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БОДЕРЖАННЯ ГЕМ-ДИФТОР-ЕНІНОВИХ СПОЛУК ТА ДОСЛІДЖЕННЯ РЕАКЦІЇ ЇХ ГІДРОСИЛІЛЮВАННЯ

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ABSTRACT

Organofluorine compounds hold a significant position in pesticide development and pharmaceutical research due to the unique properties of fluorine atom. However, the synthesis of organofluorine compounds is highly challenging, and effectively introducing fluorinated groups has become one of the major obstacles in the design of new drugs and agricultural chemicals. Among all fluorinated groups, difluoromethyl (CF_2H) has attracted considerable attentions due to its potential to significantly influence or modulate the physical and chemical properties as well as pharmacological characteristics of molecules based on the design of their electronic distribution in biology. Therefore, exploring new reaction systems for introducing difluoromethyl groups is of great interest in synthetic chemistry. Therefore, this thesis focuses on the synthesis of embedded *gem*-difluoro-1,4-ene-ynes and related functional molecules through the propargylation reaction of various nucleophiles with quaternary ammonium salt substrates, without the need for metal catalysts. Additionally, subsequent functional group transformations of these molecules, including the asymmetric hydrosilylation reaction of *gem*-difluoro-1,3-enynes, were studied in this work. The main scientific findings obtained are as follows:

（1）A systematic investigation was conducted on the propargylation reaction of *gem*-difluoro-1,3-dienes with carbon nucleophiles. By utilizing the hydrolithiation reaction of terminal alkynes with lithium metal, an alkyne lithium intermediate was generated, which then reacted with *gem*-difluoro-1,3-dienes substituted with different groups of quaternary ammonium salts. This process enabled the efficient synthesis of multiply substituted *gem*-difluoro-1,4-enyne compounds within a short timeframe (2 hours), achieving outstanding regioselectivity and high yields, up to 99%. The synthesized building blocks can be applied in pharmaceutical molecules. The involvement of metal reagents enhances the nucleophilicity of carbon nucleophiles and increases reaction activity, thus improving reaction rates. The synthesized *gem*-difluoro-enynes can undergo a series of functionalization reactions, reacting with various nucleophilic reagents to yield structurally diverse *gem*-difluoro compounds.

（2）In the context of catalytic construction of silicon-stereogenic centers, we explored the catalytic asymmetric hydrosilylation reaction of *gem*-difluoro-1,3-dienes. Using (3,3-difluoro-1-propynyl)benzene and dihydrosilane as substrates, under the action of palladium catalysts and chiral phosphoramidite ligands, the one-pot reaction procedure was employed to obtain *gem*-difluoro-1,3-dienes containing silicon-stereogenic centers. Preliminary screening of reaction conditions was conducted in this work, in which the chiral phosphoramidite ligand featured a bulky tert-butyl substituent at the meta position of aryl ring, achieving good yield and promising enantioselectivity, with a maximum of 89:11 *er*.

In summary, this thesis primarily focuses on the catalytic reaction systems for the efficient synthesis of *gem*-difluoro-enyne compounds and explores the application of these novel functionalized compounds in the construction of silicon-stereogenic centers. This research provides a new avenue for the synthesis of *gem*-difluoro compounds and their asymmetric catalytic transformations.

Key words: Organofluorine, *gem*-difluoro-enyne compounds, asymmetric catalysis, hydrosilylation reaction

CONTENT

INTRODUCTION

The synthesis and transformation of fluorine-containing functional molecules and their applications in the fields of medicine, energy, and materials science have become an important part of organic chemistry research [1-4]. Since the first introduction of trifluoromethyl group into the psychotropic drug Fluphenazine in 1956 and the synthesis of the first fluorine-containing anticancer drug 5-Fluorouracil in 1957, a large number of fluorine-containing drugs have been reported and clinically applied, the exploration of fluorine chemistry in the field of chemistry has never stopped. Among them, the sidodifluoroalkyl skeleton has attracted much attention because such skeleton possesses unique steric and electronic effects, which can greatly change the bioavailability, lipolysis, affinity, and metabolic stability of organic molecules, etc. At the same time, this kind of skeleton is also widely considered as a metabolically inert bioelectronic isoform of alcohols, carbonyls, and other polar functional groups [5-9] as shown in Fig. 1-1. However, as far as current studies are concerned, there are relatively few examples of selective introduction of difluoromethylene (CF_2) into organic molecules.

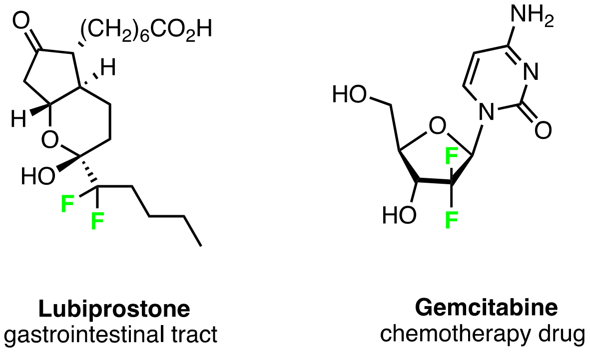


Fig. 1-1 Bioactive fragments containing the kai-difluoroalkyl skeleton

The traditional methods for introducing difluoromethylene mainly include (1) deoxyfluorination, in which aldehydes and ketones and other compounds convert the carbonyl group to difluoromethylene under the action of nucleophilic fluorination reagents [10], but this type of method has a high cost of the reaction, is cumbersome to operate, and has harsh reaction conditions; (2) direct fluorination, in which a free radical or an electrophilic reaction is used to convert the C-H bond to difluoromethylene directly [11-12], this synthetic method is low-cost but poorly operable while the selectivity of the reaction is difficult to control; (3) Fluorine-containing block synthesis, in which the target molecule is obtained from a multistep reaction of a starting fluorinated reagent or fluorinated substrate containing a difluoromethylene [13], which is more feasible, but the reaction steps are complex and require multiple steps to achieve;(4) Ring-opening reaction of difluorocyclopropanes[14-17], in which olefins are cyclopropanated to obtain difluorocyclopropane molecules, which are then ring-opened to obtain the product of ketodifluoromethylenation, but the method has a large limitation in the range of substrates and is poorly generalised (Figure 1-2).

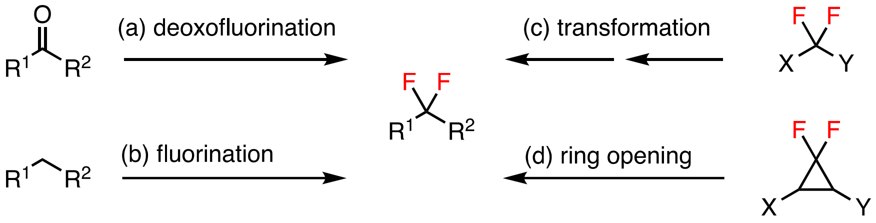


Fig. 1-2 Different strategies for conventional introduction of difluoromethylene

In recent years, with the vigorous development of transition metal-catalysed difluoroalkylation reactions, more new methods have been developed to achieve the effective introduction of difluoromethylene[18-24]. Among them, the ability to use more efficient and simple reaction systems to accomplish the effective introduction of difluoromethylene is of great significance for the advancement of medicinal chemistry and materials science. In this thesis, we reviewed the trifluoromethyl compound defluorination reactions, different types of difluoroalkylation reactions, and the preparation and application of highly efficient and general fluorination reagents developed in recent years, and on the basis of which, we individually summarized, collated, and summarized the preparation and application of new and practical, stable, and highly active sidodifluoroallylation reagents developed in recent years, with the aim of exploring the new difluoroalkylation reactions and synthesizing novel and practical fluorine-containing reagents. Synthesis of novel and practical fluorine-containing functional molecules**.**

1 LITERATURE REVIEW

1.1 Reaction and conversion studies of halogenated difluoroalkyl reagents

1.1.1 Difluoroalkylation in the presence of a difluorocarbin reagent

Difluorocarbines are important intermediates used in the synthesis of fluorinated organic compounds, and the reactions in which they are involved play important roles in the fields of pharmaceuticals, pesticides, and materials, etc. In 2013, the group of Jin-Bo Hu[25] reported an efficient and practical new methodology for the construction of C-C multiple bonds and the difluoromethylation reaction of heteroatom reagents. A novel class of difluorocarbene reagents, namely bromodifluoromethyltrimethylsilane ($TMSCF_2Br$)**1**, was developed, which is a powerful synthetic tool as a difluorocarbene source that can produce difluorocarbenes under mild reaction conditions, has a wide range of substrate applicability, and exhibits nearly orthogonal reactivity for a variety of functional groups that can be reacted with difluorocarbenes. The method reported by this group uses a simple synthetic means to prepare kedifluorocyclopropanes **3** using olefins **2** as the reaction substrate, while this type of carbene reagent can be converted to kedifluorocyclopropenes **5** with mono- and disubstituted alkynes **4** in high yields, and the reaction can be carried out smoothly when both electron-withdrawing and electron-donating groups are introduced on the alkynes; it is worth noting that propargyl ester and alkynyl sulfide can also be used to promote the reaction in the reaction conditions. promote the reaction, which is the first demonstration of the completion of difluoromethylation of alkynes using a difluorocarbin reagent (Fig. 1-3).

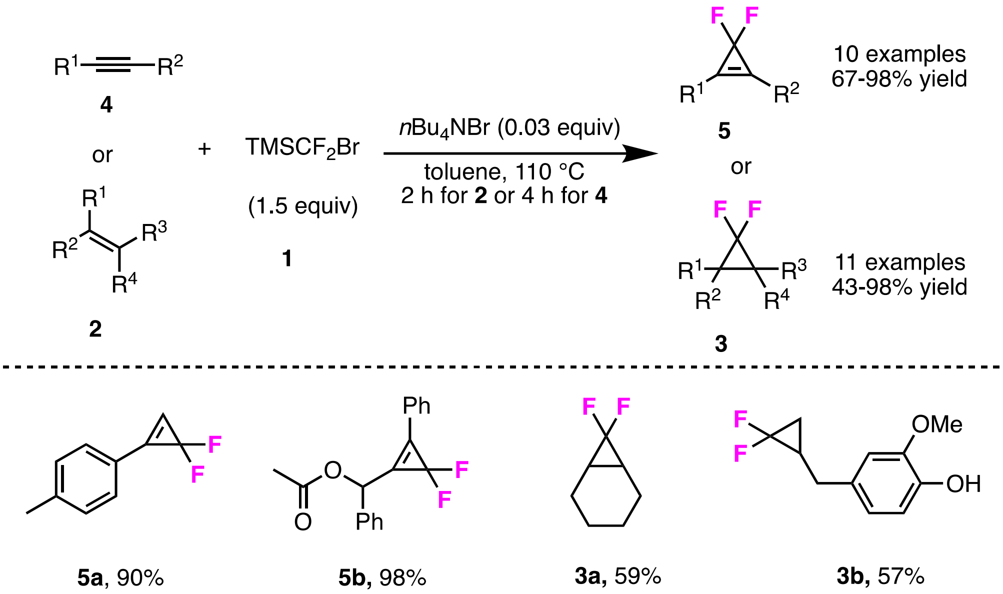


Fig. 1-3 Difluoromethylation reactions involving diflocarbine

Based on the development of this class of reagents, in 2019, a three-component strategy was realised by the group of Jinbo Hu[26] using $TMSCF_2Br$ **1**. The reaction proceeds by in situ generation of difluorocarbin, which is subsequently trapped by $PhSO_2Na$ **7** or ArSNa **8** to form the corresponding $PhSO_2^-$ or $ArSNa^-$ anion, and then undergoes nucleophilic addition with the aldehyde 6 to obtain the desired difluoromethylated product **9**, **10**; this three-component strategy allows $TMSCF_2Br$ as a source of difluoromethylene and $PhSO_2^-$ or ArS^- as a nucleophilic reagent for rapid introduction of difluoromethylene into aldehydes, which avoids the need to prepare $PhSO_2CF_2X$ or $PhSCF_2X$ (X = H, Br, TMS) reagents in multiple steps beforehand, allows the introduction of different aromatic thiols into the target product through the use of differently substituted aromatic thiols, and with the ability to simultaneously change both ends of the $-SCF_2-$ group, the method has a great potential for the rapid construction of analogues substituted with $-SCF_2-$ potential, which is favourable for drug development and late modification of bioactive molecules. In the reaction due to the weak electrophilicity of aldehydes, they promoted the reaction by adding metal salts as Lewis acids to activate the carbonyl group (Fig. 1-4).

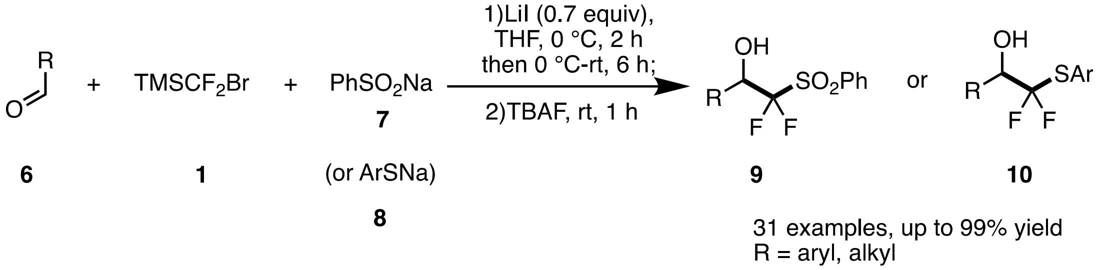


Fig. 1-4 Nucleophilic difluoromethylation of aldehydes by TMSCF$_2$Br

This three-component strategy proposes a rational mechanistic recycling route, where CF$_2$ is generated by a Lewis base activator (LB- = PhSO$_2^-$, PhS$^-$, or **10**), which is captured by a nucleophilic reagent (Nu-= PhSO$_2^-$ or PhS$^-$), and a difluoromethyl carbon negative ion is given to generate NuCF$_2^-$. This carbon negative ion undergoes nucleophilic addition with the aldehyde activated by LiI to give the alcohol salt **11** (path A). Since TMSCF$_2$Nu was observed as a by-product in the reaction, another pathway was also proposed in which NuCF$_2^-$ reacted with TMSCF$_2$Br to produce TMSCF$_2$Nu, which then reacted with the aldehyde (upon activation by the Lewis base activator) to produce **11** (Pathway B). The reaction of **10** with TMSCF$_2$Br to give **12** is accompanied by the formation of difluorocarbin, which is immediately followed by desilication of **11** using TBAF to give the final product **9** or **10** (Fig. 1-5).

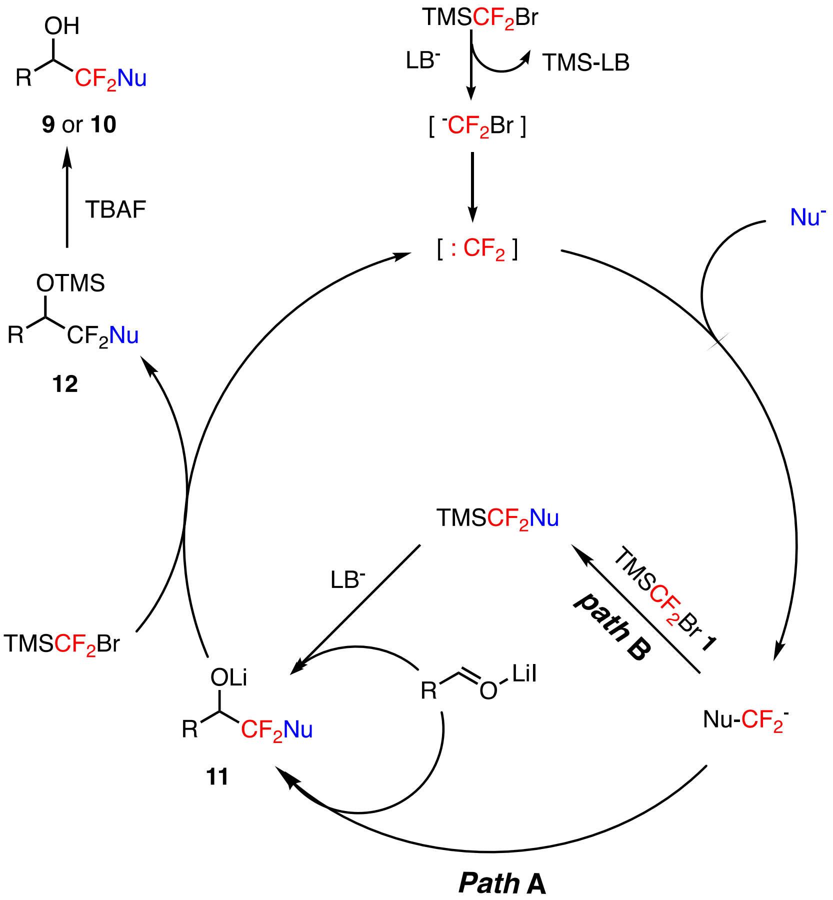


Figure 1-5 Mechanism loop diagram for realising the three-component strategy

Inspired by the above three-component strategy, a three-component reaction for the efficient synthesis of α-difluoro-β-amino amides **15** was reported by the group of Jianbo Wang[27] in 2019. The reaction utilised isonitrile compound **14** and difluorocarbin reagent **1** to synthesise an unreported difluoroalkenimine **16**, which subsequently undergoes a [2+2] addition reaction with N-sulfonimine **13** in situ, which is further hydrolysed to give the target product α-difluoro-β-amino amide **15**. The obtained difluoroalkenimine **16** can be used as a difluoroethylenone (difluoroethylenone is very unstable, it's highly susceptible to decomposition, irreversibly breaking down to CO and difluorocarbin) as a substitute. The reaction conditions are mild, the yield can reach 94 %, the compatibility of substrate functional groups is good and the synthesis can be achieved on the gram scale. The presence of the difluoroalkenimine **16** intermediate was demonstrated in the mechanistic validation by signal peaks in19 FNMR and high-resolution mass spectra (Fig. 1-6).

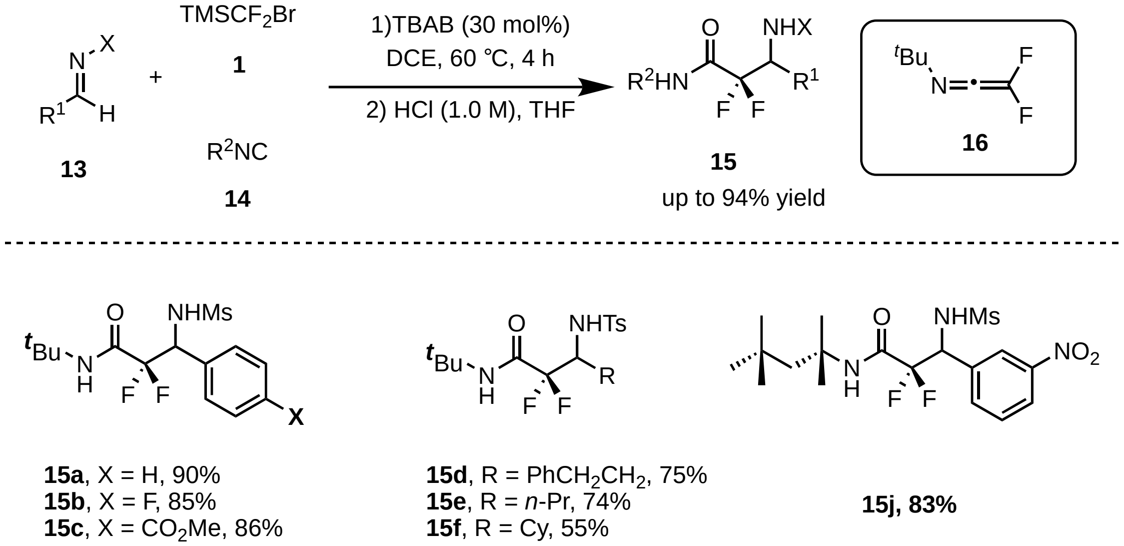


Fig. 1-6 [2+2] cyclisation via a three-component strategy

Inspired by this reaction intermediate, in 2022, the group of Jinbo Hu[28] envisioned whether the reaction of fully selective insertion of a difluoromethylene into a C-H bond could be achieved by forming an intermediate. Therefore they reported the first synthesis of the relatively stable 2, 2, 3, 3-tetrafluorocyclopropanol methylsilyl ether intermediate **18** using the difluorocarbene reagent $TMSCF_2Br$ **1** to achieve the first fully controllable insertion of a difluoromethylene into the C-H bond of an aldehyde in the absence of transition-metal catalysis as an example of the first fully controllable insertion of a difluoromethylene into an aldehyde **17**, and controlling C1 (single CF_2 insertion) and C2 (double CF_2 insertion) to achieve the fully selective insertion. Complete conversion of intermediate **18** can be achieved in the reaction to obtain structurally diverse ketones **19** containing CF_2 or CF_2CF_2 structures, which is difficult to achieve using transition metal mediation. The intermediate permits reaction with a variety of electrophilic reagents and can not only be protonated by aqueous hydrochloric acid to give the target product, but can also be successfully halogenated, enabling it to be used in the synthesis of other halodifluoromethyl ketones and halotrifluoroethyl ketones. Notably, the synthesis of this intermediate is critical for the controlled insertion of CF_2 into the reaction successfully (Fig. 1-7).

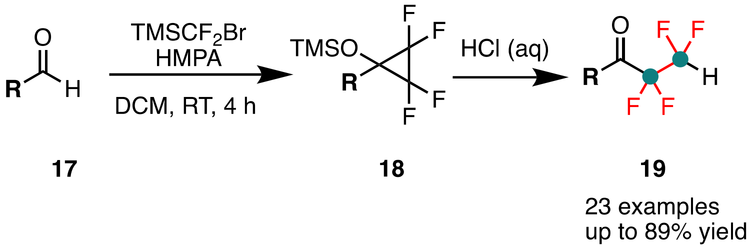


Fig. 1-7 Difluoromethylene controlled insertion reaction of aldehyde C-H bonds under the action of $TMSCF_2Br$

In 2024, Jinbo Hu's[29] group again utilised the difluorocarbene reagent $TMSCF_2Br$ **1** as the sole fluorine source in the reaction, and achieved trifluoroalkenylation and pentafluoroalkenylation of aldehydes via a controlled carbon-fluorine chain extension strategy. The reaction starts with $TMSCF_2Br$ as a source of $TMSCF_2$ radicals, followed by a coupling reaction to generate $TMSCF_2CF_2TMS$ **21**, and the unisolated $TMSCF_2CF_2TMS$ **21** with aldehyde **20** to form trifluoroolefin **22** containing two fluorinated carbon atoms, and then $TMSCF_2Br$ was utilised as a difluorocarbene precursor (:CF_2) to react with in situ formed trifluoroolefin **22** to undergo a [2+1] cycloaddition reaction to produce pentafluorocyclopropane **23** containing three fluorinated carbon atoms, the first time from C1 to C2 and from C1 to C3 was achieved. The key to the success of this approach lies in the unique and diverse chemical reactivity of $TMSCF_2Br$ **1**, which can be used as two different reaction precursors, i.e., the $TMSCF_2$ radical precursor and the difluorocarbene precursor. The wide range of substrates for this reaction, aromatic aldehydes substituted with different functional groups were successfully converted to the corresponding trifluoroolefins and pentafluorocyclopropanes under standard conditions, and the single-crystal structural characterisation of the compounds further confirmed that the new products had a pentafluorocyclopropyl alcohol structure, and the gram-scale reaction also successfully proved the potential application of the methodology (Fig. 1-8).

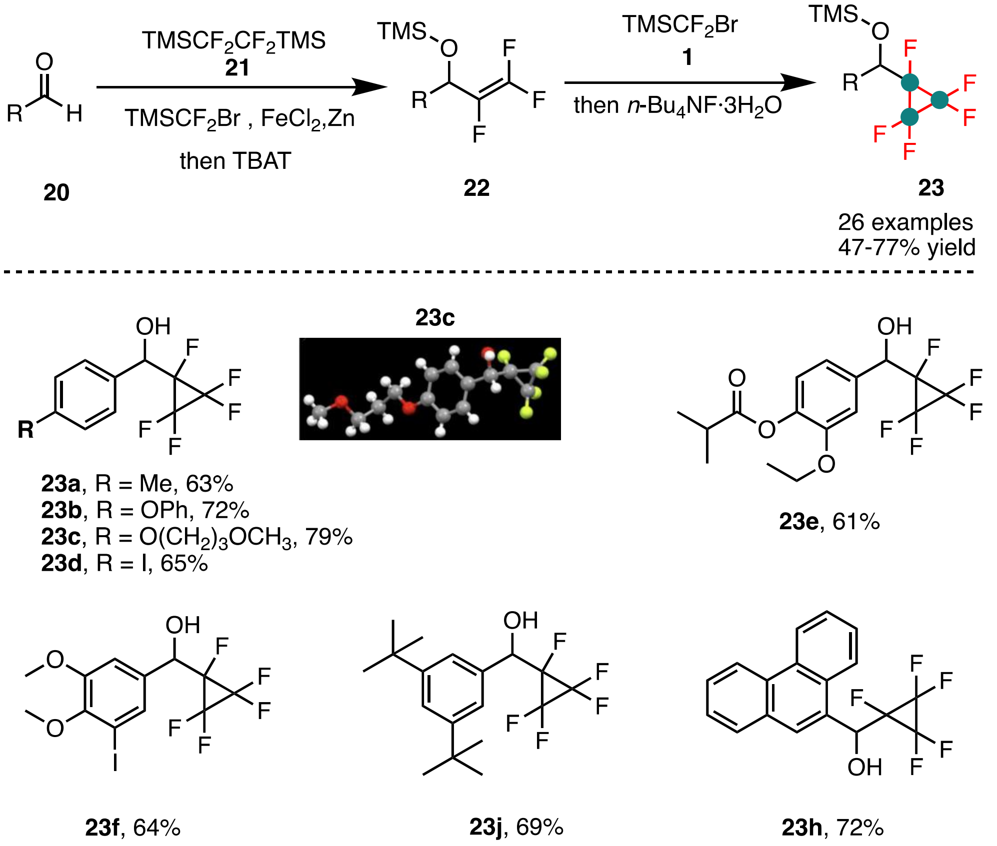


Fig. 1-8 Trifluoroalkenylation and pentafluorocyclopropylation of aldehydes by TMSCF$_2$Br reagent

1.1.2 Fluorohalogen-substituted radical difluoroalkylation reactions

In 2015, Xinguang Zhang's[30] group reported the synthesis of 6-difluoroalkylphenanthridine derivatives **26** by the radical addition reaction of 2-isocyanatobiphenyl compounds **24** with difluoroalkyl halides **25** in the presence of a palladium catalyst, which was the first difluoroalkylation reaction catalysed by the use of a transition metal. The reaction has a wide range of substrates and is highly applicable, and it is noteworthy that when the isocyanide reaction with a pyridine rather than a benzene ring was still able to proceed smoothly, the target product was obtained in 76 % yield, thus proving the potential application of this reaction in medicinal chemistry; at the same time, it was reflected in the experimental process that the reaction is not limited to difluoroalkyl bromides, and perfluoroalkyl iodides are also applicable substrates for the reaction, which once again proves the versatility of the method was again demonstrated. In the control experiments, it was found that the target products were not observed in the absence of palladium catalyst or phosphine ligand, proving that both palladium and phosphine ligands do play an important role in promoting the reaction (Fig. 1-9).

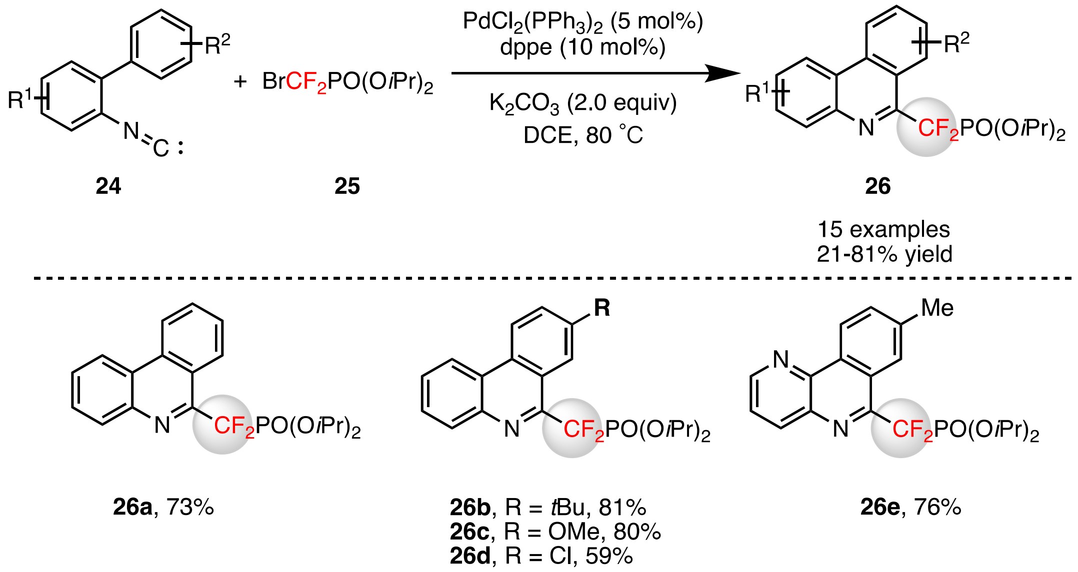


Fig. 1-9 Palladium-catalysed difluoroalkylation of difluoroalkyl bromide reagents with isocyanides

A rational reaction mechanism was subsequently proposed for this reaction. The reaction is initiated by the [Pd0(Ln)]-promoted SET pathway to produce the difluoroalkyl radical **27** and [PdI(Ln)X]. Subsequently **27** reacts with isocyanide **24** to form the cyclohexadienyl radical **29**. Subsequent to the use of a base to capture the proton from **29** to produce the radical anion **30**, **30** reacts with [PdI(Ln)X] via the SET pathway to obtain the product **26** and regenerate [Pd0(Ln)] (Pathway I). However an alternative pathway via the SET process via **30** reaction with difluoroalkyl bromide **25** to obtain the product **26** and the difluoroalkyl radical still cannot be excluded. In addition, recombination of [PdI(Ln)X] with **29** to produce the palladium complex **31** followed by *β*-hydrogen elimination to produce the product **26** and simultaneous regeneration of [Pd0(Ln)] is also a possible pathway (Pathway II) (Fig. 1-10).

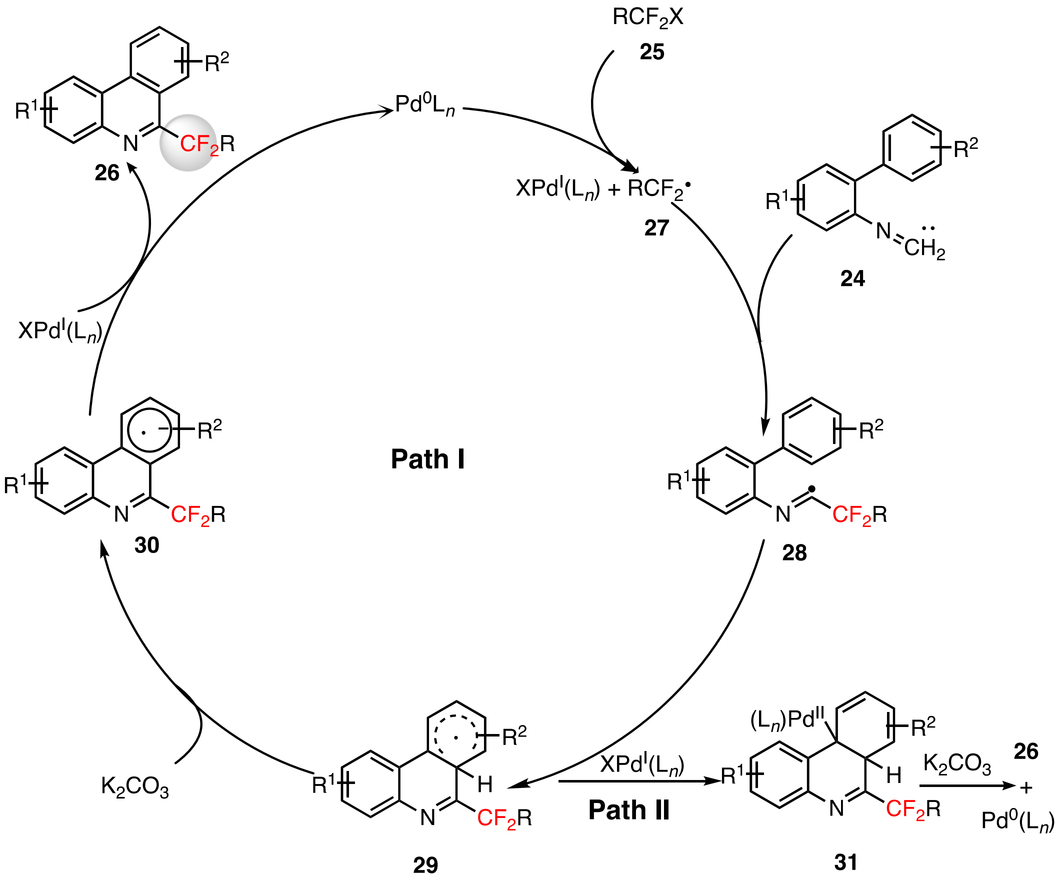
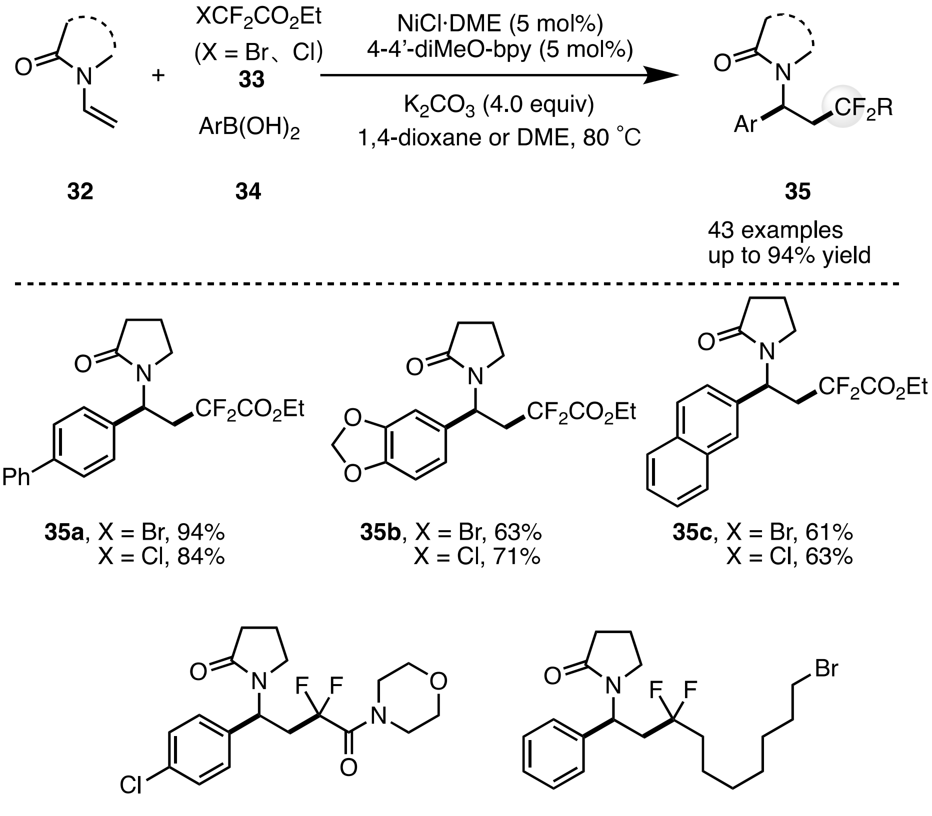


Fig. 1-10 Cyclic diagram of the mechanism of the palladium-catalysed difluoroalkylation reaction of difluoroalkyl bromides with isocyanides

Inspired by this transition metal catalytic mechanism, in 2016, the group of Xingang Zhang[31] reported a three-component strategy for the first nickel-catalysed tandem alkenamide difluoroalkylation/aromatisation reaction. By capturing the difluoroalkyl radical using an olefin, chelating the nickel complex with the aid of a ligand group in commercially available electron-rich olefinic enamides **32** having a carbonyl group as a chelating group, and facilitating its recombination with the newly formed alkyl group to obtain the final target product **35**. The development of this methodology was able to avoid the formation of a number of other by-products; the reaction is characterised by a low catalyst cost, a simple synthetic pathway, the possession of a wide The reaction has the advantages of low catalyst cost, simple synthetic route, wide range of substrates, and high reaction efficiency, and the scope of the reaction can be extended to a variety of different substituents of arylboronic acids **34** and difluoroalkyl halides **33** , and chlorodifluoroacetic acid, which is relatively less reactive, is also resistant to the reaction, which demonstrates that the reaction has a wide range of applications; this nickel-catalysed three-component reaction will promote the research of the synthesis of alkyl fluoride compounds from simple substrates at low cost, and provide an opportunity for the development of nickel-catalysed three-component reaction to obtain the final target product **35**. This nickel-catalysed three-component reaction will facilitate the low-cost synthesis of fluoroalkylated compounds from simple substrates and provide a new idea for the enantioselective synthesis of difluoroalkylated compounds by nickel-catalysed radical/cross-coupling reactions (Fig. 1-11).



35a, X = Br, 94%
X = Cl, 84%

35b, X = Br, 63%
X = Cl, 71%

35c, X = Br, 61%
X = Cl, 63%

35d, 63%

35e, 60%

Fig. 1-11 Nickel-catalysed difluoroalkylation/aromatisation of tandem enamides

In 2018, Pengfei Xu's[32] group reported for the first time the use of a difluoroalkyl bromine reagent **36** to generate difluoroalkyl radicals **37** under visible-light induction, which, together with p-methylene quinone analogues **38** to generate radical precursors of diarylmethyl radical intermediates 39 via a photocatalytic one-electron reduction process, followed by a radical-radical cross-coupling reaction to synthesise biologically active as well as potentially Diaryl difluoroalkyl compounds **40** with biological activity and potential medicinal value were synthesised; the presence of diarylmethyl radical39 and difluoroalkyl radical **37** was detected in the system using high-resolution mass spectrometry in the radical capture experiments; the reaction was mild, efficient, and had wide functional group compatibility, and the reaction was able to take place smoothly for both p-methylene quinone compounds substituted with electron-donating and electron-absorbing groups, and was also supported by ester, carbonyl, amide, and amide radicals. group, carbonyl group, amide group, heteroaryl group and other substituents modified by ester group, carbonyl group, amide group, heteroaryl group and other substituents also have good reactivity, and the reaction system can be effectively applied to monofluoroalkylated diaryl compounds, and finally the structure of the products of the reaction was further confirmed by X-ray single-crystal diffraction analysis (Fig. 1-12).

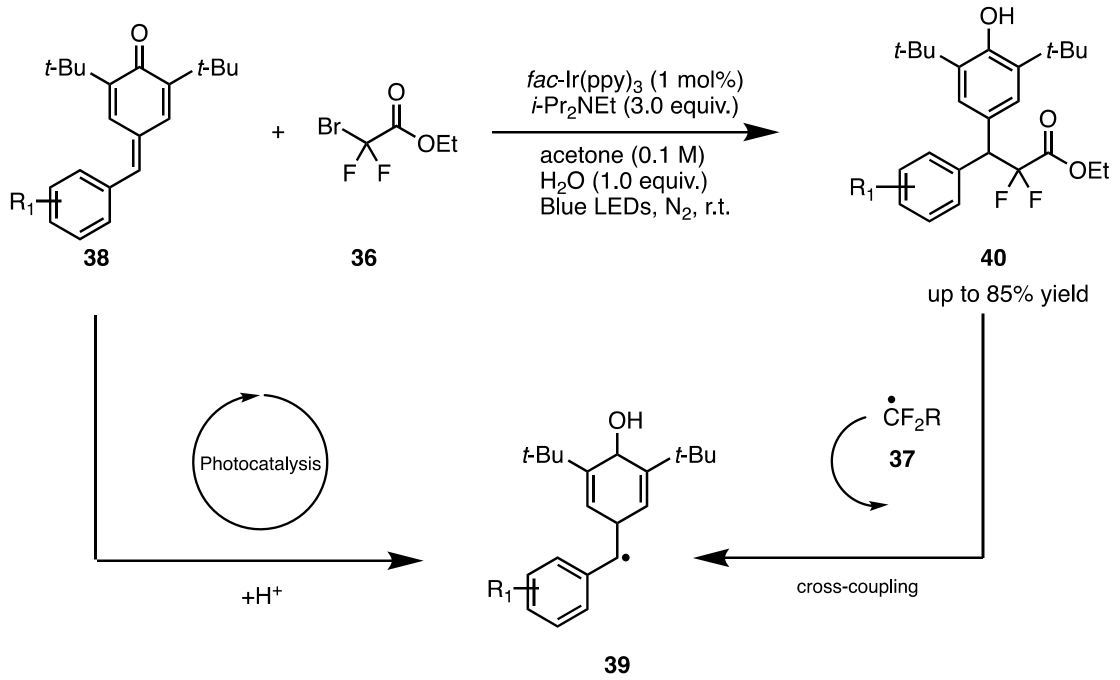


Fig. 1-12 Visible light-induced radical-radical cross-coupling reaction

Currently, most of the nickel-catalysed olefin difunctionalization reactions focus on bis-arylation or aryl-alkylation reactions, while fewer reports have been made on the bis-alkylation of olefins, mainly due to the fact that there are great challenges associated with this type of reactions, including how to avoid β-hydrogen elimination of alkyl-nickel species and how to inhibit cross-coupling reactions of the two competing components, which have been unresolved issues for a long time. Therefore, in 2019, the group of Xinguang Zhang[33] reported the difluoroalkyl-alkylation reaction of vinyl-containing pyrrolidone compounds **41** with difluoroalkyl bromine reagents **42** and dialkyl zinc **43** in the presence of a nickel catalyst. This report presents the first bisalkylation of an alkene based on a CGA strategy to simultaneously construct two C-C bonds in a single step to synthesise a series of structurally diverse ketodifluoropyrrolidinones **44**, which are of great value for applications in medicinal chemistry. The reaction conditions are mild, substrate universality is good, and it is well compatible with a wide range of difluoroalkyl halides as well as various types of dialkyl zinc reagents, while the reaction can be extended to other types of alkenylamines; it is worth noting that the carbonyl group in the pyrrolidinone is essential in facilitating the reaction, similarly to the results of the group's research in 2016[31]. The role of the carbonyl group is to chelate with the nickel complex in order to facilitate the recombination of the nickel complex with the newly formed alkyl radical material, thus facilitating the catalytic cycle to obtain the final target product **44**. In the mechanistic validation it was demonstrated that the reaction produces a difluoroalkyl radical (Fig. 1-13).

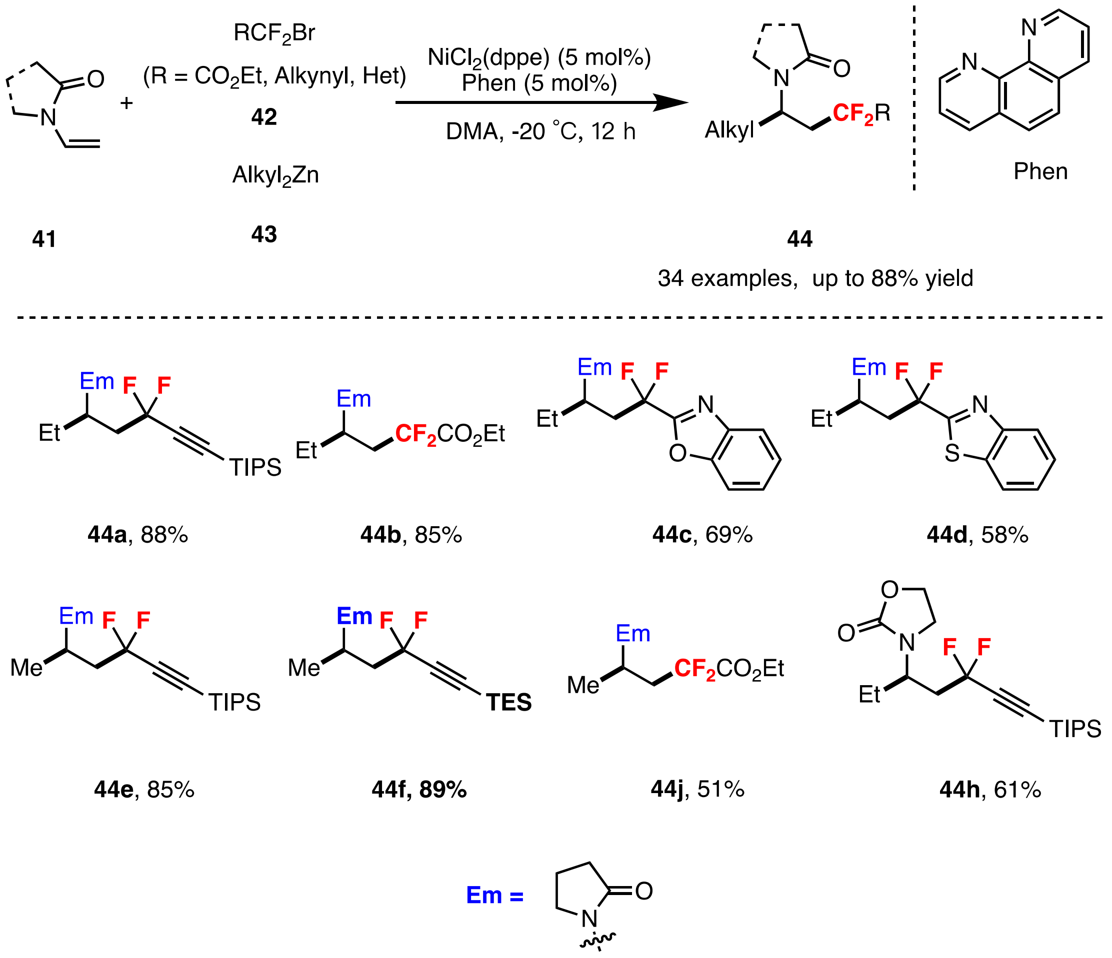


Fig. 1-13 Nickel-catalysed enamide difluoroalkyl-alkylation reaction

Due to the unique chemical properties of fluoroalkyl groups, olefins with substitution by fluoroalkyl groups have great application value in life sciences as well as in the field of materials, among which fluoroalkyl alkenyl borates are important building blocks for the synthesis of fluorinated olefins, but so far there are very few methods to construct fluoroalkyl alkenyl borates efficiently and with high stereoselectivity. Therefore, in 2019, Xingang Zhang's[34] group successfully achieved the palladium-catalysed trans-fluoroalkylation-boronation reaction of alkynes **45** with fluoroalkyl iodides **46** and bipinacol boronic esters **47** based on the above metal-catalysed radical cross-coupling reaction. The synthesis of this system is applicable to different difluoroalkyl as well as perfluoroalkyl iodides, and can highly selectively convert various alkynes (including endoalkynes and terminal alkynes) into trans-fluoroalkyl alkenyl boronates **49**, which are difficult to obtain by conventional routes, and a variety of important functional groups, such as halogens and azides, are compatible with the reaction. The reaction product **49** can also serve as an important synthetic building block for numerous transformations; in radical trapping experiments, it was demonstrated that fluoroalkyl radicals are produced during this reaction and in kinetic experiments, it was shown that the reaction generates the key reaction intermediate fluoroalkylated alkenyl iodo substituent **48**, but its generation is not the decisive rate step of the overall reaction, the subsequent boronisation reaction determines the overall rate of the reaction; it is worth noting that It is noteworthy that all the trisubstituted and tetrasubstituted fluoroalkylated alkenyl boronic esters, which have never been reported before, are now synthesised by this reaction and can be used as generic structural units for the synthesis of fluorinated complex molecules for use in the life and materials sciences (Fig. 1-14).

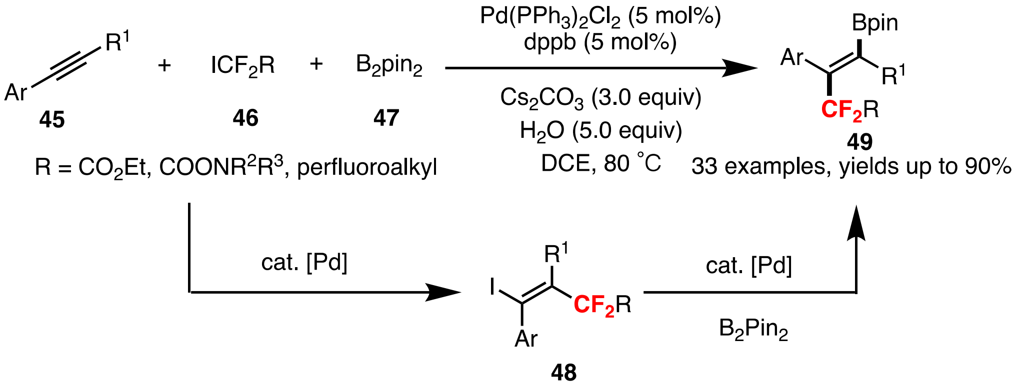
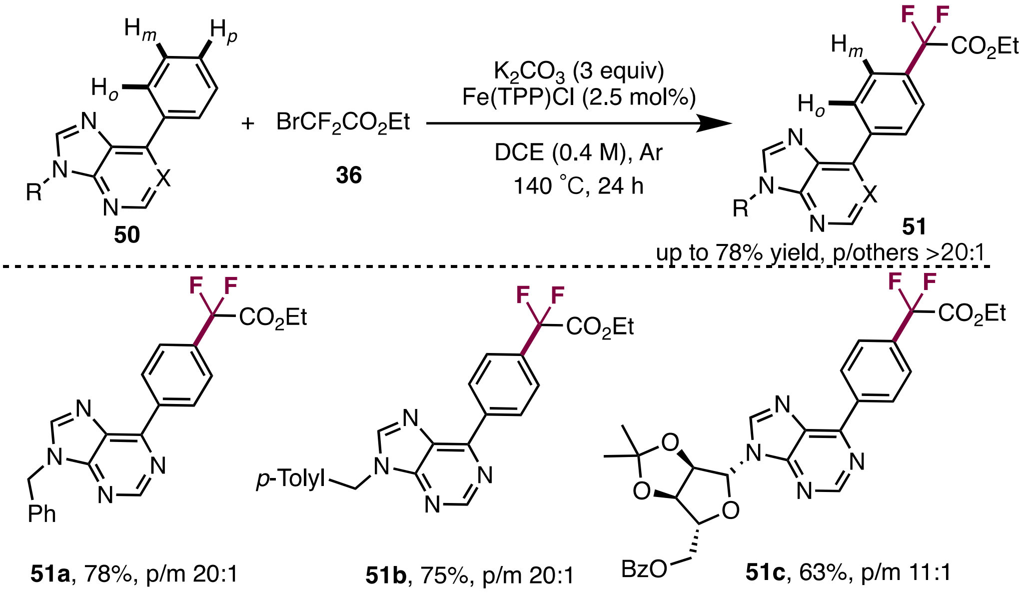


Fig. 1-14 Palladium-catalysed trans-fluoroalkylation-boronation of alkynes with fluoroalkyl iodides

In 2020, Ying-Sheng Zhao's[35] group successfully realised a highly para-selective difluoromethylation reaction of aromatic hydrocarbons via iron-catalyzed, catalyst and heteroatom transient coordination activation substrate strategy; the reaction was performed with a benzyl-protected aryl purine **50** as a template substrate, using $BrCF_2CO_2Et$ **36** as a difluoromethyl source, and catalysed by Fe(TPP)Cl iron catalysts to obtain the target product in 78 % yield and 20:1 (para:meta) selectivity to obtain the target product **51**. The reaction has a wide range of substrates, both benzyl-substituted and alkyl-substituted, and the difluoromethylated product was obtained in good to excellent yields with high chemoselectivity. It is noteworthy that the nucleoside substrates likewise showed a good tolerance to the reaction; preliminary mechanistic studies showed that the iron catalyst in the preliminary mechanistic study showed that the ethyl difluoroacetate radical was generated under the action of the iron catalyst, and the iron complex not only activated the aromatic hydrocarbons, but also induced the highly para-difluoromethylation reaction by using the spatial site-blocking effect of its own tetraphenylporphyrin (TPP) (Fig. 1-15).



51a, 78%, p/m 20:1 **51b**, 75%, p/m 20:1 **51c**, 63%, p/m 11:1

Fig. 1-15 Iron-catalysed highly para-selective difluoromethylation of aromatic hydrocarbons

1.2 Selective defluorination of trifluoromethyl compounds

1.2.1 Selective defluorination of trifluoromethyl aromatic hydrocarbons

In 2017, Konig's group[38] reported for the first time the successful activation and breaking of C(sp^3) -F single bonds in trifluoromethyl aromatic hydrocarbons by combining the Ir photoredox catalytic process with the Lewis acid activation reaction. Using the capture reagent methacrylamide **52** as the proton source and p-cyanoyl-substituted trifluorotoluene **54** as the reaction substrate, fac-Ir(ppy)$_3$ was selected as the photocatalyst to construct the defluorination reaction of trifluoromethyl aryl hydrocarbons under the blue light irradiation (455 nm), and the aryl difluoromethylated product with the breakage of the C(sp^3)-F single bond was obtained **53**. In the reaction, frequency the combination of the naphthol borane (HBpin) and the amine TMP with no α-H in the spatial site resistance significantly improved the reaction efficiency, whereas no target product was observed for this reaction in the absence of either HBpin or TMP. The novelty of the reaction is that it provides a simple and highly atom-economical method to construct aryl difluoroalkyl backbones, which are highly investigated in medicinal chemistry, and controlled single $C(sp^3)$ - F bond breakage through the synergistic effect of spatial and electronic effects, with the disadvantage of poor substrate universality and major limitations (Fig. 1- 16).

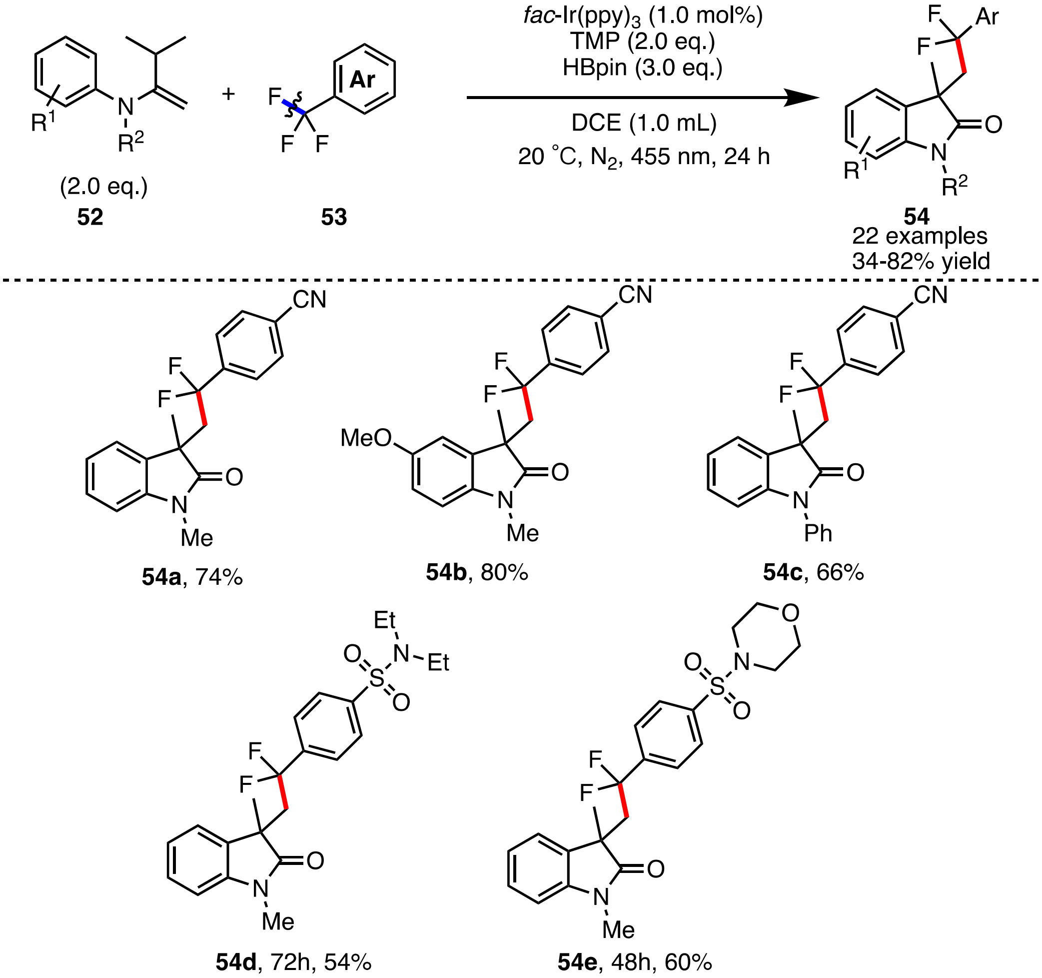


Fig. 1-16 Photocatalytic selective defluorination of trifluorotoluene with enamides

In 2018, Jui's group[39] reported a new catalytic approach using two cheap and readily available organic small molecule catalysts (as photoredox catalysts) as catalytic drivers, and regeneration of the two catalysts via sodium formate **57**, which acted synergistically in order to accomplish the transfer of electrons and hydrogen atoms. Under commercial blue LED irradiation, using trifluoromethyl aryl hydrocarbons **55** as substrates, their one-electron reduction leads to the formation of difluorobenzyl radicals **58** via a C-F bond cleavage mechanism, followed by further intermolecular coupling of such radicals **58** with olefins **56** during defluorinated alkylation, wherein radical abortion is achieved via a polar inversion catalyst, with light and sodium formate **57** as stoichiometric reagents to construct a catalytic defluorinated alkylation reaction of trifluoromethyl aryl hydrocarbons with unactivated olefins. The reaction conditions were mild and compatible with a wide range of functional groups, where the conversion of mono-substituted, 1, 1-disubstituted and trisubstituted olefins gave the target product **59** in good yields (78-89 %) with full regiocontrol (Fig. 1-17).

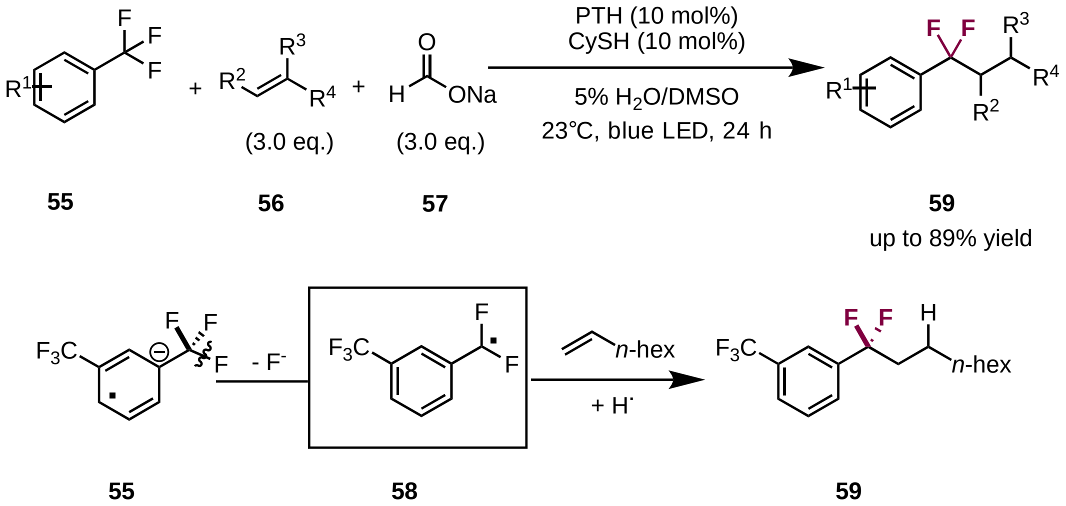


Fig. 1-17 Photocatalytic defluorinated alkylation of trifluoromethyl aromatic hydrocarbons with unactivated olefins

In 2019, Bandar's[40] group used trifluoromethylaromatics **60** and allyltrimethylsilanes **61** as substrates to obtain allylated α,α-difluorobenzyl derivatives by coupling via a single electron transfer (SET) mechanism **62**. In this reaction, for 2-substituted allyltrimethylsilanes a single 1, 1-disubstituted allyl compound can be obtained; whereas asymmetric allylsilanes (e.g., 3, 3-(dimethyl)allyltrimethylsilane) yield regional isomers, and the method is equally applicable to the derivatisation of aprepitant, an antiemetic drug approved for marketing by the FDA, to prepare the corresponding allyl derivatives. Some allyl compounds are unstable and difficult to isolate and purify, but the advantage of this method is that such difficult-to-purify allyl compounds can be converted to a variety of functional groups, such as Schwartz's reagent and iodine to iodoalkanes, and Heck coupling with aryl halides to obtain stable products (Fig. 1-18).

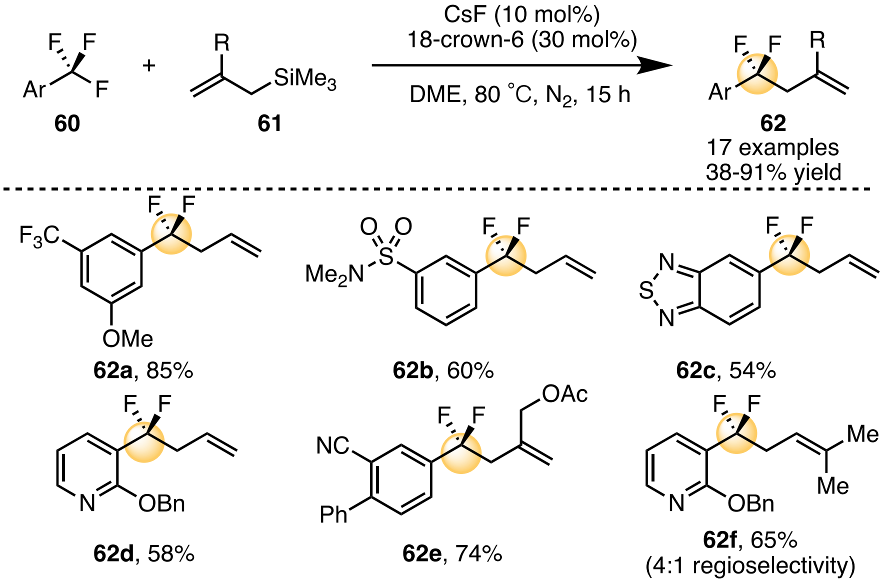


Fig. 1-18 Selective defluorination of trifluoromethyl aromatics with silyl-substituted allyl compounds

Although the above method is highly practical, the above reaction can only yield difluoroalkyl substituents with allyl coupled fragments. To address this limitation, the group of Bandar[41] in 2022 proposed a base-promoted, silane-mediated reductive coupling reaction of trifluoromethyl aromatics. This work focused on the use of a reactive silane reagent [tris(trimethylmethylsilyl)silane] **64** which was coupled to trifluoromethyl aryl hydrocarbons **63** to synthesise a series of valuable difluorobenzyl products **65**. In this case, catalytic quantities of Lewis bases interacted with the ethylsilyl reagent in the formamidic solvent to promote the single fluorine atom in the trifluoromethyl group to be methanosilylated hemiacetalyl amine functional groups The reaction proceeds by generating a difluorobenzylsilane intermediate which can also be isolated. The reaction has a wide range of substrates and is highly applicable, but trifluorotoluene, which lacks the electron-withdrawing group substitution, is unreactive under current reaction conditions, whereas substrates with electrophilic functional groups (e.g., ketones) compete for the reaction with silanes (Fig. 1-19).

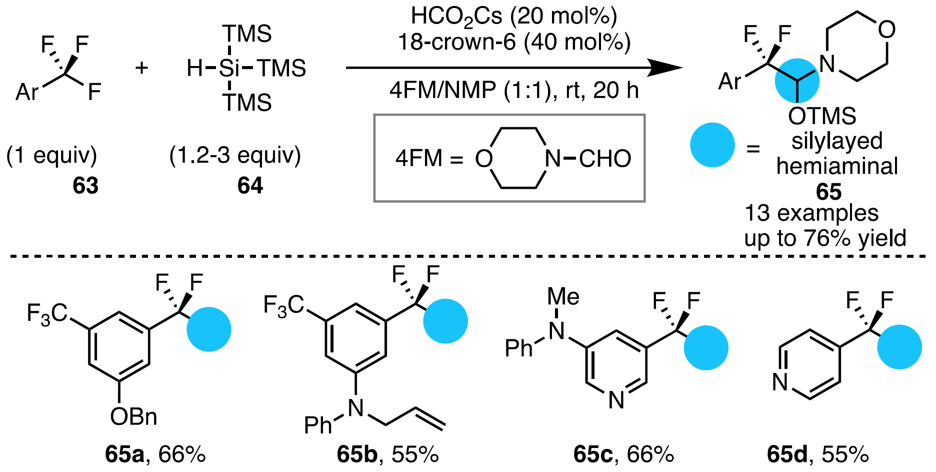


Fig. 1-19 Base-promoted divergent defluorination reductive coupling reaction of trifluoromethyl aryl hydrocarbons

As an alternative to the above reaction, the use of transition metals to activate C-F bonds in trifluoromethyl aryl hydrocarbons is a more promising strategy for development. In 2022, the group of Zhang Xingang[42] proposed transition metal-catalysed cross-coupling by oxidative addition of C(sp^3) -F bonds in trifluoromethyl aryl hydrocarbons **66** . A readily available and moisture-insensitive arylboronic acid **67** was chosen as one of the coupling mates for this reaction, and the diaryl difluoromethyl compounds **68** were obtained by modulation of the palladium catalyst $Pd(tBu_2PhP)_2Cl_2$ and the bidentate phosphine ligand Xantphos, using a blue LED (12 W × 2) irradiation without exogenous photocatalysts.The diaryl difluoromethyl compounds **68** were then obtained by the use of arylboronic acids and trifluoromethyl compounds with different substituent groups. groups of arylboronic acids and trifluoromethylaromatics for substrate generalisation, which revealed that the reaction was compatible with most functional groups and a range of target products were obtained in moderate yields (Fig. 1-20).

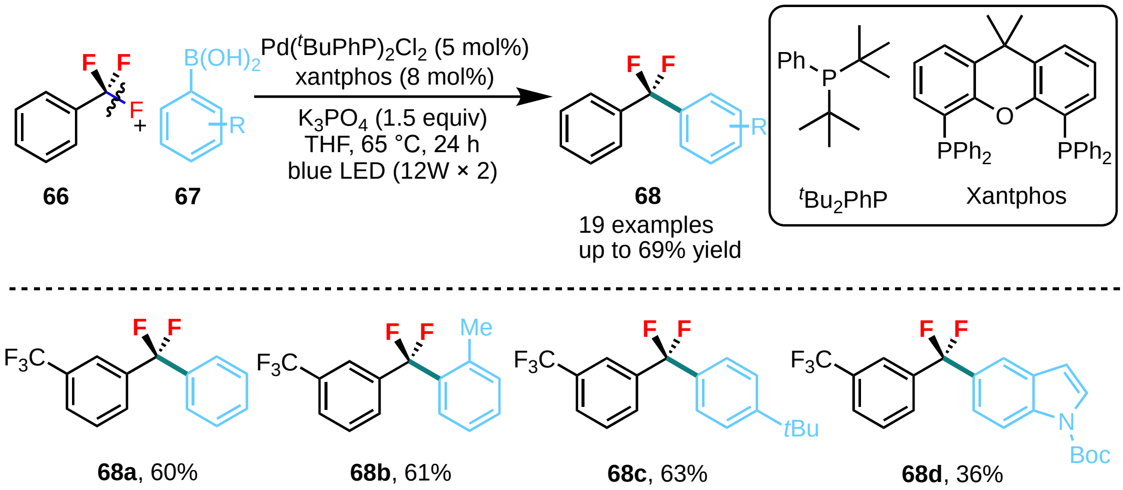


Fig. 1-20 Palladium-catalysed visible light-induced selective defluorinated arylation of trifluoromethyl aryl hydrocarbons with arylboronic acids

1.2.2 Selective defluorination of trifluoromethyl olefins

While breakthroughs in the functionalisation of individual carbon-to-fluorine bonds in trifluoromethyl aryl hydrocarbons have allowed the selective functionalisation of most CF^3-derivatives, similar transformations remain elusive with respect to trifluoromethyl olefins. Olefinic compounds with C-F bonds in such molecules (towards radicals or anions) are considered to be the source of this difficulty. So far there is no example of a general method to achieve single C-F bond functionalisation of trifluoromethyl olefins. Therefore, in 2019, the group of Dagang Yu[43] reported the first case of copper-catalysed selective formaldehyde carboxylation of single C-F bonds under CO_2 (1 atm) atmosphere. Using trifluoromethyl olefin **69** as the reaction substrate and a copper catalyst, a bioactive molecule with a difluoromethylene structure at the benzyl position was obtained with high chemoselectivity and stereoselectivity under relatively mild reaction conditions **70**. The advantage of this method is that it is simple to synthesise and can be mass-produced, and it is compatible with a wide range of functional groups (Fig. 1-21).

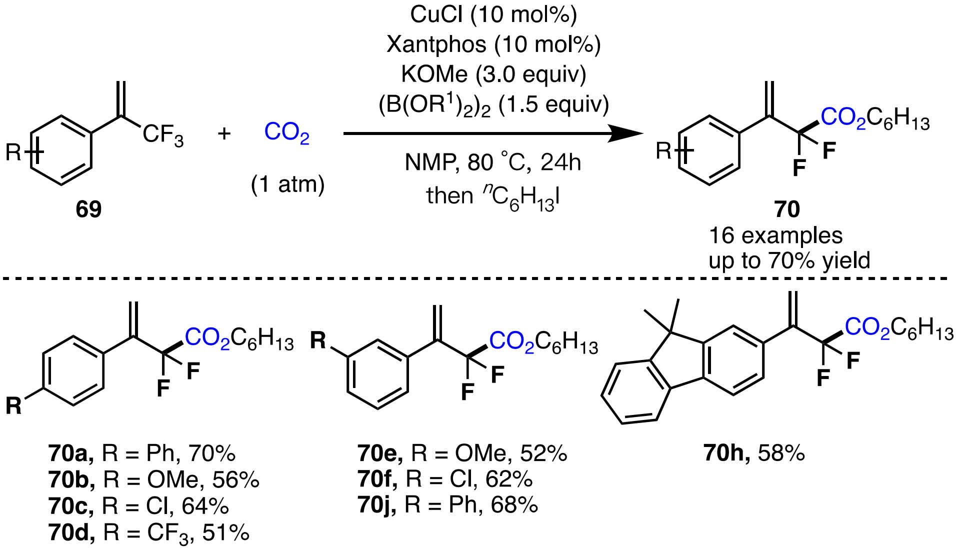


Fig. 1-21 Copper-catalysed selective formaldehyde carboxylation of trifluoromethyl olefins

In 2020, Crimmin's[44] group reported a simple reaction pathway to construct new C-C bonds by highly selectively breaking individual C(sp^3)-F bonds from trifluoromethyl groups using a substrate **71** containing a C(sp^2)-F bond to obtain the novel method for the target product **72**. The method relies on a special boron reagent **73** , which is explained by the fact that the boron site of this reagent plays a dual role in the reaction sequence, i.e., it is nucleophilic for boron in the C-F bond cleavage step (S_N2) but electrophilic for boron in the C-C bond formation step (S_E2), and the high selectivity of the reaction is attributed to the high selectivity along the S_N2 / S_E2 reaction sequence. No catalysts, additives or transition metal catalysis is required for this reaction, which is carried out in a "one-pot" fashion at room temperature, and can be facilitated by both electron-rich and electron-deficient aldehydes and ketones during the course of the reaction (Fig. 1-22).

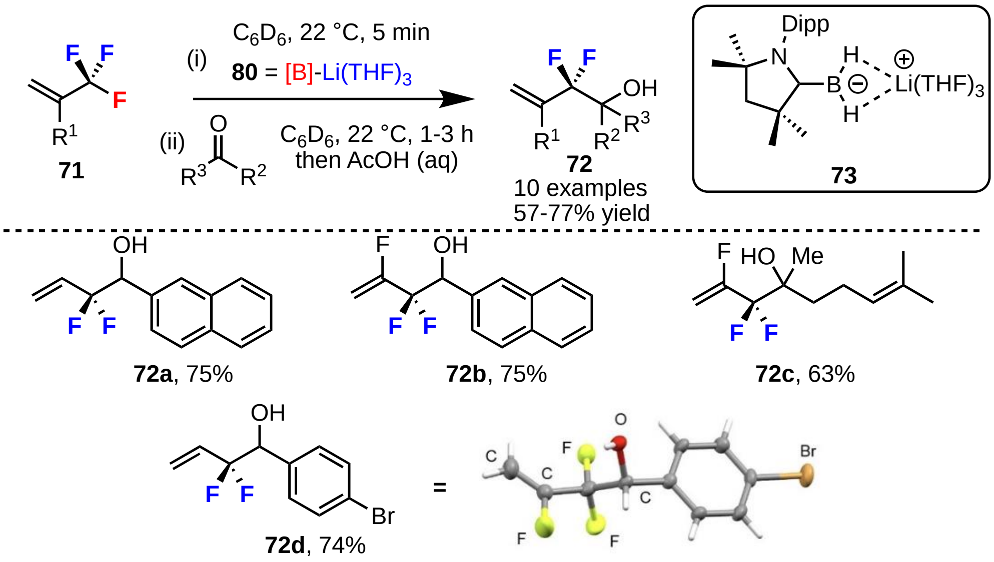


Fig. 1-22 Breakage of the C(sp^3)-F bond in trifluoromethyl olefins and their alkylation reactions

In 2021, Chao Feng[45] used a catalytic amount of TBAF (5 mol%) in his group with trifluoromethyl olefin **74** as the reaction substrate and allylsilane **75** as the allyl donor, and the selective carbon-fluorine bonded allylation of trifluoromethyl olefin could be achieved by heating. The reaction was carried out under mild conditions and was applicable to a wide range of trifluoromethyl vinyl substrates containing different electron-withdrawing and electron-donating substituents on the benzene ring (e.g., R^2 = Ph) to obtain the target product **76** in high yield; however, the introduction of the substituent group at the R1 position of the olefin resulted in a decrease in the efficiency of the reaction due to spatial site resistance, and the reaction was still able to proceed well when aryl was replaced by allyl, but the substitution of either the alkyl group or the electron-deficient substrate resulted in the reduction of the efficiency of the reaction. group substituted substrates all resulted in the reaction not proceeding (Fig. 1-23).

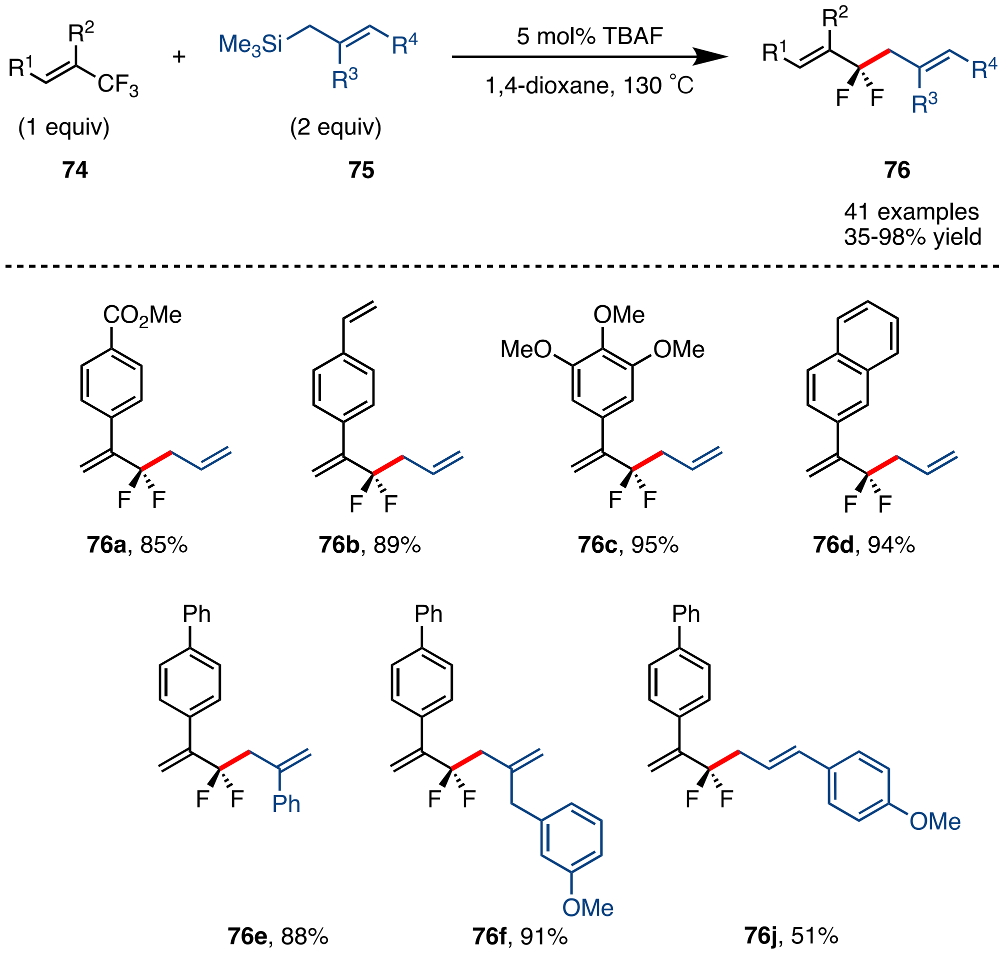


Fig. 1-23 C-F bond-selective allylation of trifluoromethyl olefins

In 2022, the group of Shen Xiao[46] presented the first case of one-step efficient construction of a thickened ketodifluorooxetane compound **79** using an extremely accessible silyl-substituted cyclopropanol **77** with α-trifluoromethyl-substituted olefin **78** under 460 nm light. The reaction has the advantages of simple operation, mild reaction conditions, and a wide range of substrates, and the synthesised thickened cyclic product can be efficiently subjected to subsequent transformation, reflecting the potential application value of this reaction (Fig. 1-24).

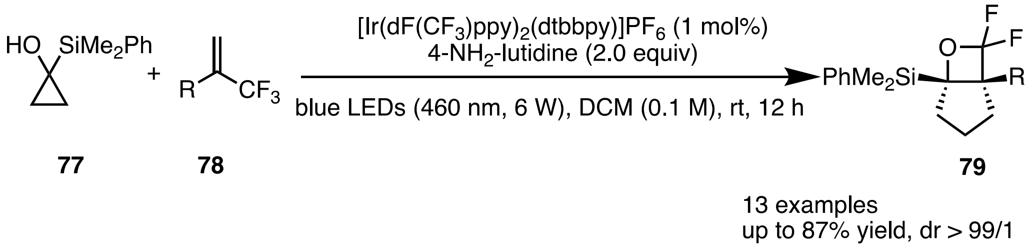


Fig. 1-24 Photocatalytic free radical cascade reaction of α-trifluoromethyl olefin

The above reaction, which efficiently constructs both two rings and three bonds in a single step, its a radical tandem reaction that involves photocatalytic redox as well as energy transfer catalysis, or direct photoexcitation, and is highly investigative as it combines two types of photochemical processes in a single reaction. A rational reaction cycle route is now proposed, where firstly the reaction uses an alcohol **77** activated by a Lewis base, which is triggered by the reduction of photoexcited PC* to PC^- via the PCET process, leading to the formation of the alkoxy radical intermediate **80**. The alkoxy radical **80** can then undergo radical *β*-carbon elimination to produce the alkyl radical intermediate **81**. Alkyl radical **81** generates benzyl radical intermediate **82** by radical addition reaction with *α*-CF_3-olefin **78**, which is then reduced to benzyl anion **83** by PC^- while regenerating the photocatalyst. Intermediate **83** then undergoes *β*-fluoroelimination to give difluoroolefin **84**. since $[Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6]$ is a known triple state energy transfer catalyst with higher triple state energy than acylsilanes, the acylsilane portion of compound **84** can be sensitised by the triple state energy transfer from the excitation of the photocatalyst to form a biradical **85** which then undergoes an intramolecular reaction with the difluoroolefin to form the product **79** (Fig. 1-25).

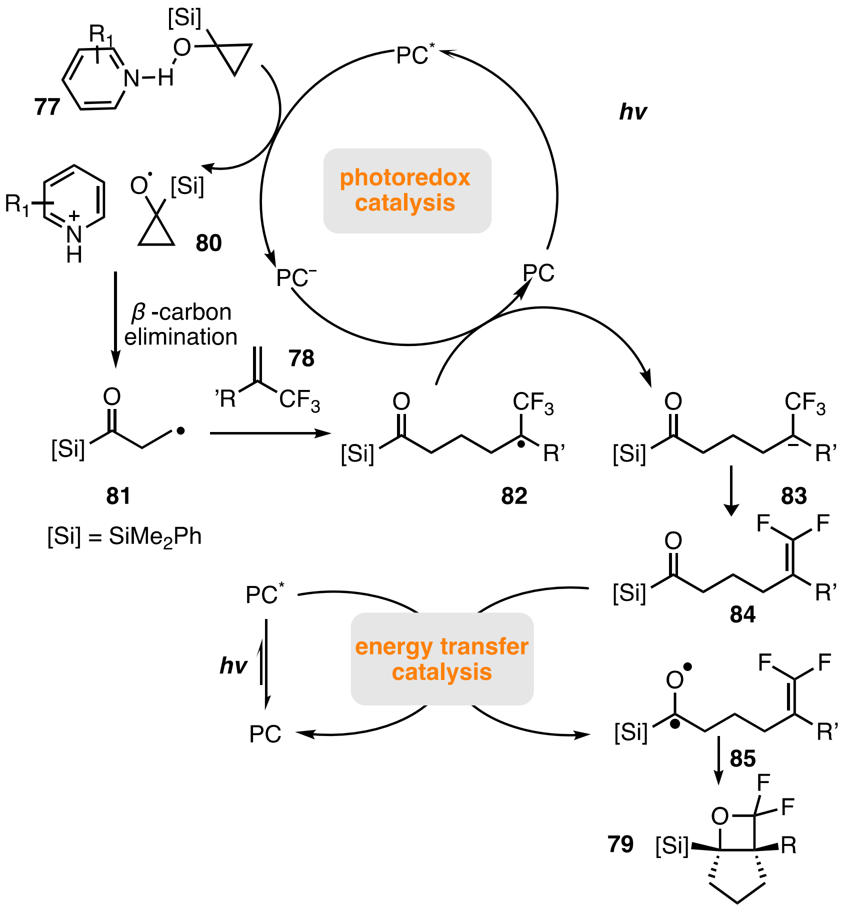


Fig. 1-25 Photocatalytic α-trifluoromethyl olefin free radical tandem reaction mechanism cycle

1.3 Preparation and conversion reaction studies of ketodifluoroalkyl reagents

In 2020, Toste's[47] group reported an electrophilic bromination strategy using a simple and readily available 1, 1-difluoroolefin lactam **86** as a nucleophilic reagent and electrophilic bromination reagents $[(DAB^1)_2Br](BF_4)_3$, $[(DAB^3)_2Br](BF_4)_3$ as an electrophilic bromine source to obtain oxazolines **88** in 49 % yield and 91% *ee* through a catalytic strategy of chiral anionic phase transfer (CATP). ee to obtain oxazolines **87** and tetrasubstituted bromodifluoromethylated stereocentric oxazines **88** compounds in 80 % yield, 96% *ee*, achieving enantioselective and regioselective brominated cyclization of difluoroolefins and highlighting the utility of the reaction through the synthesis of analogues of efavirenz, a drug used in the treatment of AIDS. The reaction has good substrate tolerance, and the yield and enantioselectivity of the reaction were found to be almost completely independent of the spatial site resistance and electrical properties of the nucleophilic reagent in the examination of oxazolines as substrates, and similar to oxazolines substrates, oxazolines were obtained in good yields (> 75%) and excellent enantioselectivities (> 94%), irrespective of whether the nucleophilic reagent was charged with an electron-donating substituent or an electron-withdrawing substituent *ee*) to obtain optically pure target products. It is noteworthy that the change of the alkyl component (R') on the difluoroolefin of this type of substrate has no effect on the yield and enantioselectivity of the reaction; it is noteworthy that both cyclic and acyclic compounds with tetra-substituted stereogenic centres of difluoromethylidene and difluoromethylidene can be obtained by further derivatization of such bromodifluoromethylated products **87**, **88**,. This further demonstrates the potential application value of this class of compounds (Figure 1-26).

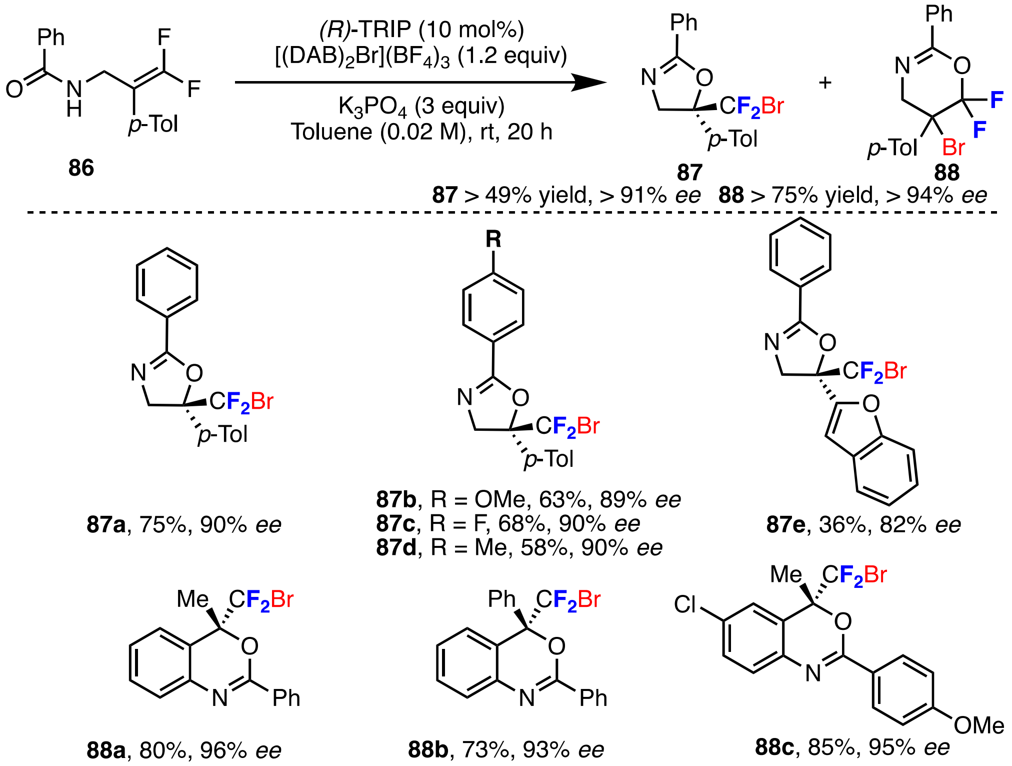


Fig. 1-26 Regioselective and enantioselective bromocyclisation of difluoroolefins

If 1,1, 2-, tri- and tetra-substituted olefins are used, the regioselectivity of the Ma rule will allow the construction of difluoroalkylated quaternary carbons. Since selective introduction of quaternary carbons can enhance conformational restriction is now considered an effective strategy to improve bioactive compounds[48-51], molecules with difluoromethylated quaternary carbons are the focus of medical research, and since the formation of the C-C bond between the polysubstituted olefin and the fluorinated reagent is affected by the spatial site-barrier, and the difficulty of regulating the regioselectivity, currently any free-radical strategies are not possible. Based on the above challenges, in 2020, Zhou Jian's[52] group proposed the use of $Mg(ClO_4)_2$-$6H_2O$ acid catalysts to achieve the martensitic region-selective difluoroalkylation reaction of simple olefins **89** with difluoroalkenyloxysilanes **90**, which are more reactive and readily available difluoroalkylation reagents than non-fluorinated reagents, to obtain more valuable α-difluoroalkylated ketones **91** (where the *β*-positions are tertiary carbonate). The advantages of the reaction include mild conditions, the use of inexpensive and easily handled catalysts, and a broad substrate range including mono-, di-, tri-, and tetra-substituted olefins that are compatible with the reaction, proving the usefulness of the reaction. The reaction is also suitable for the modification of natural products and drug derivatives, and preliminary biological studies have shown that this type of difluoroketone product has great medicinal value and can be used for the treatment of colorectal cancer (Fig. 1-27).

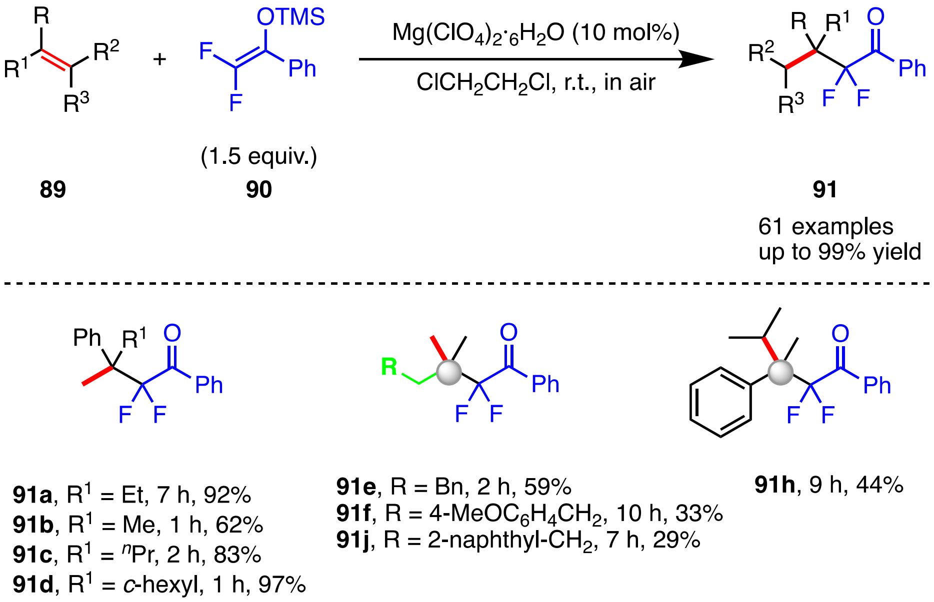


Fig. 1-27 Acid-catalysed olefin regioselective difluoroalkylation of difluoroalkenoxysilanes

In 2022, the group of Teng Huailong[53] reported a 1, 3-dipolar cycloaddition reaction of the azomethine Yelid **92** with the less active 1, 1-difluoro **93** and 1, 1, 2-trifluorostyrene **94** via Cu(I)-catalyzed azomethine. This reaction is an efficient way to obtain enantiomerically enriched 3, 3-difluoro **95** and 3, 3, 4-trifluoro **96** pyrrolidine derivatives (Fig. 1-28).

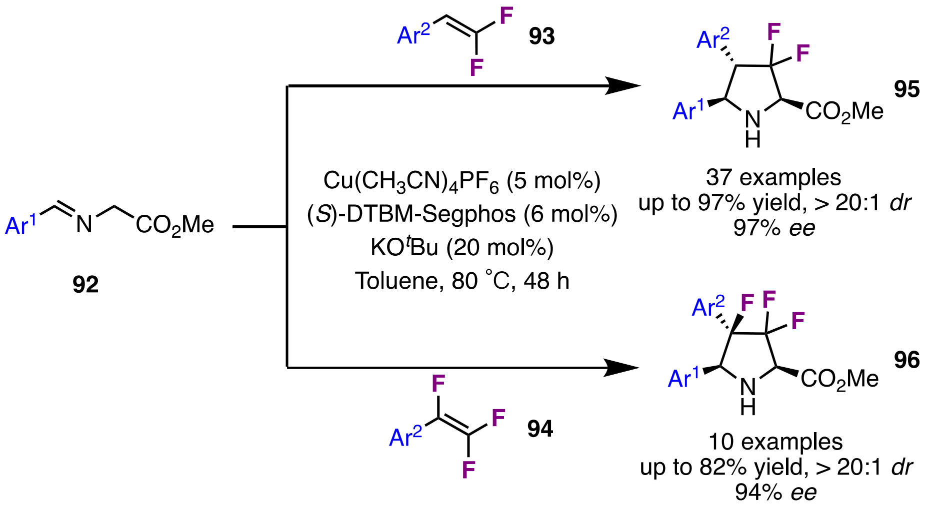
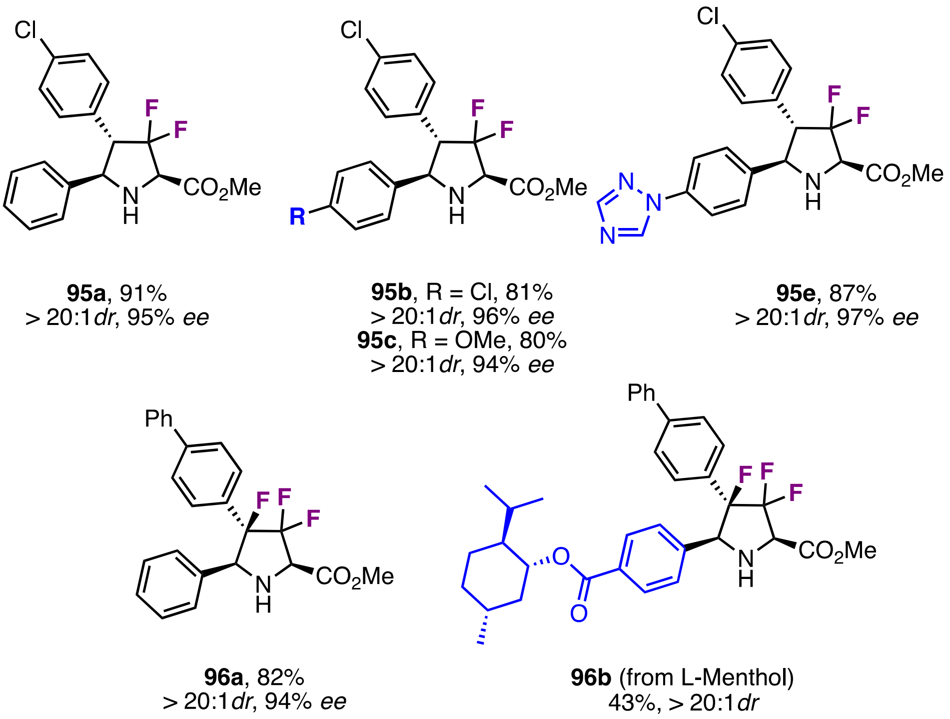


Fig. 1-28 Copper-catalysed cycloaddition of the azomethine yeridol with fluorinated olefins

A series of unreported fluorinated pyrrolidines were synthesised in reactions with yields up to 96 % and stereoselectivities as high as 20:1 *dr* and 97% *ee*, and these unique structural inserts can be easily introduced into a number of natural compounds and drugs. Among the compounds in which such fragments were introduced, the inhibitory activities of four common plant fungi were investigated, and the results showed that some of the compounds had better biological activities compared with those of the corresponding non-fluorinated compounds, and that the fluorine atoms on the pyrrolidine ring played a crucial role in the inhibitory activities of the compounds (Fig. 1-29).



95a, 91%
> 20:1 *dr*, 95% *ee*

95b, R = Cl, 81%
> 20:1 *dr*, 96% *ee*
95c, R = OMe, 80%
> 20:1 *dr*, 94% *ee*

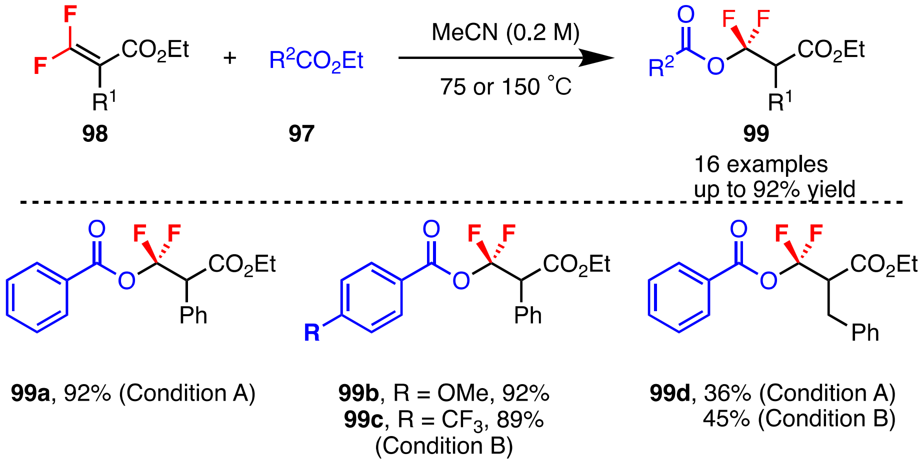
95e, 87%
> 20:1 *dr*, 97% *ee*

96a, 82%
> 20:1 *dr*, 94% *ee*

96b (from L-Menthol)
43%, > 20:1 *dr*

Fig. 1-29 Copper-catalysed cycloaddition reaction for the synthesis of fluorinated pyrrolidines

In 2024, Tsui's[54] group proposed the hydroacetoxylation reaction of difluoroacrylates using carboxylic acid **97** as an effective nucleophilic reagent with a readily available difluoroalkylation reagent, difluoroacrylate **98**, to produce trisubstituted or tetrasubstituted *β,β*-difluoroacrylates **99** by a regioselective addition via simple heating, without the need for a catalyst or additives. And the scope of the reaction can be extended to sulfonic acids, the mechanism of the reaction is still unclear, but the authors propose a possible reaction process in which, due to the strong electron-withdrawal of the two F atoms and the positive charge of the *β*-C portion, the ester group of **98** is protonated by the carboxylic acid and the oxygen of the acid attacks the *β*-C, the resulting enol intermediate interconjugate isomerises to the final product **99**. This pathway will also avoid *β*-F elimination by-products (Fig. 1-30).



Condition A: 10 equiv of carboxylic acid at 75 °C.
Condition B: 3.0 equiv of carboxylic acid at 150 °C.

Fig. 1-30 Hydroacetoxylation of carboxylic acids with difluoroacrylates

1.4 Preparation and conversion reaction studies of ketodifluoroallyl reagents

1.4.1 Preparation and transformation reactions of ketodifluoroallyl brominated reagents

The use of transition metal catalysis for the introduction of fluorinated functional groups into organic molecules is currently one of the most popular viable routes for fluorination reactions, and sai-difluoroallyl ($CF_2CH = CH_2$) is very attractive due to the versatile functionalisation of the carbon-carbon double bond. Yet useful methods for synthesising this valuable structure are rare. Therefore, in 2014, the group of Xingang Zhang[55] reported for the first time the reaction of sialylation with organoboron compounds **101** using 3-bromo-3, 3-difluoropropene (BDFP) **100** as the starting reagent for sialylation. The reaction permits the sidodifluoroallylation of a wide range of organoborons, including (hetero)aryl and vinylboronic acids, borates and potassium salts of trifluoroborate, to obtain a diverse range of difluoroallylated products under mild and easy-to-operate conditions and at low catalyst loadings (0.8 to 0.01 mmol%) **102**. The reaction can also be extended to BDFPs substituted by other functional groups, and its application can be achieved to modify the activity of fluorinated organisms in an efficient and practical manner, thus providing a new route for the development of biomedical and new drugs and the practical application of subsequent drugs. However, the coupling of BDFP with aliphatic nucleophilic reagents remains an unsolved problem, as its regional isomer difluoroolefin by-products are more likely to be formed in the reaction (Fig. 1-31).

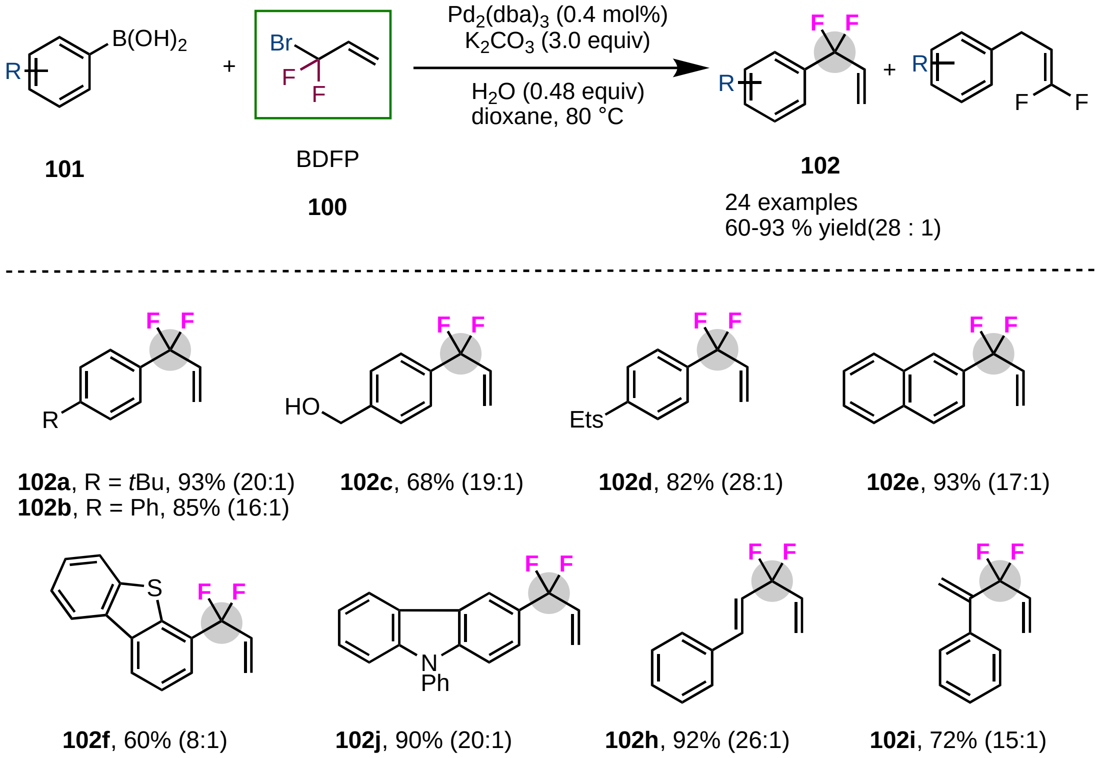


Fig. 1-31 Palladium-catalysed ketodifluoroallylation of BDFP with organoboron compounds

Since BDFP is readily available commercially and has high chemical stability and the potential to be able to be further converted. Therefore, in 2022, the group of Zhang Ao[58] reported the realisation of the reaction of aryltributyltin **103** with 3-bromo-3, 3-difluoropropene (BDFP) **100** in the presence of a palladium catalyst to achieve the reaction of ketodifluoroallylation. A series of (hetero)aryl/vinyl-3, 3-difluoropropenes **104** were synthesised efficiently with full *α*-substitution and regioselectively using Pd(OH)$_2$/C as a catalyst, and the palladium catalyst used for the reaction had a strong influence on the chemoselectivity of the reaction. The reaction has a broad substrate range and various substituents are well tolerated by both substrates (Fig. 1-32).

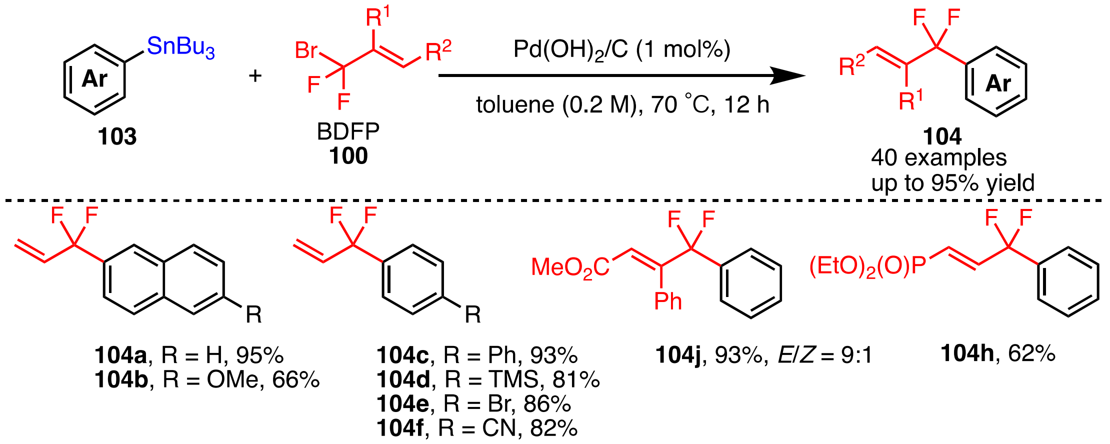


Fig. 1-32 Palladium-catalysed Doyle-Kirmse reaction of aryltributyltin over BDFP in ketodifluoroallylation

Remarkably, this reaction can be readily extended in the form of ketodifluoroallylation to the late modification of many biologically active molecules with good chemoselectivity (Fig. 1-33).

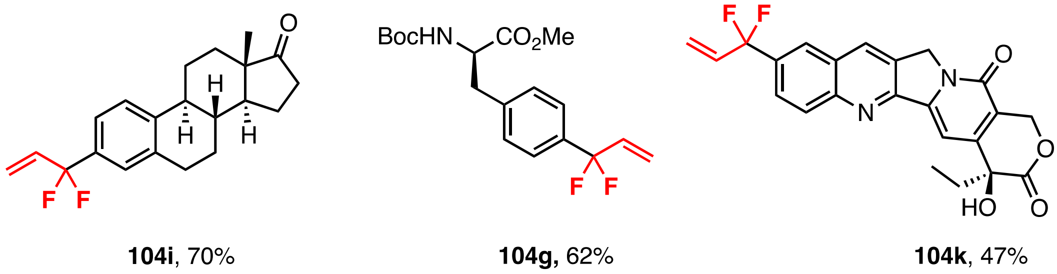


Fig. 1-33 Fragments of biologically active molecules that are kadaiodifluoroallylated

1.4.2 Preparation and conversion reactions of ketodifluoroallyl sulfonic acid reagents

The reaction of BDFP with phenylzinc chloride or tributylphenyltin still yielded defluorinated products. To address this critical issue, in 2016, Zhang Xingang's[59] group proposed the use of a palladium catalyst to achieve a highly regioselective and stereoselective sai-difluoroallylation reaction of difluoroallyl acetate **105** with arylboronic acid **106**. The reaction was found to have good substrate tolerance, allowing a wide range of boronic esters to react with difluoroolefins, and the yield of electron-rich arylboronic acid was significantly higher than that of electron-deficient arylboronic acid.The reason for the high regioselectivity of the reaction may be due to the spatial site-barrier effect of the substituent groups, and water was considered to be an effective additive. It is noteworthy that the toluenesulfonyloxy group is compatible with the reaction as no generation of diaromatised by-products was detected in the reaction, whilst moderate to high yields of the embedded difluoroolefin target product **107** were obtained in the absence of observed branched isomers, although the reaction mechanism has not yet been concretely demonstrated (Fig. 1-34).

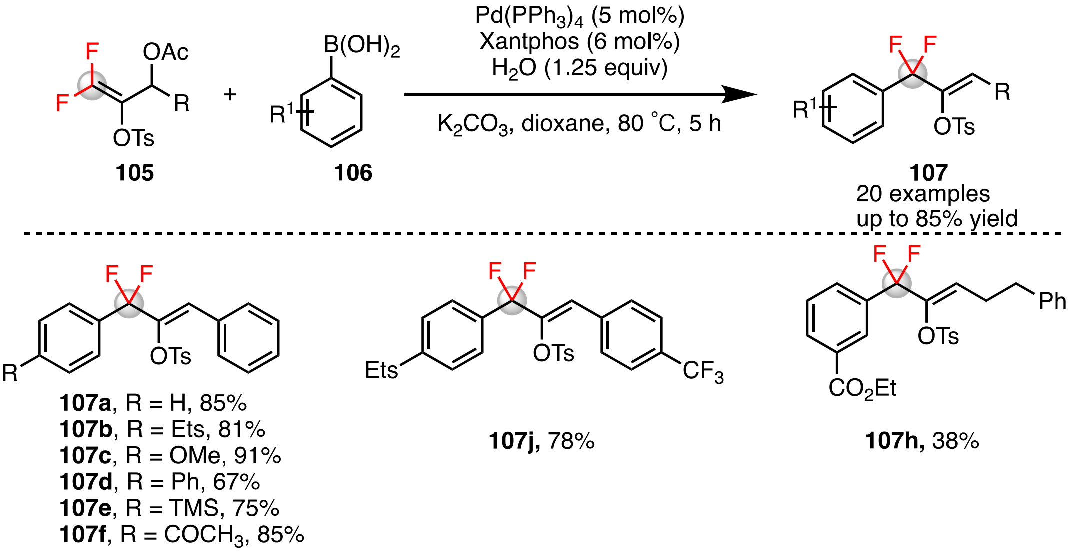
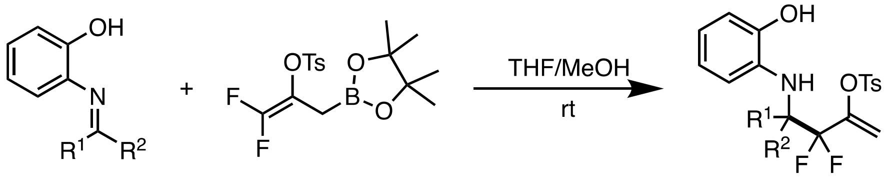


Fig. 1-34 Palladium-catalysed sai-difluoroallylation of arylboronic acids with difluoroallyl sulfonate reagents

1.4.3 Preparation and conversion reactions of ketodifluoroallylboron reagents

Allylboronates have been shown to have several advantages over allylmetalates, including stability, non-toxicity, and easy accessibility. In 2018, the group of Yiyong Huang[60] reported an unprecedented fluorination addition reaction of kainedifluoroallylboronates **108** and imines **109** (*N*-protecting group adjacent to the phenol group) without the use of a catalyst to obtain a series of racemic allyl amine compounds **110** in good to excellent yields (up to 98 % yield) to obtain a series of racemic silydifluoroallylamine compounds **110**, thus enabling the construction of racemic silydifluoroallylamine derivatives. The presence of an adjacent phenol group in the imine electrophile was found to be necessary in the experiments, and its presence enabled highly selective imine addition reactions with the seledifluoroallylboron reagent at room temperature without the need for catalyst action (Fig. 1-35).



109 **108** **110**

39 examples
up to 98% yield

Entry	Imine	Product	*t*/h	Yield/%
1	R^1 = H, R^2 = Ph	110a	18	97
2	R^1 = H, R^2 = 4-Me-C_6H_4	110b	20	98
3	R^1 = H, R^2 = 3-Br- C_6H_4	110c	18	95
4	R^1 = H, R^2 = 2-F- C_6H_4	110d	24	90
5	R^1 = H, R^2 = 1-naphthyl	110e	48	83
6	R^1 = H, R^2 = 2-thienyl	110f	24	92
7	R^1 = H, R^2 = (*E*)-phCH=CH	110j	7	94
8	R^1 = H, R^2 = *c*-hexyl	110h	20	94

Fig. 1-35 Imine addition reaction of pinacol with difluoroallylboronic acid ester

In 2018, Ito's[61] group reported for the first time the copper-catalysed asymmetric *γ*-boronyl reaction of CF_3-containing olefin compounds **111**.

The reaction of bis-boronic acid pinacol esters with CF_3-substituted different olefins was catalysed by a Cu(I)/Josiphos catalyst to give the corresponding difluoroallylboronic acid ester reagents **112** with high optical activity in high enantioselectivity (Fig. 1-36).

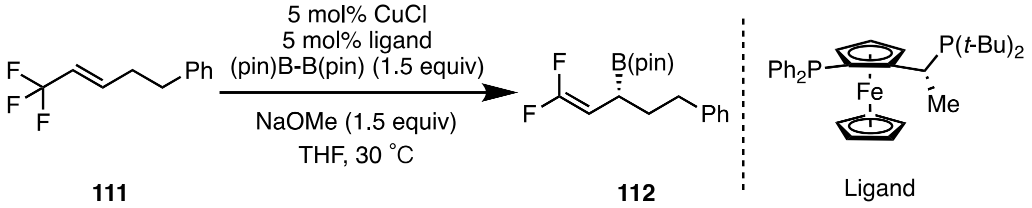


Fig. 1-36 Copper-catalysed asymmetric *γ*-boronyl substitution of CF_3-substituted olefins

The obtained *γ,γ*-difluoroallylboronate reagent **112** can be converted to the corresponding higher allylic compounds with difluoromethylidene by a highly stereoselective directed allylation reaction **113**. The proposed methodology represents the first example of an enantioselective boron substitution/stereoselective allylation sequence, which is of great potential application value (Fig. 1-37).

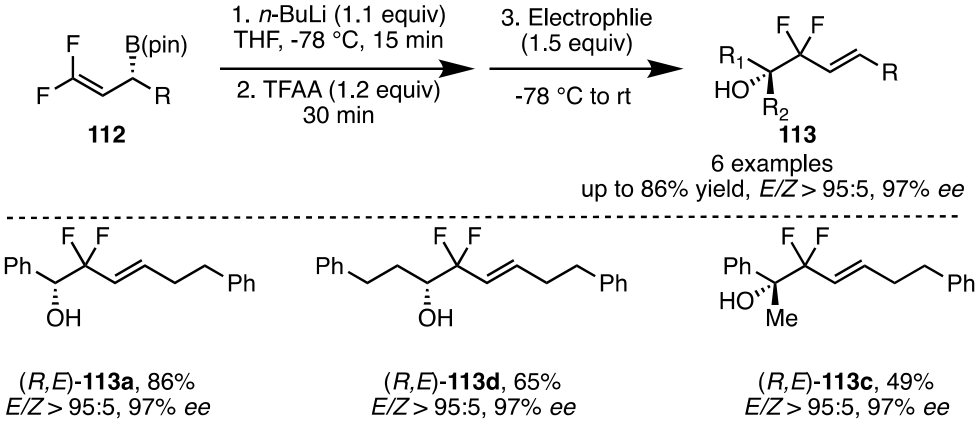


Fig. 1-37 Enantioselective boron substitution/stereoselective allylation reaction

In 2019, Xingang Zhang's[62] group reported a palladium-catalysed cross-coupling reaction of an unactivated alkyl zinc reagent with 2-bromo-3, 3, 3-trifluoropropene (BTP) as a key step in the preparation of a series of trifluoromethylated and difluoromethylated amino acids, and in the derivatisation experiments of the reaction the first palladium-catalyzed cross-coupling of an aryl halide **115** with the 3, 3-difluoroalanyl borate compound **114**, giving the difluoromethylallylated product **116** (Fig. 1-38).

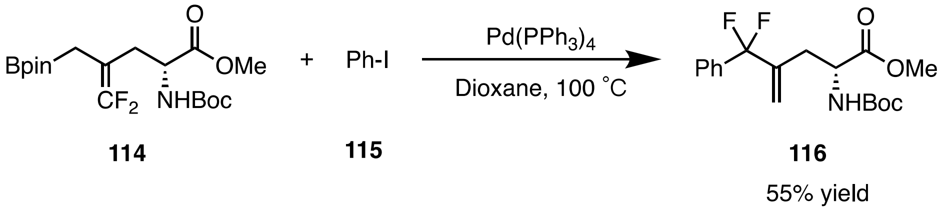


Fig. 1-38 Palladium-catalysed cross-coupling reaction of aryl halides with difluoroallyl borates

Since the above example requires iodide as a leaving group on the aromatic hydrocarbon and occurs with a high catalytic loading (10 mol% [Pd]) in moderate yield (55 %). Inspired by this reaction, the group of Hartwig[63] in 2021 first reported the catalytic defluoroborylation of 3, 3, 3-trifluoropropene **117** with cuprous chloride and tricyclohexylphosphine to obtain the difluoroallylboron reagent **118** in 89 % isolated yield (Fig. 1-39).

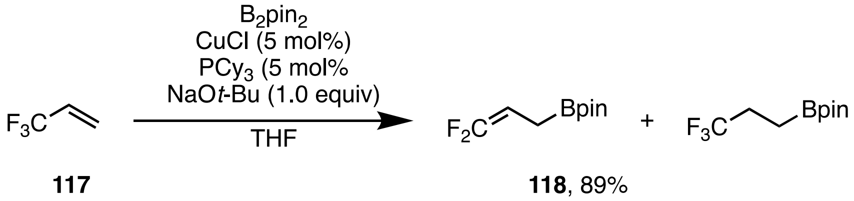
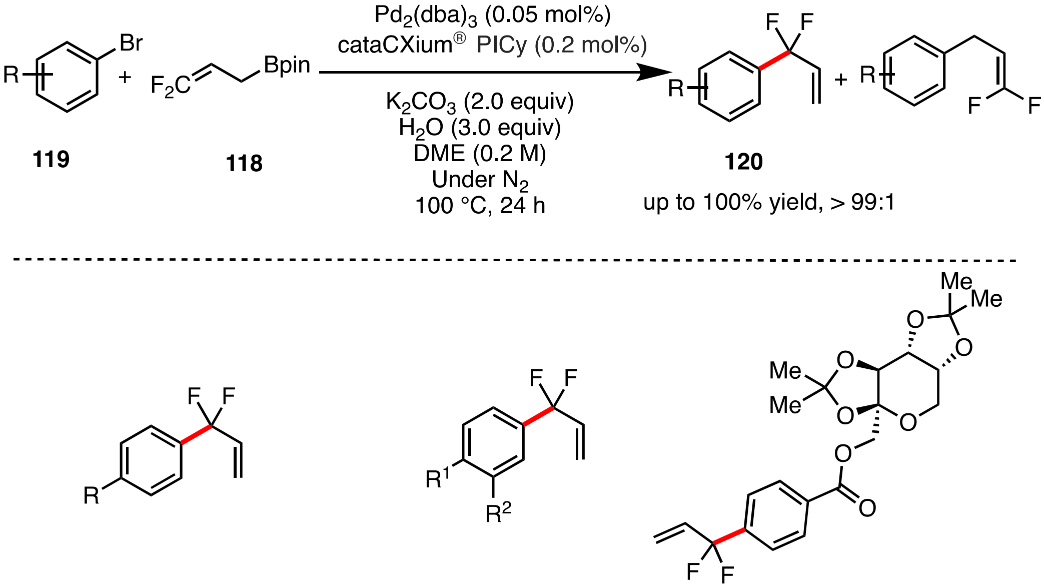


Fig. 1-39 Defluoroborylation of 3, 3, 3-trifluoropropene

Subsequently, aryl halides and mimetic halides **119** in the presence of a low catalyst loading (0.1 mol% [Pd]) are cross-coupled with the difluoroallylboron reagent 3, 3-difluoroallylboronate **118** to form ketodifluoroallylaromatics **120** as the target product to achieve diflurorallylation, and formation of a coupled product will be observed during the reaction; the reaction is high yielding, regioselective, and possesses good substrate tolerance, including primary alcohols, secondary amines, ethers, ketones, esters, amides, aldehydes, nitriles, halides, and nitroxides, as well as the fact that the reaction substrate can be extended to aryl iodides, chlorides, and trifluoromethanesulfonates, as well as substituted difluoroallylboronic acid esters for cross-coupling, providing a versatile methodology to synthesise difluoroallylaryl aryl hydrocarbons (Fig. 1-40).



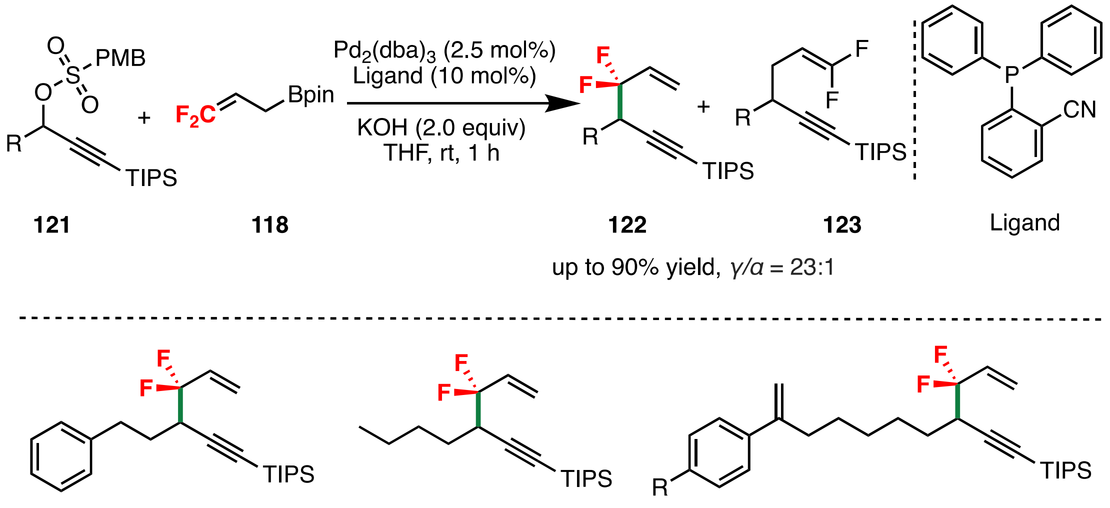
120a, R = *t*-Bu, 97% (>99:1)
120b, R = H, 100% (>99:1)
120c, R = Ph, 87% (>99:1)
120d, R = $CH=CH_2$, 86% (>99:1)
120e, R = Cl, 57%, 81 % (30:1)
120f, R = OTf, 66% (24:1)

120j, R^1 = H, R^2 = Ph,86% (>99:1)
120h, R^1 = H, R^2 = CO_2Et,84% (>99:1)
120i, R^1 = F, R^2 = CO_2Et,90% (79:1)

120k, 98% (>99:1)

Fig. 1-40 Palladium-catalysed sidodifluoroallylation of halides and mimetic halides by difluoroallylboron reagents

Inspired by the above reaction, in 2023, Xingang Zhang's[64] group used a palladium catalyst to achieve a difluoroallylation reaction of propargyl sulfonate **121** with a ketodifluoroallylboron reagent **118** to obtain the target 3, 3-difluoroalkynes product **122** with high regioselectivity. The advantages of this reaction are the mild conditions, the simplicity of the synthetic operation, and the simultaneous good functional group tolerance. The obtained difluorinated product **122** can be used as a versatile building block for the synthesis of fluorinated compounds. No target product generation was observed in the reaction using copper catalysts. A versatile reagent with potential applications in medicinal chemistry was used. The obtained difluorinated product **122** can be used as a versatile synthetic building block for the diversification of fluorinated compounds and is a versatile reagent with potential applications in medicinal chemistry. In the reaction, no generation of the target product was observed with the use of copper catalysts, and a small amount of the ketodifluoroalkenyne isomer **123** was still generated during the reaction under palladium-catalysed conditions, which is in agreement with the above reported (Fig. 1-41).



122a, 90% (γ/α = 23:1) **122b**, 65% (γ/α = 14.5:1) **122c**, R = NO_2, 75% (γ/α = 11.5:1)
122d, R = Br, 88% (γ/α = 21:1)

Fig. 1-41 Palladium-catalysed sai-difluoroallylation of difluoroallylboronic acid esters with propargyl sulphonates

1.4.4 Preparation and conversion reactions of ketodifluoroallyl quaternary ammonium salt reagents

Selective synthesis of fluorinated organic molecules is important for bioactive compounds (agrochemicals and pharmaceuticals) as well as for the development of unique materials, but effective generic quaternary ammonium reagents for the introduction of $-CF_2-$ groups have been largely neglected in the currently established synthetic methods for the introduction of fluorinated units[65-68]. Against this research background, in 2019, Chao Feng's[69] group proposed to obtain a difluoroolefin intermediate **125** by directly using trifluoromethyl olefin **124** as a reaction substrate, given the precedent of using an ammonium functional group as a leaving group in a cross-coupling reaction of a transition metal, and strategically incorporating S*N*2 amination to obtain a quaternary ammonium salt in almost quantitative yield by *N*-alkylation to give a difluoroolefin intermediate **125**, which was readily obtained in almost quantitative yield by *N*-alkylation **126**, and finally by using palladium catalysis to complete the allylic substitution reaction to synthesise an unprecedented *α,α*-difluoroallyl aryl/olefin structure **127**, successfully solving the above problem. High selectivity in the reaction controls the selective occurrence of nucleophilic substitution of the ketodifluoroallylpalladium complex on the fluorene-containing carbon atom. The reaction is characterised by its broad substrate range relative to both trifluoromethyl olefins **124** and arylboronic acid derivatives **128**, and it is noteworthy that the properties of the copper salt additives and their stoichiometric ratios are critical for the onset of allylic substitution in this reaction. However, the exact role of copper salts in the arylation step is currently unclear (Fig. 1-42).

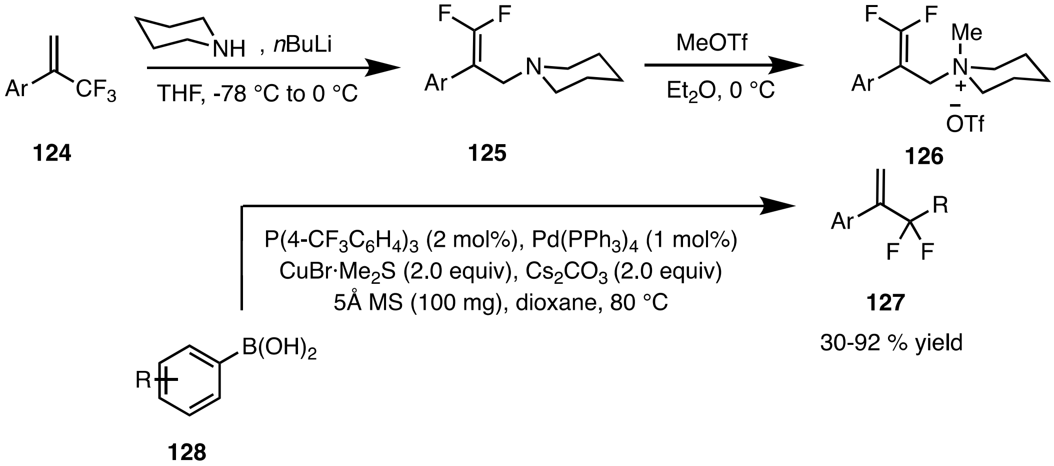


Fig. 1-42 Palladium-catalysed selective single C-F bond arylation of trifluoromethyl olefin derivatives

In 2021, Beller's[70] group developed a highly stable and versatile ketodifluoroallylating reagent 3, 3-difluoropropenylammonium salts

(DFPAs) **129** using 3, 3, 3-trifluoropropene **130** as a starting material, a commercial raw material used in the preparation of various products (e.g., in cosmetics, chemical manufacturing, etc.), with piperidine Base-mediated amination was carried out to smoothly obtain *γ*,*γ*-difluoroallylpiperidine as a colourless oil. Subsequent selective N-methylation gave the desired 3, 3-difluoropropen-1-ylammonium salt **129**, which is a crystalline white powder that does not require chromatography or other cumbersome purification methods, in an overall yield of 56 % (Fig. 1-43).

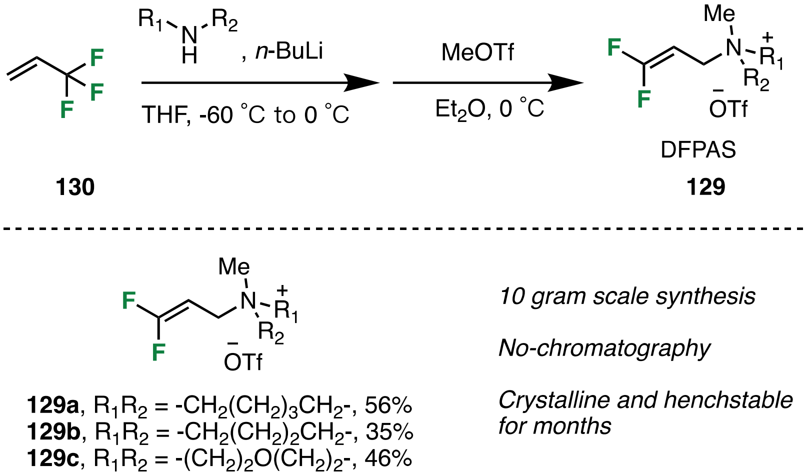


Fig. 1-43 Preparation of 3, 3-difluoropropenylammonium salts (DFPAs) of the kadaiodifluoroallylated reagent

The ammonium salt reagent allows *γ*-regioselective silylidene-difluoro-allylation reactions with a wide range of nucleophilic reagents (X : N-, O-, S-, Se-, and C-)**131** to be carried out under mild conditions without the need for transition-metal catalysis, leading to silylidene-difluoro-allylation products **132** that are uniquely regioselective and difficult to obtain by conventional methods with stability in both air and water; the reaction has a wide range of substrates. The reaction has a wide range of substrates and the target product can be obtained in good yields using different S-, Se-, N-, and activated carbon-nucleophilic reagents, while aryl and alkyl mercaptans and phenyl selenols with electron-donating or electron-absorbing groups undergo the desired S- or Se-difluoroallylation to obtain the target product, and it is noteworthy that less common oxygen nucleophilic reagents such as oximes and hydroxylamines are also well compatible with the reaction (Fig. 1- 44).

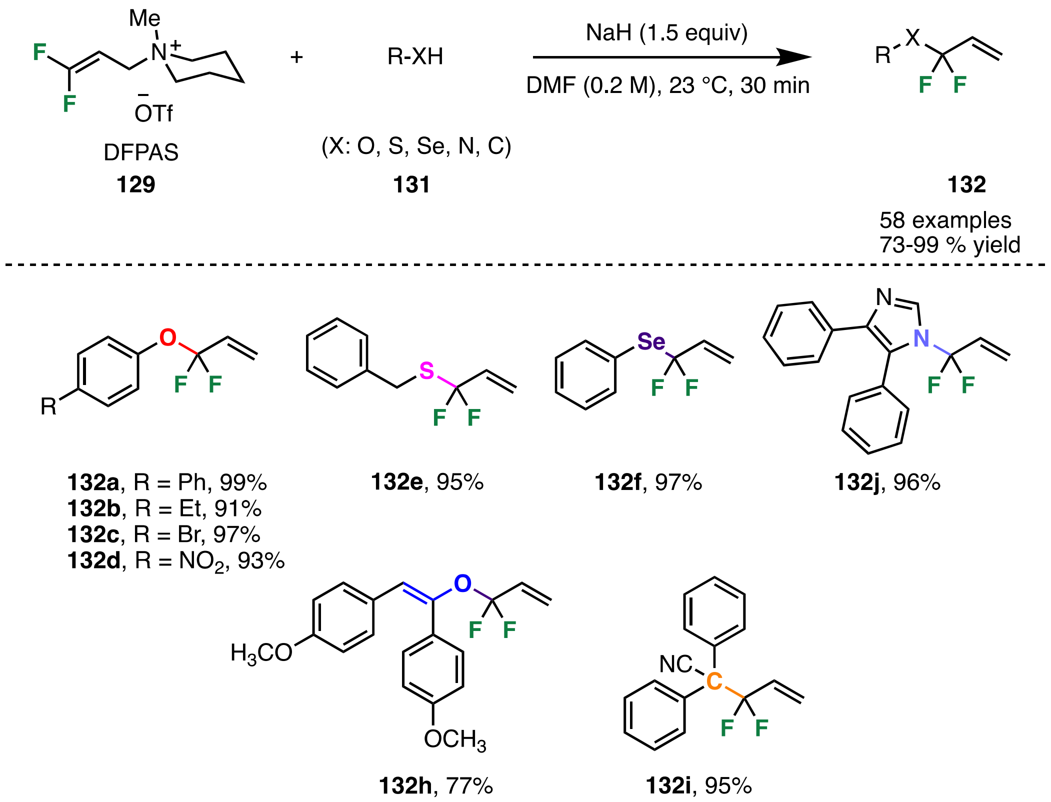
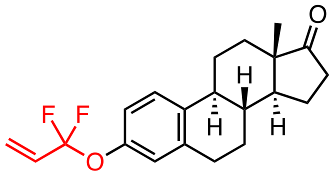
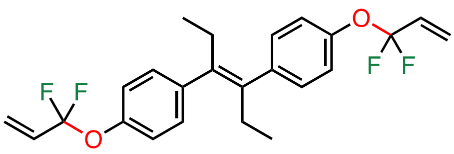


Fig. 1-44 Reaction of DFPAs with nucleophilic reagents for sai-difluoroallylation

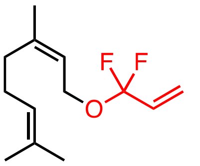
This ketodifluoroallylated ammonium salt reagent **129** also allows the direct preparation of many analogues of existing drugs, and the successful introduction of the allyldifluoromethylene structural unit achieved by this method provides a new avenue for the study of fluorine-containing molecular backbones (Fig. 1-45).



132g, 97% from Estrone



132k, 92% from Diethlstillbestrol



132l, 97% from (*Z*)-Nerol

Fig. 1-45 Preparation of existing drug analogues by the reaction of ketodifluoroallylation of DFPAs

1.4.5 Preparation and conversion reactions of ketodifluoroallyl sulphide reagents

In 2019, the group of Tiebo Xiao[56] reported the first blue-light-mediated Doyle-Kirmse reaction for the sidodifluoroallylation of aromatic diazo esters **134**, choosing to use 2-bromo-3, 3-difluoroallyl sulphide **133** as the sidodifluoroallyl source, which can be readily prepared by the commercially available S_N2-′-type reaction of 2-bromo-3, 3, 3-trifluoroacrylates with thiol salts. The reaction resulted in the synthesis of a series of sulphur- and bromine-substituted highly functionalized chalcidodifluoroallyl esters under mild, catalyst- and additive-free conditions using only blue light irradiation **135**. This reaction represents the first example of a rearrangement-based strategy for the formation of a C-CF$_2$ bond, which will have potential applications in drug discovery and development (Fig. 1-46).

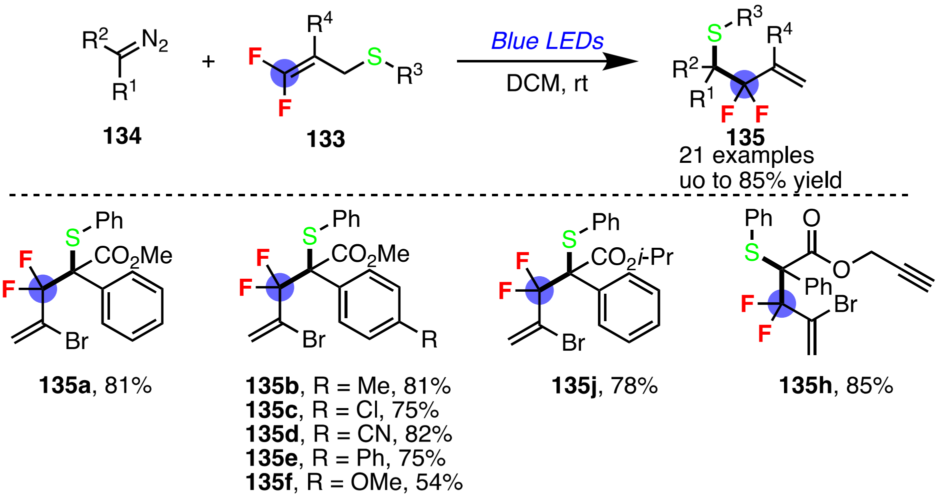


Fig. 1-46 Low-energy blue light-mediated Doyle-Kirmse reaction for the sai-difluoroallylation of aromatic diazo esters

Based on the above studies, in 2021, Tiebo Xiao's[57] group again utilised 3, 3-difluoroallyl sulphide **133** and *N*-sulfonyl-1, 2, 3-triazole **136** to achieve a kain-difluoroallylated Doyle-Kirmse reaction to synthesise a variety of compounds containing kain-difluoroallyl multifunctional quaternary carbons **137**. The reaction proceeds via a simple Rh(II)-catalyzed [2, 3] -σ migratory rearrangement reaction, the Doyle-Kirmse reaction of N-sulfonyl-1, 2, 3-triazole **136** with 3, 3-difluoroallyl sulfide led to the synthesis of an aryl, imino, thio, and bromo containing sidodifluoroallyl multifunctional quaternary carbon centre. The reaction was characterised by a wide range of substrates and moderate yields, and the utility of such methods was confirmed by gram-scale synthesis and further transformation of the product (Fig. 1-47).

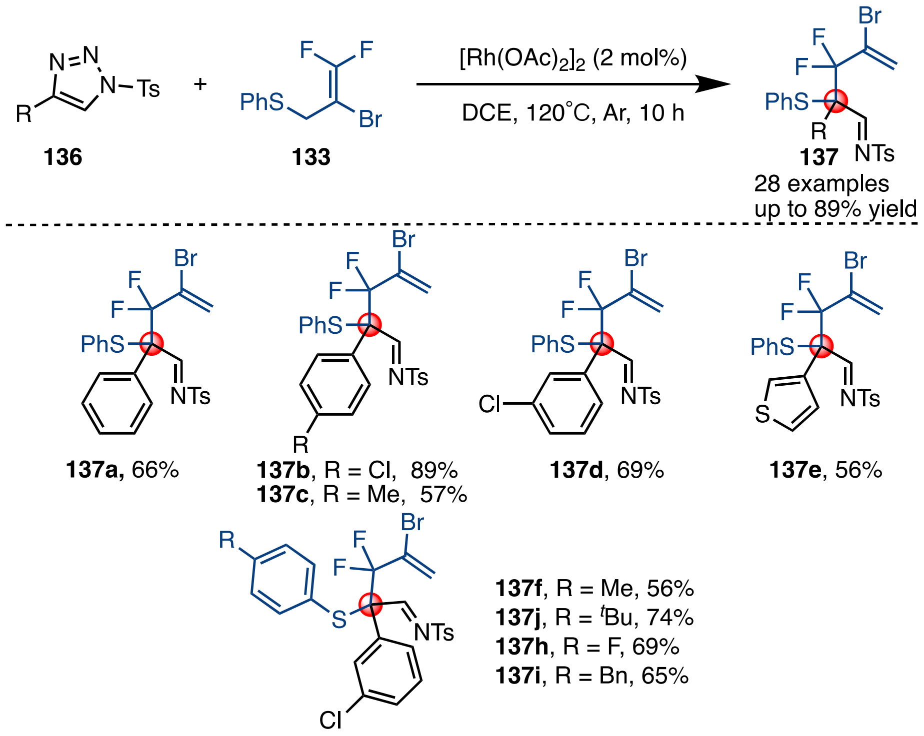
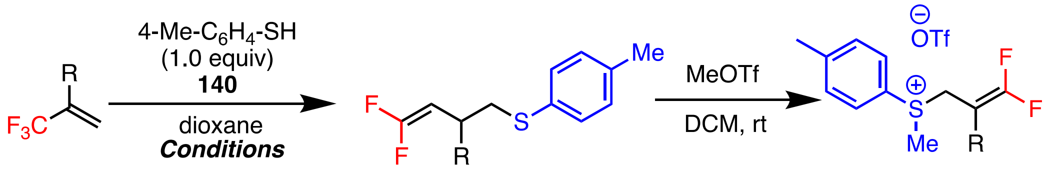


Fig. 1-47 Rhodium-catalysed Doyle-Kirmse reaction of ketodifluoroallylation

1.4.6 Preparation and conversion reactions of ketodifluoroallyl sulfide reagents

Due to the ability of the above method to construct C(sp^3) -CF_2R bonds, in 2022, Zhang Xinguang's[71] group again reported a new practical, stable and at the same time highly active kai-difluoroallylated sulfide reagent 3, 3-difluoroallyl sulfide (DFAS) **138**. DFAS was synthesised in a simple and practical way, using 3, 3-trifluoropropene (TFP) **139** and commercially available 4-methylbenzenethiol **140**, reacted in dioxane at 120 °C to efficiently obtain 3, 3-difluoroallyltoluene sulfide **141**, which is subsequently methylated by MeOTf at room temperature, and DFAS **138** can be obtained in a scale of more than 10 grams after a two-step reaction and can be stabilised in air for several months, and DFAS **138** can also be synthesised by reacting in aqueous solution in aqueous solution in aqueous solution. This type of synthesis can also be used to obtain differently substituted DFASs (R=Br) by attaching differently substituted leaving groups to the ketodifluoroallylated reagent (Fig. 1-48).



139 **141** **138**

Condition A: NaOH, 120 ˚C, 12h
Condition B: NaH, rt, 8h

141a, R = H (condition A)
141b, R = Br (condiy

138a, R = H, 56% (2 steps), **10.4 g**
138b, R = Br, 72% (2 steps), **15.2 g**

Fig. 1-48 Preparation of DFAS, a reagent for kadaiodifluoroallylated sulphide salts

This reagent allows a variety of organozinc reagents (including aryl, dialkyl, sec-alkyl and tert-alkyl zinc reagents)**142** to undergo highly efficient and highly regioselective ketodifluoroallylation reactions catalysed by low catalyst loadings (0.1-2.5 mol%) of copper under mild reaction conditions, generating a range of difluoroallylated products, **143** providing an efficient and practical method for the construction of C(sp^2) -CF_2R and C(sp^3) -CF_2R bonds provides an efficient and practical method. The method is highly efficient, has good functional group compatibility, a wide range of substrates, and even primary, secondary, and tertiary alkyl zinc reagents are suitable for the method, and more importantly, the method allows for rapid fluorination modification of biologically active molecules, which provides a convenient pathway for their synthetic applications in medicinal chemistry. It is noteworthy that although copper-catalysed fluoroalkylation reactions have made great progress, catalytic reactions utilising copper catalyst loadings as low as 0.1 mol% have not been reported so far, which allow the preparation of target products on a 6 mmol scale with only 0.1 mol% of CuBr, with virtually unaffected yields and selectivities; in addition, the obtained ketodifluoroallyl compounds **143** versatile transformation and rapid synthesis of bioactive molecules and natural product analogues further demonstrate the synthetic utility of DFAS (Fig. 1-49).

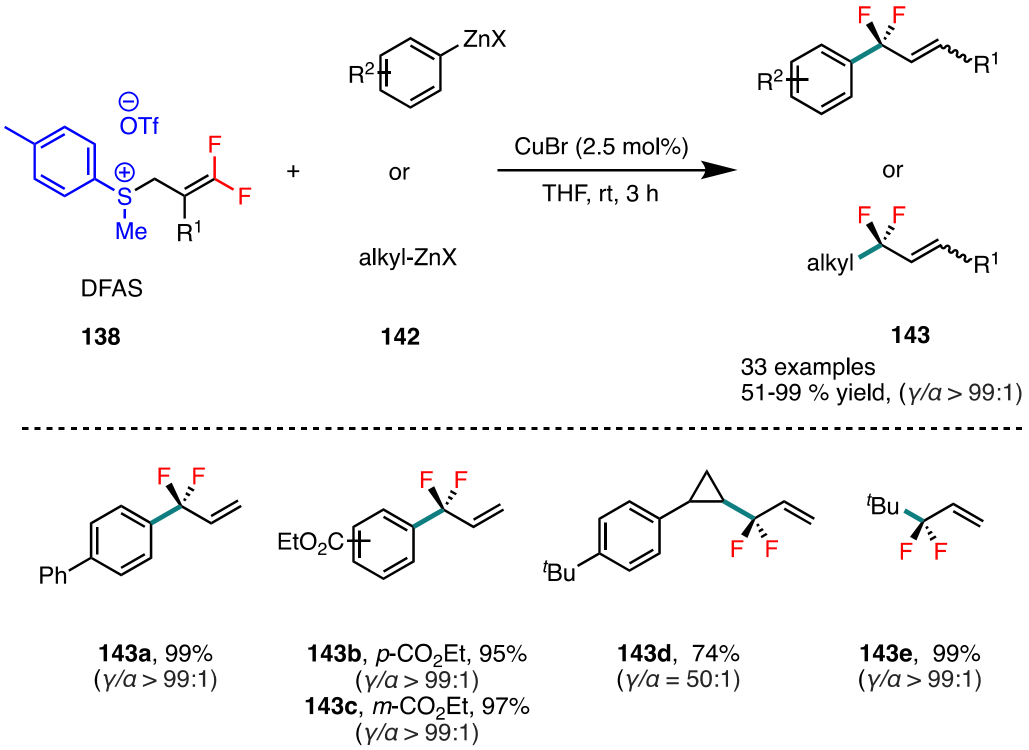
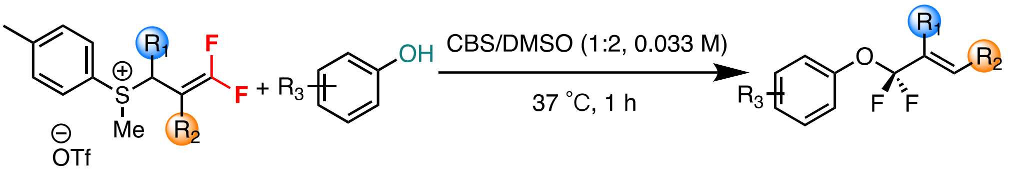


Fig. 1-49 Copper-catalysed difluoroallylation of difluoroallylated salt reagents

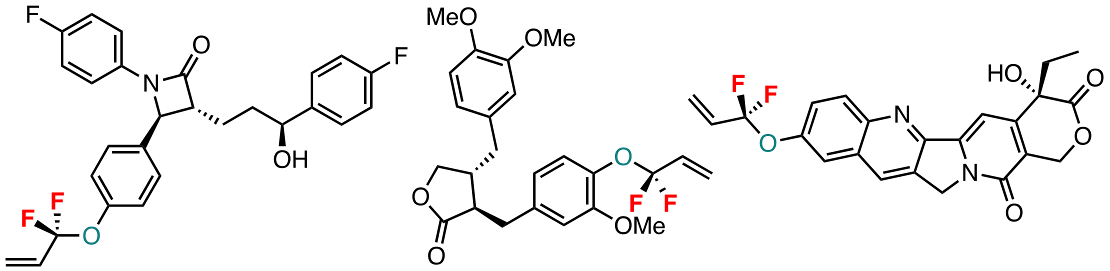
In 2023, Zhang Xingang's[72] group again synthesised a series of biologically active ketodifluoroallylated products **146** by investigating an effective method of late selective modification of phenol **145** in biologically active molecules and peptides by a stable and highly active fluoroalkylation reagent, 3, 3-difluoroallyl sulfonium salts (DFASs) **144** to achieve O-fluorinated alkylation (Fig. 1-50).



DFASs
144 **145** **146**
23 examples
up to 96% yield, α:γ > 20:1

Fig. 1-50 Late sidodifluoroallylation of phenol in biologically active molecules and peptides by difluoroallyl reagents

The reaction was carried out in a mildly alkaline buffer solution (pH=11.6) with high efficiency, high biocompatibility and excellent regioselectivity and chemoselectivity, and a variety of oligopeptides and phenolic-containing biologically active molecules including carbohydrates and nucleosides were selectively *O*-fluoroalkylated, while a range of saccharides, nucleosides and nucleophilic amino acid residues including tryptophan, histidine, methionine and threonine, all exhibit bioorthogonal reactivity to the reaction, showing the promise of the method in chemical biology. Notably, the unique nature of the CF_2 moiety not only makes DFAS more reactive than its non-fluorinated counterparts, but also makes the ketodifluoroallyl group a reactive radical acceptor for radical addition, adding a new tool for modification of the toolbox of biologically active molecules (Fig. 1-51).



from ezetimibe
146a, 80%
α:γ > 20:1

from (-)-arctigenin
146b, 83%
α:γ = 14.3:1

from 10-hydroxycamptothecin
146c, 42%
α:γ > 20:1

Fig. 1-51 Late modification of biologically active molecules by difluoroallyl reagents

1.5 Preparation and conversion reaction studies of ketodifluoroalkynyl reagents

Alkynes are extremely important in organic chemistry[73-75]. Conceptually, the substitution of methylene (CH_2) with its difluorinated counterpart (CF_2) at the alkyne position may lead to the discovery of new reactions and the development of molecules of interest with applications in life and materials sciences, e.g., difluorinated alkyne can be used for biological applications, i.e., to form a useful part of the in vivo click chemistry for molecular imaging techniques. Indeed, *α,α*-difluoromethylene propargyls are becoming increasingly important in the synthesis of various fluorinated molecules and in click chemistry. Various methods have been developed for the synthesis of such sidodifluoroalkynylated molecules[76], including direct sidodifluoroalkynylation[77,78] and indirect conversion[79]. Although direct synthetic methods are more attractive, most reported examples are limited to electrophilic reagents: e.g. nucleophilic seledifluoropropargylation of aldehydes and imines (Fig. 1-52).

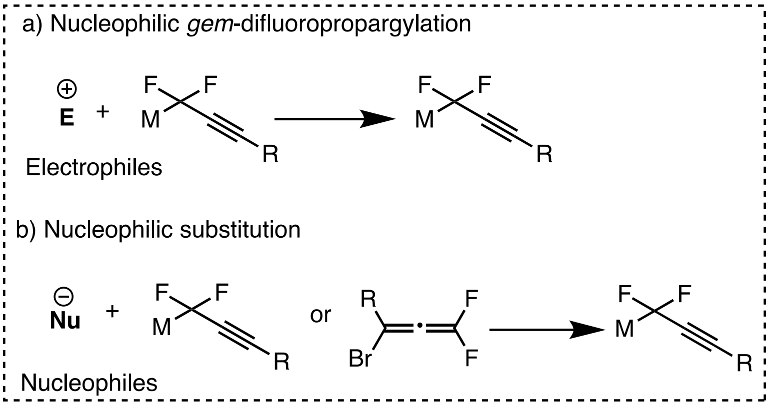


Figure 1-52 Direct ketodifluoropropargylation reaction

Therefore, in 2014, the group of Xingang Zhang[80] reported the reaction of sidodifluoropropargylation of sidodifluoropropargyl bromide reagent **147** with arylboronic acid **148**, which successfully realised the first synthesis of sidodifluoropropargyl compounds **149** under palladium catalysis. A simple P(o-Tol)3 ligand is crucial for the efficiency of this reaction, which in previous reports has been realised with phosphine ligands with large occlusion angles[81] or extremely bulky substituents[82] to achieve reductive elimination from the arylpalladium-fluoroalkyne complexes to obtain the target product. The reaction which is characterised by mild reaction conditions, high regioselectivity, a wide range of substrates and good functional group compatibility, it has provided an attractive route for drug discovery and development by the synthesis of a series of previously unknown compounds with a ketodifluoroalkynyl group for the synthesis of complex fluorine-containing compounds **149** (Fig. 1-53).

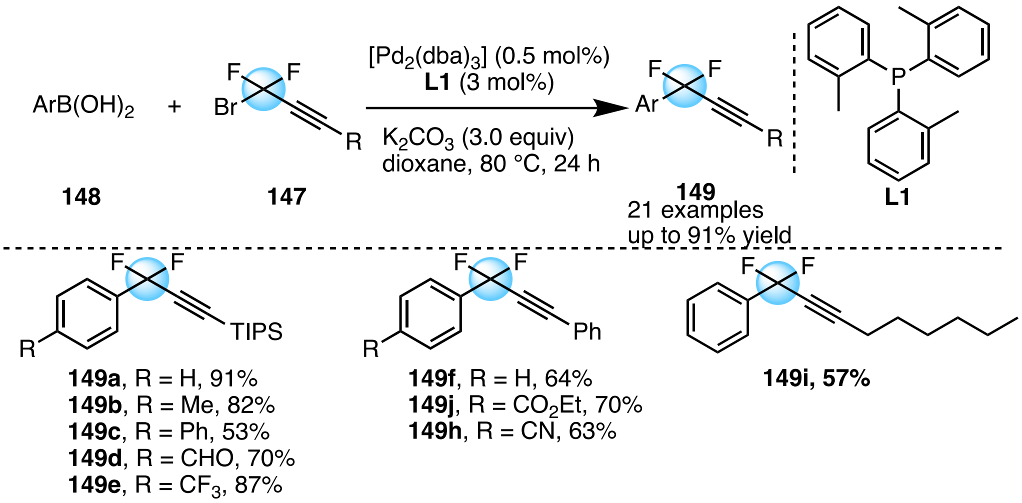


Fig. 1-53 Palladium-catalysed sidodifluoropropargylation of arylboronic acids with difluoropropargyl reagents

In 2018, Cheng Xu's[83] group reported the synthesis of a series of sidodifluoropropargyl compounds **153** by the visible-light-induced reaction of sidodifluoropropargylation of bromo-substituted difluoropropargyl compounds **151** with simple olefins **152** catalysed by sulphur radicals using benzothiazoline **150** as the key reductant, and the protection of triethylsilyl groups. Unsubstituted benzothiazoline **150** is a known but under-utilised reagent that is critical to the success of this reaction. The silyl-protected difluoropropargylated product **153** has good functional group tolerance (Fig. 1-54).

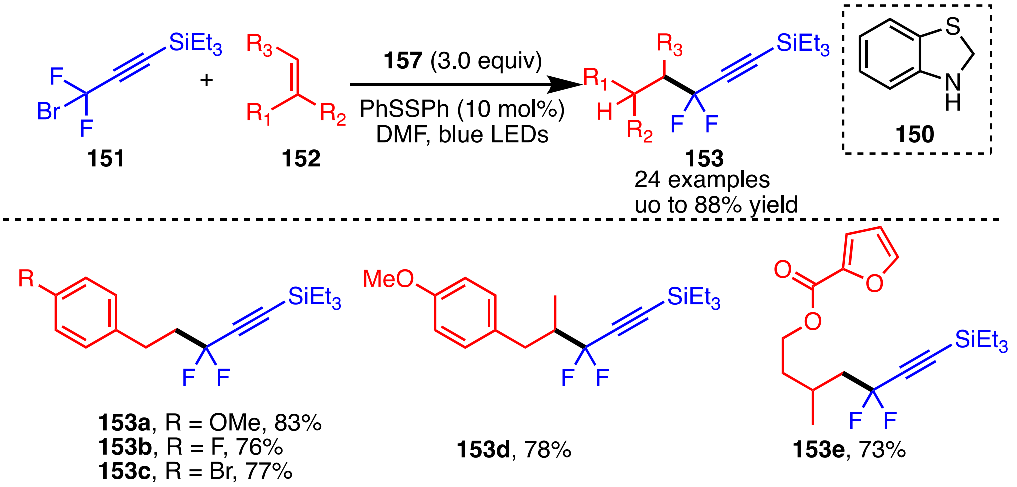


Fig. 1-54 Visible light-induced ketodifluoropropargylation of bromodifluoropropargyls with olefins

The radical-catalysed reaction presents the corresponding reaction mechanism, where firstly, under the irradiation of a blue LED, diphenyl disulphide undergoes homolytic cleavage to produce a thio radical. This radical undergoes a HAT reaction with **150** to give phenylthiophenol and benzothiazoline radicals **154**. this radical **154** gives an electron to **151** to produce the difluorinated hydrocarbyl radical **155** and benzothiazole **156**, which can be separated after the reaction. **155** binds to the olefin **152** to form the intermediate **157**. a radical chain process initiated by transfer of halogen atoms from the bromine reagent of **151** gives the product **153** (Fig. 1-55).

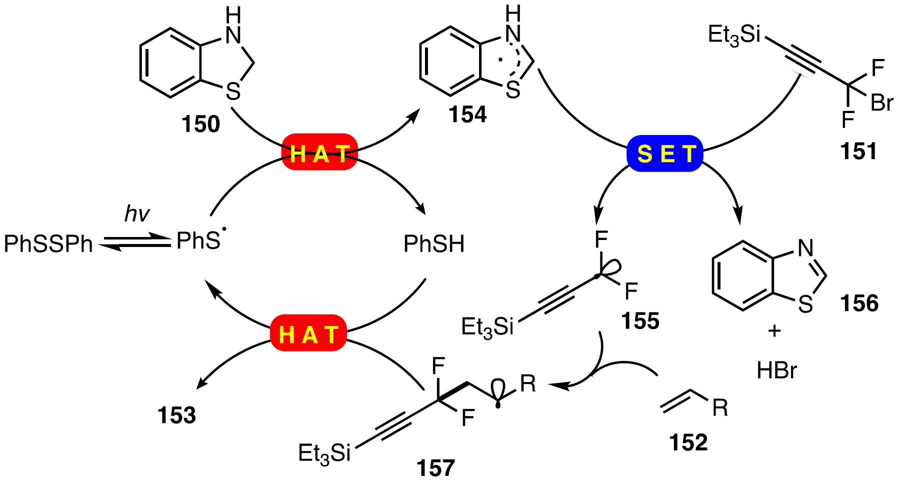


Fig. 1-55 Mechanism of visible light-induced reaction of bromodifluoropropargylation with olefins by ketodifluoropropargylation

1.6 Summary of the chapter

Based on the above literature survey, the authors have analysed and summarized some representative research progresses of the difluoroalkylation reactions in recent years, especially the highly efficient and versatile difluoroallylation reagents, and it can be found that the selective introduction of difluoro-methylene functional groups into organic molecules has become one of the most important means of new drugs, agrochemicals and advanced functional materials. Because of the wide range of applications of ketodifluoroallyl structures in life and material sciences, the development of an efficient ketodifluoroallylation reaction for the successful introduction of difluoromethylene functional groups has become one of the key research topics for scientists in recent years, which makes the development of an efficient and versatile ketodifluoroallylation reaction a necessity.

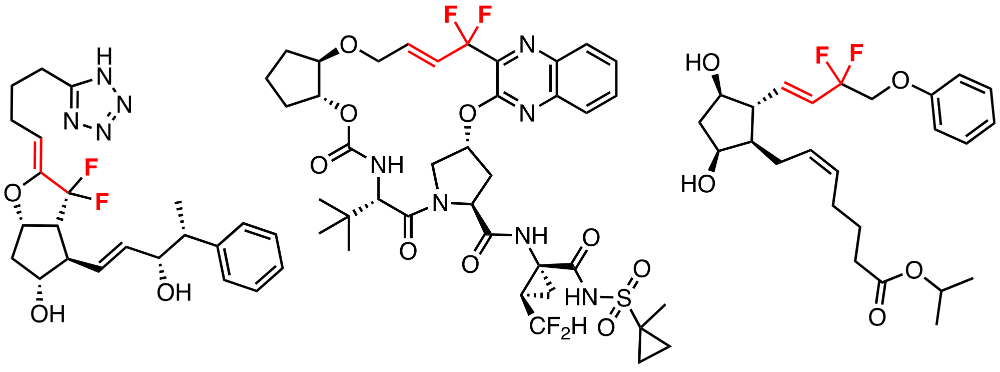
Through the above literature research, it is concluded that the introduction of suitable leaving groups on the difluoroallylated reagents to fine-tune their reactivity, such as the use of quaternary ammonium salts, which are stable, simple to obtain, and have a long storage time as the raw material for the reaction, and the use of a reaction system that does not need to be catalysed by a metal, breaks through the limitations in the construction of the C-CF_2R bond through the transformation of its carbon-carbon double bond, and the use of difluoroallyl as a widely used The development of this method has achieved the successful introduction of allyl difluoromethylene units and provided a new route for the study of fluorine-containing molecular skeletons.

Thinking on the basis of the above synthetic strategies, we adopted quaternary ammonium salts containing leaving groups as research objects and envisaged the use of metal reagents capable of enhancing their reactivity to react with terminal alkynes to generate alkynyl lithium intermediates, which, together with quaternary ammonium salts with different substituent groups, could efficiently construct highly regioselective difluoroallylation reactions under mild reaction conditions without metal catalysis, so that we could, with an easy-to-operate synthetic approach this work demonstrates that β-difluoro-1,4-alkynes are difficult to obtain by conventional methods.

2 Reaction studies on the preparation of embedded difluoromethylene 1, 4-alkynes and their transformation

2.1 Research background

The difluoroallyl structure is a bioisomer of the carbonyl group, which enhances the bioavailability and lipophilicity of the target molecule and has properties comparable to those of carbonyl compounds in terms of both electronic effects and spatial site resistance. After replacing the carbonyl structure in artemisinin with the kaidifluoroallyl group, scientists have found not only greater stability in human metabolism, but also a significant enhancement of antimalarial effects[84-86]. Currently compounds containing ketodifluoroallyl groups are present in existing drugs through a wide variety of subsequent functionalizations, as shown in Fig. 2-1, providing great attraction for organic molecules containing ketodifluoroallyl backbones. Therefore the introduction of difluoroallyl groups has become one of the most important synthetic strategies for designing new drugs. Great efforts have been made by academia and industry to achieve this transformation, but so far the development of biologically active compounds containing difluoroallyl groups is significantly less and only few commercially available therapeutic agents exist[87-92].



KAG-308
Kaken Pharmaceutical

Glecaprevir
Hepatitis C virus treatment

Tafluprost
ocular hypertension drug

Fig. 2-1 Bioactive fragments containing embedded difluoromethylenes

So far known methods of direct intermolecular preparation with preparation of difluoroallyl products have been reported rarely[93-105]. This is mainly due to the lack of efficient difluoroallyl reagents and highly selective synthetic methods. 3-Bromo-3, 3-difluoropropene (BDFP) is an effective class of difluoroallylation reagents[56] as shown in Fig. 2-2, however the use of BDFP has limitations due to its physical properties such as volatility and substrate range. In addition, the regioselectivity of the synthesised ketodifluoroallylated products requires the help of stoichiometric noble metals or catalysts. In conclusion, so far a universal approach to achieve good substrate tolerance and high selectivity of the sidodifluoroallylation reaction remains elusive.

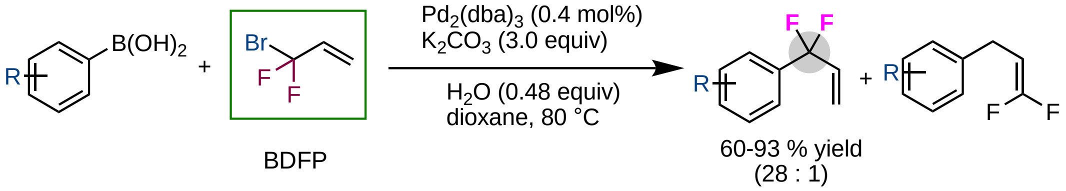
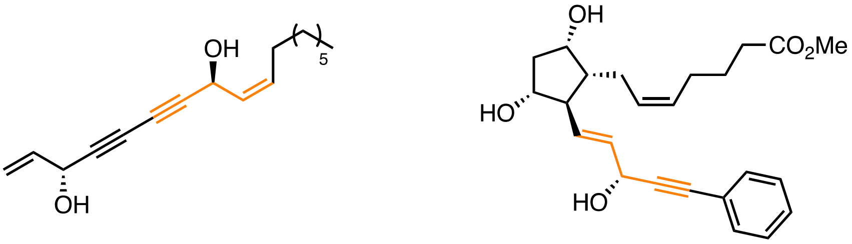


Fig. 2-2 Palladium-catalysed ketodifluoroallylation of arylboronic acid with BDFP

1, 4-Alkynes are valuable and versatile synthons for the synthesis of natural products, organometallic complexes and novel molecules, as shown in Fig. 2-3. In particular, enantiomerically enriched 1, 4-alkynes have proven to be an important component of organic synthesis due to the reliable and controlled downstream transformations of olefinic and alkynic units. For example, 1, 4-enynes can undergo a variety of transformations via special methylene interruption units, such as stereospecific proton migration[106,107], cycloaddition[108-110], and cycloisomerisation[111-113][114-118]. As a result, various efficient synthetic methods have been developed to achieve this class of transformations.

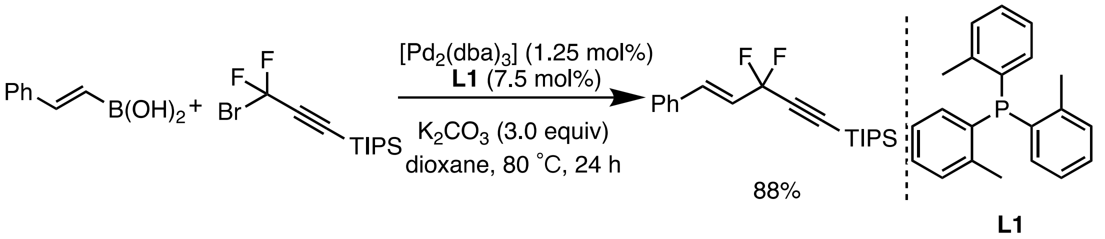


Falcarindiol
(anticancer antimutagenic)

Prostaglandin analogues
(antinidatory effects)

Fig. 2-3 Bioactive molecules containing 1, 4-alkynes

Theoretically, simultaneous substitution of the methylene group (CH$_2$) linking the alkynes by their difluorinated counterparts (CF$_2$) could lead to the formation of more stable 1, 4-alkynes due to the reciprocal isomeric instability of the CH$_2$-bridged alkynes and their susceptibility to the formation of linkages as well as polymerisation. In particular, the unique properties of the sidodifluoroallyl group allow sidodifluoro 1, 4-alkynes to discover new and interesting molecules in medicinal chemistry and materials science. In addition, a number of difluorinated natural products derived from this structural motif can also be used as probes in drug discovery and development, but effective methods for the preparation of kainodifluoro-1, 4-enyne compounds are very limited. So far, only two examples have been demonstrated. Firstly, in 2014, the group of Xingang Zhang[80] achieved the first reaction of kaidifluoroalkynyl bromide with boronic acid for the reaction of kaidifluoroalkynylation using a palladium catalyst. The reaction is carried out under mild conditions and is characterised by high regioselectivity, a wide range of substrates and good compatibility of functional groups. The reaction can also be extended to alkenylboronic acids, in which the reaction of straight-chain alkenylboronic acids with kaidifluoroalkynyl bromide generates the first kaidifluoro 1, 4-alkynyl analogues, realising the first synthesis of compounds containing such molecular backbones.



In 2016, Xingang Zhang's[119] group proposed the synthesis of sidodifluoro 1, 4-diynes via palladium-catalysed cross-coupling reaction of terminal alkynes with sidodifluoroallyl bromo reagents, and synthesized sidodifluoro 1, 4-alkynes in derivatisation experiments by hydrogenation in 89 % yield, which was obtained after a multi-step reaction under harsh reaction conditions as shown in Fig 2-5.

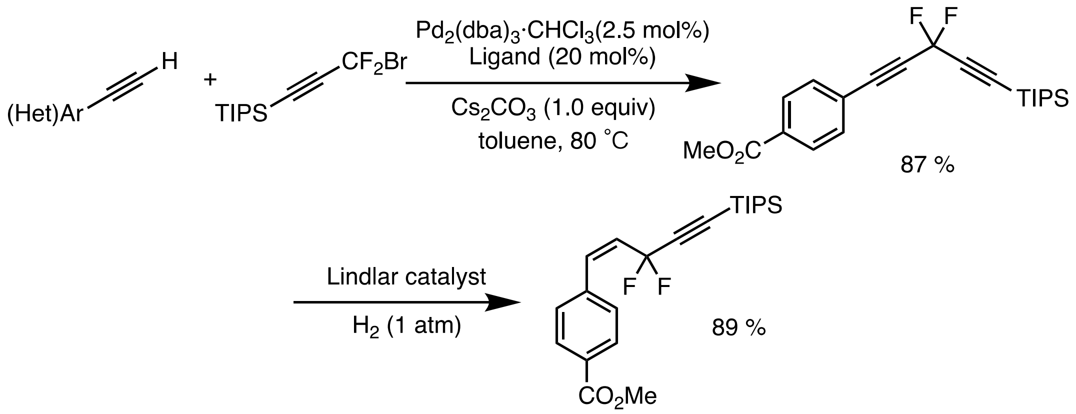


Fig. 2-5 Synthesis of kai-difluoro-1, 4-enyne compounds

Inspired by the above, we realised that there was still much room for exploration to develop a simple and versatile synthetic method to achieve a wide range of substrates and high regioselectivity for the sidodifluoroallylation reaction, and considering that the generated sidodifluoro 1, 4-alkynes had great application prospects as well as synthetic value, we attempted to explore the use of lithium alkynes intermediates activated by metal reagents as hard nucleophilic reagents for the difluoroallylation reaction with the quaternary ammonium salts, with a view to completing the synthesis of functional molecules with embedded difluoromethylene 1, 4-alkynes in high yields and high regioselectivity as shown in Fig. 2-6.

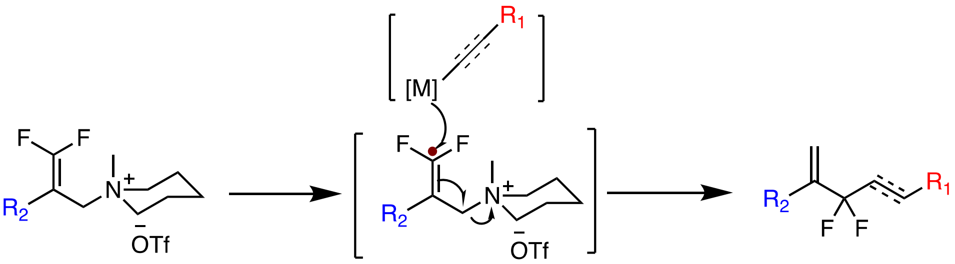
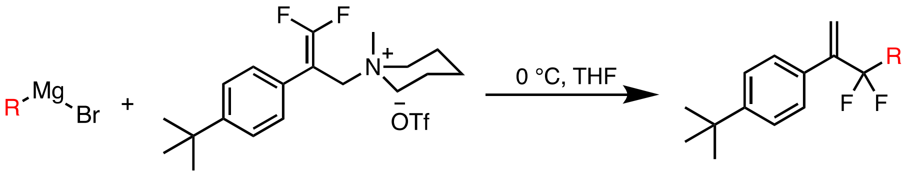


Fig. 2-6 Reaction of difluoroolefin quaternary reagents with terminal alkynes by sidodifluoroallylation

2.2 Experimental results and discussion

2.2.1 Exploration and optimisation of reaction conditions

We began the initial stage of designing the reaction by exploring whether the Grignard reagent is sufficiently nucleophilic to undergo direct sialylation with tetra-tert-butyldifluoroolefin quaternary ammonium salt (**1a**) at 0 °C to produce the expected target product (**2a**). Unfortunately, most of the less active Grignard reagents were incompatible for this reaction, and none of the target products were obtained under this reaction condition, and only the reaction with unstable Grignard reagents such as phenyl, benzyl, and allyl existed to obtain the target products with R substituted with phenyl (**2a**), benzyl (**2b**), and allyl (**2c**), which proves that such reactions require highly active metal-based reagents as nucleophilic reagents to be realised, as shown in Table 2-1.



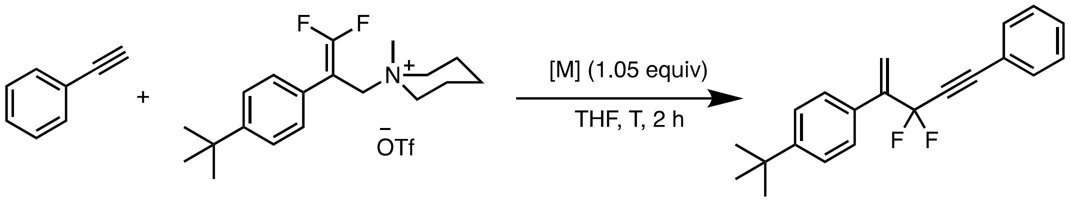
1a **2a**

Table 2-1 Influence of difluoroolefin quaternary ammonium salts by the reaction of different format reagents

Entry	R	Temp (℃)	Solvent	Yield (%)[a]
1	Me	0 ℃	THF	-
2	Et	0 ℃	THF	-
3	*t*-Bu	0 ℃	THF	-
4	*c*-Pen	0 ℃	THF	-
5	*c*-Pr	0 ℃	THF	-
6	Pr	0 ℃	THF	Trace
7	Ph	0 ℃	THF	62 (**2a**)
8	*t*-Butylbenzene	0 ℃	THF	-
9	*p*-Xylene	0 ℃	THF	-
10	Bn	0 ℃	THF	99(**2b**)
11	Vi	0 ℃	THF	-
12	allyl	0 ℃	THF	78(**2c**)
13	ethinyl	0 ℃	THF	-

Reaction conditions: 1a (0.2 mmol), RMgBr (0.22 mmol), Solvent (2 mL), the reaction mixture was stirred at 0 °C under N2 atmosphere for 1h 4a. [a] isolated yield.

And then phenylacetylene (**3a**) and tetra-tert-butyldifluoroolefin quaternary ammonium salt (**1a**) were chosen as the stencil substrate for the reaction. The effect of different metal reagents on the conversion of this reaction was firstly tried using the stencil substrate at 0 °C. After screening the metal reagents and additives, we found that most of the metal reagents did not show reactivity in this reaction (Table 2-2 entries2, 4, 5). Through literature research and analysis[120,121], copper has the effect of activating alkynes and did not promote the reaction at -40 °C when CuCN was used as an additive (Table 2-2 entries7-8), but it did not promote the reaction when lithium diisopropylamidoacetate(LDA), ethylmagnesium bromide, and n-butyllithium were used as hard nucleophilic reagents for reacting with the terminal alkynes to form alkynyl lithium. lithium reaction intermediates, the expected target product 1-tert-butyl-4-(3, 3-difluoro-5-phenylpent-1-en-4-yn-2-yl)benzene (**4a**) was generated with the quaternary ammonium substrate in a relatively short reaction time in a reaction system without any additives, as shown in Table 2-2.



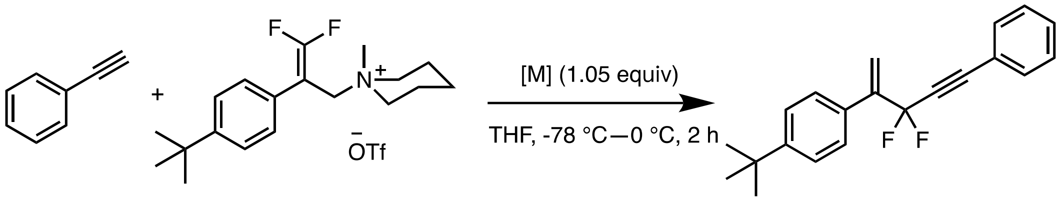
3a 1a 4a

Table 2-2 Effect of metal reagents on the reaction of difluoroallylation

Entry	[M]	Temp (°C)	Time (h)	Salts[b]	Yield(%)[a]
1	LDA	0 °C	2 h	-	53
2	Et_2Zn	0 °C	2 h	-	-
3	EtMgBr	0 °C	2 h	-	16
4	MeMgBr	0 °C	2 h	-	-
5	*i*PrMgCl·LiCl	0 °C	2 h	-	-
6	*n*-BuLi	0 °C	2 h	-	22
7	EtMgBr	-40 °C	2 h	CuCN	-
8	MeMgBr	-40 °C	2 h	CuCN	-

Reaction conditions: 3a (0.2 mmol), 1a (0.22 mmol), Solvent (2 mL), the reaction mixture was stirred at 0 °C or -40 °C under N2 atmosphere for 1h and continue strring for 1h after adding 1a. [a] isolated yield. [b] CuCN (2.2 eq.) was used.

When examining the reaction temperature of the metal reagent with the terminal alkynes, it was found that when LDA was used as the metal reagent, the temperature did not promote or inhibit the reaction, but when n-butyllithium was used as the metal reagent, the temperature had a greater effect on the generation of the lithium alkynes intermediate, and within a certain range of lowering the temperature even inhibited the reaction, and when the temperature was consistently lowered to -78 °C, the yield of the reaction was significantly improved. When the temperature was consistently lowered to -78 °C, the yield of the reaction was significantly improved, and the authors finally determined that the optimum temperature for the reaction was 0 °C for the reaction with the quaternary ammonium salt substrate after the reaction to generate the alkynyl lithium intermediate at -78 °C. Subsequently, further optimisation of the reaction conditions was carried out on this basis, as shown in Tables 2-3.



3a **1a** **4a**

Table 2-3 Effect of temperature on the reaction of difluoroallylation

Entry	**[M]**	**Temp (℃)**	**Time (h)**	**Solvent**	**Yield (%)[a]**
1	LDA	0 ℃	2 h	THF	53
2	LDA	-78 ℃	2 h	THF	58
3	n-BuLi	0 ℃	2 h	THF	22
4	n-BuLi	-40 ℃	2 h	THF	-
5	n-BuLi	-78 ℃	2 h	THF	98

Reaction conditions: 3a (0.2 mmol), 1a (0.22 mmol), Solvent (2 mL), the reaction mixture was stirred at different temperature under N2 atmosphere for 1h and continue strring for 1h after adding 1a. [a] isolated yield.

In the solvent screening stage the authors investigated using common laboratory solvents such as hexane, ether and tetrahydrofuran. It was found that when the less polar hexane was used as a solvent, the reaction was completely inhibited, when ether was used as a solvent, only trace amounts of product were generated, and only when tetrahydrofuran was used as a solvent was the reaction nearly completely converted. Ultimately, the authors determined that the optimal conditions for the reaction of **1a** with **3a** in a ketodifluoroallylation reaction to produce **4a** were: 0.2 mmol **3a** and 1.05 equiv n-butyllithium in 1 mL of tetrahydrofuran solution stirred for one hour at -78 °C, and the obtained reaction intermediate and 0.22 mmol **1a** in 1 mL of tetrahydrofuran solution stirred for one hour at 0 °C to obtain the target Product. Under this reaction condition, kedifluoro 1, 4-enyne compound 4a was obtained in 98 % isolated yield as shown in Tables 2-4.

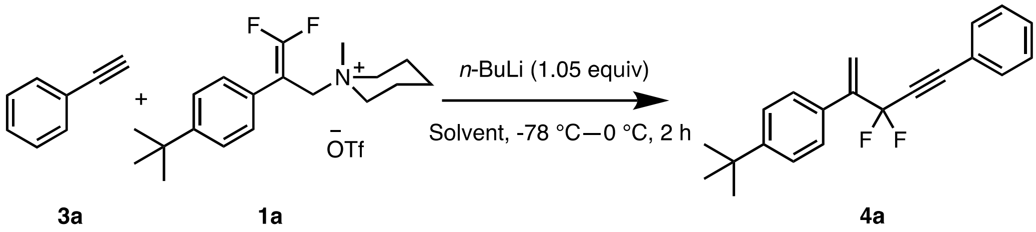


Table 2-4 Effect of solvent on the reaction of ketodifluoroallylation

Entry	**[M]**	**Temp (°C)**	**Time (h)**	**Solvent**	**Yield (%)[a]**
3	n-BuLi	-78 °C	2 h	Hexane	-
4	n-BuLi	-78 °C	2 h	Et2O	10
5	n-BuLi	-78 °C	2 h	THF	98

Reaction conditions: 3a (0.2 mmol), 1a (0.22 mmol), Solvent (2 mL), the reaction mixture was stirred at -78 °C under N2 atmosphere for 1h and continue strring for 1h after adding 1a. [a] isolated yield.

2.2.2 Reaction Substrate Expansion

After establishing the optimal reaction conditions, the substrate universality of the reaction was investigated using quaternary ammonium salt substrates with different substituents with terminal alkynes. Firstly, we established a template reaction and examined the substrate range of terminal alkynes using phenylethynes (**3a**) and tetra-tert-butyldifluoroolefin quaternary ammonium salts (**1a**) as the template substrates, and found that the reaction occurs in high yields with both electron-donating and electron-withdrawing groups in the aryl para-position of aromatic terminal alkynes, while the reaction system is equally suitable for bulky substituents such as naphthalene (**4b**, 86% yield), and aryl 3- and 5-positions with electron-withdrawing groups. This system is also applicable to bulky substituents such as naphthalene (**4b**, 86% yield), as well as to aryl groups with electron-withdrawing groups at the 3- and 5-positions, where the reaction still occurs in high yield. Subsequently, we examined a series of aliphatic terminal alkynes and found that the conversion of terminal alkynes with electron-withdrawing groups was significantly lower than that with electron-donating groups (e.g., **4k**, R^1=TMS, 56% yield and **4n**, 66% yield), and that the reaction proceeded smoothly with heterocyclic molecular segments in the terminal alkynes, as shown in Fig. 2-7.

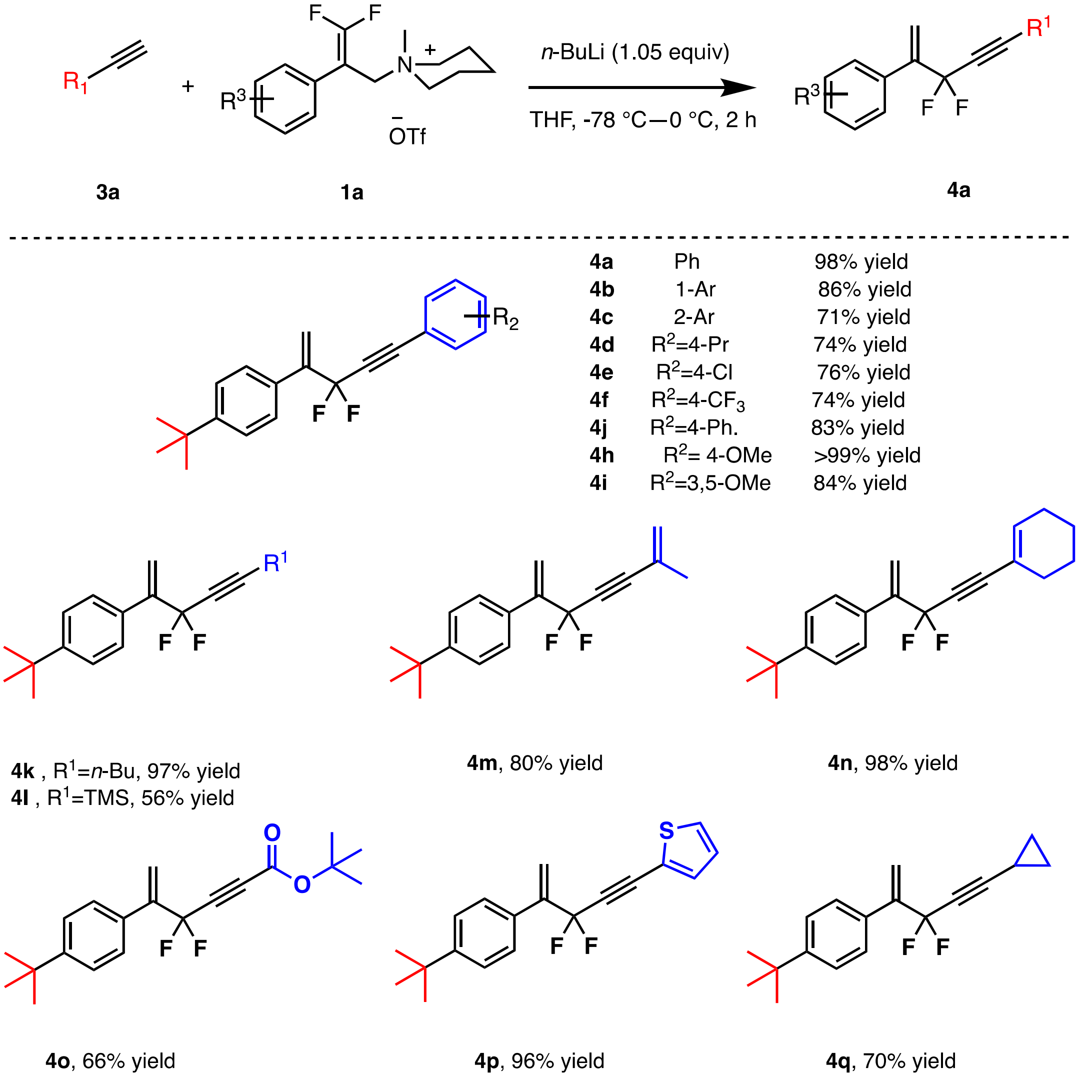
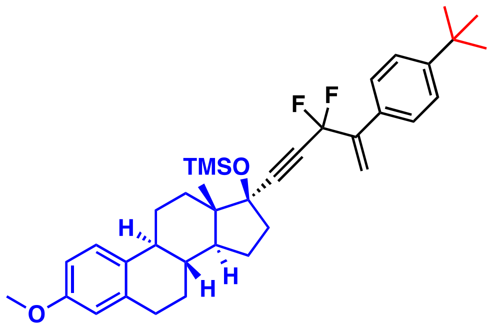


Fig. 2-7 Examination of substrate universality

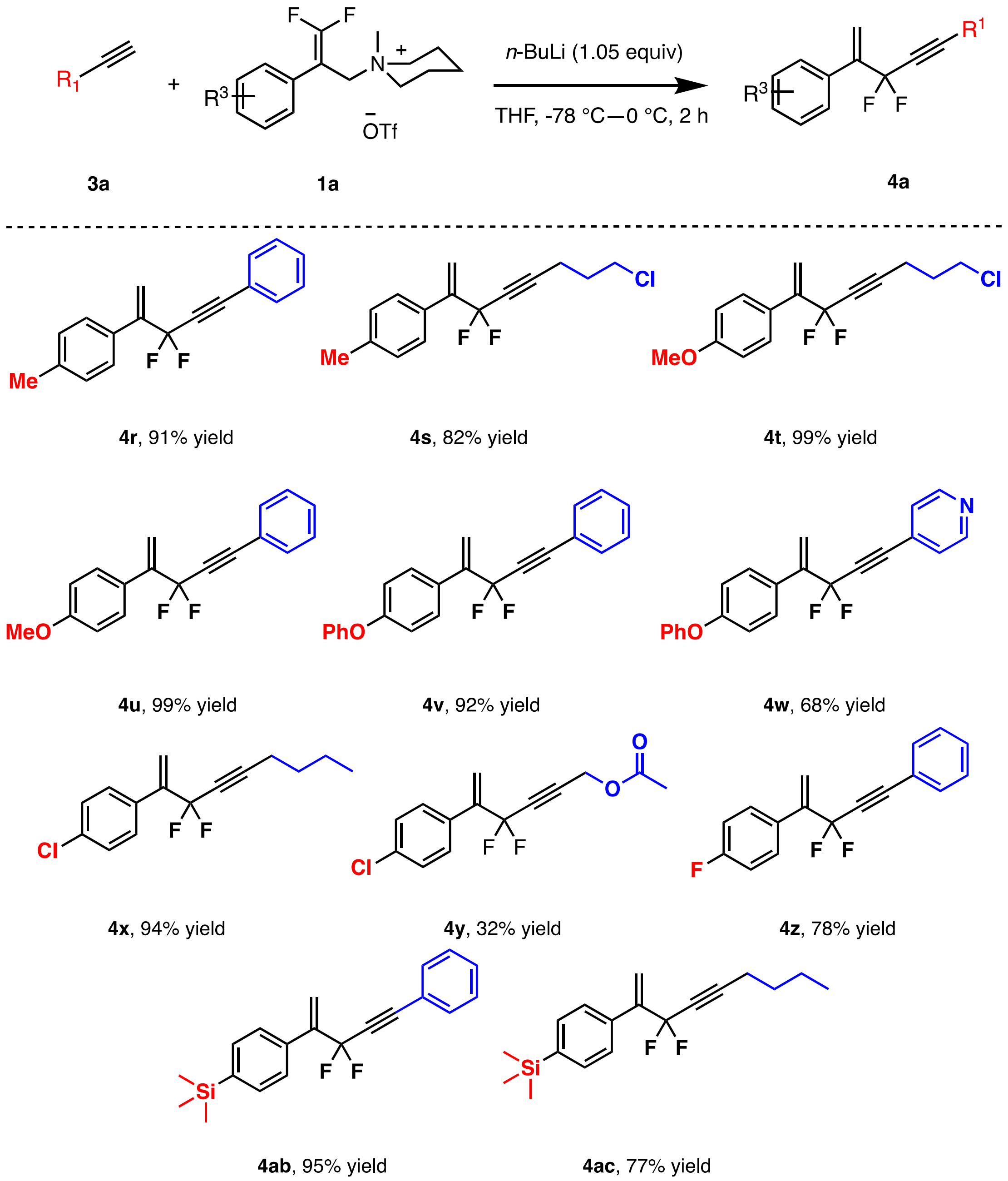
In substrate extension we tried to combine such structures with drug fragments to obtain an example of biologically active alkenyne compound **4g** in 98 % isolated yield as shown in Figure 2-8.



4g, 98% yield

Fig. 2-8 Examination of substrate universality

Subsequently, we examined the substrate universality of the quaternary ammonium substrates, and the experiments showed that the reaction system was still applicable to quaternary ammonium substrates with different substituents. We firstly synthesised quaternary ammonium substrates with aryl para-methyl, methoxy, phenoxy, fluoro, chloro halogen groups and TMS silyl substituents, and found that the reaction could occur well in the quaternary ammonium salt aryl para with both electron-donating and electron-supplying groups, and at the same time, when transforming terminal alkynes para-substituent, the majority of the functional groups showed a promotional effect on the reaction, and the yield could reach up to 99%. However, it was found that the yield of phenyl para-chloro-substituted quaternary ammonium salt substrate reacted with ester-terminated alkynes decreased dramatically (**4x**, 32% yield), while the reaction yield slightly decreased when the terminal alkynes were substituted with pyridine groups in the para-position (**4v**, 68% yield), which may be attributed to the weak activity of the pyridine ring in the electrophilic substitution reaction, as shown in Fig. 2-9. The experimental results show that this novel reaction system without the need for metal catalysis with exclusive regioselectivity and without the addition of any catalyst has good substrate tolerance.



3a **1a** **4a**

4r, 91% yield **4s**, 82% yield **4t**, 99% yield

4u, 99% yield **4v**, 92% yield **4w**, 68% yield

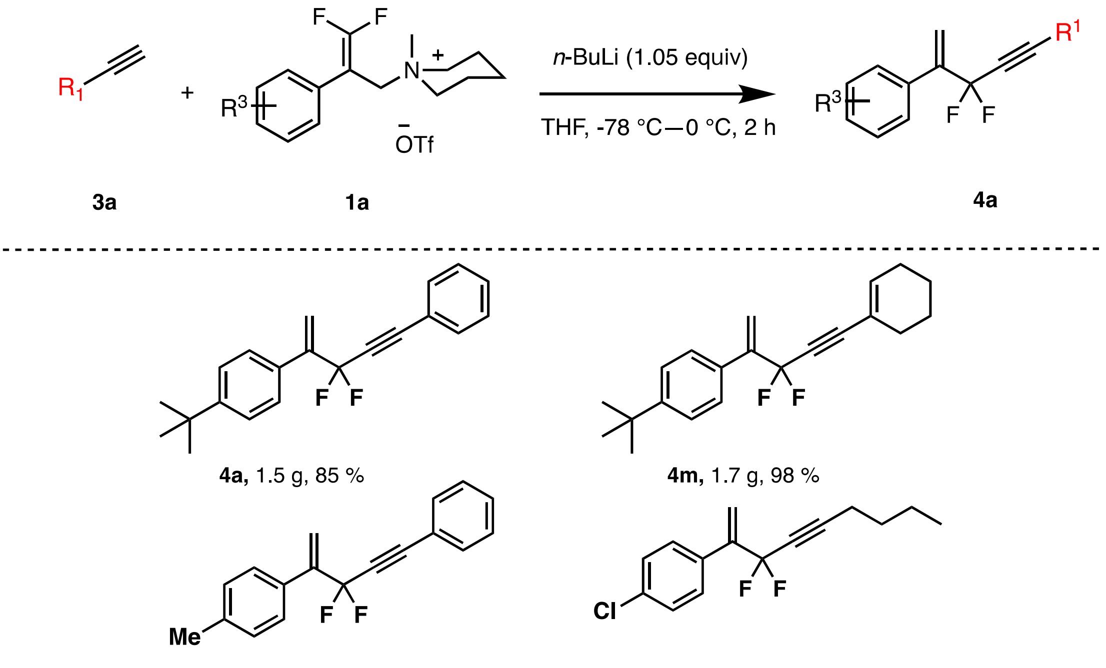
4x, 94% yield **4y**, 32% yield **4z**, 78% yield

4ab, 95% yield **4ac**, 77% yield

Fig. 2-9 Examination of substrate universality

2.2.3 Scale-up experiments and derivatisation reactions

We performed scale-up experiments for this reaction and found that the yields of the target products **4a**, **4m**, **4q**, and **4w** with different substituents could be maintained at the same reaction level as in the small-volume reaction, as shown in Fig. 2-10.



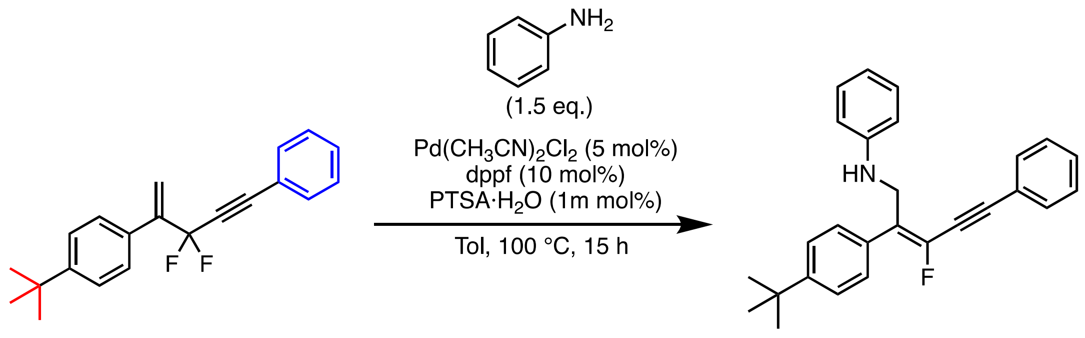
3a **1a** **4a**

4a, 1.5 g, 85 % **4m,** 1.7 g, 98 %

4q, 1.3 g, 94 % **4w,** 1.1 g, 90 %

Fig. 2-10 Gram-scale products obtained in the amplification experiment

In the process of derivatisation reaction, we have carried out a large number of reaction attempts, and found that the rigid structure of this kind of kainedifluoro 1, 4-alkynyne product **4** makes it difficult to carry out the carbonylation and intramolecular cyclisation reaction, and it is also difficult to carry out the hydrogenation reaction of the terminal alkene position by hydrogenation; after a series of attempts, experimental phenomena show that this kind of compounds can be allyl substitution reaction with different nitrogen and sulphur nucleophilic reagents under the palladium catalysis and obtain a series of different alkene position monosubstituted and disubstituted products **5**, **6**, **7** as shown in Fig. 2-11.



4a **5,** 31 %

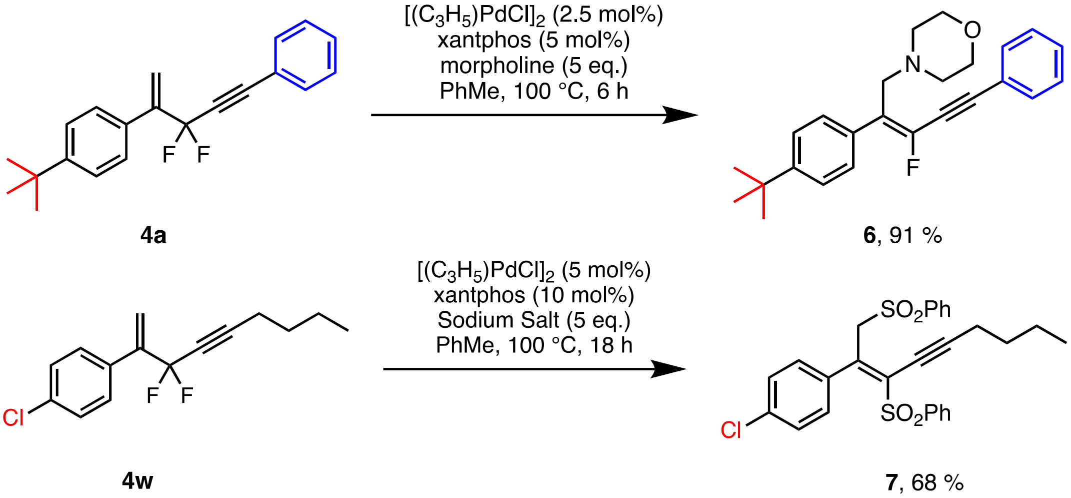


Fig. 2-11 Derivatisation of products

Continuing with the boronation reaction attempt using the obtained embedded difluoromethylene gram product, the generation of the target product was observed based on TLC monitoring, but the boronation product could not be obtained by column chromatographic separation technique, and when the reaction was attempted again, the borane was oxidised to form a hydroxyl group by H_2O, H_2O_2, and NaOH (aq) after the target product was observed at the end of the reaction, and the boronation product was obtained by column chromatographic separation technique in a 40 % separation yield was successfully obtained for the olefinic site disubstituted derivatisation product 8, as shown in Fig. 2-12.

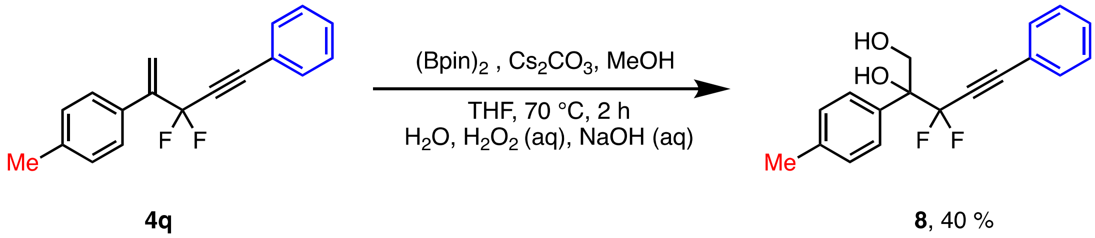
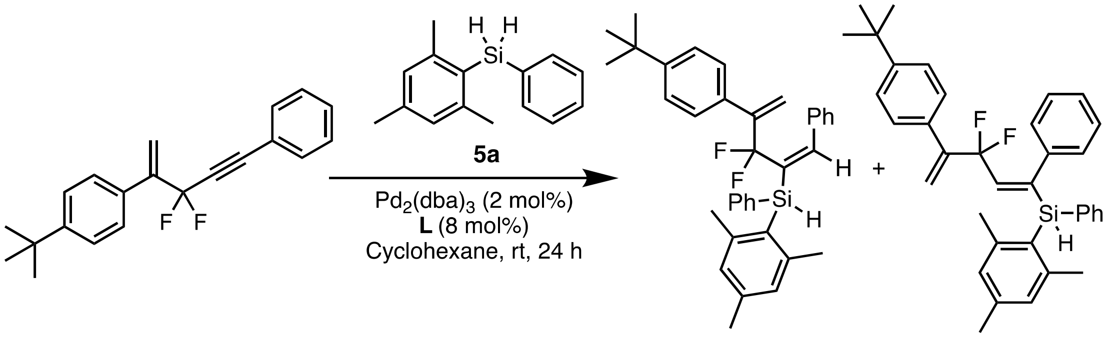


Fig. 2-12 Derivatisation of products

The extensibility of the alkyne site in the gram-scale product was then examined to construct fluorosilicon compounds containing a silicon stereocentre using an asymmetric catalytic strategy to catalyse the silylhydrogen addition reaction of sidodifluoro 1, 4-enylic alkynes with a stable palladium-phosphine ligand complex developed by our group.

Firstly, the authors used 4a as a template substrate and reacted with asymmetric diaryldisilahydrogen 5a in the presence of transition metal palladium catalyst as a palladium source and cyclohexane as a solvent at room temperature for 24 h. The range of applicability of the racemic phosphine ligands was screened to obtain the target products **6a**, **6b**. It is noteworthy that some of the commercially available phosphine ligands did not act as a catalyst for the reaction to take place in this reaction (Tables 2-5). and only three of the eight phosphine ligands were effective for this reaction. When using the 1, 3-bis(diphenylphosphino)propane (dppp) phosphine ligand (Table 2-5 entries 5), the racemic target products **6a** and **6b** were obtained in a total yield of 49 % with a good enantioselectivity (6a/6b=86:14) and more surprisingly the phosphinamidite ligand of the racemic biphenylphenol skeleton was also able to stimulate the reaction (Table 2-5 entries 4) with 15 % of the total yield. To obtain the target products in 15 % isolated yield, which provided a new idea for our chiral ligand screening, as shown in Table 2-5.

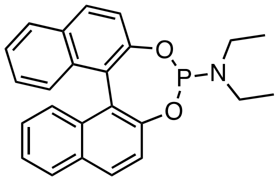


4a **6a** **6b**

Table 2-5 Screening of the phosphine-coated ligand

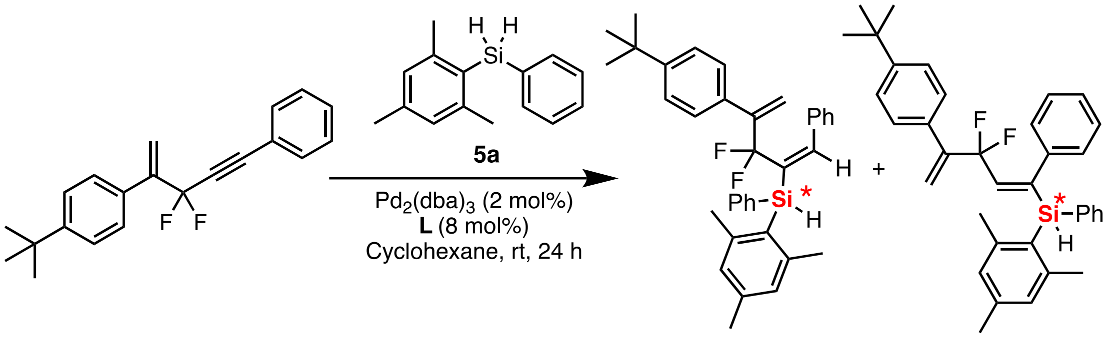
Entry	[Pd]	Ligand	Yield(%)	Ratio[a]
1	$Pd_2(dba)_3$	Xantphos	-	-
2	$Pd_2(dba)_3$	dppf	-	-
3	$Pd_2(dba)_3$	dppb	-	-
4	$Pd_2(dba)_3$	L1	15	78:22
5	$Pd_2(dba)_3$	dppp	49	86:14
6	$Pd_2(dba)_3$	PPh_3	35	90:10
7	$Pd_2(dba)_3$	Xphos	-	-
8	$Pd_2(dba)_3$	$nBuPAd_2$	-	-

Reaction conditions: **4a** (0.2 mmol), R_2SiH_2 (0.2 mmol), [Pd] (2 mol%), Ligand (8 mol%), Solvent (1 mL), rt, 24 h. [a] isolated yield.



L1

After confirming the structure of the racemic product, the authors screened the chiral ligands and found that the common commercially available ligands such as phosphine ligand (**L3**) of TADDOL backbone were not satisfactory. Based on the idea of screening the racemic ligands, we tried to synthesise a series of chiral phosphoramidite ligands with different substituents of the binaphthol backbone, and found that the phosphoramidite ligands of the binaphthol backbone were able to be applied to the reaction when the reaction was attempted. However, when the benzene ring of the binaphthol skeleton was substituted with a large-site-resistance straight-chain aliphatic group (tert-butyl) in the para-position of the benzene ring of the binaphthol skeleton, the results of several attempts of the reaction were unsatisfactory (Tables 2-6 entries4, 6, 8). When the benzene ring of the binaphthol skeleton was substituted with a large-site-resistance silica-substituted TMS group in the para-position of the benzene ring of the binaphthol skeleton, and the symmetrical substitution of the N on the N in the phosphoramidite ligand by npentane(**L10**), the yields of the target products, enantioselectivities After comparing the data, we finally confirmed the use of **L10** as the best chiral ligand for this reaction, as shown in Table 2-6.

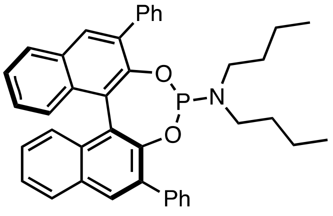


4a **6a** **6b**

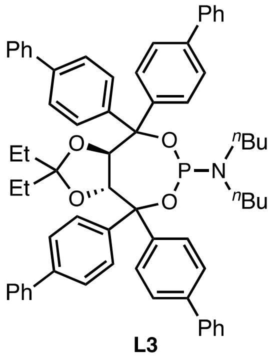
Table 2-6 Screening of chiral phosphine ligands

Entry	Ligand	Yield[a]	ee(%)[b]	rr(%)[b]
1	L2	80	77	64:36
2	L3	80	22	30:70
3	L4	trace	-	-
4	L5	trace	-	-
5	L6	84	76	87:13
6	L7	trace	-	-
7	L8	78	92	78:22
8	L9	trace	-	-
9	L10	86	90	81:19

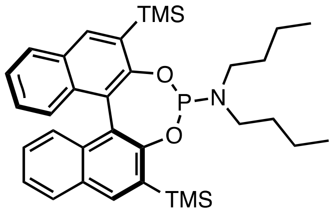
Reaction conditions: **4a** (0.2 mmol), R_2SiH_2 (0.2 mmol), [Pd] (2 mol%), Ligand (8 mol%), Solvent (1 mL), rt, 24 h. [a] isolated yield, [b] Determined by chiral HPLC analysis.



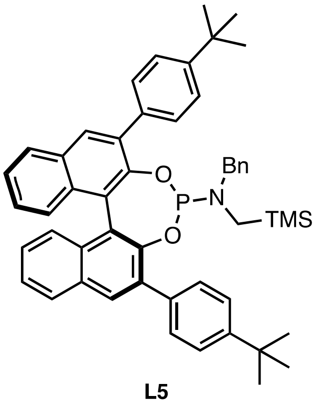
L2



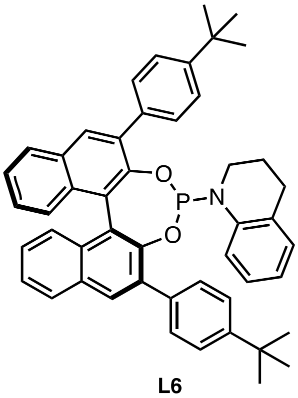
L3



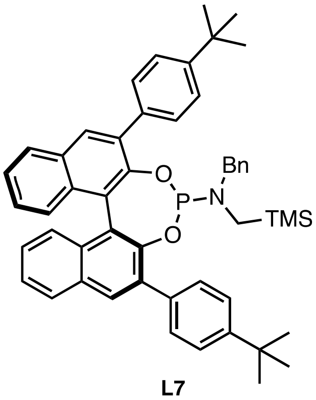
L4



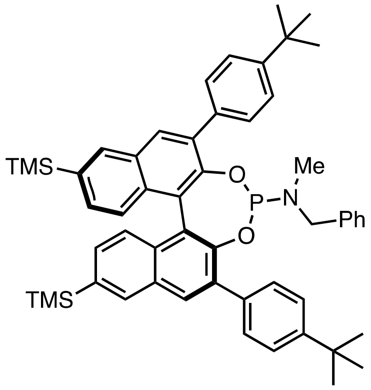
L5



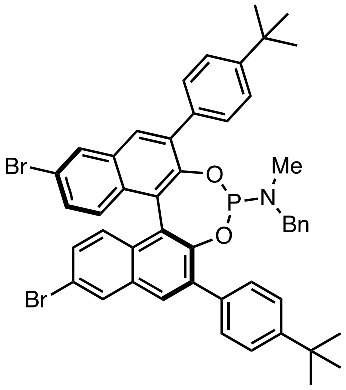
L6



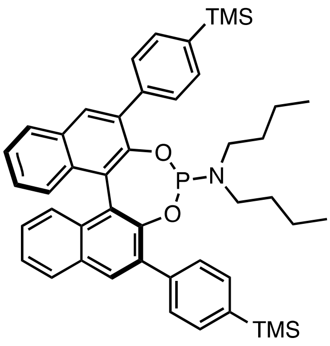
L7



L8

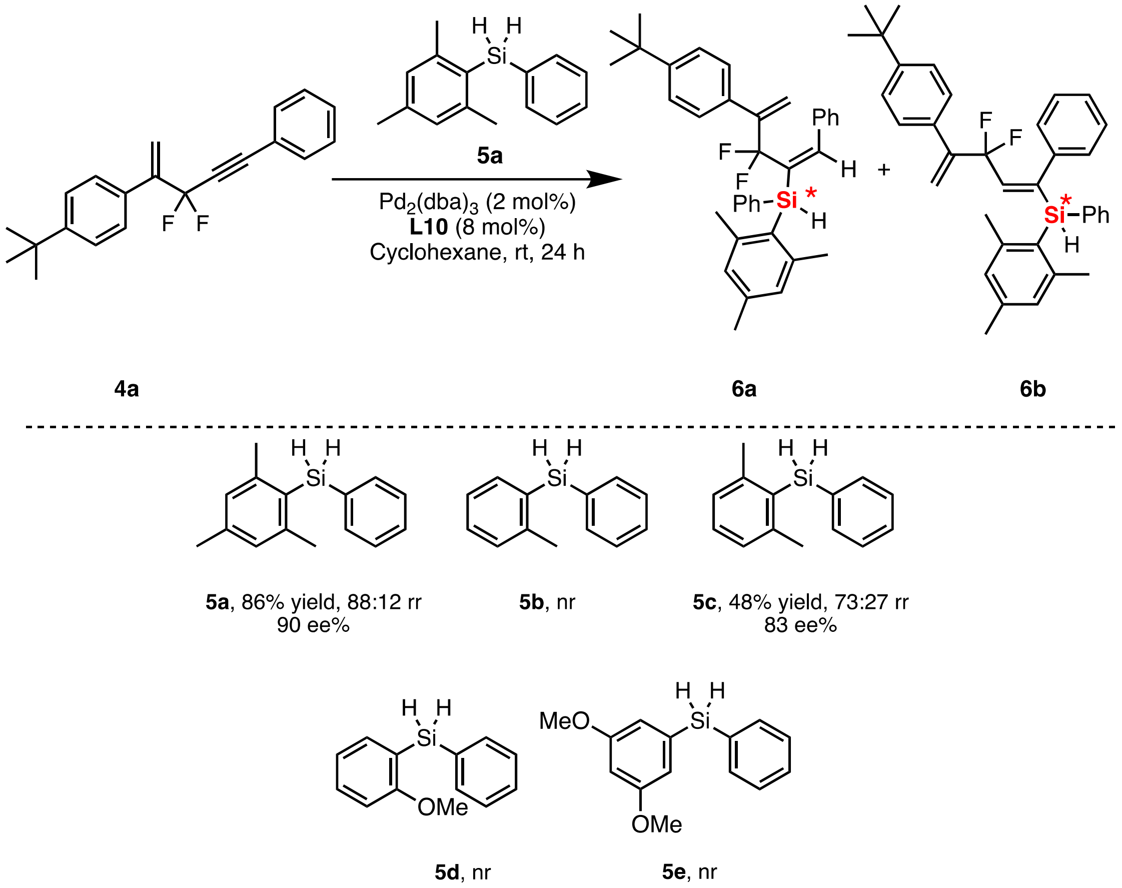


L9



L10

After determining the optimal conditions for this reaction, we synthesized a series of asymmetric dihydrosilanes to examine the reaction for silane universality, through which we found that monosubstituted silylhydrides in the asymmetric aryl group on the silanes (**5b**) were unreactive, as well as the aryl group was unreactive by both monosubstitution and disubstitution by methoxy (**5d, 5e**), and that when the aryl group was dibenzhydridized with methyl (**5c**), the yields, regioselectivities, as well as the enantioselectivity all decreased (48% yield, 73:27 *rr*, 83% *ee*), as shown in Fig. 2-13.



4a **6a** **6b**

5a, 86% yield, 88:12 rr
90 ee%

5b, nr

5c, 48% yield, 73:27 rr
83 ee%

5d, nr

5e, nr

Fig. 2-13 Dihydrosilane Substrate Range Expansion

2.3 EXPERIMENTAL PART

2.3.1 Experimental apparatus and data

In the above mentioned, all the difluoroallylation and silylhydrogen addition reactions were carried out in an anhydrous and oxygen-free Shrike reaction tube under nitrogen atmosphere, and all the solvents used in all the experiments were ultra-drying and deoxygenated solvents, and such solvents were taken in an anhydrous and an oxygen-free state by using dry long needles, and the quaternary ammonium substrate substrates and phosphinic acid amide ligands were synthesised in an anhydrous and oxygen-free nitrogen atmosphere. The product is mainly purified and separated by column chromatography, the silica gel powder used is 200-

300 mesh, and the eluents used are petroleum ether and ethyl acetate purchased by Sinopharm.

Large instruments and equipment: Brucker Advance (400/500M) NMR, Bruker MicroTOF-instrument (ESI or APCI) High Resolution Mass Spectrometer, Agilent 1260 HPLC High Performance Liquid Chromatography (HPLC), Agilent 7890 GC-MS Gas Chromatography (GC-MS), Waters UPLC high performance liquid chromatography.

2.3.2 experimental step

The synthesis of quaternary ammonium salts has been reported in the literature, and difluoroolefin quaternary ammonium salt substrates with different substituents in the aryl para position have been synthesised according to the known reports.

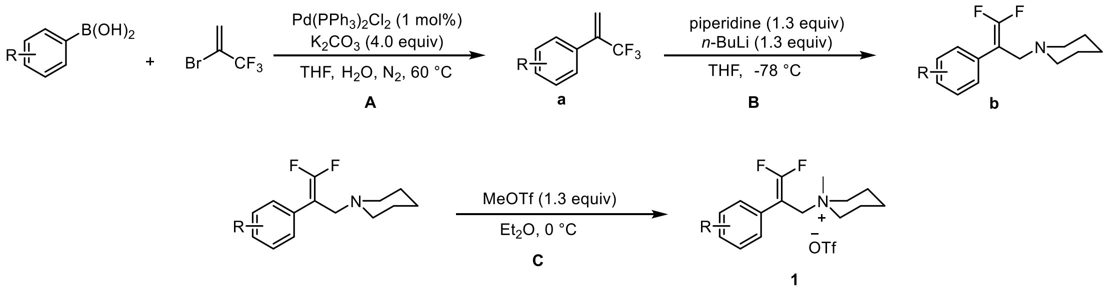
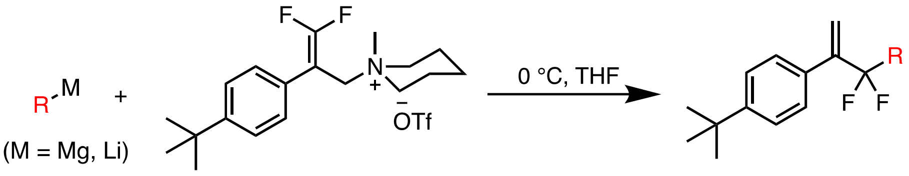


Figure 2-14 Generic synthesis of quaternary ammonium substrates with different substituents

Step A: Phenylboronic acid (20 mmol), 2-bromo-3, 3, 3-trifluoropropene (40 mmol), bis(triphenylphosphine)dichloropalladium (0.14 g, 0.2 mmol), anhydrous and oxygen-free tetrahydrofuran (60 mL), anaerobic water (30 mL), and anhydrous potassium carbonate (79.6 mmol) were sequentially added to a 500 mL Shriek's tube fitted with a magnetic stir bar. The resulting solution was stirred continuously at 60 ℃ for 24 h. The completion of the reaction was monitored using TLC, and the turbid liquid obtained from the reaction was cooled to room temperature after showing that all the ingredients had reacted, and it was quenched using saturated aqueous NH_4Cl solution (30 mL), and the solution of the target product was obtained by extraction and then concentrated under reduced pressure. The crude product obtained was purified by fast chromatography to give a colourless liquid a.

Step B: Piperidine (13.4 mmol) and anhydrous tetrahydrofuran (30 mL) were added to an oven-dried 250 mL flask equipped with a stir bar under nitrogen protection. The flask was cooled to -78 °C using a dry ethanol bath and a 2.5 M hexane solution of n-butyllithium (12.4 mmol) was added dropwise to the flask after 10 min of cooling. The solution was stirred at -78 °C for 1.5 h, then heated to 0 °C in an ice-water bath and stirred for 1 h. The flask was cooled to -78 °C using a dry ethanol bath, and after cooling for 10 min, the pentachromic solution a (2.4 g, 10.3 mmol) was added dropwise to the flask for more than 5 min. The resulting mixture was stirred at -78 °C for 3 h, then heated to 0 °C in an ice-water bath and stirred for 1 h, and then quenched with an aqueous solution of NH_4Cl (20 mL). The target product solution was obtained by extraction and then concentrated under reduced pressure. The residue was purified by fast chromatography to give a colourless liquid b.

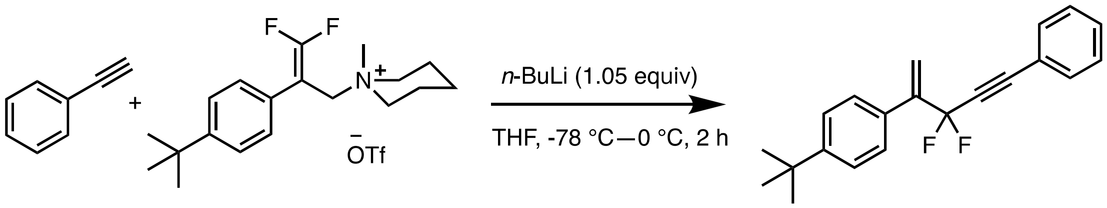
Step C: Add b (5.6 mmol) and anhydrous, oxygen-free ether (12 mL) to a Shrike tube fitted with a magnetic stir bar. The flask was cooled to 0 °C using an ice water bath and methyl trifluoromethanesulfonic acid (7.28 mmol) was added dropwise to the flask for more than 5 min. The solution was stirred at 0 °C for 1 h. The reaction solution became turbid and milky white, and after the formation of milky white flocculent was observed, the resulting mixed solution was filtered and washed repeatedly with dry ether. Vacuum drying for 5 h to obtain the pure product 1, as shown in Fig. 2-14.



1a **2a**

Fig. 2-15 Preparation of embedded difluoro-terminated alkene compounds

1a (0.3 mmol) and anhydrous anaerobic tetrahydrofuran (1.5 mL) were added to a 25 mL Shrek reaction tube equipped with a magnetic stir bar. The flask was cooled to 0 °C in a dry ethanol bath, and then Grignard's reagent (0.33 mmol ,1 mol/L) was slowly dripped into the flask using a dry long needle. The solution was stirred at 0 °C for 1 h and then quenched with aqueous NH_4Cl solution (3 ml). The target product solution was obtained by extraction and then concentrated under reduced pressure. The residue was purified by rapid chromatography to give a pale yellow oily liquid 2a, as shown in Fig. 2-15.



3a **1a** **4a**

Fig. 2-16 Preparation of embedded difluoroalkyne analogues

A 25 mL Shrek reaction tube equipped with a magnetic stirring bar was charged with alkyne 3a (0.3 mmol) and anhydrous oxygen-free tetrahydrofuran (1.5 mL). The flask was cooled to -78 °C using a dry ethanol bath and after 10 min of cooling, a 2.6 M hexane solution of n-butyllithium (0.315 mmol) was added dropwise to the flask. The solution was stirred at -78 °C for 1 h. 1a (0.36 mmol) was dissolved in dry tetrahydrofuran solution (1.5 mL) and added dropwise to the flask over more than 5 min using a dry, long needle, then heated to 0 °C in an ice-water bath and stirred for 1 h. The solution was then quenched with aqueous NH_4Cl solution (3 mL). The target product solution was obtained by extraction and then concentrated under reduced pressure. The residue was purified by rapid chromatography to give a pale yellow oily liquid 4a, as shown in Fig. 2-16.

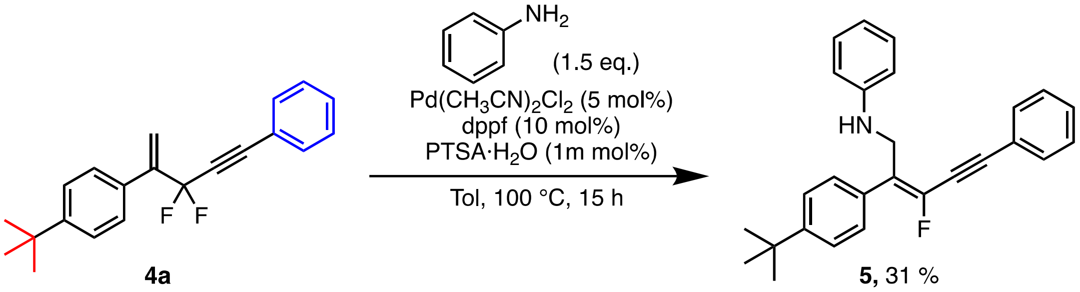


Fig. 2-17 Preparation of Derivatisation Product 5

4a (0.2 mmol), aniline (0.375 mmol), bis(acetonitrile) palladium(II) chloride (0.0125 mmol), dppf (0.025 mmol), PTSA-H_2O (0.025 mmol), and toluene (2 mL) were added to a 25 mL Shrek tube, which was filled with nitrogen. The obtained solution was stirred at 100 °C for 15 h. The completion of the reaction was monitored using TLC, and the turbid liquid obtained from the reaction was cooled to room temperature after showing that all the reaction of ingredient 4a had been completed, and it was quenched using saturated aqueous NH_4Cl solution (2 mL), and the solution of the target product was obtained by extraction and then concentrated under reduced pressure. The resulting crude product was purified by fast chromatography to give yellow liquid 5 in 31 % isolated yield as shown in Fig. 2-17.

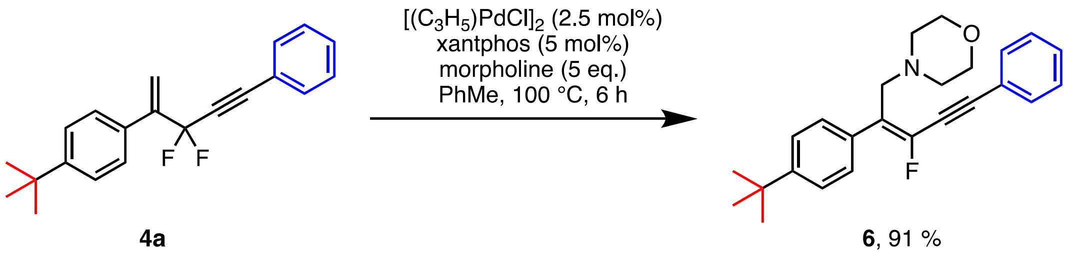


Fig. 2-18 Preparation of Derivatisation Products

4a (0.2 mmol), morpholine (1 mmol), Xantphos (0.02 mmol), allylpalladium(II) chloride dimer (0.005 mmol), and toluene (0.9 mL) were added to a 25 mL Shrek reaction tube which was filled with nitrogen. The obtained solution was stirred at 100 °C for 6 h. The completion of the reaction was monitored using TLC, and the turbid liquid obtained from the reaction was cooled to room temperature after showing that all of the reaction of ingredient 4a had been completed, and it was quenched using saturated aqueous NH_4Cl solution (2 mL), and the solution of the target product was obtained by extraction and then concentrated under reduced pressure. The resulting crude product was purified by fast chromatography to give yellow liquid 6 in 91 % isolated yield, as shown in Fig. 2-18.

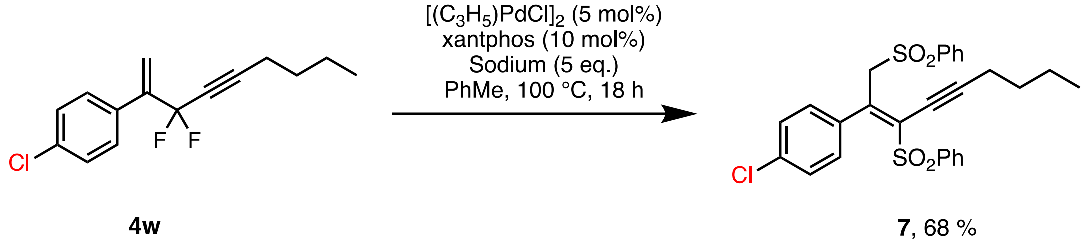


Fig. 2-19 Preparation of Derivatisation Product 7

4w (0.2 mmol), sodium salt (1 mmol), Xantphos (0.02 mmol), and allylpalladium(II) chloride dimer (0.01 mmol) were added to a 25 mL Shrek reaction tube which was filled with nitrogen. Toluene (1 mL) was added. The obtained solution was stirred at 100 °C for 18 h. The reaction mixture was cooled to room temperature and lithium hydroxide (2 M) was added, and the reaction was carried out at room temperature for 2 h. The mixed solution obtained from the reaction was quenched with saturated aqueous NH_4Cl solution (2 mL), and the target product solution was obtained by extraction and concentrated under reduced pressure. The resulting crude product was purified by fast chromatography to give yellow liquid 7 in 68 % isolated yield, as shown in Fig. 2-19.

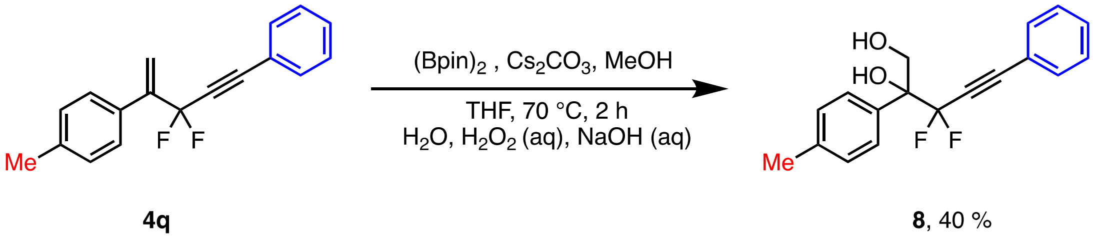
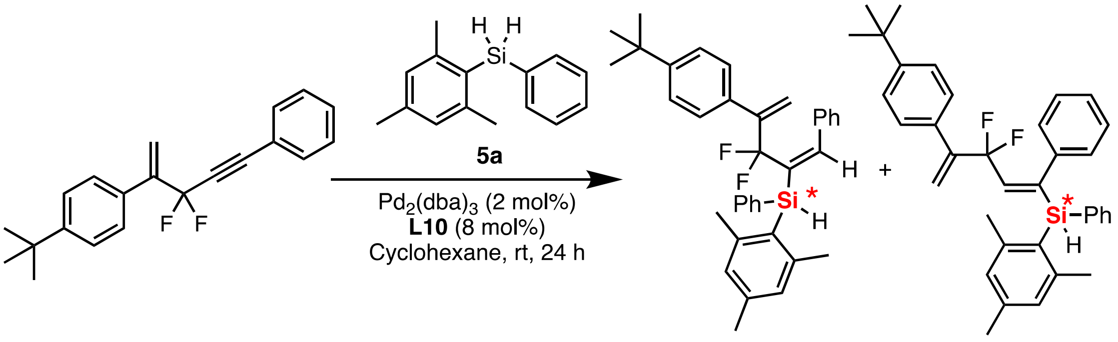


Fig. 2-20 Preparation of Derivatisation Product 8

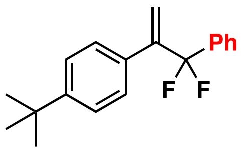
4q (0.2 mmol), pinacol ester of bisboronic acid (1 mmol), Cs_2CO_3 (0.02 mmol), and ultra-dry MeOH (0.01 mmol) were added to a 25 mL Shrike's reaction tube, which was filled with nitrogen. Anhydrous and oxygen-free tetrahydrofuran (1 mL) was added. The obtained solution was stirred at 70 °C for 2 h. The raw materials were monitored using TLC to see if they were all consumed, and the reaction mixture was cooled to room temperature after it was observed that the raw materials were consumed, sodium hydroxide (2 M), H_2O (2 mL), and H_2O_2 (aq) (2 mL) were added, and the reaction was carried out at room temperature for 2 h. TLC was used to monitor whether the borane was completely oxidised, and the reaction was carried out after it showed that all of the reaction was complete. The resulting turbid liquid was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and extracted to obtain a solution of the target product which was concentrated under reduced pressure. The resulting crude product was purified by fast chromatography to give a yellow liquid 8 in 40 % isolated yield, as shown in Fig. 2-20.



4a **6a** **6b**

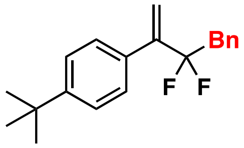
Fig. 2-21 Preparation of Derivatisation Products 6a, 6b

2.3.3 Characterisation data for representative products



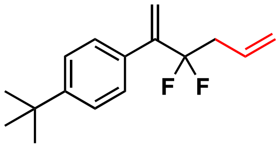
1-(tert-butyl)-4-(3,3-difluoro-3-phenylprop-1-en-2-yl)benzene (2a):

The mobile phase for flash chromatography: hexane. colourless oil. (56 mg, 63 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 - 7.54 (m, 2H), 7.43 - 7.40 (m, 3H), 7.33 - 7.27 (m, 4H), 5.65 (d, J = 4.0 Hz, 2H), 1.31 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.1, 145.1 (t, J = 26.0 Hz), 136.5 (t, J = 27.3 Hz), 133.4, 129.9, 129.3, 128.3, 127.7, 126.0 (t, J = 5.5 Hz), 125.1, 120.7 (d, J = 240.7 Hz), 118.9 (t, J = 8.2 Hz), 34.5, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -90.41 (s, 2F). **HRMS** (EI): calculated for $C_{19}H_{20}F_2$ [Na]+ :309.1423, found: 309.1425.



1-(tert-butyl)-4-(3,3-difluoro-4-phenylbut-1-en-2-yl)benzene (2b):

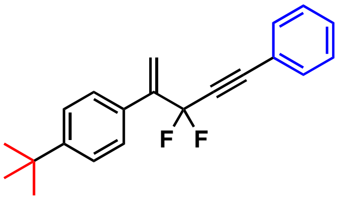
The mobile phase for flash chromatography: hexane. colourless oil. (95 mg, 99 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 12.4, 8.4 Hz, 4H), 7.25 - 7.23 (m, 2H), 7.19 - 7.12 (m, 3H), 5.52 (s, 1H), 5.38 (s, 1H), 3.21 (t, J = 16.4 Hz, 2H), 1.34 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.4, 144.1 (t, J = 22.8 Hz), 141.8, 134.0, 132.9 (t, J = 3.9 Hz), 130.6, 128.5, 128.2, 128.0, 127.3, 126.0, 125.4, 121.6 (d, J = 243.1 Hz), 118.3 (t, J = 8.8 Hz), 43.0 (t, J = 27.0 Hz), 38.1, 34.7, 31.4; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -94.05 (t, J = 15.0 Hz, 2F). **HRMS** (EI): calculated for $C_{10}H_{22}F_2$ [Na]+ :203.1582, found: 203.1558.



1-(tert-butyl)-4-(3,3-difluorohexa-1,5-dien-2-yl)benzene (2c):

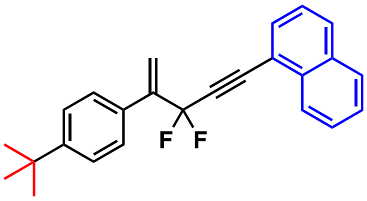
The mobile phase for flash chromatography: hexane. yellow oil. (58 mg, 77 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 12.0, 8.8 Hz, 4H), 5.81 - 5.72 (m, 1H), 5.71 (s, 1H), 5.49 (s, 1H), 5.20 - 5.08 (m, 2H), 2.72 (td, J = 16.0, 7.2 Hz, 2H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ

151.2, 144.2 (t, *J* = 22.7 Hz), 133.9, 129.1 (t, *J* = 5.2 Hz), 127.8, 125.3, 121.4 (d, *J* = 242.2 Hz), 120.1, 117.9 (t, *J* = 8.9 Hz), 41.3, 41.0, 40.8, 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -95.57 (t, *J* = 15.0 Hz, 2F). **HRMS** (EI): calculated for $C_{16}H_{20}F_2$ [Na]+ :273.1425, found: 273.1423.



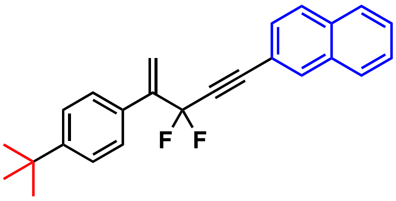
1-(tert-butyl)-4-(3,3-difluoro-5-phenylpent-1-en-4-yn-2-yl)benzene (4a):

The mobile phase for flash chromatography: hexane. White solid. (91.6 mg, 98 % yield). **M.P.** 49-51 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.43 - 7.40 (m, 3H), 7.35 - 7.33 (m, 2H), 6.03 (s, 1H), 5.69 (s, 1H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.5, 143.7 (t, *J* = 26.2 Hz), 132.3, 132.1, 129.9, 128.4, 127.7, 125.2, 120.2, 118.9 (t, *J* = 7.1 Hz), 112.7 (t, *J* = 230.4 Hz), 88.6, 81.7 (t, *J* = 40.9 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.45 (s, 2F). **HRMS** (EI): calculated for $C_{21}H_{20}F_2$ $[Na]^+$: 333.1425, found: 333.1416.



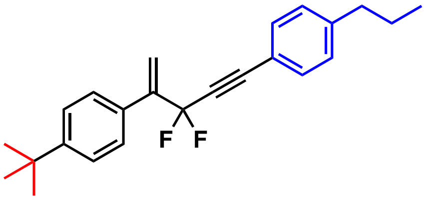
1-(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)naphthalene (4b):

The mobile phase for flash chromatography: hexane. White solid. (250 mg, 71 % yield). **M.P.** 57-59 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (td, *J* = 26.8, 7.2 Hz, 3H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.60 - 7.44 (m, 5H), 6.10 (s, 1H), 5.74 (s, 1H), 1.37 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.6, 143.8 (t, *J* = 25.3 Hz), 133.2, 132.9, 132.5, 131.7, 130.5, 128.4, 127.8, 127.3, 126.7, 125.7, 125.3, 125.0, 118.6 (t, *J* = 7.3 Hz), 112.7 (t, *J* = 231.3 Hz), 87.0 (t, *J* = 6.3 Hz), 86.3 (t, *J* = 40.9 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.26 (s, 2F). **HRMS** (EI): calculated for $C_{25}H_{22}F_2$ $[Na]^+$: 383.1582, found: 383.1569.



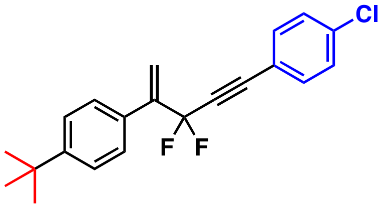
2-(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)naphthalene (4c):

The mobile phase for flash chromatography: hexane. White solid. (93 mg, 86 % yield). **M.P.** 80-83-51 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.69 (d, J = 8.6 Hz, 3H), 7.45 – 7.41 (m, 4H), 7.33 (t, J = 9.2 Hz, 3H), 5.97 (s, 1H), 5.61 (s, 1H), 1.25 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.6, 143.8 (t, J = 25.8 Hz), 133.5, 132.8, 132.6, 132.4, 128.3, 128.0, 127.8 (d, J = 6.2 Hz), 127.5, 126.9, 125.2, 119.0 (t, J = 7.0 Hz), 117.4, 112.8 (t, J = 230.7 Hz), 89.0 (t, J = 6.1 Hz), 81.9 (t, J = 40.9 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -79.28 (s, 2F). **HRMS** (EI): calculated for $C_{25}H_{22}F_2$ $[Na]^+$: 383.1582, found: 383.1580.



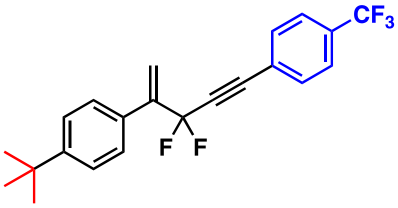
1-(tert-butyl)-4-(3,3-difluoro-5-(4-propylphenyl)pent-1-en-4-yn-2-yl)benzene (4d):

The mobile phase for flash chromatography: hexane. Yellow oil. (71.0 mg, 74 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 2H), 7.39 (q, J = 8.4 Hz, 4H), 7.16 (d, J = 8.0 Hz, 2H), 6.02 (s, 1H), 5.67 (s, 1H), 2.24 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.6 Hz, 4H), 1.35 (s, 9H), 0.94 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.4, 145.0, 143.8 (t, J = 26.2 Hz), 132.4, 132.0, 128.6, 127.7, 125.2, 118.8 (t, J = 7.1 Hz), 117.3, 112.8 (t, J = 230.4 Hz), 89.0, 81.1 (t, J = 40.9 Hz), 38.0, 34.6, 31.3, 24.3, 13.7; **^{19}F NMR** (500 MHz, $CDCl_3$) *δ* -77.87 (s, 2F). **HRMS** (EI): calculated for $C_{24}H_{26}F_2$ $[Na]^+$: 375.1895, found: 375.1894.



1-(tert-butyl)-4-(5-(4-chlorophenyl)-3,3-difluoropent-1-en-4-yn-2-yl)benzene (4e):

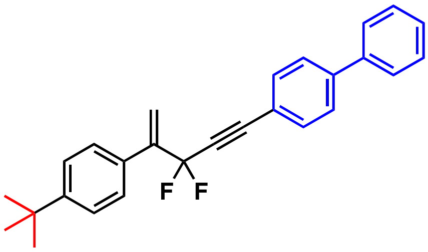
The mobile phase for flash chromatography: hexane. White solid. (67.8 mg, 65 % yield). **M.P.** 89-92 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (q, *J* = 8.8 Hz, 4H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.02 (s, 1H), 5.70 (s, 1H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 151.6, 143.6 (t, *J* = 25.7 Hz), 136.2, 133.3, 132.2, 128.9, 127.7, 125.2, 118.9 (t, *J* = 7.1 Hz), 118.6, 112.6 (t, *J* = 231.1 Hz), 87.4 (t, *J* = 6.1 Hz), 82.6 (t, *J* = 41.0 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.74 (s, 2F). **HRMS** (EI): calculated for $C_{21}H_{19}ClF_2$ $[K]^+$: 383.0775, found: 383.0703.



1-(tert-butyl)-4-(3,3-difluoro-5-(4-(trifluoromethyl)phenyl)pent-1-en-4-yn-2-yl)benzene (4f):

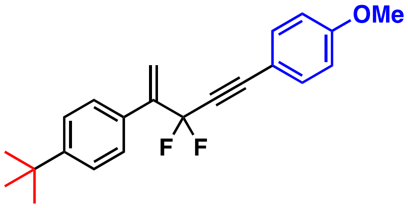
The mobile phase for flash chromatography: hexane. White solid. (84 mg, 74 % yield). **M.P.** 82-84 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.58 (dd, *J* = 24.0, 8.0 Hz, 4H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.02 (s, 1H), 5.70 (s, 1H), 1.35 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 151.7, 143.5 (t, *J* = 26.0 Hz), 132.4, 132.1, 131.8, 131.5, 127.7, 125.4 (q, *J* = 3.7 Hz), 125.2, 123.9, 122.2, 119.0 (t, *J* = 7.1 Hz), 112.4 (t, *J* = 230.0 Hz), 86.8 (t, *J* = 6.0 Hz), 83.7 (t, *J* =41.0 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$)

δ -63.07 (s, 1F), -79.27 (s, 2F). **HRMS** (EI): calculated for $C_{18}H_{20}F_2$ $[Na]^+$: 401.1299, found: 401.1256.



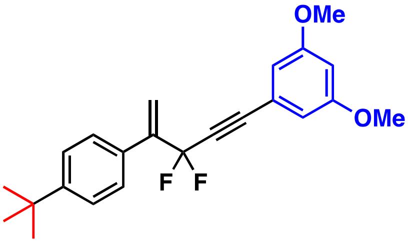
4-(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)-1,1'-biphenyl (4j):

The mobile phase for flash chromatography: hexane. White solid. (96 mg, 83 % yield). **M.P.** 88-90 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.6, 2.0 Hz, 3H), 7.52 (d, *J* = 10.4 Hz, 4H), 7.48 - 7.39 (m, 6H), 6.04 (s, 1H), 5.69 (s, 1H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.5, 143.7 (t, *J* = 26.5 Hz), 142.7, 139.9, 132.5, 132.3, 128.9, 127.7, 127.1, 125.2, 118.9 (t, *J* = 7.0 Hz), 112.8 (t, *J* = 230.2 Hz), 88.6 (t, *J* = 6.1 Hz), 82.2 (t, *J* = 40.6 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.37 (s, 2F). **HRMS** (EI): calculated for C27H24F2 $[H]^+$: 387.1895, found: 387.1894



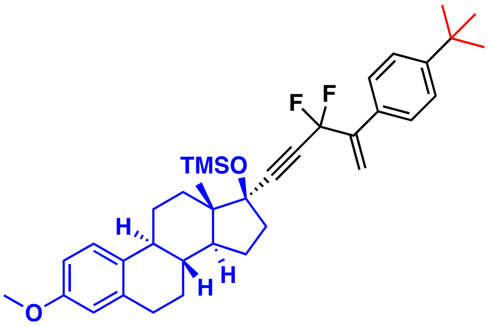
1-(tert-butyl)-4-(3,3-difluoro-5-(4-methoxyphenyl)pent-1-en-4-yn-2-yl)benzene (4h):

The mobile phase for flash chromatography: hexane. Yellow oil. (117 mg, 99 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.43 - 7.39 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.03 (s, 1H), 5.68 (s, 1H), 3.83 (s, 3H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 150.3, 142.8 (t, *J* = 26.5 Hz), 132.6, 131.4, 126.9, 126.7, 124.1, 117.7 (t, *J* = 7.0 Hz), 113.0, 111.8 (t, *J* = 230.2 Hz), 111.0, 87.9 (t, *J* = 6.1 Hz), 79.5 (t, *J* = 40.6 Hz), 54.2, 33.5, 30.2; ^{19}**F NMR** (500 MHz, $CDCl_3$) δ -77.86 (s, 2F). **HRMS** (EI): calculated for $C_{22}H_{22}OF_2$ $[H]^+$: 341.1711, found: 341.1690.



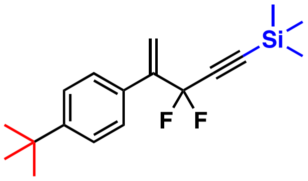
1-(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)-3,5-dimethoxybenzene (4i):

The mobile phase for flash chromatography: hexane. Yellow oil. (115.7 mg, 84 % yield). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.51 (s, 2H), 6.41 (t, *J* = 4.0 Hz, 1H), 5.92 (s, 1H), 5.58 (s, 1H), 3.67 (s, 6H), 1.24 (s, 9H);^{13}**C NMR** (100 MHz, $CDCl_3$) δ 160.6, 151.5, 143.7 (t, *J* = 26.0 Hz), 132.3, 127.8, 125.2, 121.4, 119.0 (t, *J* = 7.0 Hz), 112.7 (t, *J* = 231.0 Hz), 109.8, 103.3, 88.6 (t, *J* =6.0 Hz), 81.1 (t, *J* =40.0 Hz), 55.5, 34.6, 31.3, 29.7; ^{19}**F NMR** (500 MHz, CDCl3) δ -78.41 (s, 2F). **HRMS** (EI): calculated for $C_{23}H_{24}F_2O_2$ $[K]^+$:409.1376, found: 409.1378.



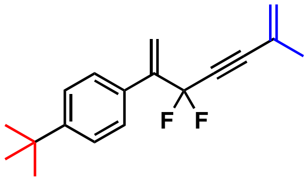
(((8R,9S,13S,14S,17S)-17-(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)oxy)trimethylsilane (4g):

The mobile phase for flash chromatography: hexane. yellow oil. (200 mg, 98 % yield). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.06 (s, 1H), 6.56 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.48 (s, 1H), 5.74 (s, 1H), 5.47 (s, 1H), 3.62 (s, 3H), 2.71 - 2.67 (m, 2H), 2.12 - 1.63 (m, 6H), 1.48 - 1.23 (m, 6H), 1.14 (s, 9H), 0.84 - 0.75 (m, 1H), 0.62 (s, 3H), 0.00 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.7, 149.8, 141.9 (t, *J* = 24.9 Hz), 136.2, 130.7 (d, *J* = 8.3 Hz), 127.8, 125.9, 124.7, 123.5, 116.0 (t, *J* = 7.5 Hz), 112.1, 110.1 (t, *J* = 231.5 Hz), 91.6 (t, *J* = 6.3 Hz), 78.8, 78.1 (t, *J* = 40.7 Hz), 53.5, 46.7 (d, *J* = 4.2 Hz), 41.8, 38.1, 37.7, 32.9, 30.9, 29.6, 28.1, 25.7, 24.7, 21.3, 11.1, 0.0; ^{19}F NMR (500 MHz, $CDCl_3$) δ -77.94-- -79.91 (t, *J* = 15.0 Hz, 2F). **HRMS** (EI): calculated for $C_{37}H_{48}F_2O_2Si$ $[Na]^+$:613.3284, found: 613.3285.



(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)trimethylsilane (4i):

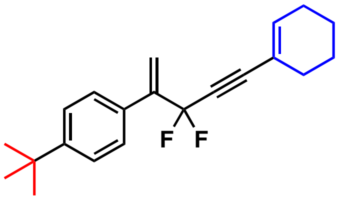
The mobile phase for flash chromatography: hexane. Yellow oil. (52 mg, 56 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 5.95 (d, *J* = 2.3 Hz, 1H), 5.62 (s, 1H), 1.33 (s, 9H), 0.19 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.2, 144.3 (t, *J* = 26.0 Hz), 133.1, 128.6, 125.9, 120.0 (t, *J* = 7.0 Hz), 112.4 (t, *J* = 230.0 Hz), 97.3 (t, *J* = 41.0 Hz), 96.3 (t, *J* =6.0 Hz), 35.4, 32.1, 0.0; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -79.27 (s, 2F). **HRMS** (EI): calculated for $C_{18}H_{24}F_2Si$ $[K]^+$: 345.1247, found: 345.1228.



1-(tert-butyl)-4-(3,3-difluoro-6-methylhepta-1,6-dien-4-yn-2-yl)benzene (4m):

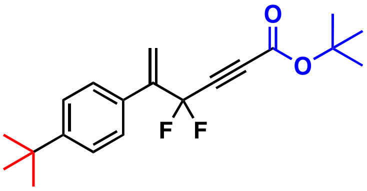
The mobile phase for flash chromatography: hexane. Yellow oil. (99.1 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.29

(d, *J* = 8.0 Hz, 2H), 5.84 (s, 1H), 5.52 (s, 1H), 5.30 (d, *J* = 20.0 Hz, 2H), 1.77 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 151.5, 143.8 (t, *J* = 26.2 Hz), 132.4, 127.8, 125.2, 118.8 (t, *J* = 7.0 Hz), 112.7 (t, *J* = 230.3 Hz), 89.7 (t, *J* = 6.2 Hz), 80.7 (t, *J* =40.5 Hz), 34.6, 31.3, 22.4, 19.1, 13.7; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.38 (s, 2F). **HRMS** (EI): calculated for $C_{18}H_{20}F_2$ $[Na]^+$: 297.1425, found: 297.1500.



1-(tert-butyl)-4-(5-(cyclohex-1-en-1-yl)-3,3-difluoropent-1-en-4-yn-2-yl)benzene (4n):

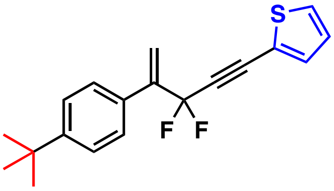
The mobile phase for flash chromatography: hexane. Yellow oil. (2.5 g, 98 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.46 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.26 (s, 1H), 5.94 (s, 1H), 5.62 (s, 1H), 2.11 (t, *J* = 4.4 Hz, 4H), 1.63 - 1.59 (m, 5H), 1.34 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 151.3, 144.0 (t, *J* = 26.6 Hz), 139.1, 132.5, 127.7, 125.1, 118.5 (t, *J* = 3.0 Hz), 112.9 (t, *J* = 229.7 Hz), 90.6 (t, *J* = 6.3 Hz), 79.2 (t, *J* = 40.4 Hz), 34.6, 31.3, 28.1, 25.7, 21.9, 21.2; **^{19}F NMR** (500 MHz, $CDCl_3$) *δ* -77.57 (s, 2F). **HRMS** (EI): calculated for $C_{21}H_{24}F_2$ $[Na]^+$: 337.1738, found: 337.1733.



tert-butyl 5-(4-(tert-butyl)phenyl)-4,4-difluorohex-5-en-2-ynoate (4o):

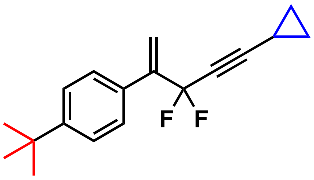
The mobile phase for flash chromatography: hexane.colourless oil. (110.3 mg, 66 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.31 - 7.26 (m, 4H), 5.84 (s, 1H), 5.57 (s, 1H), 1.38 (s, 9H), 1.21 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 150.7, 149.7, 141.4 (t, *J* = 25.0 Hz), 130.2, 126.6, 124.3, 119.1 (t, *J* = 7.1 Hz), 110.8 (t, *J* = 233.2 Hz), 84.1, 78.3 (t, *J* = 6.2 Hz), 73.5 (t, *J*

= 42.0 Hz), 33.5, 30.2, 26.8; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -80.91 (s, 2F). **HRMS** (EI): calculated for $C_{20}H_{24}F_2O_2$ [H]+ :335.1817, found: 335.1912.



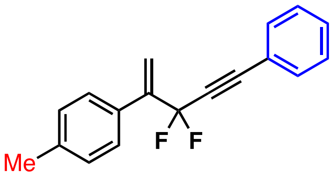
2-(4-(4-(tert-butyl)phenyl)-3,3-difluoropent-4-en-1-yn-1-yl)thiophene (4p):

The mobile phase for flash chromatography: hexane. Yellow oil. (92 mg, 96 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 5.1 Hz, 1H), 7.35 (d, *J* = 3.5 Hz, 1H), 7.03 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.05 (s, 1H), 5.72 (s, 1H), 1.39 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.6, 143.6 (t, *J* = 26.0 Hz), 134.5, 132.2, 129.5, 127.8, 127.3, 125.3, 119.8 (t, *J* = 3.0 Hz), 119.1 (t, *J* = 7.1 Hz), 112.8 (t, *J* = 232.0 Hz), 85.3 (t, *J* = 41.2 Hz), 82.4 (t, *J* = 6.1 Hz), 34.6, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.46 (s, 2F). **HRMS** (EI): calculated for $C_{19}H_{18}F_2S$ $[Na]^+$: 339.0989, found: 339.0987.



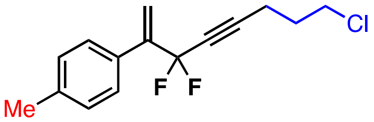
1-(tert-butyl)-4-(5-cyclopropyl-3,3-difluoropent-1-en-4-yn-2-yl)benzene (4q):

The mobile phase for flash chromatography: hexane. Yellow oil. (58 mg, 70 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 5.94 (s, 1H), 5.62 (s, 1H), 1.38 (s, 9H), 1.35 - 1.31 (m, 1H), 0.90 - 0.85 (m, 2H), 0.80 - 0.76 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.2, 144.8 (t, *J* = 26.4 Hz), 133.3, 128.5, 125.9, 119.3 (t, *J* = 7.0 Hz), 113.2 (t, *J* = 229.5 Hz), 94.7 (t, *J* = 5.8 Hz), 69.5 (t, *J* = 40.3 Hz), 35.4, 32.1, 9.3, 0.0; ^{19}**F NMR** (500 MHz, $CDCl_3$) δ -76.97 (s, 2F). **HRMS** (EI): calculated for $C_{18}H_{20}F_2$ $[Na]^+$: 297.1425, found: 297.1462.



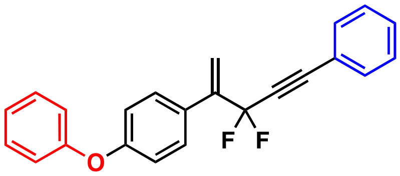
1-(3,3-difluoro-5-phenylpent-1-en-4-yn-2-yl)-4-methylbenzene (4r):

The mobile phase for flash chromatography: hexane. Yellow oil. (73 mg, 91% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.46 (t, *J* = 6.4 Hz, 4H), 7.41 - 7.33 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 1H), 5.66 (s, 1H), 2.38 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 143.8 (t, *J* = 26.0 Hz), 138.4, 132.4, 132.1 (t, *J* = 2.2 Hz), 129.9, 129.0, 128.4, 128.0, 120.2 (t, *J* = 2.9 Hz), 118.9 (t, *J* = 7.1 Hz), 112.7 (t, *J* = 230.6 Hz), 88.5 (t, *J* = 6.1 Hz), 81.6 (t, *J* =41.2 Hz), 21.2; ^{19}**F NMR** (500 MHz, $CDCl_3$) δ -78.37 (s, 2F). HRMS (EI): calculated for C18H14F2 $[Na]^+$: 291.0956, found: 291.0953.

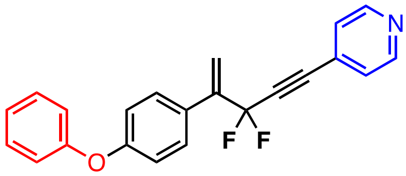


1-(8-chloro-3,3-difluorooct-1-en-4-yn-2-yl)-4-methylbenzene (4s):

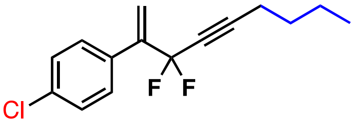
The mobile phase for flash chromatography: hexane. Yellow oil. (66 mg, 82 % yield). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.92 (t, *J* = 2.0 Hz, 1H), 5.60 (d, *J* = 1.3 Hz, 1H), 3.49 (t, *J* = 6.3 Hz, 2H), 2.50 - 2.44 (m, 2H), 2.39 (s, 3H), 1.97 - 1.91 (m, 2H). ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 143.9 (t, *J* = 25.0 Hz), 138.1, 132.5, 129.0, 127.9, 118.3 (t, *J* = 7.0 Hz), 112.0 (t, *J* = 231.0 Hz), 88.7 (t, *J* = 6.0 Hz), 74.8 (t, *J* = 40.0 Hz), 43.1, 30.3, 21.2, 15.9; ^{19}**F NMR** (500 MHz, $CDCl_3$) δ -77.88 (s, 2F). **HRMS** (EI): calculated for $C_{15}H_{15}F_2Cl$ $[H]^+$: 269.0902, found: 268.0886.



1-(3,3-difluoro-5-phenylpent-1-en-4-yn-2-yl)-4-phenoxybenzene (4v): The mobile phase for flash chromatography: hexane. Yellow oil. (96 mg, 92 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.48 - 7.46 (m, 2H), 7.42 - 7.40 (m, 1H), 7.38 - 7.33 (m, 4H), 7.16 - 7.12 (m, 1H), 7.07 - 7.05 (m, 2H), 7.03 - 6.99 (m, 2H), 6.03 (t, *J* = 2.0 Hz, 1H), 5.66 (d, *J* = 1.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.7, 156.7, 143.3 (t, *J* = 26.2 Hz), 132.1, 130.1, 130.0, 129.8, 129.6, 128.5, 123.6, 120.1 (t, *J* = 3.0 Hz), 119.3, 118.9 (d, *J* = 7.1 Hz), 118.2, 112.6 (t, *J* = 230.2 Hz), 88.7 (t, *J* = 6.0 Hz), 81.5 (t, *J* = 40.3 Hz); **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.59 (s, 2F). **HRMS** (EI): calculated for $C_{23}H_{16}F_2O$ $[Na]^+$: 369.1061, found: 369.1072.

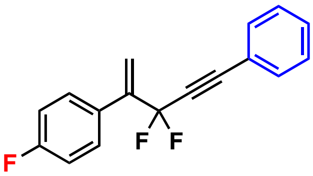


4-(3,3-difluoro-4-(4-phenoxyphenyl)pent-4-en-1-yn-1-yl)pyridine (4w): The mobile phase for flash chromatography: hexane. Yellow oil. (71 mg, 68 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 6.0 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.38 - 7.31 (m, 4H), 7.16 - 7.12 (m, 1H), 7.06 - 6.99 (m, 4H), 6.00 (t, *J* = 2.0 Hz, 1H), 5.68 (d, *J* = 1.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 156.5, 150.0, 142.7 (t, *J* = 26.0 Hz), 129.9, 129.6, 129.5, 128.2 (t, *J* = 2.0 Hz), 125.7, 123.8, 119.4, 119.3, 119.2, 118.2, 112.1 (t, *J* = 232.0 Hz), 85.4 (t, *J* = 41.0 Hz); **^{19}F NMR** (500 MHz, $CDCl_3$) δ -79.80 (s, 2F). **HRMS** (EI): calculated for $C_{22}H_{15}F_2NO$ $[H]^+$: 348.1194, found: 348.1192.



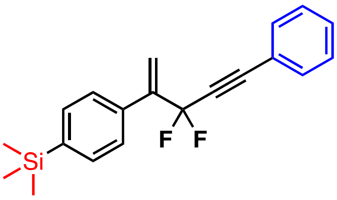
1-chloro-4-(3,3-difluoronon-1-en-4-yn-2-yl)benzene (4x):

The mobile phase for flash chromatography: hexane.colourless oil. (87 mg, 94 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.96 (s, 1H), 5.59 (s, 1H), 2.30 - 2.24 (m, 2H), 1.52 - 1.45 (m, 2H), 1.38 - 1.29 (m, 2H), 0.89 (t, *J* = 8.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.2 (t, *J* = 26.0 Hz), 134.4, 133.9, 129.4, 128.3, 119.4 t, *J* = 7.0 Hz), 111.9 (t, *J* = 229.0 Hz), 91.3 (t, *J* =5.0 Hz), 73.5 (t, *J* =40.0 Hz), 29.6, 21.7, 18.1, 13.4; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -77.45 (s, 2F). **HRMS** (EI): calculated for $C_{15}H_{15}F_2Cl$ $[H]^+$:269.0903, found: 269.0931.



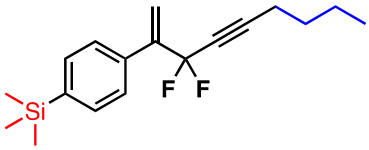
1-(3,3-difluoro-5-phenylpent-1-en-4-yn-2-yl)-4-fluorobenzene (4z):

The mobile phase for flash chromatography: hexane. yellow oil. (63.4 mg, 78 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.8, 5,6 Hz, 2H), 7.47 (d, *J* = 6.8 Hz, 2H), 7.42 - 7.34 (m, 3H), 7.09 (t, *J* = 8.4 Hz, 2H), 6.07 (s, 1H), 5.66 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.1, 161.7, 143.1 (t, *J* = 26.4 Hz), 132.1 (t, *J* = 2.2 Hz), 131.4 (d, *J* = 3.4 Hz), 130.1, 130.0, 128.5, 120.0 (t, *J* = 2.7 Hz), 119.6 (t, *J* = 6.9 Hz), 115.3, 115.1, 112.5 (t, *J* = 230.6 Hz), 88.9 (t, *J* = 6.0 Hz), 81.3 (t, *J* = 40.5 Hz); **^{19}F NMR** (500 MHz, $CDCl_3$) δ -78.64 (s, 2F), -113.29 (1F). **HRMS** (EI): calculated for $C_{17}H_{11}F_3$ [H]+ :273.0886, found: 273.0794.



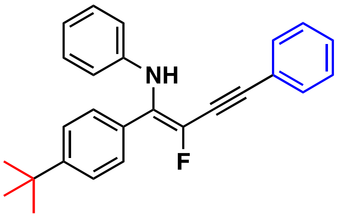
(4-(3,3-difluoro-5-phenylpent-1-en-4-yn-2-yl)phenyl)trimethylsilane (4ab):

The mobile phase for flash chromatography: hexane. yellow oil. (93.5 mg, 95 % yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.42 (s, 4H), 7.30 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 5.93 (s, 1H), 5.56 (s, 1H), 0.17 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 145.2 (t, J = 26.2 Hz), 142.1, 136.8, 134.4, 133.2, 131.1, 129.6, 128.5, 121.3, 120.6 (t, J = 7.1 Hz), 113.8 (t, J = 230.2 Hz), 89.9 (t, J = 6.1 Hz), 82.8 (t, J = 41.0 Hz), 0.0; **^{19}F NMR** (500 MHz, CDCl$_3$) δ -78.21 (s, 2F). **HRMS** (EI): calculated for $C_{20}H_{20}F_2Si$ [Na]+ :349.1195, found: 349.1100.



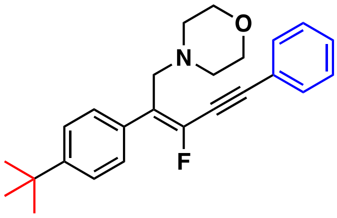
(4-(3,3-difluoronon-1-en-4-yn-2-yl)phenyl)trimethylsilane (4ac):

The mobile phase for flash chromatography: hexane. Yellow oil. (71 mg, 77 % yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.40 - 7.35 (m, 4H), 5.82 (s, 1H), 5.48 (s, 1H), 2.16 -2.13 (m, 2H), 1.39 - 1.31 (m, 2H), 1.23 - 1.16 (m, 2H), 0.74 (t, J = 8.0 Hz, 3H), 0.15 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 145.4 (t, J = 27.0 Hz), 141.8, 137.0, 134.3, 128.4, 120.2 (t, J = 7.0 Hz), 113.3 (t, J = 230.0 Hz), 92.1 (t, J = 6.0 Hz), 74.9 (t, J =40.0 Hz), 30.8, 22.9, 19.3, 14.6, 0.0; **^{19}F NMR** (500 MHz, CDC13) δ -77.17 (s, 2F). **HRMS** (EI): calculated for $C_{18}H_{24}F_2Si$ [Na]$^+$: 329.1508, found: 329.1507.



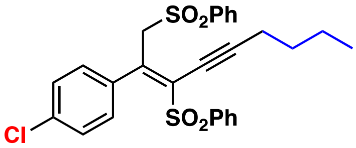
(*E*)-N-(1-(4-(tert-butyl)phenyl)-2-fluoro-4-phenylbut-1-en-3-yn-1-yl)aniline (5):

The mobile phase for flash chromatography: hexane. yellow oil. (29.1 mg, 31 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 7.6, 1.6 Hz, 2H), 7.44 - 7.34 (m, 7H), 7.19 (t, J = 8.0 Hz, 2H), 6.76 - 6.68 (m, 3H), 1.34 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.3, 147.8, 138.7, 131.7 (d, J = 2.7 Hz), 130.7, 129.5, 129.2, 128.5, 128.2 (d, J = 5.2 Hz), 125.5, 117.9, 113.3, 97.0, 80.4 (d, J = 42.3 Hz), 45.7, 34.7, 31.2, 1.1; ^{19}F NMR (500 MHz, $CDCl_3$) δ -86.95 (d, J = 13.5 Hz, 1F).**HRMS** (EI): calculated for $C_{26}H_{24}FN$ [H]+ :370.1966, found: 370.1967.



(*E*)-4-(2-(4-(tert-butyl)phenyl)-3-fluoro-5-phenylpent-2-en-4-yn-1-yl)morpholine (6):

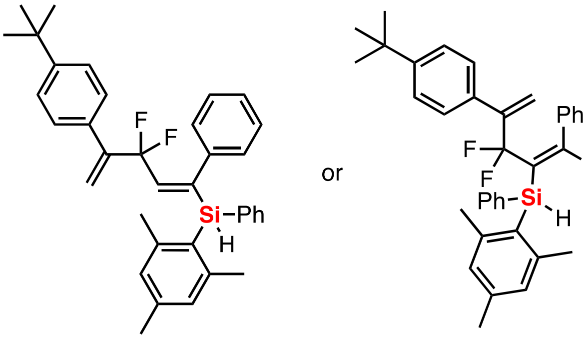
The mobile phase for flash chromatography: hexane. yellow oil. (68 mg, 91 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 4.9, 2.0 Hz, 2H), 7.30 - 7.26 (m, 5H), 3.58 (t, J = 3.7 Hz, 4H), 3.44 (s, 2H), 2.47 (t, J = 4.4 Hz, 4H), 1.23 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.9, 142.0, 139.6, 132.4 (d, J = 2.7 Hz), 131.5 (d, J = 2.2 Hz), 129.4, 128.6, 128.3 (d, J = 5.3 Hz), 125.1, 122.9 (d, J = 13.3 Hz), 121.5 (d, J = 2.2 Hz), 96.7 (d, J = 6.5 Hz), 81.1 (d, J = 41.7 Hz), 67.1, 60.0 (d, J = 2.9 Hz), 53.4, 34.7, 31.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -105.77 (s, 1F). **HRMS** (EI): calculated for $C_{28}H_{28}FNO$ $[Na]^+$:400.2047, found: 400.2040.



(*E*)-(2-(4-chlorophenyl)non-2-en-4-yne-1,3-diyldisulfonyl)dibenzene (7):

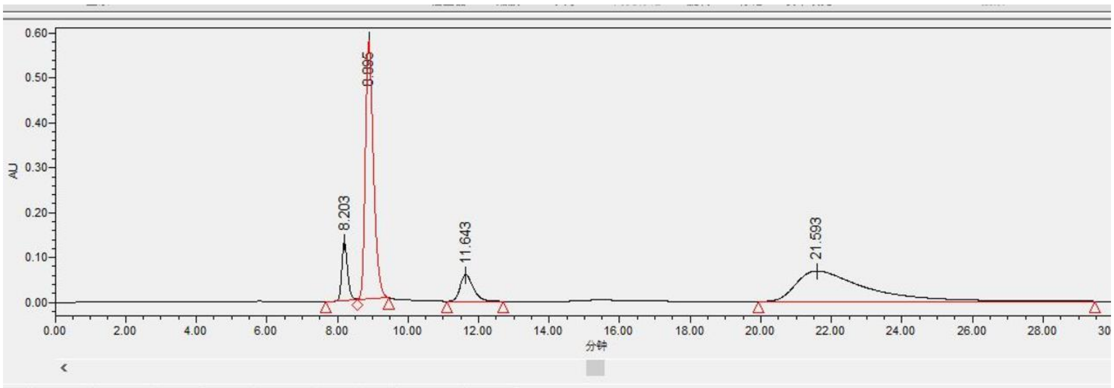
The mobile phase for flash chromatography: hexane. yellow oil. (66.8 mg, 68 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 1H), 7.65

(d, J = 7.6 Hz, 2H), 7.51 - 7.37 (m, 6H), 7.18 - 7.11 (m, 5H), 4.30 (s, 2H), 2.22 (q, J = 6.8 Hz, 2H), 1.45 - 1.39 (m, 2H), 1.35 - 1.29 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.5, 142.0, 141.6, 138.6, 134.0, 133.8, 133.2, 131.3 (d, J = 2.8 Hz), 129.8 (d, J = 4.4 Hz), 129.3, 128.9, 128.5, 127.6, 114.6 (d, J = 2.2 Hz), 100.6, 71.3 (d, J = 41.1 Hz), 59.9, 29.9, 22.0, 19.2, 13.6; **HRMS** (EI): calculated for $C_{27}H_{25}ClO_4S_2$ $[K]^+$:551.0514 :, found: 551.0556.

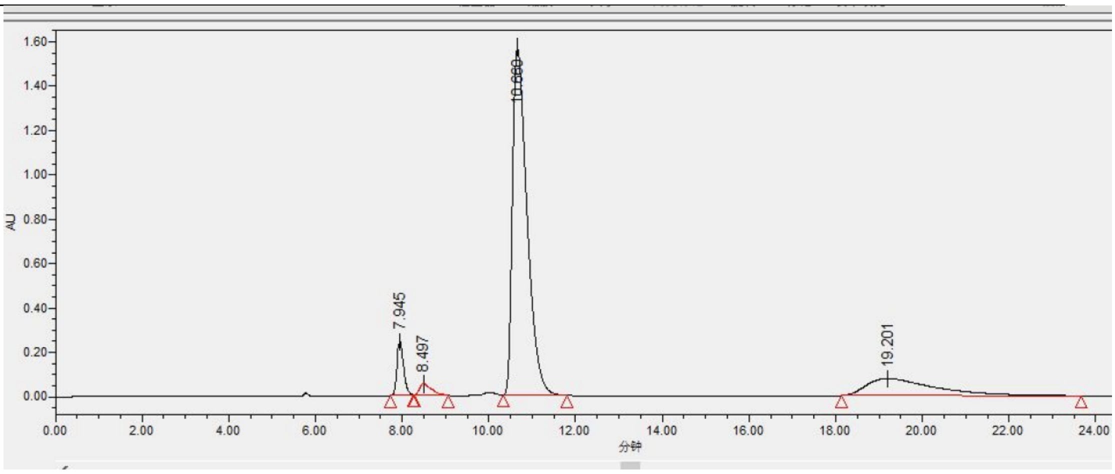


(E)-(4-(4-(*tert*-butyl)phenyl)-3,3-difluoro-1-phenylpenta-1,4-dien-1-yl)(mesityl)(phenyl)silane(6a/6b)

The mobile phase for flash chromatography: hexane. yellow oil. (98 mg, 86 % yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, J = 5.8 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.42 - 7.34 (m, 5H), 7.30 - 7.28 (m, 3H), 7.24 - 7.19 (m, 5H), 7.05 - 7.01 (m, 3H), 6.99 - 6.97 (m, 0.6H), 6.88 (s, 2H), 6.82 (s, 0.5H), 6.26 (t, J = 12.0 Hz, 0.3H), 5.59 (s, 2H), 5.37 (d, J = 10.4 Hz, 0.5H), 5.30 (s, 0.3H), 5.25 (s, 1H), 2.33 (s, 3H), 2.30 (s, 0.8H), 2.26 (s, 6H), 2.14 (s, 1.5H), 1.40 (s, 2H), 1.35 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.1, 150.8, 150.0, 145.6, 143.4, 140.2, 139.9, 139.6, 136.5, 135.8, 135.7, 134.2, 133.9, 129.5, 129.4, 128.9, 128.8, 128.3, 128.0, 127.8, 127.6, 125.1, 124.8, 119.7, 34.5, 31.4, 24.4, 21.3; **^{19}F NMR** (500 MHz, $CDCl_3$) δ -74.95 (dd, J = 306.5 Hz, 288.5 Hz, 2F), 84.0 (dd, J = 12.0 Hz, 0.5F); **HRMS** (EI): calculated for $C_{27}H_{25}ClO_4S_2$ $[Na]^+$:577.2509 :, found: 577.2575.



Entry	Time/min	Area	Area/%
1	8.203	1514241	7.06
2	8.895	9203890	42.92
3	11.643	1536110	7.16
4	21.593	9192462	42.86



Entry	Time/min	Area	Area/%
1	7.945	2577605	5.31
2	8.497	954415	1.97
3	10.660	365556414	75.33
4	19.201	8436989	17.39

2.4 Summary of the chapter

In summary, we have developed an efficient difluoroallylation method for the synthesis of biologically active sidodifluoro 1, 4-enyne compounds that can be used for the late modification of biologically active molecules. The key factor for the success of the reaction is the use of stable and highly reactive difluoroolefin quaternary reagents under mild reaction conditions to obtain the products of allylation of chalcidodifluoro 1, 4-alkynes in isolated yields of up to 99 %. The reaction is characterised by ease of synthesis, high efficiency, functional group tolerance, as well as excellent regioselectivity and chemoselectivity; notably, the unique nature of the CF_2 moiety not only makes this class of quaternary reagents more reactive than their non-fluorinated counterparts, but the synthesis of difluoroallyl alkynes using them adds the newest tool in the toolbox of biologically active molecules for modification. We anticipate that synthesised compounds of this type containing a chalcodifluoro 1, 4 allyne fragment will offer great attraction to the field of medicinal chemistry, and the synthesis of chalcodifluoroallylated products with the drug fragments and the versatile transformation of the obtained chalcodifluoroallylated compounds further demonstrate the synthetic utility of this class of compounds. The successful development of this novel difluoroallylation reaction is expected to provide a new approach to the synthesis of complex allyl fluorinated molecules in the life sciences and materials fields.

3 Palladium-catalysed asymmetric silylhydrogen addition studies of silylene-substituted 1, 3-alkynyl compounds

3.1 Research background

With the continuous development of transition metal catalysis, the strategy of constructing intramolecular or intermolecular asymmetric silica-hydrogen addition reactions using unsaturated carbon-carbon triple bonds with various types of hydroxysilanes with pre-chiral properties in the presence of metal catalysts has been a hot and difficult research topic for the preparation of chiral organosilicon compounds in recent years. Hydrogen silanes usually have different stability from alkyl groups as well as considerable reactivity in functionalization and derivatization reactions[122,123]. Since the first Rh-catalysed intramolecular silica-hydrogen addition reaction was reported by Tamao et al. in 1996, the de-symmetrization strategy of dihydrosilanes has been widely used for the synthesis of chiral organosilanes.

In this field, many outstanding works have been reported by national and international groups[124]. Compared to simple alkynes, alkynes compounds containing other electron-deficient groups are more challenging to undergo asymmetric silylhydrogen addition reactions. In 2021, the group of Li-Wen Xu[124] proposed a catalytic system using a low loading palladium catalyst (2 mol%) and a phosphinamido ligand of the binaphthol skeleton, and succeeded in constructing the intermolecular silylhydrogen of alkynone compounds with asymmetric achiral dihydrosilanes addition reaction to construct alkynone compounds containing silicon stereocentres with high regioselectivity and enantioselectivity, as shown in Fig. 3-1.

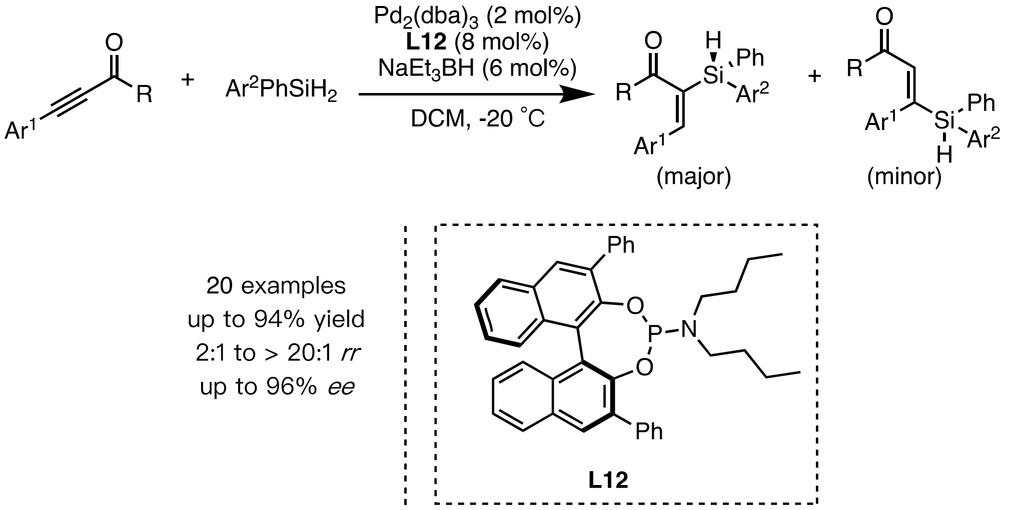


Fig. 3-1 Palladium-catalysed asymmetric silylhydrogen addition of acetylenic ketones

In 2023, Li-Wen Xu's[125] group again used this reaction system to successfully realize the silylhydrogen addition strategy of 1, 3-diyne analogues with dihydrosilanes, and obtained a series of multifunctionalized silicon-containing stereogenic centres of 1, 3-alkynyl organosilicon compounds in good yields with excellent regioselectivities and enantioselectivities under mild reaction conditions, and experimentally proved that this catalytic system The catalytic system possesses very good stability and is insensitive to air and moisture, which further provides an effective catalytic scheme for the asymmetric silylhydrogen addition strategy of alkynes containing electron-deficient functional groups, as shown in Fig. 3-2.

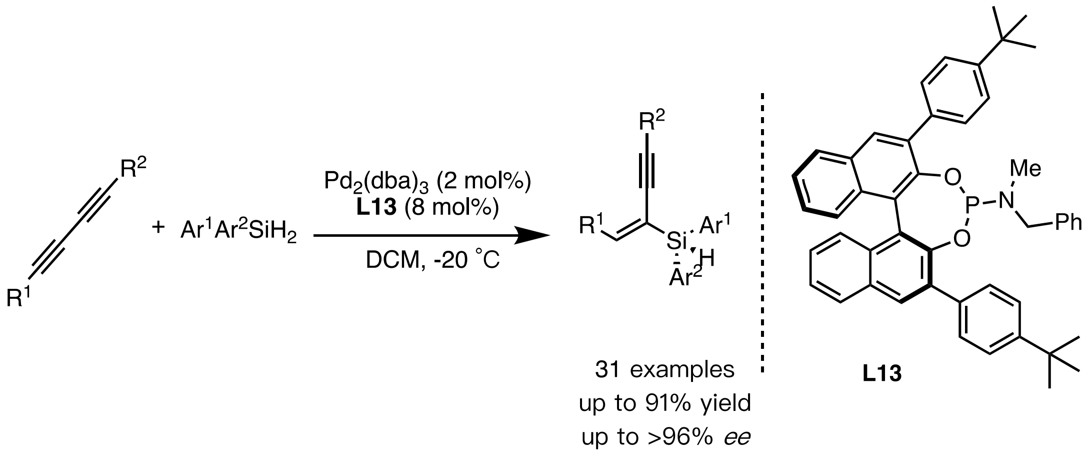


Fig. 3-2 Palladium-catalysed asymmetric silica-hydrogen addition reactions of diynes

1, 3-Dienes are one of the most common backbones in biologically active natural products as well as in organic functional materials[126] and are commonly used as key intermediates in total synthesis, while molecules of such backbones can be transformed in versatile ways, as shown in Fig. 3-3. Conventional strategies used for the construction of conjugated dienes rely mainly on elimination reactions of dihalogenated compounds, complexation or enolisation of unsaturated carbonyl compounds, transition metal-catalysed cross-coupling reactions[127]. The construction of fluorinated 1, 3-dienes compounds via asymmetric silylhydrogen addition strategies has been reported very rarely so far. Therefore, the development of efficient methods for the synthesis of polyfunctionalized fluorinated 1, 3-dienes from simple starting materials is highly valued.

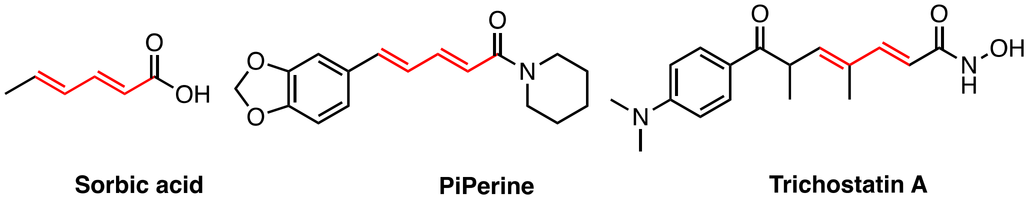
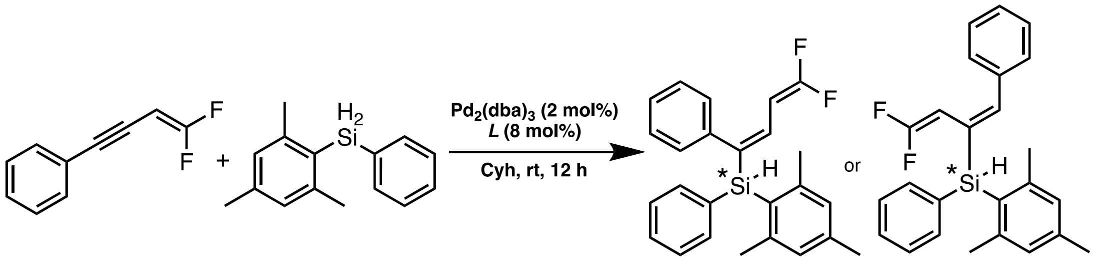

Sorbic acid **PiPerine** **Trichostatin A**

Fig. 3-3 Bioactive molecules of the 1, 3-diene skeleton

Based on the above background, we envisioned an efficient preparation of silylene-difluoroconjugated dienes by using silylene-difluoroconjugated 1, 3-alkyne compounds, which also have electron-deficient properties, as substrates with pre-chiral dihydrosilanes in the presence of metal catalysts using asymmetric silylene-hydrogen addition strategy. The reaction was performed by trying to control the regioselectivity of alkyne addition to synthesize silyl stereocentric 1, 3-diene fluoro-silyl analogues with high stereoselectivity and regioselectivity, which are difficult to prepare by existing methods, as shown in Fig. 3-4.

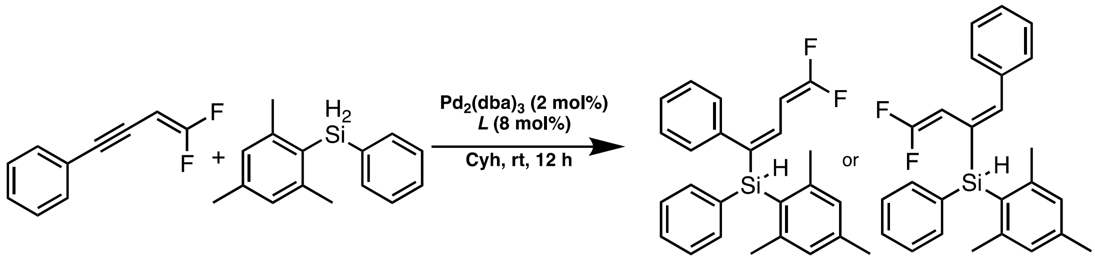


7a **5a** **8a** **8b**

Fig. 3-4 Silicon-hydrogen addition reactions of difluoroalkynes

3.2 Exploration and optimisation of reaction conditions

Based on our work on the synthesis of racemic as well as chiral fluorosilane products **6a** and **6b** by the silylhydrogen addition reaction of sidodifluoro 1, 4-alkynes with dihydrosilanes achieved in the derivatisation experiments in the second chapter of the contents, we have further investigated the silylhydrogen addition reaction of such difluroroenyne compounds and have completed the exploration of the initial conditions for this work. The effect of the racemic phosphine ligand on this silylhydroaddition reaction was investigated by using the simple structure of the sidodifluoro 1, 3-enyne compound **7a** as a template substrate, the same asymmetric diaryldihydrosilane 5a as a source of silylchirality as in the above reaction, $Pd_2(dba)_3$ (2 mol%) as a palladium source, and ultra-dry n-hexane as the reaction solvent for 24 h at room temperature. As we expected, some of the commercially available phosphine ligands did not play a role in facilitating the reaction (Tables 3-1 entris 2-3, 6-7) and only three of the eight phosphine ligands were effective in this reaction. When the 1, 3-bis(diphenylphosphino)propane (dppp) phosphine ligand was used (Table 3-1 entris4), it was possible to achieve the target products **8a**, **8b** in 20 % isolated yield, and the reaction exhibited excellent enantioselectivity (**8a/8b**=96:4). More surprisingly, the phosphoramidite ligand of the racemic binaphthol backbone was also able to promote the reaction, and the target products were obtained in 12 % isolated yield (Table 3-1 entris1), which provided direction for the screening of chiral phosphine ligands, as shown in Table 3-1.

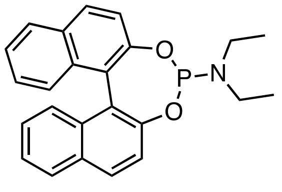


7a **5a** **8a** **8b**

Table 3-1 Screening of the phosphine-coated ligands

Entry	Ligand	Solvent	Yield(%)[a]	Ratio[b]
1	L1	Cyclohexane	12	53:47
2	Xantphos	Cyclohexane	-	-
3	dppf	Cyclohexane	-	-
4	dppp	Cyclohexane	20	96:4
5	PPh_3	Cyclohexane	19	85:15
6	Xphos	Cyclohexane	-	-
7	$nBuPAd_2$	Cyclohexane	-	-

Reaction conditions: **7a** (0.3 mmol), **R_2SiH_2** (0.3 mmol), **[Pd]** (2 mol%), **Ligand** (8 mol%), Solvent (1 mL), rt, 24 h. [a] isolated yield, [b] Determined by chiral HPLC analysis.



L1

After determining the structure of the racemic product, we then examined the effect of a series of chiral phosphine ligands on this reaction, focusing on the synthesis of a large number of phosphinamido ligands with different substituents in the binaphthol backbone (**L10-L24**). As expected, chiral phosphine ligands of other backbones (**L1-L9**), except for this type of chiral phosphine ligand, did not give satisfactory results in this reaction, and the yields and regioselectivities of the target products 8a and 8b obtained when using chiral phosphine-amidite ligands of the binaphthol backbone (**L10**) were significantly improved, and on the basis of these results, we carried out the modification of ligands. It was found that when the benzene ring of the binaphthol skeleton was substituted with methyl group (**L10**), methyl-substituted phenyl group (**L11, L12**), phenyl-substituted trifluoromethyl group (**L13**) and phenyl-substituted fluorine group (**L15**), the results of several attempts were unsatisfactory (Table 3-2 entries10-13, 14), and the yields and selectivity of the products were significantly improved when the benzene ring of the dinaphthol skeleton was substituted with the large site-resistant aliphatic tertiary-butyne moiety (Table 3-3 entries10-13, 14). When the para-position of the benzene ring of the binaphthol skeleton was substituted with a large site-resistant aliphatic chain tert-butyl group, the yield, enantioselectivity, and regioselectivity of the product increased slightly, and thus we determined the basic backbone of the ligand in the binaphthol skeleton with the para-position of the benzene ring substituted with a tert-butyl group. Immediately after that, we improved the substituent group on N. The results showed that when the N in the phosphoramidite ligand was substituted by asymmetric alkyl and phenyl groups (**L21-L23**), the yield of the product was significantly improved, but its enantioselectivity was still at a moderate level. Finally, when the N in the modified phosphoramidite ligand was replaced by quinoline ring (**L24**), the yield and enantioselectivity of the product were significantly improved, and the regioselectivity was also further enhanced (Table 3-2 entries24). After comparing the data, we finally confirmed that we used **L24** as the optimal chiral ligand for the reaction, and completed the preliminary screening of the conditions for the reaction as shown in Table 3-2.

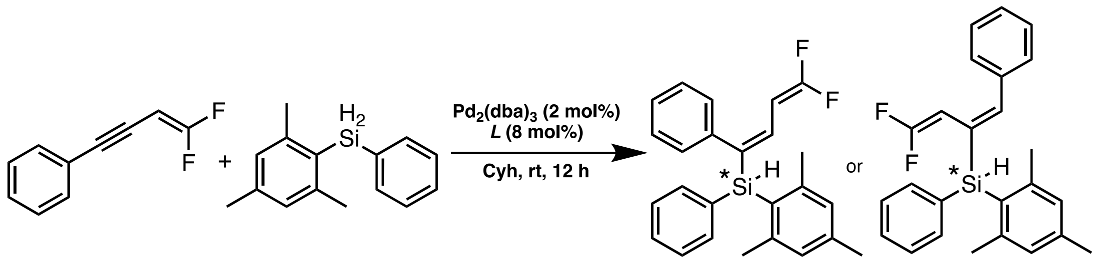
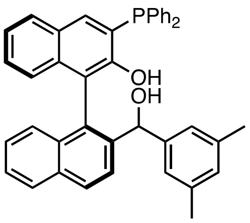


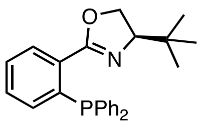
Table 3-2 Screening of chiral ligands

Entry	Ligand	Yield[a]	*ee*(%)[b]	*rr*(%)[b]
1	L1	13	4	62:38
2	L2	trace	-	-
3	L3	12	10	70:30
4	L4	13	5	93:7
5	L5	13	5	48:52
6	L6	12	13	84:16
7	L7	24	35	70:30
8	L8	9	4	47:53
9	L9	trace	-	-
10	L0	21	7	88:12
11	L11	20	3	90:10
12	L12	10	29	90:10
13	L13	11	55	98:2
14	L14	60	51	95:5
15	L15	46	55	93:7
16	L16	trace	-	-
17	L17	22	45	93:7
18	L18	49	55	97:3
19	L19	13	54	88:12
20	L20	48	51	96:4
21	L21	57	63	96:4
22	L22	70	50	96:4
23	L23	68	63	96:4
24	L24	68	79	97:3

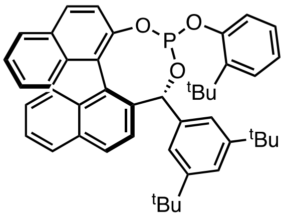
Reaction conditions: **7a** (0.3 mmol), **R_2SiH_2** (0.3 mmol), **[Pd]** (2 mol%), **Ligand** (8 mol%), Solvent (1 mL), rt, 24 h, [a] isolated yield, [b] Determined by chiral HPLC analysis.



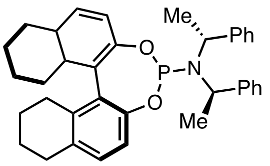
L1



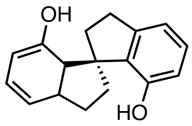
L2



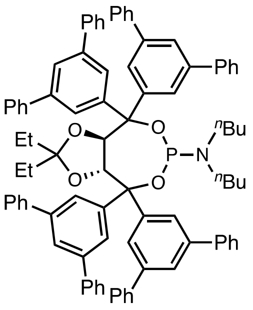
L3



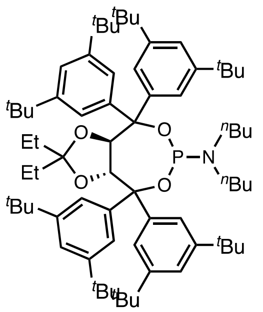
L4



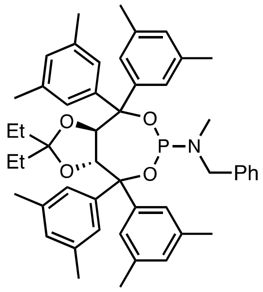
L5



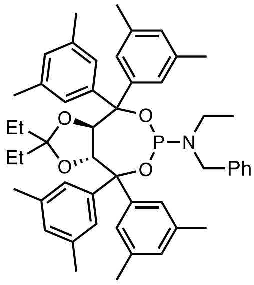
L6



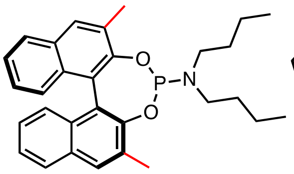
L7



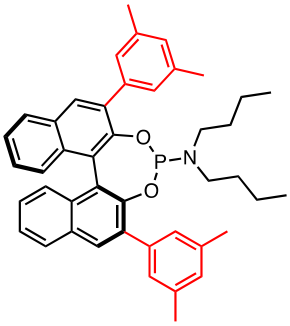
L8



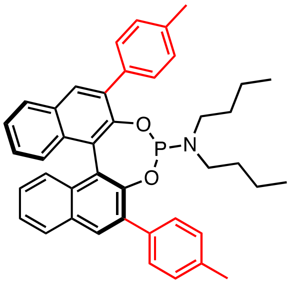
L9



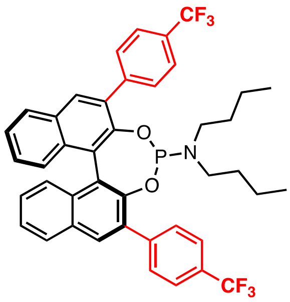
L10



L11



L12



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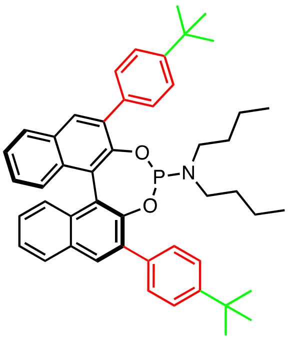

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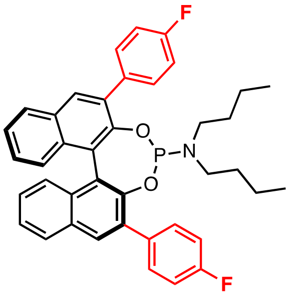

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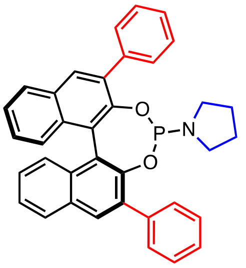
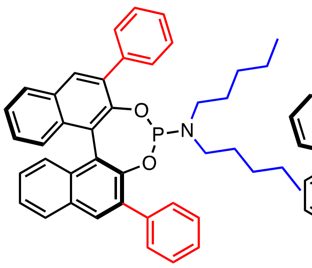
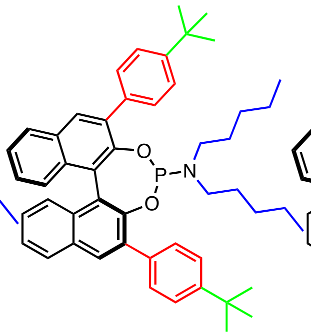


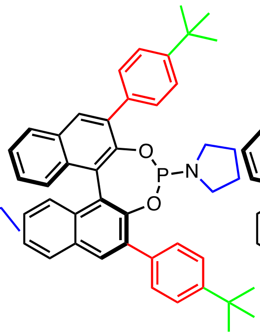
L16



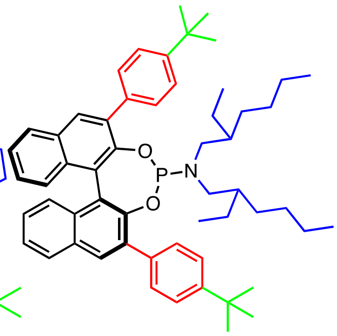
L17



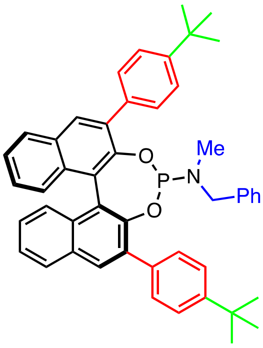
L18

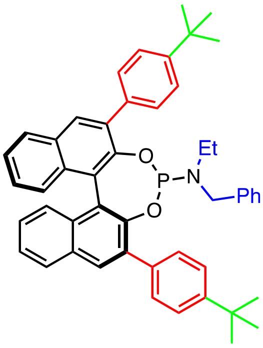


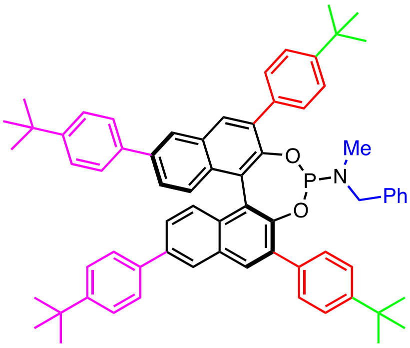
L19

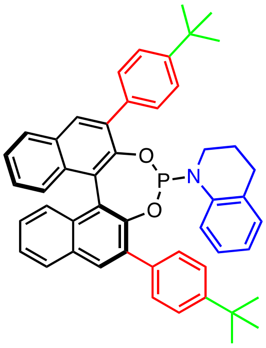


L20

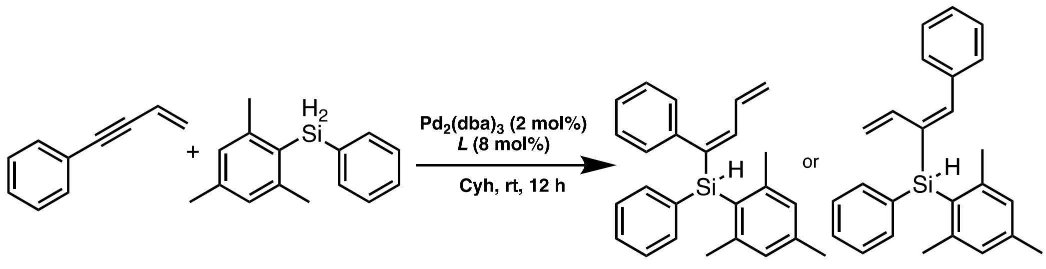

L21


L22


L23


L24

In order to verify the influence of the electron-deficient effect of elemental fluorine on the regioselectivity and enantioselectivity of this reaction, we synthesised a similar 1, 3-alkynyne substrate **9a** by controlled experiments, and reacted it under identical reaction conditions, using asymmetric diaryldihydrosilane **5a** as a chiral source, catalysed by $Pd_2(dba)_3$ (2 mol%) as a palladium source, and ultra-dry n-hexane as a reaction solvent The reaction was carried out at room temperature for 24 h to investigate the effect of the racemic phosphine ligand on the silylhydrogen addition reaction of 1, 3-alkynyl substrates without elemental fluorine. In this reaction, the target products **10a**, **10b** were obtained in 15 % isolated yield only when 1, 3-bis(diphenylphosphino)propane (dppp) phosphine ligand (Table 2-7 entris4) was used, Table 3-3.

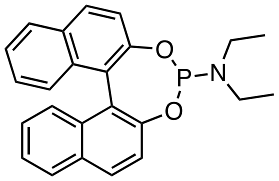


9a **5a** **10a** **10b**

Table 3-3 The effect of the racemic phosphine ligand on this reaction

Entry	Ligand	Solvent	Yield(%)[a]	Ratio[b]
1	L1	Cyclohexane	-	-
2	Xantphos	Cyclohexane	-	-
3	dppf	Cyclohexane	-	-
4	dppp	Cyclohexane	15	77:23
5	PPh_3	Cyclohexane	-	-
6	Xphos	Cyclohexane	-	-
7	$nBuPAd_2$	Cyclohexane	-	-

Reaction conditions: **9a** (0.2 mmol), **R_2SiH_2** (0.2 mmol), **[Pd]** (2 mol%), **Ligand** (8 mol%), Solvent (1 mL), rt, 24 h. [a] isolated yield, [b] Determined by chiral HPLC analysis.



L1

After determining the structure of the racemic product, we immediately followed the comparison with the same reaction conditions using the ligand (**L23**) which had obtained the better reaction in the above experimental results, and found that there was a significant decrease in the yield and regioselectivity of the silyl chiral compounds obtained by silylhydrogen addition reaction of alkenyne compounds without difluorine under the same reaction conditions (18% yield, 67:33 *rr*), but a slight increase in enantioselectivity over fluorosilanes8 (83% *ee*), as shown in Fig. 3-5. The experiments preliminarily demonstrated that the electron-deficient group played a positive role in this reaction to generate fluorosilanes with silicon stereocentres, and also provided a new idea for the realization of asymmetric silylhydrogen addition strategy for alkyne compounds with electron-deficient groups.

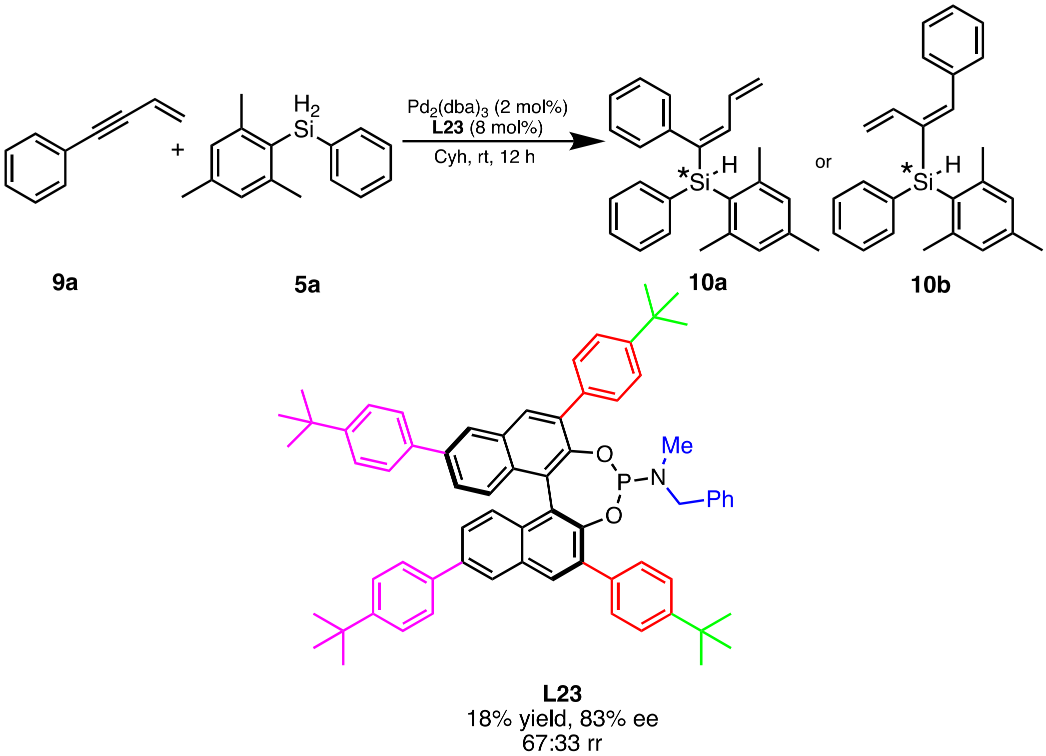


Fig. 3-5 Synthesis of dienesilanes from chiral phosphine ligands

3.3 EXPERIMENTAL PART

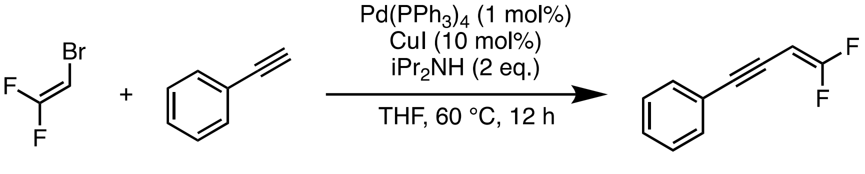
3.3.1 Experimental apparatus and data

In the above mentioned, all the silica-hydrogen addition reactions were carried out in anhydrous and oxygen-free Shrike reaction tubes under nitrogen atmosphere, all the solvents used in the experiments were ultra-dry and deoxidised solvents, and such solvents were taken in anhydrous and oxygen-free condition using dry long needles, and the substrates and ligands were synthesized under anhydrous and oxygen-free nitrogen atmosphere. The product is mainly purified and separated by column chromatography, the silica gel powder used is 200-300 mesh, and the eluents used are petroleum ether and ethyl acetate purchased by Sinopharm.

Large instruments and equipment: Brucker Advance (400/500M) NMR, Bruker MicroTOF-instrument (ESI or APCI) high-resolution mass spectrometer, Agilent 1260 HPLC high-performance liquid chromatography, Agilent 7890 GC-MS gas-mass spectrometer, Waters UPLC high performance liquid chromatography.

3.3.2 experimental step

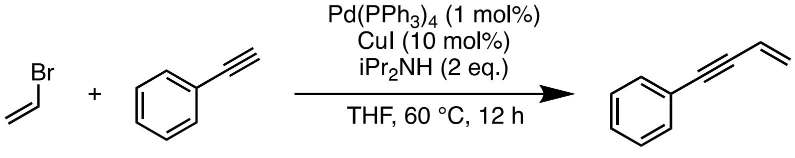
Preparation of ketodifluorosubstituted 1, 3-alkynes has been reported in the literature. Such substrates were synthesised in Ref.



7a

Fig. 3-6 Synthesis of difluoroalkynyl substrates

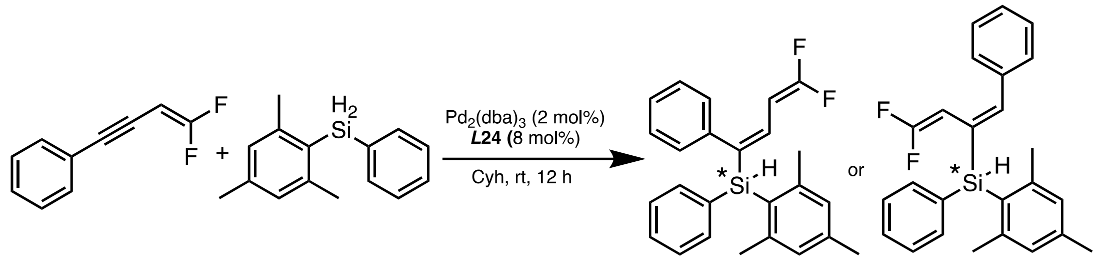
2-Bromo-1, 1-difluoroethylene (20 mmol), phenylacetylene (40 mmol), palladium tetrakis(triphenylphosphine) (0.2 mmol), cuprous iodide (2 mmol), and anhydrous, oxygen-free diisopropylamine (40 mmol) were added to a 500 mL reaction flask which was filled with nitrogen. Ultra-dry tetrahydrofuran solution (100 mL) was added to the reaction system using a dry long needle. The obtained solution was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature and the reaction mixture was quenched with saturated aqueous NH_4Cl solution to obtain the target product solution by extraction and then concentrated under reduced pressure. The crude product was purified by fast chromatography and a yellow oily liquid 7a was obtained in 50 % isolated yield, as shown in Fig. 3-6.



9a

Fig. 3-7 Synthesis of alkynyl substrates

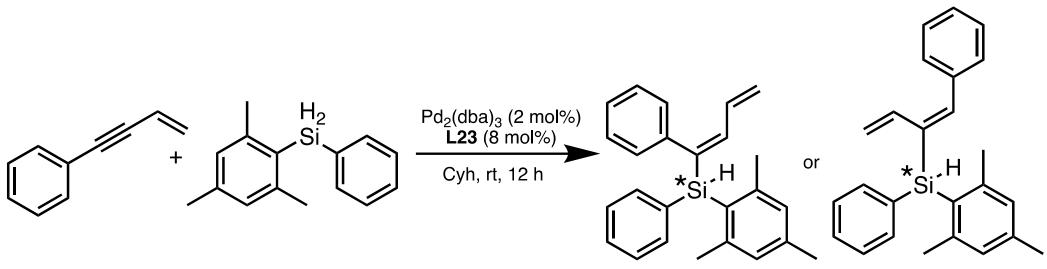
2-Bromoethylene (20 mmol), phenylacetylene (40 mmol), palladium tetrakis(triphenylphosphine) (0.2 mmol), cuprous iodide (2 mmol), and anhydrous and oxygen-free diisopropylamine (40 mmol) were added to a 500 mL anhydrous and oxygen-free reaction flask that was filled with nitrogen. Ultra-dry tetrahydrofuran solution (40 mL) was added to the reaction system using a dry long needle. The obtained solution was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature and the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the target product solution was obtained by extraction and then concentrated under reduced pressure. The crude product was purified by fast chromatography and a yellow oily liquid 9a was obtained in 68 % isolated yield, as shown in Fig. 3-7.



7a **5a** **8a** **8b**

Fig. 3-8 Preparation of chiral fluorosilane products

7a (0.2 mmol), 5a (0.2 mmol), $Pd_2(dba)_3$ (0.004 mmol) and L24 (0.016 mmol), and ultra-dry cyclohexane solution (1 mL) were added to a 10 mL Shrike's reaction tube which was filled with nitrogen. The obtained solution was stirred at room temperature for 24 h. The reaction was monitored using TLC and after observing the end of the reaction was filtered using diatomaceous earth and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by fast chromatography to obtain yellow liquid 8a, 8b, as shown in Fig. 3-8.

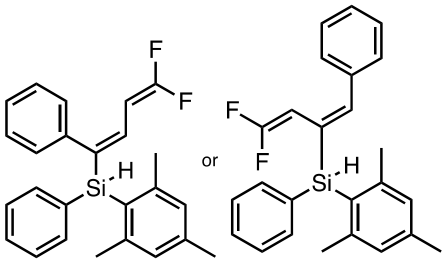


9a **5a** **10a** **10b**

Fig. 3-9 Preparation of chiral fluorosilane products

9a (0.2 mmol), 5a (0.2 mmol), Pd$_2$(dba)$_3$ (0.004 mmol) and L24 (0.016 mmol), and ultra-dry cyclohexane solution (1 mL) were added to a 10 mL Shrike's reaction tube which was filled with nitrogen. The obtained solution was stirred at room temperature for 24 h. The reaction was monitored using TLC and filtered using diatomaceous earth after it was observed that the raw material was completely consumed and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by fast chromatography to obtain the yellow liquid 10a, 10b, as shown in Fig. 3-9.

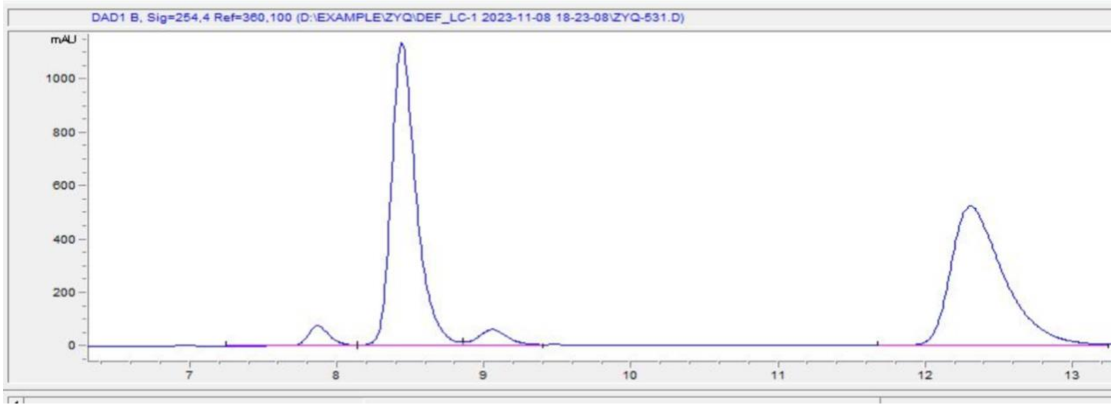
3.3.3 Characterisation data for representative products



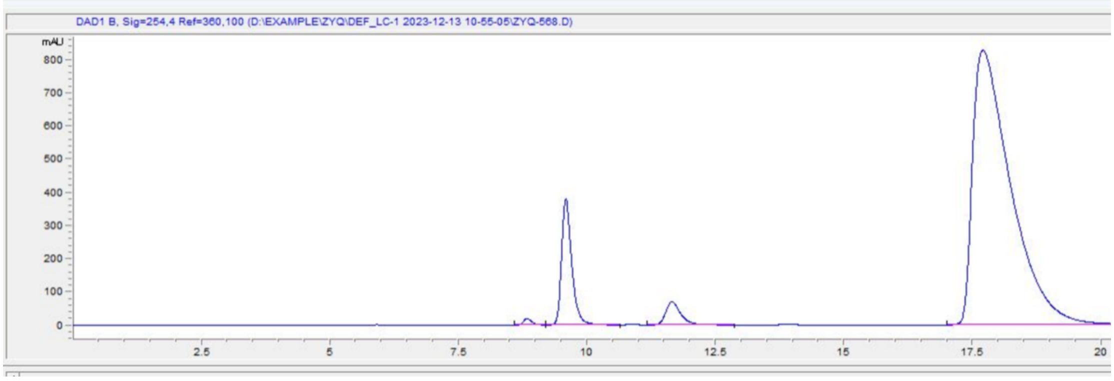
(*E*)-(4,4-difluoro-1-phenylbuta-1,3-dien-1-yl)(mesityl)(phenyl)silane(8a)

(*E*)-(4,4-difluoro-1-phenylbuta-1,3-dien-2-yl)(mesityl)(phenyl)silane(8b)

The mobile phase for flash chromatography: hexane. Yellow oil. (88 mg, 68 % yield). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.48 (d, *J* = 7.0 Hz, 2H), 7.29 - 7.18 (m, 8H), 6.79 (s, 2H), 6.69 (s, 1H), 2.28 (s, 1H), 2.21 (s, 1H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 145.5, 144.4, 144.3, 144.2, 140.0, 137.6, 135.9, 133.7, 129.7, 129.0, 128.9, 128.4, 128.2, 127.3, 127.2, 127.1, 126.7, 81.9, 81.7, 81.6, 81.4. 24.4, 21.3.^{19}**F NMR** (500 MHz, $CDCl_3$) δ -78.65 (s, 1F), -78.77 (s, 1F).. **HRMS** (EI): calculated for $C_{21}H_{19}ClF_2$ $[Na]^+$: 413.1508, found: 413.1517.



Entry	Time/min	Area	Area/%
1	7.866	767.7	2.736
2	8.437	13337.2	47.353
3	9.052	896.6	3.183
4	12.305	13164	46.738



Entry	Time/min	Area	Area/%
1	8.833	228.5	0.458
2	9.586	5233.9	10.501
3	11.65	1440.8	2.891
4	17.703	42938.5	86.150

3.4 Summary of the chapter

In summary, we have completed a preliminary screening of conditions for the palladium-catalyzed/phosphine ligand system of the si-hydrogen addition reaction of 1, 3-difluoroalkynes for the construction of highly enantiomerically enriched silicon stereocentric compounds. Stereospecific Si-H activation by silylhydrogenation of difluoroalkynes provides a synthetic method for the synthesis of silyl stereocentric conjugated dienofluorosilanes with 68 % yield, > 20:1 regioselectivity and 89:11 enantioselectivity. We believe that fluorosilanes with silyl chirality synthesized from this class of difluoro-1, 3-alkynes constructed with silicon stereocentres will have great application prospects.

CONCLUSIONS

Due to the unique properties of fluorine atoms, the selective introduction of fluorine-containing functional groups into organic molecules has become one of the most important tools for the discovery of new drugs, agrochemicals and advanced functional materials. In the past decade or so, although important progress has been made in fluorination and trifluoromethylation reactions, the selective introduction of difluoromethylene (CF_2) functional groups into organic molecules has been less studied. In this thesis, a new method for the one-step synthesis of embedded difluoromethylene functional molecules in high yields and high chemoselectivity in a mild reaction system without the need for exclusive regioselective metal catalysts as well as without the need for any additives is investigated.

Structurally diverse embedded difluoromethylene 1, 4-alkynes were efficiently constructed using synthetically simple and easily conserved difluoroolefin quaternary ammonium salts as well as compounds with terminal alkynes as substrates in optimal reactions using n-butyllithium as an activating reagent. Examples of combination with drug fragments were included in the substrate extension and all were successfully reacted in moderate to excellent yields (up to 99 %) to obtain the target products. This reaction system, with its simplicity of operation, mild conditions and high efficiency, is considered to be one of the simplest and most efficient routes for the preparation of functional difluoromethylene molecule analogues, with fluoro-silane products with silicon stereocentres obtained in high yields and high enantioselectivities (86 % yield, 90 % *ee*) during the subsequent selective conversion of the alkyne groups in the resulting alkenyne products, although the specific conformation of the generated products has not yet been Although the specific configuration of the generated product has not yet been determined, this is the first asymmetric catalytic strategy to achieve a transition metal-catalysed silylhydrogen addition reaction of selenodifluoroalkynes to obtain 1, 4-dienylfluorosilanes, which further demonstrates the utility of this class of difluoroalkynes and the potential application of this synthetic method.

On the basis of the above work, we have further investigated the use of asymmetric catalytic strategy to obtain 1, 3-dienylfluorosilanes with silyl stereocentres by using simple sidodifluoro 1, 3-enynes, and although only the preliminary condition screening has been completed so far, the target products can be obtained with high regioselectivity (97:3 *rr*) as well as good enantioselectivity (89:11 *er*). Here we not only solved the difficult problem of regulating the regioselectivity when the difluoromethylene group was introduced, but also successfully completed the construction of p-silicon-chiral fluorosilicon compounds using such alkynes on this basis.

In our future research work, we will continue to focus on the silylation reaction of difluoroalkynes with a view to synthesizing functionalized ketodifluoroorganosilicon compounds with higher enantioselectivity and chemoselectivity.

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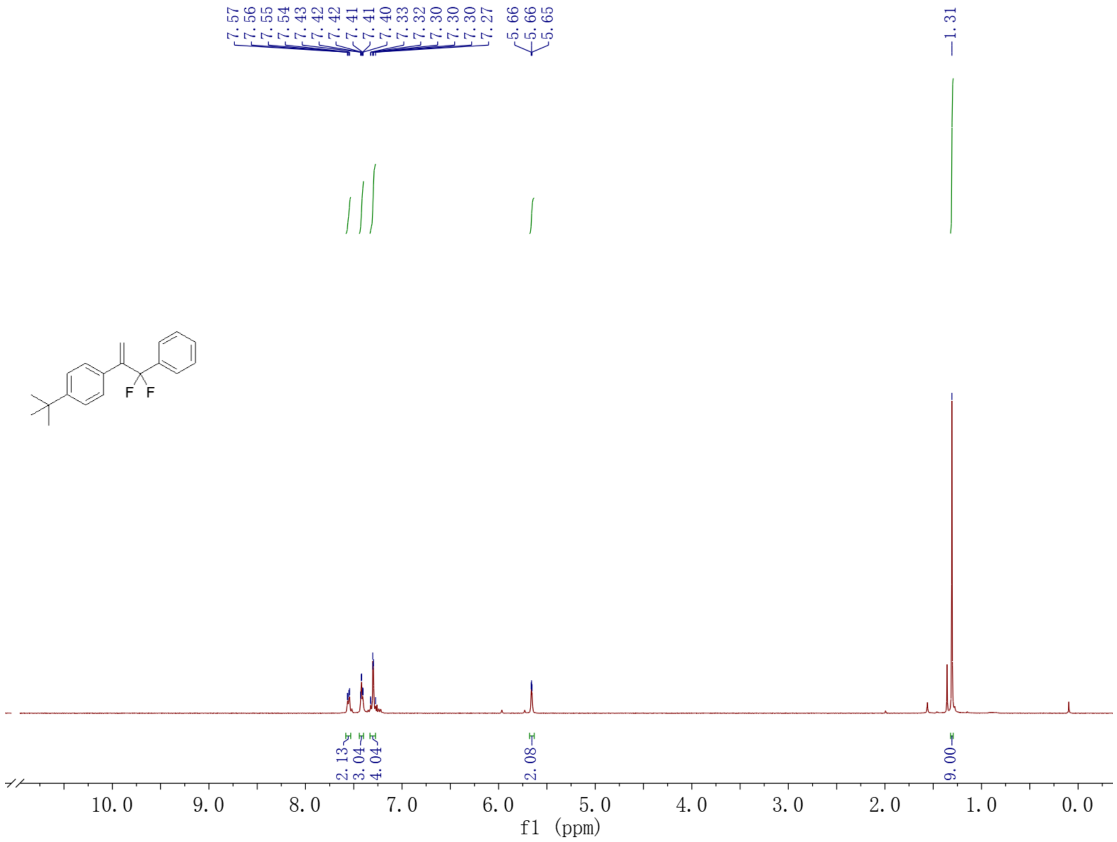
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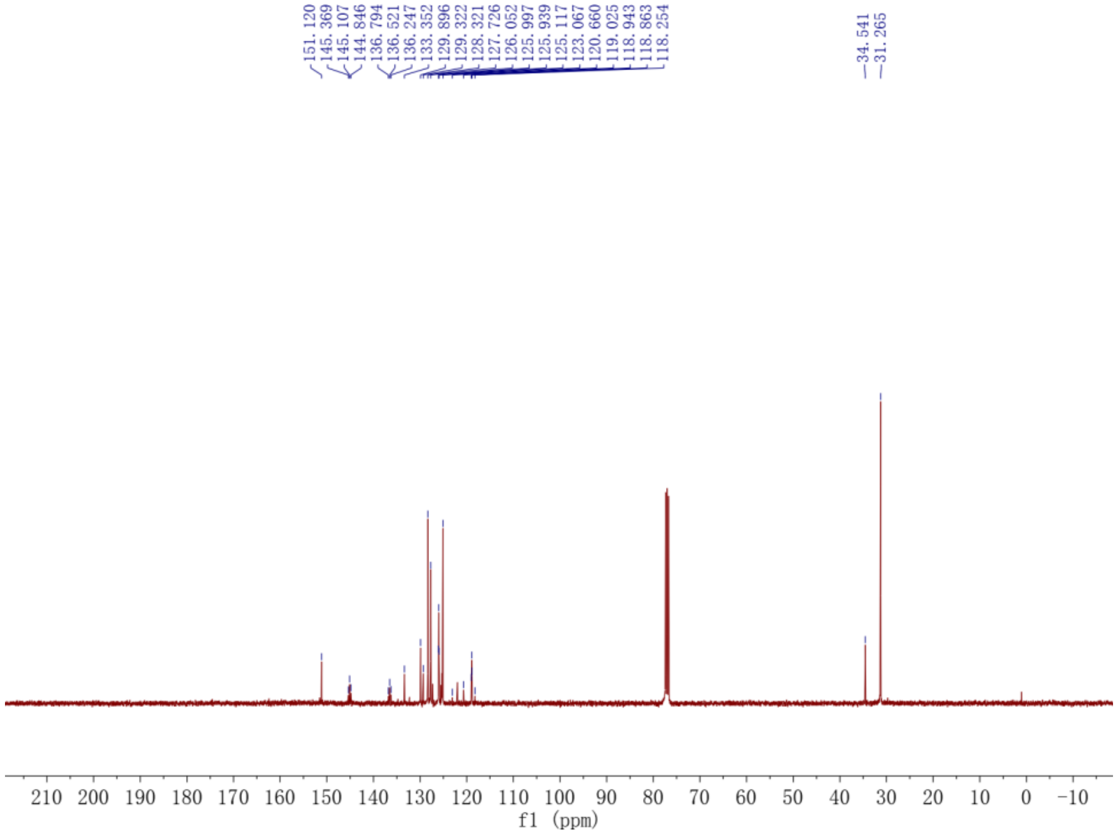
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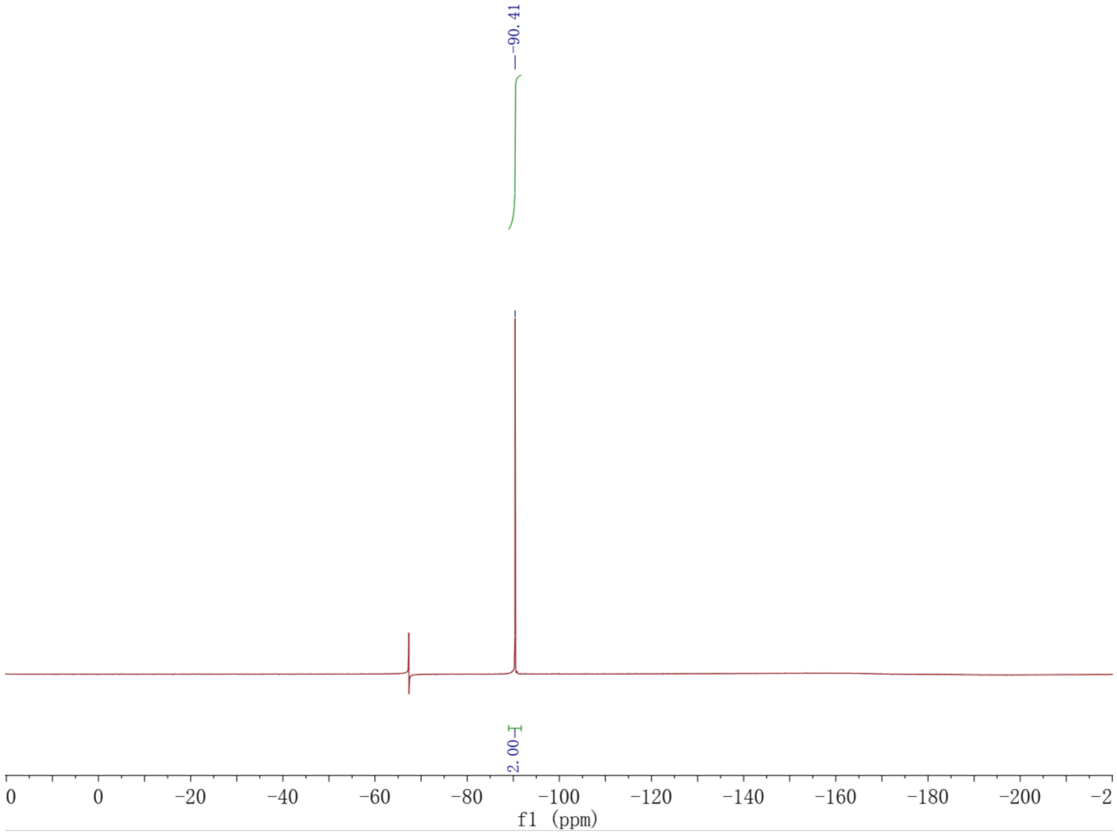
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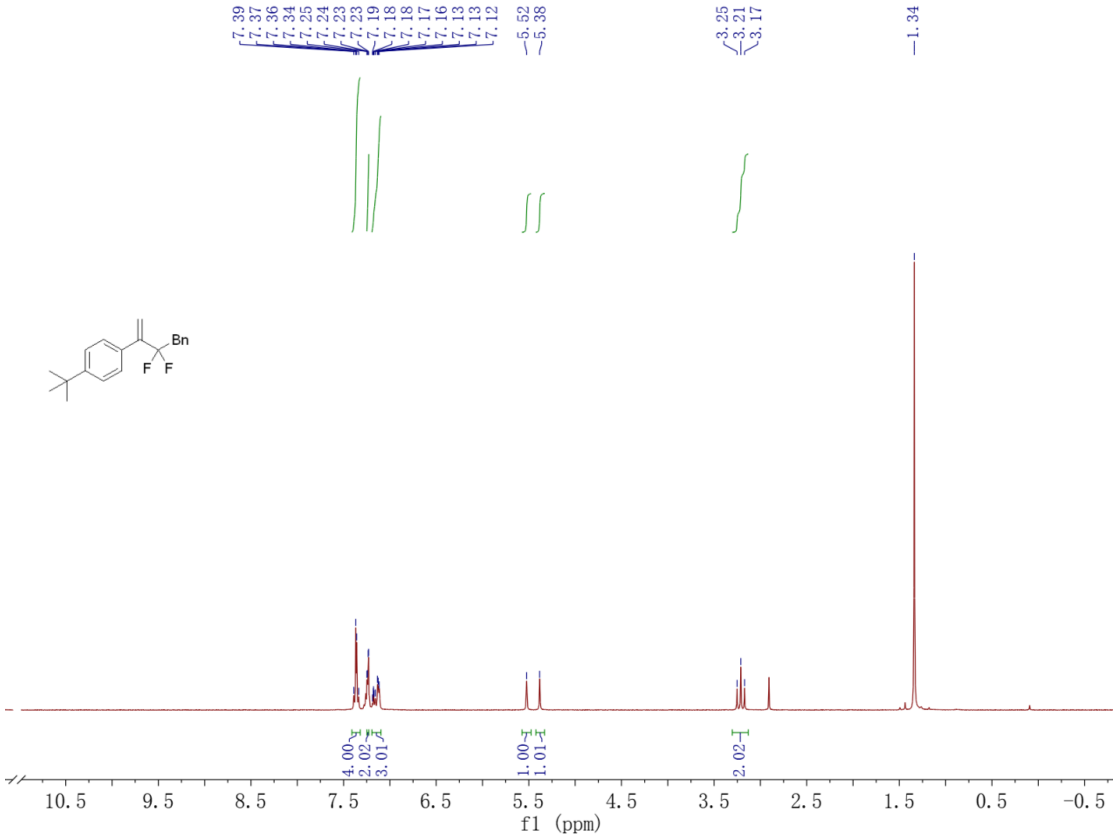
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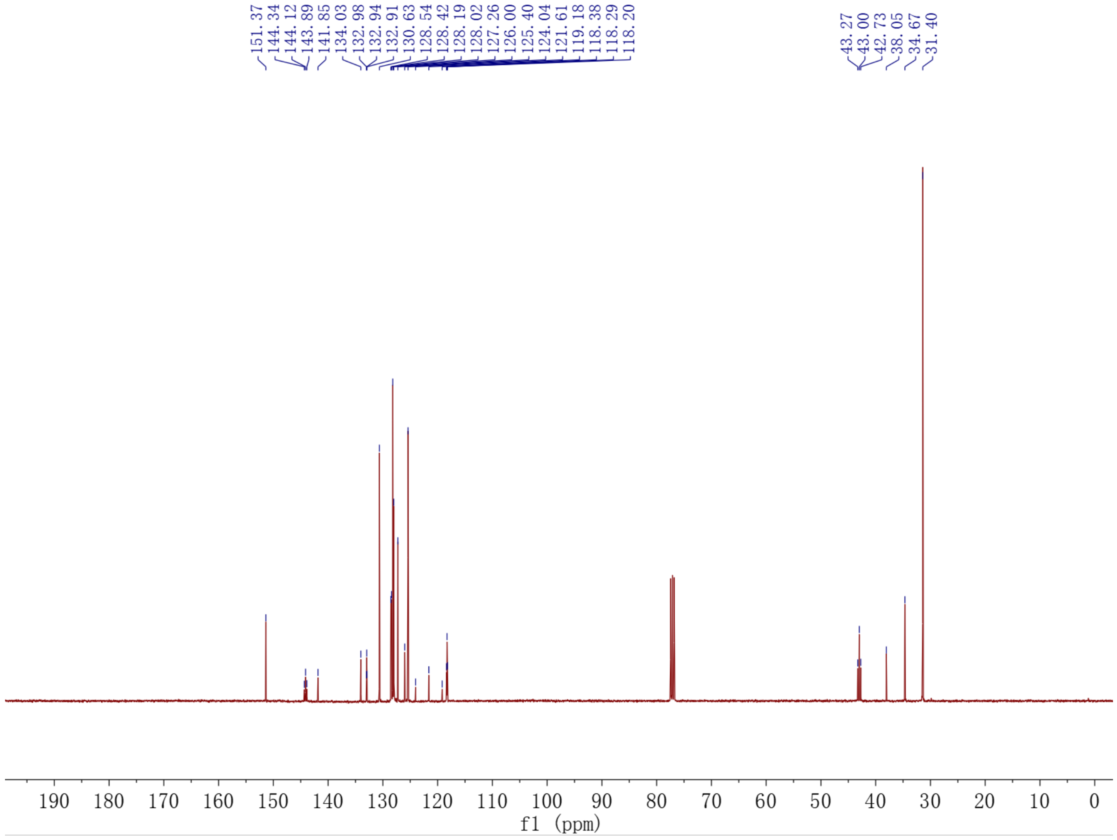
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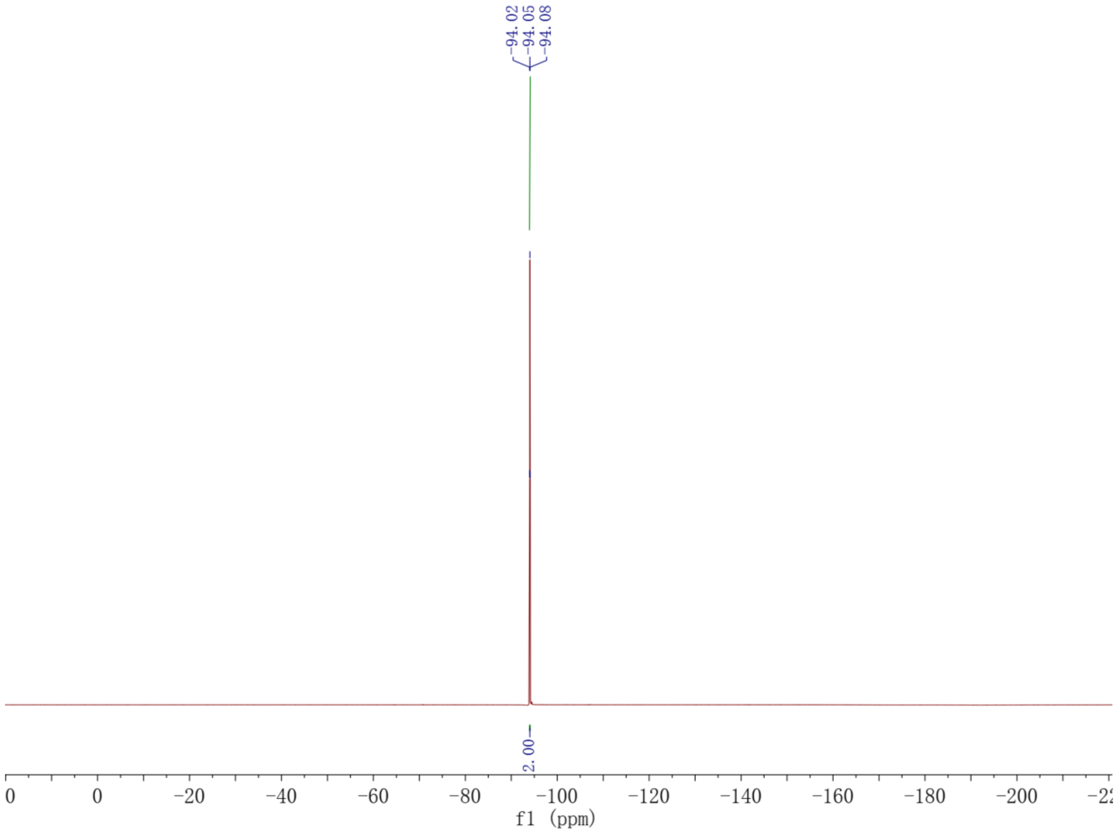
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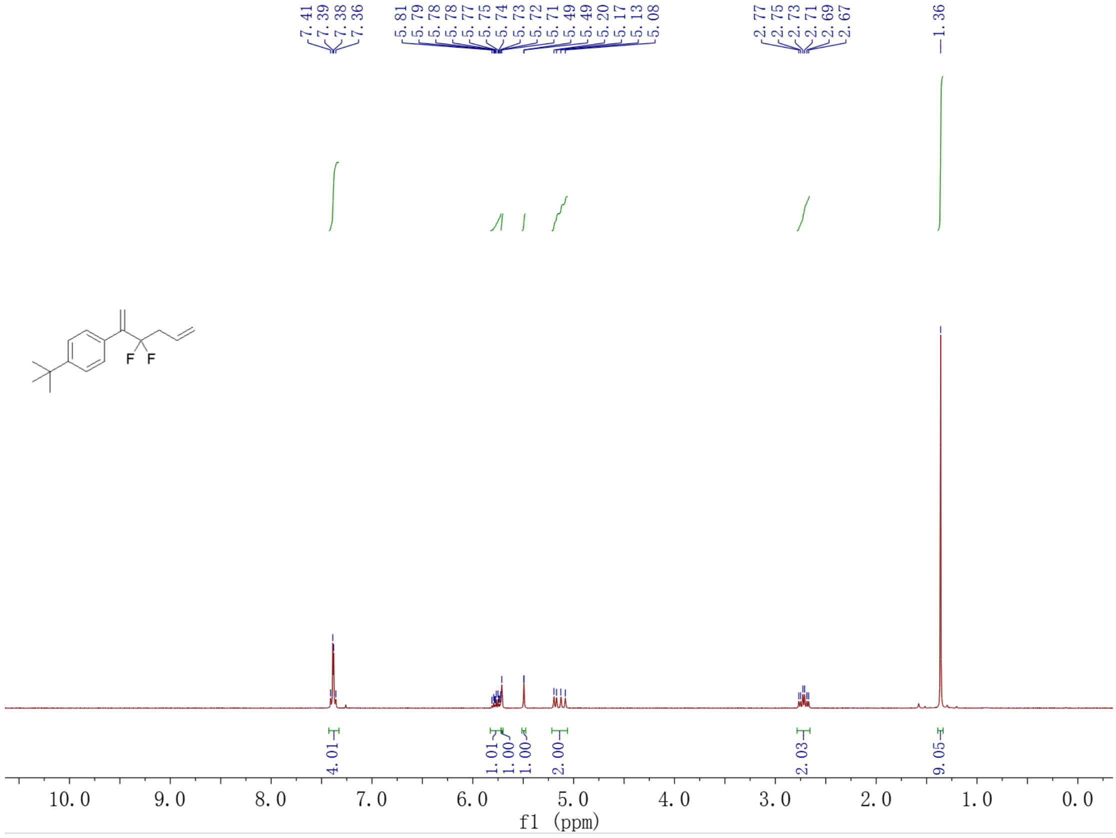
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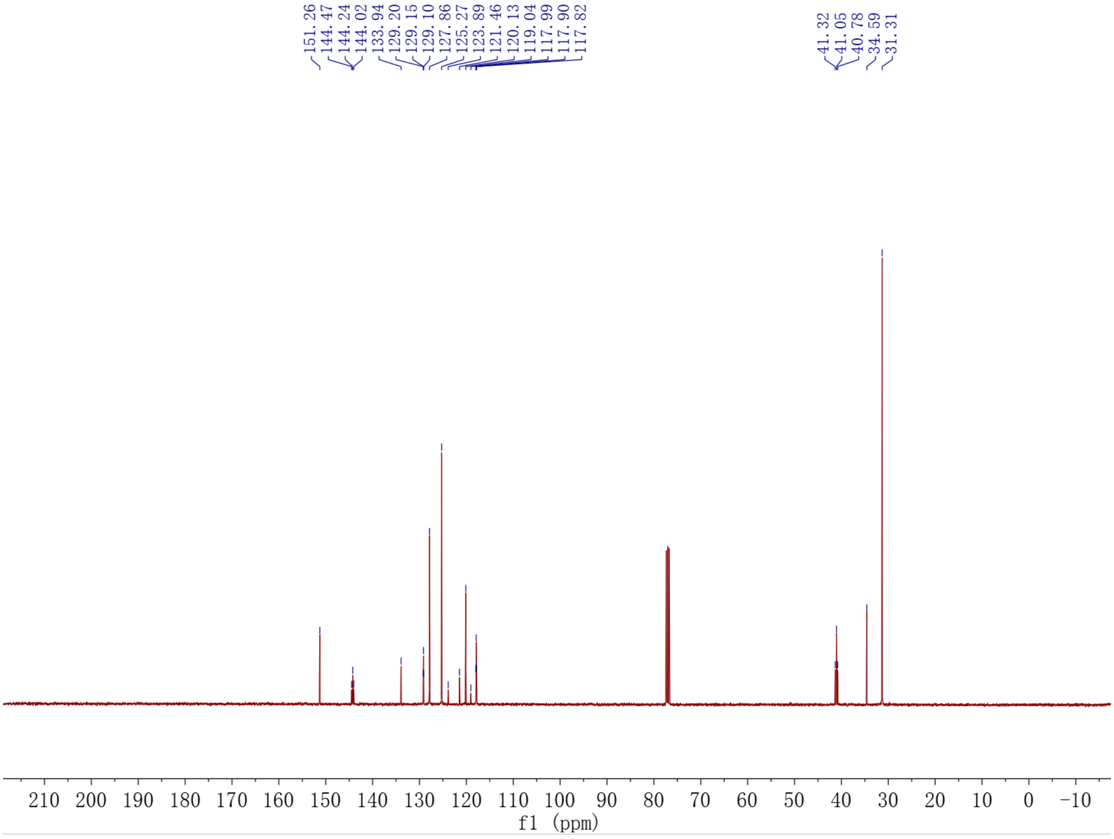
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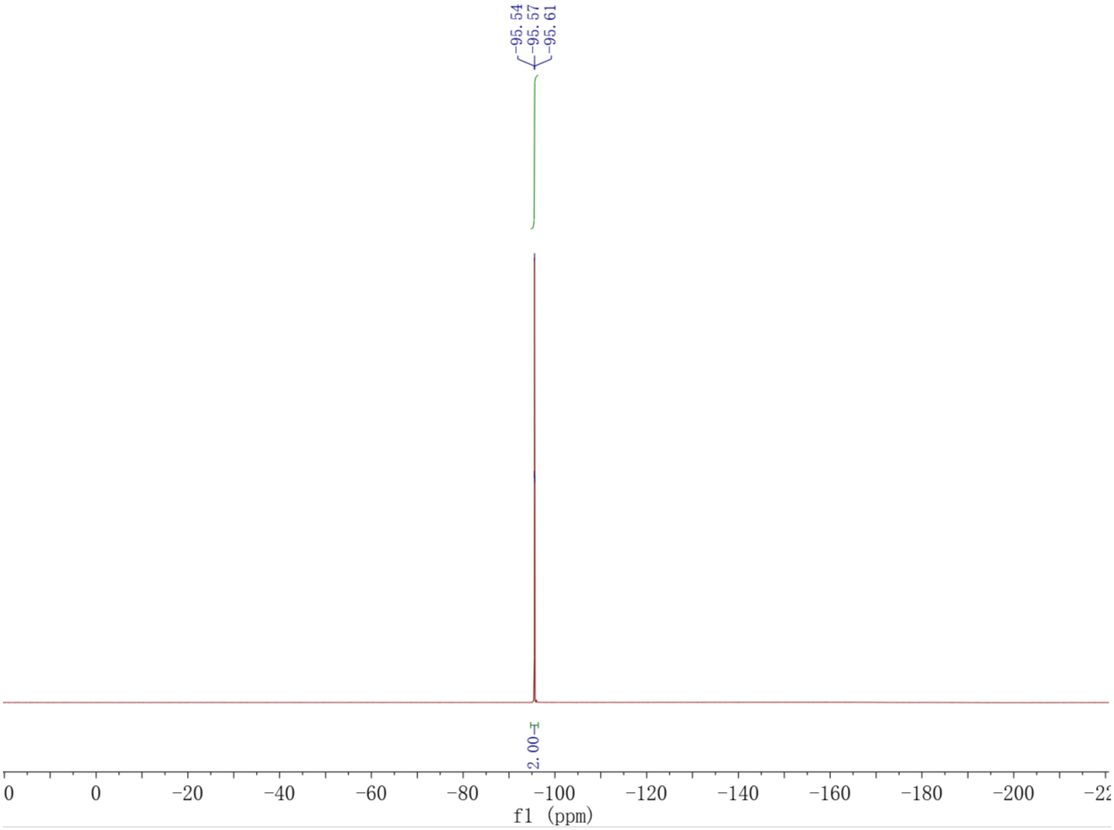
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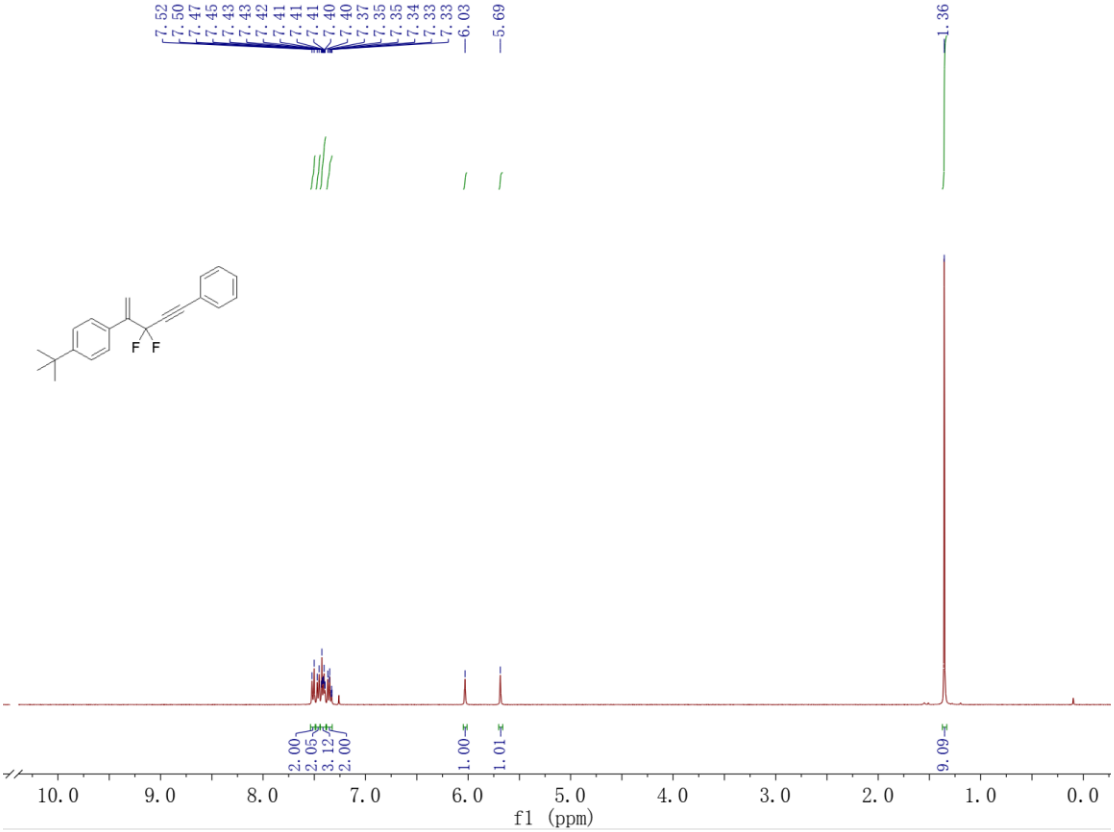
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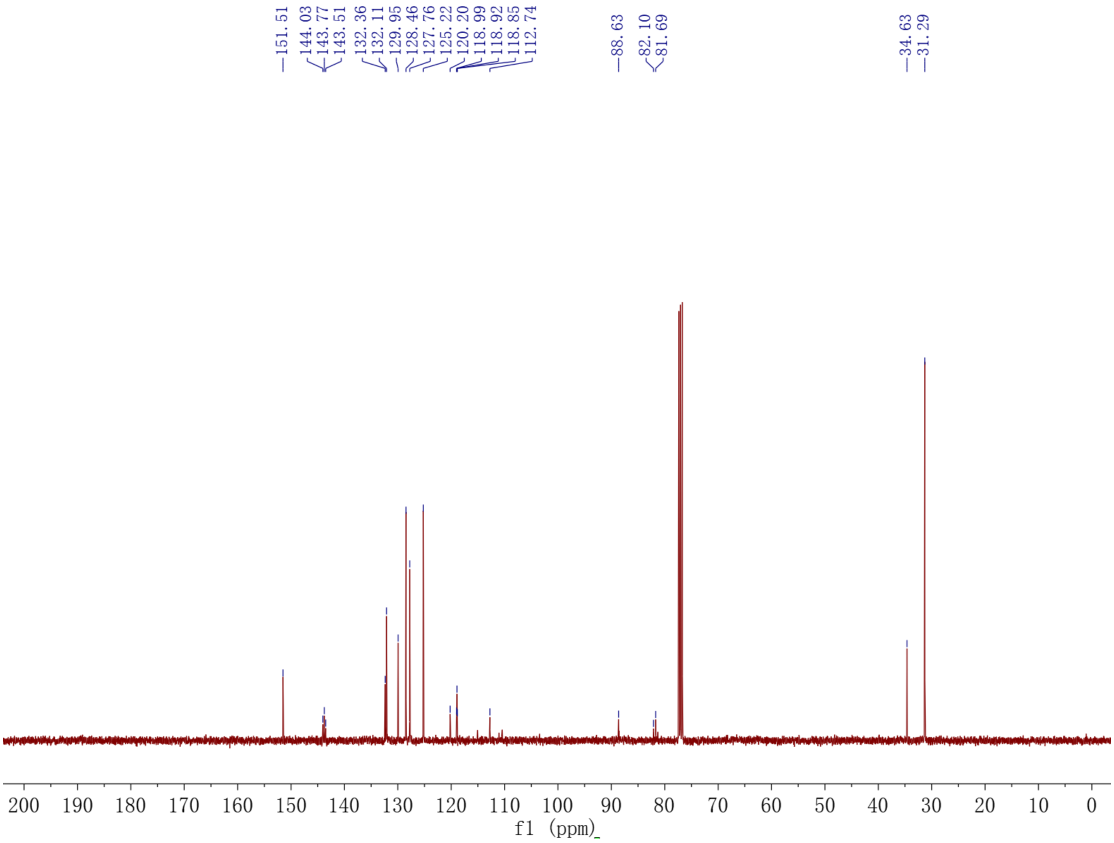
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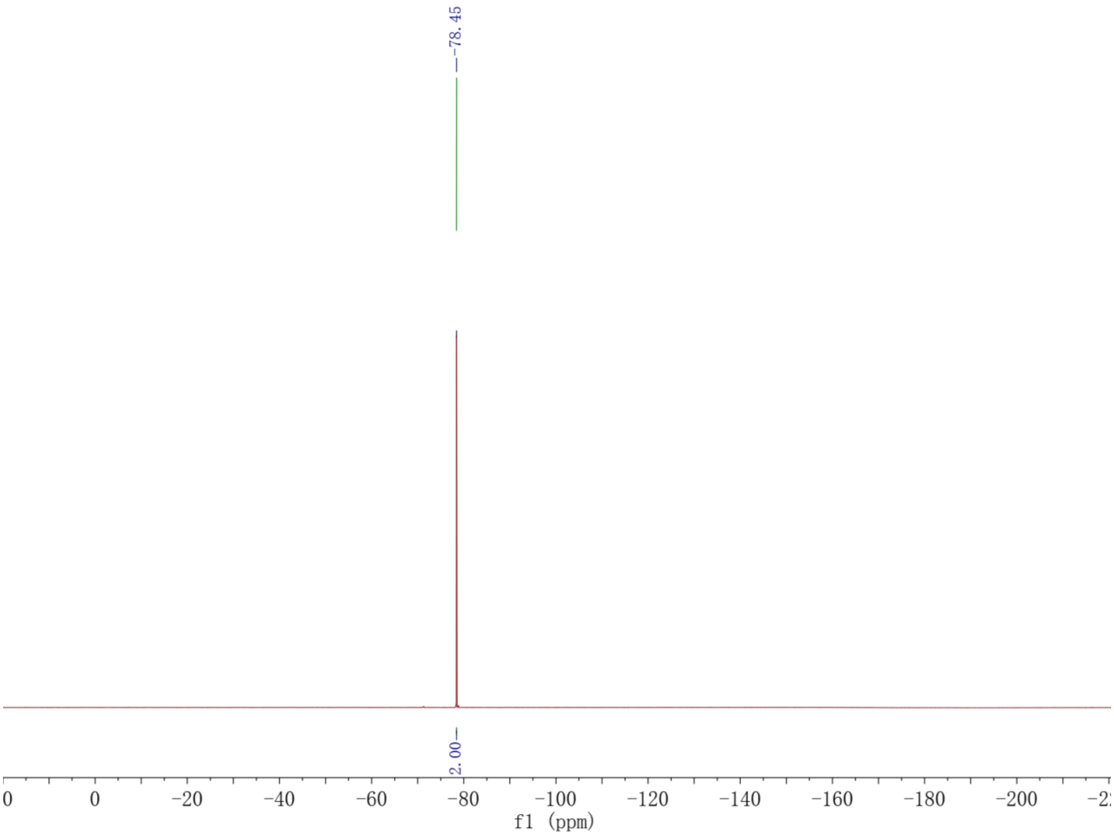

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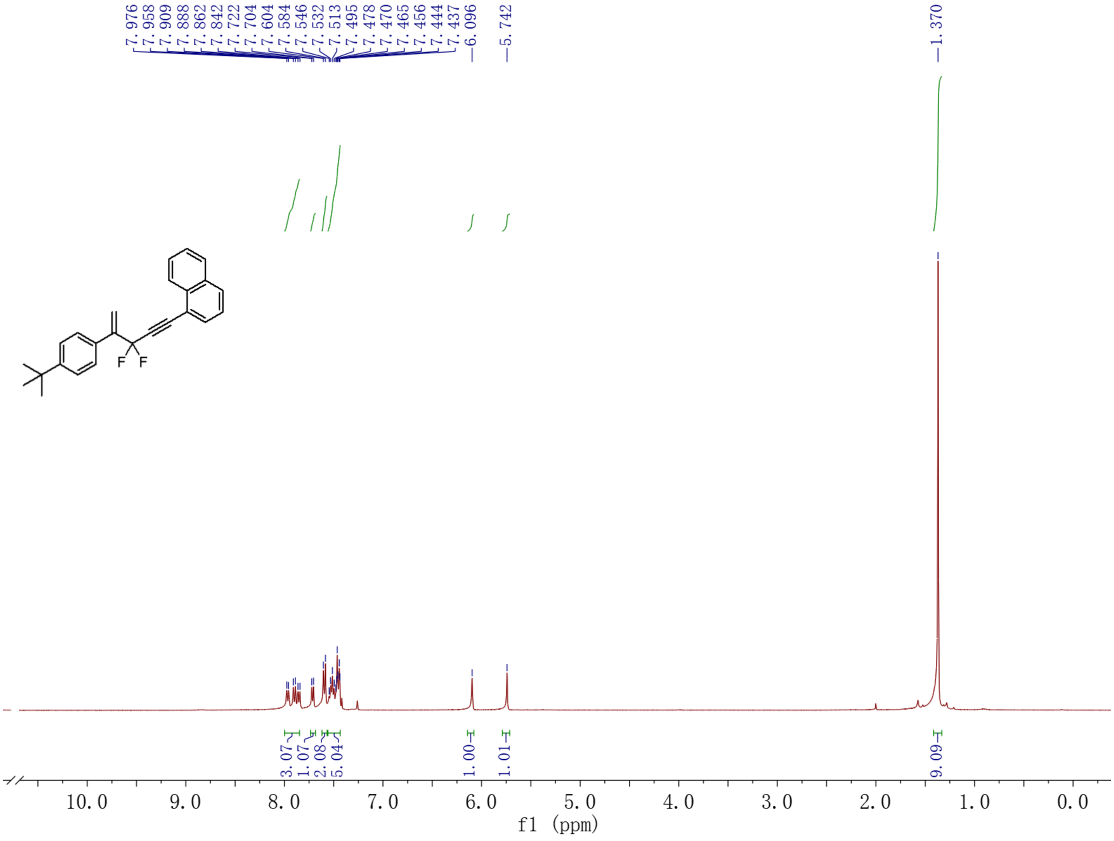

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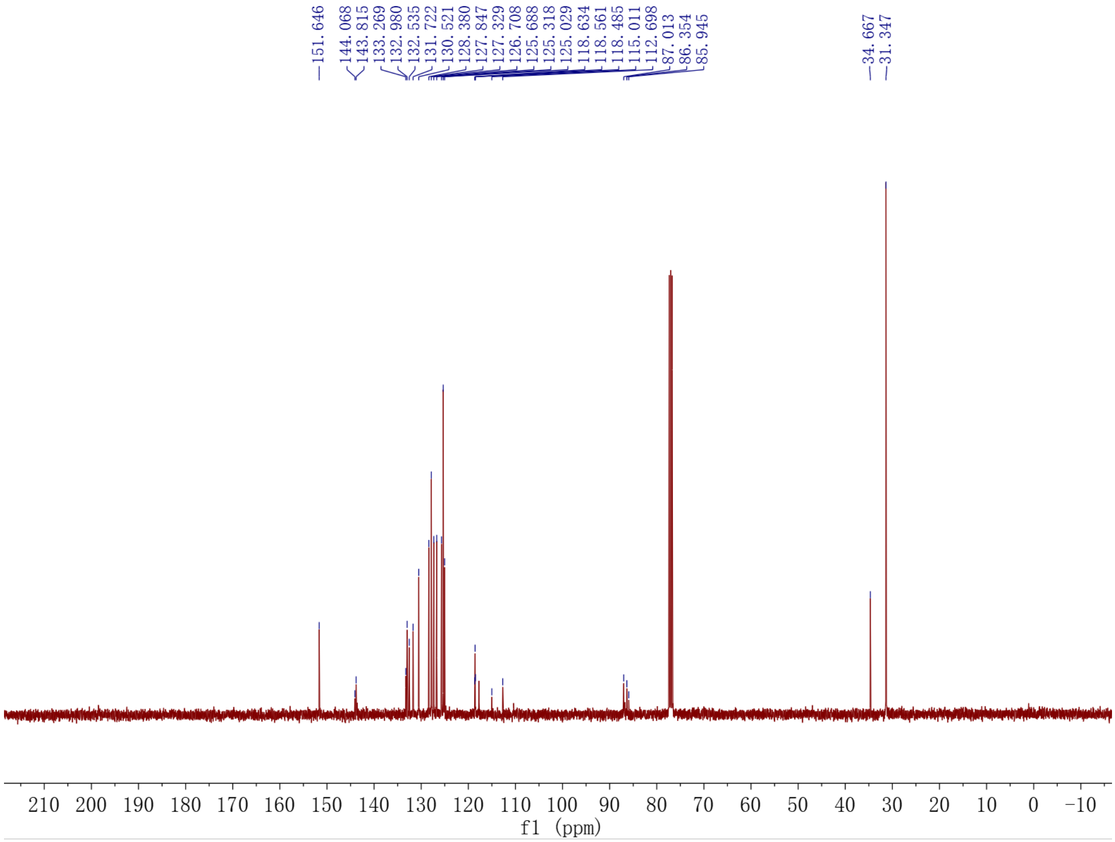
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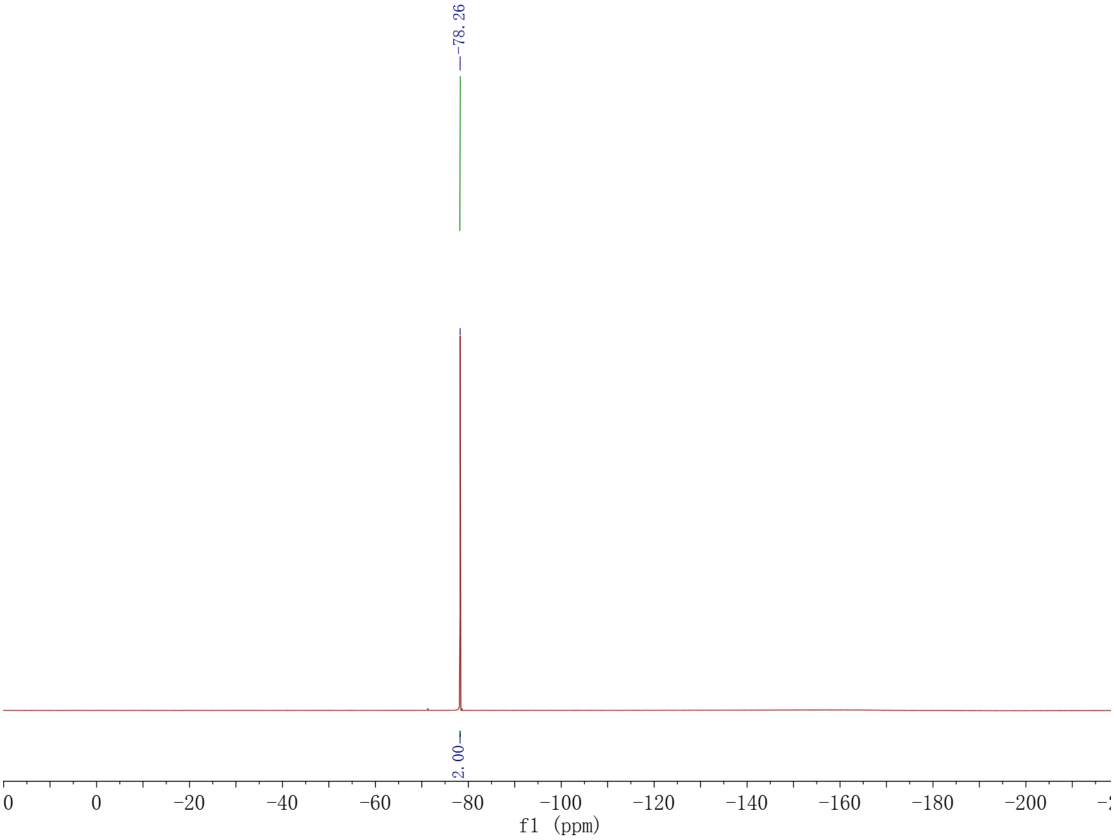

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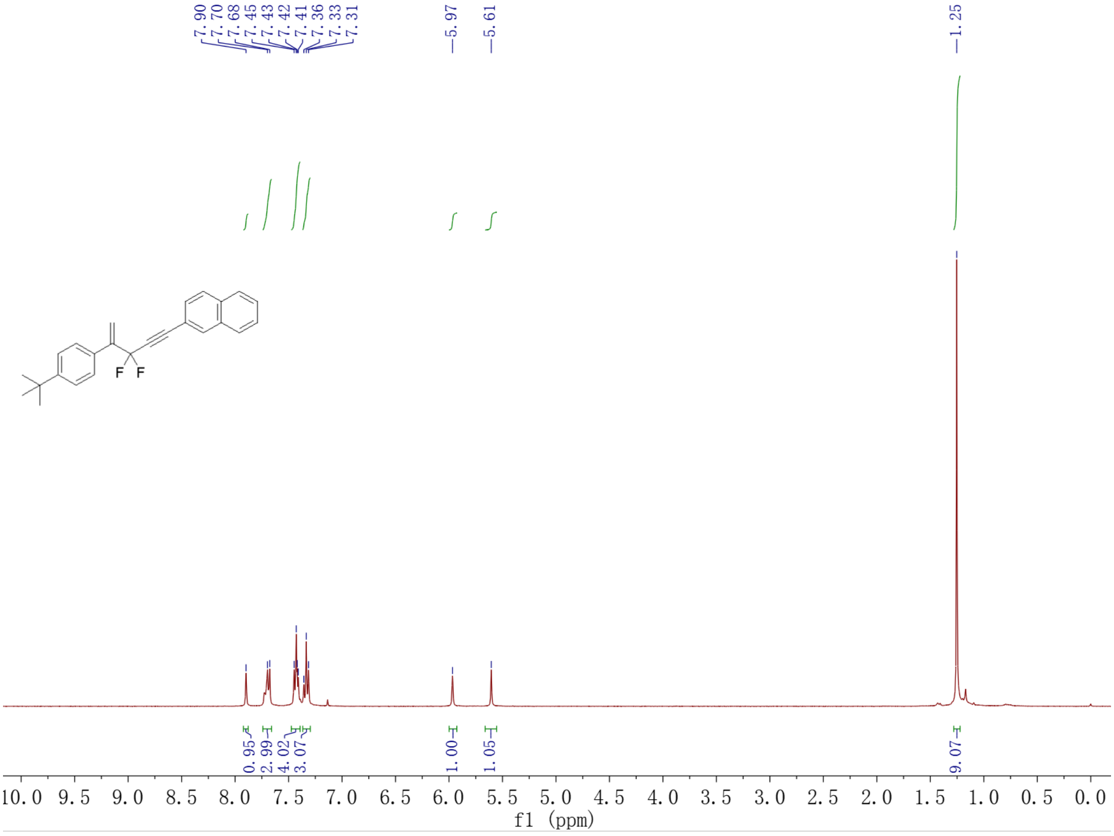

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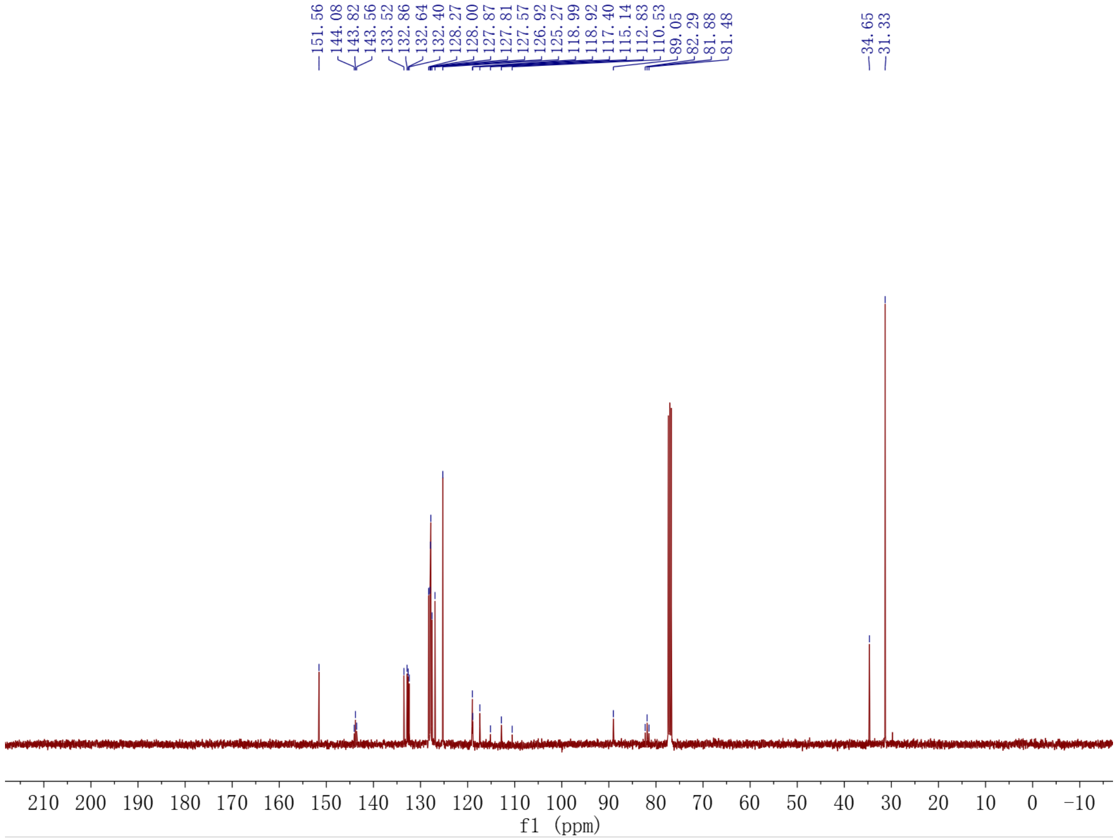
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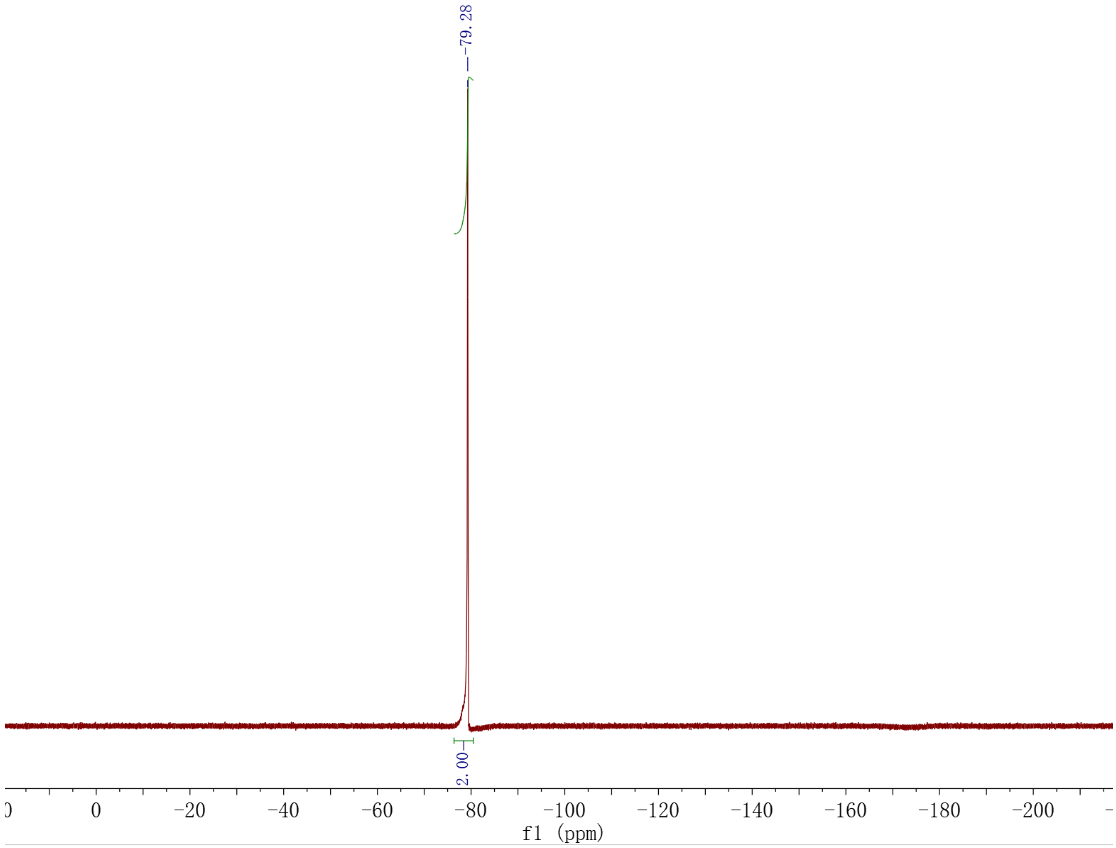
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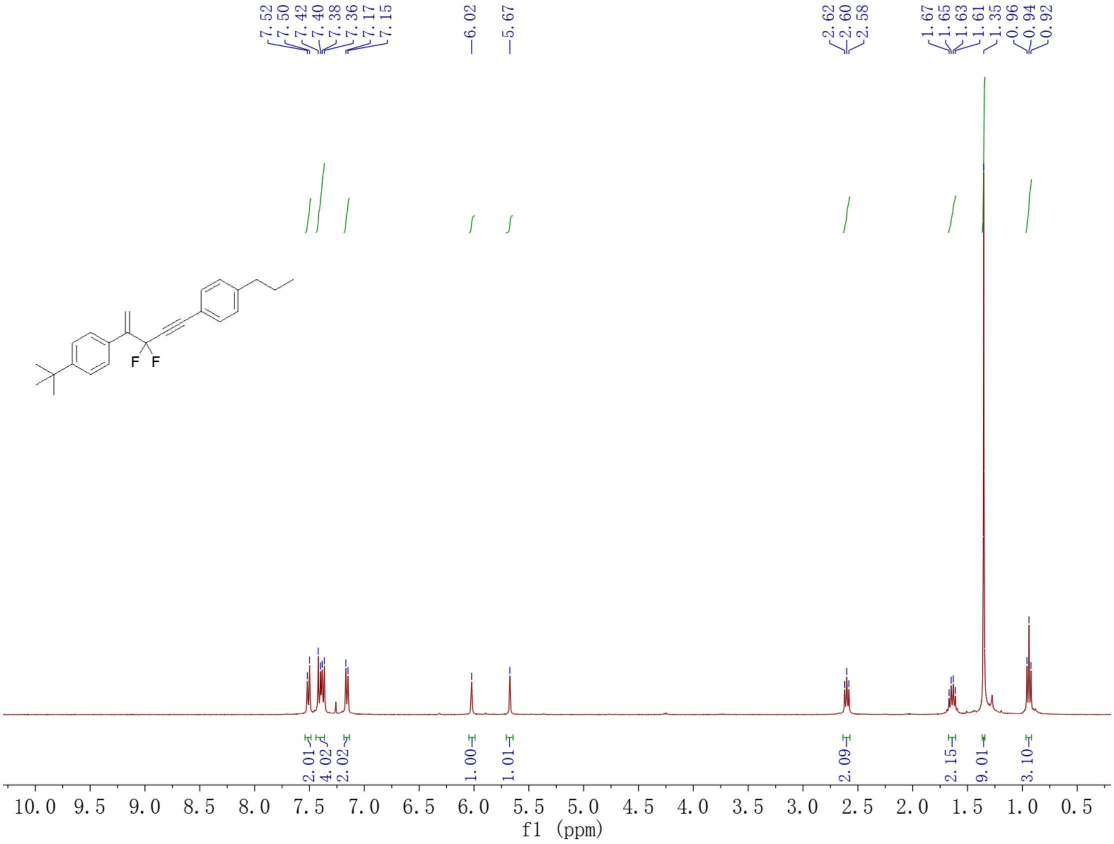
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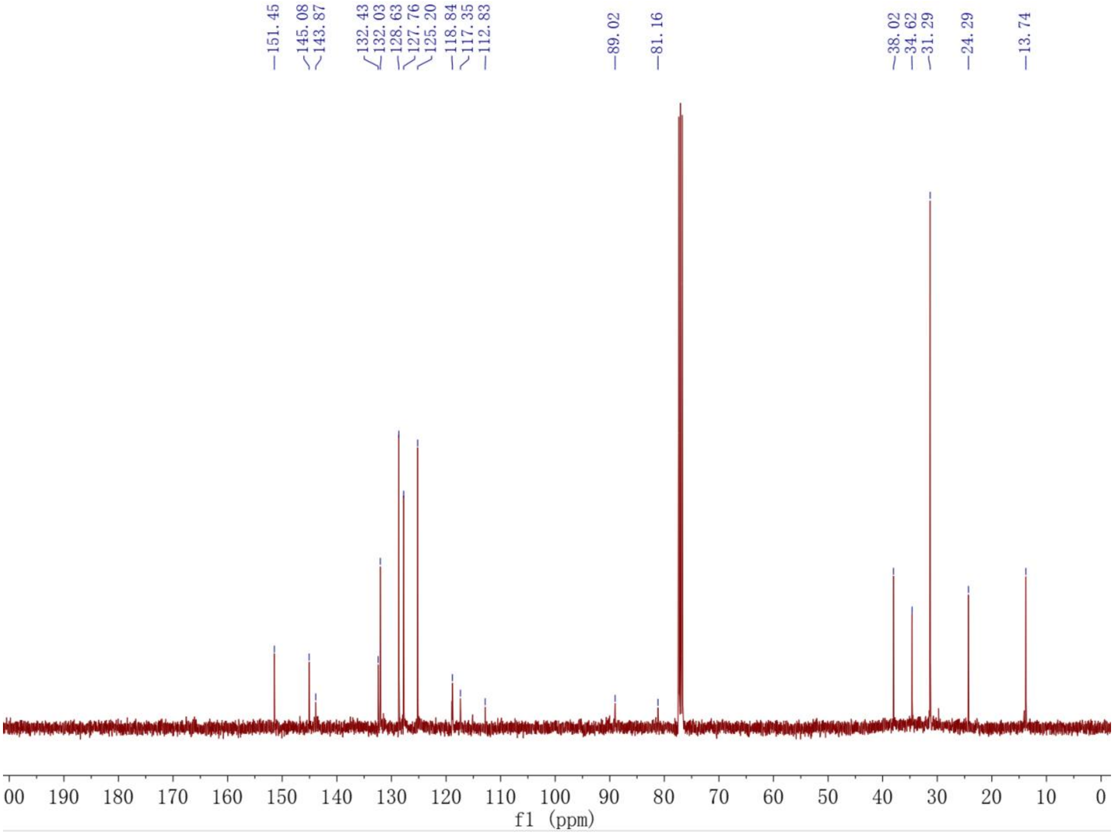
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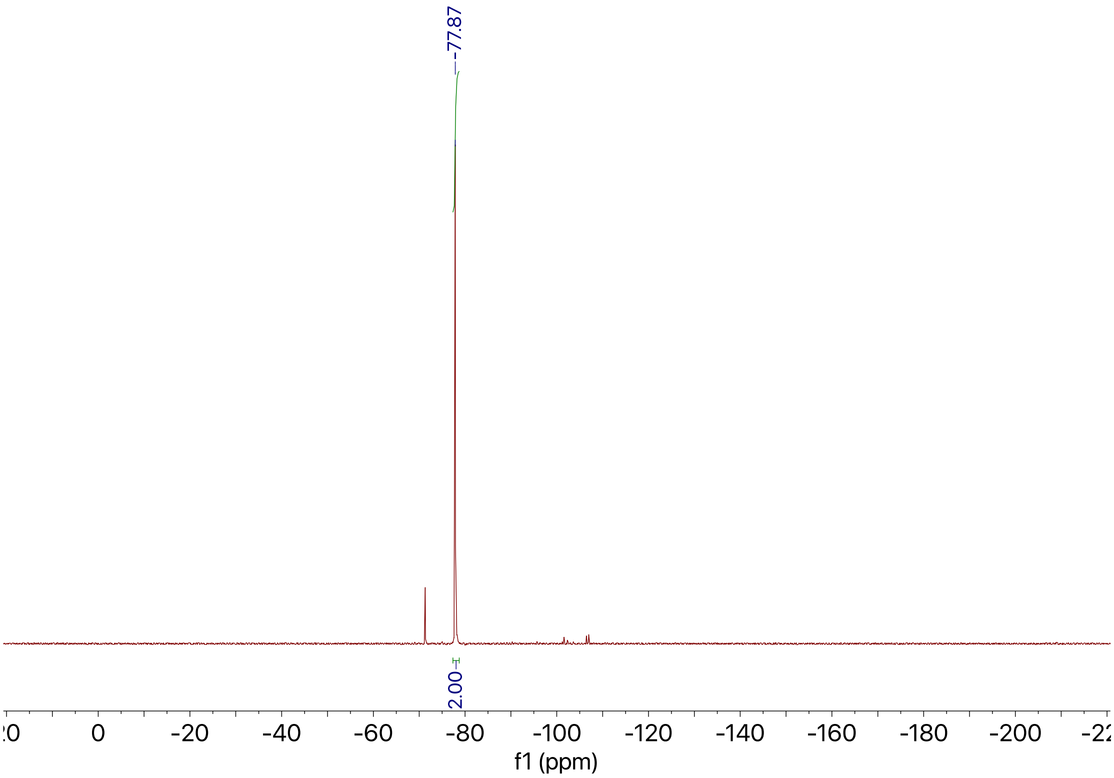
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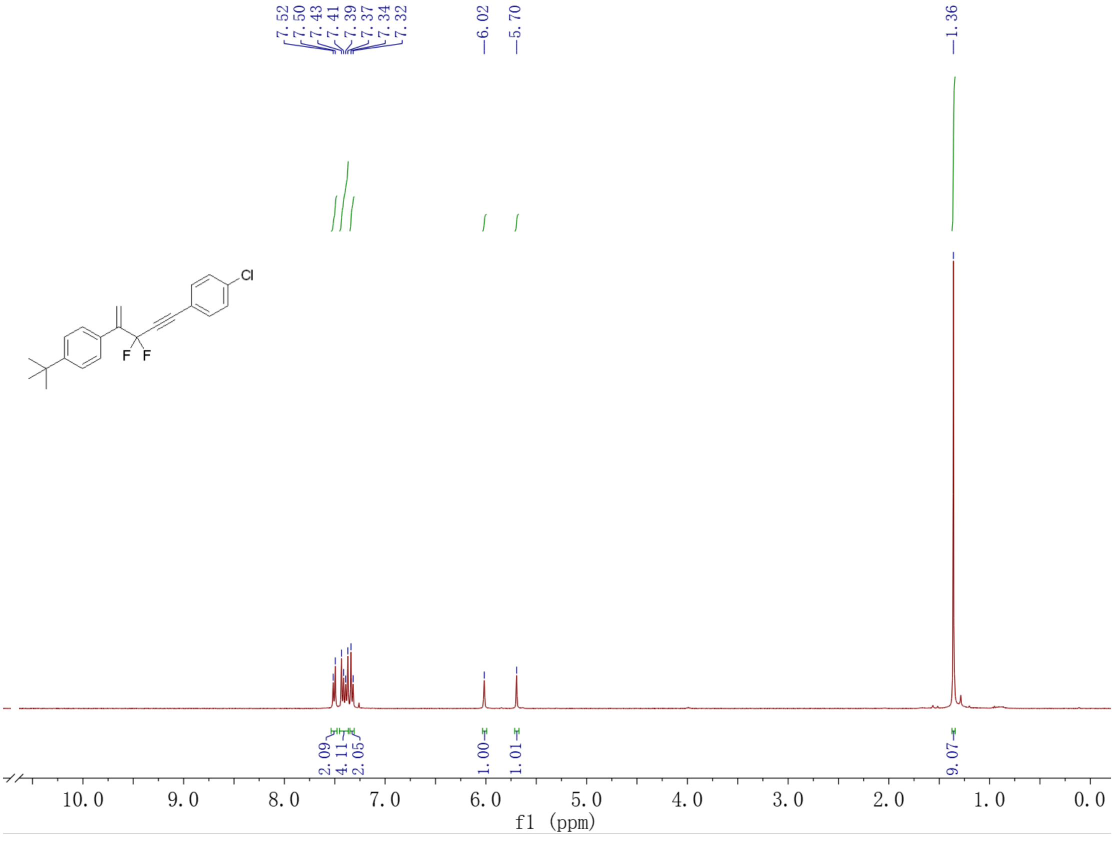
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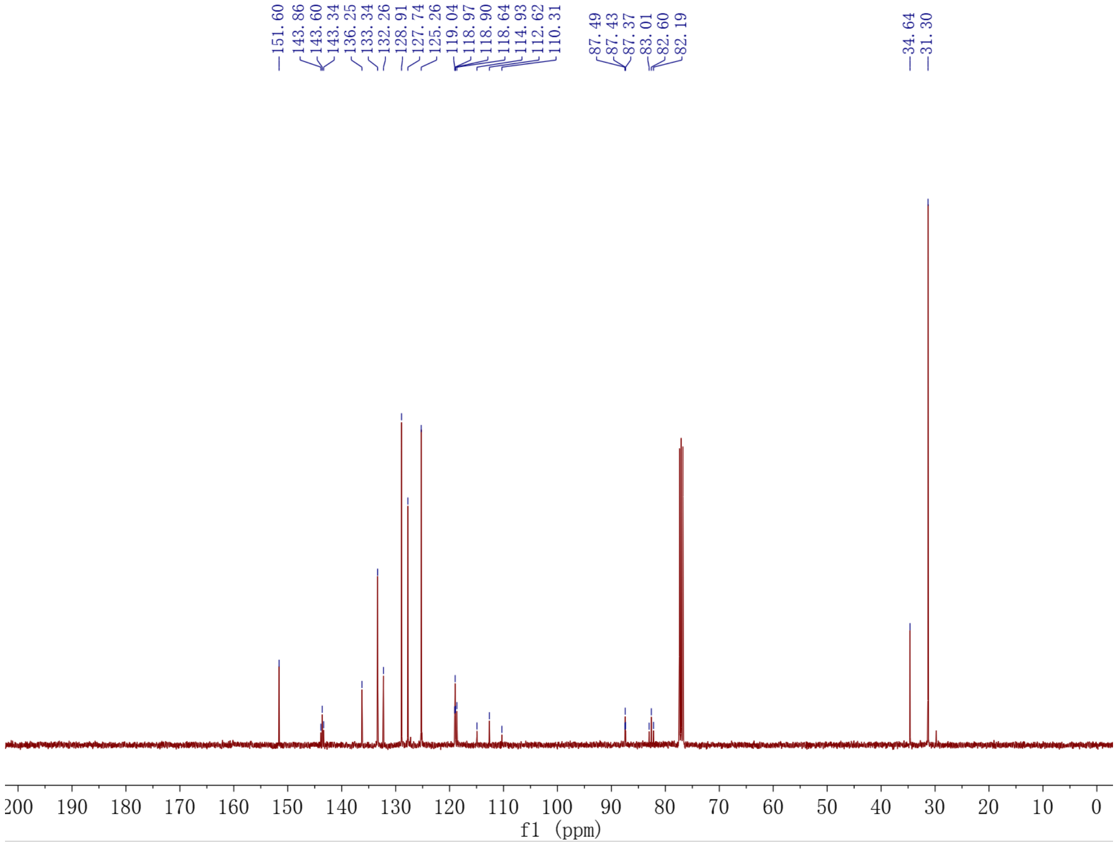
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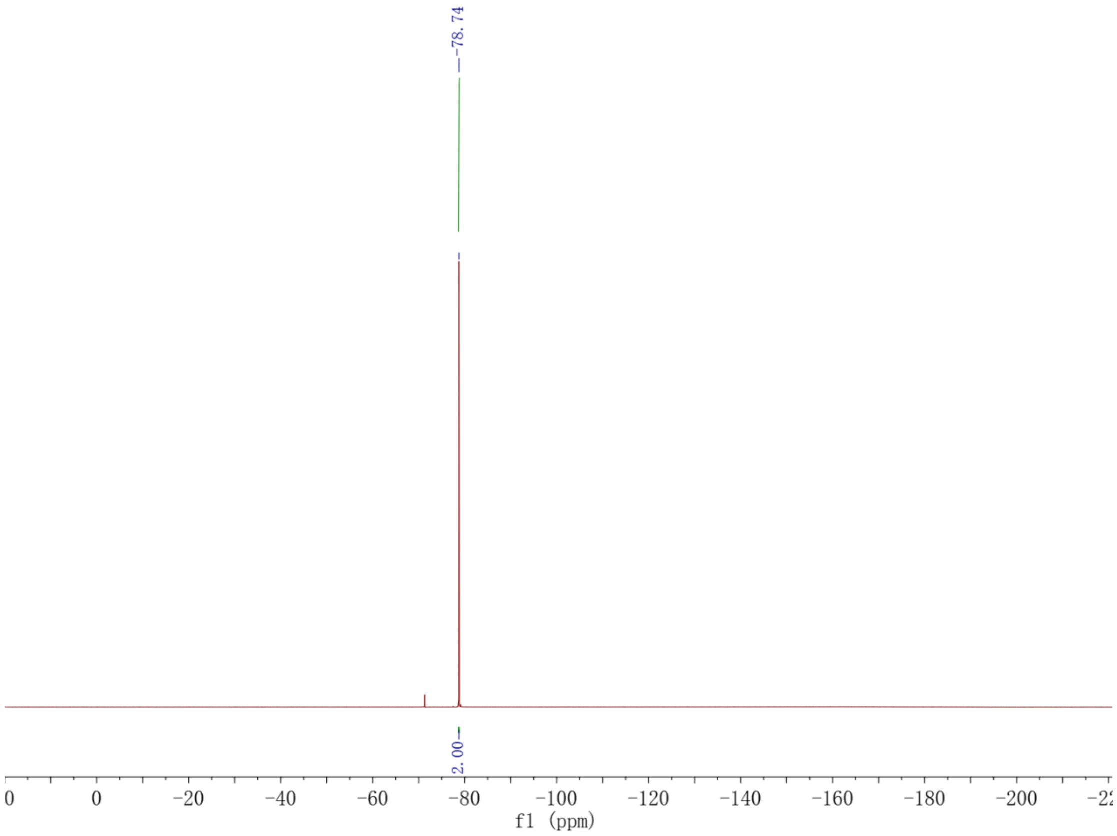
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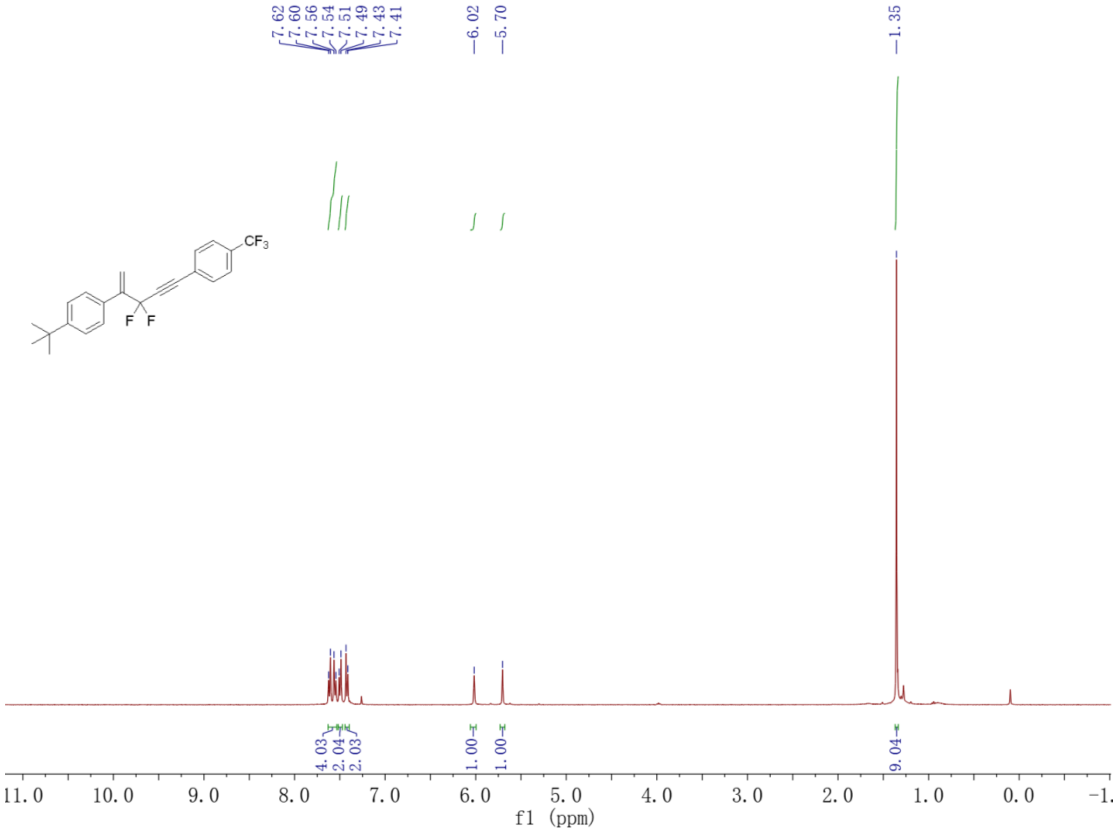
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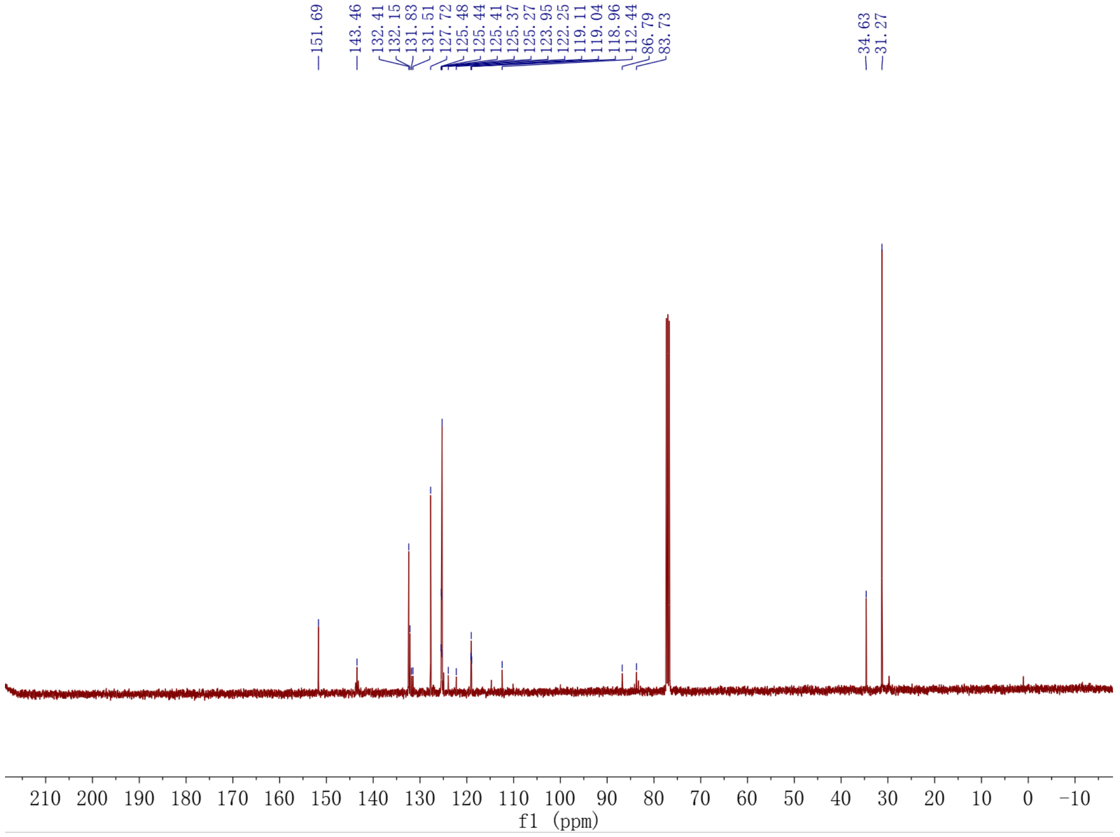
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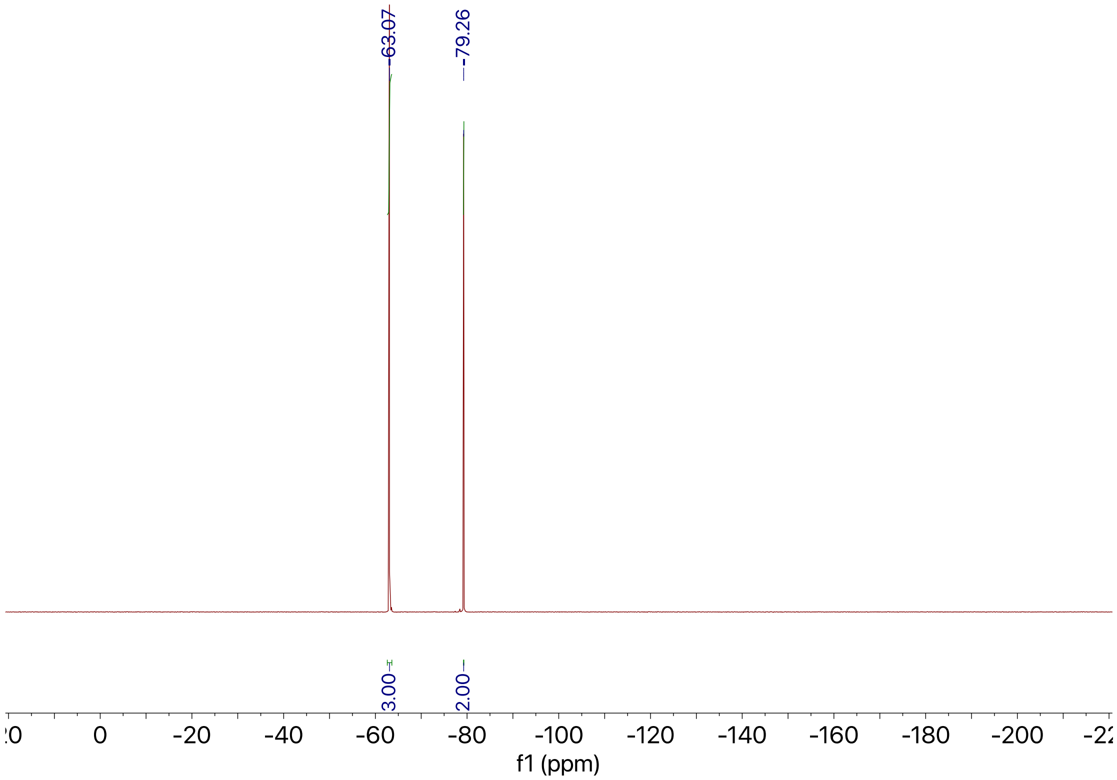
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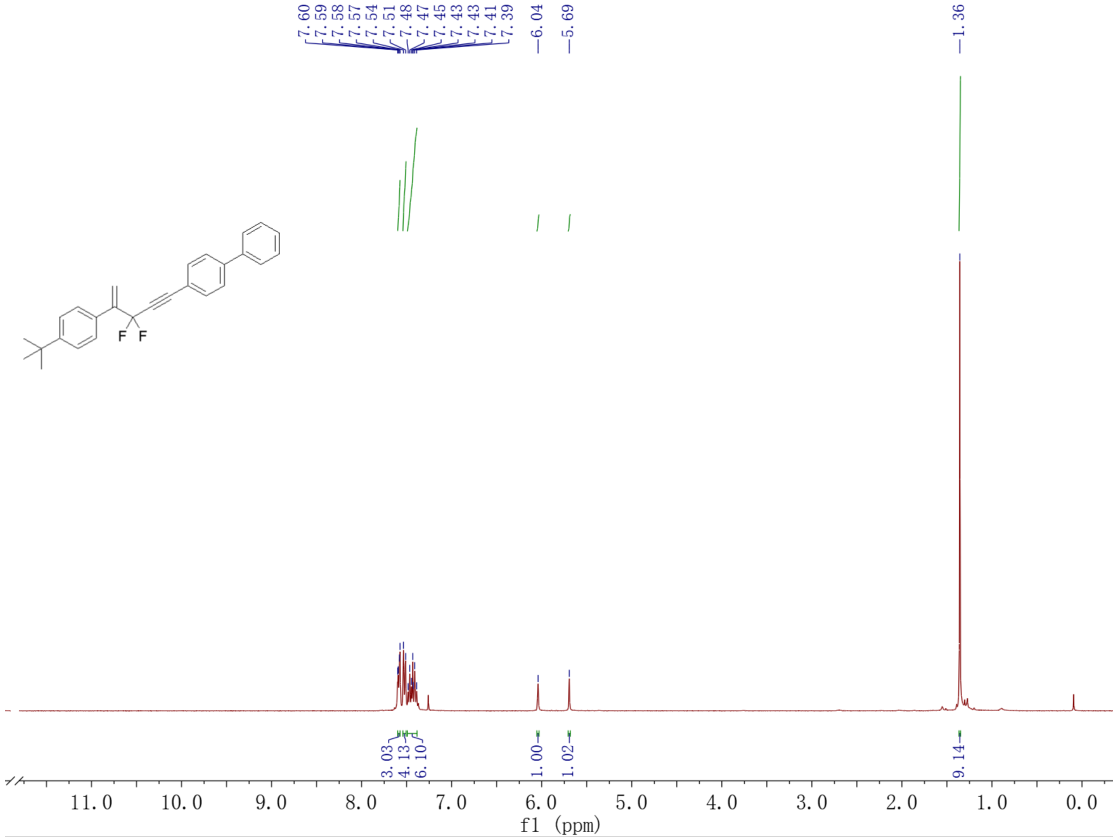
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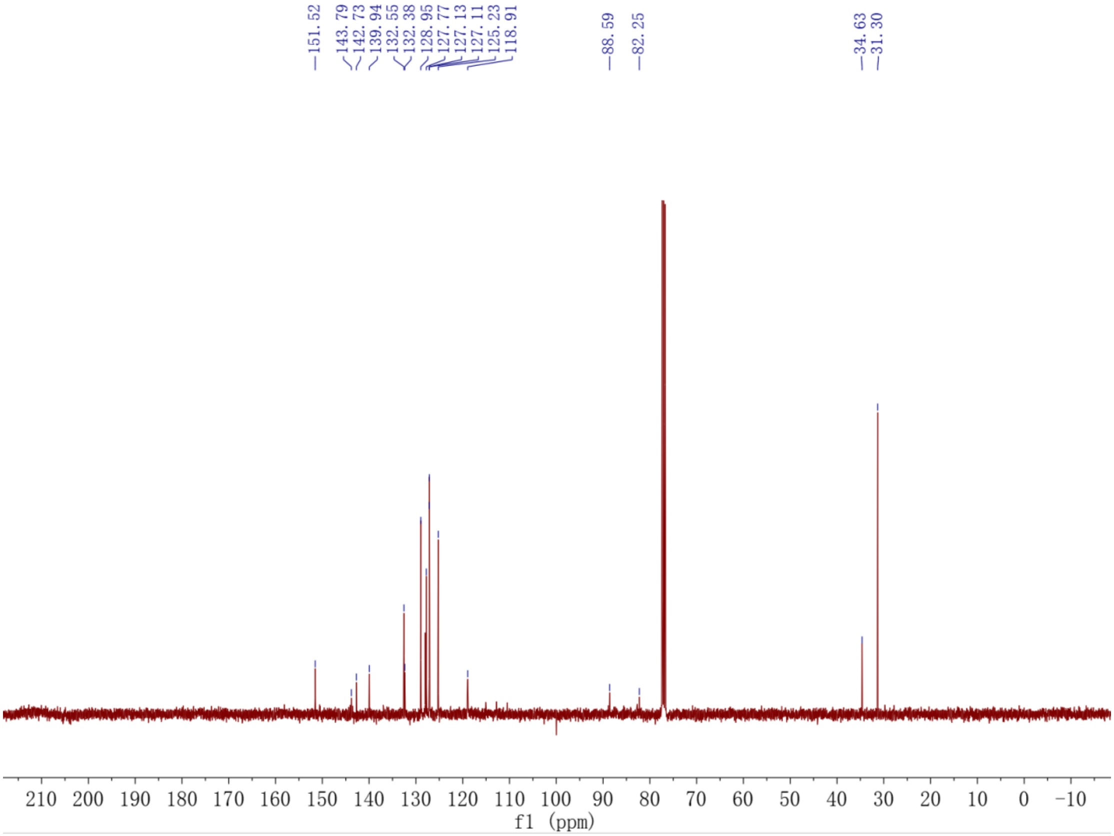

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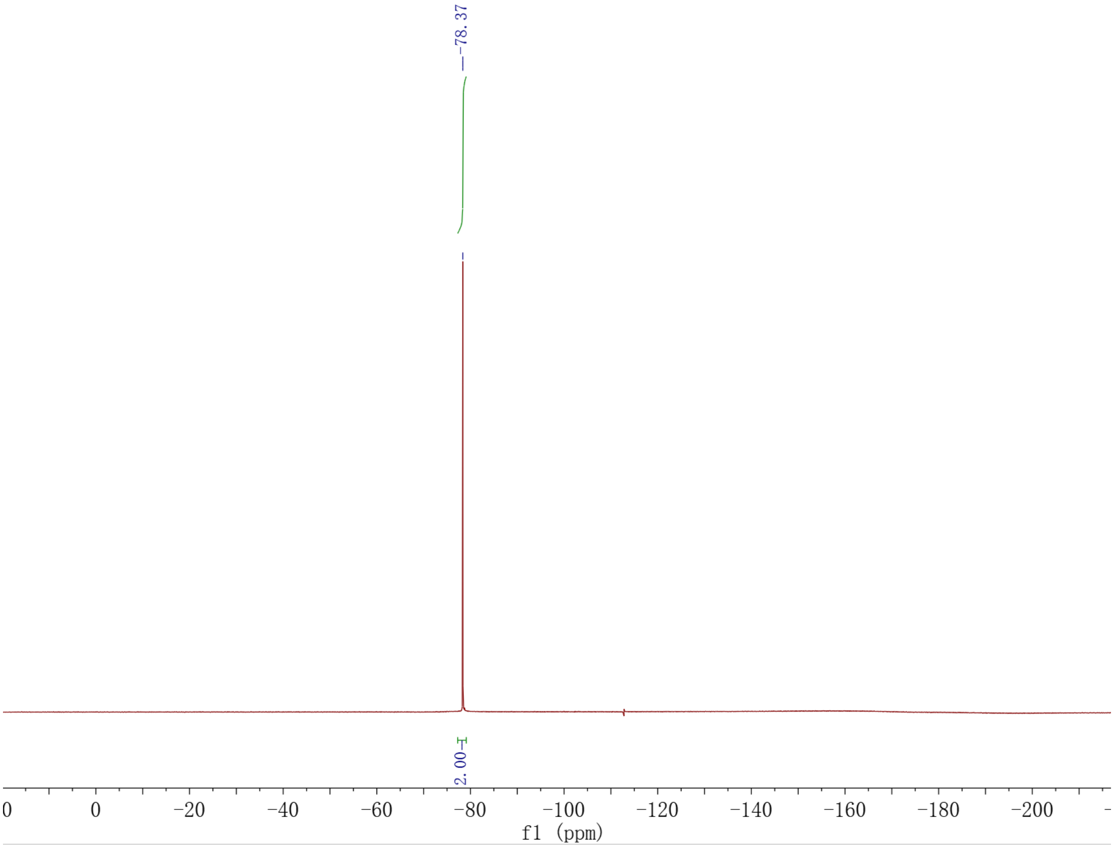

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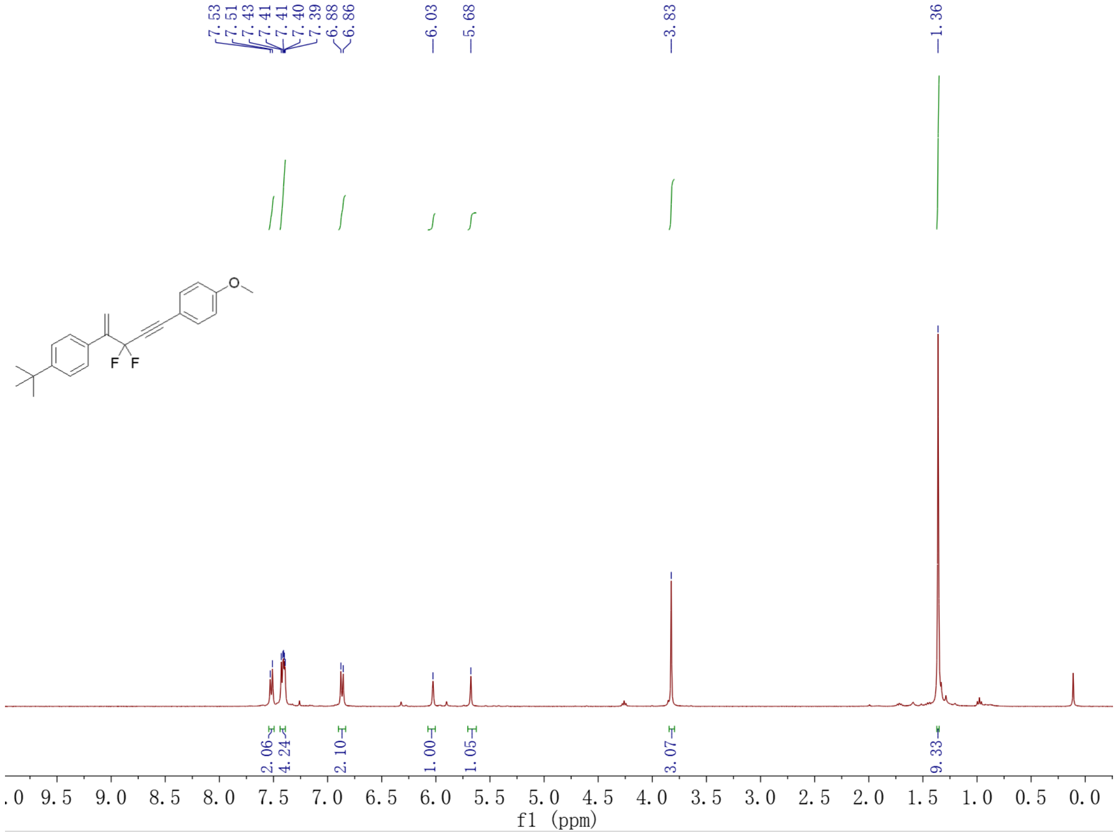
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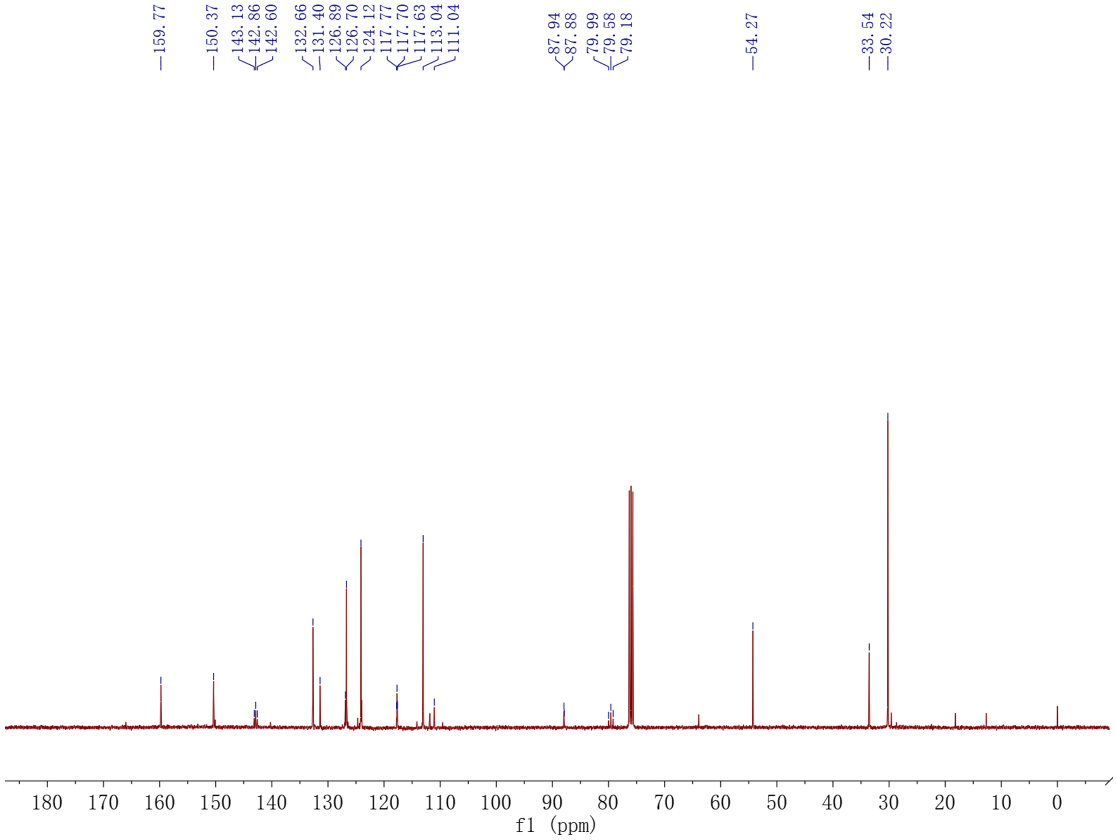
7.40
7.39
6.88
6.86
6.03
5.68
3.83
1.36
F
F
O
2.06
4.24
2.10
1.00
1.05
3.07
9.33
.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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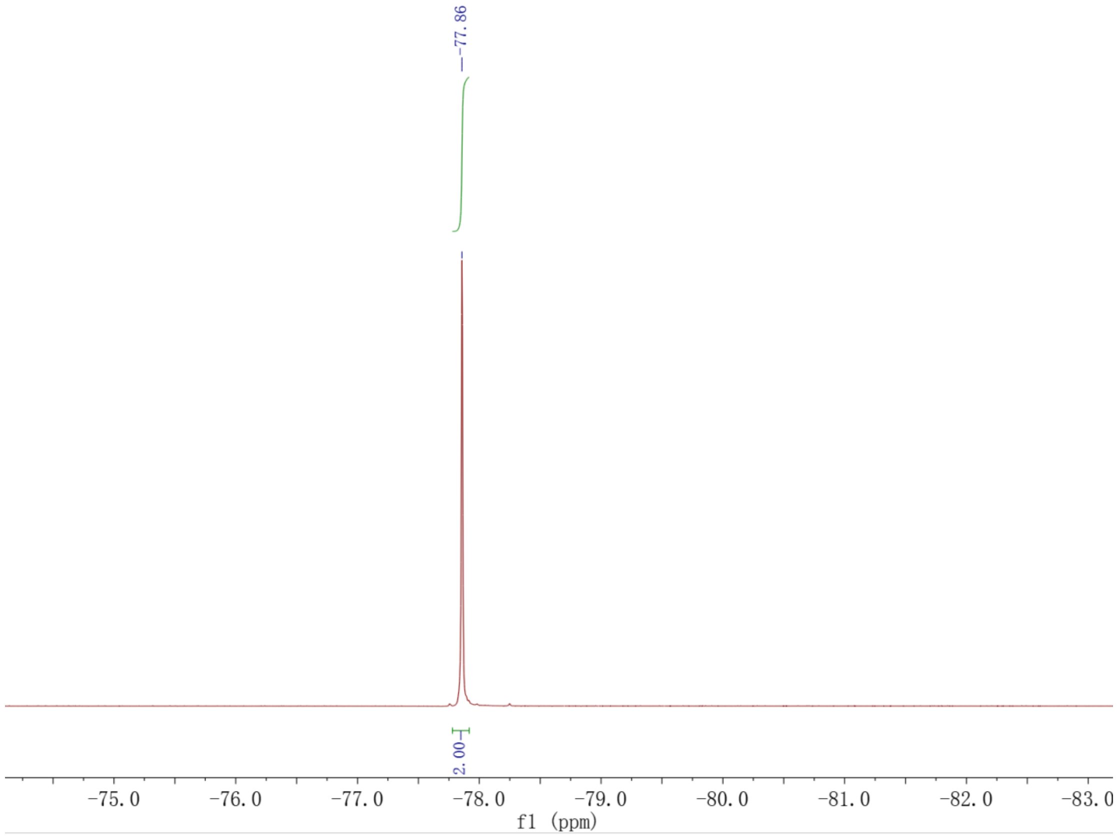
142.60
132.66
131.40
126.89
126.70
124.12
117.77
117.70
117.63
113.04
111.04
87.94
87.88
79.99
79.58
79.18
54.27
33.54
30.22
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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2.00
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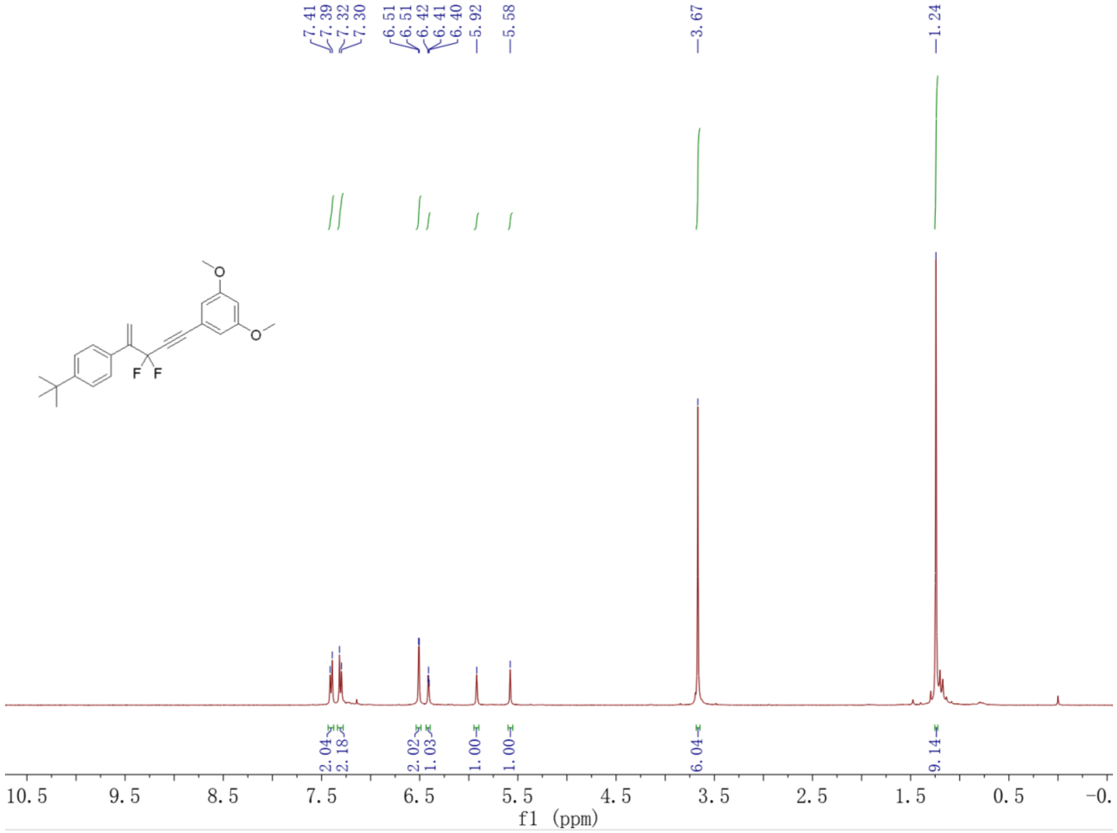
-76.0
-77.0
-78.0
-79.0
-80.0
-81.0
-82.0
-83.0
f1 (ppm)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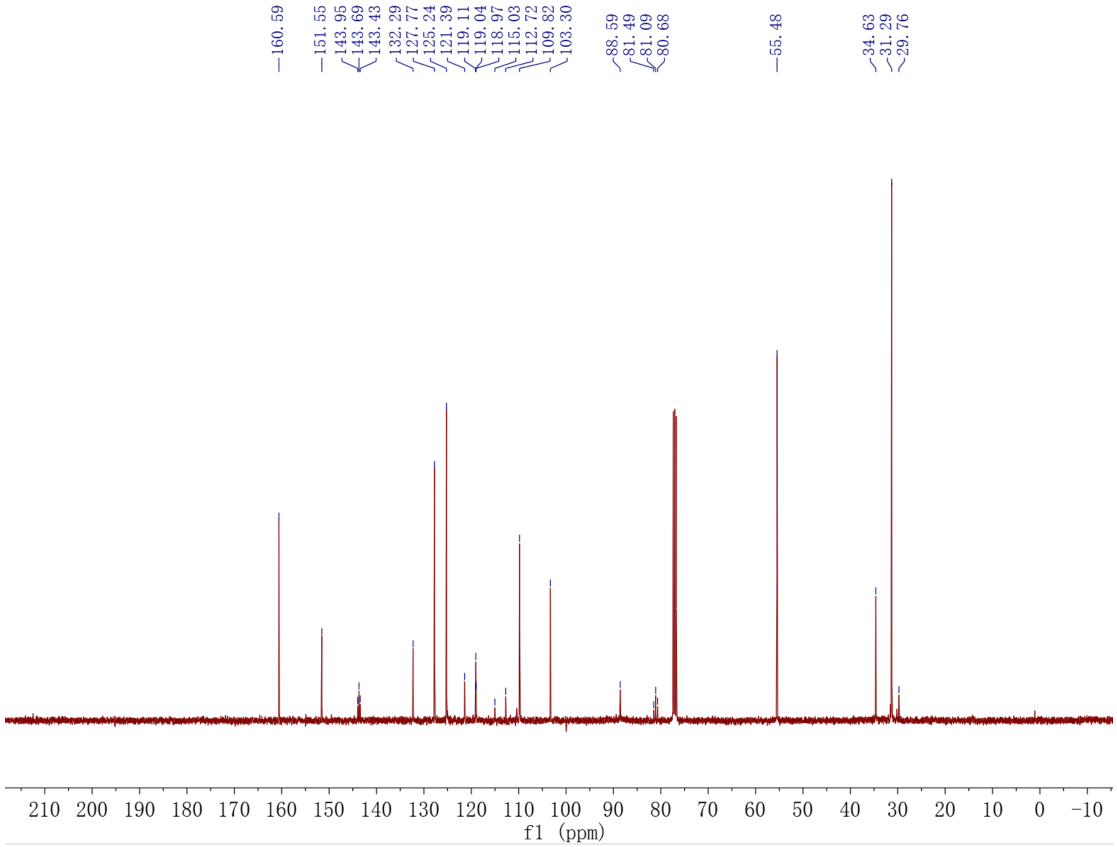
7.39
7.32
7.30
6.51
6.51
6.42
6.41
6.40
5.92
5.58
3.67
1.24
O
O
F
F
2.04
2.18
2.02
1.03
1.00
1.00
6.04
9.14
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.
f1 (ppm)


160.59
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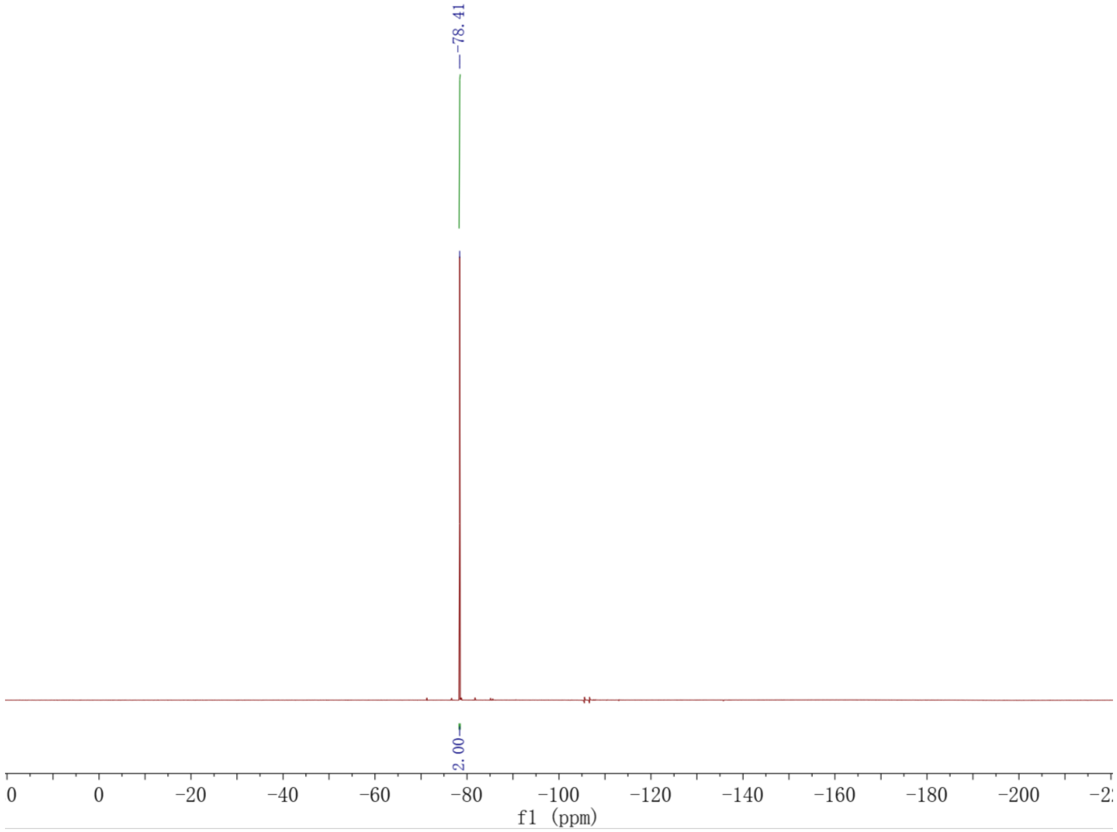
143.43
132.29
127.77
125.24
121.39
119.11
119.04
118.97
115.03
112.72
109.82
103.30
88.59
81.49
81.09
80.68
55.48
34.63
31.29
29.76
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


−78.41
2.00
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−20
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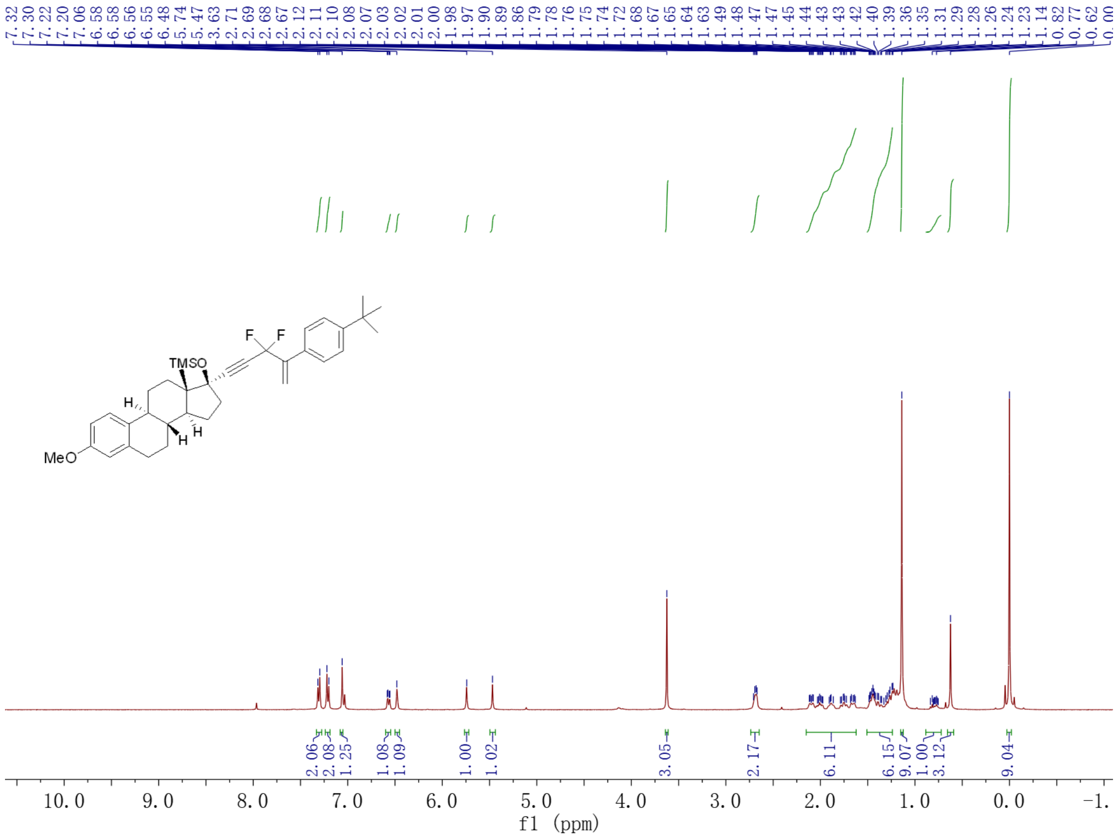
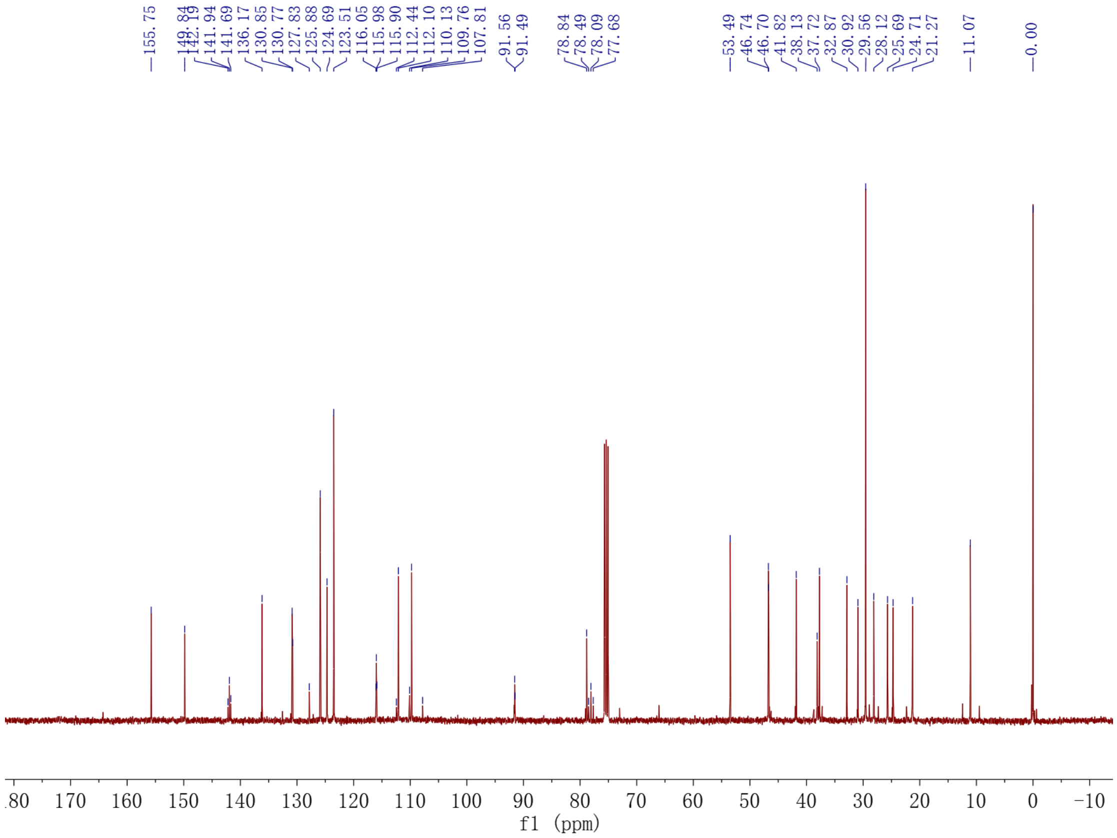
−60
−80
−100
−120
−140
−160
−180
−200
−2
f1 (ppm)


7.32
7.30
7.22
7.20
7.06
6.58
6.58
6.56
6.55
6.48
5.74
5.47
3.63
2.71
2.69
2.68
2.67
2.12
2.11
2.10
2.08
2.07
2.03
2.02
2.01
2.00
1.98
1.97
1.90
1.89
1.86
1.79
1.78
1.76
1.75
1.74
1.72
1.68
1.67
1.65
1.64
1.63
1.49
1.48
1.47
1.45
1.44
1.43
1.43
1.42
1.40
1.39
1.36
1.35
1.31
1.29
1.28
1.26
1.24
1.23
1.14
0.82
0.77
0.62
0.00
F
F
TMSO
H
H
H
MeO
2.06
2.08
1.25
1.08
1.09
1.00
1.02
3.05
2.17
6.11
6.15
9.07
1.00
3.12
9.04
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.
f1 (ppm)


155.75
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130.77
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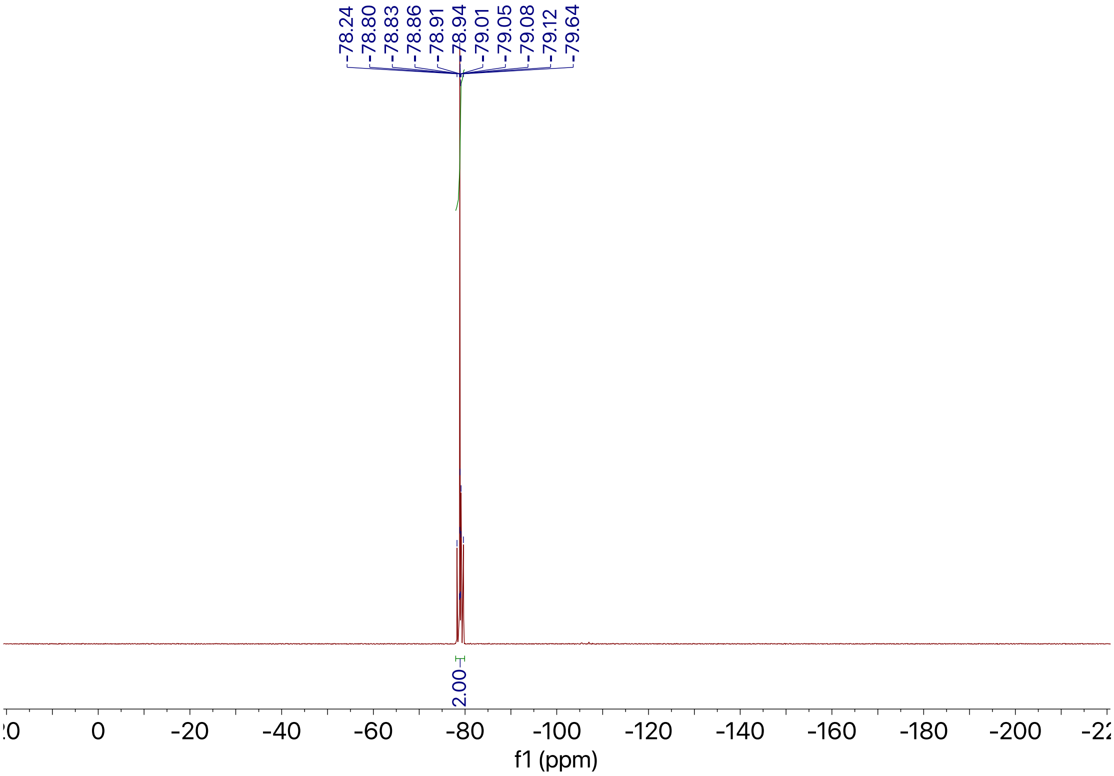
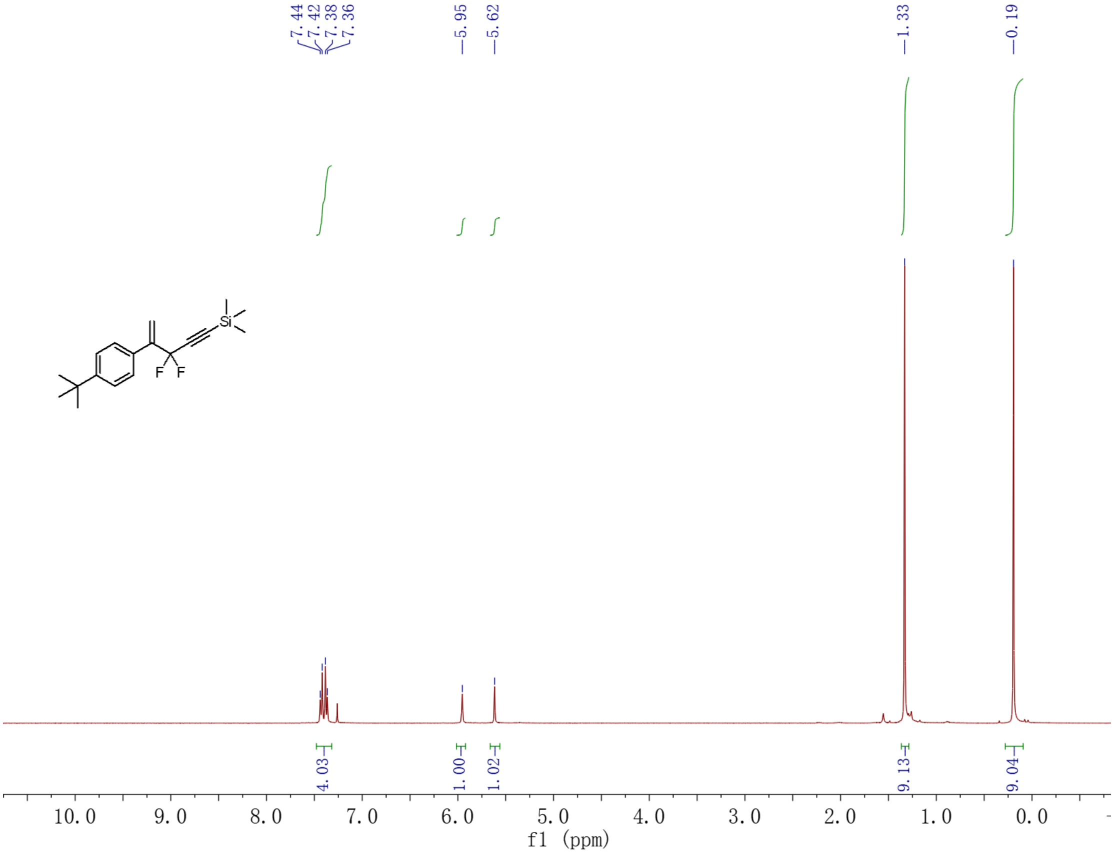
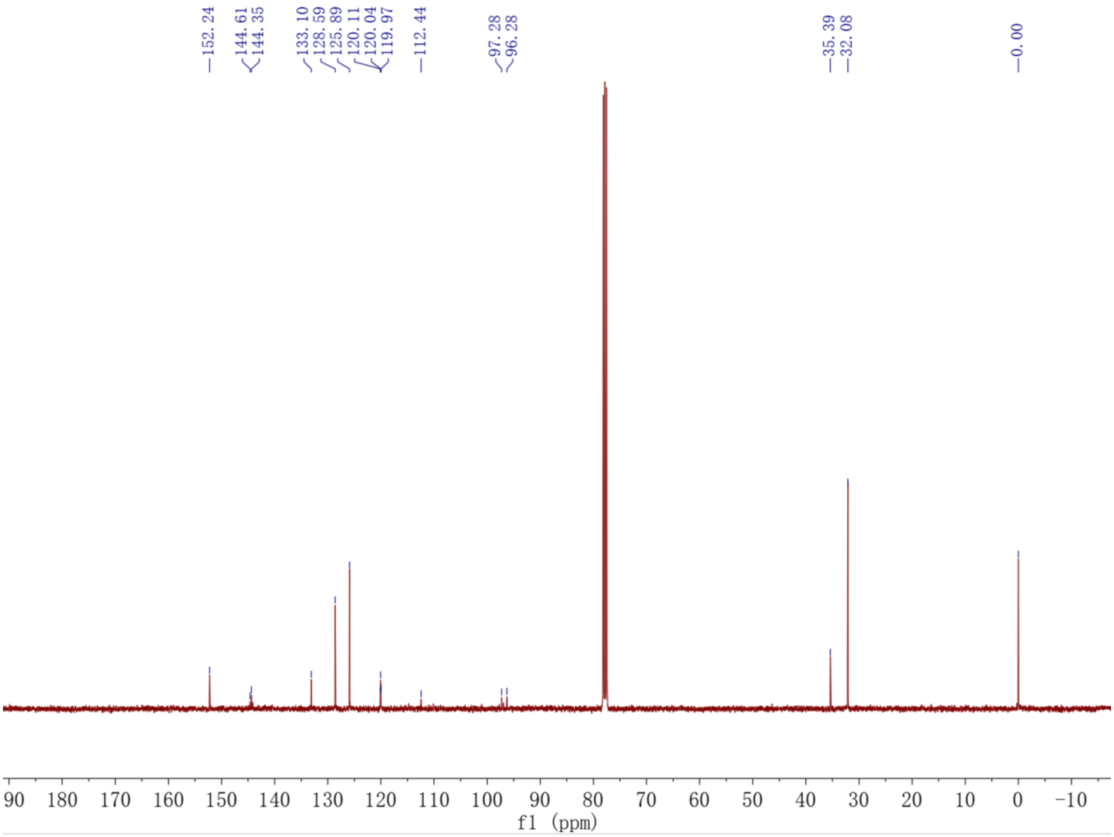
125.88
124.69
123.51
116.05
115.98
115.90
112.44
112.10
110.13
109.76
107.81
91.56
91.49
78.84
78.49
78.09
77.68
53.49
46.74
46.70
41.82
38.13
37.72
32.87
30.92
29.56
28.12
25.69
24.71
21.27
11.07
-0.00
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-78.24
-78.80
-78.83
-78.86
-78.91
-78.94
-79.01
-79.05
-79.08
-79.12
-79.64
2.00
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)


7.44
7.42
7.38
7.36
5.95
5.62
1.33
0.19
Si
F
F
4.03
1.00
1.02
9.13
9.04
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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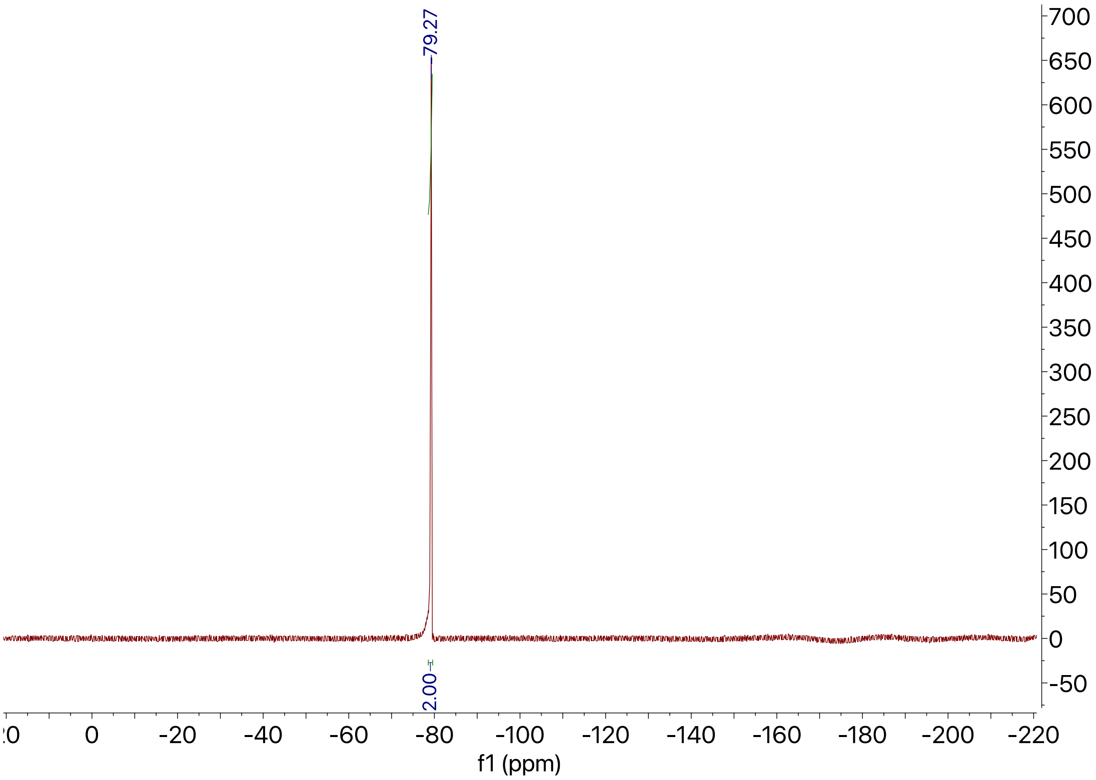
144.61
144.35
133.10
128.59
125.89
120.11
120.04
119.97
112.44
97.28
96.28
35.39
32.08
0.00
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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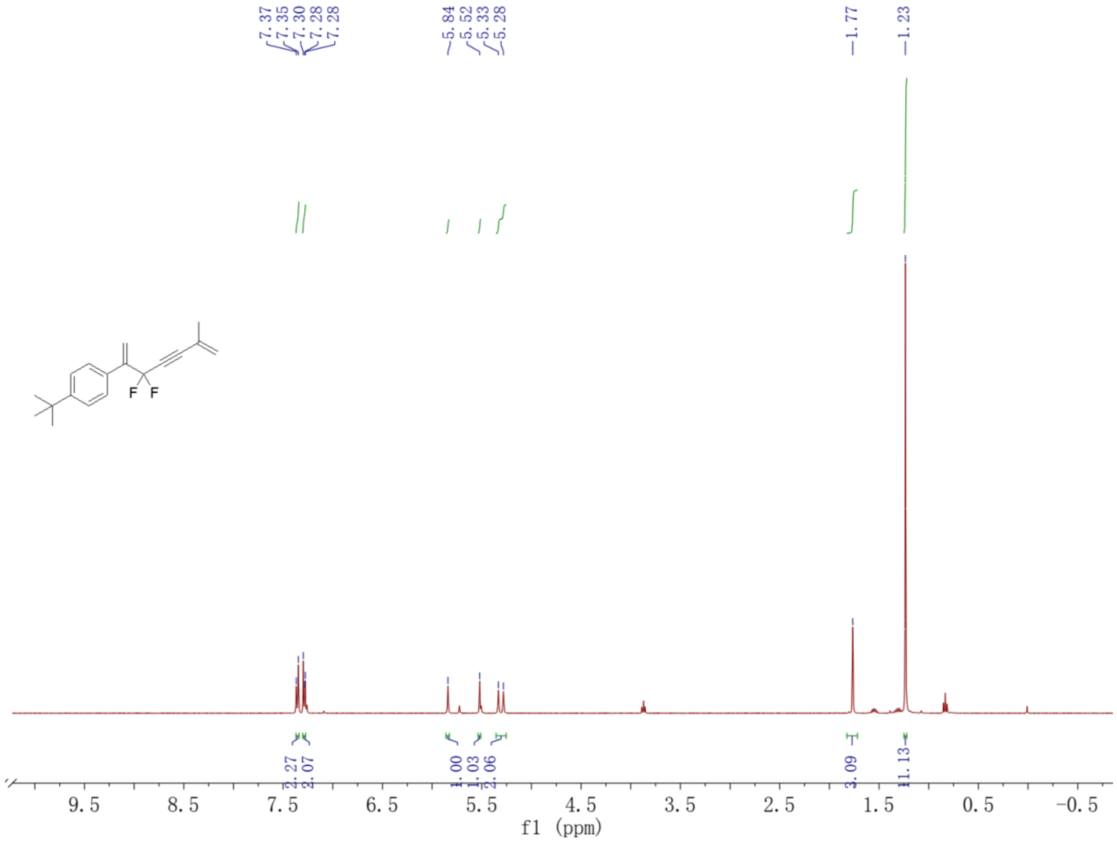
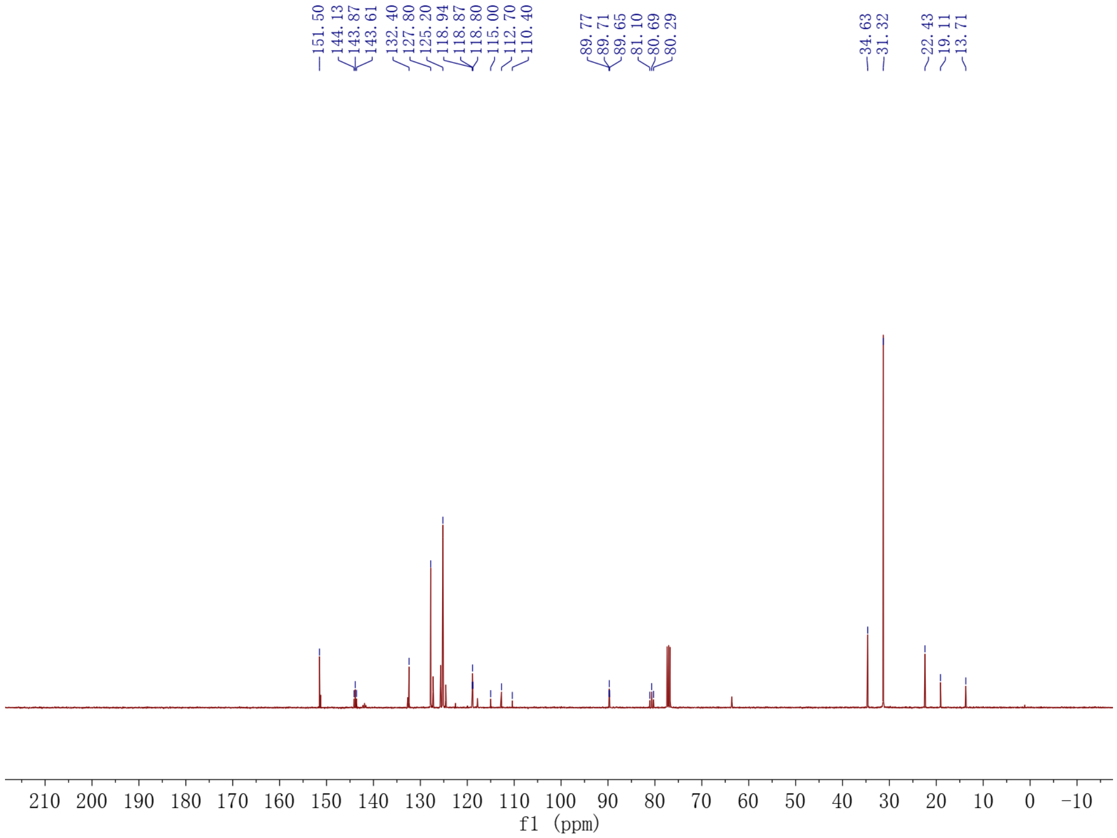
2.00
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)



7.37
7.35
7.30
7.28
7.28
5.84
5.52
5.33
5.28
1.77
1.23
F
F
2.27
2.07
1.00
1.03
2.06
3.09
11.13
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)



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144.13
143.87
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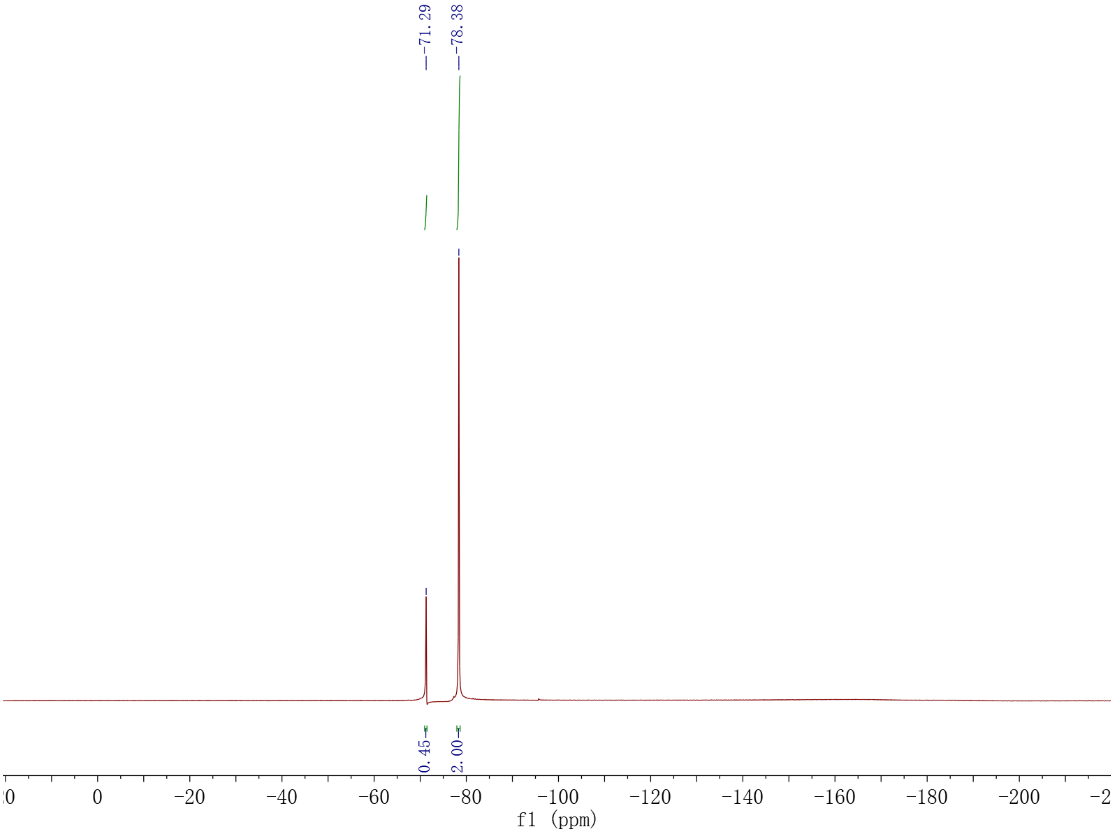
127.80
125.20
118.94
118.87
118.80
115.00
112.70
110.40
89.77
89.71
89.65
81.10
80.69
80.29
34.63
31.32
22.43
19.11
13.71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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-78.38
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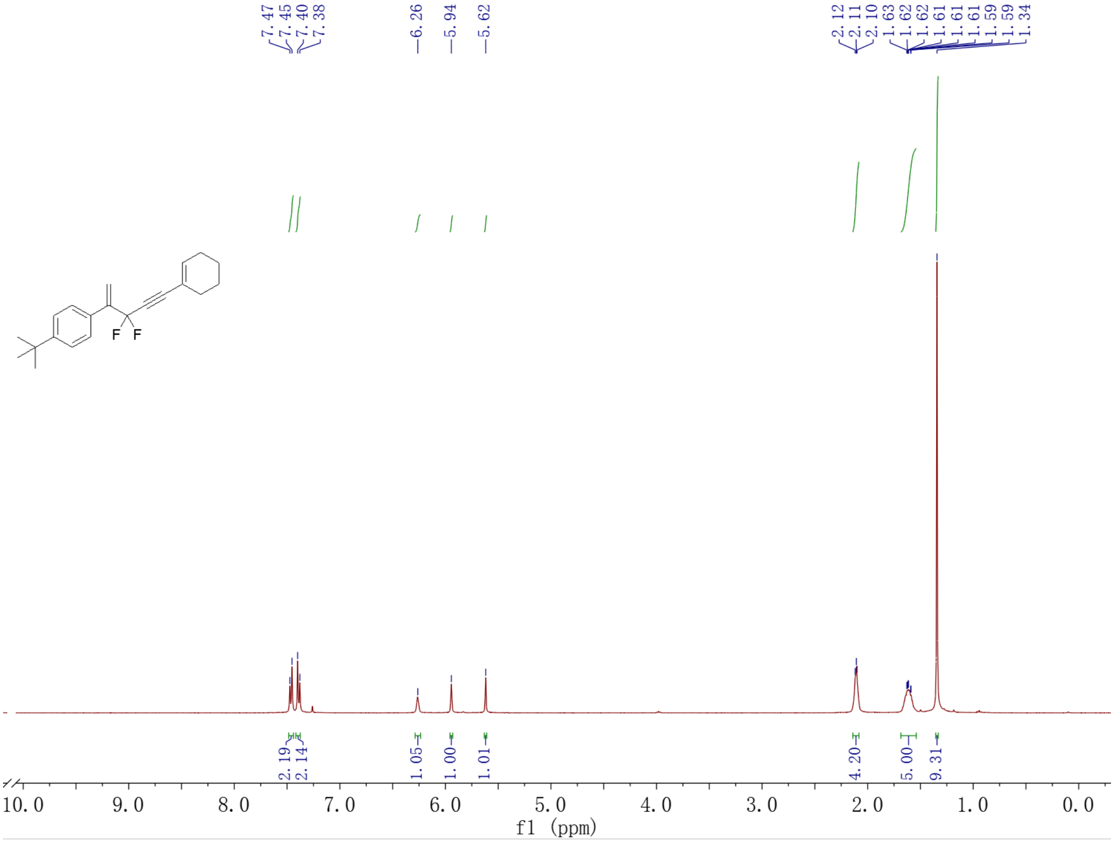
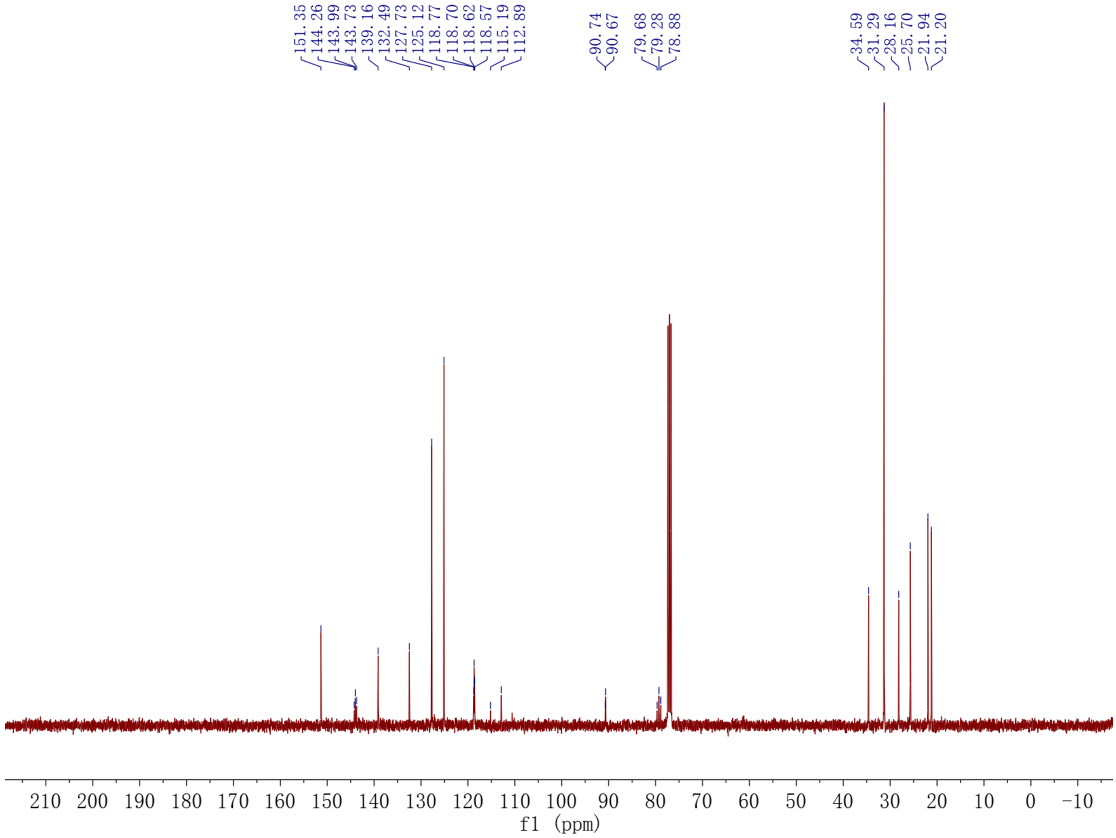
2.00
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)


7.47
7.45
7.40
7.38
6.26
5.94
5.62
2.12
2.11
2.10
1.63
1.62
1.62
1.61
1.61
1.61
1.59
1.59
1.34
F
F
2.19
2.14
1.05
1.00
1.01
4.20
5.00
9.31
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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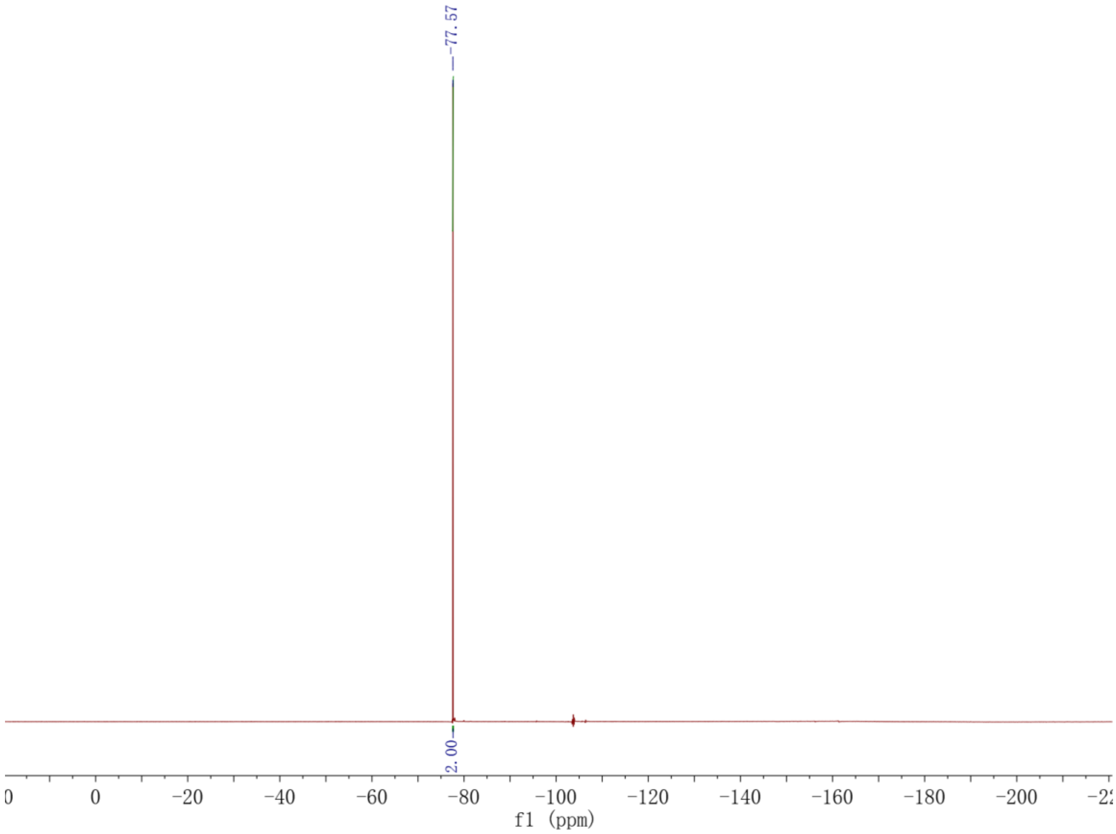
125.12
118.77
118.70
118.62
118.57
115.19
112.89
90.74
90.67
79.68
79.28
78.88
34.59
31.29
28.16
25.70
21.94
21.20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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−60
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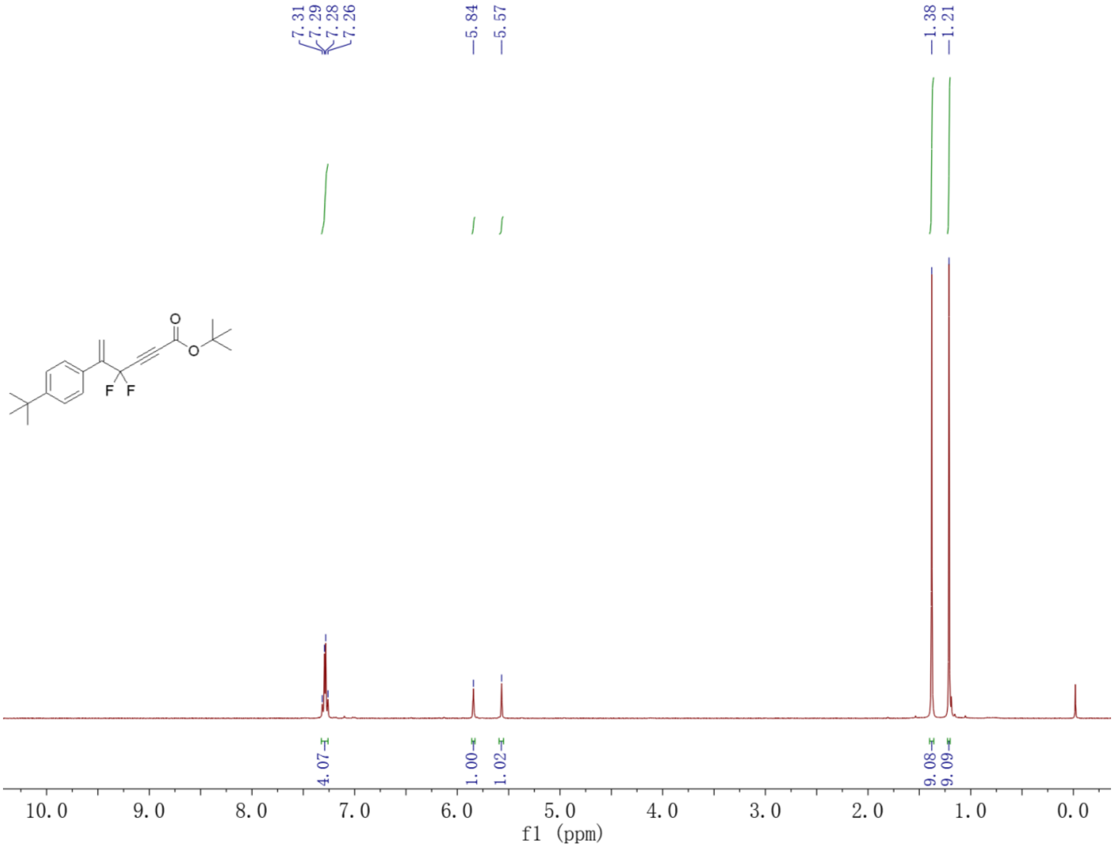
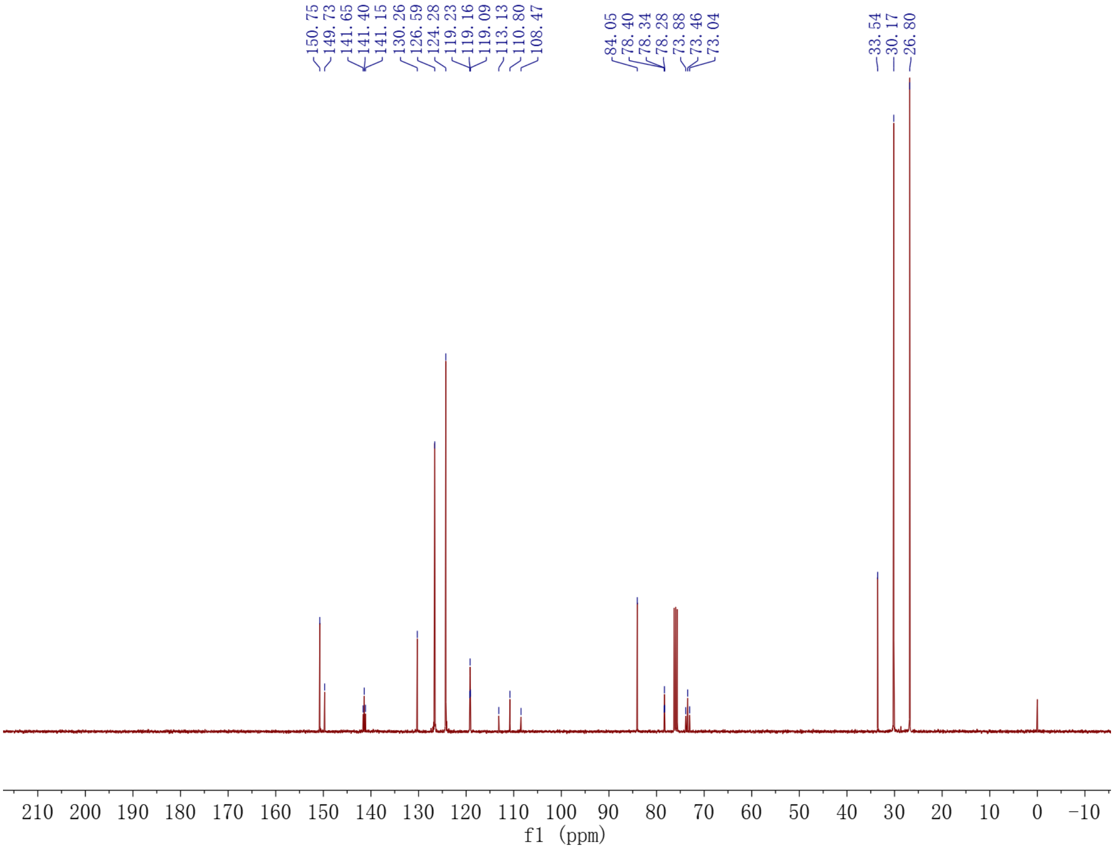
−200
f1 (ppm)


7.31
7.29
7.28
7.26
5.84
5.57
1.38
1.21
F
F
O
O
4.07
1.00
1.02
9.08
9.09
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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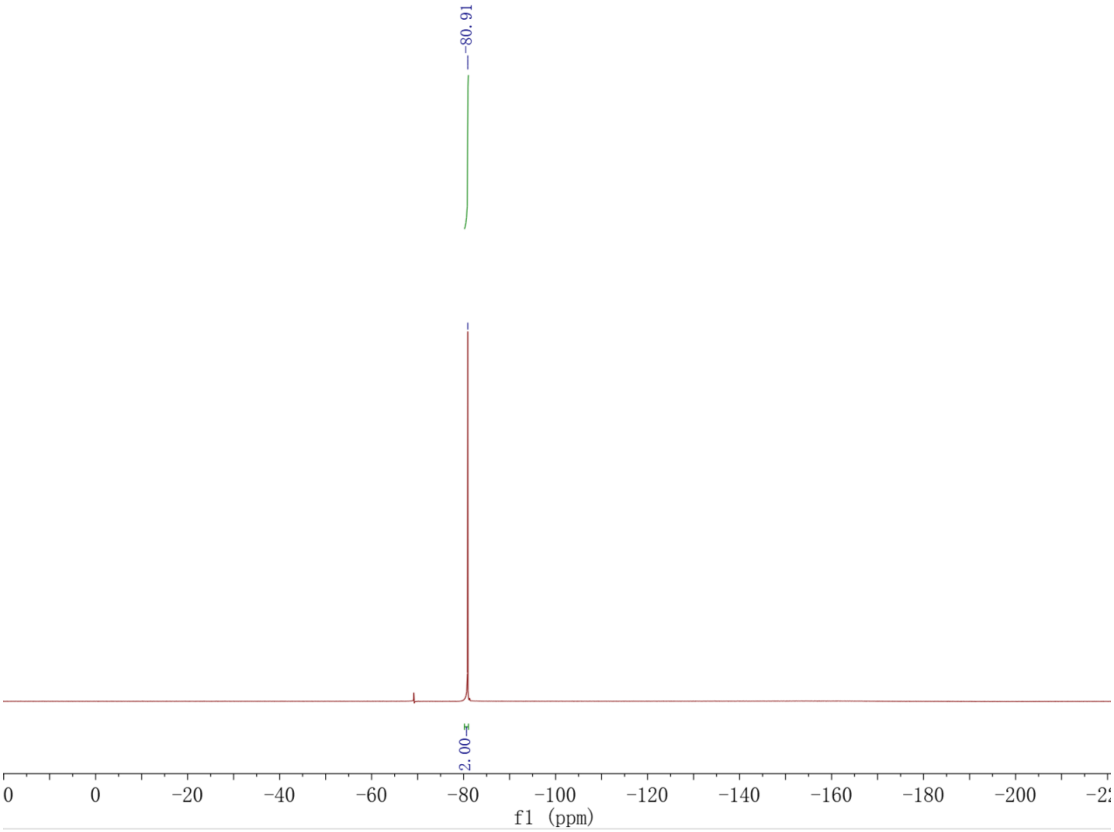
141.40
141.15
130.26
126.59
124.28
119.23
119.16
119.09
113.13
110.80
108.47
84.05
78.40
78.34
78.28
73.88
73.46
73.04
33.54
30.17
26.80
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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-20
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-80
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-120
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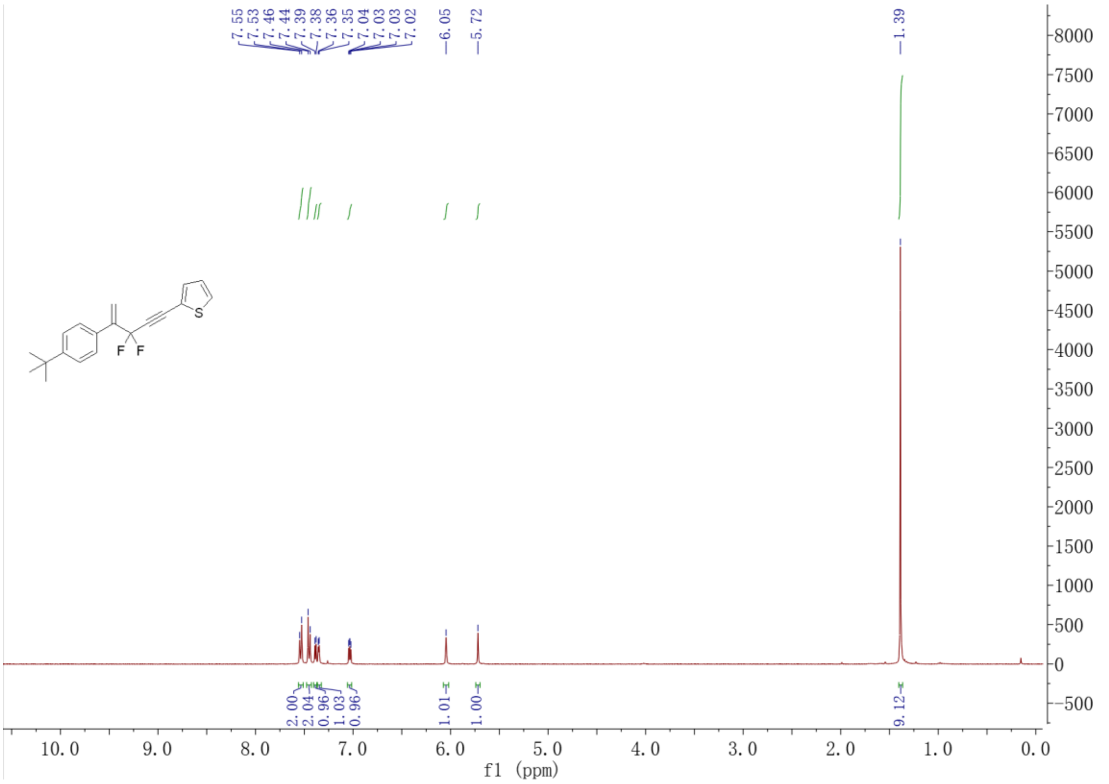
-160
-180
-200
-2
f1 (ppm)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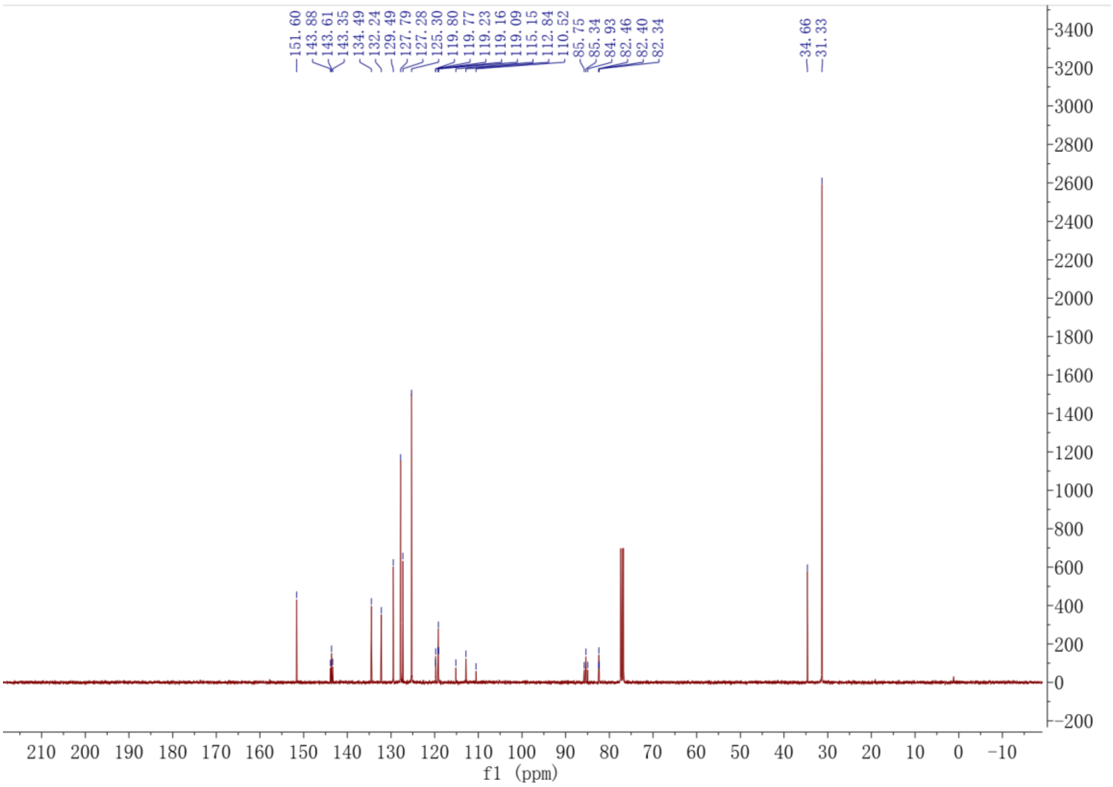
7.44
7.39
7.38
7.36
7.35
7.04
7.03
7.03
7.02
6.05
5.72
1.39
F
F
S
2.00
2.04
0.96
1.03
0.96
1.01
1.00
9.12
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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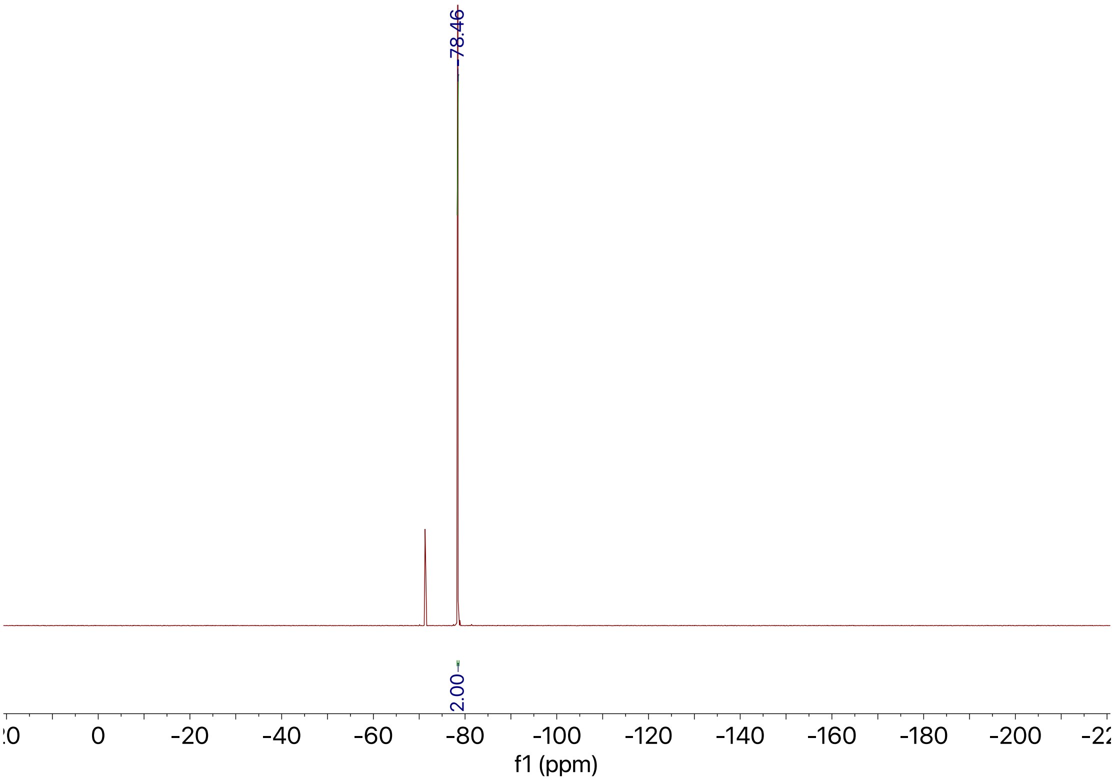
125.30
119.80
119.77
119.23
119.16
119.09
115.15
112.84
110.52
85.75
85.34
84.93
82.46
82.40
82.34
34.66
31.33
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)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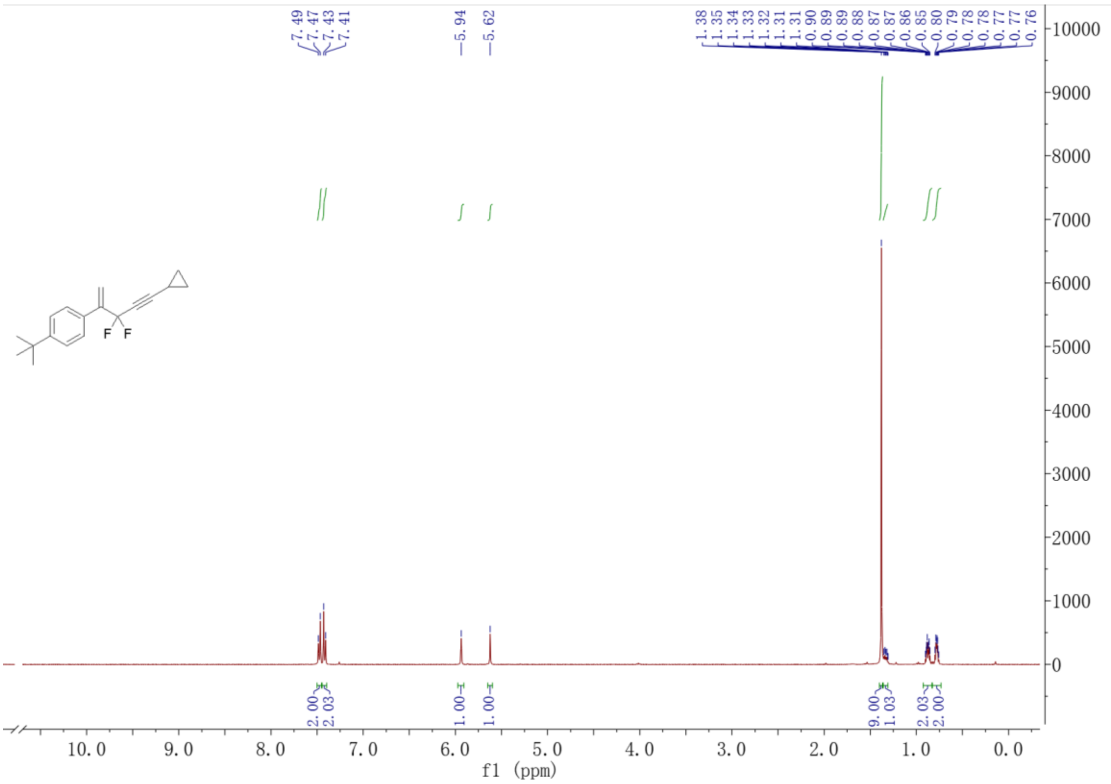
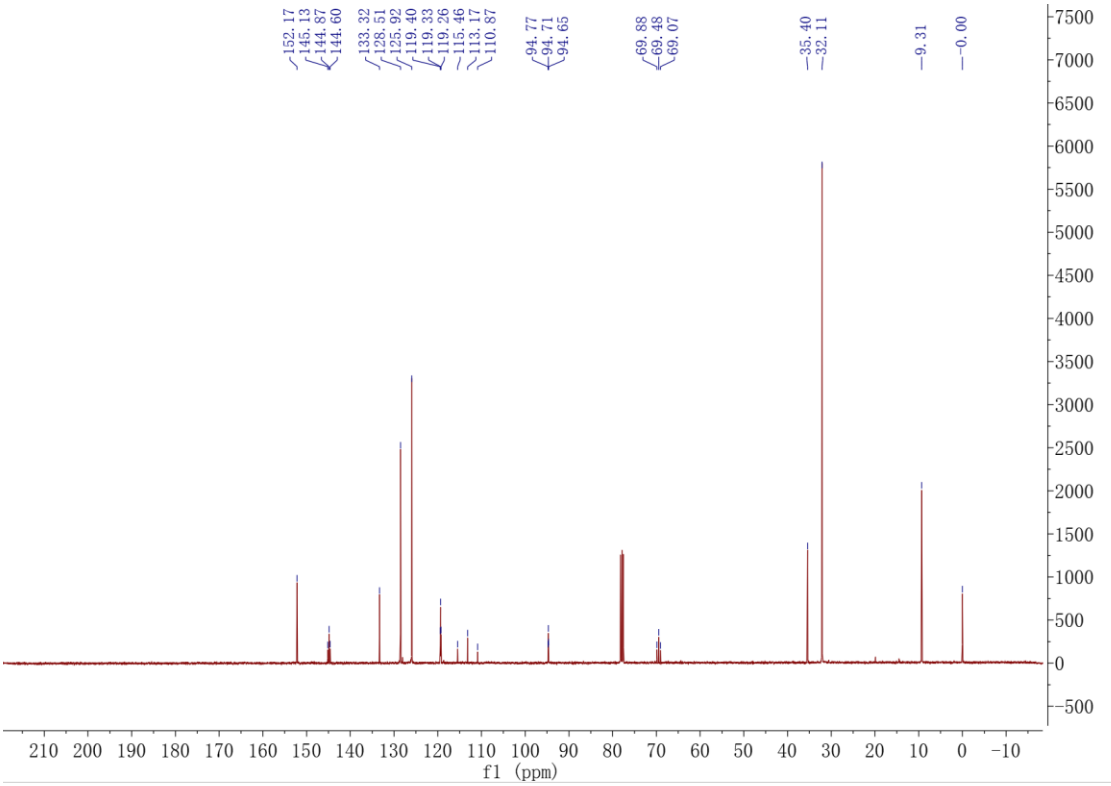
-180
-200
f1 (ppm)


7.49
7.47
7.43
7.41
5.94
5.62
1.38
1.35
1.34
1.33
1.32
1.31
0.90
0.89
0.89
0.88
0.87
0.87
0.86
0.85
0.80
0.79
0.78
0.78
0.77
0.77
0.76
F
F
2.00
2.03
1.00
1.00
9.00
1.03
2.03
2.00
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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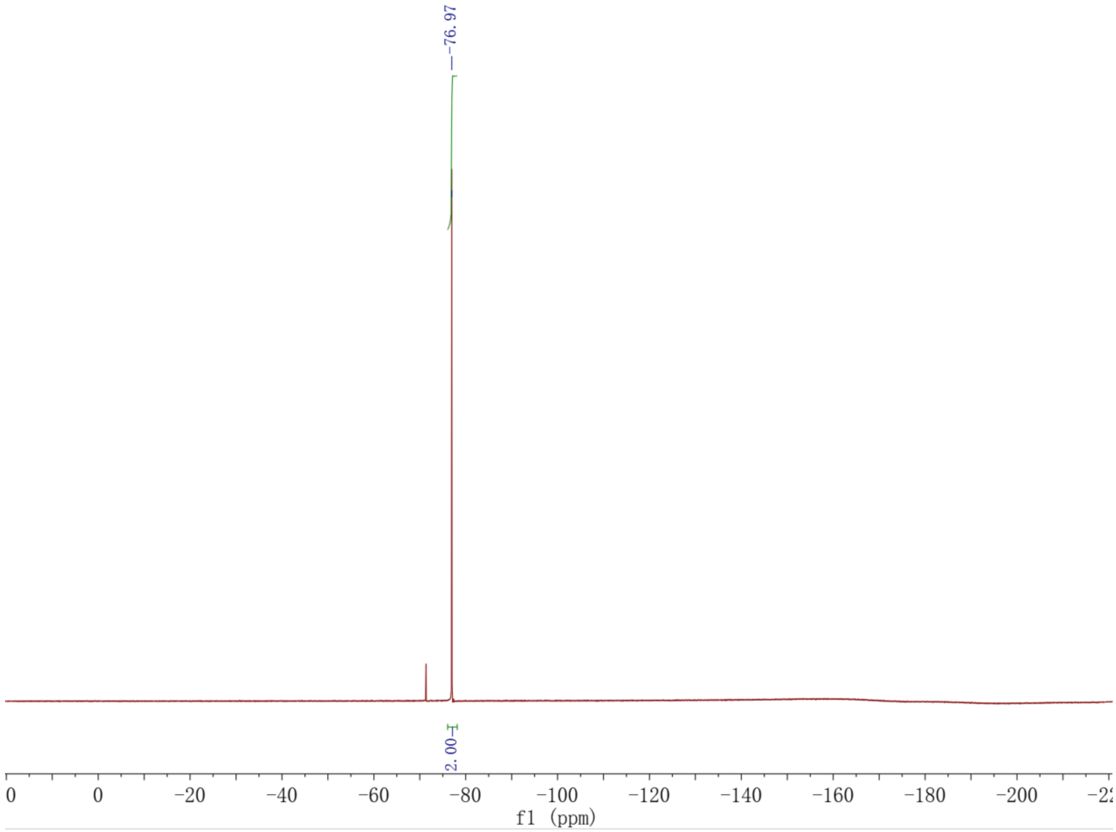
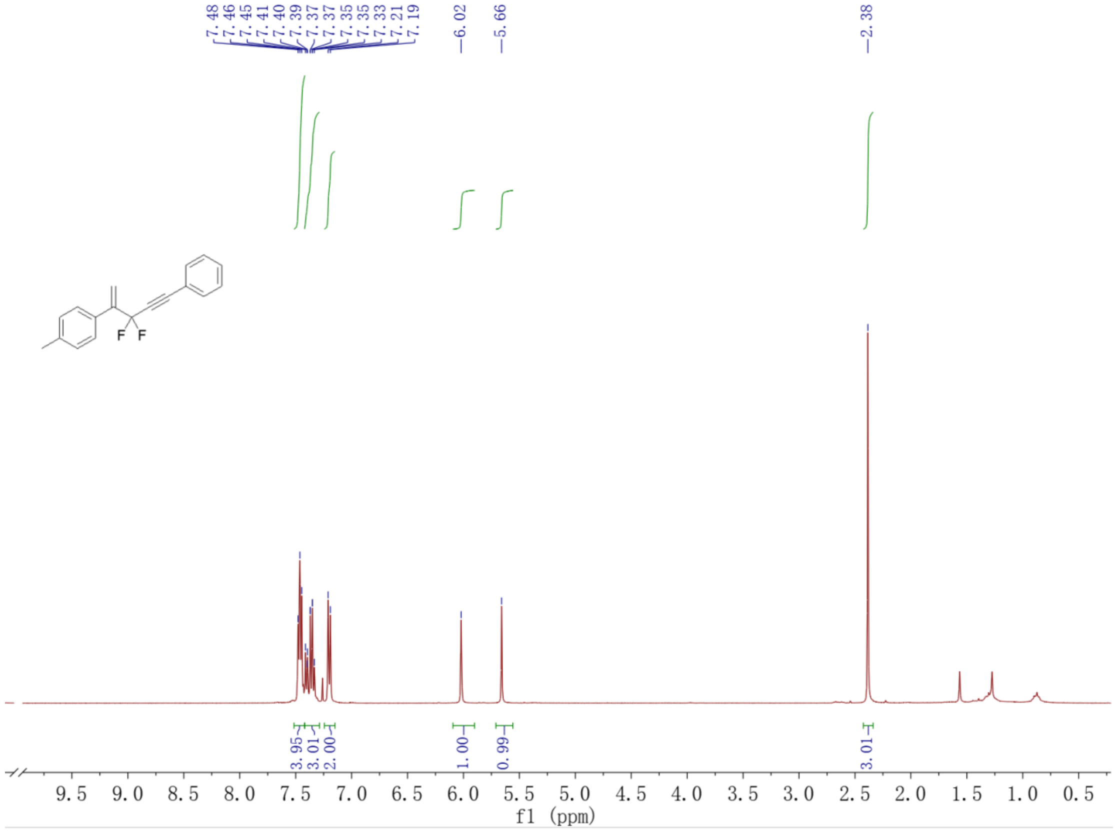
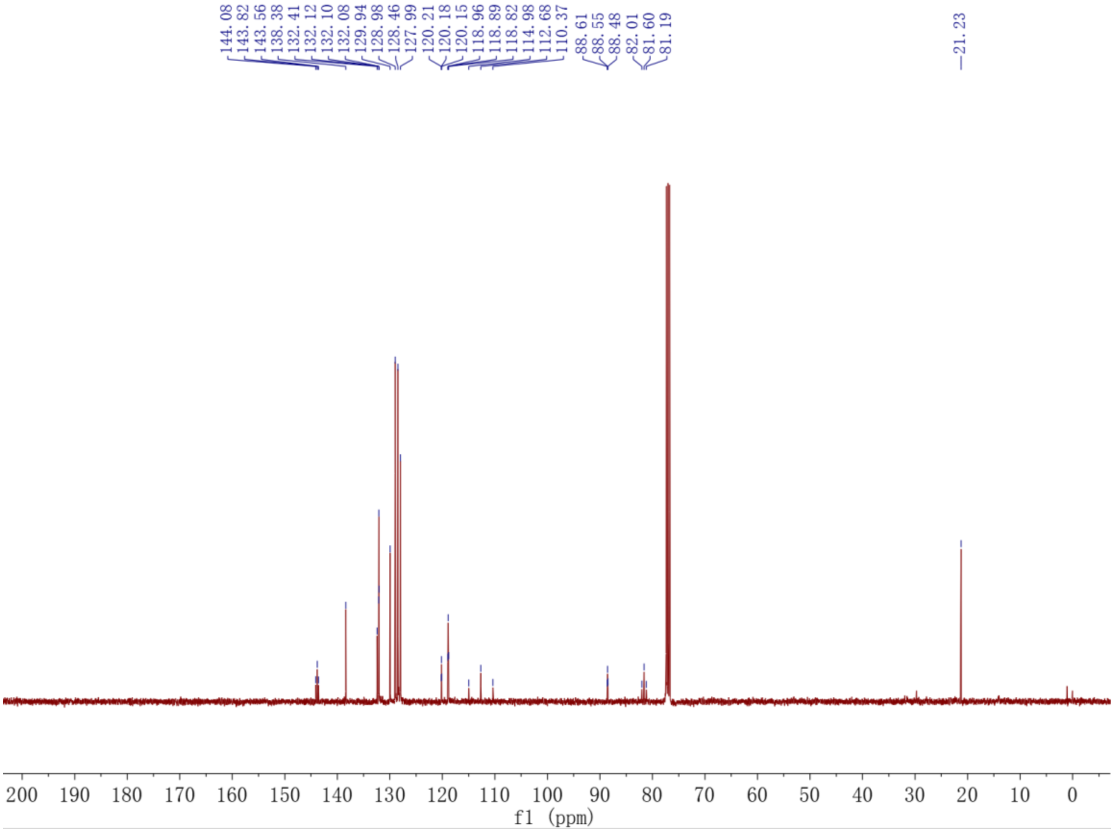
119.40
119.33
119.26
115.46
113.17
110.87
94.77
94.71
94.65
69.88
69.48
69.07
35.40
32.11
9.31
-0.00
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-76.97
2.00
0
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
−200
−2
f1 (ppm)


7.48
7.46
7.45
7.41
7.40
7.39
7.37
7.37
7.35
7.35
7.33
7.21
7.19
6.02
5.66
2.38
F
F
3.95
3.01
2.00
1.00
0.99
3.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


144.08
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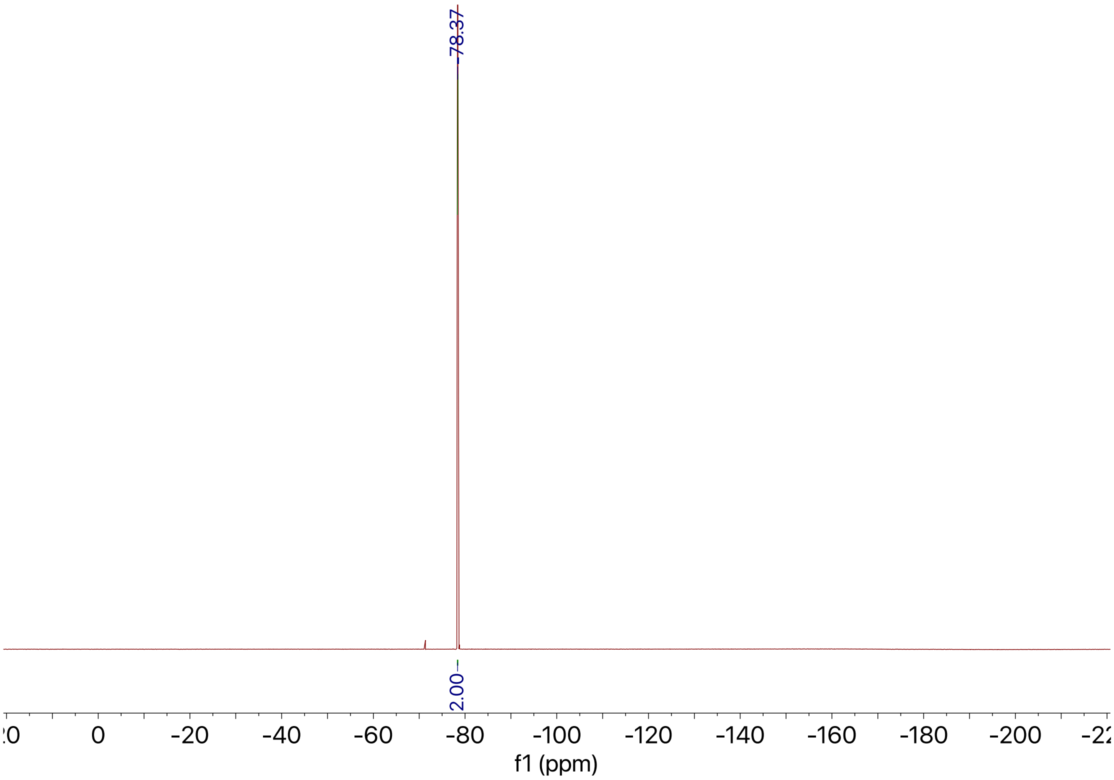
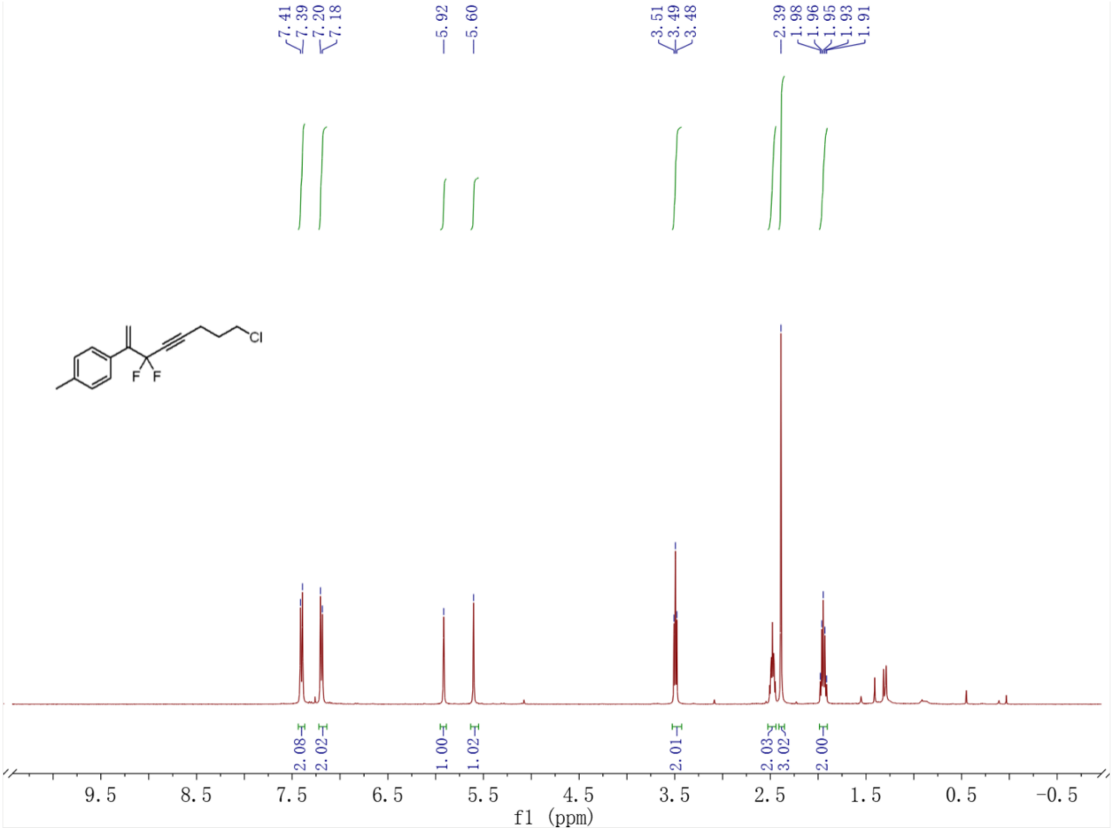
143.56
138.38
132.41
132.12
132.10
132.08
129.94
128.98
128.46
127.99
120.21
120.18
120.15
118.96
118.89
118.82
114.98
112.68
110.37
88.61
88.55
88.48
82.01
81.60
81.19
21.23
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-78.37
2.00
0 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -2
f1 (ppm)


7.41
7.39
7.20
7.18
5.92
5.60
3.51
3.49
3.48
2.39
1.98
1.96
1.95
1.93
1.91
Cl
F
F
2.08
2.02
1.00
1.02
2.01
2.03
3.02
2.00
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6.5
5.5
4.5
3.5
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1.5
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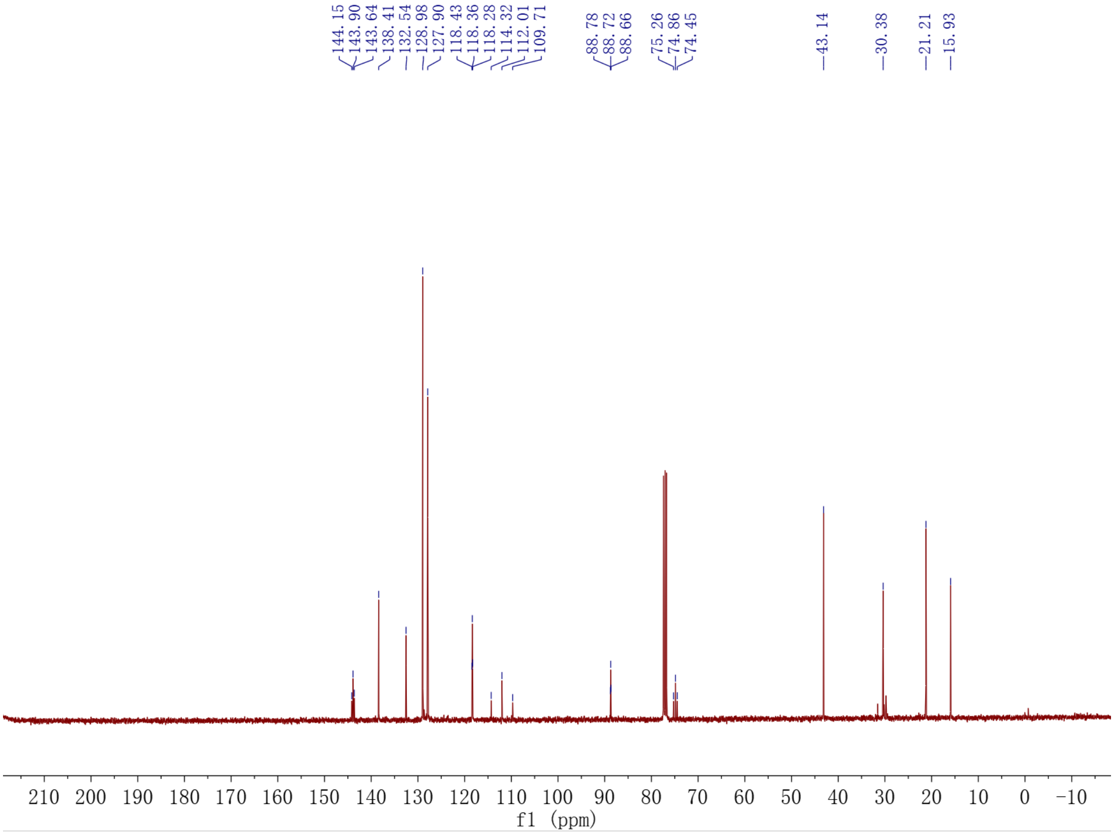
f1 (ppm)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127.90
118.43
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118.28
114.32
112.01
109.71
88.78
88.72
88.66
75.26
74.86
74.45
43.14
30.38
21.21
15.93
210
200
190
180
170
160
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140
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120
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100
90
80
70
60
50
40
30
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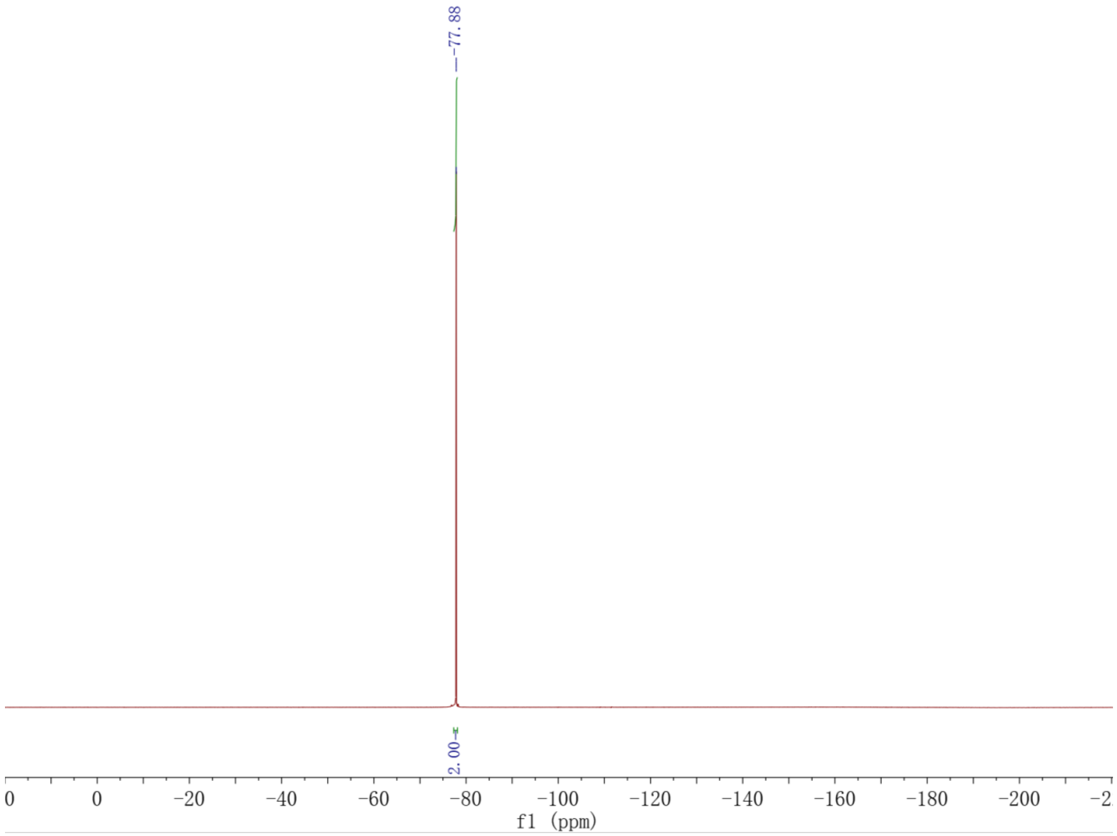
0
-10
f1 (ppm)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−120
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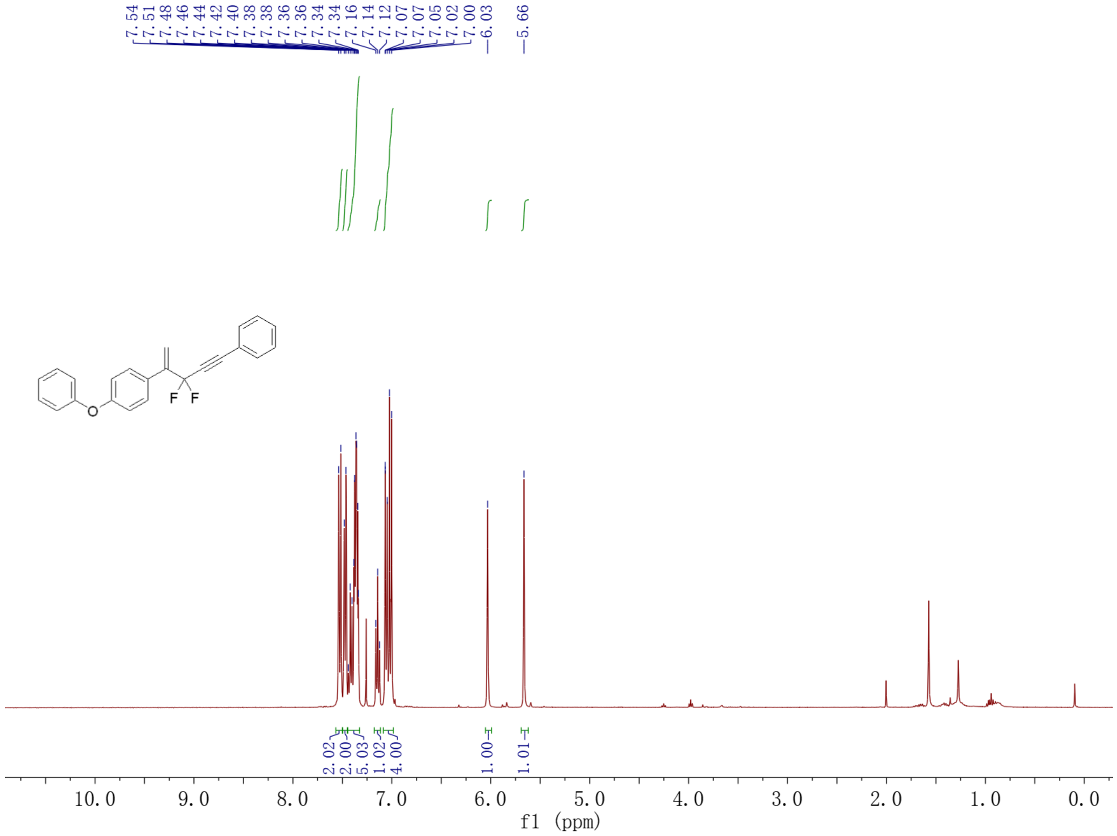
−180
−200
−2
f1 (ppm)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7.34
7.16
7.14
7.12
7.07
7.07
7.05
7.02
7.00
6.03
5.66
O
F
F
2.02
2.00
5.03
1.02
4.00
1.00
1.01
10.0
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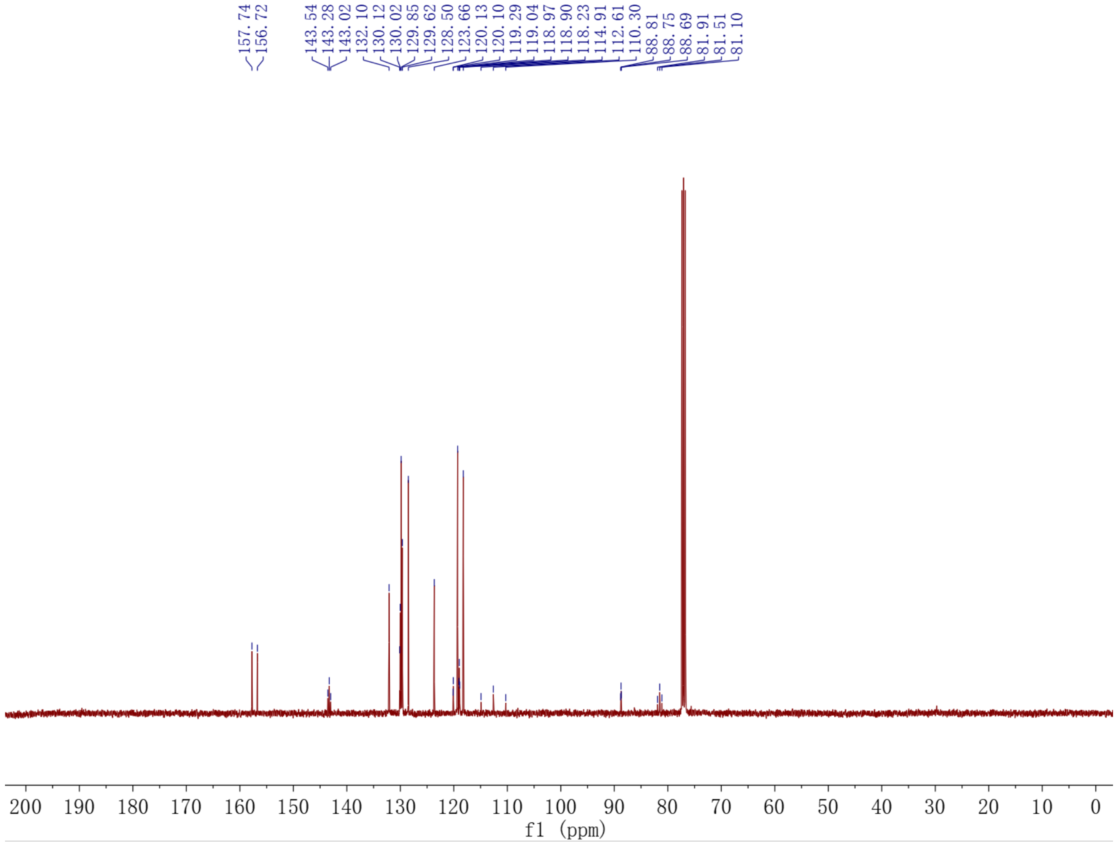
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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130.02
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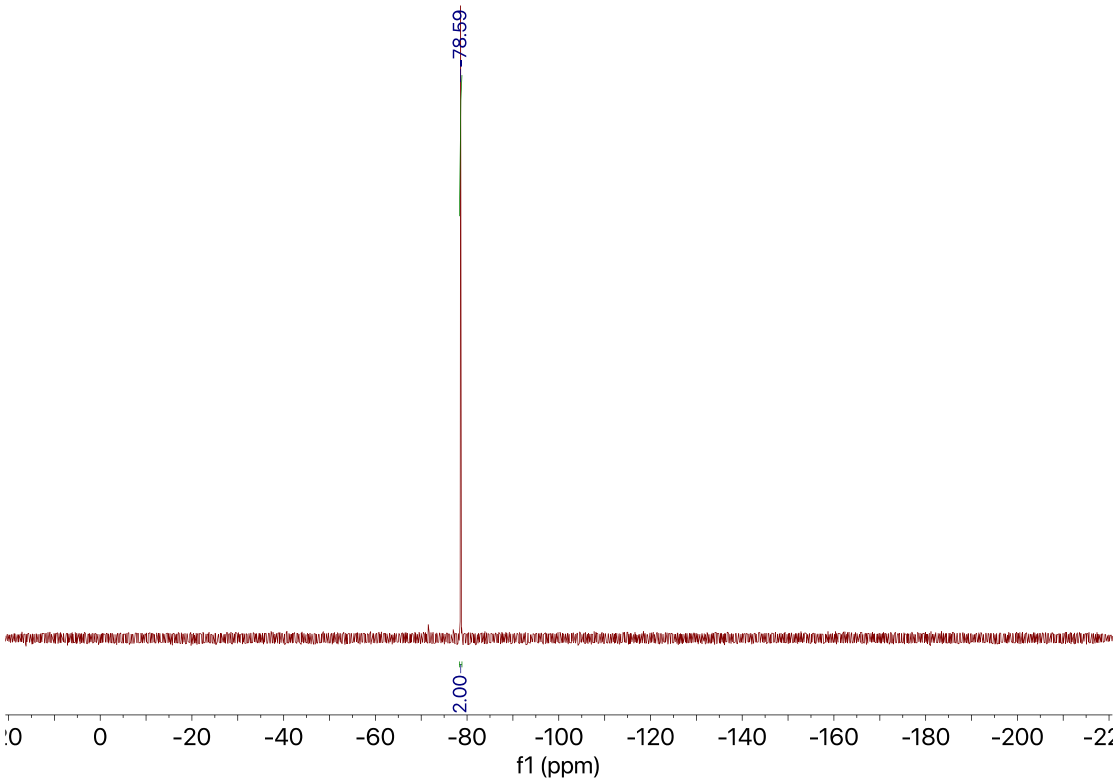
123.66
120.13
120.10
119.29
119.04
118.97
118.90
118.23
114.91
112.61
110.30
88.81
88.75
88.69
81.91
81.51
81.10
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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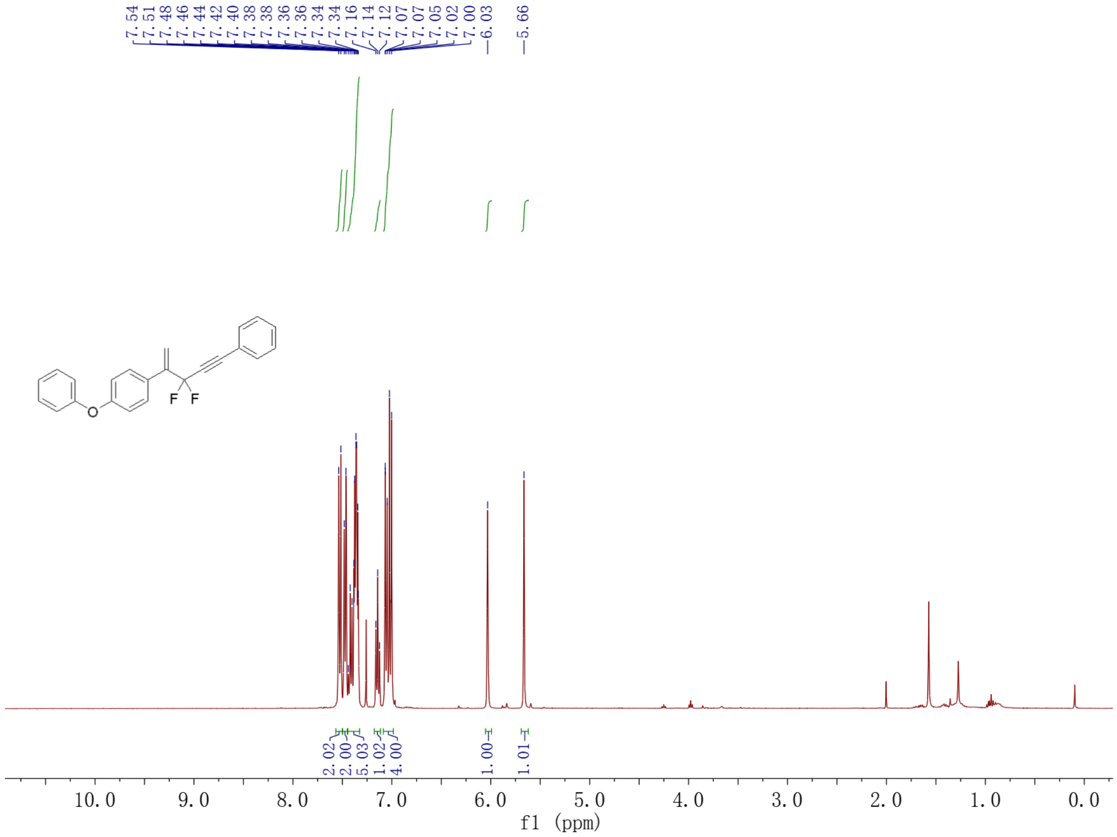
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200
f1 (ppm)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7.38
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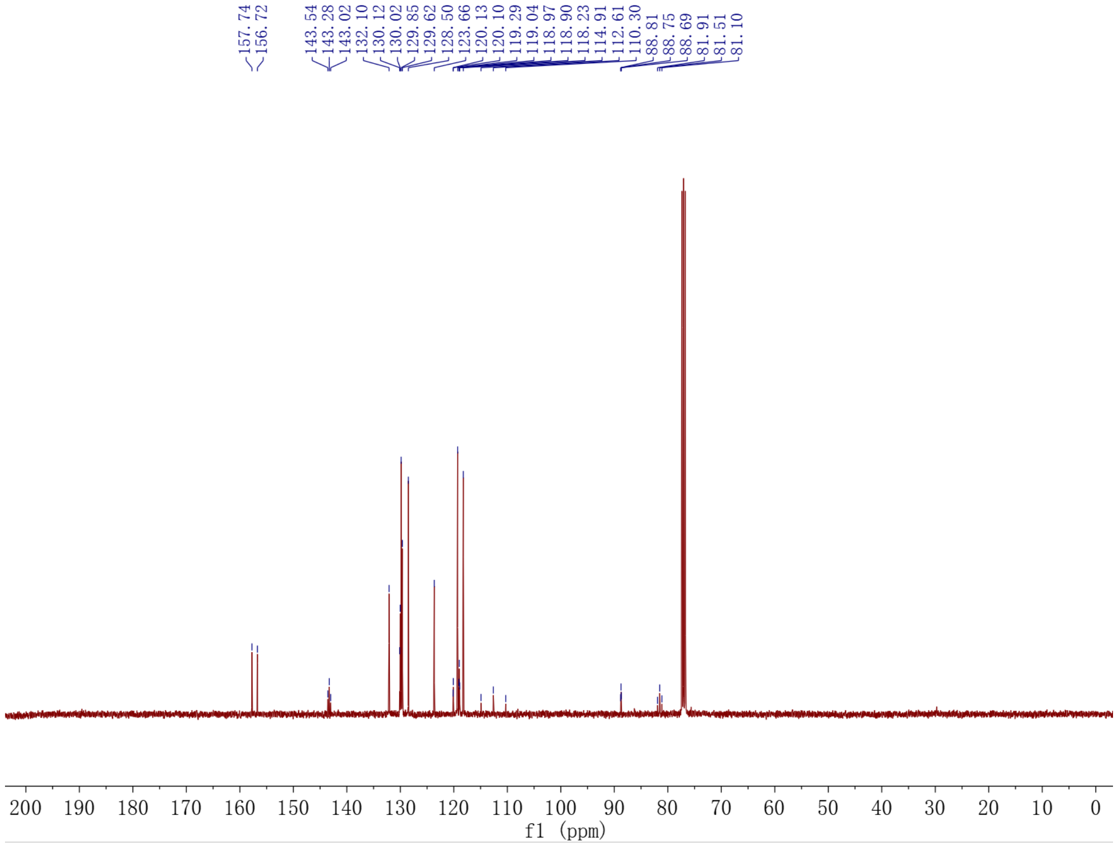
7.36
7.34
7.34
7.16
7.14
7.12
7.07
7.07
7.05
7.02
7.00
6.03
5.66
F
F
O
2.02
2.00
5.03
1.02
4.00
1.00
1.01
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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130.12
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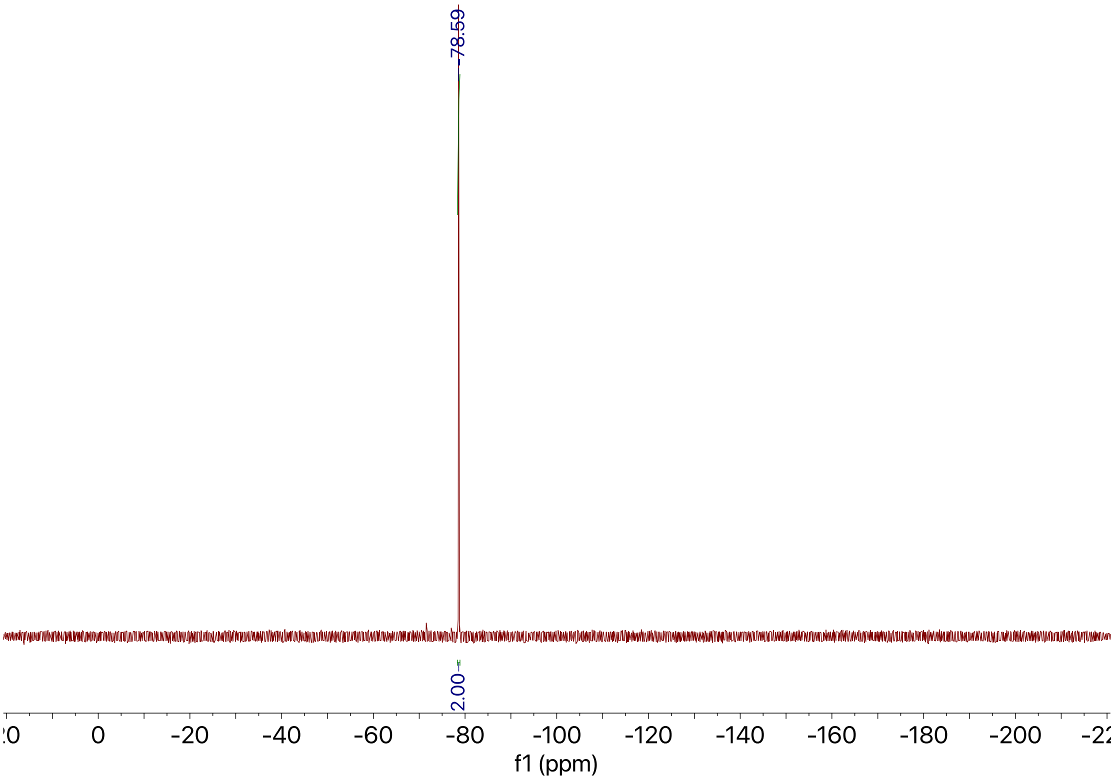
129.62
128.50
123.66
120.13
120.10
119.29
119.04
118.97
118.90
118.23
114.91
112.61
110.30
88.81
88.75
88.69
81.91
81.51
81.10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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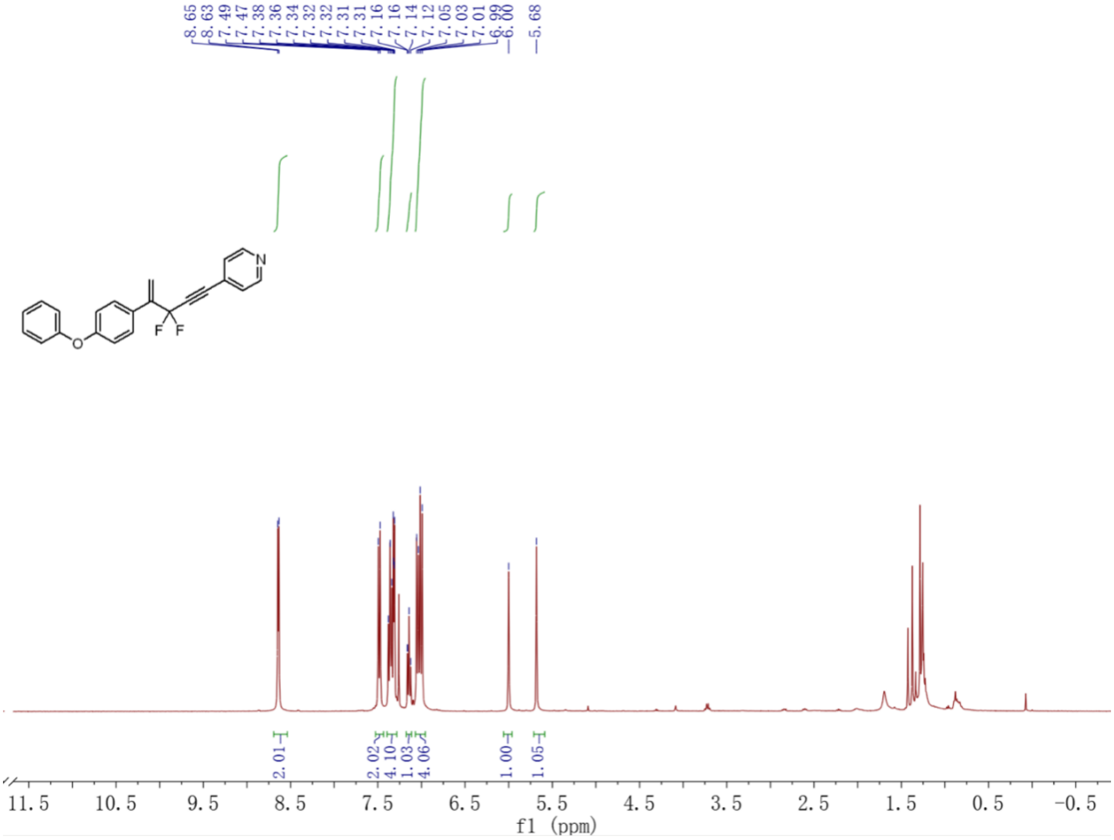
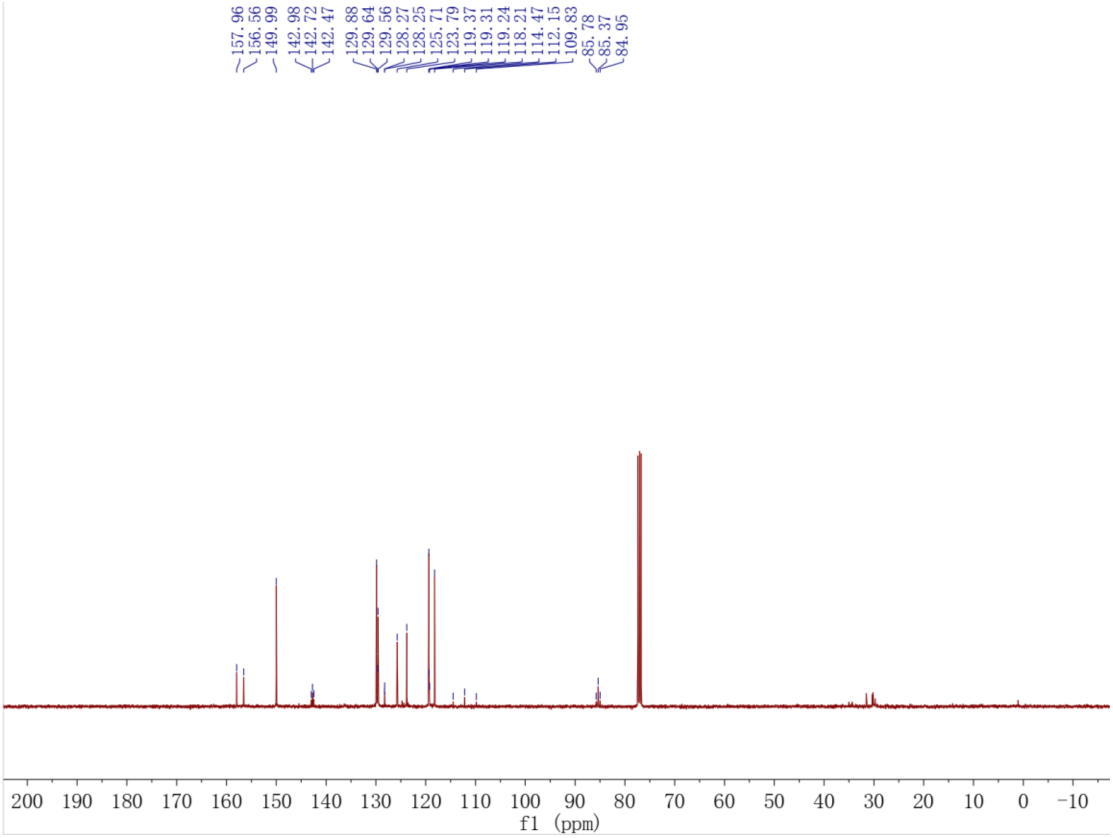
2.00
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)



8.65
8.63
7.49
7.47
7.38
7.36
7.34
7.32
7.32
7.31
7.31
7.16
7.16
7.14
7.12
7.05
7.03
7.01
6.99
6.00
5.68
N
O
F
F
2.01
2.02
4.10
1.03
4.06
1.00
1.05
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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142.47
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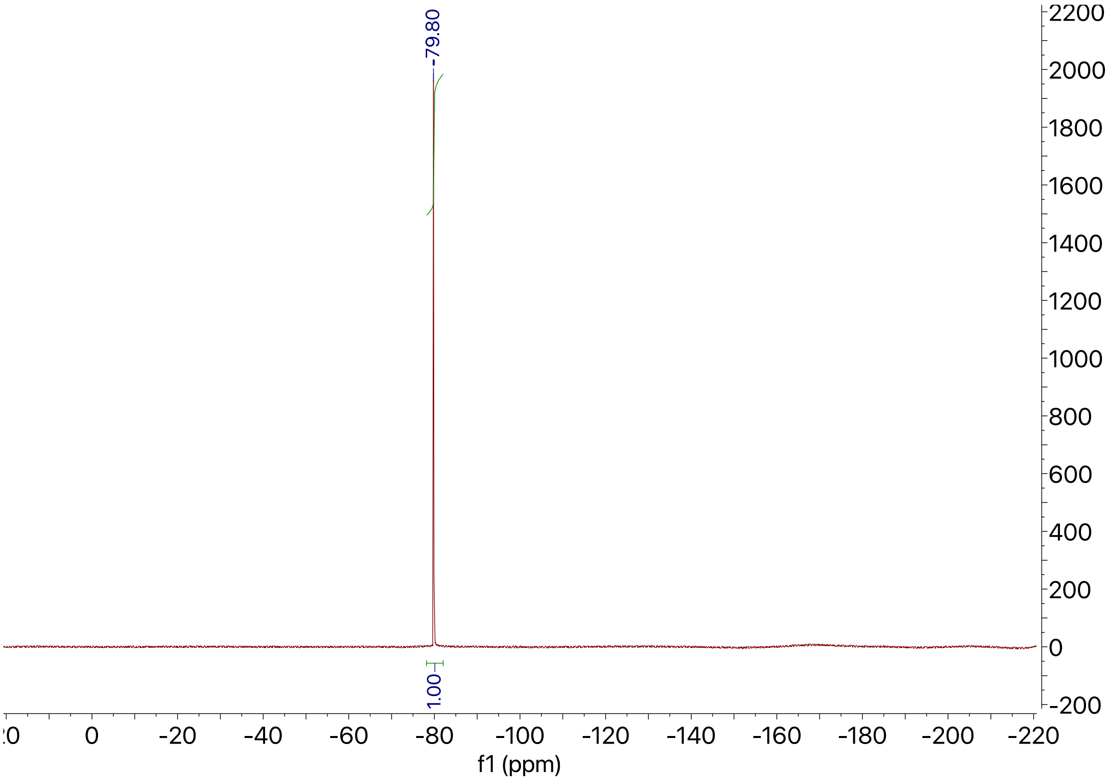
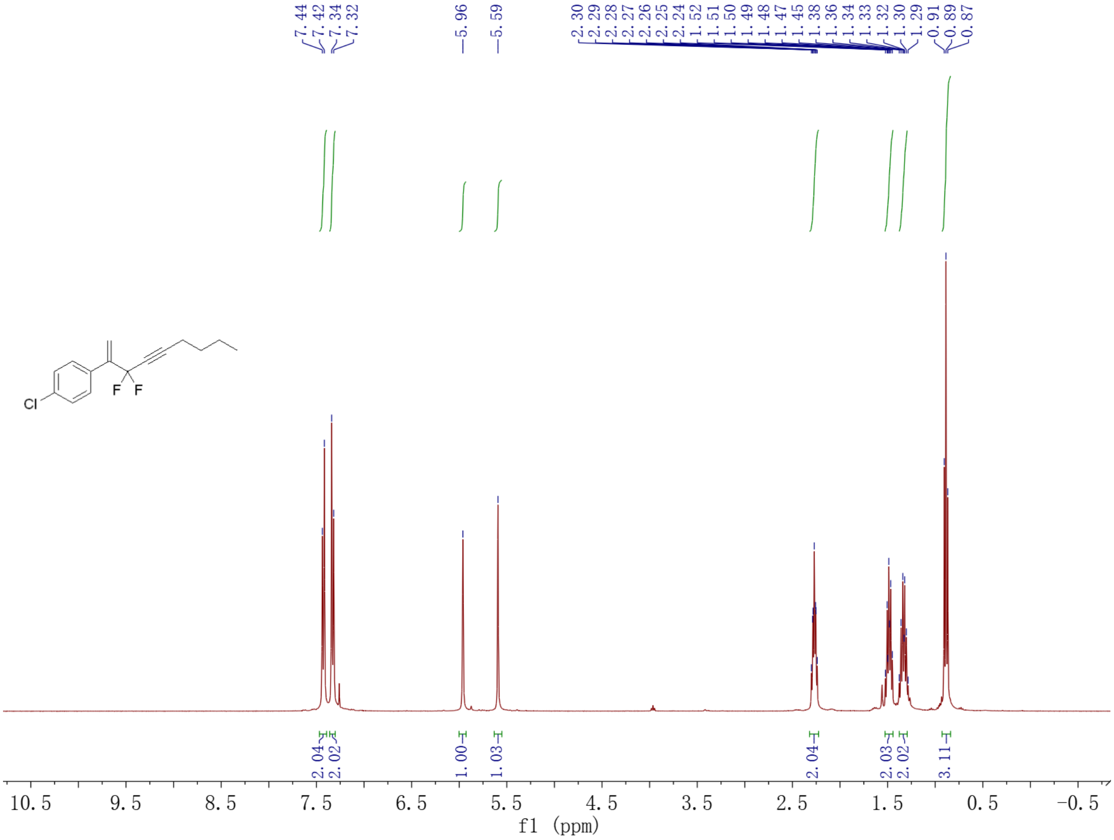
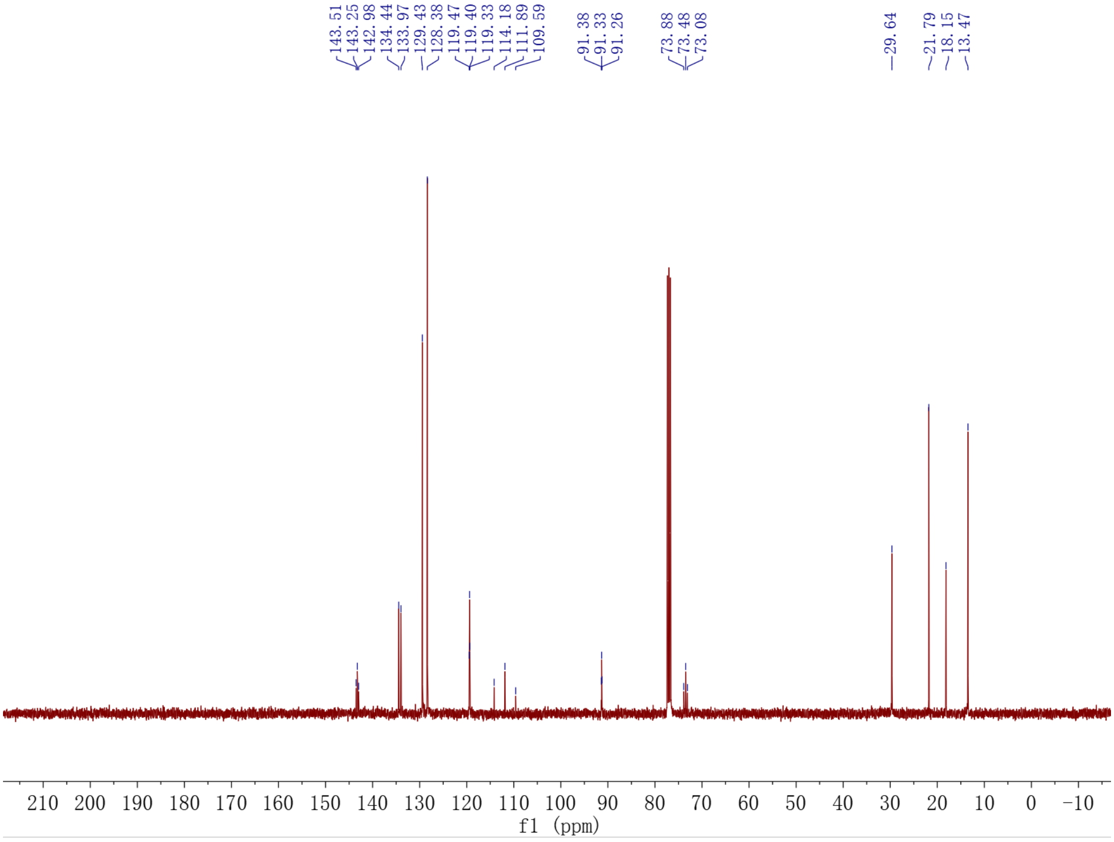
129.64
129.56
128.27
128.25
125.71
123.79
119.37
119.31
119.24
118.21
114.47
112.15
109.83
85.78
85.37
84.95
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


-79.80
1.00
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220
f1 (ppm)


7.44
7.42
7.34
7.32
5.96
5.59
2.30
2.29
2.28
2.27
2.26
2.25
2.24
1.52
1.51
1.50
1.49
1.48
1.47
1.45
1.38
1.36
1.34
1.33
1.32
1.30
1.29
0.91
0.89
0.87
Cl
F F
2.04
2.02
1.00
1.03
2.04
2.03
2.02
3.11
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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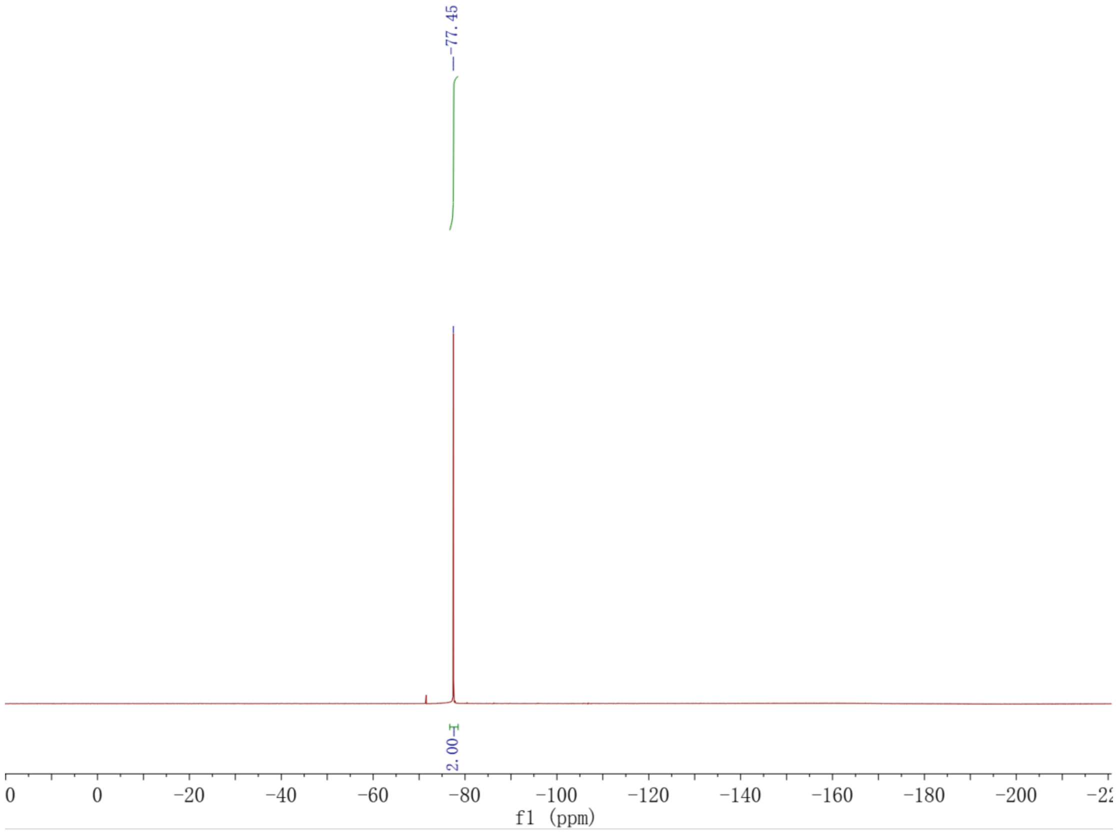
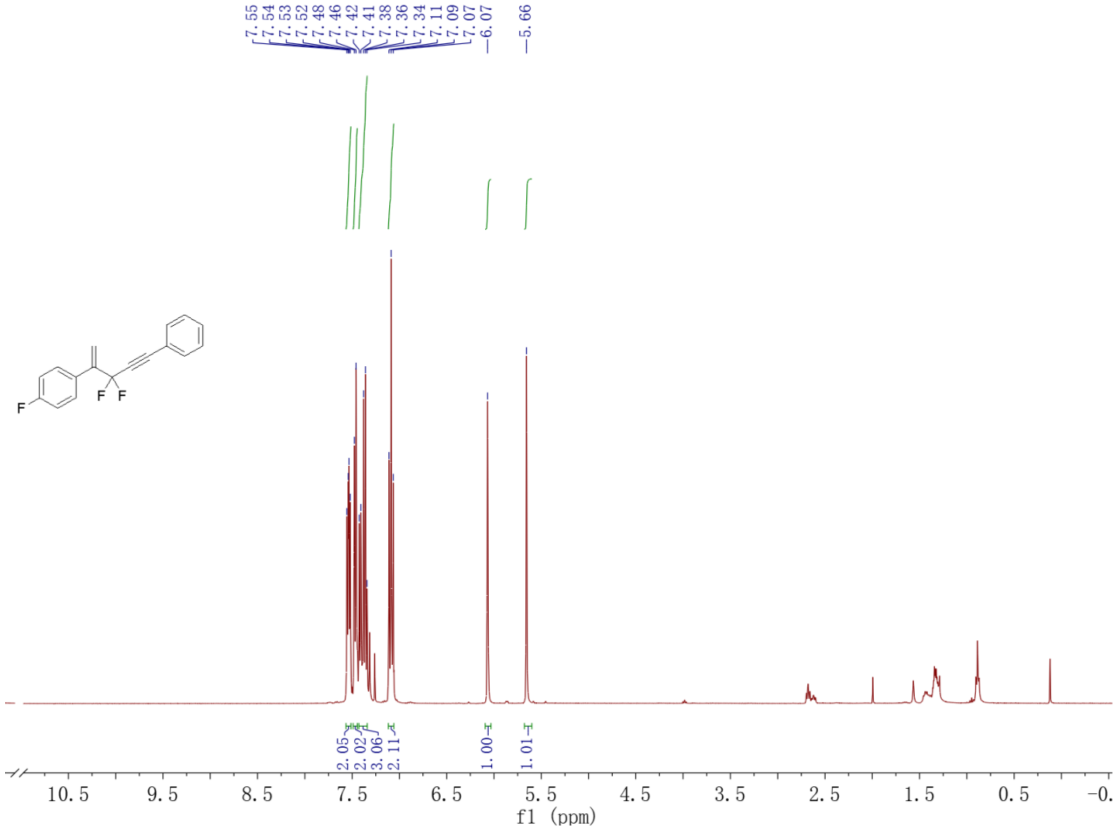
142.98
134.44
133.97
129.43
128.38
119.47
119.40
119.33
114.18
111.89
109.59
91.38
91.33
91.26
73.88
73.48
73.08
29.64
21.79
18.15
13.47
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



-77.45
2.00
0
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-2
f1 (ppm)



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7.54
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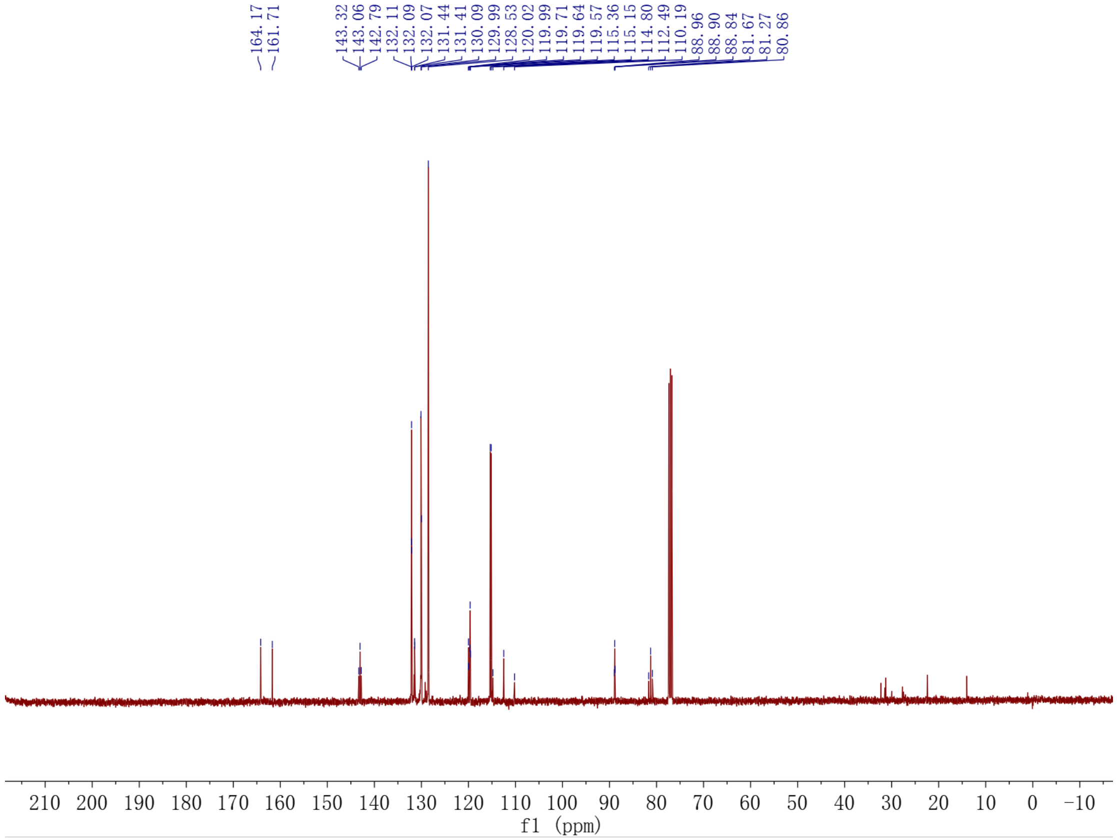
7.46
7.42
7.41
7.38
7.36
7.34
7.11
7.09
7.07
6.07
5.66
F
F F
2.05
2.02
3.06
2.11
1.00
1.01
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.
f1 (ppm)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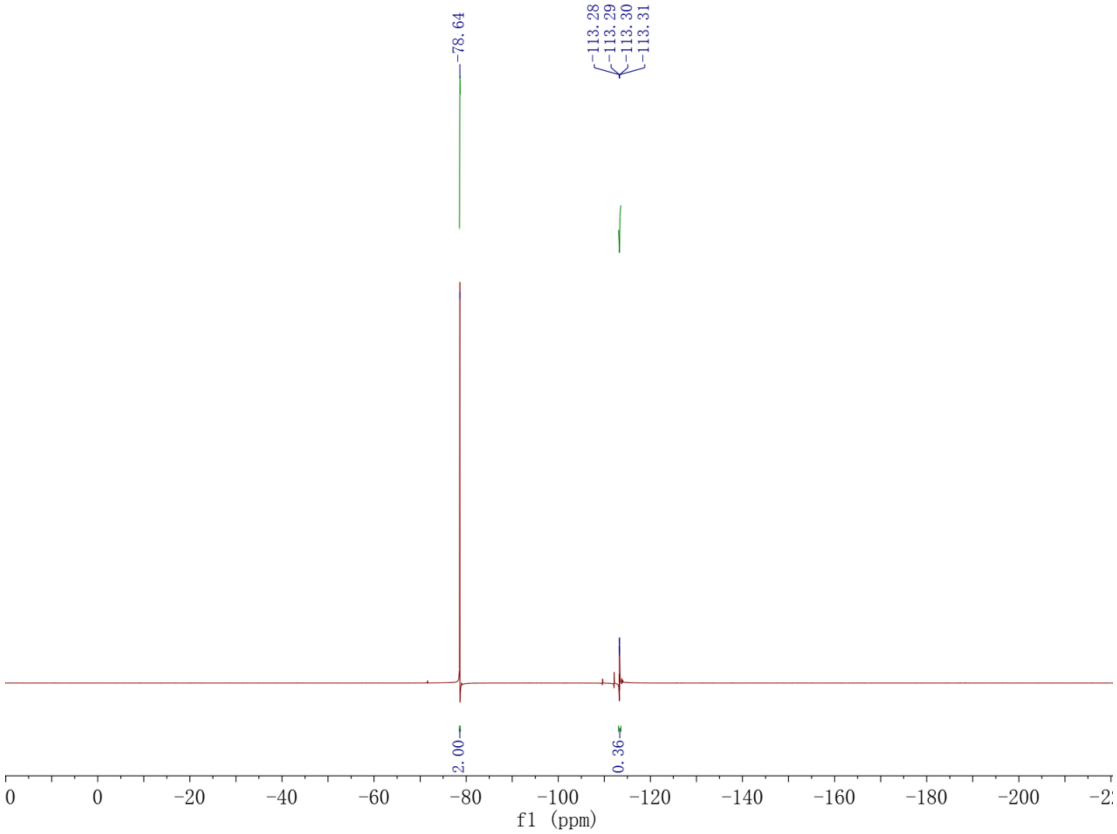
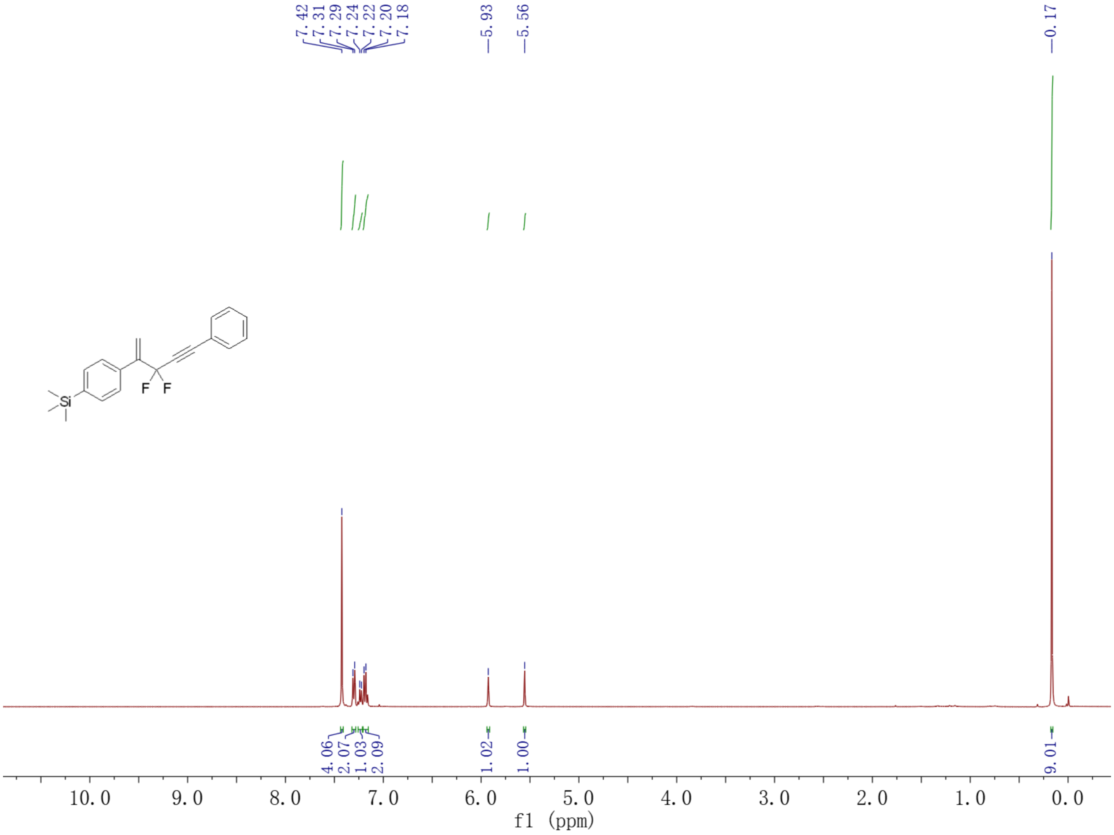
161.71
143.32
143.06
142.79
132.11
132.09
132.07
131.44
131.41
130.09
129.99
128.53
120.02
119.99
119.71
119.64
119.57
115.36
115.15
114.80
112.49
110.19
88.96
88.90
88.84
81.67
81.27
80.86
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


−78.64
−113.28
−113.29
−113.30
−113.31
2.00
0.36
0 0 −20 −40 −60 −80 −100 −120 −140 −160 −180 −200
f1 (ppm)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7.31
7.29
7.24
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7.20
7.18
5.93
5.56
0.17
Si
F
F
4.06
2.07
1.03
2.09
1.02
1.00
9.01
10.0
9.0
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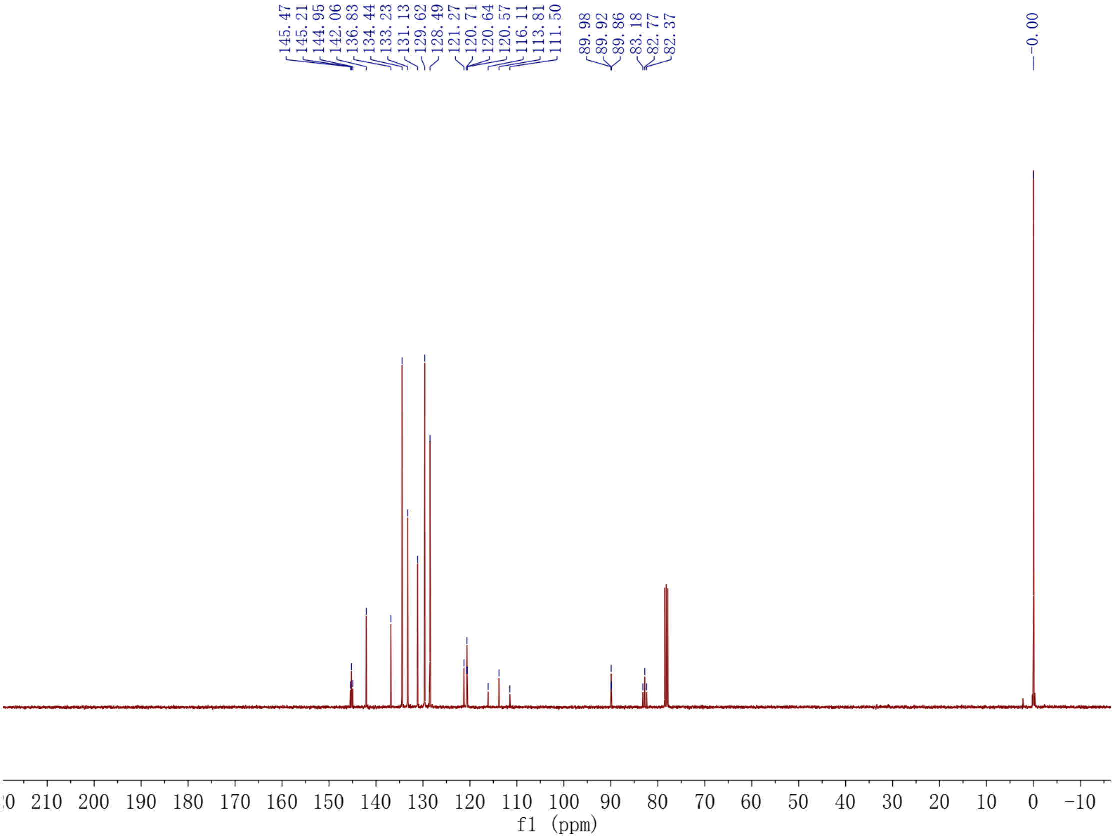
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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145.21
144.95
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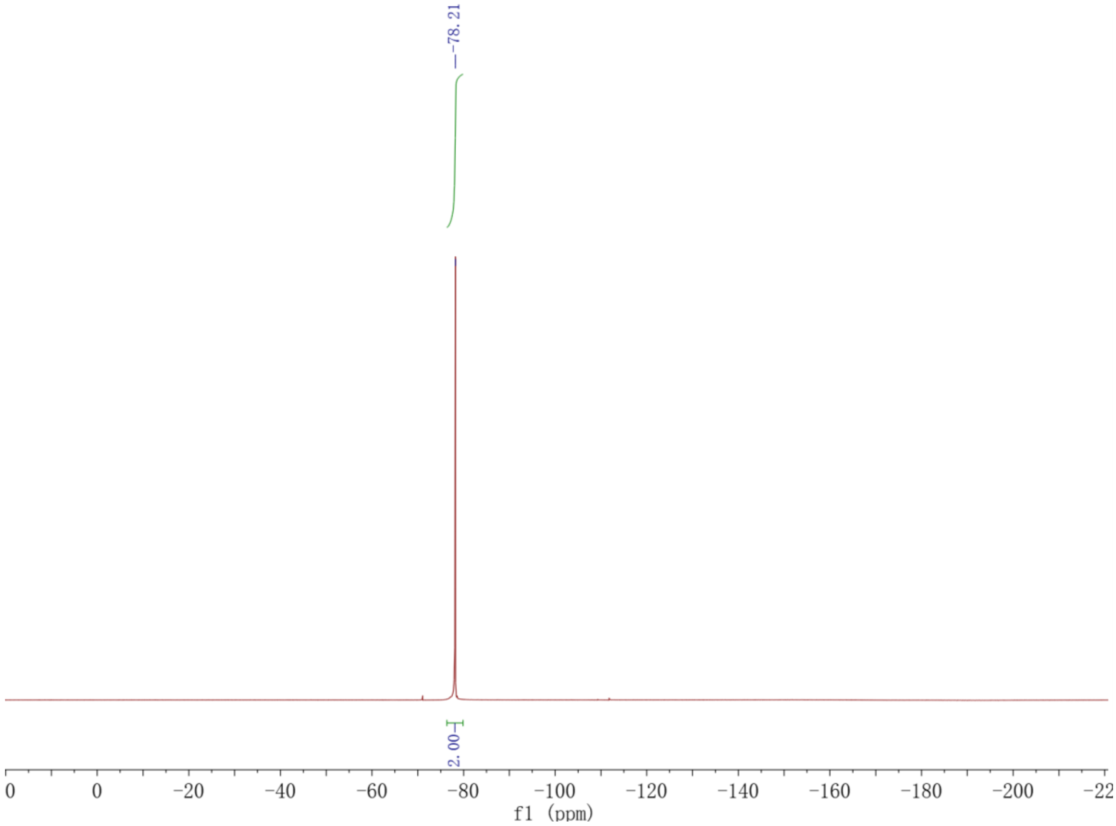
136.83
134.44
133.23
131.13
129.62
128.49
121.27
120.71
120.64
120.57
116.11
113.81
111.50
89.98
89.92
89.86
83.18
82.77
82.37
-0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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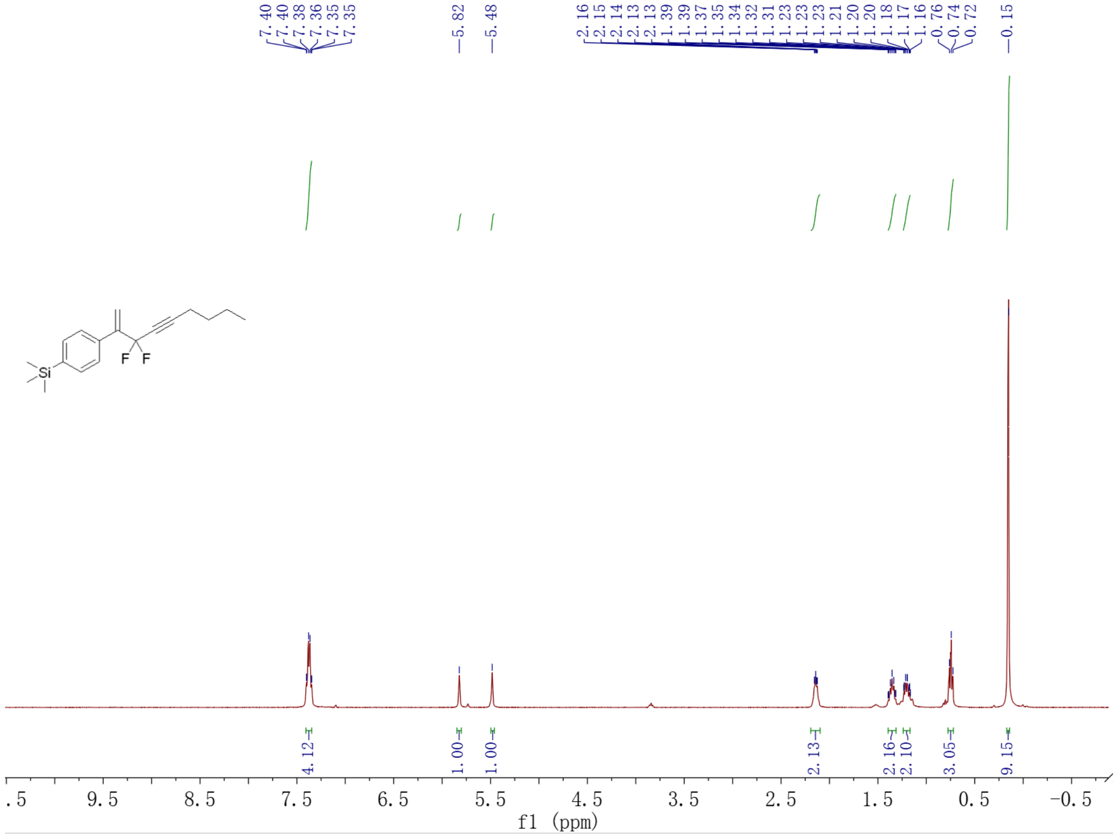
-120
-140
-160
-180
-200
-22
f1 (ppm)


7.40
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7.35
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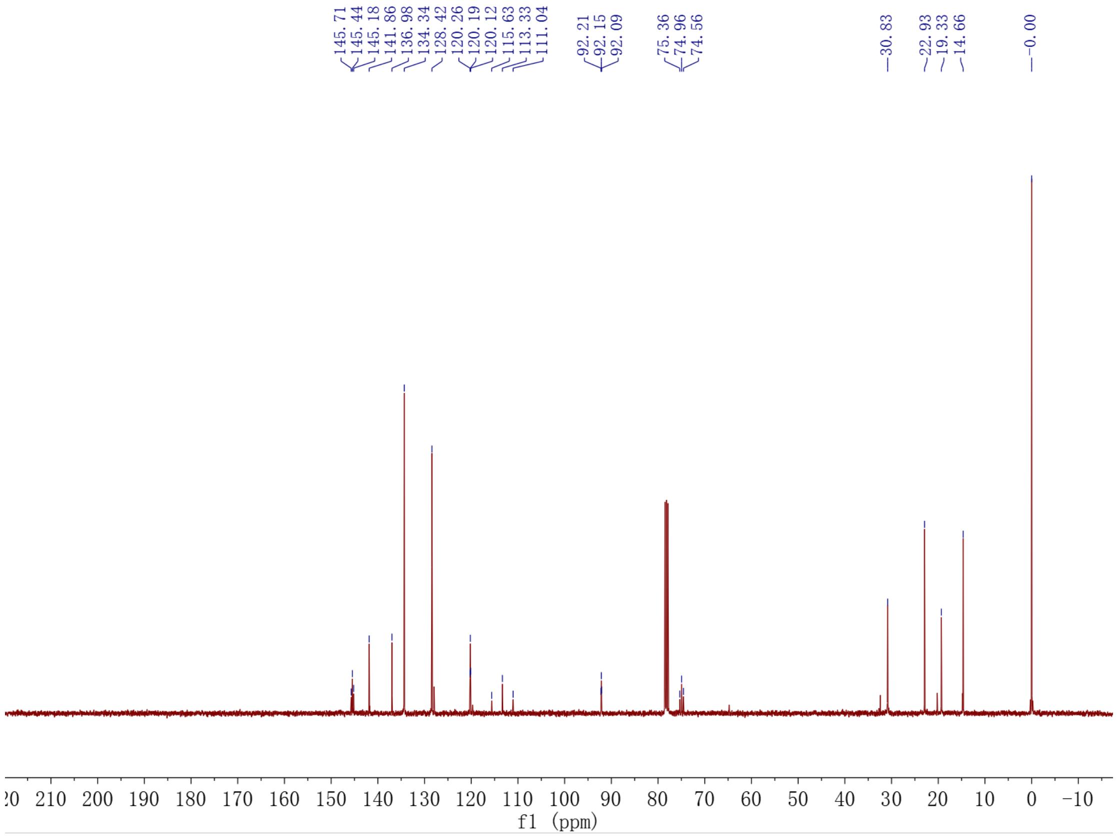
5.48
2.16
2.15
2.14
2.13
2.13
1.39
1.39
1.37
1.35
1.34
1.32
1.31
1.23
1.23
1.23
1.21
1.20
1.20
1.18
1.17
1.16
0.76
0.74
0.72
0.15
Si
F
F
4.12
1.00
1.00
2.13
2.16
2.10
3.05
9.15
.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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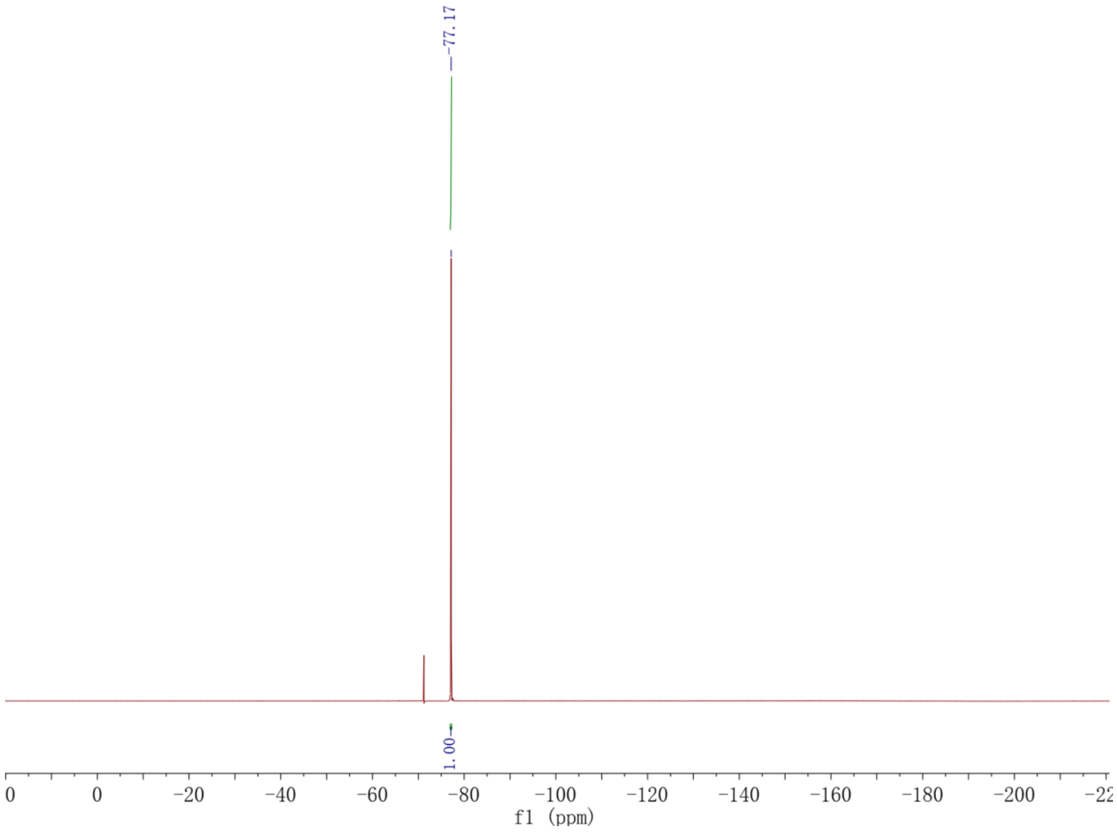
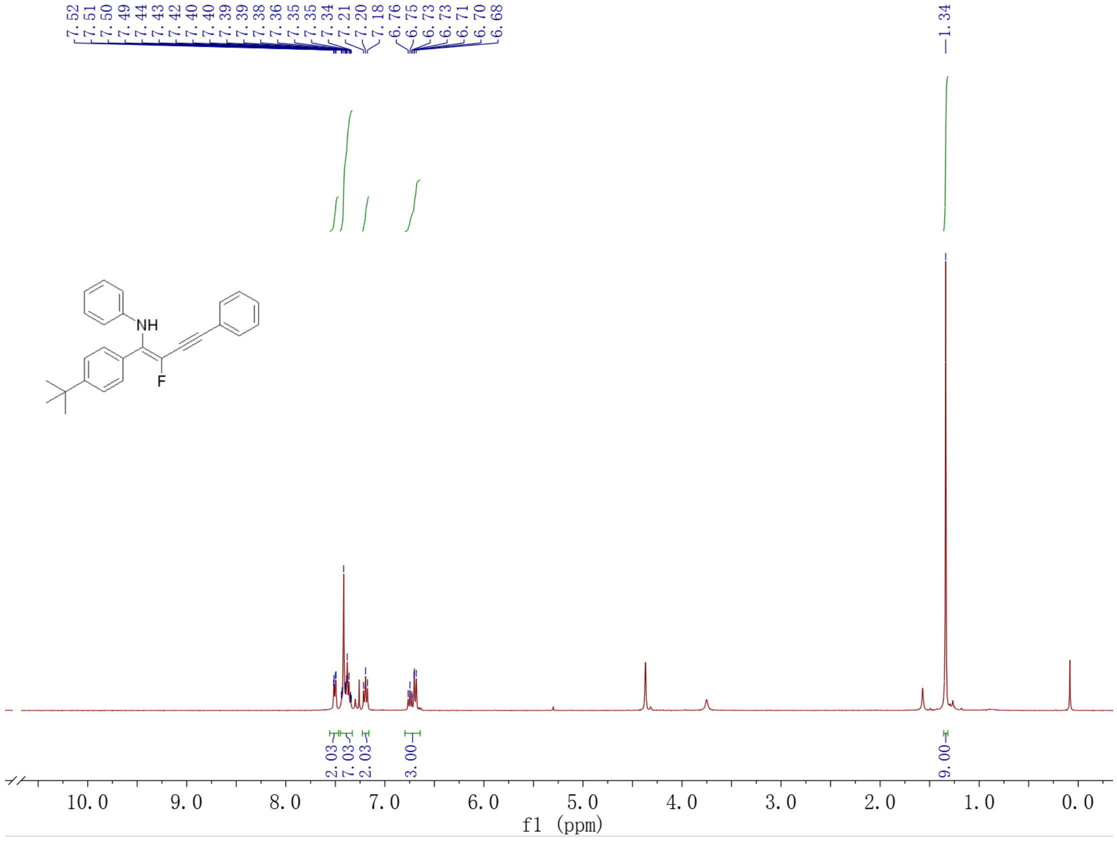
136.98
134.34
128.42
120.26
120.19
120.12
115.63
113.33
111.04
92.21
92.15
92.09
75.36
74.96
74.56
30.83
22.93
19.33
14.66
0.00
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


−77.17
1.00
0 0 −20 −40 −60 −80 −100 −120 −140 −160 −180 −200 −22
f1 (ppm)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7.40
7.39
7.39
7.38
7.36
7.35
7.35
7.34
7.21
7.20
7.18
6.76
6.75
6.73
6.73
6.71
6.70
6.68
1.34
NH
F
2.03
7.03
2.03
3.00
9.00
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9.0
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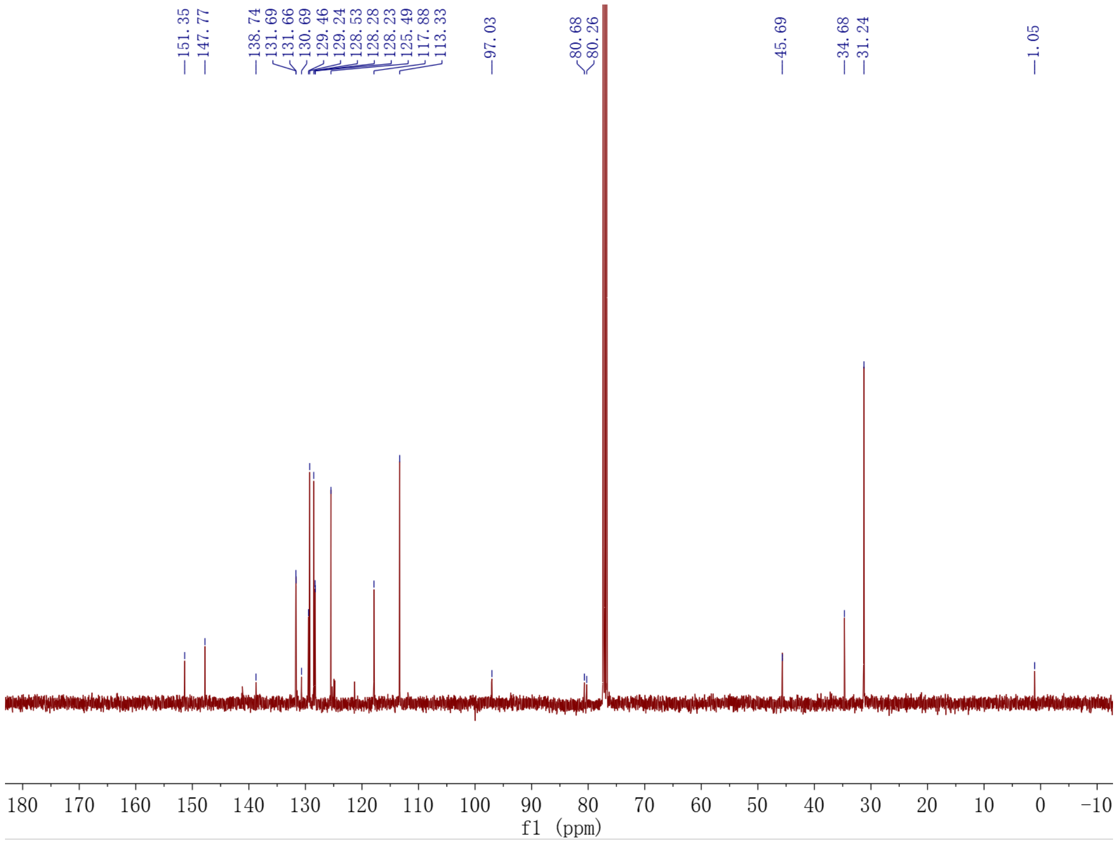
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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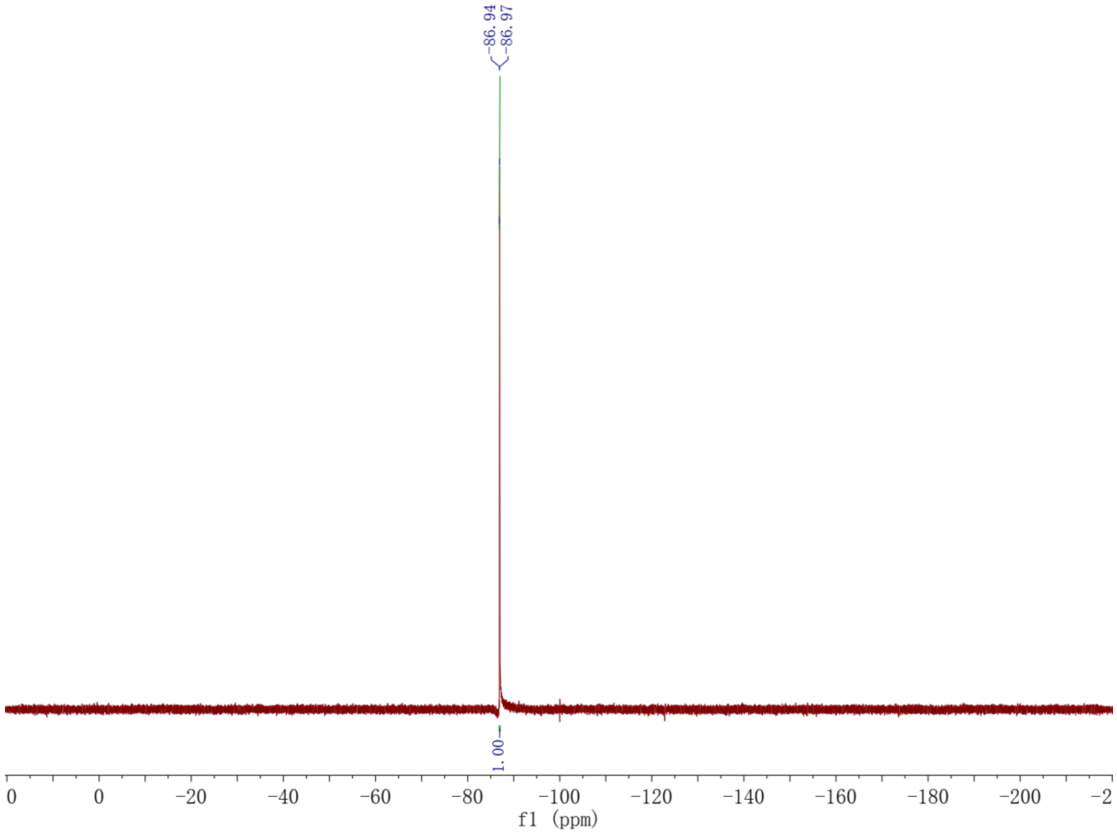
128.28
128.23
125.49
117.88
113.33
97.03
80.68
80.26
45.69
34.68
31.24
1.05
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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-86.97
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−120
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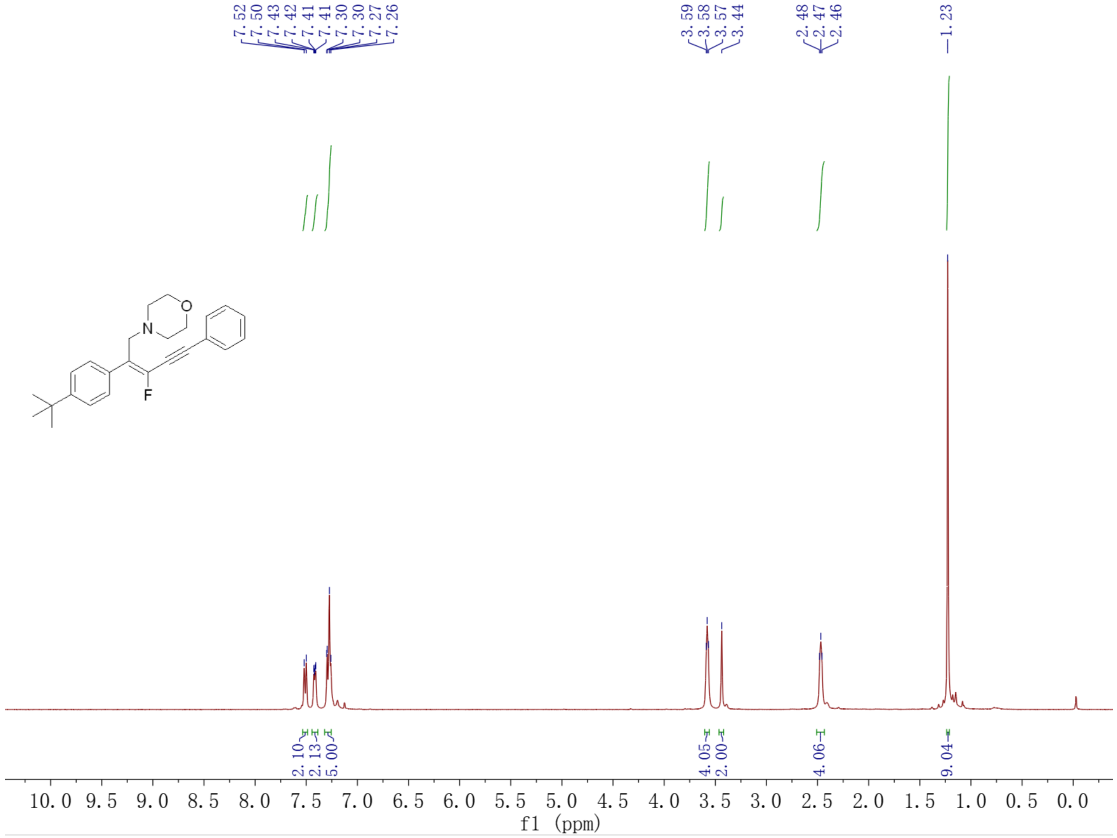
−160
−180
−200
−2
f1 (ppm)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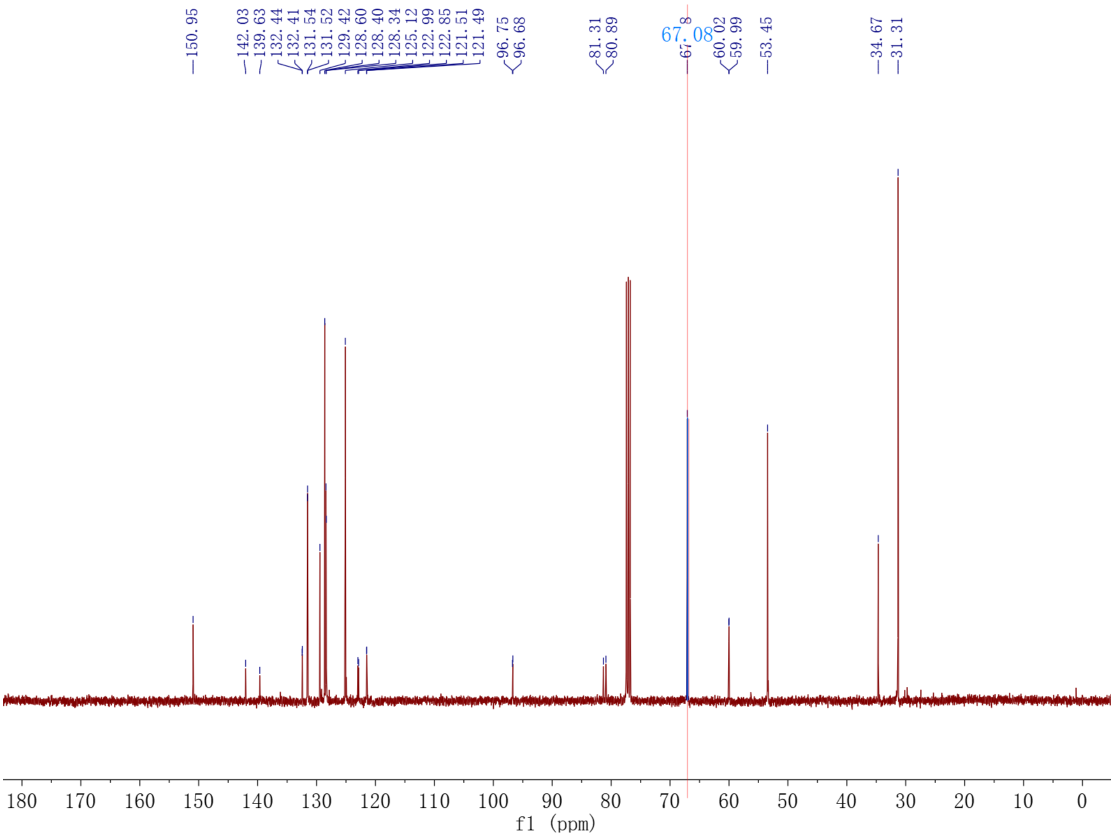
7.30
7.27
7.26
3.59
3.58
3.57
3.44
2.48
2.47
2.46
1.23
N
O
F
2.10
2.13
5.00
4.05
2.00
4.06
9.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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131.54
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129.42
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128.40
128.34
125.12
122.99
122.85
121.51
121.49
96.75
96.68
81.31
80.89
67.08
60.02
59.99
53.45
34.67
31.31
180
170
160
150
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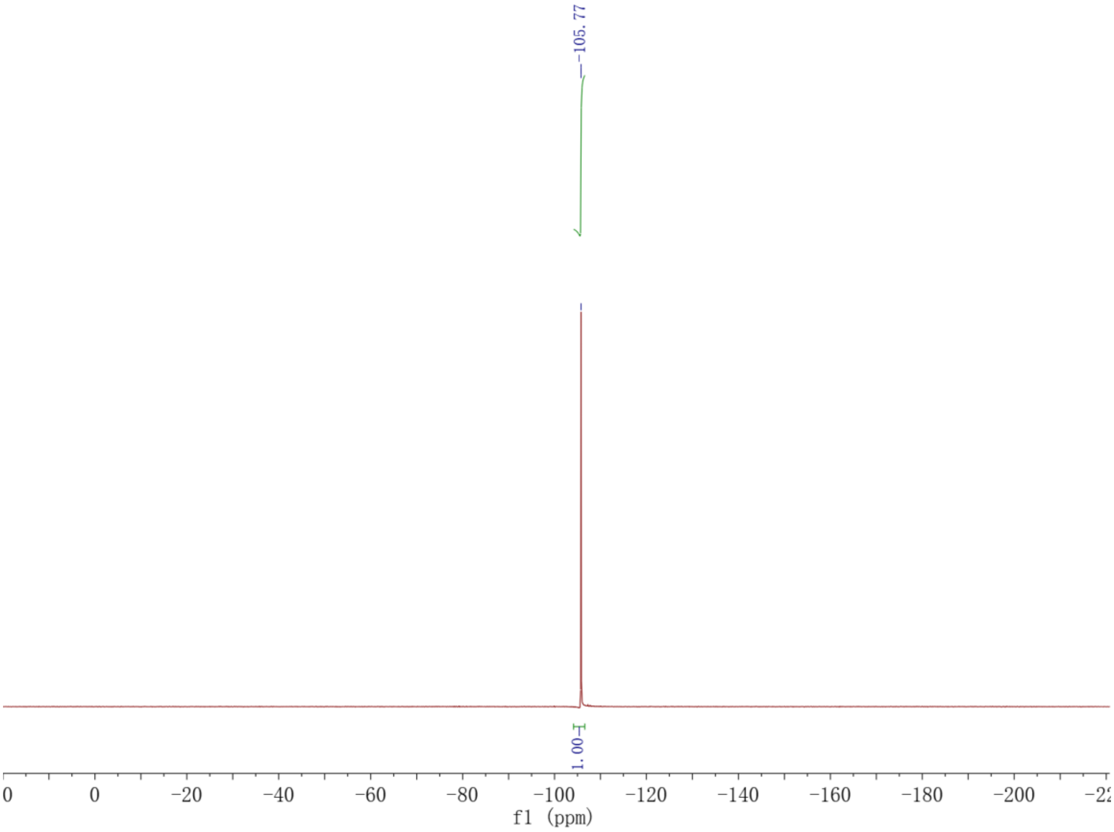
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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−120
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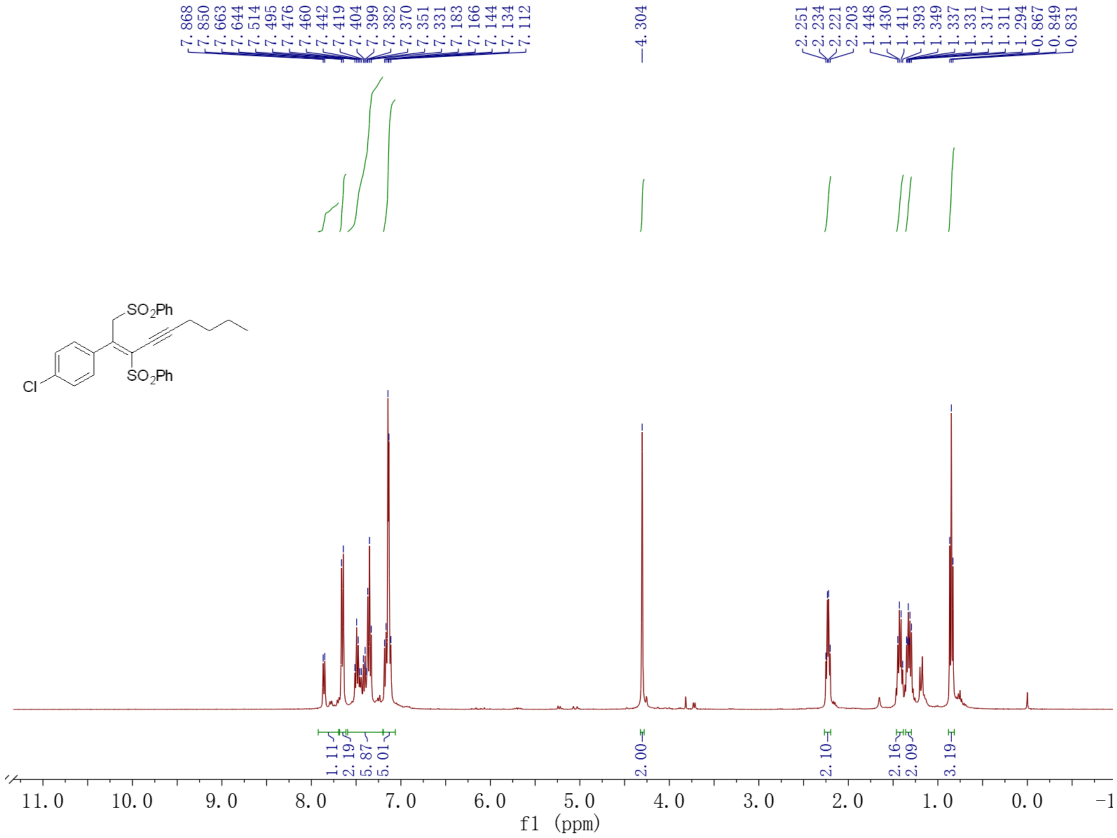
−180
−200
−2
f1 (ppm)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7.644
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7.495
7.476
7.460
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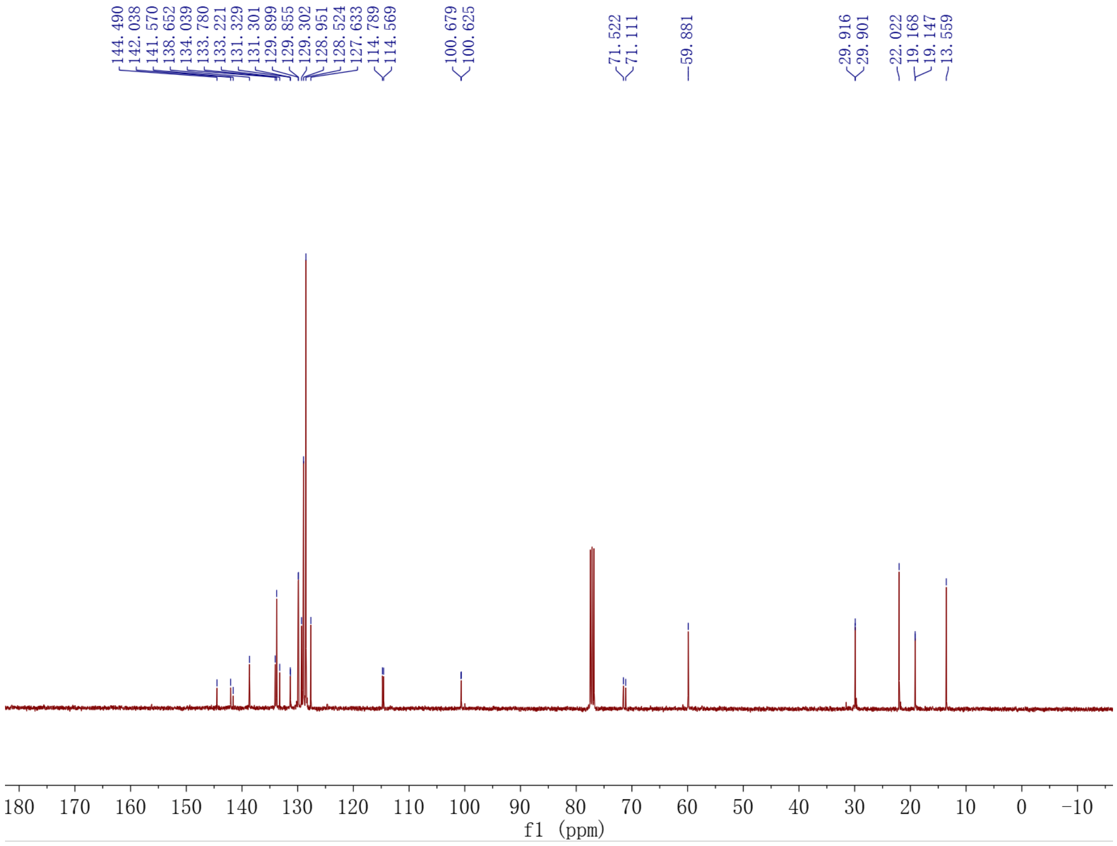
7.419
7.404
7.399
7.382
7.370
7.351
7.331
7.183
7.166
7.144
7.134
7.112
4.304
2.251
2.234
2.221
2.203
1.448
1.430
1.411
1.393
1.349
1.337
1.331
1.317
1.311
1.294
0.867
0.849
0.831
SO2Ph
SO2Ph
Cl
1.11
2.19
5.87
5.01
2.00
2.10
2.16
2.09
3.19
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1
f1 (ppm)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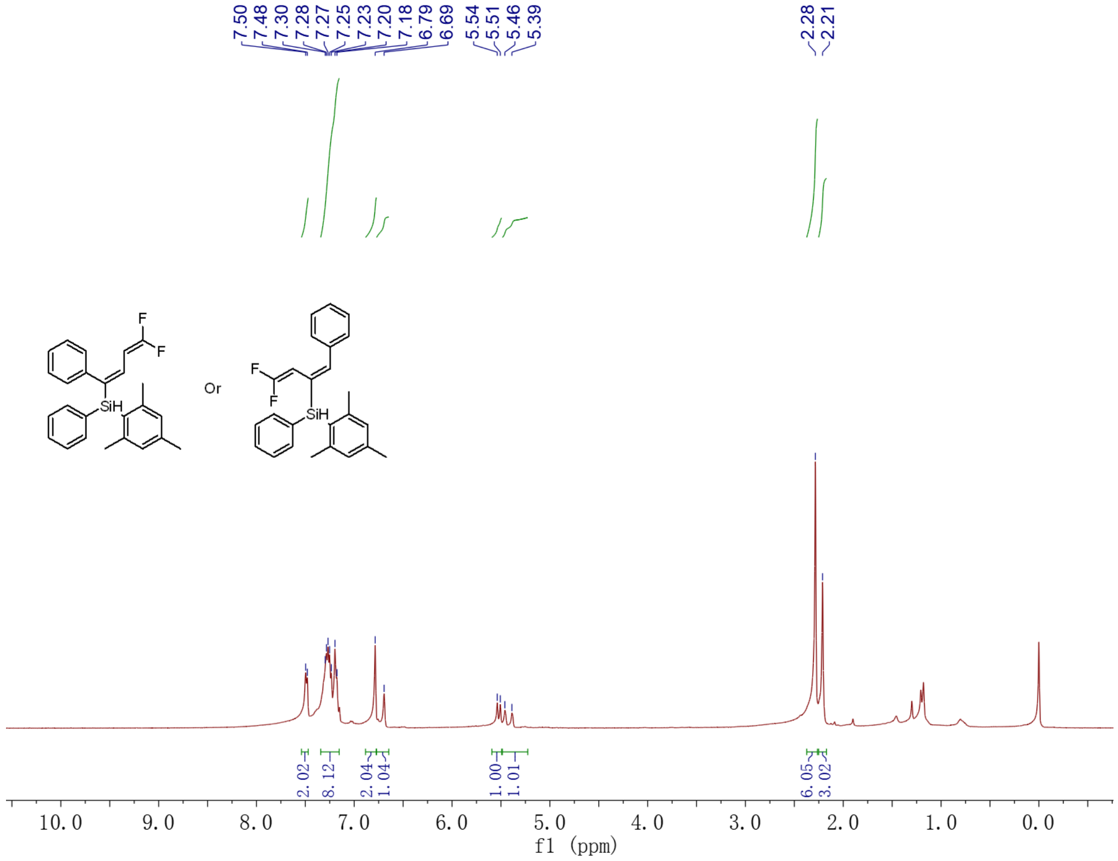
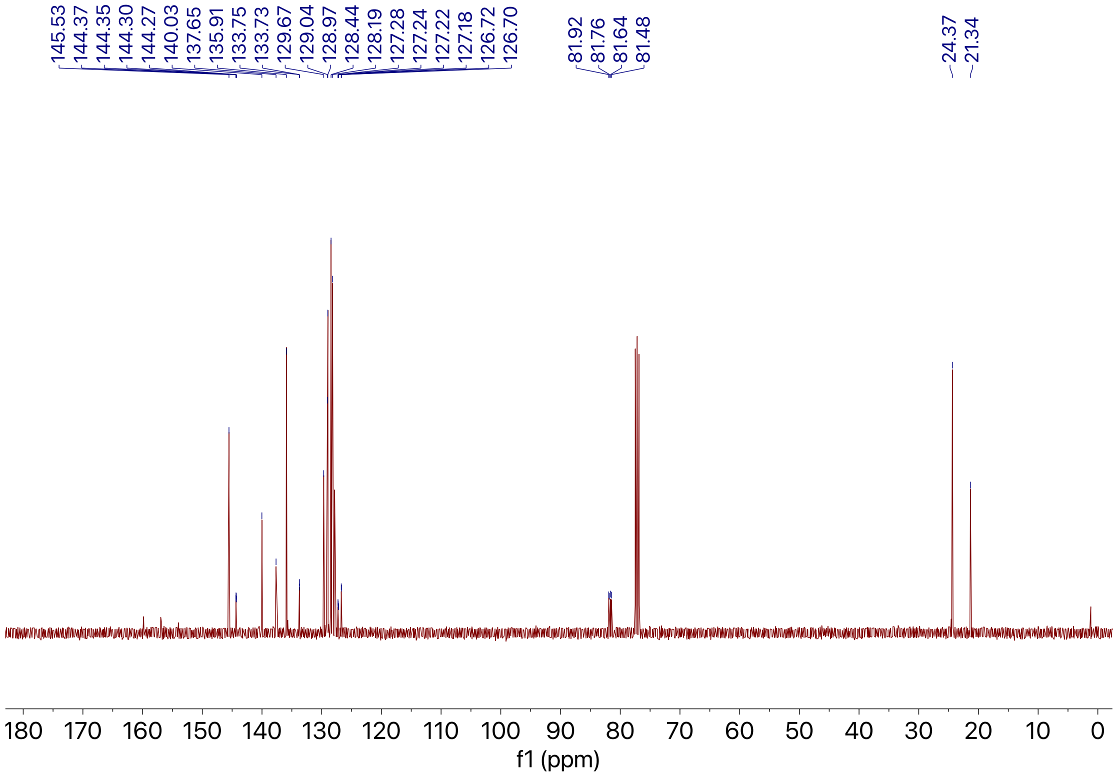
141.570
138.652
134.039
133.780
133.221
131.329
131.301
129.899
129.855
129.302
128.951
128.524
127.633
114.789
114.569
100.679
100.625
71.522
71.111
59.881
29.916
29.901
22.022
19.168
19.147
13.559
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.50
7.48
7.30
7.28
7.27
7.25
7.23
7.20
7.18
6.79
6.69
5.54
5.51
5.46
5.39
2.28
2.21
F
F
SiH
Or
F
F
SiH
2.02
8.12
2.04
1.04
1.00
1.01
6.05
3.02
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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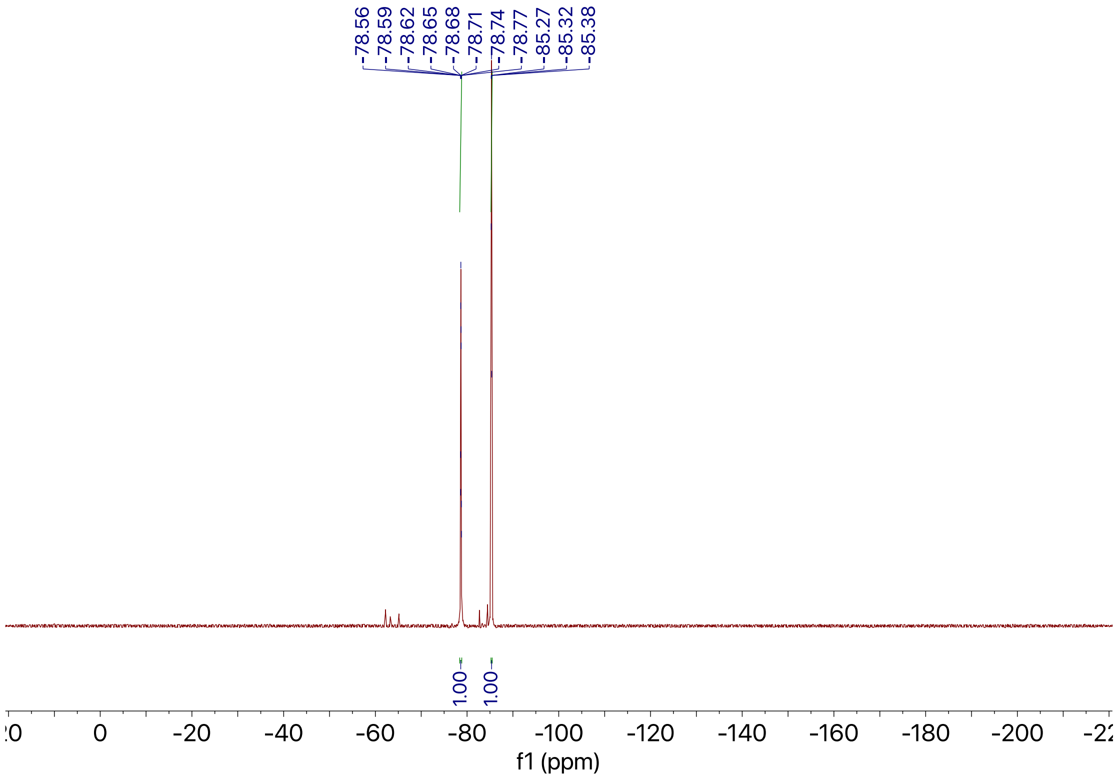
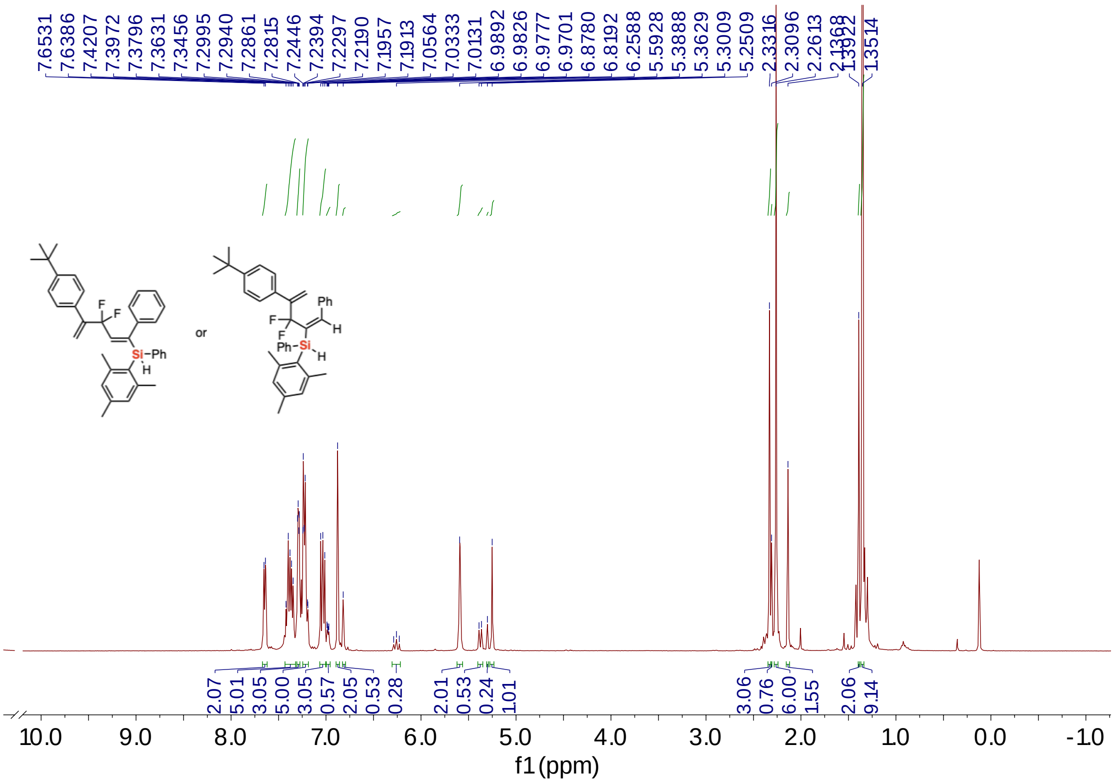
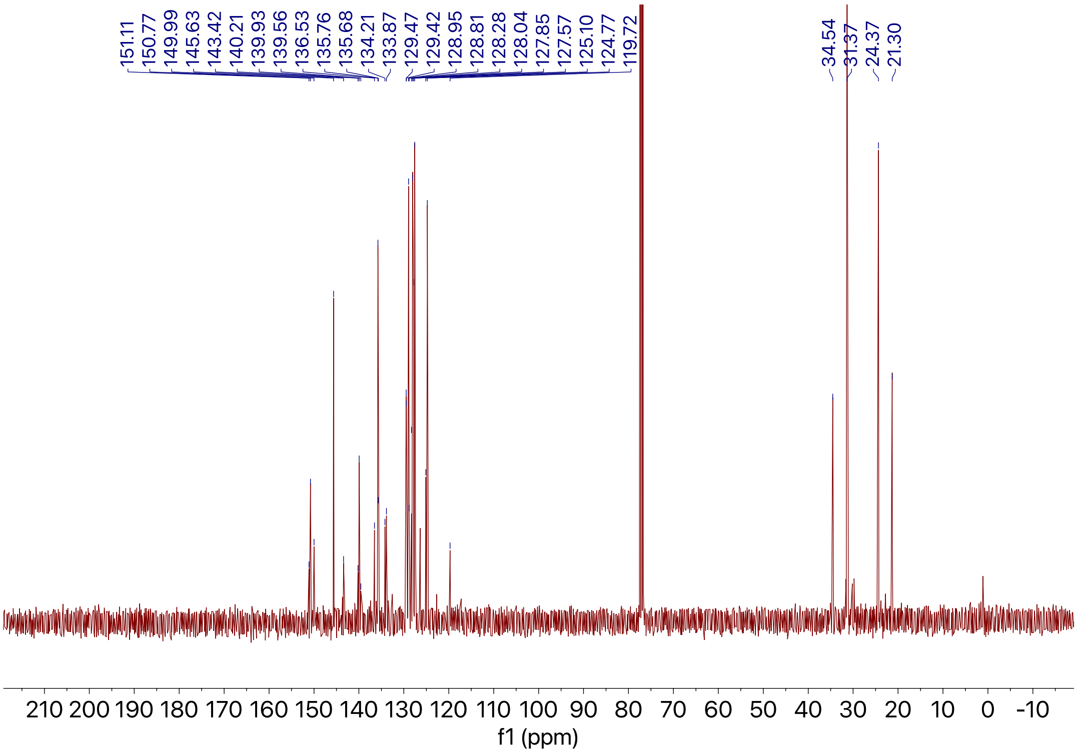
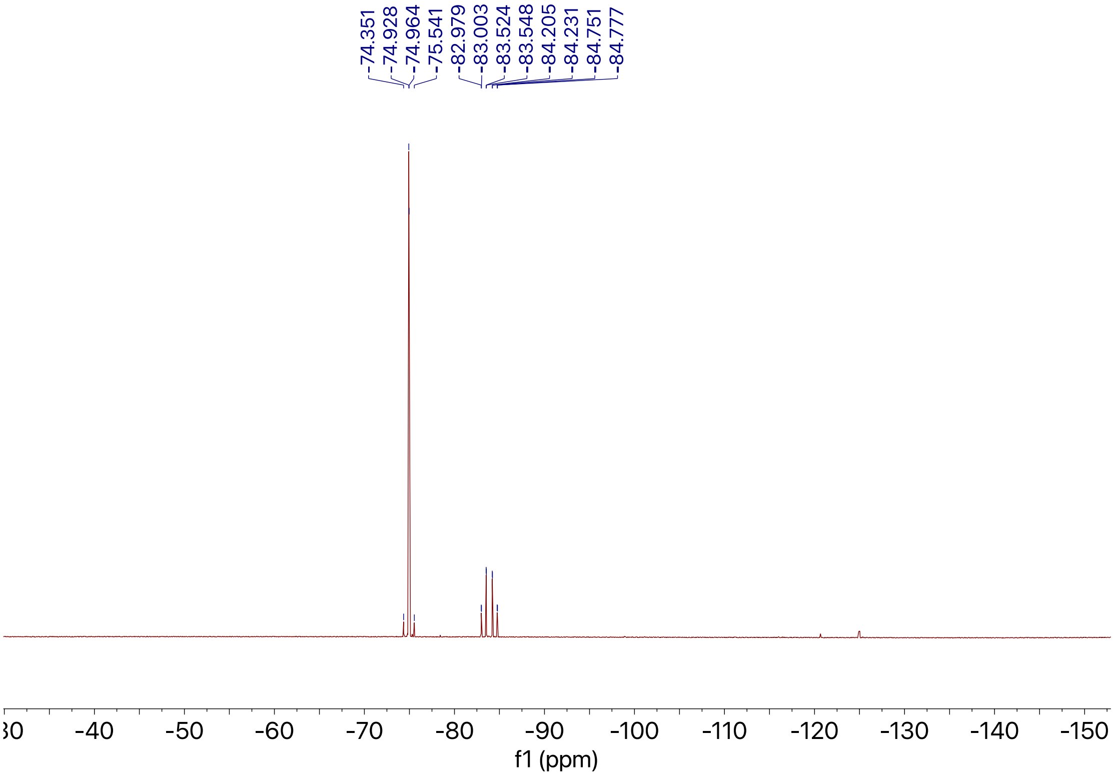
144.35
144.30
144.27
140.03
137.65
135.91
133.75
133.73
129.67
129.04
128.97
128.44
128.19
127.28
127.24
127.22
127.18
126.72
126.70
81.92
81.76
81.64
81.48
24.37
21.34
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-78.56
-78.59
-78.62
-78.65
-78.68
-78.71
-78.74
-78.77
-85.27
-85.32
-85.38
1.00
1.00
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)


7.6531
7.6386
7.4207
7.3972
7.3796
7.3631
7.3456
7.2995
7.2940
7.2861
7.2815
7.2446
7.2394
7.2297
7.2190
7.1957
7.1913
7.0564
7.0333
7.0131
6.9892
6.9826
6.9777
6.9701
6.8780
6.8192
6.2588
5.5928
5.3888
5.3629
5.3009
5.2509
2.3316
2.3096
2.2613
2.1368
1.3922
1.3514
F
F
Si
Ph
H
or
Ph
F
F
H
Ph
Si
H
2.07
5.01
3.05
5.00
3.05
0.57
2.05
0.53
0.28
2.01
0.53
0.24
1.01
3.06
0.76
6.00
1.55
2.06
9.14
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)


151.11
150.77
149.99
145.63
143.42
140.21
139.93
139.56
136.53
135.76
135.68
134.21
133.87
129.47
129.42
128.95
128.81
128.28
128.04
127.85
127.57
125.10
124.77
119.72
34.54
31.37
24.37
21.30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-74.351
-74.928
-74.964
-75.541
-82.979
-83.003
-83.524
-83.548
-84.205
-84.231
-84.751
-84.777
-40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
f1 (ppm)