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Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl Ethers

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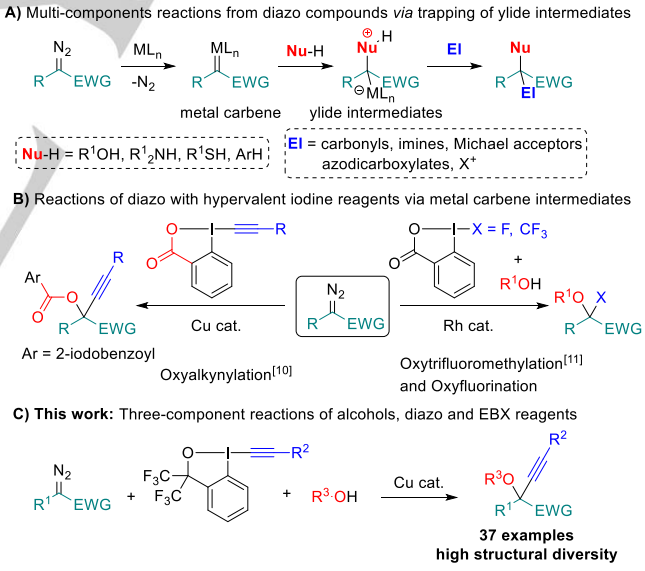
Abstract: Multicomponent reactions provide efficient means to access molecular complexity. Herein, we report a copper-catalyzed three-component reaction of diazo compounds, alcohols and ethynyl benziodoxole (EBX) reagents for the synthesis of propargyl ethers. Extensive variations of the three partners of the reaction is possible, leading to highly functionalized and structurally diverse products under mild conditions. Alkynylation of a copper ylide intermediate is postulated as key step for this transformation.

Multicomponent reactions are ideally suited for a fast entry into molecular complexity.[1] It is therefore not surprising that classical multicomponent reactions such as the Ugi or the Passerini reactions have had a major impact on both synthetic and medicinal chemistry.[2] Recently, diazo compounds have emerged as ideal partners in multicomponent reactions, with or without the help of transition metal catalysts.[3] In particular, transient ylide intermediates generated from the insertion of protic nucleophiles (alcohols, amines, thiols and aromatic compounds) into metal-carbenes generated from diazo compounds have been intercepted with various electrophiles (carbonyl compounds, imines, Michael acceptors, azodicarboxylates, electrophilic halogen sources,…) to simultaneously generate two new bonds (Scheme 1A).[4] To further develop the use of this strategy in multicomponent reactions, it is now important to extend the scope of compatible nucleophiles/electrophiles for achieving a higher molecular diversity.

In this context, hypervalent iodine reagents in general[5] and cyclic derivatives in particular[6] have demonstrated their versatility for the Umpolung of the reactivity of functional groups, giving access to a broad range of non-classical electrophiles. However, their use in multi-component reactions involving diazo compounds is not yet well established. In the absence of a metal-catalyst, Murphy and co-workers have first reported dihalogenation reactions.[7] More recent examples involve acetoxyaminoalkylation[8] and azidoaminoalkylation.[9] The first transformations involving metal carbene intermediates were reported independently by our group[10] and Szabo and co-workers.[11] We developed a copper-catalyzed oxy-alkynylation using ethynylbenziodoxolone (EBX) reagents, whereas Szabo and co-workers successfully implemented a rhodium-catalyzed oxy-fluoro/trifluoromethylation with benziodoxole reagents (Scheme 1B). These two transformations constitute efficient multi-bond forming reactions combining hypervalent iodine reagents and diazo compounds and most probably proceed *via* ylide intermediates generated from metal carbenes. Nevertheless, they remain strongly limited in the diversity of structures accessible: our work allowed exclusively the introduction of iodo-benzoate derivatives as nucleophilic partners in the three-component reaction, whereas the work of Szabo-and co-workers was limited to fluoride or trifluoromethyl as one of the partners. Therefore, there is an urgent need for more general three-component reactions of diazo compounds, nucleophiles and hypervalent iodine reagents, allowing for extensive variation of the three partners with diverse functional groups in order to maximize the structural diversity of the products.

Herein, we report the copper-catalyzed three-component reaction of diazo compounds, ethynylbenziodoxoles (EBXs) and alcohols, which overcomes this limitation (Scheme 1C). The three components of the reaction can be extensively varied, leading to a broad range of important propargylic ether building blocks with high structural diversity.[12] In particular, primary, secondary and tertiary alcohols, as well as a broad range of functional groups (including alkene, alkyne, fluoro, chloro, bromo, ether, ester, ketone, carbamate, imide, cyano, boronic ester and heterocyclic groups) were well tolerated, which would be difficult to achieve using traditional etherification methods under strongly basic or acidic conditions. The transformation can be performed using simple copper salts as catalyst, and does not require the use of one of the partners in large excess.



Scheme 1. Multi-component reactions of diazo compounds involving ylide intermediates and new disconnections enabled by hypervalent iodine reagents.

We first investigated the three-component reaction of TIPS-EBX (**1**), ethyl diazoacetate (**3a**) and ethanol (**4a**) (Table 1). In our previous work on the two-component process, diimine an bisoxazoline ligands on the copper catalyst led to best results.[10] Using $Cu(MeCN)_4BF_4$ as catalyst, diimine **8** or *tert*-butyl bisoxazoline (*t*Bu-BOX (**9**)) as ligands and ethanol as solvent, the desired product **5a** could be obtained in 50% and 63% yield, respectively (entries 1 and 2). However, despite using ethanol as solvent, a significant amount (30-32%) of the two-component product **7a** was still obtained. Furthermore, when only 10

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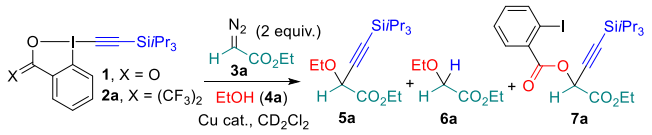
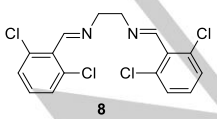
equivalents of ethanol were used, the yield of **6a** dropped to 22% (entry 3), showing that these conditions would not be useful to develop a general three-component reaction.

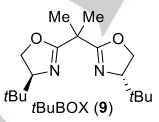
Table 1. Optimization of the three-component reaction



Entry	EBX	Equiv EtOH (**4a**)	Catalyst/Ligand(additive)	Yield **5a**/**6a**/**7a** [%][a]
1	**1**	as solvent	4 mol% $Cu(MeCN)_4BF_4$/**8**	50/n.d./32
2	**1**	as solvent	4 mol% $Cu(MeCN)_4BF_4$/**9**	63/n.d./30
3	**1**	10	4 mol% $Cu(MeCN)_4BF_4$/**9**	22/n.d./52
4	**2a**	as solvent	4 mol% $Cu(MeCN)_4BF_4$/**9**	62/n.d./-
5	**2a**	as solvent	4 mol% $Cu(MeCN)_4BF_4$	100/48/-
6	**2a**	10	4 mol% $Cu(MeCN)_4BF_4$	100/47/-
7	**2a**	4	4 mol% $Cu(MeCN)_4BF_4$	80/49/-
8	**2a**	2	4 mol% $Cu(MeCN)_4BF_4$	53/51/-
9	**2a**	2	10 mol% $Cu(MeCN)_4BF_4$	62/38/-
10	**2a**	2	10 mol% $Cu(MeCN)_4PF_6$	74/18/-
11	**2a**	2	10 mol% CuOTf-toluene	60/33/-
12	**2a**	2	10 mol% $CuOTf_2$	47/11/-
13	**2a**	2	10 mol% CuBr	16/24/-
14	**2a**	2	10 mol% $CuCl_2$	30/17/-
15	**2a**	2	10 mol% CuTC	10/40/-
16[b]	**2a**	2	10 mol% $Cu(MeCN)_4BF_4$/$NaHCO_3$	50/36/-
17	**2a**	4	10 mol% $Cu(MeCN)_4PF_6$	94/11/-
18[c]	**2a**	1	10 mol% $Cu(MeCN)_4PF_6$	37/17/-

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. The hypervalent iodine reagent **1**/**2a** and the diazo compound **3a** are used as limiting reagents to calculate the yield of **5a**/**7a** and **6a** respectively. Reactions were run on a 0.08 mmol scale. n.d. = not determined. [b]With 2 equivalents of sodium bicarbonate. [c]One equivalent of diazo compound **3a** was used.

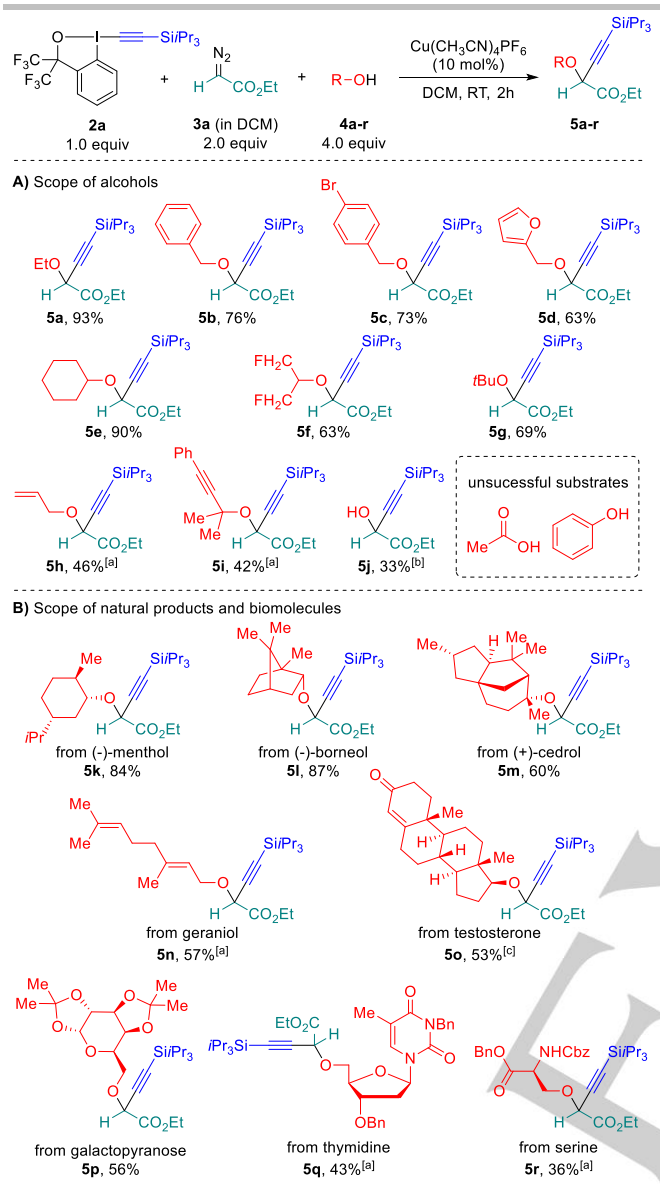




We therefore decided to modify the hypervalent iodine reagent. We turned to hexafluoro*iso*propanol derivative **2a**,[13] expecting a lower nucleophilicity of the oxygen atom. Indeed, in this case only the three-component product **5a** was obtained in 62% yield (entry 4). An enhanced reactivity was observed in absence of the BOX ligand, resulting in quantitative formation of product **5a** together with O-H insertion product **6a** (entry 5). Gratifyingly, the same result was obtained when only 10 equivalents of ethanol (**4a**) were used (entry 6). The yield of **5a** decreased to 80% and 53% respectively with 4 and 2 equivalent of ethanol (**4a**) (entries 7 and 8). Using a higher catalyst loading, **5a** could be still obtained in 62% with only 2 equivalents of ethanol (**4a**) (entry 9). At this point, different copper salts were examined. Complexes with non-coordinating counterions performed better (entries 10-12) than copper halogenides (entries 13 and 14) or thiophenecarboxylate (TC, entry 15).[14] The best result was obtained with PF_6^- as counterion, giving **5a** in 74% yield, with only 18% of O-H insertion product **6a** formed (entry 10). We then wondered if basic condition may slow down the formation of **6a**. However, a lower yield was observed in presence of sodium hydrogen carbonate (entry 16) and the reaction completely stopped in presence of other bases such as carbonate, acetate or hydroxide salts (result not shown, see Supporting Information). For cheap alcohols a larger excess is reasonable, and **5a** could be obtained in 94% yield with 4 equivalents of ethanol (**4a**) (entry 17). Unfortunately, the formation of the alcohol insertion side product cannot be fully suppressed and it was observed for most transformations described in this study. Nevertheless, **5a** was still formed in 37% yield when EBX **2a**, diazo compound **3a** and ethanol (**4a**) were used in equimolar amounts (entry 18).

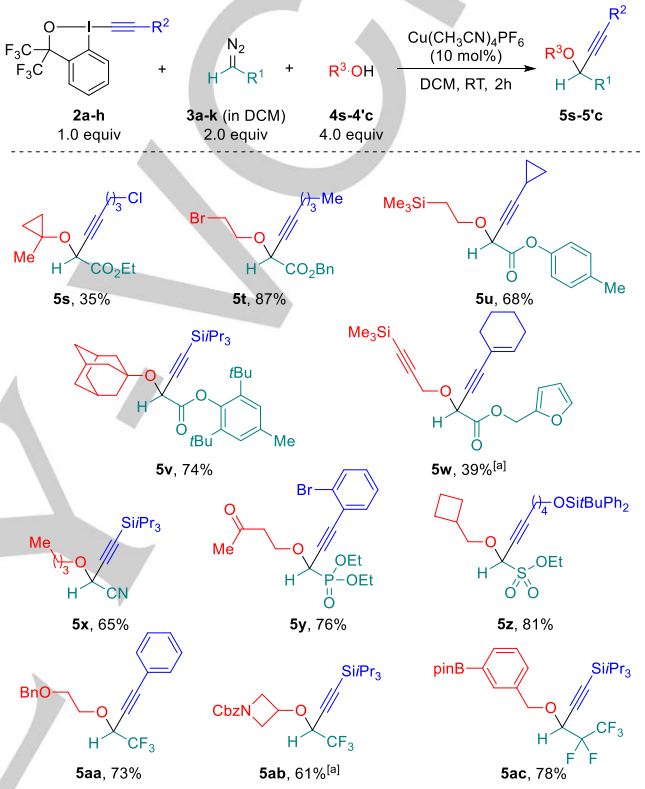
With optimized conditions in hand, we started to investigate the scope of the three-component reaction. First, we employed a variety of alcohols with EBX **2a** and ethyl diazo acetate **3a** as the two other partners (Scheme 2A). On 0.3 mmol scale, propargylic ether **5a** was isolated in 93% yield.[15] Benzyl alcohol provided the corresponding product **5b** in a slightly diminished yield. Introducing a bromo substituent in the *para* position gave **5c** in 73% yield. A heteroaromatic ring was also tolerated providing product **5d** from furfuryl alcohol in 63% yield. We also examined secondary alcohols. Cyclohexanol was well tolerated and furnished the corresponding product **5e** in 90% yield. We were pleased to see that the more electron-poor 1,3-difluoro-2-propanol gave the desired product **5f** in good yield. Sterically hindered *tert*-butanol still reacted remarkably well to give the corresponding three-component product **5g** in 69% yield. Such *tert*-butyl ethers represent a synthetic challenge and are classically accessed by strong acid-catalyzed addition of isobutene to alcohols.[16] In the case of an allyl substituent, no reaction was observed at room temperature, but at 40 °C **5h** was obtained in moderate yield. A similar temperature was needed to access the bis-propargyl ether derivative **5i** in 42% yield. These results may indicate a coordination of π bonds to the cationic copper catalyst.[17] Dissociation would be needed to allow the diazo compound to coordinate and form the metal carbene, requiring a higher reaction temperature. We then examined other O-nucleophiles than alcohols. Water was a suitable partner and gave the functionalized propargylic alcohol **5j** in 33% yield. However, only trace amount of the desired product was observed with acetic acid, while a complex reaction mixture was obtained with phenol.

Next, we turned our attention to more complex alcohol-containing natural products (Scheme 2B). We were pleased to see that several terpenes such as (-)-menthol and (-)-borneol were easily functionalized and gave the corresponding three-component products **5k** and **5l** in very good yields. (+)-Cedrol, possessing a tertiary alcohol, was converted to **5m** in 60% yield. Geraniol was a successful nucleophile partner, providing **5n** in 57% yield, despite the presence of two potentially coordinating double bonds. Other types of natural products and biomolecules were then engaged in the three-component reaction. Notably, testosterone, protected galactose, protected thymidine and protected serine all furnished the desired propargylic ether (**5o**, **5p**, **5q** and **5r**) in moderate yields showing the breadth of the scope for alcohols.



Scheme 2. Copper(I)-catalyzed three-component reaction of alcohols with ethyl diazoacetate and TIPS-EBX. Unless otherwise noted, the reaction conditions are as follows: **2a** (0.3 mmol), **3a** solution in 1.0 mL DCM (0.6 mmol), **4a-r** (1.2 mmol), DCM (2.0 mL). All yields refer to the isolated products. When applicable, ca. 1:1 d.r. was obtained. [a]Reaction conducted at 40 °C. [b]10.0 equiv. of water was used. [c]3.0 equiv. of alcohol was used.

The main strength of multi-component reactions resides in the structural diversity of accessible compounds. Therefore, we decided to simultaneously vary each of the three components of the reaction to further investigate the flexibility of our methodology, (Scheme 3). We were pleased to see that diazo esters bearing various substituents, such as alkyl (**5s** and **5t**), aryl (**5u**), bulky aryl (**5v**) or heteroaromatic (**5w**) were tolerated. Diazo amides were not suitable reagents, furnishing only traces of the desired 3-component products (not shown). Other diazo compounds bearing diverse versatile functionalities (nitrile (**5x**), phosphonate (**5y**), sulfonate (**5z**), and perfluorinated alkyls (**5aa, 5ab** and **5ac**)) were successfully applied. The scope of EBX partners was also broad, including alkyl chains (**5s, 5t, 5u** and **5z**), alkenyl (**5w**) and aromatic substituents (**5y** and **5aa**) that contained several functional groups like halide (**5s** and **5y**) or a silyl ether (**5z**) and carbocycles, such as a cyclopropane (**5u**). In addition, further versatile functional groups were tolerated on the alcohols, including a bromide (**5t**), a ketone (**5y**), protected hydroxy (**5u** and **5aa**) or a boronic ester (**5ac**) groups. Several carbocyclic or heterocyclic motifs important for medicinal chemistry such as cyclopropyl (**5s**), cyclobutyl (**5z**), azetidinyl (**5ab**), or adamantyl (**5v**) were also tolerated on the alcohol. In general, the reactions occurred smoothly, affording products in good yields. By-products and a diminished yield were obtained for the synthesis of **5s**, cyclopropyl alcohols being prone to ring-opening in presence of Cu(I) catalyst.[18] The multiple unsaturations of substrate **5w** could explain why only partial conversion of the EBX reagent was observed, resulting in a moderate yield.

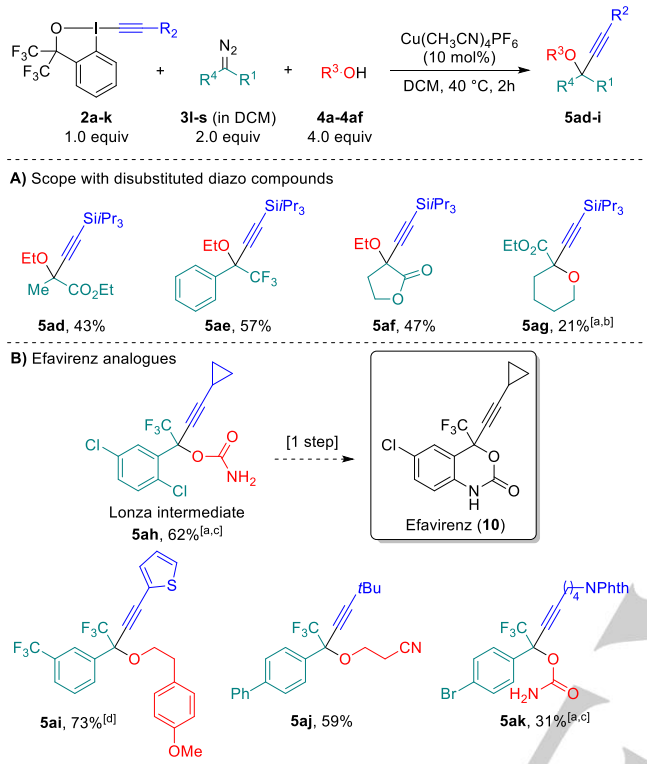


Scheme 3. Substrate scope with simultaneous variation of the three components. Unless otherwise noted, the reaction conditions are as follows: **2a-h** (0.3 mmol), **3a-k** solution in 1.0 mL DCM (0.6 mmol), **4s-4ac** (1.2 mmol), DCM (2.0 mL). All yields refer to the isolated products. [a]Reaction conducted at 40 °C.

Next, we used disubstituted diazo compounds (Scheme 4A). Diazo compounds bearing a methyl or a phenyl substituent furnished **5ad** and **5ae** in 43% and 57% yield respectively, without the need to reoptimize the reaction conditions. A cyclic diazo compound provided **5af** in moderate yield. Finally, we investigated a substrate having a pendant hydroxy group for intramolecular nucleophile attack. The desired tetrahydropyran **5ag** was formed, albeit in low yield.

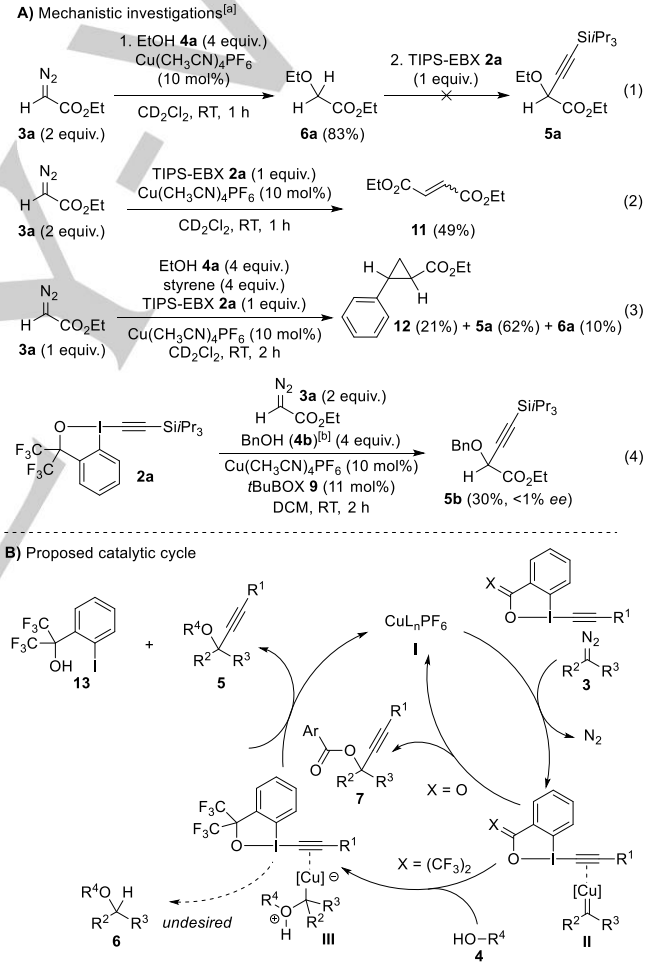
The high efficiency of the three-component reaction with trifluoromethyl-substituted diazo compounds is especially interesting, as organofluorine compounds are of significant importance in the pharmaceutical, agrochemical and materials industry.[19] For example, Efavirenz (**10**), which contains a CF_3-propargyl motif, is one of the most frequently prescribed antiretroviral drug used in HIV treatment. We decided to apply our methodology to access the Lonza intermediate **5ah**, a direct precursor to Efavirenz (**10**) (Scheme 4B).[20] We envisaged the use of *tert*-butyl carbamate as nucleophile, anticipating that O-attack followed by loss of the *tert*-butyl group could generate the desired NH_2-carbamate. In this case, the number of equivalents of reagents, as well as the catalyst loading, could be reduced as

there was no competitive O-H insertion pathway. The desired molecule **5ah** was obtained in good yield without the formation of products from N-H insertion.[21] Our methodology also gave access to structurally diverse analogues. The poly-trifluoromethylated compound **5ai**, bearing a thiophene on the alkyne, was synthesized in good yield, as well as ether **5aj** bearing a nitrile group.[22] Finally, the carbamate derivative **5ak** containing a protected amine and an aryl bromide was obtained in 31% yield.



Scheme 4. Substrate scope with disubstituted diazo compounds and Efavirenz analogues. Unless otherwise noted, the reaction conditions are as follows: **2a-k** (0.3 mmol), **3l-s** solution in 1.0 mL DCM (0.6 mmol), **4a-4af** (1.2 mmol), DCM (2.0 mL). All yields refer to the isolated products. [a]The reaction was conducted at RT. [b]No alcohol was used. [c]$BocNH_2$ **4ad** (1.3 equiv), **3p-s** (1.3 equiv) and $Cu(CH_3CN)_4PF_6$ (5 mol%) were used. [d]Yield determined by ^{19}F NMR spectroscopy.

To gain insights into the mechanism, several control experiments were carried out (Scheme 5A). First, when ethyl diazoacetate (**3a**) was reacted with ethanol (**4a**) in presence of 10 mol% of $Cu(CH_3CN)_4PF_6$, we observed the formation of **6a** by ^1H NMR spectroscopy analysis of the reaction mixture (Eq. (1)). However, no three-component product **5a** was observed after the subsequent addition of TIPS-EBX (**2a**) to this solution. This indicates that **6a** is not an intermediate in the catalytic cycle. When mixing reagent **2a** and diazo **3a** in the presence of the copper catalyst, rapid evolution of nitrogen occurred and we mainly observed the formation of diethyl fumarate/maleate (**11**) (Eq. (2)).[3d] Other products resulting from a minor decomposition (ca. 10%) of the hypervalent iodine reagent **2a** could not be identified. A ^1H NMR titration experiment was then carried out using $Cu(CH_3CN)_4PF_6$ in combination with EBX **2a**. Progressive shifts of the aromatic ^1H were observed upon addition of the copper salt, with a significant diminution after one equivalent (See Figure S3 in Supporting Information). A ^{13}C NMR spectrum of an equimolar mixture of $Cu(CH_3CN)_4PF_6$ and **2a** in CD_2Cl_2 showed major changes in the ^{13}C-alkyne signals, while other peaks remained nearly constant (See Figure S5 in Supporting Information). When ethanol (4 equiv.) and $Cu(CH_3CN)_4PF_6$ (1 equiv.) were mixed together in CD_2Cl_2, no ligand exchange was observed (See Figure S6 in Supporting Information). These NMR studies indicated an interaction between the Cu catalyst and the EBX reagent **2a**, probably through the alkyne, but no complete reaction, making oxidative addition of the reagent onto copper to form a Cu(III) intermediate a less probable pathway.[23] We then attempted the trapping of a potential Cu-carbene intermediate through a cyclopropanation reaction using one equivalent of ethyl diazoacetate (**3a**) and 4 equivalents of ethanol (**4a**) and styrene (Eq. (3)). Cylcopropane **12** was obtained in 21% NMR yield, and the three-component product **5a** was formed in 62% yield. Aside from supporting the existence of a metal carbene, this competitive experiment, also shows that attack of ethanol to form a putative oxonium ylide is faster than cyclopropanation. Finally, we re-examined the reaction of **2a**, **3a** and benzyl alcohol (**4b**) in presence of chiral ligand **9** under the optimized reaction conditions. The product **5a** was obtained in poor yield as a racemic compound (Eq. (4)). This may indicate that ligand decomplexation is required for the reaction to proceed, making the development of an enantioselective method highly challenging.



Scheme 5. Mechanistic studies and proposed catalytic cycle. [a]Yields determined by ^1H NMR analysis of the crude reaction mixture.

Based on the results of our control experiments and the relevant literature on metal-ylide based multicomponent reactions,[3] our proposed catalytic cycle is presented in Scheme 5B. Starting with Cu(I) catalyst **I**, reaction with diazo compound **3** and the hypervalent iodine reagents generates electrophilic copper-carbene **II** with alkyne-bound EBX. At this stage, it is difficult to establish if coordination of the hypervalent iodine

reagents is occurring before or after carbene formation. From **II**, two pathways are possible: With carboxylate reagent **1**, intramolecular oxygen attack directly followed by alkynylation leads to two-component product **7**; With bis-trifluoromethyl reagents **2**, the oxygen atom of the benziodoxole is not nucleophilic enough, and attack of the external alcohol **4** forms oxonium-ylide intermediate **III**. Intramolecular alkynylation by EBX reagent **2** with simultaneous deprotonation then generates the 3-component product **5** and iodide **13**, releasing the copper catalyst. Undesired 1,2-H shift on the transient ylide **III** produces the O-H insertion product **6**. Further studies will be needed to establish the mechanism of the alkynylation step.

In conclusion, we have reported a general copper-catalyzed three-component reactions of alcohols, diazo compounds and alkynyl benziodoxole reagents. The reaction can be done under mild conditions and each of the three partners can be extensively varied, leading to maximal structural diversity. Preliminary mechanism investigations support a mechanism involving subsequent formation of copper carbene and ylide intermediates, followed by electrophilic alkynylation. Future work in our laboratory will focus on a more in-depth understanding of the reaction mechanism, the development of an enantioselective variation and the use of other classes of nucleophilic partners in the three-component transformation.

Acknowledgements

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Keywords: multi-component reactions (MCR); copper catalysis; molecular complexity; hypervalent iodine reagents; carbenes.

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[15] On scope scale, better results were obtained when diazo compound **3** was added slowly as a solution in CH_2Cl_2 (0.6 M, addition rate 1 mL/h).

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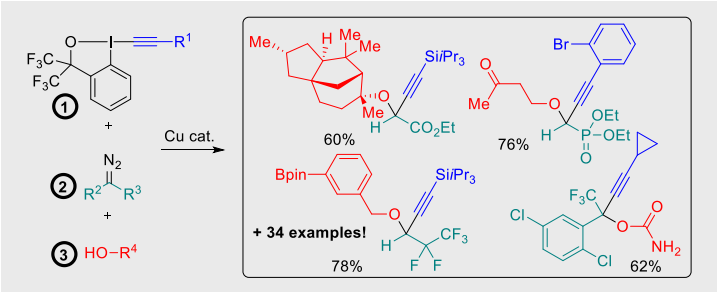
COMMUNICATION



***Power 3**: A copper-catalyzed three-component reaction of hypervalent iodine reagents, diazo compounds and alcohols has been developed. The transformation gives access to functionalized propargylic ethers with high structural diversity, as variation of the three partners with numerous functional groups was tolerated. The reaction is speculated to proceed via a copper oxonium ylide intermediate.*

*Guillaume Pisella, Alec Gagnebin and Jerome Waser**

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Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl Ethers

Supporting Information

(110 pages)

Authors contributions: G. P. performed and planned the experiments and prepared the manuscript and the experimentals part, A. G. performed the experiments as a laboratory technician in formation under the supervision of G. P., J. W. supervised the project, prepared the manuscript and corrected the experimental part.

Table of Contents

1. General Methods

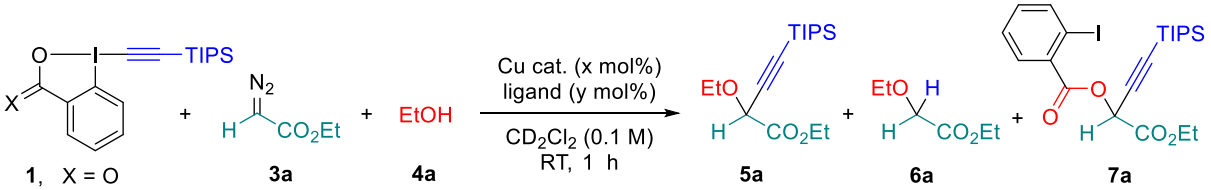
All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, *Karl-Fischer* titration). The solvents were degassed by Freeze-Pump-Thaw method when mentioned. All chemicals were purchased from Acros, Aldrich, Fluka, Fluorochem, TCI, VWR or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC aluminium plates and visualized with UV light, permanganate stain or 4-anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in $CDCl_3$, DMSO-d_6 , CD_2Cl_2 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm, the internal dichloromethane signal at 5.32 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ^{13}C NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in $CDCl_3$, DMSO-d_6, CD_2Cl_2, or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm, the internal dichloromethane signal at 54.0 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurements were done on a Agilent 1260 Infinity autosampler using a CHIRALPAK IA column from DAICEL Chemical.

2. Optimization of the reaction conditions

a) Screening of the electrophilic alkynyl source, catalyst loading and ligands

In a N_2-filled glovebox, a catalytic solution was prepared by mixing $Cu(CH_3CN)_4BF_4$ (x mol%) and ligand (**8 - 9**) (y mol%) (when applicable) in CD_2Cl_2 (2.00 mL) at room temperature for 1 h.
The catalytic solution was prepared in EtOH when used as solvent.

0.40 mL of the catalytic solution was then added to a stirring solution of hypervalent iodine reagent (**1**, **2a** or **14**) (0.08 mmol, 1.00 equiv.), EtOH (**4a**) (w equiv.) and ethyl diazoacetate (**3a**) (v equiv.) in CD_2Cl_2 (0.40 mL). The resulting reaction mixture was stirred at room temperature for 1 h. After this time, a ^1H NMR spectrum of the reaction mixture was recorded. Yields were obtained by comparing the integration of the signals at 8.43-8.36 ppm for **2a**, 8.17 ppm for the corresponding alcohol, 4.72 ppm for **5a** and 4.03 ppm for **6a**, and are not calibrated.

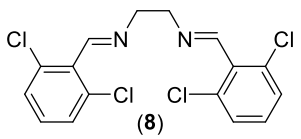


1, X = O
2a, X = $(CF_3)_2$

3a **4a** **5a** **6a** **7a**

entry	EBX (1 equiv.)	EDA 3a (v equiv.)	EtOH 4a (w equiv.)	Cu cat. (x mol%)	ligand (y mol%)	yield 5a/6a/7a [%][a]
1	**1**	2.00	as solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**8** (4 mol%)	50/n.d./32
2	**1**	2.00	as solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**9** (4 mol%)	63/n.d./30
3	**1**	2.00	10.0	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**9** (4 mol%)	22/n.d./52
4	**2a**	2.00	as solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**9** (4 mol%)	62/n.d./-
5	**14**	2.00	as solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	**9** (4 mol%)	-/n.d./-
6	**2a**	2.00	as solvent	$Cu(CH_3CN)_4BF_4$ (4 mol%)	-	100/48/-
7	**2a**	2.00	10.0	$Cu(CH_3CN)_4BF_4$ (4 mol%)	-	100/47/-
8	**2a**	2.00	4.00	$Cu(CH_3CN)_4BF_4$ (4 mol%)	-	80/49/-
9	**2a**	2.00	2.00	$Cu(CH_3CN)_4BF_4$ (4 mol%)	-	53/51/-
10	**2a**	**2.00**	**2.00**	**$Cu(CH_3CN)_4BF_4$ (10 mol%)**	**-**	**62/38/-**
11	**2a**	1.00	2.00	$Cu(CH_3CN)_4BF_4$ (10 mol%)	-	34/42/-

[a] Determined by ^1H NMR analysis



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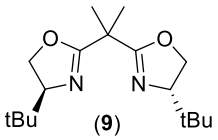
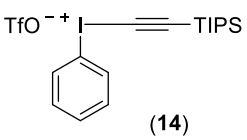


(**9**)

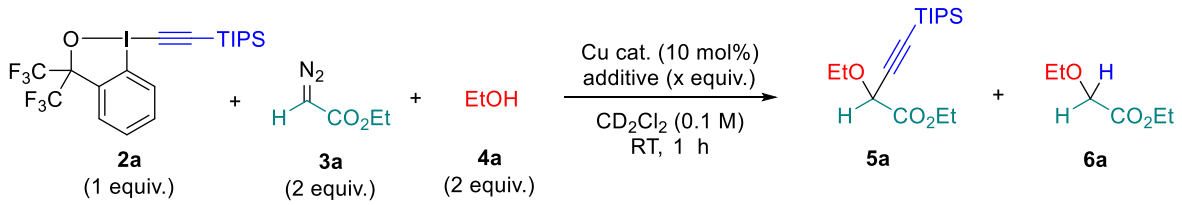


(**14**)

It was found that reagent **2a** was converted only to the desired three-component product **5a**. The absence of a ligand was beneficial for the formation of **5a**. Increasing the Cu catalyst loading to 10 mol% improved the formation of **5a**.

b) Screening of additives

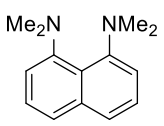
In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4BF_4$ (2.52 mg, 8.00 µmol, 0.10 equiv.), TIPS-EBX **2a** (44.0 mg, 80.0 µmol, 1.00 equiv.) and the additive (x equiv.), if solid. The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by EtOH (**4a**) (9.34 µL, 160 µmol, 2.00 equiv.), the additive (x equiv.), if liquid, and ethyl diazoacetate (**3a**) (19.0 µL, 160 µmol, 2.00 equiv., 87%wt in DCM). The resulting reaction mixture was stirred at room temperature for 1 h. After this time, ^{1}H NMR spectrum of the reaction mixture was recorded.



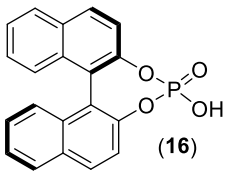
2a (1 equiv.) + **3a** (2 equiv.) + **4a** (2 equiv.) → **5a** + **6a**

entry	Cu cat. (10 mol%)	additive (x equiv.)	yield 5a/6a [%][a]
1	$Cu(CH_3CN)_4BF_4$	proton sponge (**15**) (2.00)	no reaction
2	$Cu(CH_3CN)_4BF_4$	LiOH (2.00)	no reaction
3	$Cu(CH_3CN)_4BF_4$	Cs_2CO_3 (2.00)	no reaction
4	$Cu(CH_3CN)_4BF_4$	NaOAc (2.00)	no reaction
5	$Cu(CH_3CN)_4BF_4$	$NaHCO_3$ (2.00)	50/36
6	$Cu(CH_3CN)_4BF_4$	HFIP (40.0)	0/100
7	$Cu(CH_3CN)_4BF_4$	CPA (**16**) (5 mol%)	13/85

[a] Determined by ^{1}H NMR analysis



(**15**)



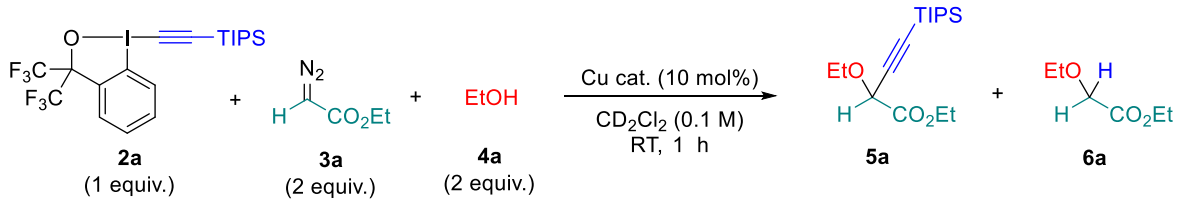
(**16**)

None of the additives screened above were found to improve the formation of the three-component product **5a**.

c) Screening of the copper catalysts

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with Cu cat. (8.00 µmol, 0.10 equiv.) and TIPS-EBX **2a** (44.0 mg, 80.0 µmol, 1.00 equiv.). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by EtOH (**4a**) (9.30 µL, 160 µmol, 2.00 equiv.) and ethyl diazoacetate (**3a**) (19.0 µL, 160 µmol, 2.00 equiv., 87%wt in DCM). The resulting reaction mixture

was stirred at room temperature for 1 h. After this time, ^{1}H NMR spectrum of the reaction mixture was recorded.



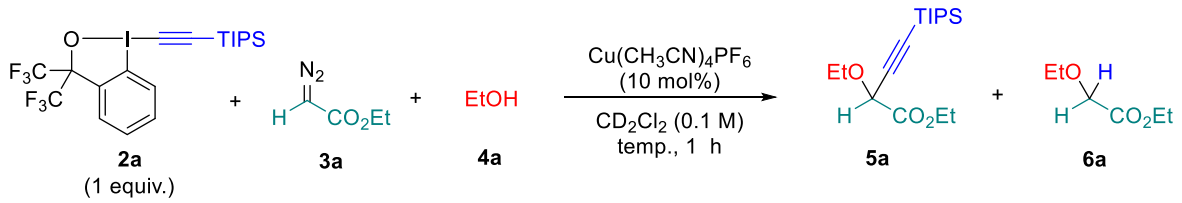
entry	Cu cat.	yield 5a/6a [%][a]
1	**$Cu(CH_3CN)_4PF_6$**	**74/18**
2	CuOTf•toluene	60/33
3	$Cu(OTf)_2$	47/11
4	$CuCl_2$	30/17
5	CuBr	16/24
6	CuI	no reaction
7	CuTC	10/40
8	CuCN	no reaction
9	CuOAc	no reaction
10	$Cu(C_5H_4F_3O_2)_2$	no reaction
11	$Cu(OAc)_2$	no reaction

[a] Determined by ^{1}H NMR analysis

It was found that $Cu(CH_3CN)_4PF_6$ was superior to $Cu(CH_3CN)_4BF_4$ to catalyze the formation of the three-component product **5a**.

d) Fine-tuning of the last parameters

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_4CN)_4PF_6$ (2.52 mg, 8.00 µmol, 0.10 equiv.) and TIPS-EBX **2a** (44.0 mg, 80.0 µmol, 1.00 equiv.). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by EtOH (**4a**) (w equiv.) and ethyl diazoacetate (**3a**) (v equiv.). The resulting reaction mixture was stirred at room temperature for 1 h. After this time, ^{1}H NMR spectrum of the reaction mixture was recorded.



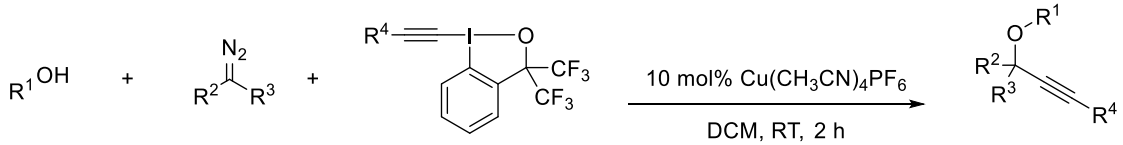
entry	EDA 3a (v equiv.)	EtOH 4a (w equiv.)	temp. (° C)	yield 5a/6a [%][a]
1	2	4	25	94 (84)[b]/11
2	2	4	0	95/11
3[c]	**2**	**4**	**25**	**94[b]/n.d.**
4	1	1	25	37/17

[a] Determined by ^{1}H NMR analysis [b] Isolated yield [c] The diazo compounds was added as a 0.6 M solution in DCM in 1 h *via* seringe pump. Reaction perfomed on scope scale (**2a**, 0.3 mmol)

It was found that 4 equivalents of EtOH **4a** was beneficial for the formation of the three-component product **5a**. It was found that the slow addition of a diluted solution of EDA **3a** improved the yield of **5a**.

3. 3-component reaction of alcohols, diazo compounds and EBX reagents

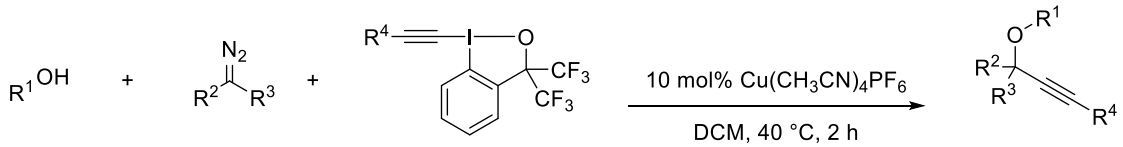
General procedure A: Three-component reaction at 25 °C.



4a - 4'f **3a - 3s** **2a - 2k** **5a - 5ak**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv.), EBX reagent (**2a – 2k**) (0.30 mmol, 1.00 equiv.) and alcohol (**4a – 4af**) (1.20 mmol, 4.00 equiv.), if solid. The vial was capped, removed from the glovebox and dry DCM (2.0 mL) was added. The alcohol was added at this point if liquid. To the resulting solution was added a 0.6 M solution of diazo compound (**3a – 3s**) (0.60 mmol, 2.00 equiv.) in dry DCM in 1 h *via* seringe pump at 25 °C. The system was mainted isobaric with a filled balloon with N_2. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography using EtOAc/pentane as eluent (the solvent ratio indicated in the R_f measurement was used), directly without further work-up to afford the corresponding product (**5a – 5ak**).

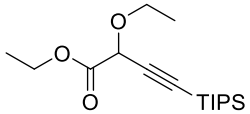
General procedure B: Three-component reaction at 40 °C.



4a - 4'f **3a - 3s** **2a - 2k** **5a - 5ak**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv.), EBX reagent (**2a – 2k**) (0.30 mmol, 1.00 equiv.) and alcohol (**4a – 4af**) (1.20 mmol, 4.00 equiv.), if solid. The vial was capped, removed from the glovebox and dry DCM (2.0 mL) was added. The alcohol was added at this point if liquid. To the resulting solution was added a 0.6 M solution of diazo compound (**3a – 3s**) (0.60 mmol, 2.00 equiv.) in dry DCM in 1 h *via* seringe pump at 40 °C. The system was mainted isobaric with a filled balloon with N_2. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography using EtOAc/pentane as eluent (the solvent ratio indicated in the R_f measurement was used), directly without further work-up to afford the corresponding product (**5a – 5ak**).

Ethyl 2-ethoxy-4-(triisopropylsilyl)but-3-ynoate (5a)

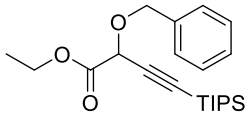


5a

Following general procedure A, starting from ethanol (**4a**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**6a**) as a colorless oil (87 mg, 0.28 mmol, 93%). R_f = 0.29 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1H, *H*CC≡C), 4.35 – 4.17 (m, 2H, C*H*$_2$OC(O)), 3.79 (dq, *J* = 9.1, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 3.65 (dq, *J* = 9.2, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 1.29 (m, 6H, 2 x OCH$_2$C*H*$_3$), 1.13 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 100.4, 89.2, 69.2, 64.6, 62.0, 18.7, 15.2, 14.2, 11.2; IR (ν_{max},

cm^{-1}) 2943 (m), 2867 (m), 2175 (w), 1759 (s), 1464 (m), 1281 (m), 1192 (m), 1116 (s), 1032 (s), 882 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{32}NaO_3Si^+$ 335.2013; Found 335.2009.

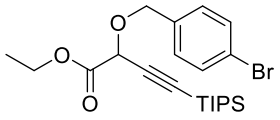
Ethyl 2-(benzyloxy)-4-(triisopropylsilyl)but-3-ynoate (5b)



5b

Following general procedure A, starting from benzyl alcohol (**4b**) (124 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5b**) as a colorless oil (85 mg, 0.23 mmol, 76%). R_f = 0.33 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H, ArH), 4.86 – 4.79 (m, 1H, OC*H*$_2$Ph), 4.79 – 4.69 (m, 2H, OC*H*$_2$Ph and *H*CC≡C), 4.35 – 4.16 (m, 2H, OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.13 – 0.97 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 136.9, 128.7, 128.6, 128.2, 100.0, 90.0, 70.4, 68.1, 62.0, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2175 (w), 1756 (s), 1463 (m), 1275 (m), 1192 (s), 1111 (s), 1031 (s), 882 (s), 739 (m), 697 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{34}NaO_3Si^+$ 397.2169; Found 397.2172.

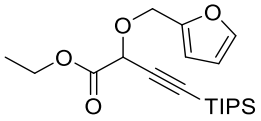
Ethyl 2-((4-bromobenzyl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5c)



5c

Following general procedure A, starting from 4-bromobenzyl alcohol (**4c**) (224 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5c**) as a colorless oil (99 mg, 0.22 mmol, 73%). R_f = 0.29 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H, Ar*H*), 7.32 – 7.24 (m, 2H, Ar*H*), 4.80 – 4.72 (m, 2H, OC*H*$_2$Ar and *H*CC≡C), 4.68 (m, 1H, OC*H*$_2$Ar), 4.35 – 4.16 (m, 2H, OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.96 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 136.1, 131.7, 130.2, 122.2, 99.7, 90.4, 69.6, 68.2, 62.1, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2892 (m), 2866 (m), 1755 (s), 1489 (m), 1463 (m), 1367 (m), 1279 (m), 1194 (s), 1112 (s), 1070 (s), 1039 (s), 1012 (s), 882 (s), 801 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{33}BrNaO_3Si^+$ 475.1275; Found 475.1279.

Ethyl 2-(furan-2-ylmethoxy)-4-(triisopropylsilyl)but-3-ynoate (5d)

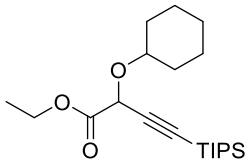


5d

Following general procedure A, starting from furfuryl alcohol (**4d**) (104 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5d**) as a colorless oil (69 mg, 0.19 mmol, 63%). R_f = 0.28 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.9, 0.8 Hz, 1H, Ar*H*), 6.39 (dd, *J* = 3.2, 0.8 Hz, 1H, Ar*H*), 6.34 (dd, *J* = 3.2, 1.9 Hz, 1H, Ar*H*), 4.81 – 4.67 (m, 3H, *H*CC≡C and C*H*$_2$Ar), 4.33 – 4.16 (m, 2H, OC*H*$_2$CH$_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.96 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 150.5, 143.4, 110.8, 110.5, 99.6, 90.4, 67.8, 62.1, 61.9, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (s), 2866 (s), 2174 (w),

1756 (s), 1464 (m), 1277 (m), 1193 (s), 1151 (s), 1097 (s), 1043 (s), 1015 (s), 921 (m), 883 (s), 737 (s), 676 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{20}H_{32}NaO_4Si^+$ 387.1962; Found 387.1974.

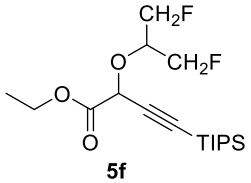
Ethyl 2-(cyclohexyloxy)-4-(triisopropylsilyl)but-3-ynoate (5e)



5e

Following general procedure A, starting from cyclohexanol (**4e**) (127 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5e**) as a colorless oil (99 mg, 0.27 mmol, 90%). R_f = 0.33 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H, *H*CC≡C), 4.36 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 3.65 (tt, *J* = 9.6, 3.9 Hz, 1H, O-C*H*-$_{cyclohexyl}$), 2.04 – 1.90 (m, 2H, 2 x C*H*-$_{cyclohexyl}$), 1.82 – 1.69 (m, 2H, 2 x C*H*-$_{cyclohexyl}$), 1.56 – 1.12 (m, 9H, 2 x C*H*$_2$-$_{cyclohexyl}$ and OCH$_2$C*H*$_3$), 1.11 – 0.93 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 101.3, 88.6, 77.1, 67.2, 61.9, 32.9, 31.9, 25.8, 24.5, 24.3, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2175 (w), 1756 (s), 1463 (m), 1275 (m), 1192 (s), 1111 (s), 1040 (s), 882 (s), 739 (m), 697 (s), 676 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{38}NaO_3Si^+$ 389.2482; Found 389.2487.

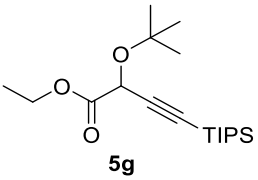
Ethyl 2-((1,3-difluoropropan-2-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5f)



5f

Following general procedure A, starting from 1,2-difluoro-2-propanol (**4f**) (93.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5f**) as a colorless oil (68 mg, 0.19 mmol, 63%). R_f = 0.27 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H, *H*CC≡C), 4.78 – 4.64 (m, 2H, 2 x C*H*$_2$F), 4.64 – 4.52 (m, 2H, 2 x C*H*$_2$F), 4.36 – 4.17 (m, 3H, OC*H* and OC*H*$_2$CH$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.95 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 99.4, 90.9, 81.5 (ddd, *J* = 171.5, 15.9, 6.5 Hz), 74.6 (t, *J* = 20.6 Hz), 69.2, 62.2, 18.6, 14.2, 11.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2945 (m), 2894 (m), 2867 (m), 2176 (w), 1755 (s), 1464 (m), 1282 (m), 1200 (s), 1121 (s), 1091 (s), 1028 (s), 970 (m), 882 (s), 677 (s), 660 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{32}F_2NaO_3Si^+$ 385.1981; Found 385.1987.

Ethyl 2-(tert-butoxy)-4-(triisopropylsilyl)but-3-ynoate (5g)

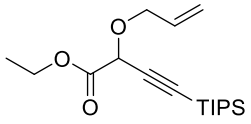


5g

Following general procedure A, starting from *tert*-butanol (**4g**) (115 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5g**) as a colorless oil (70 mg, 0.21 mmol, 69%). R_f = 0.40 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 1H, *H*CC≡C), 4.34 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 1.31 – 1.26 (m, 12H, *t*Bu

and OCH_2CH_3), 1.10 – 0.93 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 103.6, 87.3, 76.5, 63.2, 61.9, 28.1, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2961 (m), 2943 (m), 2866 (m), 2177 (w), 1766 (s), 1741 (m), 1464 (m), 1367 (s), 1275 (m), 1254 (m), 1188 (s), 1096 (s), 1033 (s), 882 (s), 750 (m), 677 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{36}NaO_3Si^+$ 363.2326; Found 363.2329.

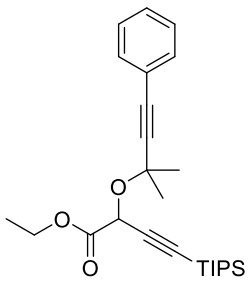
Ethyl 2-(allyloxy)-4-(triisopropylsilyl)but-3-ynoate (5h)



5h

Following general procedure B, starting from allyl alcohol (**4h**) (115 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5h**) as a colorless oil (45 mg, 0.14 mmol, 46%). R_f = 0.31 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (dddd, *J* = 17.0, 10.3, 6.5, 5.4 Hz, 1H, C*H*=CH_2), 5.34 (dq, *J* = 17.2, 1.6 Hz, 1H, CH=CH_2), 5.25 (dq, *J* = 10.4, 1.2 Hz, 1H, CH=CH_2), 4.79 (s, 1H, *H*CC≡C), 4.36 – 4.12 (m, 4H, OCH_2CH and OC$H_2$$CH_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.12 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 133.6, 118.9, 100.1, 89.7, 69.7, 68.2, 62.0, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (s), 2175 (w), 1758 (s), 1464 (m), 1270 (m), 1189 (s), 1111 (s), 1038 (s), 996 (s), 921 (m), 882 (s), 676 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{32}NaO_3Si^+$ 347.2013; Found 347.2008.

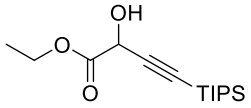
Ethyl 2-((2-methyl-4-phenylbut-3-yn-2-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5i)



5i

Following general procedure B, starting from 4-phenyl-2-methyl-3-butyn-2-ol (**4i**) (192 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5i**) as a colorless oil (54 mg, 0.13 mmol, 42%). R_f = 0.38 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 3H, Ar*H*), 5.20 (s, 1H, *H*CC≡C), 4.35 – 4.12 (m, 2H, OC$H_2$$CH_3$), 1.68 (s, 3H, C(C$H_3$)$_2$), 1.62 (s, 3H, C(C$H_3$)$_2$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.09 – 0.93 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 131.9, 128.6, 128.4, 122.5, 102.8, 90.1, 88.0, 85.8, 73.7, 65.4, 61.9, 30.0, 29.4, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2178 (w), 1765 (s), 1741 (m), 1464 (m), 1283 (m), 1269 (m), 1184 (s), 1152 (s), 1091 (s), 1038 (s), 882 (s), 756 (s), 690 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{26}H_{38}NaO_3Si^+$ 449.2482; Found 449.2485.

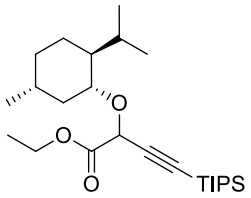
Ethyl 2-hydroxy-4-(triisopropylsilyl)but-3-ynoate (5j)



5j

Adapted from general procedure A, starting from water (**4j**) (54 µL, 3.0 mmol, 10.0 equiv.), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol, 1.00 equiv.), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM, 2.00 equiv.), afforded the title compound (**5j**) as a colorless oil (28 mg, 0.10 mmol, 33%). R_f = 0.11 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, *J* = 5.2 Hz, 1H, *H*CC≡C), 4.41 – 4.20 (m, 2H, OC*H*$_2$CH$_3$), 3.00 (br d, *J* = 7.0 Hz, 1H, O*H*), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.09 – 1.02 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 102.3, 87.4, 62.8, 62.1, 18.6, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 3469 (br w), 2943 (s), 2866 (s), 2177 (w), 2099 (m), 1745 (s), 1465 (m), 1301 (m), 1259 (m), 1202 (m), 1093 (s), 1028 (s), 882 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{15}H_{28}NaO_3Si^+$ 307.1700; Found 307.1700.

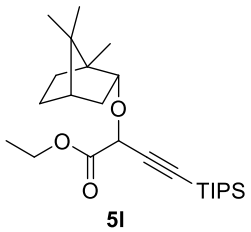
Ethyl 2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5k)



5k + 5k'

Following general procedure A, starting from (-)-menthol (**4k**) (188 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5k**) (50:50 *dr* in the crude ^{1}H NMR) as a colorless oil (107 mg, 0.25 mmol, 84%). A pure analytical sample of each diastereoisomer was isolated by PTLC using EtOAc/pentane 4:96 as eluent. Diaster **5k**: R_f = 0.35 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H, *H*CC≡C), 4.36 – 4.12 (m, 2H, OC*H*$_2$CH$_3$), 3.51 (td, *J* = 10.6, 4.2 Hz, 1H, OC*H*-$_{cyclohexyl}$), 2.31 (pd, *J* = 7.0, 2.8 Hz, 1H, C*H*-$_{cyclohexyl}$), 2.09 – 2.00 (m, 1H, C*H*-$_{cyclohexyl}$), 1.70 – 1.58 (m, 2H, C*H*-$_{cyclohexyl}$), 1.40 – 1.24 (m, 6H, C*H*-$_{isopropyl}$, C*H*-$_{cyclohexyl}$ and OCH$_2$C*H*$_3$), 1.11 – 1.03 (m, 22H, C*H*-$_{cyclohexyl}$ and TIPS), 0.90 (m, 7H, C*H*-$_{cyclohexyl}$ and 2 x C*H*$_3$-$_{isopropyl}$), 0.82 (d, *J* = 7.0 Hz, 3H, C*H*$_3$-$_{methyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 101.0, 88.8, 78.4, 67.1, 61.9, 47.8, 39.8, 34.6, 31.7, 25.7, 23.7, 22.4, 21.0, 18.7, 16.6, 14.2, 11.3; Diaster **5k'**: R_f = 0.36 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 1H, *H*CC≡C), 4.16 – 4.00 (m, 2H, OC*H*$_2$CH$_3$), 3.21 (td, *J* = 10.6, 4.4 Hz, 1H, OC*H*-$_{cyclohexyl}$), 2.10 (m, 2H, C*H*-$_{cyclohexyl}$), 1.51 – 1.42 (m, 2H, C*H*-$_{cyclohexyl}$), 1.24 – 1.05 (m, 6H, C*H*-$_{isopropyl}$, C*H*-$_{cyclohexyl}$ and OC*H*$_2$CH$_3$), 0.90 (s, 22H, C*H*-$_{cyclohexyl}$ and TIPS), 0.73 (m, 7H, C*H*-$_{cyclohexyl}$ and 2 x C*H*$_3$-$_{isopropyl}$), 0.60 (d, *J* = 6.9 Hz, 3H, C*H*$_3$-$_{methyl}$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 102.1, 88.6, 80.9, 69.1, 61.9, 48.3, 41.7, 34.4, 31.8, 25.5, 23.4, 22.3, 21.1, 18.7, 16.3, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2952 (s), 2925 (s), 2867 (s), 1766 (s), 1744 (m), 1463 (m), 1367 (m), 1274 (m), 1186 (s), 1107 (s), 1038 (s), 882 (s), 677 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{25}H_{46}NaO_3Si^+$ 445.3108; Found 445.3116.

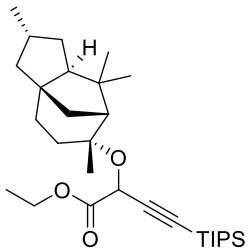
Ethyl 4-(triisopropylsilyl)-2-(((2*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)but-3-ynoate (5l)



5l

Following general procedure A, starting from (-)-borneol (**4l**) (185 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5l**) (55:45 *dr* in the crude ^{1}H NMR) as a colorless oil (110 mg, 0.260 mmol, 87%). R_f = 0.45 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 and 4.68 (2 x s, 1H, *H*CC≡C), 4.33 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 4.06 – 3.92 (m, 1H, OC*H*), 2.25 – 1.99 (m, 2H, CH-$_{bicyclo[2.2.1]heptan-2-yl}$), 1.77 – 1.59 (m, 2H, CH-$_{bicyclo[2.2.1]heptan-2-yl}$), 1.34 – 1.15 (m, 6H, CH-$_{bicyclo[2.2.1]heptan-2-yl}$ and OCH$_2$C*H*$_3$), 1.12 – 0.94 (m, 21H, TIPS), 0.92- 0.88 (m, 3H, CH_3), 0.87 – 0.81 (m, 6H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 168.0, 101.7, 101.5, 88.9, 88.5, 84.6, 83.7, 69.6, 68.7, 61.8, 61.7, 49.6, 49.5, 48.0, 45.2, 36.7, 36.0, 28.3, 28.2, 26.8, 26.7, 19.9, 19.0, 18.9, 18.7, 14.2, 14.0, 13.7, 11.3; Not all signals could be resolved. IR (ν_{max}, cm^{-1}) 2943 (m), 2891 (m), 2866 (m), 2178 (w), 1765 (s), 1741 (m), 1464 (m), 1269 (m), 1184 (s), 1152 (s), 1091 (s), 1038 (s), 882 (s), 756 (s), 690 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{25}H_{44}NaO_3Si^+$ 443.2952; Found 443.2966.

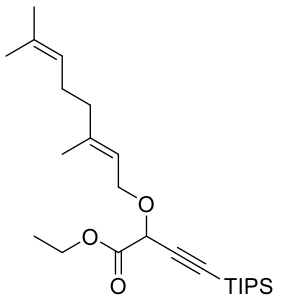
Ethyl 2-(((2*R*,3a*R*,6*R*,7*R*,8a*R*)-2,6,8,8-tetramethyloctahydro-1*H*-3a,7-methanoazulen-6-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5m)



5m

Following general procedure A, starting from (+)-cedrol (**4m**) (267 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5m**) (50:50 *dr* in the crude ^{1}H NMR) as a colorless oil (88 mg, 0.18 mmol, 60%). R_f = 0.36 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 and 4.82 (2 x s, 1H, *H*CC≡C), 4.31 – 4.15 (m, 2H, OC*H*$_2$CH$_3$), 2.12 – 1.17 (m, 22H, C*H*-$_{alphatic}$ and OCH$_2$C*H*$_3$), 1.10 – 0.93 (m, 24H, C*H*$_3$ and TIPS), 0.83 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 168.9, 103.7, 103.1, 87.9, 87.3, 82.3, 82.3, 62.6, 62.2, 61.8, 61.7, 57.7, 57.1, 57.1, 57.0, 54.1, 54.1, 43.5, 43.4, 41.5, 41.4, 41.3, 37.2, 37.2, 32.9, 32.3, 31.5, 31.4, 29.1, 29.0, 27.7, 27.6, 25.5, 25.3, 25.0, 18.7, 15.8, 14.2, 11.3; Not all signals could be resolved. IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 2178 (w), 1765 (s), 1741 (m), 1464 (m), 1283 (m), 1269 (m), 1184 (s), 1152 (s), 1091 (s), 1038 (s), 882 (s), 756 (s), 690 (s), 677 (s), 661 (s); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{30}H_{52}NaO_3Si^+$ 511.3578; Found 511.3582.

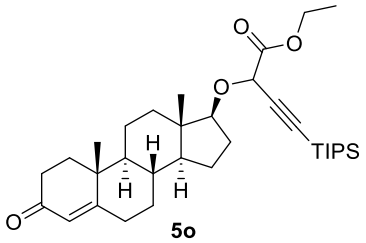
(*E*)-Ethyl 2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5n)



5n

Following general procedure B, starting from geraniol (**4n**) (211 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5n**) as a colorless oil (72 mg, 0.17 mmol, 57%). R_f = 0.38 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (ddt, *J* = 8.3, 7.0, 1.3 Hz, 1H, C*H*CH_2O), 5.08 (ddp, *J* = 7.0, 5.8, 1.4 Hz, 1H, $(H_3C)_2$C=C*H*), 4.77 and 4.68 (2 x s, 1H, *H*CC≡C), 4.34 – 4.18 (m, 4H, CHCH_2O and OC$H_2$$CH_3$), 2.16 – 2.01 (m, 4H, C$H_2CH_2$), 1.69 (m, 6H, 2 x C$H_3$), 1.60 (d, *J* = 1.4 Hz, 3H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.13 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 142.5, 132.0, 124.0, 119.6, 100.6, 89.2, 67.7, 64.9, 62.0, 39.8, 26.4, 25.8, 18.7, 17.8, 16.6, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2959 (s), 2942 (s), 2893 (m), 2866 (s), 2174 (w), 1758 (s), 1463 (m), 1271 (m), 1189 (s), 1103 (s), 1040 (s), 883 (s), 677 (s), 662 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{44}NaO_3Si^+$ 443.2952; Found 443.2953.

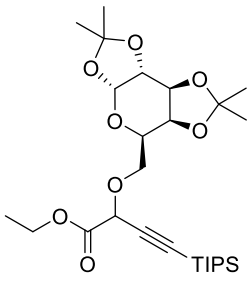
Ethyl 2-(((8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)oxy)-4-(triisopropylsilyl)but-3-ynoate (5o)



5o

Adapted from general procedure A, starting from testosterone (**4o**) (260 mg, 0.900 mmol, 3 equiv.), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol, 1.00 equiv.), and ethyl 2-diazoacetate (**3a**) (1.00 mL, 0.60 mmol, 0.6 M in DCM, 2.00 equiv.), afforded the title compound (**5o**) (55:45 *dr* in the crude ^{1}H NMR) as a thick colorless oil (88 mg, 0.16 mmol, 53%). R_f = 0.45 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H, *H*C=C), 4.76 – 4.65 (m, 1H, *H*CC≡C), 4.34 – 4.14 (m, 2H, OC$H_2$$CH_3$), 3.77 – 3.60 (m, 1H, OC*H*), 2.50 – 2.16 (m, 4H, C*H*-$_{alkyl}$), 2.13 – 1.90 (m, 3H, C*H*-$_{alkyl}$), 1.88 – 1.77 (m, 1H, C*H*-$_{alkyl}$), 1.76 – 1.50 (m, 5H, C*H*-$_{alkyl}$), 1.50 – 0.77 (m, 36H, C*H*-$_{alkyl}$, CH_3, CH_3, OCH_2CH_3 and TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 199.7, 171.4, 171.3, 168.0, 167.8, 124.0, 101.4, 101.3, 89.0, 88.6, 88.2, 88.2, 87.7, 69.2, 68.9, 61.9, 61.8, 54.0, 54.0, 50.7, 50.6, 43.1, 43.0, 38.8, 38.8, 37.6, 37.1, 35.9, 35.6, 34.1, 32.9, 31.7, 31.6, 28.2, 27.7, 23.5, 20.8, 20.7, 18.7, 17.5, 14.2, 11.8, 11.7, 11.3; Not all signals could be resolved. IR (ν_{max}, cm^{-1}) 2919 (s), 2850 (m), 1759 (m), 1672 (m), 1659 (m), 1464 (m), 1268 (m), 1230 (m), 1188 (m), 1158 (m), 1115 (s), 1101 (s), 1016 (m), 882 (s), 779 (m), 679 (s); HRMS (ESI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd. for $C_{34}H_{55}O_4Si^+$ 555.3864; Found 555.3859.

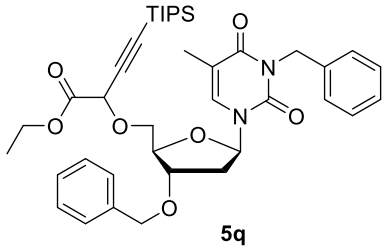
Ethyl 2-(((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-d]pyran-5-yl)methoxy)-4-(triisopropylsilyl)but-3-ynoate (5p)



5p

Following general procedure A, starting from 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (**5p**) (312 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5p**) (58:42 *dr* in the crude ^{1}H NMR) as a colorless oil (88 mg, 0.17 mmol, 56%). R_f = 0.62 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (d, *J* = 5.0 Hz, 1H, OC*H*$_{anomer}$), 4.94 and 4.89 (2 x s, 1H, *H*CC≡C), 4.60 (ddd, *J* = 8.0, 3.7, 2.4 Hz, 1H, OC*H*), 4.34 – 4.15 (m, 4H, 2 x OC*H* and OC*H*$_2$CH$_3$), 4.11 – 3.96 (m, 1H, OC*H*), 3.96 – 3.79 (m, 2H, OC*H*$_2$), 1.56 – 1.52 (m, 3H, C(C*H*$_3$)$_2$), 1.45 – 1.41 (m, 3H, C(C*H*$_3$)$_2$), 1.35 – 1.31 (m, 6H, C(C*H*$_3$)$_2$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.6, 109.4, 109.4, 108.8, 108.7, 100.1, 100.0, 96.5, 96.4, 89.7, 89.7, 71.4, 71.0, 70.8, 70.6, 69.6, 69.3, 67.5, 67.5, 67.0, 66.5, 62.0, 61.9, 29.7, 26.2, 26.1, 25.1, 24.7, 24.6, 18.7, 14.2, 11.2; Not all signals could be resolved. IR (ν_{max}, cm^{-1}) 2941 (m), 2867 (w), 1757 (m), 1463 (w), 1382 (m), 1371 (m), 1255 (m), 1211 (s), 1169 (m), 1109 (s), 1069 (s), 1003 (s), 919 (m), 884 (m), 866 (m), 677 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{27}H_{46}NaO_8Si^+$ 549.2854; Found 549.2855.

Ethyl 2-(((2*R*,3*S*,5*R*)-5-(3-benzyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(benzyloxy)tetrahydrofuran-2-yl)methoxy)-4-(triisopropylsilyl)but-3-ynoate (5q)

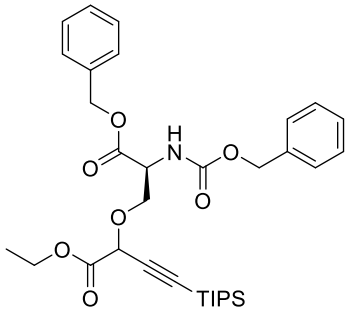


5q

Following general procedure B, starting from 3-benzyl-1-((2R,4S,5R)-4-(benzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**4q**) (507 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5q**) (53:47 *dr* in the crude ^{1}H NMR) as a thick colorless oil (89 mg, 0.13 mmol, 43%). R_f = 0.38 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 and 7.73 (2 x d, *J* = 1.4 Hz, 1H, *H*C=C), 7.52 – 7.44 (m, 2H, Ar*H*), 7.41 – 7.20 (m, 8H, Ar*H*), 6.48 (td, *J* = 8.2, 5.6 Hz, 1H, OC*H*N), 5.12 (s, 2H, NC*H*$_2$Ar), 4.78 (s, 1H, *H*CC≡C), 4.57 (dd, *J* = 11.7, 4.1 Hz, 1H, OC*H*$_2$Ar), 4.49 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.37 – 4.16 (m, 4H, OC*H*$_2$CH$_3$, BnOC*H* and OC*H*$_2$CH), 4.09 – 4.01 (m, 0.5H, OC*H*$_2$CH), 3.94 – 3.80 (m, 1H, OCH$_2$C*H*), 3.70 – 3.61 (m, 0.5H, OC*H*$_2$CH), 2.46 (dddd, *J* = 13.4, 5.5, 3.9, 1.7 Hz, 1H, C*H*$_{2\text{-cyclic}}$), 2.22 – 2.07 (m, 1H, C*H*$_{2\text{-cyclic}}$), 1.93 (dd, *J* = 3.7, 1.2 Hz, 3H, C*H*$_3$), 1.29 (td, *J* = 7.1, 1.4 Hz, 3H, OCH$_2$C*H*$_3$), 1.12 – 0.91 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.9, 163.7, 163.7, 151.3, 151.3, 137.7, 137.7, 137.2, 137.2, 134.6, 134.4, 129.3, 129.3, 128.6, 128.5, 128.0, 127.7, 127.6, 127.6, 110.6, 110.4, 99.2, 99.0, 91.1, 90.5, 86.0, 85.9, 83.6, 83.6, 80.4, 80.1, 71.4, 71.3, 69.2, 69.1, 68.8, 68.7, 62.2, 44.6, 44.6, 37.6, 37.6, 18.7, 18.6, 14.2, 13.3, 13.2, 11.2; IR (ν_{max}, cm^{-1}) 2947 (m), 2867 (m), 2175

(w), 1754 (m), 1701 (s), 1649 (s), 1458 (s), 1273 (m), 1200 (s), 1084 (s), 921 (m), 885 (m), 739 (m), 690 (s), 672 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{39}H_{52}N_2NaO_7Si+$ 711.3436; Found 711.3433.

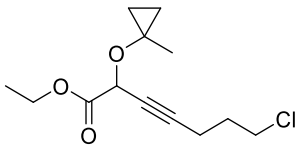
Ethyl 2-((S)-3-(benzyloxy)-2-(((benzyloxy)carbonyl)amino)-3-oxopropoxy)-4-(triisopropylsilyl)but-3-ynoate (5r)



5r

Following general procedure B, starting from *N*-carbobenzoxy-L-serine benzyl ester (**4r**) (395 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5r**) (53:47 *dr* in the crude ^{1}H NMR) as a colorless oil (65 mg, 0.11 mmol, 36%). R_f = 0.55 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 10H, Ar*H*), 6.03 and 5.83 (2 x d, 8.4 Hz, 1H, N*H*), 5.28 – 5.05 (m, 4H, 2 x CH_2OAr), 4.85 – 4.76 (m, 1H, *H*CC≡C), 4.63 – 4.54 (m, 1H, NC*H*), 4.33 – 4.08 (m, 3H, OCH_2CH and OCH_2CH$_3$), 4.00 – 3.96 (m, 1H, OCH_2CH), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.09 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 170.0, 167.5, 167.3, 156.3, 156.2, 136.5, 136.4, 135.6, 135.5, 128.7, 128.7, 128.6, 128.6, 128.4, 128.4, 128.2, 128.2, 128.2, 128.2, 128.1, 98.8, 98.6, 91.1, 91.0, 69.0, 68.8, 68.0, 67.5, 67.4, 67.2, 67.1, 62.2, 62.1, 54.5, 54.5, 18.7, 14.2, 11.2; IR (ν_{max}, cm^{-1}) 2943 (m), 2866 (m), 1746 (s), 1727 (s), 1509 (m), 1457 (m), 1336 (m), 1289 (m), 1197 (s), 1120 (s), 1053 (s), 882 (m), 735 (m), 696 (s), 677 (s), 664 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{33}H_{45}NNaO_7Si^+$ 618.2858; Found 618.2863.

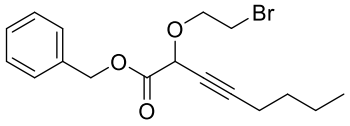
Ethyl 7-chloro-2-(1-methylcyclopropoxy)hept-3-ynoate (5s)



5s

Following general procedure A, starting from 1-methylcyclopropanol (**4s**) (68.0 µL, 1.20 mmol), 1-(5-chloropent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2b**) (141 mg, 0.300 mmol), and ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**5s**) as a colorless oil (27 mg, 0.10 mmol, 35%). R_f = 0.11 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (t, *J* = 2.2 Hz, 1H, *H*CC≡C), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.63 (t, *J* = 6.4 Hz, 2H, CH_2Cl), 2.42 (td, *J* = 6.8, 2.2 Hz, 2H, C≡CCH_2), 1.96 (p, *J* = 6.6 Hz, 2H, CH_2CH$_2$Cl), 1.43 (s, 3H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.07 – 1.00 (m, 1H, C*H*-$_{cyclopropyl}$), 0.93 – 0.85 (m, 1H, C*H*-$_{cyclopropyl}$), 0.49 – 0.37 (m, 2H, C*H*-$_{cyclopropyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 85.8, 76.4, 67.5, 62.1, 60.2, 43.6, 31.1, 21.2, 16.4, 14.2, 13.9, 13.5; IR (ν_{max}, cm^{-1}) 2963 (w), 2236 (w), 1759 (s), 1739 (s), 1445 (m), 1388 (m), 1291 (m), 1251 (s), 1187 (s), 1110 (m), 1075 (s), 1022 (s), 857 (m), 727 (m), 658 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{13}H_{19}ClNaO_3^+$ 281.0915; Found 281.0917.

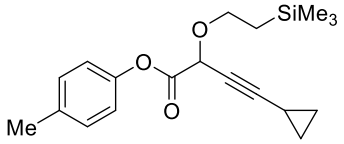
Benzyl 2-(2-bromoethoxy)oct-3-ynoate (5t)



5t

Following general procedure A, starting from 2-bromoethanol (**4t**) (85.0 µL, 1.20 mmol), 1-(hex-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2c**) (135 mg, 0.300 mmol), and benzyl 2-diazoacetate (**3b**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5t**) as a colorless oil (92 mg, 0.26 mmol, 87%). R_f = 0.21 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H, Ar*H*), 5.31 – 5.18 (m, 2H, C*H*$_2$Ar), 4.85 (t, *J* = 2.2 Hz, 1H, *H*CC≡C), 4.04 – 3.87 (m, 2H, OC*H*$_2$CH$_2$Br), 3.50 (t, *J* = 6.5 Hz, 2H, C*H*$_2$Br), 2.24 (td, *J* = 7.0, 2.2 Hz, 2H, C≡CC*H*$_2$), 1.55 – 1.44 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.44 – 1.27 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.89 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 135.3, 128.7, 128.6, 128.3, 89.7, 72.8, 69.1, 68.4, 67.5, 30.4, 29.8, 22.0, 18.6, 13.7; IR (ν_{max}, cm^{-1}) 2959 (w), 2933 (w), 1742 (m), 1256 (s), 1213 (s), 1180 (s), 1148 (s), 1110 (s), 963 (m), 947 (m), 926 (m), 756 (s), 729 (s), 698 (s), 680 (m); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{17}H_{21}BrNaO_3^+$ 375.0566; Found 375.0571.

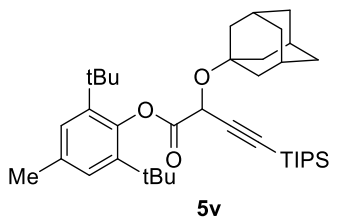
***p*-Tolyl 4-cyclopropyl-2-(2-(trimethylsilyl)ethoxy)but-3-ynoate (5u)**



5u

Following general procedure A, starting from 2-(trimethylsilyl)ethanol (**4u**) (172 µL, 1.20 mmol), 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2d**) (130 mg, 0.300 mmol), and *p*-tolyl 2-diazoacetate (**3c**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**5u**) as a colorless oil (67 mg, 0.20 mmol, 68%). R_f = 0.34 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 2H, Ar*H*), 7.05 – 6.98 (m, 2H, Ar*H*), 4.85 (d, *J* = 2.0 Hz, 1H, *H*CC≡C), 3.84 – 3.75 (m, 1H, OC*H*$_2$), 3.75 – 3.66 (m, 1H, OC*H*$_2$), 2.34 (s, 3H, ArC*H*$_3$), 1.37 – 1.27 (m, 1H, C*H*-$_{cyclopropyl}$), 1.09 – 1.00 (m, 2H, C*H*$_2$TMS), 0.86 – 0.72 (m, 4H, C*H*-$_{cyclopropyl}$), 0.04 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 148.4, 135.9, 130.1, 121.0, 91.8, 68.8, 68.6, 66.8, 21.0, 18.2, 8.5, 8.5, -0.3, -1.3; IR (ν_{max}, cm^{-1}) 2953 (w), 2895 (w), 2238 (w), 1775 (m), 1507 (m), 1248 (m), 1195 (s), 1166 (s), 1095 (s), 857 (s), 835 (s), 695 (m); HRMS (ESI/QTOF) m/z: [M+Na]$^+$ Calcd. for $C_{19}H_{26}NaO_3Si^+$ 353.1543; Found 353.1543.

2,6-Di-tert-butyl-4-methylphenyl 2-((3s,5s,7s)-adamantan-1-yloxy)-4-(triisopropylsilyl)but-3-ynoate (5v)

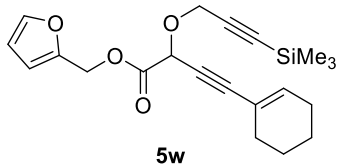


5v

Following general procedure A, starting from 1-adamantanol (**4v**) (183 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and 1,3-di-*tert*-butyl-2-(diazomethyl)-5-methylbenzene (**3d**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**5v**) as a viscous colorless oil (132 mg, 0.220 mmol, 74%). R_f = 0.43 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H, Ar*H*), 5.18 (s, 1H,

*H*CC≡C), 2.31 (s, 3H, C*H*$_3$), 2.24 – 2.15 (m, 3H, 3 x C*H*), 2.01 – 1.87 (m, 6H, C(C*H*$_2$)$_3$), 1.73 – 1.59 (m, 6H, 3 x C*H*$_2$), 1.35 (m, 18H, 2 x *tBu*), 1.08 (s, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 146.4, 142.3, 142.1, 134.8, 127.1, 127.1, 103.8, 89.0, 76.2, 62.5, 42.3, 36.4, 35.5, 35.5, 31.8, 31.7, 30.9, 21.7, 18.7, 18.7, 11.4; IR (ν_{max}, cm^{-1}) 2912 (m), 2865 (m), 2251 (w), 2176 (w), 1760 (m), 1462 (m), 1421 (m), 1364 (m), 1271 (m), 1200 (m), 1183 (m), 1144 (m), 1104 (s), 1074 (s), 1018 (m), 909 (s), 883 (m), 733 (s), 677 (s); HRMS (ESI/QTOF) m/z: $[M+K]^+$ Calcd. for $C_{38}H_{60}KO_3Si^+$ 631.3943; Found 631.3958.

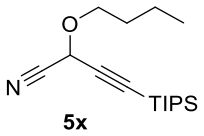
Furan-2-ylmethyl 4-(cyclohex-1-en-1-yl)-2-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)but-3-ynoate (5w)



5w

Following general procedure B, starting from 3-trimethylsilyl-2-propyn-1-ol (**4w**) (148 µL, 1.20 mmol), 1-(cyclohex-1-en-1-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2e**) (119 mg, 0.300 mmol), and furan-2-ylmethyl 2-diazoacetate (**3e**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**5w**) as a viscous colorless oil (36 mg, 0.10 mmol, 39%). R_f = 0.21 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.9, 0.9 Hz, 1H, Ar*H*), 6.49 – 6.42 (m, 1H, Ar*H*), 6.36 (dd, *J* = 3.3, 1.9 Hz, 1H, Ar*H*), 6.16 (p, *J* = 2.1 Hz, 1H, C=C*H*), 5.25 – 5.13 (m, 2H, OC*H*$_2$Ar), 5.08 (s, 1H, *H*CC≡C), 4.37 (s, 2H, OC*H*$_2$C≡C), 2.14 – 2.04 (m, 4H, C*H*-$_{cyclohexenyl}$), 1.68 – 1.51 (m, 4H, C*H*-$_{cyclohexenyl}$), 0.16 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 148.8, 143.6, 137.6, 119.7, 111.4, 110.8, 100.0, 92.9, 90.0, 78.7, 67.5, 59.5, 56.7, 28.9, 25.8, 22.3, 21.5, -0.1; IR (ν_{max}, cm^{-1}) 2934 (m), 2862 (w), 1753 (m), 1444 (w), 1251 (m), 1181 (m), 1090 (s), 1009 (m), 846 (s), 753 (m); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{26}NaO_4Si^+$ 393.1493; Found 393.1491.

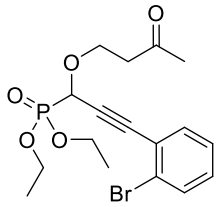
2-Butoxy-4-(triisopropylsilyl)but-3-ynenitrile (5x)



5x

Following general procedure A, starting from 1-butanol (**4x**) (110 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and 2-diazoacetonitrile (**3f**) (1.20 mL, 0.600 mmol, 0.50 M in DCM), afforded the title compound (**5x**) as a colorless oil (57 mg, 0.19 mmol, 65%). R_f = 0.14 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1H, *H*CC≡C), 3.82 – 3.72 (m, 1H, OC*H*$_2$), 3.69 – 3.61 (m, 1H, OC*H*$_2$), 1.63 (tt, *J* = 8.3, 6.3 Hz, 2H, OCH$_2$C*H*$_2$), 1.47 – 1.35 (m, 2H, C*H*$_2$CH$_3$), 1.14 – 0.97 (m, 21H, TIPS), 0.93 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 114.9, 96.3, 91.8, 68.3, 58.0, 31.3, 19.3, 18.6, 13.9, 11.1; IR (ν_{max}, cm^{-1}) 2945 (m), 2867 (m), 1740 (m), 1717 (m), 1464 (m), 1253 (m), 1091 (s), 1029 (m), 882 (s), 836 (m), 776 (m), 678 (s), 662 (s); HRMS (APCI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{32}NOSi^+$ 294.2248; Found 294.2251.

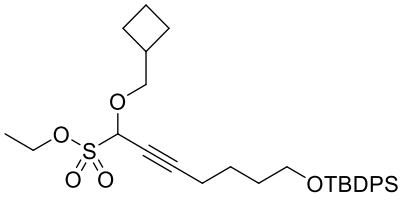
Diethyl (3-(2-bromophenyl)-1-(3-oxobutoxy)prop-2-yn-1-yl)phosphonate (5y)



5y

Following general procedure A, starting from 4-hydroxy-2-butanone (**4y**) (103 µL, 1.20 mmol), 1-((2-bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2f**) (165 mg, 0.300 mmol) and diethyl (diazomethyl)phosphonate (**3g**) (1.00 mL, 0.600 mmol, 0.60 M in DCM), afforded the title compound (**5y**) as a colorless oil (95 mg, 0.23 mmol, 76%). R_f = 0.17 (EtOAc/pentane 20:80), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar*H*), 7.30 – 7.23 (m, 1H, Ar*H*), 7.20 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 4.73 (d, *J* = 19.4 Hz, 1H, *H*CC≡C), 4.34 – 4.18 (m, 5H, 2 x POCH_2CH$_3$ and OCH_2), 3.92 (ddd, *J* = 9.6, 6.8, 5.9 Hz, 1H, OCH_2), 2.88 – 2.70 (m, 2H, CH_2COCH$_3$), 2.20 (s, 3H, COCH_3), 1.36 (tt, *J* = 7.0, 1.0 Hz, 6H, 2 x POCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 133.9 (d, *J* = 2.8 Hz), 132.6, 130.2, 127.2, 125.7 (d, *J* = 3.1 Hz), 124.3 (d, *J* = 3.6 Hz), 87.7 (d, *J* = 10.0 Hz), 86.1 (d, *J* = 5.2 Hz), 67.1 (d, *J* = 175.3 Hz), 66.0 (d, *J* = 12.5 Hz), 64.1 (dd, *J* = 11.1, 6.7 Hz), 43.6, 30.5, 16.7 (dd, *J* = 5.7, 3.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.3; IR (ν_{max}, cm^{-1}) 2917 (w), 2849 (w), 1715 (m), 1469 (w), 1236 (m), 1165 (w), 1097 (m), 1021 (s), 977 (m), 756 (m); HRMS (APPI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{23}BrO_5P^+$ 417.0461; Found 417.0455.

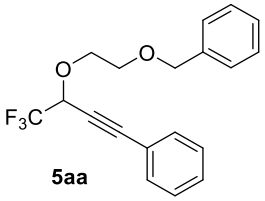
Ethyl 7-((tert-butyldiphenylsilyl)oxy)-1-(cyclobutylmethoxy)hept-2-yne-1-sulfonate (5z)



5z

Following general procedure A, starting from cyclobutanemethanol (**4z**) (113 µL, 1.20 mmol), ((6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane (**2g**) (211 mg, 0.300 mmol), and ethyl diazomethanesulfonate (**3h**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**5z**) as a colorless oil (132 mg, 0.240 mmol, 81%). R_f = 0.35 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H, Ar*H*), 7.49 – 7.33 (m, 6H, Ar*H*), 5.25 (t, *J* = 1.6 Hz, 1H, *H*CC≡C), 3.80 – 3.45 (m, 6H, 3 x OCH_2), 2.58 (hept, *J* = 7.4 Hz, 1H, OCH$_2$C*H*), 2.31 – 2.21 (m, 2H, CH_2-$_{aliphatic}$), 2.13 – 2.00 (m, 2H, CH_2-$_{aliphatic}$), 1.98 – 1.80 (m, 2H, CH_2-$_{aliphatic}$), 1.80 – 1.59 (m, 6H, CH_2-$_{aliphatic}$), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH$_3$), 1.05 (s, 9H, tBu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.1, 129.7, 127.8, 91.7, 86.5, 76.0, 69.4, 63.4, 61.0, 35.0, 31.9, 27.0, 25.3, 25.2, 25.0, 19.4, 18.7, 18.6, 15.2; IR (ν_{max}, cm^{-1}) 2931 (m), 2859 (m), 2245 (w), 1428 (m), 1389 (w), 1359 (m), 1148 (m), 1108 (s), 1041 (s), 1008 (m), 740 (m), 701 (s), 613 (m); HRMS (APPI/LTQO) m/z: $[M-C_2H_5O_3S]^+$ Calcd. for $C_{28}H_{37}O_2Si^+$ 433.2557; Found 433.2543.

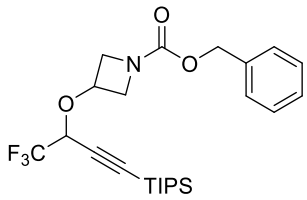
(3-(2-(Benzyloxy)ethoxy)-4,4,4-trifluorobut-1-yn-1-yl)benzene (5aa)



5aa

Following general procedure A, starting from 2-(benzyloxy)ethanol (**4aa**) (171 µL, 1.20 mmol), 1-(phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2h**) (141 mg, 0.300 mmol), and 2,2,2-trifluorodiazoethane (3**i**) (1.62 mL, 0.600 mmol, 0.37 M in DCM), afforded the title compound (**5aa**) as a colorless oil (73 mg, 0.22 mmol, 73%). R_f = 0.27 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H, Ar*H*), 7.41 – 7.26 (m, 8H, Ar*H*), 4.90 (q, *J* = 5.9 Hz, 1H, *H*CC≡C), 4.60 (s, 2H, C*H*$_2$Ar), 4.06 – 3.98 (m, 1H, OC*H*$_2$), 3.98 – 3.90 (m, 1H, OC*H*$_2$), 3.80 – 3.66 (m, 2H, C*H*$_2$OBn); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 132.2, 129.5, 128.6, 128.5, 127.9, 127.8, 122.7 (q, *J* = 281.8 Hz), 121.3, 88.8, 79.3 (q, *J* = 2.4 Hz), 73.5, 69.8 (q, *J* = 35.1 Hz), 69.4, 69.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.8; IR (ν_{max}, cm^{-1}) 2871 (w), 1720 (w), 1703 (w), 1491 (w), 1454 (w), 1362 (w), 1272 (s), 1184 (s), 1141 (s), 1095 (s), 1028 (m), 756 (s), 690 (s); HRMS (APPI/LTQ-Orbitrap) m/z: $[M]^+$ Calcd. for $C_{19}H_{17}F_3O_2^+$ 334.1175; Found 334.1173.

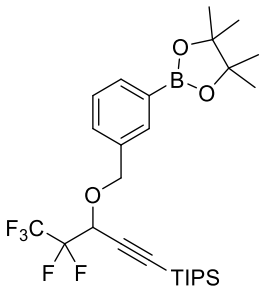
Benzyl 3-((1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-yl)oxy)azetidine-1-carboxylate (5ab)



5ab

Following general procedure B, starting from benzyl 3-hydroxyazetidine-1-carboxylate (**4ab**) (249 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and 2,2,2-trifluorodiazoethane (**3i**) (1.67 mL, 0.600 mmol, 0.36 M in DCM), afforded the title compound (**5ab**) as a colorless oil (86 mg, 0.18 mmol, 61%). R_f = 0.09 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, Ar*H*), 5.10 (s, 2H, OC*H*$_2$Ar), 4.73 – 4.63 (m, 1H, OC*H*), 4.55 (q, *J* = 5.8 Hz, 1H, *H*CC≡C), 4.30 – 4.16 (m, 2H, NC*H*$_2$), 4.11 (ddd, *J* = 9.7, 4.4, 1.1 Hz, 1H, NC*H*$_2$), 4.01 (ddd, *J* = 9.8, 4.4, 1.2 Hz, 1H, NC*H*$_2$), 1.14 – 0.95 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 136.6, 128.6, 128.2, 128.1, 122.1 (q, *J* = 281.9 Hz), 95.7, 93.5, 68.2 (q, *J* = 35.5 Hz), 67.7, 67.0, 57.9 – 56.3 (m), 18.6, 11.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.0; IR (ν_{max}, cm^{-1}) 2946 (m), 2867 (m), 1713 (s), 1456 (m), 1418 (s), 1352 (m), 1272 (m), 1181 (s), 1146 (s), 1093 (s), 1039 (m), 1001 (m), 882 (m), 736 (m), 697 (m), 680 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{34}F_3NNaO_3Si_+$ 492.2152; Found 492.2164.

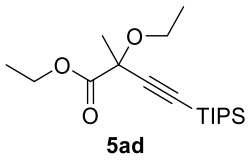
Triisopropyl(4,4,5,5,5-pentafluoro-3-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)pent-1-yn-1-yl)silane (5ac)



5ac

Following general procedure A, starting from (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (**4ac**) (281 mg, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2i**) (165 mg, 0.300 mmol), and 3-diazo-1,1,1,2,2-pentafluoropropane (**3j**) (1.67 mL, 0.600 mmol, 0.36 M in DCM), afforded the title compound (**5ac**) as a colorless oil (128 mg, 0.234 mmol, 78%). R_f = 0.40 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H, Ar*H*), 7.49 (dt, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.44 – 7.34 (m, 1H, Ar*H*), 4.88 (d, *J* = 11.7 Hz, 1H, CH_2O), 4.77 – 4.66 (m, 1H, CH_2O), 4.66 – 4.54 (m, 1H, *H*CC≡C), 1.35 (s, 12H, 4 x CH_3), 1.19 – 0.96 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 134.9, 134.9, 131.4, 129.4 (br s), 128.2, 118.8 (tq, *J* = 287.0, 35.0 Hz), 111.8 (qdd, *J* = 256.8, 36.3, 5.0 Hz), 95.9, 93.3, 84.0, 71.0, 67.3 (dd, *J* = 29.5, 24.8 Hz), 25.01 (d, *J* = 4.7 Hz), 18.6, 11.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.1, -119.9 (d, *J* = 273.9 Hz), -125.3 (d, *J* = 274.2 Hz); IR (ν_{max}, cm^{-1}) 2945 (m), 2868 (m), 2181 (w), 1464 (w), 1434 (w), 1358 (s), 1321 (m), 1216 (s), 1198 (s), 1144 (s), 1099 (m), 1079 (m), 988 (m), 965 (m), 883 (m), 853 (m), 743 (m), 708 (s), 672 (s); HRMS (APCI/QTOF) m/z: $[M+NH_4]^+$ Calcd. for $C_{27}H_{44}BF_5NO_3Si^+$ 564.3098; Found 564.3115.

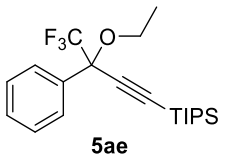
Ethyl 2-ethoxy-2-methyl-4-(triisopropylsilyl)but-3-ynoate (5ad)



5ad

Following general procedure B, starting from ethanol (**4a**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and ethyl 2-diazopropanoate (**3k**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5ad**) as a colorless oil (42 mg, 0.13 mmol, 43%). R_f = 0.37 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 – 4.12 (m, 2H, (O)COCH_2), 3.81 (dq, *J* = 8.7, 7.1 Hz, 1H, OCH_2CH$_3$), 3.59 (dq, *J* = 8.9, 7.0 Hz, 1H, OCH_2CH$_3$), 1.67 (s, 3H, CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, (O)COCH$_2$CH_3), 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH$_3$), 1.08 (s, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 104.4, 87.9, 75.0, 62.4, 61.9, 27.7, 18.7, 15.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (m), 2868 (m), 1748 (s), 1460 (m), 1247 (m), 1196 (m), 1124 (s), 1065 (m), 881 (m), 670 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{34}NaO_3Si^+$ 349.2169; Found 349.2172.

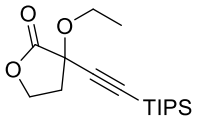
(3-Ethoxy-4,4,4-trifluoro-3-phenylbut-1-yn-1-yl)triisopropylsilane (5ae)



5ae

Following general procedure B, starting from ethanol (**4a**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and (1-diazo-2,2,2-trifluoroethyl)benzene (**3l**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5ae**) as a colorless oil (66 mg, 0.17 mmol, 57%). R_f = 0.65 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H, Ar*H*), 7.45 – 7.37 (m, 3H, Ar*H*), 3.83 (dq, *J* = 8.9, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 3.44 (dq, *J* = 9.0, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 1.28 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 1.21 – 0.95 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 129.6, 128.3, 128.3, 123.1 (q, *J* = 285.2 Hz), 99.5, 93.2, 79.5 (q, *J* = 31.1 Hz), 61.7, 18.7, 15.4, 11.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.7; IR (ν_{max}, cm^{-1}) 2947 (m), 2869 (m), 1460 (m), 1272 (m), 1180 (s), 1120 (m), 1068 (s), 952 (m), 884 (m), 763 (m), 708 (m), 672 (s); HRMS (ESI/QTOF) m/z: $[M+Ag]^+$ Calcd. for $C_{21}H_{31}AgF_3OSi^+$ 491.1142; Found 491.1136.

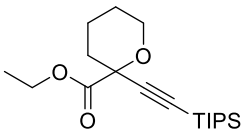
3-Ethoxy-3-((triisopropylsilyl)ethynyl)dihydrofuran-2(3*H*)-one (5af)



5af

Following general procedure B, starting from ethanol (**4a**) (70.0 µL, 1.20 mmol), ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol), and 3-diazodihydrofuran-2(3*H*)-one (**3m**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound (**5af**) as a colorless oil (44 mg, 0.14 mmol, 47%). R_f = 0.26 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 – 4.27 (m, 2H, OC*H*$_2$CH$_2$), 3.99 – 3.81 (m, 2H, OC*H*$_2$CH$_3$), 2.66 – 2.46 (m, 2H, OCH$_2$C*H*$_2$), 1.23 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 1.13 – 0.94 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 100.7, 91.9, 73.4, 65.4, 62.4, 38.9, 18.7, 15.5, 11.2; IR (ν_{max}, cm^{-1}) 2944 (s), 2867 (m), 2170 (w), 1787 (s), 1463 (m), 1377 (m), 1224 (m), 1155 (s), 1060 (s), 1026 (s), 884 (m), 764 (m), 671 (s); HRMS (APCI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{31}O_3Si^+$ 311.2037; Found 311.2030.

Ethyl 2-((triisopropylsilyl)ethynyl)tetrahydro-2*H*-pyran-2-carboxylate (5ag)

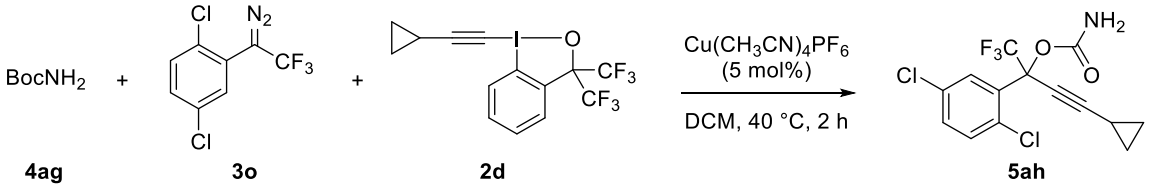


5ag

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (11.2 mg, 30.0 µmol, 0.10 equiv.) and ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) (165 mg, 0.300 mmol). To the resulting solution was added a 0.6 M solution of ethyl 2-diazo-6-hydroxyhexanoate (**3n**) (0.60 mmol, 2.00 equiv.) in dry DCM in 1 h via seringe pump at 25 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (EtOAc/pentane) directly without further work-up, affording the title compound (**5ag**) as a colorless oil (21 mg, 62 µmol, 21%). R_f = 0.17 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (qq, *J* = 7.1, 3.6 Hz, 2H, OC*H*$_2$CH$_3$), 4.09 – 3.96 (m, 1H, OC*H*$_2$), 3.96 – 3.85 (m, 1H, OC*H*$_2$), 2.09 – 2.00 (m, 1H, C*H*-$_{aliphatic}$), 2.00 – 1.69 (m, 3H, C*H*-$_{aliphatic}$), 1.67 – 1.39 (m, 2H, C*H*-$_{aliphatic}$), 1.29 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.16 – 0.84 (m, 21H, TIPS); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 169.7, 102.9, 89.4, 74.4, 64.3, 62.0, 34.6, 25.0, 20.0, 18.7, 14.2, 11.3; IR (ν_{max}, cm^{-1}) 2943 (s), 2865 (s), 2166 (w), 1762 (s), 1742 (s), 1464 (m), 1289 (m), 1255 (s), 1203 (s), 1149 (s), 1095 (m), 1066 (s), 1018 (s), 920 (m), 882 (s), 759 (m), 676 (s), 660 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{34}NaO_3Si^+$ 361.2169; Found 361.2174.

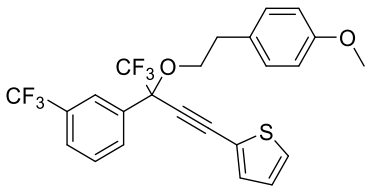
2-(4-Bromophenyl)-8-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluorooct-3-yn-2-yl carbamate (5ah)



4ag **3o** **2d** **5ah**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (5.59 mg, 15.0 µmol, 0.05 equiv.), 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2d**) (130 mg, 0.300 mmol, 1.00 equiv.) and *tert*-butyl carbamate (**4ag**) (45.7 mg, 0.390 mmol, 1.30 equiv.). The vial was capped, removed from the glovebox and dry DCM (5.35 mL) was added. To the resulting solution was added a 0.6 M solution of 1,4-dichloro-2-(1-diazo-2,2,2-trifluoroethyl)benzene (**3o**) (0.65 mL, 0.39 mmol, 1.30 equiv.) in dry DCM in 1 h via seringe pump at 25 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography, using DCM as eluent, directly without further work-up affording the title compound (**5ah**) as a white solid (65 mg, 0.19 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.3 Hz, 1H, Ar*H*), 7.33 – 7.29 (m, 1H, Ar*H*), 7.29 – 7.24 (m, 1H, Ar*H*), 4.88 (br s, 2H, NH_2), 1.42 (tt, *J* = 8.2, 5.2 Hz, 1H, C*H*-$_{cyclopropyl}$), 0.94 – 0.83 (m, 4H, C*H*-$_{cyclopropyl}$); ^{13}C NMR (101 MHz, $CDCl_3$) 152.5, 133.3, 132.8, 132.1, 131.9, 131.1, 130.7, 122.5 (q, *J* = 285.8 Hz), 95.3, 77.9 (q, *J* = 33.3 Hz), 67.1, 8.8, 8.7, -0.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.5. The values of the NMR spectra are in accordance with reported literature data.[1]

2-(4,4,4-Trifluoro-3-(4-methoxyphenethoxy)-3-(3-(trifluoromethyl)phenyl)but-1-yn-1-yl)thiophene (5ai)



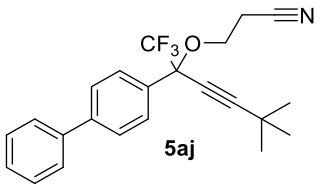
5ai

Following general procedure B, starting from 4-methoxyphenethyl alcohol (**4ae**) (183 mg, 1.20 mmol), 1-(thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxole (**2i**) (143 mg, 0.300 mmol), and 1-(1-diazo-2,2,2-trifluoroethyl)-3-(trifluoromethyl)benzene (**3p**) (1.0 mL, 0.60 mmol, 0.60 M in DCM), afforded the title compound (**5ai**) as an unseparable mixture with the corresponding O-H insertion product. The yield was estimated to be 73% by ^{19}F NMR spectroscopy. A pure analytical sample was isolated by PTLC using toluene/acetone 95:5 as eluent. R_f = 0.31 (EtOAc/pentane 3:97), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, Ar*H*), 7.75 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.69 – 7.63 (m, 1H, Ar*H*), 7.48 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.41 – 7.36 (m, 2H, Ar*H*) , Ar*H*, 7.16 – 7.10 (m, 2H, Ar*H*), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H, Ar*H*), 6.86 – 6.80 (m, 2H, Ar*H*), 4.04 – 3.95 (m, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.59 – 3.51 (m, 1H, OCH_2), 2.94 (t, *J* = 6.9 Hz, 2H, CH_2Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 135.4, 134.2, 131.7, 131.0 (q, *J* = 32.7 Hz), 130.4, 130.2, 129.1, 129.0, 127.4, 126.7 (q, *J* = 3.1 Hz), 125.2 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 272.3 Hz), 122.8 (q, *J* = 285.9 Hz), 120.5, 114.0, 84.8, 84.7, 79.5 (q, *J* = 31.7 Hz), 67.6, 55.4, 35.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6, -78.2; IR (ν_{max}, cm^{-1}) 2931 (w), 2226 (w), 1515 (m),

[1] D. Dai, X. Long, A. Kulesza, J. Reichwagen, B. Luo and Y. Guo (Lonza Ltd), PCT Int. Appl. *WO2012097510*, **2012**.

1329 (m), 1252 (m), 1178 (s), 1130 (s), 1082 (m), 1039 (m), 910 (w), 815 (w), 713 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{24}H_{19}F_6O_2S^+$ 485.1004; Found 485.1006.

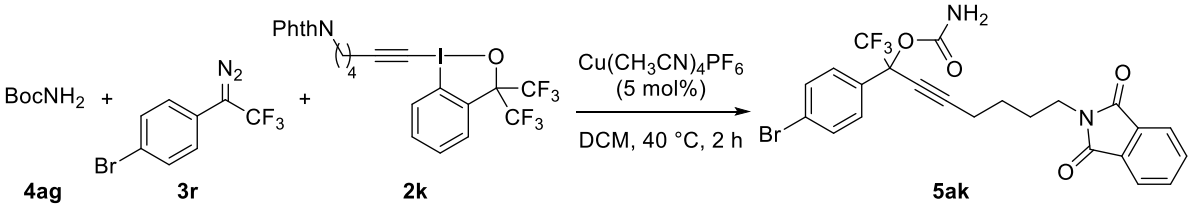
3-((2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoro-5,5-dimethylhex-3-yn-2-yl)oxy)propanenitrile (5aj)



5aj

Following general procedure B, starting from 3-hydroxypropionitrile (**4af**) (81.0 µL, 1.20 mmol), 1-(3,3-dimethylbut-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2j**) (135 mg, 0.300 mmol), and 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (**3q**) (1.0 mL, 0.60 mmol, 0.6 M in DCM), afforded the title compound **5aj** as a colorless oil (68 mg, 0.18 mmol, 59%). R_f = 0.24 (EtOAc/pentane 5:95), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.75 (m, 2H, Ar*H*), 7.69 - 7.57 (m, 4H, Ar*H*), 7.51 - 7.43 (m, 2H, Ar*H*), 7.42 - 7.35 (m, 1H, Ar*H*), 3.96 (dt, *J* = 9.4, 6.1 Hz, 1H, OCH_2), 3.67 (ddd, *J* = 9.4, 7.5, 6.1 Hz, 1H, OCH_2), 2.83 - 2.63 (m, 2H, CH_2CN), 1.37 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 140.3, 132.7, 129.0, 128.7, 127.9, 127.3, 127.3, 122.9 (q, *J* = 285.0 Hz), 117.4, 101.4, 79.4 (q, *J* = 31.8 Hz), 70.8, 60.4, 30.7, 28.0, 19.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.84; IR (ν_{max}, cm^{-1}) 2975 (w), 2251 (w), 1487 (m), 1290 (m), 1255 (m), 1175 (s), 1090 (s), 1007 (m), 943 (m), 884 (m), 836 (m), 766 (s), 738 (s), 697 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{22}F_3NNaO^+$ 408.1546; Found 408.1546.

2-(4-Bromophenyl)-8-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluorooct-3-yn-2-yl carbamate (5ak)



4ag **3r** **2k** **5ak**

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (5.59 mg, 15.0 µmol, 0.05 equiv.), 2-(6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)isoindoline-1,3-dione (**2k**) (179 mg, 0.300 mmol, 1.00 equiv.) and *tert*-butyl carbamate (**4ag**) (45.7 mg, 0.390 mmol, 1.30 equiv.). The vial was capped, removed from the glovebox and dry DCM (2.35 mL) was added. To the resulting solution was added a 0.6 M solution of 1-bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (**3r**) (0.65 mL, 0.39 mmol, 1.30 equiv.) in dry DCM in 1 h via seringe pump at 40 °C. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography, using EtOAc/pentane 33:67 as eluent, directly without further work-up affording the title compound (**5ak**) as a white solid (49 mg, 90 µmol, 31%). M.p. 117-118 °C; R_f = 0.54 (EtOAc/pentane 50:50), *p*-anisaldehyde; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 2H, Ar*H*), 7.75 – 7.67 (m, 2H, Ar*H*), 7.56 – 7.45 (m, 4H, Ar*H*), 5.00 (br s, 2H, NH_2), 3.72 (t, *J* = 7.0 Hz, 2H, CH_2N), 2.44 (t, *J* = 6.9 Hz, 2H, CH_2C≡C), 1.92 – 1.79 (m, 2H, CH_2), 1.74 – 1.61 (m, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 152.4, 134.1, 133.1, 132.2, 131.7, 128.8, 124.1, 123.4, 122.2 (q, *J* = 284.2 Hz), 91.1, 72.7, 72.2 (q, *J* = 32.4 Hz), 37.5, 27.8, 25.4, 18.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.5; IR (ν_{max}, cm^{-1}) 2945 (m), 2870 (m), 2358 (w), 1461 (m), 1273 (m), 1180 (s), 1117 (s), 1068 (s), 763 (m), 711 (m), 674 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{18}BrF_3N_2NaO_4^+$ 545.0294; Found 545.0284.

4. Control experiments and mechanistic studies

a) Sequential addition of the alcohol and the EBX reagent (Scheme 5, Eq. (1)):

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (3.0 mg, 8.0 µmol, 0.20 equiv.). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by EtOH (**4a**) (19 µL, 0.32 mmol, 8.00 equiv.). Ethyl diazoacetate (**3a**) (19 µL, 0.16 mmol, 4.00 equiv., 87%wt in DCM) was added dropwise and the resulting reaction mixture was stirred at room temperature for 1 h. After this time, an aliquot of the solution (0.40 mL) was taken and a ^1H NMR spectrum of the reaction mixture was recorded **(c)**. A solution of TIPS-EBX (**2a**) (22.0 mg, 40.0 µmol, 1.00 equiv.) in CD_2Cl_2 (0.40 mL) was added to the first solution and the reaction was continued for 1 h at room temperature. A ^1H NMR spectrum was recoreded **(d)**.

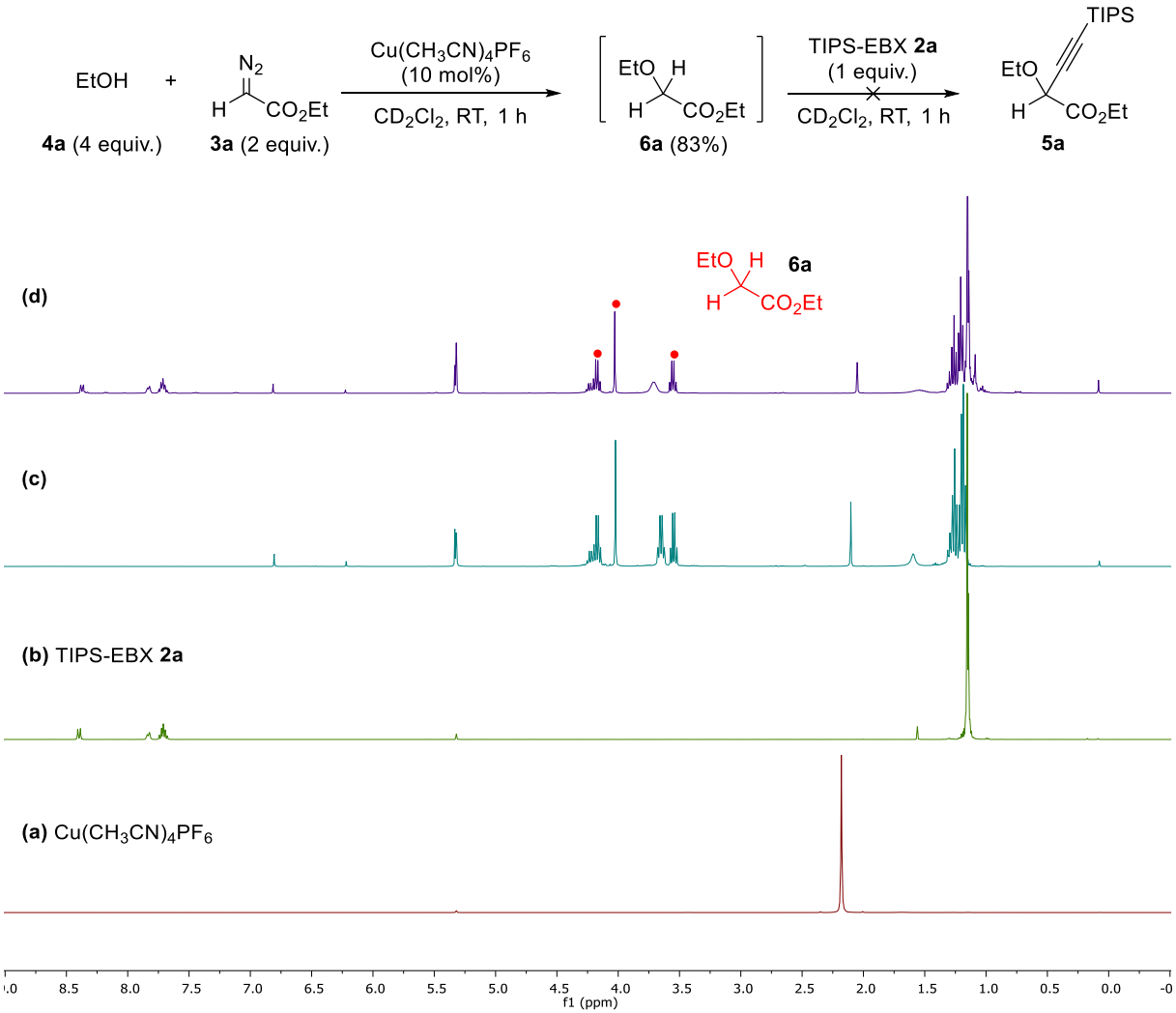


Figure S1: ^1H NMR spectra of the sequential addition of EtOH (**4a**) and TIPS-EBX (**2a**).

No NMR signal of the desired three-component product **5a** appeared after the addition of TIPS-EBX (**2a**) to the already formed O-H insertion product **6a** in presence of the copper catalyst.

b) EBX reagent and diazo compound in presence of copper catalyst (Scheme 5, Eq. (2)):

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (3.0 mg, 8.0 µmol, 0.10 equiv.) and TIPS-EBX **2a** (44 mg, 80 µmol, 1.00 equiv.). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by the dropwise addition of ethyl diazoacetate (**3a**) (19 µL, 0.16 mmol, 4.00 equiv., 87%wt in DCM). Rapid evolution of nitrogen was

observed to occur. The reaction was continued for 1 h at room temperature. A ^{1}H NMR spectrum was recorded **(c)**.

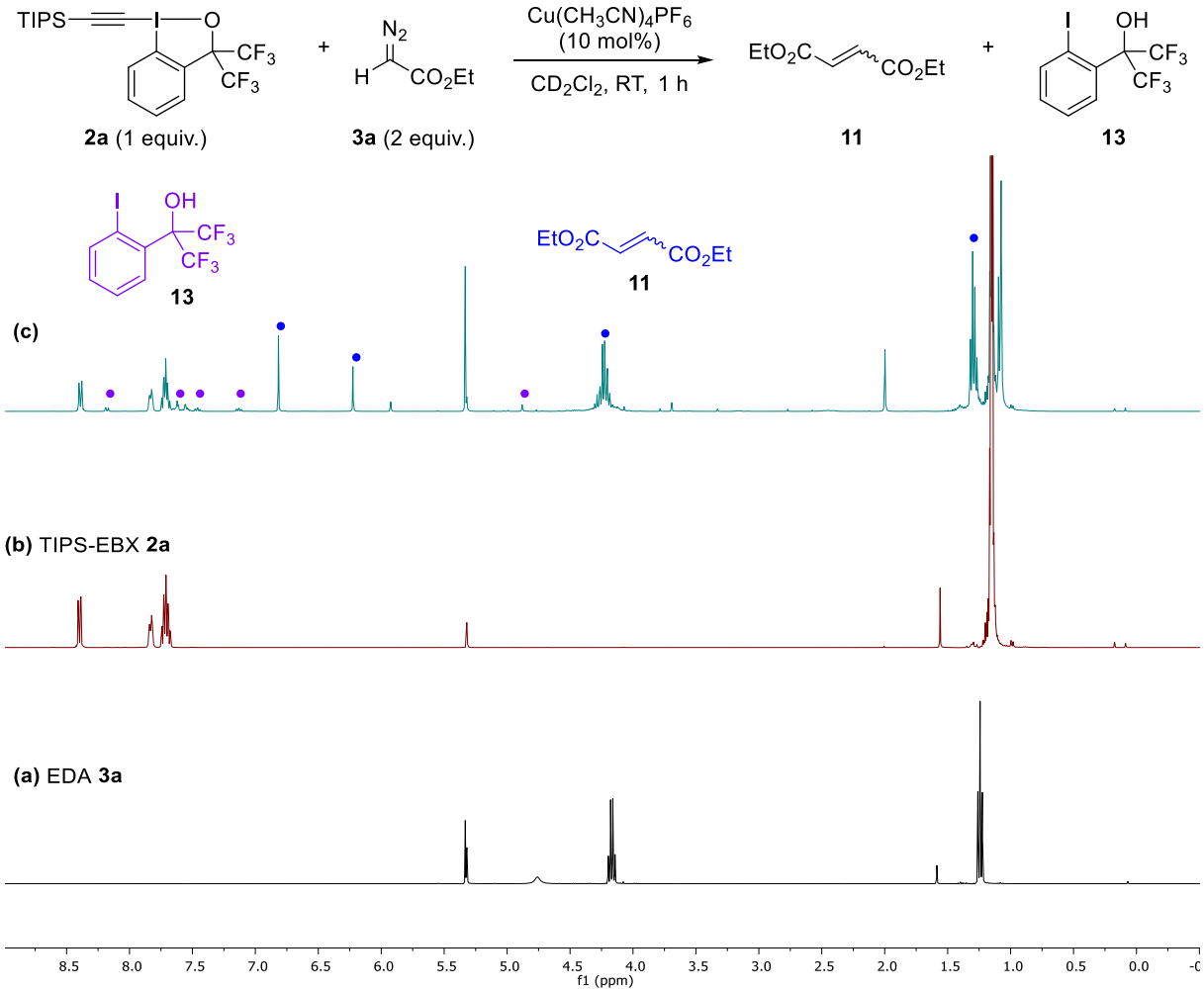
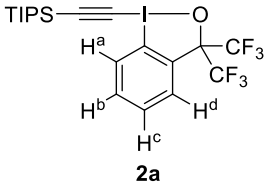


Figure S2: ^{1}H NMR spectra of the dimerization of EDA (**3a**) in presence of EBX (**2a**).

There was an obvious dimerization of ethyl diazoacetate (**3a**) to diethyl fumarate/maleate (**9**) in absence of alcohol. Approximately 10% of the EBX reagent **2a** was degraded to the precursor **13** and other unidentified by-products.

c) ^{1}H and ^{19}F NMR titration of EBX reagent with $Cu(CH_3CN)_4PF_6$:

In a N_2 filled glovebox, two differents oven-dried 10 mL microwave vials were prepared with the following solutions:
(1): 0.1 M solution of TIPS-EBX (**2a**) (110 mg, 2.00 mmol) in CD_2Cl_2 (2.0 mL).
(2): 0.1 M solution of $Cu(CH_3CN)_4PF_6$ (74.5 mg, 2.00 mmol) in CD_2Cl_2 (2.0 mL).
TIPS-EBX (**2a**) (200 µL of solution (1), 0.02 mmol, 1.00 equiv.) was then stirred for 1h at room temperature with differents equivalent of $Cu(CH_3CN)_4PF_6$ (gradient from 0 µL of solution (2), 0.00 mmol, 0.00 equiv. to 600 µL of solution (2), 0.06 mmol, 3.00 equiv.) All solutions were adjusted with CD_2Cl_2 (600 µL to 0 µL) before the addition of the solution (2) to have V_{tot} = 800 µL.



2a

$^{1}H^{a}$: δ 8.43 - 8.36 (m, 1H)
$^{1}H^{b+c}$: δ 7.76 - 7.66 (m, 2H)
$^{1}H^{d}$: δ 7.86 - 7.79 (m, 1H)
^{19}F : δ 76.5

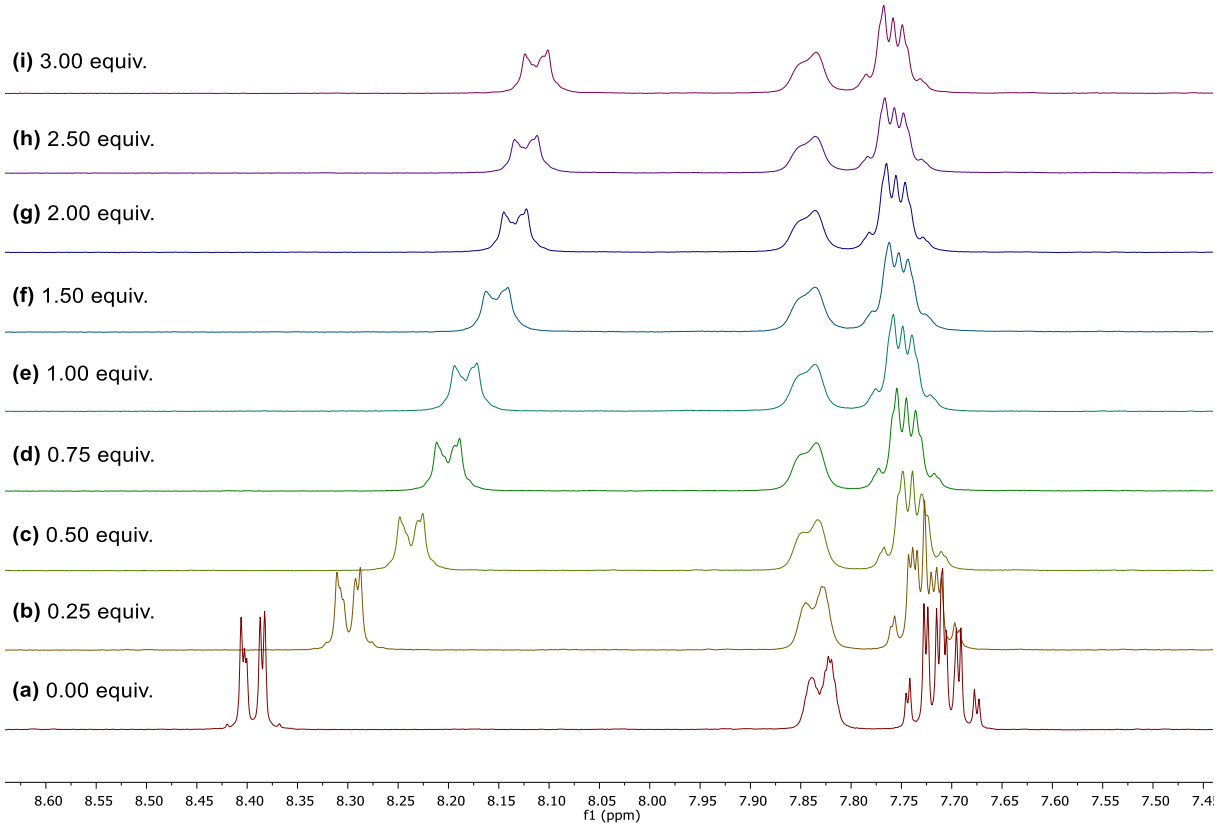


Figure S3: ^{1}H NMR titration of the EBX reagent with $Cu(CH_3CN)_4PF_6$.

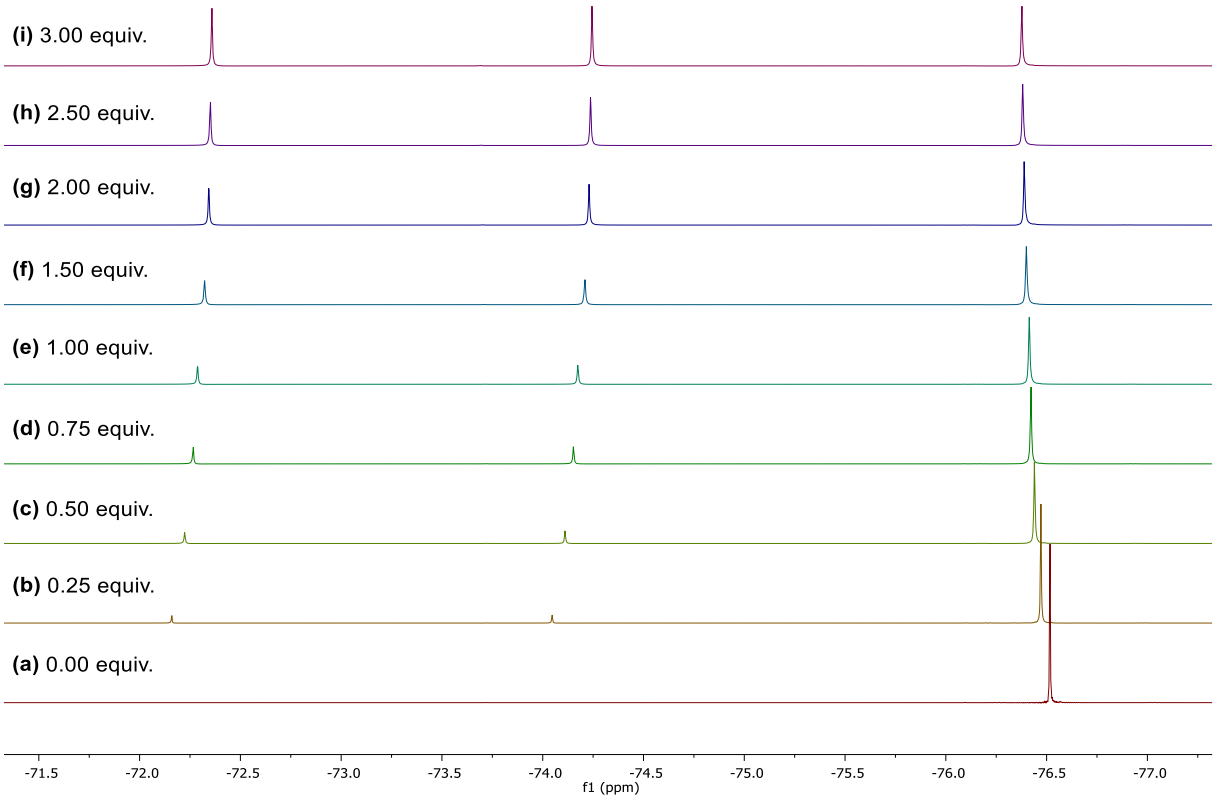


Figure S4: ^{19}F NMR titration of the EBX reagent with $Cu(CH_3CN)_4PF_6$.

Progressive shifts of the aromatic $^{1}H^{a}$ were observed upon addition of the copper salt, with a significant diminution after one equivalent. Others ^{1}H signals were less influenced by the presence of the Cu salt. Minor shift of ^{19}F signal of **2a** was observed (The new doublet appearing comes from the PF_6^-).

d) ^{13}C NMR spectrum of the complexation of the EBX reagent with $Cu(CH_3CN)_4PF_6$:

Samples **(a)** (0.00 equiv.) and **(e)** (1.00 equiv.) from the titration experiment were submitted to ^{13}C NMR analysis.

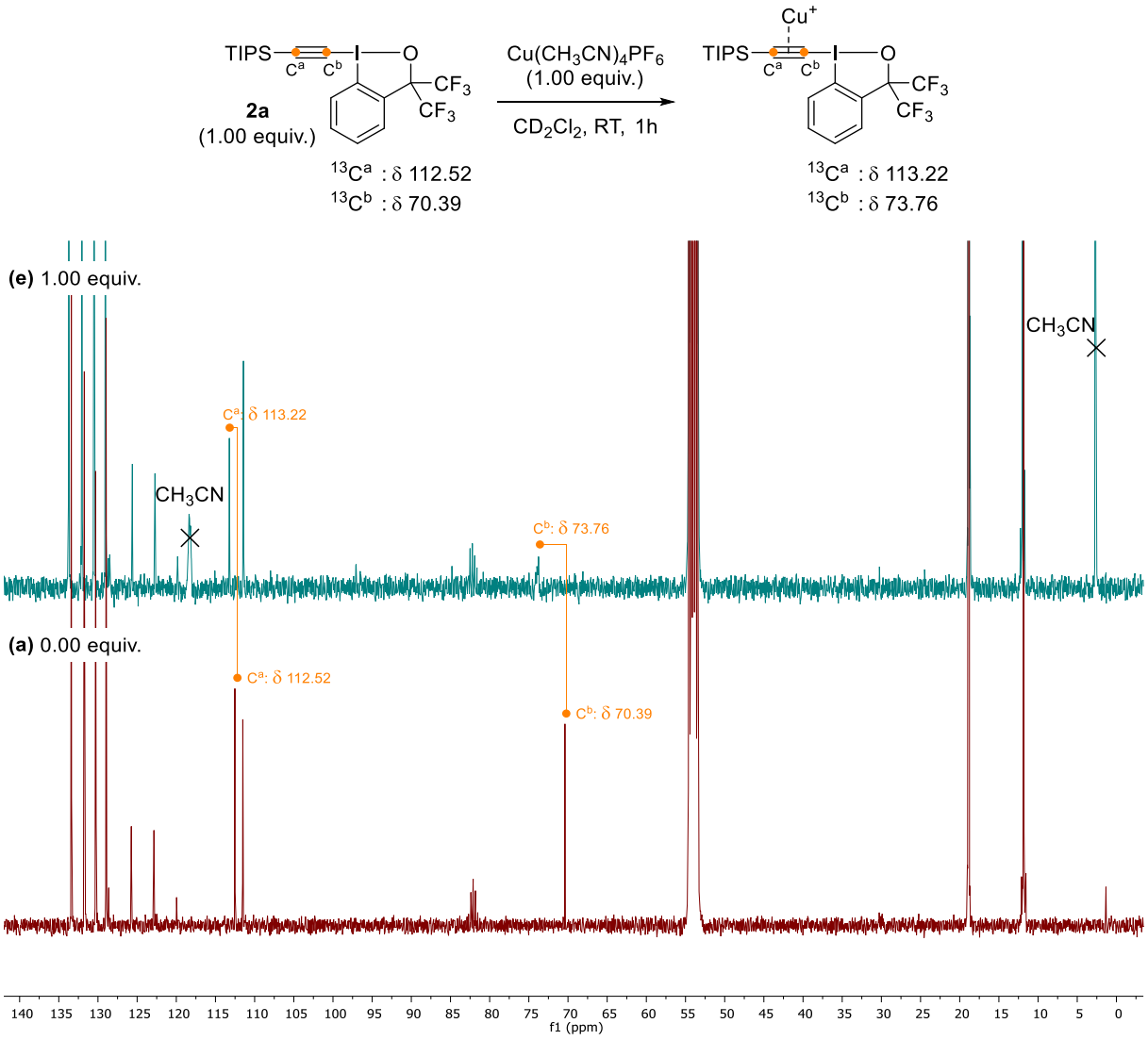


Figure S5: ^{13}C NMR spectrum of the complexation of the EBX reagent and $Cu(CH_3CN)_4PF_6$.

Major changes of $^{13}C^{a}$ ($\Delta\delta$ = 0.7 ppm, 71.1 Hz) and $^{13}C^{b}$ ($\Delta\delta$ = 3.4 ppm, 339.5 Hz) were observed. Other ^{13}C signals remained almost unchanged in presence of the Cu salt.

e) Mixing EtOH with $Cu(CH_3CN)_4PF_6$:

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (30 mg, 0.080 mmol, 1.00 equiv.). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by the addition of EtOH (**4a**) (19 µL, 0.32 mmol, 4.00 equiv.). The resulting reaction mixture was stirred at room temperature for 1 h. A ^{1}H NMR spectrum was recoreded **(c)**. The solvent was then removed under reduced pressure and a new ^{1}H NMR spectrum was recorded in CD_2Cl_2 **(d)**.

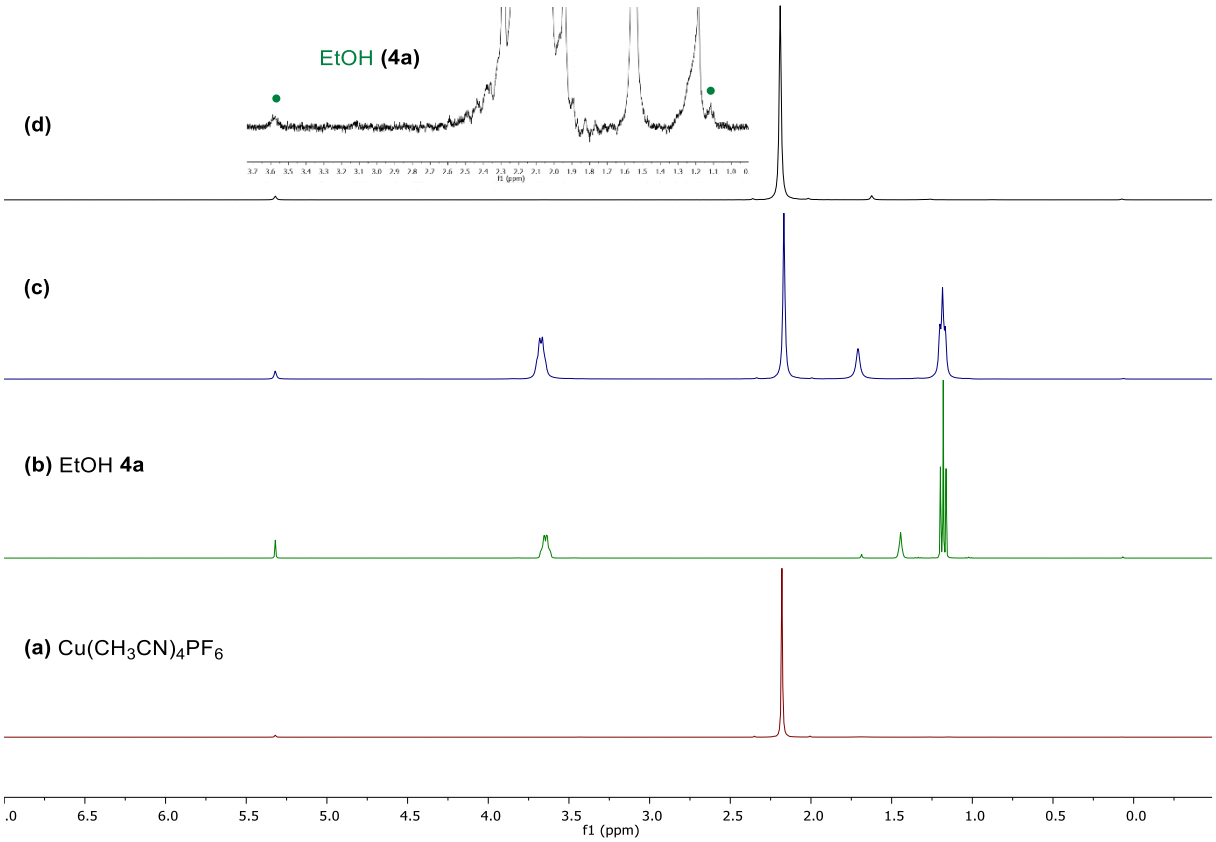


Figure S6: ^{1}H NMR spectrum of the complexation of EtOH and $Cu(CH_3CN)_4PF_6$.

No shift of ^{1}H signals of ethanol or $Cu(CH_3CN)_4PF_6$ were observed. When the reaction mixture was evaporated, the initial copper salt was recovered.

f) Cu-carbene trapping through cyclopropanation (Scheme 5, Eq (3)):

In a N_2 filled glovebox, an oven-dried 10 mL microwave vial was charged with $Cu(CH_3CN)_4PF_6$ (3.0 mg, 8.0 µmol, 0.10 equiv.) and TIPS-EBX **2a** (44 mg, 80 µmol, 1.00 equiv.). The vial was capped, removed from the glovebox and CD_2Cl_2 (0.80 mL) was added, followed by the addition of ethanol (**4a**) (19 µL, 0.32 mmol, 4.00 equiv.) and styrene (37 µL, 0.32 mmol, 4.00 equiv.). A solution of ethyl diazoacetate (**3a**) in DCM (133 µL, 80 µmol, 1.00 equiv., 0.6 M) was slowly added in 1 h via seringe pump. At the end of the addition, the reaction was continued 1 h at room temperature. ^{1}H NMR spectrum of the reaction mixture was recoreded (**d**). For comparison, control experiments missing the EBX reagent (spectrum (**c**)), ethanol (spectrum (**b**)) and EBX + ethanol (spectrum (**a**)) were done.

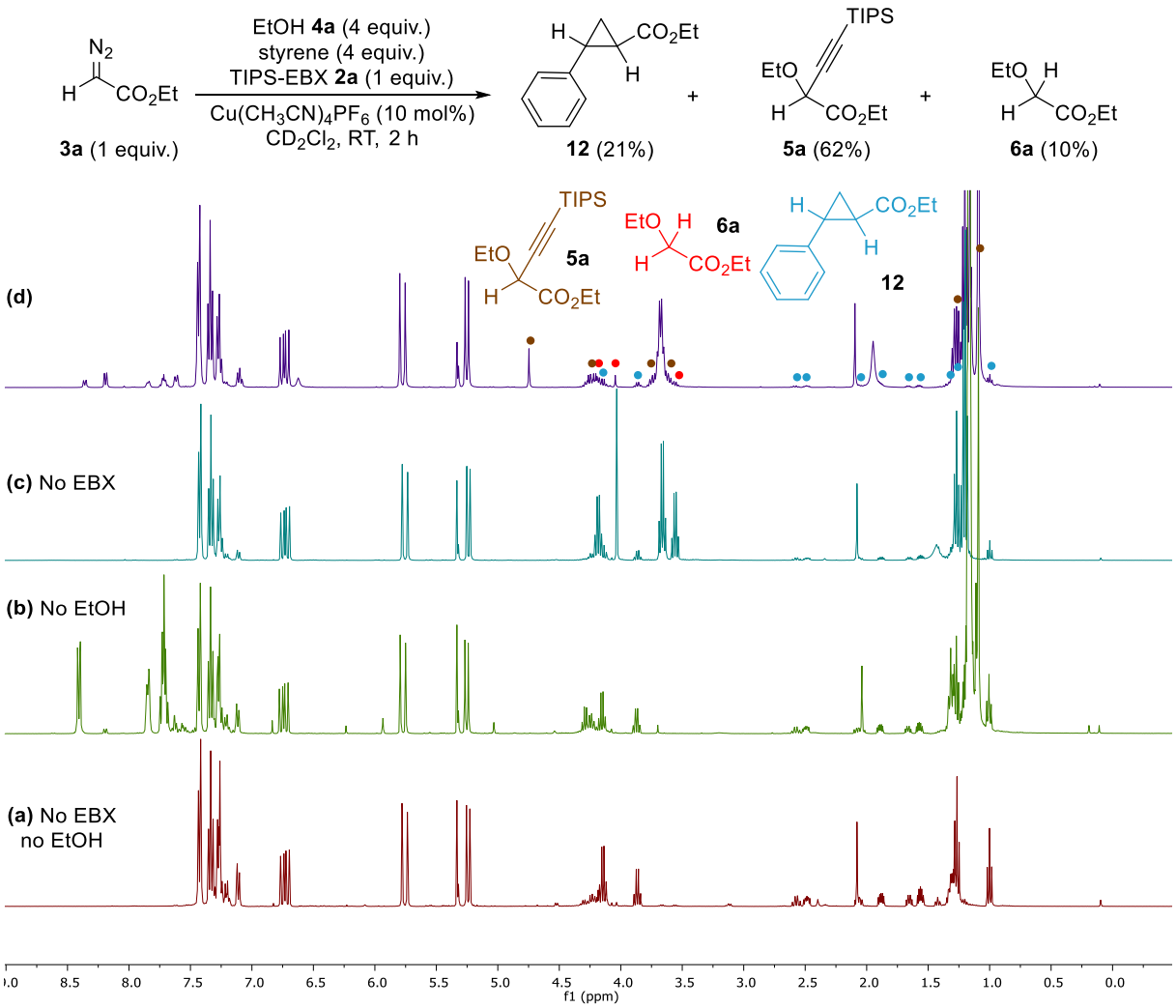
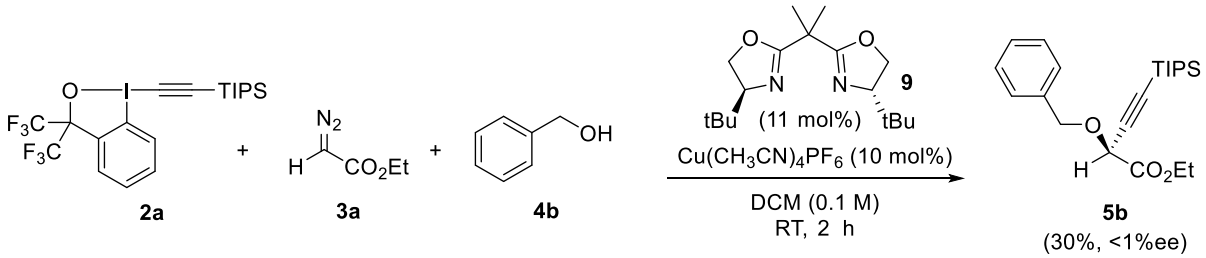


Figure S7: ^{1}H NMR spectrum of the competitive cyclopropanation with styrene.

The three-component product **5a** was the major product observed (62%). The conversion of TIPS-EBX (**2a**) was 62%. A detectable amount of cyclopropane **12** was observed (21%). The O-H insertion product **6a** was also detected (10%). In absence of EtOH, cyclopropane **12** was the major product formed (spectrum (**a**) and (**b**)). The O-H insertion product **6a** was predominant (83%) over the cyclopropane **12** (16%) when EtOH (4.00 equiv.) and styrene (4.00 equiv.) were in competition (spectrum (**c**)).

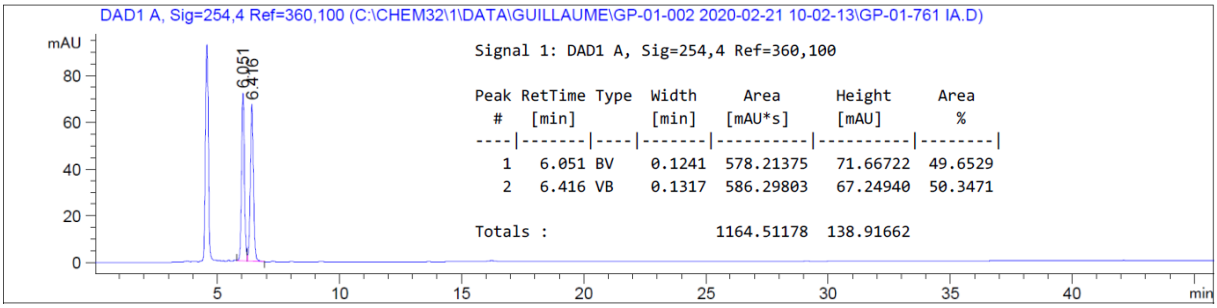
g) Effect of *t*BuBOX ligand (Scheme 5, Eq (4)):



In a N_2 filled glovebox, a catalytic solution was prepared by mixing $Cu(CH_3CN)_4PF_6$ (16.8 mg, 45.0 µmol, 0.15 equiv.) and (*S*,*S*)-(-)-2,2'-isopropylidenebis(4-*tert*-butyl-2-oxazoline) (**9**) (14.6 mg, 50.0 µmol, 0.17 equiv.) in dry DCM (3.00 mL) at room temperature for 1 h.

2.00 mL of the catalytic solution was added to an oven-dried 10 mL microwave vial previously charged with TIPS-EBX **2a** (165 mg, 0.3 mmol, 1.00 equiv.) under N_2 atmosphere followed by benzyl alcohol (**4b**)

(124 µL, 1.20 mmol, 4.00 equiv.). To the resulting solution was added ethyl 2-diazoacetate (**3a**) (1.0 mL, 0.60 mmol, 0.6 M in DCM) in 1 h *via* seringe pump at 25 °C. The system was mainted isobaric with a filled balloon with N_2. At the end of the addition, the reaction was continued for 1 h at the same temperature. The solvent was removed under reduced pressure and the resulting crude product was analyzed by ^{1}H NMR. Ethyl 2-(benzyloxy)-4-(triisopropylsilyl)but-3-ynoate (**5b**) was formed in 30% yield in the crude reaction mixture. The crude product was purified by column chromatography using EtOAc/pentane 3:97 as eluent to afford ethyl 2-(benzyloxy)-4-(triisopropylsilyl)but-3-ynoate (**5b**) (23 mg, 0.06 mmol, 20%) as a colorless oil. Chiral HPLC conditions: ee = <1%; Chiralpak IA 98:2 Hexane/iPrOH, 1.0 mL/min, 60 min. tr (1) = 6.051 min. and tr (2) = 6.416 min. λ = 254 cm^{-1}.

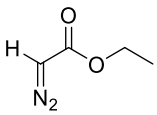


Benzyl alcohol (**4b**) was used instead of ethanol (**4a**) to facilitate HPLC analysis of the enantioselectivity.

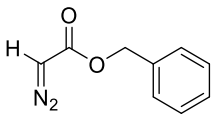
5. Synthesis of diazo-compounds

CAUTION: Diazo compounds are toxic and potentially explosive and should be handled with care in a well-ventilated hood.[2]

Ethyl 2-diazoacetate (**3a**) and benzyl 2-diazoacetate (**3b**) were directly purchased from Sigma Aldrich.

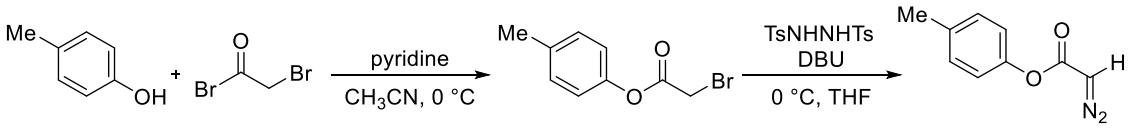


3a



3b

***p*-Tolyl 2-diazoacetate (3c)**



17 **18** **19** **3c**

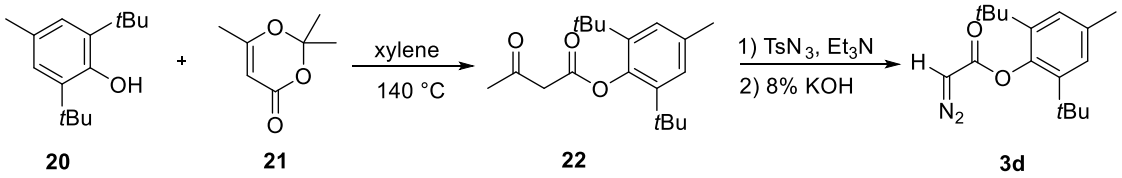
Bromoacetyl bromide (**18**) (1.31 mL, 15.0 mmol, 1.50 equiv) was added to a stirred solution of *p*-cresol (**17**) (1.08 g, 10.0 mmol, 1.00 equiv) and pyridine (1.61 mL, 20.0 mmol, 2.00 equiv) in acetonitrile (50 mL) at 0 °C over 10 minutes. The mixture was stirred for further 5 minutes at 0 °C and then quenched with water (30 mL). The reaction mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford *p*-tolyl 2-bromoacetate (**19**) as a colorless oil (2.1 g, 9.2 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 2H, Ar*H*), 7.05 – 6.95 (m, 2H, Ar*H*), 4.04 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 148.4, 136.2, 130.2, 120.9, 25.7, 21.0. The values of the NMR spectra are in accordance with reported literature data.[3]

Following a reported procedure, *N,N'*-Ditosylhydrazine (3.40 g, 10.0 mmol, 2.00 equiv) was added to a solution of *p*-tolyl 2-bromoacetate (**19**) (1.15 g, 5.00 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) and the mixture was cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (3.8 mL, 25 mmol, 5.0 equiv) was added dropwise over 20 minutes at 0 °C. The reaction was stirred 2 h at 0 °C before being quenched by a saturated aqueous $NaHCO_3$ solution (30 mL). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford *p*-tolyl 2-diazoacetate (**3c**) as a yellow oil (0.450 g, 2.55 mmol, 51%). R_f = 0.33 (EtOAc/pentane 5:95), $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H, Ar*H*), 7.03 – 6.98 (refm, 2H, Ar*H*), 4.95 (br s, 1H, C*H*N_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 148.4, 135.7, 130.1, 121.5, 46.9, 21.0; IR (ν_{max}, cm^{-1}) 3115 (w), 2112 (s), 1699 (s), 1508 (m), 1364 (s), 1342 (s), 1193 (s), 1167 (s), 1143 (s), 923 (m), 831 (m), 728 (m); HRMS (ESI) calcd. for $C_9H_9N_2O_2^+$ $[M+H]^+$ 177.0659; found 177.0656. One carbon was not resolved at 100 MHz.

[2] S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.* **2020**, *24*, 67.

[3] G. Himbert, D. Fink and K. Diehl, *Chem. Ber.* **1988**, *121*, 431.

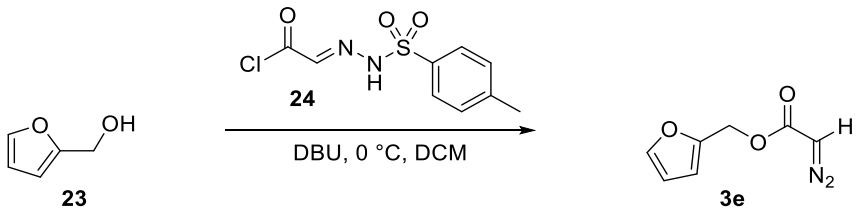
2,6-Di-*tert*-butyl-4-methylphenyl 2-diazoacetate (3d)



Following a slightly modified procedure,[4] a mixture of 2,6-di-*tert*-butyl-4-methylphenol (**20**) (5.51 g, 25.0 mmol, 1.00 equiv), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**21**) (3.32 mL, 25.0 mmol, 1.00 equiv), and xylene (5 mL) was stirred at 140 °C for 1.5 h. After cooling to room temperature, the reaction mixture was directly loaded on silica and was purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford 2,6-di-*tert*-butyl-4-methylphenyl 3-oxobutanoate (**22**) as a white solid (5.77 g, 19.0 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 0.22H, O*H* of enol form), 7.31 – 7.24 (m, 1H, Ar*H* of enol and keto form), 7.24 – 7.18 (m, 2H, Ar*H* of enol and keto form), 5.38 (s, 0.2H, vinyl *H* of enol form), 3.81 (s, 1.56H, CH_3COCH_2 of keto form), 3.03 (m, 2H, 2 x $CH(CH_3)_2$ of enol and keto form), 2.41 (s, 2.32H, CH_3COCH_2 of keto form), 2.08 (s, 0.6H, CH_3 of enol form), 1.28 – 1.21 (m, 12H, 2 x $CH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$), Enol form: δ 177.7, 171.5, 144.5, 140.5, 126.5, 123.9, 88.7, 23.7, 22.7, 21.4; ^{13}C NMR (101 MHz, $CDCl_3$), Keto form: δ 199.9, 165.7, 145.1, 140.2, 126.8, 124.0, 49.6, 30.4, 27.4, 27.3. The values of the NMR spectra are in accordance with reported literature data.[5]

Following a slightly modified procedure,[4] to a solution of 2,6-di-*tert*-butyl-4-methylphenyl 3-oxobutanoate (**22**) (5.48 g, 18.0 mmol, 1.00 equiv) in MeCN (22 mL) was added triethylamine (3.26 mL, 23.4 mmol, 1.30 equiv). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (3.90 g, 19.8 mmol, 1.1 equiv) in MeCN (22 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (90 mL) was added and stirred vigorously for 4 h. The reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 2:98 as eluent to afford 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (**3d**) as a yellow solid (4.80 g, 16.6 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 2H, Ar*H*), 5.00 (s, 1H, CHN_2), 2.32 (s, 3H, $ArCH_3$), 1.36 (s, 18H, 2 x *t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 145.1, 142.4, 134.8, 127.0, 47.3, 35.3, 31.5, 21.5. The values of the NMR spectra are in accordance with reported literature data.[6]

Furan-2-ylmethyl 2-diazoacetate (3e)



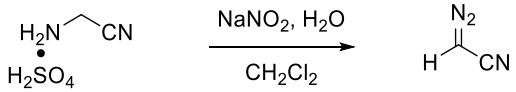
Following a slightly modified procedure,[7] to a solution of *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (**24**) (1.30 g, 5.00 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL) were added furfuryl alcohol (**23**) (475 µL, 5.50 mmol, 1.10 equiv.) and then DBU (1.89 mL, 12.5 mmol, 2.50 equiv.) dropwise at 0 °C. After

[4] P. Müller and P. Polleux, *Helv. Chim. Acta* **1994**, *77*, 645.
[5] D. P. Hari and J. Waser, *J. Am. Chem. Soc.*, 2017, **139**, 8420.
[6] M. P. Doyle, V. Bagheri, T. J. Wandless, N. K. Harn, D. A. Brinker, C. T. Eagle and K. L. Loh, *J. Am. Chem. Soc.* **1990**, *112*, 1906.
[7] T. Hashimoto, N. Uchiyama and K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380.

stirring for 2 h at the same temperature, the reaction was stirred 30 min at room temperature and then poured into saturated NH_4Cl solution (10 mL). The organic layer was then extracted with CH_2Cl_2 (3 x 10 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 3:97 as eluent to afford furan-2-ylmethyl 2-diazoacetate (**3e**) as a yellow oil (534 mg, 3.21 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.9, 0.9 Hz, 1H, Ar*H*), 6.42 (dd, *J* = 3.3, 0.8 Hz, 1H, Ar*H*), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H, Ar*H*), 5.14 (s, 2H, C*H*$_2$O), 4.78 (br s, 1H, CN$_2$*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 149.5, 143.5, 111.0, 110.7, 58.3, 46.5. The values of the NMR spectra are in accordance with reported literature data.[8]

2-Diazoacetonitrile (3f)

CAUTION: This diazo compound is reported to be explosive at high concentration.

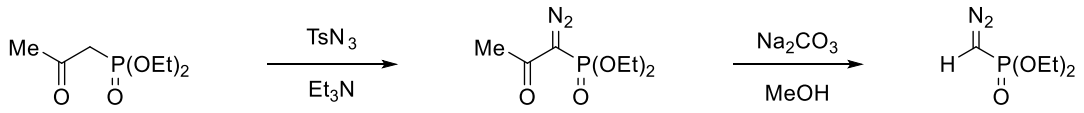


25 **3f**

Following a reported procedure,[9] to a suspension of 2-aminoacetonitrile sulfate (**25**) (3.70 g, 24.0 mmol, 1.00 equiv.) in DCM (28 mL) at -10 °C was cautiously added dropwise an aqueous solution of sodium nitrite (4.97 g, 72.0 mmol, 3.00 equiv.) in distilled water (22 mL) at such a rate that the temperature of the reaction did not rise above 0 °C. During the addition effervescence was observed. After the complete addition, the reaction was allowed to stir for 30 min at 0 °C. The organic layer was separated and the aqueous layer further extracted with DCM (20 mL). The combined organic layers were washed with 1% aqueous $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered and stored at - 18 °C.

The concentration of the solution was assumed to be 0.5 M of diazoacetonitrile (**3f**) in DCM and was used immediately without further purification.

Diethyl (diazomethyl)phosphonate (3g)



26 **27** **3g**

Following a reported procedure,[10] a mixture of diethyl (2-oxopropyl)phosphonate (**26**) (1.15 mL, 6.00 mmol, 1.00 equiv), tosyl azide (1.3 g, 6.6 mmol, 1.10 equiv) and triethylamine (6 mL) was stirred at room temperature for 18 h. After evaporation of the triethylamine under reduced pressure, the residue was dissolved in diethyl ether (50 mL). The precipitate was filtered off, the filtrate was evaporated and the residue was purified by column chromatography using EtOAc/pentane 50:50 as eluent affording the corresponding diethyl (1-diazo-2-oxopropyl)phosphonate (**27**) as a yellow oil (0.810 g, 3.68 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 – 4.19 (m, 4H, 2 x C*H*$_2$CH$_3$) 2.19 (s, 3H, C*H*$_3$), 1.30 (t, *J* = 7.0 Hz, 6H, 2 x CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (d, *J* = 13.2 Hz), 63.4 (d, *J* = 5.6 Hz), 27.1, 16.0 (d, *J* = 6.8 Hz). The values of the NMR spectra are in accordance with reported literature data.[5]

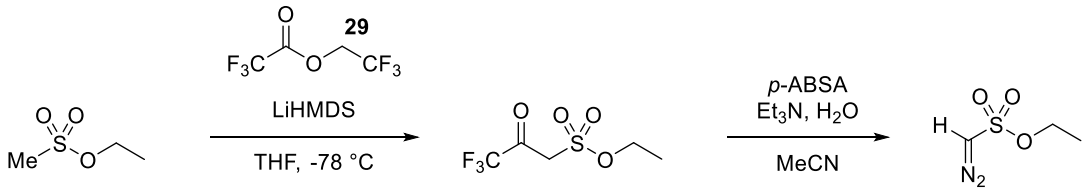
[8] S. Bew, P.-A. Ashford and D. Bachera, *Synthesis* **2013**, *45*, 903.

[9] J. Dunn and A. P. Dobbs, *Tetrahedron* **2015**, *71*, 7386.

[10] S. Chanthamath, S. Ozaki, K. Shibatomi and S. Iwasa, *Org. Lett.* **2014**, *16*, 3012.

To a solution of diethyl (1-diazo-2-oxopropyl)phosphonate (**27**) (694 mg, 3.15 mmol, 1.00 equiv) in MeOH (9.0 mL) was added Na_2CO_3 (401 mg, 3.78 mmol, 1.20 equiv). The mixture was stirred at room temperature for 15 min. The precipitate was filtered off, the filtrate was evaporated and the residue was purified by column chromatography using EtOAc/pentane 50:50 as eluent affording the corresponding diethyl (diazomethyl)phosphonate (**3g**) as a yellow oil (533 mg, 2.99 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.08 (m, 4H, 2 x C*H*$_2$CH$_3$), 3.75 (d, *J* = 11.1 Hz, 1H, C*H*N$_2$), 1.34 (td, *J* = 7.1, 0.7 Hz, 6H, 2 x CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.6 (d, *J* = 5.3 Hz), 16.1 (d, *J* = 6.9 Hz). The values of the NMR spectra are in accordance with reported literature data. One carbon was not resolved at 101 MHz.[5]

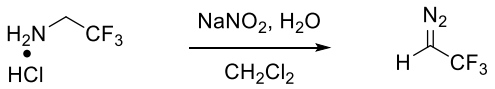
Ethyl diazomethanesulfonate (3h)



28 **30** **4i**

Following a reported procedure,[11] to a solution of ethyl methanesulfonate (**28**) (1.86 g, 15.0 mmol, 1.00 equiv) in dry THF (50 mL) was added a 1 M LiHMDS solution in hexane (18 mL, 18 mmol, 1.2 equiv) at -78 °C. After stirring the reaction mixture for 30 min at this temperature, 2,2,2-trifluoroethyl trifluoroacetate (**29**) (2.4 mL, 18 mmol, 1.2 equiv) was added rapidly in one portion *via* syringe. After 10 min, the reaction mixture was poured into a solution of diethyl ether (20 mL) and 5% HCl (50 mL). The mixture was extracted with diethyl ether (3 x 50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. The resulting ethyl 3,3,3-trifluoro-2-oxopropane-1-sulfonate (**30**) was immediately dissolved in dry MeCN (30 mL). To this solution was added *p*-ABSA (4.32 g, 18.0 mmol, 1.20 equiv), Et_3N (2.5 mL, 18 mmol, 1.2 equiv), and water (0.27 mL, 15 mmol, 1.0 equiv). After stirring the reaction mixture overnight at room temperature, the solvent was removed under reduced pressure and the residue was filtered on short plug of silica gel and washed with a mixture of ethyl acetate (100 mL) and hexane (100 mL). The filtrate was concentrated under vacuum and the residue was purified by column chromatography using EtOAc/pentane 10:90 as eluent to afford ethyl diazomethanesulfonate (**3h**) as a yellow oil (0.9 g, 6 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H, C*H*N$_2$), 4.26 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 1.41 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.4, 52.4, 14.6. The values of the NMR spectra are in accordance with reported literature data.[11]

2,2,2-Trifluorodiazoethane (3i)



31 **3i**

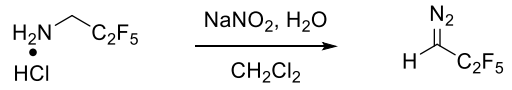
Following a reported procedure,[12] under argon, 2,2,2-trifluoroethanamine hydrochloride (**31**) (0.678 g, 5.00 mmol, 1.00 equiv) and sodium nitrite (0.379 g, 5.50 mmol, 1.10 equiv) were dissolved in degassed CH_2Cl_2 (10 mL). Degassed water (1.00 mL, 55.5 mmol, 11.1 equiv) was added slowly at 0 °C. The solution was stirred for 2 h at 0 °C and 1 h at room temperature. The aqueous layer was frozen in the freezer overnight (-18 °C) and the organic layer was dried over a plug of potassium carbonate, transferred into a vial, sealed and stored at - 18 °C. The concentration of the obtained solution was

[11] Ye T. and Zhou C., *New J. Chem.* **2005**, *29*, 1159.

[12] S. Hyde, J. Veliks, B. Liégault, D. Grassi, M. Taillefer and V. Gouverneur, *Angew. Chem. Int. Ed.,* 2016, **55**, 3785.

determined to be 0.37 M by ^{19}F NMR analysis (according to an internal reference, $PhCF_3$). ^{19}F NMR (377 MHz, CH_2Cl_2) δ -55.56. The values of the NMR spectra are in accordance with reported literature data.

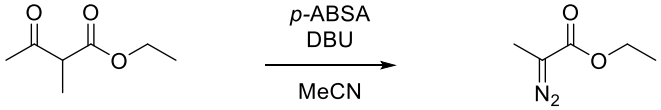
3-Diazo-1,1,1,2,2-pentafluoropropane (3j)



32 **3j**

Under argon, 2,2,2-trifluoroethanamine hydrochloride (**32**) (0.928 g, 5.00 mmol, 1.00 equiv) and sodium nitrite (0.379 g, 5.50 mmol, 1.10 equiv) were dissolved in degassed CH_2Cl_2 (10 mL). Degassed water (1.00 mL, 55.5 mmol, 11.1 equiv) was added slowly at 0 °C. The solution was stirred for 2 h at 0 °C and 1 h at room temperature. The organic layer was isolated, dried over $MgSO_4$, transferred into a vial, sealed and stored at - 18 °C. The concentration of the obtained solution was determined to be 0.36 M by ^{19}F NMR analysis (according to an internal reference, $PhCF_3$). ^{19}F NMR (377 MHz, CH_2Cl_2) δ -88.96 – -89.01 (m), -110.98 – -111.03 (m).

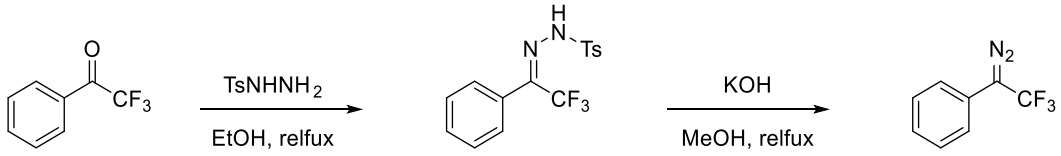
Ethyl 2-diazopropanoate (3k)



33 **3k**

Following a modified reported procedure,[13] DBU (1.8 mL, 12 mmol, 3.0 equiv) was added slowly to a stirred solution of ethyl 2-methylacetoacetate (**33**) (0.60 mL, 4.0 mmol, 1.0 equiv) and *p*-ABSA (1.4 g, 6.0 mmol, 1.5 equiv) in MeCN (80 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring for 12 h, the reaction mixture was quenched with 1 M HCl (8 mL), and extracted with hexane (3 x 40 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using Et_2O:pentane 2:98 as eluent affording the corresponding ethyl 2-diazopropanoate (**3k**) as a yellow oil (241 mg, 1.88 mmol, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 1.94 (s, 3H, N_2CCH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 60.7, 14.5, 8.4. The values of the NMR spectra are in accordance with reported literature data.[14] One carbon was not resolved at 101 MHz.

(1-Diazo-2,2,2-trifluoroethyl)benzene (3l)



34 **35** **3l**

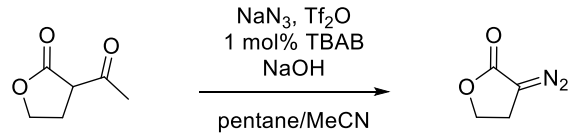
2,2,2-Trifluoroacetophenone (**34**) (702 µL, 5.00 mmol, 1.05 equiv.) was added to EtOH (18.8 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (880 mg, 4.76 mmol, 1.00 equiv.) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid.

[13] T. Hashimoto, Y. Naganawa and K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834.
[14] L. Huang and W. D. Wulff, *J. Am. Chem. Soc.* **2011**, *133*, 8892.

Then, pentane (100 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Following a reported procedure,[18] 4-methyl-N'-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonohydrazide (**35**) was disolved in a 0.4 M solution of potassium hydroxide (561 mg, 5.00 mmol, 2.00 equiv.) in MeOH (25.0 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (15 mL). The crude product was extracted with pentane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford (1-diazo-2,2,2-trifluoroethyl)benzene (**3l**) as a volatile orange oil (344 mg, 1.85 mmol, 37%). The compound was kept as a 0.6 M solution in DCM at -18 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 2H, Ar*H*), 7.23 – 7.17 (m, 1H, Ar*H*), 7.13 – 7.05 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.6, 126.1, 125.8 (q, *J* = 269.4 Hz), 123.7, 122.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[18]

3-Diazodihydrofuran-2(3*H*)-one (3m)

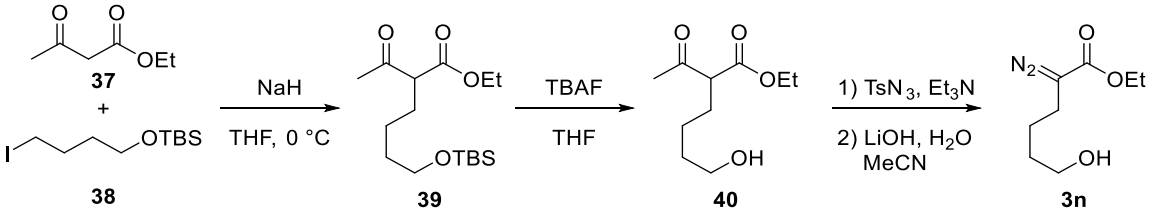


36 **3m**

Following a reported procedure,[15] sodium azide (2.42 g, 37.2 mmol, 4.00 equiv), sodium hydroxide (78 mL, 2 M in water), tetrabutylammonium bromide (30.0 mg, 93.0 µmol, 0.01 equiv), and pentane (40 mL) were mixed in a 250 mL round-bottom flask with magnetic stirring bar open to the air and allowed to cool to 0 °C. With vigorous stirring, Tf_2O (3.10 mL, 18.6 mmol, 2.00 equiv) was added dropwise. After 10 min, a solution of 2-acetyl-butyrolactone (**36**) (1.00 mL, 9.30 mmol, 1.00 equiv) in MeCN (35 mL) was poured into the round-bottom flask through a funnel, followed by additional MeCN (10 mL) to complete the transfer. The initially colorless reaction mixture immediately turned yellow. After allowing to stir for 30 min at 0 °C, the mixture was diluted with ice water (25 mL) and EtOAc (25 mL) and transferred to a separatory funnel. After phase separation and removal of the organic layer, the aqueous layer was washed with cold EtOAc (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc:pentane 50:50 as eluent affording the corresponding 3-diazodihydrofuran-2(3*H*)-one (**3m**) as a bright yellow crystalline solid (0.32 g, 2.8 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, *J* = 8.0 Hz, 2H, CH_2), 3.36 (t, *J* = 8.0 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): 170.6, 65.3, 49.4, 23.1. The values of the NMR spectra are in accordance with reported literature data.[15]

[15] E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 943.

Ethyl 2-diazo-6-hydroxyhexanoate (3n)



Adapted from a reported procedure,[16] ethyl acetoacetate (**37**) (3.79 mL, 30.0 mmol, 2.00 equiv.) was added dropwise to a stirred suspension of sodium hydride (60 % dispersion in mineral oil, 900 mg, 22.5 mmol, 1.50 equiv.) in dry THF (35.7 mL) at 0 °C. After 30 min, *tert*-butyl(4-iodobutoxy)dimethylsilane (**38**) (3.88 mL, 15.0 mmol, 1.00 equiv.) was added slowly at ambient temperature, and the reaction was refluxed for 24 h. Saturated aqueous NH_4Cl (50 mL) was added, the two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/pentane 5:95 as eluent to afford ethyl 2-acetyl-6-((*tert*-butyldimethylsilyl)oxy)hexanoate (**39**) as a colorless oil (3.66 g, 11.6 mmol, 77%). R_f = 0.30 (EtOAc/pentane 5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.59 (t, *J* = 6.3 Hz, 2H, C*H*$_2$OTBS), 3.40 (t, *J* = 7.4 Hz, 1H, C(O)C*H*C(O)), 2.22 (s, 3H, C(O)C*H*$_3$), 1.95 – 1.76 (m, 2H, CHC*H*$_2$), 1.57 – 1.48 (m, 2H, C*H*$_2$CH$_2$OTBS), 1.38 – 1.23 (m, 5H, OCH$_2$C*H*$_3$ and C*H*$_2$CH$_2$CH), 0.88 (s, 9H, Si-*tBu*), 0.03 (s, 6H, 2 x Si-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 170.0, 62.9, 61.5, 60.1, 32.6, 28.9, 28.2, 26.1, 24.0, 18.5, 14.3, -5.2; IR (ν_{max}, cm^{-1}) 2954 (m), 2930 (m), 2857 (m), 1741 (m), 1716 (s), 1360 (m), 1251 (m), 1150 (m), 1097 (s), 835 (s), 774 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{32}NaO_4Si^+$ 339.1962; Found 339.1961.

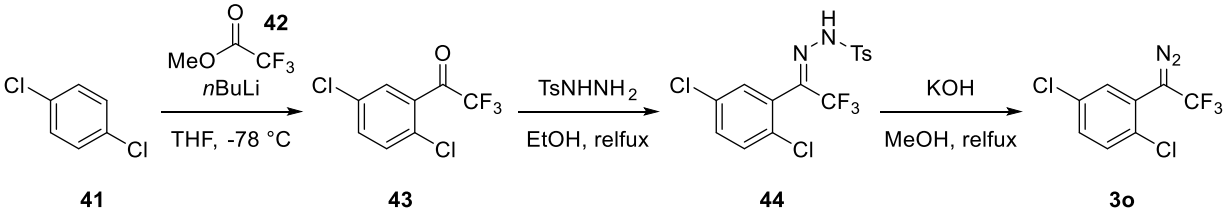
To a solution of ethyl 2-acetyl-6-((*tert*-butyldimethylsilyl)oxy)hexanoate (**39**) (3.17 g, 10.0 mmol, 1.00 equiv.) in THF (20 mL) was added TBAF (11.0 mL, 11.0 mmol, 1.10 equiv., 1.0 M in THF) slowly and the mixture was stirred overnight at room temperature. After this time, the reaction was quechend by a saturated aqueous NH_4Cl solution (20 mL) and diluted with diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography using EtOAc/pentane 50:50 as eluent to afford ethyl 2-acetyl-6-hydroxyhexanoate (**40**) as a colorless oil (1.51 g, 7.49 mmol, 75%). R_f = 0.35 (EtOAc/pentane 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (qd, *J* = 7.1, 0.9 Hz, 2H, OC*H*$_2$CH$_3$), 3.64 (t, *J* = 6.4 Hz, 2H, C*H*$_2$OH), 3.42 (t, *J* = 7.3 Hz, 1H, C(O)C*H*C(O)), 2.23 (s, 3H, C(O)C*H*$_3$), 1.93 – 1.80 (m, 2H, CHC*H*$_2$), 1.64 – 1.53 (m, 3H, C*H*$_2$CH$_2$OH and O*H*), 1.42 – 1.31 (m, 2H, C*H*$_2$CH$_2$CH), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 170.0, 62.5, 61.5, 59.9, 32.4, 29.0, 27.9, 23.8, 14.3; IR (ν_{max}, cm^{-1}) 3436 (w), 2938 (m), 2869 (w), 1736 (s), 1711 (s), 1361 (m), 1201 (s), 1149 (s), 1056 (m), 1032 (s); HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{18}NaO_4^+$ 225.1097; Found 225.1101.

Adapted from a reported procedure,[16] a 1.0 M solution of tosylazide (2.07 g, 10.5 mmol, 1.50 equiv.) in MeCN (10.5 mL) was added dropwise to a solution of 2-acetyl-6-hydroxyhexanoate (**40**) (1.46 g, 7.00 mmol, 1.00 equiv.) and triethylamine (1.46 mL, 10.5 mmol, 1.50 equiv.) in MeCN (21.2 mL) at ambient temperature. After stirring for 12 h, a solution of LiOH (0.84 g, 35 mmol, 5.0 equiv.) in water (12.7 mL) was added and the mixture was stirred for another 12 h. Brine was added, the two layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography using EtOAc/pentane 25:75 as eluent to afford ethyl 2-diazo-6-hydroxyhexanoate (**3n**) as a bright yellow oil (0.95 g, 5.1 mmol, 73%). R_f = 0.31 (EtOAc/pentane 25:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.77 – 3.61 (m, 2H, C*H*$_2$OH), 2.43

[16] S.-F. Zhu, X.-G. Song, Y. Li, Y. Cai and Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 16374.

– 2.30 (m, 2H, CH_2CN$_2$), 1.69 – 1.54 (m, 4H, CH_2CH_2), 1.51 (br s, 1H, O*H*), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 62.5, 60.9, 31.7, 24.2, 23.1, 14.7; IR (ν_{max}, cm^{-1}) 3437 (w), 2939 (w), 2868 (w), 2079 (s), 1686 (s), 1371 (s), 1328 (m), 1305 (s), 1276 (m), 1171 (s), 1119 (s), 1057 (m), 1024 (m), 740 (s); HRMS (APPI/LTQ-Orbitrap) m/z: $[M-N_2]^+$ Calcd. for $C_8H_{14}O_3^+$ 158.0937; Found 158.0937. One carbon was not resolved at 101 MHz.

1,4-Dichloro-2-(1-diazo-2,2,2-trifluoroethyl)benzene (3o)



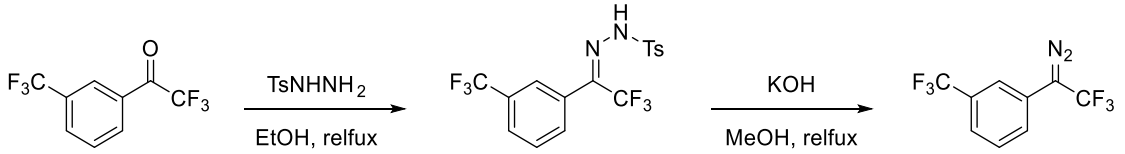
Following a modified reported procedure,[17] a solution of 1,4-dichlorobenzene (**41**) (10.0 g, 68.0 mmol, 1.00 equiv.) in anhydrous THF (150 mL) was cooled to -78 °C. Then, a 2.5 M solution of *n*-butyllithium (30.0 mL, 74.8 mmol, 1.10 equiv.) in hexanes was added dropwise. The mixture was stirred for 1 h, followed by the dropwise addition of methyl 2,2,2-trifluoroacetate (**42**) (7.66 mL, 76.0 mmol, 1.12 equiv.) in 30 min. The mixture was allowed to warm up to 0 °C, stirred for 2 h and then quenched with saturated aqueous ammonium chloride solution (50 mL). Diethyl ether (50 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation to afford 1-(2,5-dichloro-phenyl)-2,2,2-trifluoroethanone (**43**) as a colorless oil (12.2 g, 50.4 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H, Ar*H*), 7.49 – 7.54 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.8 (q, *J* = 37.6 Hz), 134.0, 133.1, 132.7, 132.1, 131.8, 129.6 (q, *J* = 2.2 Hz), 115.5 (q, *J* = 287.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.4. The values of the NMR spectra are in accordance with reported literature data.[17]

Adapted from a reported procedure,[18] 1-(2,5-dichlorophenyl)-2,2,2-trifluoroethanone (**43**) (7.29 g, 30.0 mmol, 1.05 equiv.) was added to EtOH (19 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (5.32 g, 28.6 mmol, 1.00 equiv.) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (200 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Adapted from a reported procedure,[18] *N*'-(1-(2,5-dichlorophenyl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**44**) was disolved in a 0.4 M solution of potassium hydroxide (3.37 g, 60.0 mmol, 2.00 equiv.) in MeOH (17.5 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (20 mL). The product was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford 1,4-dichloro-2-(1-diazo-2,2,2-trifluoroethyl)benzene (**3o**) as a orange oil (1.69 g, 6.09 mmol, 20%). The compound was kept as a 0.6 M solution in DCM at -18 °C. R_f = 0.95 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H, Ar*H*), 7.30 – 7.25 (m, 1H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7, 132.0, 131.8, 129.8, 129.5, 125.7 (q, *J* = 269.5 Hz), 123.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.8; IR (ν_{max}, cm^{-1}) 2096 (s), 1583 (m), 1470 (m), 1320 (s), 1251 (m), 1176 (s), 1149 (s), 1107 (s), 1060 (m), 977 (s), 815 (m), 795 (m), 729 (m); HRMS (APPI/LTQ-Orbitrap) m/z: $[M]^+$ Calcd. for $C_8H_3Cl_2F_3^+$ 225.9558; Found 225.9565. One carbon was not resolved at 101 MHz.

[17] A. S. Golubev, A. F. Shidlovskii, A. S. Peregudov and N. D. Kagramanov, *Russ Chem Bull.* **2014**, *63*, 2264.

1-(1-Diazo-2,2,2-trifluoroethyl)-3-(trifluoromethyl)benzene (3p)

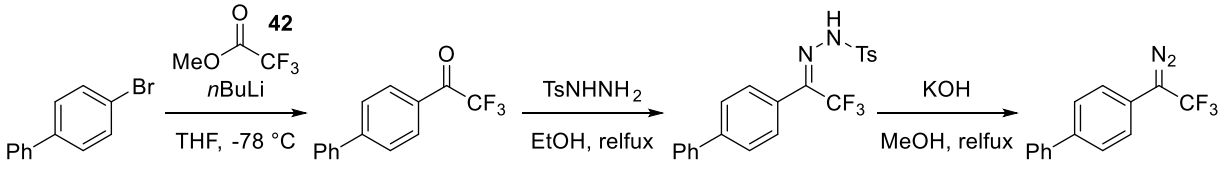


45 **46** **3p**

2,2,2-Trifluoro-1-(3-(trifluoromethyl)phenyl)ethanone (**45**) (0.605 g, 2.50 mmol, 1.05 equiv.) was added to EtOH (4.7 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (0.443 g, 2.38 mmol, 1.00 equiv.) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (100 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Adapted from a reported procedure,[18] 4-methyl-N'-(2,2,2-trifluoro-1-(3(trifluoromethyl)phenyl)ethylidene)benzenesulfonohydrazide (**46**) was disolved in a 0.4 M solution of potassium hydroxide (281 mg, 5.00 mmol, 2.00 equiv.) in MeOH (6.25 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (15 mL). The crude product was extracted with pentane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using EtOAc/pentane 1:99 as eluent to afford 1-(1-diazo-2,2,2-trifluoroethyl)-3-(trifluoromethyl)benzene (**3p**) as a volatile orange oil (233 mg, 0.834 mmol, 33%, contains 10 wt. % of eluent). The compound was kept as a 0.6 M solution in DCM at -18 °C. R_f = 0.95 (EtOAc/pentane 1:99); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (tt, *J* = 7.8, 0.8 Hz, 1H, Ar*H*), 7.49 – 7.41 (m, 1H, Ar*H*), 7.33 – 7.23 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.2 (q, *J* = 32.6 Hz), 130.1, 125.3, 125.3 (q, *J* = 269.6 Hz), 125.2, 123.8 (q, *J* = 272.5 Hz), 122.7 (q, *J* = 3.8 Hz), 118.9 – 118.6 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4, -63.1; IR (ν_{max}, cm^{-1}) 2089 (s), 1616 (w), 1591 (w), 1496 (w), 1455 (m), 1362 (m), 1338 (s), 1312 (s), 1273 (m), 1168 (s), 1111 (s), 1076 (s), 977 (m), 795 (s), 692 (s); HRMS (ESI/QTOF) m/z: $[M-N_2+H]^+$ Calcd. for $C_9H_5F_6^+$ 227.0290; Found 227.0291. One carbon was not resolved at 101 MHz.

4-(1-Diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (3q)



47 **48** **49** **3q**

A solution of 4-bromo-biphenyl (**47**) (4.66 g, 20.0 mmol, 1.00 equiv.) in anhydrous THF (100 mL) was cooled to -78 °C. Then, a 2.5 M solution of *n*-butyllithium (9.60 mL, 24.0 mmol, 1.20 equiv.) in hexanes was added dropwise. The mixture was stirred for 1 h, followed by the dropwise addition of methyl 2,2,2-trifluoroacetate (**42**) (2.21 mL, 22.0 mmol, 1.10 equiv.) in 30 min. The mixture was allowed to warm up to room temperature, stirred for 18 h and then quenched with saturated aqueous ammonium chloride solution (50 mL). Diethyl ether (50 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was

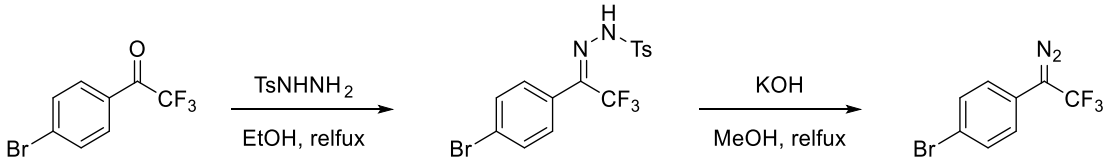
[18] E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. L. Collier, B. Liégault, M. Taillefer and V. Gouverneur, *Org. Lett.* **2014**, *16*, 6004.

purified by silica gel chromatography using pentane/EtOAc 90:10 as eluent to afford 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethanone (**48**) as a slight yellow oil (3.37 g, 13.5 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.10 (m, 2H, Ar*H*), 7.81 – 7.74 (m, 2H, Ar*H*), 7.68 – 7.62 (m, 2H, Ar*H*), 7.54 – 7.41 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3 (q, *J* = 34.8 Hz), 148.4, 139.3, 130.9 (q, *J* = 2.2 Hz), 129.3, 129.1, 128.7, 127.8, 127.5, 116.9 (q, *J* = 291.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.32. The values of the NMR spectra are in accordance with reported literature data.[18]

Following a reported procedure,[18] 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethanone (**48**) (3.36 g, 13.5 mmol, 1.05 equiv.) was added to EtOH (9 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (2.40 g, 12.9 mmol, 1.00 equiv.) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (200 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Following a reported procedure,[18] *N*'-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**49**) was disolved in a 0.4 M solution of potassium hydroxide (3.37 g, 60.0 mmol, 2.00 equiv.) in MeOH (17.5 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (20 mL). The product was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford 4-(1-Diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (**3q**) as a red solid (1.42 g, 5.44 mmol, 50%). The compound was kept at -18 °C. R_f = 0.70 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H, Ar*H*), 7.62 – 7.55 (m, 2H, Ar*H*), 7.45 (dd, *J* = 8.4, 6.9 Hz, 2H, Ar*H*), 7.41 – 7.34 (m, 1H, Ar*H*), 7.17 (d, *J* = 8.2 Hz, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 139.0, 129.1, 128.2, 127.7, 127.0, 125.8 (q, *J* = 269.6 Hz), 122.7, 122.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.32. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[18]

1-Bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (3r)



50 **51** **3r**

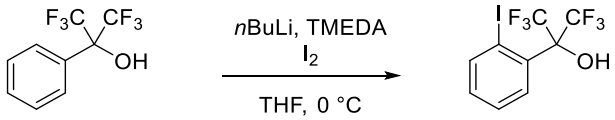
1-(4-Bromophenyl)-2,2,2-trifluoroethanone (**50**) (633 mg, 2.50 mmol, 1.05 equiv.) was added to EtOH (4.7 mL) at room temperature followed by *p*-toluenesulfonylhydrazide (0.443 g, 2.38 mmol, 1.00 equiv.) in one portion. A condenser was then attached and the contents were heated to reflux for 12 h. After this time, the solvent was removed under reduced pressure until the beginning of the formation of a solid. Then, pentane (100 mL) was added and the precipitate was collected by filtration and washed with pentane. The solid obtained was used in the next step without purification.

Following a reported procedure,[18] N'-(1-(4-bromophenyl)-2,2,2-trifluoroethylidene)-4-methylbenzenesulfonohydrazide (**51**) was disolved in a 0.4 M solution of potassium hydroxide (281 mg, 5.00 mmol, 2.00 equiv.) in MeOH (12.5 mL). A condenser was attached and the reaction mixture was stirred at reflux for 0.5 h. Then, the reaction was cooled to room temperature and diluted with water (15 mL). The crude product was extracted with pentane (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography using pentane as eluent to afford 1-bromo-4-(1-diazo-2,2,2-trifluoroethyl)benzene (**3r**) as a orange oil (146 mg, 0.551 mmol, 22%). The compound was kept as a 0.6 M solution in DCM at -18 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H, Ar*H*), 7.01 – 6.91 (m, 2H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ

132.8, 125.7 (q, *J* = 270.3 Hz), 124.0, 123.0, 119.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.5. One carbon was not resolved at 101 MHz. The values of the NMR spectra are in accordance with reported literature data.[18]

6. Preparation of EBX reagents

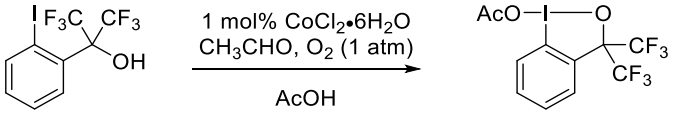
1,1,1,3,3,3-Hexafluoro-2-(2-iodophenyl)propan-2-ol (11)



52 **11**

Following a reported procedure,[19] TMEDA (1.27 mL, 8.40 mmol, 0.20 equiv.) was added to a solution of *n*-BuLi (37.0 mL, 92.0 mmol, 2.20 equiv., 2.5 M in hexanes). After 15 min, the cloudy solution was cooled to 0 °C and 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (**52**) (7.07 mL, 42.0 mmol, 1.00 equiv.) in THF (6.0 mL) was added dropwise. The reaction was stirred 30 min at 0 °C and then 18 h at room temperature. Then, THF (30.0 mL) was added, followed by the portionwise addition of I_2 (11.3 g, 44.5 mmol, 1.05 equiv.) at 0 °C and the mixture was stirred at 0 °C for 30 min and 4 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 3:97 as eluent to afford 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**11**) as a colorless oil (13.9 g, 37.5 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.9, 1.4 Hz, 1H, Ar*H*), 7.63 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.43 (dt, *J* = 8.4, 1.4 Hz, 1H, Ar*H*), 7.11 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 4.23 (s, 1H, O*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 131.4, 130.0, 129.7, 128.0, 122.6 (q, *J* = 291.4 Hz), 90.6, 78.9 (q, *J* = 32.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.4. The values of the NMR spectra are in accordance with reported literature data.[19]

3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (53)



11 **53**

Following a slightly modified procedure,[20] a 500 mL flsak was charged with glacial acetic acid (188 mL), 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**11**) (13.9 g, 37.5 mmol, 1.00 equiv.) and cobalt(II) chloride hexahydrate (89.0 g, 0.375 mmol, 0.01 equiv.). The reaction vessel was purged with O_2 for 5 min before acetaldehyde (21.4 mL, 379 mmol, 10.0 equiv.) was added in one portion. The reaction mixture was stirred under 1 atm of O_2, delivered by inflated balloon, at room temperature for 12 h. Acetaldehyde (21.4 mL, 379 mmol, 10.00 equiv.) was added and the reaction continue for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in DCM. The organic layer was washed with distilled water (50 mL) and extracted with DCM (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained residue was triturated in pentane for 0.5 h, filtered and washed with pentane (operation repeated 2 times) to afford 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) as a white solid (9.91 g, 23.2 mmol, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H, Ar*H*), 7.85 – 7.69 (m, 3H, Ar*H*), 2.19 (s, 3H, (O)CC*H*$_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.4, 134.2, 131.4, 131.0, 130.8, 129.5 – 129.0 (m), 123.1 (q, *J* = 289.5 Hz), 116.1, 84.5 – 83.7 (m), 20.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ -75.1. The values of the NMR spectra are in accordance with reported literature data.[21]

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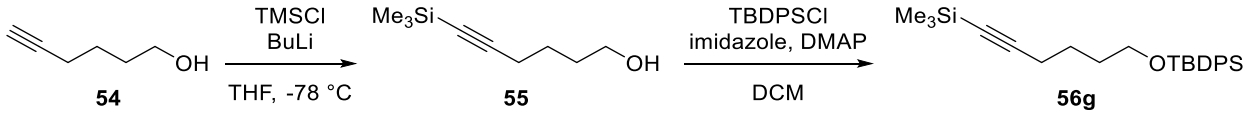
[19] J. Cvengroš, D. Stolz and A. Togni, *Synthesis* **2009**, 2818.

[20] A. Maity, S.-M. Hyun and D. C. Powers, *Nat. Chem.* **2018**, *10*, 200.

[21] P. Eisenberger, S. Gischig and A. Togni, *Chem. Eur J.* **2006**, *12*, 2579.

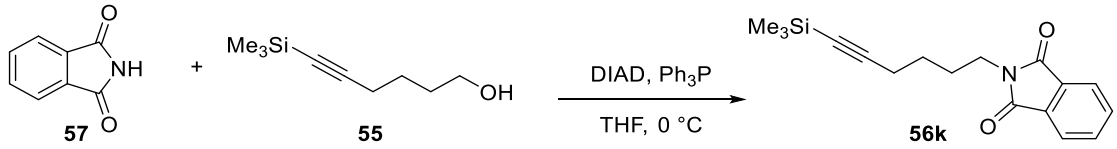
***Tert*-butyldiphenyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (56g)**



Following a reported procedure,[22] butyllithium (17.6 mL, 44.0 mmol, 2.20 equiv., 2.5 M in hexanes) was added dropwise to a stirring solution of 5-hexyn-1-ol (**54**) (2.20 mL, 20.0 mmol, 1.00 equiv.) in THF (40.0 mL) at -78 °C. Stirring was continued for 1 h, then chlorotrimethylsilane (5.58 mL, 44.0 mmol, 2.20 equiv.) was added at -78 °C. After 1 h, the reaction mixture was warmed to 0 °C. Aqueous 1M HCl (30 mL) was added dropwise and stirring was continued for 30 min at room temperature. The reaction mixture was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with water (30 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography using Et_2O/pentane 20:80 as eluent to afford 6-(trimethylsilyl)hex-5-yn-1-ol (**55**) as a colorless oil (2.12 g, 14.2 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 – 3.62 (m, 2H, CH_2OH), 2.27 (t, *J* = 6.8 Hz, 2H, C≡CCH_2), 1.80 – 1.52 (m, 4H, CH_2CH_2), 1.13 (br s, 1H, O*H*), 0.14 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.3, 84.9, 62.6, 32.0, 25.0, 19.8, 0.3. The values of the NMR spectra are in accordance with reported literature data.[22]

Following a reported procedure,[23] under an atmosphere of nitrogen, 6-(trimethylsilyl)hex-5-yn-1-ol (**55**) (511 mg, 3.00 mmol, 1.00 equiv.) was dissolved in DCM (10.00 mL). The alcohol was then treated, in succession, with imidazole (306 mg, 4.50 mmol, 1.50 equiv.), DMAP (110 mg, 0.900 mmol, 0.3 equiv.), and *tert*-butylchlorodiphenylsilane (1.17 mL, 4.50 mmol, 1.50 equiv.). The reaction was stirred at room temperature. After 1 hour, the reaction was diluted with 30 mL of water then extracted with DCM (2 x 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography using EtOAc/pentane 2:98 as eluent to afford tert-butyldiphenyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (**56g**) as a colorless oil (1.21 g, 2.95 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.62 (m, 4H, Ar*H*), 7.45 - 7.34 (m, 6H, Ar*H*), 3.67 (t, *J* = 5.9 Hz, 2H, CH_2O), 2.23 (t, *J* = 6.6 Hz, 2H, C≡CCH_2), 1.72 - 1.56 (m, 4H, CH_2CH_2), 1.05 (s, 9H, tBu), 0.14 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.2, 129.7, 127.8, 107.6, 84.6, 63.6, 31.8, 27.0, 25.3, 19.8, 19.4, 0.3. The values of the NMR spectra are in accordance with reported literature data.[23]

2-(6-(Trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (56k)



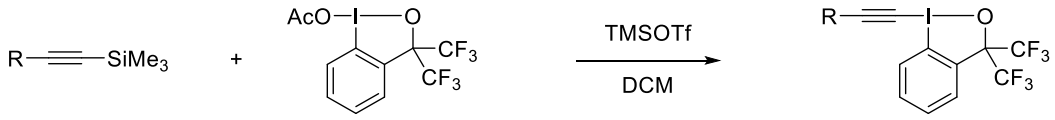
To a stirring solution of 6-(trimethylsilyl)hex-5-yn-1-ol (**55**) (852 mg, 5.00 mmol, 1.00 equiv.) in THF (16.7 mL) was added triphenylphosphine (1.44 g, 5.50 mmol, 1.10 equiv.) and DIAD (1.15 mL, 5.50 mmol, 1.10 equiv.) at 0 °C. The reaction mixture was stirred at this temperature for 15 min and then, phthalimide (**57**) (750 mg, 5.10 mmol, 1.02 equiv.) was added. The reaction was continued at room temperature for 5 h, then cold water (20 mL) was added and the product was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using Et_2O/pentane 10:90 as eluent to furnish 2-(6-(trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (**56k**) as a white solid (1.37 g, 4.58 mmol, 92%). M.p. 68-70 °C; R_f = 0.26

[22] M. Gersch, F. Gut, V. S. Korotkov, J. Lehmann, T. Böttcher, M. Rusch, C. Hedberg, H. Waldmann, G. Klebe and S. A. Sieber, *Angew. Chem. Int. Ed.* **2013**, *52*, 3009.

[23] E. C. McLaughlin and M. P. Doyle, *J. Org. Chem.* **2008**, *73*, 4317.

(Et_2O/pentane 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar*H*), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H, Ar*H*), 3.70 (t, *J* = 7.0 Hz, 2H, C*H*$_2$NPhth), 2.27 (t, *J* = 7.1 Hz, 2H, C≡CC*H*$_2$), 1.85 - 1.74 (m, 2H, C*H*$_2$), 1.61 - 1.49 (m, 2H, C*H*$_2$), 0.12 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 134.0, 132.3, 123.3, 106.7, 85.1, 37.6, 27.8, 25.9, 19.6, 0.3; IR (ν_{max}, cm^{-1}) 2955 (w), 2931 (w), 2170 (w), 1770 (w), 1705 (m), 1440 (w), 1390 (s), 1352 (m), 1324 (m), 1247 (m), 1035 (m), 904 (m), 841 (s), 761 (s), 718 (s), 638 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{22}NO_2Si^+$ 300.1414; Found 300.1413.

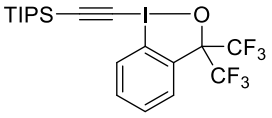
General procedure C: Synthesis of EBX reagents:



56a - 56k **53** **2a - 2k**

To a solution of 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (1.00 equiv.) in dry DCM (*c* = 0.2 M) was added trimethylsilyl trifluoromethanesulfonate (1.10 equiv.) dropwise at room temperature and the reaction mixture was stirred for 1 h. After this time, the corresponding trimethylethynylsilane (**56a – 56k**) (1.10 equiv.) was added and the mixture was stirred for 6 h at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (3 times). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/pentane as eluent to give the corresponding EBX reagent (**2a – 2k**).

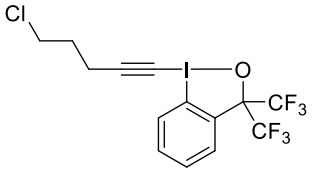
((3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (2a)



2a

Following general procedure C, starting from triisopropyl((trimethylsilyl)ethynyl)silane (**56a**) (2.80 g, 11.0 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (4.28 g, 10.0 mmol), afforded ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2a**) as a white solid (5.33 g, 9.68 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.88 – 7.81 (m, 1H, Ar*H*), 7.74 – 7.62 (m, 2H, Ar*H*), 1.23 – 1.07 (m, 21H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.3, 130.1, 130.2 – 130.0 (m), 128.3, 123.7 (q, *J* = 290.4 Hz), 112.3, 111.0, 81.6 (p, *J* = 29.5 Hz), 69.9, 18.7, 11.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[24]

1-(5-Chloropent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2b)



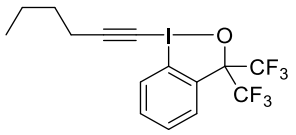
2b

Following general procedure C, starting from (5-chloropent-1-yn-1-yl)trimethylsilane (**56b**) (197 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-(5-chloropent-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-

[24] Y. Li, J. P. Brand and J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743.

benzo[*d*][1,2]iodaoxole (**2b**) as a white solid (273 mg, 0.580 mmol, 58%). M.p. 113-115 °C; R_f = 0.47 (EtOAc/pentane 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.17 (m, 1H, Ar*H*), 7.87 – 7.78 (m, 1H, Ar*H*), 7.73 – 7.64 (m, 2H, Ar*H*), 3.70 (t, *J* = 6.1 Hz, 2H, CH_2Cl), 2.74 (t, *J* = 6.9 Hz, 2H, CH_2C≡C), 2.07 (p, *J* = 6.6 Hz, 2H, CH_2CH$_2$Cl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0, 131.3, 130.1, 130.1 – 129.9 (m), 128.3, 123.7 (q, *J* = 290.5 Hz), 111.0, 105.5, 81.7 (p, *J* = 29.6 Hz), 45.2, 43.5, 31.0, 17.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2158 (w), 1441 (w), 1427 (w), 1263 (s), 1178 (s), 1145 (s), 966 (s), 946 (s), 768 (s), 753 (s), 729 (s), 660 (m); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{11}ClF_6IO^+$ 470.9442; Found 470.9446.

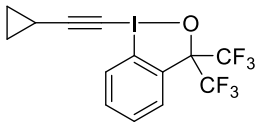
1-(Hex-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2c)



2c

Following general procedure C, starting from hex-1-yn-1-yltrimethylsilane (**56c**) (222 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-(hex-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2c**) as a white solid (285 mg, 0.630 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.18 (m, 1H, Ar*H*), 7.86 – 7.79 (m, 1H, Ar*H*), 7.73 – 7.64 (m, 2H, Ar*H*), 2.53 (t, *J* = 7.0 Hz, 2H, CH_2C≡C), 1.67 – 1.56 (m, 2H, CH_2CH$_2$C≡C), 1.53 – 1.42 (m, 2H, CH_2CH$_3$), 0.96 (t, *J* = 7.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.2, 130.2, 130.0 – 129.8 (m), 128.3, 123.8 (q, *J* = 290.7 Hz), 111.1, 108.1, 81.7 (p, *J* = 29.4 Hz), 43.5, 30.6, 22.2, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[25]

1-(Cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2d)



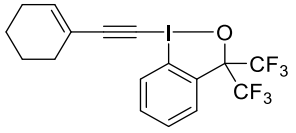
2d

Following general procedure C, starting from (cyclopropylethynyl)trimethylsilane (**56d**) (995 µL, 5.50 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (2.14 g, 5.00 mmol), afforded 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2d**) as an off-white solid (873 mg, 2.01 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.14 (m, 1H, Ar*H*), 7.88 – 7.74 (m, 1H, Ar*H*), 7.74 – 7.59 (m, 2H, Ar*H*), 1.54 (tt, J = 8.2, 5.0 Hz, 1H, C*H*C≡C), 1.00 – 0.91 (m, 2H, CH_2-cyclopropyl), 0.91 – 0.85 (m, 2H, CH_2-cyclopropyl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.2, 130.2, 130.0, 129.8, 128.2, 123.8 (q, *J* = 290.8 Hz), 81.7 (p, *J* = 29.5 Hz), 39.4, 9.5, 1.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.3. The values of the NMR spectra are in accordance with reported literature data.[26]

[25] X. Li, X. Xie, N. Sun and Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6994.

[26] J. Wu, X. Deng, H. Hirao and N. Yoshikai, *J. Am. Chem. Soc.* **2016**, *138*, 9105.

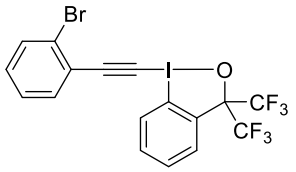
1-(Cyclohex-1-en-1-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2e)



2e

Following general procedure C, starting from (cyclohex-1-en-1-ylethynyl)trimethylsilane (**56e**) (196 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-(cyclohex-1-en-1-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2e**) as an off-white solid (213 mg, 0.450 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.13 (m, 1H, Ar*H*), 7.91 – 7.78 (m, 1H, Ar*H*), 7.73 – 7.60 (m, 2H, Ar*H*), 6.36 (p, *J* = 2.2 Hz, 1H, C=C*H*), 2.28 – 2.13 (m, 4H, 2 x CH_2C=C), 1.75 – 1.54 (m, 4H, CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 132.9, 129.8, 129.6, 128.1, 127.8, 123.4 (q, *J* = 290.3 Hz), 119.8, 111.2, 107.7, 81.3 (p, *J* = 29.6 Hz), 50.5, 28.7, 25.7, 21.9, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[27]

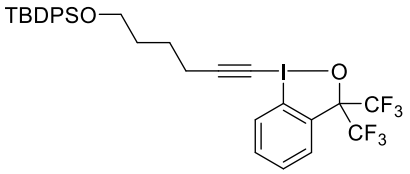
1-((2-Bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2f)



2f

Following general procedure C, starting from ((2-bromophenyl)ethynyl)trimethylsilane (**56f**) (234 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-((2-bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2f**) as a white solid (535 mg, 0.970 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.43 (m, 1H, Ar*H*), 7.90 – 7.81 (m, 1H, Ar*H*), 7.76 – 7.68 (m, 2H, Ar*H*), 7.66 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar*H*), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H, Ar*H*), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.32 – 7.24 (m, 1H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 133.2, 132.9, 131.4, 131.2, 130.2 – 129.9 (m), 130.0, 128.9, 127.5, 126.2, 123.9, 123.7 (q, *J* = 290.6 Hz), 111.6, 103.0, 81.8 (p, *J* = 29.8 Hz), 59.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.1. The values of the NMR spectra are in accordance with reported literature data.[28]

((6-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane (2g)



2g

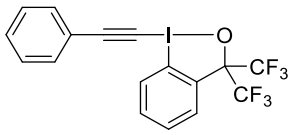
Following general procedure C, starting from tert-butyldiphenyl((6-(trimethylsilyl)hex-5-yn-1-yl)oxy)silane (**56g**) (450 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded ((6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-

[27] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz and A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547.

[28] Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129.

1(3H)-yl)hex-5-yn-1-yl)oxy)(tert-butyl)diphenylsilane (**2g**) as a white solid (355 mg, 0.500 mmol, 50%). M.p. 110-112 °C; R_f = 0.40 (EtOAc/pentane 10:90); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar*H*), 7.86 -7.78 (m, 1H, Ar*H*), 7.72 – 7.58 (m, 6H, Ar*H*), 7.46 – 7.32 (m, 6H, Ar*H*), 3.77 – 3.66 (m, 2H, C*H*$_2$OTBDPS), 2.59 – 2.49 (m, 2H, C*H*$_2$C≡C), 1.80 – 1.65 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$O), 1.06 (s, 9H, *tBu*-Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 133.8, 132.7, 131.1, 130.0, 129.9 – 129.7 (m), 129.7, 128.1, 127.7, 123.6 (q, *J* = 290.4 Hz), 110.9, 107.7, 81.5 (p, *J* = 29.5 Hz), 63.2, 43.7, 31.6, 26.9, 25.0, 20.2, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2934 (w), 2855 (w), 2155 (w), 2071 (m), 1695 (w), 1427 (m), 1266 (m), 1257 (m), 1181 (s), 1151 (s), 1107 (m), 966 (s), 946 (s), 762 (s), 732 (s), 701 (s); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{31}H_{32}F_6IO_2Si^+$ 705.1115; Found 705.1114.

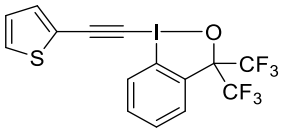
1-(Phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2h)



2h

Following general procedure C, starting from trimethyl(phenylethynyl)silane (**56h**) (192 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-(phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2h**) as a white solid (395 mg, 0.840 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.24 (m, 1H, Ar*H*), 7.86 (ddt, *J* = 7.4, 3.2, 1.4 Hz, 1H, Ar*H*), 7.75 – 7.66 (m, 2H, Ar*H*), 7.59 – 7.53 (m, 2H, Ar*H*), 7.48 – 7.37 (m, 3H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 132.8, 131.4, 130.3, 130.1, 130.0, 128.8, 128.5, 123.7 (q, *J* = 289.8 Hz), 121.4, 111.6, 105.4, 82.5 – 81.1 (m), 54.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[29]

1-(Thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2i)

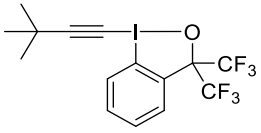


2i

Following general procedure C, starting from trimethyl(thiophen-2-ylethynyl)silane (**56i**) (182 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-(thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2i**) as an off-white solid (403 mg, 0.850 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.19 (m, 1H, Ar*H*), 7.89 – 7.80 (m, 1H, Ar*H*), 7.76 – 7.66 (m, 2H, Ar*H*), 7.44 – 7.38 (m, 2H, Ar*H*), 7.07 (dd, J = 5.1, 3.7 Hz, 1H, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.2, 131.4, 130.2, 123.0, 129.9, 128.5, 127.5, 123.7 (q, *J* = 291.2 Hz), 121.3, 111.8, 98.4, 81.8 (p, *J* = 29.7 Hz), 59.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[29]

[29] X. Wu, S. Shirakawa and K. Maruoka, *Org. Biomol. Chem.* **2014**, *12*, 5388.

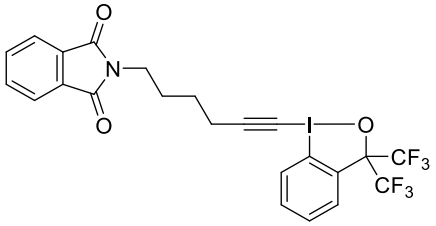
1-(3,3-Dimethylbut-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (2j)



2j

Following general procedure C, starting from (3,3-dimethylbut-1-yn-1-yl)trimethylsilane (**56j**) (229 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 1-(3,3-dimethylbut-1-yn-1-yl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2j**) as a white solid (350 mg, 0.780 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.14 (m, 1H, Ar*H*), 7.89 – 7.78 (m, 1H, Ar*H*), 7.74 – 7.64 (m, 2H, Ar*H*), 1.34 (s, 9H, *tBu*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.7, 131.1, 130.3, 130.0, 128.0, 123.9 (q, *J* = 290.3 Hz), 116.1, 111.2, 81.9 (p, *J* = 29.6 Hz), 42.0, 30.8, 29.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2. The values of the NMR spectra are in accordance with reported literature data.[27]

2-(6-(3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)isoindoline-1,3-dione (2k)

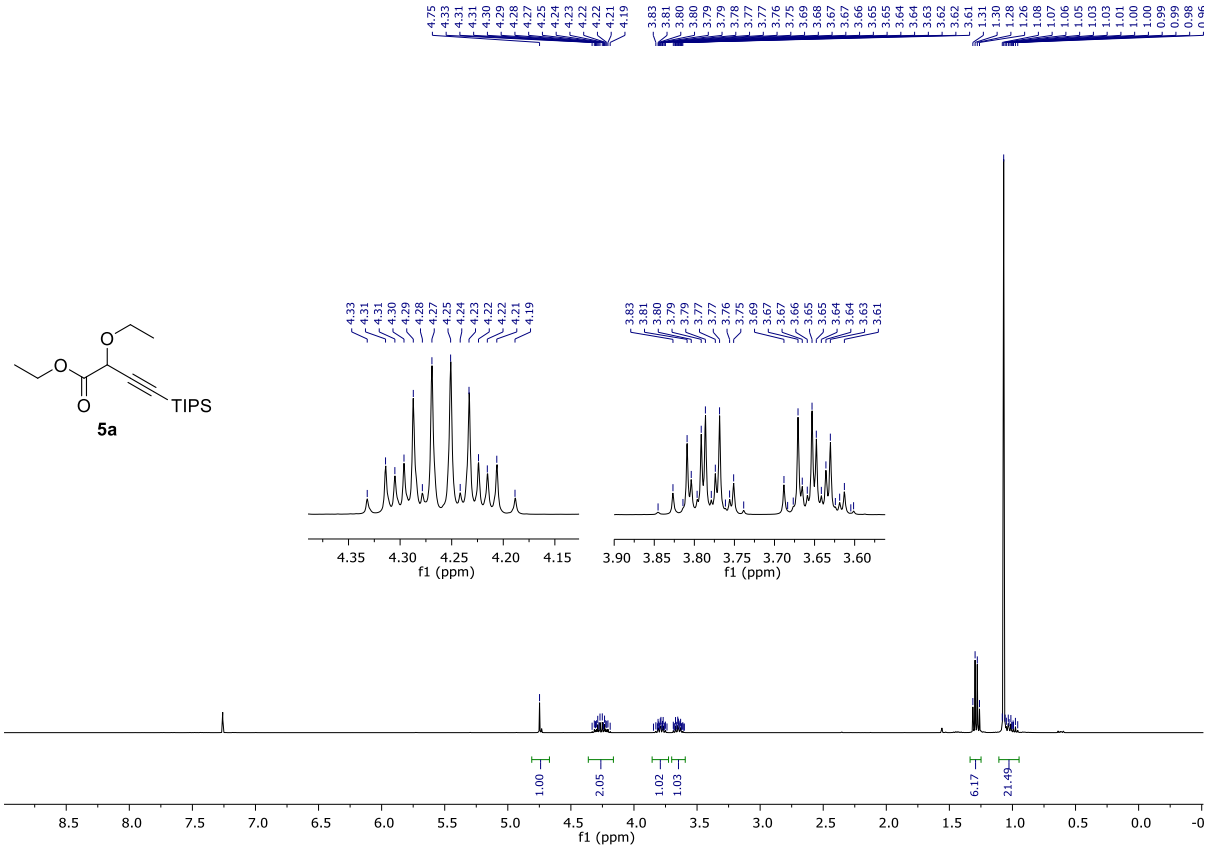


2k

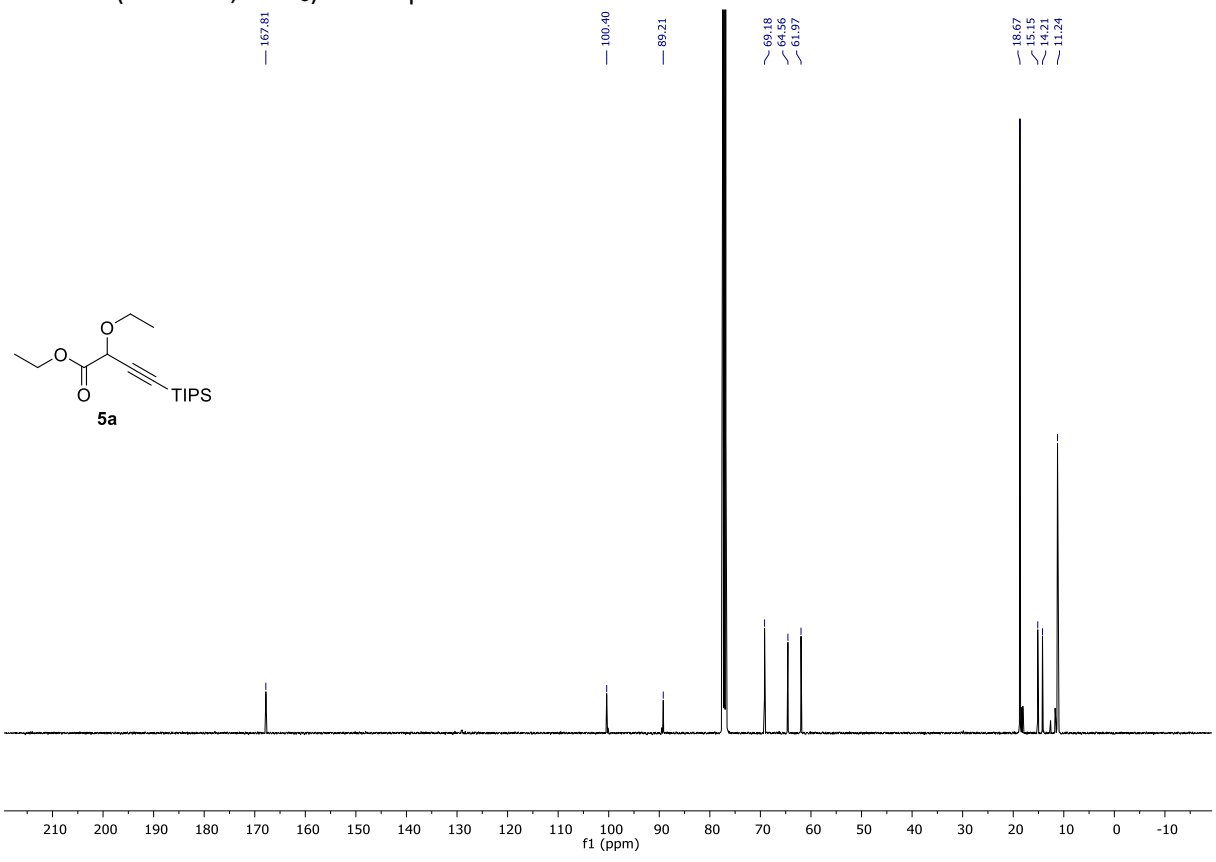
Following general procedure C, starting from 2-(6-(trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (**56k**) (330 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**53**) (428 mg, 1.00 mmol), afforded 2-(6-(3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3H)-yl)hex-5-yn-1-yl)isoindoline-1,3-dione (**2k**) as a white solid (590 mg, 0.990 mmol, 99%). M.p. 139-141 °C; R_f = 0.13 (EtOAc/pentane 15:85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 1H, Ar*H*), 7.89 – 7.78 (m, 3H, Ar*H*), 7.77 – 7.65 (m, 4H, Ar*H*), 3.75 (t, *J* = 7.0 Hz, 2H, CH_2NPhth), 2.59 (t, *J* = 7.0 Hz, 2H, CH_2C≡C), 1.87 (tt, *J* = 7.7, 6.4 Hz, 2H, CH_2CH_2N), 1.73 – 1.62 (m, 2H, CH_2CH_2C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 134.2, 133.0, 132.2, 131.2, 130.1, 130.0 – 129.8 (m), 128.4, 123.7 (q, *J* = 290.4 Hz), 123.4, 111.0, 106.9, 81.7 (p, *J* = 29.4 Hz), 44.6, 37.4, 27.8, 25.6, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2; IR (ν_{max}, cm^{-1}) 2355 (w), 2164 (w), 2099 (w), 1707 (m), 1393 (m), 1264 (m), 1180 (s), 1154 (s), 965 (m), 947 (s), 767 (s), 751 (s), 714 (s) HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calcd. for $C_{23}H_{17}F_6INO_3^+$ 596.0152; Found 596.0157.

7. Spectra of new compounds

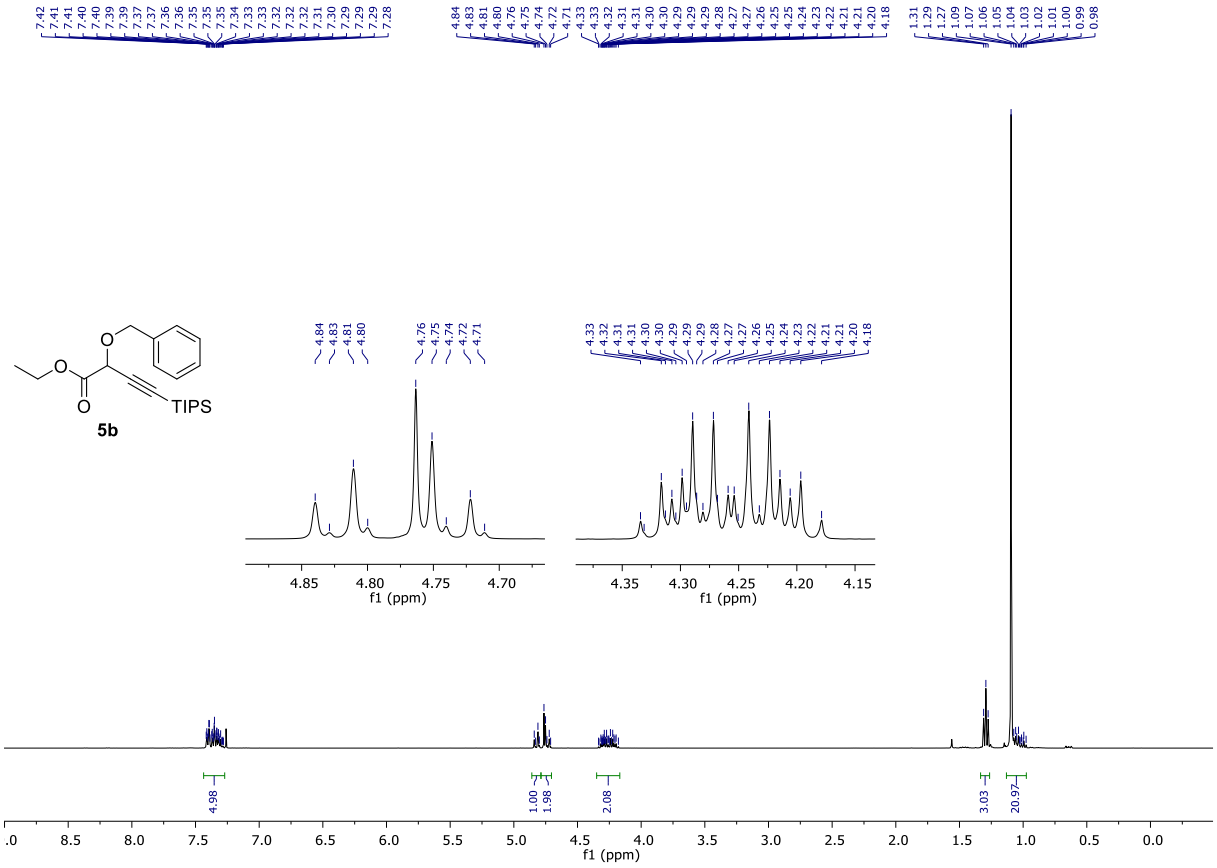
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5a**



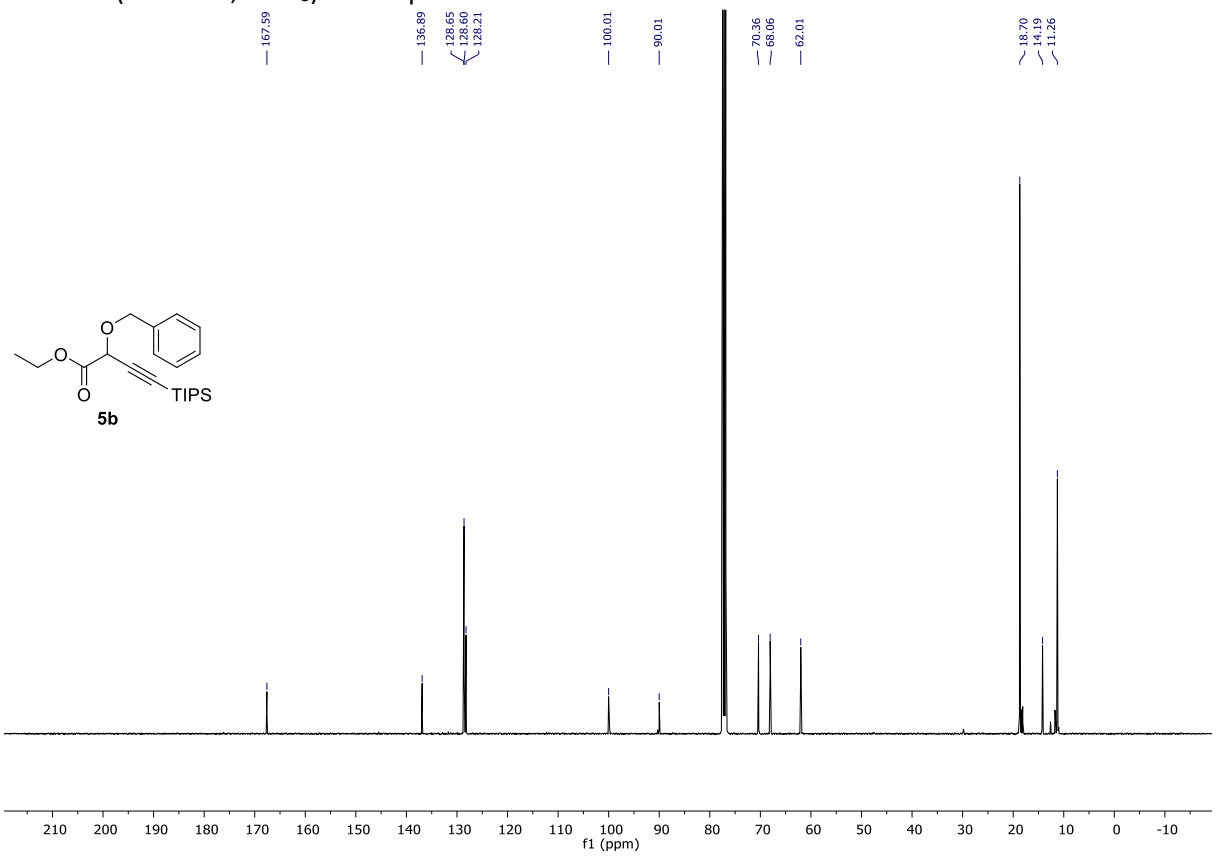
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5a**



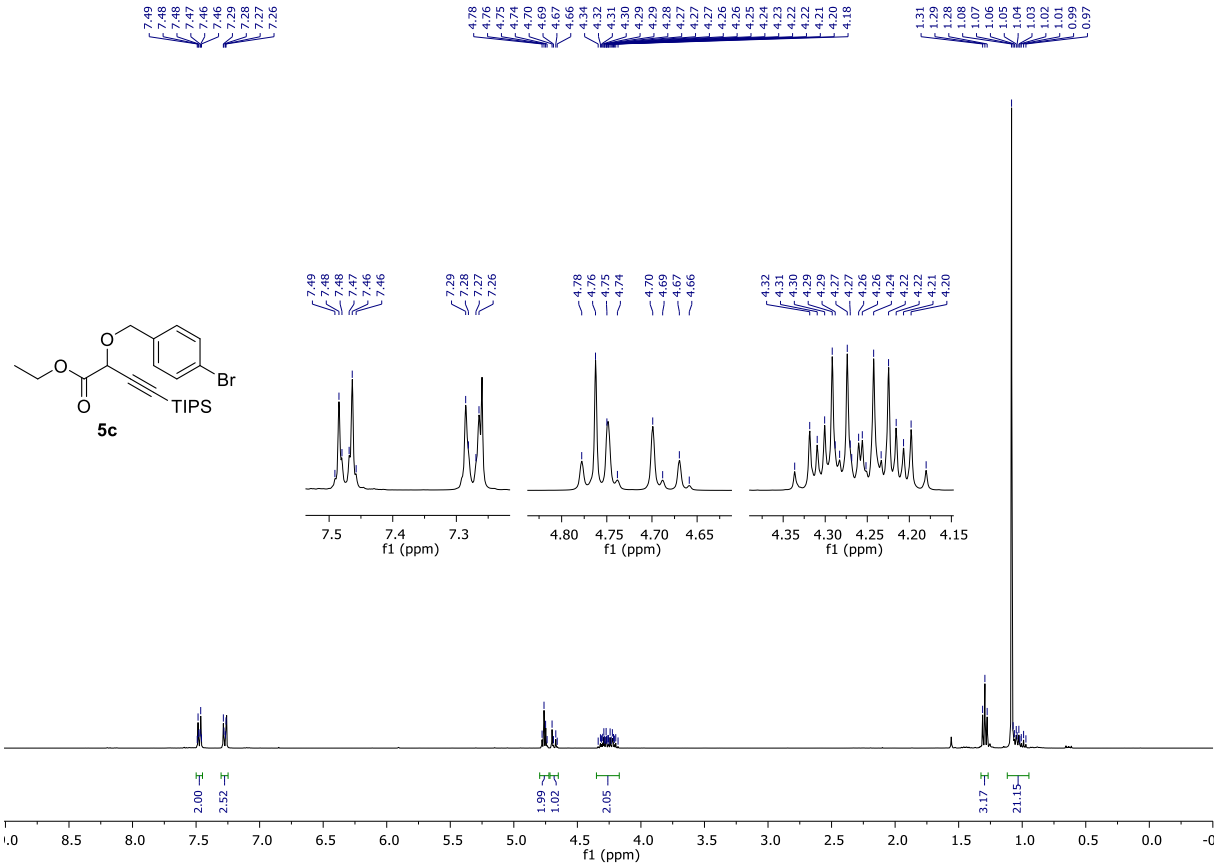
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5b**



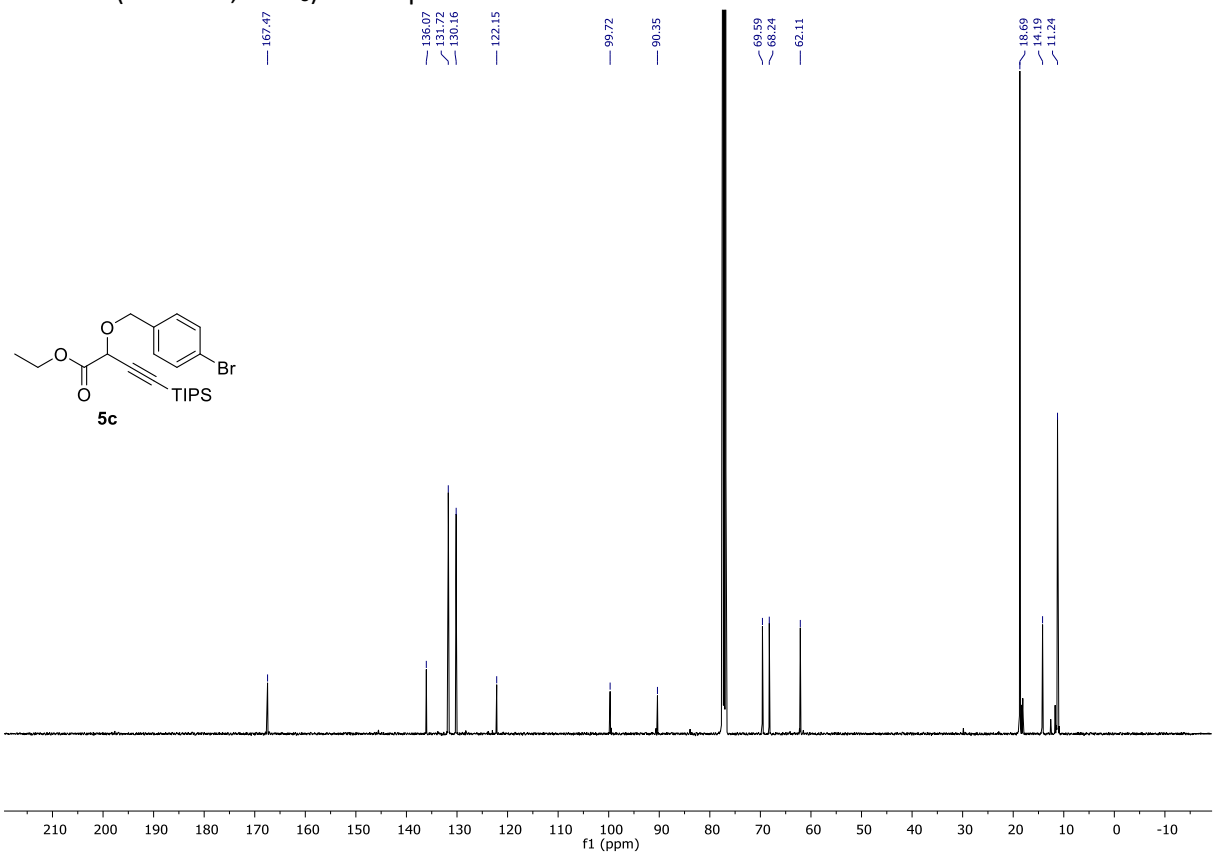
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5b**



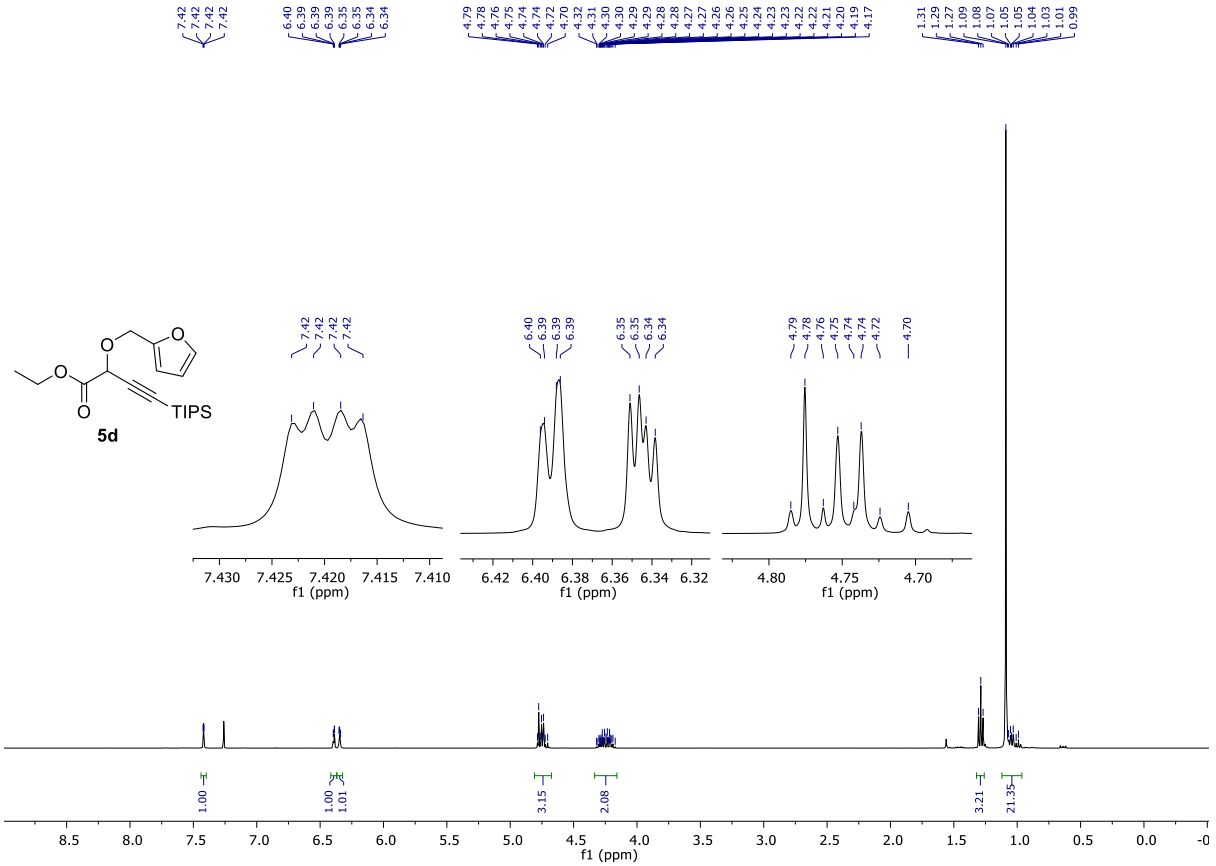
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5c**



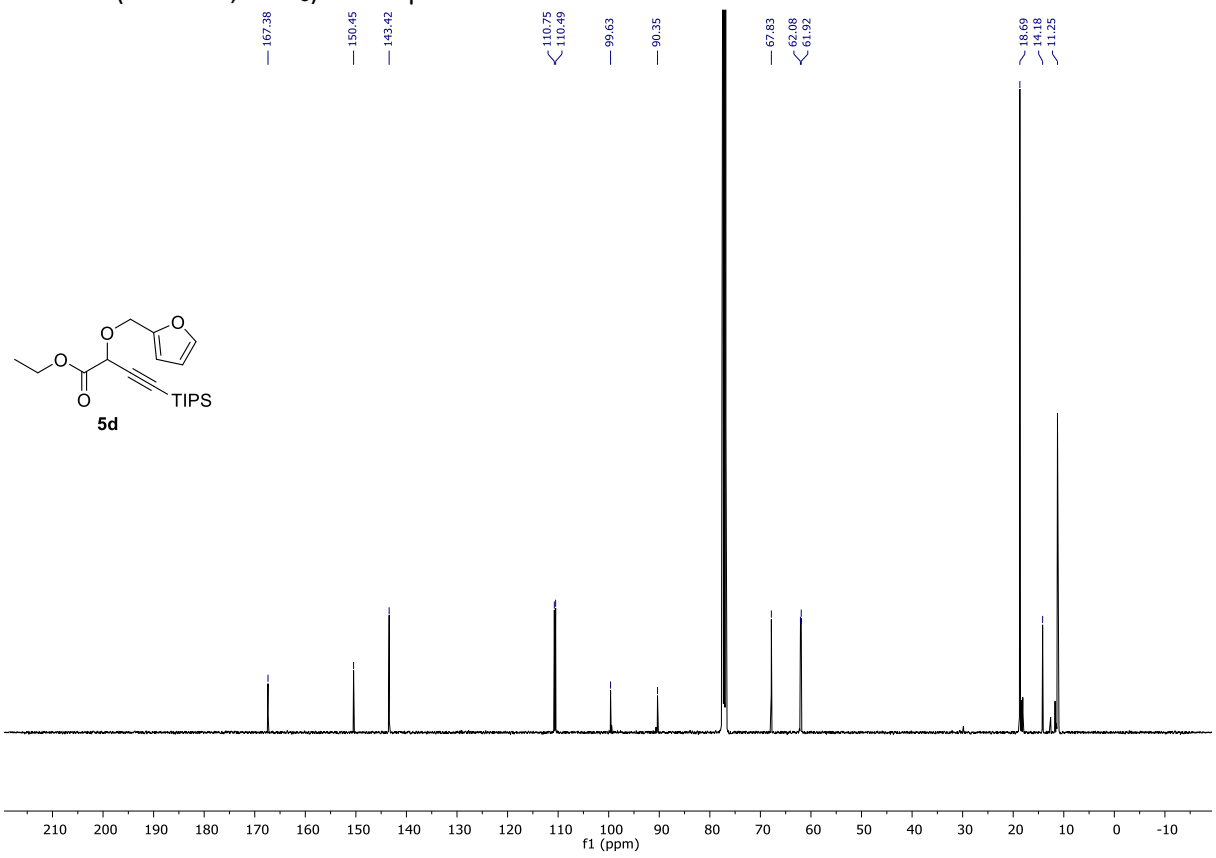
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5c**



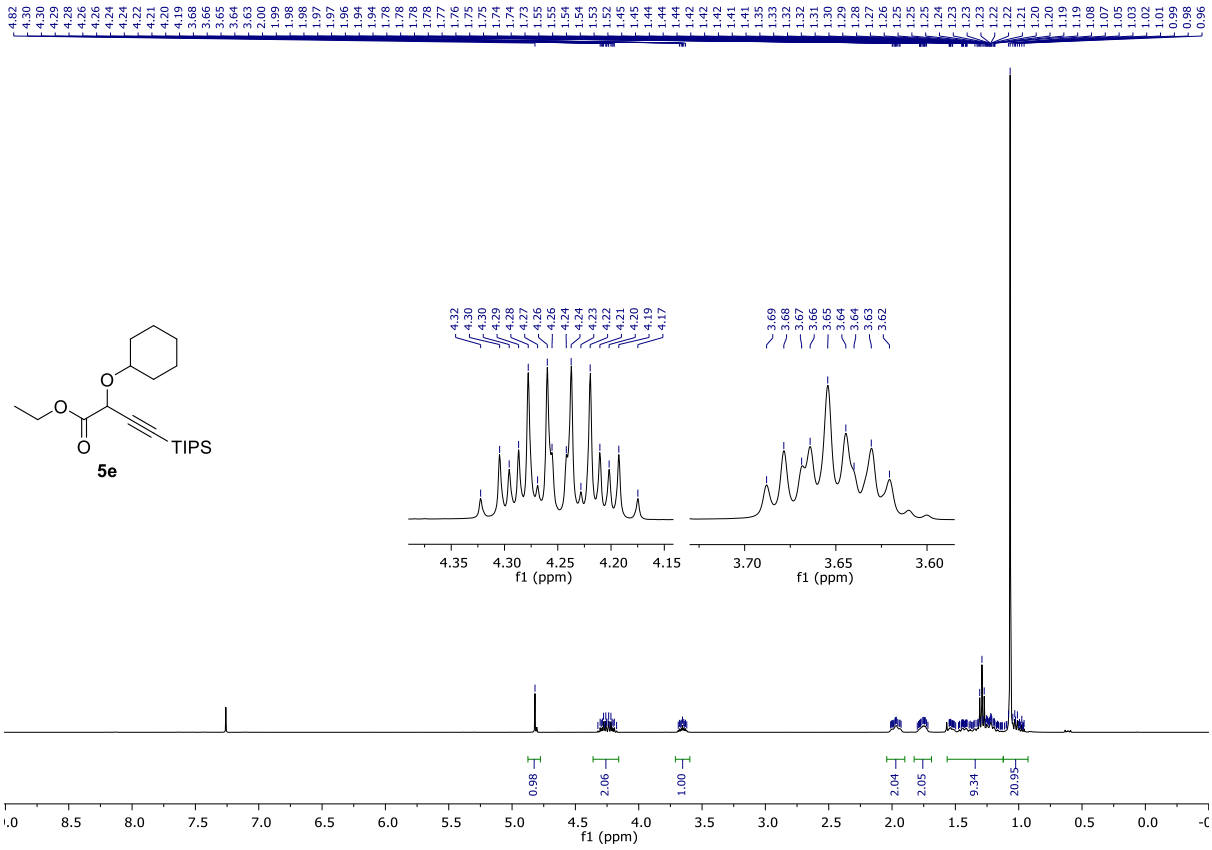
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5d**



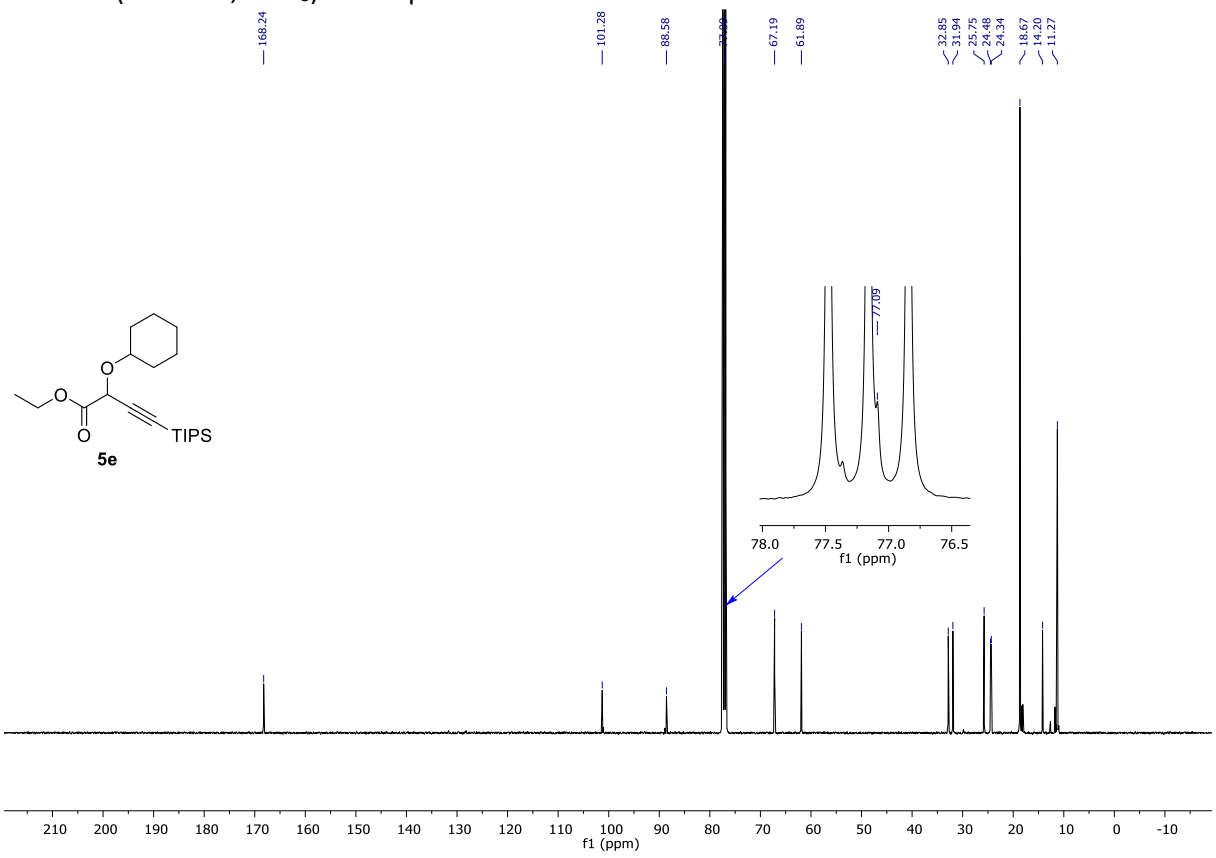
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5d**



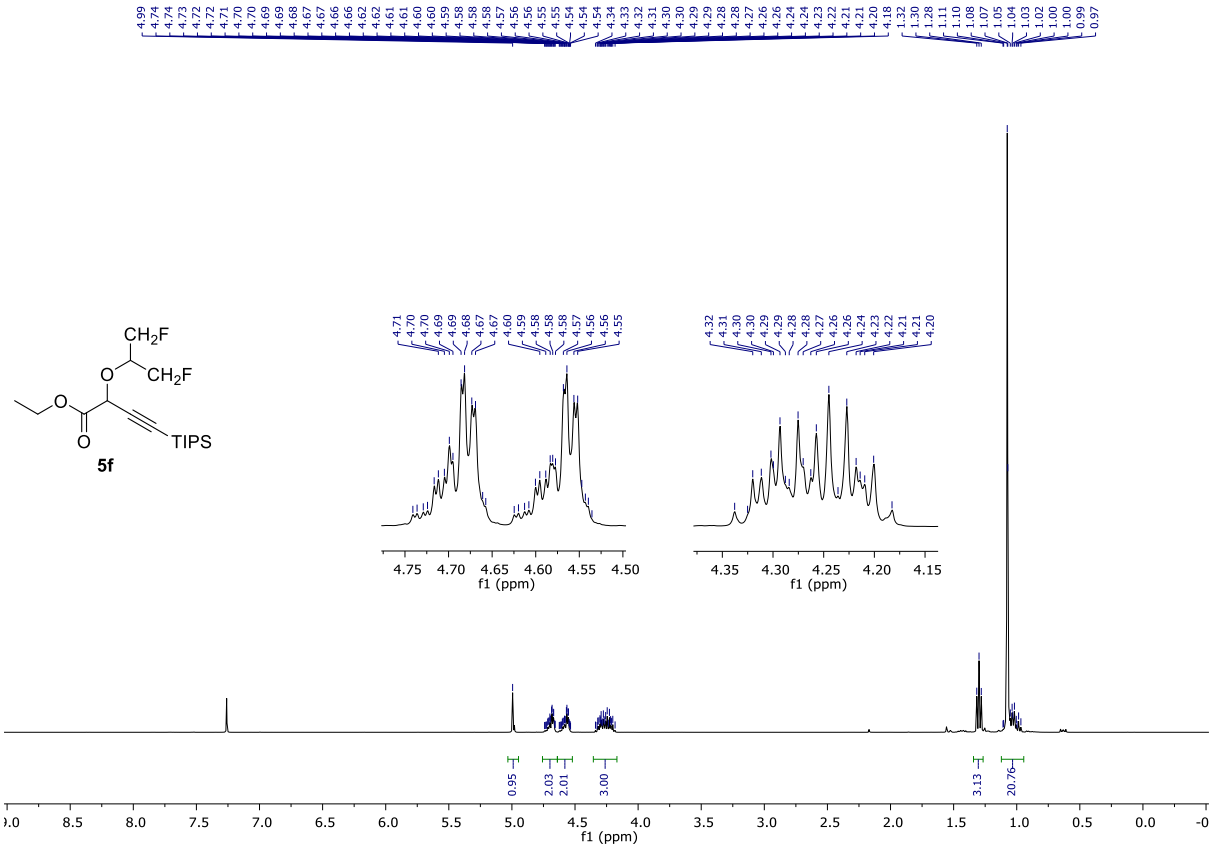
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5e**



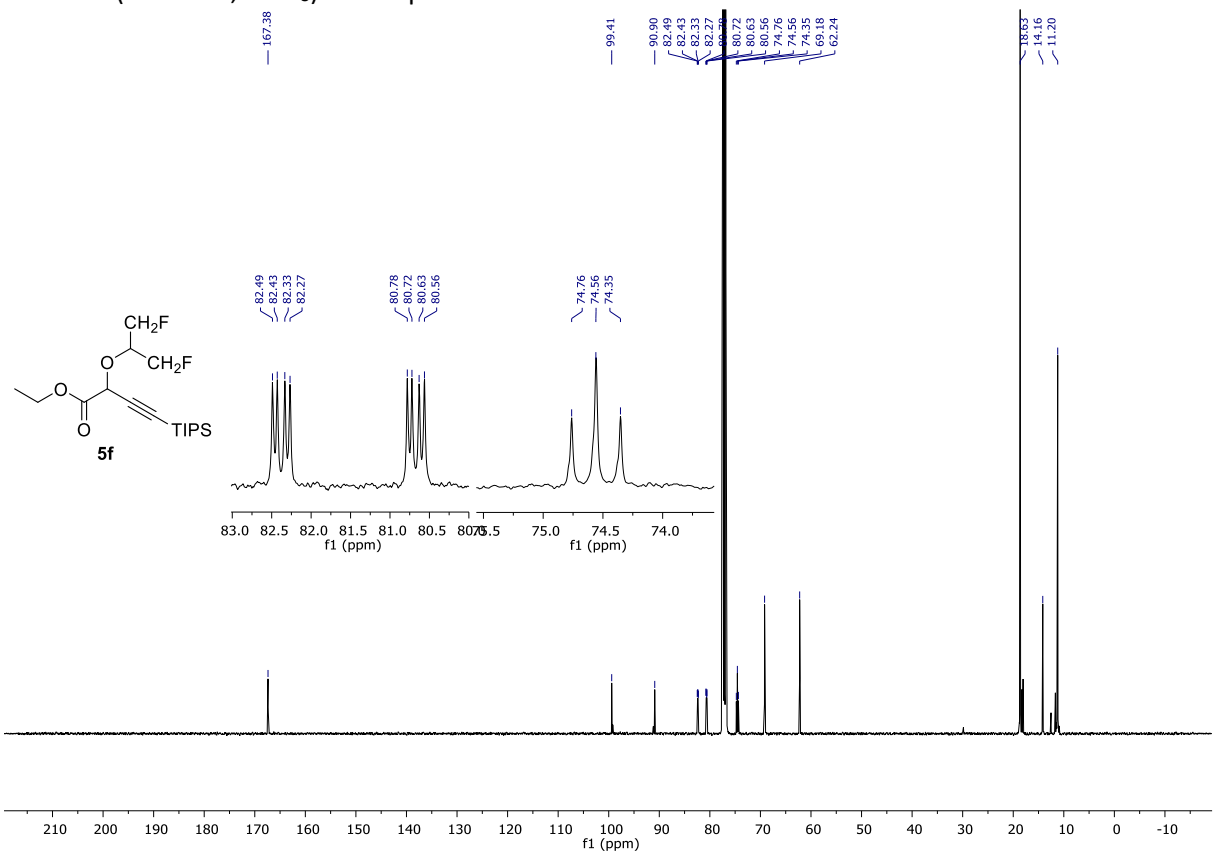
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5e**



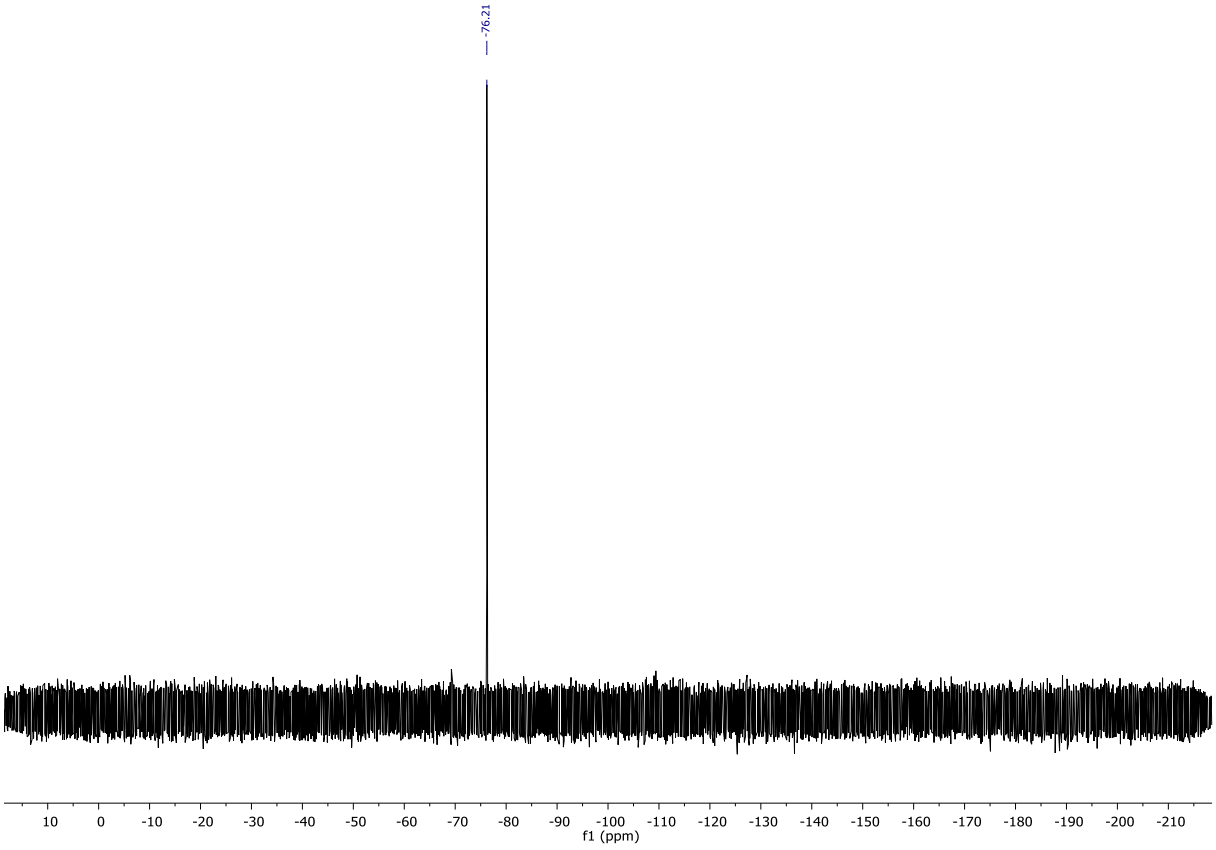
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5f**



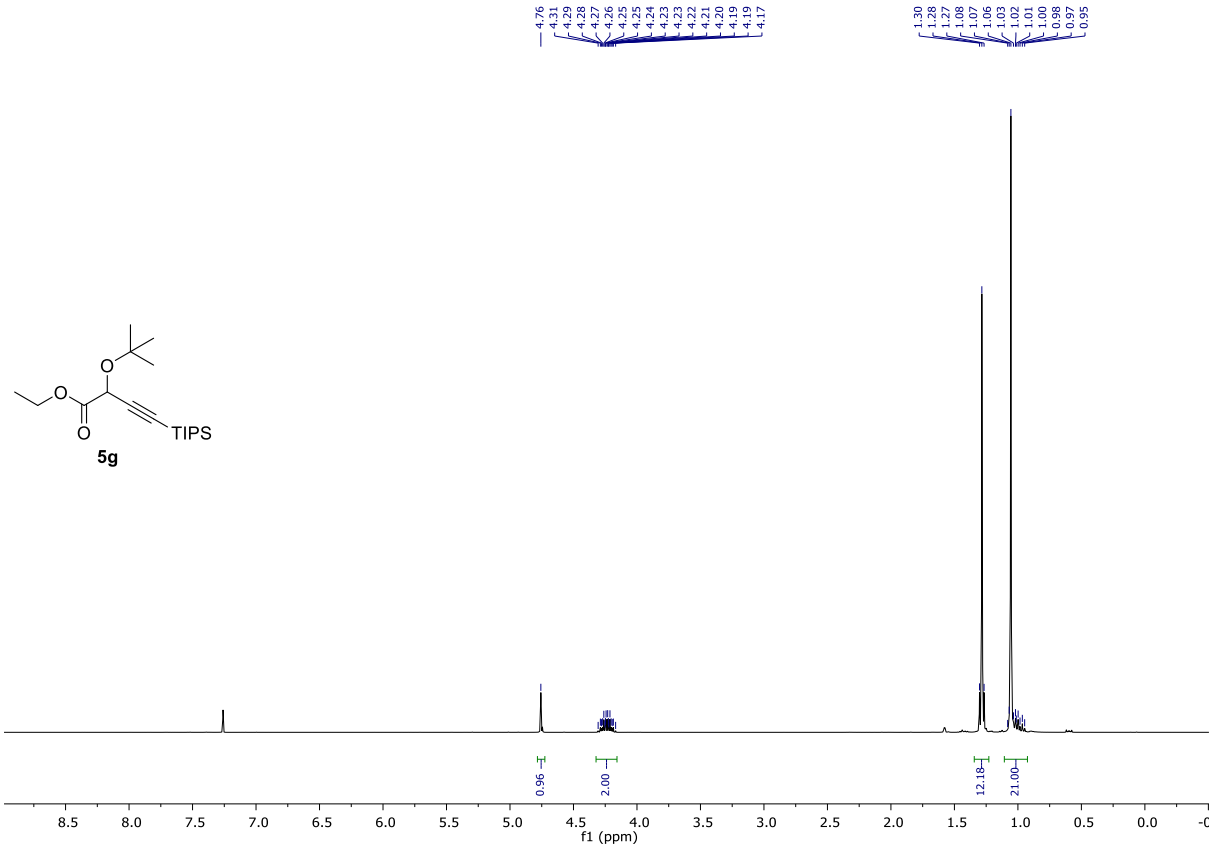
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5f**



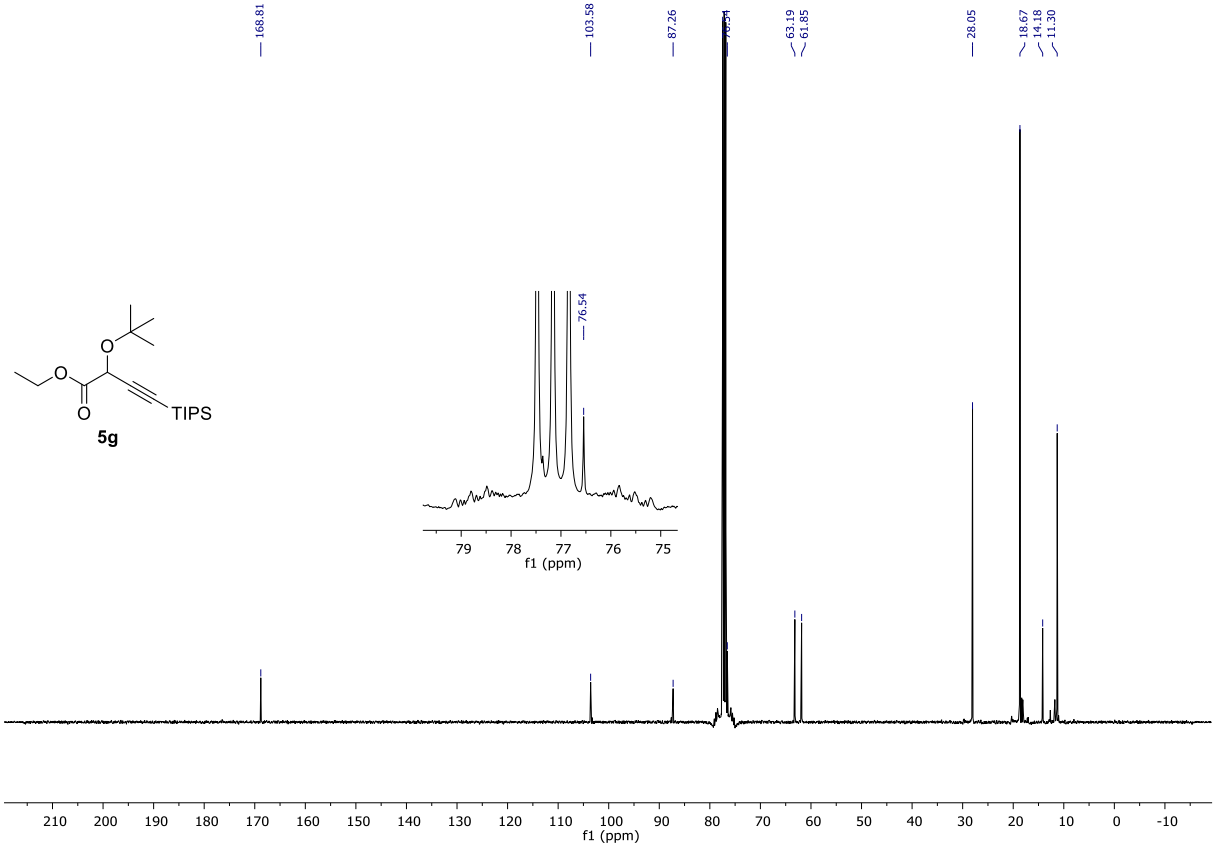
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5f**



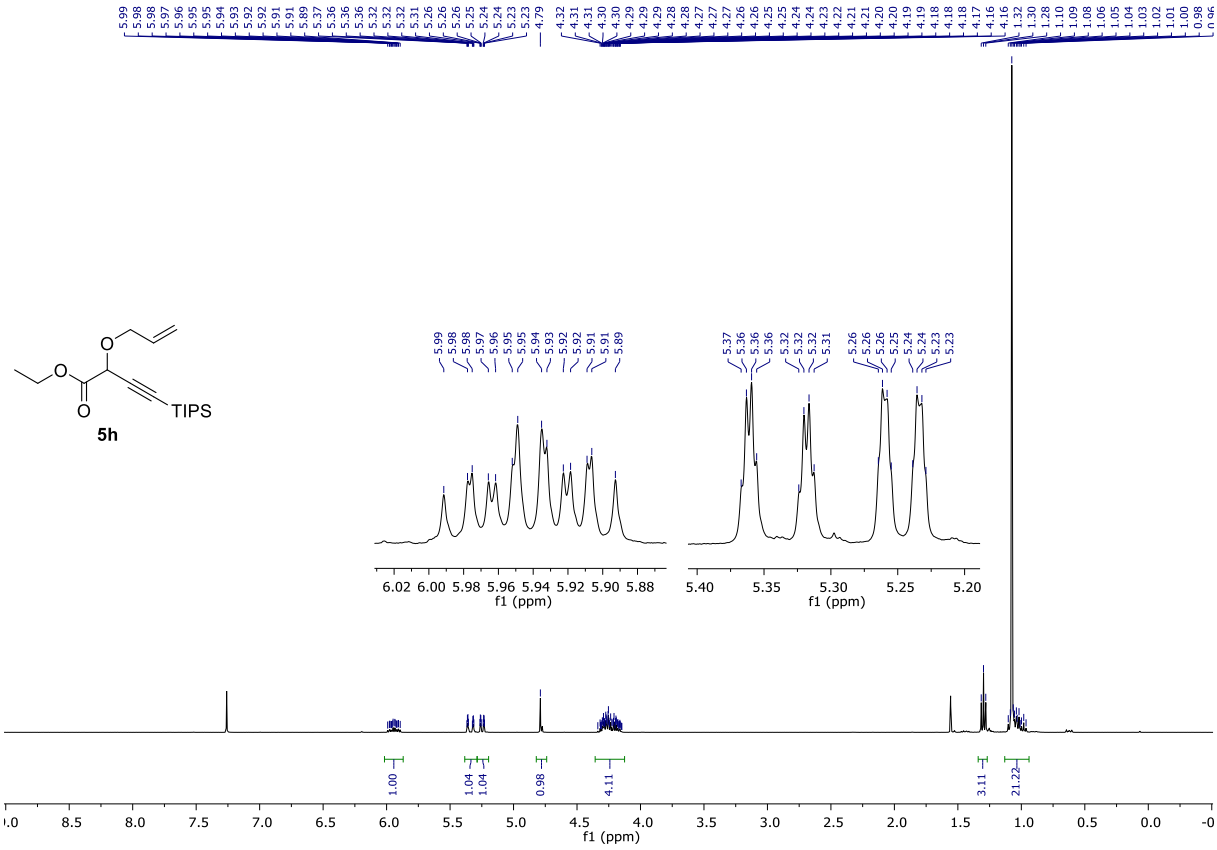
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5g**



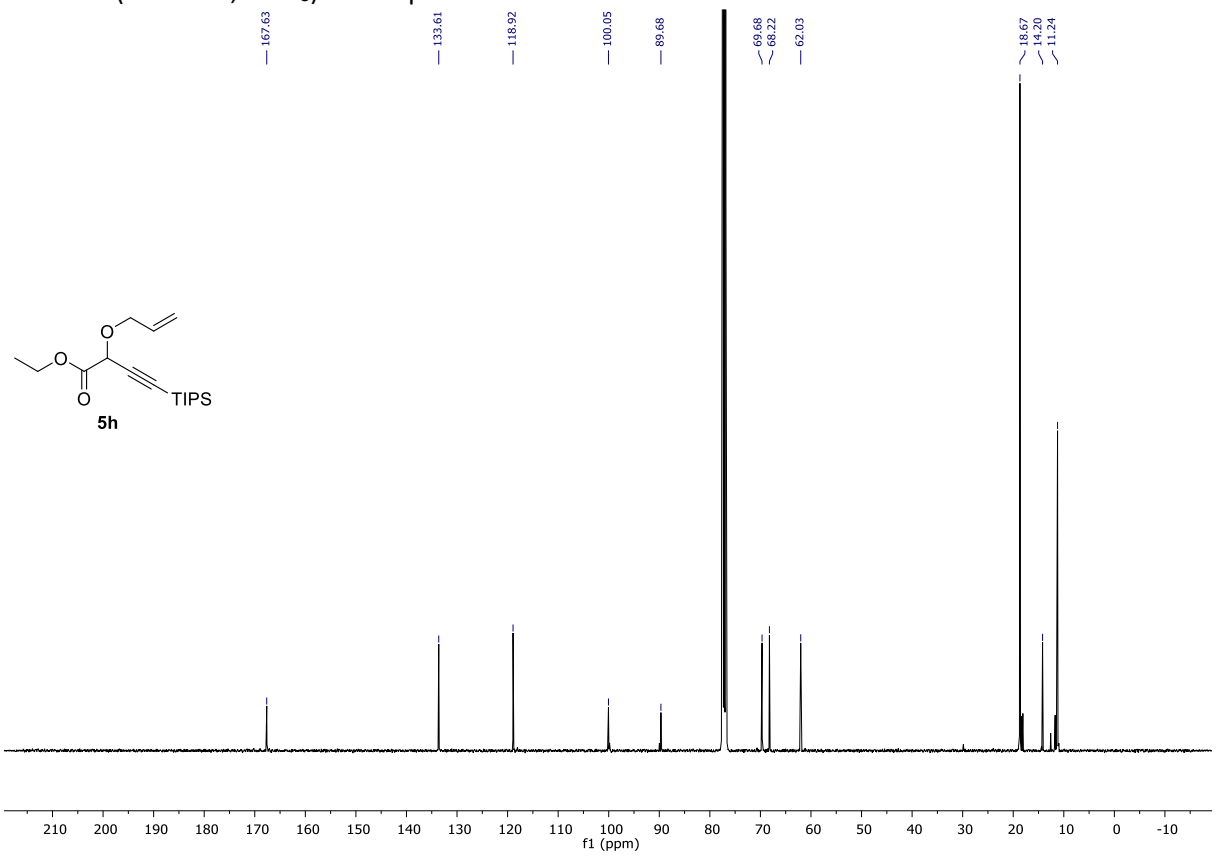
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5g**



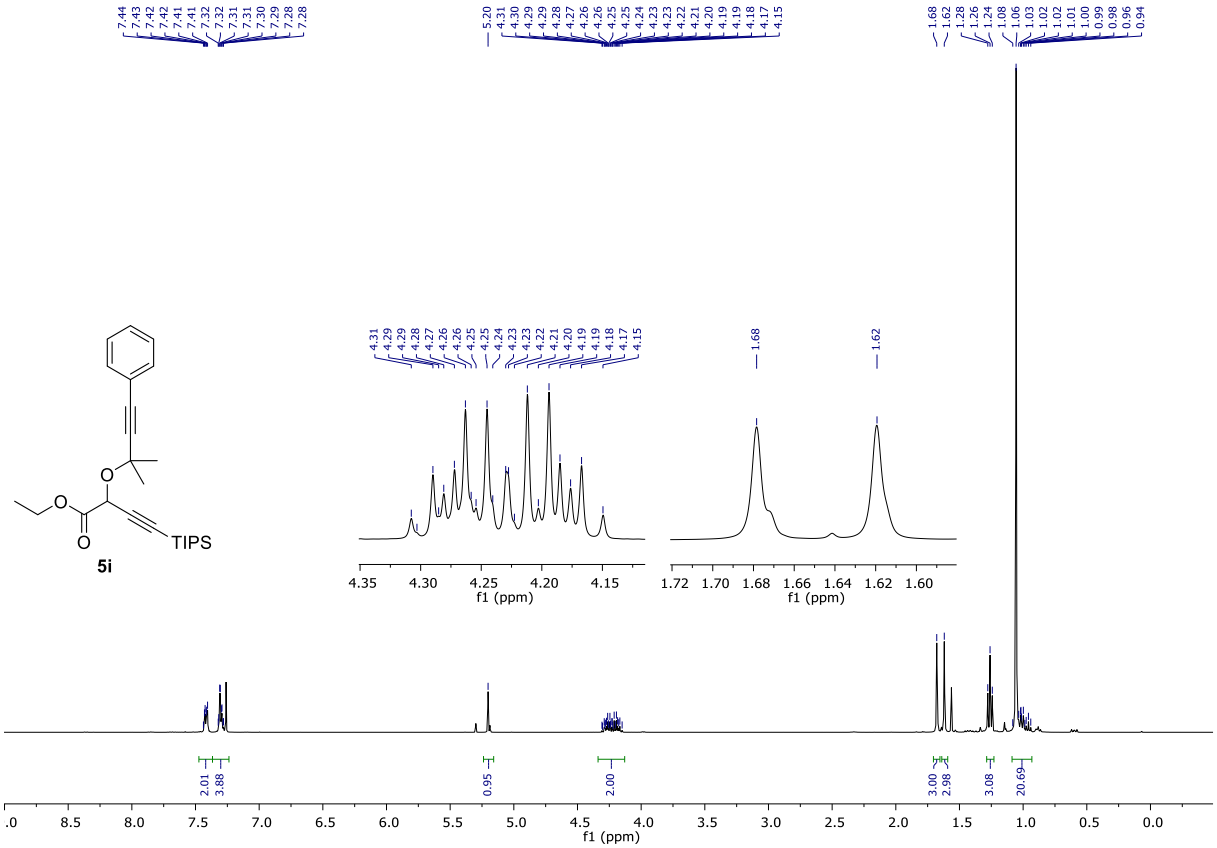
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5h**



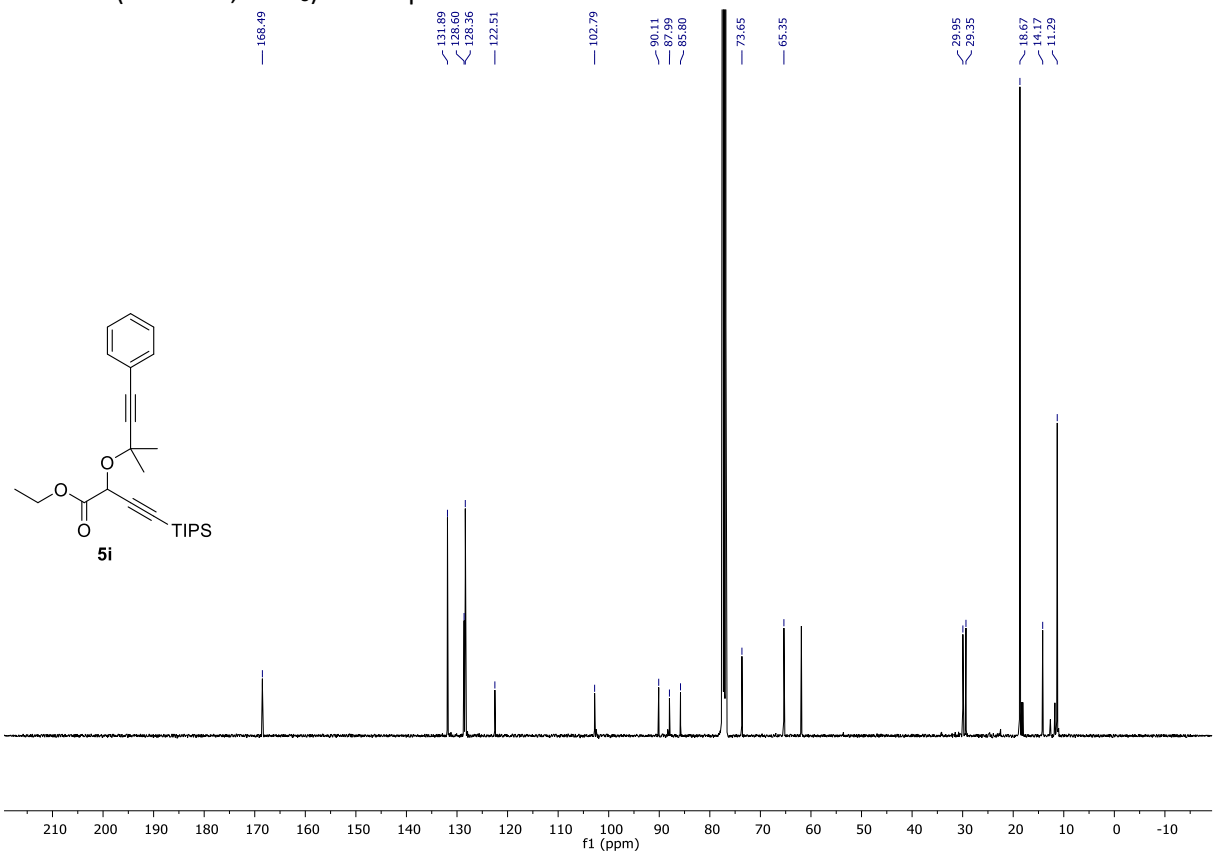
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5h**



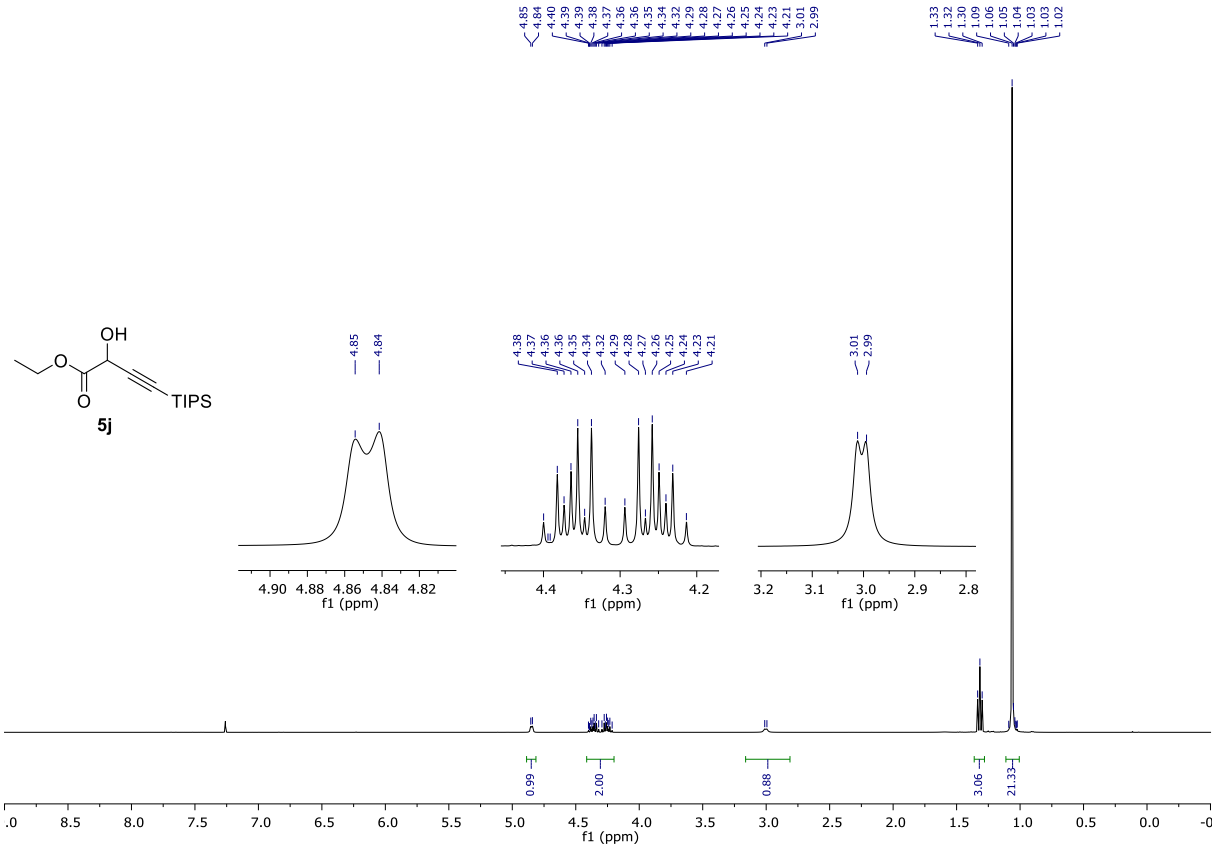
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5i**



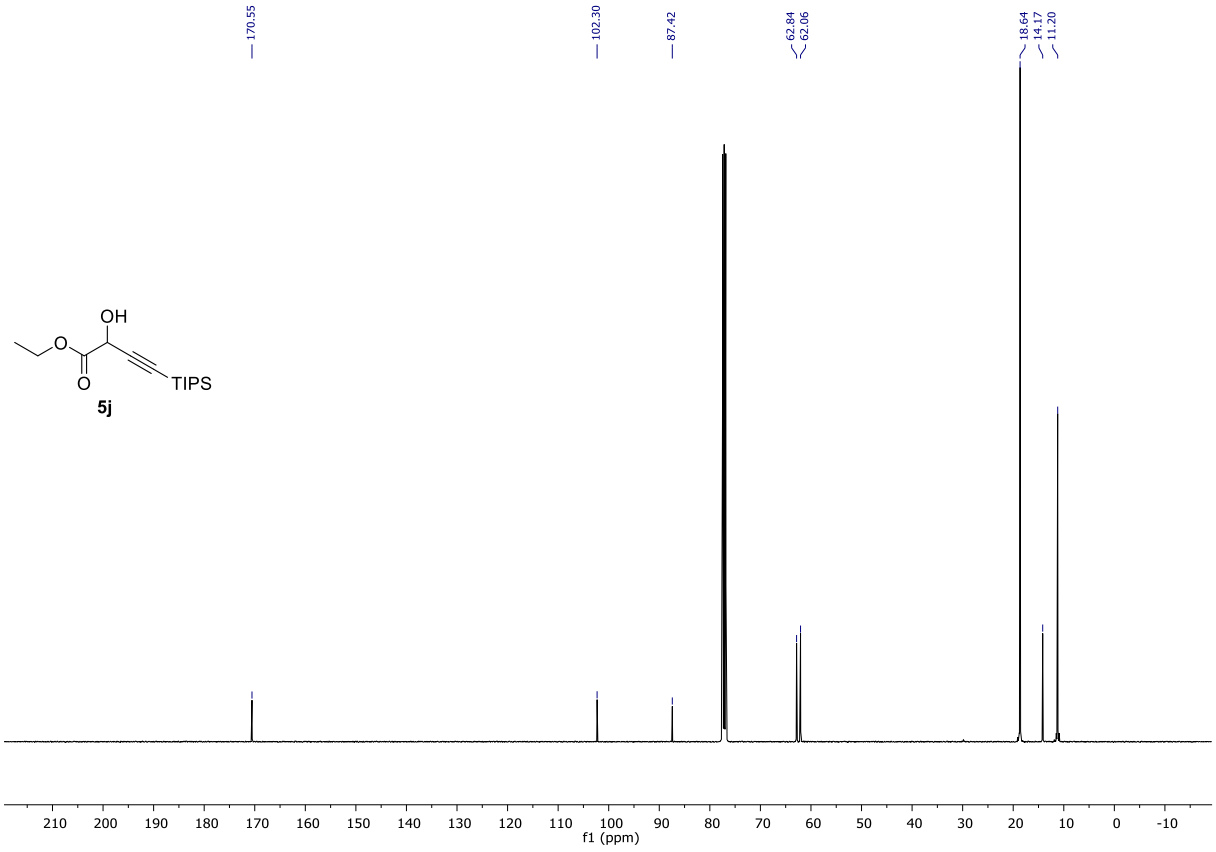
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5i**



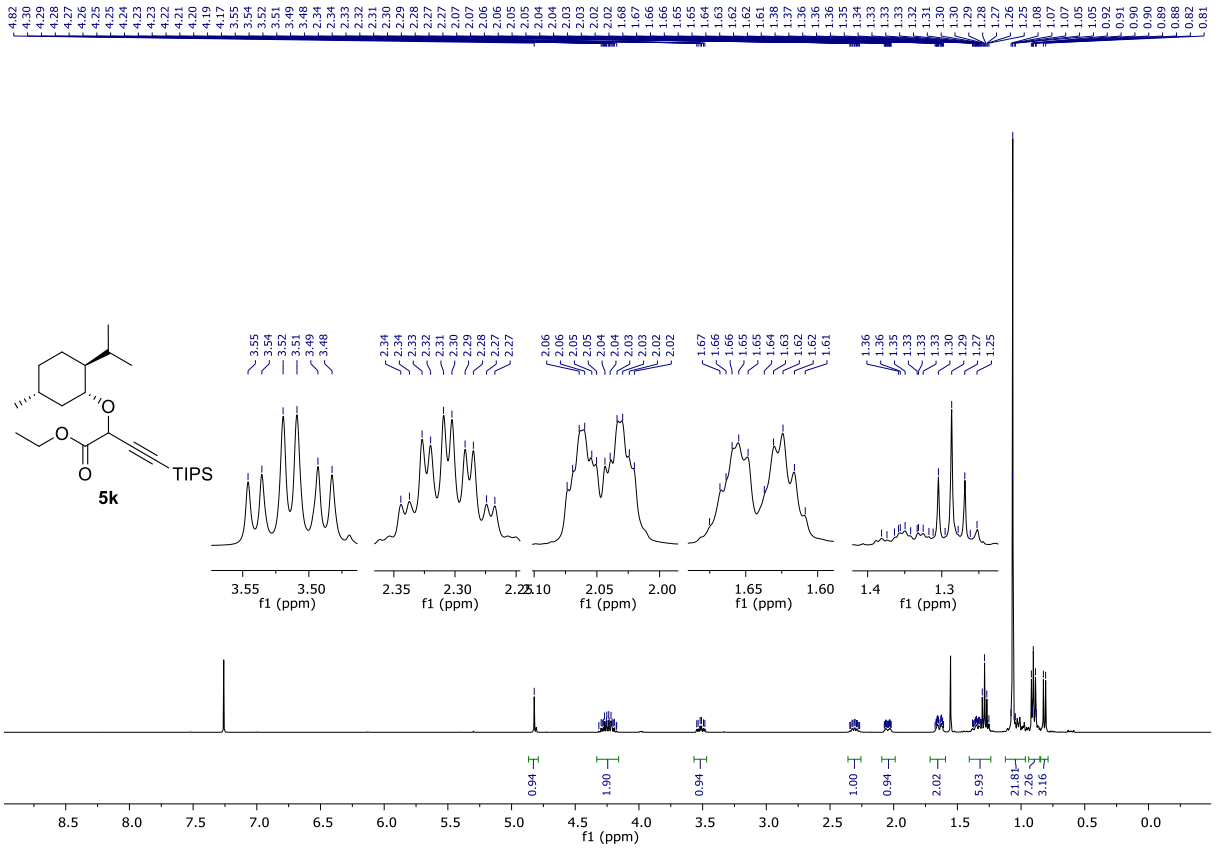
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5j**



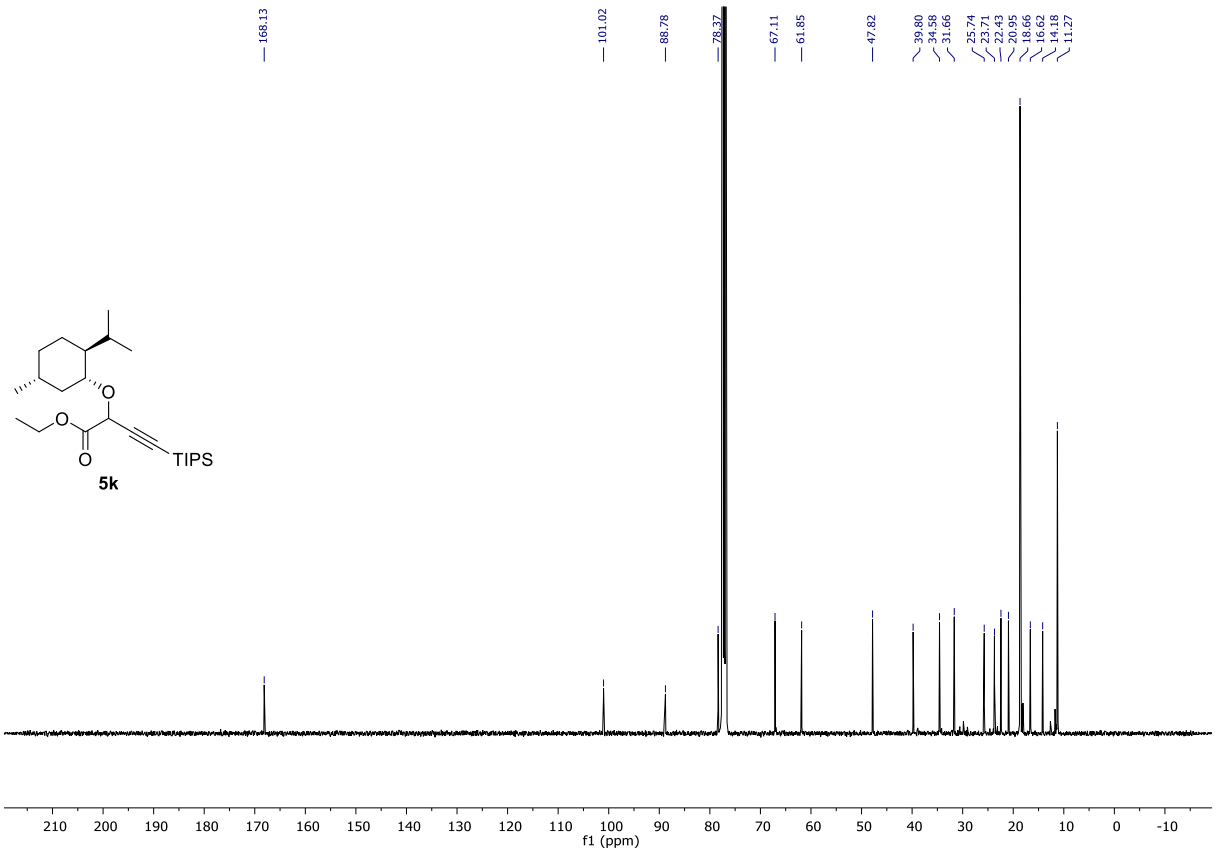
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5j**



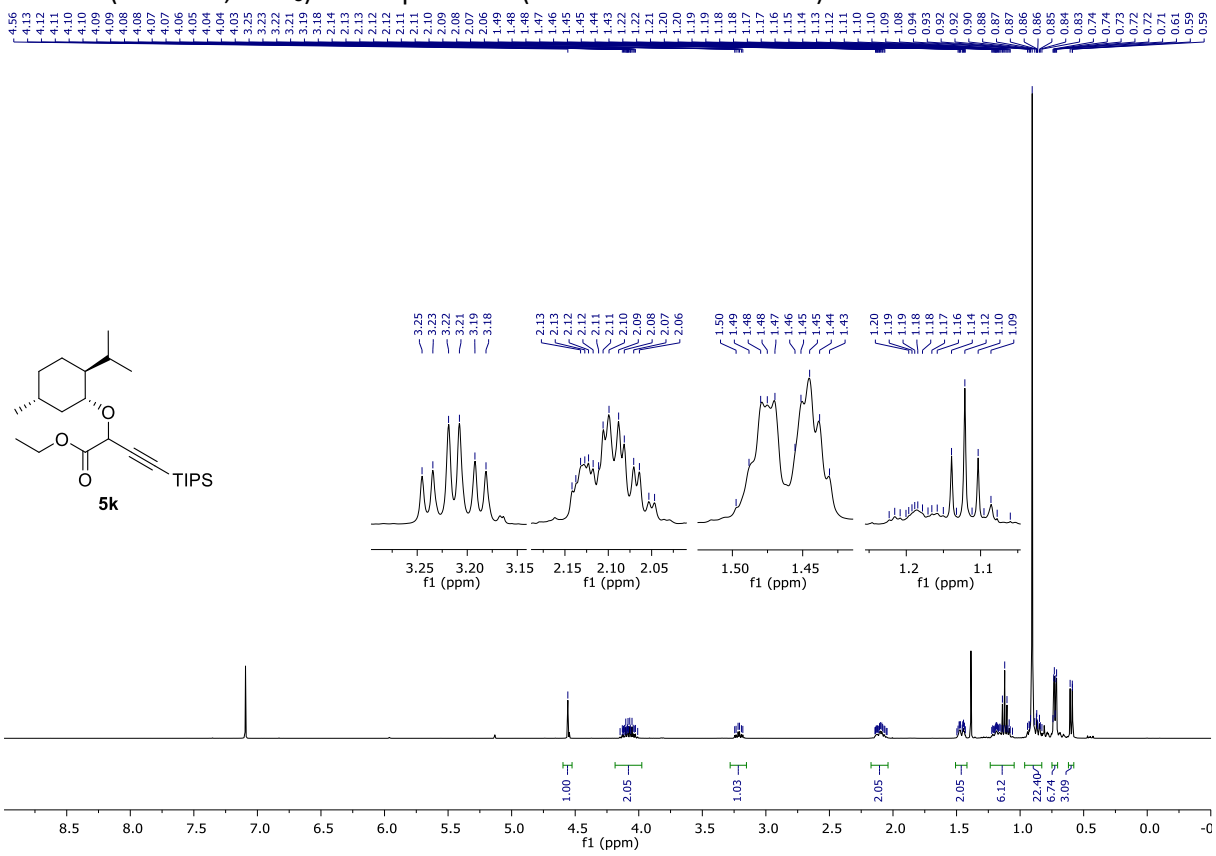
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5k** (first diastereoisomer)



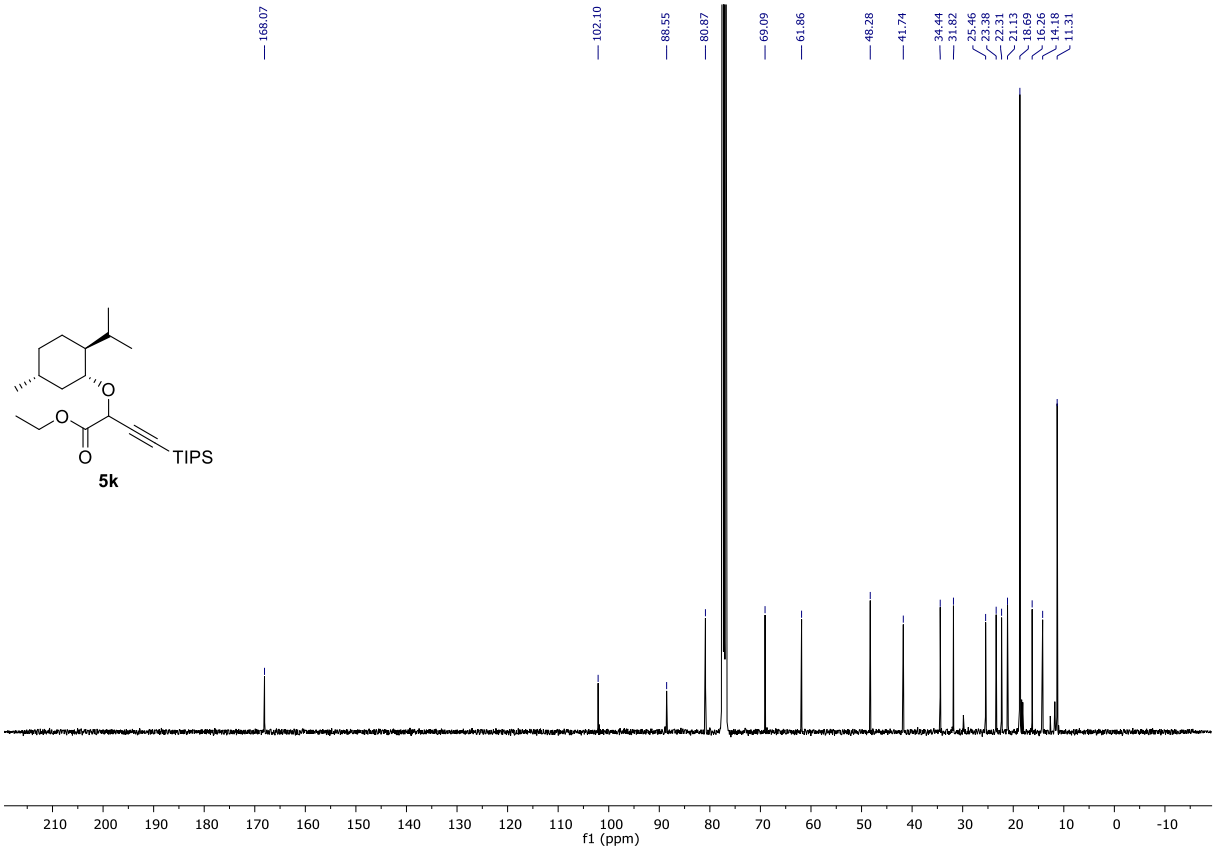
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5k** (first diastereoisomer)



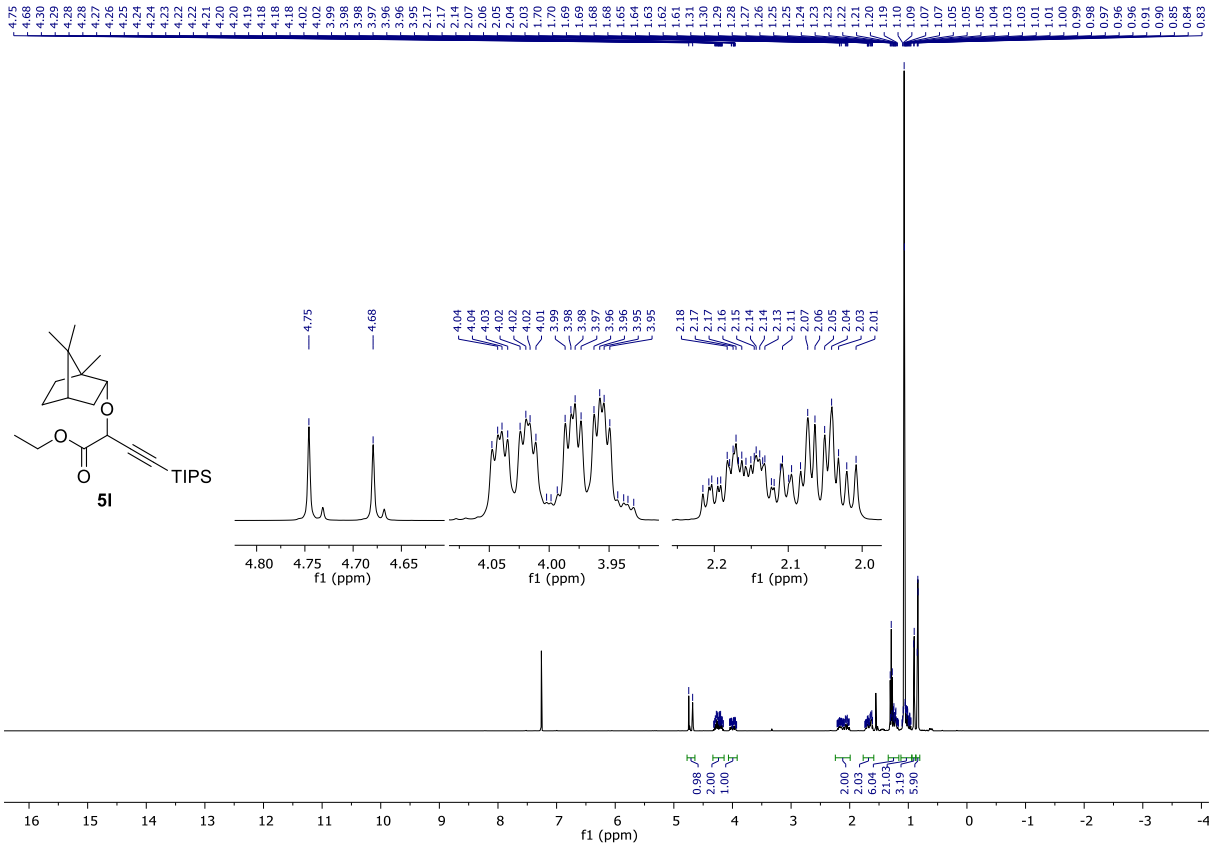
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5k** (second diastereoisomer)



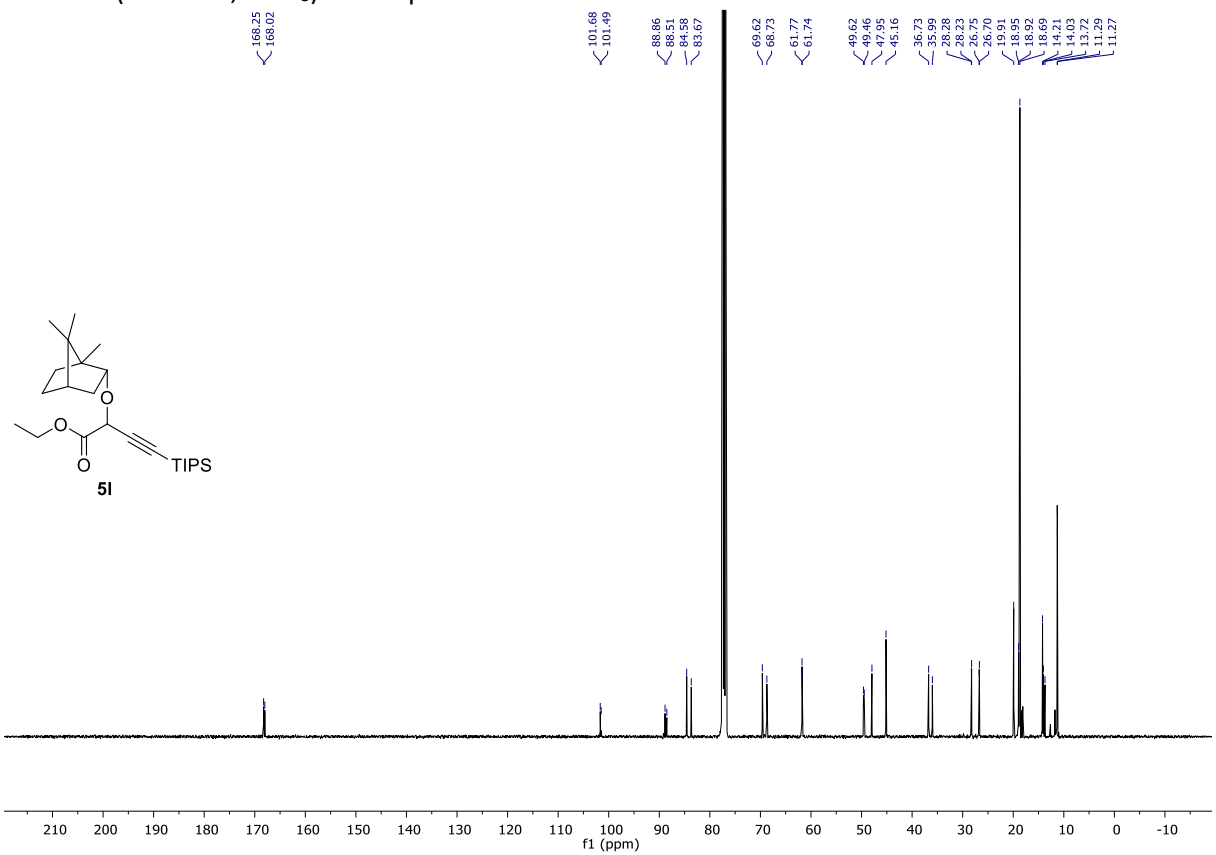
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5k** (second diastereoisomer)



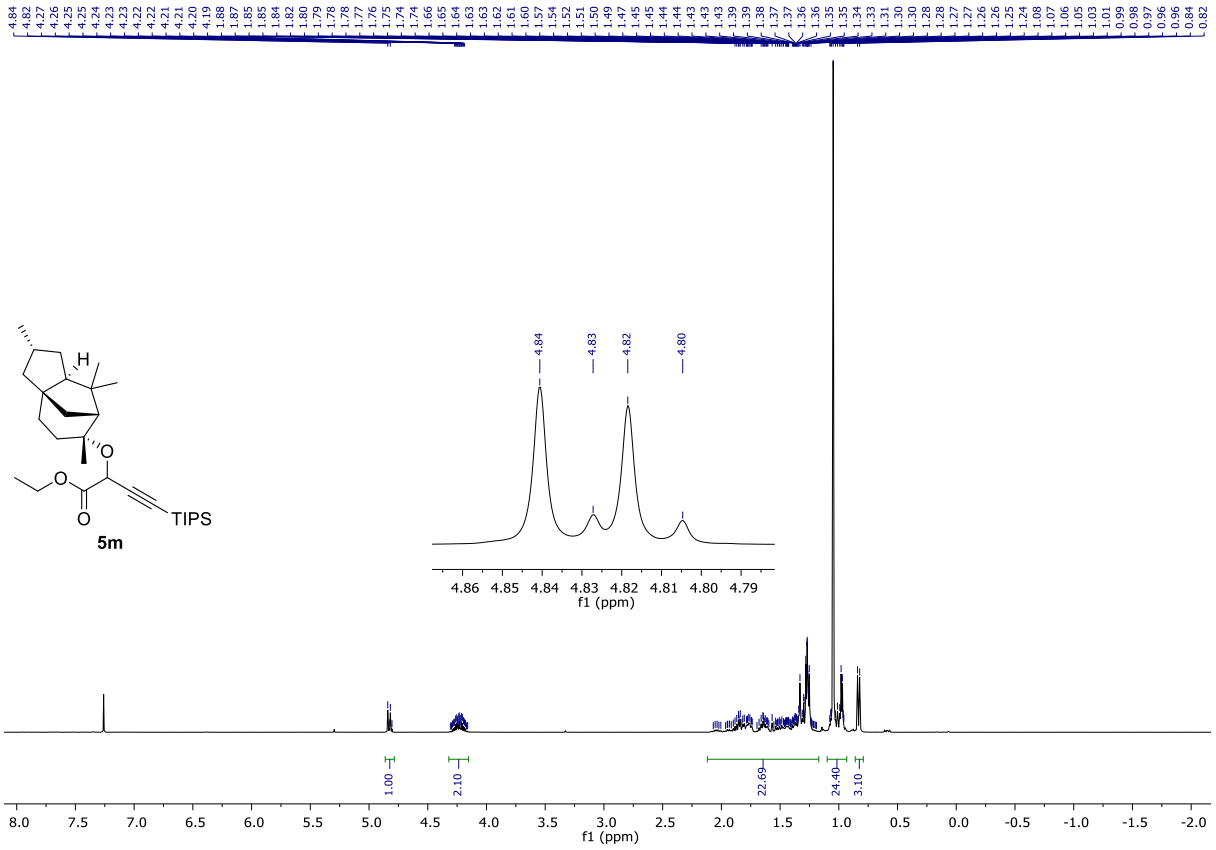
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5l**



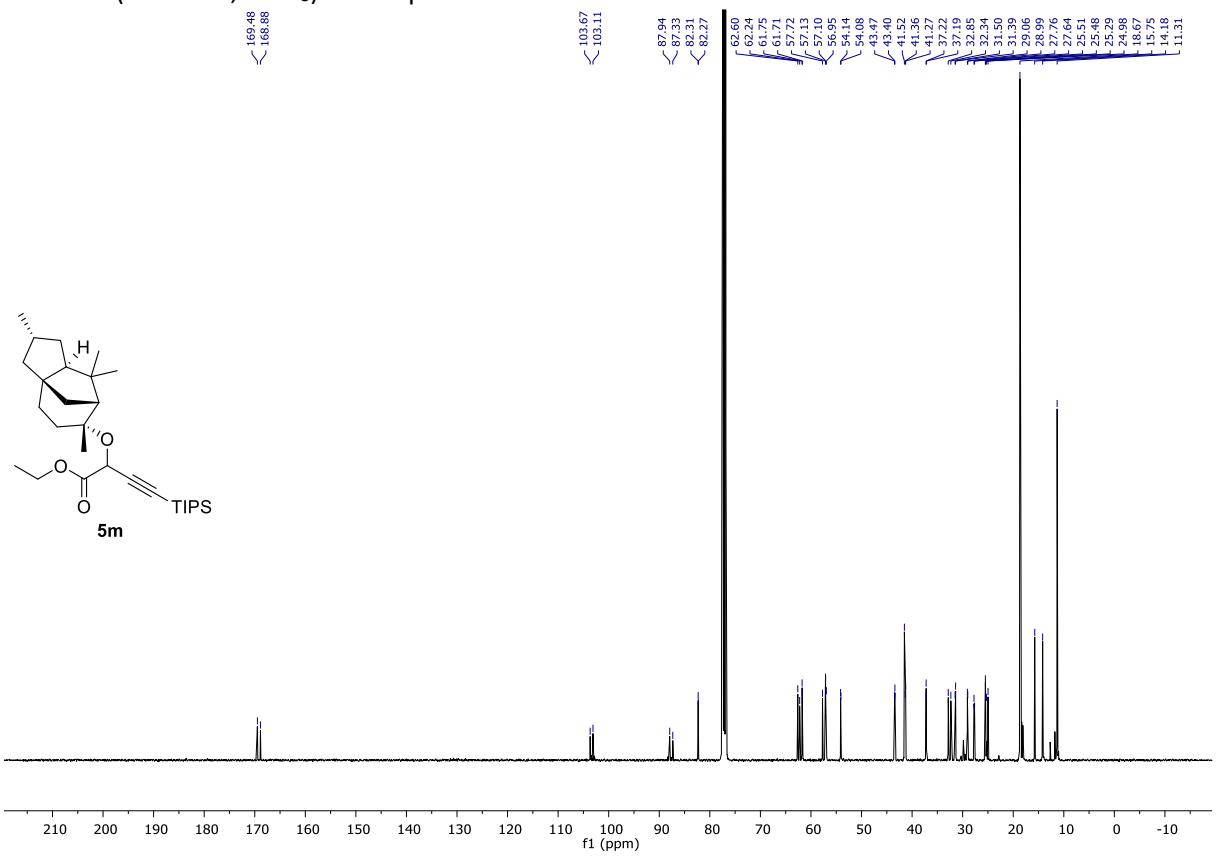
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5l**



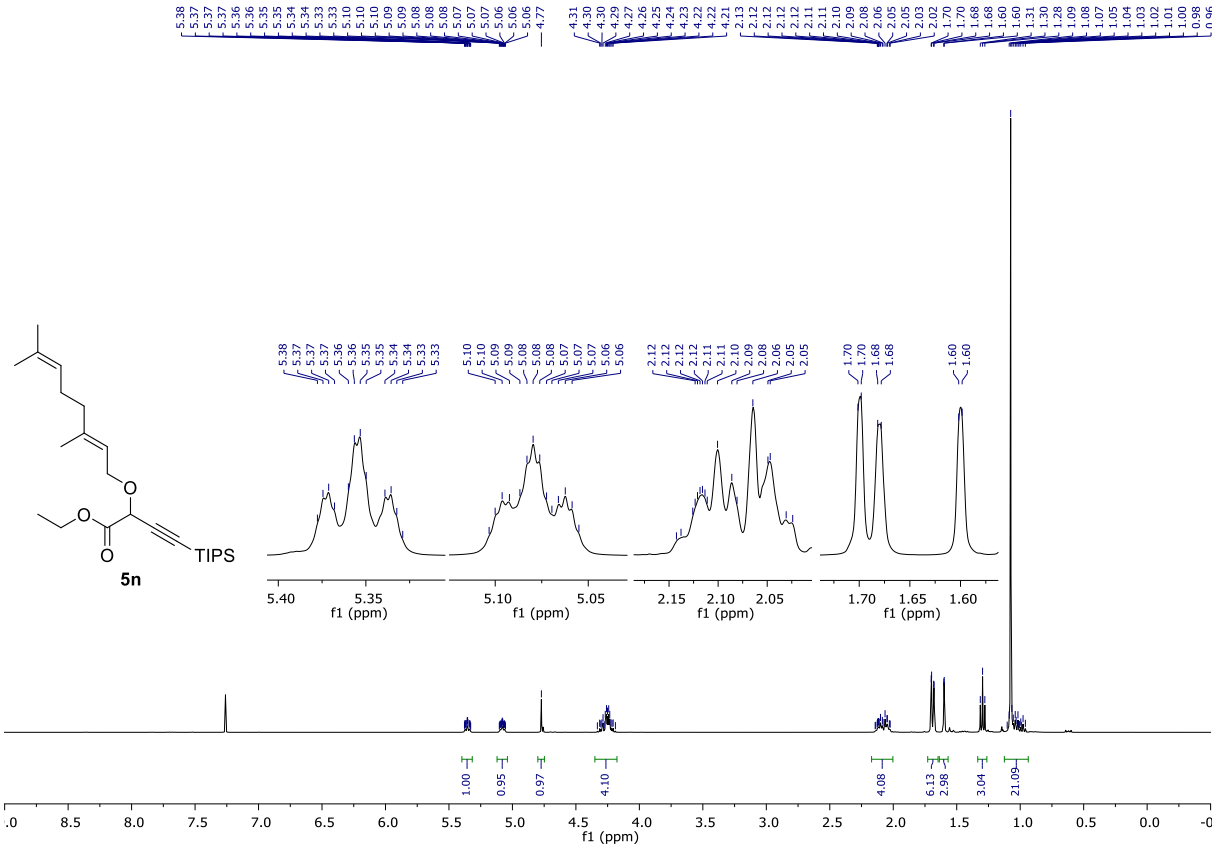
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5m**



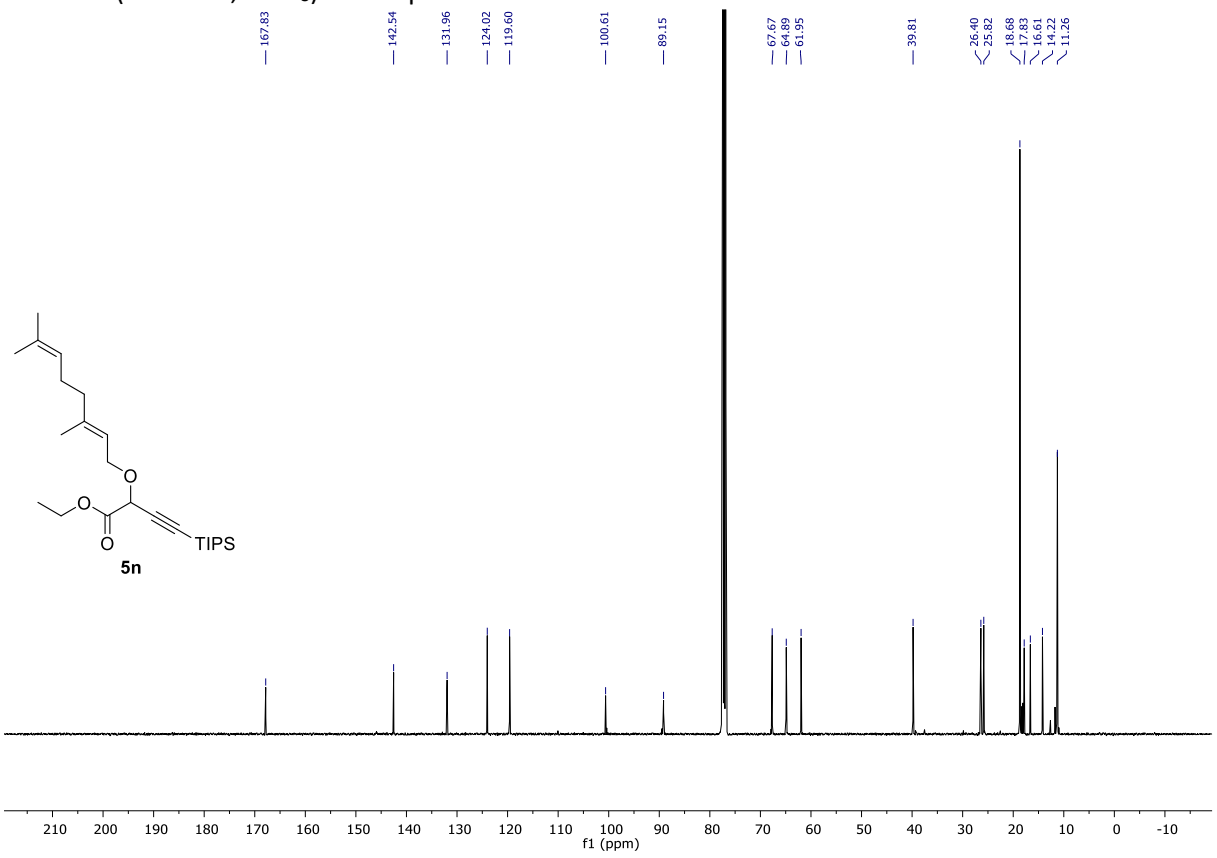
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5m**



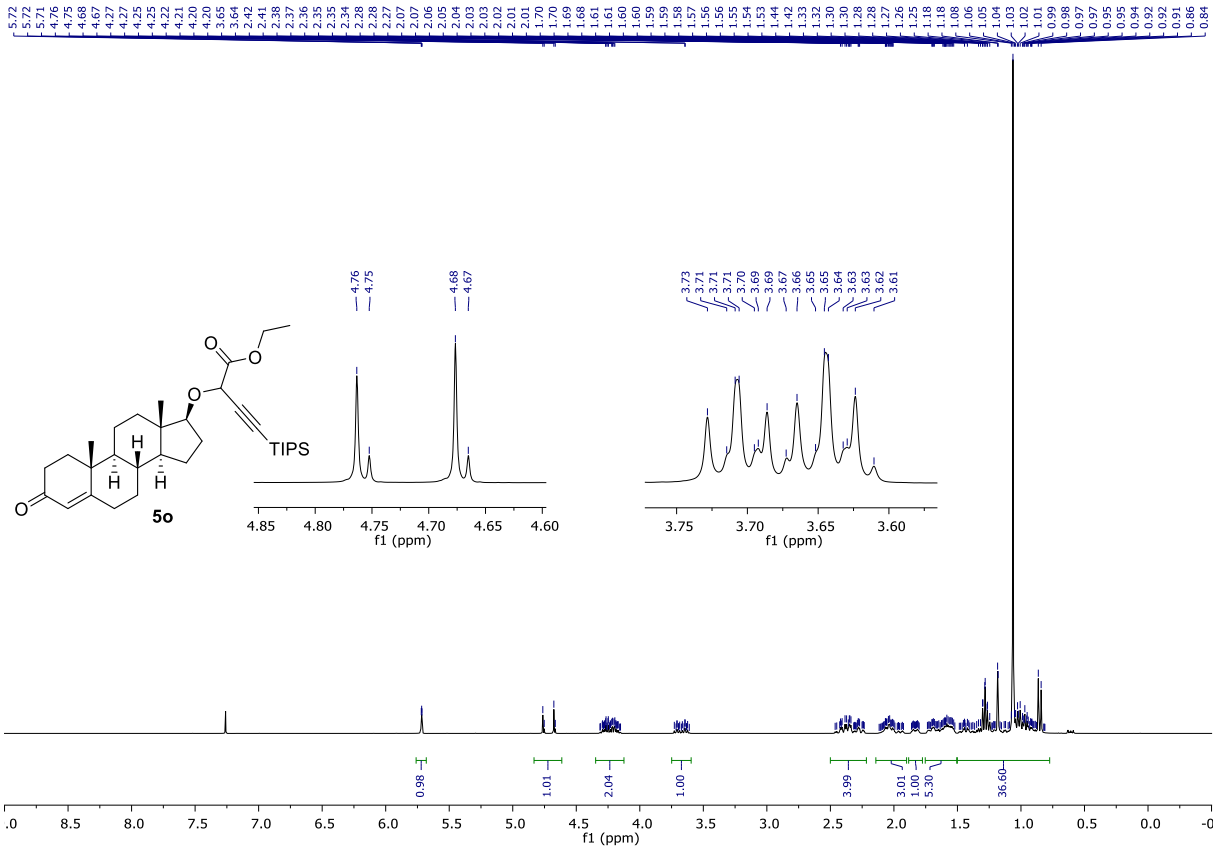
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5n**



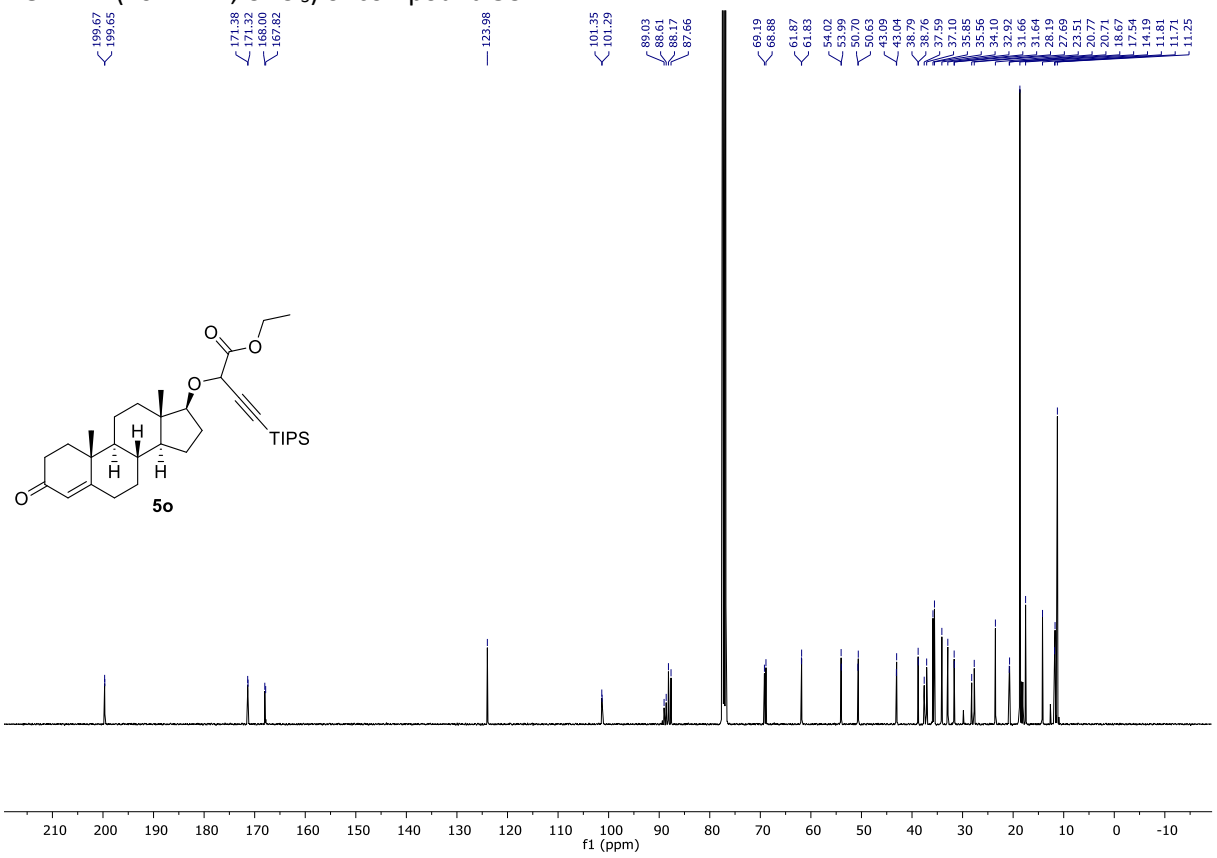
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5n**



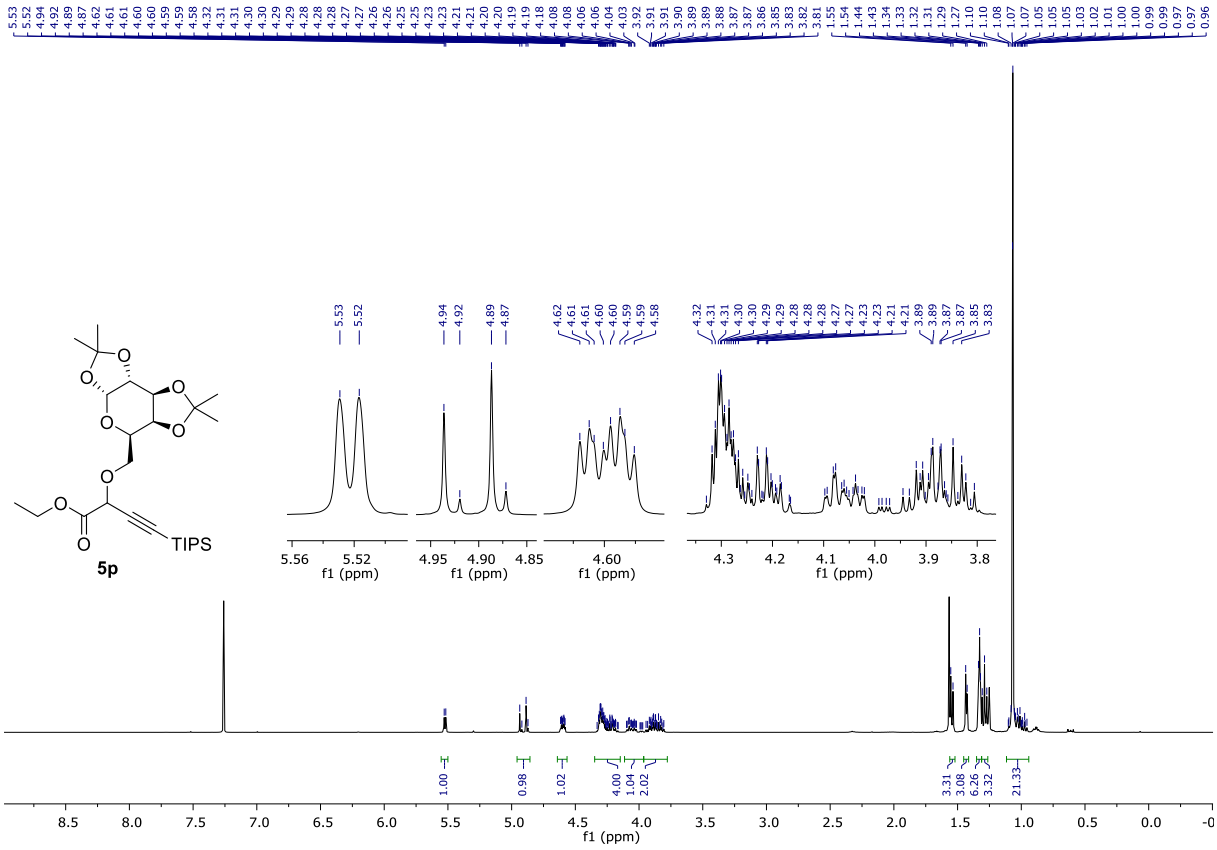
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5o**



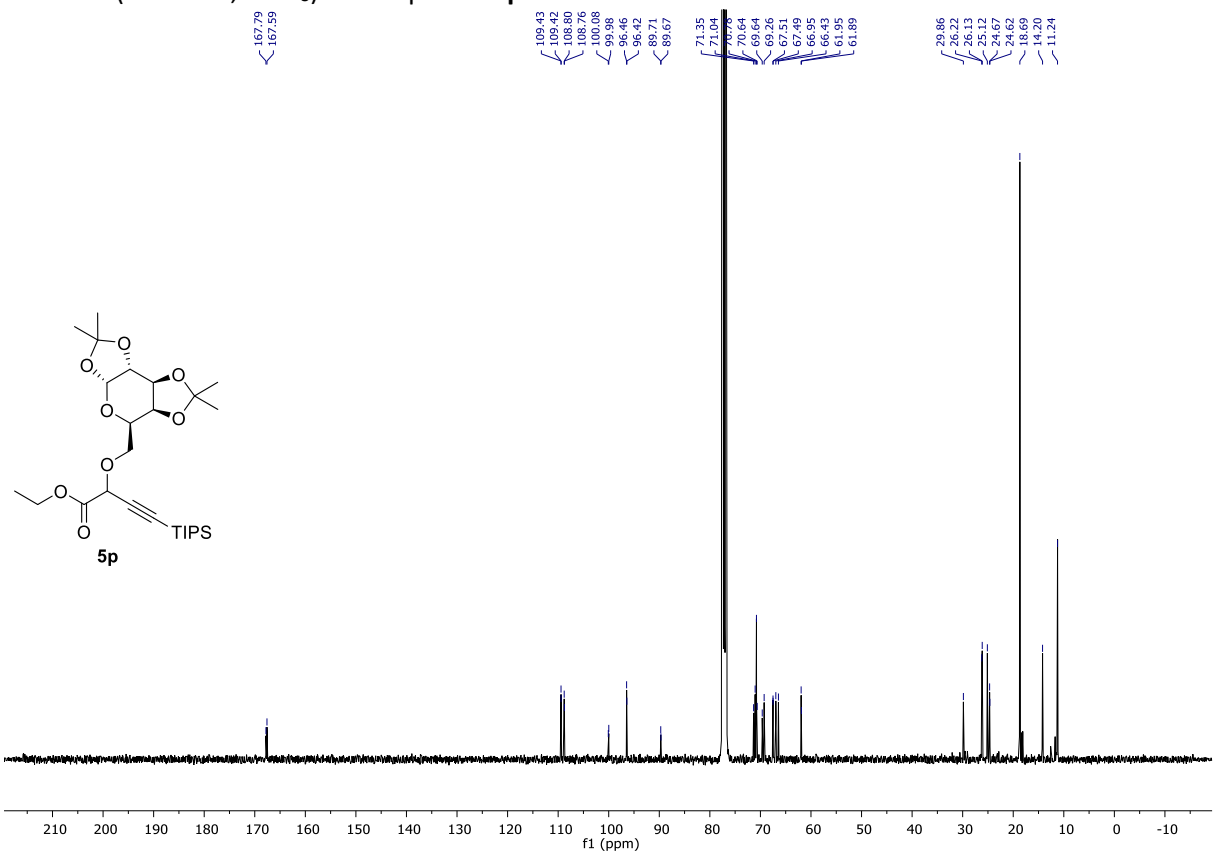
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5o**



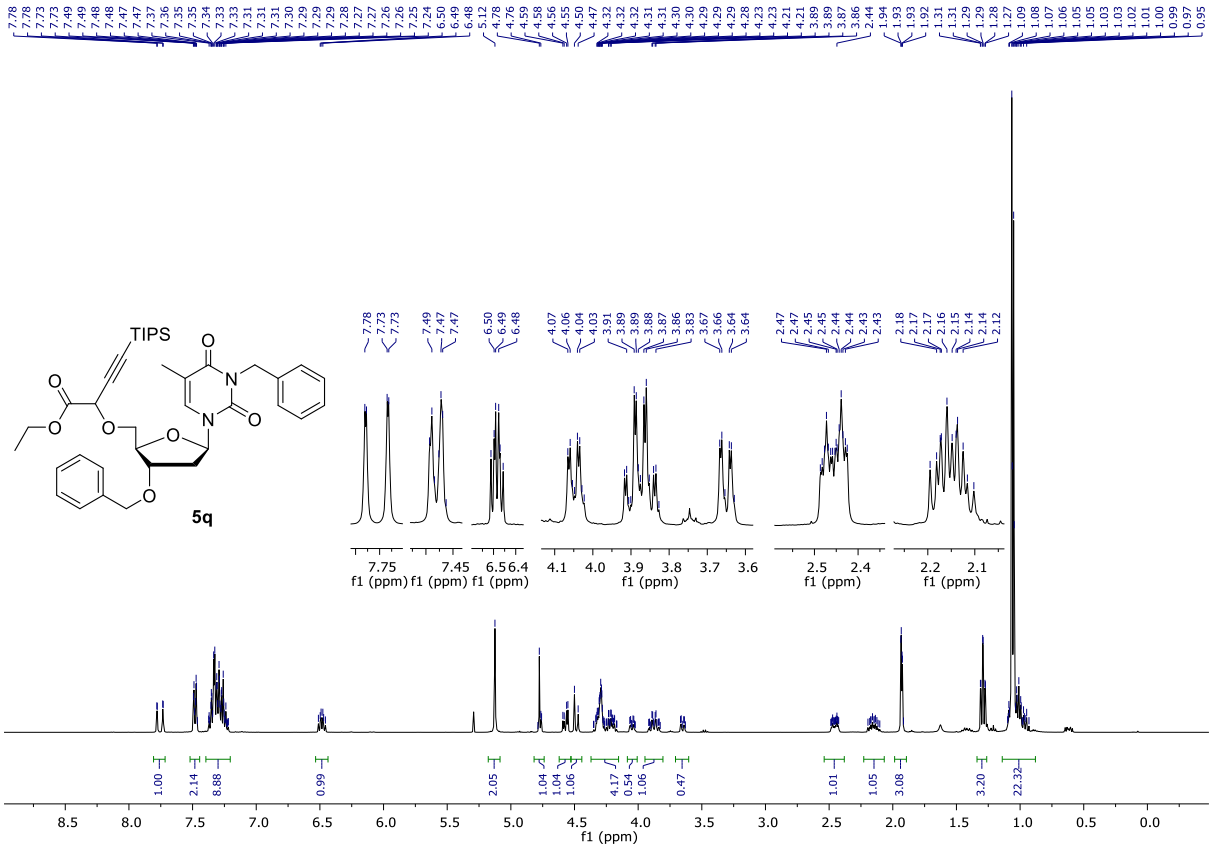
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5p**



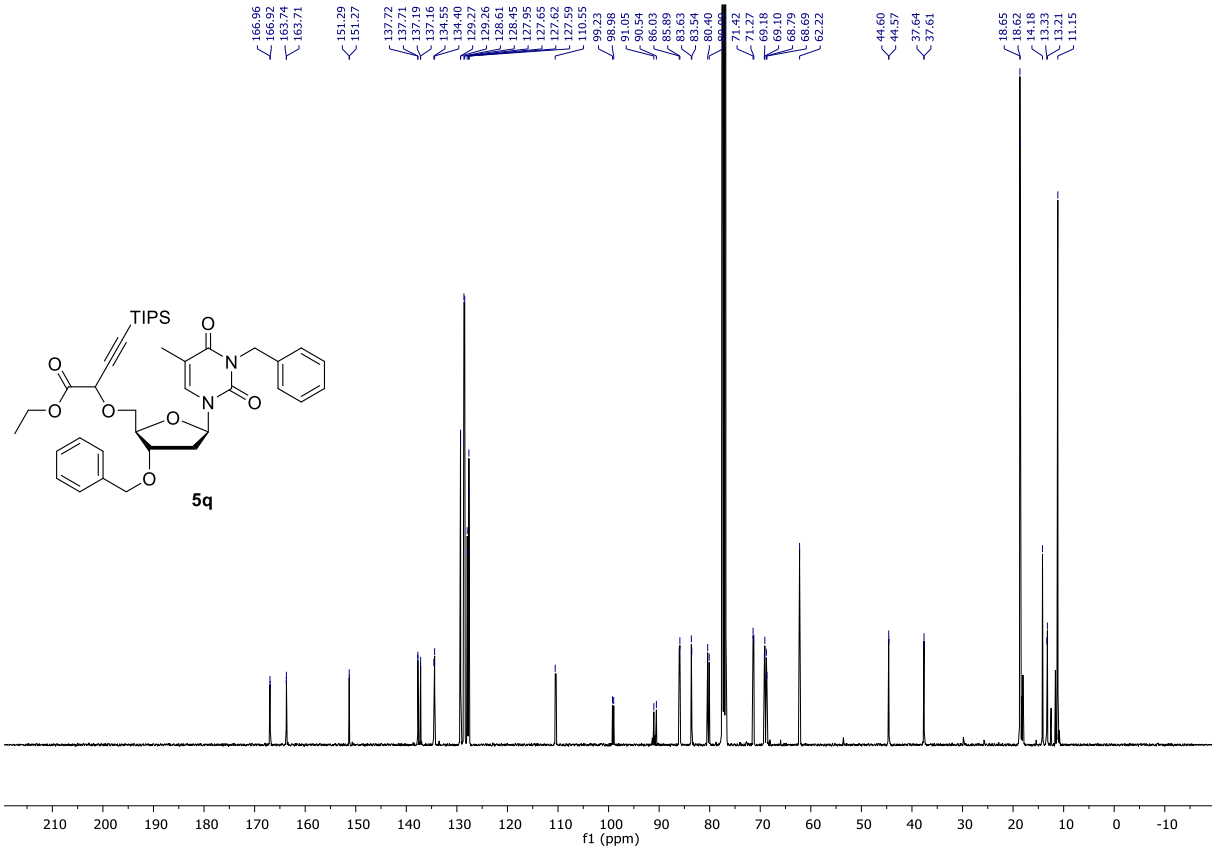
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5p**



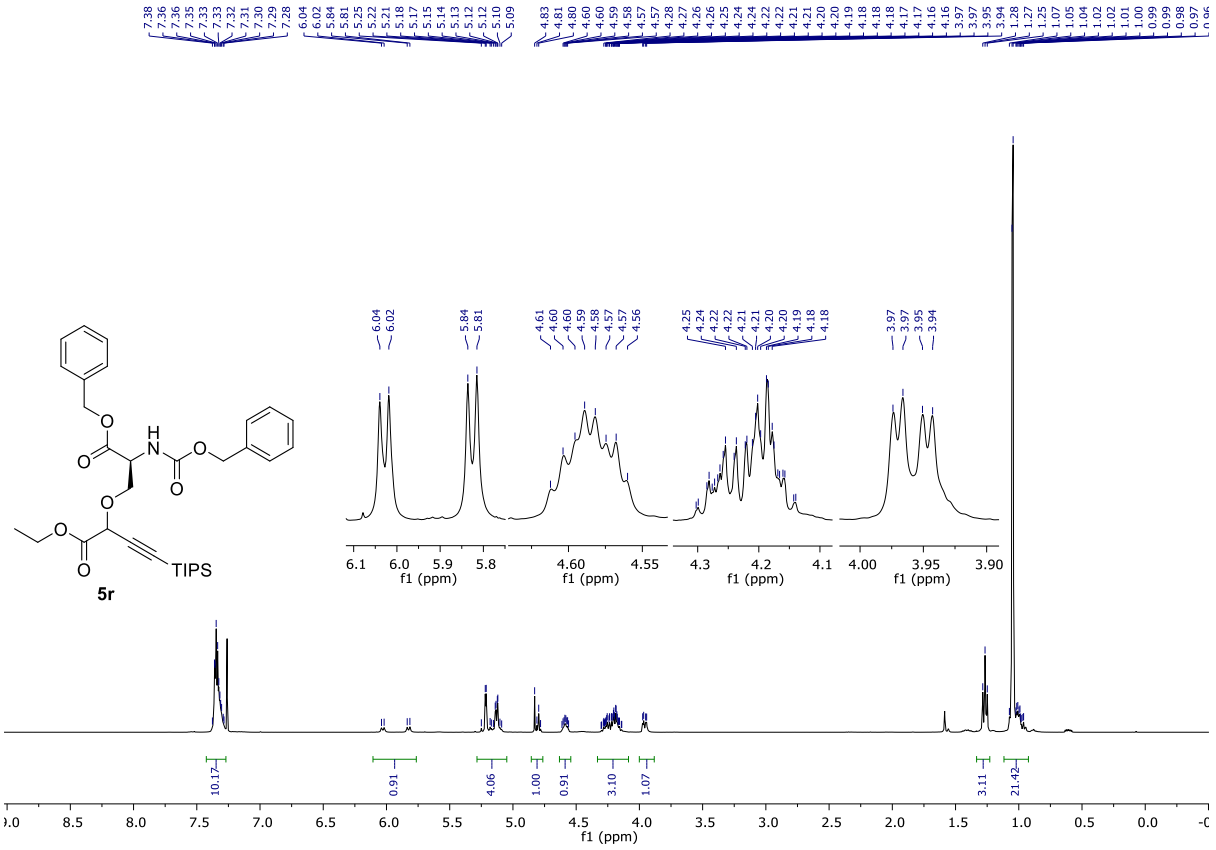
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5q**



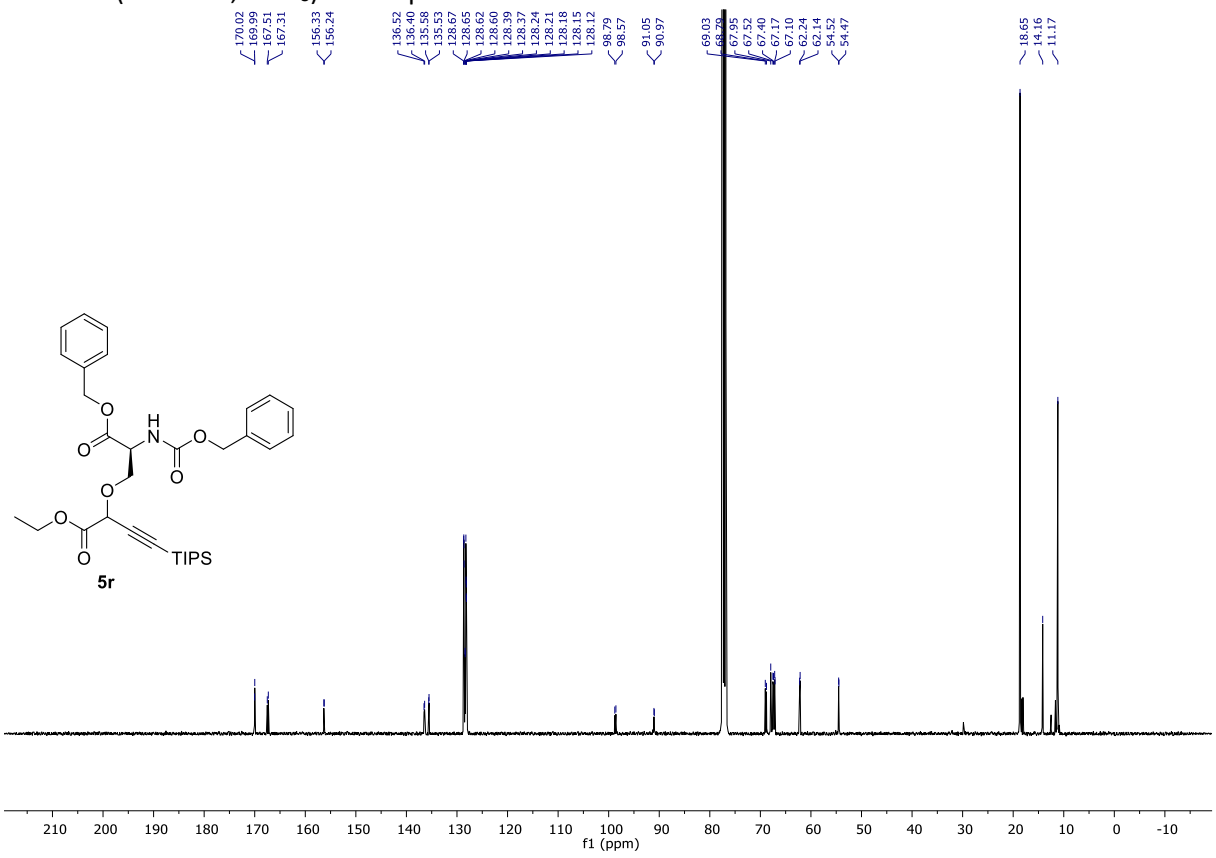
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5q**



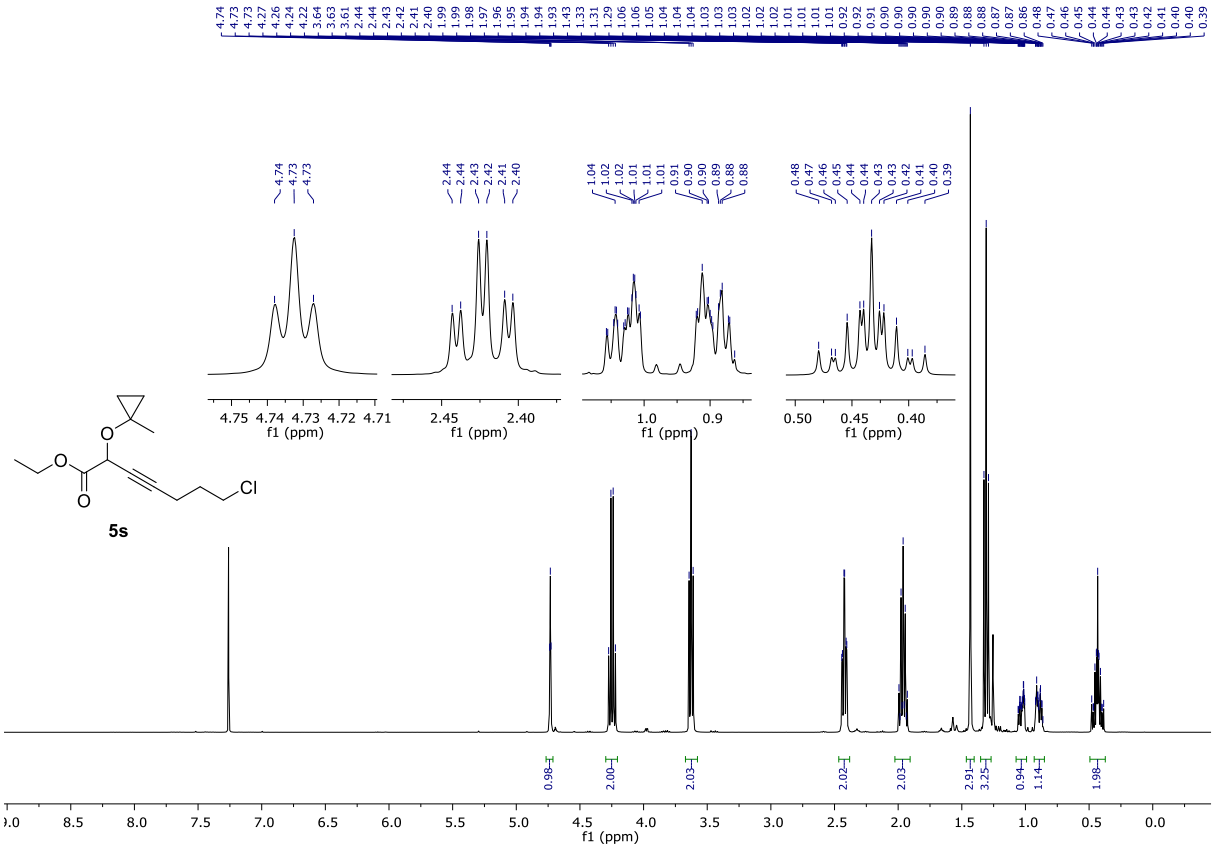
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5r**



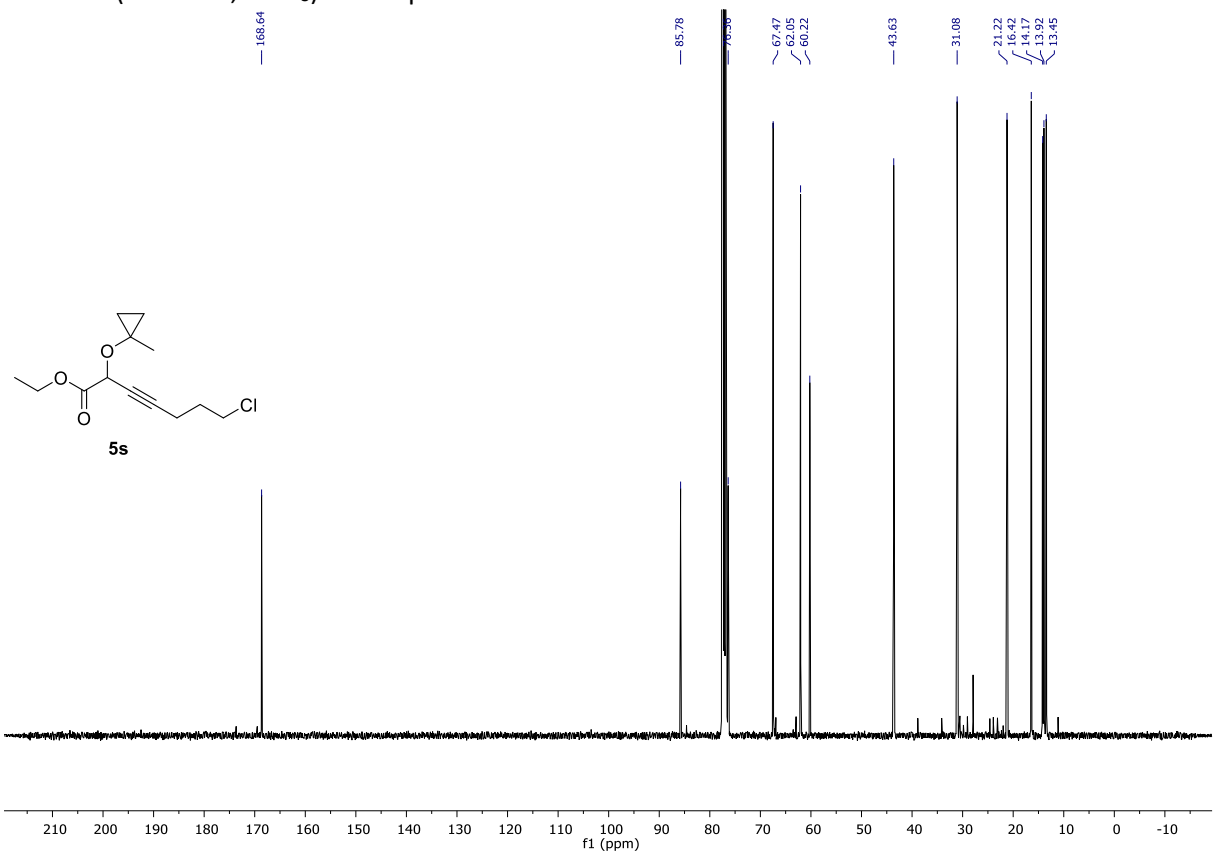
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5r**



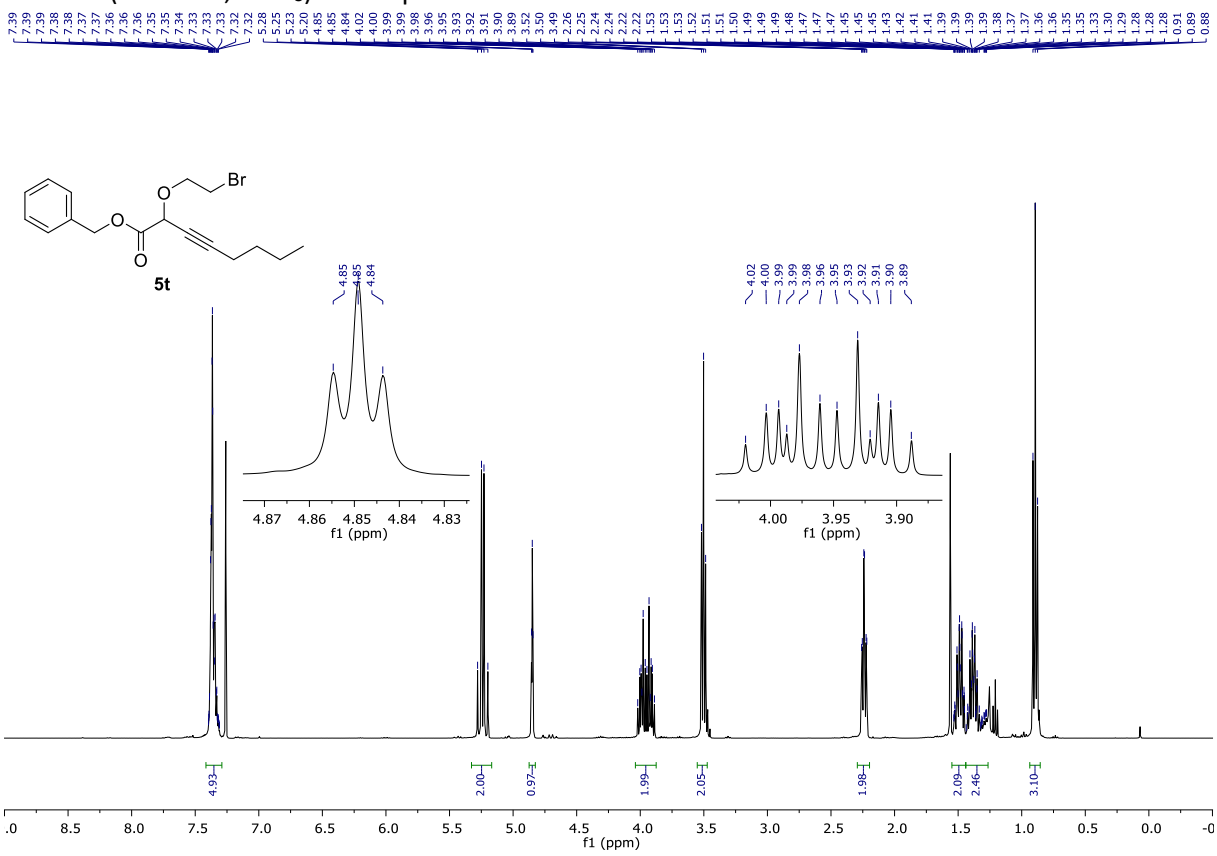
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5s**



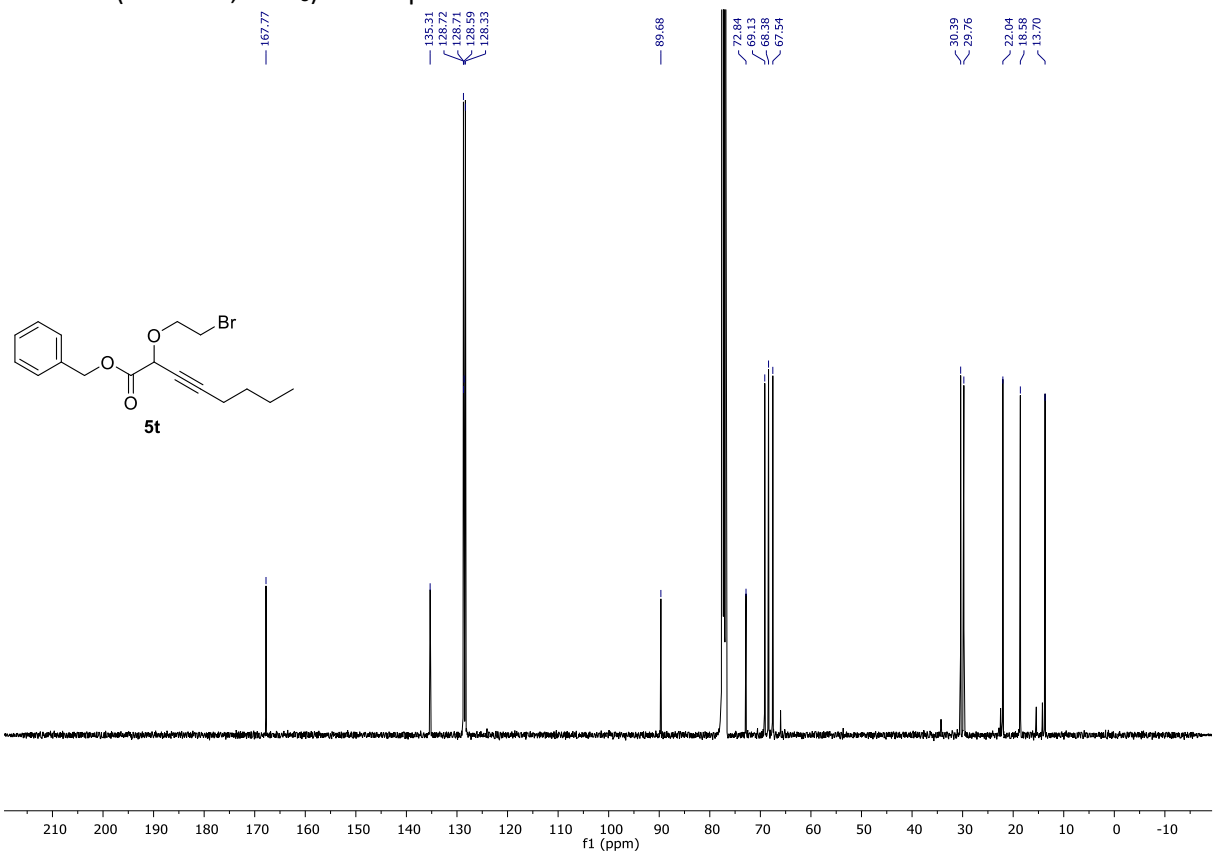
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5s**



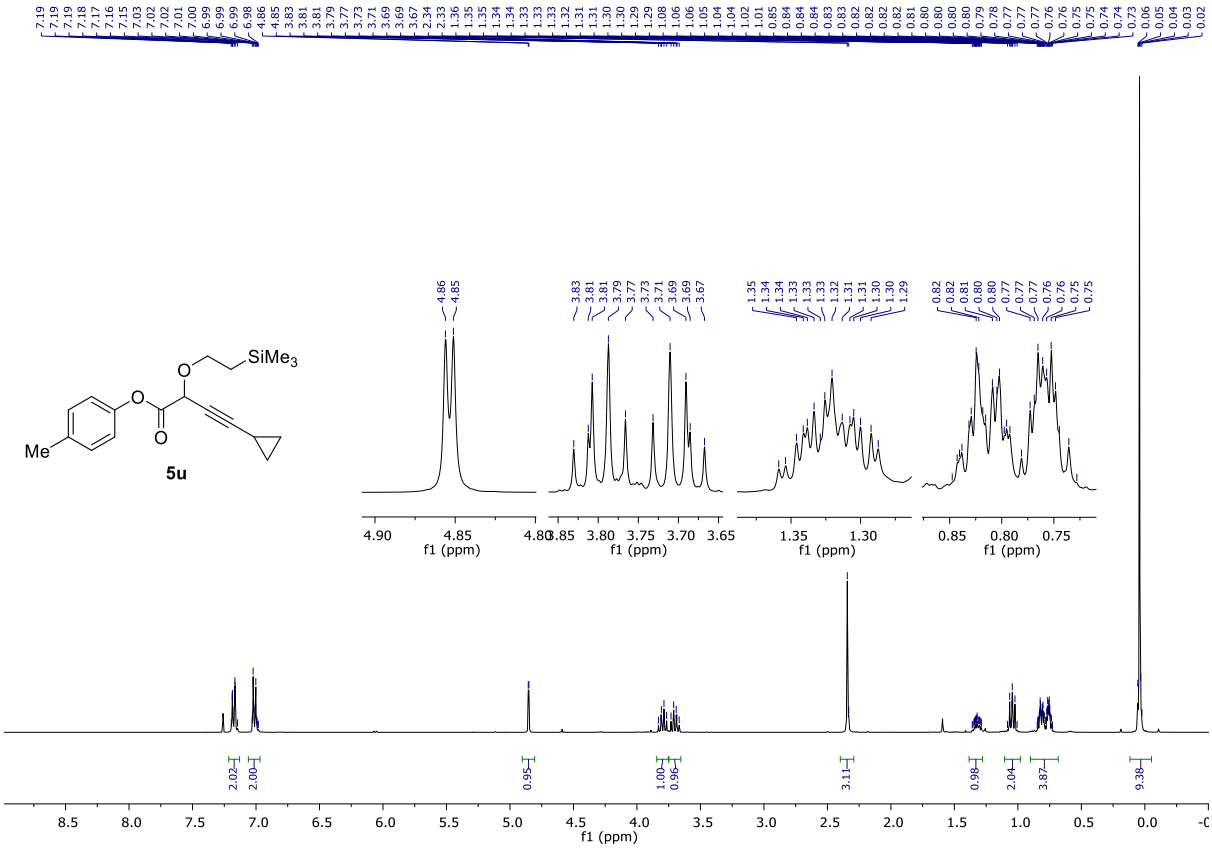
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5t**



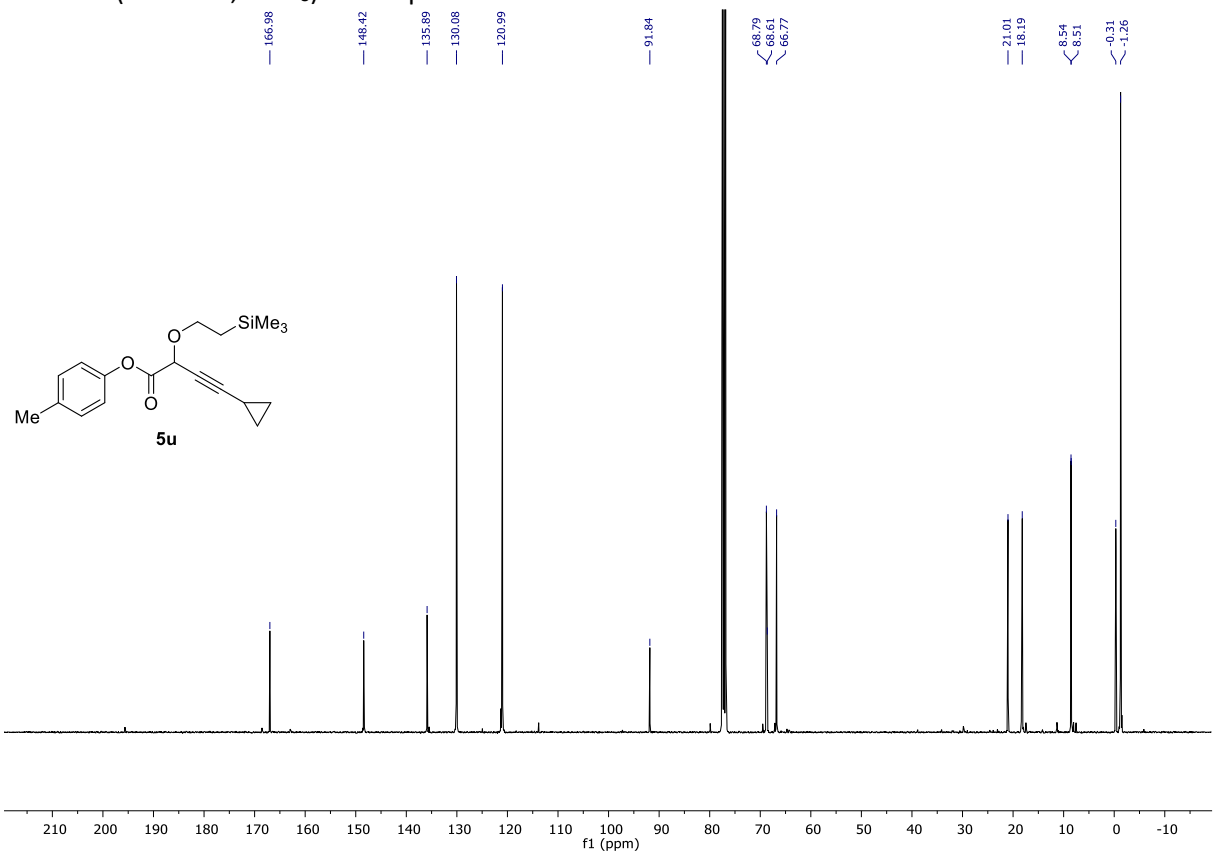
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5t**



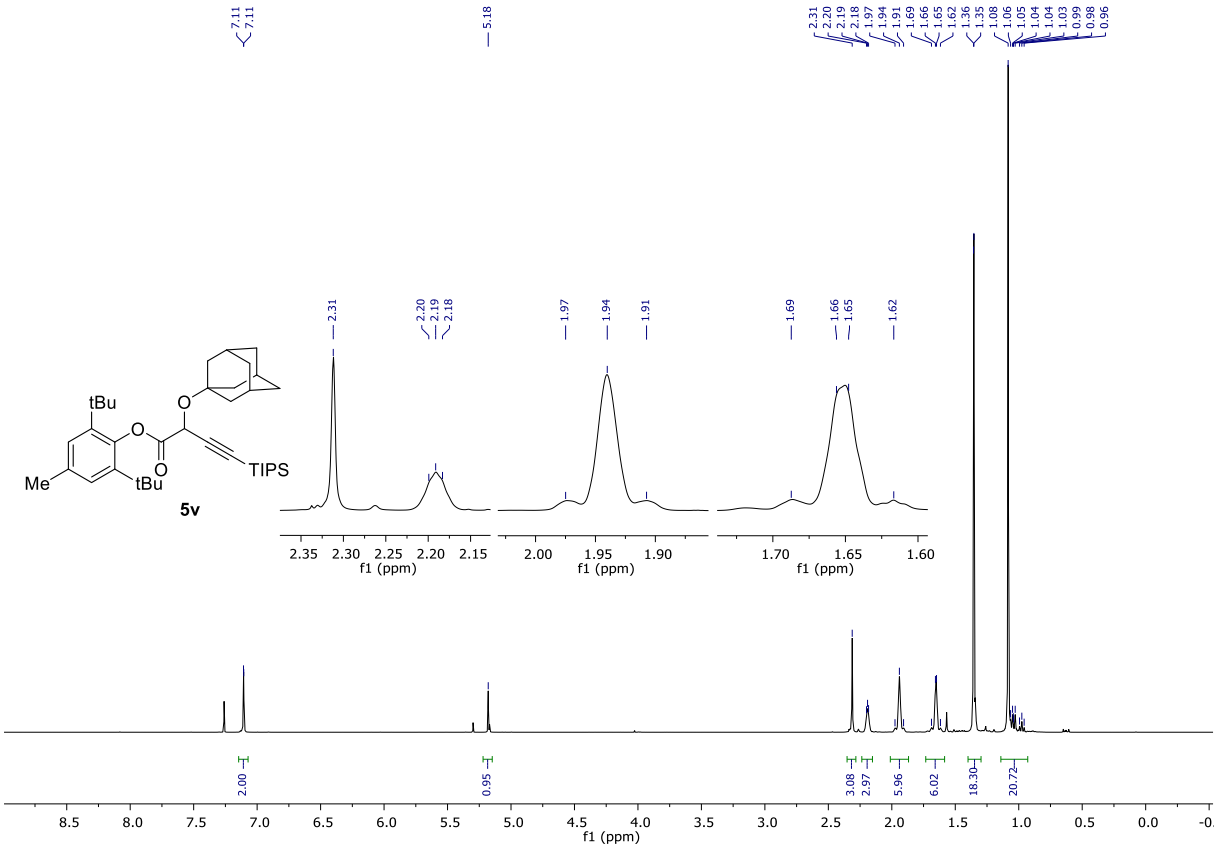
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5u**



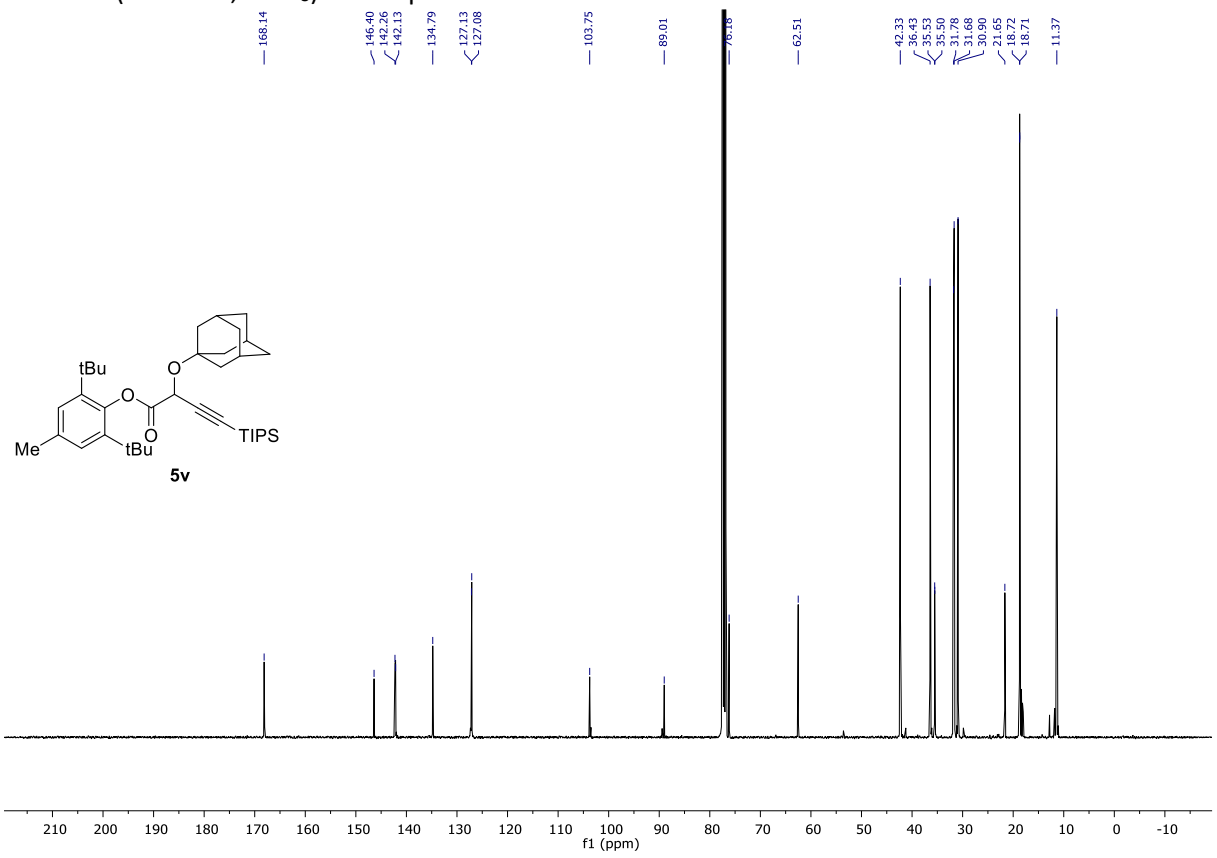
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5u**



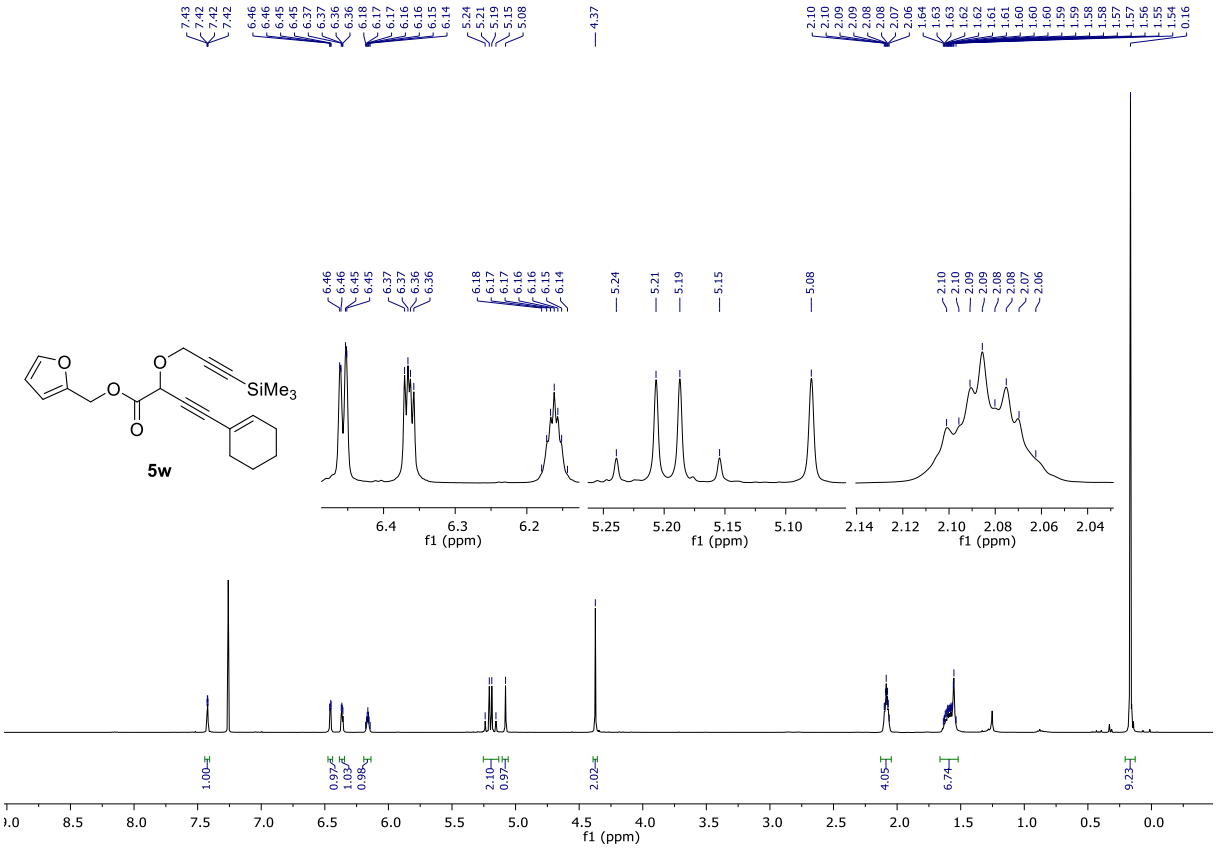
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5v**



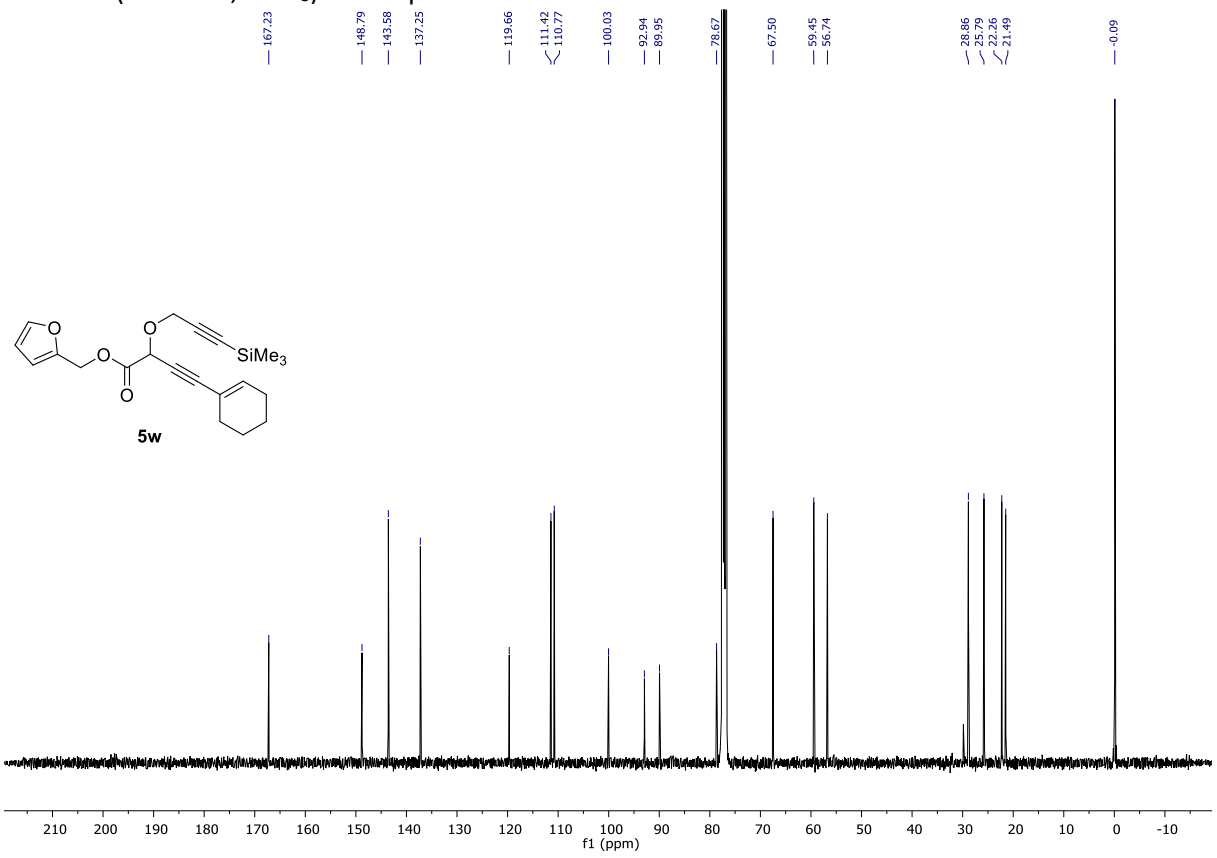
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5v**



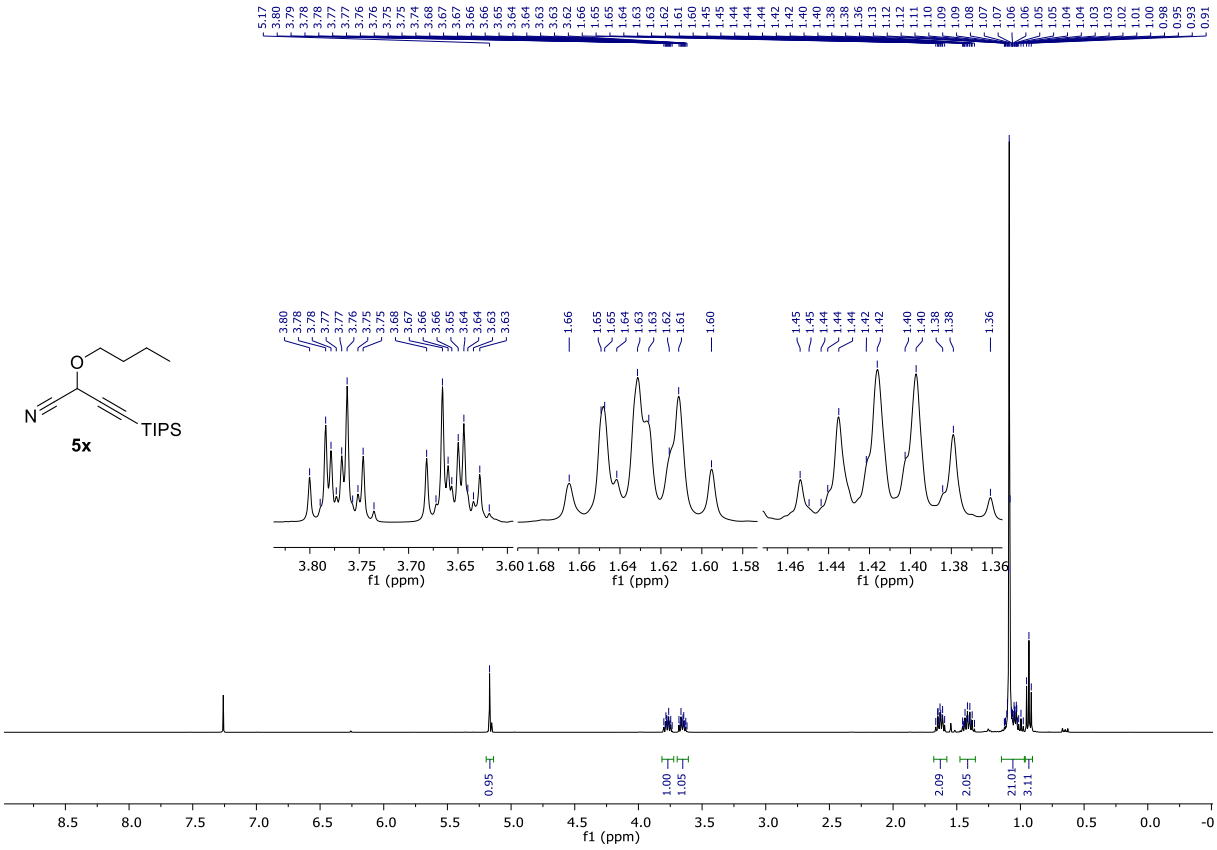
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5w**



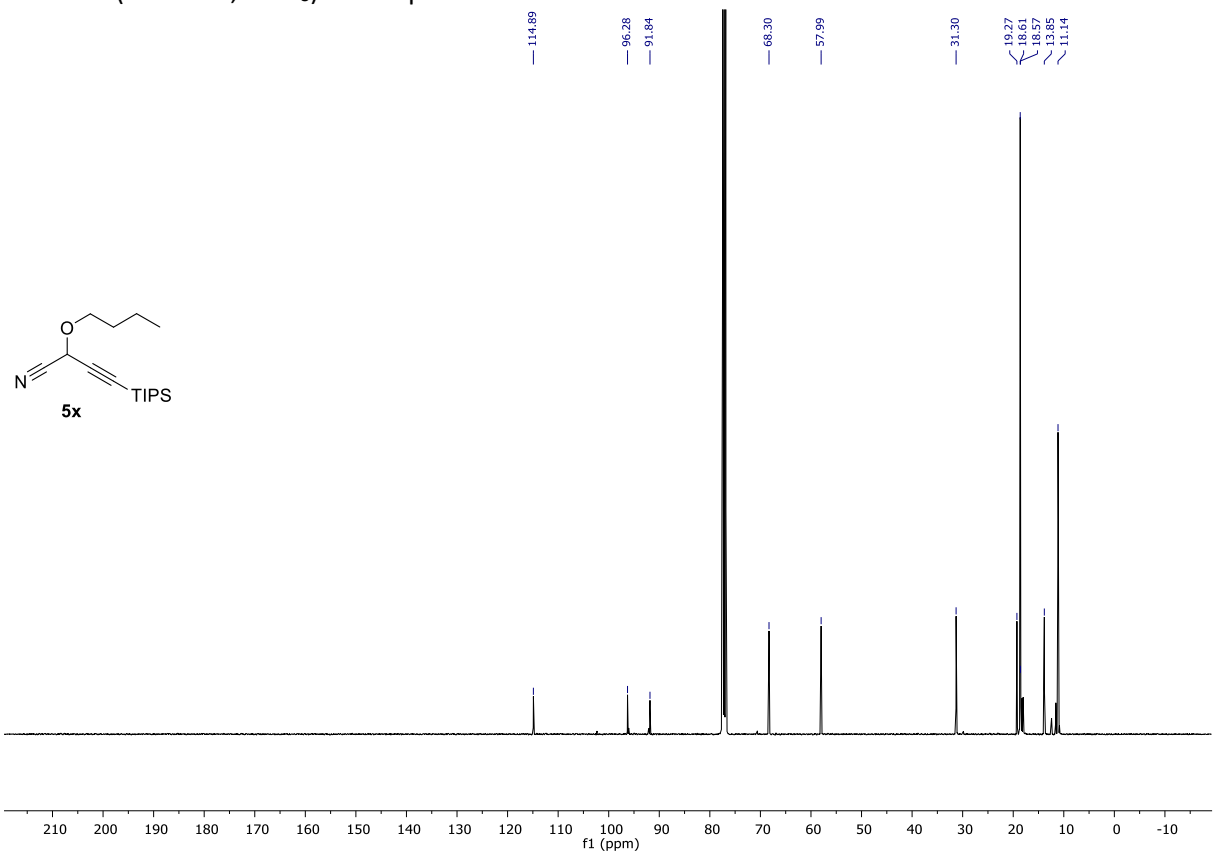
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5w**



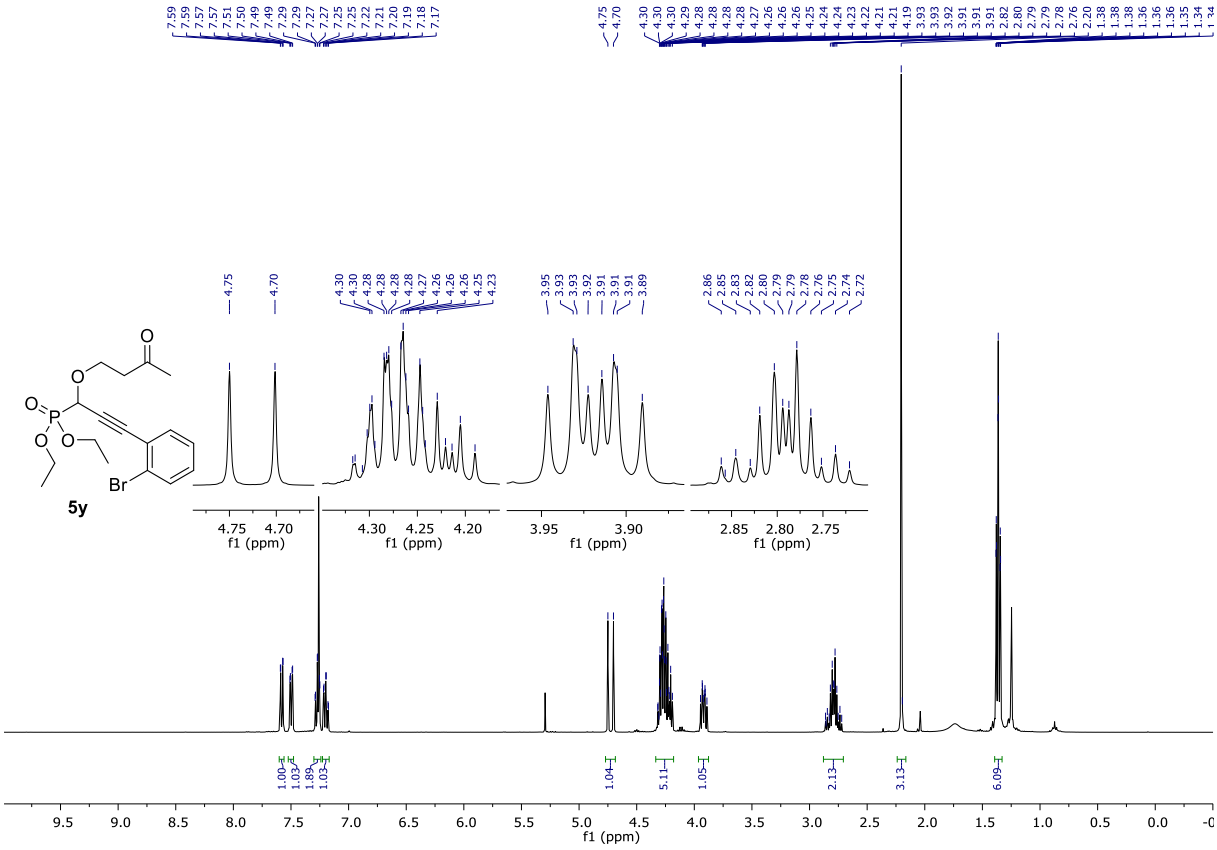
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5x**



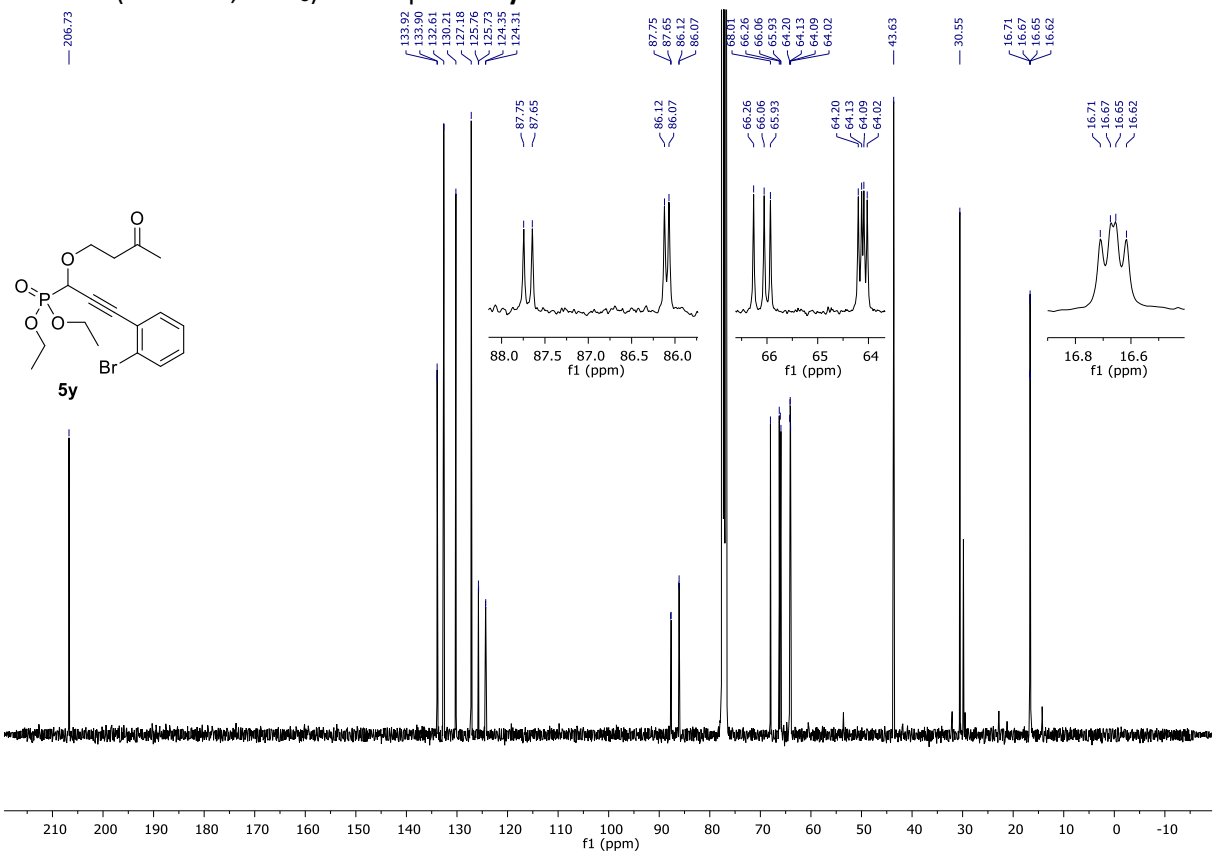
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5x**



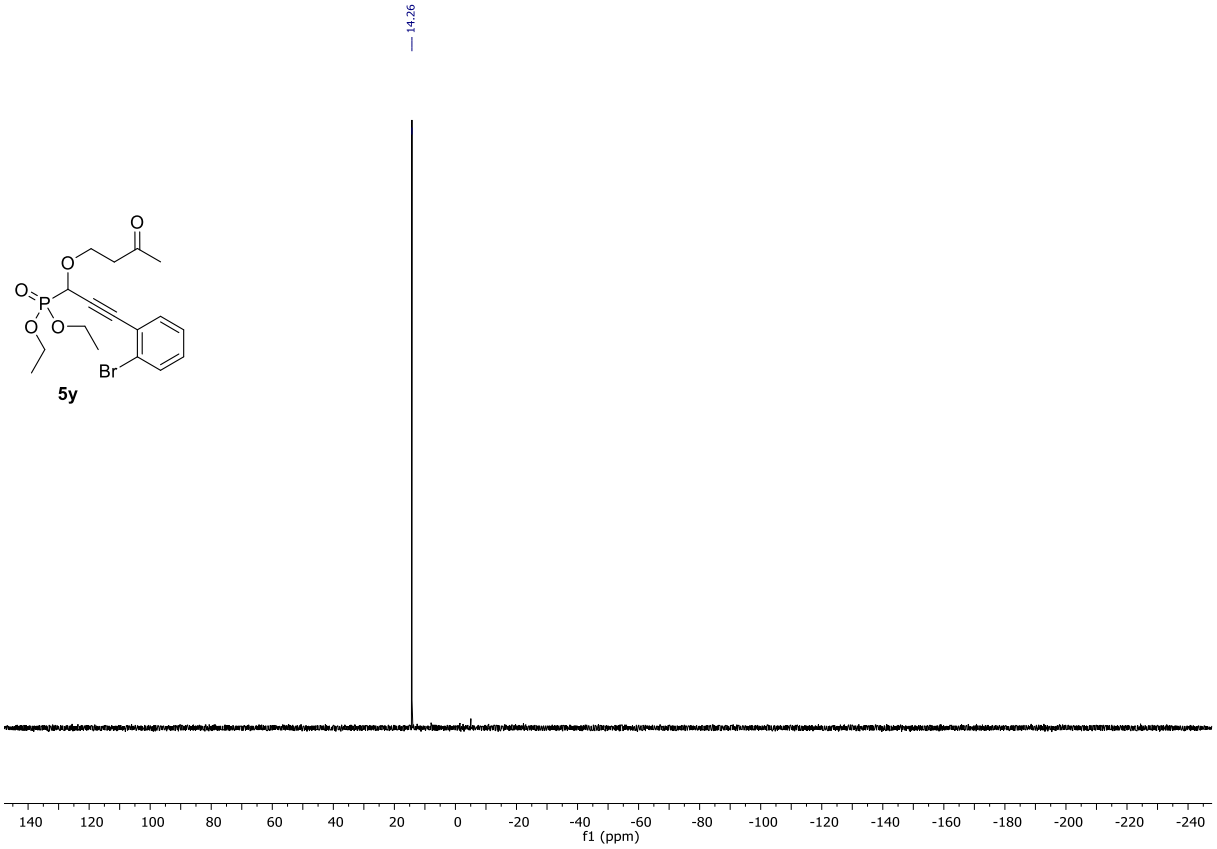
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5y**



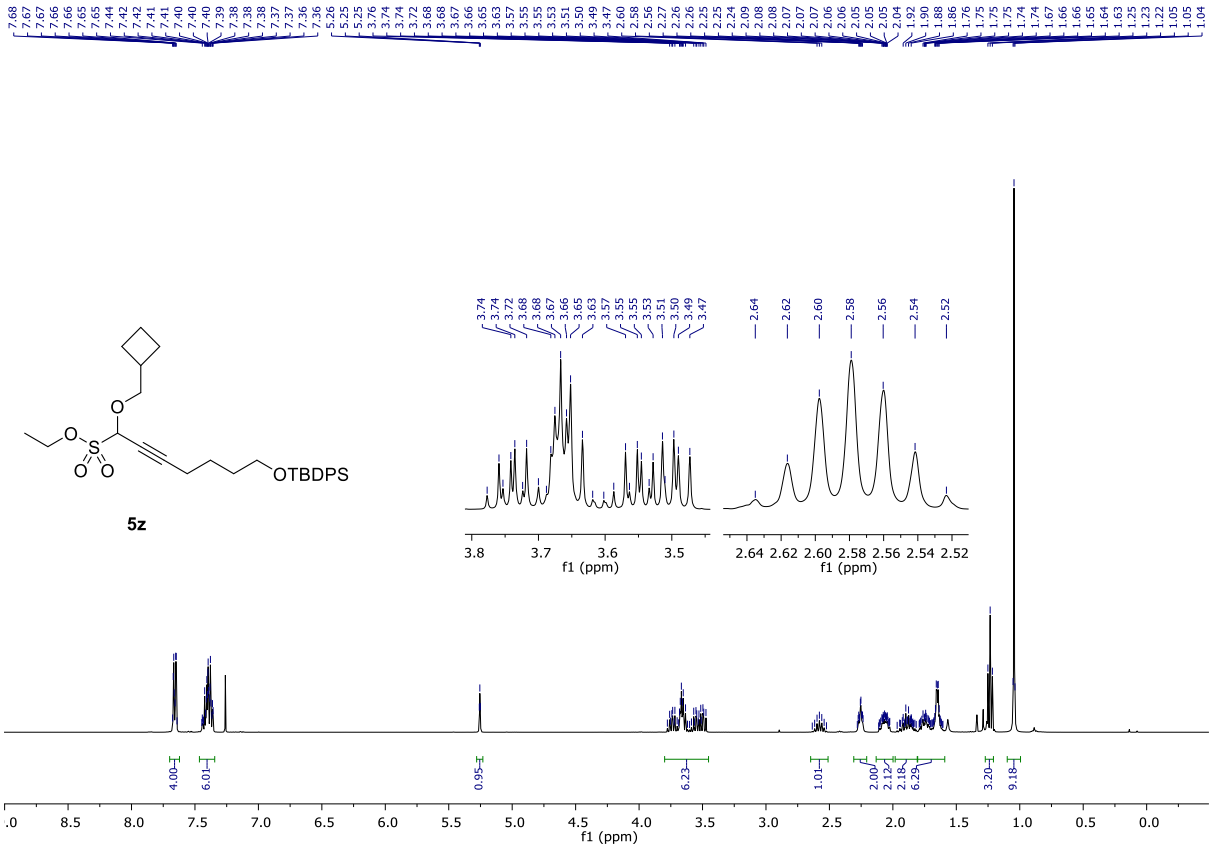
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5y**



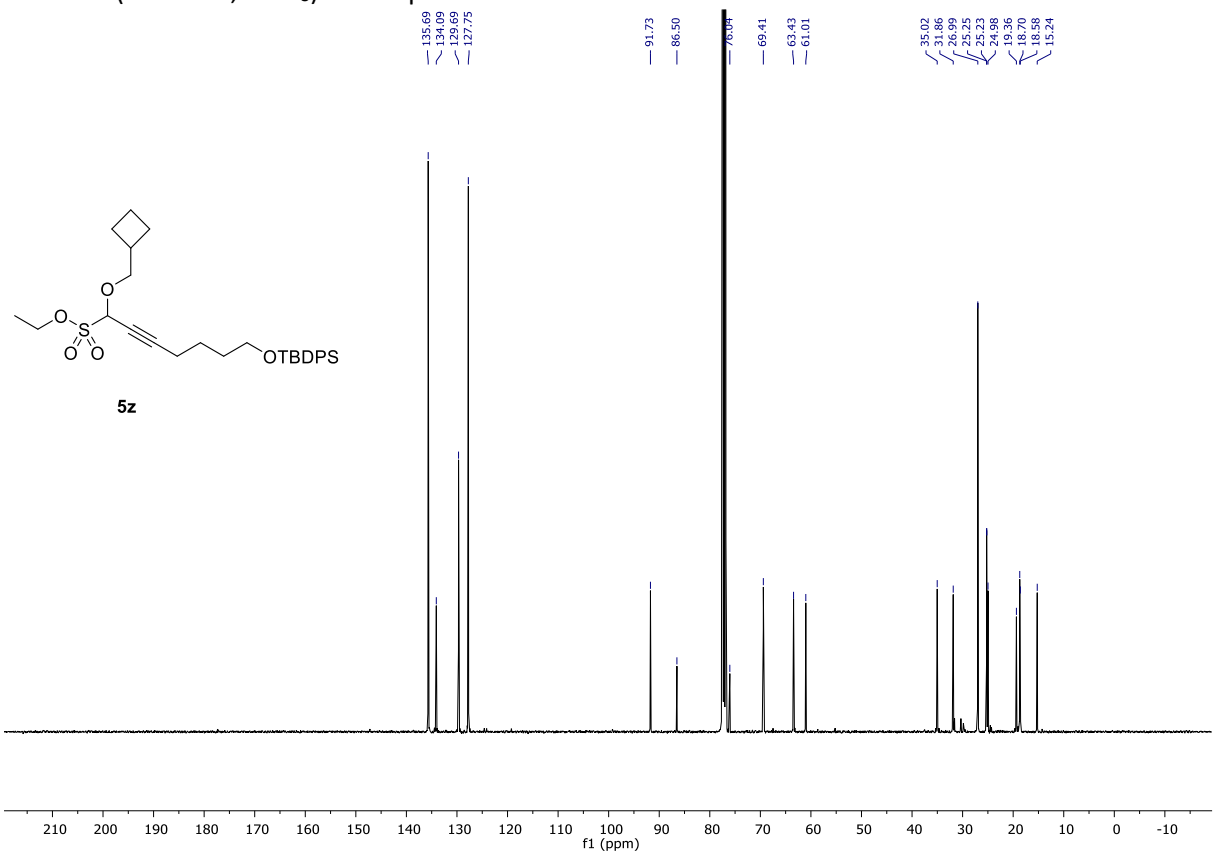
^{31}P-NMR (162 MHz, $CDCl_3$) of compound **5y**



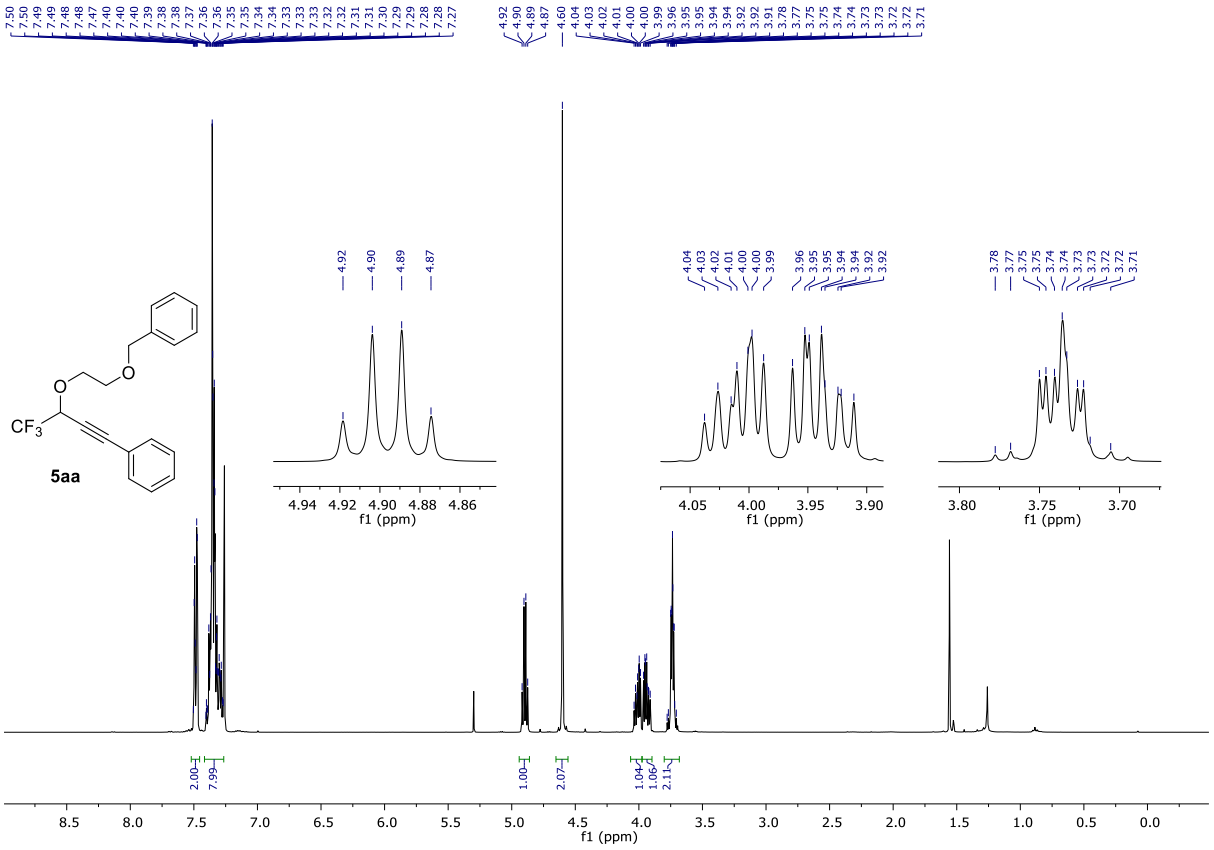
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5z**



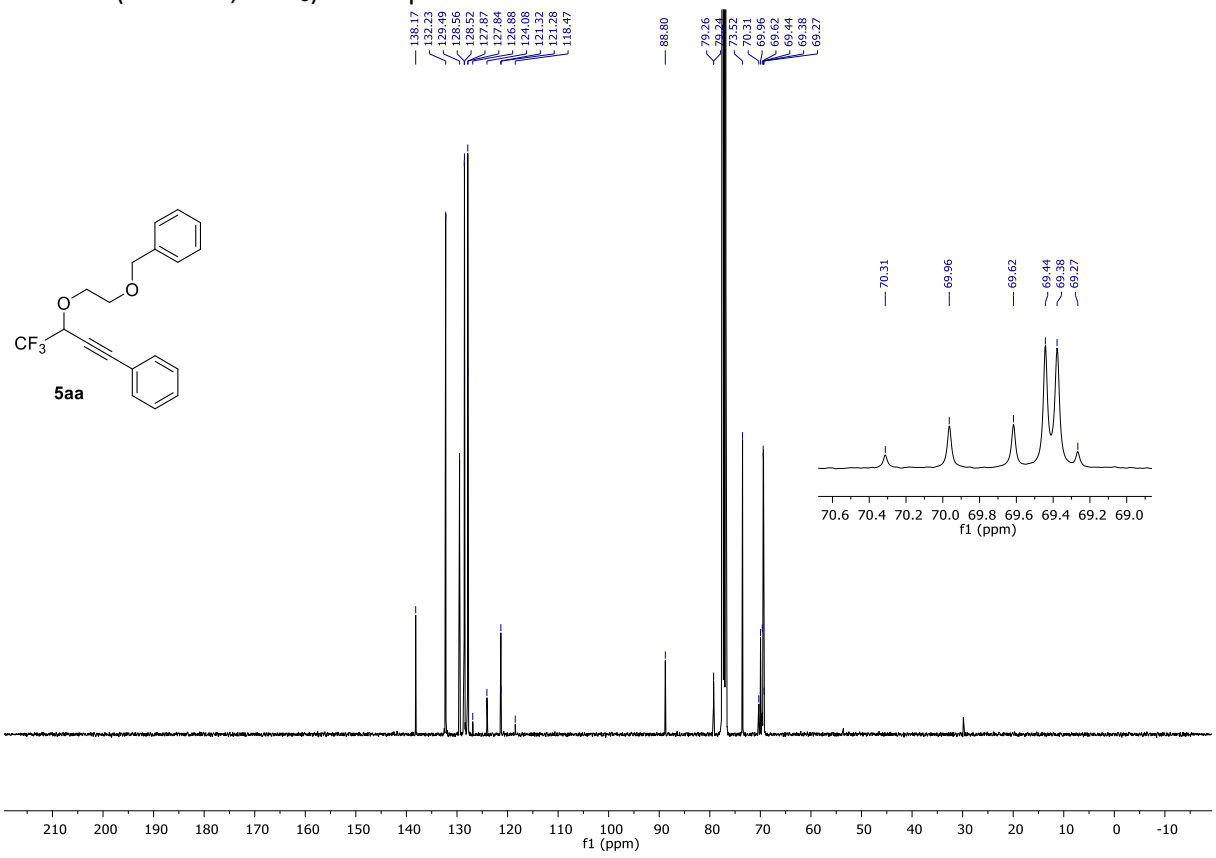
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5z**



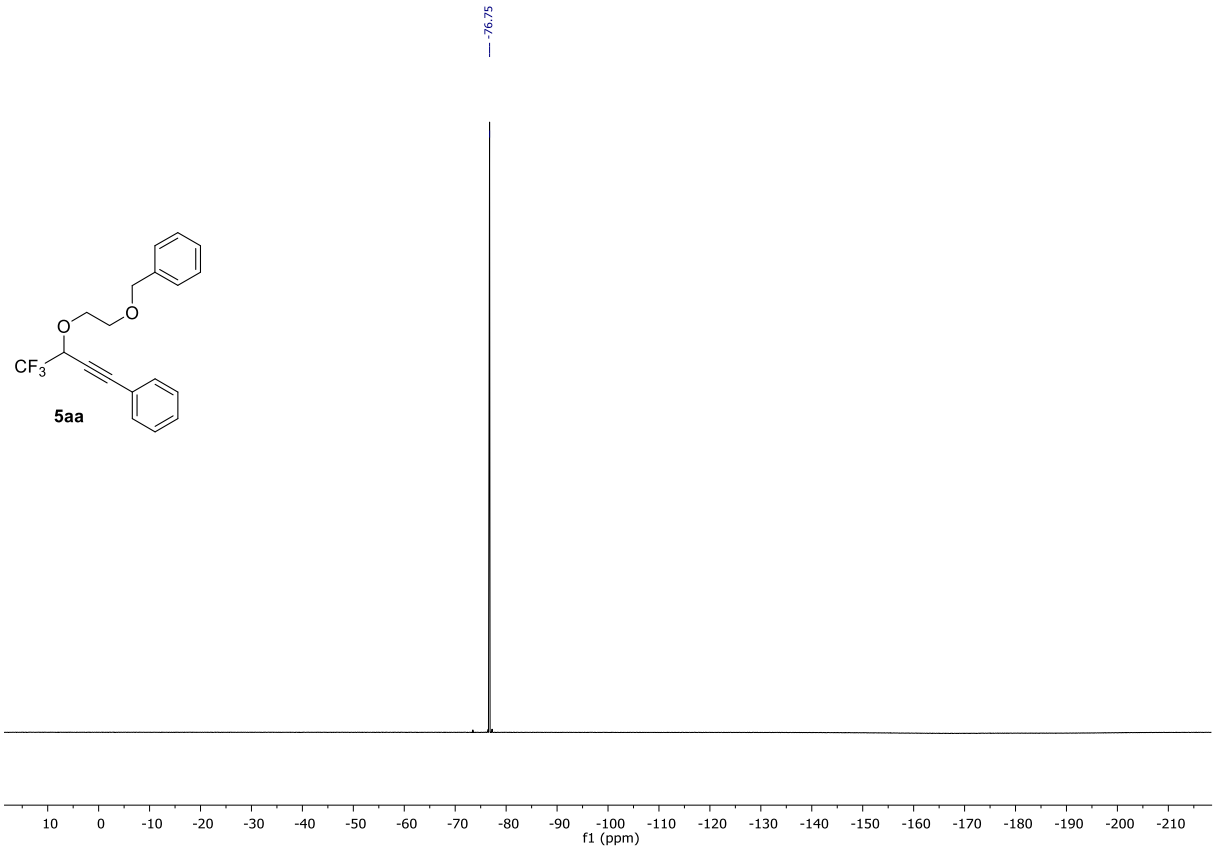
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5aa**



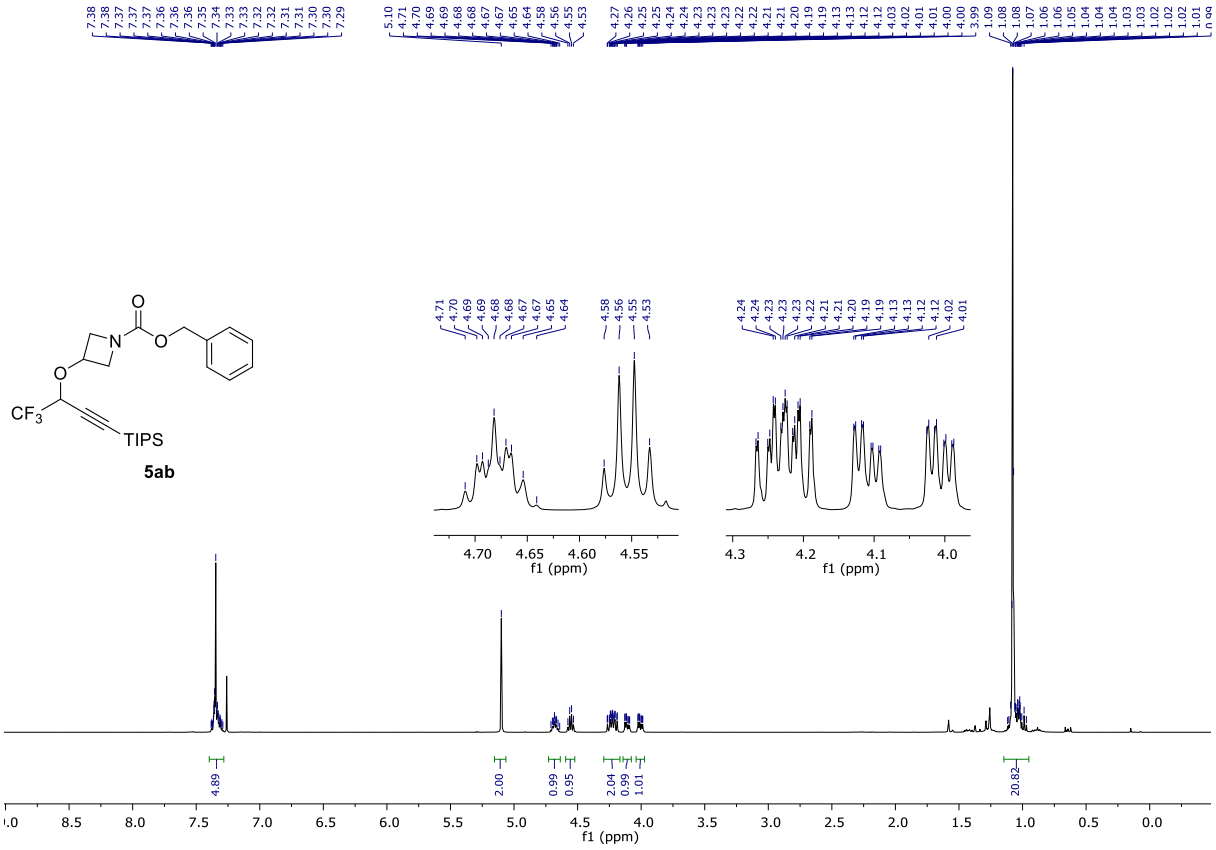
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5aa**



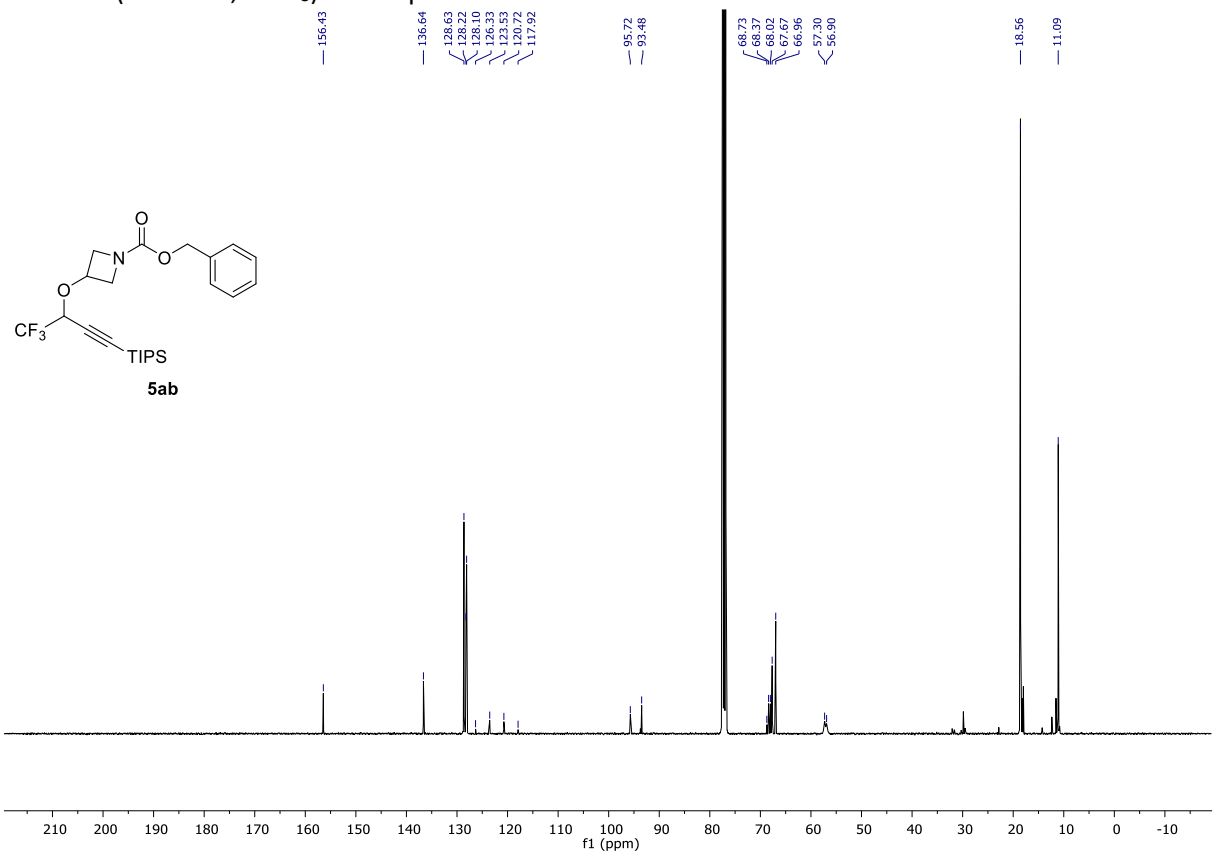
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5aa**



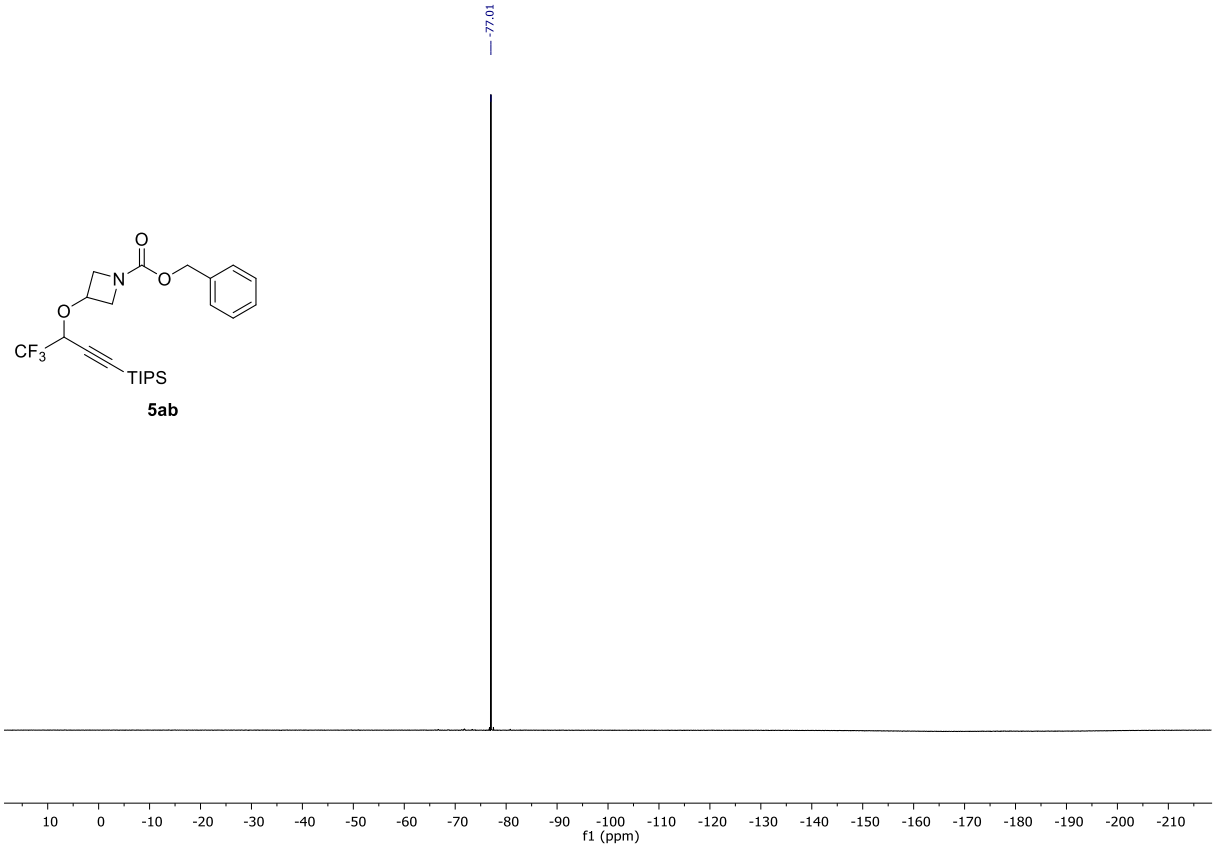
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ab**



^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ab**

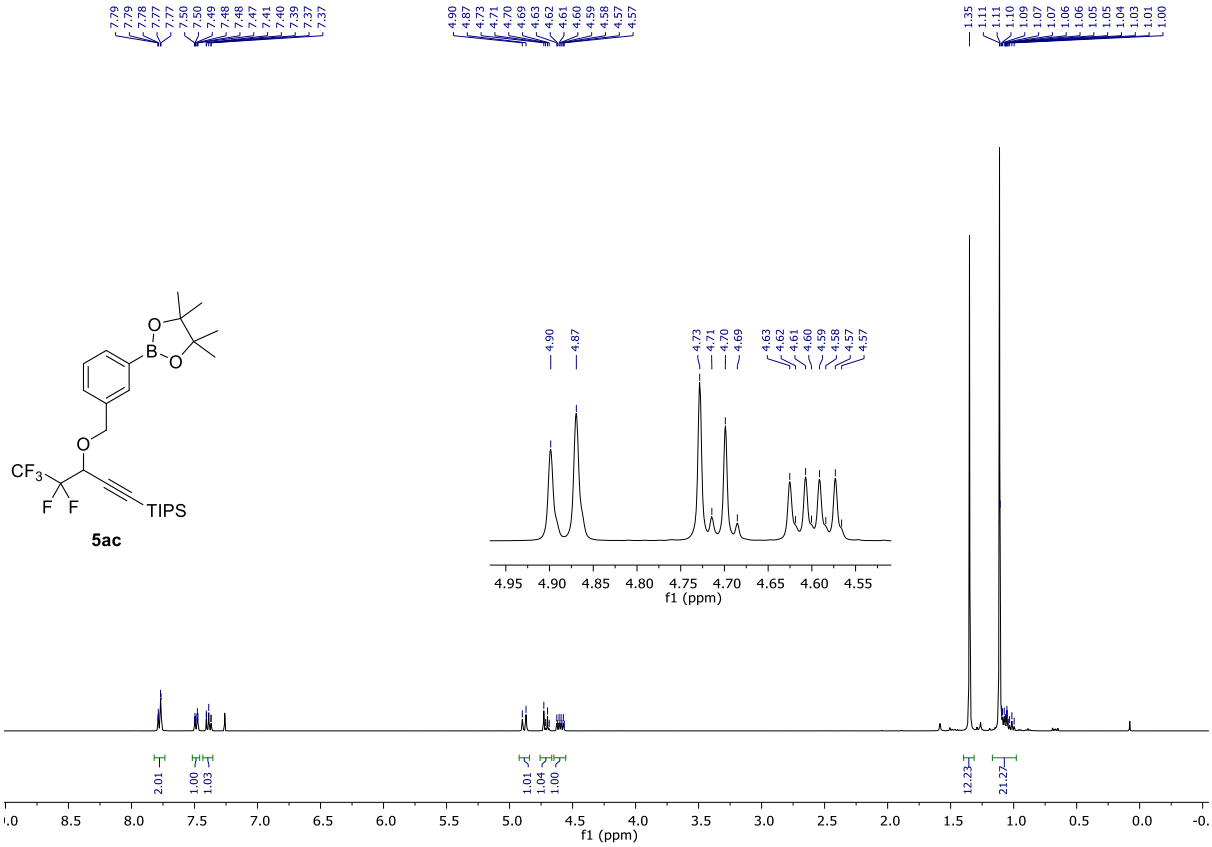


^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5ab**

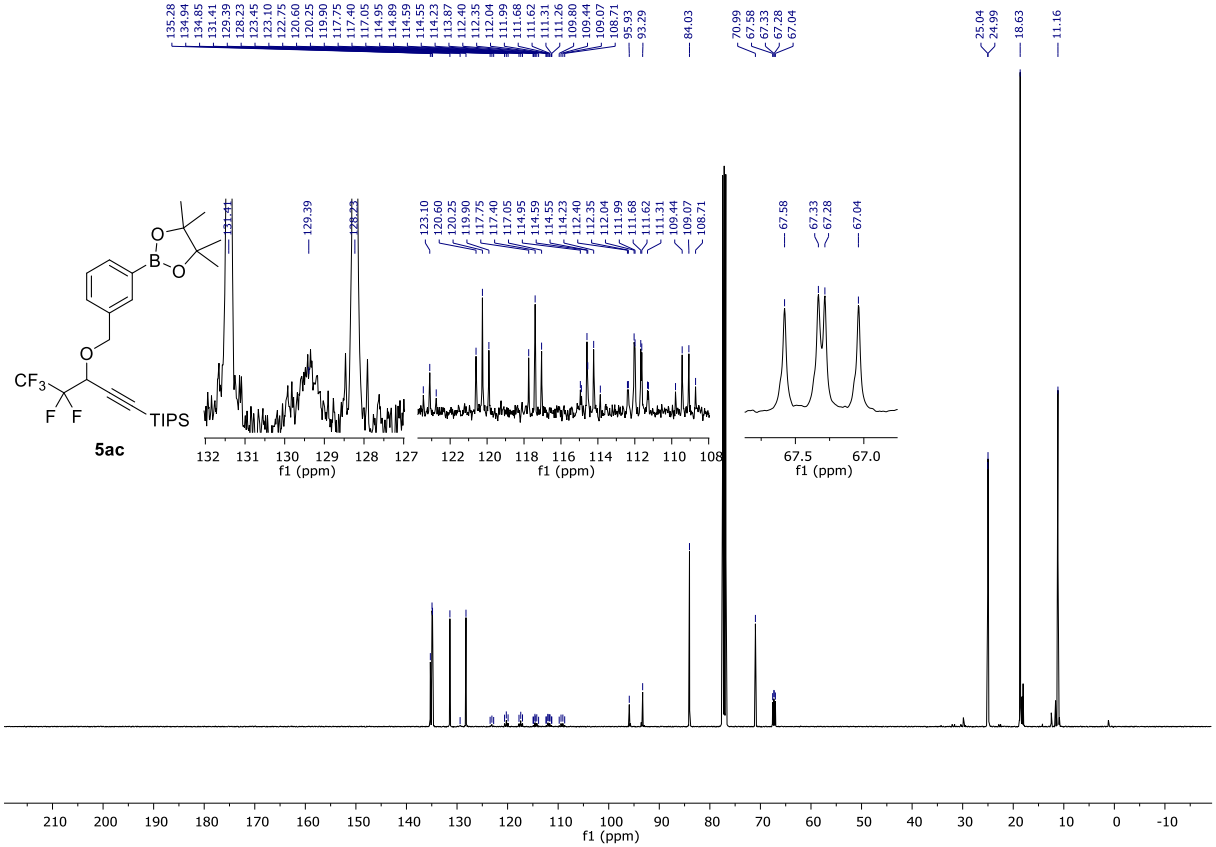


5ab

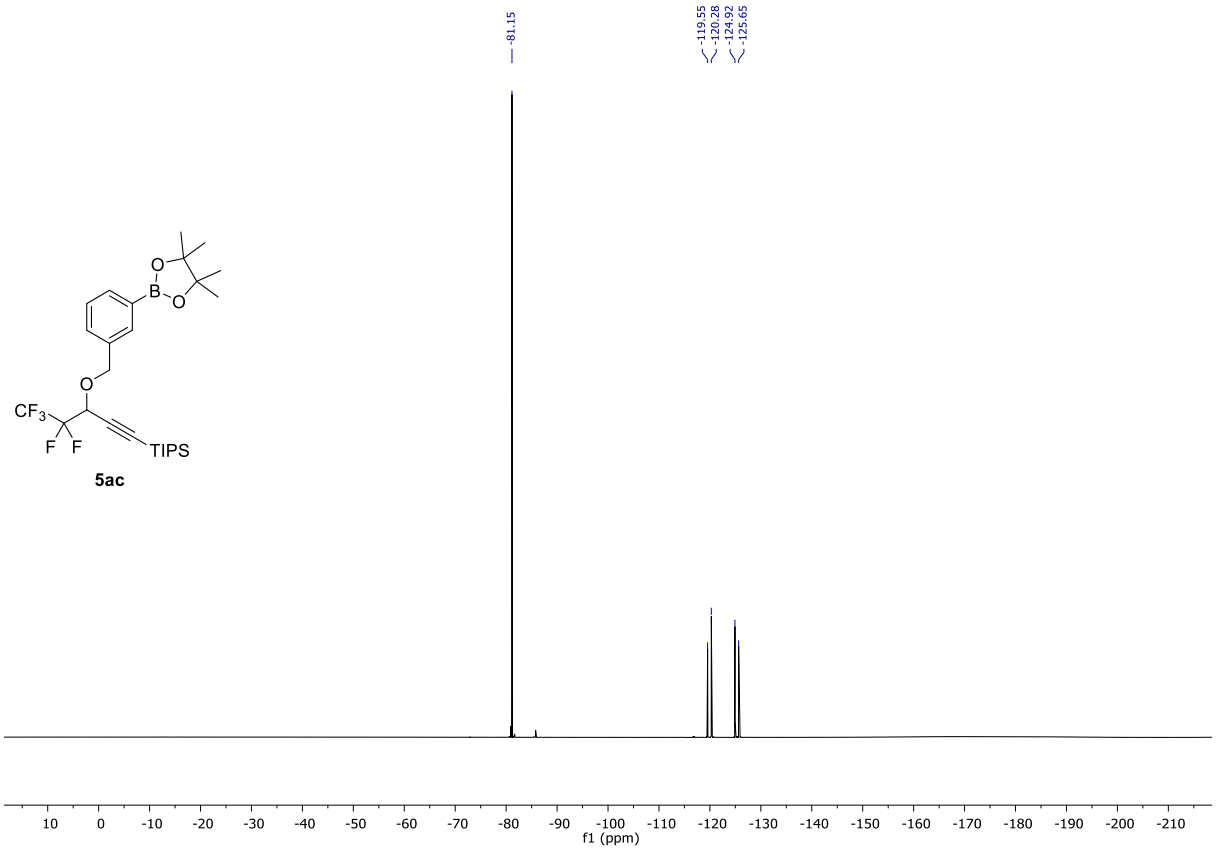
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ac**



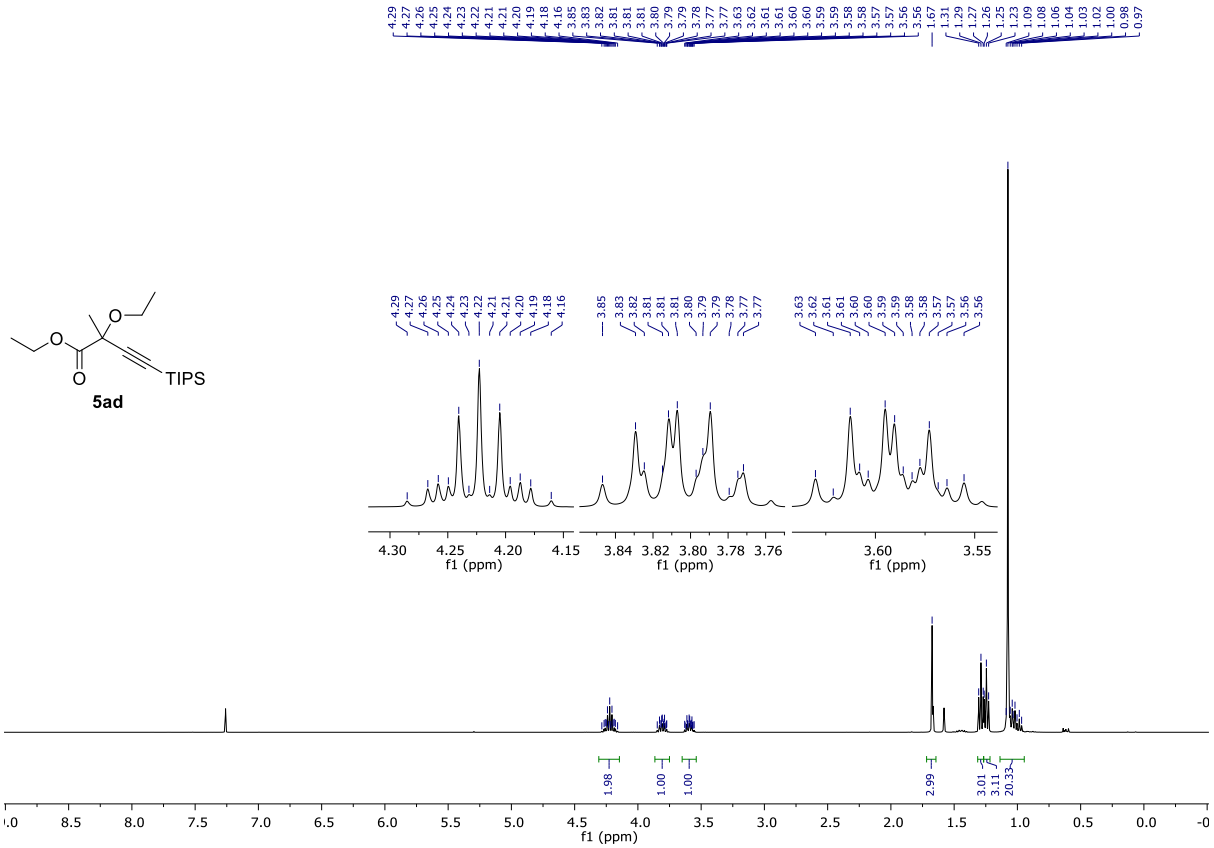
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ac**



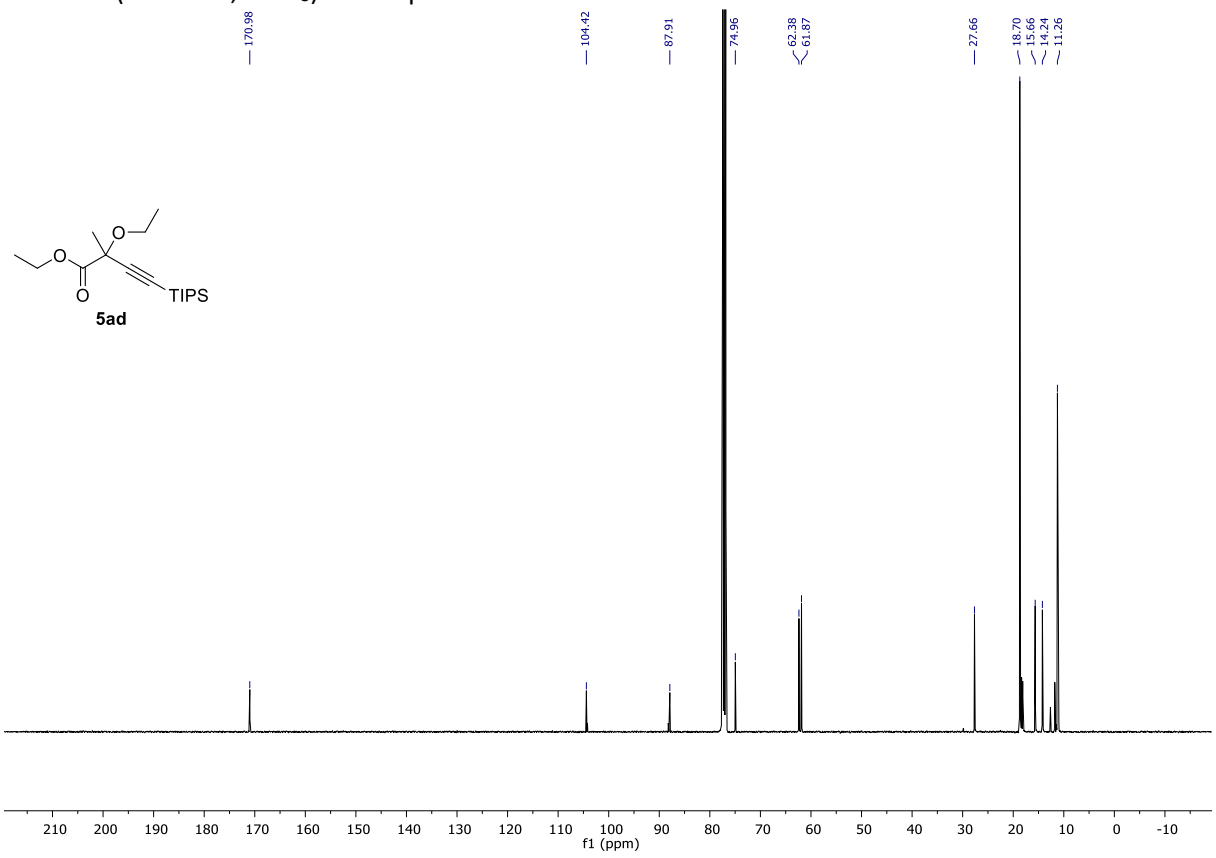
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5ac**



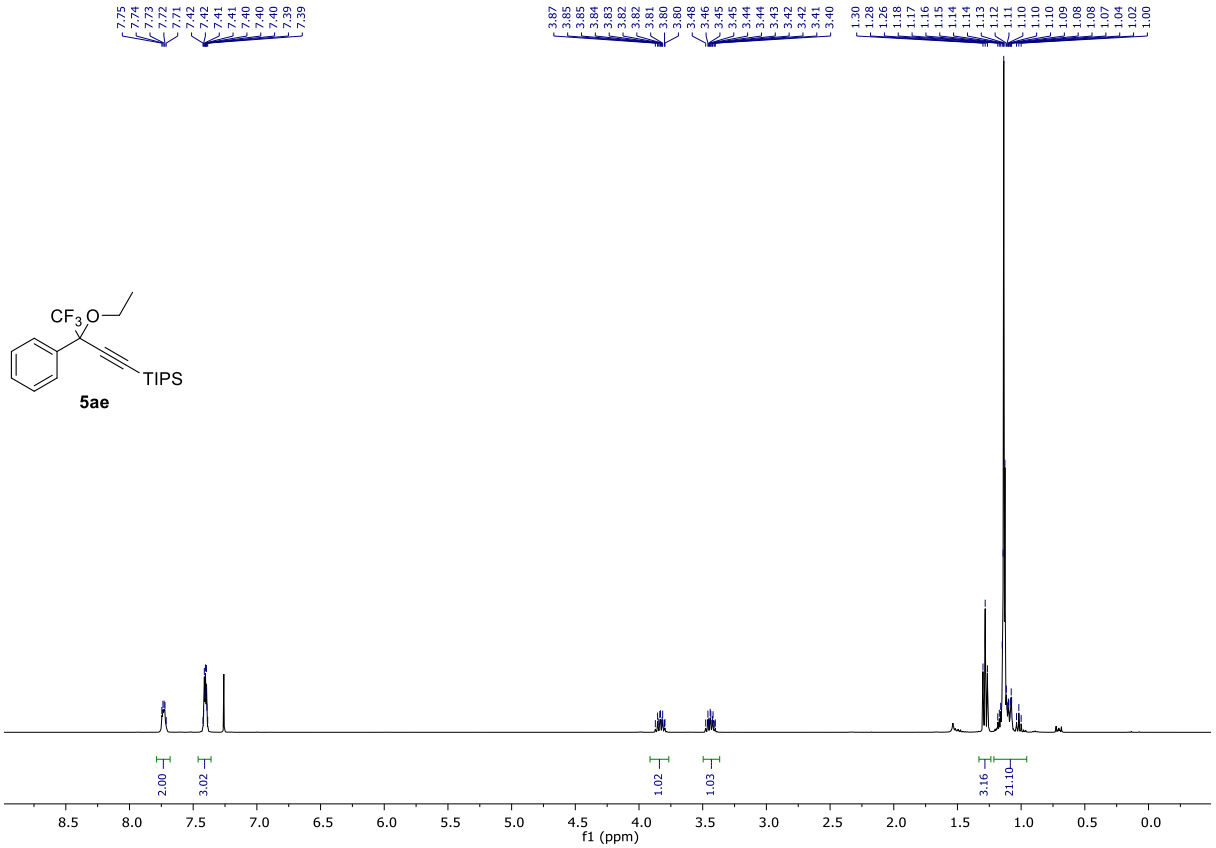
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ad**



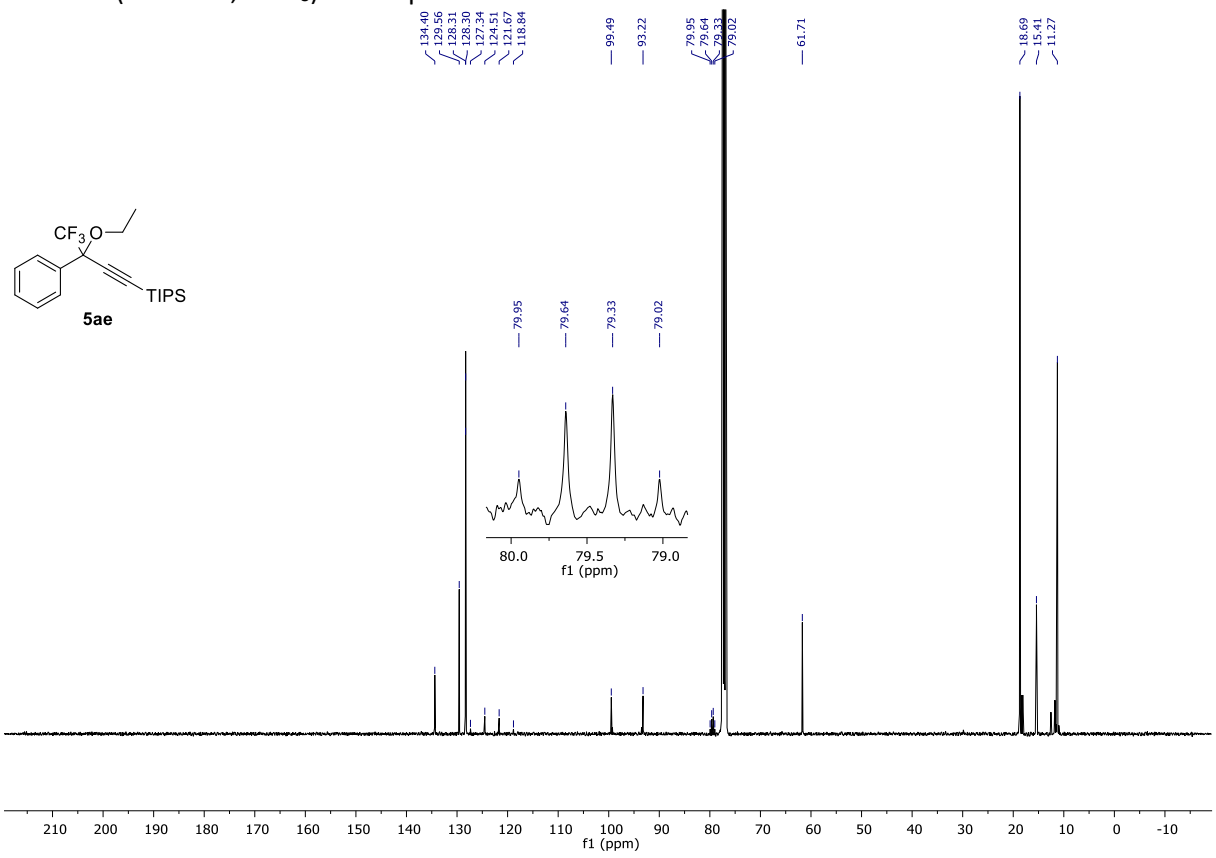
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ad**



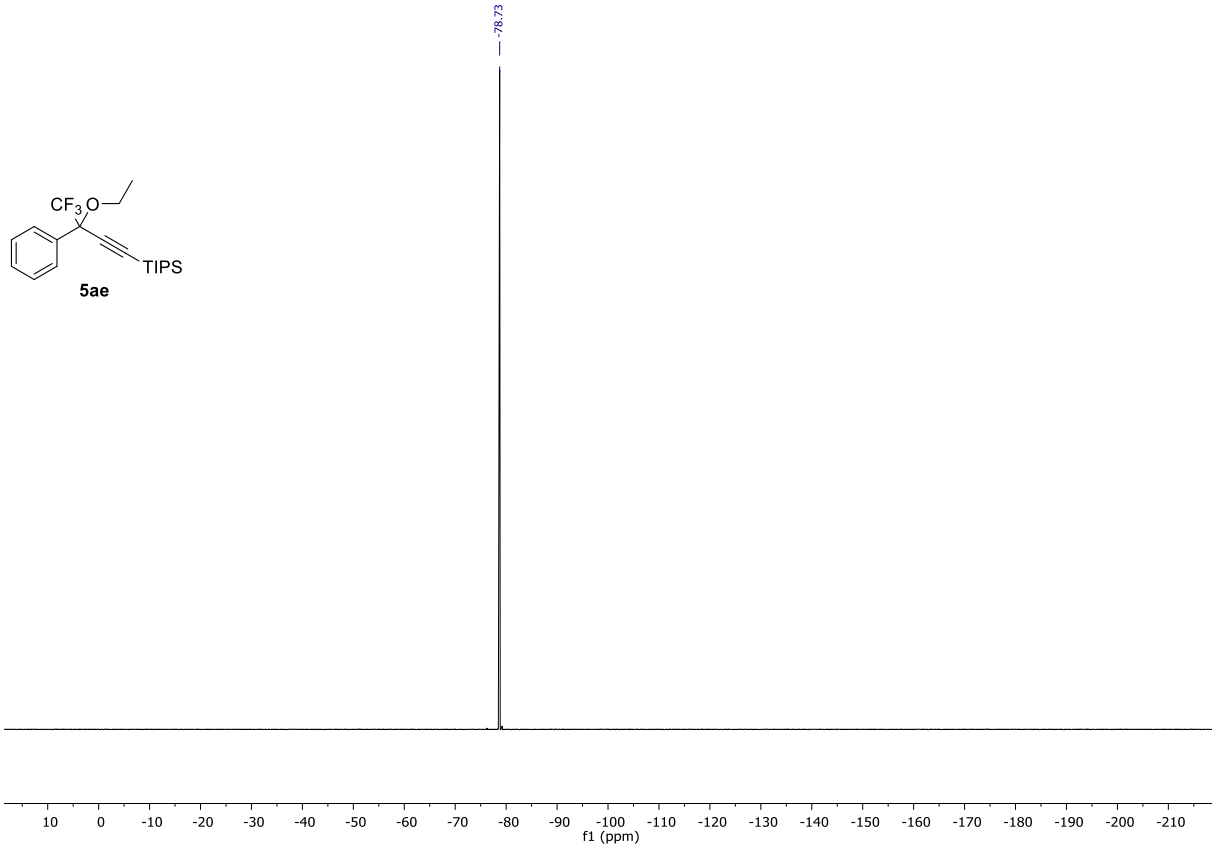
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ae**



^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ae**



^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5ae**



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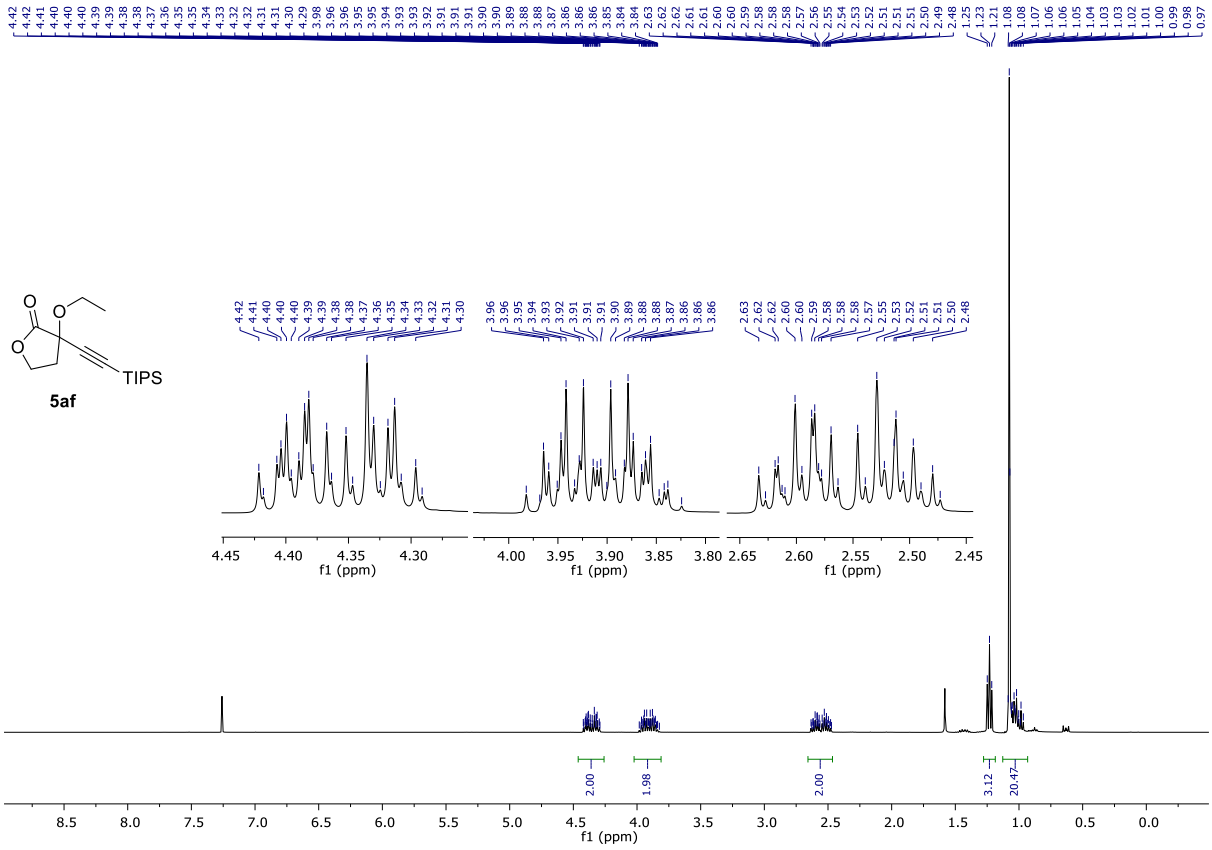
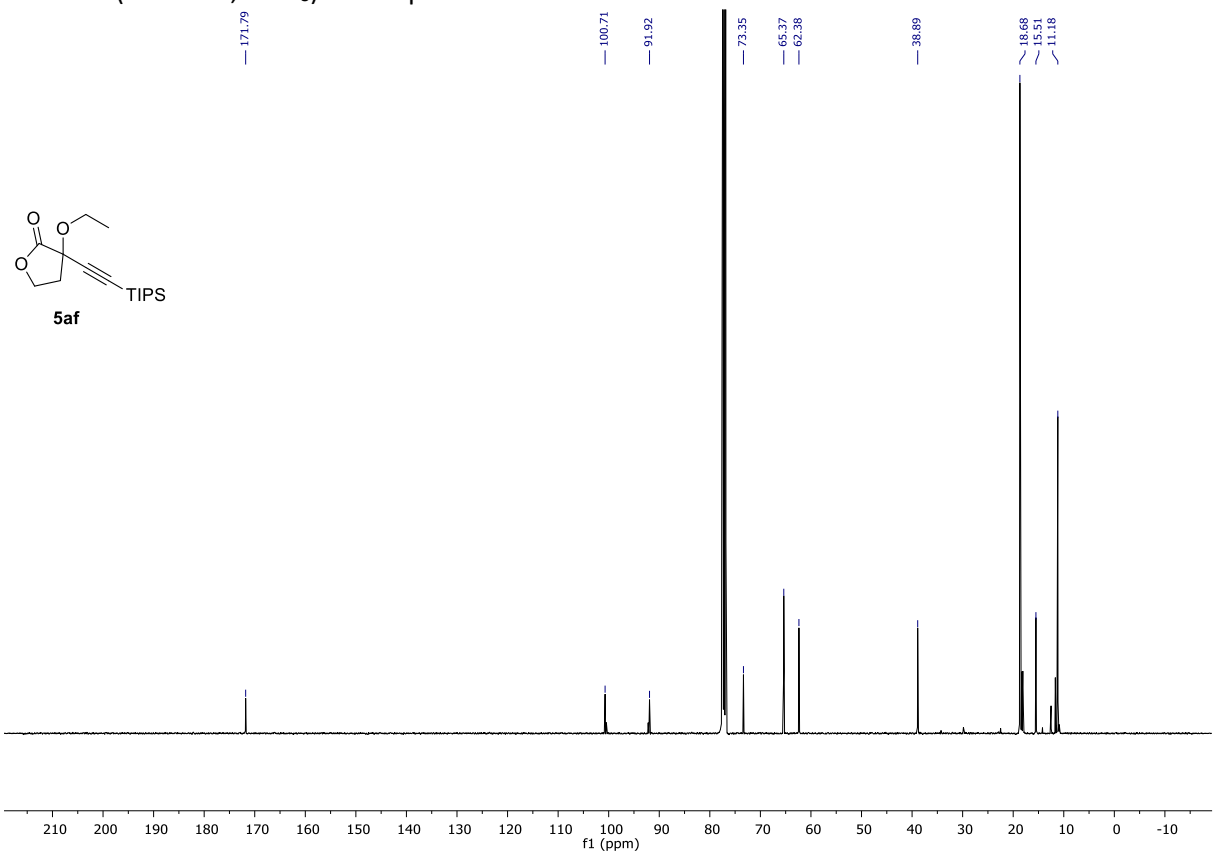
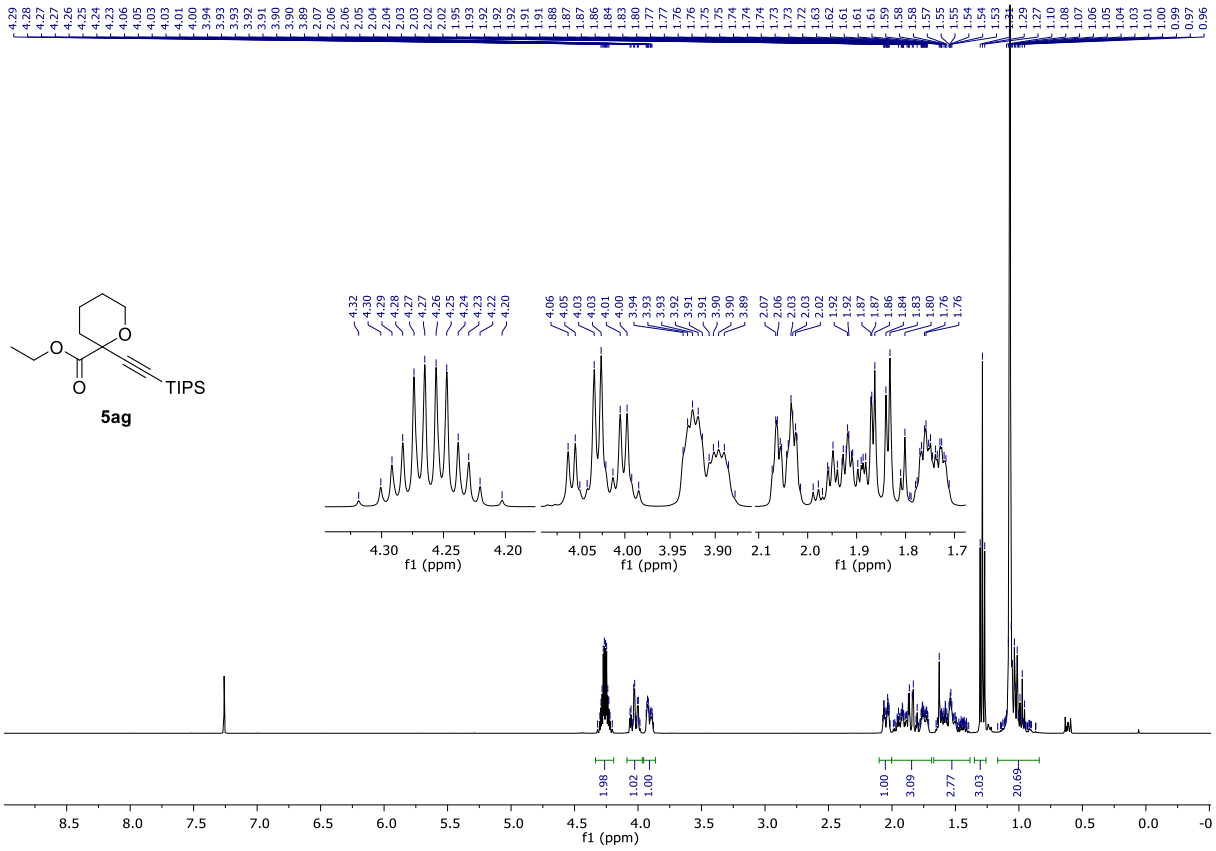


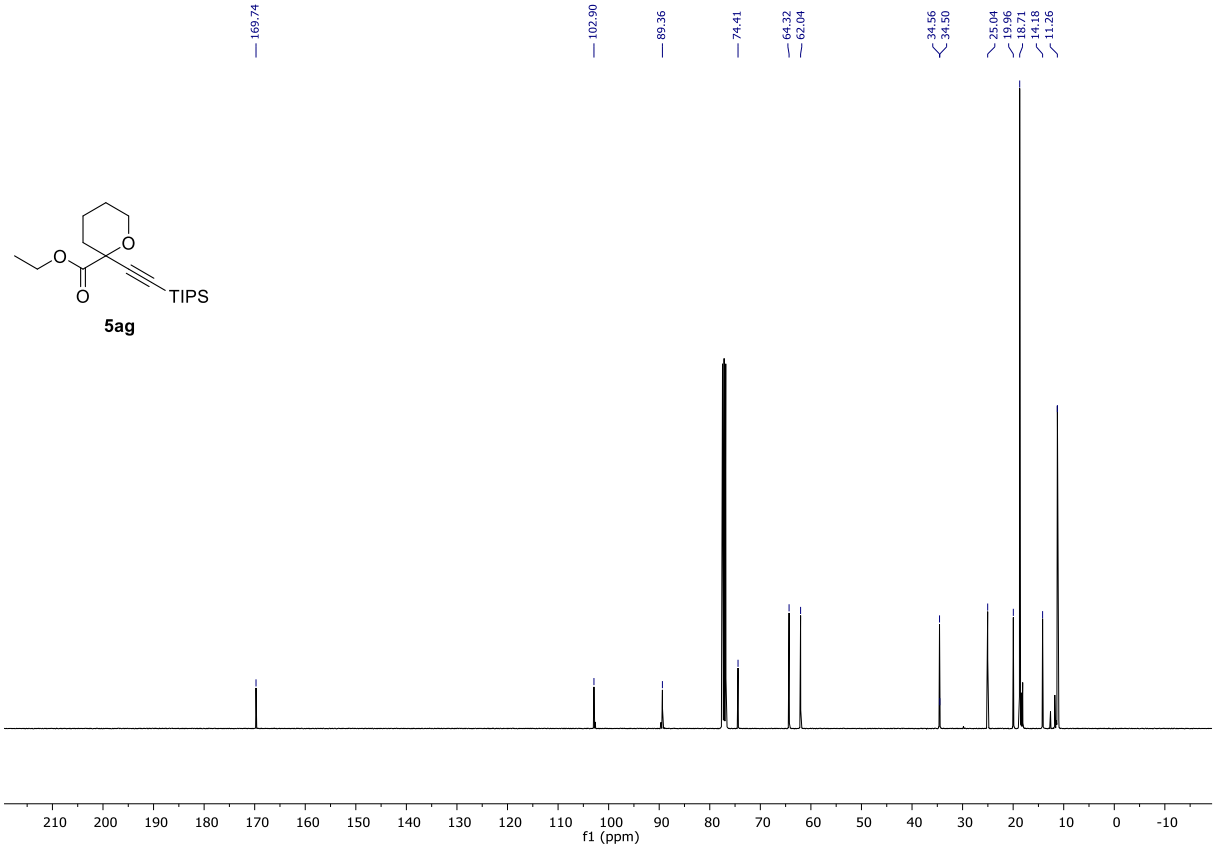
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5af**



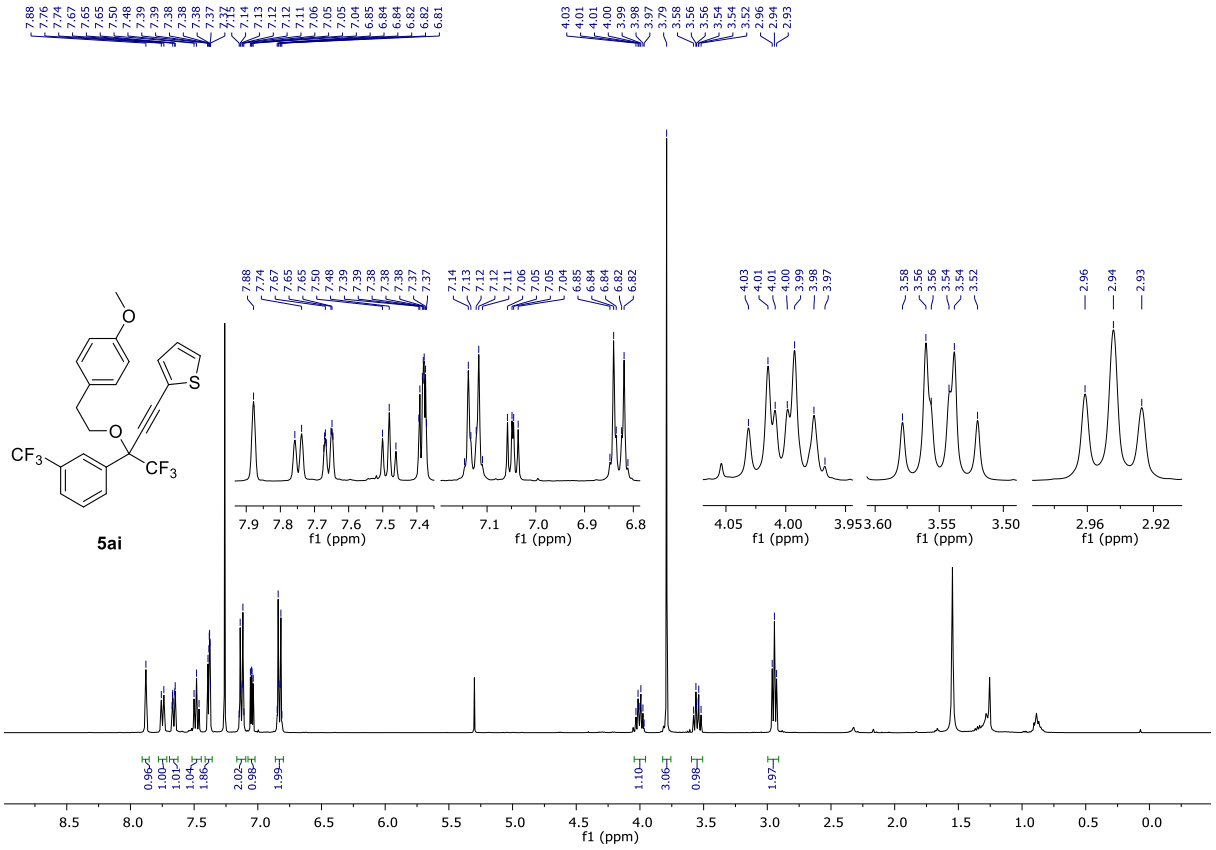
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ag**



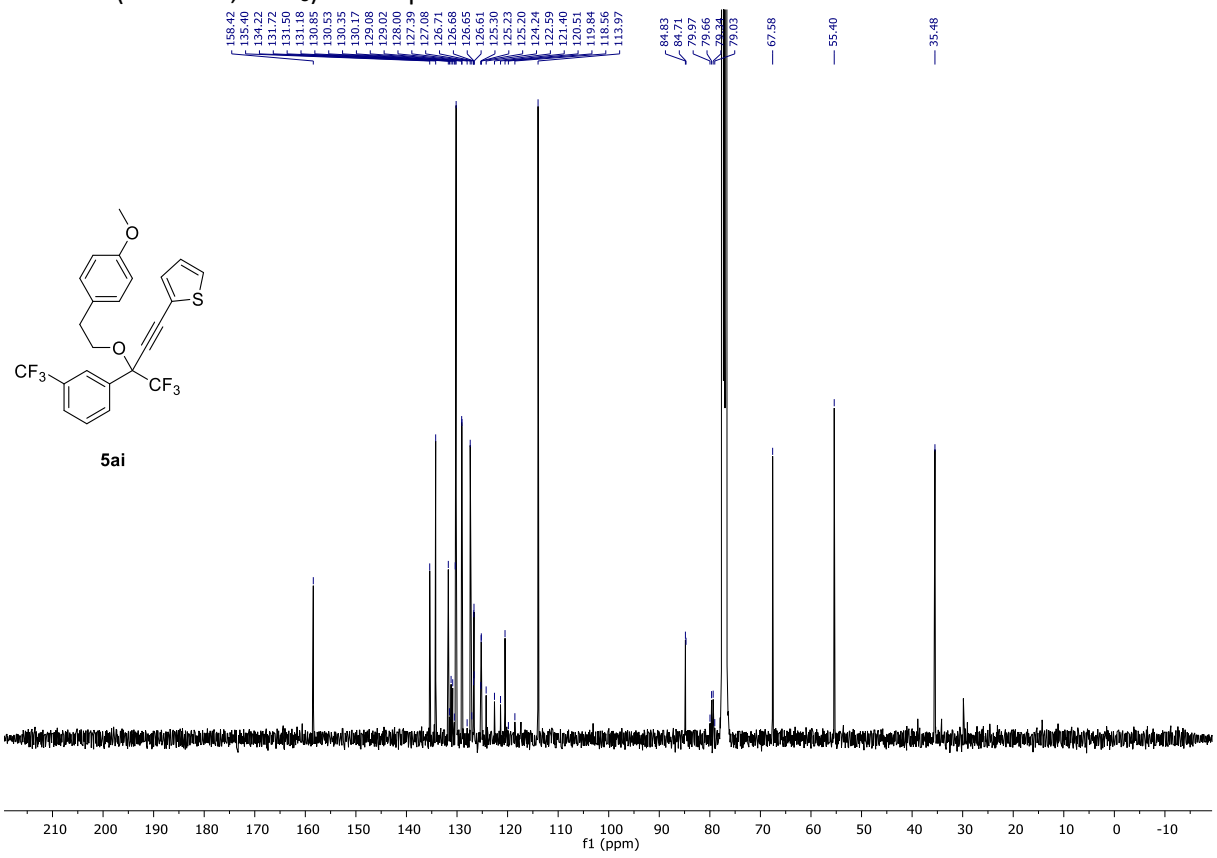
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ag**



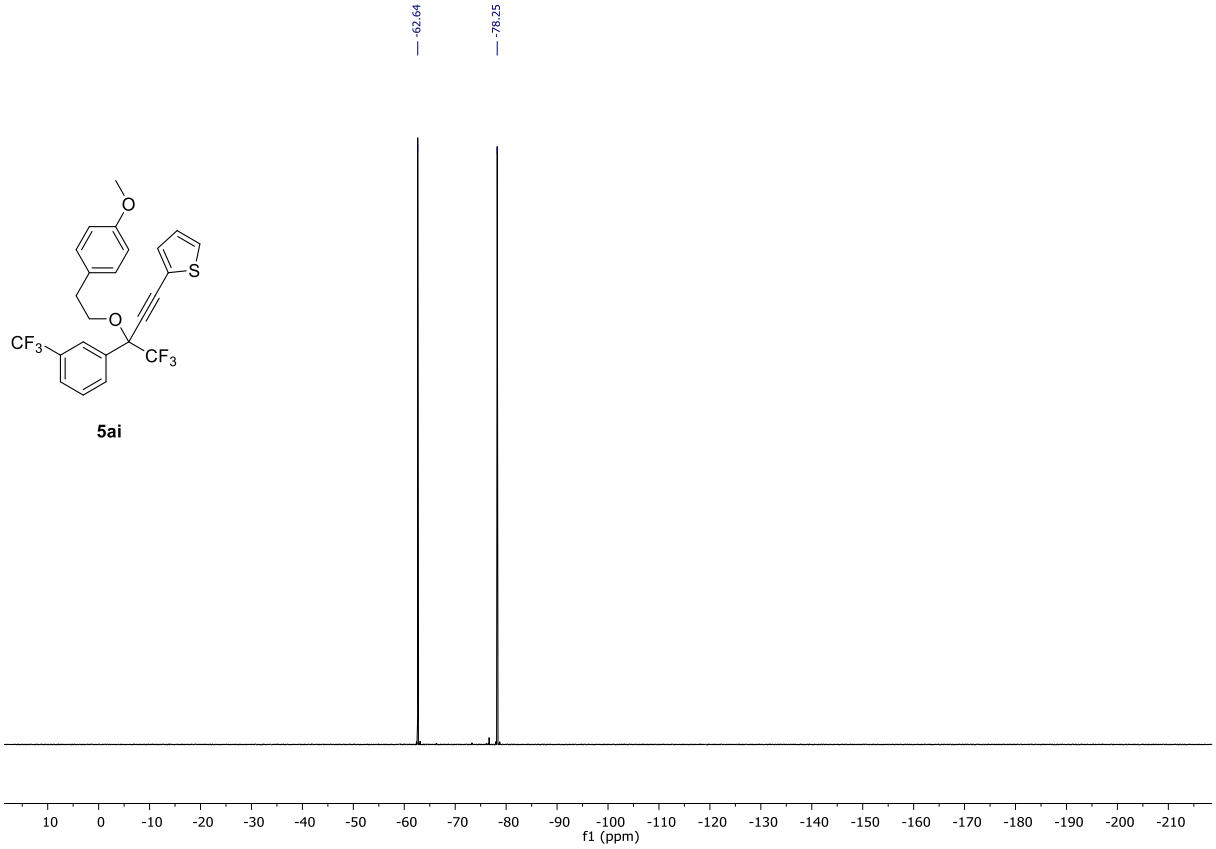
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ai**



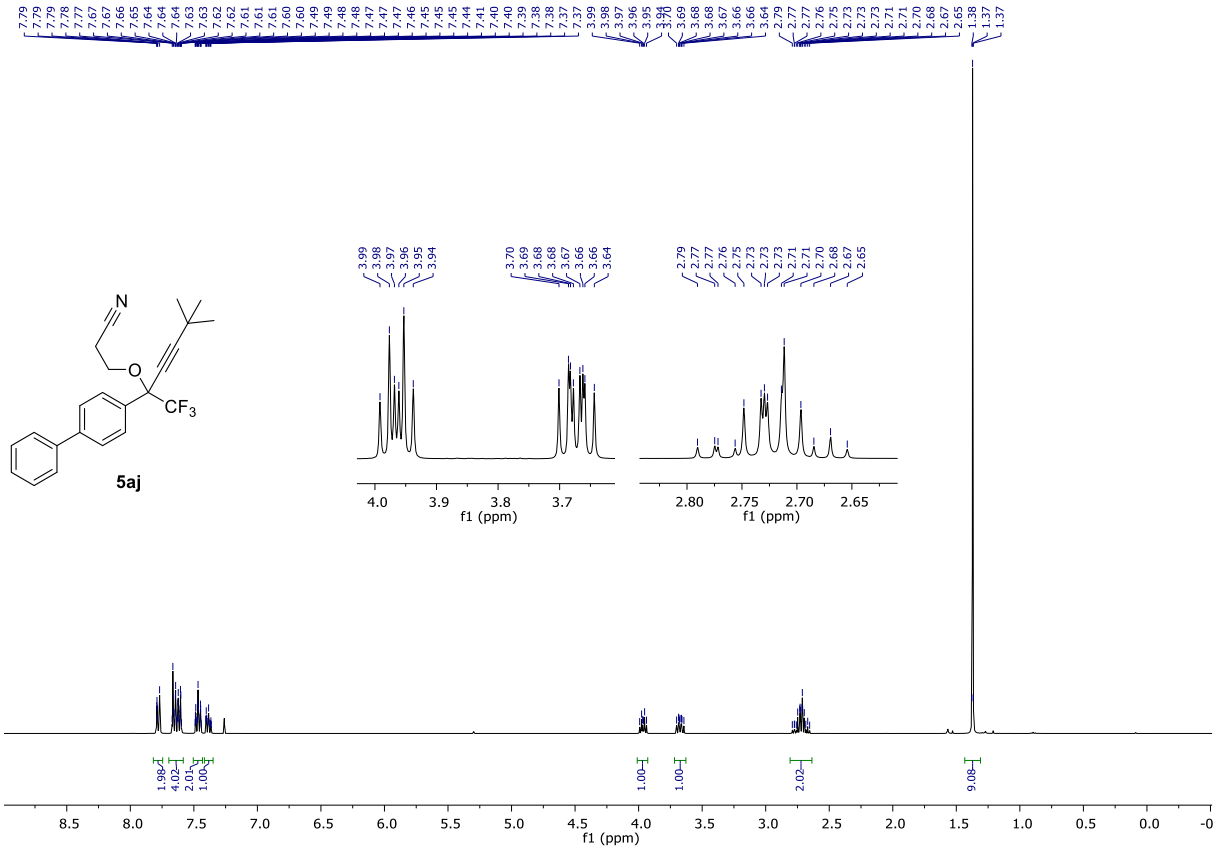
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ai**



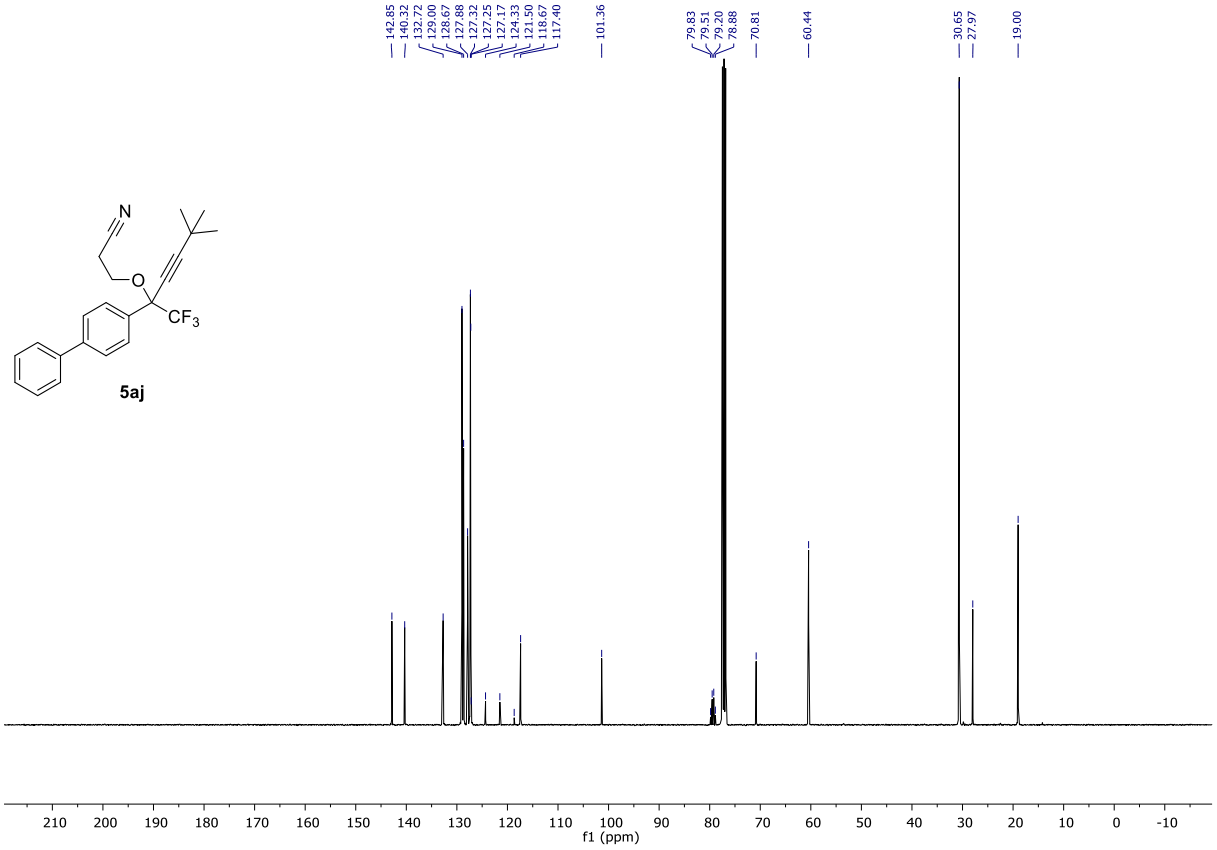
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5ai**



^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5aj**



^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5aj**



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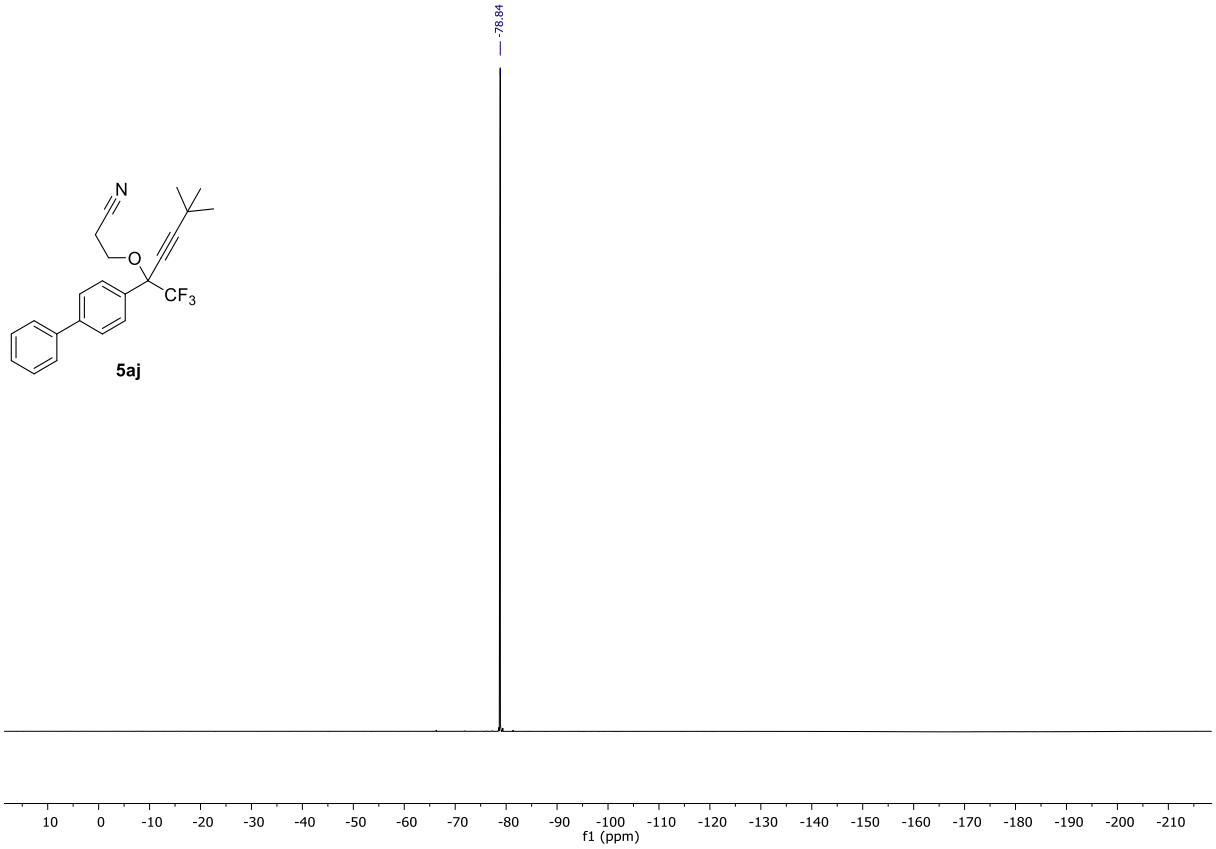
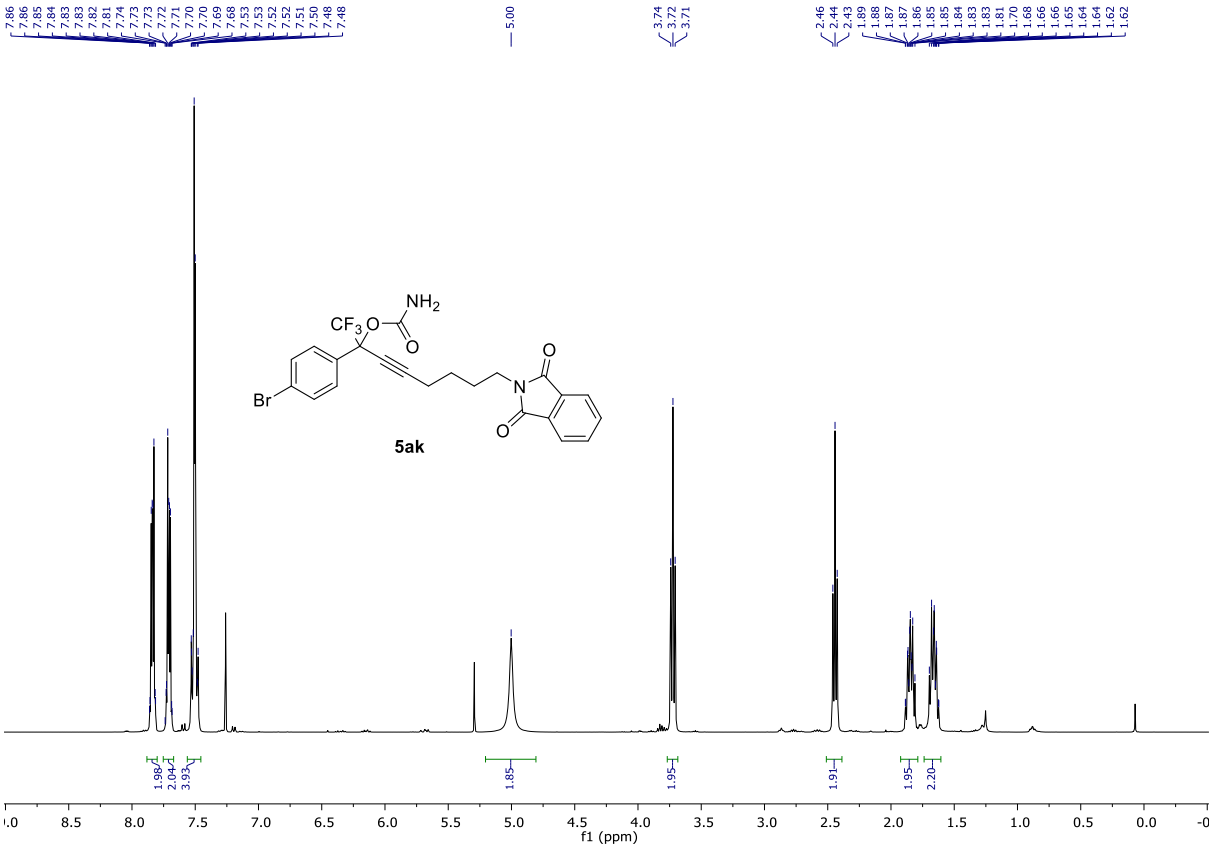
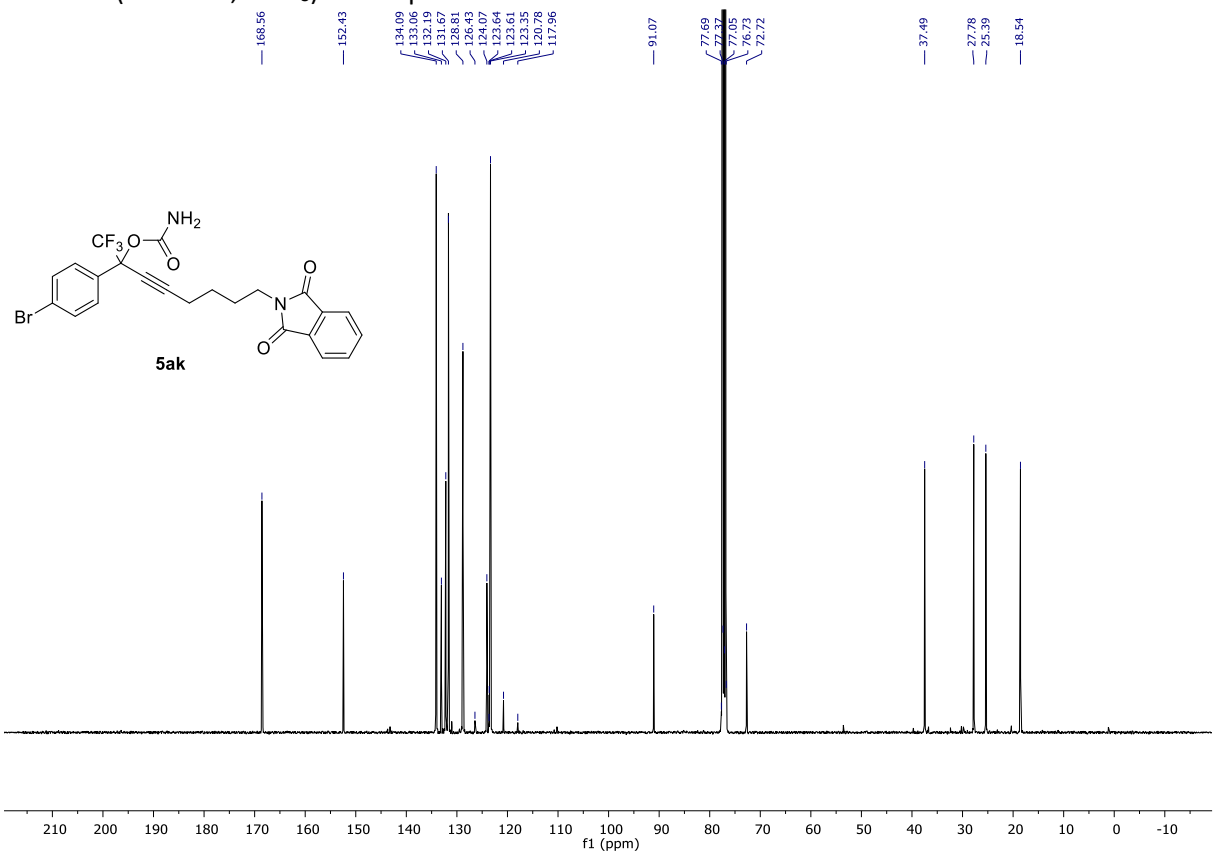


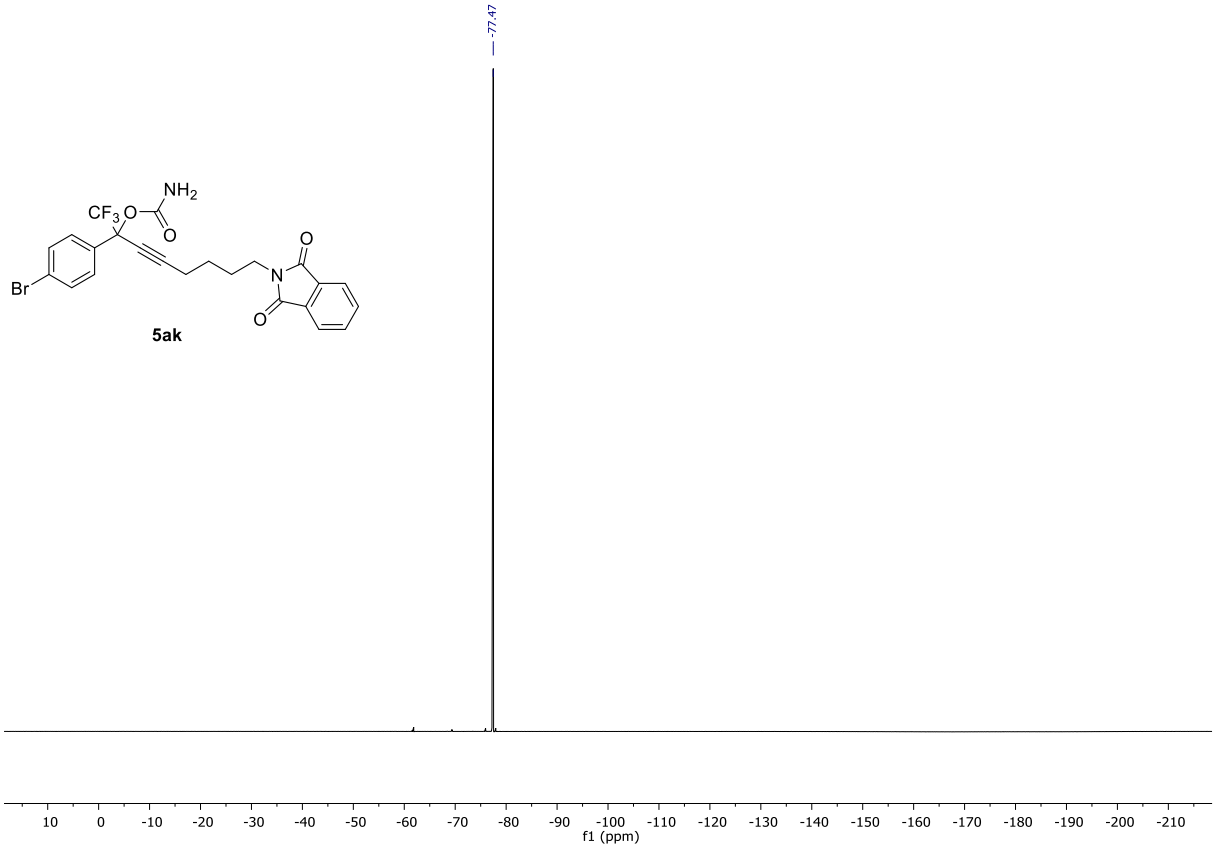
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **5ak**



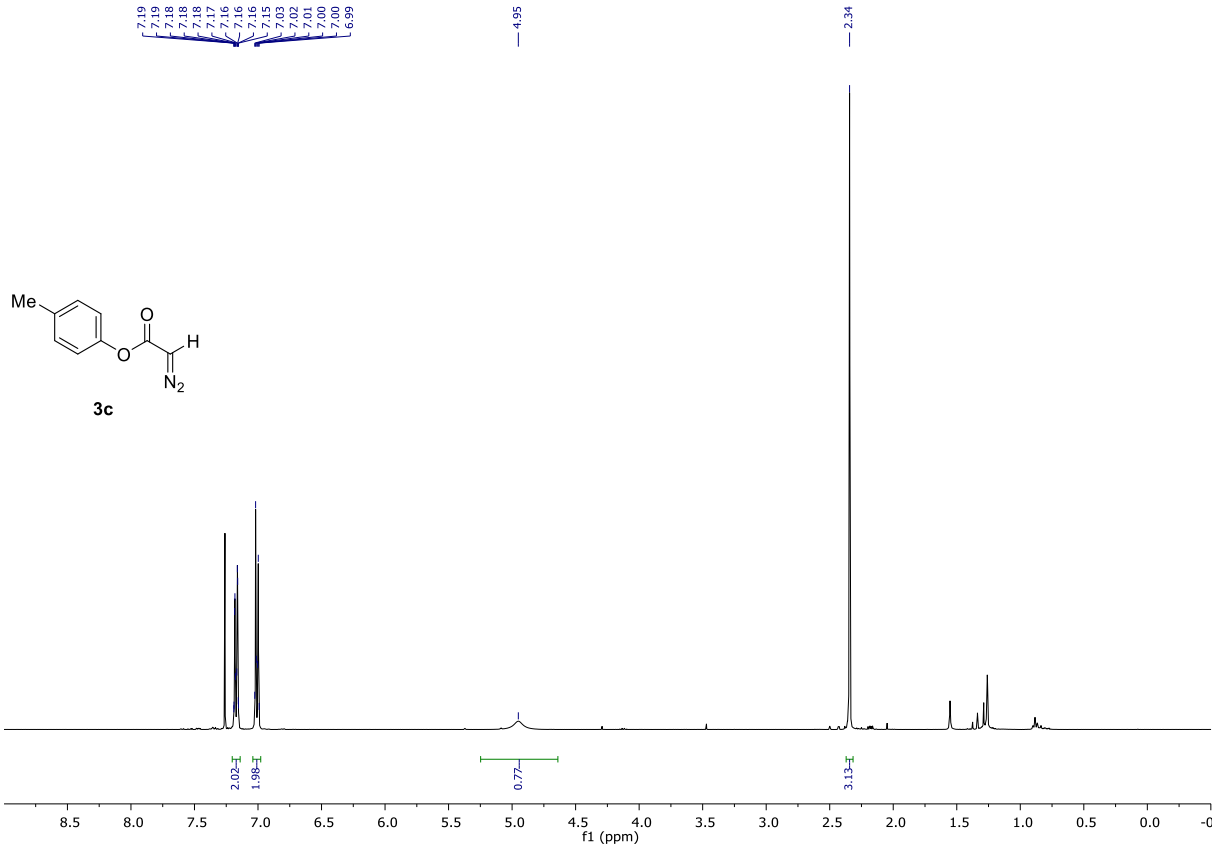
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **5ak**



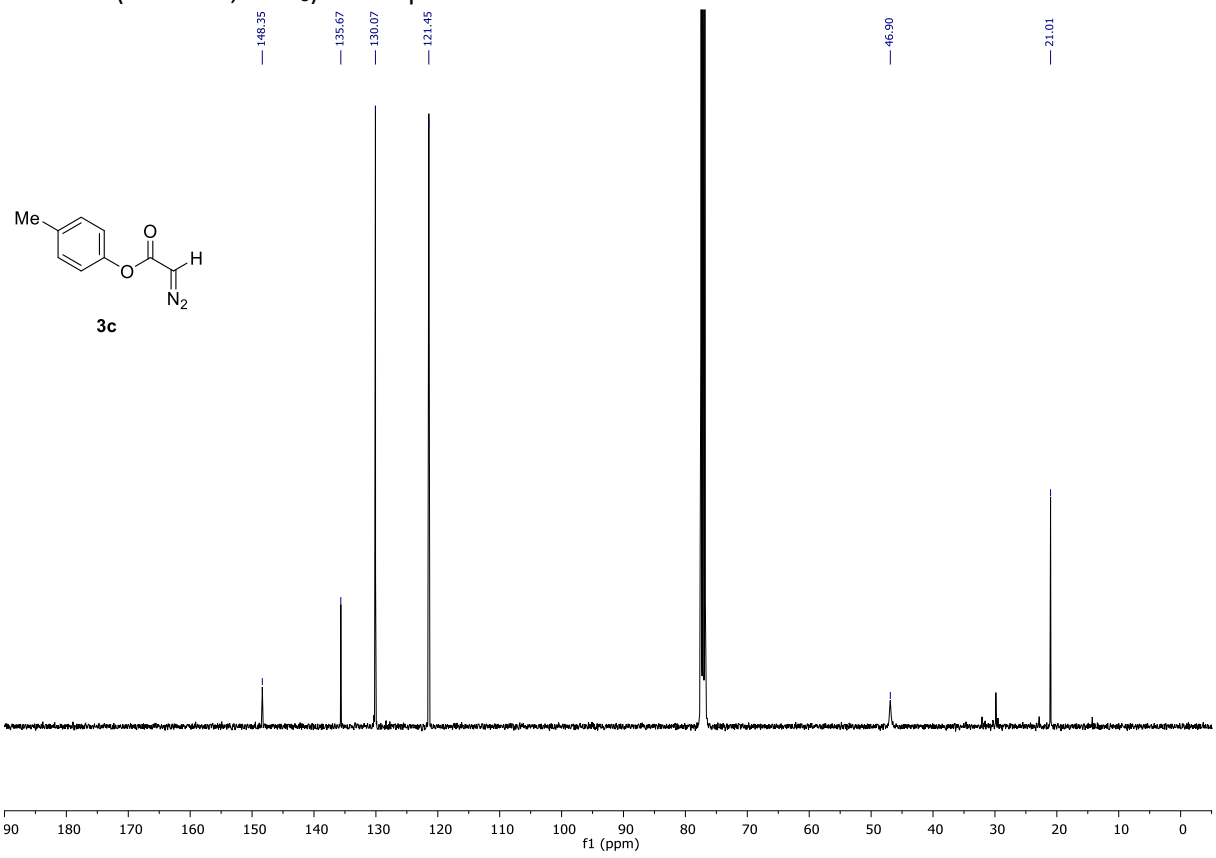
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **5ak**



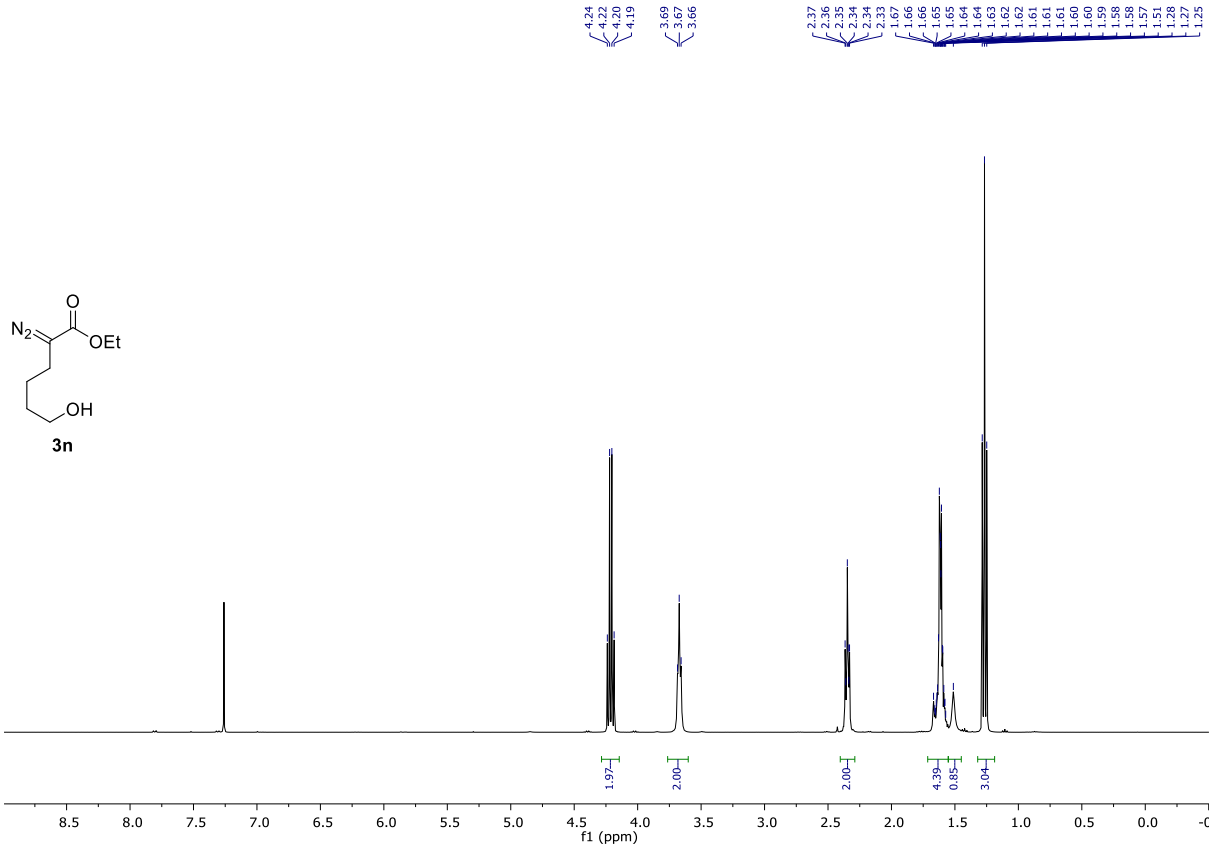
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **3c**



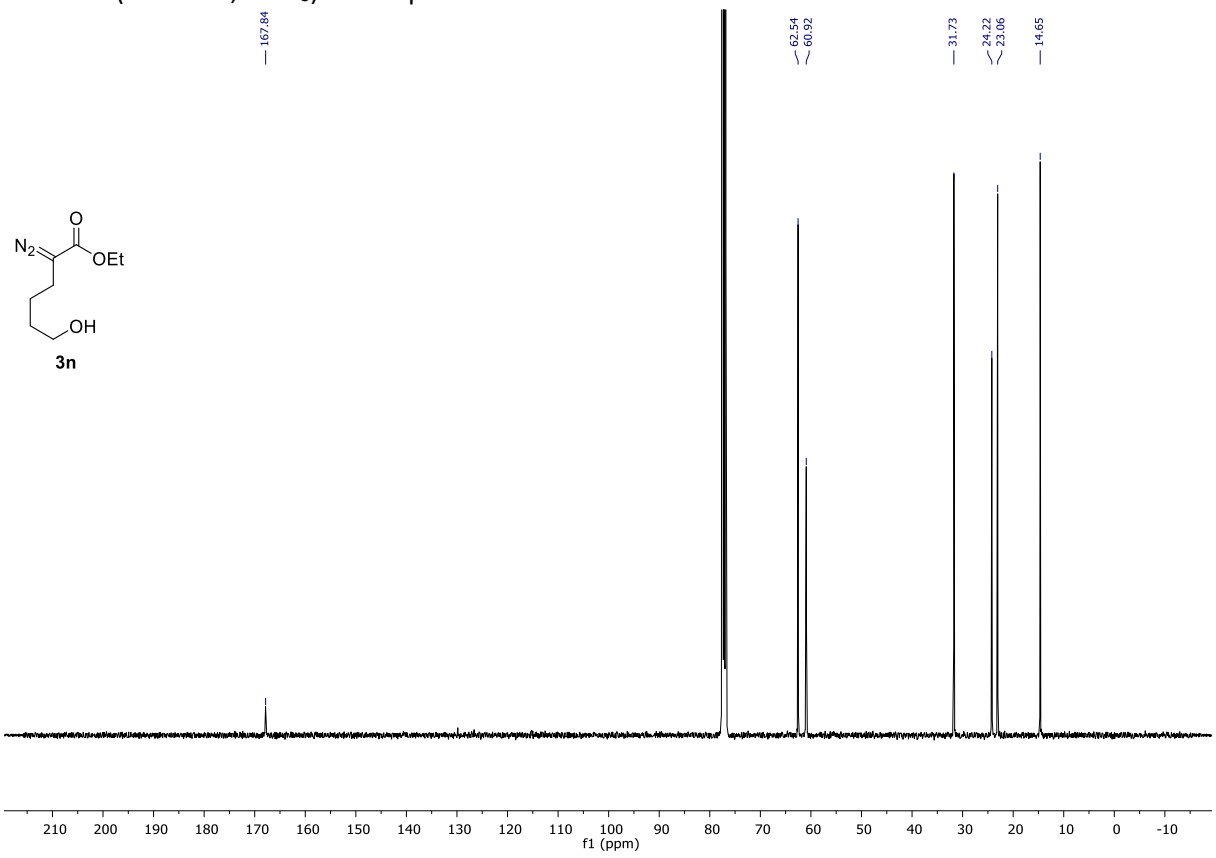
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **3c**



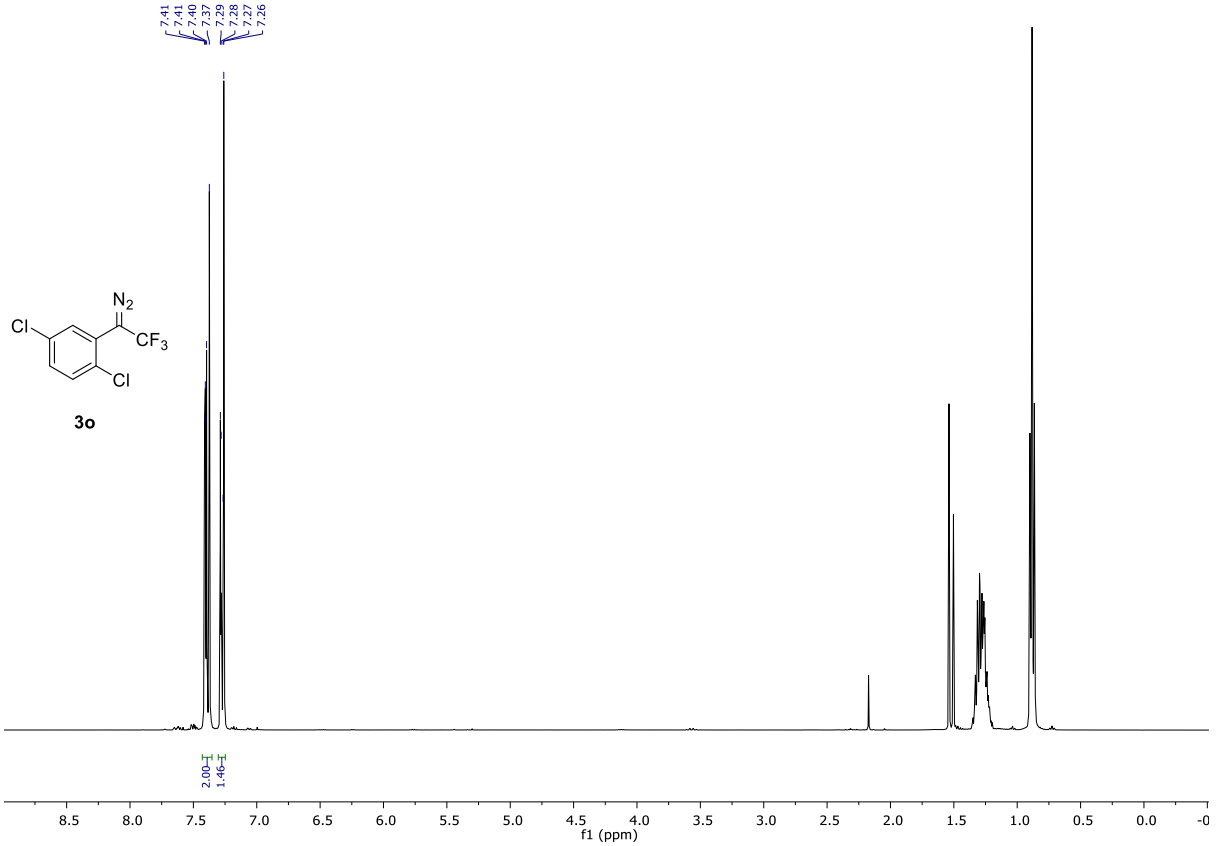
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **3n**



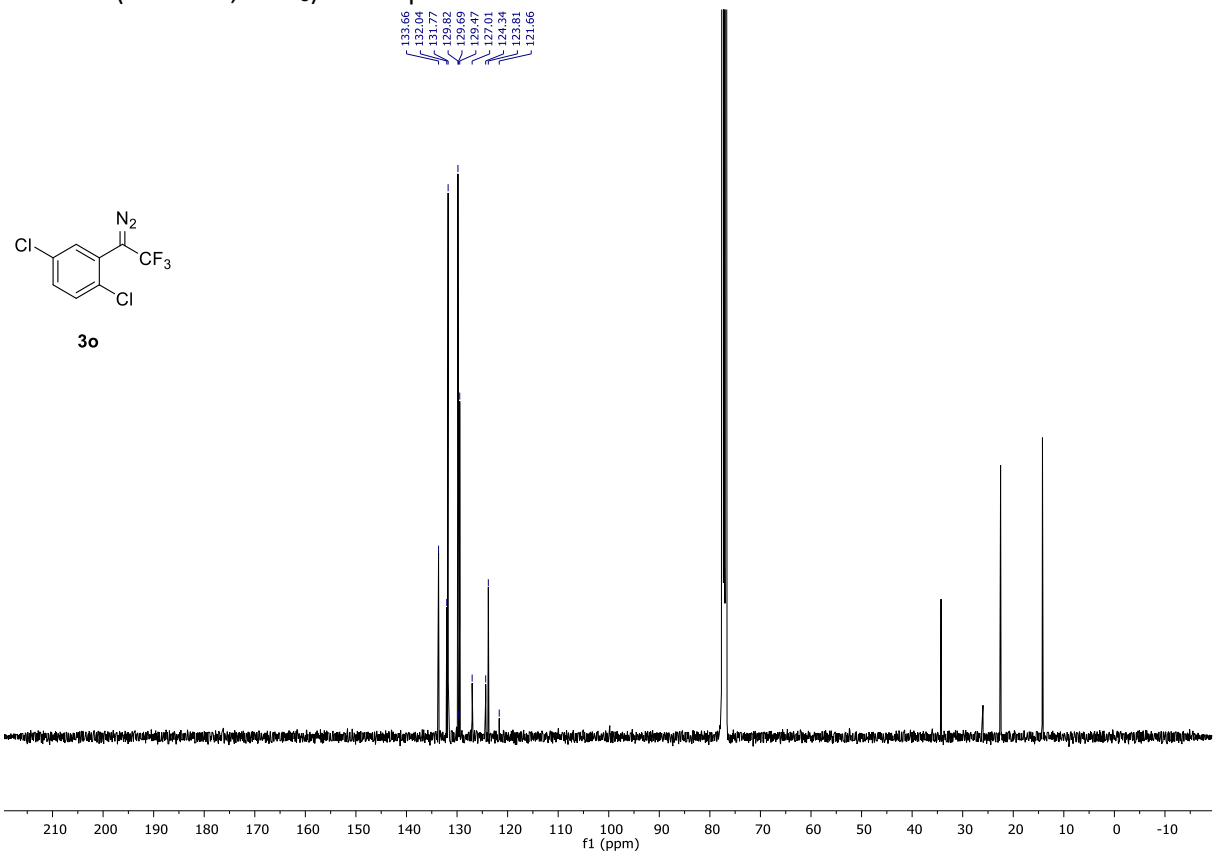
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **3n**



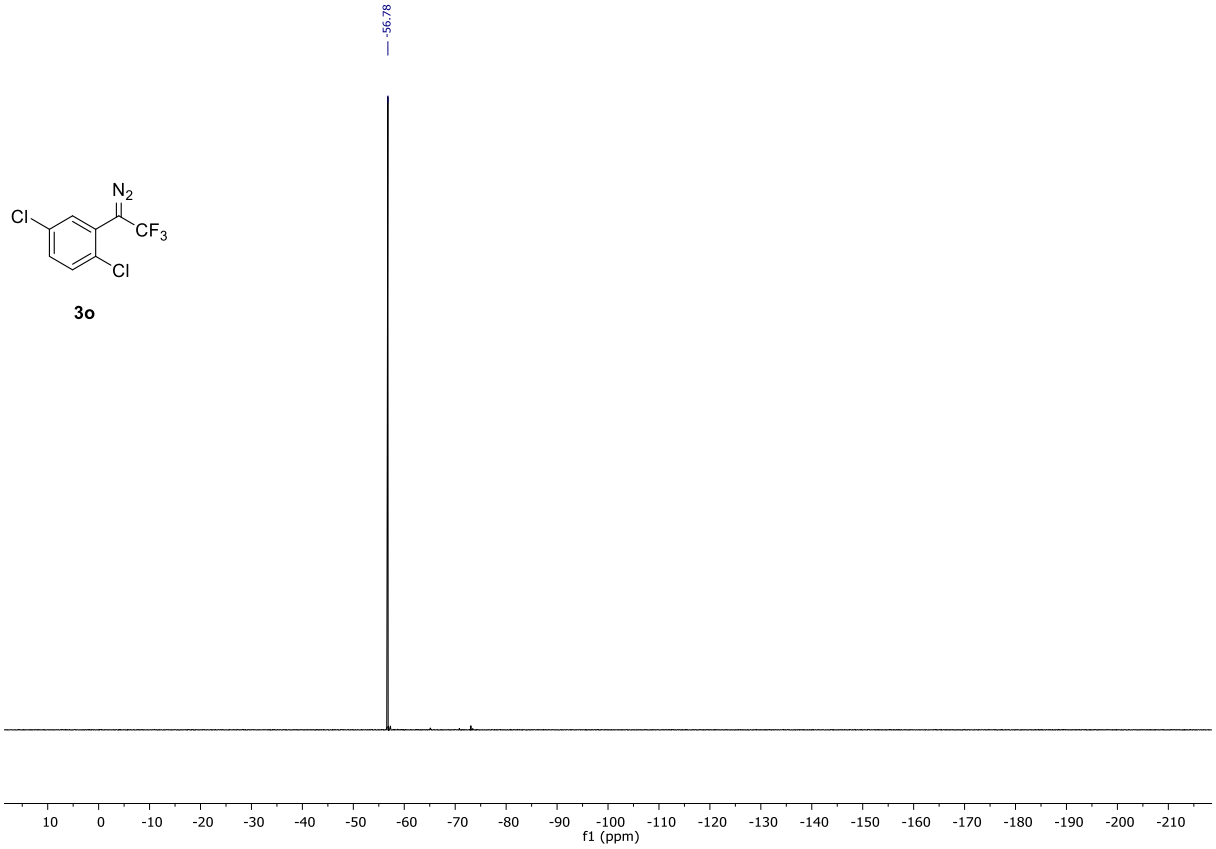
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **3o**



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

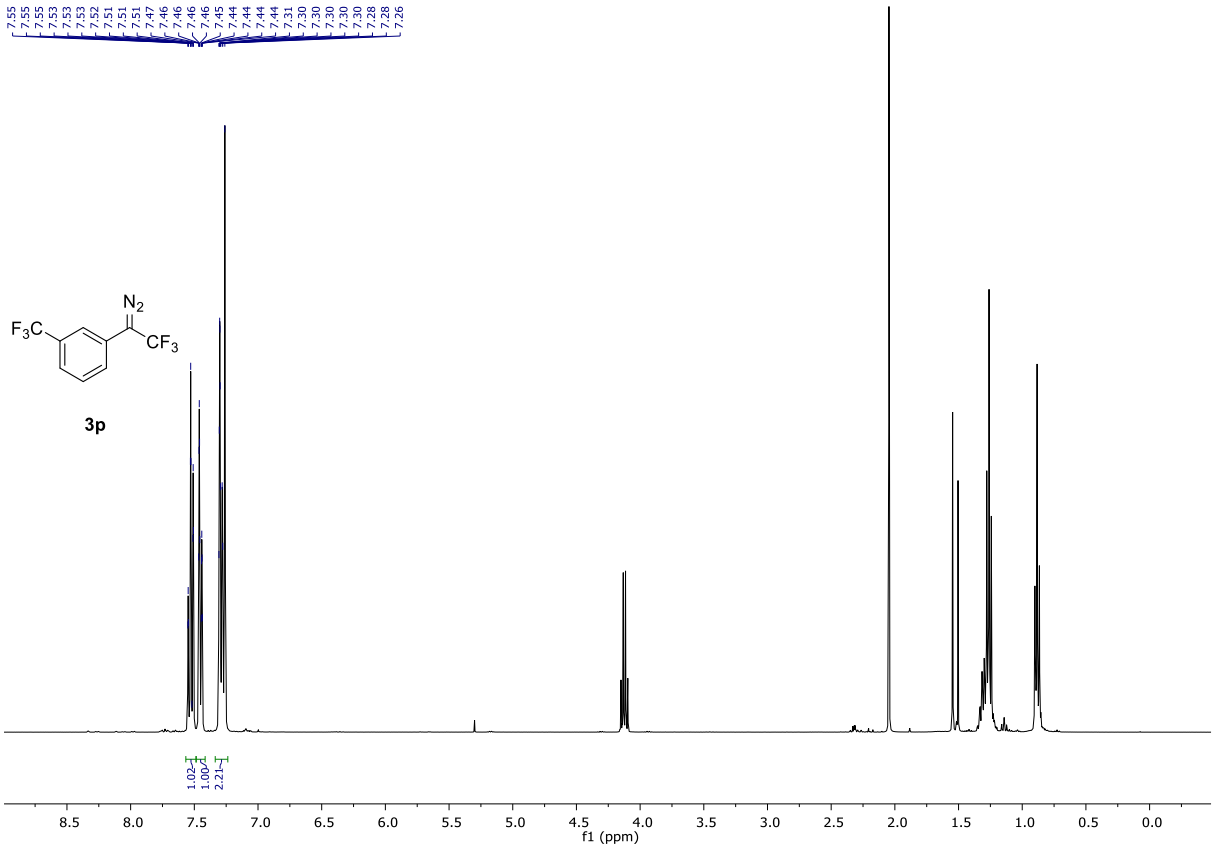


^{19}F-NMR (376 MHz, $CDCl_3$) of compound **3o**

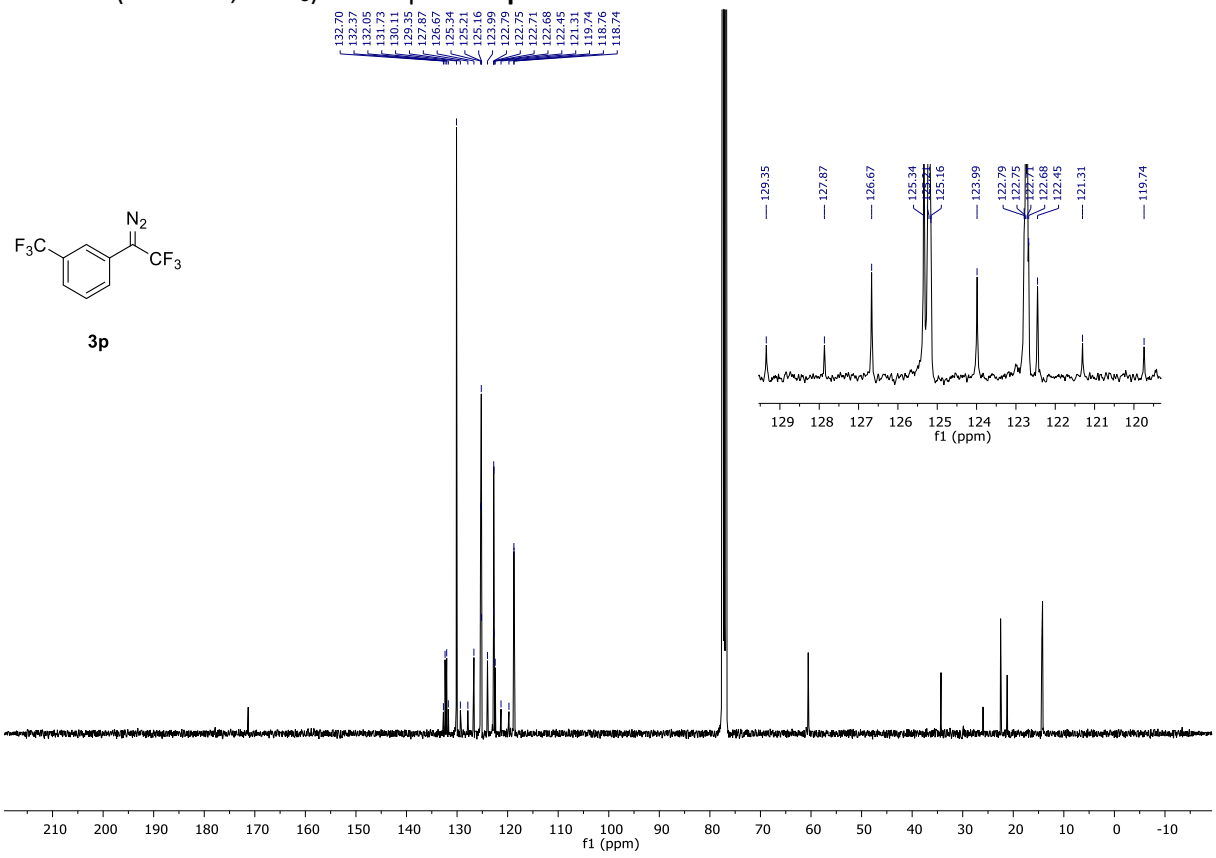


3o

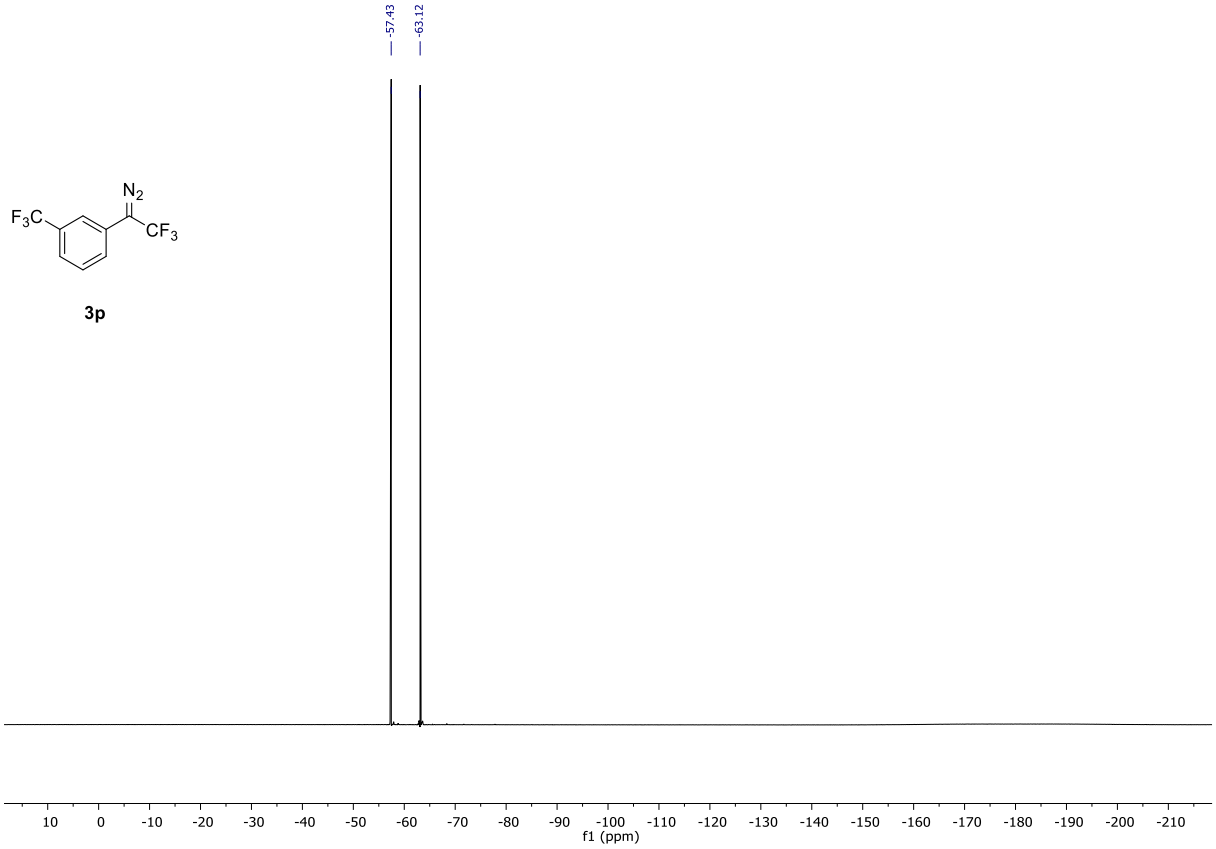
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **3p**



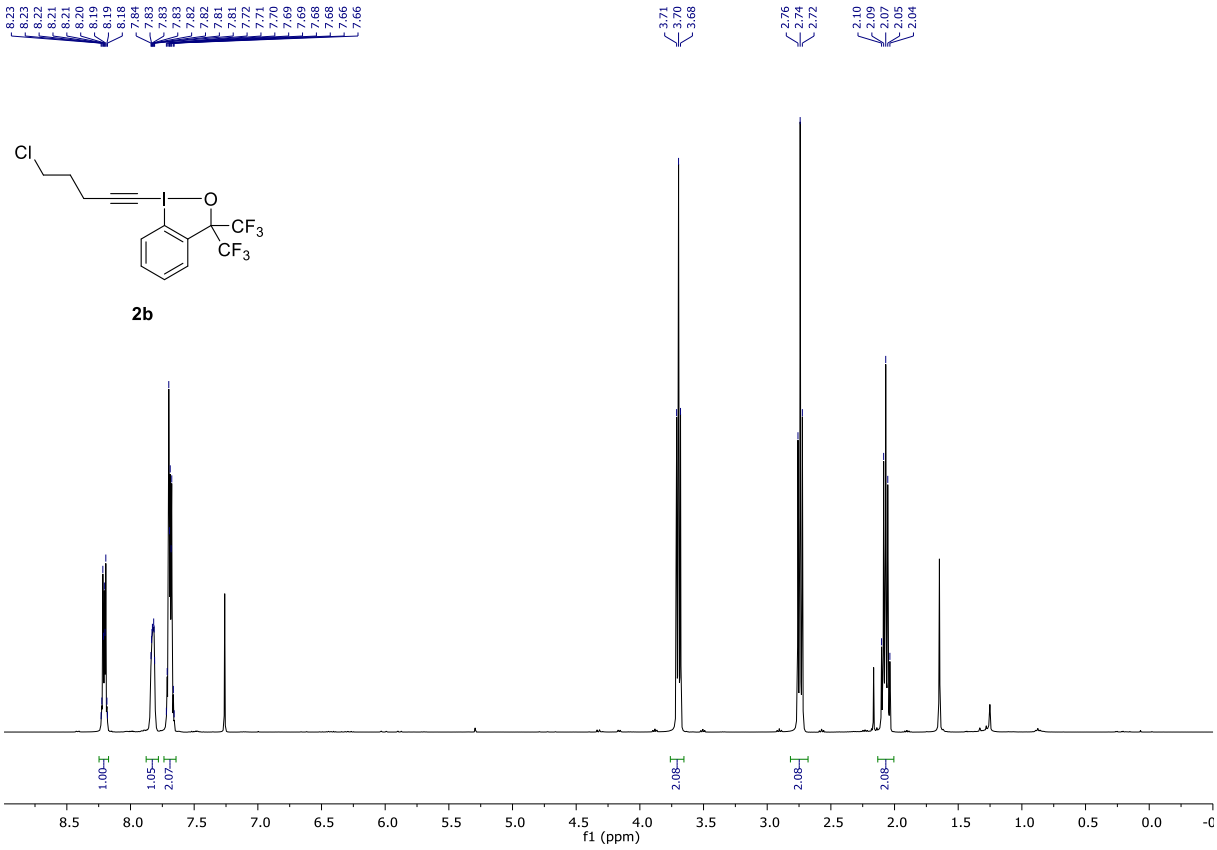
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **3p**



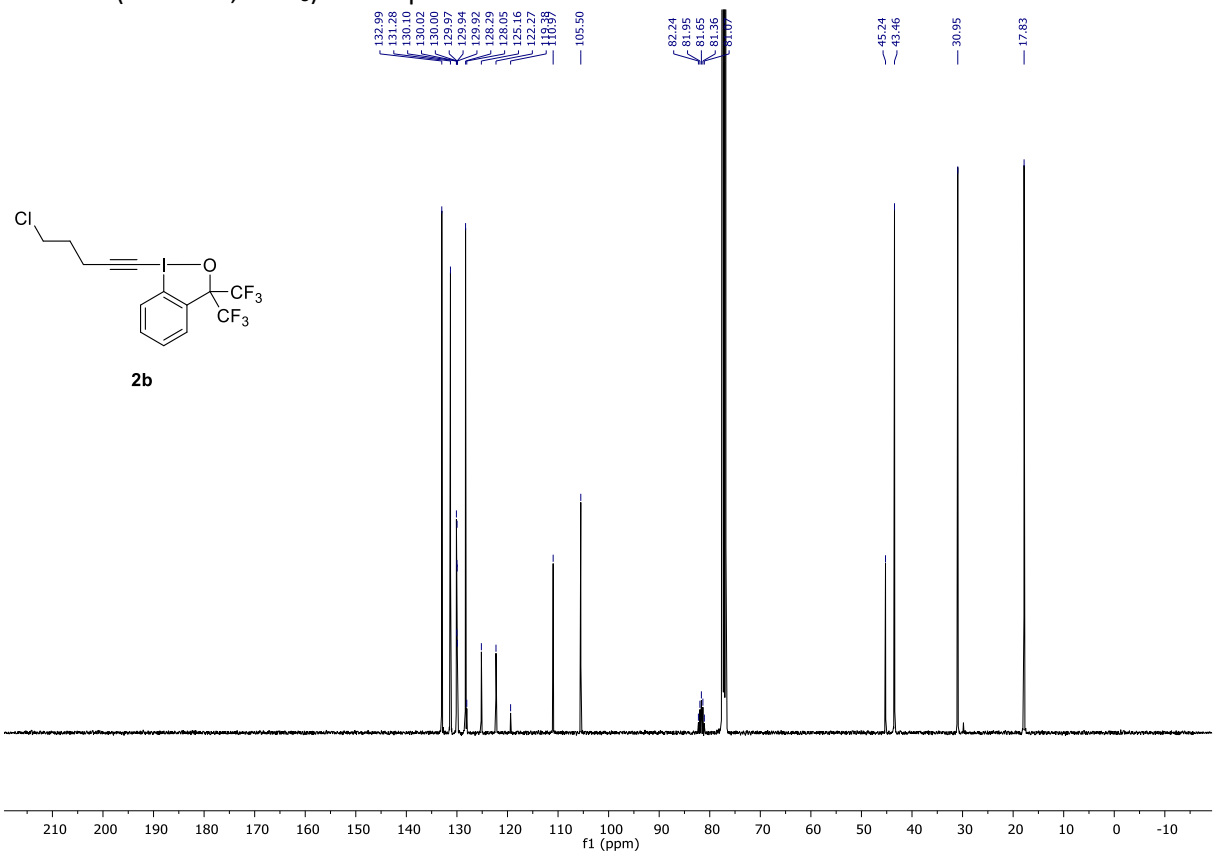
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **3p**



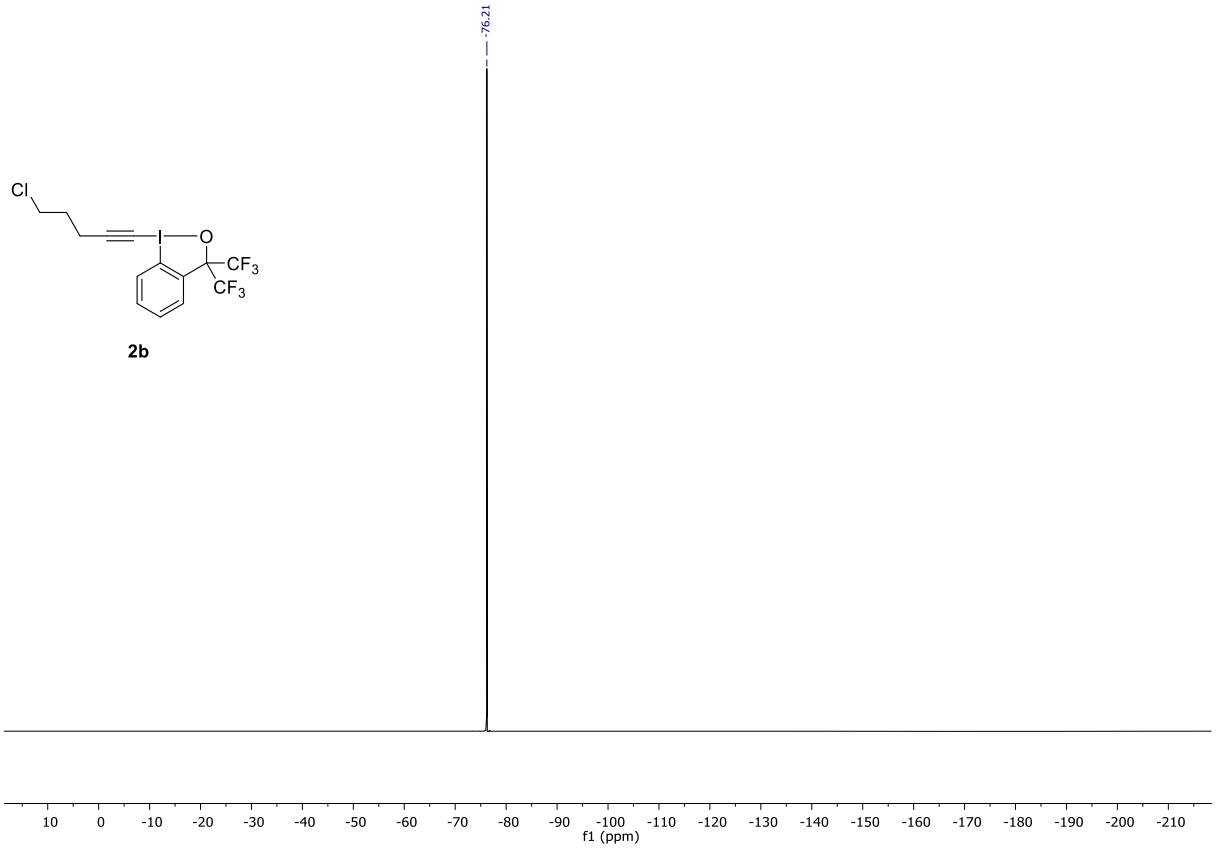
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **2b**



^{13}C-NMR (101 MHz, $CDCl_3$) of compound **2b**

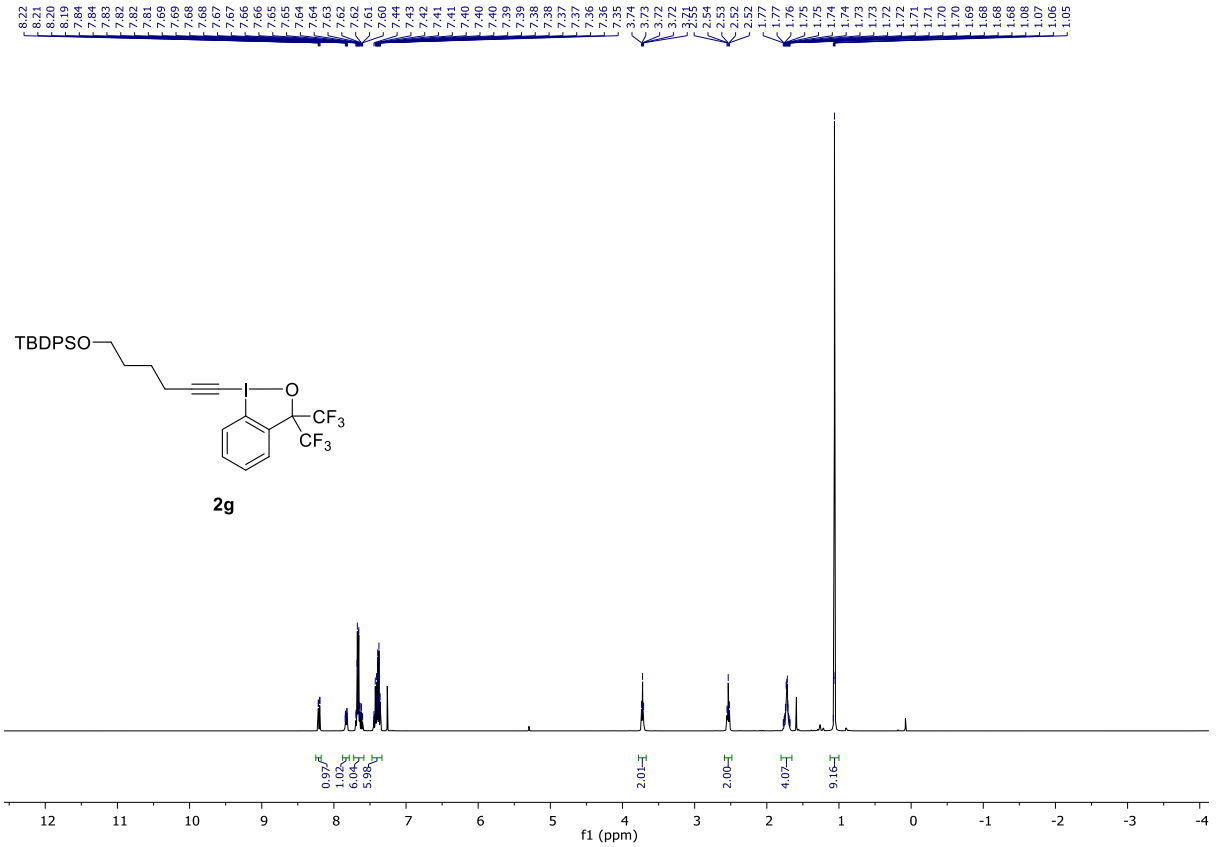


^{19}F-NMR (376 MHz, $CDCl_3$) of compound **2b**

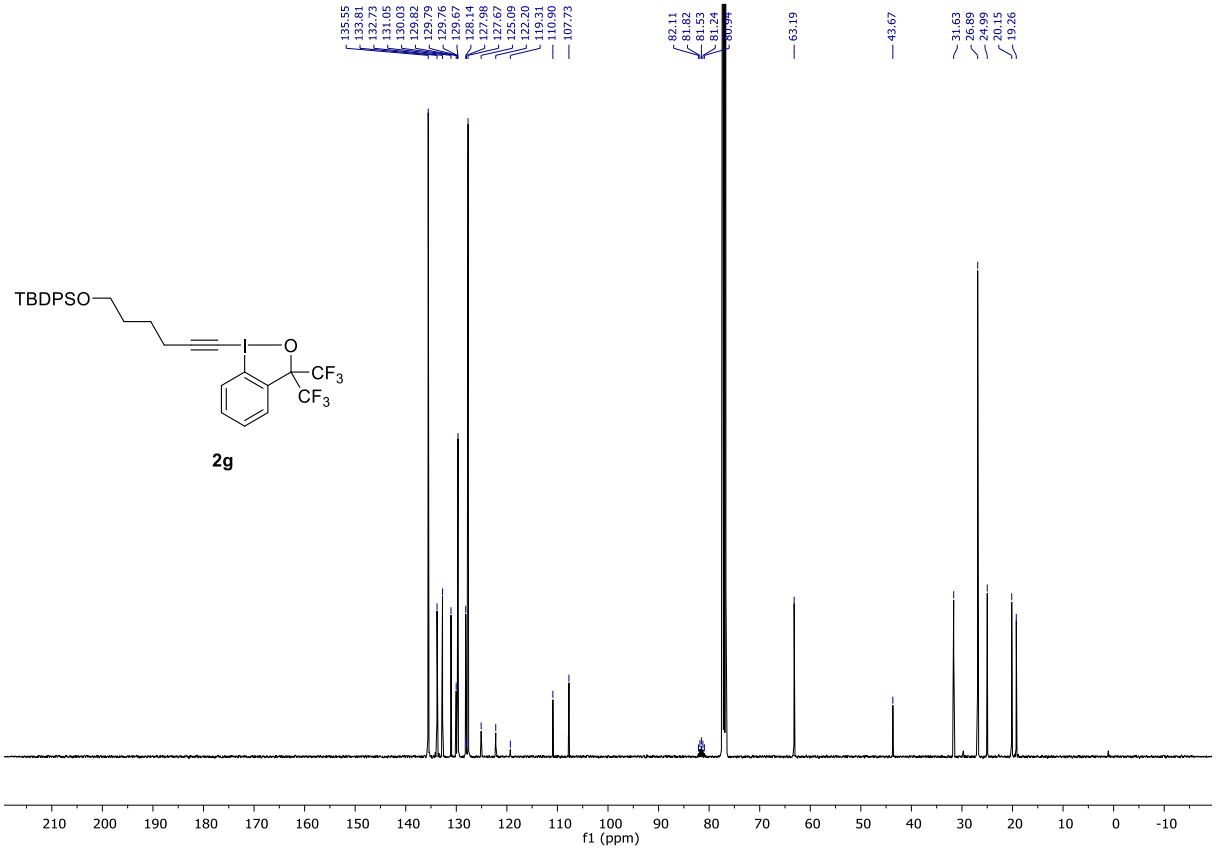


2b

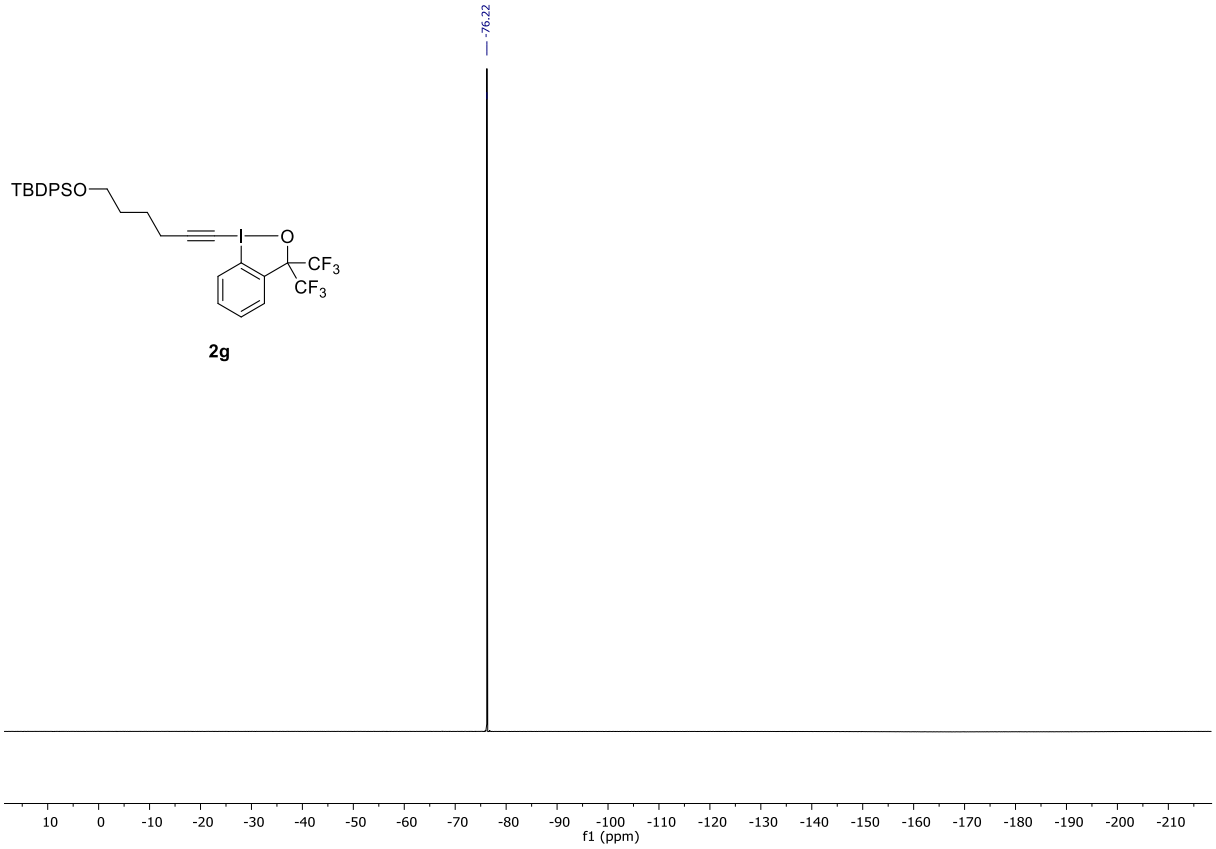
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **2g**



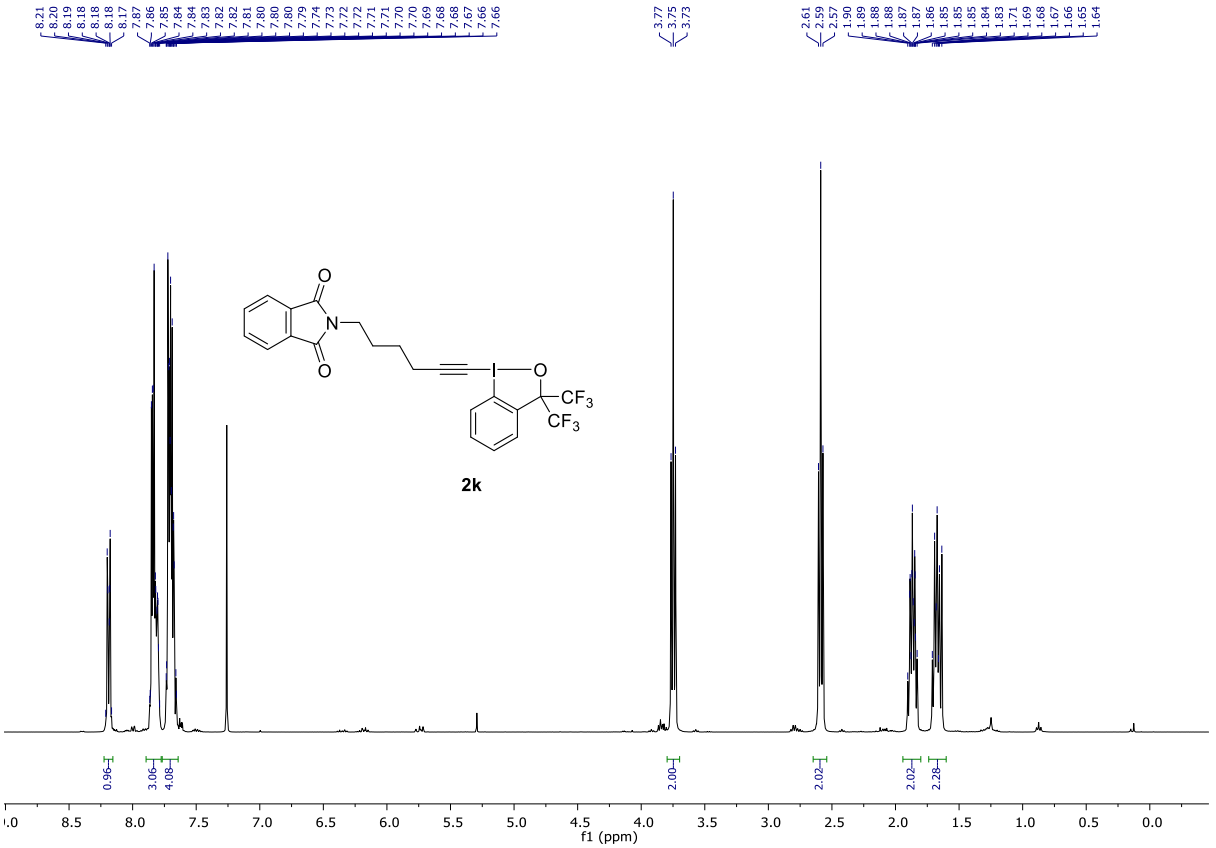
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **2g**



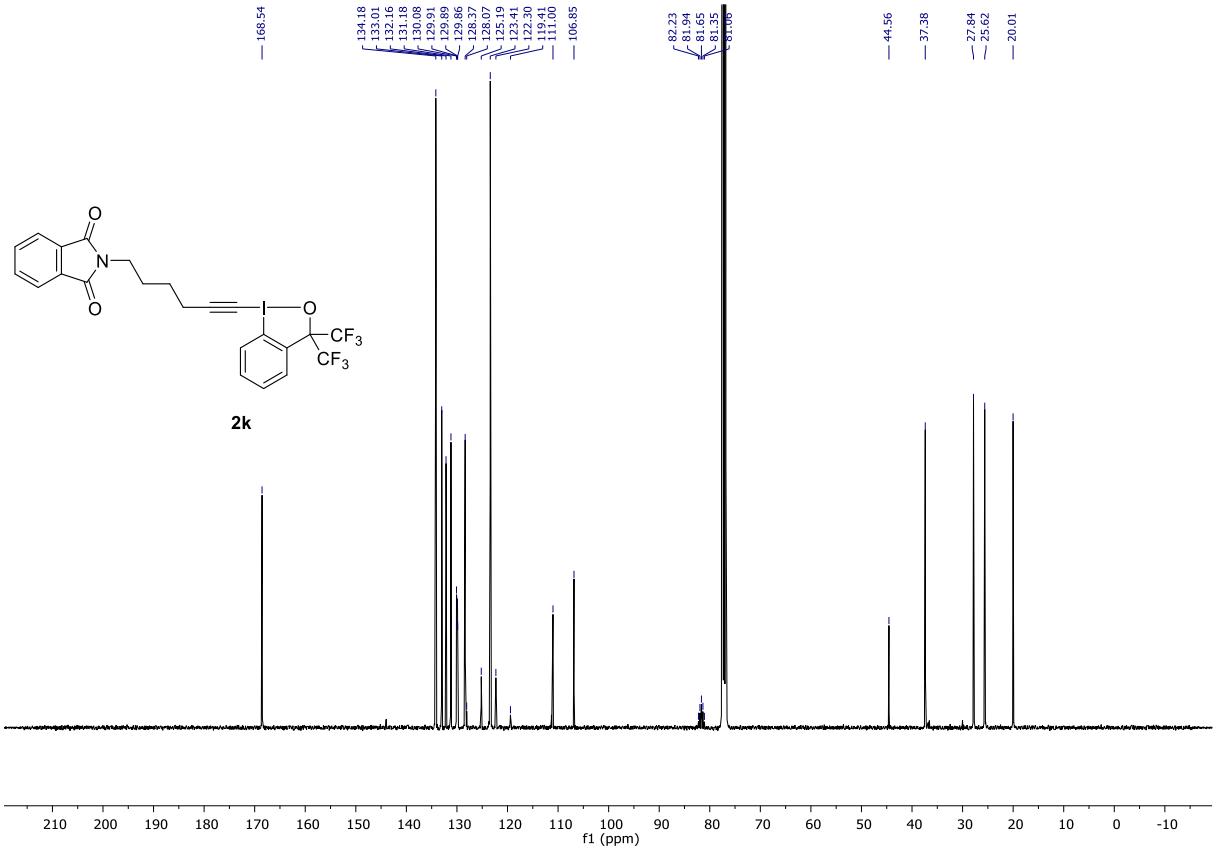
^{19}F-NMR (376 MHz, $CDCl_3$) of compound **2g**



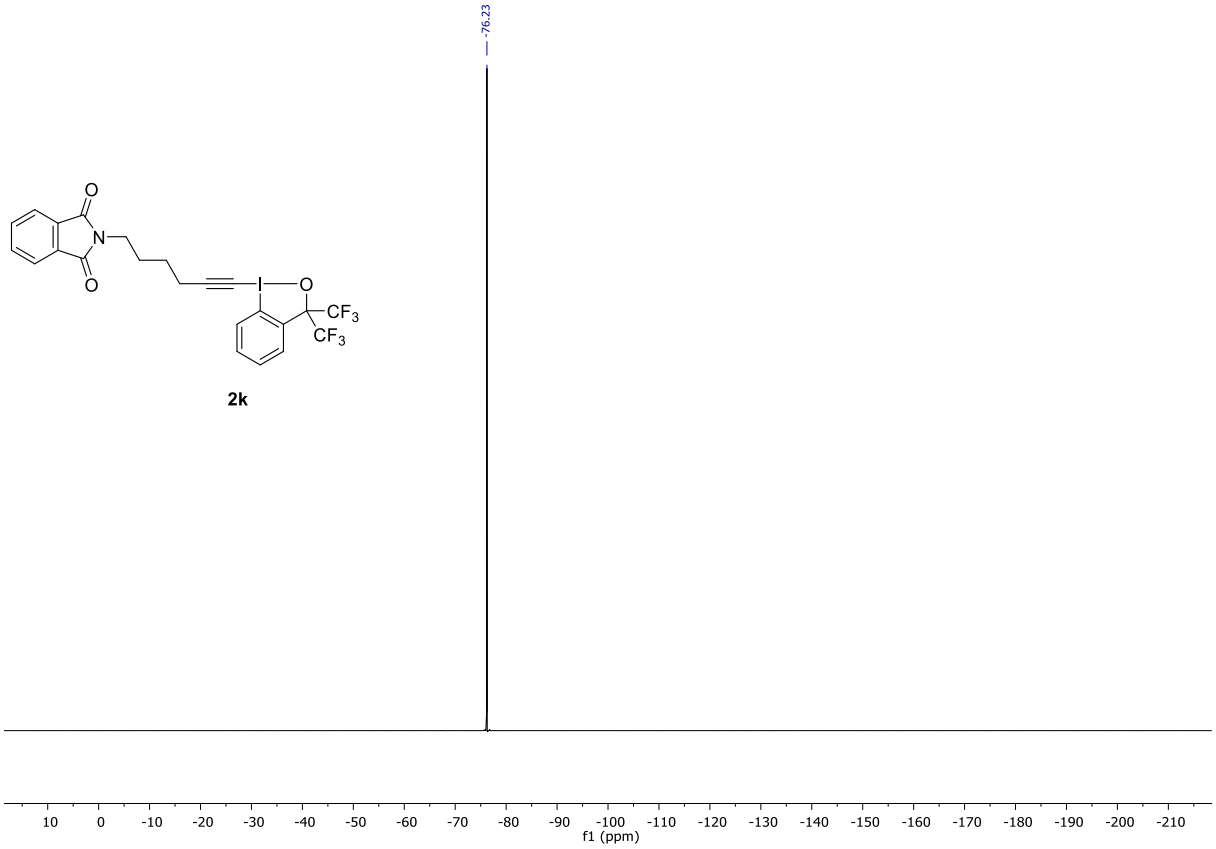
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **2k**



^{13}C-NMR (101 MHz, $CDCl_3$) of compound **2k**

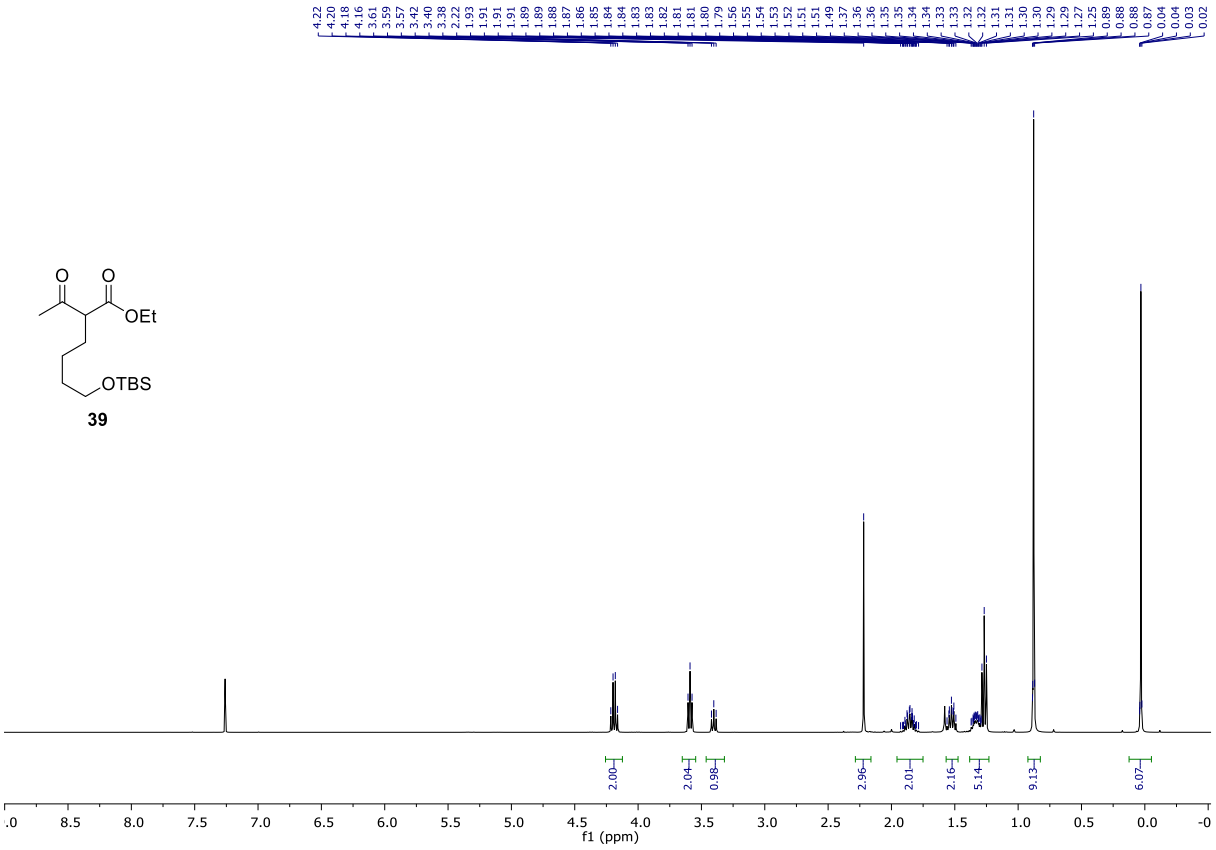


^{19}F-NMR (376 MHz, $CDCl_3$) of compound **2k**

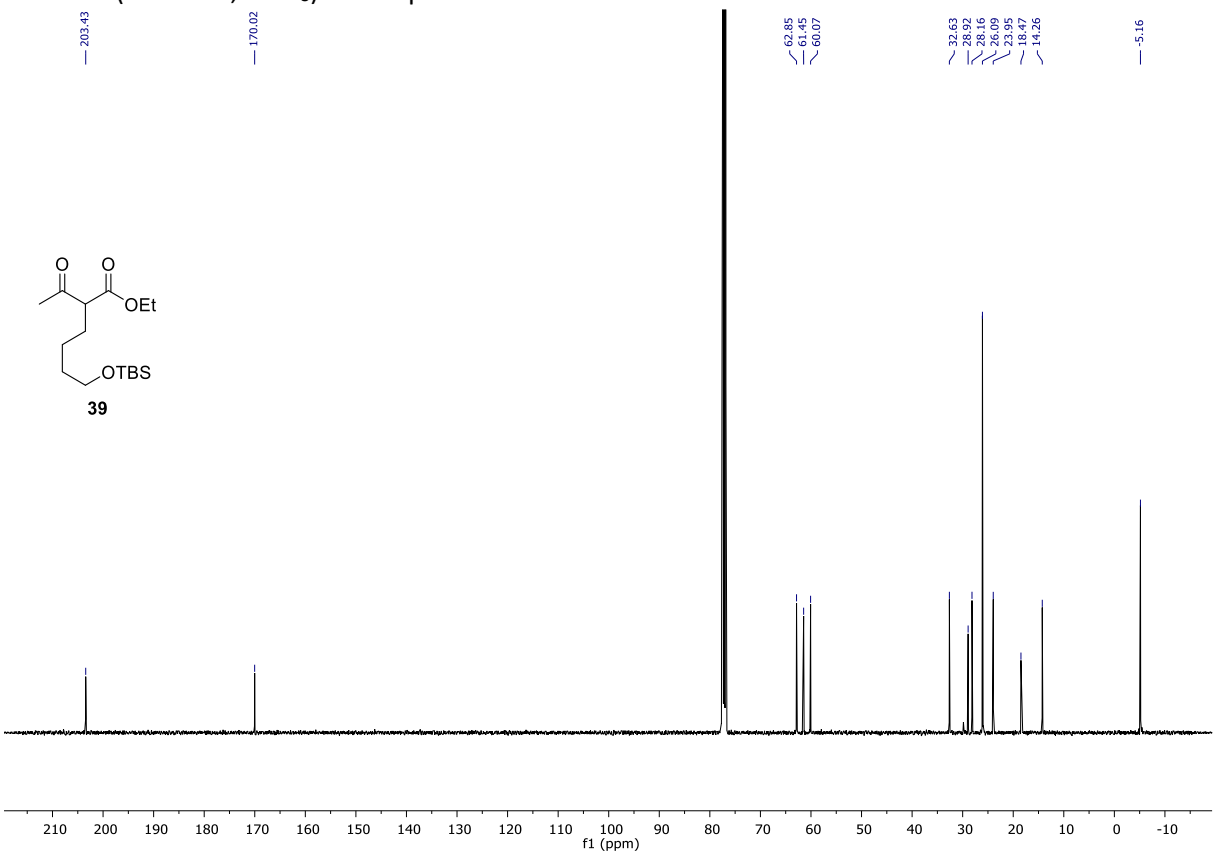


2k

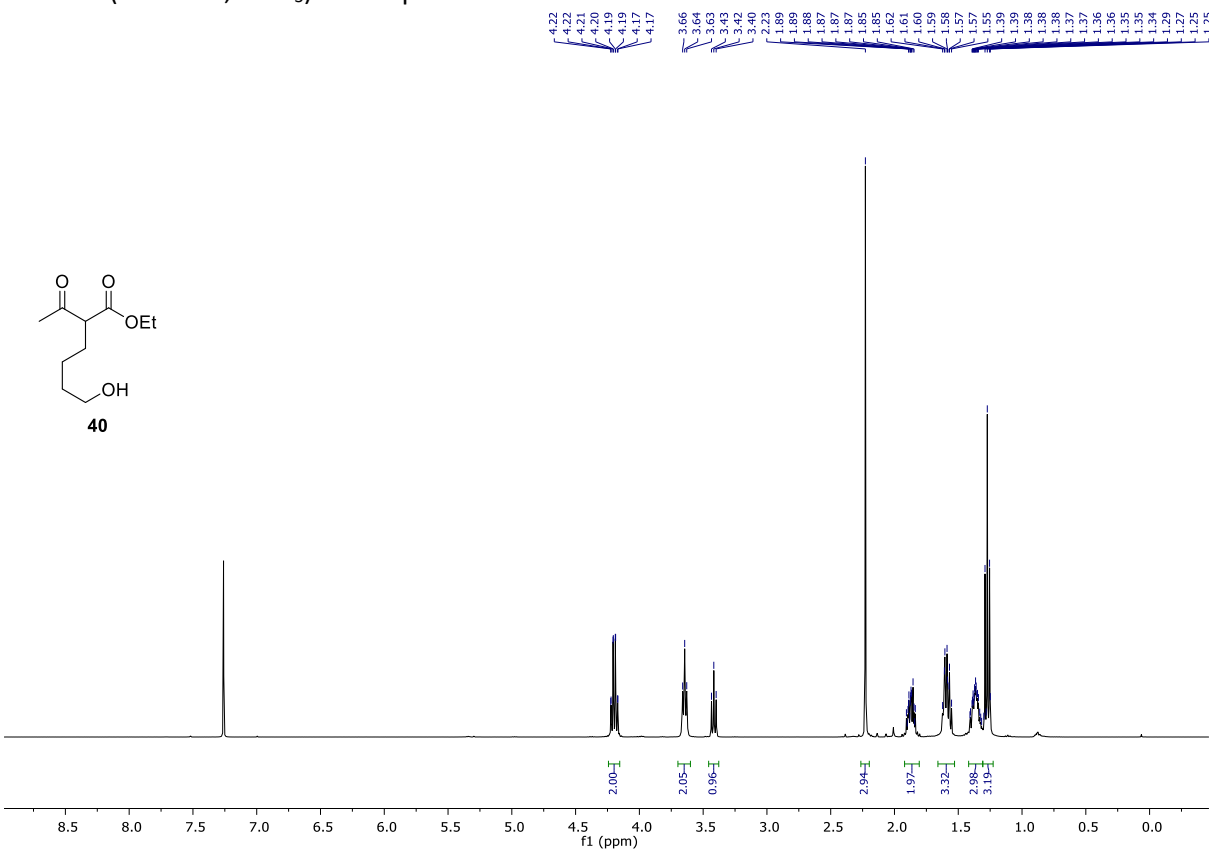
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **39**



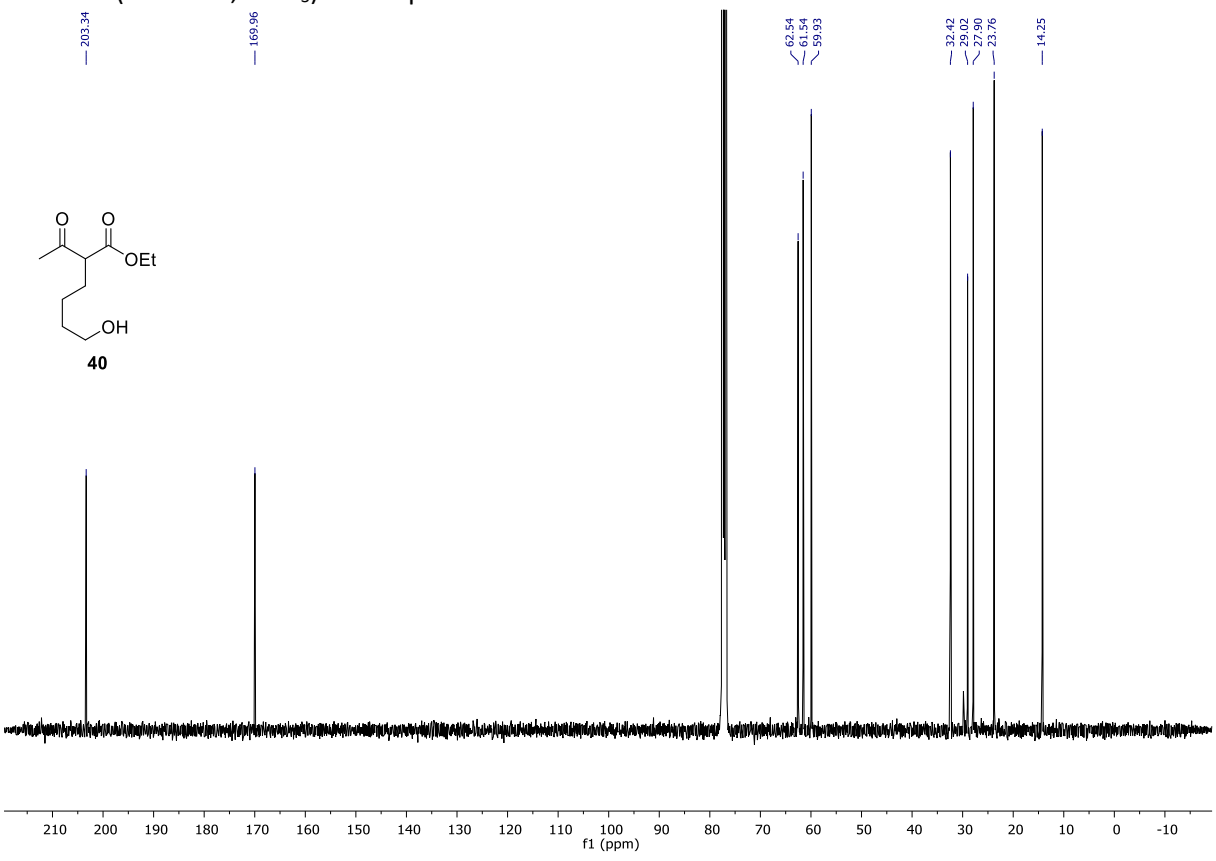
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **39**



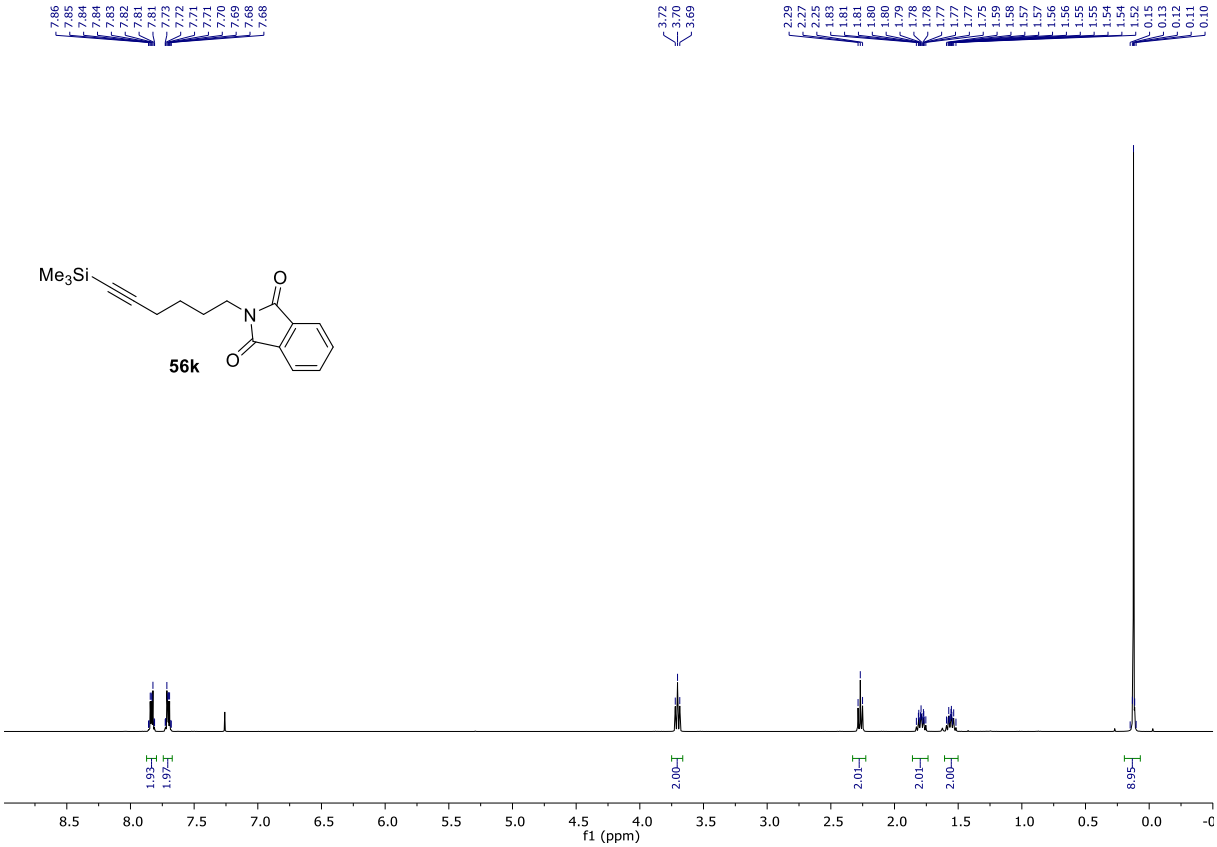
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **40**



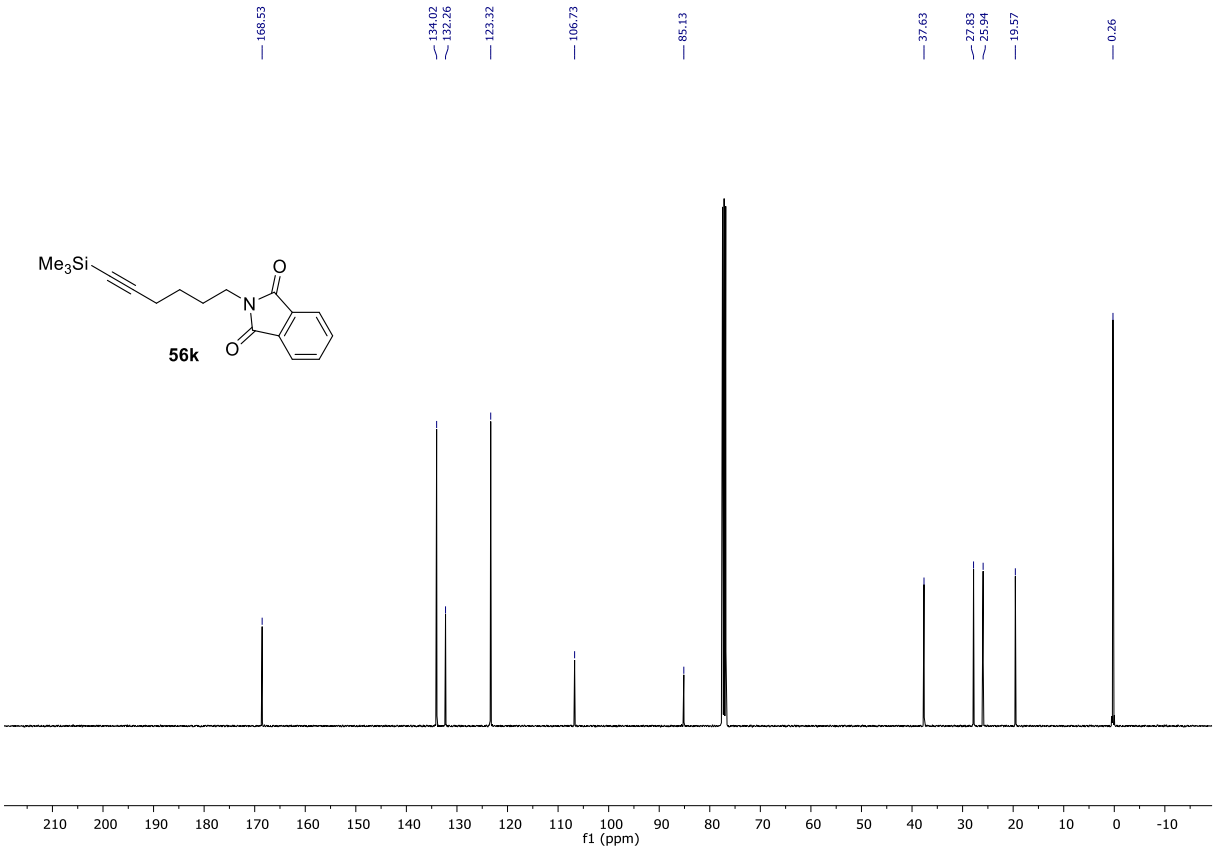
^{13}C-NMR (101 MHz, $CDCl_3$) of compound **40**



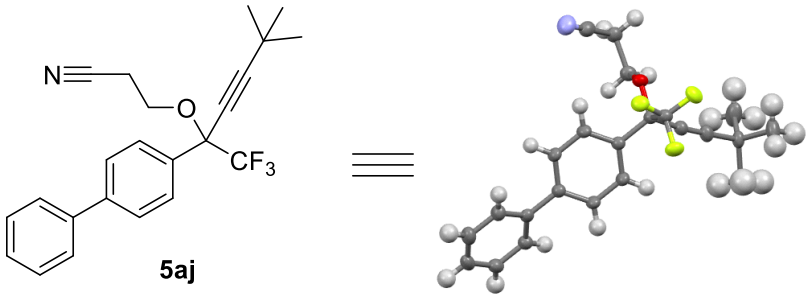
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **56k**



^{13}C-NMR (101 MHz, $CDCl_3$) of compound **56k**



8. X-ray diffraction parameters and data for 5aj



5aj

Empirical formula	$C_{23}H_{22}F_3NO$	
Formula weight	385.41	
Temperature	140.00(10) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	a = 8.81133(9) Å	α = 90°.
	b = 20.9653(2) Å	β = 90°.
	c = 22.3585(3) Å	γ = 90°.
Volume	4130.33(8) $Å^3$	
Z	8	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.785 mm^{-1}	
F(000)	1616	
Crystal size	0.440 x 0.151 x 0.120 mm^3	
Θ range for data collection	3.954 to 72.795°.	
Index ranges	-10 ≤ h ≤ 10, -25 ≤ k ≤ 25, -27 ≤ l ≤ 27	
Reflections collected	32007	
Independent reflections	4078 [R_{int} = 0.0354]	
Completeness to θ = 67.684°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.548	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4078 / 133 / 349	
Goodness-of-fit on F^2	1.053	
Final R indices [I > 2σ(I)]	R_1 = 0.0308, wR_2 = 0.0838	
R indices (all data)	R_1 = 0.0374, wR_2 = 0.0864	
Extinction coefficient	0.00022(6)	
Largest diff. peak and hole	0.275 and -0.189 e.$Å^{-3}$	