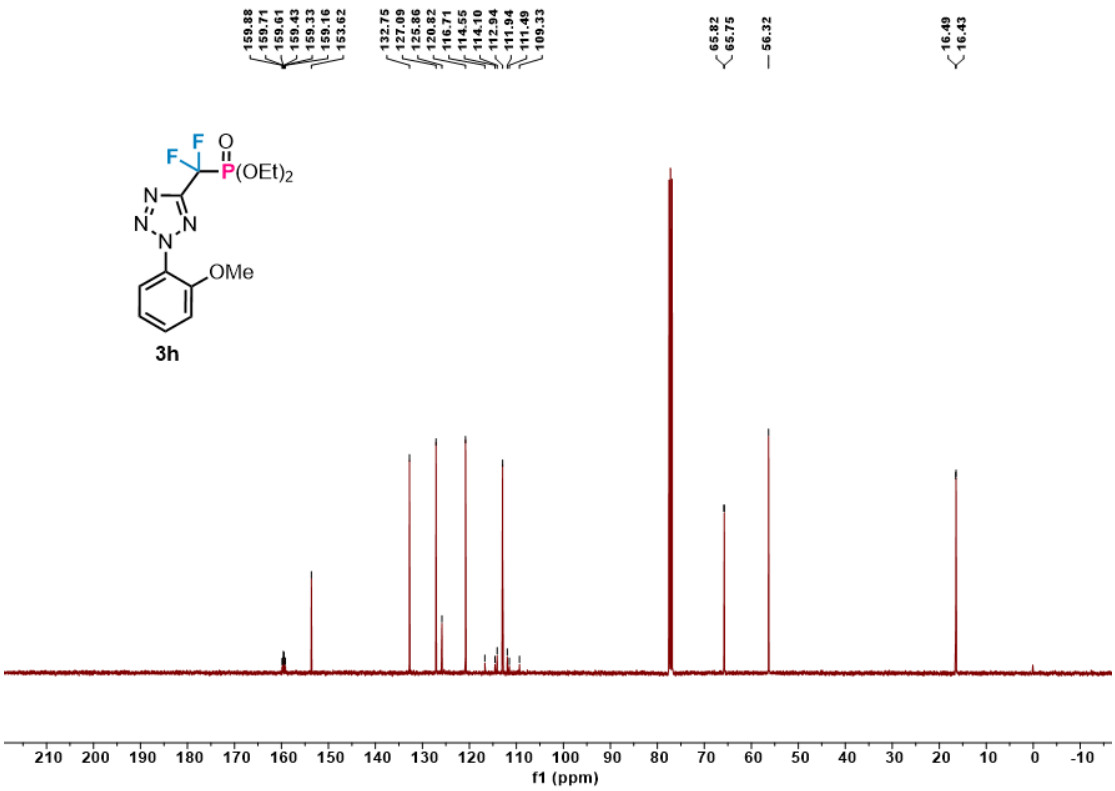
^{1}H-NMR of **3h** ($CDCl_3$, 400 M)



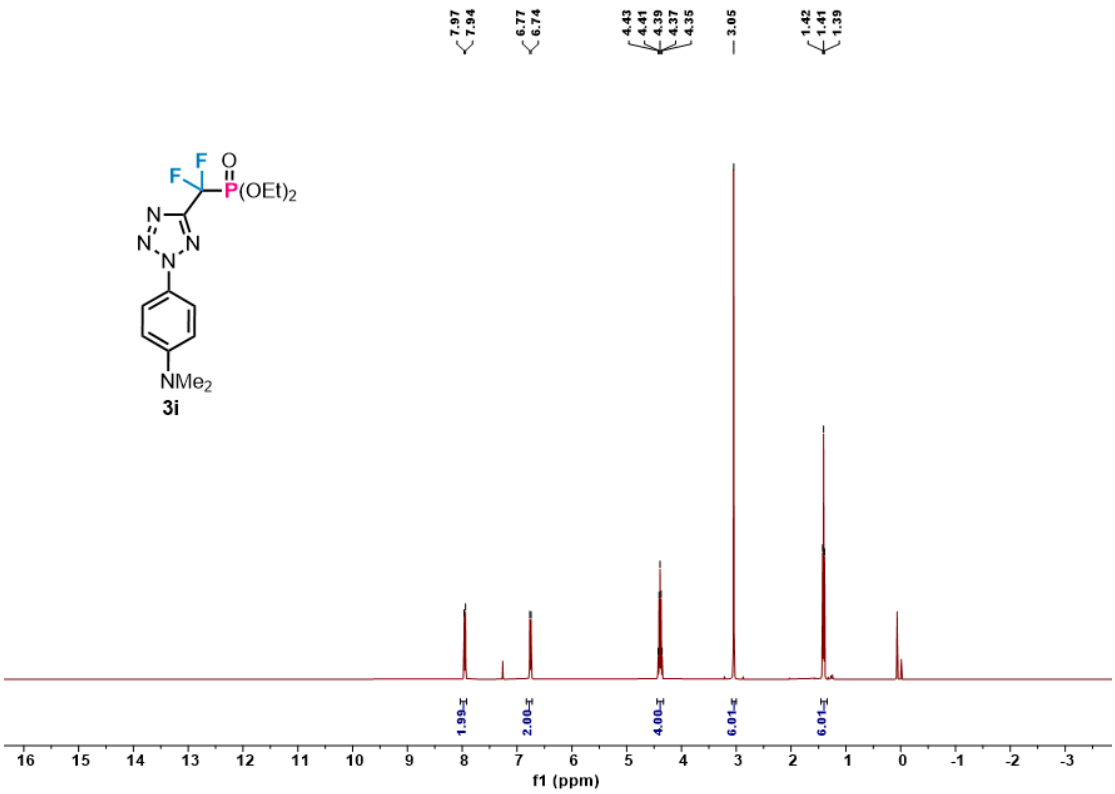
^{19}F-NMR of **3h** ($CDCl_3$, 376 M)



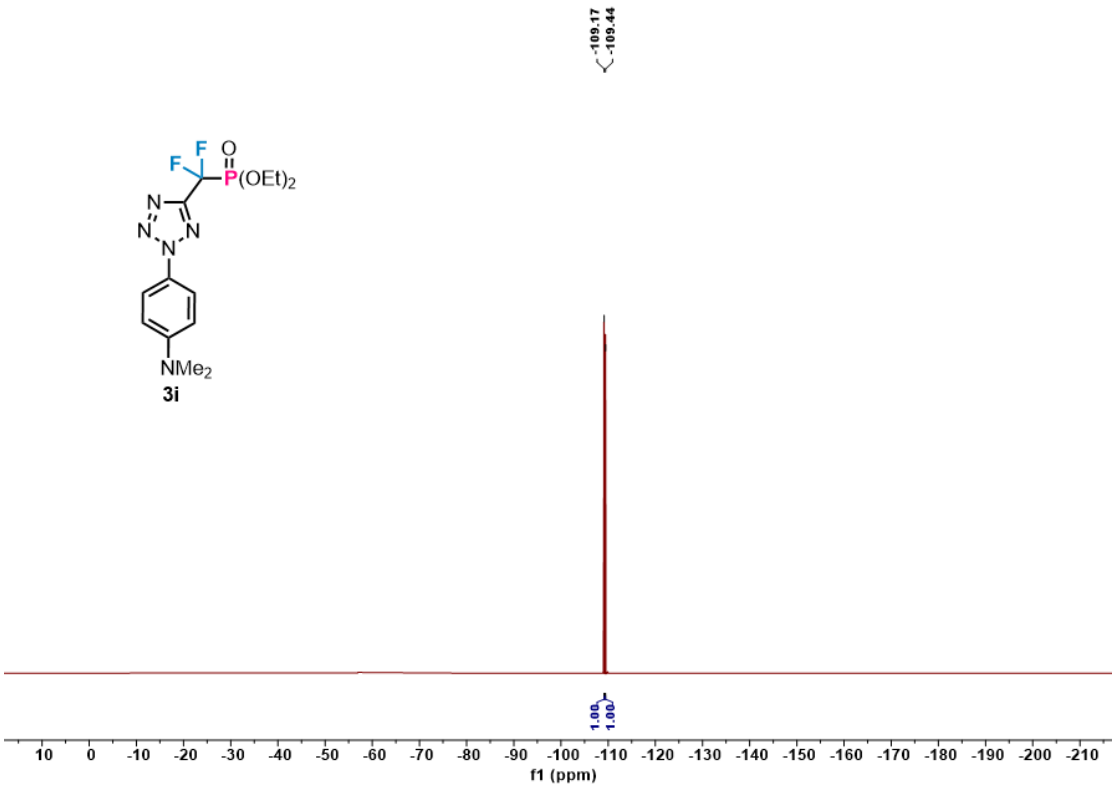
^{31}P-NMR of **3h** ($CDCl_3$, 162 M)



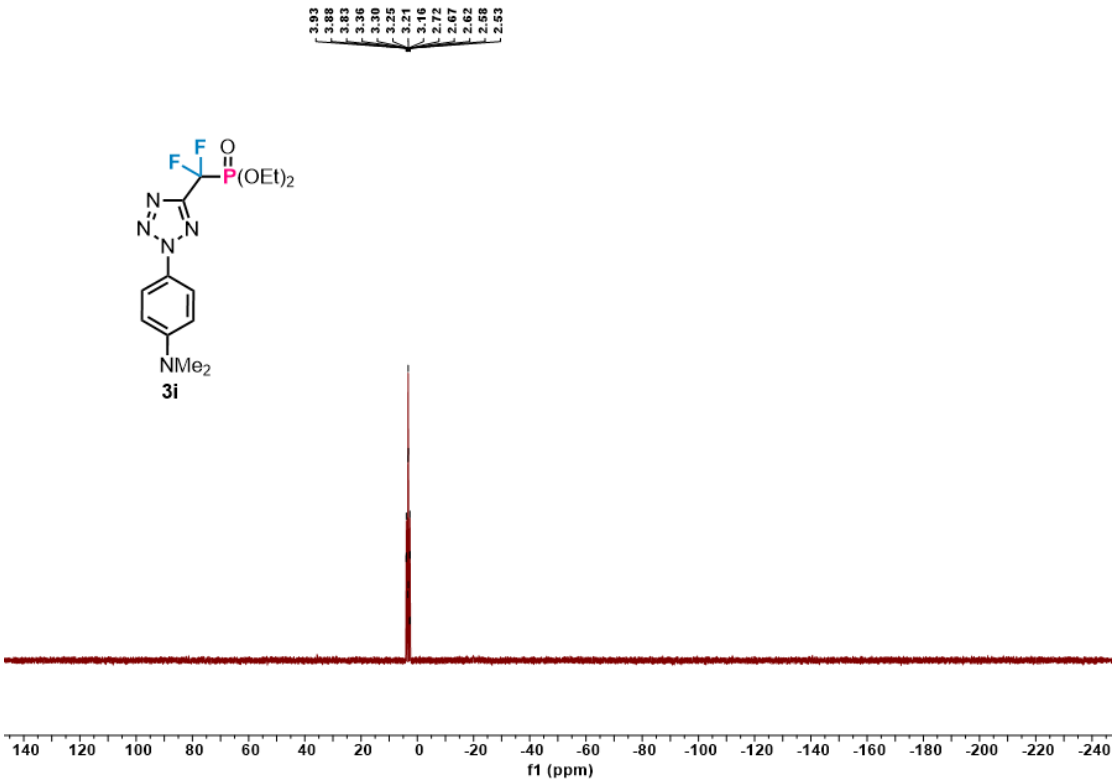
^{13}C-NMR of **3h** ($CDCl_3$, 101 M)



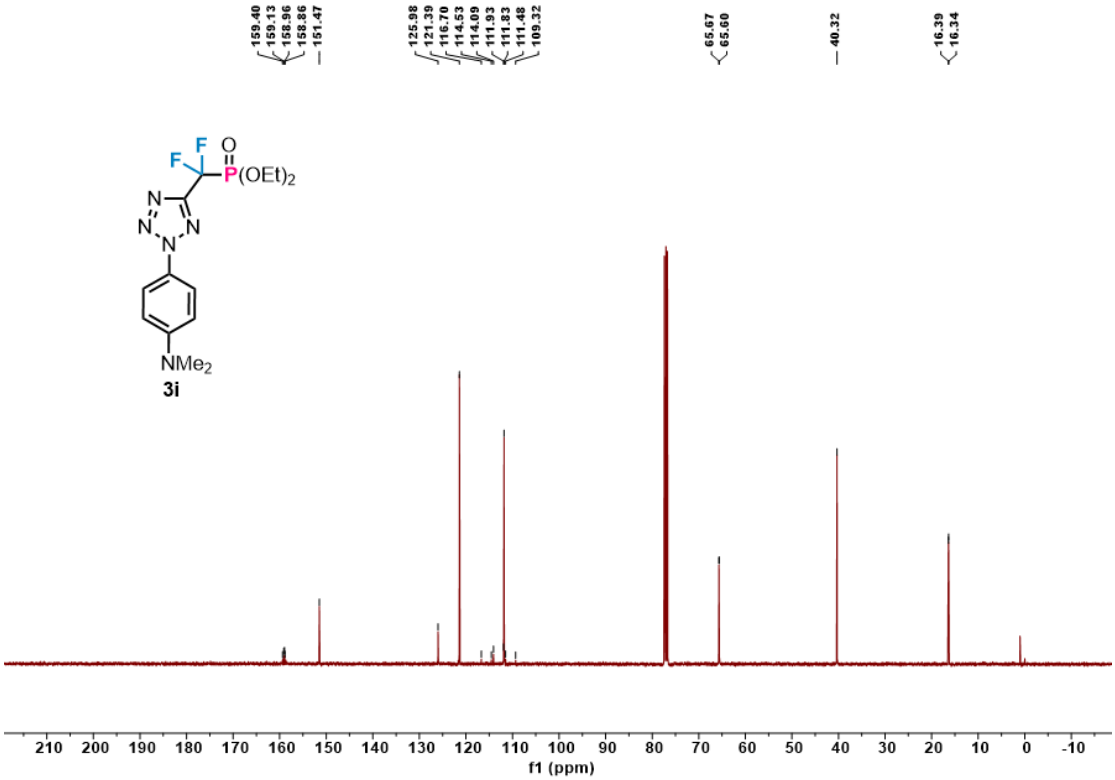
^{1}H-NMR of **3i** ($CDCl_3$, 400 M)



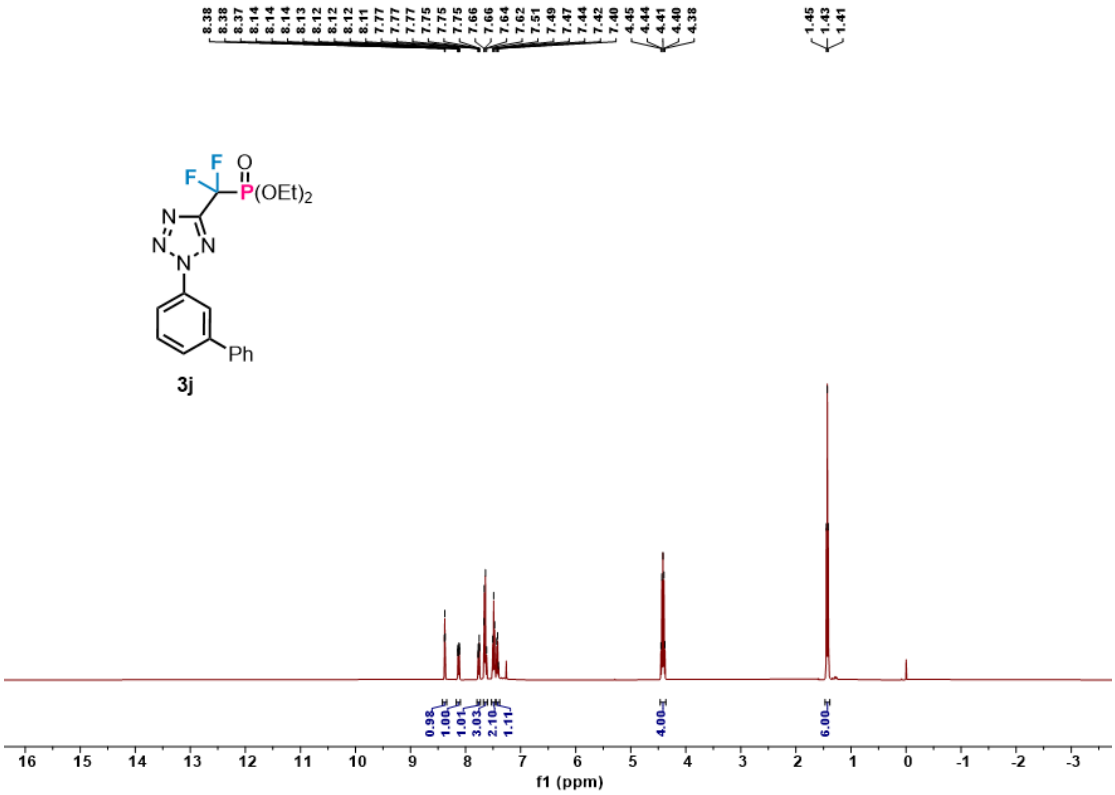
^{19}F-NMR of **3i** ($CDCl_3$, 376 M)



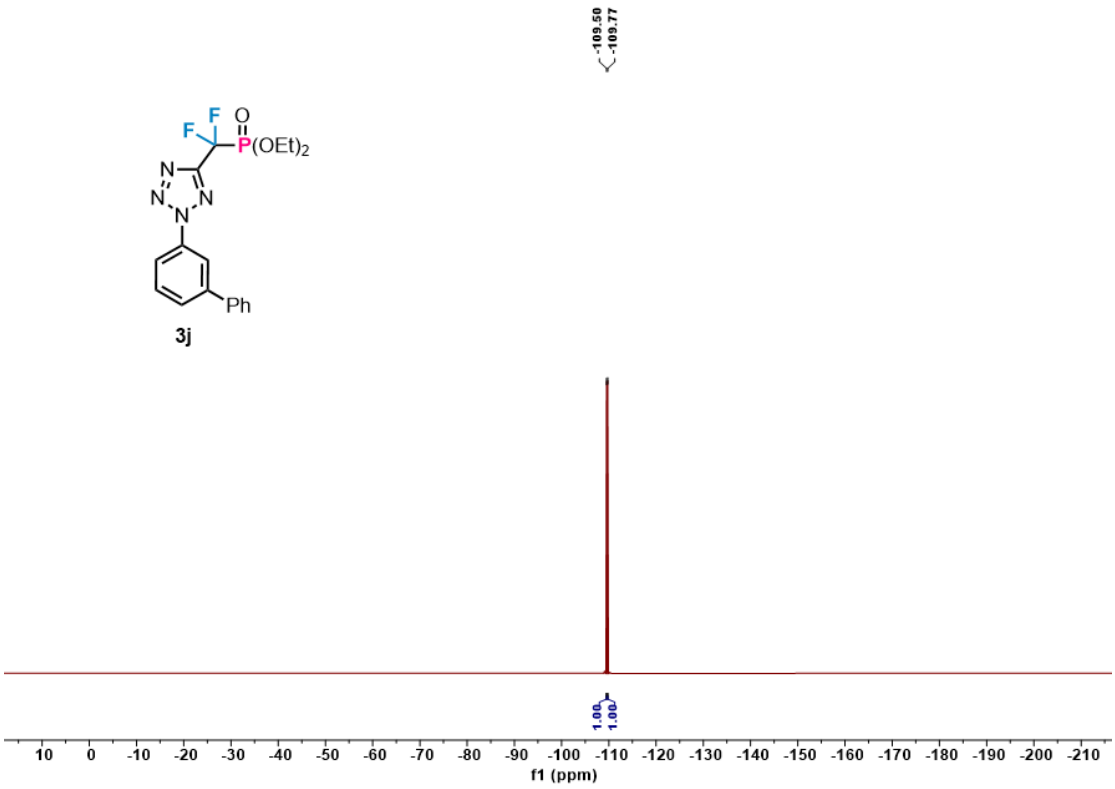
^{31}P-NMR of **3i** ($CDCl_3$, 162 M)



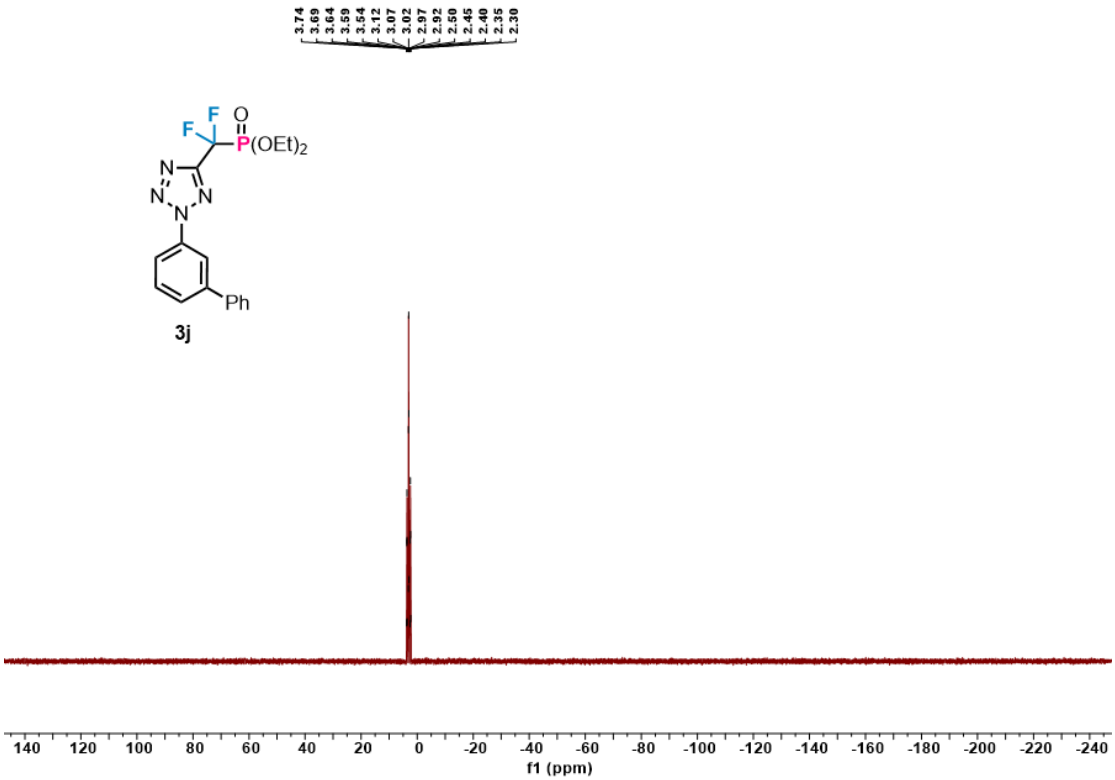
^{13}C-NMR of **3i** ($CDCl_3$, 101 M)



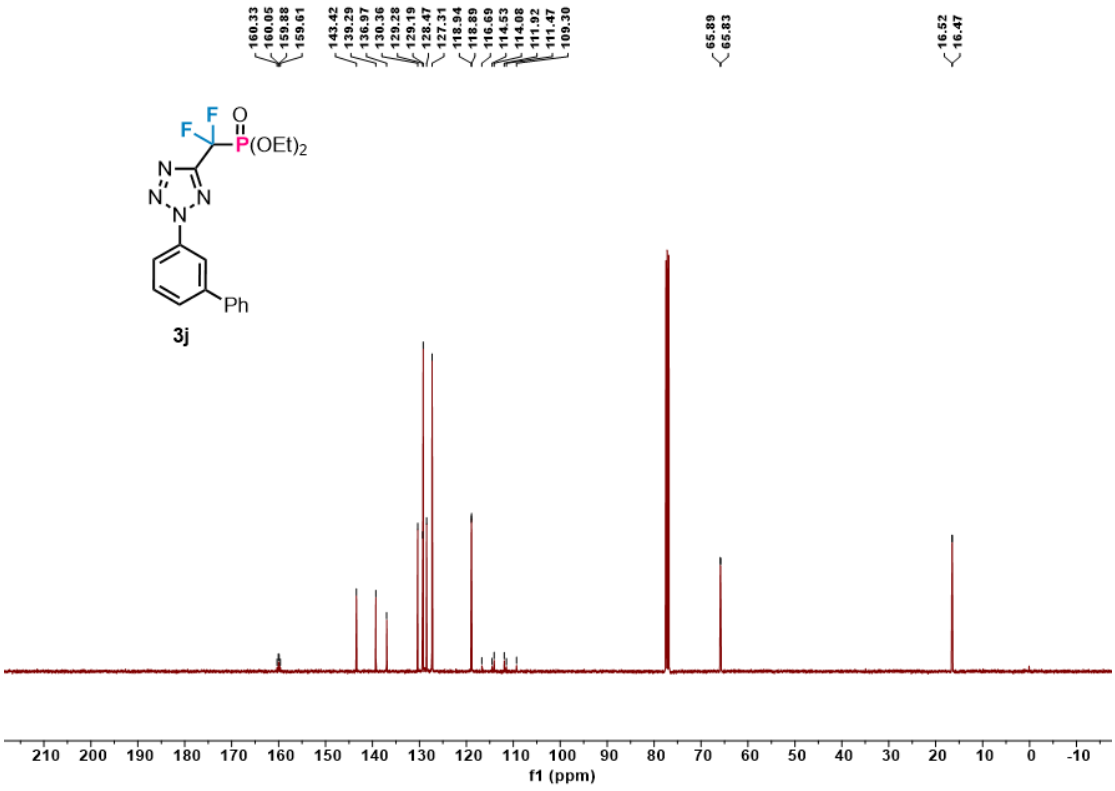
^{1}H-NMR of **3j** ($CDCl_3$, 400 M)



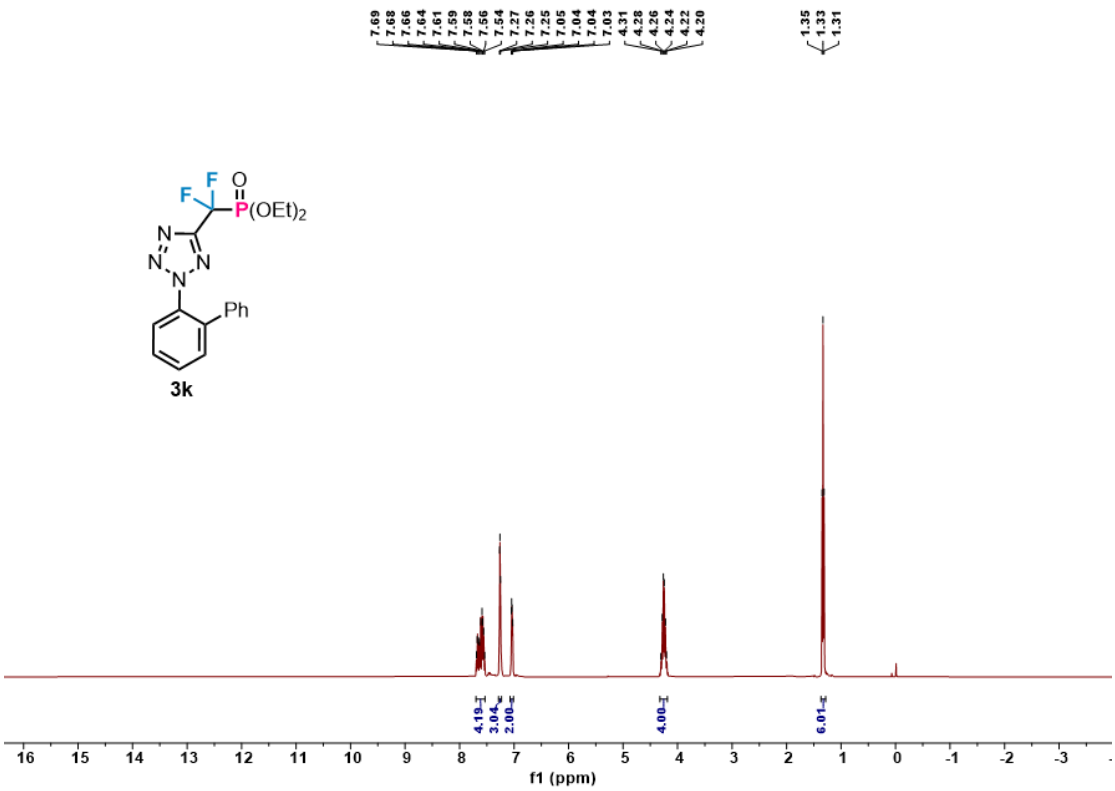
^{19}F-NMR of **3j** ($CDCl_3$, 376 M)



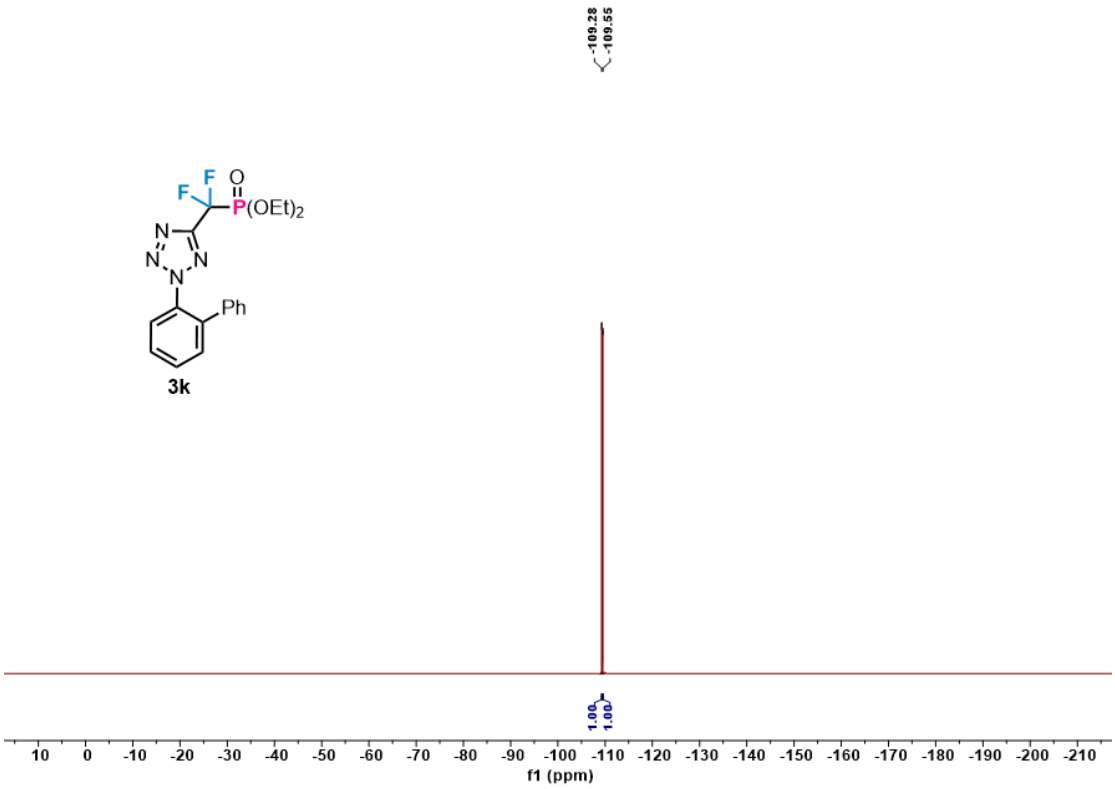
^{31}P-NMR of **3j** ($CDCl_3$, 162 M)



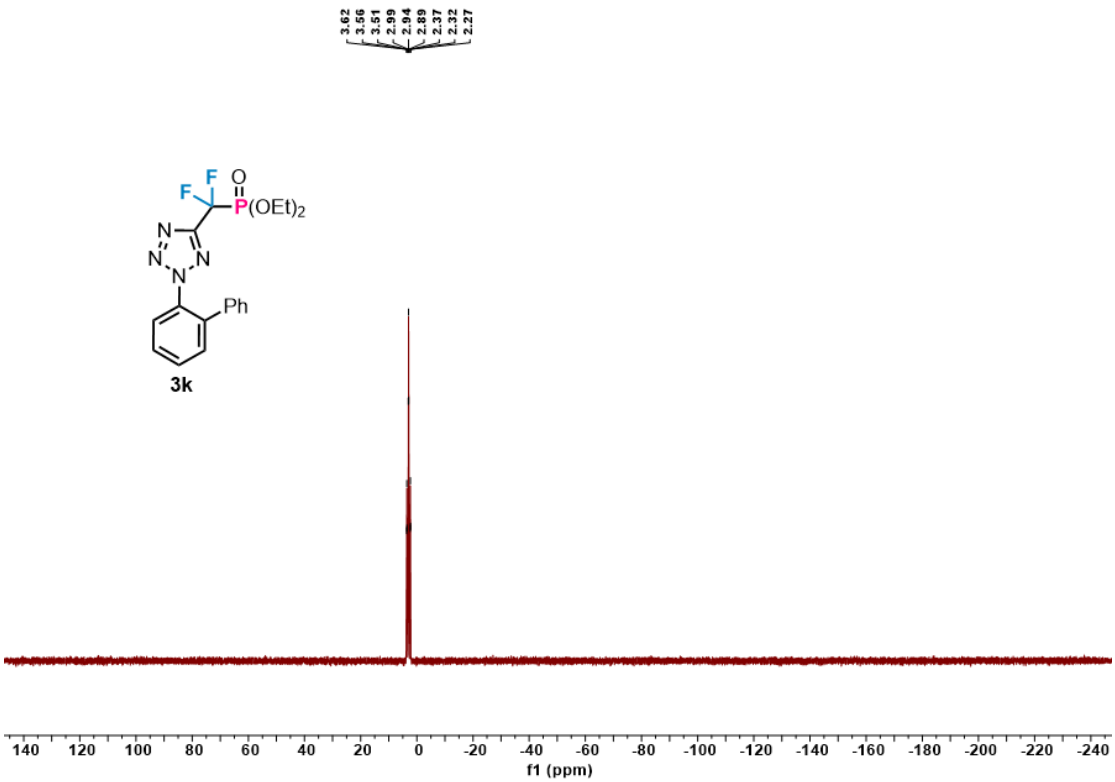
^{13}C-NMR of **3j** ($CDCl_3$, 101 M)



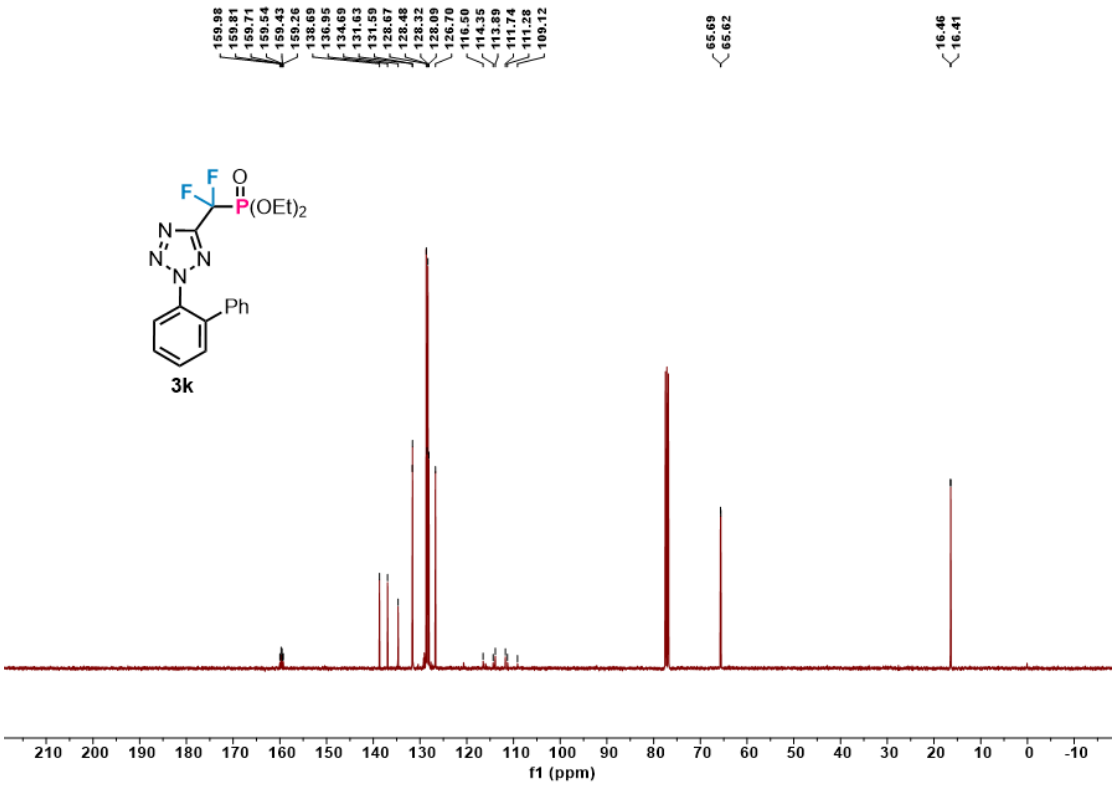
^{1}H-NMR of **3k** ($CDCl_3$, 400 M)



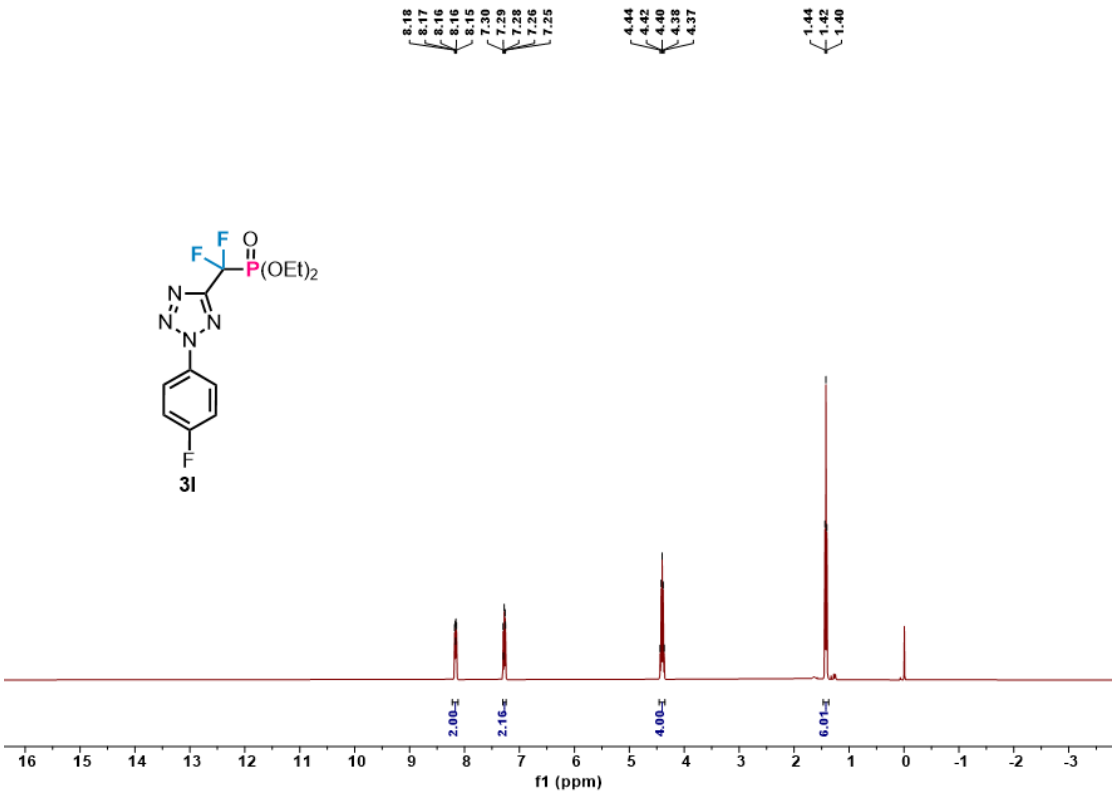
^{19}F-NMR of **3k** ($CDCl_3$, 376 M)



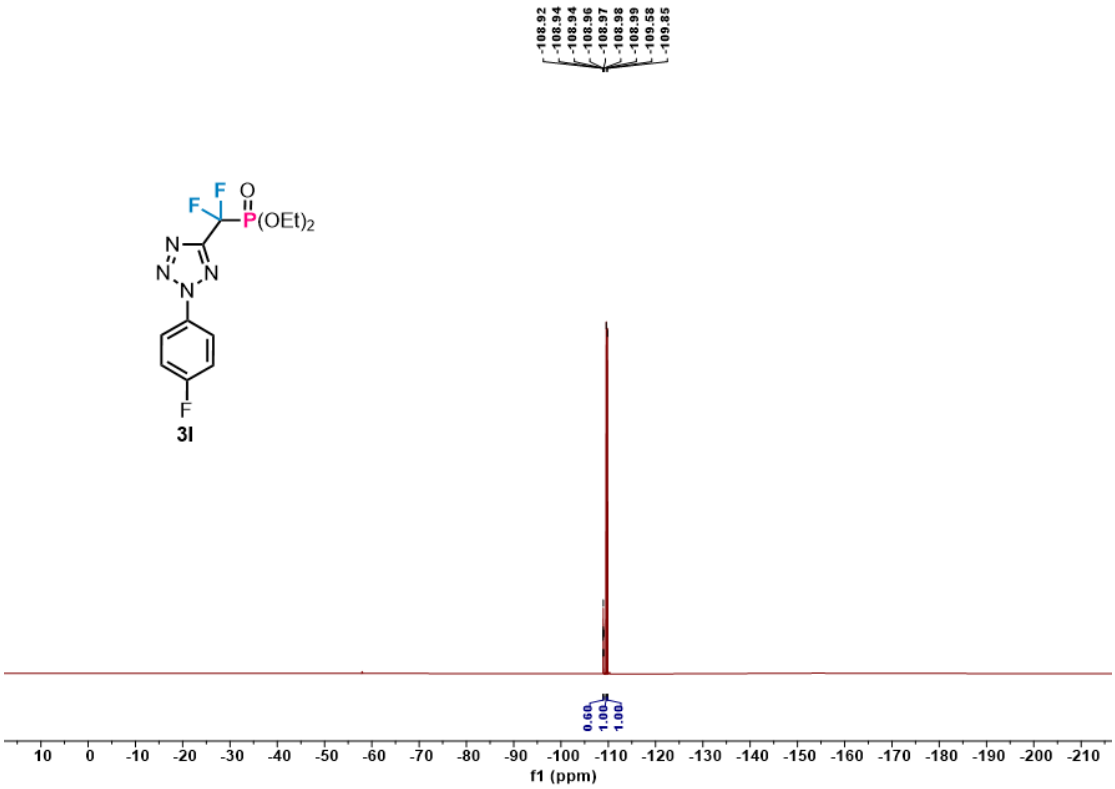
^{31}P-NMR of **3k** ($CDCl_3$, 162 M)



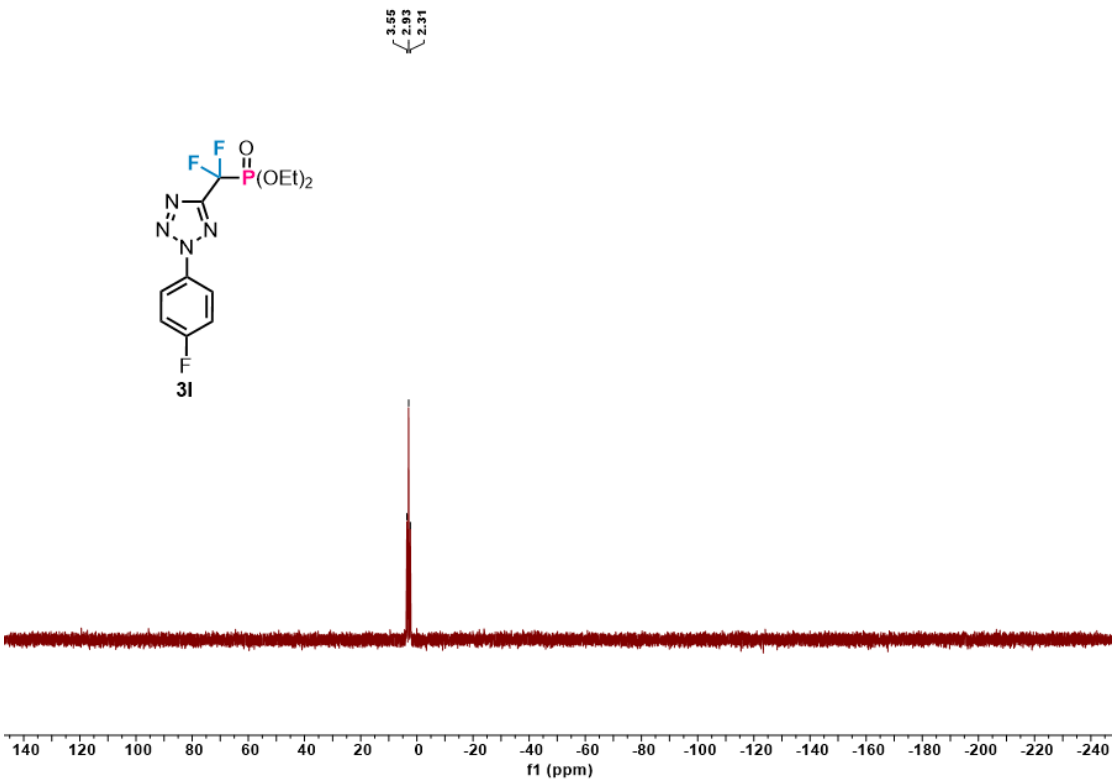
^{13}C-NMR of **3k** ($CDCl_3$, 101 M)



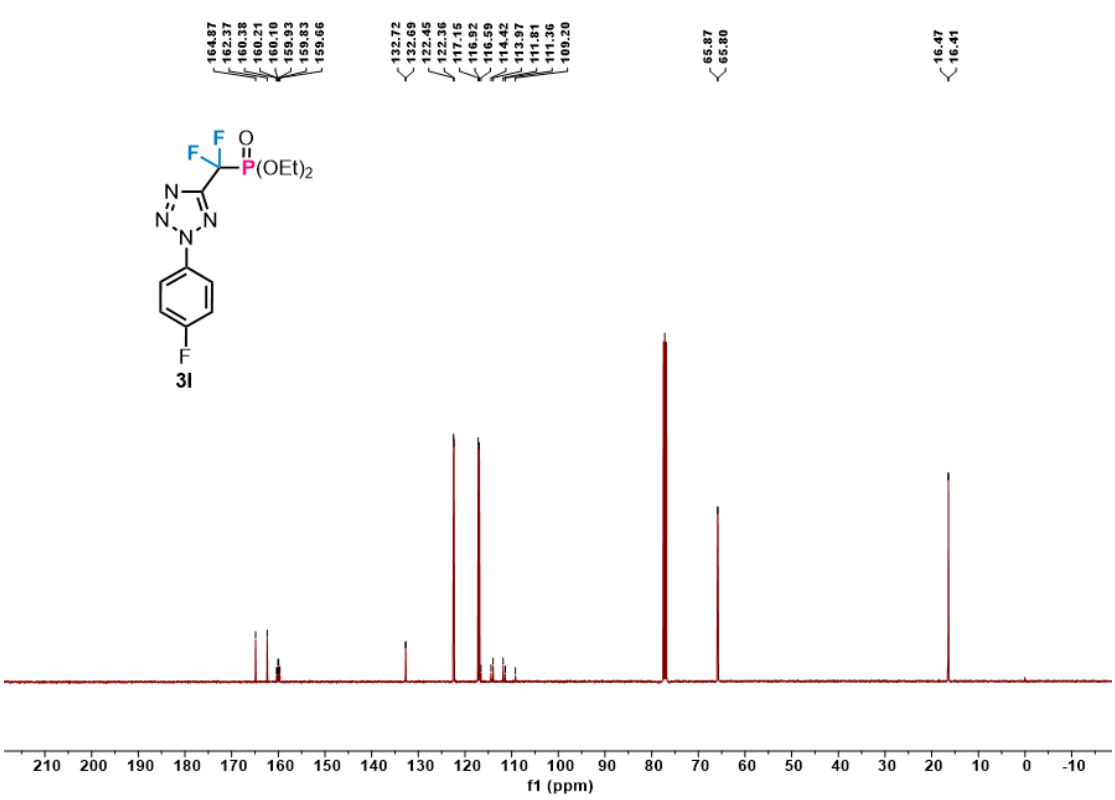
^{1}H-NMR of **3l** ($CDCl_3$, 400 M)



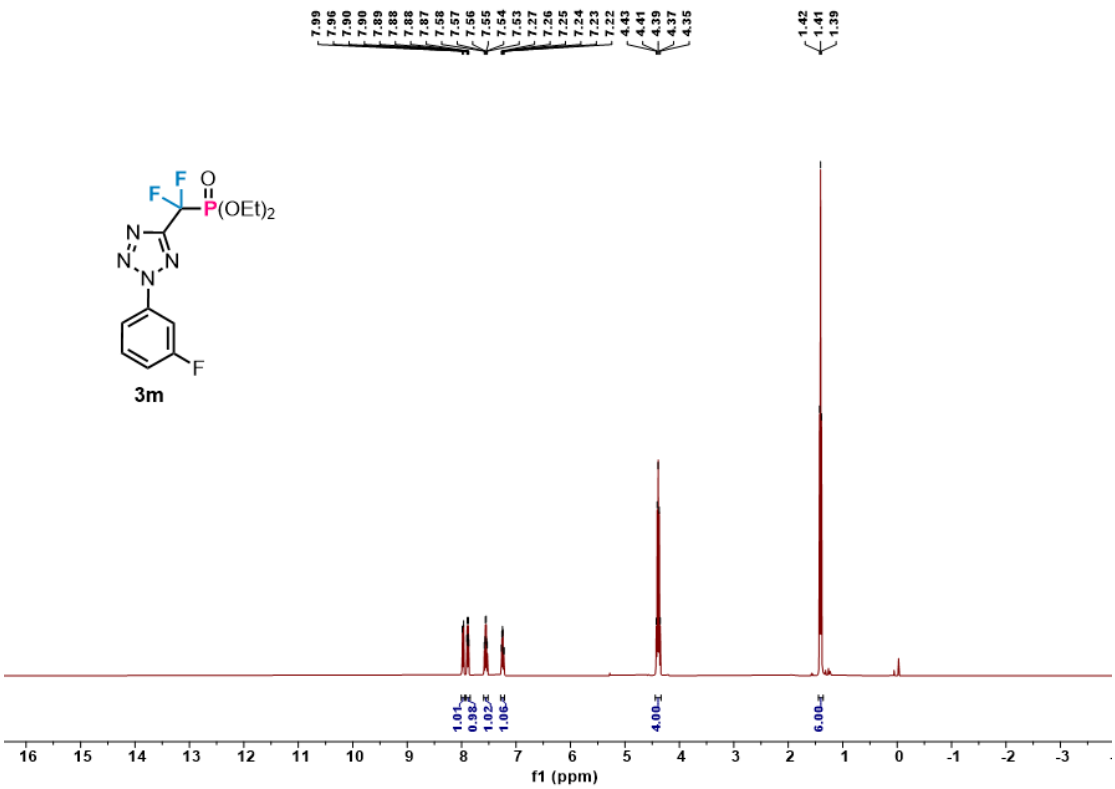
^{19}F-NMR of **3l** ($CDCl_3$, 376 M)



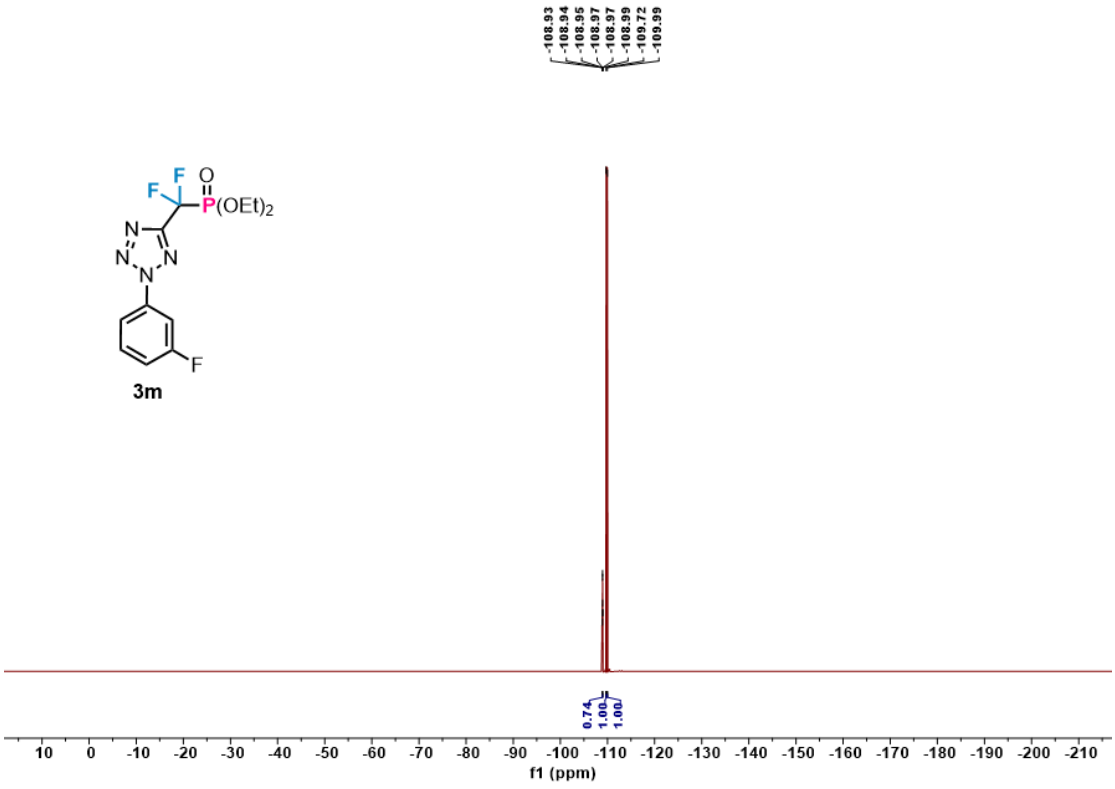
^{31}P-NMR of **3l** ($CDCl_3$, 162 M)



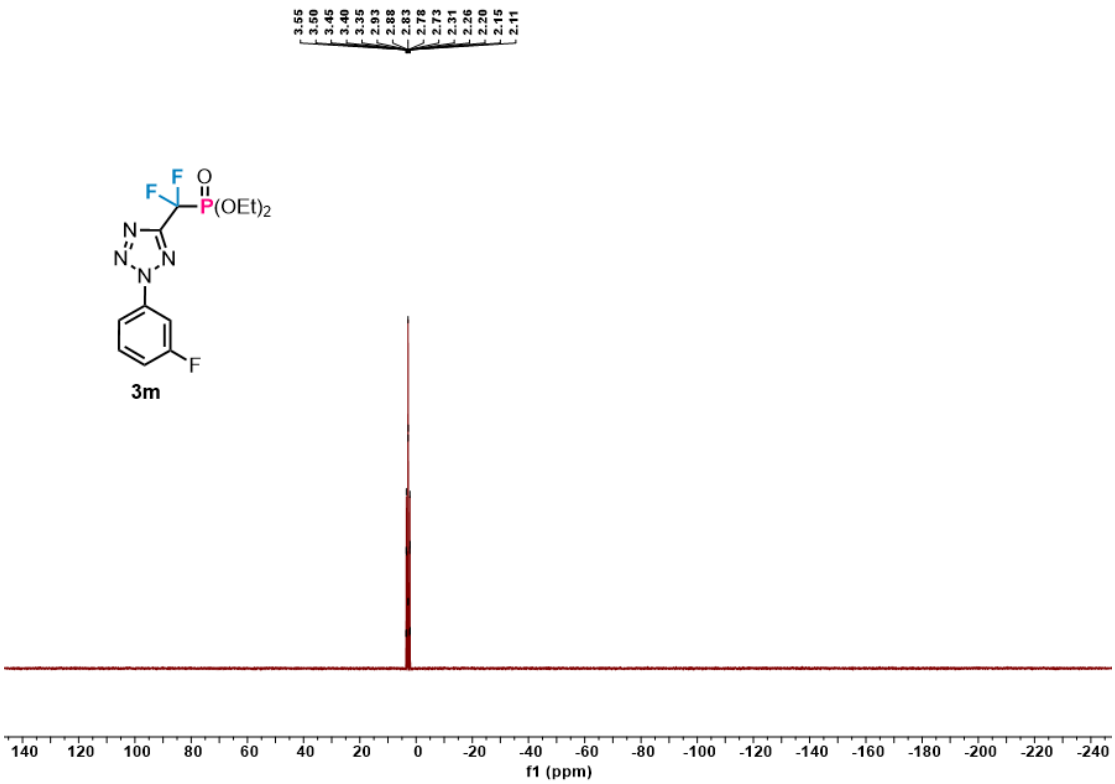
^{13}C-NMR of **3l** ($CDCl_3$, 101 M)



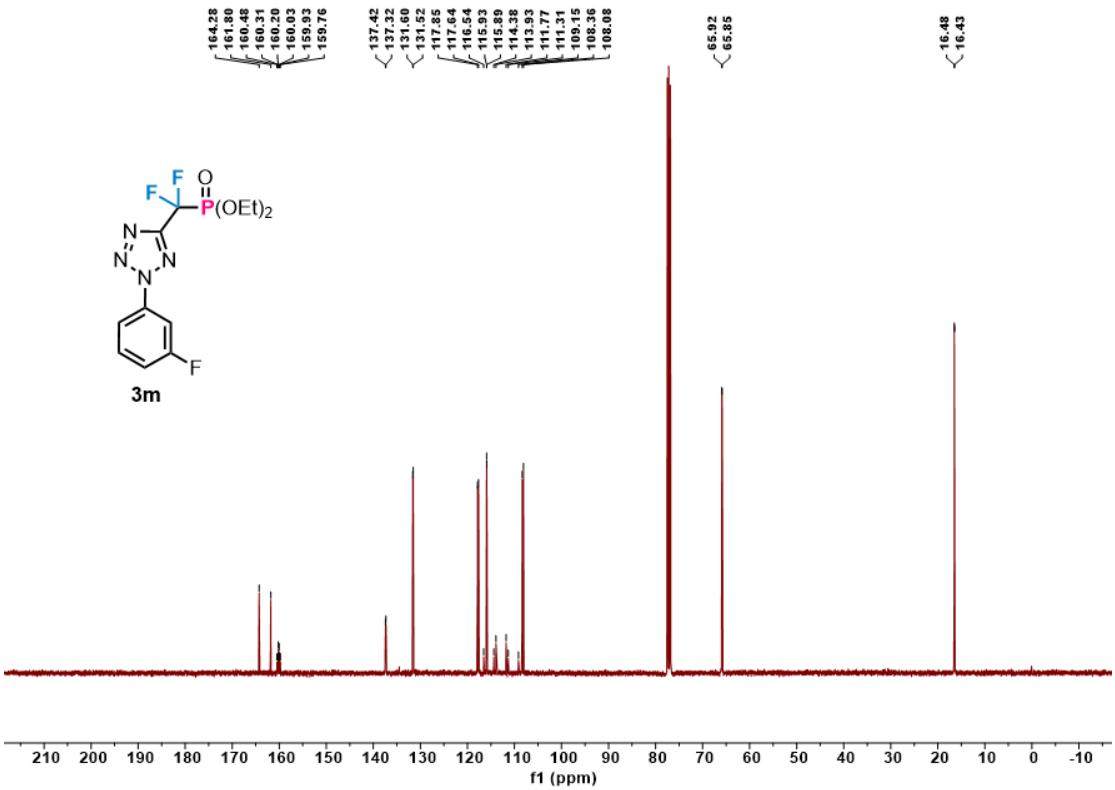
^{1}H-NMR of **3m** ($CDCl_3$, 400 M)



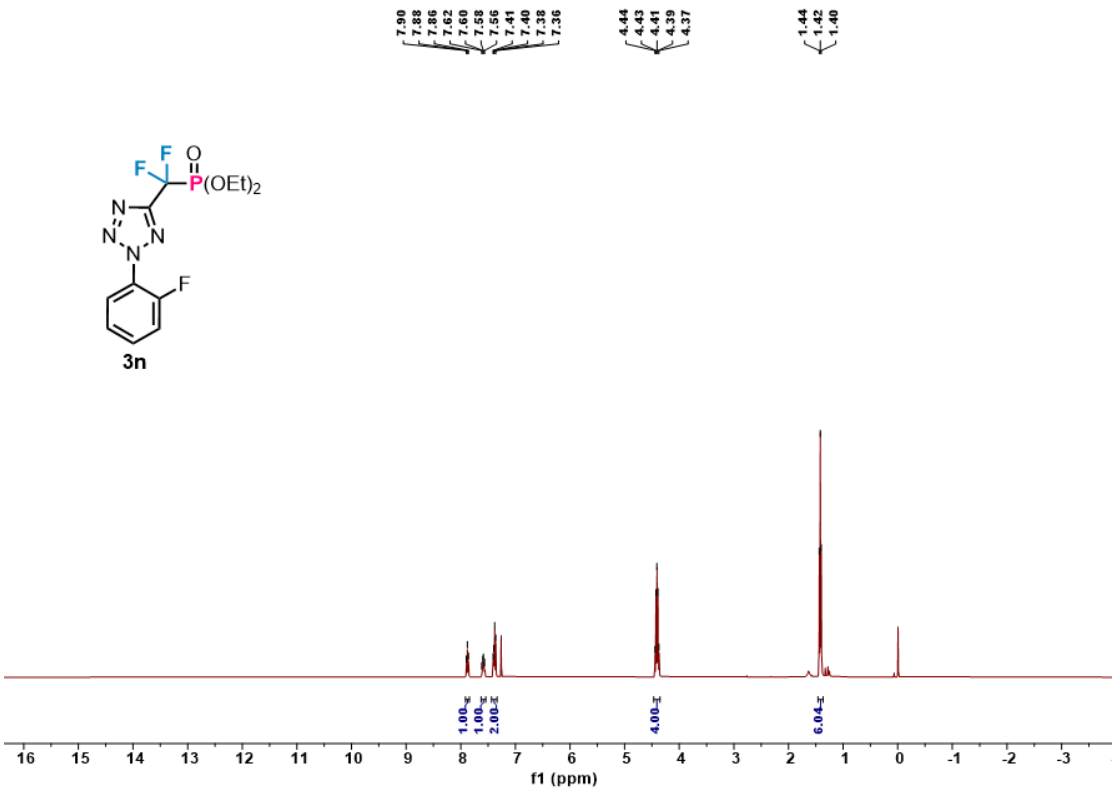
^{19}F-NMR of **3m** ($CDCl_3$, 376 M)



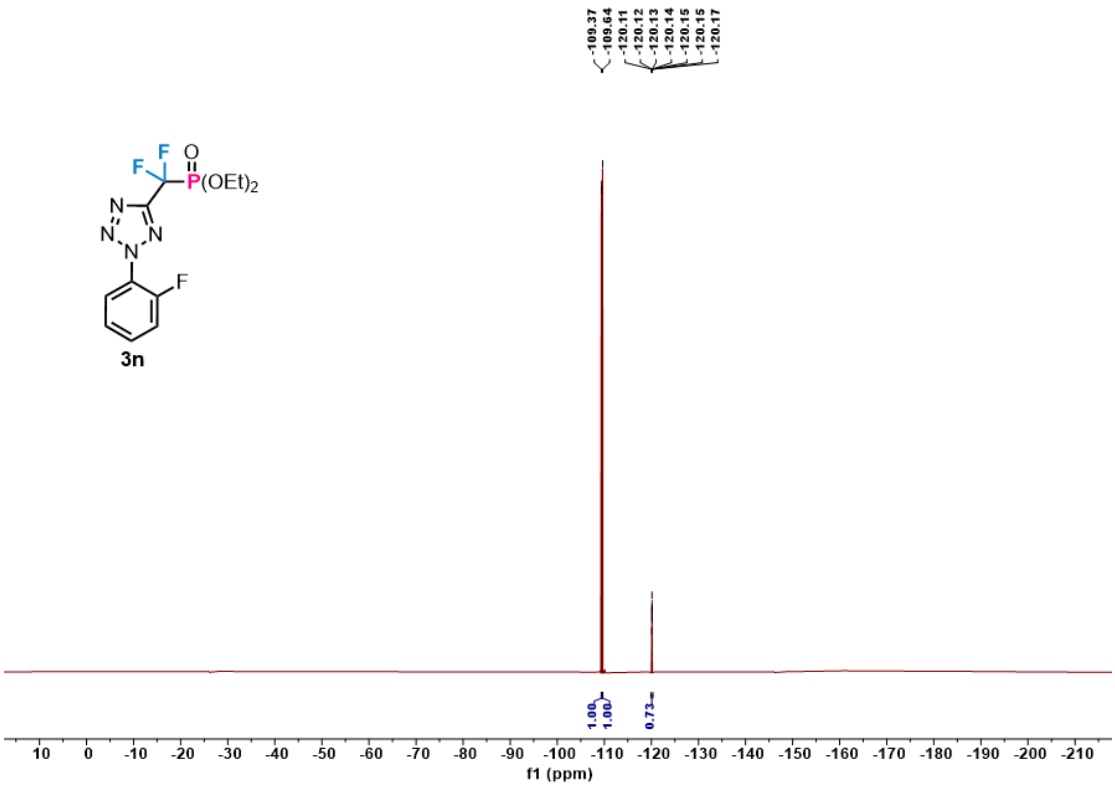
^{31}P-NMR of **3m** ($CDCl_3$, 162 M)



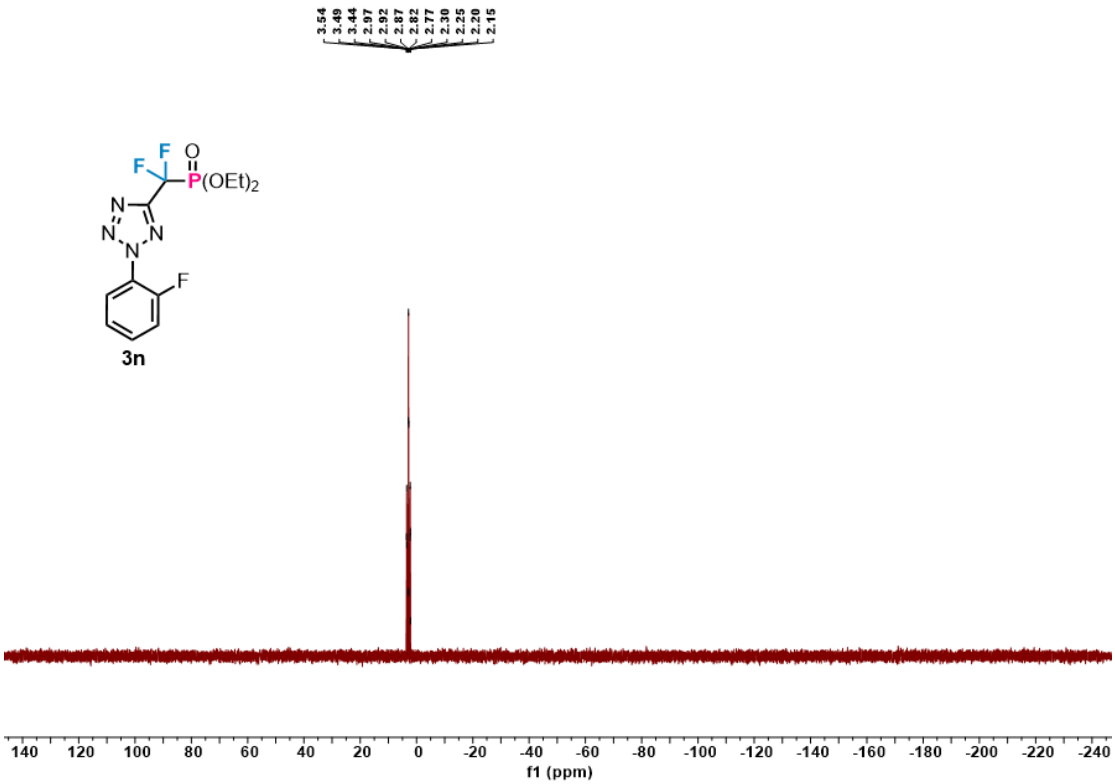
^{13}C-NMR of **3m** ($CDCl_3$, 101 M)



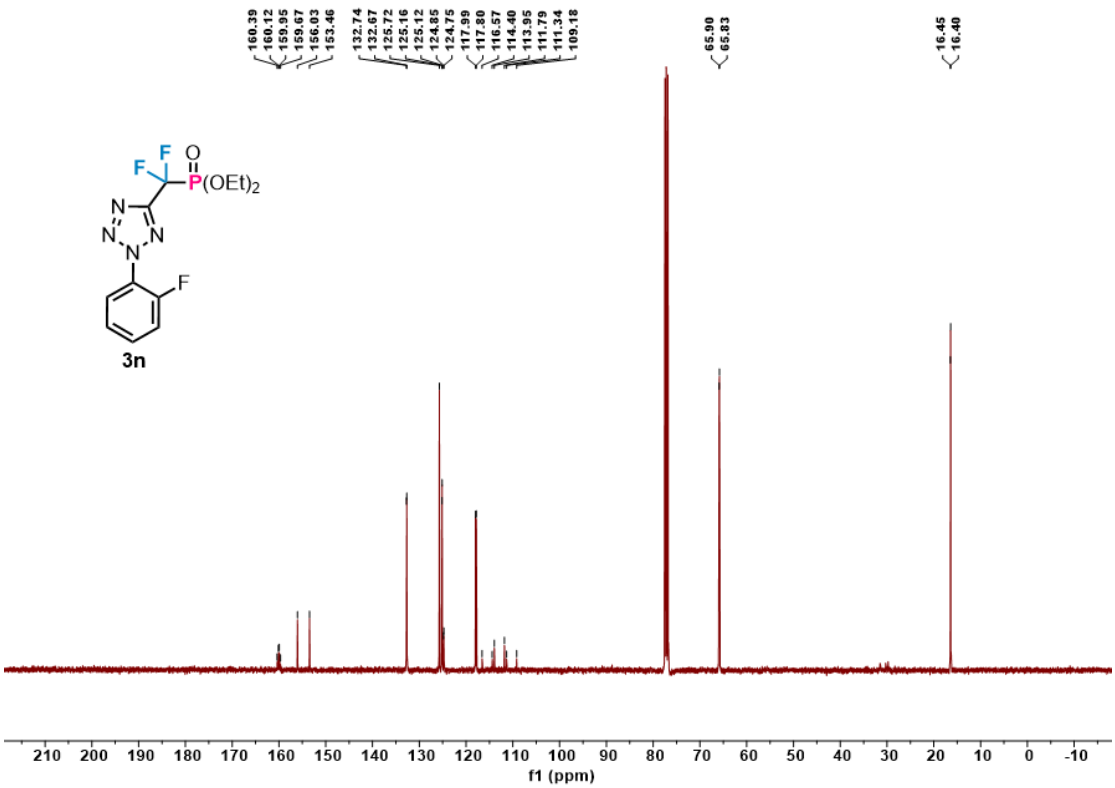
^{1}H-NMR of **3n** ($CDCl_3$, 400 M)



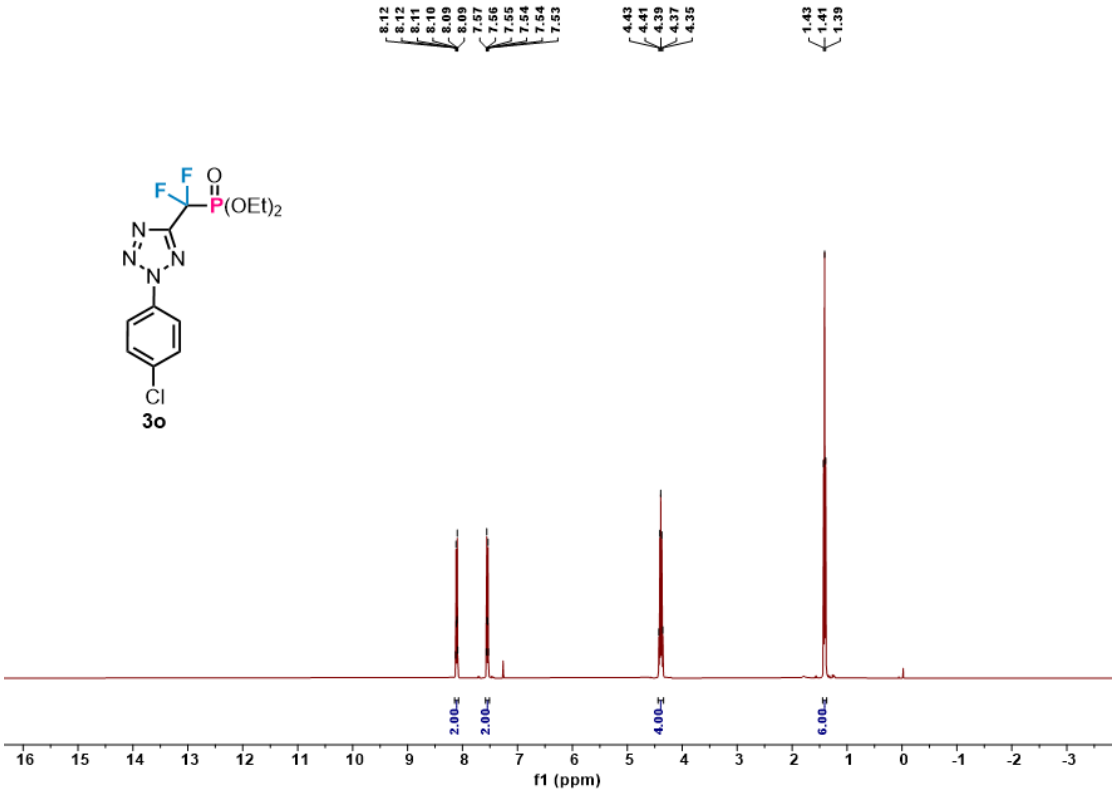
^{19}F-NMR of **3n** ($CDCl_3$, 376 M)



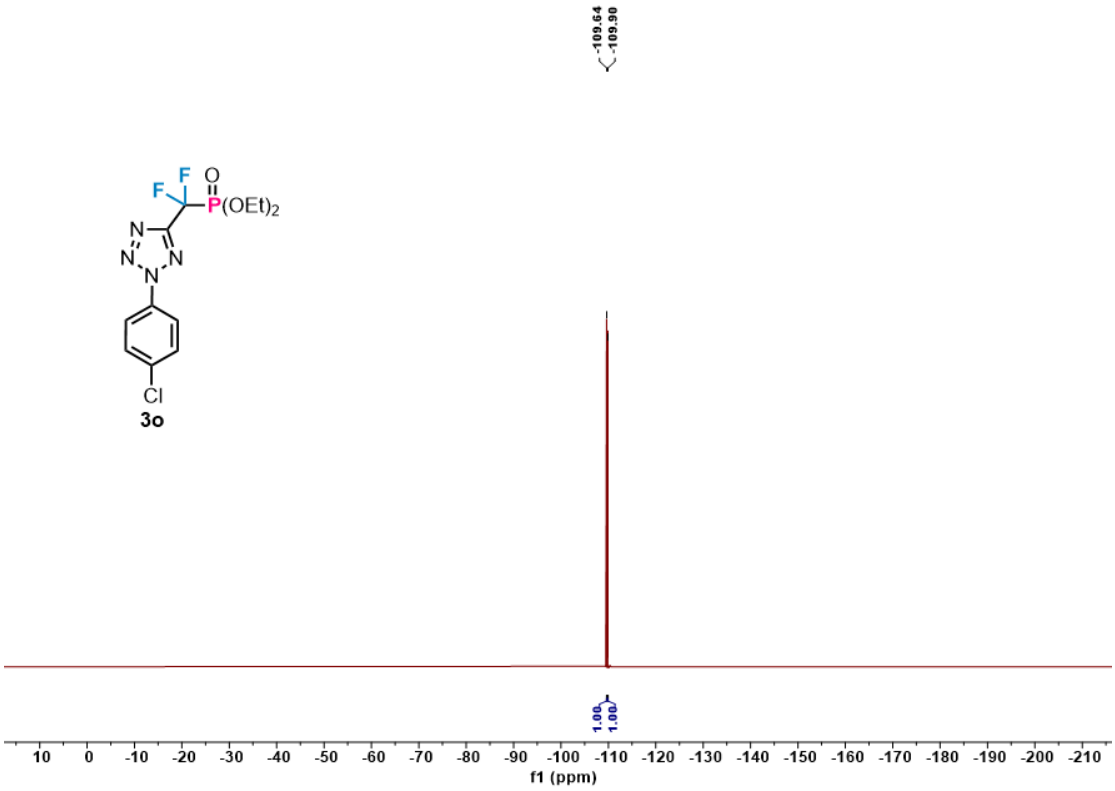
^{31}P-NMR of **3n** ($CDCl_3$, 162 M)



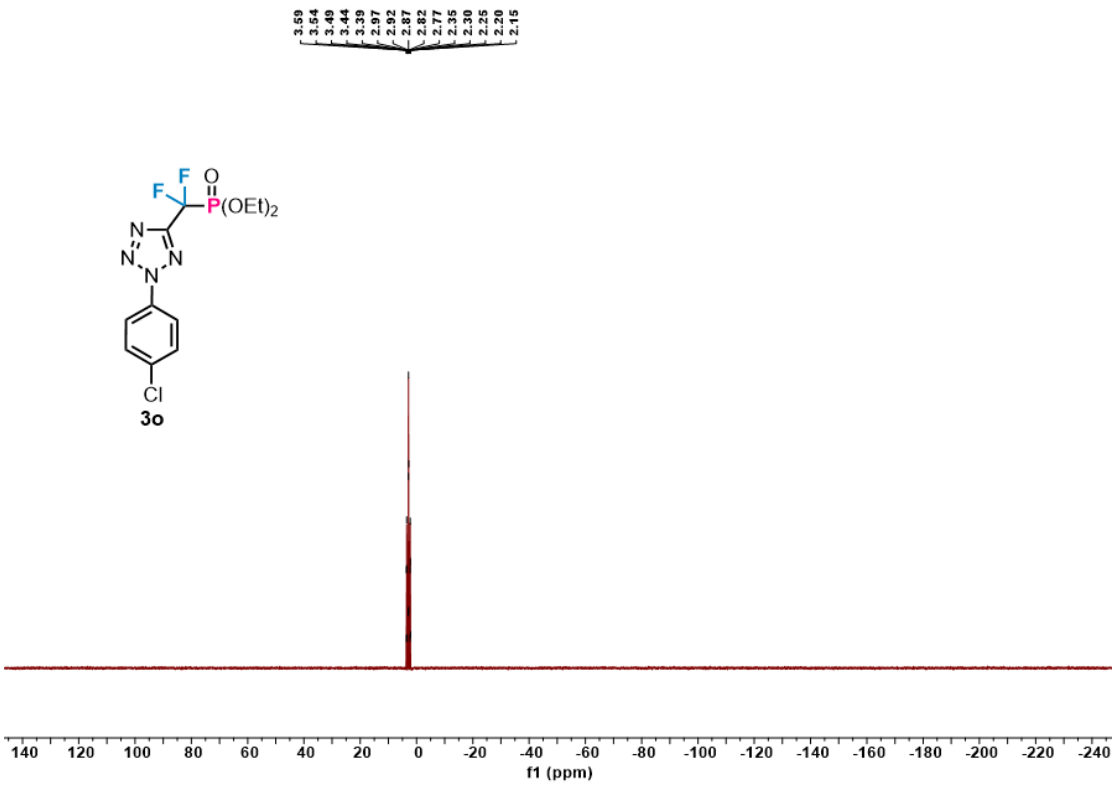
^{13}C-NMR of **3n** ($CDCl_3$, 101 M)



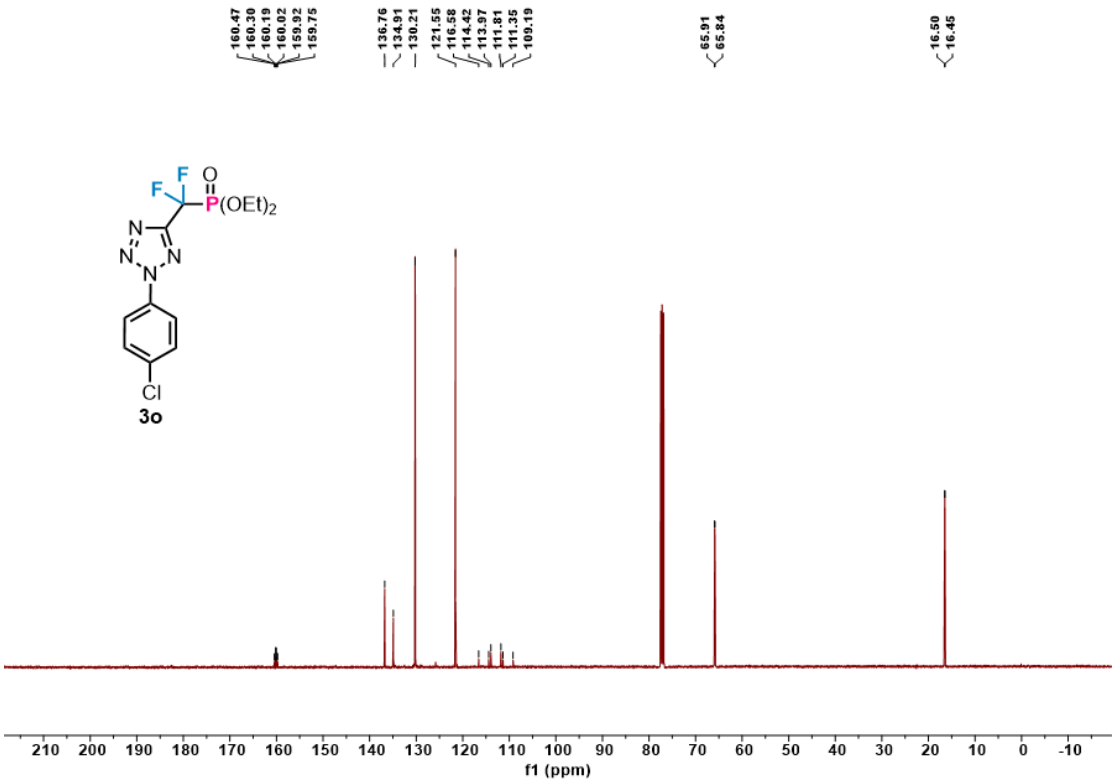
^{1}H-NMR of **3o** ($CDCl_3$, 400 M)



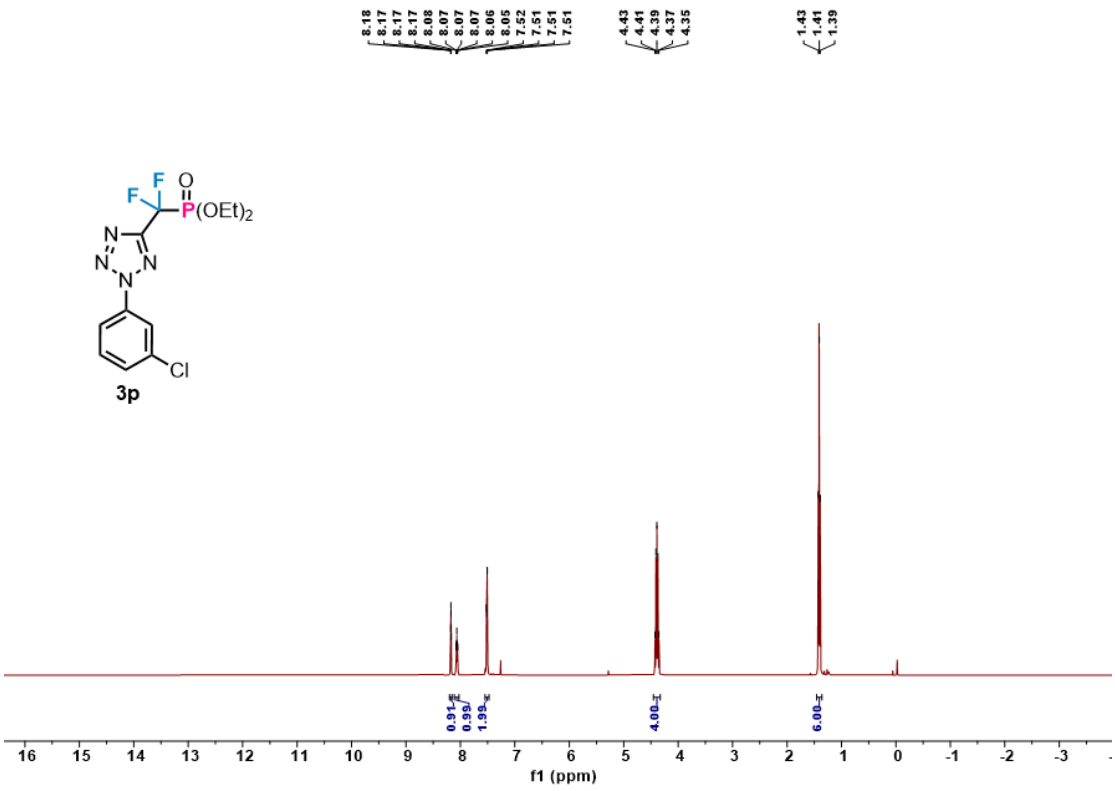
^{19}F-NMR of **3o** ($CDCl_3$, 376 M)



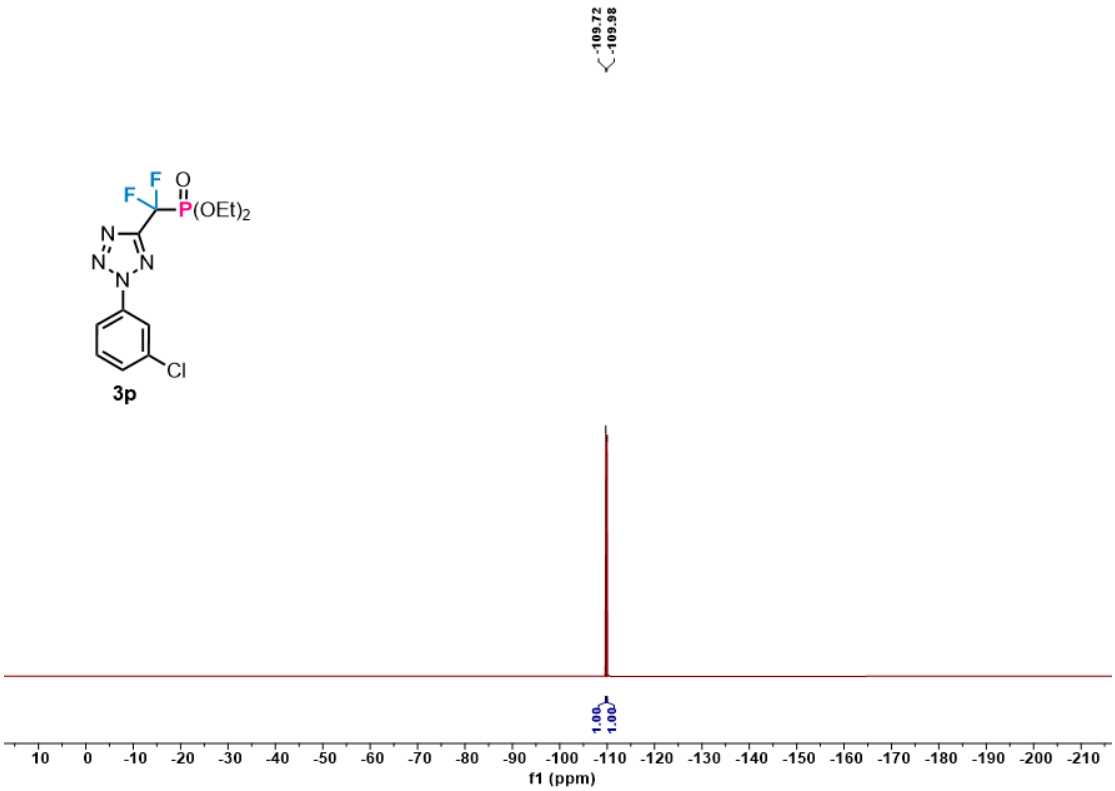
^{31}P-NMR of **3o** ($CDCl_3$, 162 M)



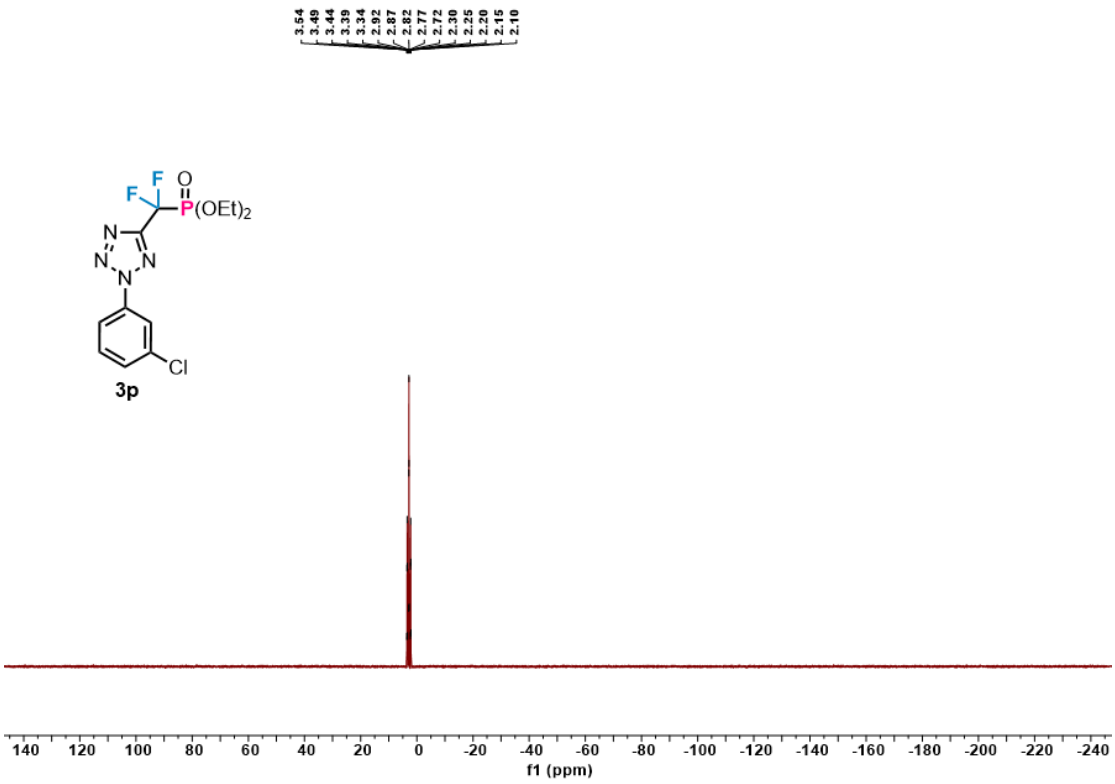
^{13}C-NMR of **3o** ($CDCl_3$, 101 M)



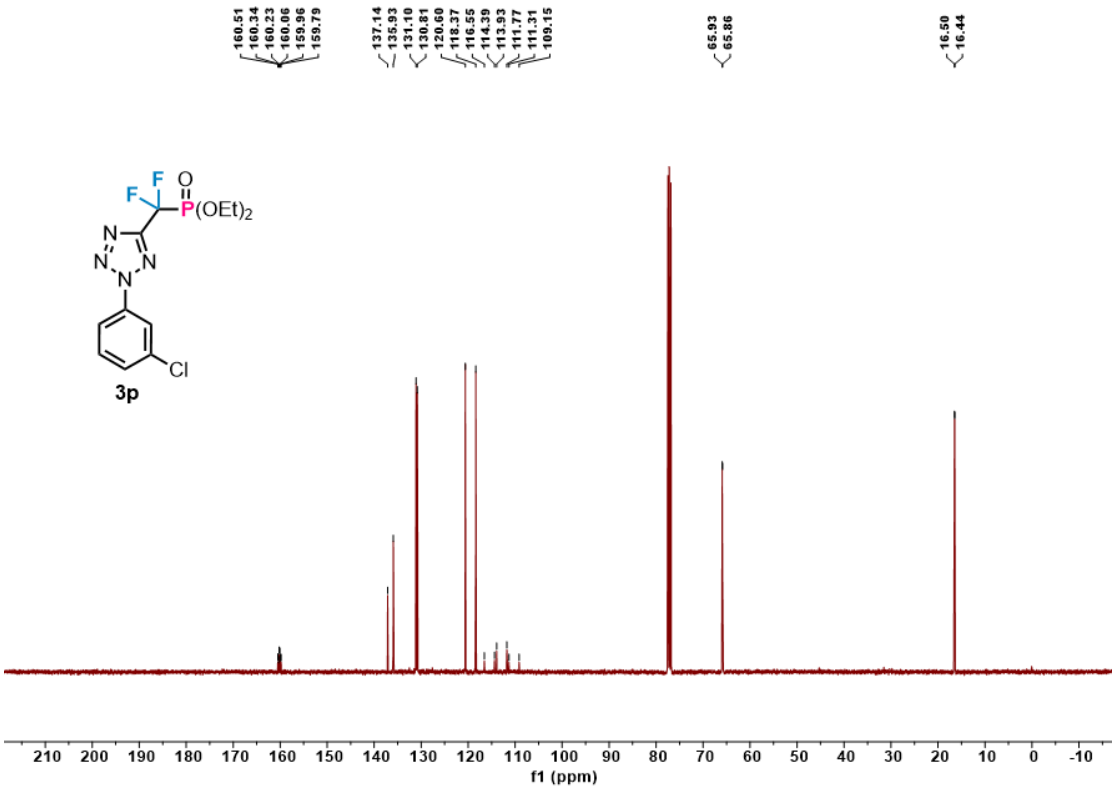
^{1}H-NMR of **3p** ($CDCl_3$, 400 M)



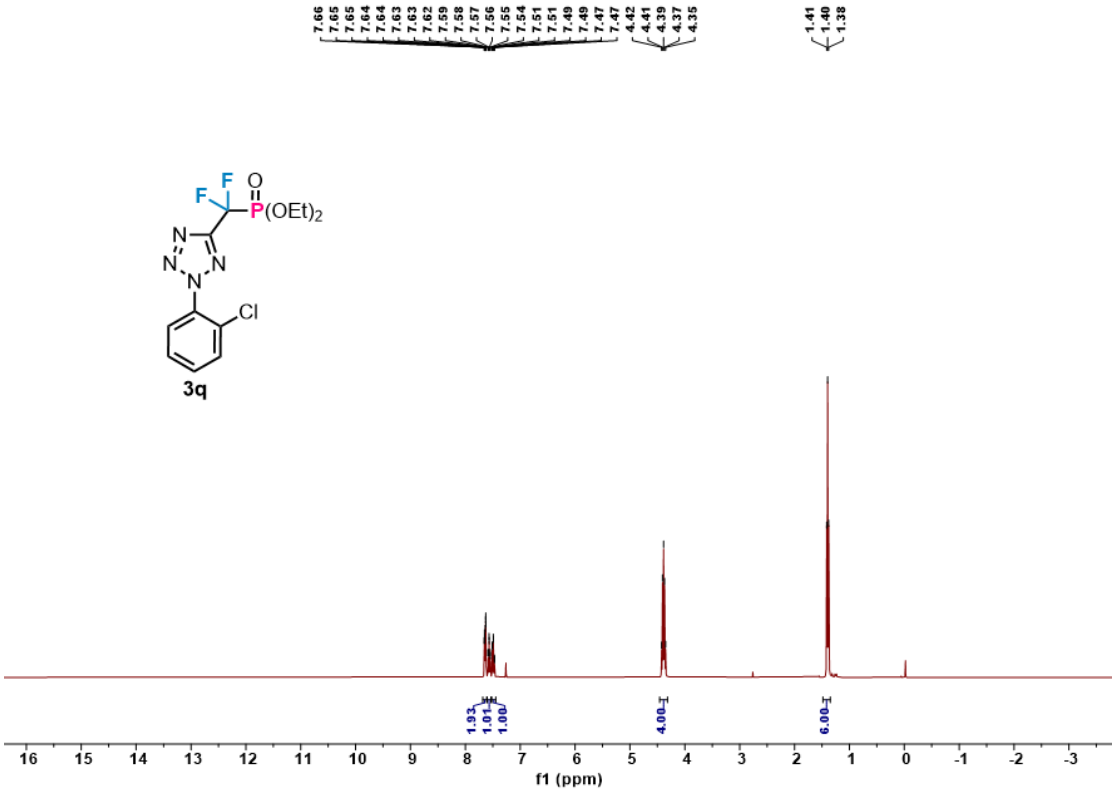
^{19}F-NMR of **3p** ($CDCl_3$, 376 M)



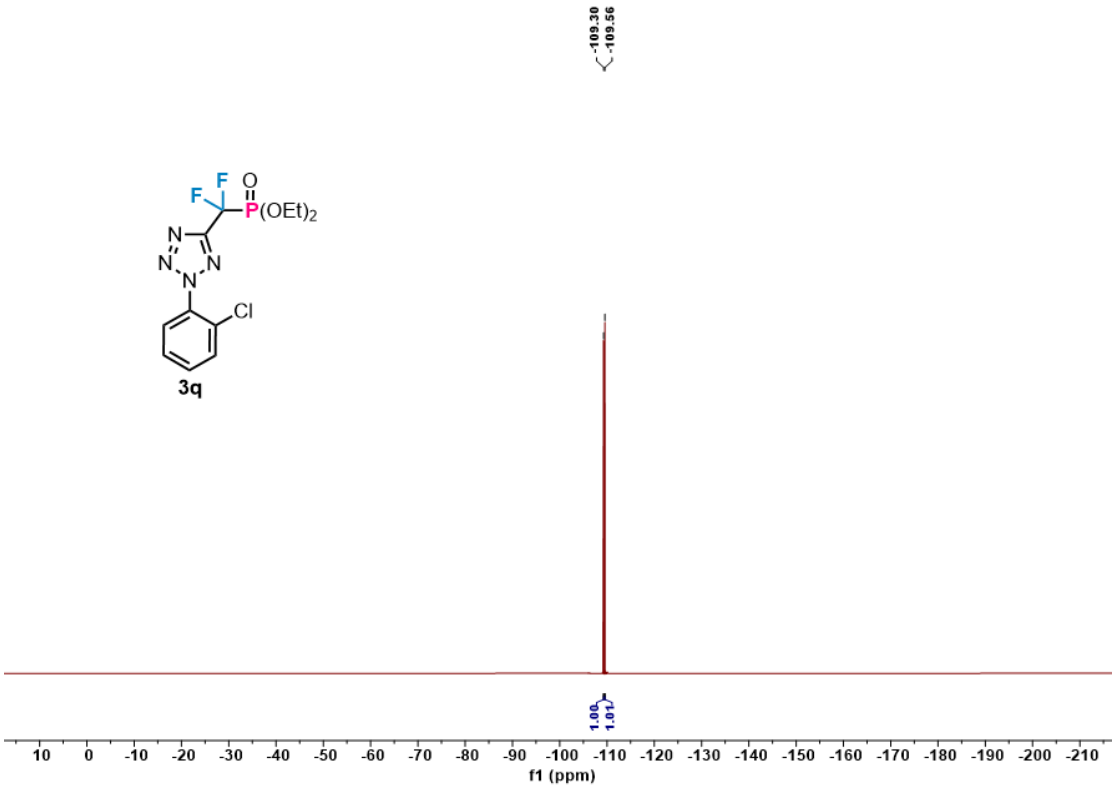
^{31}P-NMR of **3p** ($CDCl_3$, 162 M)



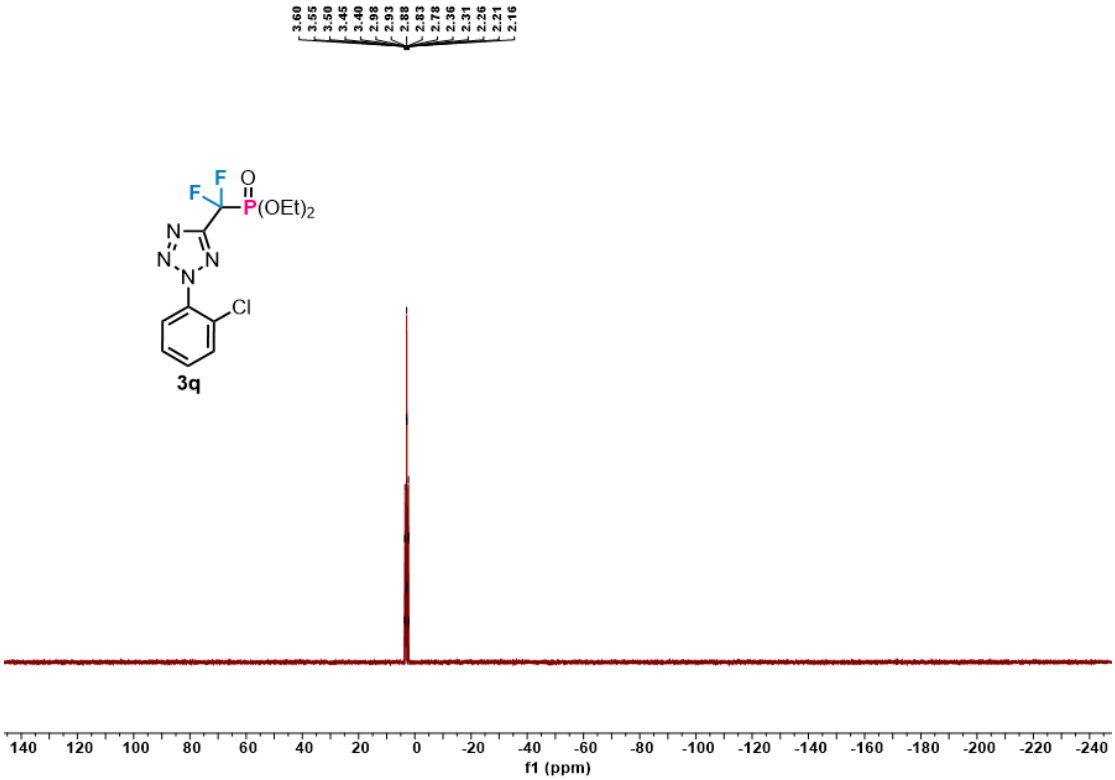
^{13}C-NMR of **3p** ($CDCl_3$, 101 M)



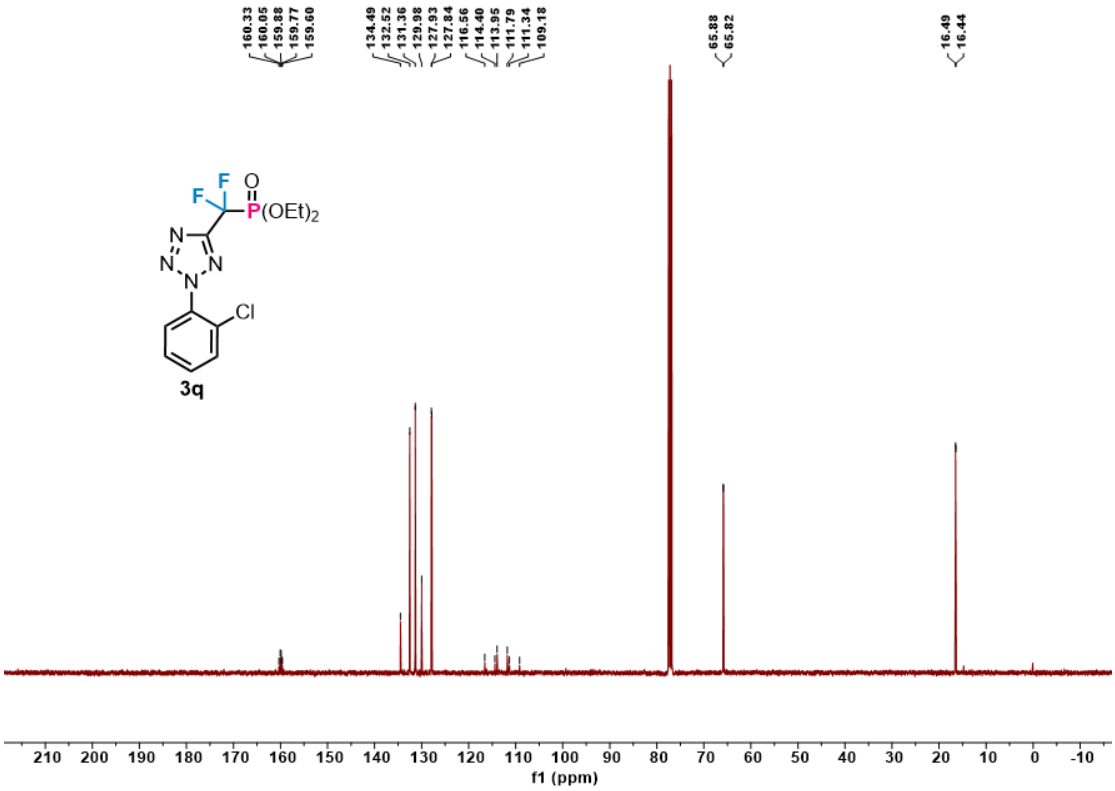
^{1}H-NMR of **3q** ($CDCl_3$, 400 M)



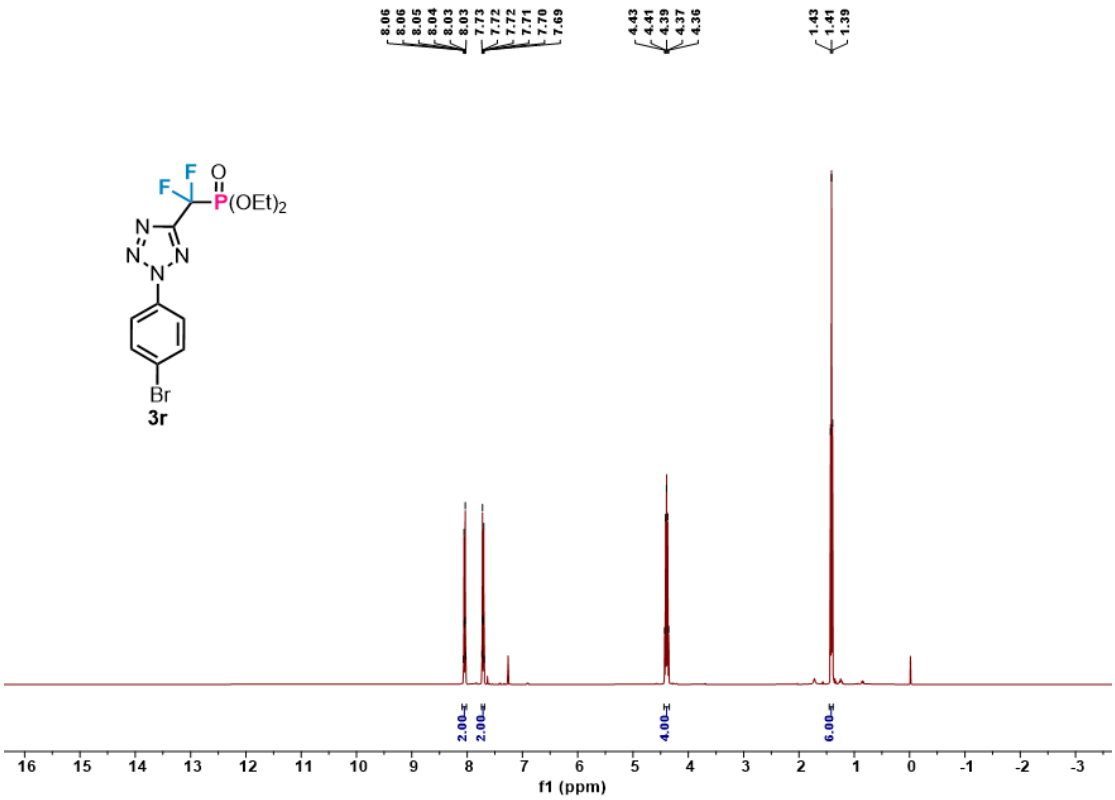
^{19}F-NMR of **3q** ($CDCl_3$, 376 M)



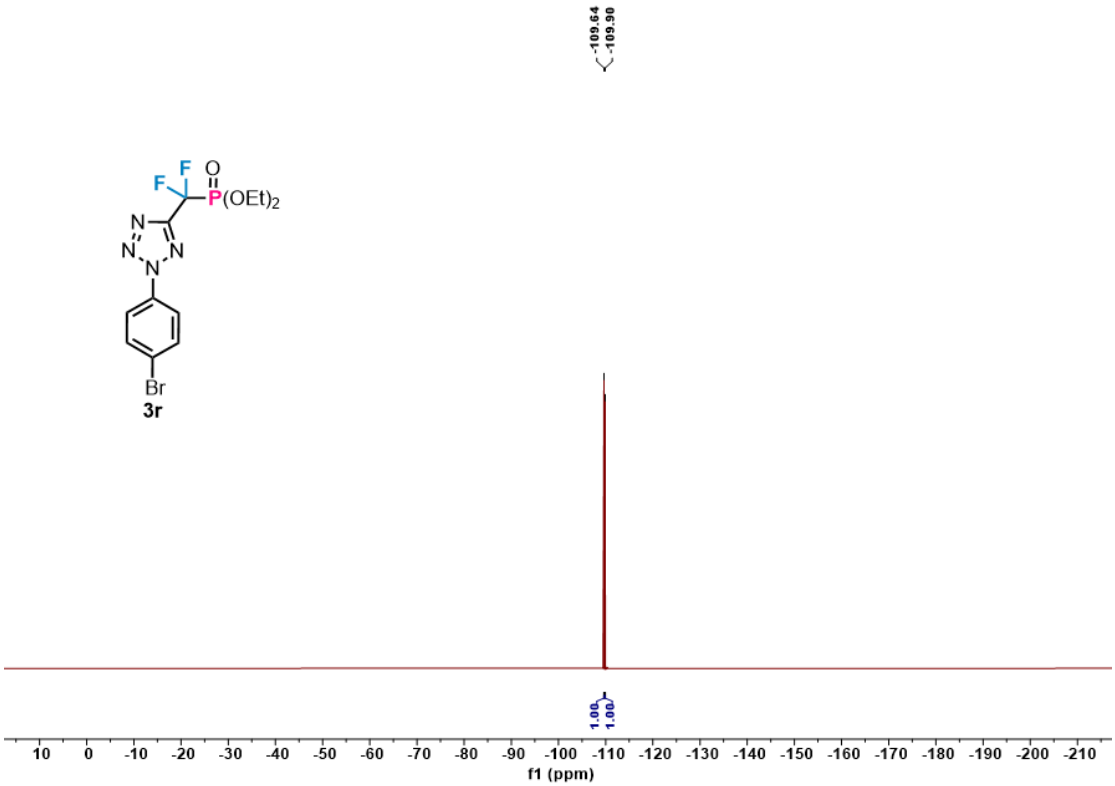
^{31}P-NMR of **3q** ($CDCl_3$, 162 M)



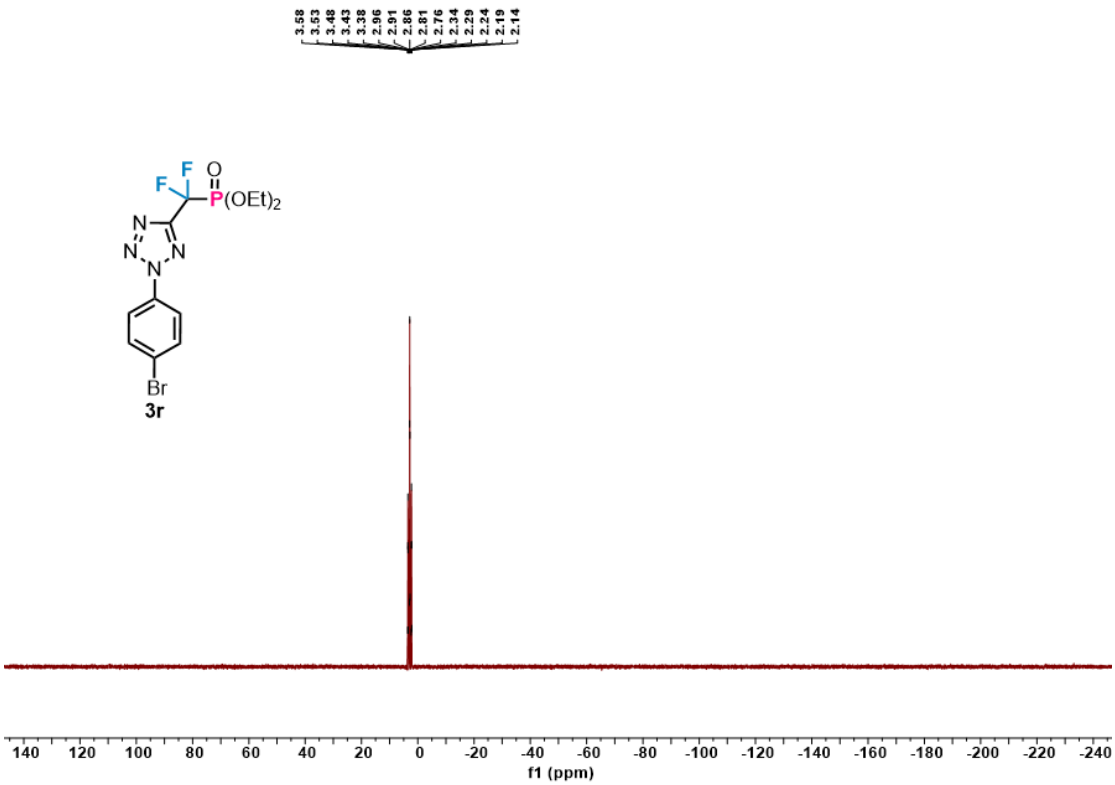
^{13}C-NMR of **3q** ($CDCl_3$, 101 M)



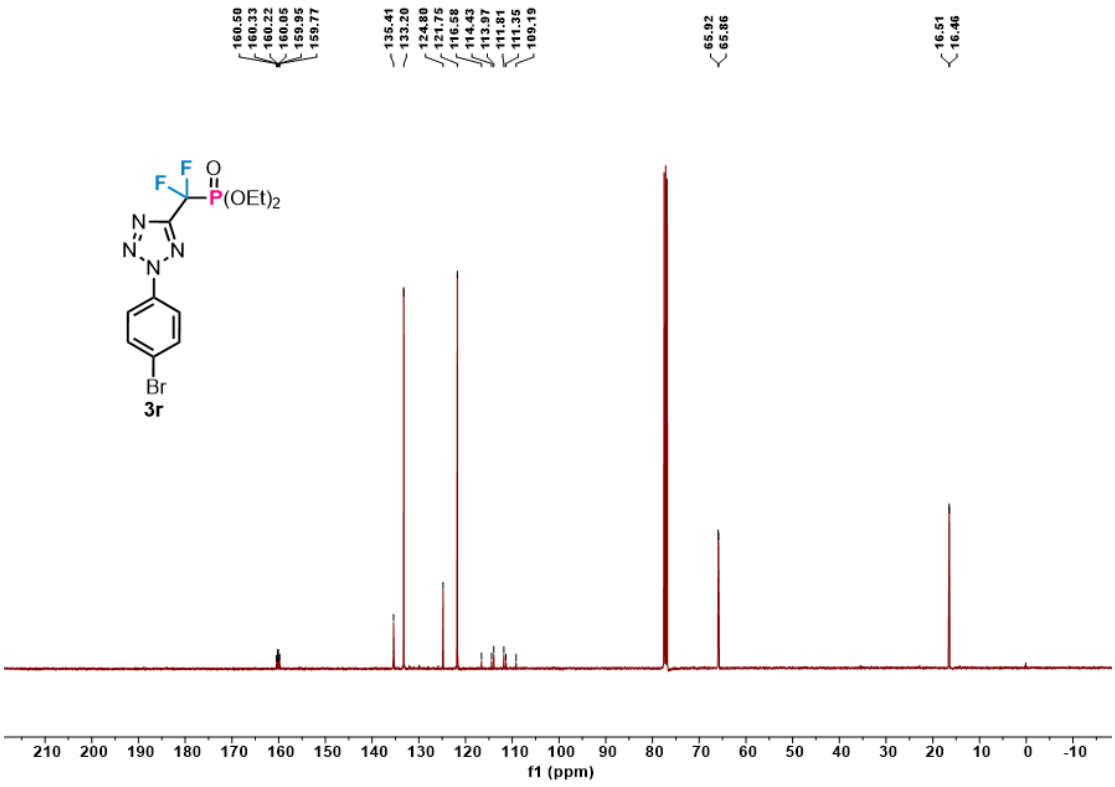
^{1}H-NMR of **3r** ($CDCl_3$, 400 M)



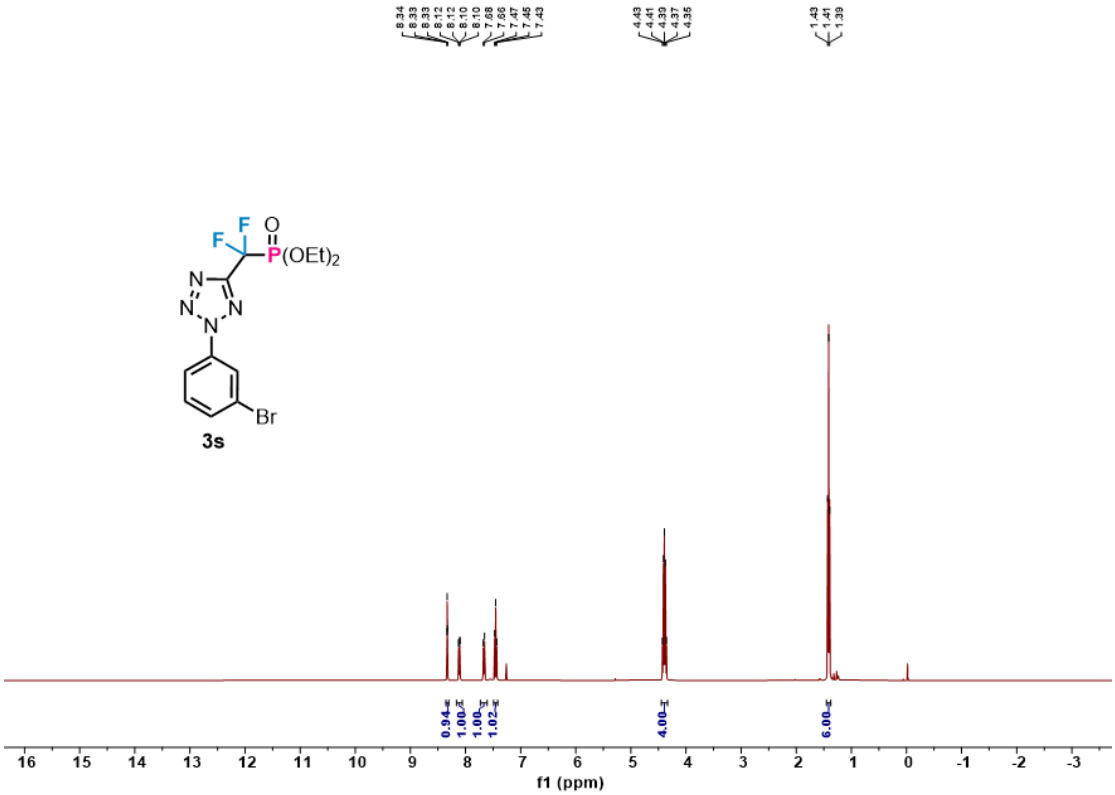
^{19}F-NMR of **3r** ($CDCl_3$, 376 M)



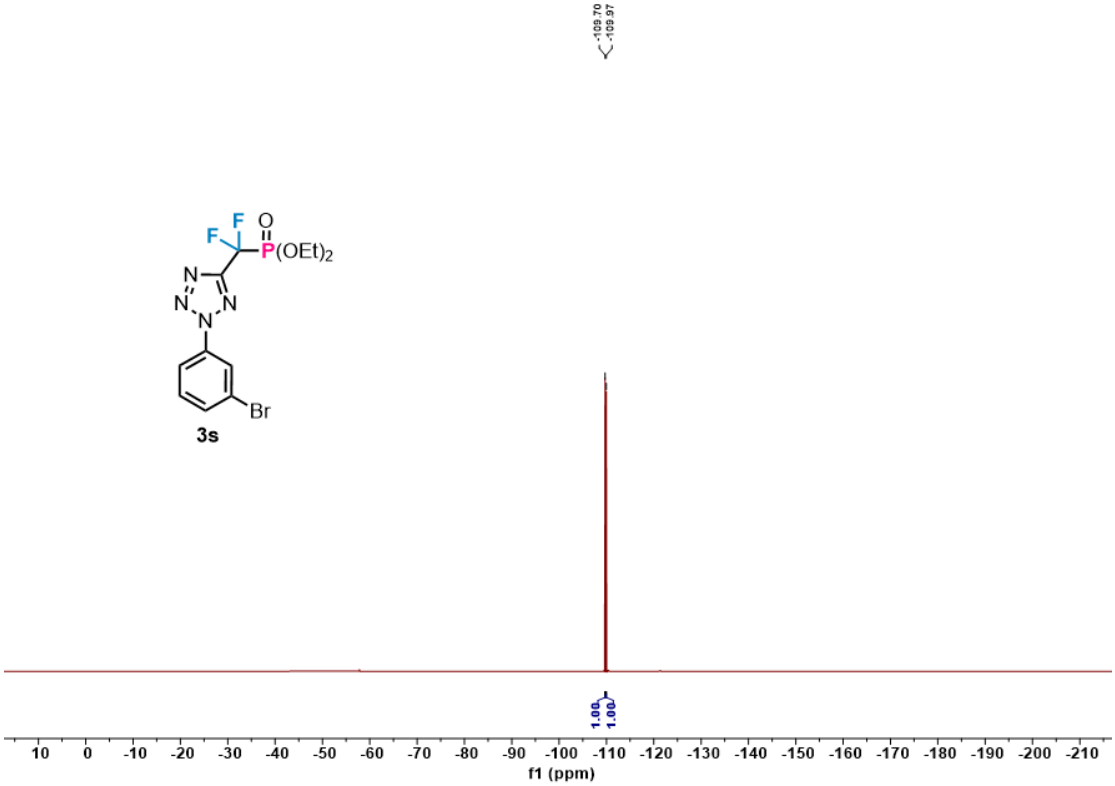
^{31}P-NMR of **3r** ($CDCl_3$, 162 M)



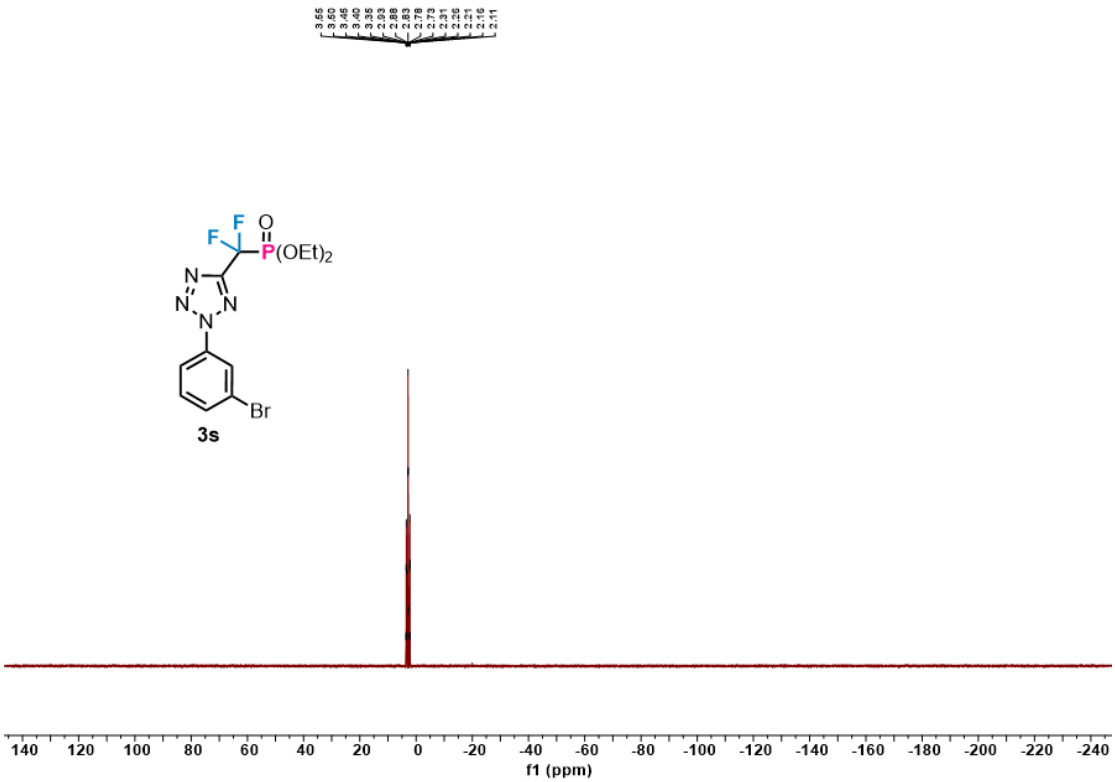
^{13}C-NMR of **3r** ($CDCl_3$, 101 M)



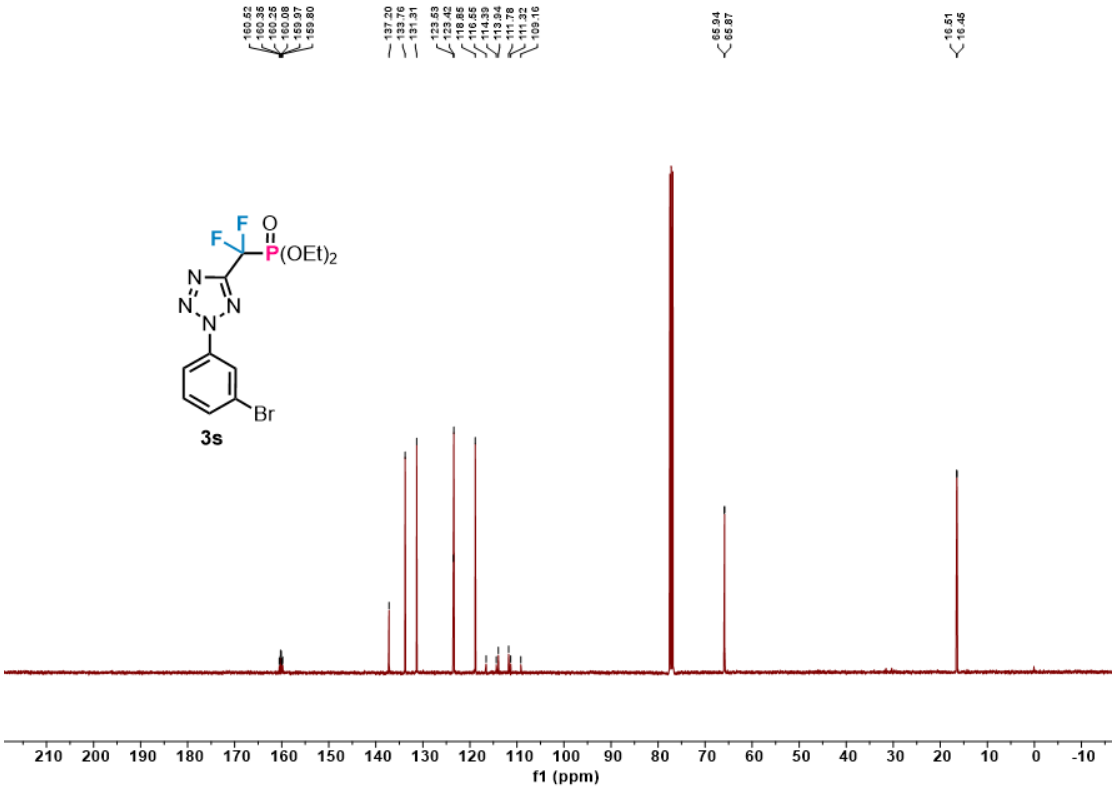
^{1}H-NMR of **3s** ($CDCl_3$, 400 M)



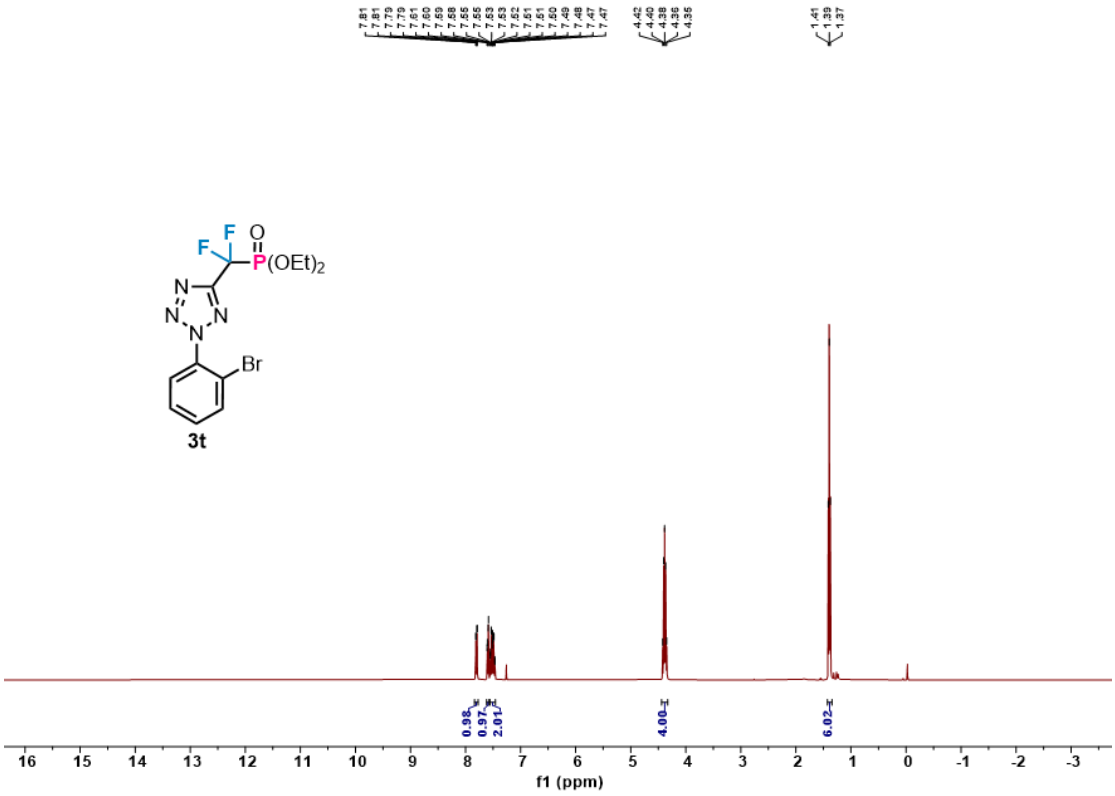
^{19}F-NMR of **3s** ($CDCl_3$, 376 M)



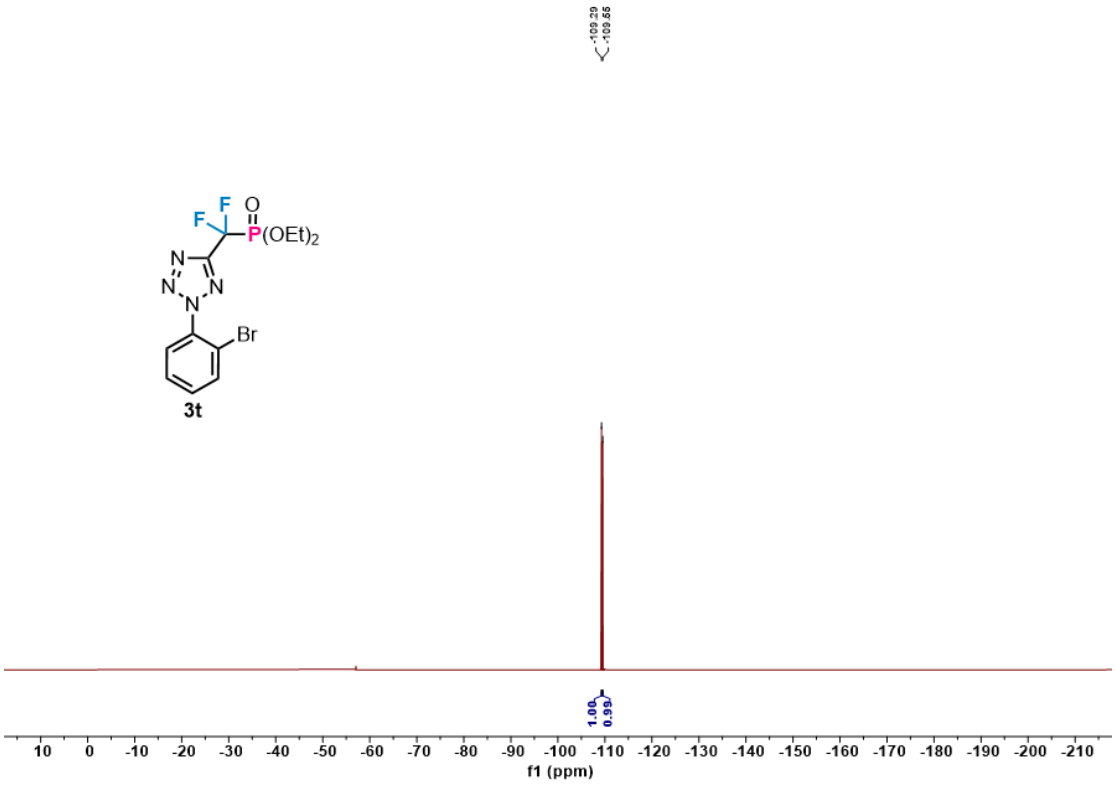
^{31}P-NMR of **3s** ($CDCl_3$, 162 M)



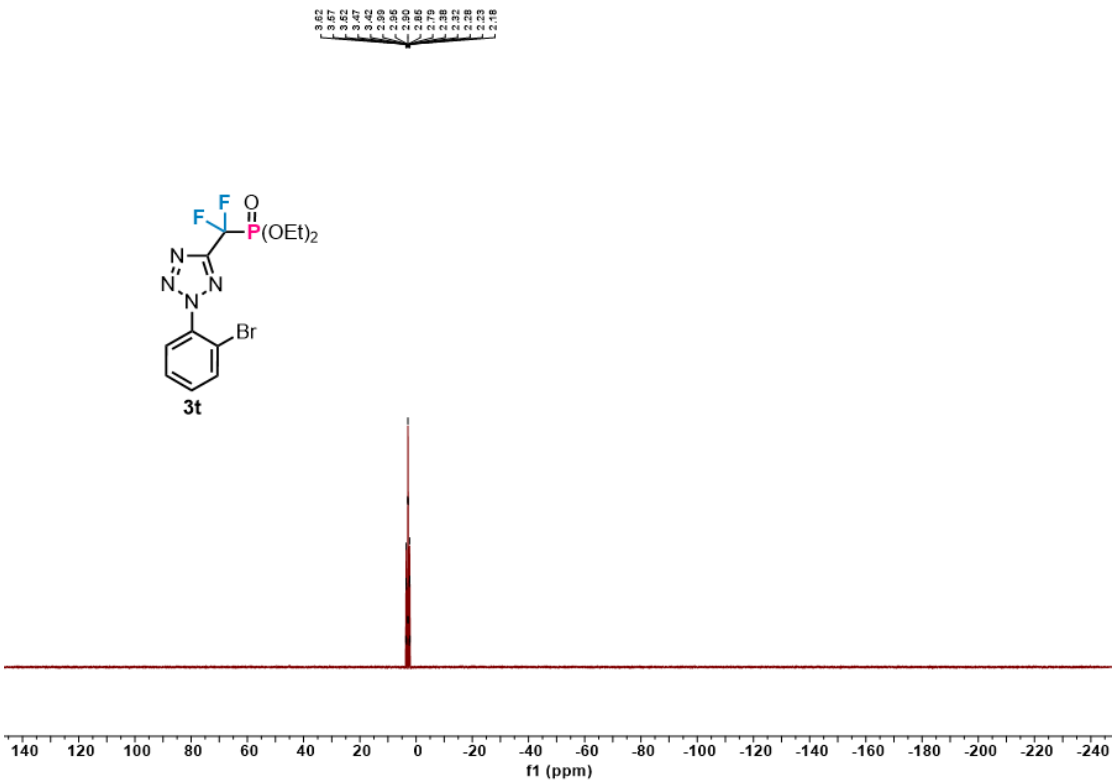
^{13}C-NMR of **3s** ($CDCl_3$, 101 M)



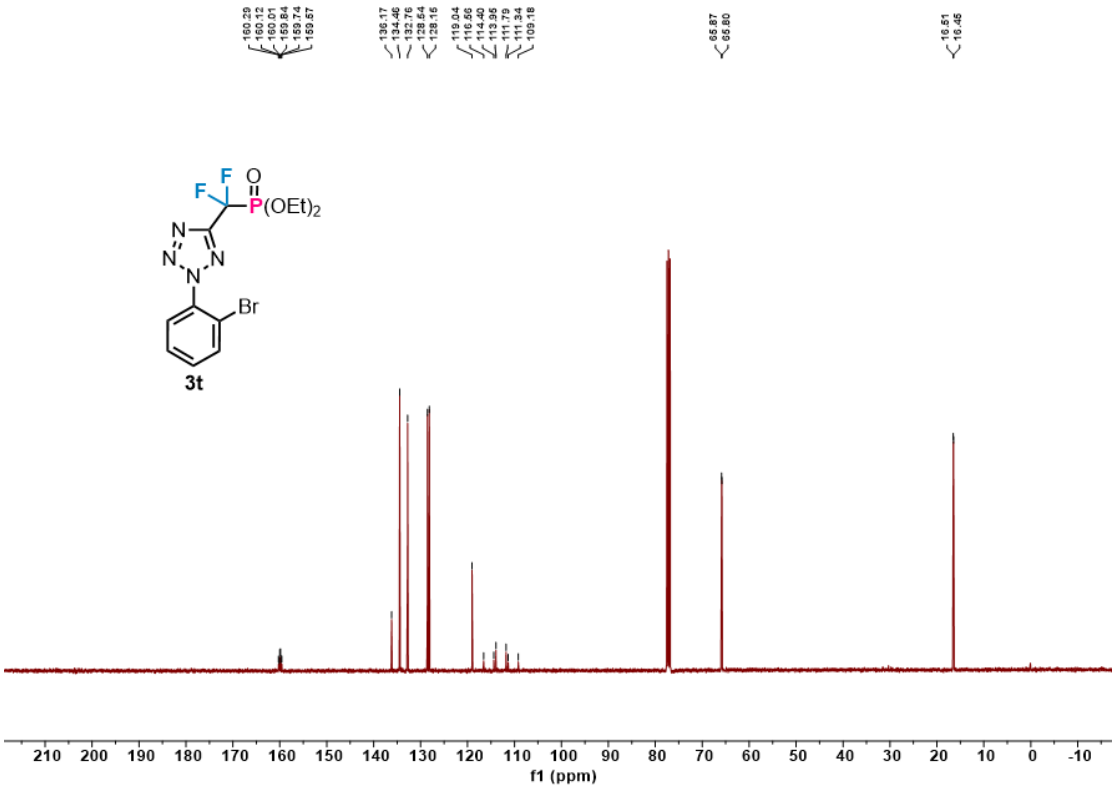
^{1}H-NMR of **3t** ($CDCl_3$, 400 M)



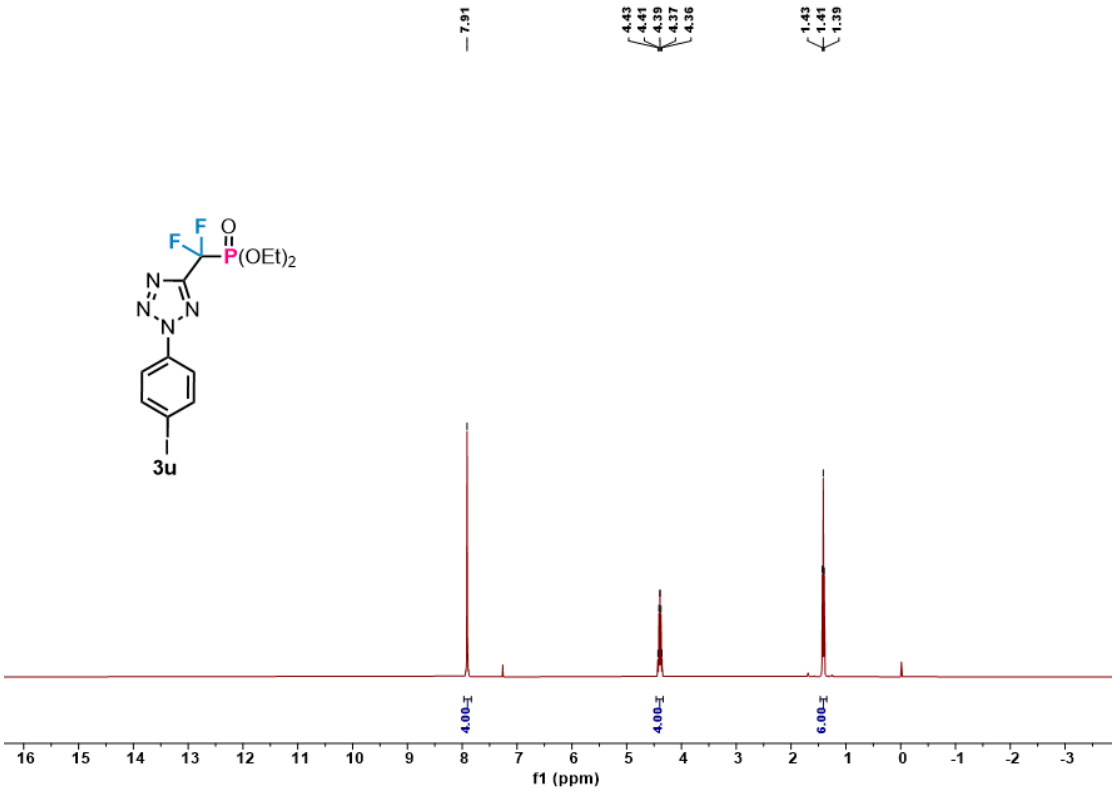
^{19}F-NMR of **3t** ($CDCl_3$, 376 M)



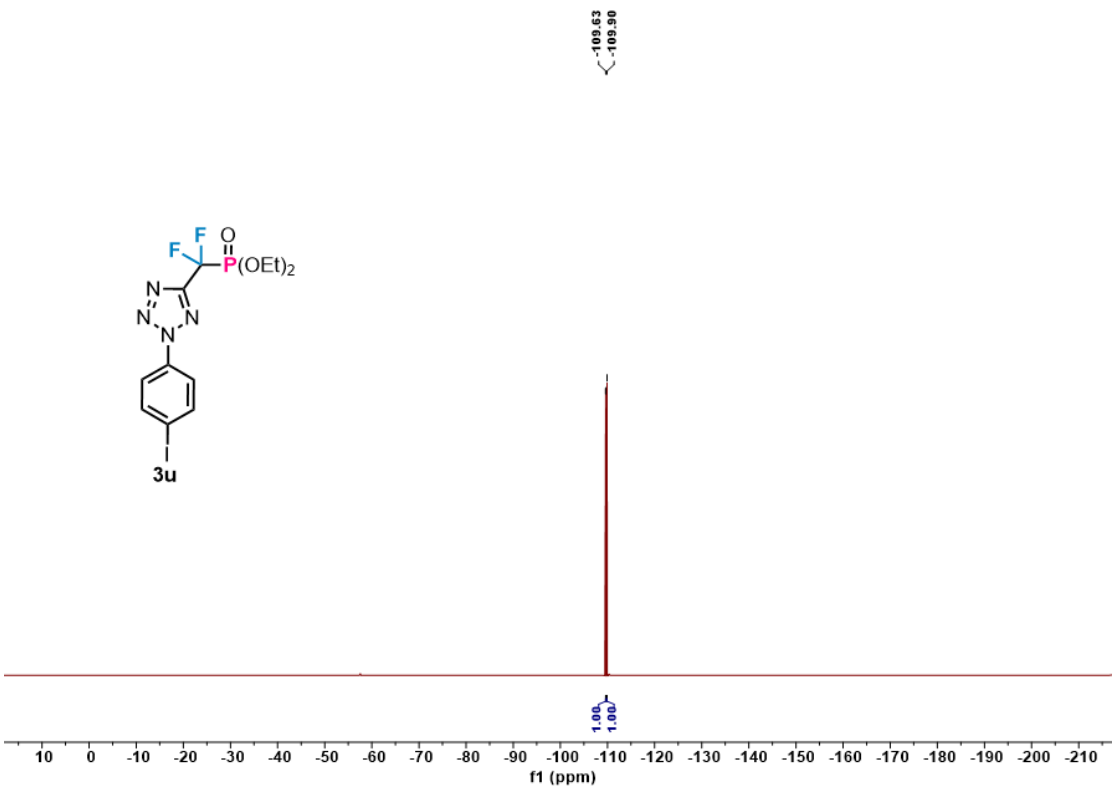
^{31}P-NMR of **3t** ($CDCl_3$, 162 M)



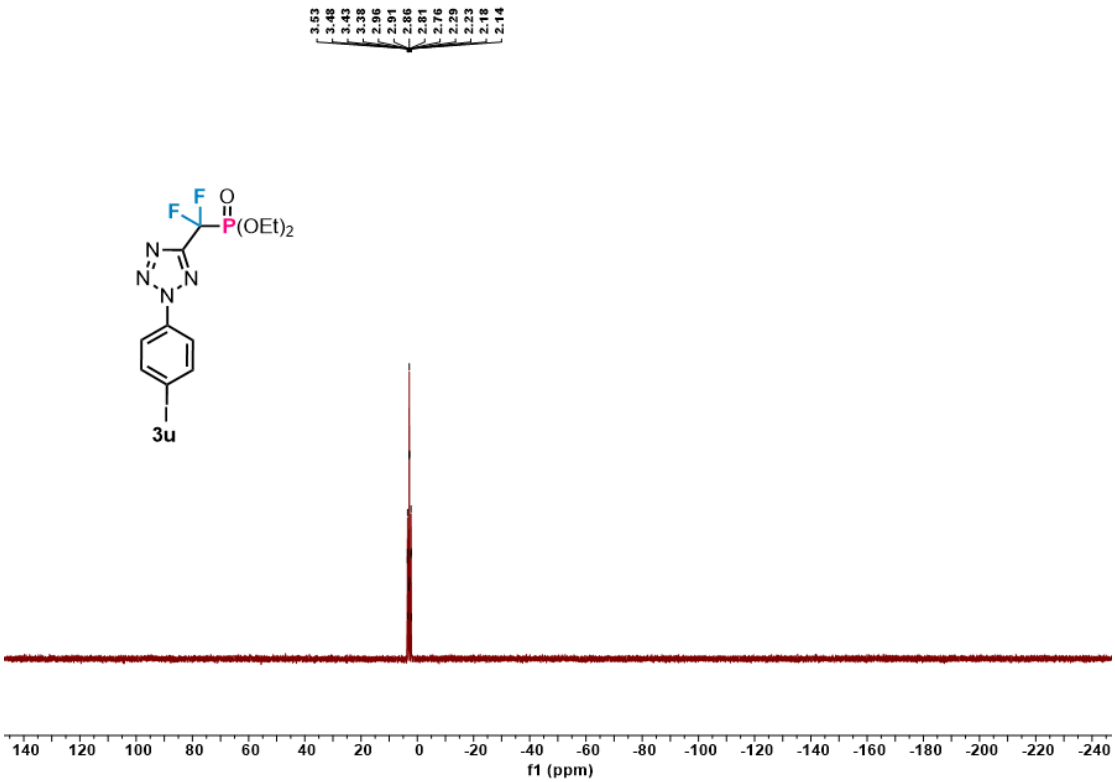
^{13}C-NMR of **3t** ($CDCl_3$, 101 M)



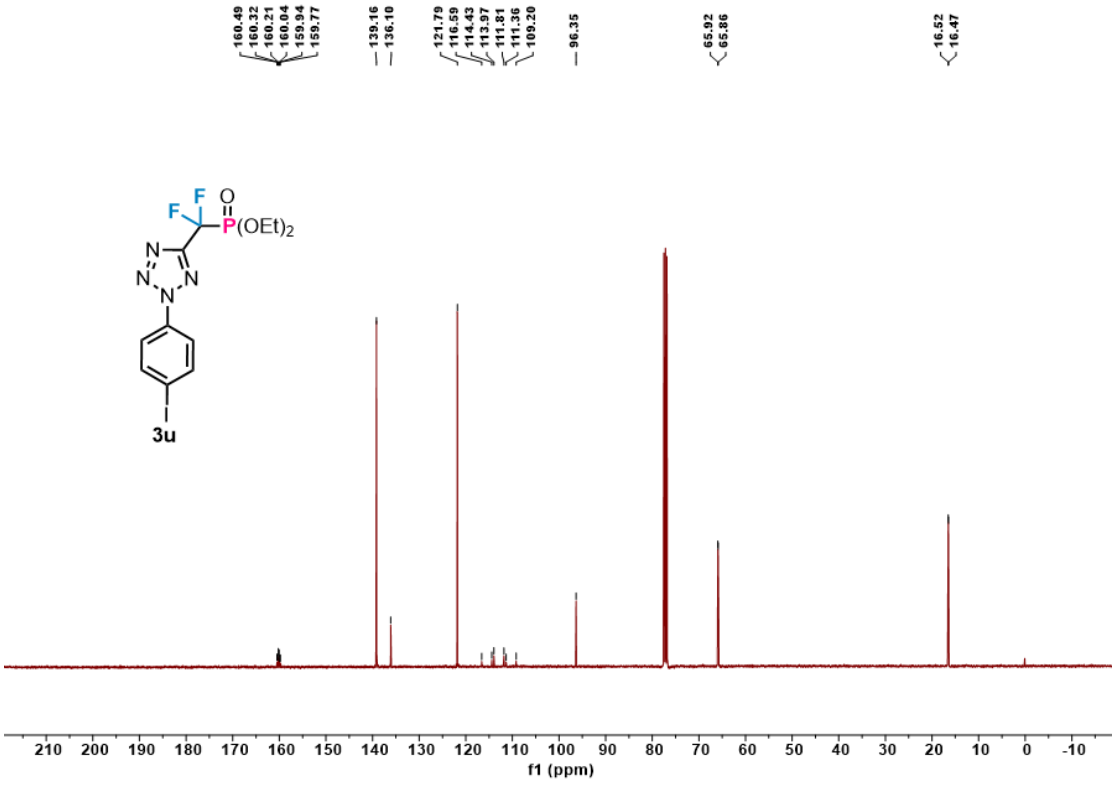
^{1}H-NMR of **3u** ($CDCl_3$, 400 M)



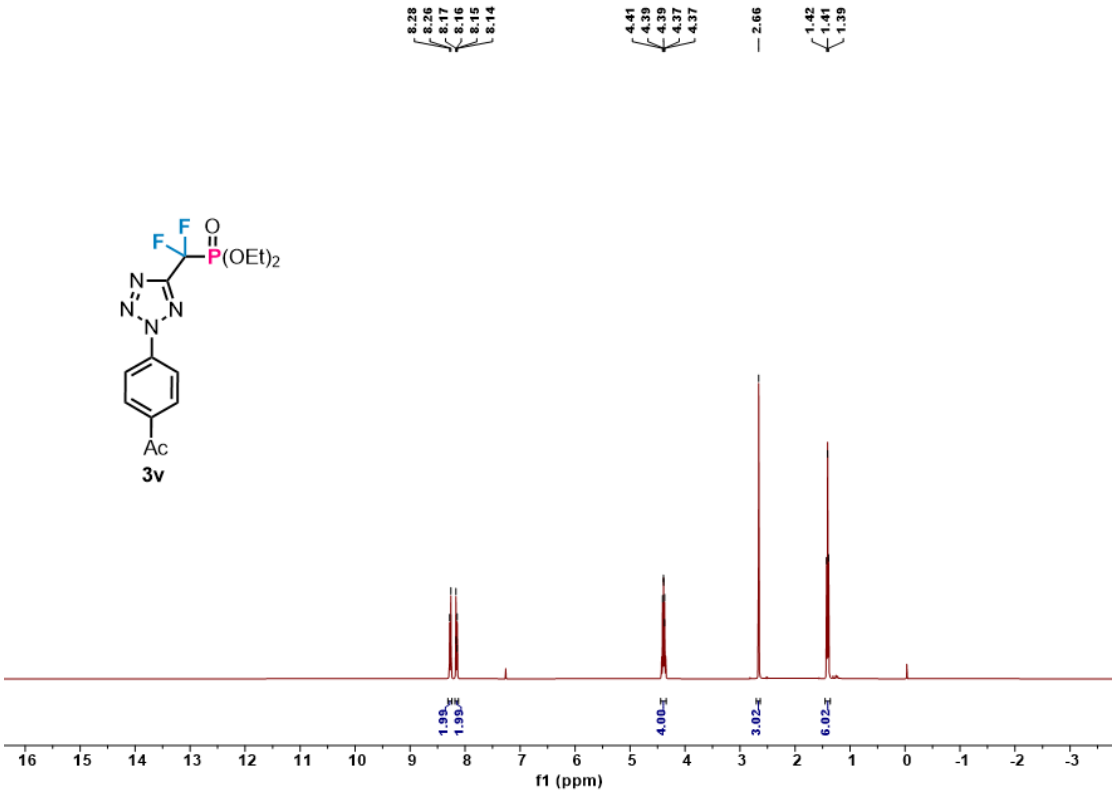
^{19}F-NMR of **3u** ($CDCl_3$, 376 M)



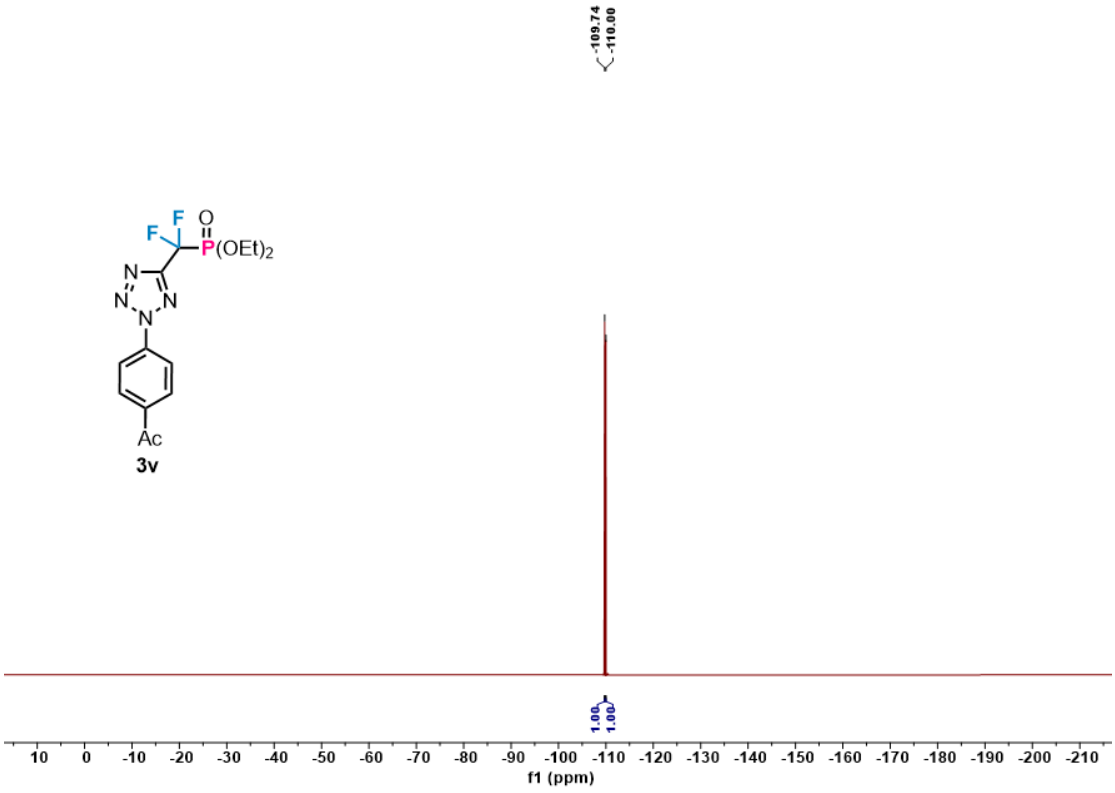
^{31}P-NMR of **3u** ($CDCl_3$, 162 M)



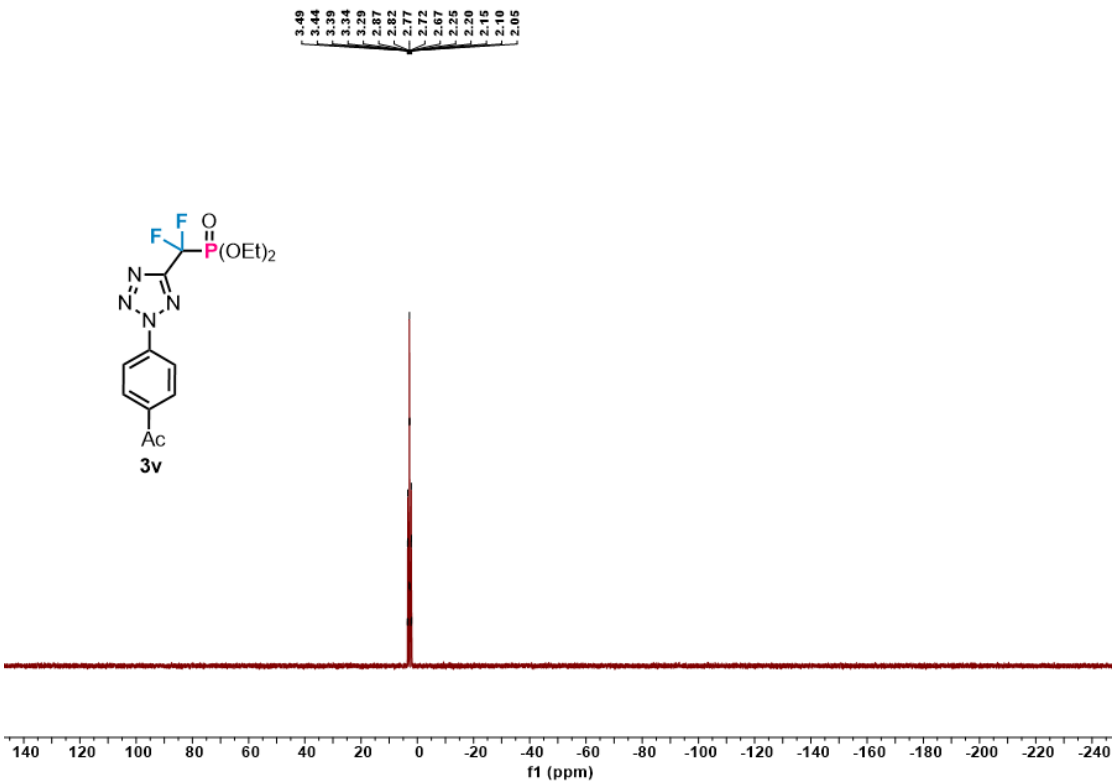
^{13}C-NMR of **3u** ($CDCl_3$, 101 M)



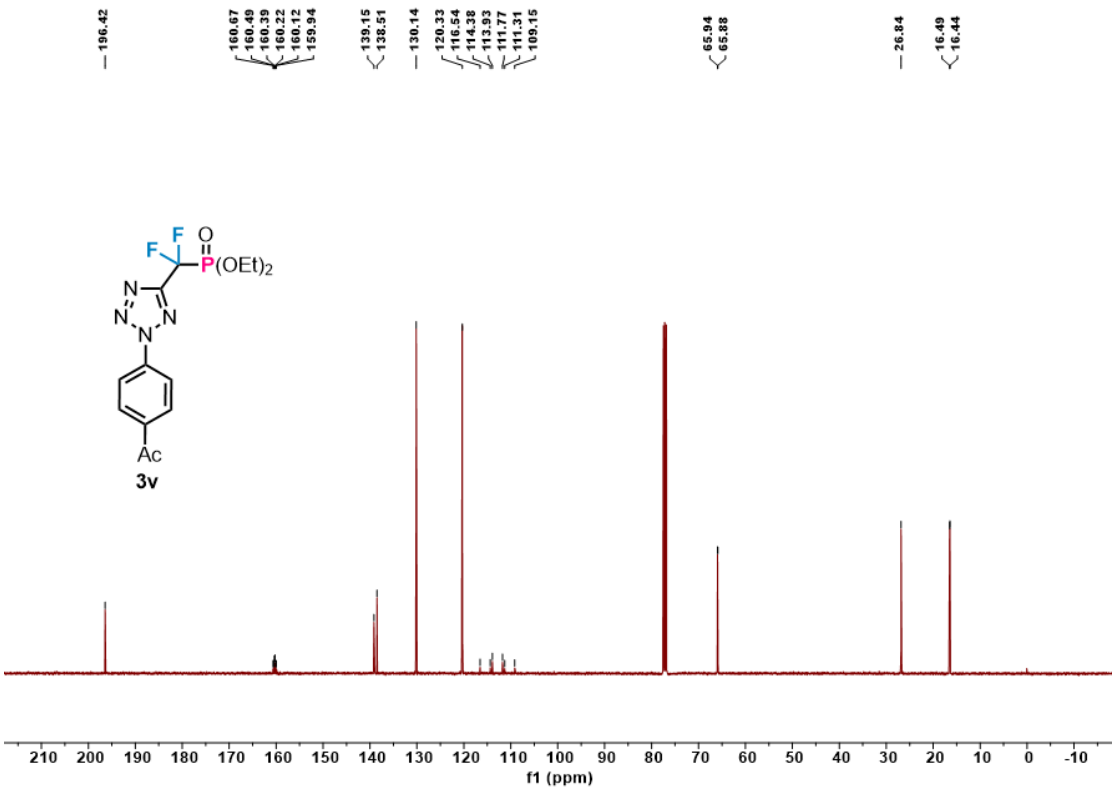
^{1}H-NMR of **3v** ($CDCl_3$, 400 M)



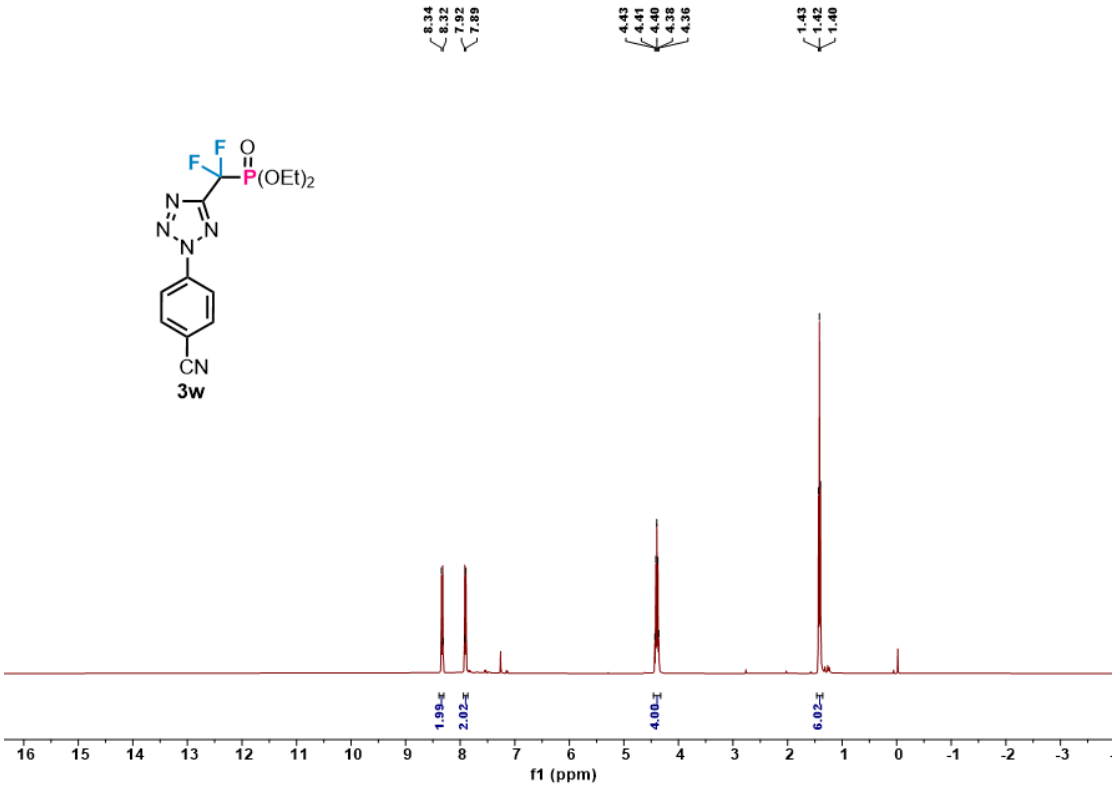
^{19}F-NMR of **3v** ($CDCl_3$, 376 M)



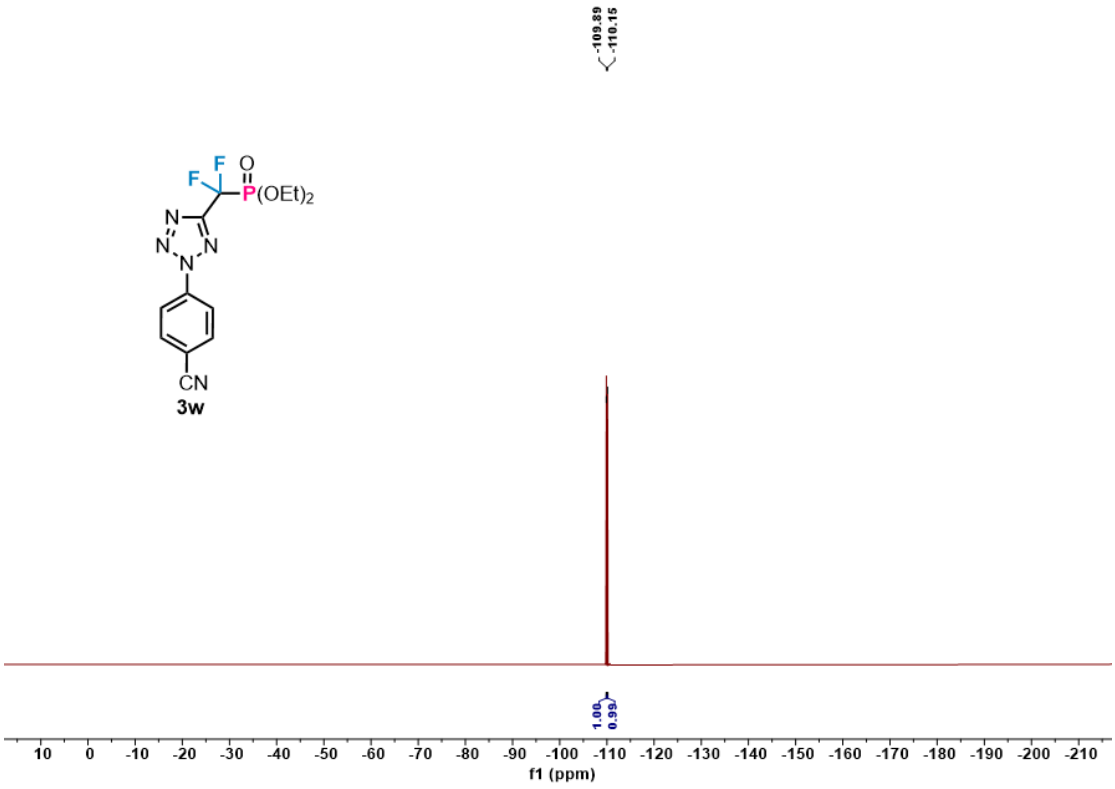
^{31}P-NMR of **3v** ($CDCl_3$, 162 M)



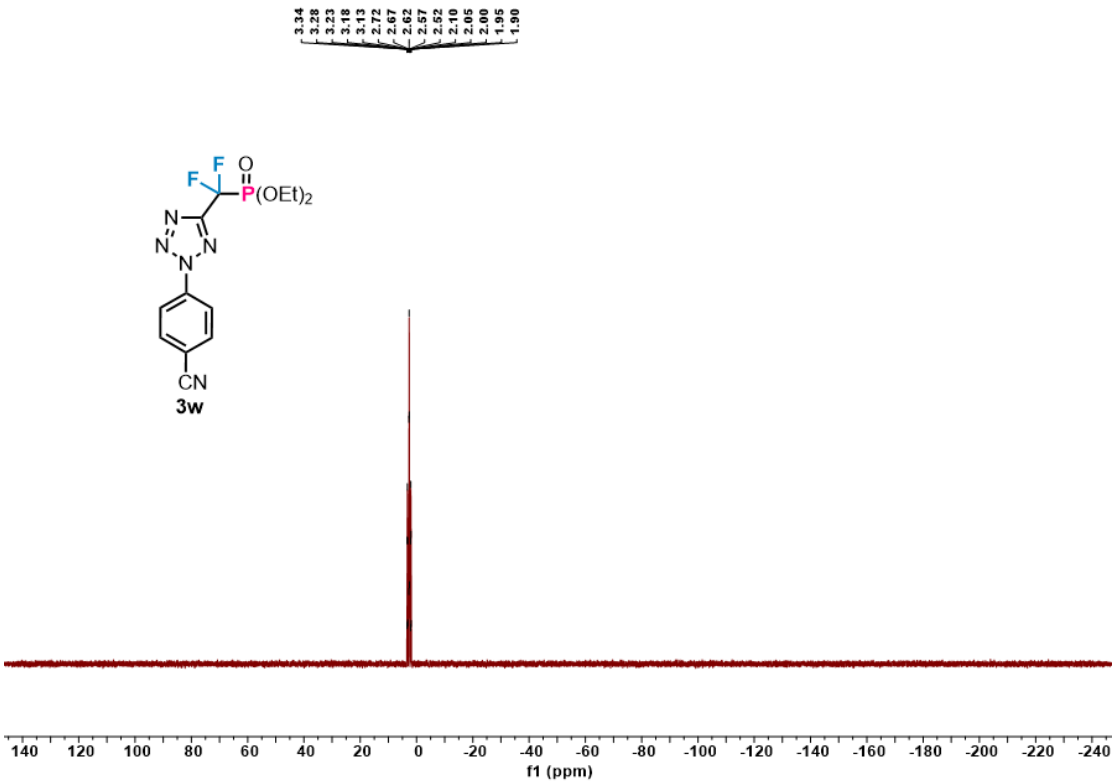
^{13}C-NMR of **3v** ($CDCl_3$, 101 M)



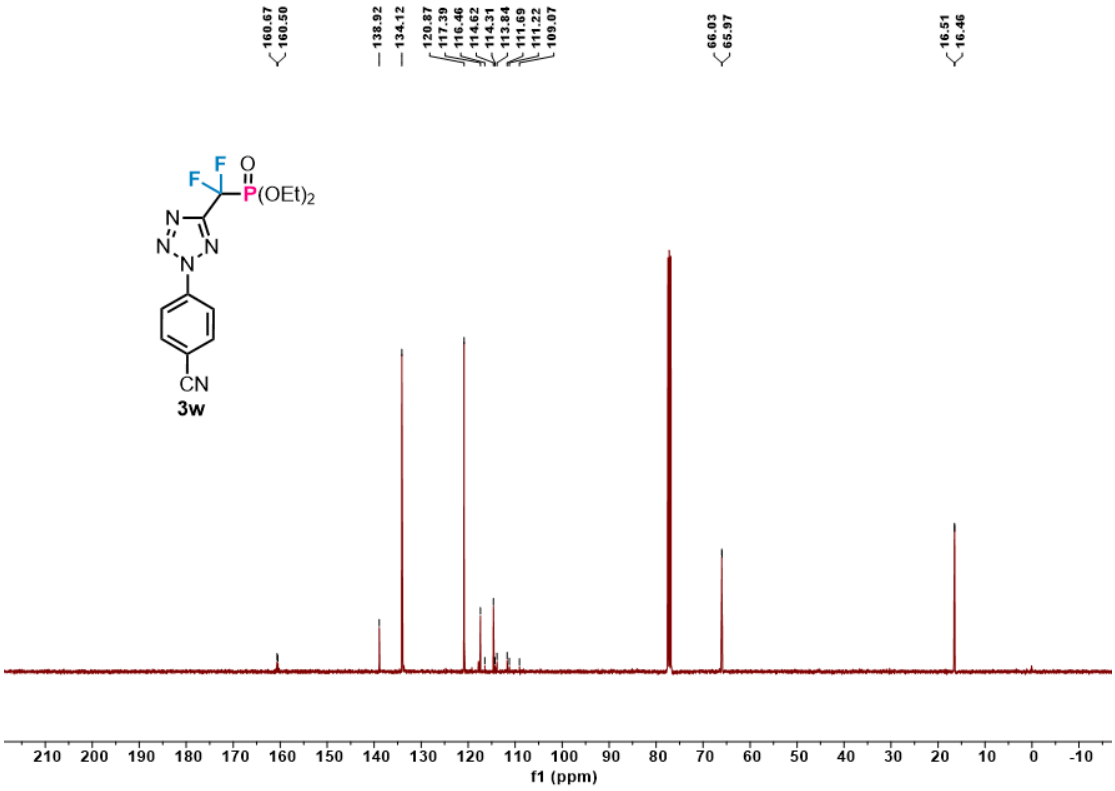
^{1}H-NMR of **3w** ($CDCl_3$, 400 M)



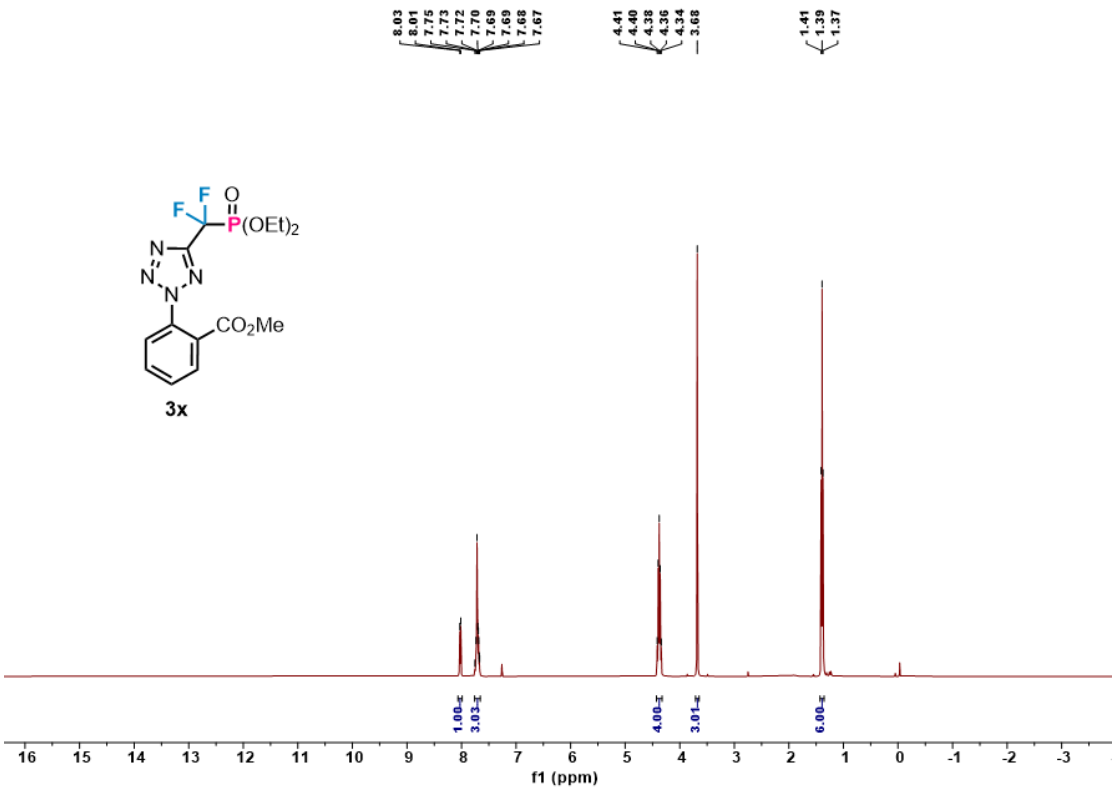
^{19}F-NMR of **3w** ($CDCl_3$, 376 M)



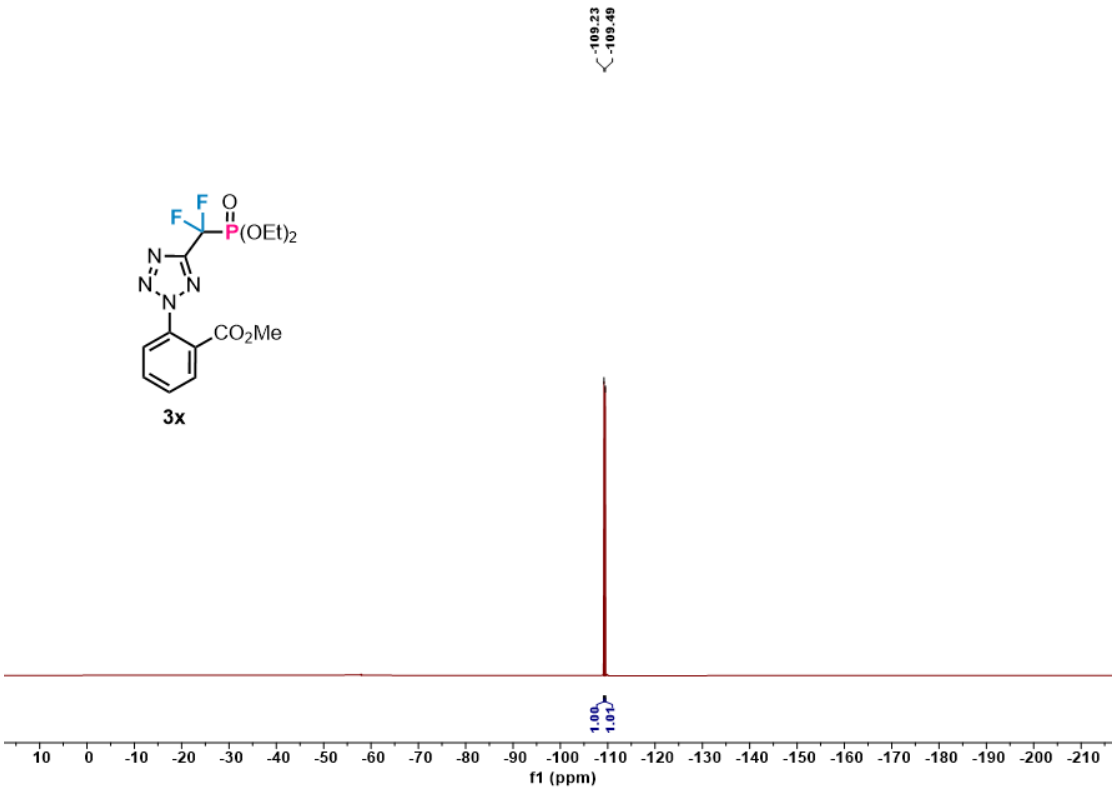
^{31}P-NMR of **3w** ($CDCl_3$, 162 M)



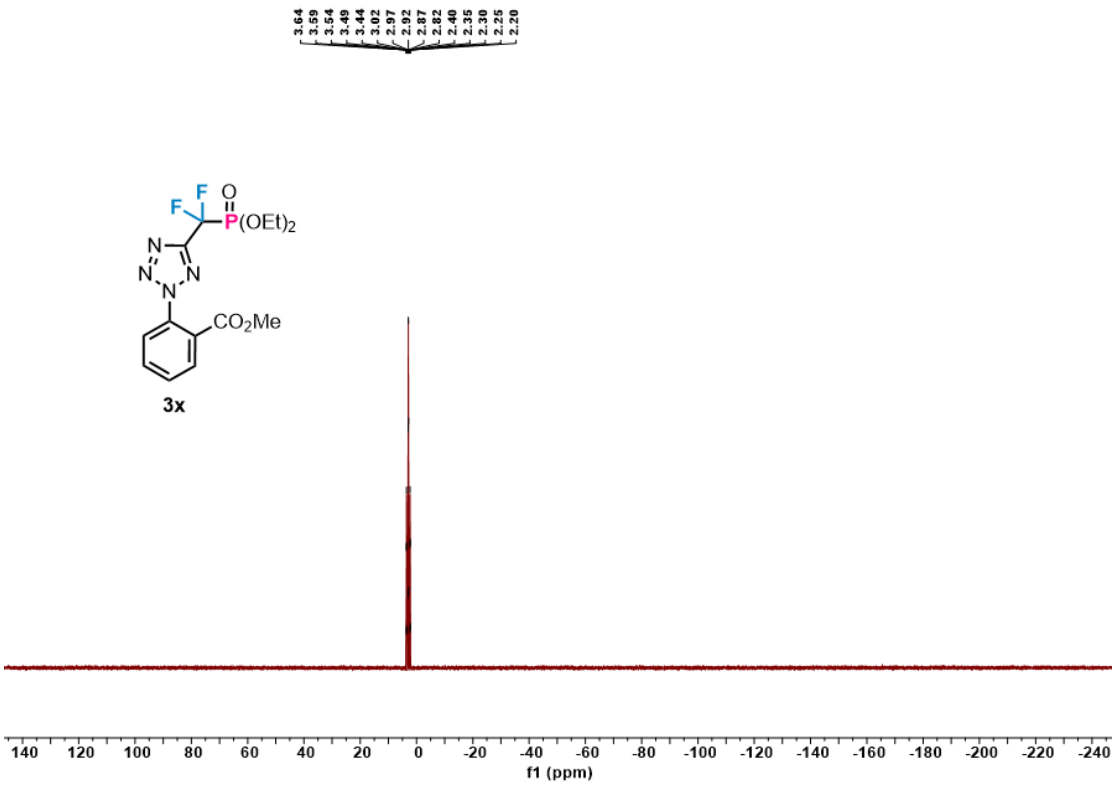
^{13}C-NMR of **3w** ($CDCl_3$, 101 M)



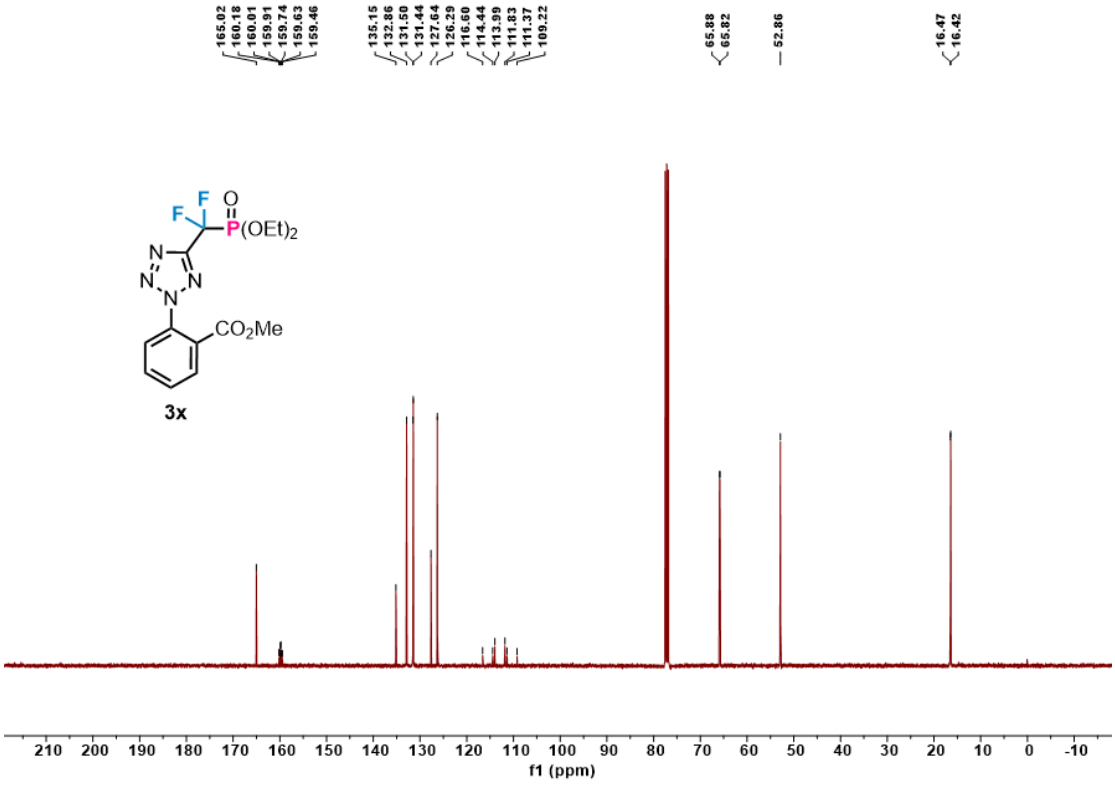
^{1}H-NMR of **3x** ($CDCl_3$, 400 M)



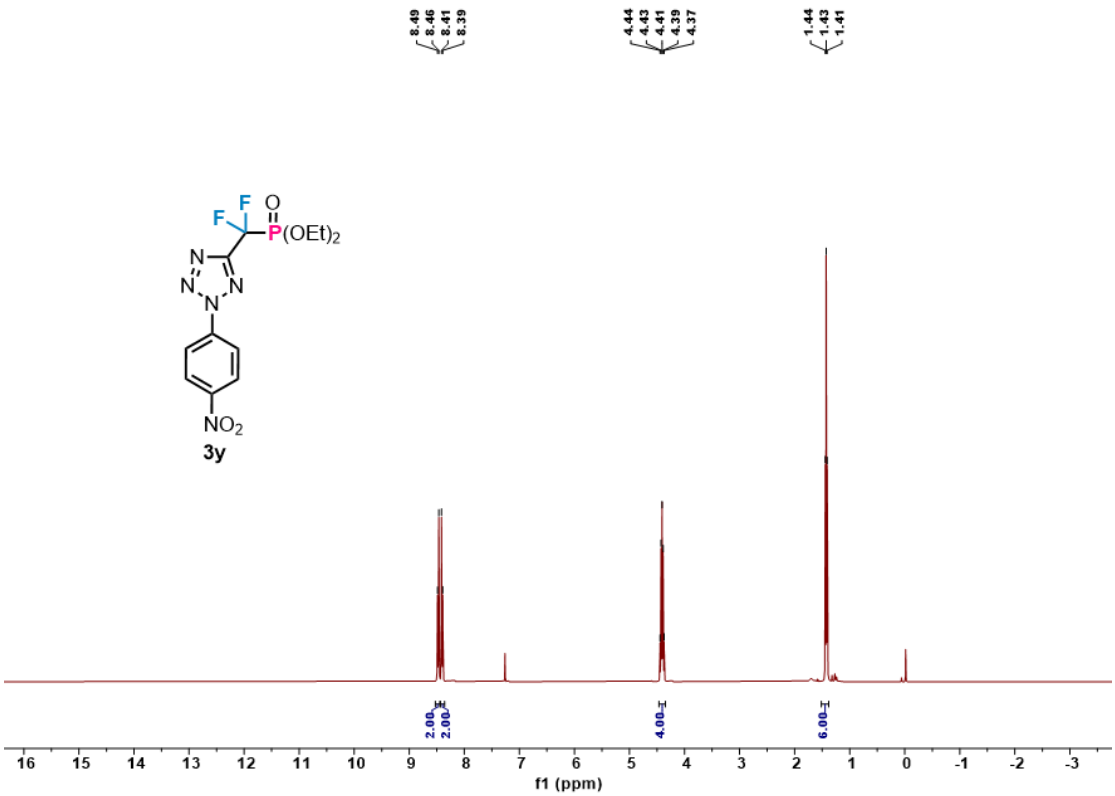
^{19}F-NMR of **3x** ($CDCl_3$, 376 M)



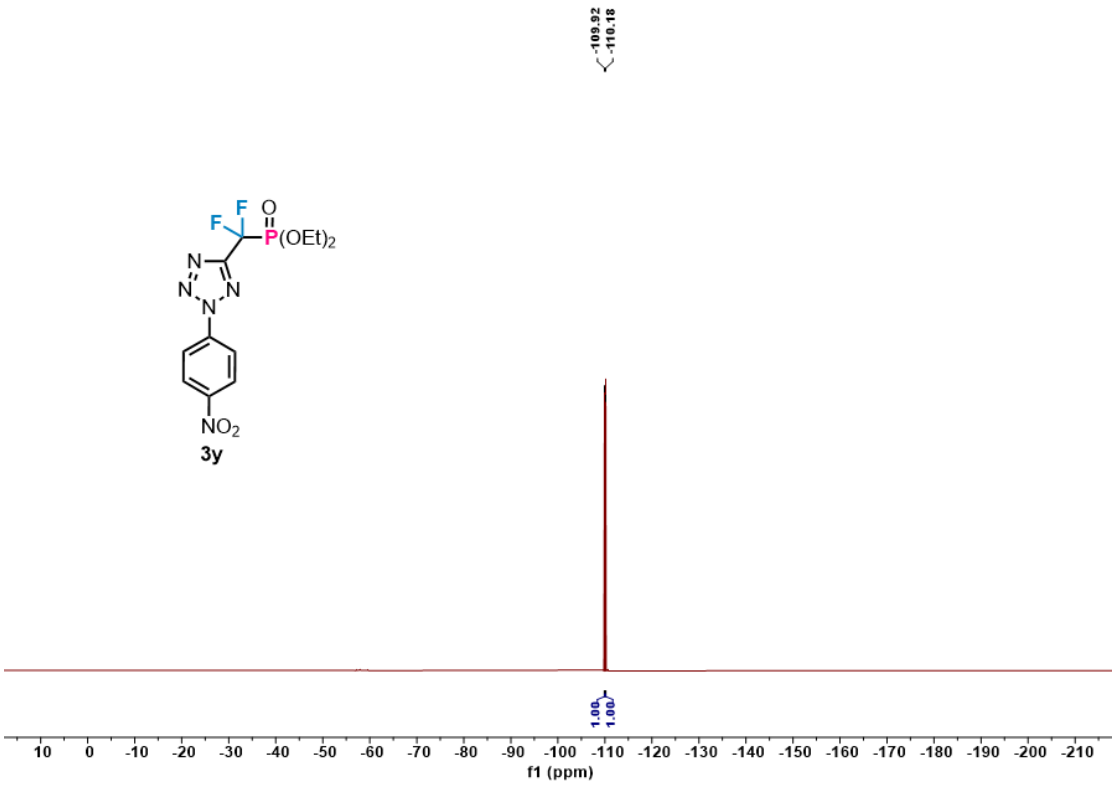
^{31}P-NMR of **3x** ($CDCl_3$, 162 M)



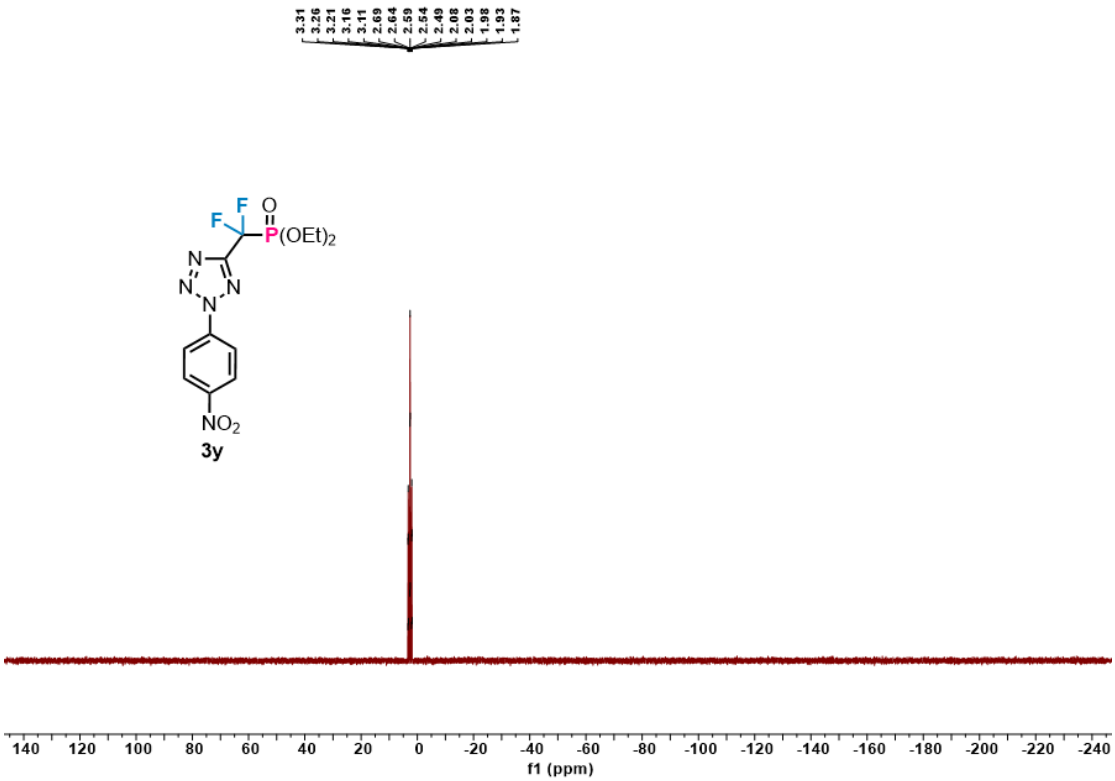
^{13}C-NMR of **3x** ($CDCl_3$, 101 M)



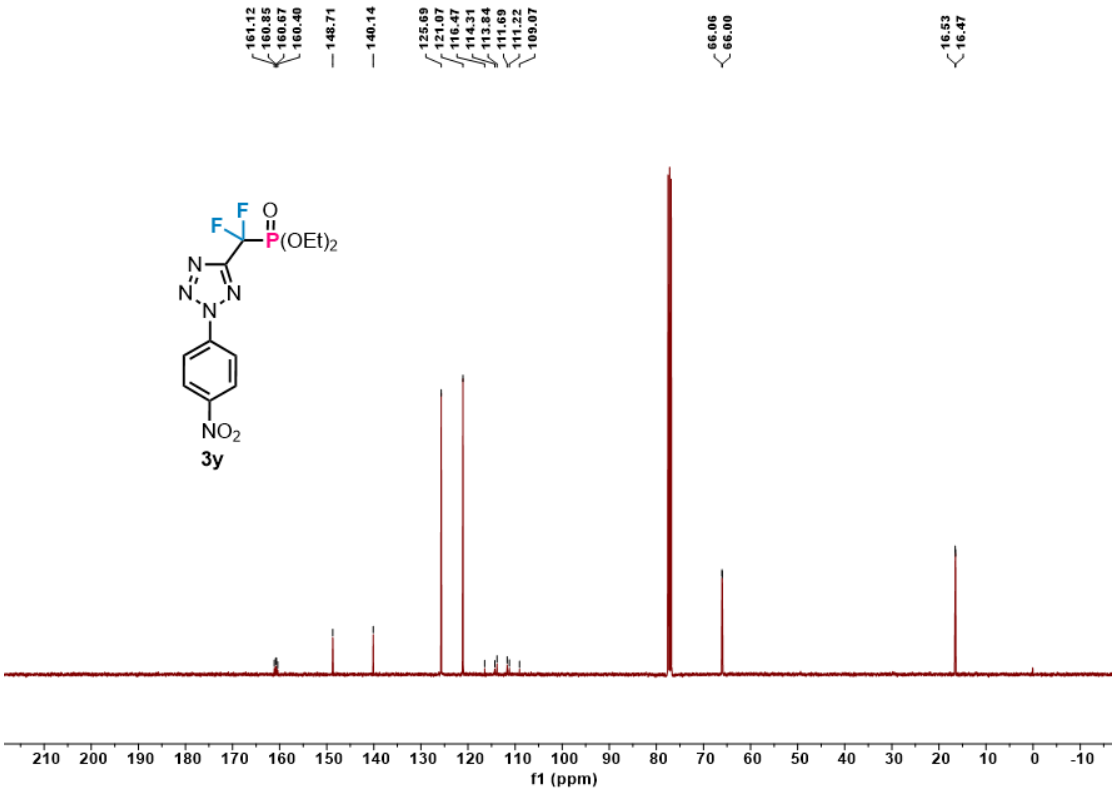
^{1}H-NMR of **3y** ($CDCl_3$, 400 M)



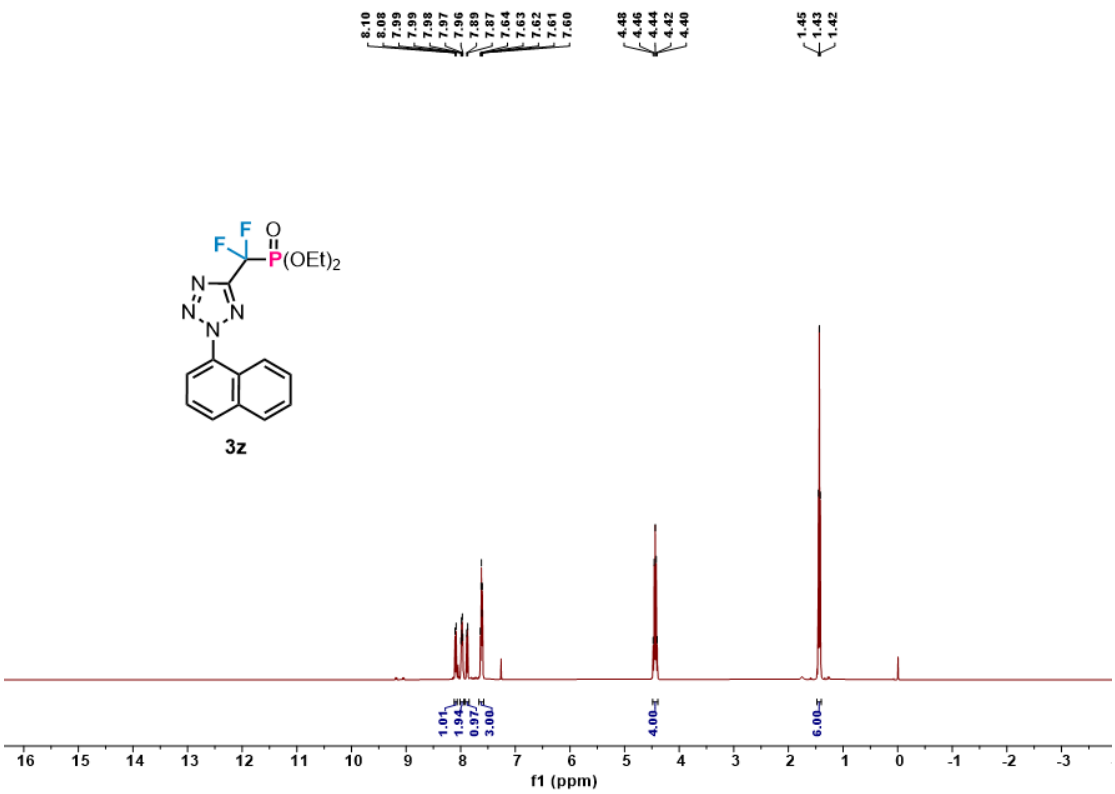
^{19}F-NMR of **3y** ($CDCl_3$, 376 M)



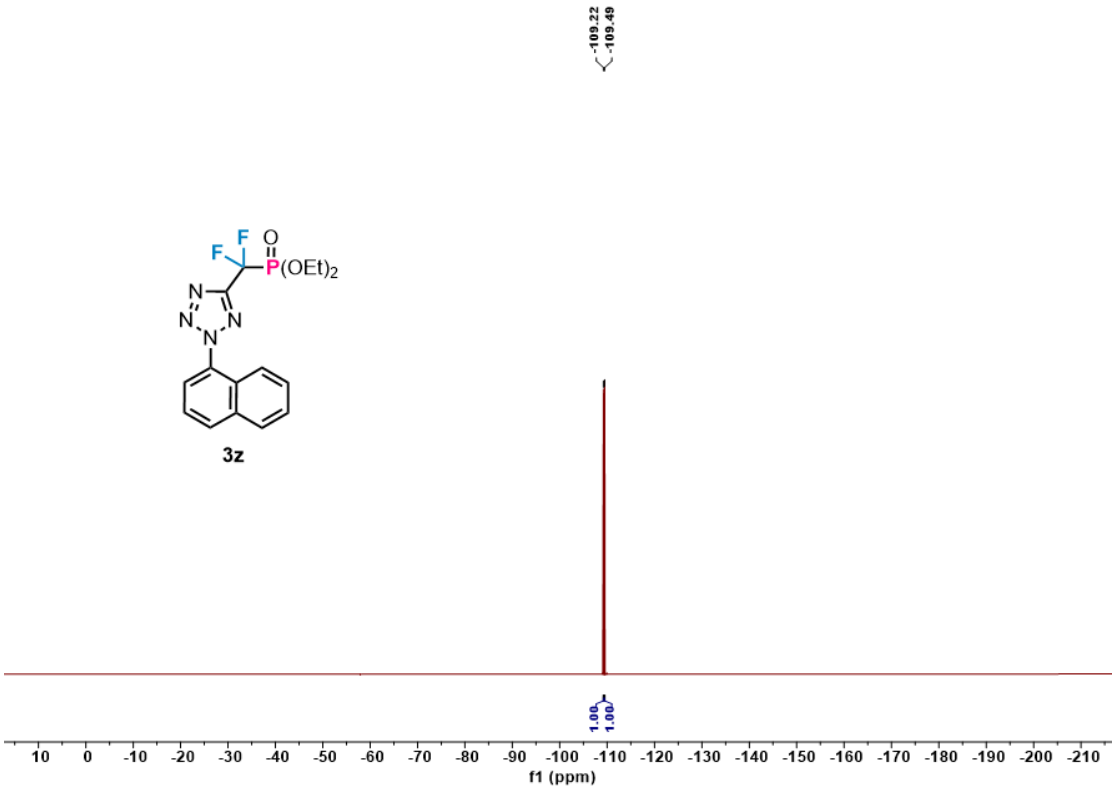
^{31}P-NMR of **3y** ($CDCl_3$, 162 M)



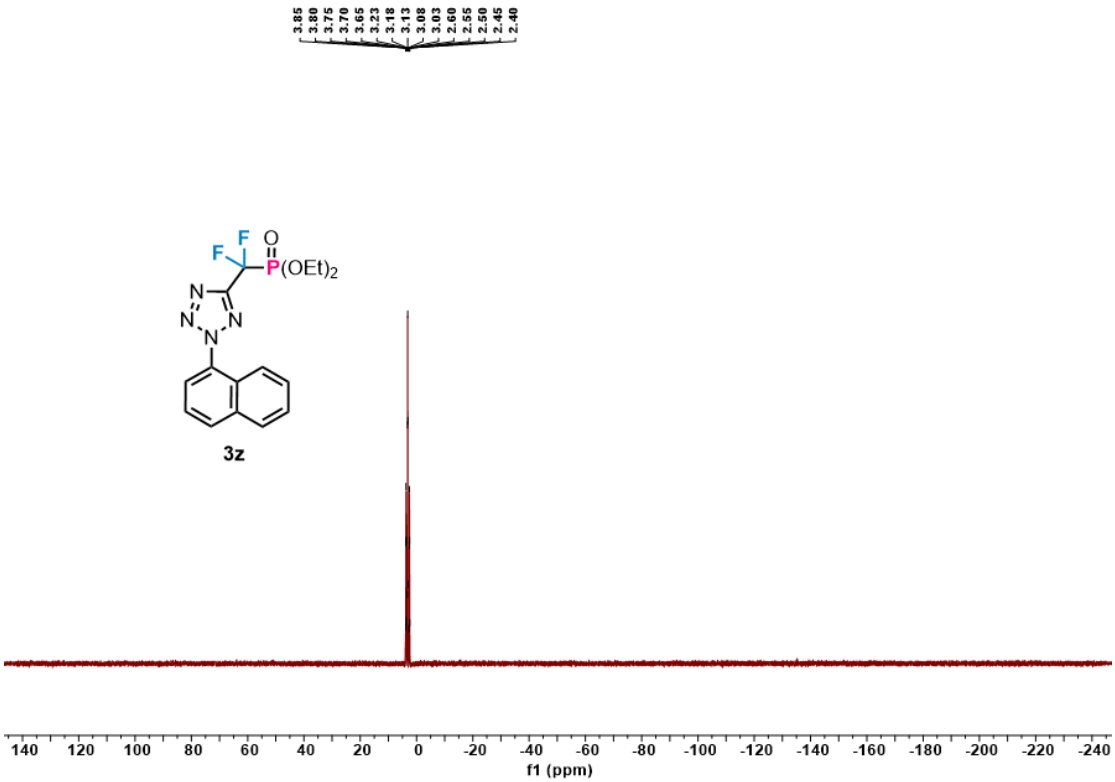
^{13}C-NMR of **3y** ($CDCl_3$, 101 M)



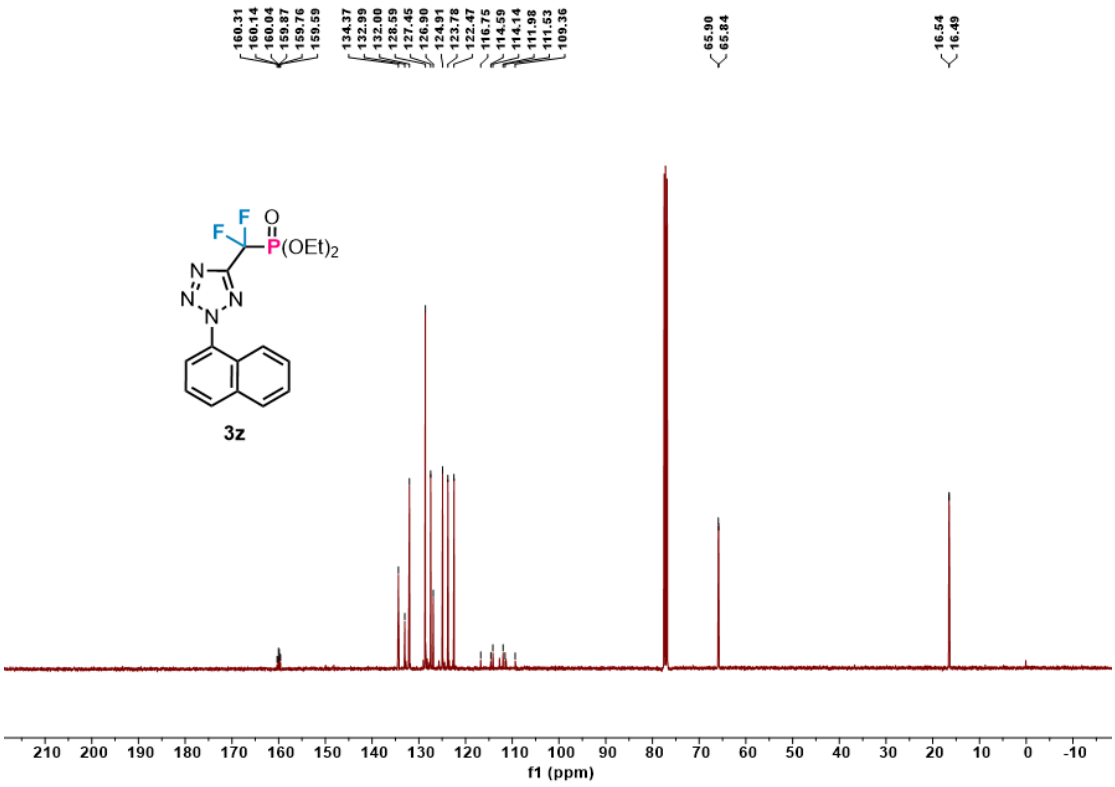
^{1}H-NMR of **3z** ($CDCl_3$, 400 M)



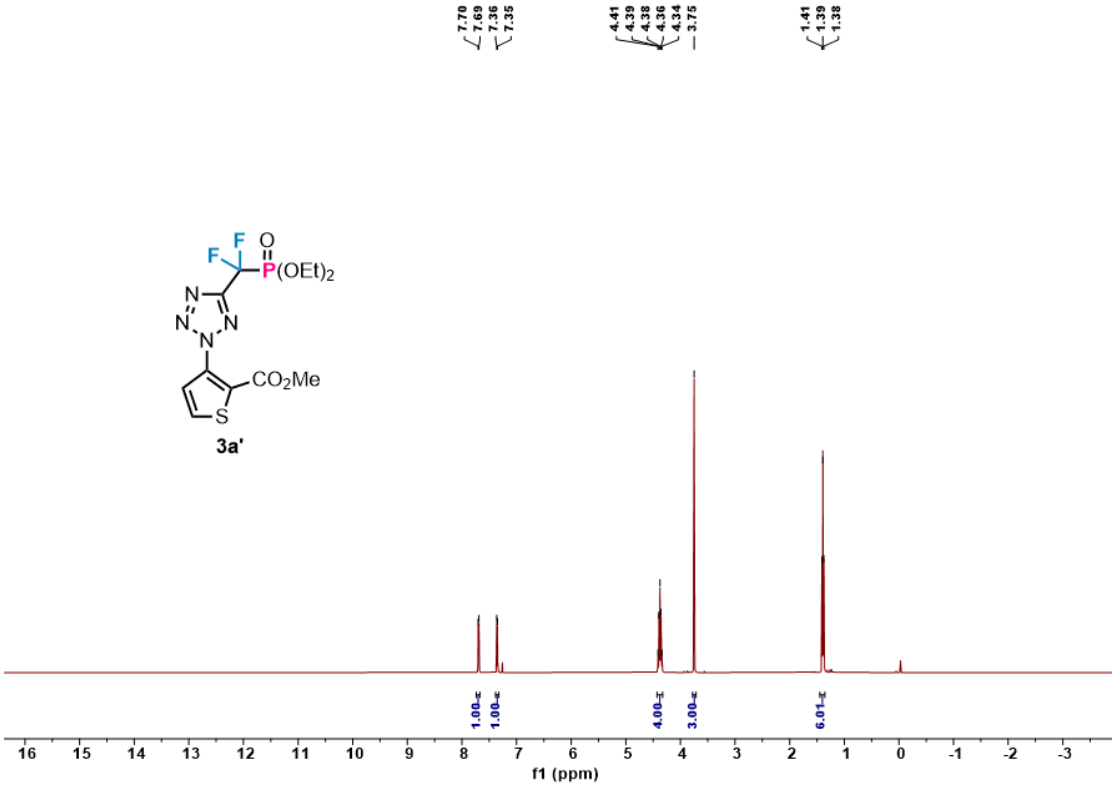
^{19}F-NMR of **3z** ($CDCl_3$, 376 M)



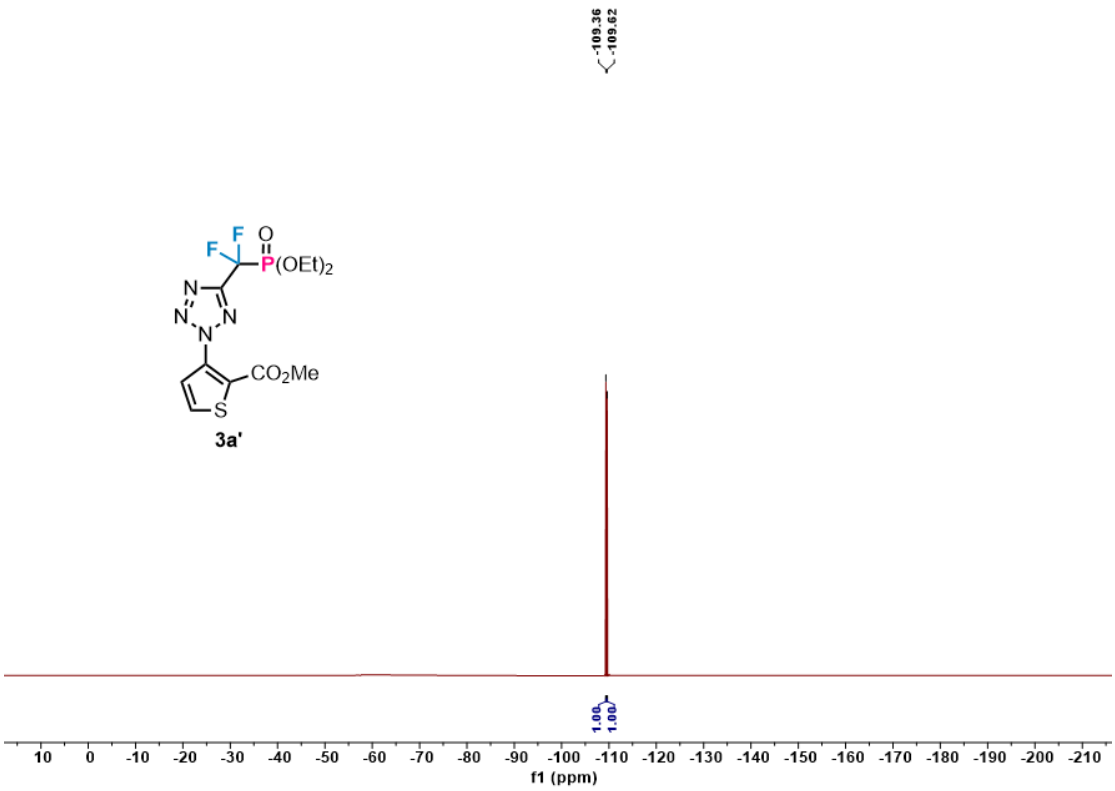
^{31}P-NMR of **3z** ($CDCl_3$, 162 M)



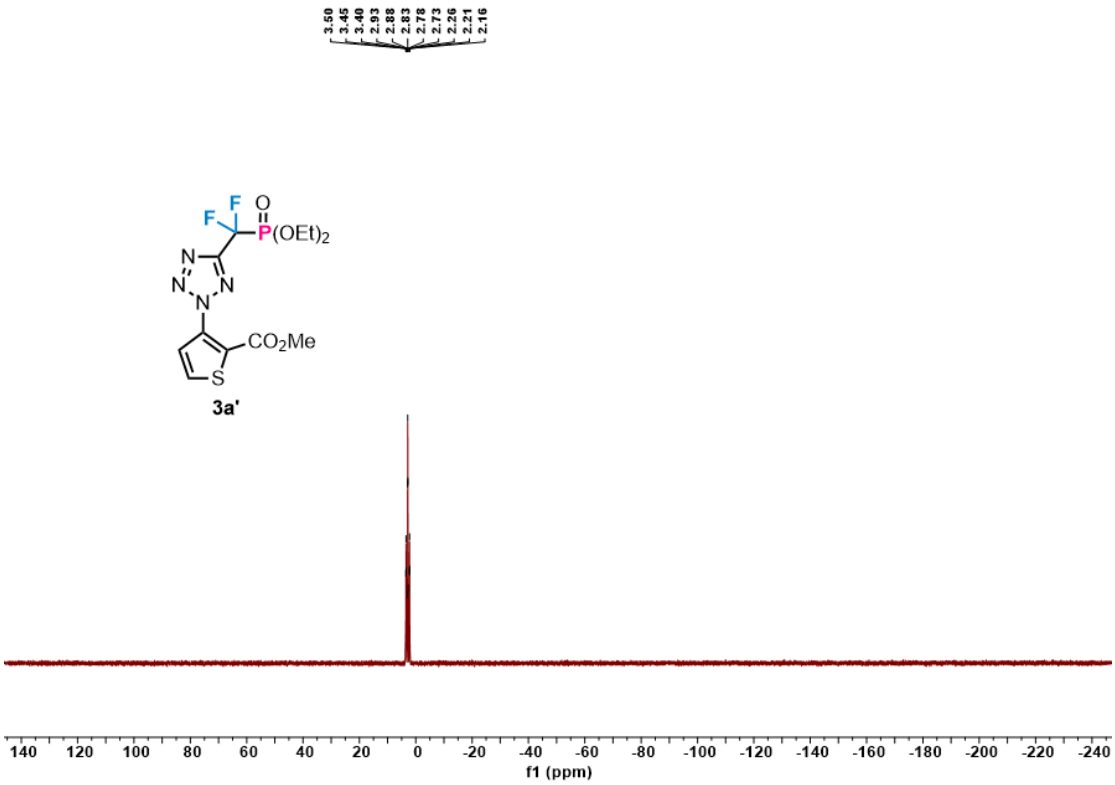
^{13}C-NMR of **3z** ($CDCl_3$, 101 M)



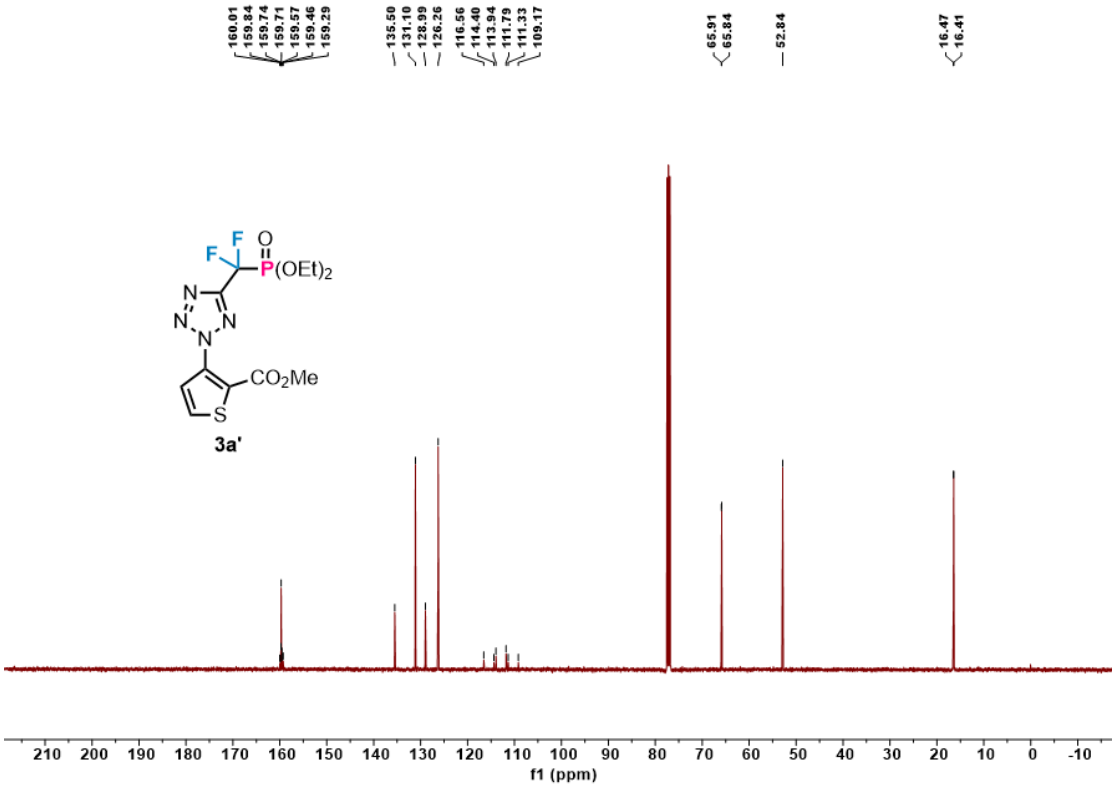
^{1}H-NMR of **3a'** ($CDCl_3$, 400 M)



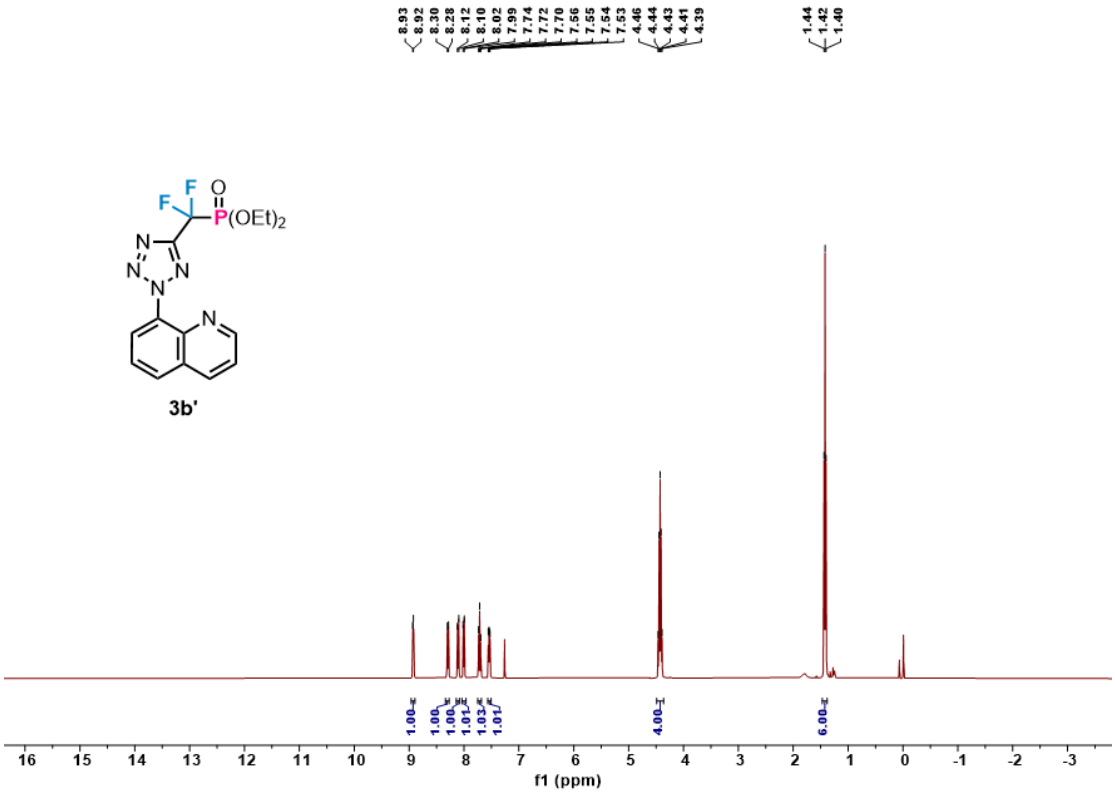
^{19}F-NMR of **3a'** ($CDCl_3$, 376 M)



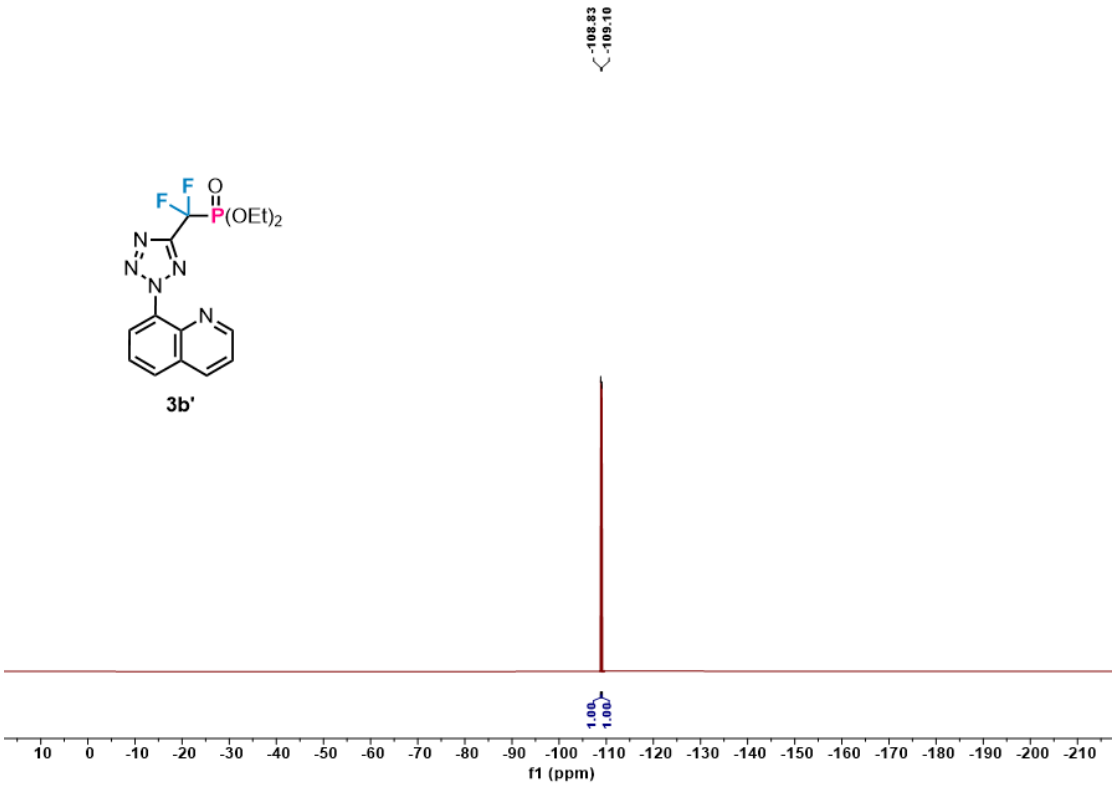
^{31}P-NMR of **3a'** ($CDCl_3$, 162 M)



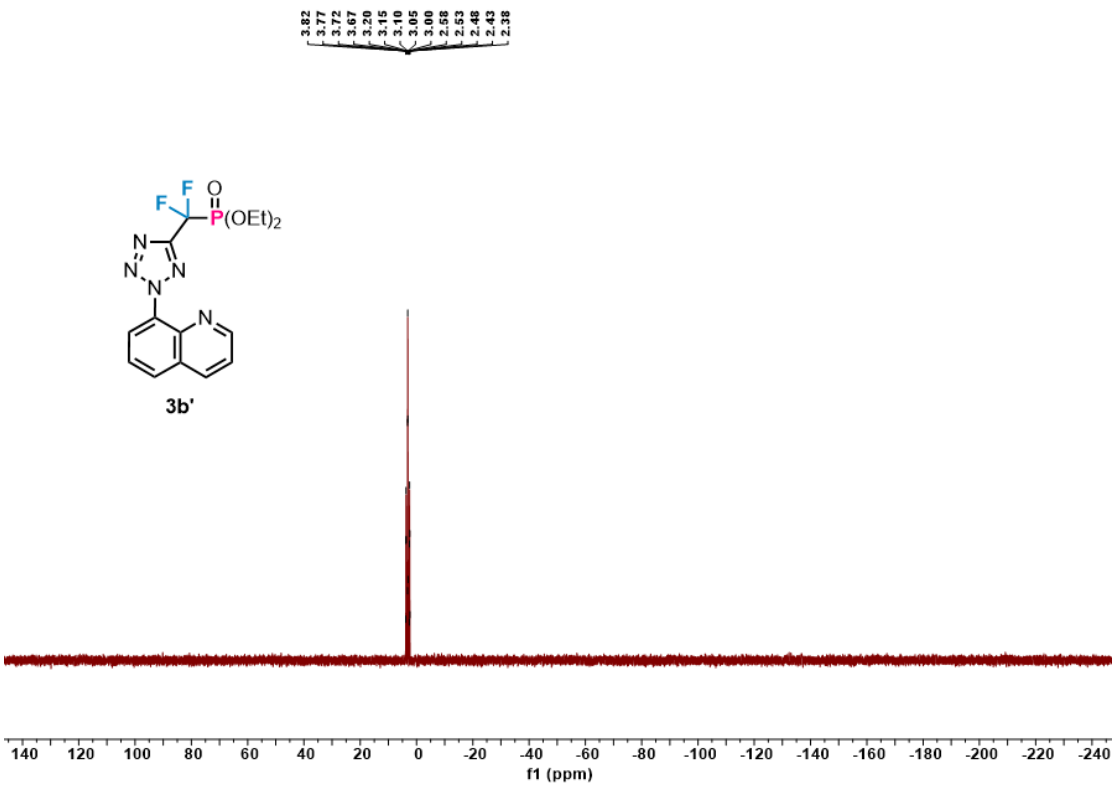
^{13}C-NMR of **3a'** ($CDCl_3$, 101 M)



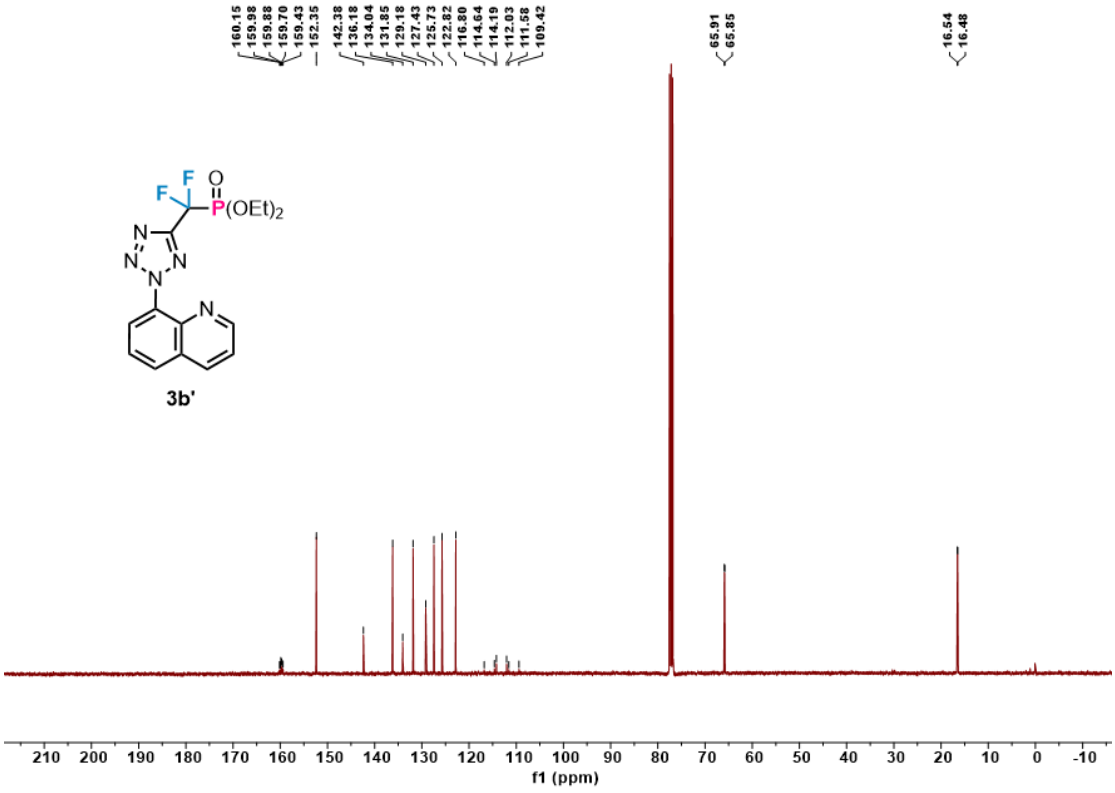
^{1}H-NMR of **3b'** ($CDCl_3$, 400 M)\



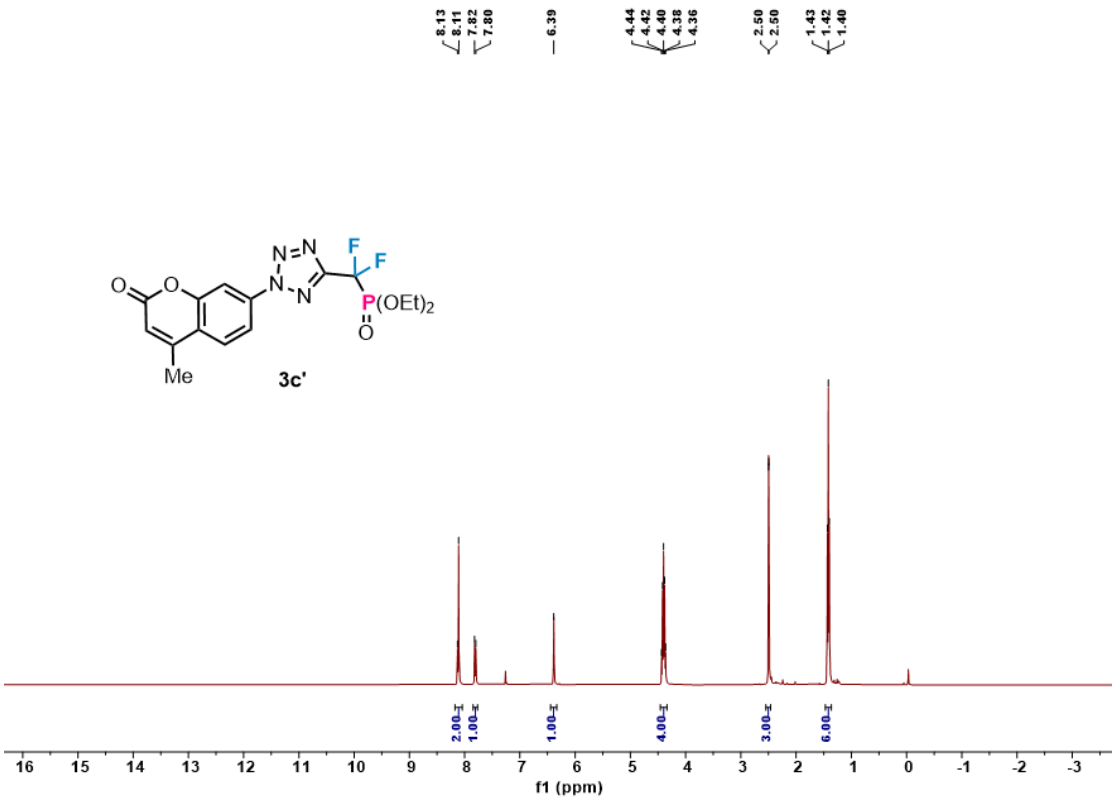
^{19}F-NMR of **3b'** ($CDCl_3$, 376 M)



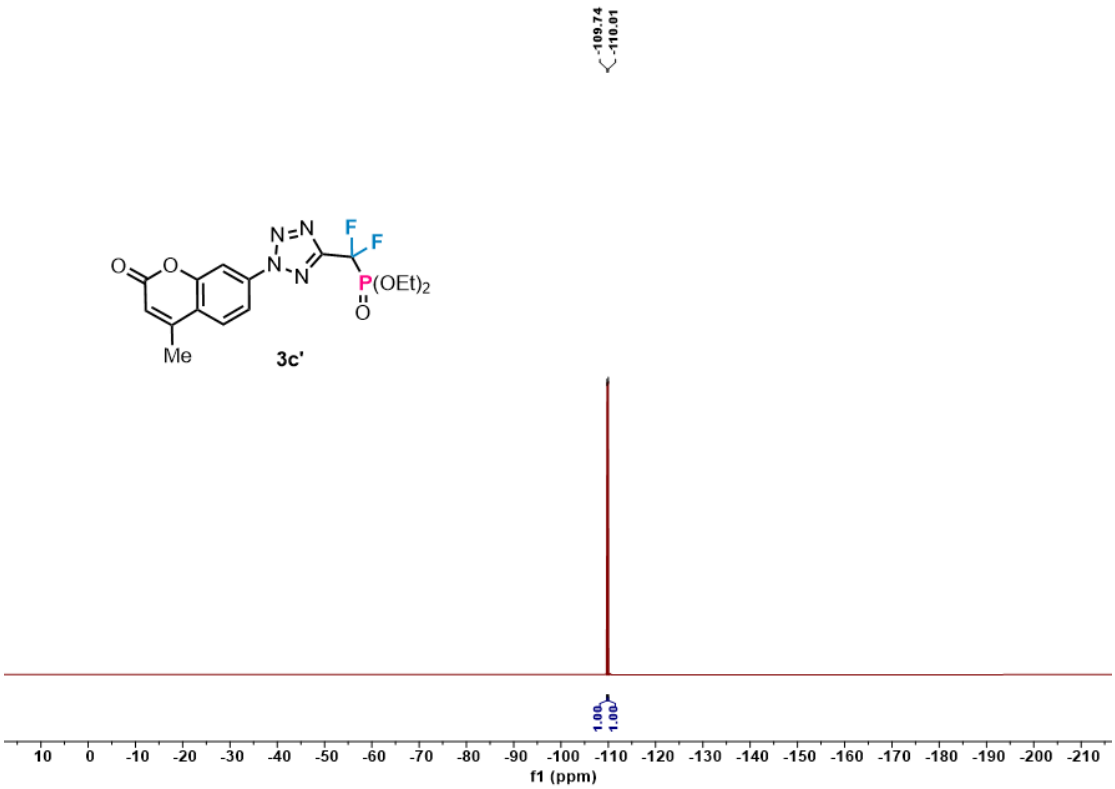
^{31}P-NMR of **3b'** ($CDCl_3$, 162 M)



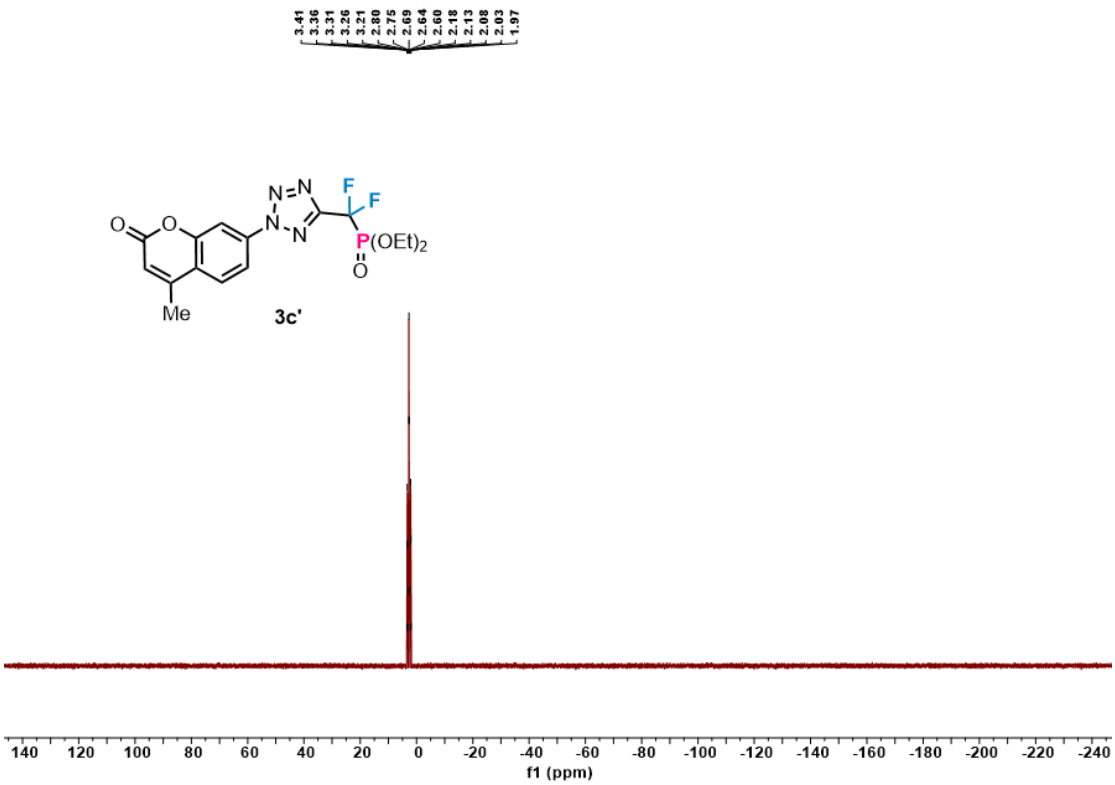
^{13}C-NMR of **3b'** ($CDCl_3$, 101 M)



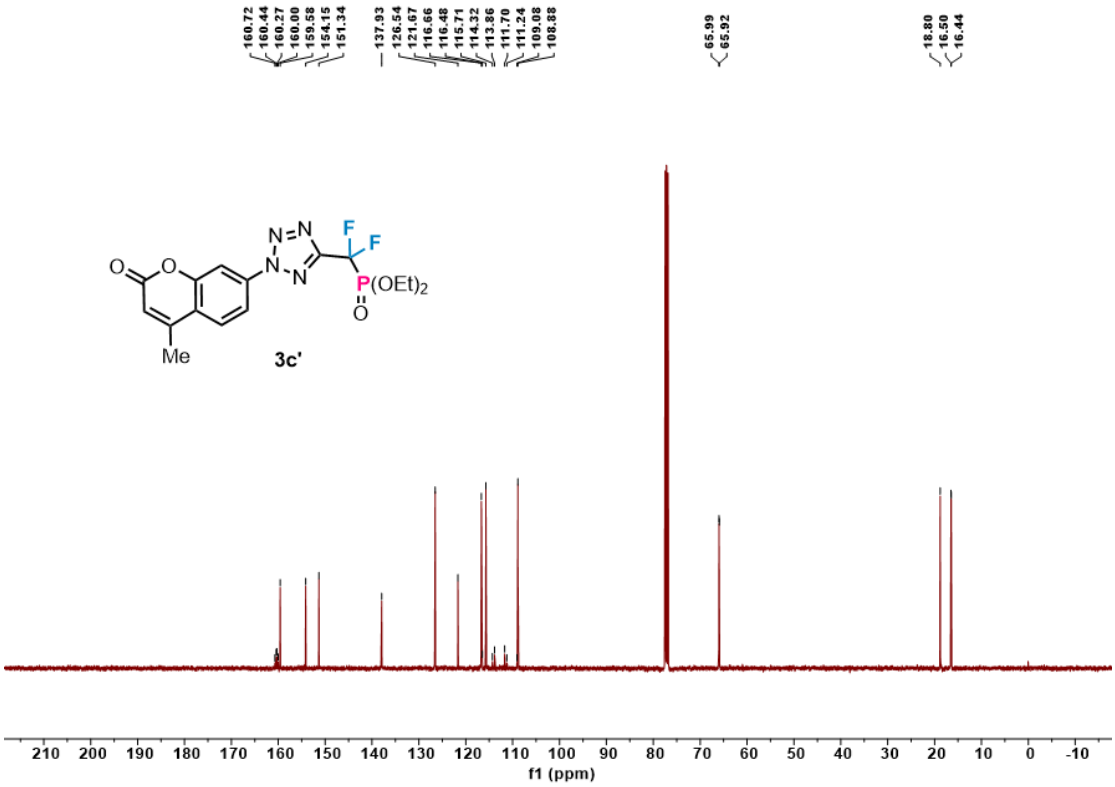
^{1}H-NMR of **3c'** ($CDCl_3$, 400 M)



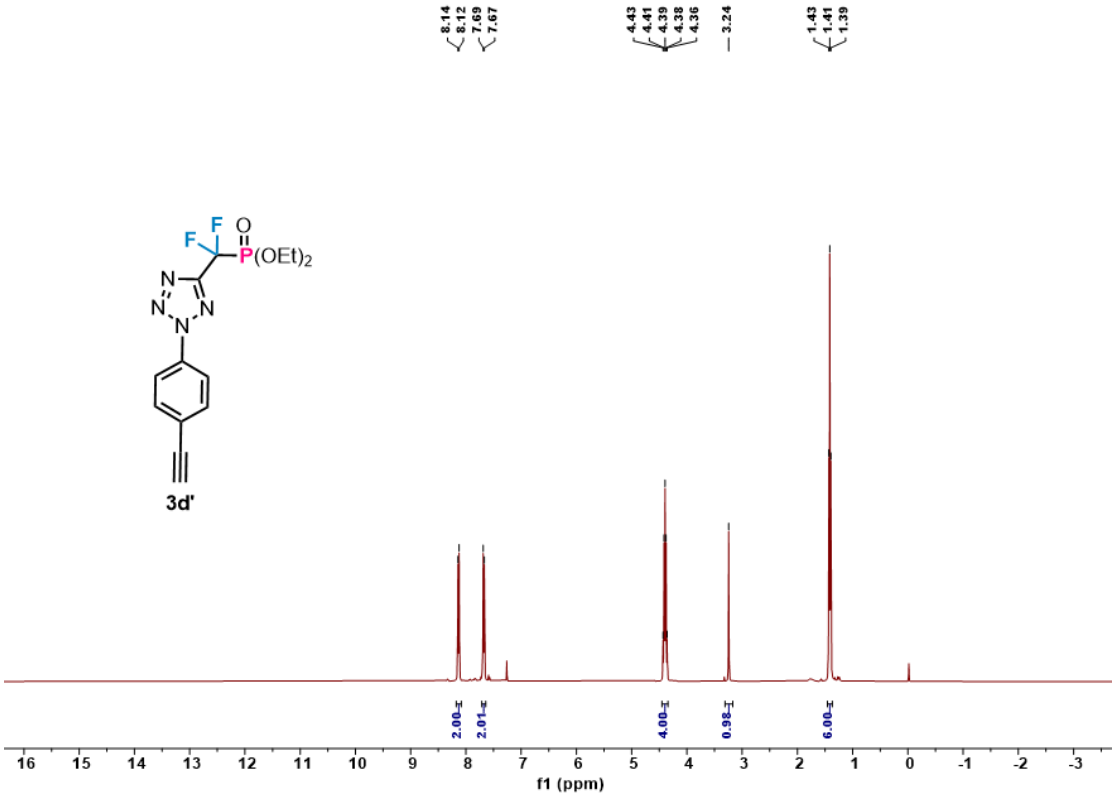
^{19}F-NMR of **3c'** ($CDCl_3$, 376 M)



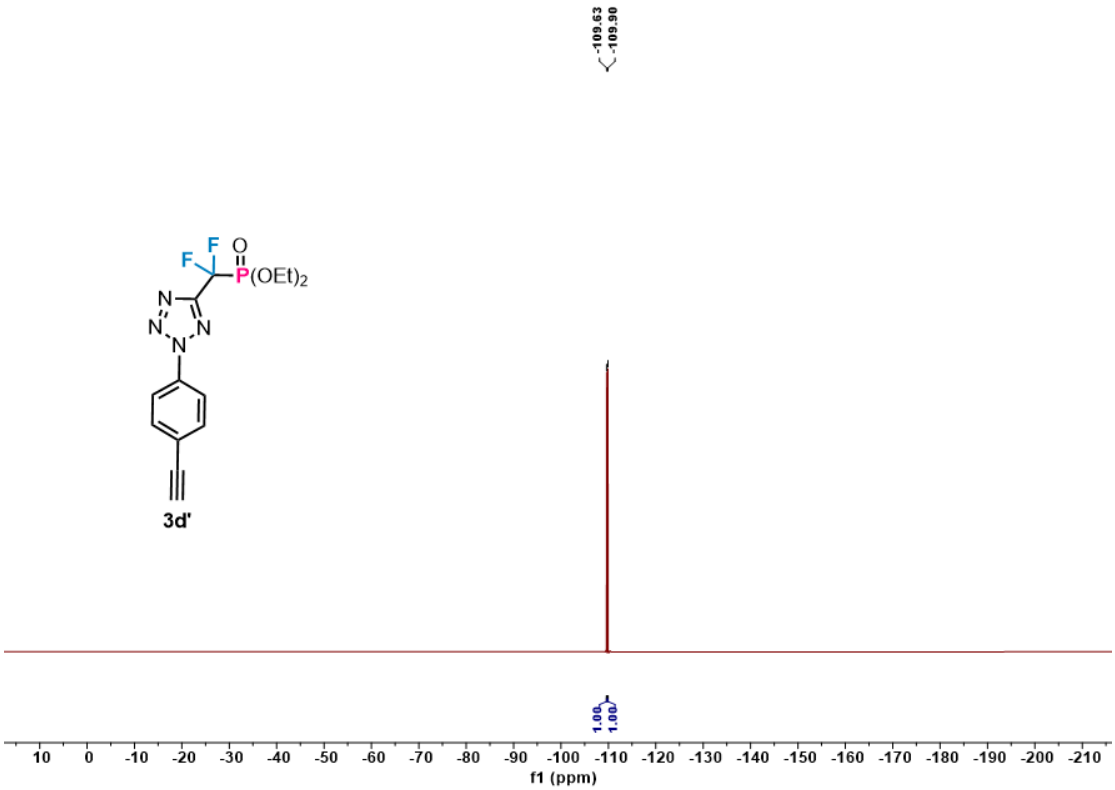
^{31}P-NMR of **3c'** ($CDCl_3$, 162 M)



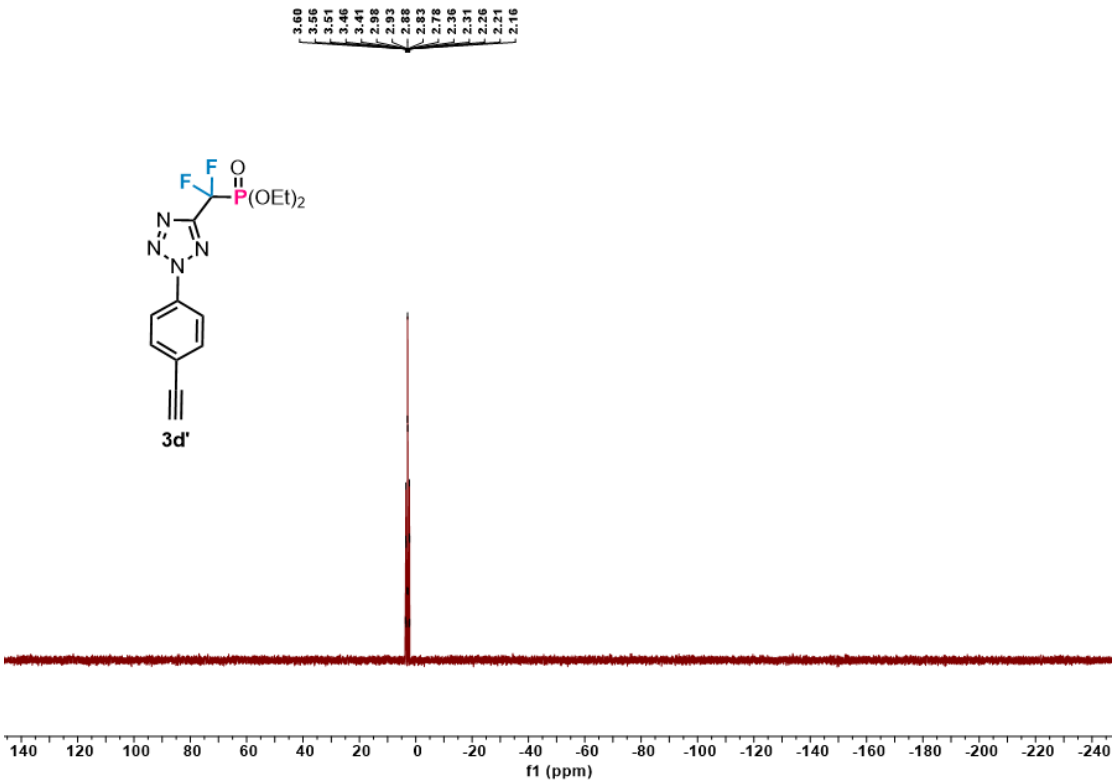
^{13}C-NMR of **3c'** ($CDCl_3$, 101 M)



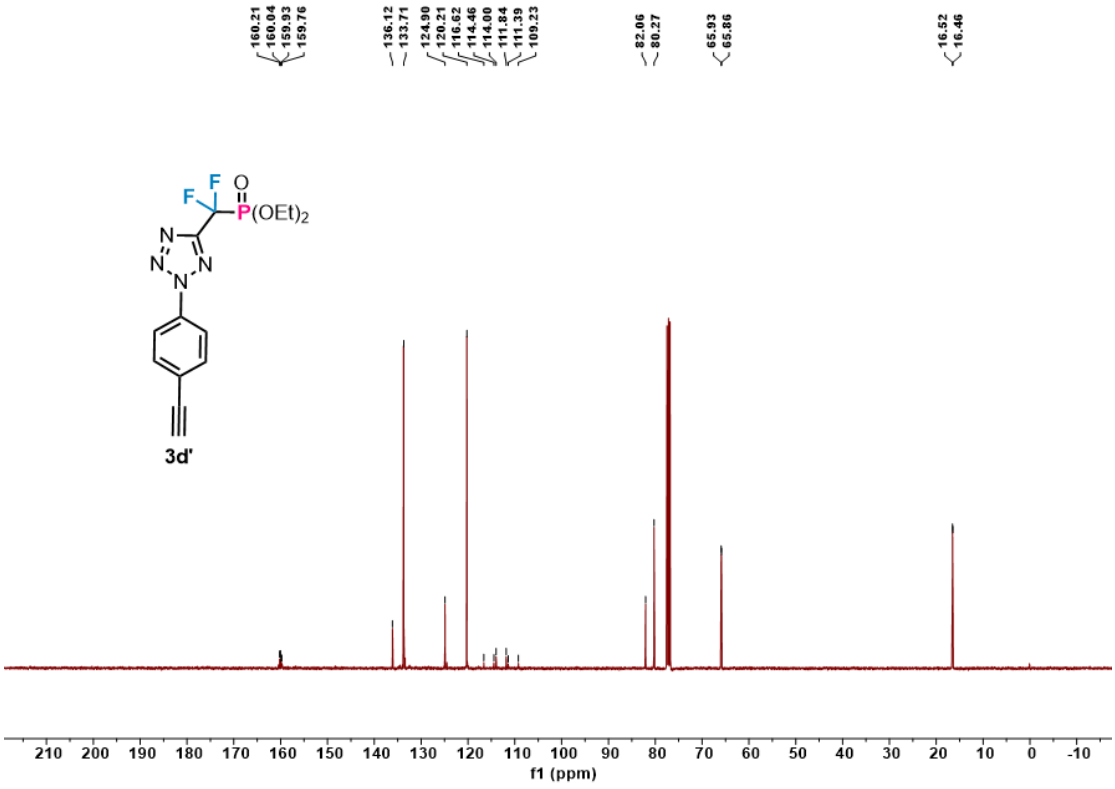
^{1}H-NMR of **3d'** ($CDCl_3$, 400 M)



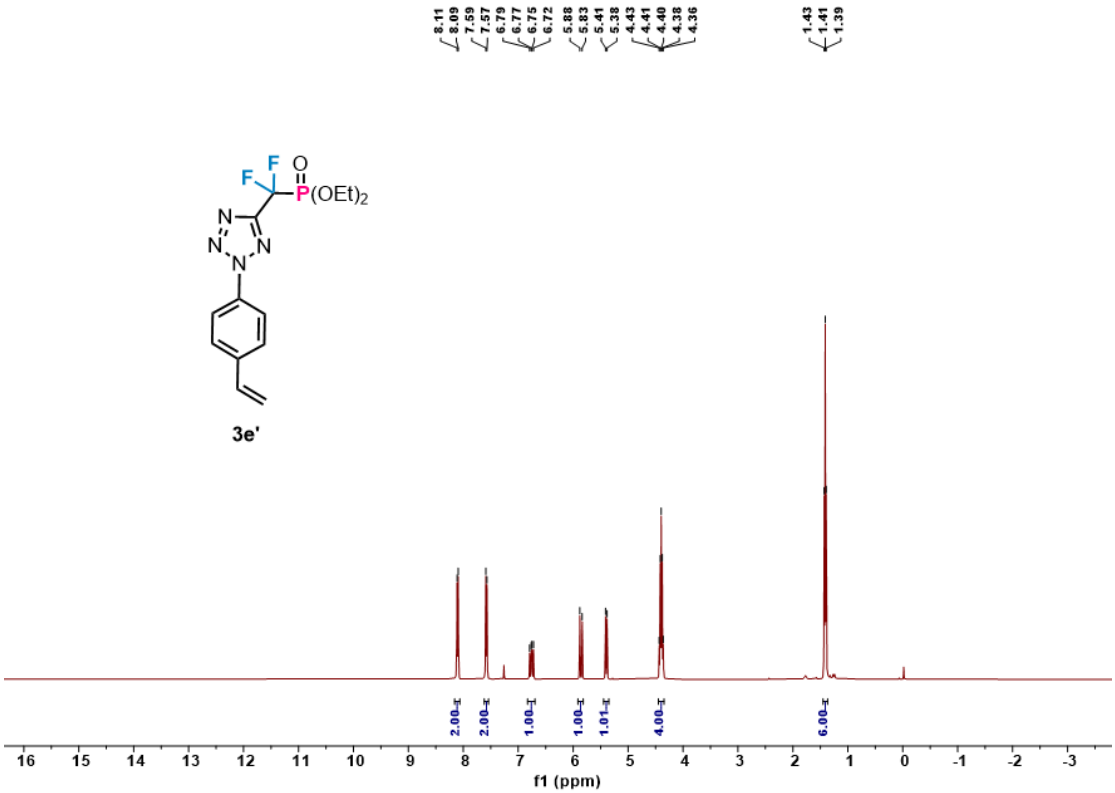
^{19}F-NMR of **3d'** ($CDCl_3$, 376 M)



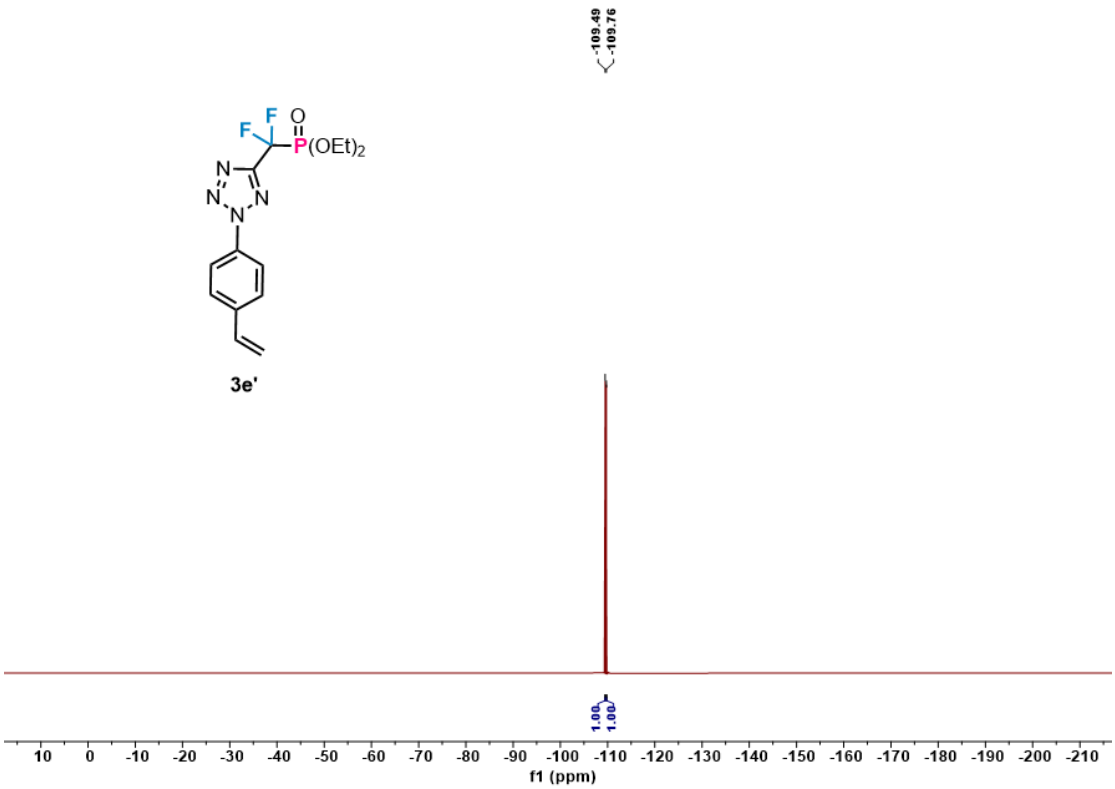
^{31}P-NMR of **3d'** ($CDCl_3$, 162 M)



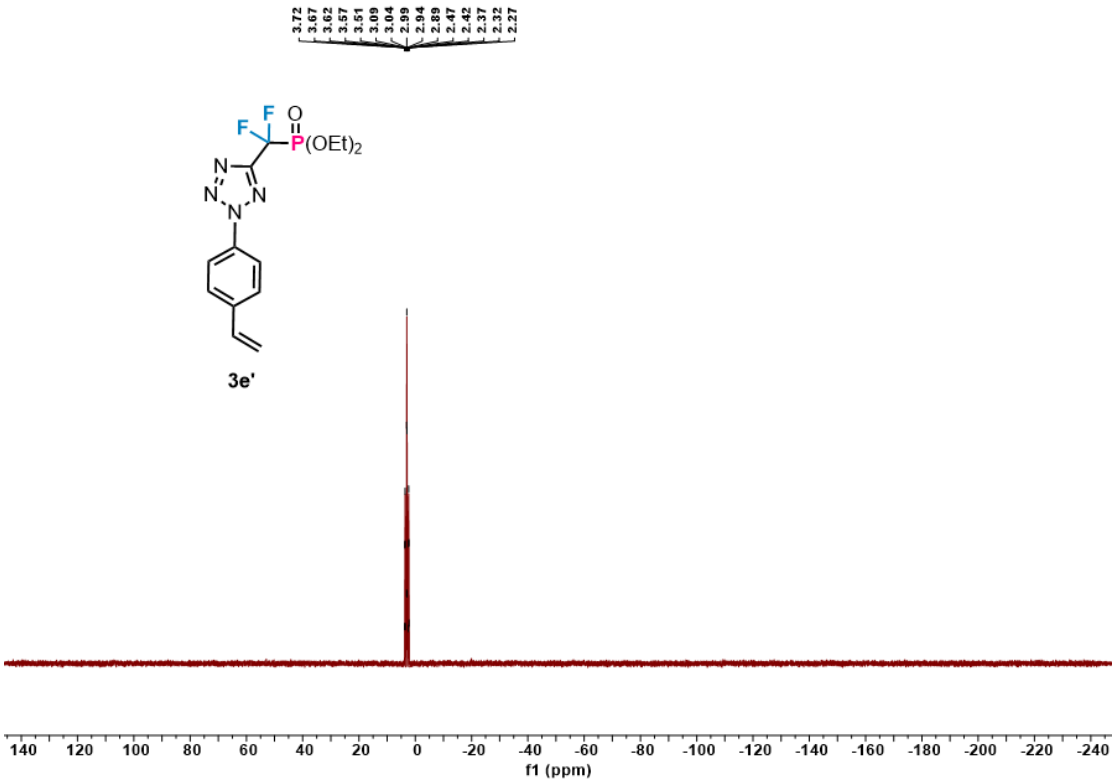
^{13}C-NMR of **3d'** ($CDCl_3$, 101 M)



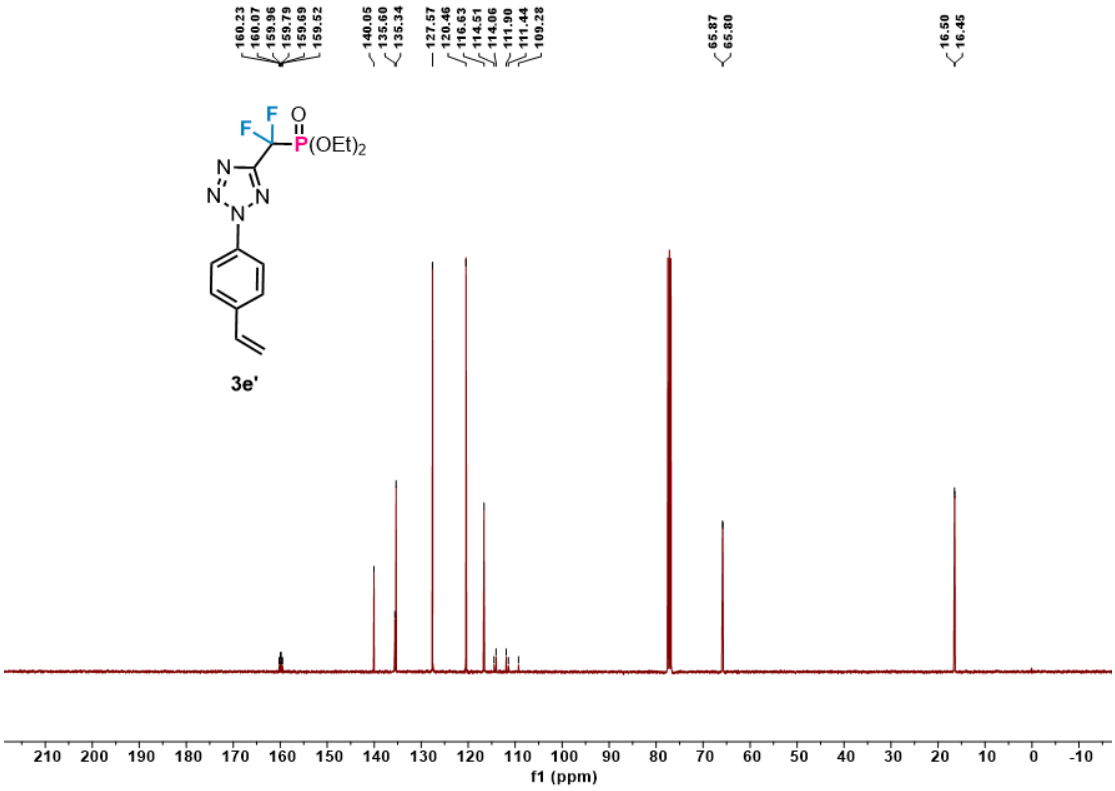
^{1}H-NMR of **3e'** ($CDCl_3$, 400 M)



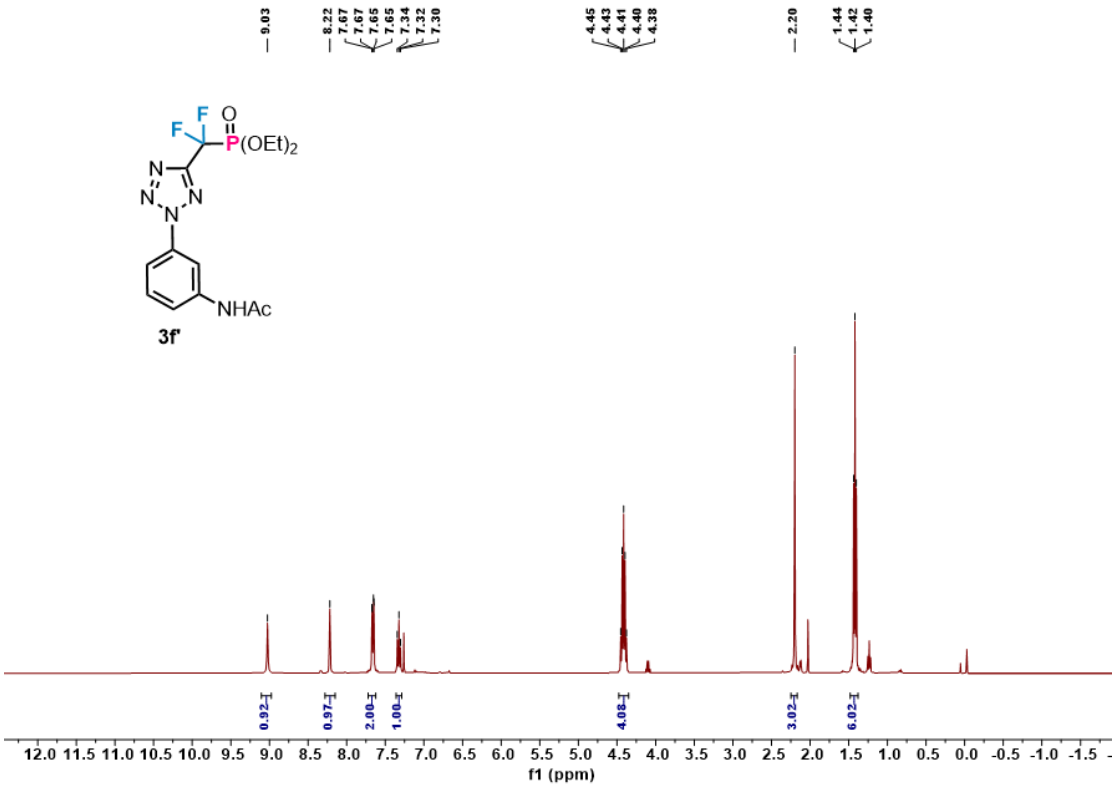
^{19}F-NMR of **3e'** ($CDCl_3$, 376 M)



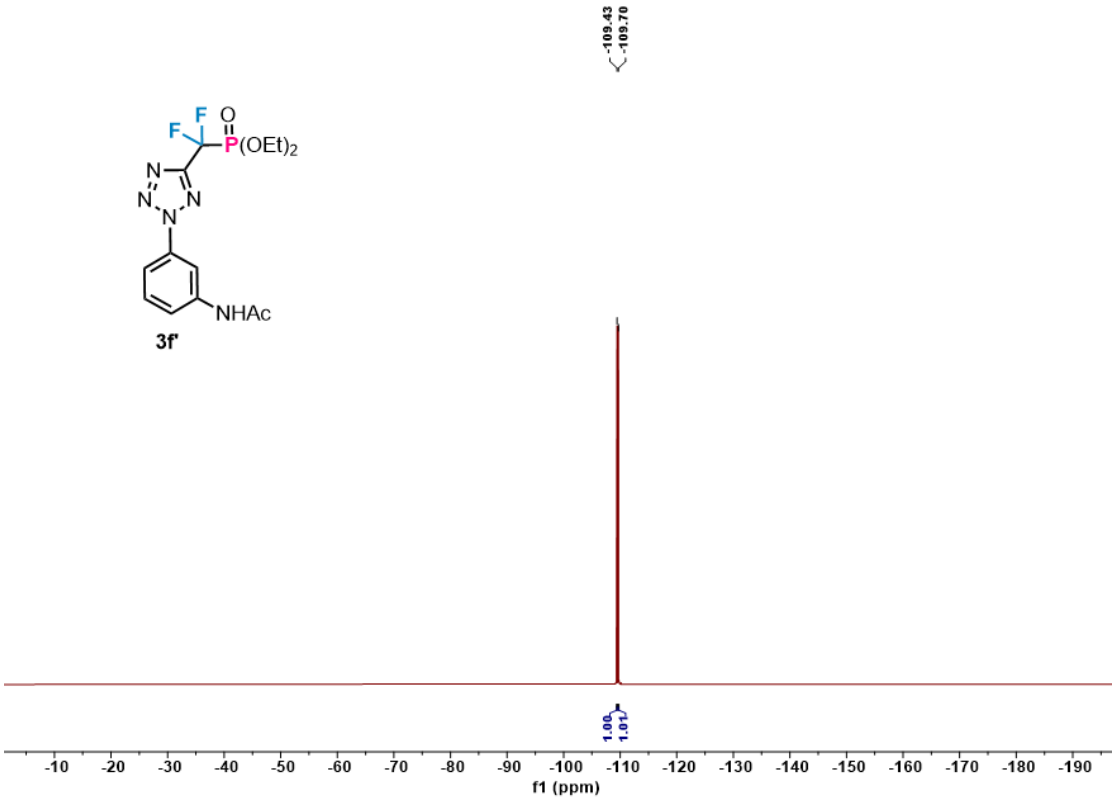
^{31}P-NMR of **3d'** ($CDCl_3$, 162 M)



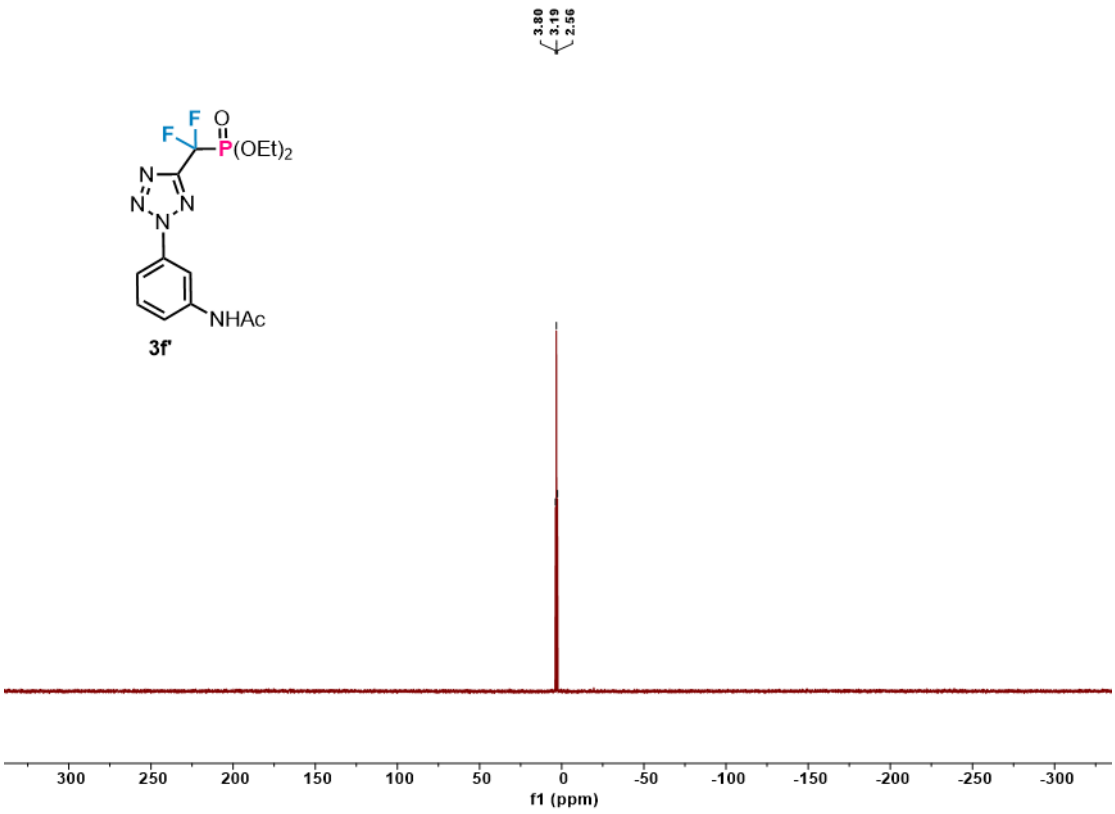
^{13}C-NMR of **3e'** ($CDCl_3$, 101 M)



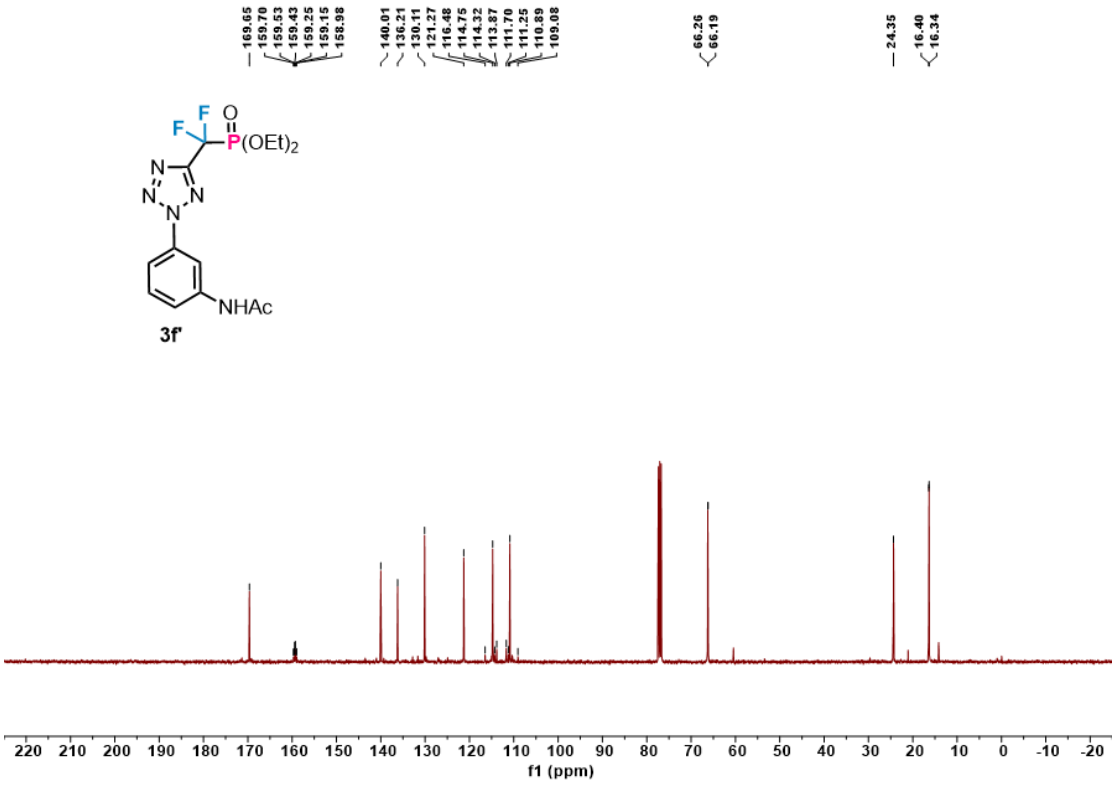
^{1}H-NMR of **3f'** ($CDCl_3$, 400 M)



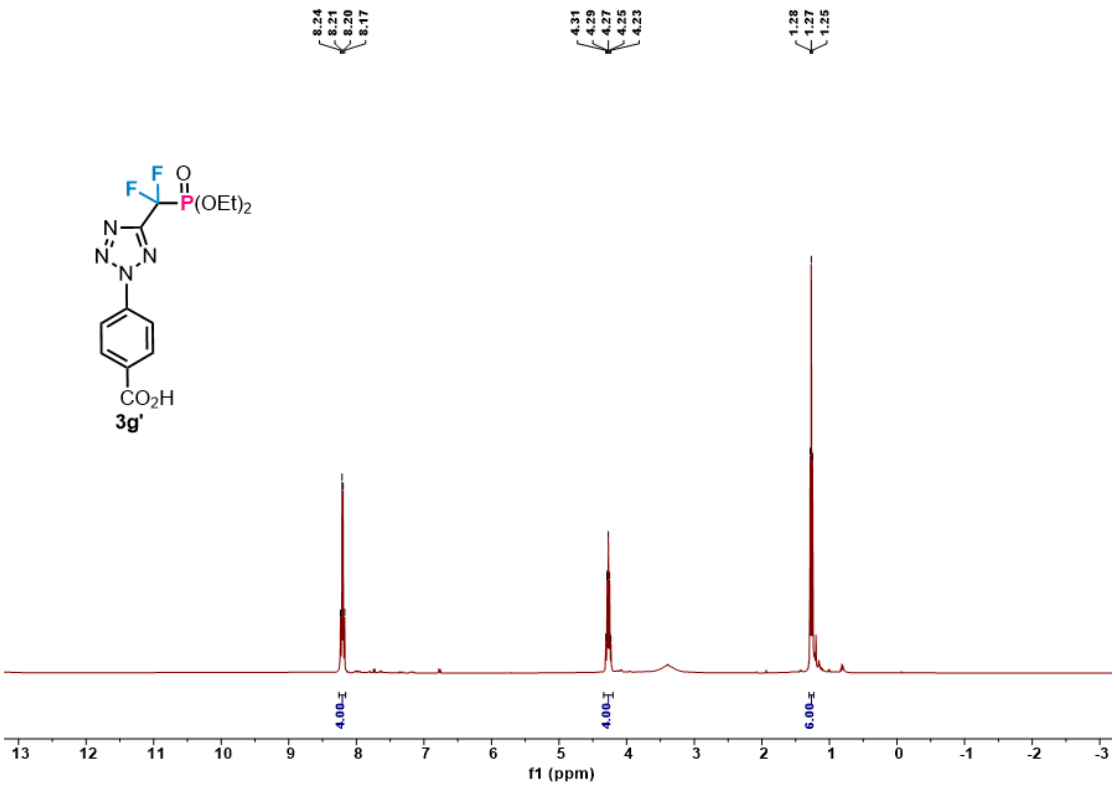
^{19}F-NMR of **3f'** ($CDCl_3$, 376 M)



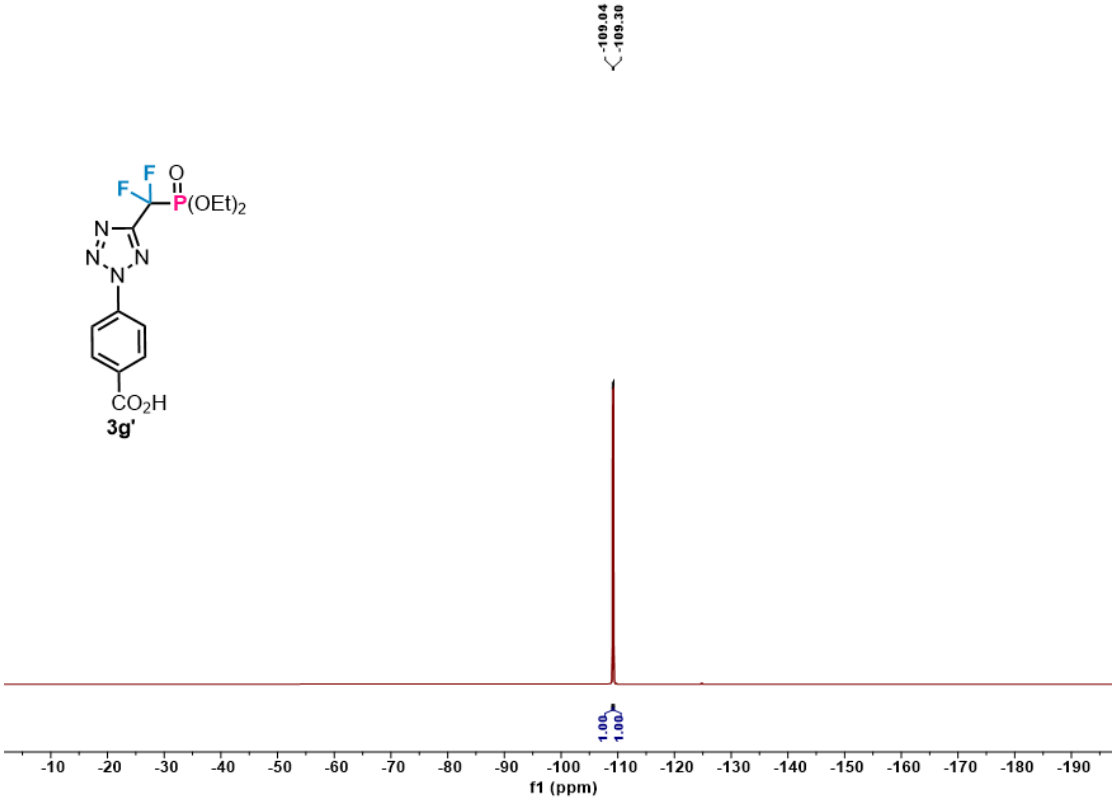
^{31}P-NMR of **3f'** ($CDCl_3$, 162 M)



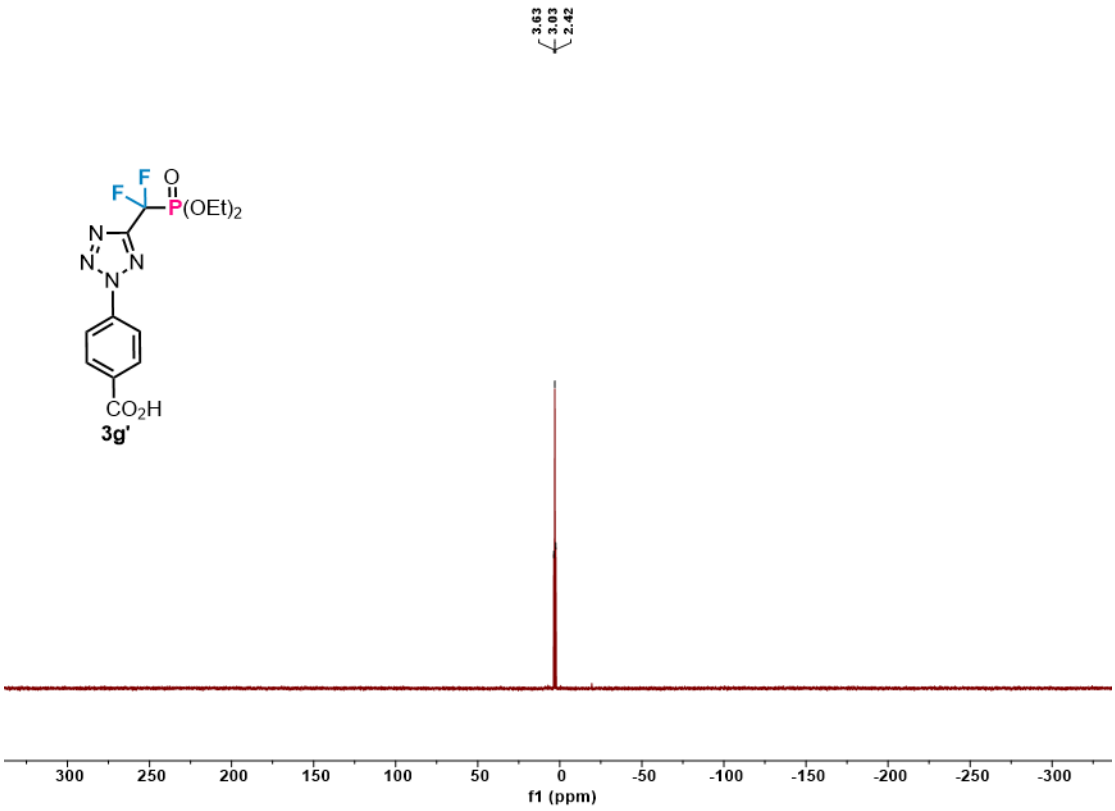
^{13}C-NMR of **3f'** ($CDCl_3$, 101 M)



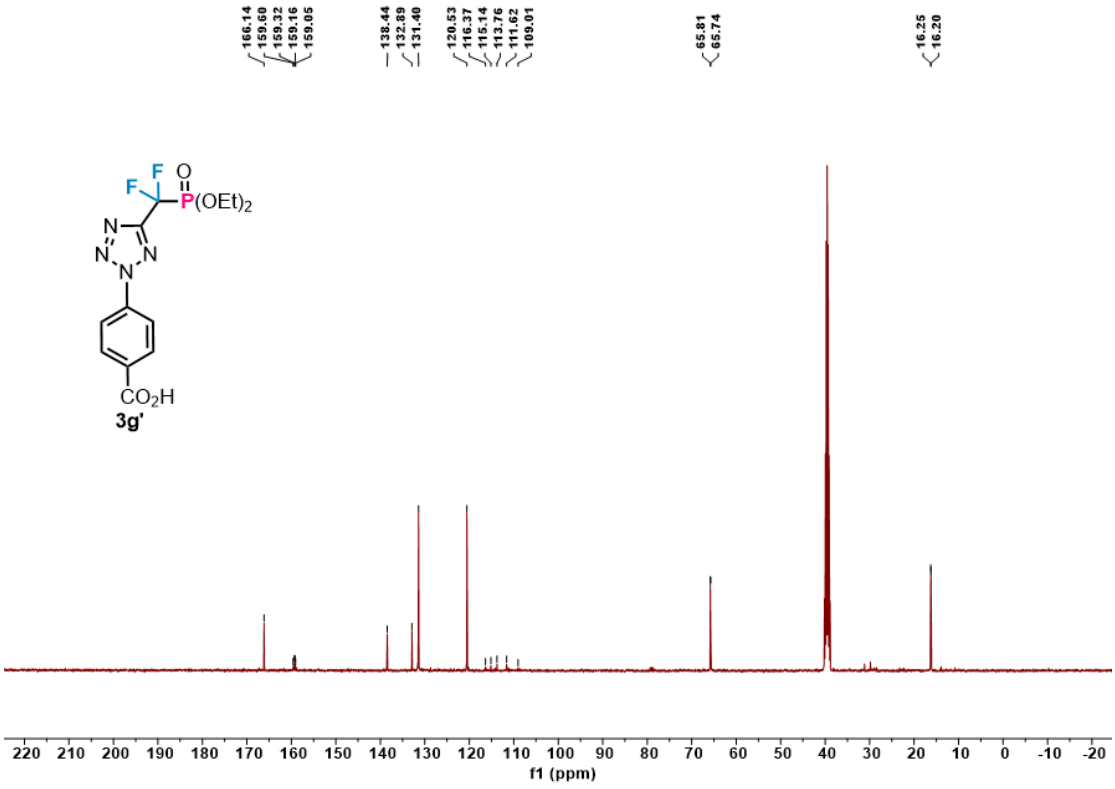
^{1}H-NMR of **3g'** (DMSO-d_6, 400 M)



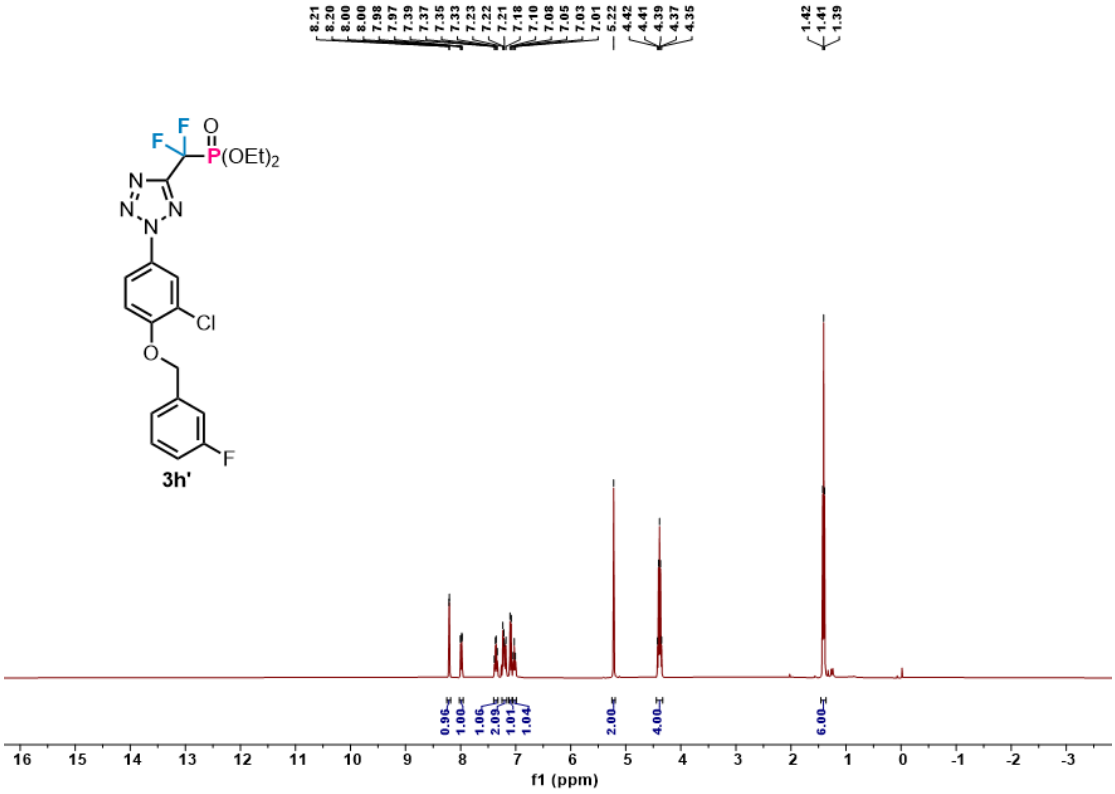
^{19}F-NMR of **3g'** (DMSO-d_6, 376 M)



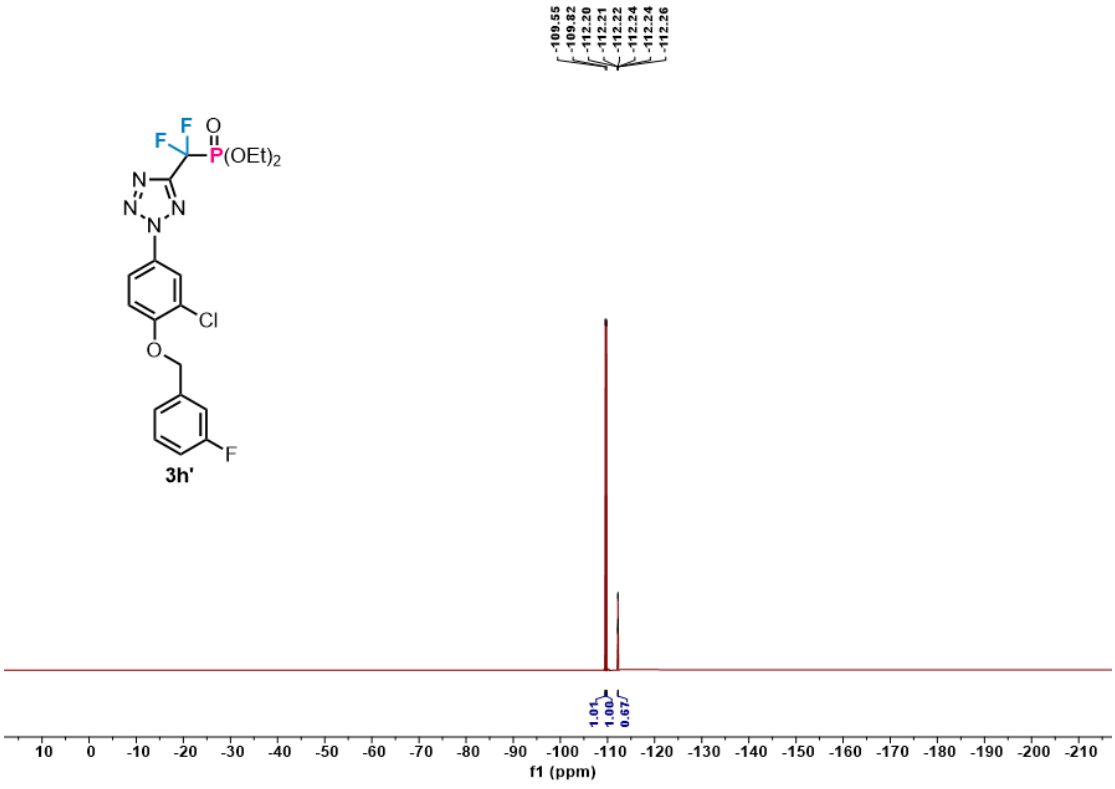
^{31}P-NMR of **3g'** (DMSO-d_6, 162 M)



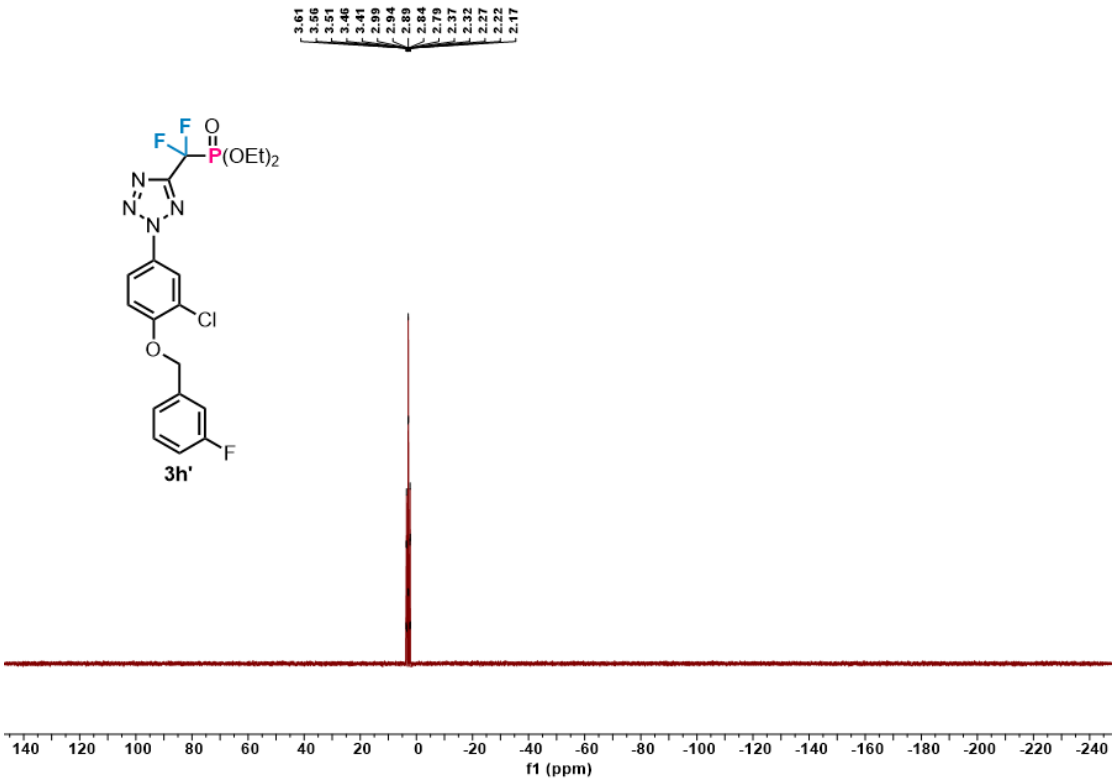
^{13}C-NMR of **3g'** (DMSO-d_6, 101 M)



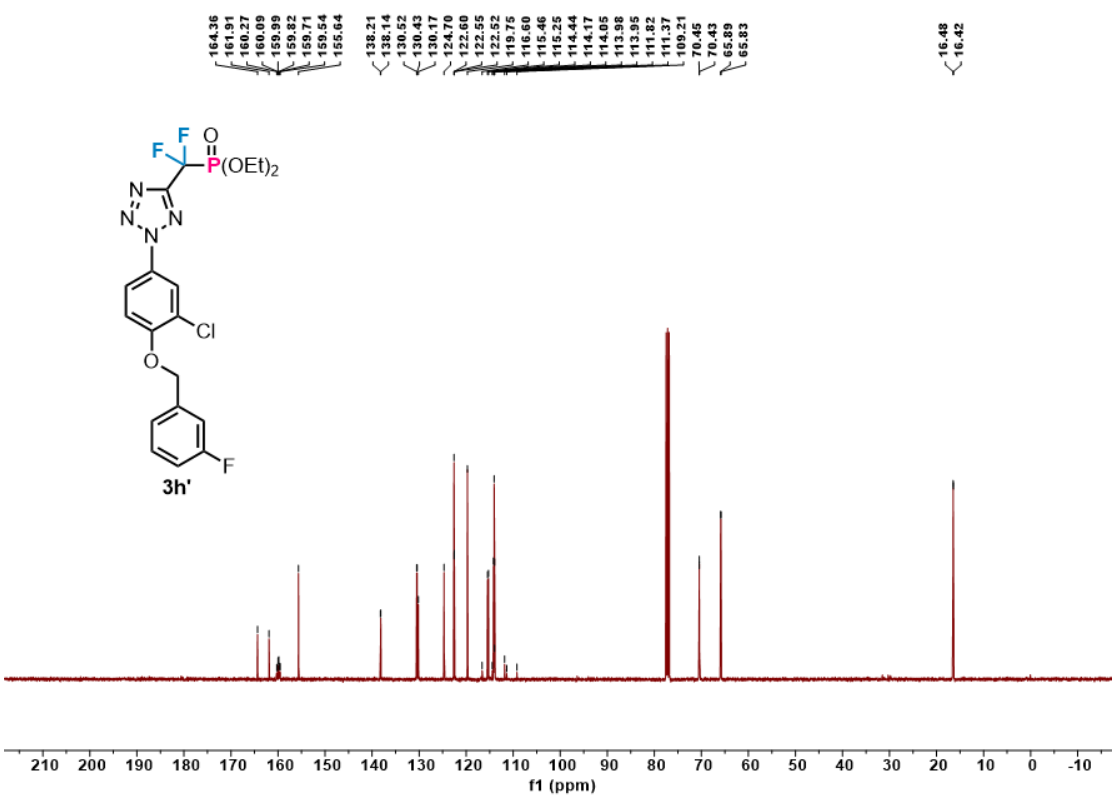
^{1}H-NMR of **3h'** ($CDCl_3$, 400 M)



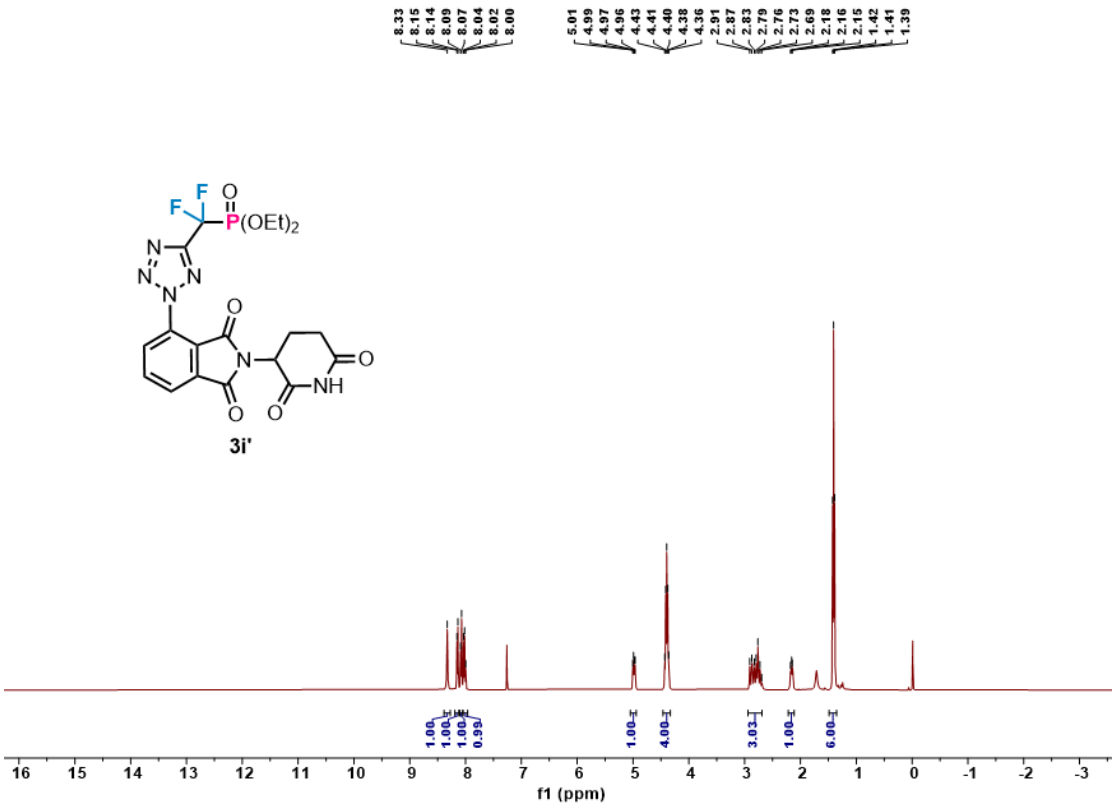
^{19}F-NMR of **3h'** ($CDCl_3$, 376 M)



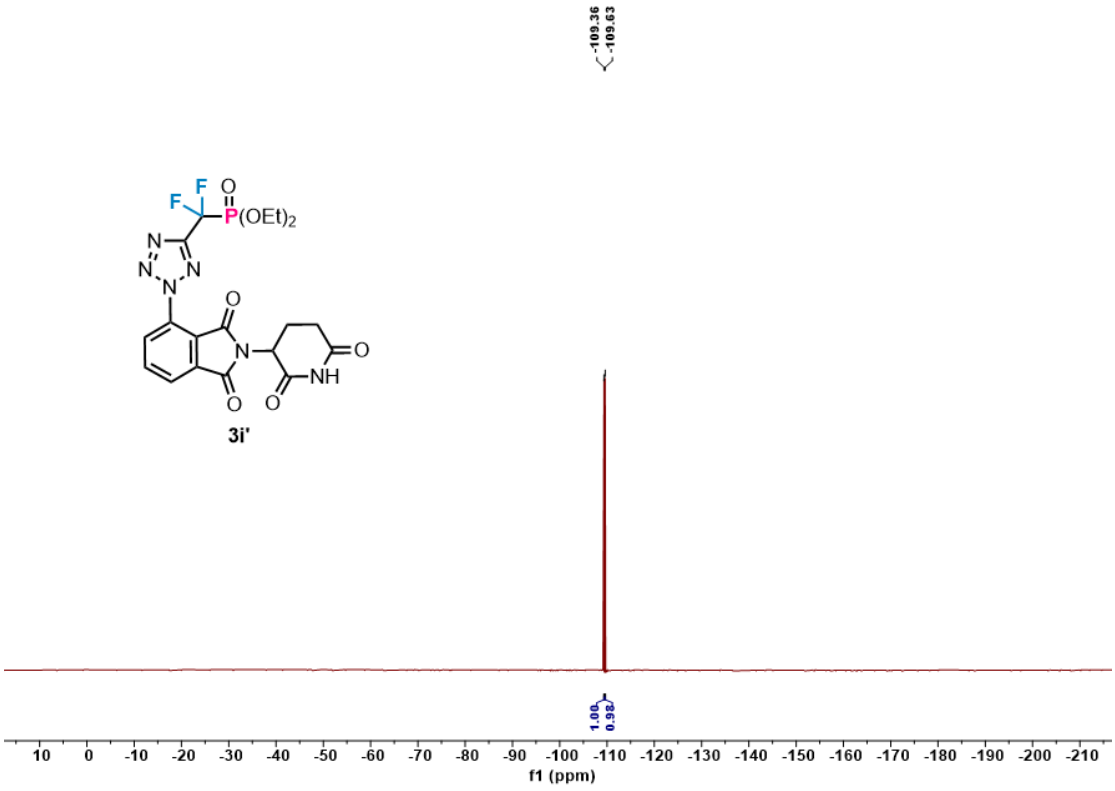
^{31}P-NMR of **3h'** ($CDCl_3$, 162 M)



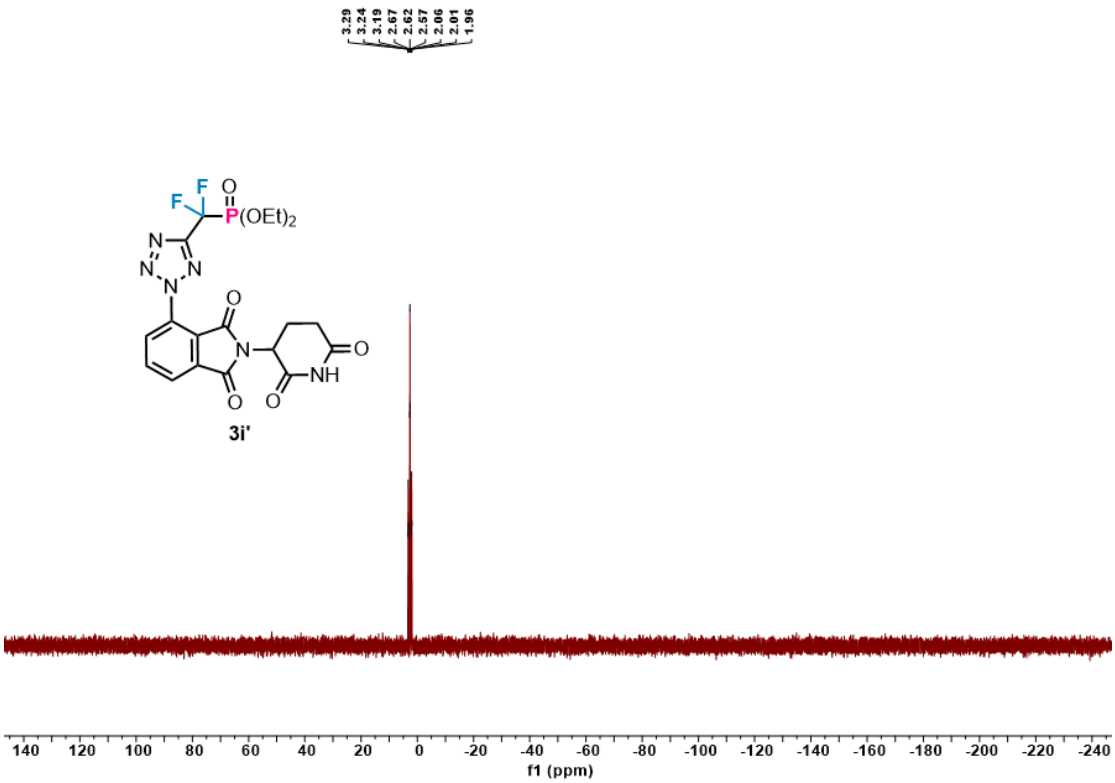
^{13}C-NMR of **3h'** ($CDCl_3$, 101 M)



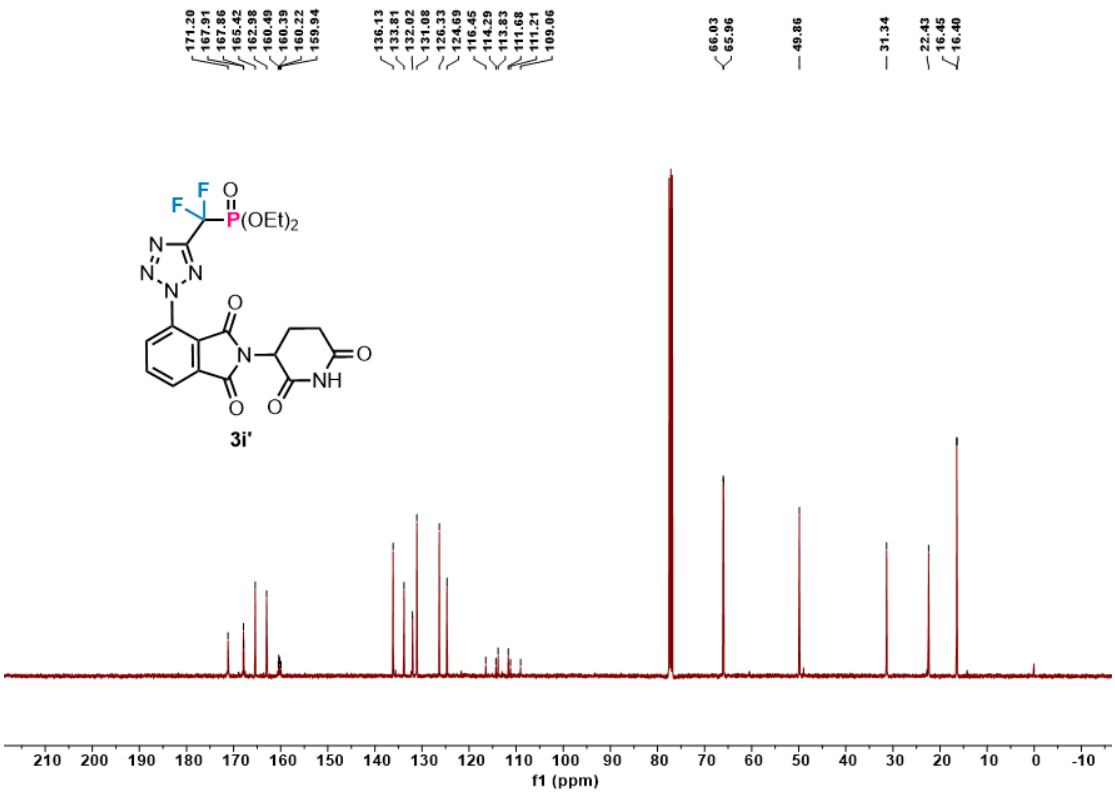
^{1}H-NMR of **3i'** ($CDCl_3$, 400 M)



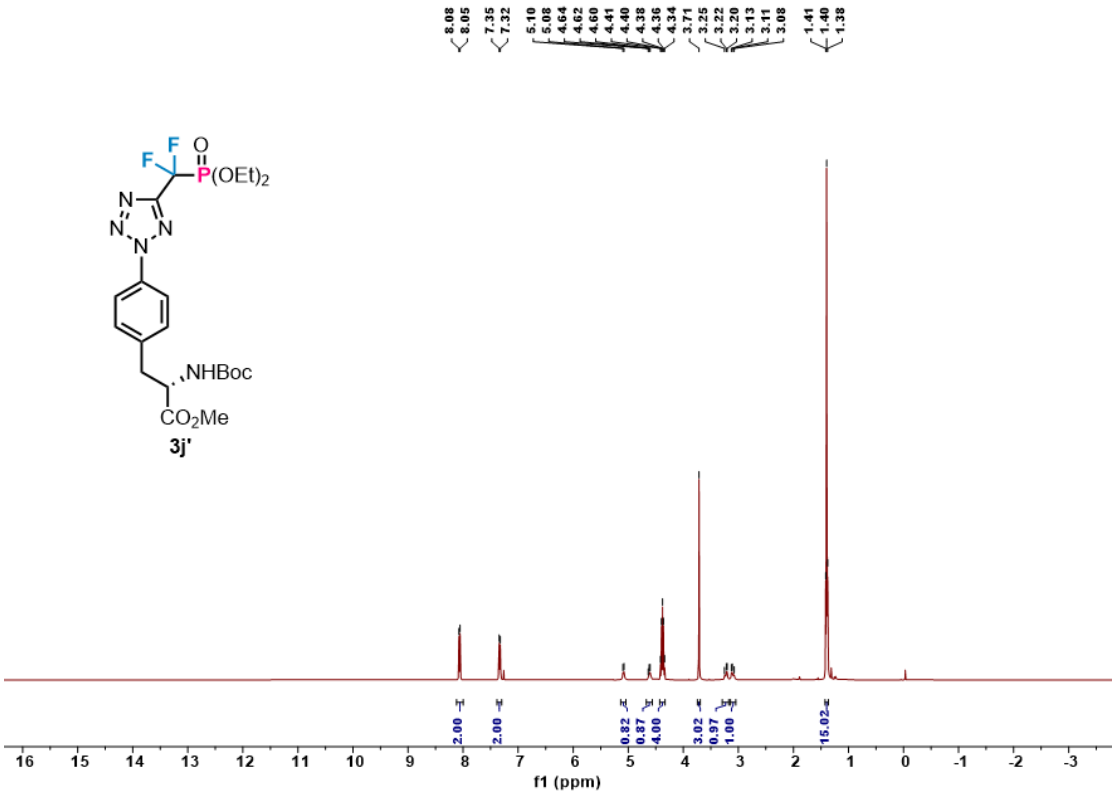
^{19}F-NMR of **3i'** ($CDCl_3$, 376 M)



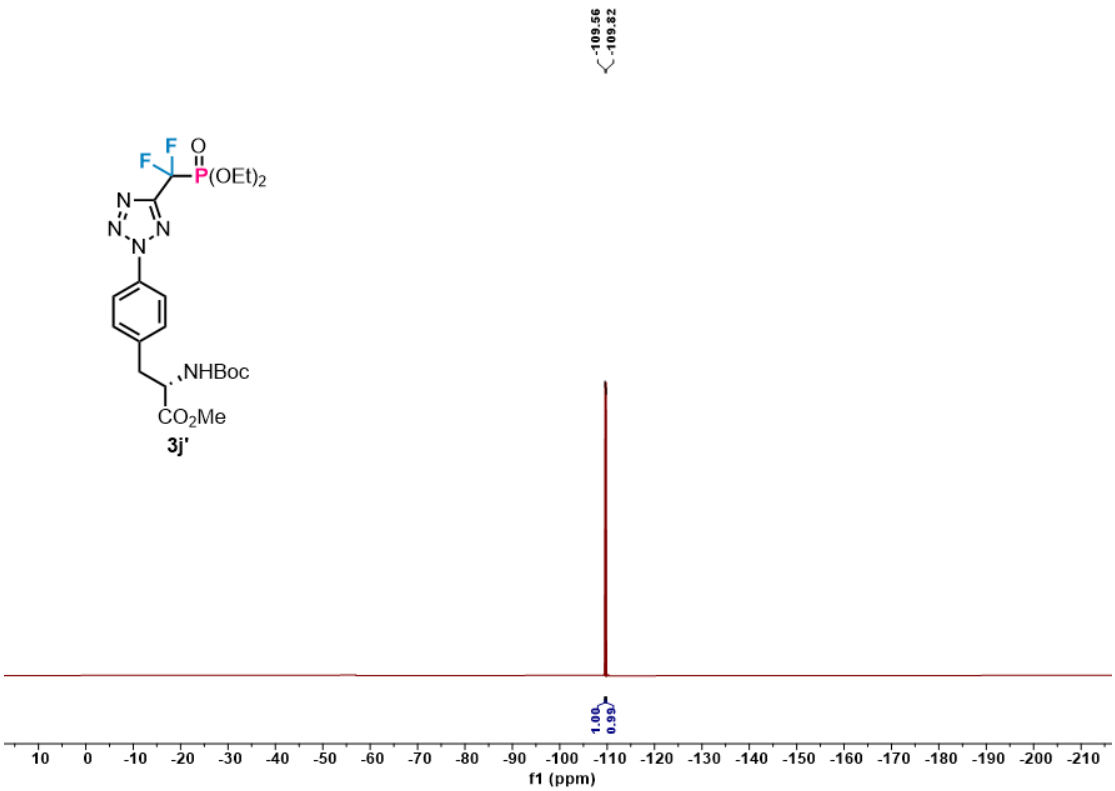
^{31}P-NMR of **3i'** ($CDCl_3$, 162 M)



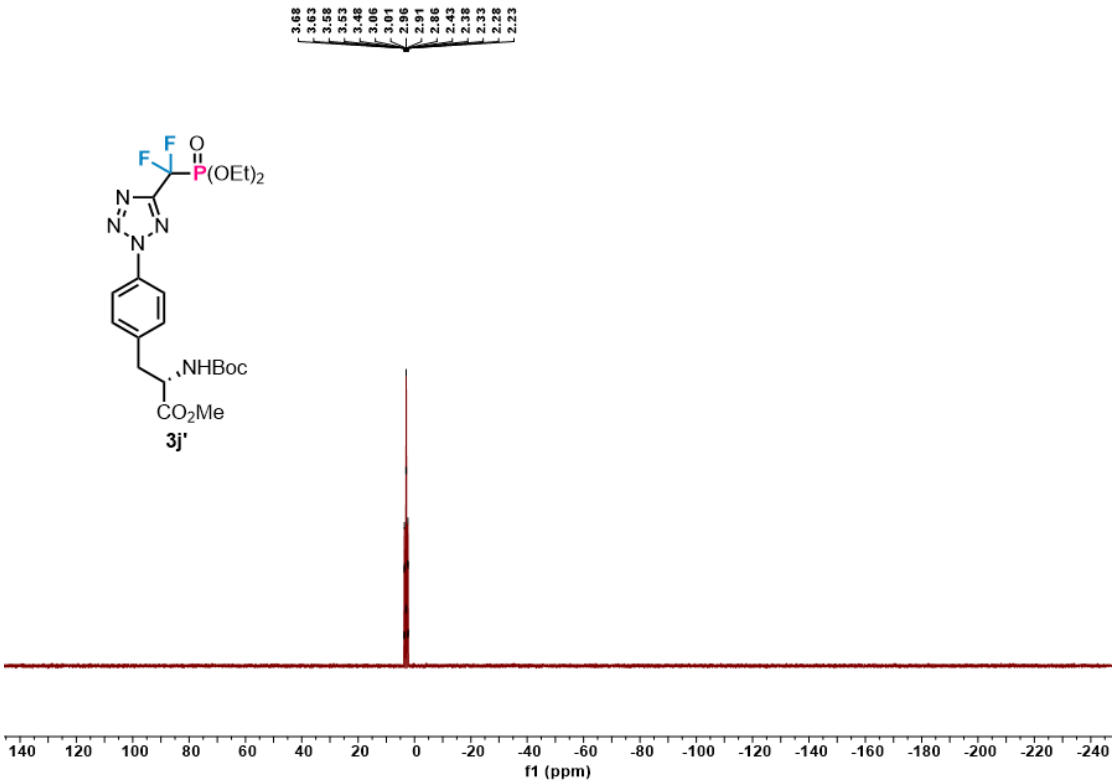
^{13}C-NMR of **3i'** ($CDCl_3$, 101 M)



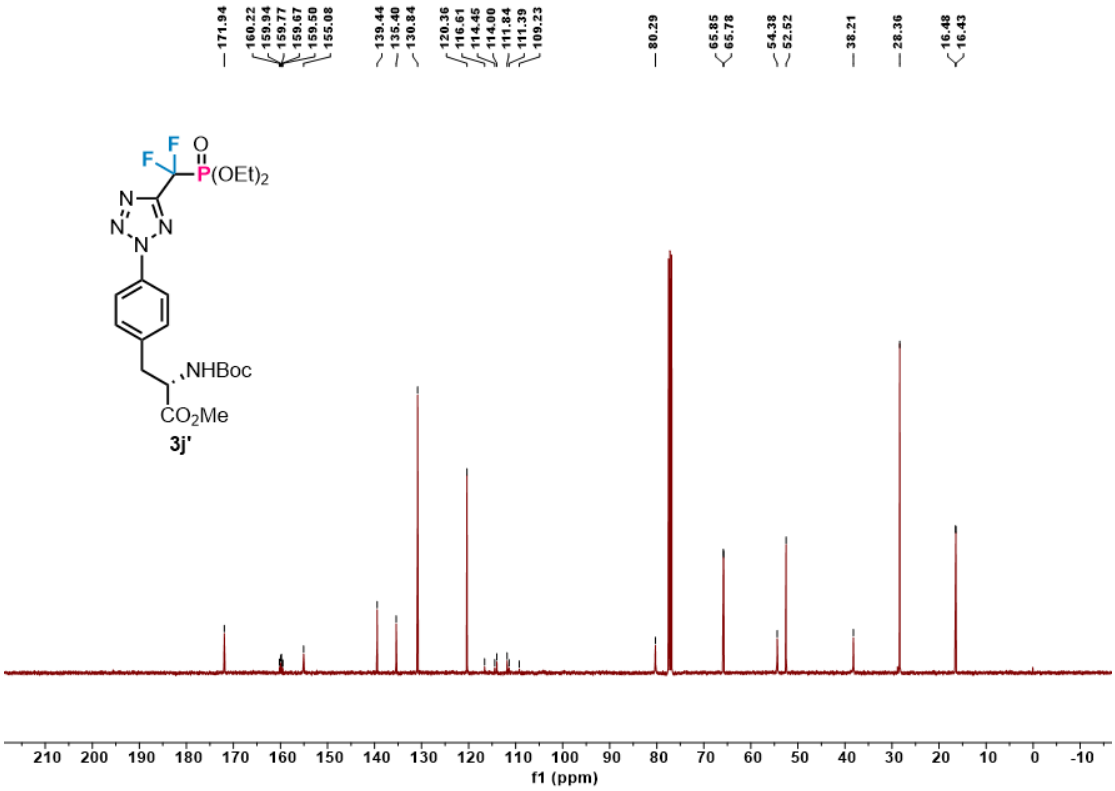
^{1}H-NMR of **3j'** ($CDCl_3$, 400 M)



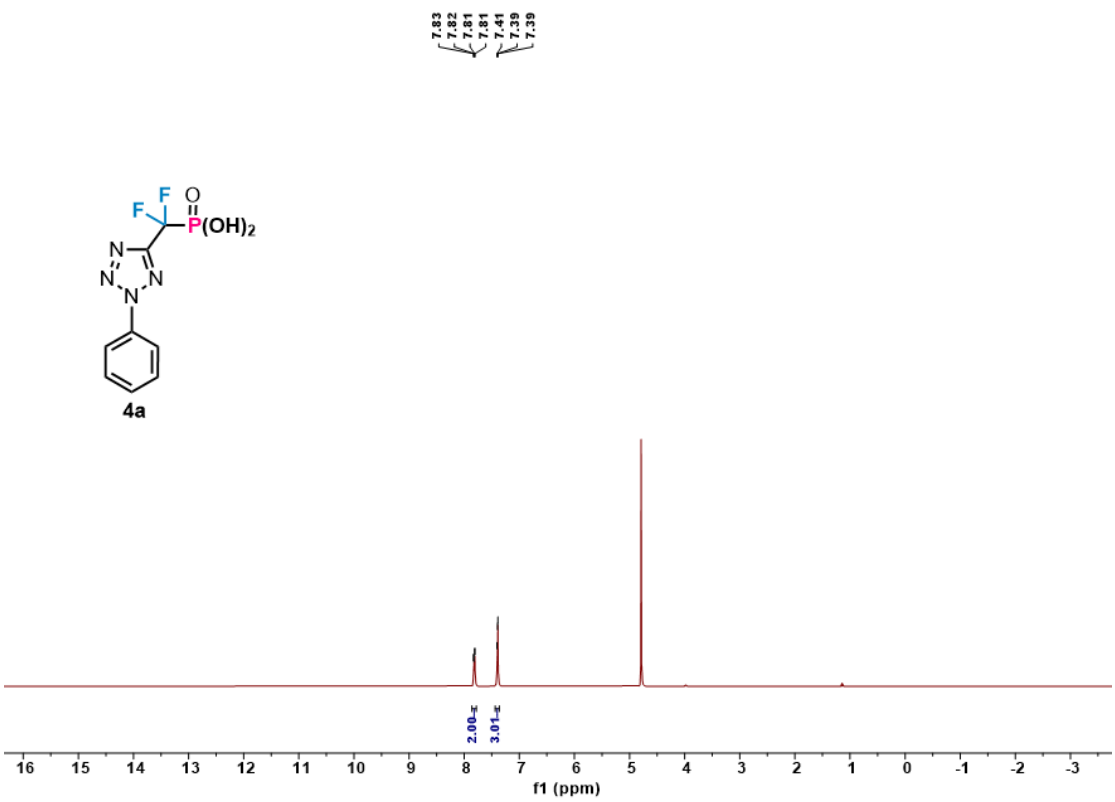
^{19}F-NMR of **3j'** ($CDCl_3$, 376 M)



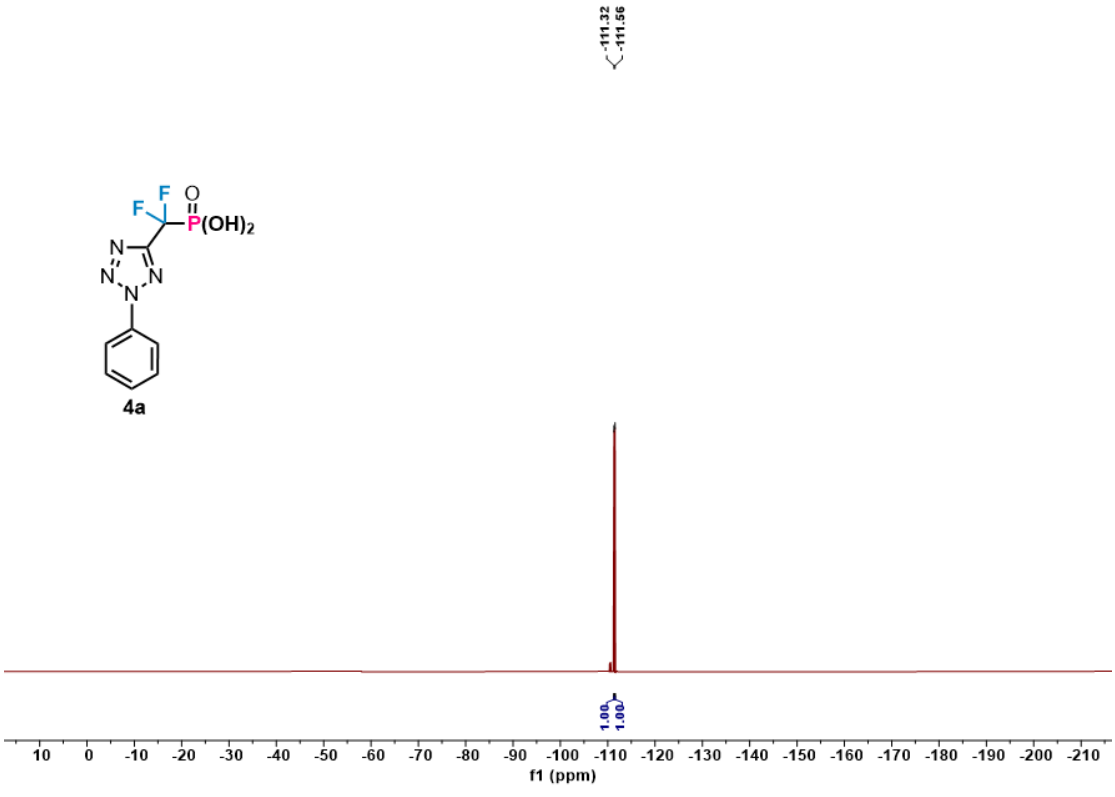
^{31}P-NMR of **3j '** ($CDCl_3$, 162 M)



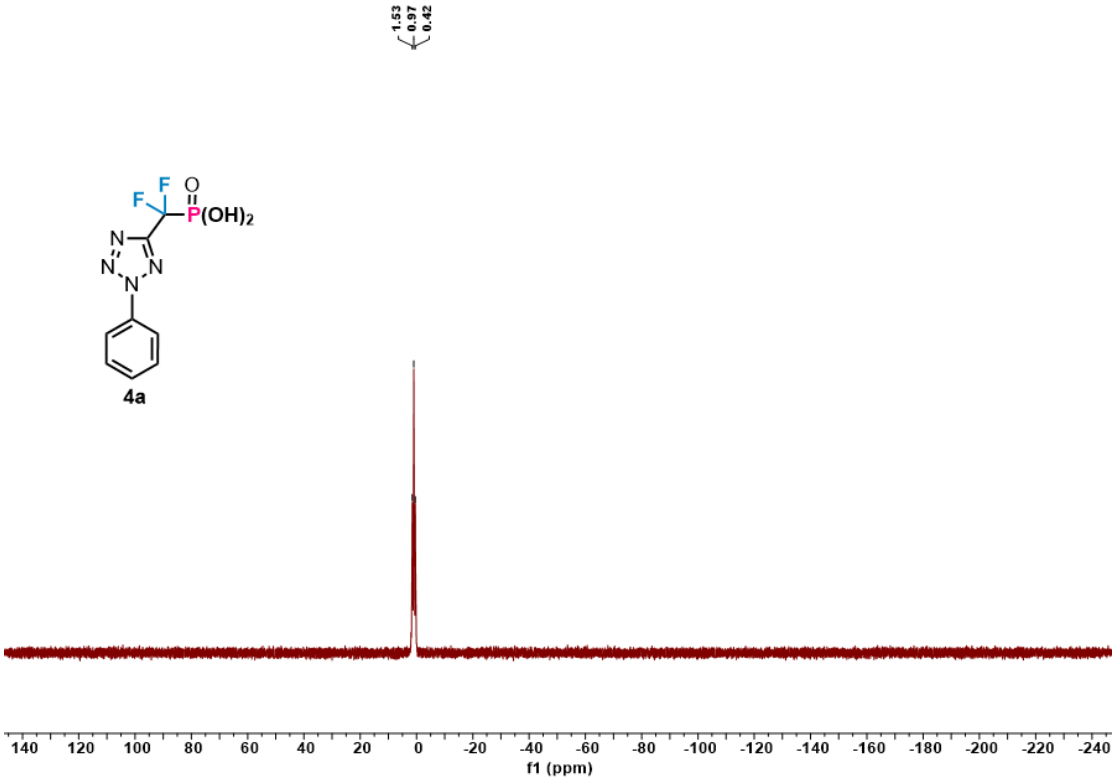
^{13}C-NMR of **3j'** ($CDCl_3$, 101 M)



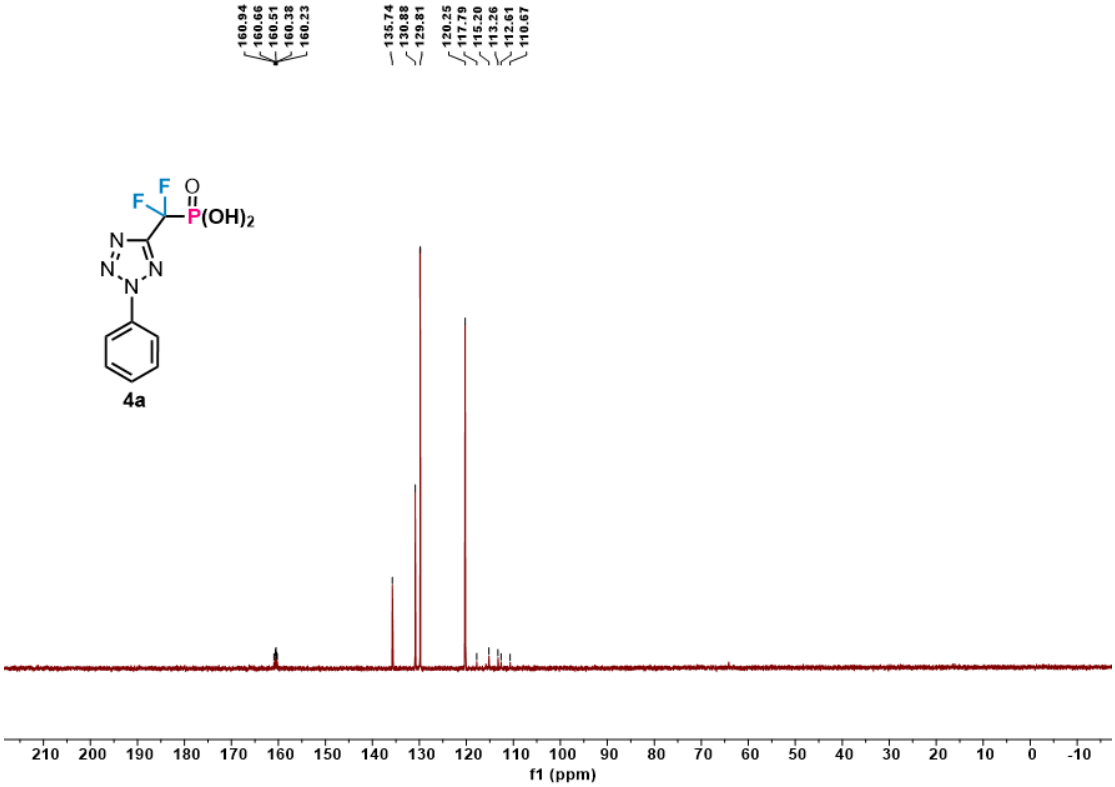
^{1}H-NMR of **4a** (D_2O, 400 M)



^{19}F-NMR of **4a** (D_2O, 376 M)



^{31}P-NMR of **4a** (D_2O, 162 M)

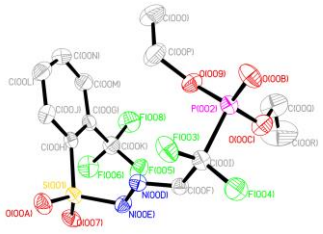


^{13}C-NMR of **4a** (D_2O, 101 M)

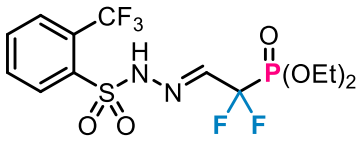
X-Ray Crystallographic Data

Crystal Structure of 1a

(CCDC No. 2014391)



X-ray structure of 1a

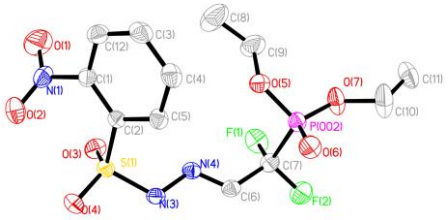


1a

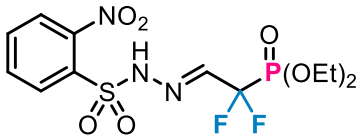
Empirical formula	$C_{13}H_{16}N_2O_5F_5PS$
Formula weight	438.31
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.7965(6)
b/Å	20.1796(13)
c/Å	10.5118(8)
α/°	90
β/°	90.352(6)
γ/°	90
Volume/Å^3	1865.9(2)
Z	4
ρ_{calc}g/cm^3	1.560
μ/mm^{-1}	0.335
F(000)	896.0
Crystal size/mm^3	0.21 × 0.16 × 0.14
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.036 to 58.418
Index ranges	$-11 \le h \le 11$, $-23 \le k \le 26$, $-11 \le l \le 13$
Reflections collected	11186
Independent reflections	4108 [R_{int} = 0.0337, R_{sigma} = 0.0449]
Data/restraints/parameters	4108/0/246
Goodness-of-fit on F^2	1.019
Final R indexes [I>=2σ (I)]	R_1 = 0.0495, wR_2 = 0.1222
Final R indexes [all data]	R_1 = 0.0801, wR_2 = 0.1339
Largest diff. peak/hole / e Å^{-3}	0.49/-0.38

Crystal Structure of 1b

(CCDC No. 2014388)



X-ray structure of 1b

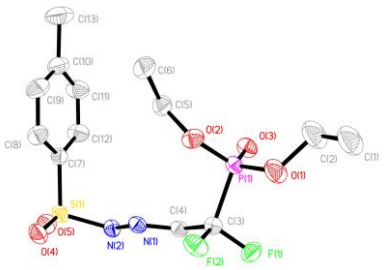


1b

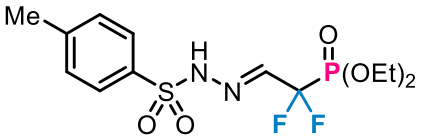
Empirical formula	$C_{12}H_{16}F_2N_3O_7PS$
Formula weight	415.31
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.9091(4)
b/Å	11.0245(6)
c/Å	11.6958(7)
α/°	111.426(5)
β/°	105.144(4)
γ/°	96.832(4)
Volume/Å^3	889.89(9)
Z	2
ρ_{calc}g/cm^3	1.550
μ/mm^{-1}	0.332
F(000)	428.0
Crystal size/mm^3	0.12 × 0.06 × 0.05
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	3.962 to 59.29
Index ranges	-10 ≤ h ≤ 7, -14 ≤ k ≤ 15, -16 ≤ l ≤ 15
Reflections collected	12321
Independent reflections	4130 [R_{int} = 0.0249, R_{sigma} = 0.0278]
Data/restraints/parameters	4130/6/241
Goodness-of-fit on F^2	1.071
Final R indexes [I>=2σ (I)]	R_1 = 0.0428, wR_2 = 0.1148
Final R indexes [all data]	R_1 = 0.0590, wR_2 = 0.1235
Largest diff. peak/hole / e Å^{-3}	0.28/-0.30

Crystal Structure of 1c

(CCDC No. 2014390)



X-ray structure of 1c

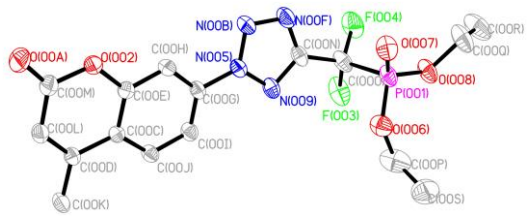


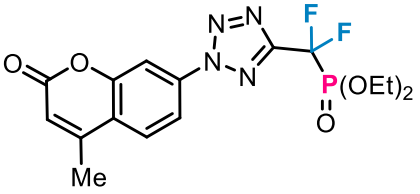
1c

Empirical formula	$C_{13}H_{19}F_2N_2O_5PS$
Formula weight	384.33
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.5115(4)
b/Å	10.6785(4)
c/Å	11.5265(8)
α/°	111.547(5)
β/°	104.967(5)
γ/°	96.358(4)
Volume/$Å^3$	916.40(9)
Z	2
$\rho_{calc}g/cm^3$	1.393
μ/mm^{-1}	0.307
F(000)	400.0
Crystal size/mm^3	0.18 × 0.15 × 0.13
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.014 to 59.15
Index ranges	$-11 \leq h \leq 9$, $-11 \leq k \leq 13$, $-15 \leq l \leq 13$
Reflections collected	12104
Independent reflections	4259 [R_{int} = 0.0271, R_{sigma} = 0.0256]
Data/restraints/parameters	4259/21/214
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0536, wR_2 = 0.1546
Final R indexes [all data]	R_1 = 0.0650, wR_2 = 0.1646
Largest diff. peak/hole / e $Å^{-3}$	0.68/-1.04

Crystal Structure of 3c'

(CCDC No. 2083296)



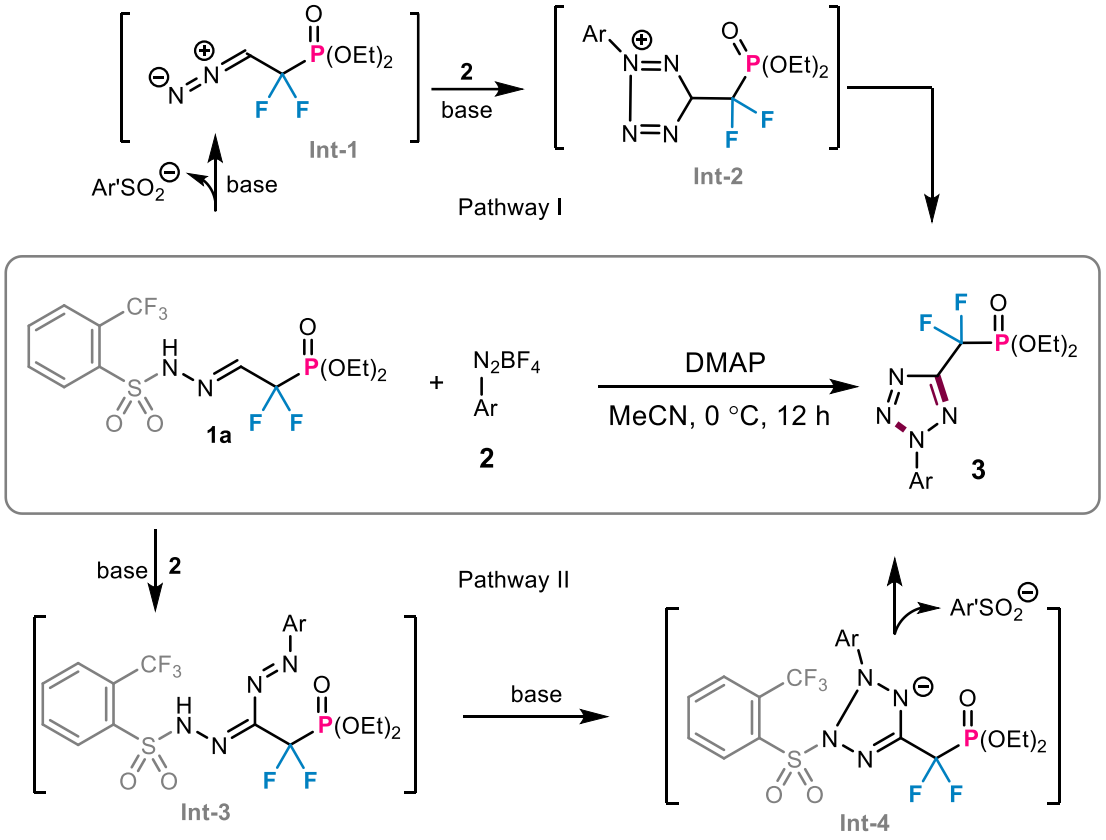


X-ray structure of 3c' **3c'**

Empirical formula	$C_{16}H_{17}F_2N_4O_5P$
Formula weight	414.30
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.7849(4)
b/Å	8.2796(4)
c/Å	15.9785(7)
α/°	100.034(4)
β/°	94.761(4)
γ/°	110.336(5)
Volume/Å^3	939.38(8)
Z	2
ρ_{calc}g/cm^3	1.465
μ/mm^{-1}	0.202
F(000)	428.0
Crystal size/mm^3	0.32 × 0.26 × 0.18
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.444 to 58.806
Index ranges	-9 ≤ h ≤ 10, -8 ≤ k ≤ 10, -20 ≤ l ≤ 19
Reflections collected	11993
Independent reflections	4296 [R_{int} = 0.0759, R_{sigma} = 0.1076]
Data/restraints/parameters	4296/0/256
Goodness-of-fit on F^2	1.010
Final R indexes [I>=2σ (I)]	R_1 = 0.0582, wR_2 = 0.1272
Final R indexes [all data]	R_1 = 0.1237, wR_2 = 0.1461
Largest diff. peak/hole / e Å^{-3}	0.23/-0.28

Proposed Mechanism

We proposed two possible mechanisms for this reaction as shown below. In pathway I, hydrazone **1a** was first transformed to the diazo intermediate **Int-1** via eliminating arylsulfone moiety under basic conditions. 1,3-Dipolar cycloaddition reaction of **Int-1** with aryldiazonium salt **2** proceeded to give the cycloadduct **Int-2**. Final aromatization process led to the tetrazole product **3**. On the other hand, it is also possible that hydrazone **1a** first underwent nucleophilic addition to aryldiazonium salt **2** to generate a formazan intermediate **Int-3**. Then intramolecular cyclization and arylsulfone elimination steps proceeded to give the tetrazole product **3**. We have treated hydrazone **1a** with DMAP in the absence of aryldiazonium salt and didn't observe the formation of diazo species **Int-1**. This control experiment indicated that pathway II is probably more practicable, but pathway I still couldn't be fully excluded.



Checkcif for compound 3c'

X-ray data for compound 1a

Click here to access/download

Crystallographic Data (.zip)

X-ray data for compound 1a.cif

X-ray data for compound 1b

Click here to access/download

Crystallographic Data (.zip)

X-ray data for compound 1b.cif

X-ray data for compound 1c

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Crystallographic Data (.zip)

X-ray data for compound 1c.cif

X-ray data for compound 3c'

Click here to access/download

Crystallographic Data (.zip)

X-ray data for compound 3c.cif

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
