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Multicomponent Reaction

Copper (I)-BOX Catalyzed Asymmetric 3-Component Reaction for the Synthesis of Trifluoromethylated Propargylic Ethers and Anilines**

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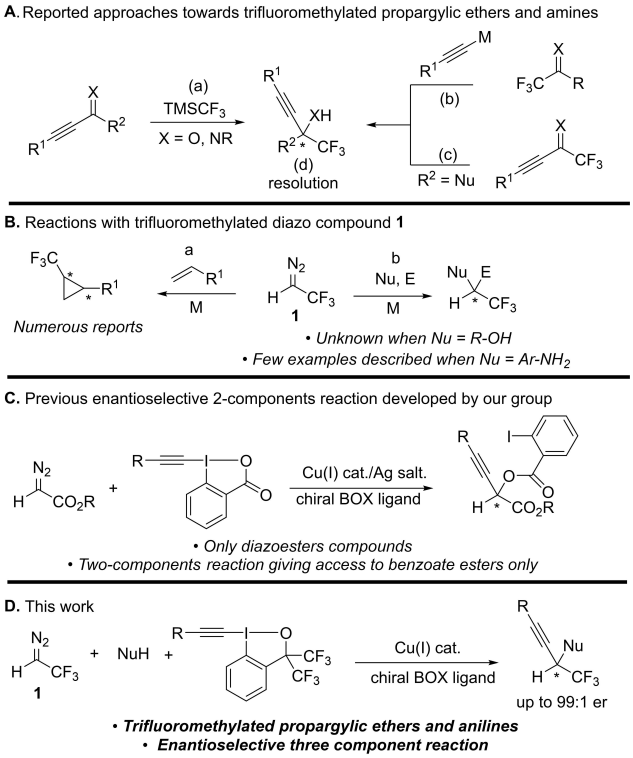
Abstract: An asymmetric 3-component reaction between EthynylBenziodoXoles (EBXs), 2,2,2-trifluorodiazoethane and nucleophiles catalyzed by a Cu^{I}-BOX (Bisoxazoline) catalyst is described. This protocol gives access to chiral trifluoromethylated propargyl ethers and anilines, which are valuable building blocks in synthetic and medicinal chemistry. The reaction proceeds with high enantioselectivity and yield with different nucleophiles such as primary, secondary and tertiary alcohols, as well as both electron-rich and electron-poor anilines. Aryl-, alkyl- and silyl-substituted alkynes can be successfully introduced as electrophiles. In case of chiral substrates, high catalyst control was observed, leading to good diastereoselectivity.



Scheme 1. State of the art for the synthesis of fluorinated propargylic ethers and anilines and our approach.

The unique physico-chemical properties of the fluorine atom have been extensively used for drugs, agrochemicals and materials design.[1–3] In particular, trifluoromethylated propargylic ethers and amines[4,5] are valuable building blocks for synthetic and medicinal chemistry.[6] Reported catalytic enantioselective methods[7] for the synthesis of trifluoromethylated carbinols and anilines are based on (a) the addition of CF_3-based nucleophiles to ynones,[7a,8] (b) the addition of acetylides onto carbonyl compounds or imines,[9,10] (c) the addition of carbon nucleophiles to trifluoromethylated alkynyl ketones or the reduction of the corresponding trifluoromethylated propargyl imines,[11,12] or (d) the kinetic resolution of the propargyl alcohols (Scheme 1A).[6a] Nevertheless, stoichiometric amounts of strong bases, lower or higher temperatures, expensive catalysts (Rh, Pd, among others), and/or additives are sometimes needed, leading to a narrow scope. Furthermore, most methods give access only to alcohols, requiring extra synthetic steps if the ethers are targeted.

In this context, Multi-Component Reactions (MCRs) involving diazo compounds have demonstrated their synthetic potential.[13–15] Recently, fluorinated diazo compounds, such as 2,2,2-trifluorodiazoethane (HN_2CCF_3, **1**, Scheme 1B), have been used in the synthesis of trifluoromethylated compounds.[16] Nevertheless, enantioselective methods have been mostly limited to cyclopropanation.[17] In the case of MCRs, there are only examples of the use of amines as nucleophiles to access aziridines, triazolines or 1,2-diamines.[18] To the best of our knowledge, the use of alcohols as nucleophiles in asymmetric MCRs with fluorinated diazo compounds has never been reported.

In 2016, our group reported an oxyalkynylation reaction of diazo esters using EthynylBenziodoXolones (EBXs) and a copper catalyst.[19] Later, an enantioselective variation of

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this reaction was developed using BOX ligands (Scheme 1C).[20] Despite copper being one of the most earth-abundant transition metals, it has been only rarely used in carbene-based enantioselective MCRs.[21] Recently, we could extend the use of copper catalysis to a 3-CR (Three Component Reaction) reaction between modified EBX derivatives, diazo compounds, and nucleophiles, such as alcohols[22] or anilines.[23] However, the development of an enantioselective method has not yet been reported.

Herein, we describe the first asymmetric 3-CR between 2,2,2-trifluorodiazoethane (**1**), EBX derivatives and nucleophiles for the synthesis of trifluoromethylated propargylic ethers and anilines (Scheme 1D). The reaction proceeds with high enantioselectivity for non-chiral alcohols and anilines and high diastereoselectivity under catalyst control for chiral alcohols. In the case of alcohol nucleophiles, primary, secondary and tertiary alcohols could all be used, the latest being challenging targets for traditional etherification reactions.[24]

As a model system, we chose the 3-CR of 2,2,2-trifluorodiazoethane (**1**),[25] EthynylBenziodoxole (EBX) **2a** and cyclohexanol (**3a**) (Table 1). After optimization, the enantioselective 3-CR could be performed using commercially available $Cu(MeCN)_4BF_4$ and BOX ligand **L1** at room temperature in DCE to give product **4aa** in 85% yield and 96:4 er (Table 1, entry 1). On 0.20 mmol scale, **4aa** was isolated in 83% yield. With indaBOX ligand **L2**, a quantitative yield, but lower selectivity was obtained (Table 1, entry 2). Using similar conditions than in our previous work[20b] led to similar results (Table 1, entries 3 and 4). Other counterions, such as SbF_6^-, PF_6^- or OTf^- gave **4aa** in similar or lower yields and er (Table 1, entries 5–7).

Different Cu^I catalysts, such as Cu(OTf)·PhMe, CuI or CuTc, (Table 1, entry 8 and Supporting Information) were also tested, but no improvement was observed. Using Cu^{II} salts, such as $Cu(OAc)_2$ or $Cu(OTf)_2$ was less efficient (Table 1, entries 9–10). A larger excess of **3a** did not lead to a significant improvement (Table 1, entry 11). Using only 1.5 equiv. of **3a** afforded compound **4aa** in lower yield (Table 1, entry 12). No reaction was observed with MeCN and a lower yield and similar selectivity than with DCE when using PhMe. (Table 1, entries 13 and 14). The use of further solvents and conditions did not lead to any improvement (See Supporting Information for more information).

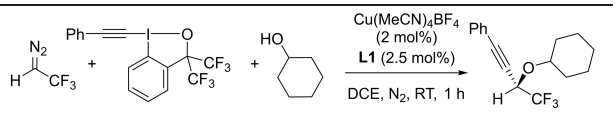
With these optimized conditions in hand, we explored the scope of the reaction between **1**, **2a** and different alcohols **3a**–**3p** (Scheme 2). Enantiopure (*S*)-2-phenylethanol (**2b**) afforded compound **4ab** in 70% yield and 95:5 dr. Switching to tertiary alcohols, *tert*-butanol (**3c**) gave **4ac** in 72% yield and 96:4 er. *Tert*-amyl alcohol (**3d**) afforded the corresponding propargylic ether **4ad** in 70% yield and 94:6 er. The presence of an arene in the aliphatic chain (**3e**–**g**) was tolerated, yielding products **4ae**–**g** in 43–65% yield with 97:3–98:2 er.[26] Cyclic alcohol **3h** gave **4ah** in 55% yield and 95:5 er. Trifluoromethylated propargylic ethers **4ai** and **4aj** containing pharmaceutically relevant adamantyl substituents[27] were obtained in good yield and enantioselectivity.

We then turned to primary alcohols. Benzyl alcohol (**3k**) gave **4ak** in 78% and 93:7 er. With hexanol (**3l**), the use of a stoichiometric ratio between the Cu^I salt and **L1** was needed to afford **4al** in good enantioselectivity (93:7 er) (See Supporting Information for more information). Ethanol (**3m**) afforded **4am** in 85% yield and 93:7 er. The presence of a trimethylsilyl group (**3n**) was well tolerated to give **4an** in 58% yield and 90:10 er. At 1 mmol scale product **4an** was obtained in 51% yield and 93:7 er. Switching to the less nucleophilic trifluoroethanol (**3o**), we observed poor selectivity and moderate yield, probably due to the higher acidity of the propargylic hydrogen.[28,29]

Finally, we studied substitution on the alkyne. A strong electron withdrawing nitro group in *para*-position of the phenyl ring led to high enantioselectivity: Compounds **4bp** and **4ba** were obtained in 55% yield/98:2 er and 87% yield/97:3 er, respectively. *Ortho*-substitution with a bromine group gave product **4ca** in 82% yield and 93:7 er. Importantly, silyl alkynes giving access to synthetically useful terminal alkynes were also tolerated. Product **4de** was obtained in 60% yield and 99:1 er. A 93:7 diastereoselectivity was obtained in the case of enantiopure alcohol **3b**. Compound **4eb** containing a cyclopropylalkyne was formed in 63% yield and 92:8 diastereoselectivity.

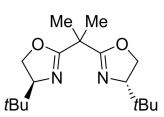
Enantiopure alcohols are widely found in nature. Considering the impressive catalyst control observed with (*S*)-2-phenylethanol (**2b**), we investigated more complex sub-

Table 1: Optimization of the MCR reaction.

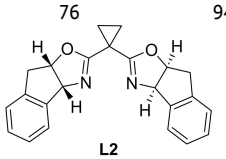


1 (2 equiv.) (0.33 - 0.40 M in DCM) | **2a** (1 equiv.) (0.15 M in DCE) | **3a** (2 equiv.) | **4aa**

Entry	Modifications	Yield **4aa**	er
1	none	85 (83)[b]	96:4
2	L2	quant.	11:89
3	$CuCl/AgNTf_2$	75	93:7
4	$CuCl/AgNTf_2$ and L2	95	11:89
5	$Cu(MeCN)_4SbF_6$	89	92:8
6	$Cu(MeCN)_4PF_6$	69	89:11
7	$Cu(MeCN)_4OTf$	77	93:7
8	Cu(OTf)•PhMe	78	95:5
9	$Cu(OAc)_2$	69	85:15
10	$Cu(OTf)_2$	68	96:4
11	4 equiv of **3a**	88	94:6
12	1.5 equiv of **3a**	65	95:5
13	MeCN	n.d.	n.d.
14	PhMe	76	94:6

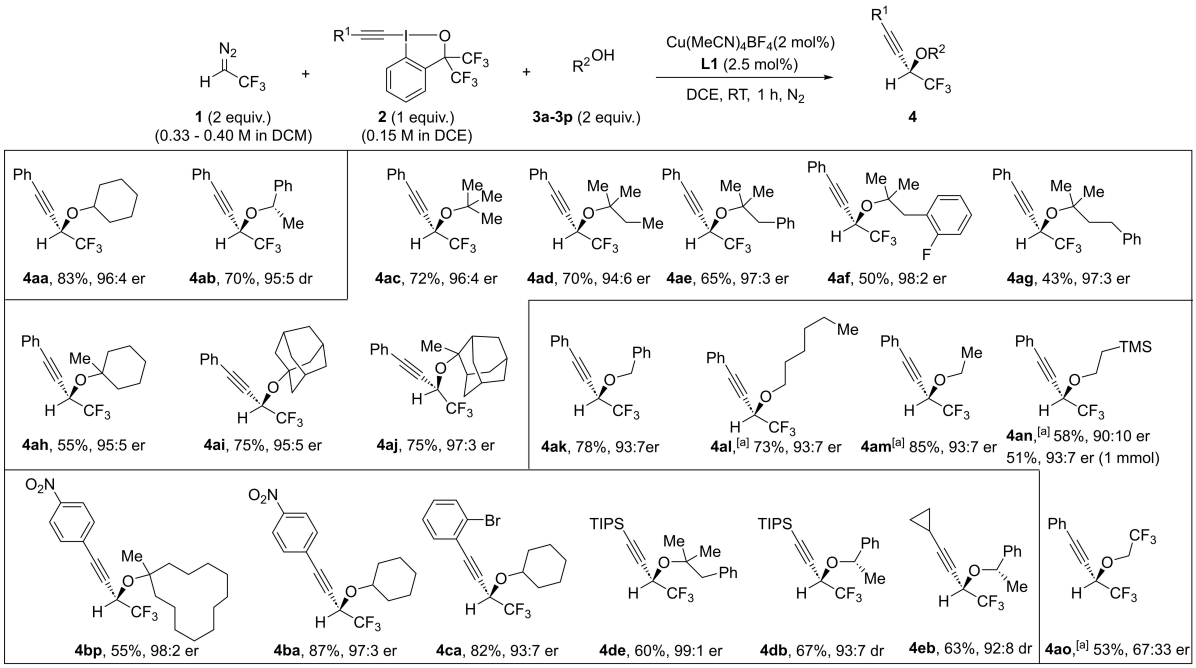


L1



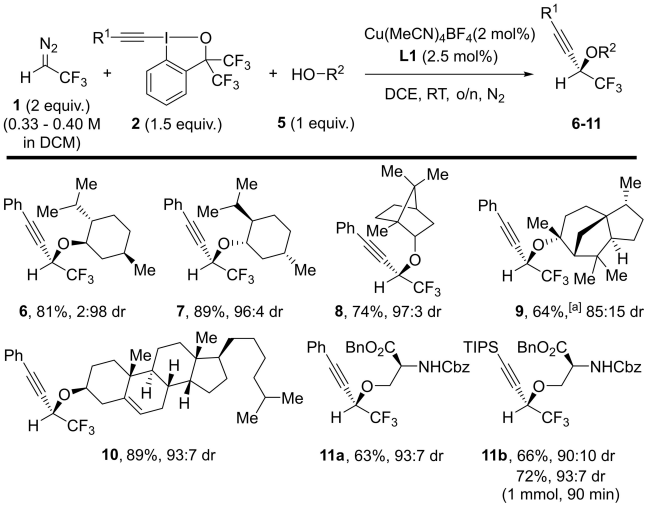
L2

Conditions: [a] The reactions were performed with 0.15 mmol of **2a**. The chiral complex was formed mixing the Cu^I catalyst with **L1** or **L2** in the reaction solvent during 1 h. The yield was determined by ^{19}F NMR using 1 equiv of $PhCF_3$ as internal standard. The er was determined by chiral HPLC. [b] Isolated yield at 0.20 mmol scale is indicated in brackets.



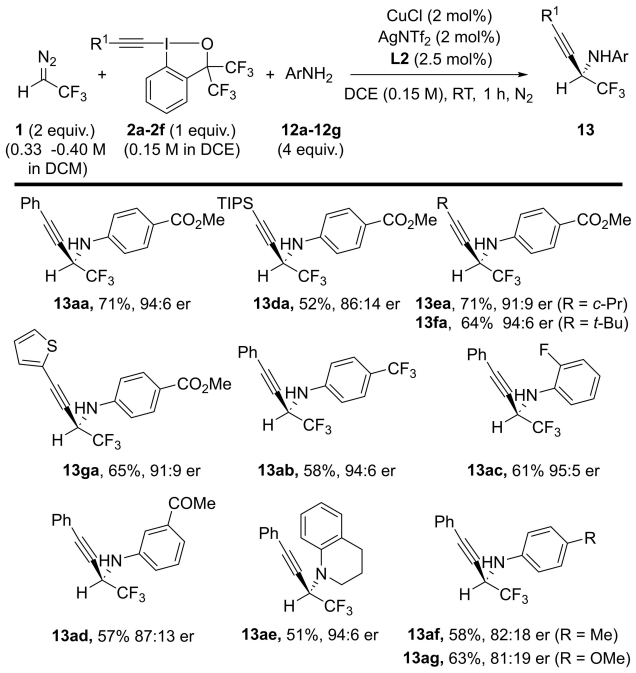
Scheme 2. Scope of the 3-CR with 2,2,2-trifluorodiazoethane (**1**) and different alcohols (**3**) and EBXs (**2**). The reactions were performed at 0.20 scale and isolated yields are given. The enantiomeric excess was obtained by chiral HPLC after flash column purification. The diastereomeric ratio was obtained from the crude reaction mixture by ^{19}F NMR. [a] 2 mol% $Cu(MeCN)_4BF_4$ and 2 mol% **L1**.

strates (Scheme 3). We first reoptimized the reaction for the use of the alcohol as limiting reagent (See Supporting Information for more information). The use of 1 equiv. of (−)-menthol (**5a**) gave alkyne **6** in 81% yield and 2:98 dr. When (+)-menthol (**5b**) was submitted to the same conditions, product **7** was obtained in 89% yield and 96:4 dr, displaying an excellent catalyst control. Other terpene derived alcohols gave products **8**–**10** in 64–89% yield and 85:15–97:3 dr. With protected serine derivative **5f**, ether **11a** was obtained in 63% yield and 93:7 dr. The reaction of alcohol **5f** was also performed with TIPS-substituted reagent **2d**, giving compound **11b** in 66% yield and 90:10 dr. Compound **11b** was obtained in slightly higher yield and diastereoselectivity at a 1 mmol scale.



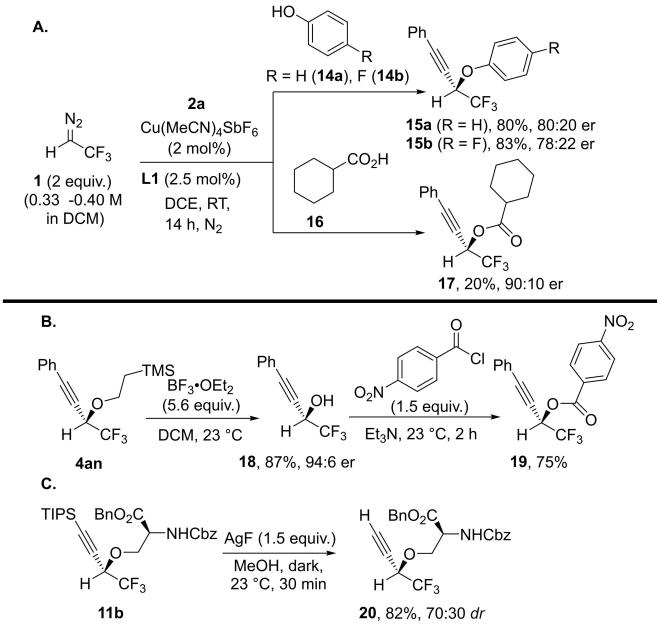
Scheme 3. Scope of the 3-CR with 2,2,2-trifluorodiazoethane (**1**) and chiral alcohols (**5**). Reaction conditions: Unless otherwise indicated, the reactions were performed at 0.25 mmol scale. Isolated yields by flash column chromatography are given. The diastereomeric ratio was obtained from the crude reaction mixture by ^{19}F NMR. [a]Using $Cu(MeCN)_4SbF_6$, 1 equiv of **2a** and 4 equiv of alcohol **5d**.

Next, we studied anilines as nucleophiles (Scheme 4).[23] We studied first the reaction between **1**, **2a** and methyl 4-aminobenzoate (**12a**). Unfortunately, despite the good er obtained (98:2); the desired product (**13aa**) was obtained in only 66% yield with low reproducibility using the conditions optimized for alcohols. After screening of different BOX ligands, Cu^I catalysts, solvents, concentrations and temperatures, **L2** in combination with the cationic complex formed from $CuCl/AgNTf_2$ in DCE afforded compound **13aa** in 71% yield and 94:6 er with high reproducibility (See Supporting Information for more information). Compound **13da** was obtained in 52% yield and 86:14 er. Both cyclopropyl (*c*-Pr) and *tert*-butyl (*t*-Bu)-substituted alkynes gave products **13ea** and **13fa** in 71% yield and 91:9 er and 64% yield and 94:6, respectively. Thiophene substituted alkyne **13ga** was obtained in 65% yield and 91:9 er. The scope of substituted anilines was then explored. Electron withdrawing groups, such as trifluoromethyl or *para*-fluoro gave the desired products **13ab** and **13ac**[30] in similar yield and selectivity. A ketone group was also tolerated, giving product **13ad** in 57% and 87:13 er. 1,2,3,4-Tetrahydroquinoline afforded compound **13ae** in moderated yield and good enantioselectivity. The presence of a methyl or methoxy in *para* position led to lower enantioselectivity (products **13af** and **13ag**).



Scheme 4. Scope of the 3-CR with 2,2,2-trifluorodiazoethane (**1**) and anilines (**12**). The reactions were performed at 0.25 mmol scale. Isolated yields are given. The enantiomeric excess was obtained by chiral HPLC after PTLC.

We also examined phenols and carboxylic acids as nucleophiles (Scheme 5A). In this case, the combination of $Cu(MeCN)_4SbF_6$ and an excess of the nucleophile afforded the best results. With phenols **14a** and **14b**, compounds **15a** and **15b** were obtained in good yield and moderate selectivity. In contrast, using 2-cyclohexanecarboxylic acid (**16**), we reached good enantioselectivity for ester **17**, but the reaction did not go to completion. To determine the absolute configuration of the propargylic ether products, **4an** was deprotected using BF_3OEt_2 to give alcohol **18** in 87 % yield (Scheme 5B). Compound **18** was reacted with *p*-nitrobenzoyl chloride to give ester **19**, which allow us to determine the absolute configuration via X-ray analysis.[30] Deprotection of the TIPS group was performed on compound **11b** by treatment with AgF, giving terminal alkyne **20** in 82 % yield, albeit with a lower dr (Scheme 5C).



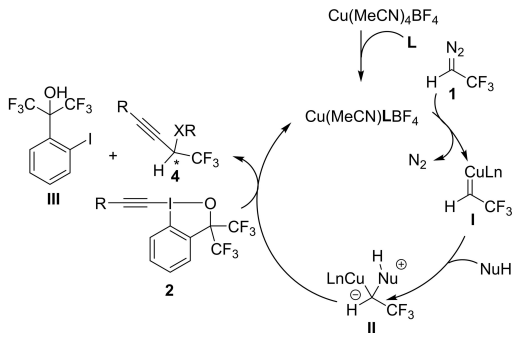
Scheme 5. Scope extension (A) and products modification (B and C). The reactions were performed at 0.20 mmol scale. Isolated yields are given. The enantiomeric excess was obtained by chiral HPLC after flash column purification.

According to our previous work,[19,20] we propose the following speculative mechanism (Scheme 6): The preformed chiral Cu^I complex would first react with **1** generating Cu carbene **I**, which then would react with the nucleophile forming the metal-ylide **II**. Finally, electrophilic alkyne transfer from EBX reagent **2** would give the desired product **4** and bistrifluoromethylated alcohol **III** as by product. For the alkynylation step, a redox mechanism on copper can tentatively be proposed, as reported in case of gold,[31] but further work is needed to better understand this step as well as the observed asymmetric induction (See Supporting Information for more information).

In summary, we have developed the first asymmetric enantioselective 3-CR between hypervalent iodine reagents, 2,2,2-trifluorodiazoethane (**1**) and nucleophiles using a Cu^I catalyst. Tertiary, secondary and primary alcohols as well as electron-rich and electron-poor anilines can be used as nucleophiles affording fluorinated propargylic ethers and anilines in up to 99:1 er. Alkyl-, aryl- and silyl-substituted EBXs could be used in the process, giving access to structurally diverse alkynes. With chiral substrates, high catalyst control was observed leading to good diastereoselectivity.

Supporting Information

The authors have cited additional references within the Supporting Informatio[32–39] Optimization tables, experimental procedures and analytical data for all new compounds. ^1H NMR, ^{13}C NMR, ^{19}F NMR spectra and chiral HPLC traces are included. Raw data for NMR, IR, MS and HPLC



Scheme 6. Plausible mechanism. Ln = (MeCN)**L**.

are freely available on the platform zenodo: https://doi.org/10.5281/zenodo.7991566.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Alkynes · Asymmetric Catalysis · Fluorinated Diazo Compounds · Multi-Component Reactions · Nucleophiles

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[28] Less nucleophilic alcohols, such as HFIP did not show any reactivity.
[29] When an alcohol or an aniline containing a nitrile group was used, only traces of product could be observed, probably due to catalyst deactivation.
[30] Deposition Numbers 2216834 (for **13ac**) and 2225295 (for **19**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
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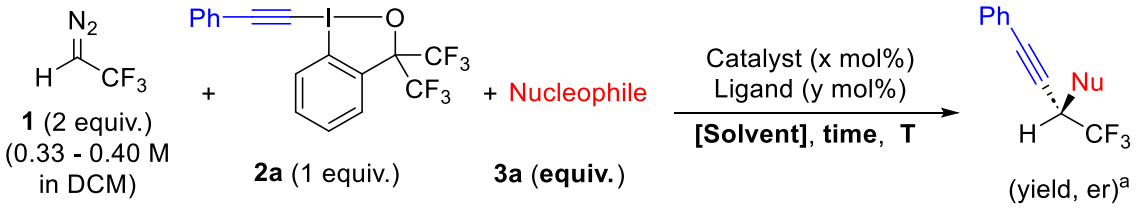
Table of Content

1. General Information

Reagents (precursors of HIR and diazo compounds as well as anilines) and solvents were purchased from different trading houses (Sigma-Aldrich, Fluorochem, TCI) and were used without further purification, unless otherwise stated. TLC was performed on silica gel 60 F254, using aluminum plates, and visualized by exposure with UV. Flash chromatography (FC) was carried out on hand-packed columns of silica gel 60 (230−400 mesh). Infrared (IR) analysis was performed with a JASCO FT/IR b4100 spectrophotometer equipped 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 spectra were performed by the mass spectrometry service of ISIC at EPFL on a MICROMASS (ESI) Ultima API (Waters Instrument). The NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F. The chemical shift (δ) for 1 H and 13C is given in ppm and referenced to residual signals of the solvents (chloroform-d 7.26 ppm ^{1}H NMR and 77.16 ppm ^{13}C NMR). ^{13}C NMR spectra were recorded with 1 H decoupling and ^{19}F NMR as ^{19}F nondecoupling. Coupling constants are given in hertz. The data is reported using the following abbreviations: s, singlet; d, doublet; q, quartet; m, multiplet; bs, broad signal; app, apparent. $Cu(MeCN)_4SbF_6$ was prepared according to a reported procedure.[1] Racemic samples were prepared according to our previous protocol.[2]

[1] Kubas, G. J.; Monzyk, B.; Crumblis, A. L. in Inorganic Synthesis (Ed.; R. J. Angelici), Wiley & Sons, Inc., Hoboken, NJ, USA 2007, pp. 68-70

2. Optimization Studies

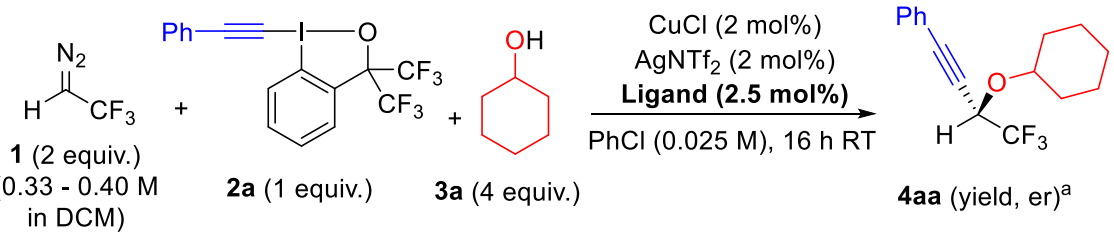


Stock solution of the catalyst: In an oven-dried microwave vial, **catalyst (x mol%)** and **ligand (y mol%)** were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry solvent **[concentration]** was added into the vial and the resulting colourlesss solution was stirred (430 rpm) at room temperature during 1 h.

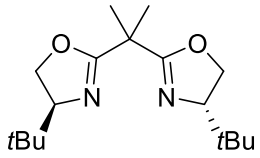
Procedure: In an oven-dried microwave vial, compound **2a** (70 mg, 0.15 mmol, 1.00 equiv.) and **nucleophile (if solid) (equiv)** were added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2, followed by the addition of **1** (0.40 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and **nucleophile (if liquid) (equiv).** The resulting reaction mixture was stirred at RT under N_2 atmosphere and the catalytic solution **[concentration]** was added dropwise. After **t** of reaction, the reaction was monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2** (unless otherwise noticed). The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (10 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography according to the conditions described for each compound.

A) Optimization for Alcohols

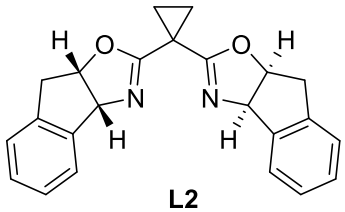
2.1. Influence of the BOX Ligands



1 (2 equiv.) (0.33 - 0.40 M in DCM) + **2a** (1 equiv.) + **3a** (4 equiv.) → **4aa** (yield, er)[a]



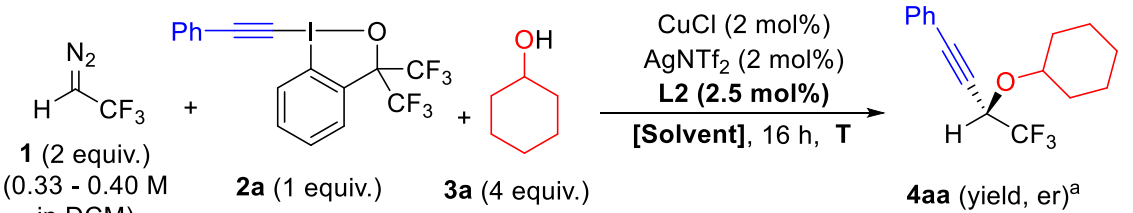
L1
(65%, 93:6 er)



L2
(61%, 92:8 er)[b]

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC. b) The opposite enantiomer was obtained.

2.2. Influence of Solvent, Temperature and Concentration

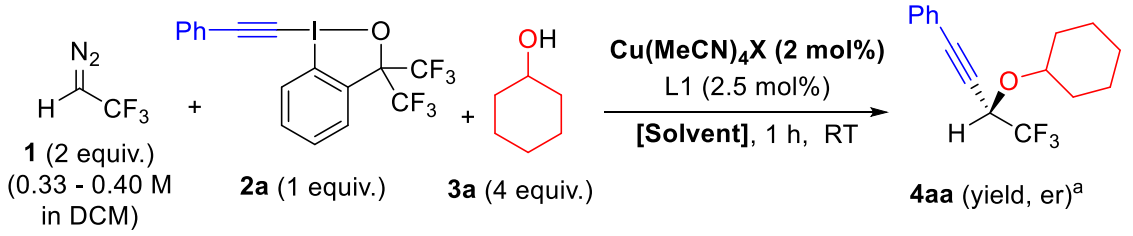


1 (2 equiv.) (0.33 - 0.40 M in DCM) + **2a** (1 equiv.) + **3a** (4 equiv.) → **4aa** (yield, er)[a]

Entry	Solvent/[M]	Temperature	Yield	er
1	PhCl [0.5 M]	RT	90	91:9
2	DCE [0.15 M]	50 °C	quantitative	86:14
3	DCE [0.15 M]	RT	95	89:11

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC. b) The opposite enantiomer was obtained.

2.3. Screening of Copper (I) Catalysts and Solvents



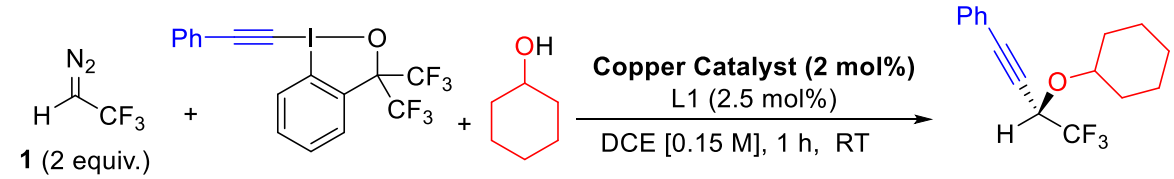
1 (2 equiv.) (0.33 - 0.40 M in DCM) + **2a** (1 equiv.) + **3a** (4 equiv.)

4aa (yield, er)[a]

Entry	Copper (I) catalyst	Solvent	Yield	er
1	$Cu(MeCN)_4SbF_6$	DCE	quantitative	89:11
2	**$Cu(MeCN)_4BF_4$**	**DCE**	**88**	**94:6**
3	$Cu(MeCN)_4SbF_6$	MeCN	n.d.	n.d.
4	$Cu(MeCN)_4SbF_6$	PhMe	82	93:7
5	$Cu(MeCN)_4SbF_6$	THF	78	92:8

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

2.4. Screening of the Stoichiometry and Copper Catalysts Stoichiometry using 3a and Copper (I) Catalyst



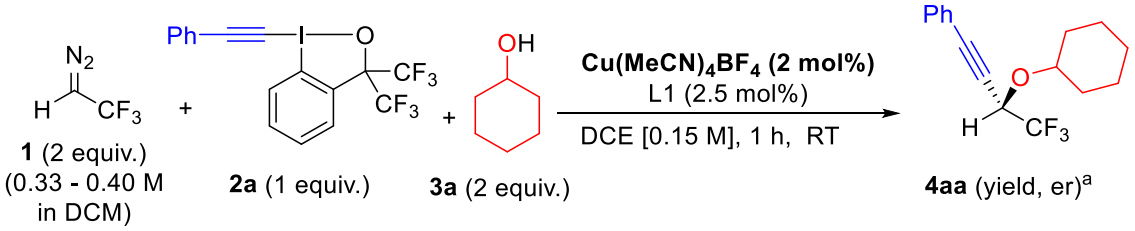
1 (2 equiv.) (0.33 - 0.40 M in DCM) + **2a** (1 equiv.) + **3a** (2 equiv.)

4aa (yield, er)[a]

Entry	Copper (I) catalyst	Equiv of 3a	Yield	er
1	$CuCl/AgNTf_2$	2	75	93:7
2	$CuCl/AgNTf_2$ and L2	2	95	89:11
3	CuI	2	64	89:11
4	CuTC	2	81	87:13
5	Cu(OTf)xPhMe	2	78	95:5
6	**$Cu(MeCN)_4BF_4$**	**2**	**83**	**96:4**
7	$Cu(MeCN)_4BF_4$	1.5	65	95:5
8	$Cu(MeCN)_4SbF_6$	2	89	92:8
9	$Cu(MeCN)_4PF_6$	2	69	89:11
10	$Cu(MeCN)_4OTf$	2	77	93:7
11	$Cu(OAc)_2$	2	69	85:15
12	$Cu(OTf)_2$	2	68	96:4

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

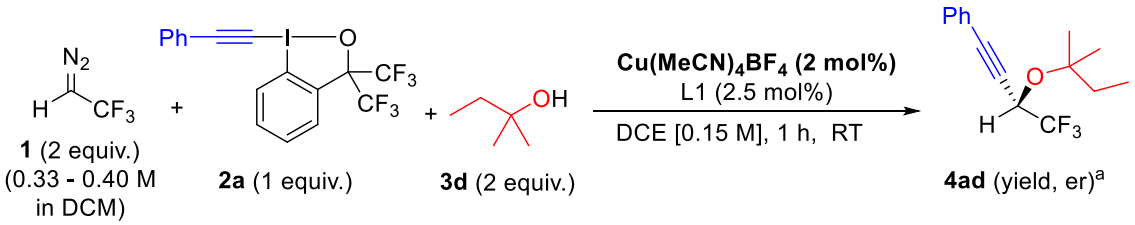
2.5. Final screening



Entry	Solvent and modifications	Yield	er
1	**DCE**	**83**	**96:4**
2	PhMe	76	94:6
3	MeCN	n.d.	n.d.
4	2:1 Cu(I)/L1	75	87:13

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

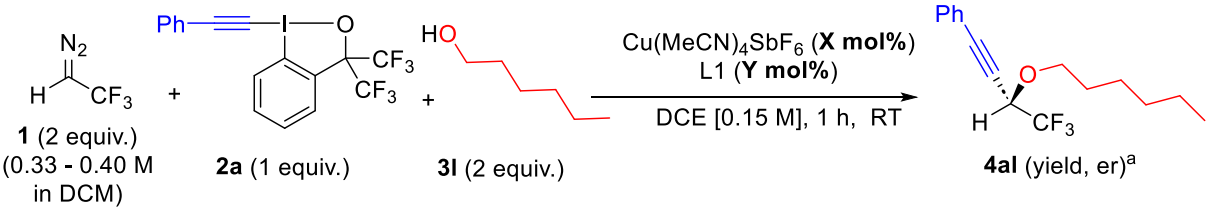
2.6. Optimization for Tertiary Alcohols



Entry	Modifications	Yield	er
1	**none**	**70**	**94:6**
2	$Cu(MeCN)_4SbF_6$	72	95:5
3	$Cu(MeCN)_4SbF_6$, 0 °C and 4 equiv. **3d**	61	95.5:4.5
4	$CuCl/AgNTf_2$	49	95:5
5	CuCl and $AgNTf_2$ and L2 in PhCl (0.025 M)	56	96:4
6	$Cu(MeCN)_4SbF_6$ and L2	84	96:4[a]
7	$Cu(MeCN)_4SbF_6$ and L2 in DCM	66	91:9

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC. [a]Although these conditions gave slightly better results for tertiary alcohols, they were not well suited for secondary alcohols. To keep a single procedure, we therefore preferred to keep the conditions of entry 1 also for tertiary alcohols.

2.7. Optimization for Primary Alcohols

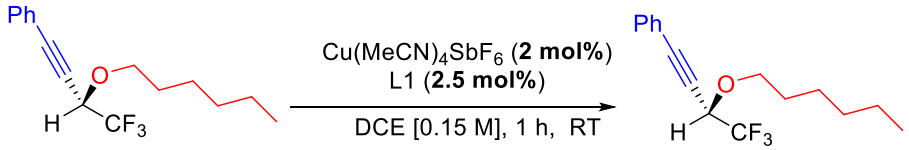


1 (2 equiv.) (0.33 - 0.40 M in DCM) + **2a** (1 equiv.) + **3l** (2 equiv.) → **4al** (yield, er)[a]

Entry	$Cu(MeCN)_4SbF_6$ (X mol%)	L1 (X mol%)	Yield (%)	er
1	**2**	**2**	**90**	**93:7**
2	2	2.5	91	85:15
3	2	4	84	84:16
4	4	2	74	93:7

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

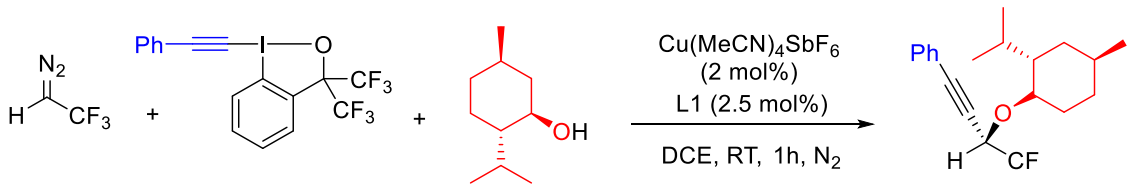
2.8. Control for the Absence of Racemization under the Reaction Conditions



4al 93:7 *er* → **4al** 93:7 *er*

Enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

2.9. Optimization for Chiral Alcohols

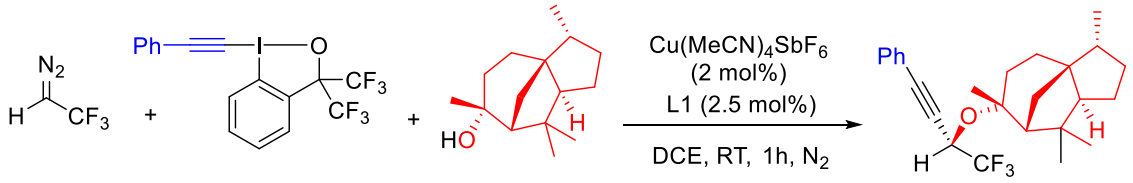


1 (2 equiv.) (0.33 - 0.40 M in DCM) + **2a** (X equiv.) + **5a** (Y equiv.) → **6** (yield, dr)[a]

Entry	Equiv. 2a	Equiv. 5a	Yield (%)	dr
1	1	4	68	96:4
2	**1.5**	**1**	**70**	**97:3**
3	2	2	59	94:4

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and dr determined by ^{19}F NMR of the crude reaction mixture.

2.10. Optimization for Cedrol (5d)



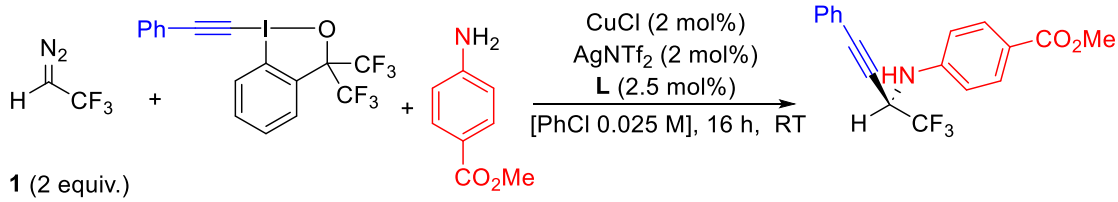
1 (2 equiv.) (0.33 - 0.40 M in DCM) | **2a** (X equiv.) | **5a** (Y equiv.) | **9** (yield, er)[a]

Entry	Equiv. 2a	Equiv. 5d	Yield (%)	dr
1	**1**	**4**	**64**	**85:15**
2	1.5	1	37	97:3
3[b]	**1.5**	1	33	97:3

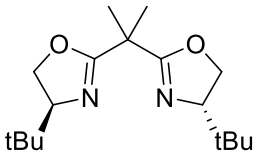
Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and dr determined by ^{19}F NMR of the crude reaction mixture. b) $Cu(MeCN)_4BF_4$ was used instead of $Cu(MeCN)_4SbF_6$

B) Optimization for Anilines

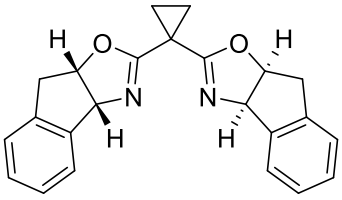
2.11. Screening of Ligands



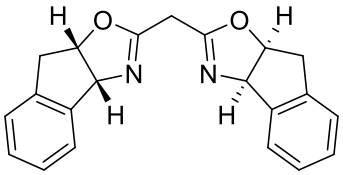
1 (2 equiv.) (0.33 - 0.40 M in DCM) | **2a** (1 equiv.) | **12a** (4 equiv.) | **13aa** (yield, er)[a]



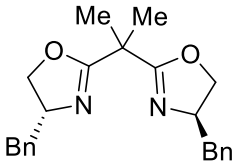
L1 (66%, 98:2 er)



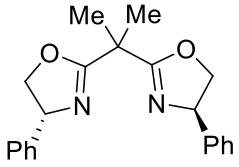
L2 (98%, 8:92 er)



L3 (62%, 13:87 er)



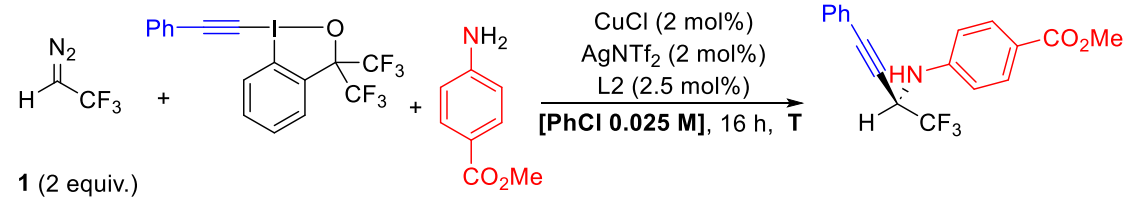
L4 (57%, 19:81 er)



L5 (86%, 25:75 er)

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

2.12. Screening of Temperature

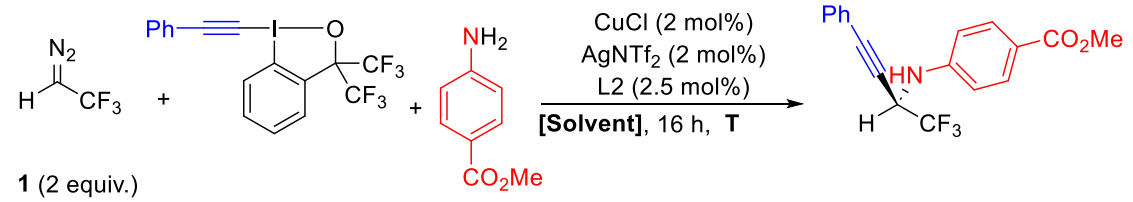


1 (2 equiv.) (0.33 - 0.40 M in DCM) | **2a** (1 equiv.) | **12a** (4 equiv.) | **13aa** (yield, er)[a]

Entry	Temperature	Yield	er
1	**RT**	**98**	**92:8**
2	0 °C to RT	quantitative	94:6
3	-10 °C	76	93.5:6.5

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

2.13. Screening of Solvent, Concentration and Temperature

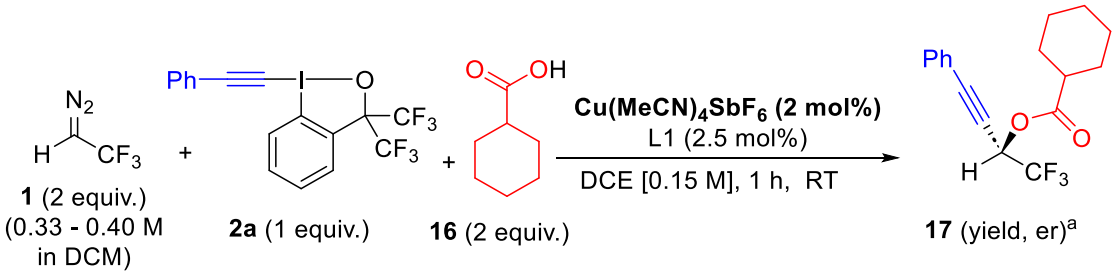


1 (2 equiv.) (0.33 - 0.40 M in DCM) | **2a** (1 equiv.) | **12a** (4 equiv.) | **13aa** (yield, er)[a]

Entry	Temperature	[Solvent]	Yield	er
1	-10	PhCl [0.15 M]	63	97:3
2	RT	PhCl [0.15 M]	93	95:5
3	0	PhCl [0.15 M]	79	96:4
4	RT	DCM [0.15 M]	89	94:6
5	**RT**	**DCE [0.15 M]**	**87**	**96:4**
6[b]	RT	DCE [0.15 M]	68	95:5

Reactions were performed at 0.15 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC. b) **L1** was used instead of **L2.**

2.14. Optimization for Carboxylic Acid (17)



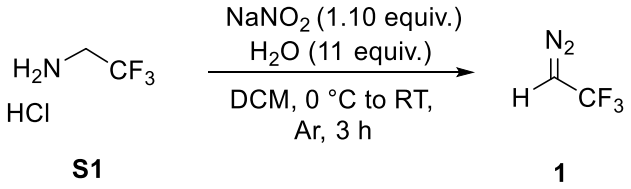
Entry	Modifications	Yield	er
1	**None, 1 h**	**20**	**90:10**
2	None, o/n	20	90:10
3	Cu(I) (4 mol%)/L1 (5 mol%)	20	90:10
4	50 °C	15	90:10
5	Na_2CO_3 (20 mol%)	20	85:15

Reactions were performed at 0.20 mmol scale. In brackets, ^{19}F NMR yield of the crude reaction mixture using $PhCF_3$ as Internal Standard (IS) (1 equiv.) and enantiomeric excess determined by chiral HPLC after purification of the crude reaction mixture by PTLC.

3. Synthesis of Starting Materials

For a better reproducibility, the following syntheses are taken directly from the cited articles reported by our group, unless otherwise is noticed.

3.1. Synthesis of 2,2,2-Trifluorodiazoethane (1)

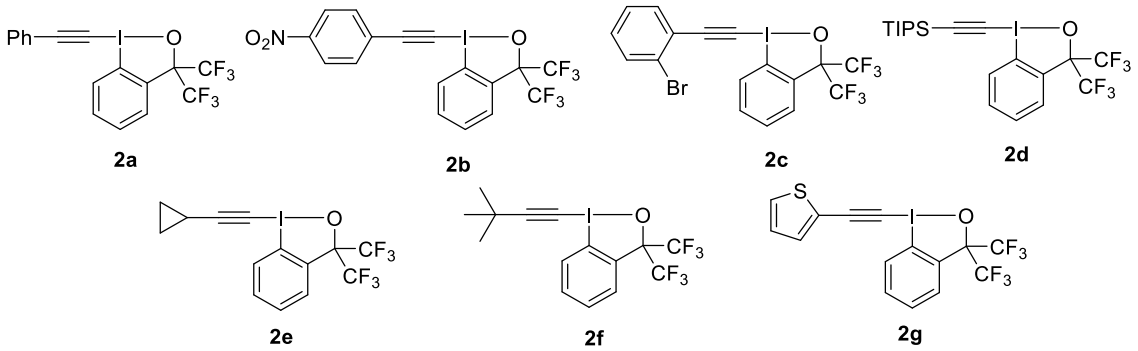


Following a reported procedure,[2] under argon, 2,2,2-trifluoroethanamine hydrochloride (**S1**) (0.678 g, 5.00 mmol, 1.00 equiv) and sodium nitrite (0.379 g, 5.50 mmol, 1.10 equiv) were dissolved in degassed DCM (10 mL). Degassed water (1.00 mL, 55.5 mmol, 11.1 equiv) was added slowly at 0 °C. The solution was stirred for 2 h at 0 °C and 1 h at room temperature. Layers were separated and the organic layer was dried over $MgSO_4$, transferred into a vial, sealed, and stored at −18 °C. The concentration of the obtained solution was determined to be 0.0.33-0.40 M by ^{19}F NMR analysis (according to an

[2] Ramirez, N.P.; Pisella, G.; Waser, J. Cu(I)-Catalyzed gem-Aminoalkynylation of Diazo Compounds: Synthesis of Fluorinated Propargylic Amines. *J. Org. Chem.* **2021**, *86*, 10928-10938.
[3] Pisella, G.; Waser, J. Three-Component Reaction for the Synthesis of Highly Functionalized Propargyl Ethers. *Chem. Eur. J.* **2020**, *26*, 10199 – 10204.

internal reference, $PhCF_3$). **^{19}F NMR (377 MHz, DCM-*d*$_2$)** δ −55.6. The values of the NMR spectra are in accordance with reported literature data.[2], [3]

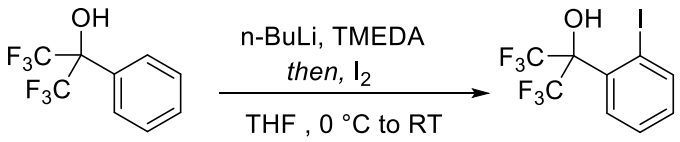
3.2. EBX Used in the Reaction



2a **2b** **2c** **2d**

2e **2f** **2g**

3.3. Synthesis of EBX derivatives



S2 **S3**

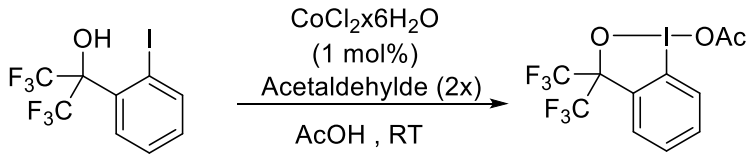
3.3.1. Synthesis of Precursors S3 and S4

1,1,1,3,3,3-Hexafluoro-2-(2-iodophenyl)- propan-2-ol (**S3**).

According to a reported procedure,[2],[3] 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 (**S2**) (7.07 mL, 42.0 mmol, 1.00 equiv) in THF (6.0 mL) was added dropwise. The reaction was stirred for 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 × 30 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/pentane 3:97 as an eluent to afford 1,1,1,3,3,3- hexafluoro-2-(2-iodophenyl)propan-2-ol (**S3**) as a colorless oil (13.9 g, 37.5 mmol, 89%): $\mathbf{R_f}$ 0.66 (95:5,

Pentane/EtOAc, visualized by exposure to UV light); **^{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.[2],[3]

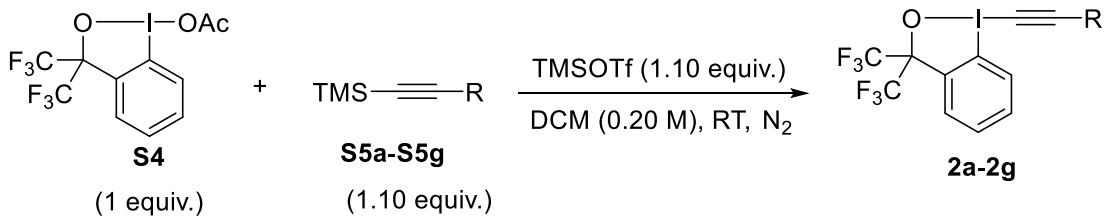
3,3-Bis(trifluoromethyl)-1λ^3 -benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**).



S3 **S4**

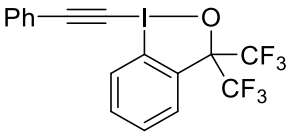
A 500 mL flask was charged with glacial acetic acid (188 mL), 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol (**S4**) (13.9 g, 37.5 mmol, 1.00 equiv.), and cobalt(II) chloride hexahydrate (89.0 mg, 0.375 mmol, 0.01 equiv.). The reaction vessel was purged with O_2 for 5 min before acetaldehyde (21.4 mL, 379 mmol, 10.0 equiv.) was added in one portion. The reaction mixture was stirred under 1 atm. of O_2, delivered by an 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 × 50 mL). The organic layer was dried over $MgSO_4$ and 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)-1λ3 -benzo[d][1,2]iodaoxol-1(3H)-yl acetate (**S4**) 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, -OCH_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.[2],[3]

3.3.2. Synthesis of Hypervalent Iodine Reagents (EBX') (2a–2g)[2],[3]



To a solution of 3,3-bis(trifluoromethyl)-1λ^3 -benzo[*d*][1,2]iodaoxol1(3*H*)-yl acetate (**S4**) (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 (**S5a**–**S5g**) (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 an eluent to give the corresponding EBX' reagent (**2a**–**2g**).

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

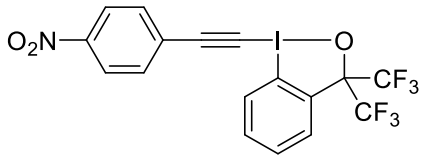


2a

Following the general procedure, starting from trimethyl(phenylethynyl)silane (**S5a**) (192 mg, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (428 mg, 1.00 mmol), afforded 1-(phenylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2b**) as a white solid (395 mg, 0.840 mmol, 84%) after purification by flash column chromatography (100% Pentane to 97:3 Pentane/EtOAc): $\mathbf{R_f}$ = 0.49 (95:5 Pentane/EtOAc, visualized by exposure to UV light); **^{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.[2],[3]

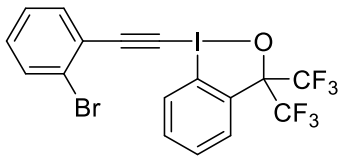
1-((4-nitrophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-λ^3-benzo[*d*][1,2]iodaoxole **(2b):**[2]



2b

Following the general procedure, starting from ((4-nitrophenyl)ethynyl)trimethylsilane (**S5b**)[4] (241. mg, 1.10 mmol) and and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (428 mg, 1.00 mmol), afforded 1-((4-nitrophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2b**) as a yellow amorphous solid (232 mg, 0.450 mmol, 45%) after purification by flash column chromatography (100% Pentane to 90:10 Pentane/EtOAc): $\mathbf{R_f}$ = 0.19 (95:5 Pentane/EtOAc, visualized by exposure to UV light); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.30 - 8.25 (m, 2H Ar*H*), 8.24 - 8.21 (m, 1H, Ar*H*), 7.90 - 7.84 (m, 1H, Ar*H*), 7.78 - 7.68 (m, 4H, Ar*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 148.2, 133.5, 133.3, 131.7, 130.2 (br s), 130.1, 128.5, 128.1, 127.9, 124.0, 123.6 (q, *J* = 289.8 Hz) 111.4, 102.3, 81.8 (m), 61.3; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.1. The values of the NMR spectra are in accordance with reported literature data.[2]

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

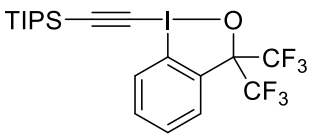


2c

[4] Chuprun, S.; Acosta, C. M.; Mathivathanan, L.; Bukhryakov, K. V. Molybdenum Benzylidene Complexes for Olefin Metathesis Reactions. *Organometallics* **2020**, *39*, 3453-3457.

Following general procedure, starting from ((2-bromophenyl)ethynyl)trimethylsilane (**S5c**) (234 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3 -benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (428 mg, 1.00 mmol), afforded 1-((2-bromophenyl)ethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ3 - benzo[d][1,2]iodaoxole (**2c**) as a white solid (535 mg, 0.970 mmol, 97%) after purification by flash column chromatography (100% Pentane to 95:5 Pentane/EtOAc): **R_f** = 0.34 (95:5 Pentane/EtOAc, visualized by exposure to UV light); **^{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.[3]

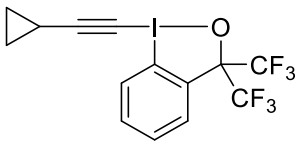
<u>((3,3-Bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane **(2d)**</u>:[2],[3]



2d

Following the general procedure, starting from triisopropyl((trimethylsilyl)ethynyl)silane (**S5d**) (2.80 g, 11.0 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (4.28 g, 10.0 mmol), afforded ((3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl)ethynyl)triisopropylsilane (**2d**) as a white solid (5.33 g, 9.68 mmol, 97%) after purification by flash column chromatography (100% Pentane to 97:3 Pentane/EtOAc): **R_f** = 0.82 (95:5 Pentane/EtOAc, visualized by exposure to UV light); **^{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.[2],[3]

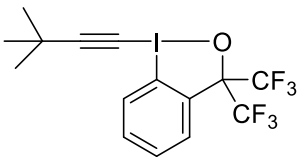
1-(Cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3 -benzo[*d*][1,2]iodaoxole (**2e**): [3]



2e

Following general procedure, starting from (cyclopropylethynyl)trimethylsilane (**S5e**) (995 µL, 5.50 mmol) and 3,3-bis(trifluoromethyl)-1λ^3 -benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (2.14 g, 5.00 mmol), afforded 1-(cyclopropylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3 - benzo[*d*][1,2]iodaoxole (**2e**) as an off-white solid (873 mg, 2.01 mmol, 40%) after purification by flash column chromatography (100% Pentane to 97:3 Pentane/EtOAc): R_f = 0.26 (95:5 Pentane/EtOAc, visualized by exposure to UV light); **^{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, 2*H*, 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.[3]

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

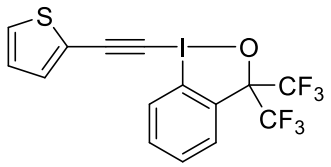


2f

Following the general procedure, starting from (3,3-dimethylbut-1-yn-1-yl)trimethylsilane (**S5f**) (229 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (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 (**2f**) as a white solid (350 mg, 0.780 mmol, 78%) after purification by flash column chromatography (100% Pentane to 97:3 Pentane/EtOAc): R_f = 0.34 (95:5

Pentane/EtOAc, visualized by exposure to UV light); **^{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.[2]

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

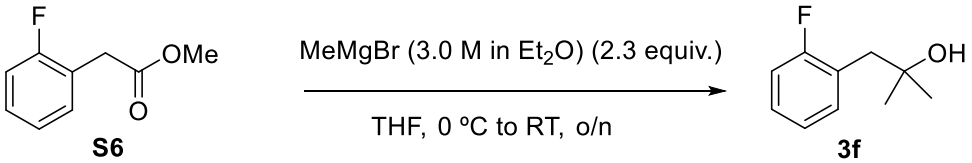


2g

Following general procedure, starting from trimethyl(thiophen-2-ylethynyl)silane (**S5g**) (182 µL, 1.10 mmol) and 3,3-bis(trifluoromethyl)-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate (**S4**) (428 mg, 1.00 mmol), afforded 1-(thiophen-2-ylethynyl)-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ^3-benzo[*d*][1,2]iodaoxole (**2g**) as an off-white solid (403 mg, 0.850 mmol, 85%) after purification by flash column chromatography (100% Pentane to 95:5 Pentane/EtOAc): R_f = 0.34 (95:5 Pentane/EtOAc, visualized by exposure to UV light); **^{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.[2]

3.4. Synthesis of alcohols 3f and 3p

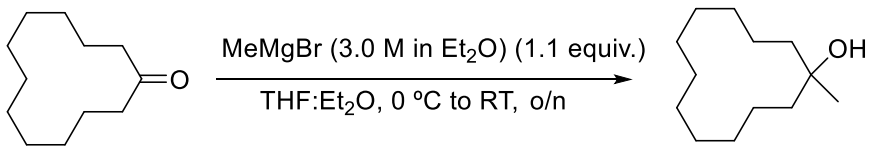
3.4.1. Preparation of 1-2-fluorophenyl)-2-methylpropan-2-ol (3f)



S6 **3f**

Following a reported procedure,[4] in a two-necked round bottom flask, a solution of **S6** was prepared (1.0 mL, 6.8 mmol, 2.3 equiv.) in dry THF (60 mL). The reaction mixture was cooled down to 0 °C and a solution of MeMgBr (5.2 mL, 16 mmol, 2.3 equiv., 3.0 M in Et_2O) in dry THF (10 mL) was added dropwise. The resulting reaction mixture was allowed to reach room temperature and stirred overnight at room temperature under N_2 atmosphere. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL, aprox.) and stirred for 15 min. Then, aqueous layer was extracted with EtOAc (3 x 40 mL). Organics were recombined, washed with water (2 x 30 mL), brine (1 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Compound **3f** was obtained after flash column chromatography (Pentane/EtOAc, 90:10 to 80:20) as a colorless oil (815 mg, 4.84 mmol, 71%): **Rf** = 0.28 (Pentane/EtOAc, 9:1), visualized by exposure to UV light; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.18 - 7.11 (m, 2H, Ar*H*), 7.04 - 6.96 (m, 2H, Ar*H*), 2.76 (d, *J* = 1.8 Hz, 2H, -CH_2-), 1.18 (d, *J* = 1.0 Hz, 6H, 2 x -CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -116.1 (m). The values of the NMR spectra are in accordance with reported literature data.[4]

3.4.2. Preparation of 1-2-fluorophenyl)-2-methylpropan-2-ol (3p)



S7 **3p**

Following a reported procedure:[4]In an oven-dried two necked flask, a solution of cyclododecanone **S7** (1.0 g, 5.5 mmol, 1.00 equiv.) in Et_2O (25 mL) was prepared. The solution was cooled down to 0 °C and MeMgBr (2.0 mL, 6.0 mmol, 1.1 equiv. 3.0 M in Et_2O) diluted with THF (4 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred overnight under N_2 atmosphere. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and the resulting suspension was stirred for 15 min. After this time, H_2O (15 mL) and EtOAc (30 mL) were added, and the layers were separated. Aqueous layer was separated and extracted with EtOAc (3 x 20

[4] Amos, S.G.E., Cavalli, D.; Le Vaillant, F.; Waser, J. Direct Photoexcitation of Ethynylbenziodoxolones: An Alternative to Photocatalysis for Alkynylation Reactions. *Angew. Chem. Int. Ed.* **2021**, *60*, 23827–23834.

mL). Organics were recombined, washed with brine (1x 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (100% to 95:5, Pentane/EtOAc), affording compound **3p** as a white solid (567 mg, 2.90 mmol, 52%): R_f = 0.26 (95:5 Pentane/EtOAc, stained with $KMnO_4$); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 1.59 - 1.49 (m, 2H), 1.45 - 1.24 (m, 21 H), 1.17 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 73.8, 36.3, 29.2, 26.6, 26.2, 22.7, 22.2, 20.1. The values of the NMR spectra are in accordance with reported literature data.[4]

4. Synthesis of L2 and L3[5]

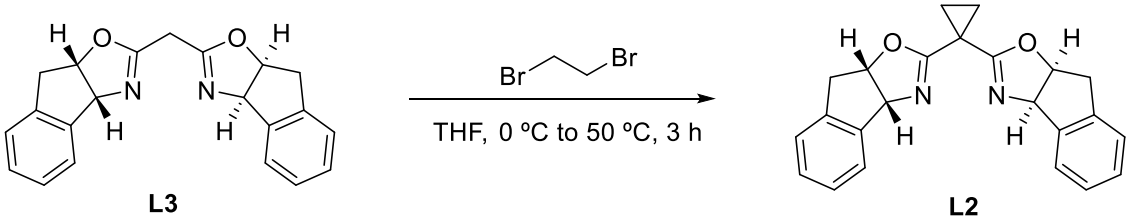
4.1. Preparation of L3

S8 **S9** **L3**

In a round bottom flask, diethyl malonimidate dihydrochloride (1.2 g, 5.0 mmol, 1.00 equiv.) and (1*R*, 2*S*)-(+)-cis-1-amino-2-indanol (1.6 g, 10 mmol, 2.11 equiv.) were added. The system was backfilled with N_2-vacumm cycles (3 times). Then, dry DCM (15 mL) was added, and the purple suspension was stirred at reflux under N_2 atmosphere during 24h. The reaction was allowed to reach room temperature and H_2O (70 mL) was added. Layers were separated and aqueous layer was extracted with DCM (3 x 70 mL). Organic layers were recombined, washed with brine (1 x 10 mL), dried over anydrous $MgSO_4$, filtered and concentrated under reduced pressure, affording a pale-brown solid, which was recrystallized with EtOH (20 mL). Compound **L3** was obtained as a white solid (1.25 g, 3.71 mmol 74%): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.51 - 7.44 (m, 2H, Ar*H*), 7.30 - 7.23 (m, 6H, Ar*H*), 5.58 (d, *J* = 8.8 Hz, 2H, -C*H*$_2$Ar), 5.39 – 5.32 (m, 2H, -C*H*$_2$Ar), 3.40 (dd, *J* = 17.6, 6.7 Hz, 2H, -C*H*O-), 3.28 (s, 2H, -C*H*$_2$C=N-), 3.23 – 3.12 (m, 2H, -C*H*O-): **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.1, 141.7, 139.8, 128.6, 127.6, 125.6, 125.4, 83.7, 76.8, 39.8, 28.8. The values of the NMR spectra are in accordance with reported literature data.[5]

[5] Hofstra, L.; DeLano, T. J.; Reisman, S. E. Synthesis of Chiral Bisoxazoline Ligands: (3aR,3a'R,8aS,8a'S)-2,2'-(cyclopropane-1,1-diyl)bis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole). *Org. Synth.* **2020**, *97*, 172-188.

4.2. Preparation of L2



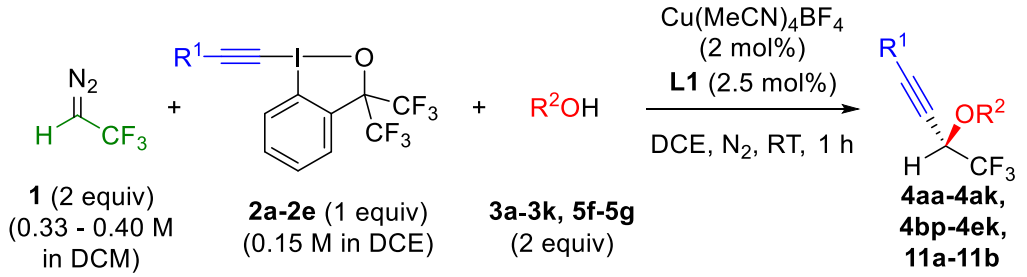
L3 **L2**

In an oven dried two-necked round bottomed flask, a solution of **L3** (502 mg, 1.52 mmol, 1.00 equiv.) in dry THF (11.8 mL) was prepared and the mixture was cooled down to 0 ºC and stirred during 15 min. Then, NaH (60% dispersion in mineral oil) (182 mg, 4.56 mmol, 3.00 equiv.) is added portionwise during 5 min. The mixture was vigorously stirred during 5 min and then, the reaction was allowed to reach room temperature and heated to 50 ºC during 2 h. After this time, the reaction was allowed to reach room temperature and cooled again to 0 ºC. The reaction mixture was quenched with NH_4Cl (10 mL) and diluted with H_2O (7 mL). Then, DCM (20 mL) was added and layers were separated. Aqueous layer was extracted with DCM (3 x 20 mL) and organics were recombined, washed with brine (1 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure affording a pale-yellow solid, which was recrystallyzed Hexane/EtOAc (2:1, 15 mL), providing **L2** as a white solid (385 mg, 1.08 mmol, 71%): **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 - 7.41 (m, 2H, Ar*H*), 7.24 - 7.21 (m, 6H, Ar*H*), 5.52 (dd, *J* = 7.9, 0.8 Hz, 2H, -C*H*$_2$Ar), 5.33 (ddd, *J* = 8.0, 7.0, 1.9 Hz, 2H, -C*H*$_2$Ar), 3.38 (dd, *J* = 17.7, 6.9 Hz, 2H, -C*H*Ar), 3.19 (dd, *J* = 17.9, 1.9 Hz, 2H, -C*H*Ar), 1.38 – 1.30 (m, 2H, -cyclopropyl), 1.30 – 1.23 (m, 2H, cyclopropyl): **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.0, 141.9, 139.9, 128.5, 127.49, 125.8, 125.3, 83.5, 76.5, 39.8, 18.5, 15.9. The values of the NMR spectra are in accordance with reported literature data.[5]

5. Procedures and Compound Characterization for the Enantioselective 3-Component Reaction between 1, 2 and Alcohols (3, 5)

In order to avoid reproducibility issues, a stock solution of the catalyst was prepared triplicating the corresponding amount of $Cu(MeCN)_4BF_4$, L1 and DCE belonging to a 0.20 mmol scale 3-CR reaction. Then, the same catalytic stock solution was used for 2 reactions.

Procedure A: Synthesis of Trifluoromethylated Propargylic Ethers **4aa-4ak**, **4bp-4eb**, **11a-11b**.



1 (2 equiv) (0.33 - 0.40 M in DCM)

2a-2e (1 equiv) (0.15 M in DCE)

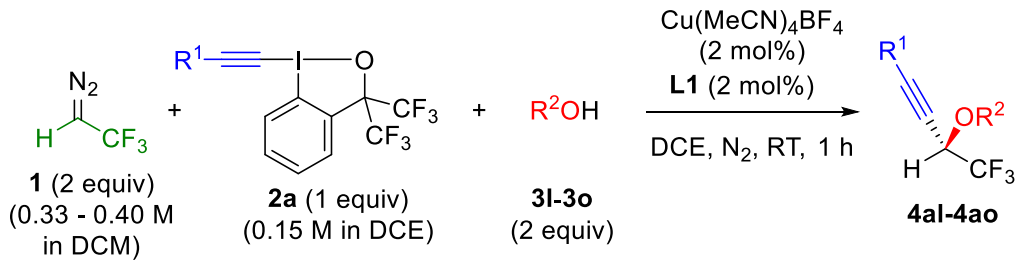
3a-3k, 5f-5g (2 equiv)

4aa-4ak, 4bp-4ek, 11a-11b

Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (3.8 mg, 1.2 µmol, 0.06 equiv.) and **L1** (4.4 mg, 1.5 µmol, 0.075 equiv.) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (3.9 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

Procedure: In an oven-dried microwave vial, compound **2** (0.20 mmol, 1.00 equiv.) and alcohol **3** (if solid) (0.40 mmol, 2.00 equiv.) were added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2, followed by the addition of **1** (0.40 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and alcohol **3** (if liquid) (0.40 mmol, 2.00 equiv.). The resulting reaction mixture was stirred at RT under N_2 atmosphere and the catalytic solution (1.30 mL) was added dropwise. After 1h of reaction, the reaction was monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2** (unless otherwise noticed). The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (15 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography according to the conditions described for each compound.

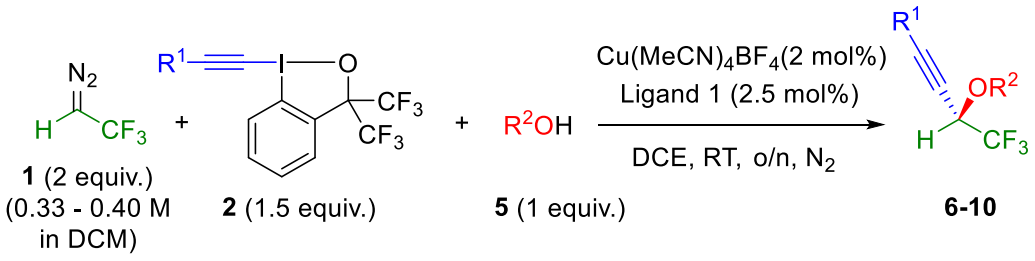
Procedure B: Synthesis of Trifluoromethylated Propargylic Ethers **4al-4an**.



Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (3.8 mg, 1.2 µmol, 0.060 equiv) and **L1** (3.5 mg, 1.2 µmol, 0.060 equiv) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (3.9 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

Procedure: In an oven-dried microwave vial, compound **2a** (94 mg, 0.20 mmol, 1.00 equiv.) was added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2, followed by the addition of **1** (0.40 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and alcohol **3l-3n** (0.40 mmol, 2.00 equiv.). The resulting reaction mixture was stirred at RT under N_2 atmosphere and the catalytic solution (1.30 mL) was added dropwise. After 1 h of reaction, the reaction was monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2** (unless otherwise noticed). The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (15 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography according to the conditions described for each compound.

Procedure C: Synthesis of Trifluoromethylated Propargylic Ethers **6-10**.

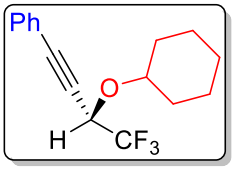


Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (3.8 mg, 1.2 µmol mmol, 0.060 equiv.) and **L1** (4.4 mg, 1.5 µmol, 0.075 equiv.) were charged and

the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (3.9 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

Procedure: In an oven-dried microwave vial, compound **2** (0. 30 mmol, 1.50 equiv.) and alcohol (**5a**-**5e**) (if solid) (0.20 mmol, 1.00 equiv.) were added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N2, followed by the addition of **1** (0.40 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and alcohol (**5a-5e**) (if liquid) (0.20 mmol, 1.00 equiv.). Finally, the catalytic solution (1.30 mL) was added dropwise and the resulting reaction mixture was stirred overnight at RT under N_2 atmosphere. The reaction was monitored by TLC (90:10, Pentane/EtOAc) observing full conversion of **5** (unless otherwise noticed). The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (15 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography according to the conditions described for each compound.

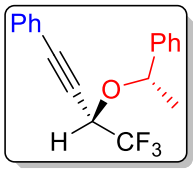
(*S*)-(3-(Cyclohexyloxy)-4,4,4-trifluorobut-1-yn-1-yl)benzene (**4aa**):



Compound **4aa** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and cyclohexanol **3a** (42 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (46.8 mg, 0.166 mmol, 83%): The enantiomeric ratio (er) resulted to be 96:4 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.8 min, $t_{R(major)}$ = 6.2 min; $\boldsymbol{\alpha_D^{23}}$ = 127.6 (c = 0.375, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.63 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2937 (m), 2861 (w), 2229 (w), 1491 (w), 1447 (w), 1440 (w), 1361 (w), 1274 (m), 1254 (m), 1219 (m), 1184 (s), 1143 (s), 1100 (m), 770 (s), 761 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 - 7.30 (m, 3H, Ar*H*), 7.49 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar*H*), 4.76 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 3.75 (td, *J* = 9.2, 4.5 Hz, 1H, -OC*H*-), 2.01 - 1.87 (m, 2H, -CH_2 *cyclohexyl*), 1.84 - 1.74 (m, 2H, -CH_2

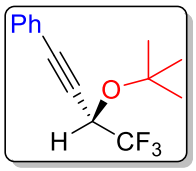
cyclohexyl), 1.58 - 1.48 (m, 2H, -CH_2 *cyclohexyl*), 1.44 - 1.23 (m, 4H, -CH_2 *cyclohexyl*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 132.2, 129.3, 128.5, 127.1, 122.9 (q, *J* = 281.5 Hz), 121.5, 87.6, 80.5 (q, *J* = 2.4 Hz), 78.1, 67.1 (q, *J* = 34.8 Hz), 32.7, 31.4, 25.7, 24.0, 23.8; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.3 (d, *J* = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}F_3O^+$ 283.1304; Found 283.1306.

(*S*)-4,4,4-Trifluoro-3-((*S*)-1-phenylethoxy)but-1-yn-1-yl)benzene (**4ab**):



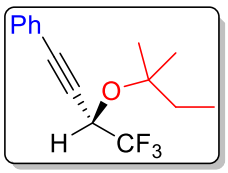
Compound **4ab** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and (*S*)-1-phenylethanol (**3b**) (50 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (42.6 mg, 0.140 mmol, 70%): The diastereomeric ratio (dr) resulted to be 95:5 and was determined by ^{19}F NMR of the crude mixture; **α_D^{23}** = 65.2 (c = 0.2, $CHCl_3$); **TLC** ***R_f*** = 0.75 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2962 (m), 2946 (m), 2904 (w), 2874 (w), 2146 (w), 1490 (m), 1473 (m), 1467 (m), 1444 (m), 1380 (m), 1270 (s), 1260 (s), 1218 (s), 1191 (s), 1186 (s), 1148 (s), 1141 (s), 967 (m), 946 (m), 930 (m), 772 (s), 758 (s), 730 (m); **^{1}H NMR (400 MHz, $CDCl_3$, , mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.50 – 7.29 (m, 10H, Ar*H*), 4.87 (q, *J* = 6.5 Hz, 1H, -OC*H*-), 4.64 (q, *J* = 5.7 Hz, 1H, -OC*H*CF_3), 1.56 (d, *J* = 6.4 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 142.0, 132.1, 129.3, 128.7, 128.4, 128.3, 127.4, 126.7, 124.2 (q, *J* = 281.9 Hz), 121.5, 87.8, 80.1 (q, *J* = 2.5 Hz), 79.7, 67.8 (q, *J* = 34.8 Hz), 23.6; **^{19}F NMR (376 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ -76.7 (d, *J* = 5.4 Hz, minor diastereoisomer), -76.8 (d, *J* = 6.1 Hz, major diastereoisomer); **HRMS (APPI/LTQ-Orbitrap)** *m/z*: [M]+ Calcd for $C_{18}H_{15}F_3O^+$ 304.1070; Found 304.1067.

(*S*)-(3-(tert-butoxy)-4,4,4-trifluorobut-1-yn-1-yl)benzene (**4ac**):



Compound **4ac** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and *tert*-butanol (**3c**) (40 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (37.0 mg, 0.144 mmol, 72%): The enantiomeric ratio (er) resulted to be 96:4 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 5.6 min, $t_{R(minor)}$ = 6.1 min; α_D^{23} = -147.9 (c = 0.1, $CHCl_3$); **TLC *Rf*** = 0.54 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2981 (w), 2936 (w), 1368 (w), 1350 (w), 1276 (m), 1254 (m), 1220 (m), 1184 (s), 1141 (s), 1087 (m), 898 (m), 772 (s), 763 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (dd, *J* = 7.8, 1.8 Hz, 2H, Ar*H*), 7.37 – 7.30 (m, 3H, Ar*H*), 4.74 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 1.35 (s, 9H, (-CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 132.0, 129.2, 128.5, 127.2, 123.0 (q, *J* = 281.3 Hz), 86.6, 82.5 (q, *J* = 2.2 Hz), 77.4, 62.9 (q, *J* = 35.0 Hz), 27.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -77.4 (d, *J* = 5.5 Hz); **HRMS (Sicrit plasma/LTQ-Orbitrap)** *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}F_3O^+$ 257.1148; Found 257.1139.

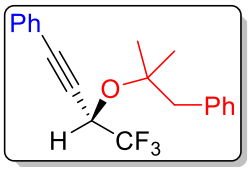
(*S*)-(4,4,4-Trifluoro-3-(tert-pentyloxy)but-1-yn-1-yl)benzene (**4ad**):



Compound **4ad** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 2-methylbutan-2-ol (3d) (45 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (37.8 mg, 0.140 mmol, 70%): The enantiomeric ratio (er) resulted to be 94:6 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 5.3 min, $t_{R(minor)}$ = 6.0 min; α_D^{23} = -127.8 (c = 0.1, $CHCl_3$); **TLC *Rf*** = 0.53 (99:1

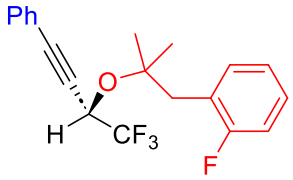
Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2975 (m), 2939 (w), 2885 (w), 1491 (m), 1465 (m), 1445 (w), 1389 (m), 1375 (m), 1354 (m), 1324 (m), 1274 (s), 1255 (m), 1217 (m), 1181 (s), 1141 (s), 1087 (s), 938 (m), 921 (w), 889 (m), 878 (m), 771 (s), 755 (s)**; ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 - 7.43 (m, 2H, Ar*H*), 7.36 - 7.30 (m, 3H, Ar*H*), 4.74 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 1.72 - 1.52 (m, 2H, -C$H_2$$CH_3$), 1.31 (s, 3H, -C$H_3$), 1.27 (s, 3H, CH_3), 0.97 (t, *J* = 7.5 Hz, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 132.0, 129.1, 128.5, 123.0 (q, *J* = 281.2 Hz), 121.9, 86.6, 82.6, 79.7, 62.7 (q, *J* = 35.0 Hz), 33.8, 25.5, 24.9, 8.5; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.3 (d, *J* = 5.4 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z: [M + Na]$^+$* Calcd for $C_{15}H_{17}F_3NaO^+$ 293.1124; Found 293.1125.

(*S*)-(2-Methyl-2-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)propyl)benzene (**4ae**):



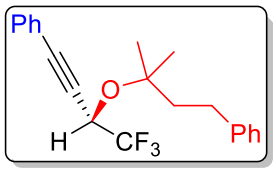
Compound **4ae** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 2-methyl-1-phenylpropan-2-ol (**4e**) (63µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (43.2 mg, 0.130 mmol, 65%): The enantiomeric ratio (er) resulted to be 97:3 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 10.5 min, $t_{R(minor)}$ = 12.7 min; **α_D^{23}** = -112.3 (c = 0.1, $CHCl_3$); **TLC** Rf 0.45 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 2975 (m), 2934 (w), 2240 (w), 2226 (w), 1491 (m), 1465 (m), 1445 (w), 1389 (m), 1373 (m), 1350 (m), 1324 (m), 1273 (s), 1255 (m), 1242 (m), 1219 (m), 1181 (s), 1141 (s), 1088 (s), 1008 (w), 990 (m), 938 (m), 920 (w), 889 (m), 877 (m), 770 (s), 755 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar*H*), 7.37 – 7.19 (m, 8H, Ar*H*), 4.81 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 2.97 (d, *J* = 13.4 Hz, 1H, -C*H*Ph), 2.85 (d, *J* = 13.4 Hz, 1H, -C*H*Ph), 1.34 (s, 3H, -CH_3), 1.22 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 137.6, 132.0, 130.8, 129.2, 128.5, 128.1, 126.5, 121.5 (q, *J* = 280.6 Hz), 121.8, 86.9, 82.5 (q, *J* = 2.1 Hz), 79.8, 62.9 (q, *J* = 35.2 Hz), 48.4, 25.6, 24.8; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -77.2 (d, *J* = 5.5 Hz); **HRMS (Sicrit plasma/LTQ-Orbitrap)** *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{20}F_3O^+$ 333.1461; Found 333.1449.

1-Fluoro-2-(2-methyl-2-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)propyl)benzene (**4af**)



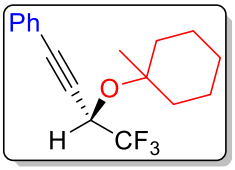
Compound **4af** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 1-(3-fluorophenyl)-2-methylpropan-2-ol (**3f**) (67.3 mg, 0.400 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (35.0 mg, 0.100 mmol, 50%): The enantiomeric ratio (er) resulted to be 98:2 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 0.5 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 16.3 min, $t_{R(minor)}$ = 18.4 min; $\boldsymbol{\alpha_D^{23}}$ = -123.0 (c = 0.1, $CHCl_3$); **TLC** Rf 0.58 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2937 (w), 2863 (w), 2859 (w), 1596 (w), 1524 (m), 1491 (m), 1456 (w), 1346 (s), 1274 (m), 1254 (m), 1213 (w), 1185 (s), 1143 (s), 1105 (m), 857 (m), 772 (s), 763 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 - 7.40 (m, 2H, Ar*H*), 7.37 - 7.30 (m, 5H, Ar*H*), 7.09 - 7.00 (m, 2H, Ar*H*), 4.81 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 2.97 (s, 2H, -CH_2), 1.26 (s, 6H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.5 (d, *J* = 244.9 Hz), 133.4 (q, *J* = 4.4 Hz), 132.7, 132.0, 129.2, 128.6, 128.5, 128.4 (d, *J* = 8.4 Hz), 124.5 (q, *J* = 15.3 Hz), 123.2 (q, *J* = 285.0 Hz), 123.8 (q, *J* = 3.3 Hz), 115.2 (d, *J* = 23.3 Hz), 87.0, 79.9 (q, *J* = 2.0 Hz), 62.9 (q, *J* = 35.7 Hz), 40.4, 25.5, 24.5; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.2 (d, *J* = 5.5 Hz), -116.1 – -116.7 (m); **HRMS (APPI/LTQ-Orbitrap)** *m/z: [M]$^+$* Calcd for $C_{20}H_{18}F_4O^+$ 350.1288; Found 350.1290.

(*S*)-(3-Methyl-3-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)butyl)benzene (**4ag**):



Compound **4ag** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 2-methyl-4-phenylbutan-2-ol (**3g**) (69 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (30 mg, 0.087 mmol, 43%): The enantiomeric ratio (er) resulted to be 97:3 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 14.0 min, $t_{R(minor)}$ = 16.8 min; $\boldsymbol{\alpha_D^{23}}$ = -112.2 (c = 0.1, $CHCl_3$); **TLC R*f*** = 0.65 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 3029 (w), 2973 (w), 2936 (w), 1491 (m), 1375 (m), 1350 (m), 1272 (m), 1182 (s), 1139 (s), 1083 (m), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 (d, *J* = 6.6 Hz, 1H, Ar*H*), 7.16 - 709 (m, 3H, Ar*H*), 7.07 - 7.03 (m, 3H, Ar*H*), 7.01 - 6.95 (m, 3H, Ar*H*), 4.60 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 2.62 (td, *J* = 13.0, 5.1 Hz, 1H, -CH_2-), 2.52 (td, *J* = 12.9, 5.1 Hz, 1H, -CH_2-), 1.76 (td, *J* = 13.1, 5.1 Hz, 1H, -CH_2-), 1.70 – 1.59 (m, 1H, -CH_2-), 1.20 (s, 3H, -CH_3), 1.17 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.5, 132.1, 129.2, 128.51, 128.50, 128.47, 125.9, 123.0 (q, *J* = 281.0 Hz), 121.8, 86.9, 82.4 (q, *J* = 1.9 Hz), 79.1, 62.9 (q, *J* = 35.2 Hz), 43.3, 30.4, 26.2, 25.6; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -77.2 (d, *J* = 6.2 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z:* $[M]^+$ Calcd for $C_{21}H_{21}F_3O^+$ 346.1539; Found 346.1554.

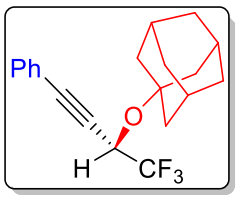
(*S*)-(4,4,4-Trifluoro-3-((1-methylcyclohexyl)oxy)but-1-yn-1-yl)benzene (**4ah**):



Compound **4ah** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 1-methylcyclohexan-1-ol (**2h**) (51 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (32.5 mg, 0.110 mmol, 55%): The enantiomeric ratio (er) resulted to be 95:5 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB

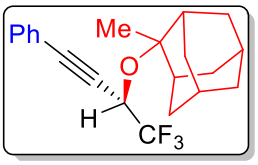
N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 5.2 min, $t_{R(minor)}$ = 6.0 min; **α_D^{23}** = -129.5 (c = 0.1, $CHCl_3$); **TLC** Rf 0.68 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2971 (w), 2936 (m), 2868 (w), 1271 (m), 1256 (m), 1219 (m), 1181 (s), 1139 (s), 1083 (m), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.48 - 7.43 (m, 2H, Ar*H*), 7.38 - 7.30 (m, 3H, Ar*H*), 4.76 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 1.88 - 1.64 (m, 4H, -CH_2 cyclohexyl), 1.51 - 1.38 (m, 5H, -CH_2 cyclohexyl), 1.36 - 1.25 (m, 4H, -CH_2 cyclohexyl + -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 132.0, 129.1, 128.5, 123.1 (q, *J* = 282.2 Hz), 121.9, 86.6, 82.7 (q, *J* = 2.2 Hz), 78.4, 62.2 (q, *J* = 35.2 Hz), 37.2, 36.6, 25.7, 25.2, 22.5, 22.2; **^{19}F NMR (377 MHz, $CDCl_3$)** *δ* -77.0 (d, *J* = 5.5 Hz); **HRMS (Sicrit plasma/LTQ-Orbitrap)** *m/z: [M + H]$^+$* Calcd for $C_{17}H_{20}F_3O^+$ 297.1461; Found 297.1450.

(3*R*,5*R*)-1-(((*S*)-1,1,1-Trifluoro-4-phenylbut-3-yn-2-yl)oxy)adamantane (**4ai**):



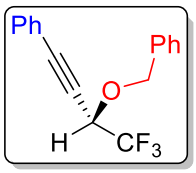
Compound **4ai** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and adamantan-1-ol (**2i**) (70 mg, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (50.0 mg, 0.150 mmol, 75%): The enantiomeric ratio (er) resulted to be 95:5 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 7.0 min, $t_{R(minor)}$ = 8.3 min; **α_D^{23}** 9.3 (c = 0.44, $CHCl_3$); **TLC R_f =** 0.76 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2971 (w), 2936 (m), 2868 (w), 1271 (m), 1256 (m), 1219 (m), 1181 (s), 1139 (s), 1083 (m), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.47 (dd, *J* = 7.7, 1.8 Hz, 2H, Ar*H*), 7.37 - 7.30 (m, 3H, Ar*H*), 4.90 (q, *J* = 6.0 Hz, 1H, -C*H*CF_3), 2.21 (br s, 3H, -ad), 1.94 - 1.78 (m, 6H, -ad), 1.73 - 1.59 (m, 6H, -ad); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 132.1, 129.1, 128.5, 121.7 (q, *J* = 278.2 Hz), 121.9, 86.4, 82.7 (q, *J* = 1.9 Hz), 76.6, 60.8 (q, *J* = 34.7 Hz), 41.8, 36.4, 30.8; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -77.3 (d, *J* = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z:* [M]$^+$ Calcd for $C_{20}H_{21}F_3O^+$ 334.1539; Found 334.1552.

(1*R*,2*S*,5*S*)-2-Methyl-2-(((*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)adamantane (**4aj**):



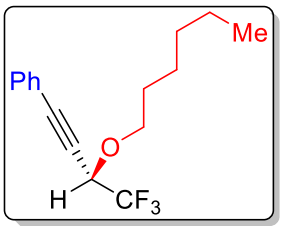
Compound **4aj** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 2-methyladamant-2-ol (**2j**) (66 mg, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (52.0 mg, 0.149 mmol, 75%): The enantiomeric ratio (er) resulted to be 97:3 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 5.7 min, $t_{R(minor)}$ = 6.2 min; $\boldsymbol{\alpha_D^{23}}$ = 69.3 (c = 0.775, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.91 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2960 (w), 2920 (w), 2877 (w), 2251 (w), 2230 (w), 1594 (w), 1494 (m), 1492 (m), 1372 (w), 1361 (w), 1277 (m), 1253 (m), 1220 (s), 1191 (m), 1188 (m), 1152 (s), 1079 (m), 1067 (m), 1004 (w), 990 (w), 877 (w), 773 (s), 757 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 – 7.44 (m, 2H, Ar*H*), 7.37 – 7.27 (m, 3H, Ar*H*), 4.84 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 1.90 – 1.74 (m, 9H, -ad), 1.62 – 1.53 (m, 4H, -ad), 1.47 – 1.48 (m, 4H, -C*H*$_3$ + -ad); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 131.9, 129.1, 128.5, 126.0 (q, *J* = 280.4 Hz), 122.0, 86.8, 82.9 (q, *J* = 1.5 Hz), 82.6, 62.0 (q, *J* = 35.0 Hz), 38.6, 37.3, 36.7, 35.4, 35.0, 33.1, 32.4, 27.7 27.1, 22.2; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -76.6 (d, *J* = 5.5 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z:* $[M]^+$ Calcd for $C_{21}H_{23}F_3O^+$ 348.1696; Found 348.1711.

(*S*)-(3-(Benzyloxy)-4,4,4-trifluorobut-1-yn-1-yl)benzene (**4ak**):



Compound **4ak** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and benzyl alcohol **3k** (42 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (45.0 mg, 0.155 mmol, 78%): The enantiomeric ratio (er) resulted to be 93:7 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 8.1 min, $t_{R(major)}$ = 8.4 min; $\boldsymbol{\alpha_D^{23}}$ = -12.6 (c = 0.1, $CHCl_3$); **TLC** Rf 0.73 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 3033 (w), 2986 (w), 2968 (w), 2936 (w), 1491 (m), 1273 (m), 1255 (m), 1219 (m), 1186 (m), 1143 (s), 1091 (m), 1086 (m), 1083 (m), 772 (s), 755 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55 - 7.49 (m, 2H, Ar*H*), 7.46 - 7.31 (m, 8H, Ar*H*), 4.95 (d, *J* = 11.9 Hz, 1H, -C*H*$_2$Ph), 4.79 (d, *J* = 11.9 Hz, 1H, -C*H*$_2$Ph), 4.73 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.2, 132.3, 129.6, 128.8, 128.6, 128.5, 128.4, 122.7 (q, *J* = 281.3 Hz), 121.3, 89.0, 79.1 (q, *J* = 2.6 Hz), 71.4, 68.1 (q, *J* = 35.4 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.5 (d, *J* = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z:* $[M]^+$ Calcd for $C_{17}H_{13}F_3O^+$ 290.0918; Found 290.0917.

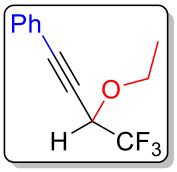
(*S*)-(4,4,4-Trifluoro-3-(hexyloxy)but-1-yn-1-yl)benzene (**4al**):



Compound **4al** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and hexan-1-ol (**3l**) (51 µL, 0.40 mmol, 2.00 equiv.) following the procedure B. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (41.5 mg, 0.146 mmol, 73%). The enantiomeric ratio (er) resulted to be 93:7 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0

hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 6.7 min, $t_{R(major)}$ = 7.6 min; **α_D^{23}** = 112.0 (c = 0.35, $CHCl_3$); **TLC *R_f*** = 0.91 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **α_D^{23}** = 112.0 (c = 0.35, $CHCl_3$); **IR** *(ν_{max}, cm^{-1})* 2953 (m), 2932 (m), 2872 (w), 2861 (w), 2236 (w), 2110 (w), 1804 (w), 1742 (w), 1491 (m), 1468 (w), 1445 (w), 1363 (w), 1318 (w), 1273 (s), 1254 (m), 1218 (m), 1184 (s), 1143 (s), 1108 (s), 1012 (w), 921 (w), 856 (w), 757 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.53 - 7.46 (m, 2H, Ar*H*), 7.42 - 7.31 (m, 3H, Ar*H*), 4.68 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 3.86 (dt, *J* = 9.2, 6.7 Hz, 1H, -OC*H*$_2$-), 3.66 (dt, *J* = 9.2, 6.7 Hz, 1H, -OC*H*$_2$-), 1.70 - 1.63 (m, 2H, -OCH_2CH_2-), 1.45 - 1.36 (m, 2H, -C*H*$_2$-), 1.36 - 1.28 (m, 4H, -CH_2CH_3), 0.91 - 0.87 (m, 3H, -C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 132.2, 129.4, 128.5, 122.7 (q, *J* = 281.9 Hz), 121.4, 88.4, 79.6 (q, *J* = 2.2 Hz), 70.6, 69.5 (q, *J* = 35.0 Hz), 31.7, 29.5, 25.7, 22.7, 14.2; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -76.8 (d, *J* = 5.4 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z:* $[M]^+$ Calcd for $C_{16}H_{19}F_3O^+$ 284.1383; Found 284.1394.

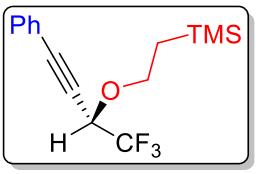
(*S*)-(3-Ethoxy-4,4,4-trifluorobut-1-yn-1-yl)benzene (**4am**):



Compound **4am** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and ethanol (**3m)** (24 µL, 0.40 mmol, 2.00 equiv.) following the procedure B. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (38.9 mg, 0.171 mmol, 85%): The enantiomeric ratio (er) resulted to be 93:7 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 8.0 min, $t_{R(minor)}$ = 8.4 min; **α_D^{23}** = -110.8 (c = 0.1, $CHCl_3$); **TLC *R_f*** = 0.45 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2982 (w), 2940 (w), 2922 (w), 2892 (w), 2233 (w), 1491 (m), 1445 (m), 1361 (m), 1318 (m), 1271 (s), 1256 (m), 1187 (s), 1148 (s), 1109 (s), 990 (m), 894 (m), 773 (m), 758 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.53 - 7.47 (m, 2H, Ar*H*), 7.41 - 7.30 (m, 3H, Ar*H*), 4.70 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 3.94 (dq, *J* = 9.2, 7.0 Hz, 1H, -OC*H*$_2$$CH_3$), 3.73 (dq, *J* = 9.2, 7.0 Hz, 1H, -OC*H*$_2$$CH_3$), 1.32 (t, *J* = 7.0 Hz, 3H, -CH_2C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 132.2, 129.5, 128.5, 122.7 (q, *J* = 281.7 Hz), 121.4,

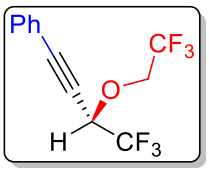
121.3, 88.4, 69.3 (q, *J* = 35.0 Hz), 79.5 (q, *J* = 2.3 Hz), 66.0, 15.1; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -76.8 (d, *J* = 5.4 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z*: $[M]^+$ Calcd for $C_{12}H_{11}F_3O^+$ 228.0757; Found 228.0754.

(*S*)-Trimethyl(2-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)ethyl)silane (**4an**):



Compound **4an** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 2-trimethylsilylethanol (**3n)** (60 µL, 0.40 mmol, 2.00 equiv.) following the procedure B. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (35.0 mg, 0.117 mmol, 58%): The enantiomeric ratio (er) resulted to be 90:10 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.9 min, $t_{R(major)}$ = 6.6 min; **α_D^{23}** = -134.3 (c = 0.1, $CHCl_3$); **TLC R_f** = 0.74 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2956 (w), 2900 (w), 2873 (w), 2233 (w), 1491 (m), 1364 (w), 1316 (w), 1274 (m), 1252 (m), 1219 (m), 1184 (s), 1143 (s), 1105 (m), 954 (w), 860 (m), 838 (s), 772 (s), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.51 - 7.46 (m, 2H, Ar*H*), 7.40 - 7.32 (m, 3H, Ar*H*), 4.68 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 3.98 (td, J = 9.1, 7.1 Hz, 1H, -OC*H*$_2$-), 3.75 (td, J = 9.2, 7.0 Hz, 1H, -OC*H*$_2$-), 1.04 (ddd, J = 9.4, 6.8, 2.3 Hz, 2H, -C*H*$_2$TMS), 0.06 (s, 9H, -Si(C*H*$_3$)$_3$)); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 132.2, 129.4, 128.5, 122.7 (q, *J* = 281.5 Hz), 121.5, 88.4, 79.6 (q, *J* = 2.6 Hz), 69.0 (q, *J* = 35.0 Hz), 68.1, 18.1, -1.3; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -76.8 (d, *J* = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z*: $[M]^+$ Calcd for $C_{15}H_{19}F_3OSi^+$ 300.1152; Found 300.1149.

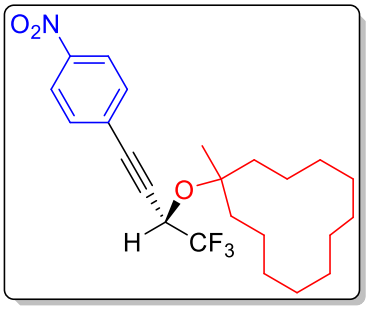
(*S*)-(4,4,4-Trifluoro-3-(2,2,2-trifluoroethoxy)but-1-yn-1-yl)benzene (**4ao**)



Compound **4ao** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 2,2,2-trifluoroethanol (**3o**) (29 µL, 0.40 mmol, 2.00 equiv.) following the procedure B. It was

purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (30.0 mg, 0.106 mmol, 53%). The enantiomeric ratio (er) resulted to be 67:33 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 9.0 min, $t_{R(major)}$ = 14.2 min; $\boldsymbol{\alpha_D^{23}}$ = 36.3 (c = 0.3, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.8 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2912 (m), 2855 (m), 1492 (m), 1455 (w), 1445 (w), 1357 (m), 1281 (m), 1269 (m), 1253 (m), 1176 (s), 1140 (s), 1108 (m), 1083 (s), 1004 (w), 986 (w), 972 (w), 940 (w), 917 (m), 867 (m), 758 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 - 7.50 (m, 2H, Ar*H*), 7.44 - 7.34 (m, 3H, Ar*H*), 4.96 (q, *J* = 5.6 Hz, 1H, -C*H*CF_3), 4.20 - 4.10 (m, 2H, -OCH_2CF3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 132.3, 130.1, 128.7, 123.5 (q, *J* = 278.8 Hz), 122.1 (q, *J* = 281.6 Hz), 120.6, 90.9, 77.4, 70.0 (q, *J* = 35.6 Hz), 65.8 (q, *J* = 35.8 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -74.0 (t, *J* = 8.2 Hz, -OCH_2CF_3), -76.7 (d, *J* = 5.4 Hz, -CF_3); **HRMS (GC/EI)** *m/z*: $[M]^+$ Calcd for $C_{12}H_8F_6O_3$ 282.0479; Found 282.000.

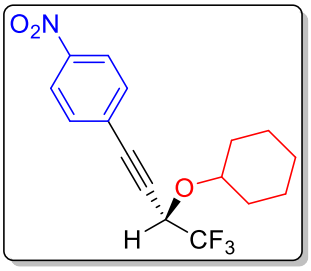
(*S*)-1-Methyl-1-((1,1,1-trifluoro-4-(4-nitrophenyl)but-3-yn-2-yl)oxy)cyclododecane (**4bp**):



Compound **4bp** was prepared from **2b** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 1-methylcyclododecan-1-ol (**3p**) (36.7 mg, 0.400 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (47.0 mg, 0.111 mmol, 55%): The enantiomeric ratio (er) resulted to be 98:2 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 19.5 min, $t_{R(minor)}$ = 21.4 min; $\boldsymbol{\alpha_D^{23}}$ = 39.9 (c = 0.2, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.69 (95:5 Hexane/EtOAc), visualized by exposure to UV light; **IR**

(ν_{max}, cm^{-1}) 2939 (m), 2856 (w), 1595 (m), 1524 (m), 1472 (m), 1376 (w), 1345 (s), 1272 (m), 1254 (m), 1220 (m), 1181 (s), 1141 (s), 1095 (m), 1083 (m), 853 (m), 770 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 (d, *J* = 8.9 Hz, 2H, Ar*H*), 7.60 (d, *J* = 8.9 Hz, 2H, Ar*H*), 4.82 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 1.28 (br s, 2H, -CH_2 cyclododecanol), 1.76 - 1.64 (m, 2H, -CH_2 cyclododecanol), 1.52 - 1.31 (m, 21H, -CH_2 cyclododecanol), 1.28 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.8, 132.2, 128.6, 123.76, 122.83 (q, *J* = 282.2 Hz), 87.9, 84.5, 82.9, 62.3 (q, *J* = 35.2 Hz), 34.6, 33.5, 26.7, 26.6, 26.1, 24.5, 22.9, 22.8, 22.4, 22.4, 19.9; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.8 (d, *J* = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z: [M]$^+$* Calcd for $C_{23}H_{30}F_3NO_3^+$ 425.2172; Found 425.2164.

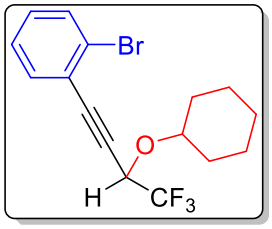
(*S*)-1-(3-(Cyclohexyloxy)-4,4,4-trifluorobut-1-yn-1-yl)-4-nitrobenzene (**4ba**):



Compound **4ba** was prepared from **2b** (94.0 mg, 0.200 mmol, 1.00 equiv.) and cyclohexanol (**3a**) (42 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (57.0 mg, 0.174 mmol, 87%): The enantiomeric ratio (er) resulted to be 97:3 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 19.8 min, $t_{R(minor)}$ = 23.6 min; **α_D^{23}** = -113.9 (c = 0.1, $CHCl_3$)**;** **TLC R_f** = 0.40 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 293 (m), 2856 (w), 1596 (m), 1523 (s), 1492 (w), 1455 (w), 1377 (w), 1346 (s), 1309 (w), 1274 (m), 1254 (m), 1184 (s), 1142 (s), 1096 (s), 856 (s), 769 (m), 750 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.64 (d, *J* = 9.0 Hz, 2H, Ar*H*), 4.77 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 3.73 (td, *J* = 9.1, 4.5 Hz, 1H,-OC*H*$(CH_2)_2$-), 2.03 - 1.90 (m, 2H, -CH_2 cyclohexyl), 1.84 - 1.72 (m, 2H, -CH_2 cyclohexyl), 1.59 - 1.39 (m, 3H, -CH_2 cyclohexyl), 1.37 - 1.22 (m, 3H, -CH_2 cyclohexyl); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.9, 133.1, 133.1, 128.2, 123.7, 123.7, 122.7 (q, *J* = 281.5 Hz), 85.6 (q, *J* = 2.3 Hz), 85.3, 78.8, 67.1 (q, *J* = 35.2 Hz), 32.6, 31.4, 25.6, 23.9, 23.7; **^{19}F NMR**

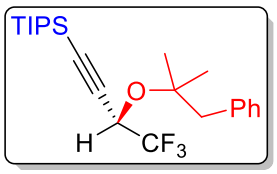
(376 MHz, $CDCl_3$) δ -77.0 (d, J = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z*: $[M]^+$ Calcd for $C_{16}H_{16}F_3NO_3^+$ 327.1077; Found 327.1075.

(*S*)-1-Bromo-2-(3-(cyclohexyloxy)-4,4,4-trifluorobut-1-yn-1-yl)benzene (**4ca**):



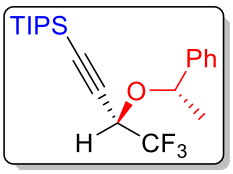
Compound **4ca** was prepared from **2c** (109.8 mg, 0.2000 mmol, 1.00 equiv.) and cyclohexanol **3a** (43 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (59.0 mg, 0.163 mmol, 82%): The enantiomeric ratio (er) resulted to be 93:7 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 7.7 min, $t_{R(minor)}$ = 8.3 min; α_D^{23} = -147.3 (c = 0.1, $CHCl_3$); **TLC** R_f = 0.66 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2936 (m), 2859 (m), 1472 (m), 1451 (w), 1435 (w), 1273 (m), 1219 (m), 1181 (s), 1142 (s), 1094 (s), 1054 (m), 1029 (m), 997 (w), 946 (w), 773 (s), 756 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.60 (dd, J = 7.9, 1.5 Hz, 1H, Ar*H*), 7.50 (dd, J = 7.6, 1.8 Hz, 1H, Ar*H*), 7.28 (td, J = 7.6, 1.4 Hz, 1H, Ar*H*), 7.22 (td, J = 7.6, 1.4 Hz, 1H, Ar*H*), 4.82 (q, J = 5.8 Hz, 1H, -C*H*CF_3), 3.82 (td, J = 9.2, 4.6 Hz, 1H, -OC*H*$(CH_2)_2$), 2.03 - 1.87 (m, 2H, -CH_2 cyclohexanol), 1.84 - 1.70 (m, 2H, , -CH_2 cyclohexanol), 1.60 - 1.48 (m, 2H, -CH_2 cyclohexanol), 1.44 - 1.15 (m, 4H, -CH_2 cyclohexanol); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 133.9, 132.7, 130.5, 127.2, 125.9, 122.8 (q, J = 281.3 Hz), 123.9, 86.1, 84.9 (q, J = 2.6 Hz), 78.01, 67.1 (q, J = 35.0 Hz), 32.7, 31.2, 25.7, 24.0, 23.8; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.0 (d, J = 6.1 Hz); **HRMS (APPI/LTQ-Orbitrap)** *m/z*: $[M]^+$ Calcd for $C_{16}H_{16}BrF_3O^+$ 360.0331; Found 360.0331.

(*S*)-Triisopropyl(4,4,4-trifluoro-3-((2-methyl-1-phenylpropan-2-yl)oxy)but-1-yn-1-yl)silane (**4de**)



Compound **4de** was prepared from **2e** (110.1 mg, 0.2000 mmol, 1.00 equiv.) and 2-methyl-1-phenylpropan-2-ol (**3e**) (62 µL, 0.40 mmol, 2.00 equiv.) after overnight reaction following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (49.3 mg, 0.120 mmol, 60%): The enantiomeric ratio (er) resulted to be 99:1 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 19.8 min, $t_{R(minor)}$ = 23.6 min; **TLC** Rf 0.94 (99:1 Hexane/EtOAc), visualized by exposure to UV light; $\boldsymbol{\alpha_D^{23}}$ = 87.3 (c = 0.36, $CHCl_3$)**IR** *(ν_{max}, cm^{-1})* 3083 (m), 3061 (m), 3031 (m), 2976 (m), 2929 (m), 1492 (m), 1447 (m), 1388 (m), 1372 (m), 1354 (m), 1274 (s), 1254 (m), 1224 (m), 1181 (s), 1141 (s), 1083 (s), 1073 (m), 895 (m), 773 (m), 759 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 - 7.21 (m, 5H, Ar*H*), 4.61 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 2.89 (q, *J* = 13.4 Hz, 2H, -CH_2Ph), 1.31 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.07 (s, 21H, TIPS); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 137.7, 130.8, 128.0, 126.5, 122.9 (q, *J* = 281.2 Hz), 100.4, 89.5, 79.5, 62.6 (q, *J* = 34.8 Hz), 48.4, 25.6, 24.8, 18.6, 11.2; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.4 (d, *J* = 6.1 Hz). **HRMS (Sicrit plasma/LTQ-Orbitrap)** *m/z:* $[M + H]^+$ Calcd for $C_{23}H_{36}F_3OSi^+$ 413.2482; Found 413.2481.

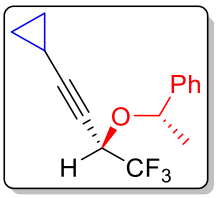
(*S*)- Triisopropyl(4,4,4-trifluoro-3-(1-phenylethoxy)but-1-yn-1-yl)silane (**4db**):



Compound **4db** was prepared from **2d** (110.1 mg, 0.2000 mmol, 1.00 equiv.) and (*S*)-phenylethanol (**3b)** (48 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colorless oil (47.0 mg, 0.122 mmol, 61%): The diastereomeric ratio (dr) resulted to

be 93:7 and was determined by ^{19}F NMR of the crude mixture; α_D^{23} = -169.6 (c = 0.1, $CHCl_3$); **TLC** R_f = 0.95 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2946 (s), 2867 (s), 1464 (m), 1382 (m), 1368 (m), 1272 (s), 1177 (s), 1141 (s), 1125 (s), 1092 (s), 1073 (s), 1030 (s), 997 (s), 995 (s), 908 (m), 883 (s), 760 (s); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.40 - 7.27 (m, 5H, Ar*H*), 4.83 (q, *J* = 6.4 Hz, 1H, -OC*H*Ph), 4.45 (q, *J* = 5.9 Hz, 1H, -C*H*CF_3), 1.52 (d, *J* = 6.4 Hz, 3H, CH_3), 1.05 (s, 21H, TIPS); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 142.1, 128.6, 128.1, 126.5, 123.1 (q, *J* = 282.4 Hz), 97.7 (q, *J* = 1.98 Hz), 90.6, 79.5, 67.7 (q, *J* = 34.7 Hz), 23.4, 18.6, 11.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.0 (d, *J* = 5.4 Hz, minor diastereoisomer), -77.2 (d, *J* = 6.1 Hz, major diastereoisomer); **HRMS (Sicrit plasma/LTQ-Orbitrap)** *m/z*: $[M + H_{-1}]^+$ Calcd for $C_{21}H_{30}F_3OSi^+$ 383.2013; Found 383.2012.

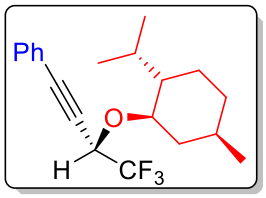
(*S*)-(1-((4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-yl)oxy)ethyl)benzene (**4eb**):



Compound **4eb** was prepared from **2e** (86.8 mg, 0.200 mmol, 1.00 equiv.) and (*S*)-phenylethanol (**3b)** (48 µL, 0.40 mmol, 2.00 equiv.) following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (33.8 mg, 0.126 mmol, 63%): The diastereomeric ratio (dr) resulted to be 92:8 and was determined by ^{19}F NMR of the crude mixture; α_D^{23} = 19.2 (c = 0.22, $CHCl_3$); **TLC** R_f = 0.49 (99:1Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2940 (m), 2858 (w), 1596 (m), 1523 (m), 1473 (m), 1346 (s), 1270 (m), 1254 (m), 1220 (m), 1181 (m), 1141 (s), 1082 (m), 856 (m), 773 (s); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.37 - 7.28 (m, 5H, Ar*H*), 4.77 (q, *J* = 6.5 Hz, 1H, -OC*H*Ph), 4.36 (qd, *J* 5.8, 1.9 Hz, 1H, -C*H*CF_3), 1.49 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24 - 1.17 (m, 1H, -C*H* cyclopropyl), 0.79 - 0.71 (m, 2H, -CH_2 cyclopropyl), 0.66 - 0.60 (m, 2H, -CH_2 cyclopropyl); **^{13}C NMR (101 MHz, $CDCl_3$, indicated peaks belongs to the major diastereoisomer)** δ 142.2, 128.6, 128.1, 126.6,

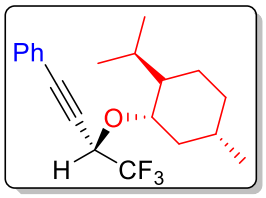
123.2 (q, *J* = 282.8 Hz), 92.2, 79.2, 67.4 (q, *J* = 34.7 HZ), 66.4 (q, *J* = 2.9 Hz), 23.5, 8.41, 8.38, -0.6; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -77.1 (d, *J* = 5.4 Hz, major diastereoisomers), -77.2 (d, *J* = 6.1 Hz, minor diastereoisomers); **HRMS (APPI/LTQ-Orbitrap)** *m/z: [M]*$^+$ Calcd for $C_{15}H_{15}F_3O^+$ 268.1070; Found 268.1064.

((*S*)-4,4,4-Trifluoro-3-(((1*R*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)but-1-yn-1-yl)benzene (**6**):



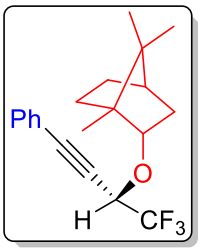
Compound **6** was prepared from **2a** (141.0 mg, 0.3000 mmol, 1.5 equiv.) and (1*R*,2*S*,5*R*)-5-methyl-2-propan-2-ylcyclohexan-1-ol (**5a)** (31.3 mg, 0.200 mmol, 1.00 equiv.) following the general procedure C. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a white solid (55.0 mg, 0.163 mmol, 81%): The diastereomeric ratio (dr) resulted to be 2:98 and was determined by ^{19}F NMR of the crude mixture; **α_D^{23}** = -182.0 (c = 0.1, $CHCl_3$); **TLC *R_f*** = 0.63 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2959 (m), 2953 (m), 2921 (m), 2870 (w), 2849 (w), 1457 (w), 1444 (m), 1372 (m), 1315 (w), 1264 (m), 1183 (s), 1137 (s), 1094 (s), 772 (m), 757 (s); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** *δ* 7.48 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar*H*), 7.39 - 7.31 (m, 3H, Ar*H*), 4.67 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 3.46 (td, *J* = 10.6, 4.3 Hz, 1H, -OC*H*-), 2.34 - 2.23 (m, 3H, -CH_2 menthol), 1.70 - 1.64 (m, 2H, -CH_2 menthol), 1.45 - 1.32 (m, 2H, -CH_2 menthol), 1.19 – 1.07 (m, 1H, -C*H* menthol), 1.04 . 0.98 (m, 1H, -C*H* menthol), 0.95 (d, *J* = 6.5 Hz, 3H, -CH_3), 0.92 (d, *J* = 7.2 Hz, 3H, -CH_3), 0.79 (d, *J* = 7.0 Hz, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** *δ* 132.1, 129.3, 128.5, 123.0 (q, *J* = 282.4 Hz), 121.7, 87.4, 82.8, 81.3 (q, *J* = 2.6 Hz), 68.6 (q, *J* = 34.8 Hz), 48.4, 41.3, 34.4, 31.7, 25.2, 23.2, 22.4, 21.1, 15.9; **^{19}F NMR (376 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** *δ* -77.0 (d, *J* = 5.5 Hz, minor diastereoisomer), -77.2 (d, *J* = 6.1 Hz, major diastereoisomer).**HRMS (APPI/LTQ-Orbitrap)** *m/z: [M]*$^+$ Calcd for $C_{20}H_{25}F_3O^+$ 338.1852; Found 338.1850.

((*S*)-4,4,4-trifluoro-3-(((1*S*,2*S*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)but-1-yn-1-yl)benzene (**7**):



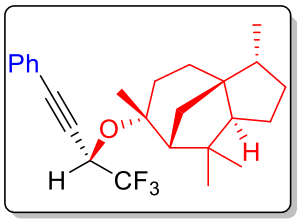
Compound 7 was prepared from **2a** (141.0 mg, 0.3000 mmol, 1.5 equiv.) and (1*S*, 2*R*, 5*S*)-5-methyl-2-propan-2-ylcyclohexan-1-ol (**5b**) (31.5 mg, 0.200 mmol, 1.00 equiv.) following the procedure C. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a white solid (60.0 mg, 0.177 mmol, 89%): The diastereomeric ratio (dr) resulted to be 96:4 and was determined by ^{19}F NMR of the crude mixture; $\boldsymbol{\alpha_D^{23}}$ =117.1(c = 0.1, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.77 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2957 (m), 2921 (m), 2874 (m), 2233 (w), 1457 (w), 1446 (w), 1386 (w), 1368 (m), 1361 (w), 1315 (m), 1275 (m), 1177 (s), 1142 (s), 1094 (s), 920 (w), 863 (w), 773 (s), 759 (s), 706 (m); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.48 (dd, *J* = 7.8, 1.8 Hz, 2H, Ar*H*), 7.40 - 7.30 (m, 3H, Ar*H*), 4.82 (q, *J* = 5.8 Hz, 1H, C*H*CF_3), 3.57 (td, *J* = 10.7, 4.3 Hz, 1H, -OC*H*-), 2.33 (pd, *J* = 7.0, 2.7 Hz, 1H, -C*H*$(CH_3)_2$), 2.12 – 2.07 (m, 1H, C*H*, menthol), 1.71 - 1.60 (m, 2H, -OC*H*CH_2), 1.44 - 1.30 (m, 4H, -CH_2 menthol), 0.94 (d, *J* = 6.8 Hz, 7H, 2x(-CH_3) + -C*H* menthol), 0.85 (d, *J* = 6.9 Hz, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 132.1, 129.3, 128.5, 122.8 (q, *J* = 280.8 Hz), 121.6, 87.7, 80.3 (q, *J* = 2.03 Hz), 78.2, 66.7 (q, *J* = 35.2 Hz), 47.9, 39.3, 34.5, 31.6, 25.61, 23.5, 22.4, 21.0, 16.4. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.03 (d, *J* = 5.4 Hz, major diastereoisomer), -77.2 (d, *J* = 5.4 Hz, minor diastereoisomer); **HRMS (APCI/QTOF)** *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{26}F_3O^+$ 339.1930; Found 339.1931.

(1*S*,2*S*,4*R*)-1,7,7-Trimethyl-2-(((*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)bicyclo[2.2.1]heptane (**8**):



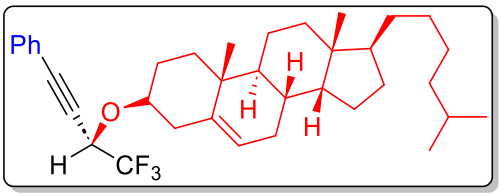
Compound **8** was prepared from **2a** (141.0 mg, 0.3000 mmol, 1.5 equiv.) and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**5c)** (30.9 mg, 0.200 mmol, 1.00 equiv.) following the procedure C. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a pale-yellow oil (50.0 mg, 0.149 mmol, 74%): The diastereomeric ratio (dr) resulted to be 97:3 and was determined by ^{19}F NMR of the crude mixture; $\boldsymbol{\alpha_D^{23}}$ = -163.5 (c = 0.1, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.95 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2955 (m), 2881 (m), 2229 (w), 1491 (m), 1455 (m), 1445 (m), 1272 (m), 1256 (m), 1217 (m), 1187 (s), 1141 (s), 1116 (s), 1103 (s), 770 (s), 756 (s); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.48 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar*H*), 7.39 - 7.31 (m, 3H, Ar*H*), 4.69 (q, *J* = 6.0 Hz, 1H, -C*H*CF_3), 3.99 (dt, *J* = 9.5, 2.6 Hz, 1H, -OC*H*-), 2.32 – 2.20 (m, 1H, -C*H* borneol), 2.07 - 2.00 (m, 1H, -CH borneol), 1.77 - 1.63 (m, 2H, -CH_2 borneol), 1.34 (dd, *J* = 13.4, 33.3 Hz), 0.92 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 1.31 - 1.21 (m, 2H), 0.86 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 132.1, 129.3, 128.5, 122.8 (q, *J* = 281.9 Hz), 121.7, 87.9, 86.8, 80.8 (q, *J* = 2.2 Hz), 69.9 (q, *J* = 34.5 Hz), 49.9, 47.8, 45.2, 36.7, 28.2, 26.5, 19.8, 19.0, 13.8; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -77.0 (d, *J* = 6.1 Hz, major diastereoisomers), -77.1 (d, *J* = 6.1 Hz, minor diastereoisomer). **HRMS (APPI/LTQ-Orbitrap)** *m/z:* $[M]^+$ Calcd for $C_{20}H_{23}F_3O^+$ 336.1696; Found 336.1706.

(3*R*,3a*S*,6*R*,7*R*,8a*S*)-3,6,8,8-Tetramethyl-6-(((*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)octahydro-1H-3a,7-methanoazulene (**9**):



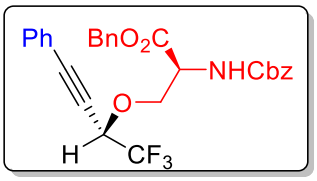
Compound **9** was prepared from **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**5d)** (181.5 mg, 0.8000 mmol, 4.00 equiv.) following procedure A, but using $Cu(MeCN)_4SbF_6$ (1.9 mg, 4.0 µmol, 2 mol%) instead of $Cu(MeCN)_4BF_4$. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a white solid (51.8 mg, 0.128 mmol, 64%): The diastereomeric ratio (dr) resulted to be 85:15 and was determined by ^{19}F NMR of the crude mixture; α_D^{23} = 14.0 (c = 0.38, $CHCl_3$); **TLC** R_f = 0.63 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2982 (m), 2958 (m), 2937 (m), 2912 (m), 2871 (m), 1491 (m), 1464 (m), 1444 (m), 1382 (m), 1351 (m), 1322 (w), 1278 (m), 1268 (m), 1253 (m), 1175 (s), 1137 (s), 1130 (m), 1105 (m), 1079 (s), 1003 (w), 989 (w), 970 (w), 921 (w), 910 (w), 896 (w), 863 (w), 763 (m), 755 (s); **^{1}H NMR (400 MHz, $CDCl_3$, major diastereoisomer)** δ 7.49 - 7.43 (m, 2H, Ar*H*), 7.41 - 7.30 (m, 3H, Ar*H*), 4.81 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 2.30 (td, *J* = 13.1, 6.1 Hz, 1H, -cedrol), 1.88 (dq, *J* = 11.9, 6.0 Hz, 1H, -cedrol), 1.82 - 1.77 (m, 2H, -CH_2 cedrol), 1.75 - 1.74 (m, 1H, -CH_2 cedrol), 1.71 - 1.61 (m, 2H, -CH_2 cedrol,), 1.57 - 1.46 (m, 3H, -C*H* + CH_2 cedrol), 1.43 - 1. 36 (m, 1H, -C*H* cedrol; s, 3H, -CH_3), 1.31 - 1.24 (m, 1H, -cedrol; s, ·3H, -CH_3), 1.40 (m, 1H, -cedrol; s, 3H, -CH_3), 1.27 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$, major diastereoisomer)** δ 131.9, 129.1, 128.5, 123.1 (q, *J* = 281.3 Hz), 122.1, 86.7, 83.1, 82.8 (q, *J* = 2.2 Hz), 62.2 (q, *J* = 35.0 Hz), 59.7, 56.9, 54.1, 43.7, 41.5, 41.5, 37.2, 31.7, 31.5, 29.1, 27.9, 25.5, 23.7, 15.8; **^{19}F NMR (376 MHz, $CDCl_3$, mixture of diastereoisomers)** δ -76.9 (d, *J* = 6.1 Hz, minor diastereoisomer), -77.2 (d, *J* = 6.1 Hz, major diastereoisomer); **HRMS (APPI/LTQ-Orbitrap)** *m/z:* $[M]^+$ Calcd for $C_{25}H_{31}F_3O^+$ 404..2327; Found 404.2327.

(3*R*,8*S*,9*S*,10*R*,13*R*,14*R*,17*S*)-10,13-Dimethyl-17-(5-methylhexyl)-3-(((*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene (**10**):



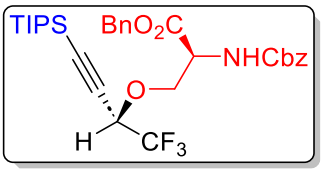
Compound **10** was prepared from **2a** (141.0 mg, 0.3000 mmol, 1.5 equiv.) and (3*S*, 8*S*, 9*S*, 10*R*, 13*R*, 14*R*)-8,10,13-trimethyl-17-[(2*R*)-6-methylheptan-2-yl]-1,2,3,4,7,9,11,12,14,16,17-dodecahydrocyclopena[a]phenanhren-3-ol (**5e)** (80.1 mg, 0.200 mmol, 1.00 equiv.) following the procedure C. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a white solid (102 mg, 0.178 mmol, 89%): The diastereomeric ratio (dr) resulted to be 93:7 and was determined by ^{19}F NMR of the crude mixture; $\boldsymbol{\alpha_D^{23}}$ = 796.3 (c = 0.75, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.93 (9:1Hexane/EtOAc), visualized by exposure to UV light; IR (vmax, cm-1) 2942 (s), 2867 (m), 1674 (w), 1491 (m), 1465 (m), 1444 (m), 1382 (m), 1375 (m), 1367 (m), 1275 (s), 1254 (m), 1180 (s), 1145 (s), 1098 (s), 1018 (m), 874 (w), 755 (s), 709 (m); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.49 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar*H*), 7.39 - 7.31 (m, 3H, Ar*H*), 5.39 (d, *J* = 5.4 Hz, 1H, -C=C*H*), 4.79 (q, *J* = 5.8 Hz, 1H, -C*H*CF_3), 3.64 (dq, *J* = 11.2, 5.7, 4.9 Hz, 1H, -C*H* choloresterol), 2.51 - 2.35 (m, 2H, -CH_2 cholesterol), 2.09 - 1.79 (m, 5H, -CH_2 cholesterol), 1.65 – 1.43 (m, 6H, -CH_2 cholesterol), 1.39 – 1.30 (m, 5H), 1.20 - 1.05 (m, 6H, -CH_2 cholesterol), 1.03 (s, 4H, -C*H* cholesterol + -CH_3), 0.93 (d, *J* = 6.5 Hz, 4H, -C*H* cholesterol + -CH_3), 0.88 (dd, *J* = 6.7, 1.9 Hz, 6H -2 x -CH_3), 0.69 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 140.4, 132.2, 129.4, 128.5, 122.8 (q, *J* = 281.5 Hz), 122.5, 121.5, 87.8, 80.3 (q, *J* = 2.2 Hz), 79.8, 67.2 (q, *J* = 34.8 Hz), 56.9, 56.3, 50.2, 42.5, 39.9, 39.7, 39.4, 37.1, 36.9, 36.3, 35.9, 32.1, 32.0, 28.4, 28.2, 27.9, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -77.20 (d, *J* = 5.5 Hz, minor diastereoisomer), -77.21 (d, *J* = 5.5 Hz, major diastereoisomer); **HRMS (APPI/LTQ-Orbitrap)** *m/z*: $[M]^+$ Calcd for $C_{37}H_{51}F_3O^+$ 568.3887; Found 568.3912.

Benzyl *N*-((benzyloxy)carbonyl)-O-((*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)-*L*-serinate (**11a**):



Compound **11a** was prepared from **2a** (94 mg, 0.20 mmol, 1.00 equiv.) and benzyl 3-hydroxy-2-(phenylmethoxycarbonylamino)propanoate (**5f**) (131.7 mg, 0.4000 mmol, 2.00 equiv.) in 16 h following the procedure A. It was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a white solid (64 mg, 0.13 mmol, 63%): The diastereomeric ratio (dr) resulted to be 93:7 and was determined by ^{19}F NMR of the crude mixture; $\boldsymbol{\alpha_D^{23}}$ = 18.4 (c = 0.05, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.13 (95:5 Hexane/EtOAc), visualized by exposure to UV light and/or $KMnO_4$; **IR** (ν_{max}, cm^{-1}) 2953 (w), 2233 (w), 1749 (m), 1725 (s), 1526 (m), 1519 (m), 1511 (m), 1506 (m), 1494 (m), 1456 (m), 1451 (w), 1341 (m), 1274 (s), 1256 (m), 1195 (s), 1188 (s), 1146 (s), 1116 (m), 1070 (m), 1064 (m), 773 (w), 755 (m), 745 (m), 741 (m), 703 (m); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ 7.51 - 7.27 (m, 15H, Ar*H*), 5.73 (d, *J* = 8.8 Hz, 1H, -C*H*NH-), 5.23 (d, *J* = 4.3 Hz, 2H, -OCH_2-), 5.12 (d, *J* = 5.1 Hz, 2H, -OCH_2-), 4.67 (q, *J* = 5.8 Hz, 2H, -C*H*CF_3), 4.25 – 4.06 (m, 2H, -OCH_2); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ 169.5, 156.1, 136.2, 135.2, 132.2, 129.7, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 122.3 (q, *J* = 283.5 Hz), 120.8, 128.2, 89.7, 78.0, 70.4, 70.0 - 69.7 (m), 67.8, 67.71 67.3, 54.4; **^{19}F NMR (376 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ -76.4 (d, *J* = 6.1 Hz, major diastereoisomer), -76.5 (d, *J* = 6.1 Hz, minor diastereoisomer); **HRMS (ESI/QTOF)** *m/z:* [M + Na]$^+$ Calcd for $C_{28}H_{24}F_3NNaO_5^+$ 534.1499; Found 534.1497.

Benzyl *N*-((benzyloxy)carbonyl)-O-((*S*)-1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-yl)-L-serinate (**11b**):

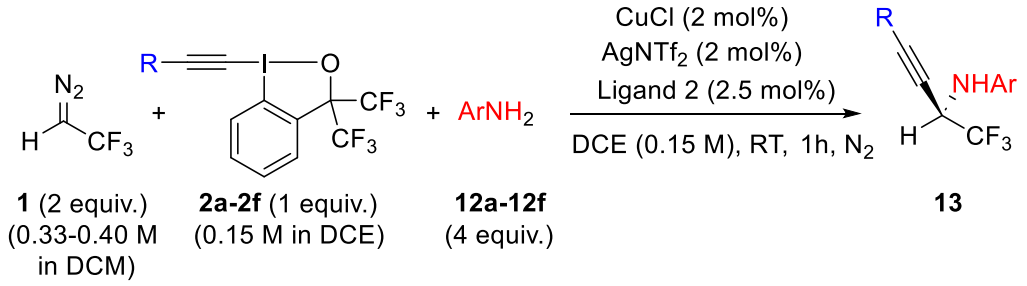


Compound **11b** was prepared from **2d** (110.1 mg, 0.2000 mmol, 1.00 equiv.) and benzyl 3-hydroxy-2-(phenylmethoxycarbonylamino)propanoate (**5f)** (131.7 mg, 0.4000 mmol, 2.00 equiv.) in 16 h following the procedure A. It was purified by flash column chromatography (100% to 90:10, Pentane/EtOAc) and obtained as a white solid (78.0 mg, 0.132 mmol, 66%): The diastereomeric ratio (dr) resulted to be 90:10 and was determined by ^{19}F NMR of the crude mixture; **α_D^{23}** = -169.7 (c = 0.1, $CHCl_3$); **TLC R_f** = 0.20 (90:10 Hexane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 2946 (m), 2871 (m), 1749 (m), 1729 (m), 1504 (m), 1462 (m), 1340 (m), 1274 (m), 1220 (m), 1187 (s), 1148 (s), 1119 (m), 1063 (m), 1057 (m), 883 (m), 773 (s); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diatereoisomers, indicated peaks belongs to the major diastereoisomer)** δ 7.39 - 7.28 (m, 10H, Ar*H*), 5.65 (d, *J* = 8.9 Hz, 1H, -N*H*-), 5.26 - 5.16 (m, 2H, -C*H*$_2$Ph), 5.14 - 5.10 (m, 2H, -C*H*$_2$Ph), 4.67 - 4.63 (m, 1H, -C*H*CO$_2$Bn), 4.44 (q, *J* = 5.8 Hz, 1H, -C*H*CF$_3$), 4.12 (dd, *J* = 9.3, 2.9 Hz, 1H, -OC*H*$_2$-), 4.05 (dd, *J* = 9.3, 3.1 Hz, 1H, -OC*H*$_2$-), 1.07 (s, 21H, -TIPS); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers, indicated peaks belongs to the major diastereoisomer**) δ 169.5, 156.1 136.2, 135.3, 128.7, 128.7, 128.6, 128.3, 128.30, 128.2, 122.1 (q, *J* = 282.1 Hz), 95.5, 93.3, 70.0 - 69.0 (m, 2C), 67.7, 67.7, 67.3, 54.3, 18.5, 11.0; **^{19}F NMR (377 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ -76.5 (d, *J* = 6.2 Hz, minor diastereoisomer), -76.8 (d, *J* = 5.5 Hz, major diastereoisomer); **HRMS (ESI/QTOF)** *m/z*: [M + Na]$^+$ Calcd for $C_{31}H_{40}F_3NNaO_5Si^+$ 614.2520; Found 614.2536.

6. Procedures and Compound Characterization for the Enantioselective 3-Component Reaction between 1, 2 and Anilines (12)

In order to avoid reproducibility issues, a Stock Solution of the catalyst was prepared triplicating the corresponding amount of CuCl, $AgNTf_2$, L2 and DCE belonging to a 0.25 mmol scale 3-CR reaction. Then, the same catalytic stock solution was used for 2 reactions.

Procedure D: Synthesis of Trifluoromethylated Propargylic Anilines **13aa**-**13af**, **13da**, **13ea**, **13fa**, **13ga**.

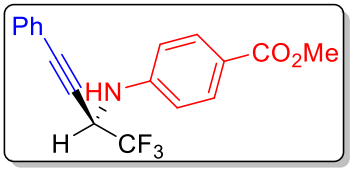


Stock solution of the catalyst: In an oven-dried microwave vial, CuCl (1.5 mg, 1.5 µmol, 0.060 equiv.), $AgNTf_2$ (5.8 mg, 1.5 µmol, 0.060 equiv.) and L2 (6.7 mg, 1.9 µmol, 0.075 equiv) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (5 mL) was added into the vial and the resulting pale-green solution was stirring (430 rpm) at room temperature during 1 h.

Procedure: In an oven-dried microwave vial, compound **2** (0.25 mmol, 1.00 equiv.) and aniline (**12**) (if solid) (1.00 mmol, 4.00 equiv.) were added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2, followed by the addition of **1** (0.40 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and aniline **12** (if liquid) (1.00 mmol, 4.00 equiv.). The resulting reaction mixture was stirred at RT under N2 atmosphere and the catalytic solution (1.70 mL) was added dropwise. After 1h of reaction, the reaction was monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2** (unless otherwise noticed). The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (15 mL). The solvent was removed under reduced pressure and the resulting residue was purified by preparative thin layer

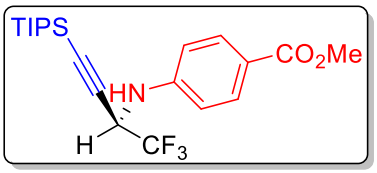
chromatography (the crude was distributed into 2 plates to favour the separation) according to the conditions described for each compound.

Methyl (*R*)-4-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)amino)benzoate (**13aa**):



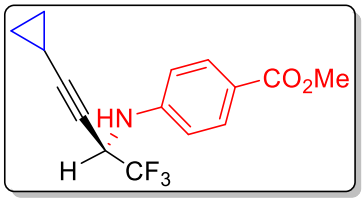
Compound **13aa** was prepared from **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and methyl 4-aminobenzoate (**12a**) (151.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a white amorphous solid. (59.0 mg, 0.178 mmol, 71%). The enantiomeric ratio (er) resulted to be 94:6 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI column: AI 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 25.1 min, $t_{R(major)}$ = 31.2 min. **α_D^{23}** = -387.7 (c = 0.1, $CHCl_3$); **TLC** ***R_f*** = 0.13 (95:5 pentane/ EtOAc); visualized by UV light; IR (vmax, cm-1) 3348 (w), 1699 (m), 1606 (s), 1530 (m), 1492 (w), 1437 (m), 1310 (m), 1288 (s), 1258 (s), 1181 (s), 1132 (s), 1116 (m), 1015 (w), 969 (w), 841 (w), 771 (m), 757 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, J = 8.8 Hz, 2H, ArH), 7.47 – 7.41 (m, 2H, ArH), 7.40 – 7.30 (m, 3H, ArH), 6.76 (d, J = 8.9 Hz, 2H, ArH), 5.03 (dq, J = 9.2, 5.9 Hz, 1H, -C*H*CF_3), 4.56 (d, *J* = 9.2 Hz, 1H, -N*H*-), 3.88 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 167.0, 148.9, 132.1, 131.7, 129.5, 128.5, 123.7 (q, *J* = 282.4 Hz) 121.5, 121.1, 113.1, 86.7, 79.7 (q, *J* = 2.6 Hz), 51.9, 49.7 (q, *J* = 35.0 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -75.6 (d, *J* = 5.5 Hz); **HRMS (ESI/QTOF)** *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{15}F_3NO_2^+$ 334.1049; Found 334.1051. The values of the NMR spectra are in accordance with reported literature data.[2],

Methyl (*R*)-4-((1,1,1-trifluoro-4-(triisopropylsilyl)but-3-yn-2-yl)amino)benzoate (**13da**):



Compound **13da** was prepared from **2d** (137.6 mg, 0.2500 mmol, 1 equiv.) and methyl 4-aminobenzoate (**12a**) (151.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a white amorphous solid. (54.0 mg, 0.131 mmol, 52%): The enantiomeric ratio (er) resulted to be 86:14 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI column: AI 95:5 hexane/isopropanol, flow rate1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.4 min, $t_{R(major)}$ = 5.7 min; $\boldsymbol{\alpha_D^{23}}$ **=** 104.1 (c = 0.275, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.14 (97:3 pentane/ EtOAc), visualized by exposure to UV light; IR (vmax, cm-1) 3357 (w), 2946 (m), 2867 (m), 1703 (s), 1699 (m), 1606 (s), 1537 (m), 1523 (m), 1465 (m), 1436 (m), 1320 (m), 1281 (s), 1252 (s), 1178 (s), 1133 (s), 1112 (s), 1044 (m), 1018 (m), 997 (m), 970 (w), 920 (w), 885 (m), 840 (m), 770 (s), 767 (s), 720 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.73 (d, *J* = 8.8 Hz, 2H, Ar*H*), 4.82 (dq, *J* = 9.0, 5.8 Hz, 1H, -C*H*CF_3), 4.33 (d, *J* = 9.2 Hz, 1H, -N*H*-), 3.87 (s, 3H, -C*H*$_3$), 1.05 (s, 21H, *TIPS*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.0, 148.9, 131.6, 123.6 (q, *J* = 284.5 Hz), 121.5, 110.9, 97.3, 89.8 (br, s), 51.9, 49.8 (q, *J* = 34.5 Hz), 18.6, 11.1**; ^{19}F NMR (376 MHz, $CDCl_3$)** δ -75.7 (d, *J* = 6.1 Hz); **HRMS (ESI/QTOF)** *m/z:* $[M + H]^+$ Calcd for $C_{21}H_{31}F_3NO_2Si^+$ 414.2071; Found 414.2075. The values of the NMR spectra are in accordance with reported literature data.[2]

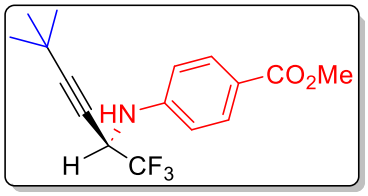
Methyl (*R*)-4-((4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-yl)amino)benzoate (**13ea**):



Compound **13ea** was prepared from **2e** (108.5 mg, 0.2500 mmol, 1 equiv.) and methyl 4-aminobenzoate (**12a**) (151.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D.

It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a white amorphous solid (53.0 mg, 0.178 mmol, 71%): The enantiomeric ratio (er) resulted to be 91:9 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI column: AI 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 15.3 min, $t_{R(minor)}$ = 17.8 min; **α_D^{23}** = 354.5 (c = 0.1, $CHCl_3$); **TLC** *Rf* 0.08 (99:1 Hexane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 3354 (m), 2250 (w), 1700 (s), 1606 (s), 1526 (m), 1437 (m), 1284 (s), 1254 (s), 1178 (s), 1130 (s), 1114 (s), 965 (m), 953 (m), 906 (m), 842 (m), 813 (m), 770 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.91 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.68 (d, *J* = 8.9 Hz, 2H, Ar*H*), 4.78 – 4.68 (m, 1H, -C*H*CF_3), 4.32 (d, *J* = 8.9 Hz, 1H, -N*H*-), 3.86 (s, 3H, -CO_2Me), 1.31 - 1.20 (m, 1H, -C*H*C-), 0.84 - 0.77 (m, 2H, -CH_2-), 0.74 - 0.67 (m, 2H, -CH_2-); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 167.1, 149.0, 131.6, 123.7 (q, *J* = 281.3 Hz), 121.24, 113.0, 91.0, 66.1 (q, *J* = 2.6 Hz), 51.9, 49.2 (q, *J* = 35.1 Hz), 8.46, -0.61; **^{19}F NMR (377 MHz, $CDCl_3$)** *δ* -76.0 (d, *J* = 5.5 Hz); **HRMS (ESI/QTOF)** *m/z: [M + H]$^+$* Calcd for $C_{15}H_{15}F_3NO_2^+$ 298.1049; Found 298.1051.

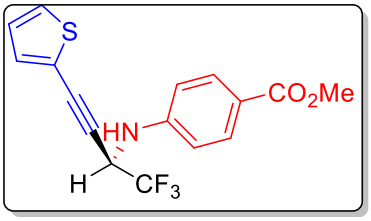
Methyl (*R*)-4-((1,1,1-trifluoro-5,5-dimethylhex-3-yn-2-yl)amino)benzoate (**13fa**):



Compound **13fa** was prepared from **2f** (112.5 mg, 0.2500 mmol, 1.00 equiv.) and methyl 4-aminobenzoate (**12a**) (151.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a white amorphous solid (50.1 mg, 0.160 mmol, 64%). The enantiomeric ratio (er) resulted to be 94:6 and was determined by chiral HPLC analysis on a Daicel Chiralpak ID column: AI 99:1 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 9.5 min, $t_{R(minor)}$ = 10.9 min; **α_D^{23}** = -20 (c = 0.33, $CHCl_3$); **TLC R_f** = 0.11 (97:3 pentane/ EtOAc), visualized by UV light; **IR (ν_{max}, cm^{-1})** 3351 (w), 2974 (w), 2953 (w), 2251 (w), 1703 (m), 1608 (s), 1527 (w), 1438 (m), 1321 (w), 1287 (m), 1264 (m), 1219 (w), 1181 (s), 1133 (m), 1115 (m), 772 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.91 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.70 (d, *J* = 8.9 Hz, 2H, Ar*H*), 4.83 – 4.71 (m, 1H, -C*H*CF_3), 4.34 (d, *J* = 8.9 Hz, 1H, -N*H*-), 3.86 (s, 3H, -

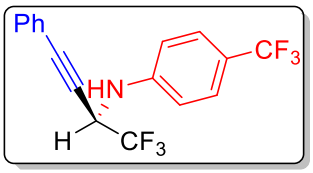
OCH_3), 1.21 (s, 9H, (-CH_3)$_3$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 167.1, 149.1, 131.6, 123. 8 (q, J = 280.4 Hz), 121.1, 112.9, 96.0, 69.6 (q, J = 2.5 Hz); 51.9, 49.1 (q, J = 34.5 Hz), 30.6 (3 x CH_3), 27.6; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -76.2 (d, J = 6.1 Hz); **HRMS (ESI/QTOF)** *m/z: [M + H]*$^+$ Calcd for $C_{16}H_{19}F_3NO_2^+$ 314.1362; Found 314.1364. The values of the NMR spectra are in accordance with reported literature data.[2]

Methyl (*R*)-4-((1,1,1-trifluoro-4-(thiophen-2-yl)but-3-yn-2-yl)amino)benzoate (**13ga**):



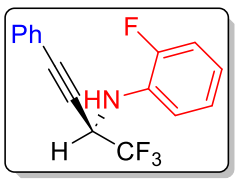
Compound **13ga** was prepared from **2g** (119.0 mg, 0.2500 mmol, 1.00 equiv.) and methyl 4-aminobenzoate (**12a**) (151.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a white amorphous solid (55.1 mg, 0.162 mmol, 65%). The enantiomeric ratio (er) resulted to be 91:9 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI column: AI 90:10 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 14.6 min, $t_{R(major)}$ = 17.4 min; **α_D^{23}** = -412.5 (c = 0.1, $CHCl_3$); **TLC R_f** = 0.11 (95:5 pentane/ EtOAc), visualized by UV light; **IR** (ν_{max}, cm^{-1}) 3357 (w), 2946 (m), 2867 (m), 1703 (s), 1699 (m), 1606 (s), 1537 (m), 1523 (m), 1465 (m), 1436 (m), 1320 (m), 1281 (s), 1252 (s), 1178 (s), 1133 (s), 1112 (s), 1044 (m), 1018 (m), 997 (m), 970 (w), 920 (w), 885 (m), 840 (m), 770 (s), 767 (s), 720 (m); **1H NMR (400 MHz, CDCl$_3$)** δ 7.94 (d, J = 8.9 Hz, 2H, ArH), 7.33 – 7.26 (m, 2H, tiophene), 6.98 (dd, J = 5.1, 3.6 Hz, 1H, tiophene), 6.75 (d, J = 8.9 Hz, 2H, ArH), 5.04 (dq, J = 9.3, 6.0 Hz, 1H, -CHCF$_3$), 4.51 (d, J = 9.3 Hz, 1H, -NH-), 3.87 (s, 3H, CH_3); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 167.0, 148.8, 133.8, 131.7, 128.6, 127.2, 123.5 (q, J = 282.4 Hz), 121.6, 120.8, 113.1, 83.5 (q, J = 2.3 Hz), 80.3, 51.9, 49.9 (q, J = 35.2 Hz); **^{19}F NMR (376 MHz, CDCl$_3$)** δ -75.4 (d, J = 6.1 Hz); **HRMS (ESI/QTOF)** *m/z:* [M + H]$^+$ Calcd for $C_{16}H_{13}F_3NO_2S^+$ 340.0614; Found 340.0614. The values of the NMR spectra are in accordance with reported literature data.[2]

(*R*)-*N*-(1,1,1-Trifluoro-4-phenylbut-3-yn-2-yl)-4-(trifluoromethyl)aniline (**13ab**):



Compound **13ab** was prepared from **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and 4-(trifluoromethyl)aniline (**12b**) (128 µL, 1.00 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a yellow oil (50.0 mg, 0.146 mmol, 65%). The enantiomeric ratio (er) resulted to be 94:6 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 10.5 min, $t_{R(major)}$ = 11.7 min; **TLC** R*f* 0.20 (97:3 pentane/EtOAc), visualized by UV light; $\boldsymbol{\alpha_D^{23}}$ = -320.5 (c = 0.1, $CHCl_3$); **IR (ν_{max}, cm^{-1})** 2939 (w), 2864 (w), 1595 (w), 1524 (m), 1491 (m), 1346 (s), 1271 (m), 1256 (m), 1217 (m), 1184 (s), 1143 (s), 1102 (m), 857 (m), 772 (s), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 – 7.44 (m, 4H, Ar*H*), 7.40 - 7.30 (m, 3H, Ar*H*), 6.82 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.99 (dq, *J* = 9.2, 5.9 Hz, 1H, -C*H*CF_3), 4.38 (d, *J* = 9.2 Hz, 1H, -N*H*-); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.7, 132.2, 129.6, 128.6, 127.0 (q, *J* = 3.7 Hz), 126.0, 124.7 (q, *J* = 271.1 Hz), 123.7 (q, *J* = 282.3 Hz). 122.0 (q, *J* = 32.6 Hz), 121.1, 113.6, 86.8, 79.7 (q, *J* = 2.6 Hz), 49.9 (q, *J* = 35.2 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -61.5, -75.6 (d, *J* = 5.4 Hz); **HRMS (ESI/QTOF)** *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{12}F_6N^+$ 344.0868; Found 344.0868. The values of the NMR spectra are in accordance with reported literature data.[2]

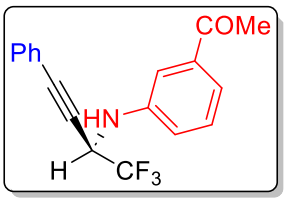
(*R*)-2-Fluoro-*N*-(1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)aniline (**13ac**):



Compound **13ac** was prepared from **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and 2-fluoroaniline (**12c**) (100 µL, 1.00 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a white amorphous solid (45.0 mg, 0.153 mmol, 61%). The enantiomeric ratio (er) resulted to be 95:5 and was

determined by chiral HPLC analysis on a Daicel Chiralpak AI N-5 column: AI 99:1 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.6 min, $t_{R(major)}$ = 6.1 min; **α_D^{23}** = -322.6 (c = 0.1, $CHCl_3$); **TLC** R_f = 0.44 (97:3 pentane/EtOAc), visualized by UV light; **IR (ν_{max}, cm^{-1})** 3437 (w), 3062 (w), 2237 (w), 1620 (w), 1516 (m), 1454 (w), 1338 (m), 1257 (s), 1184 (s), 1134 (s), 752 (s), 849 (w), 1034 (w), 991 (w); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50− 7.44 (m, 2H, Ar*H*), 7.40−7.29 (m, 3H, Ar*H*), 7.11−7.02 (m, 2H, Ar*H*), 6.92−6.87 (m, 1H, Ar*H*), 6.85−6.80 (m, 1H, ArH), 4.93 (dq, *J* = 9.4, 6.0 Hz, 1H, -C*H*CF_3), 4.37 (d, *J* = 12.8 Hz, 1H, -N*H*-); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 152.3 (d, *J* = 240 Hz), 133.5 (d, *J* = 11.4 Hz), 132.2, 129.4, 128.5, 124.8 (d, *J* = 4.0 Hz), 123.8 (q, *J* = 280 Hz), 121.3, 120.1 (d, *J* = 7.3 Hz), 115.4 (d, *J* = 18.7 Hz), 114.2, 86.6, 80.1 (q, *J* = 2.6 Hz), 50.4 (q, *J* = 34.8 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ −75.7 (d, *J* = 6.1 Hz), −134.5 (tq, *J* = 8.9, 4.1 Hz); **HRMS (ESI/QTOF)** *m/z [M + H]*$^+$ calcd for $C_{16}H_{12}F_4N^+$ 294.0900, found 294.0905. The values of the NMR spectra are in accordance with reported literature data.[2]

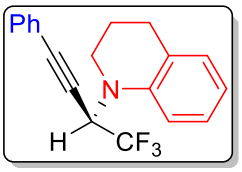
(*R*)-1-(3-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)amino)phenyl)ethan-1-one (**13ad**):



Compound **13ad** was prepared from **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and 1-(3-aminophenyl)ethan-1-one (**13d**) (135.2 mg, 1.00 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a colorless oil (45.0 mg, 0.142 mmol, 57%). The enantiomeric ratio (er) resulted to be 87:13 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI N-5 column: AI 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 18.6 min, $t_{R(major)}$ = 31.6 min; **α_D^{23}** = 18.6 (c = 0.4, $CHCl_3$); TLC Rf = 0.25 (96:4 pentane/EtOAc), visualized by UV light; IR (ν_{max}, cm^{-1}) 1681 (s), 1605 (s), 1534 (m), 1522 (m), 1491 (m), 1441 (m), 1359 (m), 1324 (m), 1303 (m), 1266 (s), 1230 (m), 1184 (s), 1134 (s), 789 (m), 765 (m), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 - 7.43 (m, 3H, Ar*H*), 7.40 - 7.37 (m, 2H, Ar*H*), 7.36 - 7.29 (m, 3H, Ar*H*), 6.99 (dd, J = 8.0, 2.7 Hz, 1H, Ar*H*), 5.00 (dq, *J* = 9.4, 6.0 Hz, 1H, -C*H*CF_3), 4.23 (d, *J* = 9.4 Hz, 1H, -N*H*-), 2.59 (s, 3H, -COC*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)**

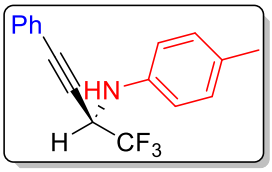
δ 198.2, 145.4, 138.5, 132.1, 129.8, 129.4, 128.5, 123.8 (q, *J* = 282.3 Hz), 121.3, 120.6, , 119.2, 113.4, 86.6, 80.1 (q, *J* = 2.3 Hz), 50.4 (q, *J* = 34.7 Hz), 26.9; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* −75.6 (d, *J* = 6.2 Hz); **HRMS (ESI/QTOF)** *m/z: [M + Na]*$^+$ Calcd for $C_{20}H_{21}NNaO_4S^+$ 394.1084; Found 394.1081.

(*R*)-1-(1,1,1-Trifluoro-4-phenylbut-3-yn-2-yl)-1,2,3,4-tetrahydroquinoline (**13ae**):



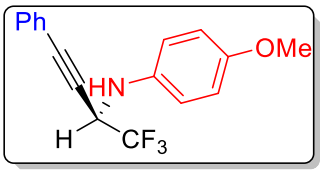
Compound **13ae** was prepared from **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and 4-(trifluoromethyl)aniline (**12e**) (130 µL, 1.00 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a yellow oil (40.1 mg, 0.127 mmol, 51%). The enantiomeric ratio (er) resulted to be 94:6 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 99:1 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.3 min, $t_{R(major)}$ = 7.6 min; **α_D^{23}** = -20 (c = 0.33, $CHCl_3$); **TLC *Rf*** = 0.39 (97:3 pentane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 3062 (w), 3028 (w), 2935 (m), 2858 (w), 2233 (w), 1604 (m), 1496 (m), 1454 (m), 1354 (m), 1304 (m), 1254 (s), 1126 (s), 1176 (s), 1057 (w), 991 (w), 891 (w), 833 (w), 752 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 7.50 (dd, J = 7.8, 1.8 Hz, 2H, Ar*H*), 7.41− 7.33 (m, 3H, Ar*H*), 7.17−7.10 (m, 1H, Ar*H*), 7.05 (d, *J* = 7.4 Hz, 1H, Ar*H*), 6.85− 6.74 (m, 2H, Ar*H*), 5.35 (q, *J* = 6.8 Hz, 1H, -C*H*CF_3), 3.76 (dt, *J* = 11.0, 5.0 Hz, 1H, -NCH_2), 3.43 (dt, *J* = 11.0, 5.0 Hz, 1H, -NCH_2), 2.83 (t, *J* = 6.5 Hz, 2H, -CH_2-), 2.06− 1.96 (m, 2H, -CH_2-); **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 144.3, 132.1, 130.0, 129.2, 128.5, 127.3, 124.5 (q, *J* = 285.4 Hz), 124.6, 121.7, 118.7, 112.8, 88.2, 78.8 (q, *J* = 2.6 Hz), 55.4 (q, *J* = 33.9 Hz), 45.7, 28.1, 21.9; **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* −73.2 (d, *J* = 6.8 Hz); **HRMS (ESI/QTOF)** m/z [M + H]$^+$ calcd for $C_{19}H_{17}F_3N^+$ 316.1308, found 316.1310. The values of the NMR spectra are in accordance with reported literature data.[2]

(*R*)-4-methyl-N-(1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)aniline (**13af**):



Compound **13af** was prepared form **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and *p*-toluidine (**12f**) (107.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a pale-yellow oil (42.0 mg, 0.145 mmol, 58%). The enantiomeric ratio (er) resulted to be 82:18 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI column: AI 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.8 min, $t_{R(major)}$ = 6.1 min; α_D^{23} = -302.7 (c = 0.1, $CHCl_3$); **TLC** R_f = 0.23 (97:3 pentane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 3371 (w), 2936 (w), 1516 (s), 1491 (m), 1466 (w), 1444 (w), 1353 (m), 1268 (m), 1239 (s), 1181 (s), 1133 (s), 1033 (m), 990 (w), 821 (m), 770 (s), 761 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 - 7.43 (m, 2H, Ar*H*), 7.37 - 7.29 (m, 3H, Ar*H*), 7.07 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.72 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.86 (dq, *J* = 9.5, 6.2 Hz, 1H, -C*H*CF_3), 3.91 (d, *J* = 9.5 Hz, 1H, -N*H*-), 2.28 (s, 3H, -CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.8, 132.1, 130.1, 129.8, 129.3, 128.5, 123.9 (q, *J* = 281.7 Hz), 121.6, 115.0, 86.2, 80.9 (q, *J* = 2.2 Hz), 51.2 (q, *J* = 34.1 Hz), 20.6; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -75.7 (d, *J* = 6.1 Hz); **HRMS (ESI/QTOF)** *m/z: [M + H]*$^+$ Calcd for $C_{17}H_{15}F_3N^+$ 290.1151; Found 290.1152. The values of the NMR spectra are in accordance with reported literature data.[2]

(*R*)-4-Methoxy-*N*-(1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)aniline (**13ag**):



Compound **13ag** was prepared form **2a** (117.5 mg, 0.2500 mmol, 1.00 equiv.) and *p*-anisidine (**12g**) (123.2 mg, 1.000 mmol, 4.00 equiv.) following the procedure D. It was purified by PTLC (95:5, Pentane/EtOAc) and obtained as a pale-yellow oil (48.0 mg, 0.157 mmol, 63%). The enantiomeric ratio (er) resulted to be 81:19 and was determined by chiral HPLC analysis on a Daicel Chiralpak AI column: AI 97:3 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 9.7 min, $t_{R(major)}$ = 10.1 min.; $\boldsymbol{\alpha_D^{23}}$ = -236.3 (c = 0.1, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ = 0.12 (97:3 pentane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2947 (w), 1512 (s), 1491 (m), 1349 (m), 1270 (m), 1240 (s), 1236 (s), 1181 (s), 1134 (s), 1033 (m), 823 (m), 773 (m), 770 (m), 759 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 - 7.41 (m, 2H, Ar*H*), 7.37 - 7.29 (m, 3H, Ar*H*), 6.87 - 6.77 (m, 4H, Ar*H*), 4.77 (dq, *J* = 9.8, 6.3 Hz, 1H, -C*H*CF_3), 3.78 - 3.76 (m, 4H, -N*H*- + -OCH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.3, 139.0, 132.1, 129.3, 128.5, 123.9 (q, *J* = 281.5 Hz), 121.6, 117.0, 115.0, 86.4, 81.0 (q, *J* = 2.6 Hz), 55.8, 52.3 (q, *J* = 33.9 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -75.7 (d, *J* = 6.8 Hz); **HRMS (ESI/QTOF)** *m/z: [M + H]$^+$* Calcd for $C_{17}H_{15}F_3NO^+$ 306.1100; Found 306.1100. The values of the NMR spectra are in accordance with reported literature data.[2],

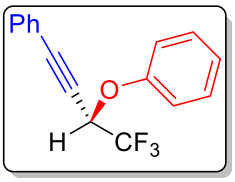
7. Procedures and Compound Characterization for the Enantioselective 3-Component Reaction between 1, 2 and Phenols (14) and Carboxylic Acids (16)

Procedure E: Synthesis of Trifluoromethylated Phenol Ethers **15a**-**15b** and ester (**17**)

Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4SbF_6$ (3.8 mg, 1.2 µmol, 0.060 equiv) and L1 (4.4 mg, 1.5 µmol, 0.075 equiv.) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (3.9 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

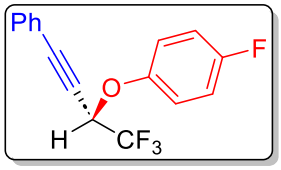
Procedure: In an oven-dried microwave vial, compound **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and phenol (**14a**-**14b**, if solid) (0.80 mmol, 4.00 equiv.) were added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N2, followed by the addition of 1 (0.40 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and phenol (**14a**-**14b**, if liquid). The resulting reaction mixture was stirred at RT under N2 atmosphere and the catalytic solution (1.30 mL) was added dropwise. After 1h of reaction, the reaction was monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2** (unless otherwise noticed). The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (15 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography according to the conditions described for each compound.

(*S*)-(4,4,4-Trifluoro-3-phenoxybut-1-yn-1-yl)benzene (**15a**):



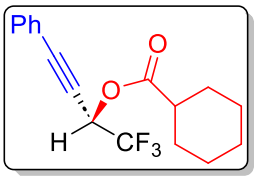
Compound **15a** was prepared form **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and phenol (**14a**) (75.3 mg, 0.800 mmol, 4.00 equiv.) following the procedure E. It was purified by flash column chromatography (100% Pentane to 97:3 Pentane/EtOAc) and obtained as a pale-yellow oil (43.2 mg, 0.160 mmol, 80%). The enantiomeric ratio (er) resulted to be 80:20 and was determined by chiral HPLC by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 10.4 min, $t_{R(major)}$ = 11.1 min. $\boldsymbol{\alpha_D^{23}}$ = -95.0 (c = 0.1, $CHCl_3$); **TLC** $\boldsymbol{R_f}$ 0.54 (99:1 pentane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2957 (w), 2918 (w), 2226 (w), 1595 (w), 1494 (m), 1278 (m), 1255 (m), 1220 (s), 1188 (m), 1148 (s), 1079 (m), 1072 (m), 877 (w), 770 (s), 767 (s)**; ^{1}HNMR (400 MHz, $CDCl_3$)** δ 7.50 - 7.44 (m, 2H, Ar*H*), 7.41 - 7.29 (m, 5H), 7.15 - 7.07 (m, 3H, Ar*H*), 5.32 (q, *J* = 5.5 Hz, 1H, -C*H*CF_3); **^{13}CNMR (101 MHz, $CDCl_3$)** δ 156.6, 132.2, 129.8, 129.7, 128.5, 122.3 (q, J = 281.2 Hz), 121.0, 118.1, 116.5, 89.4, 78.8 (d, J = 2.2 Hz), 68.6 (q, J = 36.3 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.7 (d, *J* = 5.4 Hz); **HRMS (ESI/QTOF)** *m/z:* $[M + Ag]^+$ Calcd for $C_{16}H_{11}AgF_3O^+$ 382.9807; Found 382.9807.

(*S*)-1-fluoro-4-((1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)oxy)benzene (**15b**):



Compound **15b** was prepared form **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and *p*-fluorophenol (**14b**) (89.7 mg, 0.800 mmol, 4.00 equiv.) following the general procedure E. It was purified by flash column chromatography (100% Pentane to 97:3 Pentane/EtOAc) and obtained as a pale-yellow oil (48.8 mg, 0.166 mmol, 83%). The enantiomeric ratio (er) resulted to be 78:22 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 11.1 min, $t_{R(major)}$ = 13.2 min. $\boldsymbol{\alpha_D^{23}}$ = 28.0 (c = 0.26, $CHCl_3$); **TLC** *Rf* 0.53 (99:1 pentane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 3083 (w), 3055 (w), 2936 (w), 2251 (w), 2229 (w), 1505 (s), 1492 (m), 1365 (w), 1275 (m), 1256 (m), 1241 (m), 1218 (s), 1202 (s), 1147 (s), 1098 (w), 1065 (m), 1004 (w), 990 (w), 909 (m), 884 (w), 830 (m), 774 (s), 757 (m), 735 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 - 7.42 (m, 2H, Ar*H*), 7.41 - 7.30 (m, 3H, Ar*H*), 7.11 - 7.00 (m, 4H, Ar*H*), 5.23 (q, *J* = 5.4 Hz, 1H, -C*H*CF_3). **^{13}CNMR (101 MHz, $CDCl_3$)** δ 158.9 (d, *J* = 241.3 Hz), 152.7 (d, *J* = 3 Hz), 132.2, 129.8, 128.6, 122.2 (q, *J* = 281.5 Hz), 120.9, 118.4 (d, *J* = 8.2 Hz), 116.3 (q, *J* = 23.0 Hz), 89.7, 78.5 (d, *J* = 1.6 Hz), 69.6 (q, *J* = 34.3 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.8 (d, *J* = 5.4 Hz, -CF_3), -120.3 (m). **HRMS (Sicrit plasma/LTQ-Orbitrap)** m/z: $[M + H]^+$ Calcd for $C_{16}H_{11}F_4O^+$ 295.0741; Found 295.0739.

(*S*)-1,1,1-Trifluoro-4-phenylbut-3-yn-2-yl cyclohexanecarboxylate (**17**):

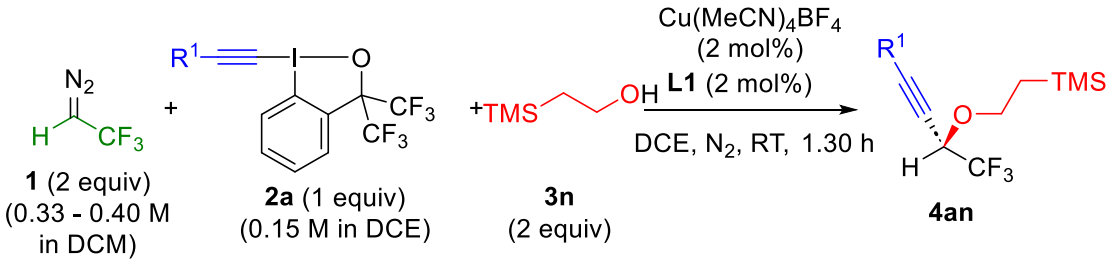


Compound **17** was prepared form **2a** (94.0 mg, 0.200 mmol, 1.00 equiv.) and cyclohexanecarboxylic acid **(16)** (90.6 mg, 0.800 mmol, 4.00 equiv.) following the general procedure E. It was purified by PTLC (100% Pentane) and obtained as a pale-yellow oil (12.4 mg, 0.0400 mmol, 20%). The enantiomeric ratio (er) resulted to be 90:10

and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(major)}$ = 8.2 min, $t_{R(minor)}$ = 8.6 min; **α_D^{23}** = 102.8 (c =0.125, $CHCl_3$); **TLC R_f** = 0.72 (99:1 pentane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 3356 (w), 3020 (w), 2931 (w), 2843 (w), 1512 (s), 1346 (m), 1242 (s), 1180 (s), 1134 (s), 1034 (m), 822 (m), 756 (m); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.51 - 7.48 (m, 2H, Ar*H*), 7.41 - 7.29 (m, 3H, Ar*H*), 6.10 (q, *J* = 5.8 Hz, 1H, -*C*HCF$_3$), 2.47 (tt, *J* = 11.2, 3.6 Hz, 1H, -COC*H*-), 2.01 - 1.94 (m, 2H, -CH_2, -cyclohexyl), 1.81 - 1.73 (m, 2H, -CH_2 cyclohexyl), 1.70 - 1.63 (m, 1H, -C*H* cyclohexyl), 1.53 - 1.42 (m, 1H, -C*H* cyclohexyl), 1.38 - 1.21 (m, 4H, -CH_2 cyclohexyl); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.7, 132.4, 129.7, 128.5, 122.1 (q, *J* = 281.2 Hz), 121.0, 88.0, 78.0 (q, *J* = 1.8 Hz), 61.7 (q, *J* = 37.2 Hz), 42.8, 29.0, 28.7, 25.7, 25.4, 25.3; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.6 (d, *J* = 5.4 Hz).

8. Scale up Procedures for Compounds 4an and 11b

8.1. Procedure for the scale up of compound 4an



Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (6.3 mg, 0.020 mmol, 0.020 equiv) and **L1** (3.5 mg, 1.2 µmol, 0.060 equiv) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (6.7 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

Procedure: In an oven-dried microwave vial, compound **2a** (470.1 mg, 1.000 mmol, 1.00 equiv.) was added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2, followed by the addition of **1** (5.6 mL, 2.0 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) and alcohol **3n** (287 µL, 2.00 mmol, 2.00 equiv.). The resulting reaction mixture was stirred at RT under N_2 atmosphere and the catalyst solution (6.7 mL) was added dropwise. After 1.30 h of reaction, the reaction was

monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2**. The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (40 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography (100% to 99:1, Pentane/EtOAc) and obtained as a colourless oil (153 mg, 0.509 mmol, 51%). The enantiomeric ratio (er) resulted to be 93:7 and was determined by chiral HPLC analysis on a Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate1 mL/min, 2 µL sample's injection, 254 nm, $t_{R(minor)}$ = 5.7 min, $t_{R(major)}$ = 6.3 min. *For characterization, see compound **4an***

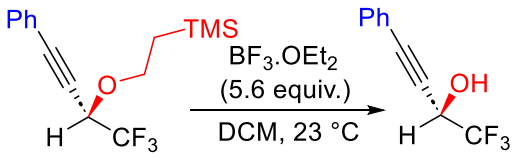
8.2. Procedure for the scale up for compound 11b

Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (6.3 mg, 0.020 mmol, 0.02 equiv.) and **L1** (7.4 mg, 0.025 mmol, 0.025 equiv.) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2. Finally, dry DCE (6.7 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

Procedure: In an oven-dried microwave vial, compound **2a** (550.4 mg, 1.000 mmol, 1.00 equiv.) and **10** (630.6 mg, 2.000 mmol, 2.00 equiv.) were added and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N_2, followed by the addition of **1** (5.6 mL, 2.0 mmol, 0.33-0.40 M in DCM, 2.00 equiv.) The resulting reaction mixture was stirred at RT under N_2 atmosphere and the catalyst solution (6.7 mL) was added dropwise. After 1 h of reaction, the reaction was monitored by TLC (95:5, Pentane/EtOAc) observing full conversion of **2**. The reaction mixture was filtered through a short pad of celite and rinsed up with EtOAc (40 mL). The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography (100% to 90:10, Pentane/EtOAc) and obtained as a white solid (425.0 mg, 0.718 mmol, 72%). The diastereomeric ratio (dr) resulted to be 97:3 and was determined by ^{19}F NMR of the crude mixture.

9. Product functionalization

9.1. Procedure for the deprotection of 4an: Synthesis of (*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (18)



4an 87%, 94:6 er **18**

Following a reported procedure,[6] a solution of **4an** (126 mg, 0.420 mmol, 1.00 equiv., 93:7 e:r) in dry DCM (6.5 mL) was prepared followed by the dropwise addition of $BF_3.OEt_2$ (396 µL, 2.35 mmol, 5.60 equiv.). The colourless solution was stirred at RT under N_2 atmosphere. After 1h, the reaction was monitored by TLC (95:5, Pentane/EtOAc) and full conversion was observed.

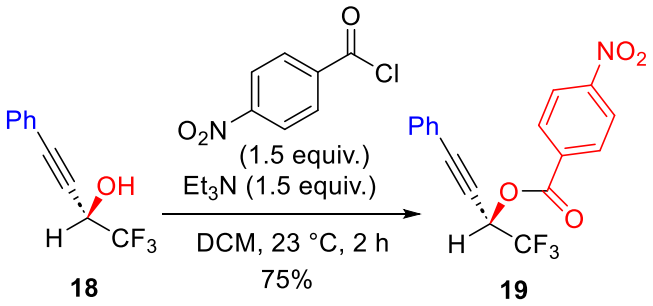
The reaction was quenched adding $NaHCO_3$ (7 mL) and the biphasic mixture was stirring during 10 min at RT. Then, layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). Organics were recombined, washed with brine (1 x 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (95:5 to 80:20, Pentane/EtOAc), yielding compound **18** as a colourless oil (73.0 mg, 0.365 mmol, 87%). The enantiomeric ratio (er) resulted to be 94:6 and was determined by chiral HPLC; $\boldsymbol{\alpha_D^{23}}$ = -10.3 (c =1, $CHCl_3$)[7,8]; **TLC** $\boldsymbol{R_f}$ = 0.020 (8:2: Hexane/EtOAc), visualized by exposure to UV light; **IR (ν_{max}, cm^{-1})** 3379 (w), 2975 (w), 2248 (w), 2229 (w), 1491 (m), 1352 (m), 1273 (m), 1256 (m), 1219 (m), 1186 (s), 1140 (s), 1087 (m), 1071 (m), 772 (s), 759 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.51 - 7.45 (m, 2H, Ar*H*), 7.41 - 7.32 (m, 3H, Ar*H*), 4.92 (p, *J* = 5.8 Hz, 1H, -C*H*CF_3), 2.75 (d, *J* = 8.2 Hz, 1H, -O*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 132.2, 129.7, 128.6, 122.9 (q, *J* =

[6] Ramasamy, M.; Lin, H.-C.; Kuo, S.-C.; Hsieh, M.-T. Lewis Acid-Catalyzed Rearrangement of Fluoroalkylated Propargylic Alohols: An Alternative Approach to *β*-Fluoroalkyl-*α*,*β*-enones. *Synlett* **2019**, *30*, 356 – 360..

[7] We found different α_D value for the same enantiomer described in the literature. This is probably due to the low rotation power of this compound. For more information, see: a) Veeraraghavan Ramachandran, P.; Gong, B.; Teodorovic, A. V.; Brown, H. C. Selective reductions. 52. Efficient Asymmetric Reduction of *α*-Acetylenic *α*'-Fluoroalkyl Ketones with Either *β*-Chlorodiisopinocamphenylborane or *β*-Isopinocampheyl-9-borabicyclo[3.3.1.]nonane in High Enantiomeric Purity. The Influence of Fluoro Groups in Such Reductions. *Tetrahedron: Asymmetry* **1994**, *5*, 1061 – 1074. b) Matsutani, H.; Kusumoto, T.; Hiyama, T. A Facile Synthesis of Optically Active 1, 1, 1 – Trifluoro-3-alkyn-2-ols by Stereospecific Substitution of Optically Active 1-Benzyloxy-2,2,2-trifluoroethyl Tosylate with Lithium Alkynyltriethylaluminates. *Chemistry Letters* **1999**, *28*, 529-530. c) Zhang, Y.-M.; Yuan, M.-L.; Liu, W.-P.; Xie, J.-H.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Transfer Hydrogenation of Alkynyl Ketones Using Sodium Formate and Ethanol as Hydrogen Sources. *Org. Lett.* **2018**, *20*, 4486 – 4489. d) Nicholson, K.; Dunne, J.; DaBell, P.; Beaton Garcia, A.; Bage, A. D.; Docherty, J. H.; Hunt, T. A.; Langer, T.; Thomas, S. P. A Boron-Oxygen Transborylation Strategy for a Catalytic Midland Reduction. *ACS Catal.* **2021**, *11*, 2034 – 2040.

281.9 Hz), 121.0, 88.1, 80.6 (q, *J* = 2.6 Hz), 63.1 (q, *J* = 36.5 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** *δ* -79.4 (d, *J* = 5.4 Hz); **HRMS (APCI/QTOF)** *m/z: [M + H]*$^+$ Calcd for $C_{10}H_8F_3O^+$ 201.0522; Found 201.0516. The values of the NMR spectra are in accordance with reported literature data.[8!

9.2. Derivation of compound 18: Synthesis of (*S*)-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl 4-nitrobenzoate (19)[8]

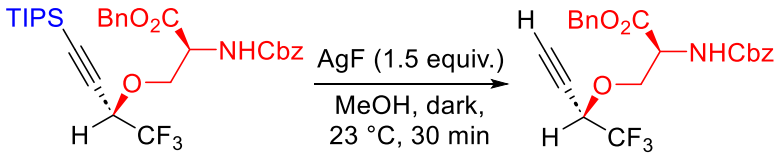


In a MW vial, a solution of **18** (72.0 mg, 0.360 mmol, 1.00 equiv.) in dry DCM (1 mL) was prepared followed by the dropwise addition of Et_3N (75 µL, 0.57 mmol, 1.50 equiv.) and the resulting solution was stirred at room temperature during 30 min. After that, *p*-nitrobenzoyl chloride (100 mg, 0.570 mmol, 1.50 equiv.) was slowly added into the solution and the reaction mixture was stirred during 2 h at room temperature. After this time, full conversion was observed (monitored by TLC, 80:20, Pentane/EtOAc) and the reaction mixture was quenched with brine (1 x 5 mL). The two-layer mixture was stirred during 15 min and then, extracted with DCM (3 x 10 mL). The organic layers were recombined and washed with $NaHCO_3$ (1 x 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **19** was obtained after purification by flash column chromatography (100% Pentane to 80:20 Pentane/EtOAc) as a white crystalline solid (94.3 mg, 0.270 mmol, 75%): **TLC** R_f = 0.31 (99:1 pentane/EtOAc), visualized by exposure to UV light; **IR** *(ν_{max}, cm^{-1})* 2946 (w), 2868 (w), 1750 (w), 1534 (w), 1347 (w), 1328 (w), 1275 (m), 1260 (m), 1219 (m), 1195 (m), 1147 (m), 1092 (w), 772 (s). **^{1}H NMR (400 MHz, $CDCl_3$)** *δ* 8.36 – 8.20 (m, 4H, Ar*H*), 7.55 - 7.47 (m, 2H, Ar*H*), 7.45 - 7.30 (m, 3H, Ar*H*), 6.33 (q, *J* = 5.6 Hz, 1H, -C*H*CF_3). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 162.6, 151.3, 133.7, 132.4, 131.6, 130.0, 128.6, 123.9, 121.9 (q, *J* = 281.2 Hz), 120.5, 89.1, 63.3 (q, *J* =

[8] Ko, S.-J.; Lim, J. Y.; Jeon, N. Y.; Won, K.; Ha, D.-C.; Kim, B. T.; Lee, H. Kinetic resolution of fluorinated propargyl alcohols by lipase-catalyzed enantioselective transesterification. *Tetrahedron: Asymmetric* **2009**, *20*, 1109 – 1114.

37.8 Hz). (One C is not resolved); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -76.3 (d, J = 5.4 Hz); **HRMS (APCI/QTOF)** m/z: $[M + H]^+$ Calcd for $C_{10}H_8F_3O^+$ 201.0522; Found 201.0516.The values of the NMR spectra are in accordance with reported literature data.[8]

9.3. Procedure for the deprotection of the TIPS group: Synthesis of benzyl *N*-((benzyloxy)carbonyl)-O-((*S*)-1,1,1-trifluorobut-3-yn-2-yl)-L-serinate (20)



11b 82%, 70:30 *dr* **20**

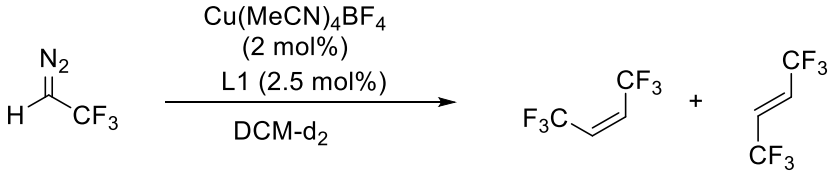
Following a reported procedure,[9] a solution of **11b** (425 mg, 0.738 mmol, 1.00 equiv. 93:7 er) in dry MeOH (7.6 mL) was prepared followed by the slowly addition of AgF (140 mg, 1.10 mmol, 1.50 equiv.). The black mixture was stirred at RT during 30 min under N_2 atmosphere. After this time, HCl (1 M, 10 mL)) was added and the resulting suspension was stirred another additional 10 min. The precipitated was filtrated and the aqueous liquors were extracted with DCM (3 x 20 mL). Organics were recombined, washed with sat. NH_4Cl (1 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (95:5 to 75:25, Pentane/EtOAc), yielding product **20** as a white solid (265.0 mg, 0.609 mmol, 82%). The diastereomeric ratio (dr) resulted to be 70:30 and was determined by ^{19}F NMR of the crude mixture; **α_D^{23}** = -174.3 (c = 0.1, $CHCl_3$); **TLC** R_f = 0.18 (95:5 Hexane/EtOAc), visualized by exposure to UV light and/or $KMnO_4$; **IR (ν_{max}, cm^{-1})** 3303 (w), 3036 (w), 2953 (w), 1744 (m), 1719 (s), 1608 (w), 1510 (m), 1465 (w), 1456 (m), 1341 (m), 1273 (s), 1217 (s), 1189 (s), 1148 (s), 1119 (s), 1057 (m), 860 (w), 772 (s), 759 (m); **^{1}H NMR (400 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ 7.37 - 7.32 (m, 10H, Ar*H*), 5.65 - 5.62 (m, 1H, -N*H*-), 5.25 - 5.16 (m, 2H, -CH_2Ph), 5.14 - 5.13 (m, 2H, -CH_2Ph), 4.63 - 4.61 (m, 1H, -C*H*CO_2Bn), 4.53 - 4.49 (m, 0.39H, C*H*CF_3), 4.43 - 4.39 (0.74H, -C*H*CF_3), 4.27 - 4.24 (m, 0.32H, -OCH_2-), 4.12 (dd, J = 9.4, 3.1 Hz, 1H, -OCH_2-), 4.04 (dd, J

[9] Kim, S.; Kim, B.; In, J. Facile Deprotection of Bulky (Trialkylsilyl)acetylenes with Silver Fluoride. *Synthesis* **2009**, *12*, 1963 – 1968.

= 9.3, 3.3 Hz, 0.82H, -OCH_2-), 3.95 - 3.92 (m, 0.31H, -OCH_2-), 2.55 (s, 0.63H, $HC\equiv C-$), 2.52 (s, 0.31H, $HC\equiv C-$); **^{13}C NMR (101 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ 169.4 (major diastereoisomer), 169.3 (minor diastereoisomer), 156.02 (major diastereoisomer), 156.00 (minor diastereoisomer), 136.2, 135.2, 128.72, 128.68, 128.64, 128.61, 128.6, 128.34, 128.31, 128.2, 122.0 (q, *J* = 282.6 Hz, minor diastereoisomer), 121.9 (q, *J* = 283.2 Hz, major diastereoisomer), 78.4 (minor diastereoisomer), 78.3 (major diastereoisomer), 73.0 (q, *J* = 2.4 Hz, major diastereoisomer), 72.9 (q, *J* = 2.2 Hz, minor diastereoisomer), 69.9, 69.5, 69.0 (q, *J* = 35.8 Hz), 68.8 (q, *J* = 35.6 Hz, minor diastereoisomer), 67.72 (minor diastereoisomer), 67.69 (major diastereoisomer, 67.3, 54.3;**^{19}F NMR (377 MHz, $CDCl_3$, mixture of inseparable diastereoisomers)** δ -76.6 (d, *J* = 5.5 Hz, minor diastereoisomer), -76.8 (d, *J* = 5.5 Hz, major diastereoisomer);**HRMS (APPI/LTQ-Orbitrap)** *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{21}F_3NO_5^+$ 436.1366; Found 436.1376.

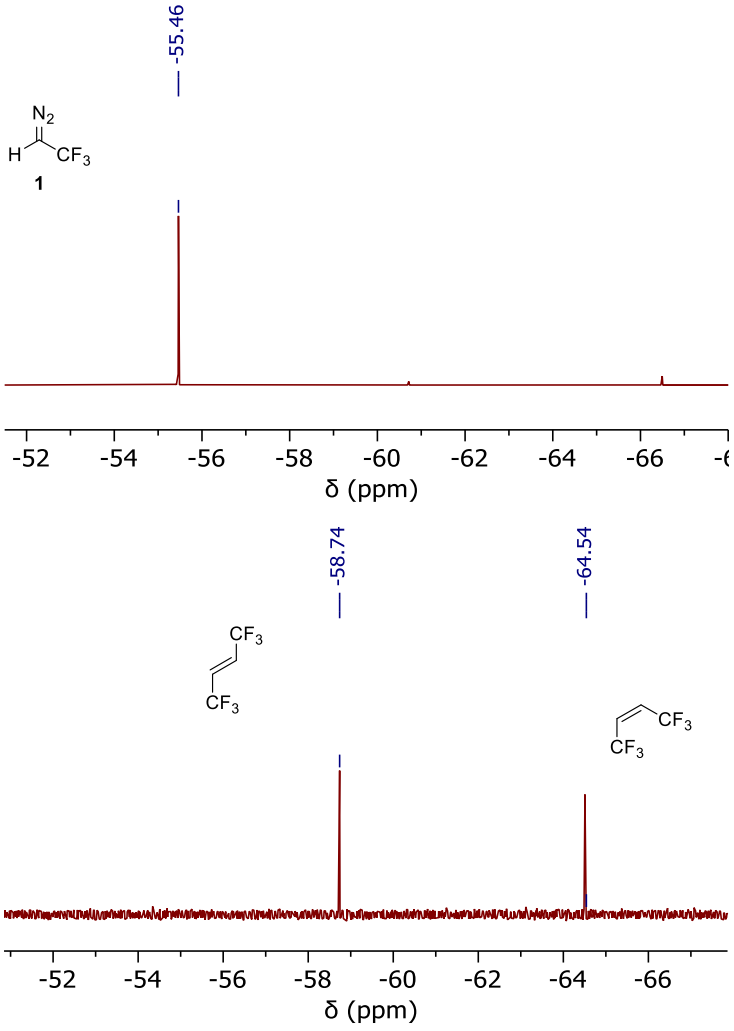
10. Preliminary mechanistic studies

- Decomposition of diazo compound under the presence of the catalytic system (catalytic loading)

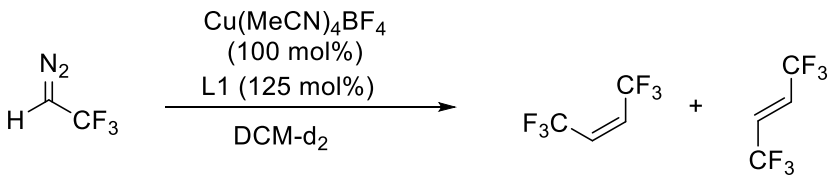


Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (0.90 mg, 3.00 µmol, 0.020 equiv) and L1 (1.10 mg, 3.70 µmol, 0.025 equiv) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N2. Finally, DCM-d_2 (1 mL) was added into the vial and the resulting colourlesss solution was stirred (430 rpm) at room temperature during 1 h.

Experiment description: In an oven dried J young NMR tube, 1 (0.430 mL, 0.150 mmol) in DCM (0.33 – 0.40 M) was added followed by the dropwise addition of the catalytic solution in DCM-d2 (1 mL). The NMR tube was sealed and the ^{19}FNMR experiment was submitted.



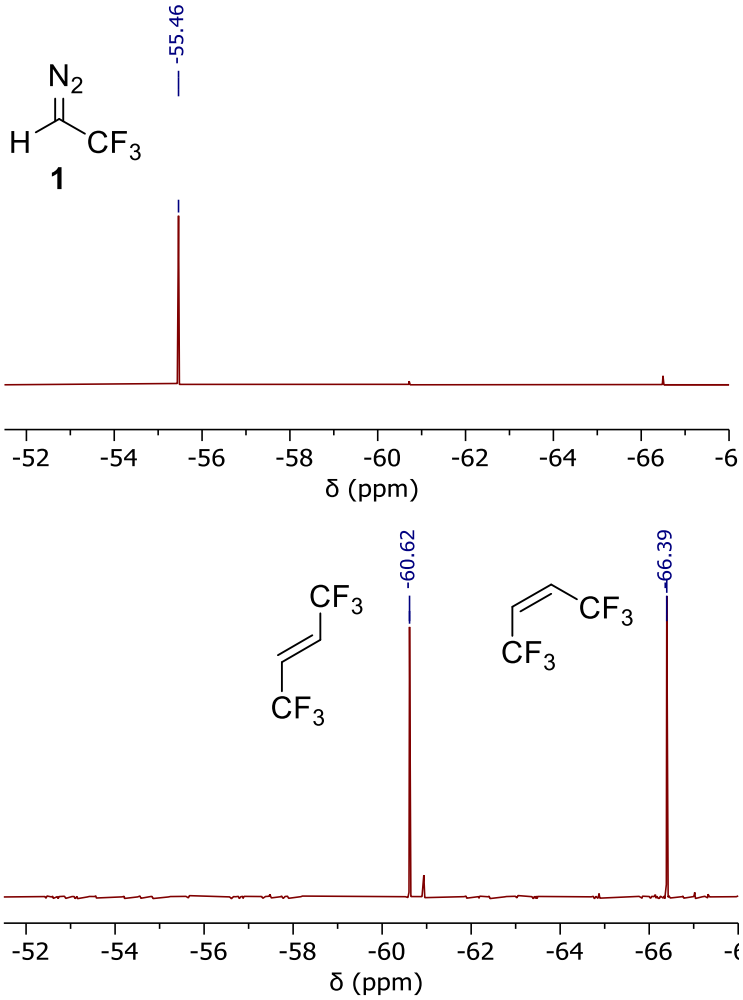
- Decomposition of diazo compound under the presence of the catalytic system (stoichiometric catalytic loading)



Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (15.7 mg, 0.05 mmol, 1.000 equiv) and L1 (18.4 mg, 63.0 µmol, 0.025 equiv) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with

3 cycles of vacuum-N_2. Finally, DCM-d2 (0.35 mL) was added into the vial and the resulting colourlesss solution was stirring (430 rpm) at room temperature during 1 h.

Experiment description: In an oven dried J young NMR tube, **1** (0.14 mL, 0.05 mmol) in DCM (0.33 – 0.40 M) was added followed by the dropwise addition of the catalytic solution in DCM-d2 (0.35 mL). The NMR tube was sealed and the 19FNMR experiment was submitted.



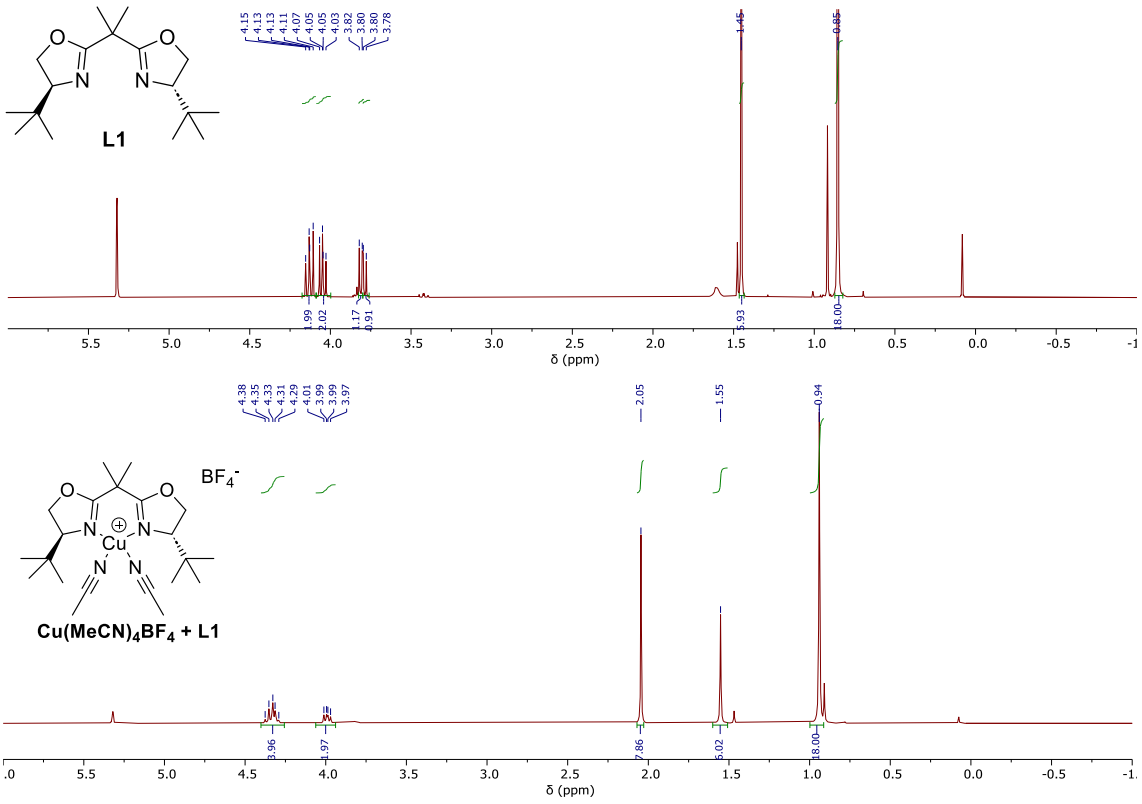
These experiments support the formation of a Copper carbene between **1** and the pre-formed Cu(I)-BOX chiral complex, allowing the formation of the *cis*- and *trans*- alkene after a fast decomposition of the Copper carbene.

- Synthesis of BOX complex

In an oven-dried J young NMR valve, $Cu(MeCN)_4BF_4$ (0.94 mg, 3.00 µmol, 0.020 equiv) and L1 (1.10 mg, 3.70 µmol, 0.025 equiv) were charged followed by the addition of DCM-d2 (1 mL). The mixture was shaken and then NMR was submitted and recorded. The comparison between the uncomplexed L1 and the complexed mixture is done below.

L1: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.13 (dd, J = 10.0, 8.7 Hz, 2H, -OCH_2-), 4.05 (dd, J = 8.7, 7.3 Hz, 2H, -OCH2-), 3.81 (d, J = 7.4 Hz, 1H, -CH-), 3.79 (d, J = 7.4 Hz, 1H, -CH-), 1.45 (s, 6H, -CH_3), 0.85 (s, 18H, -(CH_3)$_3$).

Cu(MeCN)4BF4+ L1: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.58 - 4.29 (m,4H), 3.99 (dd, J = 9.9, 6.7 Hz, 2H), 2.05 (s, 6H), 1.55 (s, 6H), 0.94 (s, 18H).



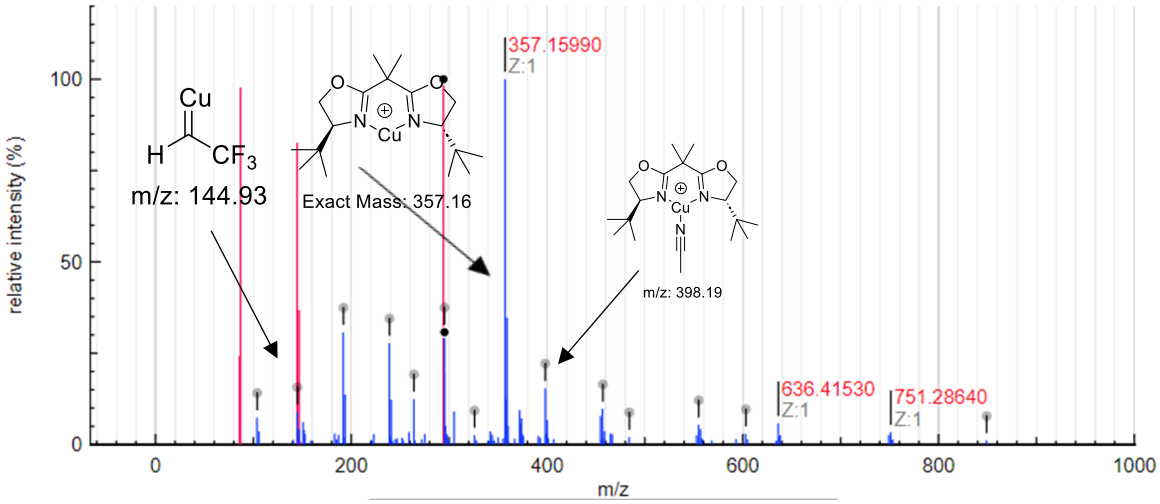
This experiment shows the complexation between L1 and the Cu(I) catalyst. As it is observable in Spectrum B, the signals appears at more downshielded in comparison to Spectrum A, which indicated coordination of Cu. Moreover, a new signal appears at 2.05

ppm belonging to the MeCN groups from the Cu(I) catalyst. The defined shape of the signals reveals that Cu(I), non paramagnetic, species are formed.

- Analysis of the reaction between **1** and the Cu(I)-BOX chiral catalytic system by Mass-Spectrometry.

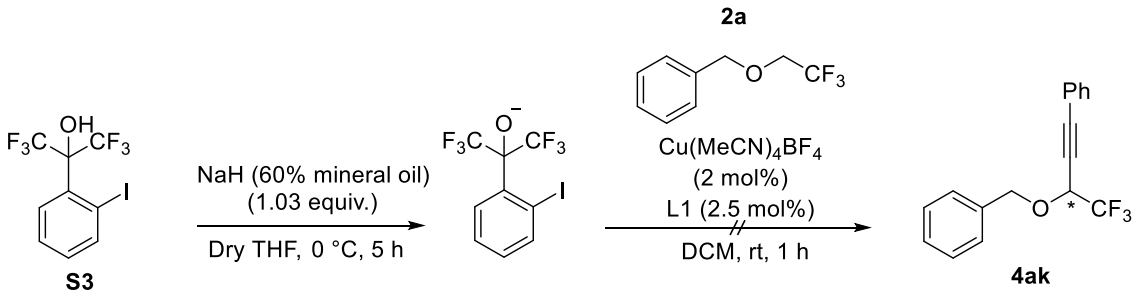
Stock solution of the catalyst: In an oven-dried microwave vial, $Cu(MeCN)_4BF_4$ (0.94 mg, 3.00 µmol, 0.020 equiv) and L1 (1.10 mg, 3.70 µmol, 0.025 equiv) were charged and the vial was capped with a septum. Then, the system was evacuated and backfilled with 3 cycles of vacuum-N2. Finally, dry DCM (1 mL) was added into the vial and the resulting colourlesss solution was stirred (430 rpm) at room temperature during 1 h.

Experiment description: In an oven dried MW vial, **1** (0.43 mL, 0.15 mmol) in DCM (0.33 – 0.40 M) was added followed by the dropwise addition of the catalytic solution in DCM- (1 mL). Then, 150 µL were transfer to a mass-vial under N_2 atmosphere and diluted with dry EtOAc (1.3 mL). The content was directly submitted to mass (ESI-QTOF).



The mass spectra shows the formation of the pre-complex between $Cu(MeCN)_4BF_4$ and **L1** (m/z = 398.19) containing 1 MeCN. Moreover, a Cu-BOX specie can be observed as a main mass (m/z = 357.16). Finally, with a m/z = 144.93 it is also possible to observe the formation of the Cu-carbene specie. Unfortunately, the copper complex bearing both L1 and the carbene could not be observed, probably due to its low stability.

- Alkyne transfer step: Deprotonation of the X-H insertion product?

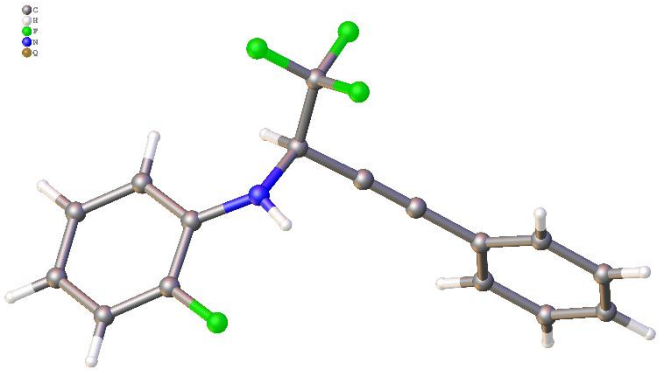


Into an oven-dried MW tube, a solution of **S3** (185 mg, 0.500 mmol, 2.00 equiv.) in dry THF (0.25 mL) was added to a suspension of NaH (60% mineral oil) (20.6 mg, 0.515 mmol, 2.06 equiv.) in dry THF (0.25 mL) at 0 °C. The resulting reaction mixture was stirred under these conditions during 5 h. After that, the reaction mixture was allowed to reach room temperature and the solvent was evaporated. Then, **2a** (117 mg, 0.250 mmol, 1.00 equiv.) followed by 2,2,2-trifluoroethoxymethylbenzene (95.1 mg, 0.500 mmol, 2.00 equiv.) were added into the flask containing the salt. Finally, the catalytic mixture (prepared according previous described protocol) was added dropwise and the reaction mixture was stirred for 1 h at RT, no observing the formation of the desired product after this reaction time..

This experiment shows that the alkyne transfer does not happen via deprotonation of the X-H insertion product by the alkoxylate from **S3.**

11. Determination of the absolute configuration

11.1. X-Ray for the Determination of the Absolute Configuration for Anilines

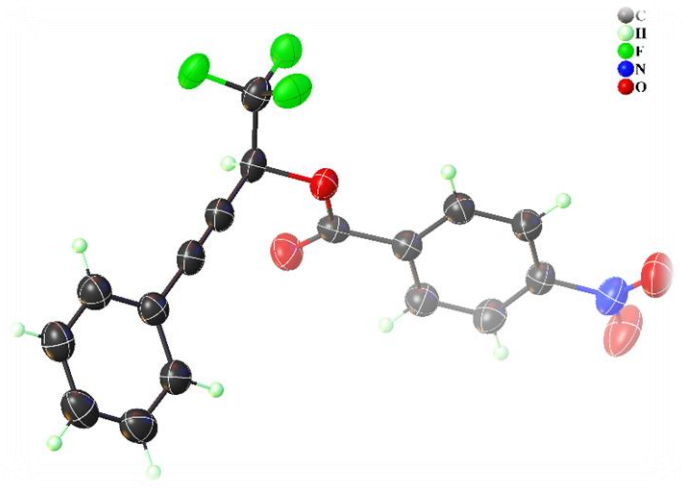


Experimental. Single clear pale colourless needle-shaped crystals of **12ac** were used as supplied. A suitable crystal with dimensions 0.57 × 0.07 × 0.06 mm^3 was selected and mounted on a SuperNova, Dual, Cu at home/near, Atlas diffractometer. The crystal was kept at a steady T = 140.00(11) K during data collection. The structure was solved with the **ShelXT** (Sheldrick, 2015) solution program using dual methods and by using **Olex2** 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on F^2.

Crystal Data. $C_{16}H_{11}F_4N$, M_r = 293.26, monoclinic, $P2_1$ (No. 4), a = 9.2957(4) Å, b = 4.7466(2) Å, c = 15.6594(7) Å, □ = 91.369(4)°, □ = □ = 90°, V = 690.75(5) $Å^3$, T = 140.00(11) K, Z = 2, Z' = 1, □(Cu K□) = 1.045, 5457 reflections measured, 2631 unique (R_{int} = 0.0272) which were used in all calculations. The final wR_2 was 0.1380 (all data) and R_1 was 0.0497 (I≥2 □(I)).

Compound	**12ac**
Formula	$C_{16}H_{11}F_4N$
$D_{calc.}$/ g cm^{-3}	1.410
□/mm^{-1}	1.045
Formula Weight	293.26
Colour	clear pale colourless
Shape	needle-shaped
Size/mm^3	0.57×0.07×0.06
T/K	140.00(11)
Crystal System	monoclinic
Flack Parameter	0.2(2)
Hooft Parameter	0.05(8)
Space Group	$P2_1$
a/Å	9.2957(4)
b/Å	4.7466(2)
c/Å	15.6594(7)
□/°	90
□/°	91.369(4)
□/°	90
V/Å^3	690.75(5)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K□
□$_{min}$/°	2.823
□$_{max}$/°	72.389
Measured Refl's.	5457
Indep't Refl's	2631
Refl's I≥2 □(I)	2398
R_{int}	0.0272
Parameters	195
Restraints	1
Largest Peak	0.265
Deepest Hole	-0.162
GooF	1.031
wR_2 (all data)	0.1380
wR_2	0.1327
R_1 (all data)	0.0539
R_1	0.0497

10.2. X-Ray for the Determination of the Absolute Configuration for Alcohols



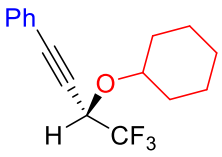
Experimental. Single colourless needle-shaped crystals of **19** were used as supplied. A suitable crystal with dimensions 0.46 × 0.04 × 0.03 mm^3 was selected and mounted on an XtaLAB Synergy R, DW system, HyPix-Arc 150 diffractometer. The crystal was kept at a steady T = 139.99(10) K during data collection. The structure was solved with the **ShelXT** 2018/2 (Sheldrick, 2015) solution program using dual methods and by using **Olex2** 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on F^2.

Crystal Data. $C_{17}H_{10}F_3NO_4$, M_r = 349.26, trigonal, $R3$ (No. 146), a = 30.7704(17) Å, b = 30.7704(17) Å, c = 4.3483(2) Å, □ = 90°, □ = 90°, □ = 120°, V = 3565.4(4) $Å^3$, T = 139.99(10) K, Z = 9, Z' = 1, □(Cu K□) = 1.115, 11947 reflections measured, 3021 unique (R_{int} = 0.0474) which were used in all calculations. The final wR_2 was 0.1248 (all data) and R_1 was 0.0489 (I≥2□(I)).

Compound	**19**
Formula	$C_{17}H_{10}F_3NO_4$
$D_{calc.}$/ g cm^{-3}	1.464
□/mm^{-1}	1.115
Formula Weight	349.26
Colour	colourless
Shape	needle-shaped
Size/mm^3	0.46×0.04×0.03
T/K	139.99(10)
Crystal System	trigonal
Flack Parameter	0.25(15)
Space Group	*R*3
a/Å	30.7704(17)
b/Å	30.7704(17)
c/Å	4.3483(2)
□/°	90
□/°	90
□/°	120
V/Å^3	3565.4(4)
Z	9
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu*K*□
□$_{min}$/°	2.872
□$_{max}$/°	75.408
Measured Refl's.	11947
Indep't Refl's	3021
Refl's I≥2□(I)	2287
R_{int}	0.0474
Parameters	226
Restraints	1
Largest Peak/e Å^{-3}	0.170
Deepest Hole/e Å^{-3}	-0.278
GooF	0.994
wR_2 (all data)	0.1248
wR_2	0.1137
R_1 (all data)	0.0709
R_1	0.0489
CCDC number	2225295

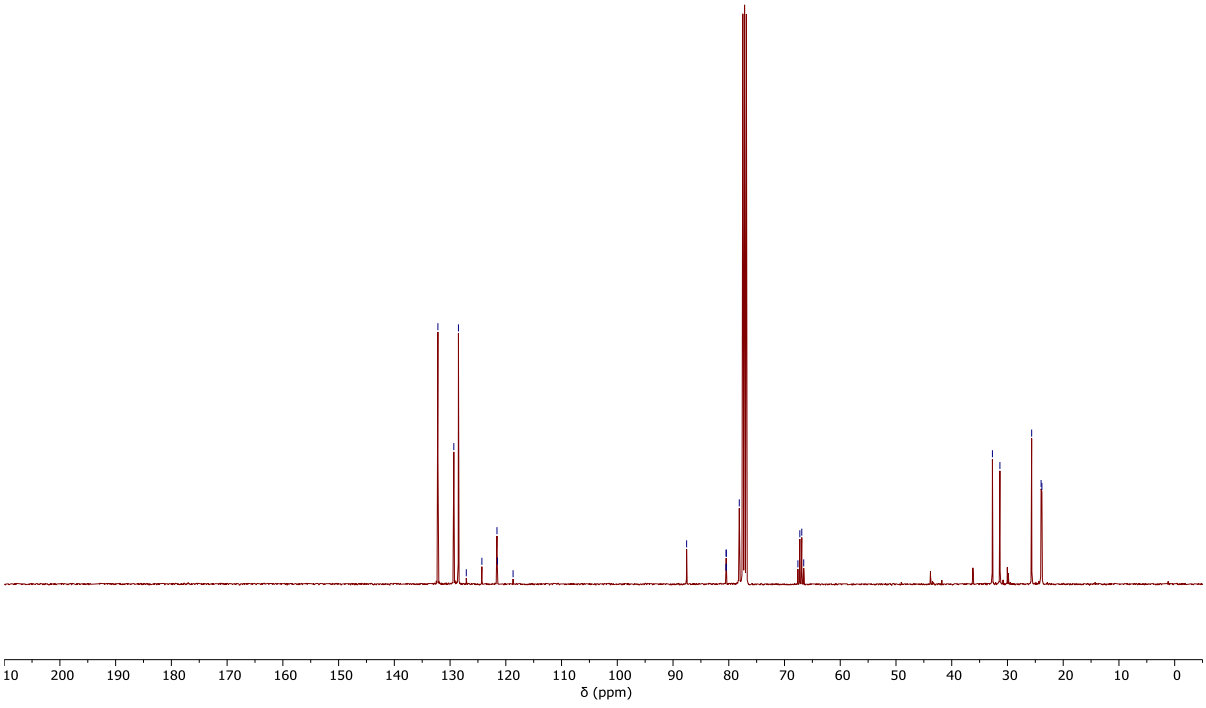
12. ^{1}H, ^{13}C and ^{19}F NMR Spectra of Trifluoromethylated Propargylic Compounds

^{1}H NMR (400 MHz, $CDCl_3$)

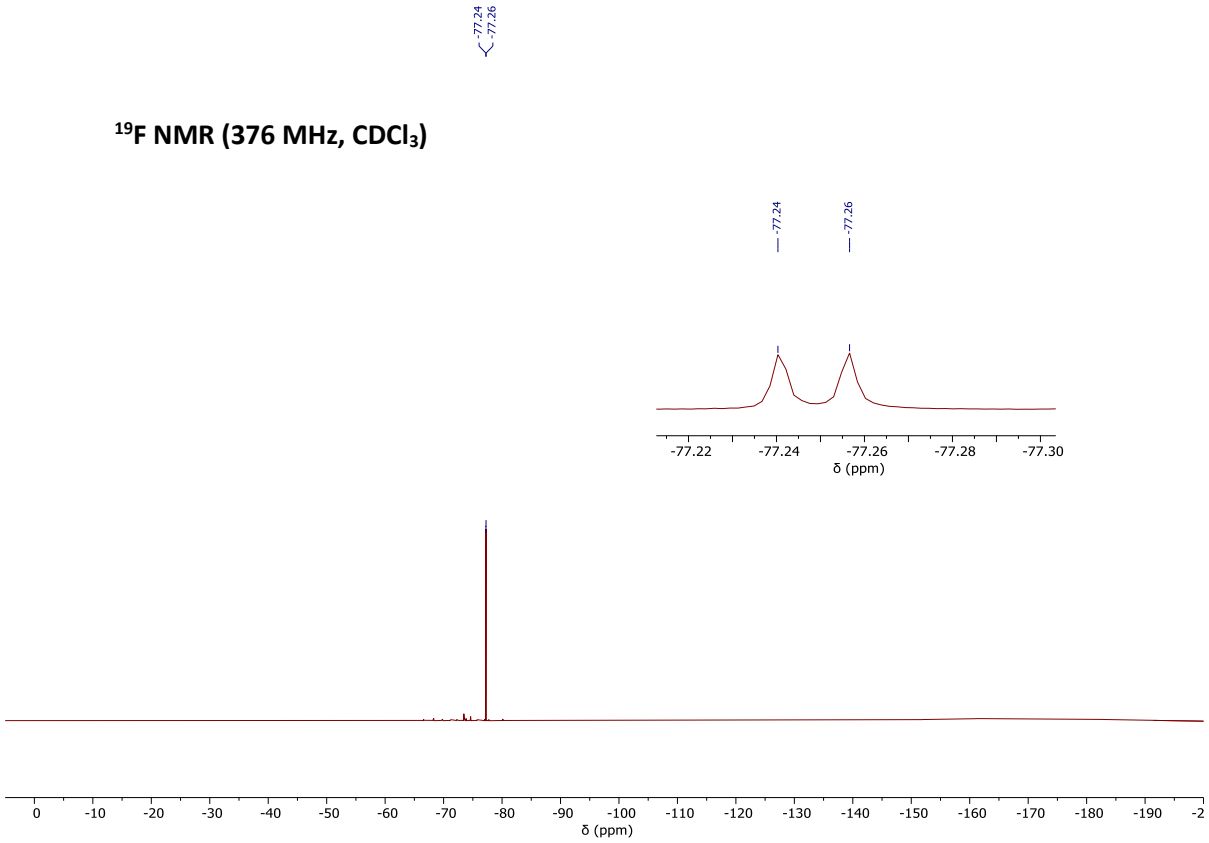


4aa

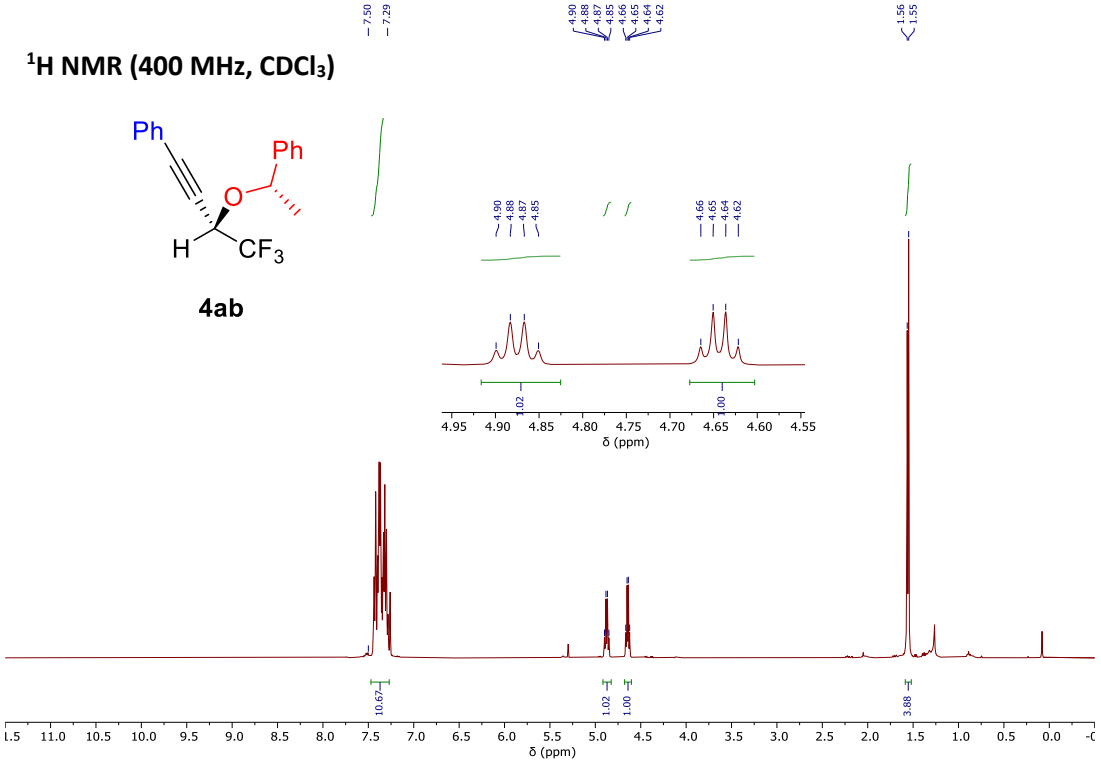
^{13}C NMR (101 MHz, $CDCl_3$)



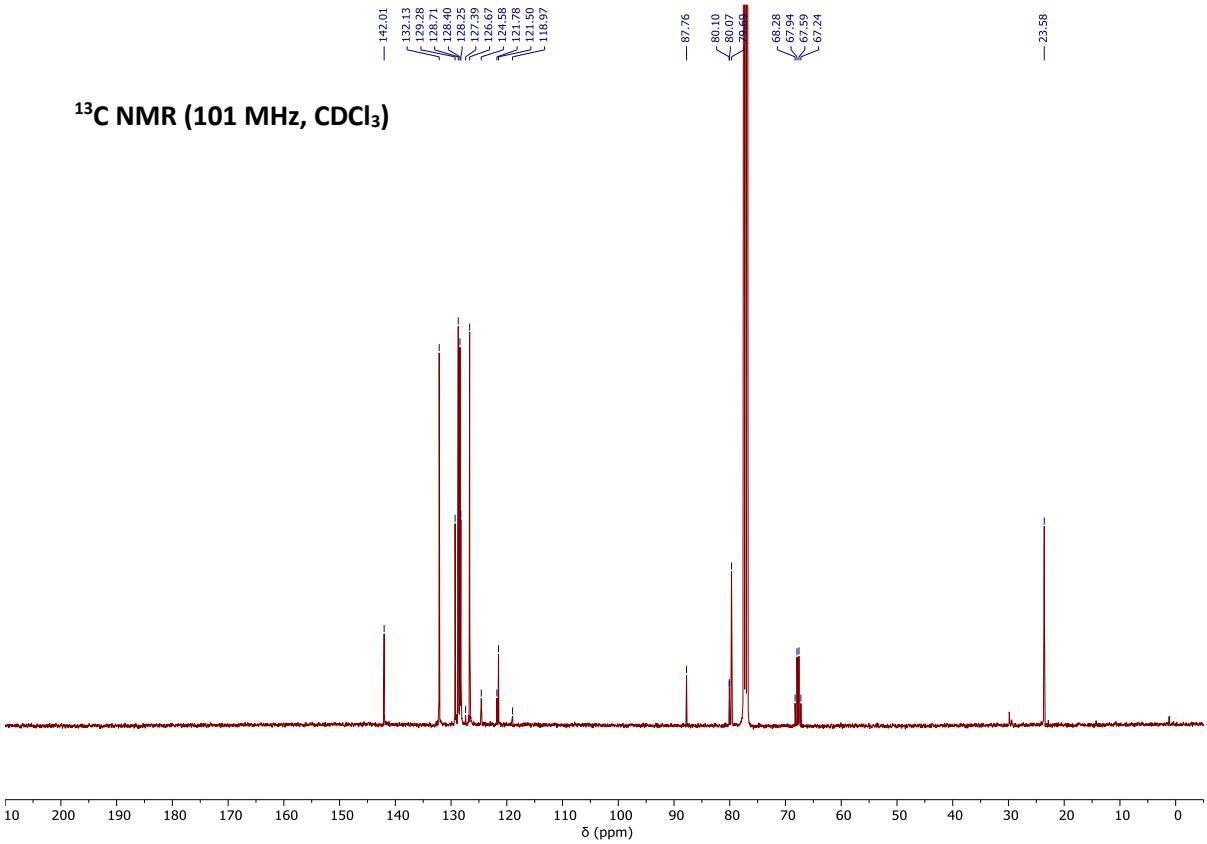
^{19}F NMR (376 MHz, $CDCl_3$)



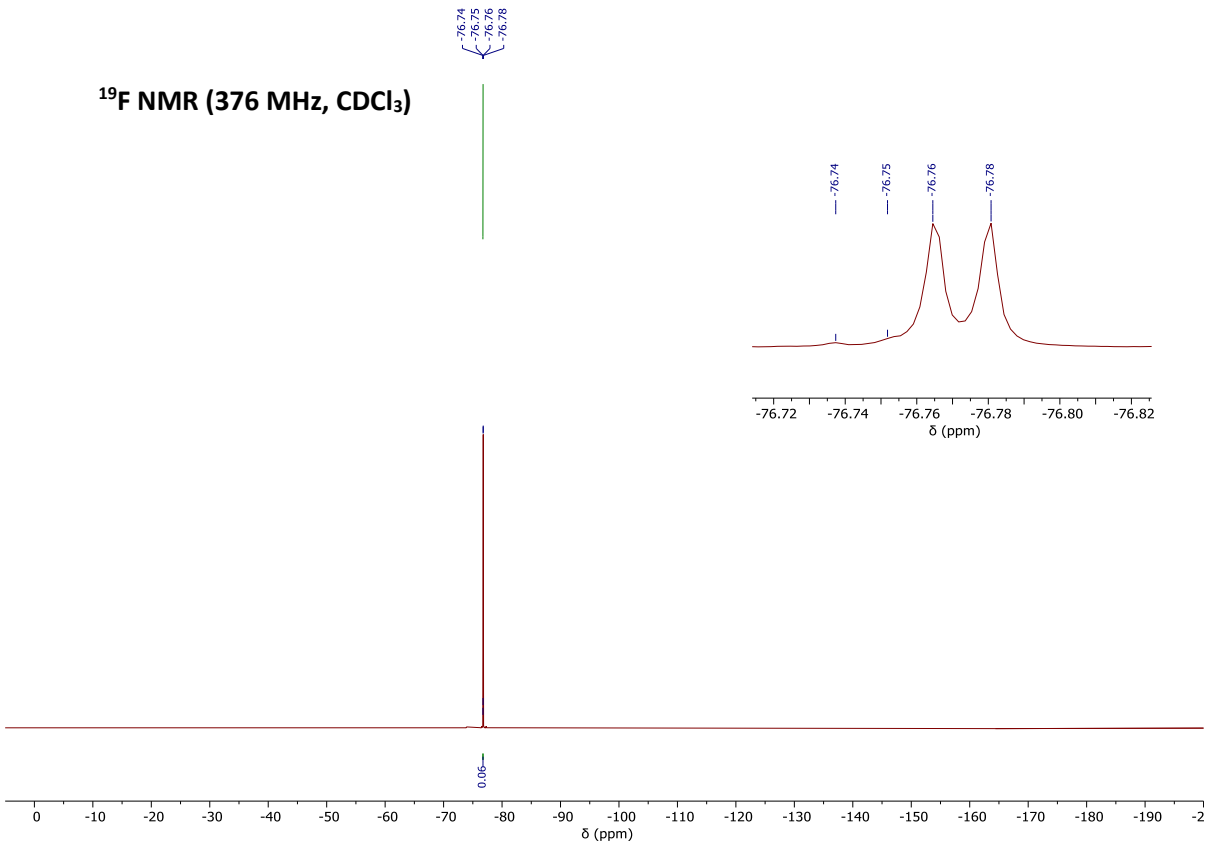
^{1}H NMR (400 MHz, $CDCl_3$)



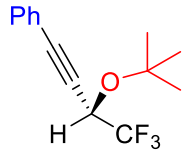
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

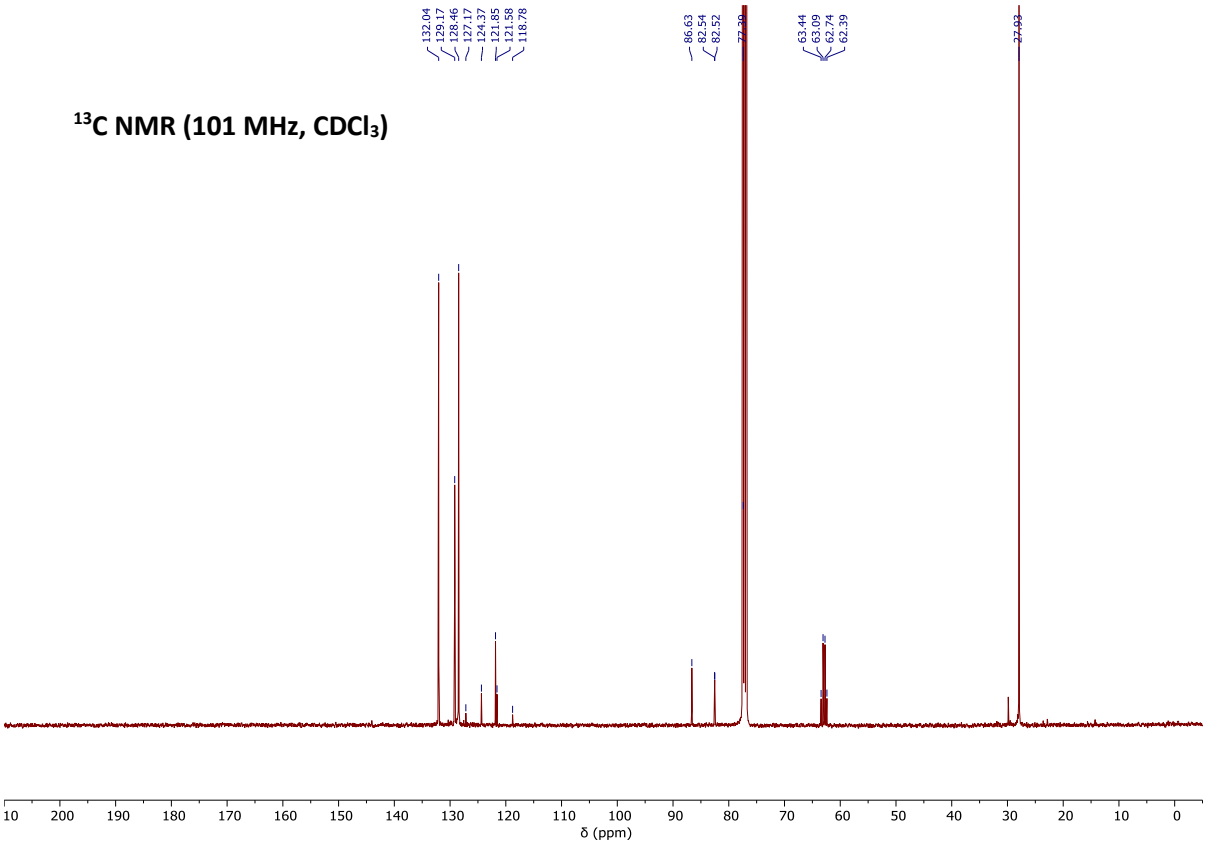


^{1}H NMR (400 MHz, $CDCl_3$)

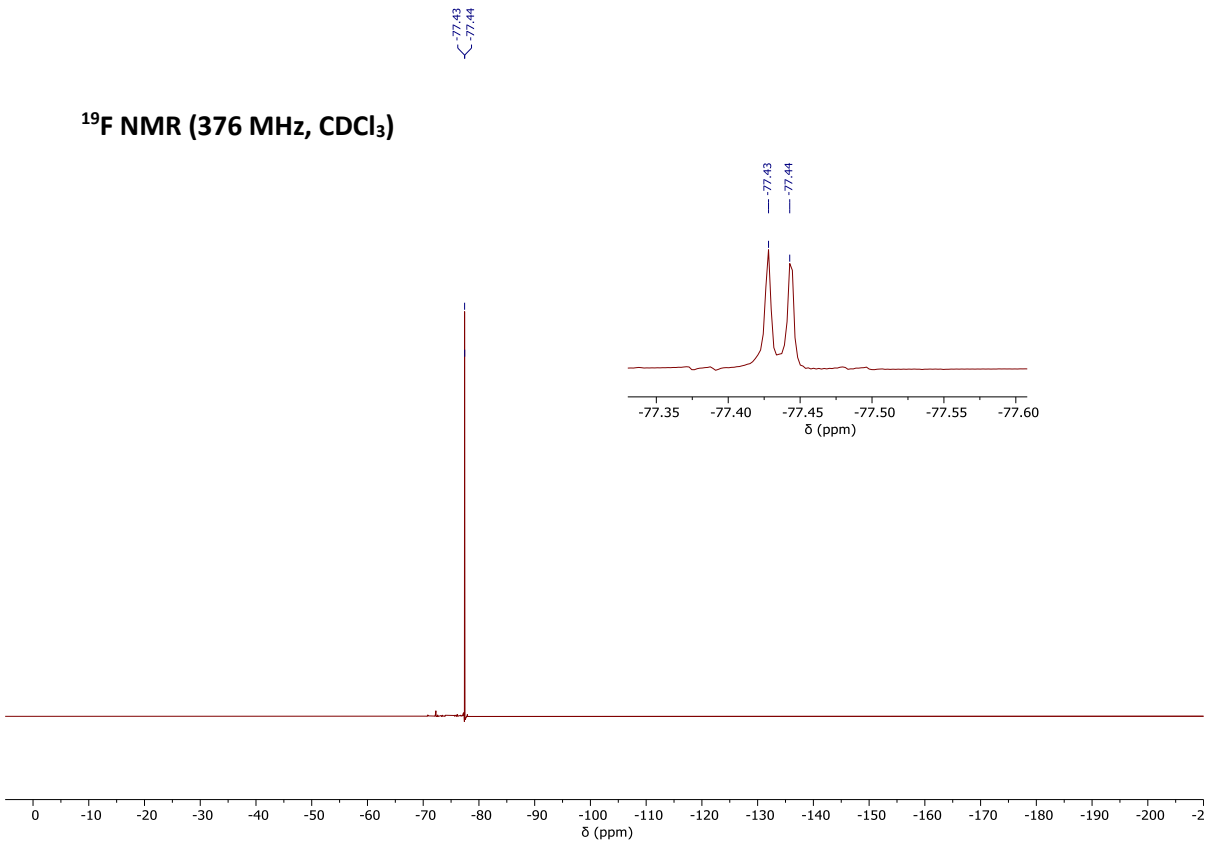


4ac

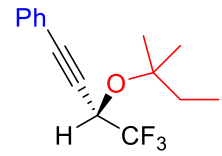
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

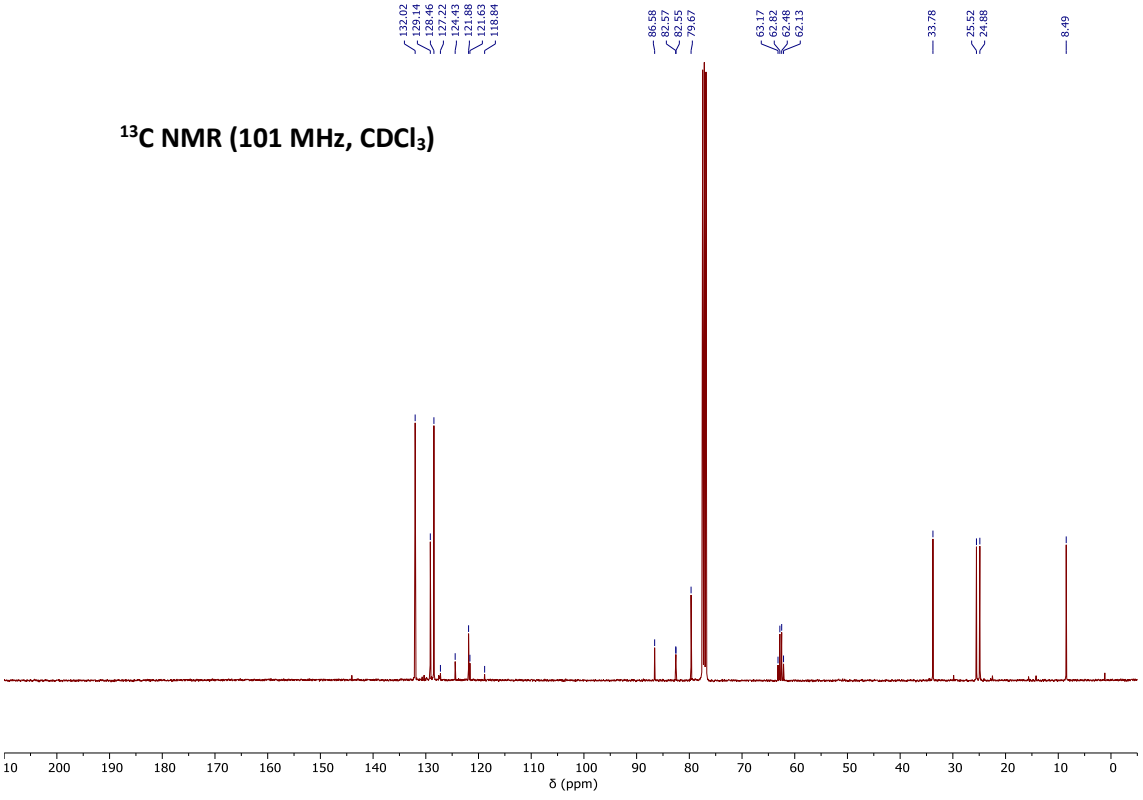


^{1}H NMR (400 MHz, $CDCl_3$)

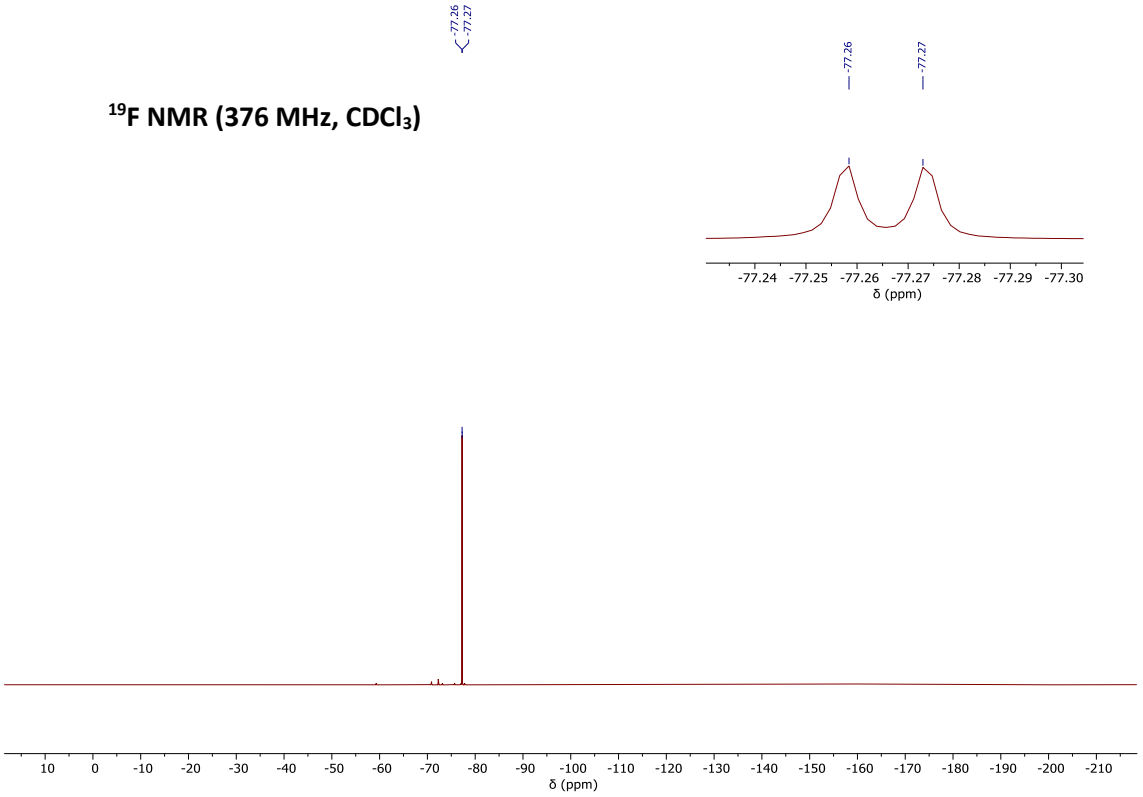


4ad

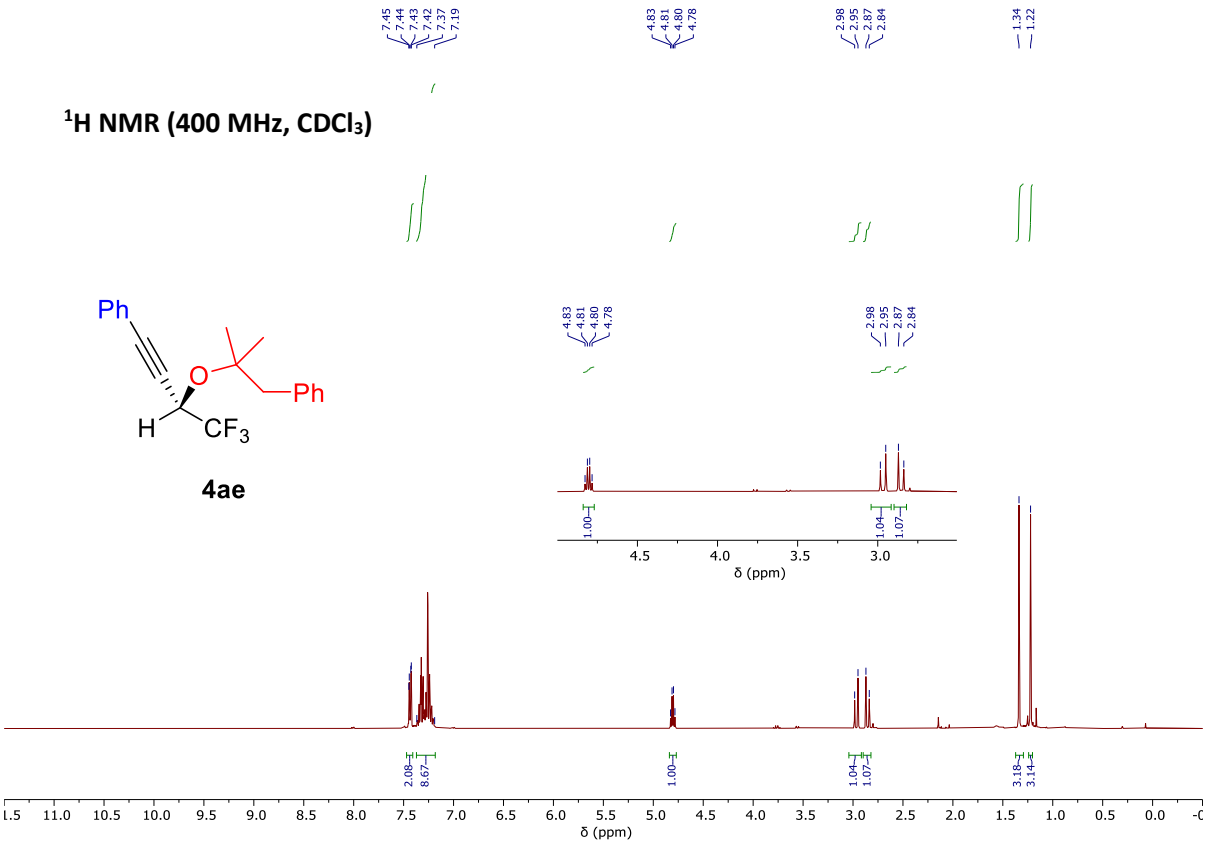
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

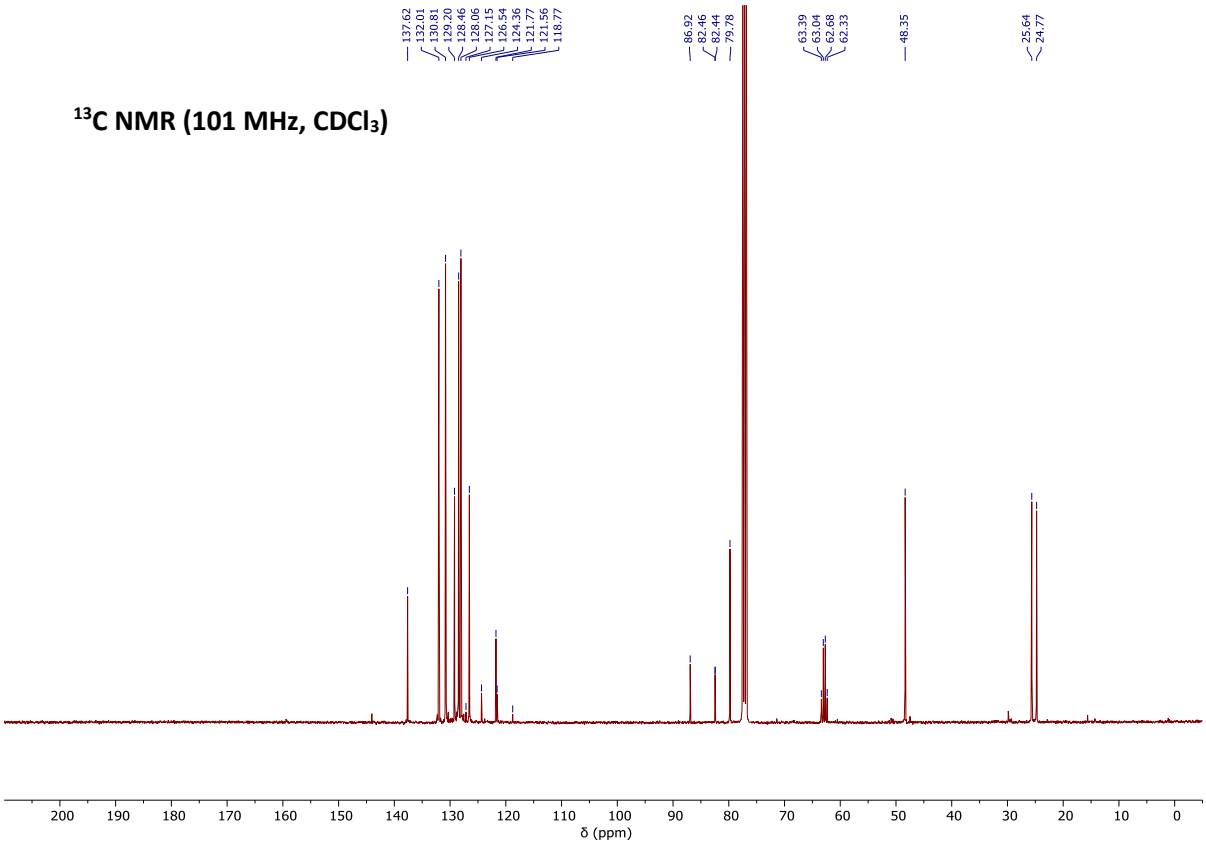


^{1}H NMR (400 MHz, $CDCl_3$)

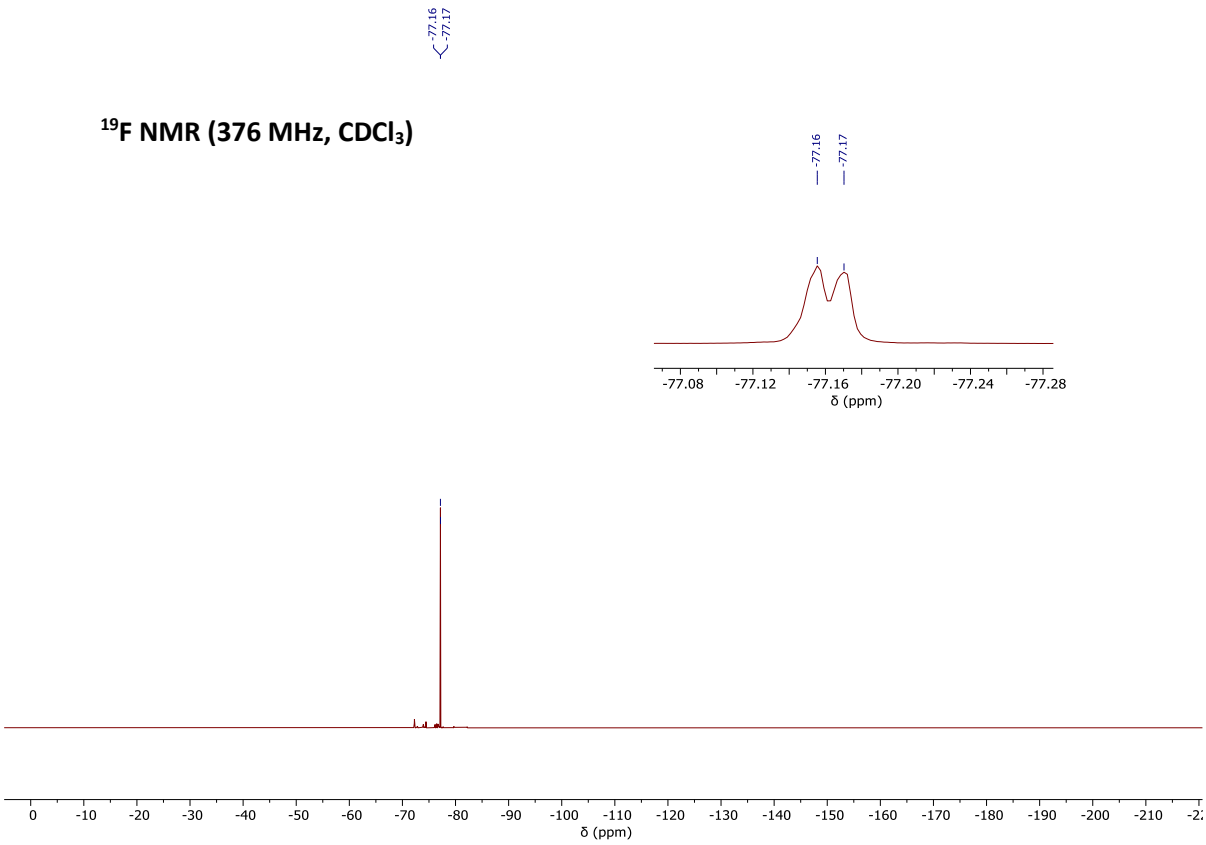


4ae

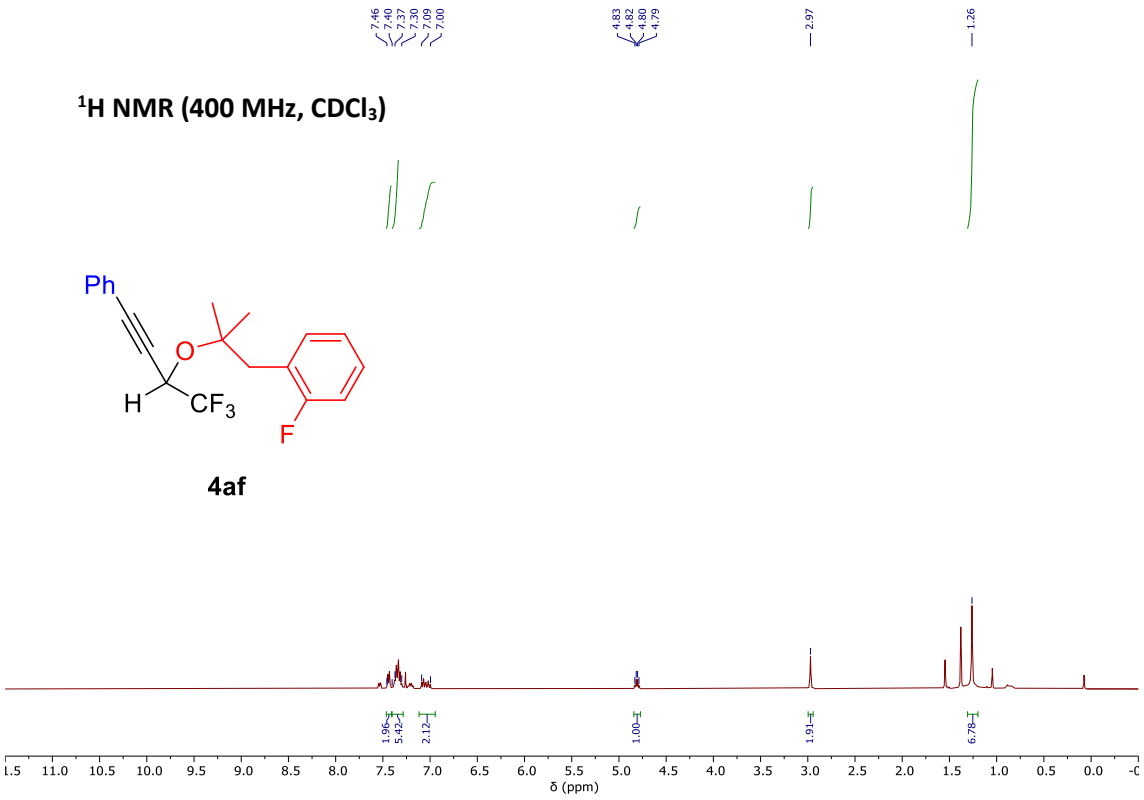
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

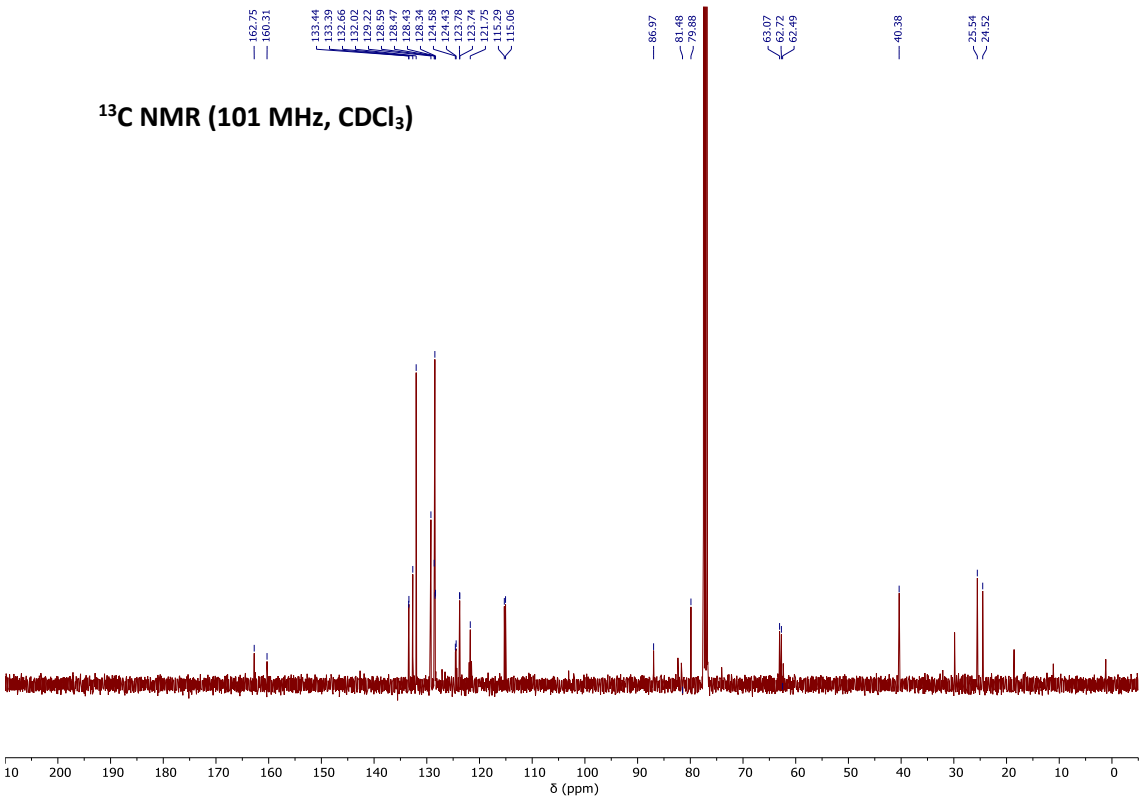


^{1}H NMR (400 MHz, $CDCl_3$)

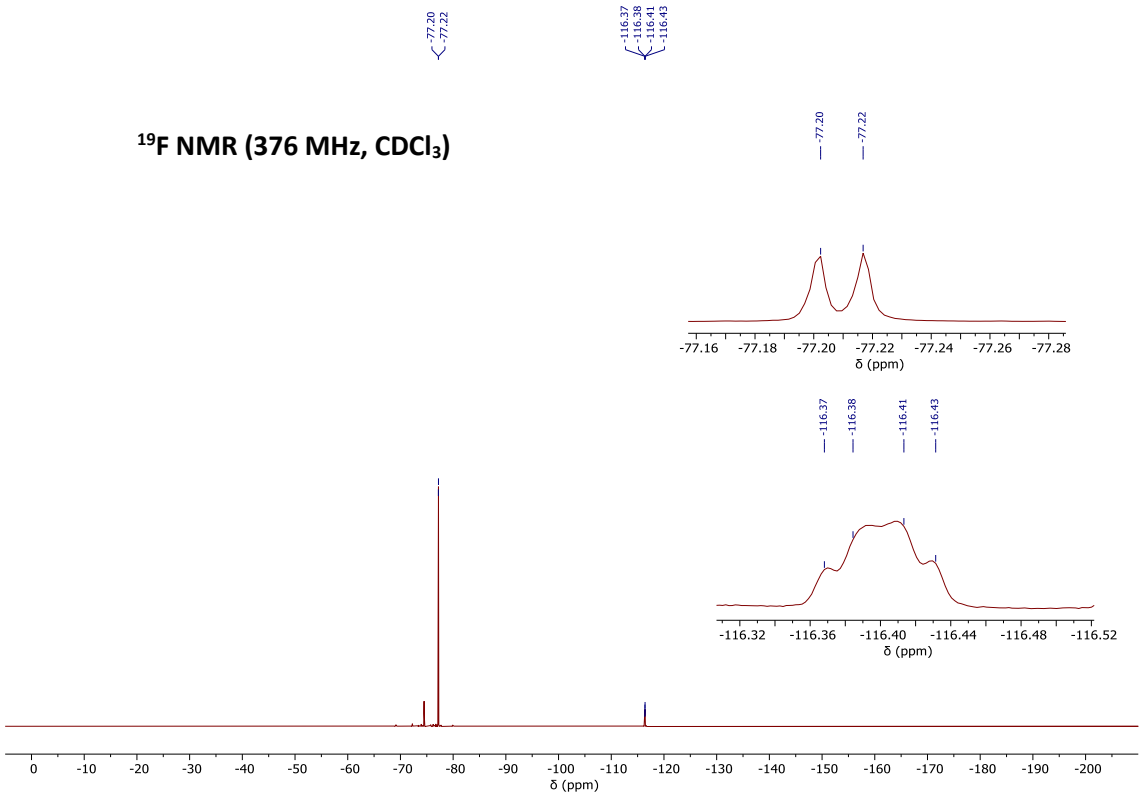


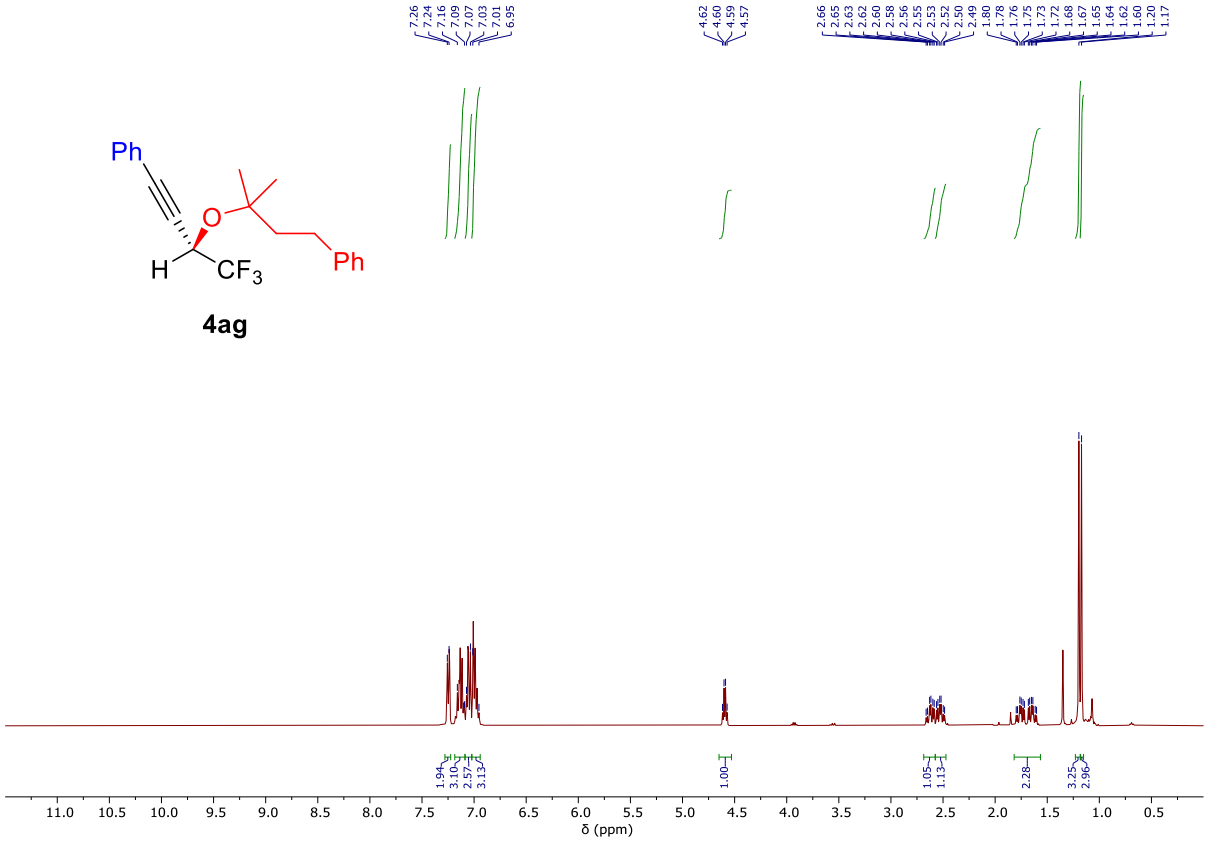
4af

^{13}C NMR (101 MHz, $CDCl_3$)



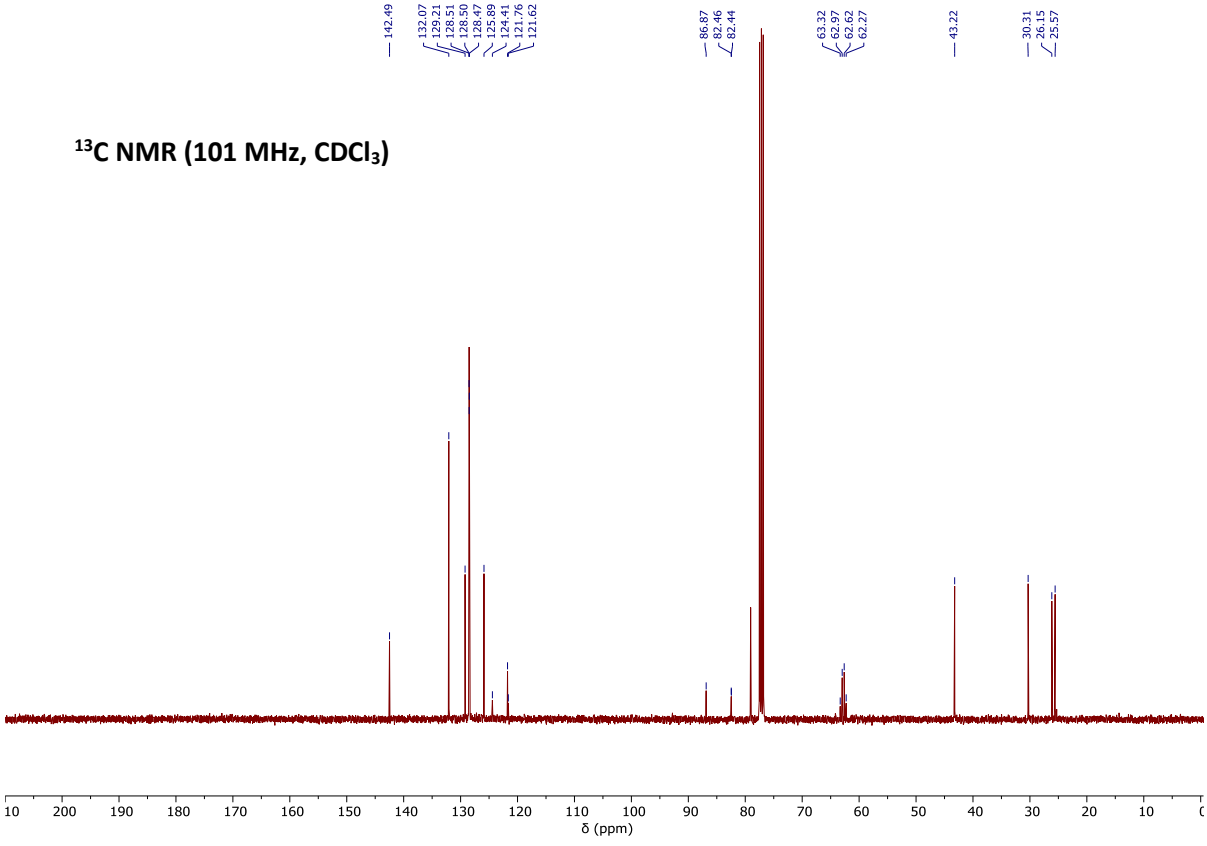
^{19}F NMR (376 MHz, $CDCl_3$)



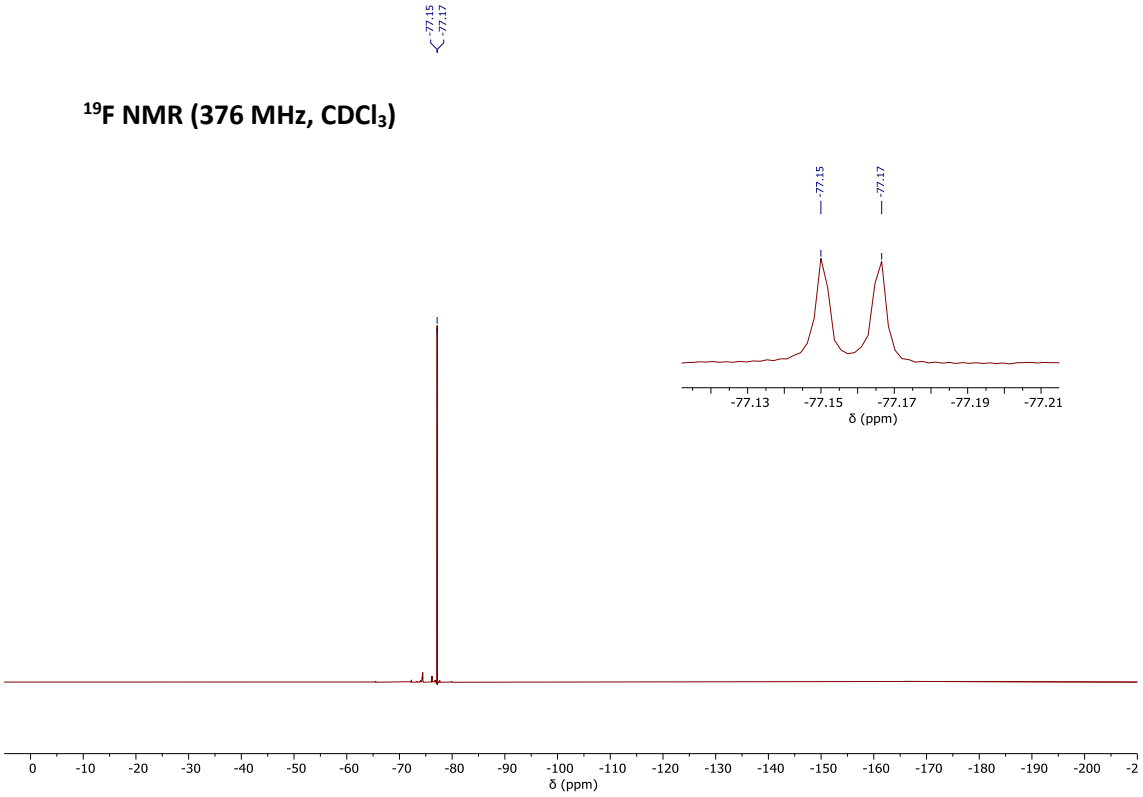


4ag

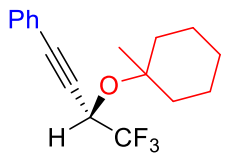
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

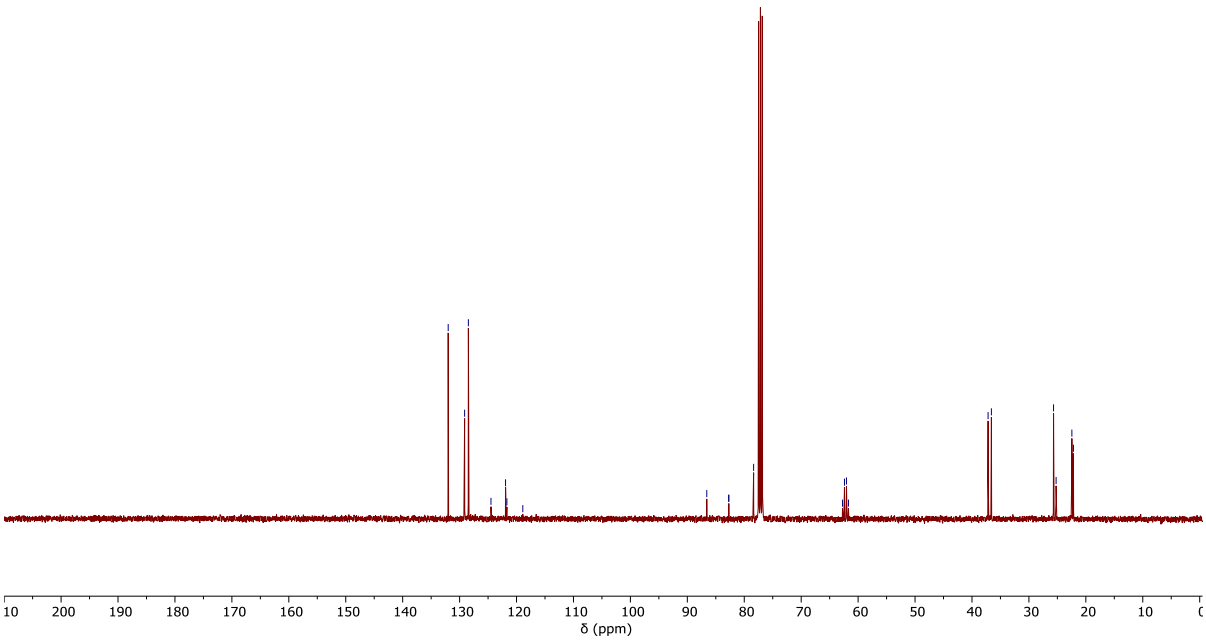


^{1}H NMR (400 MHz, $CDCl_3$)

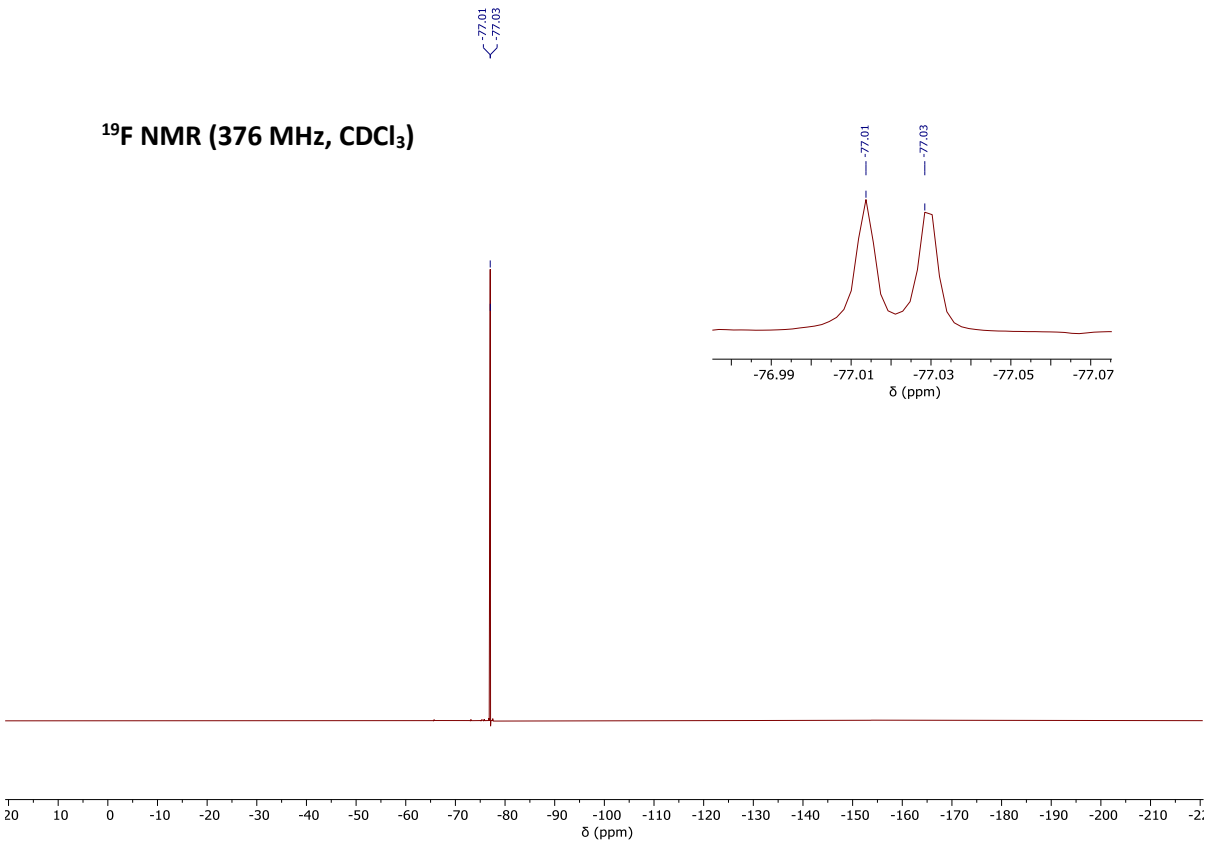


4ah

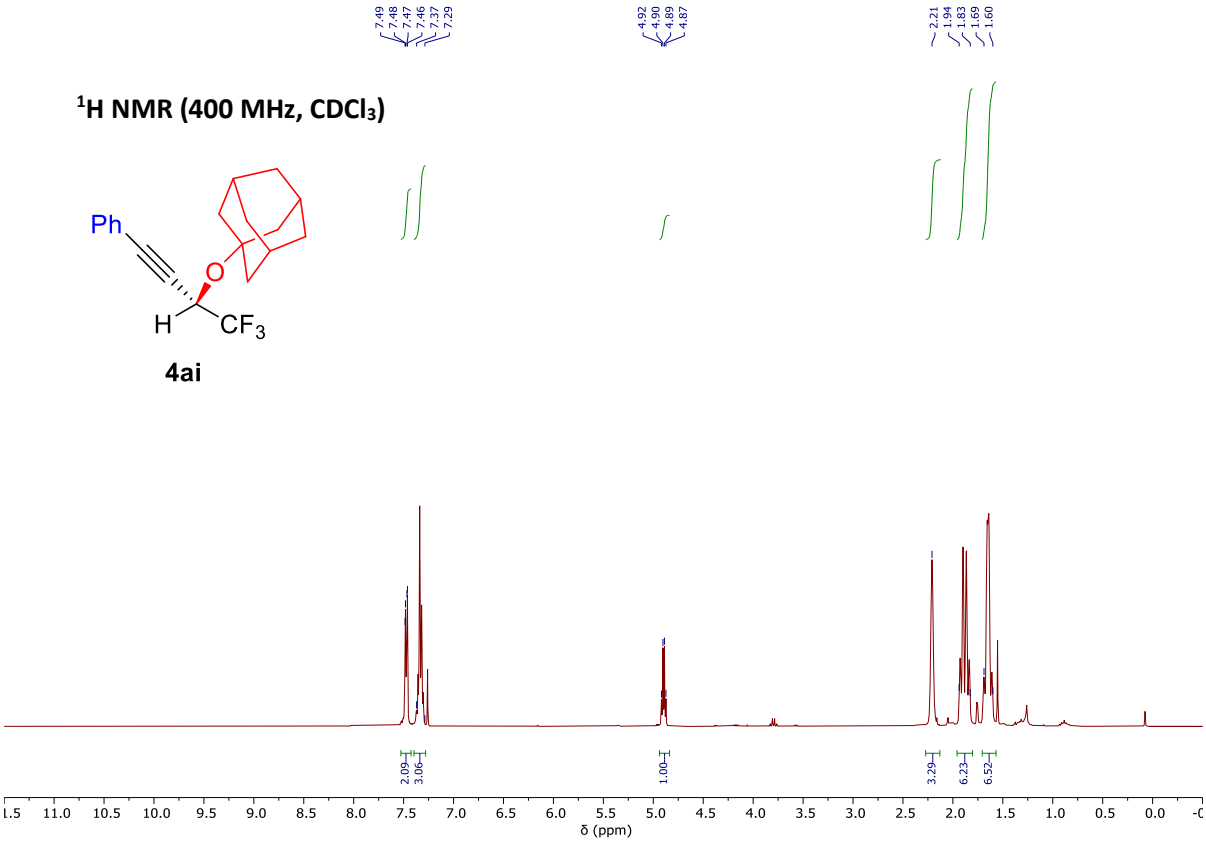
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

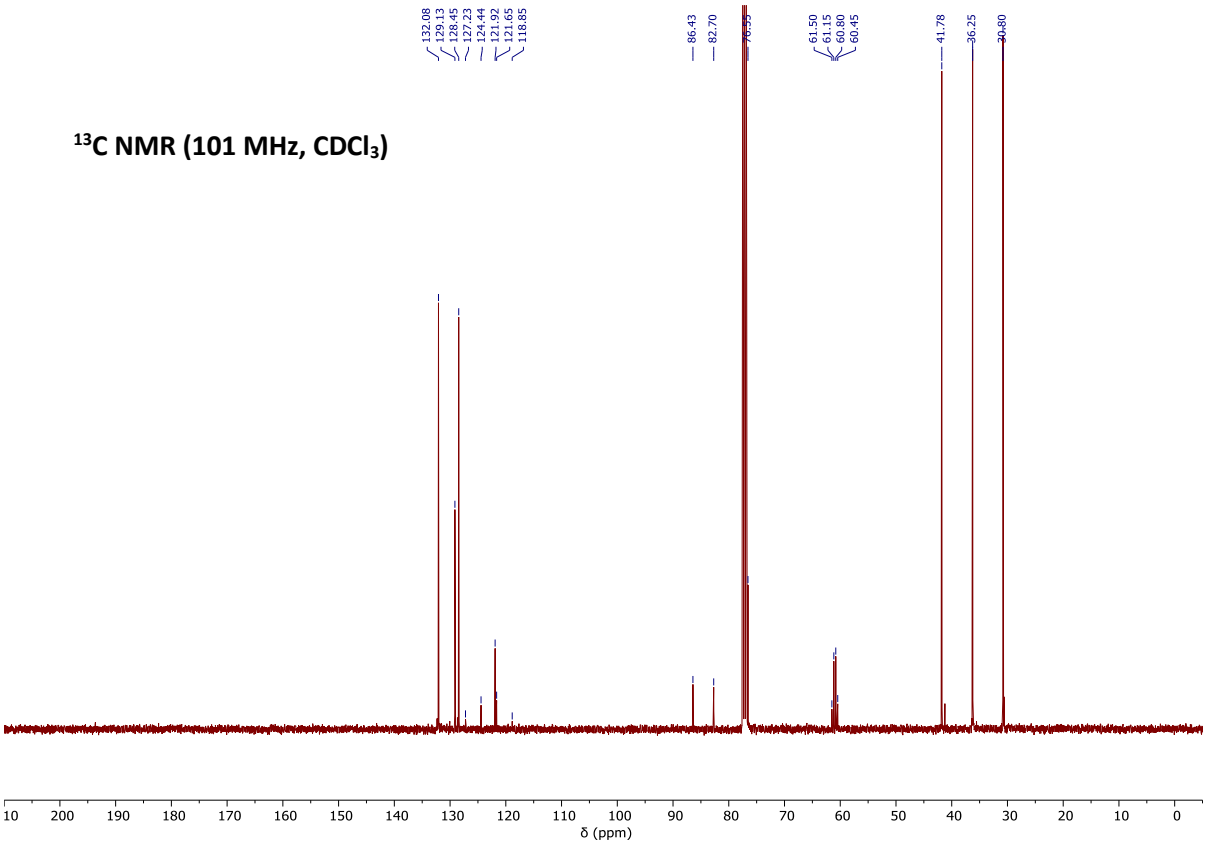


^{1}H NMR (400 MHz, $CDCl_3$)

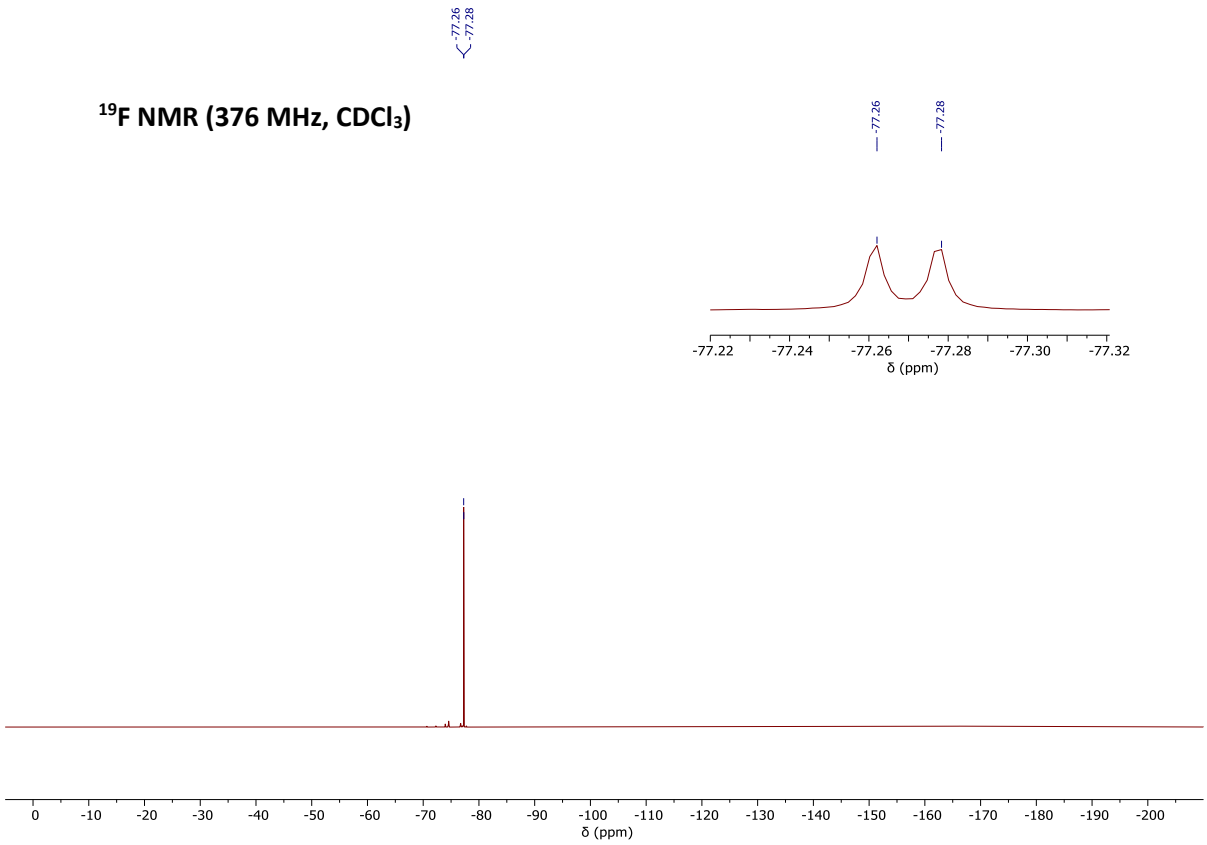


4ai

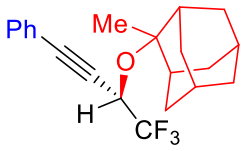
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

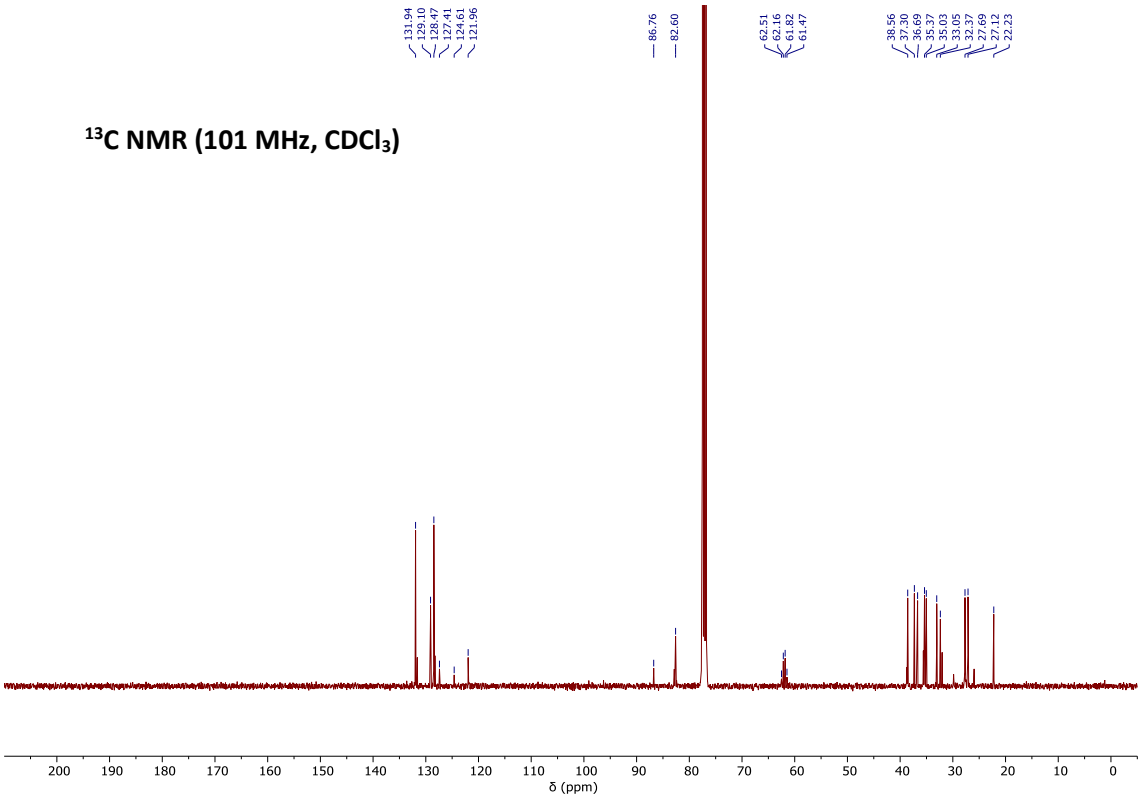


^{1}H NMR (400 MHz, $CDCl_3$)

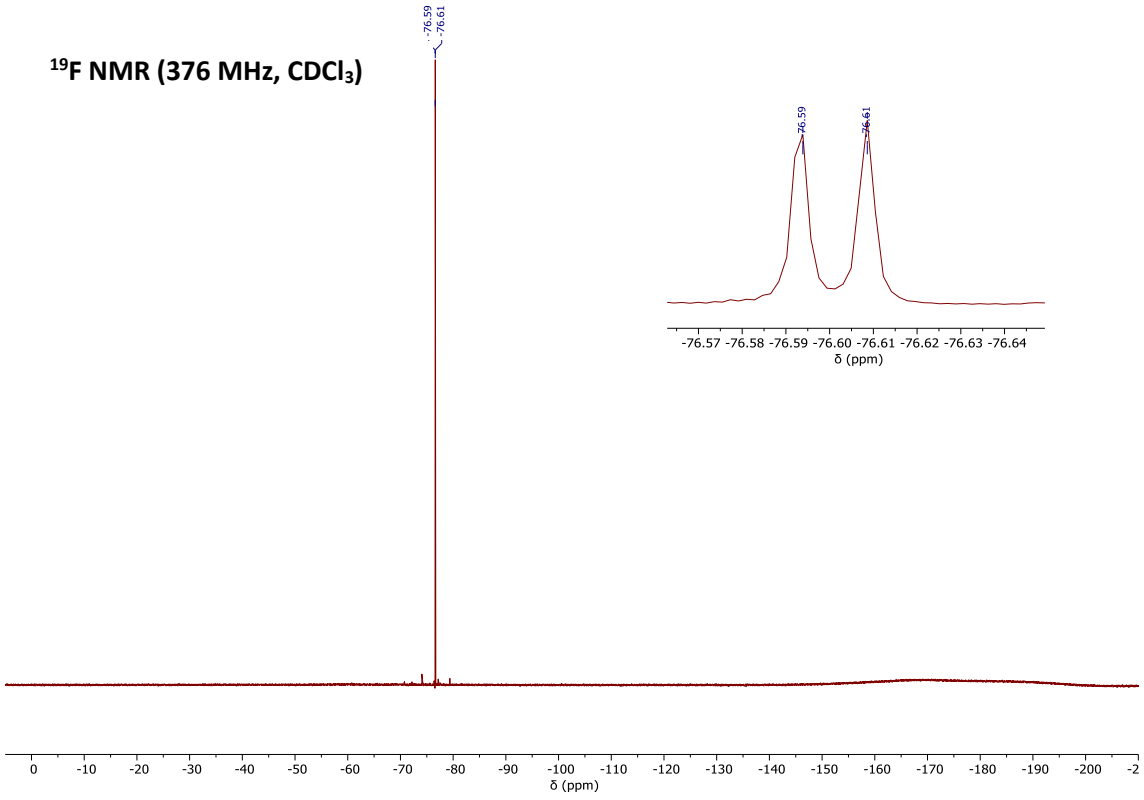


4aj

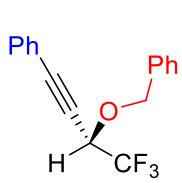
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

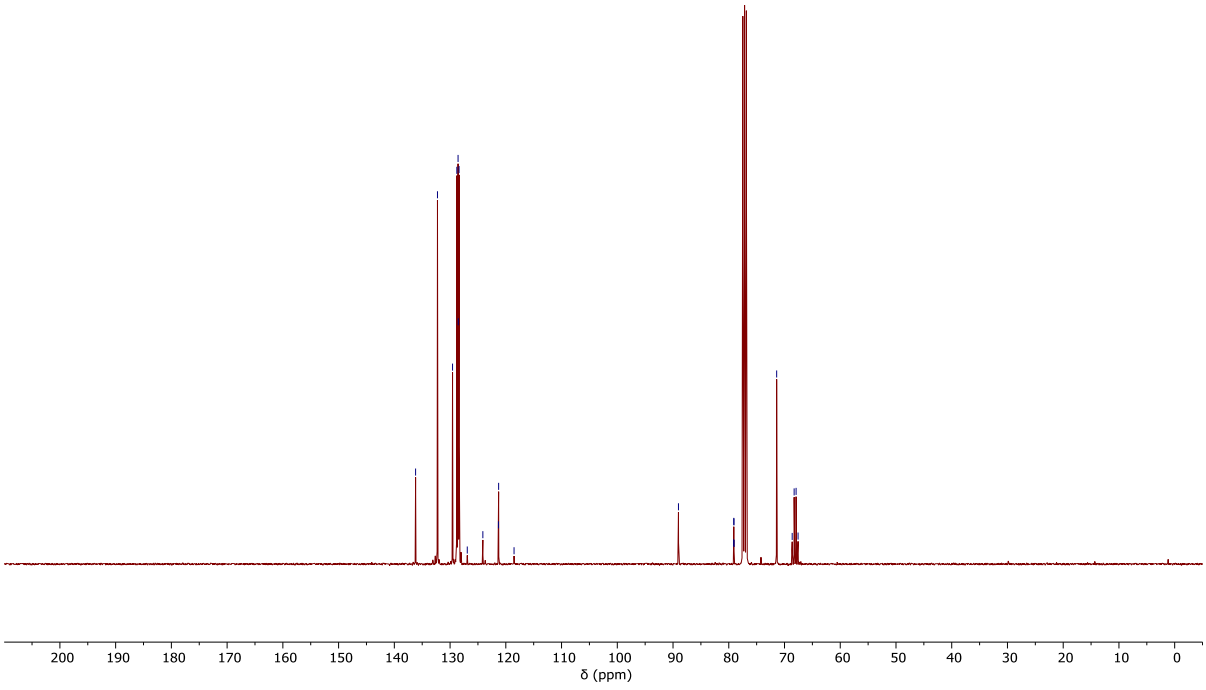


^{1}H NMR (400 MHz, $CDCl_3$)

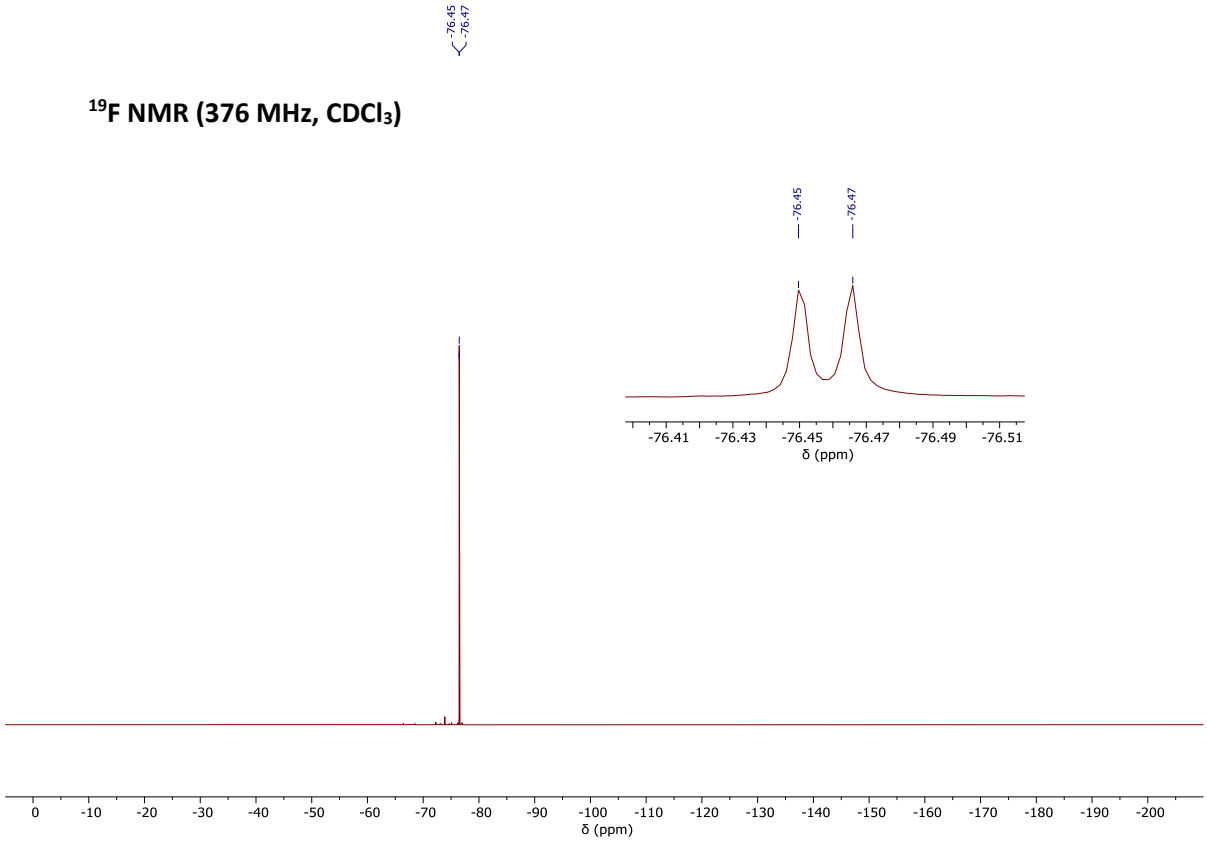


4ak

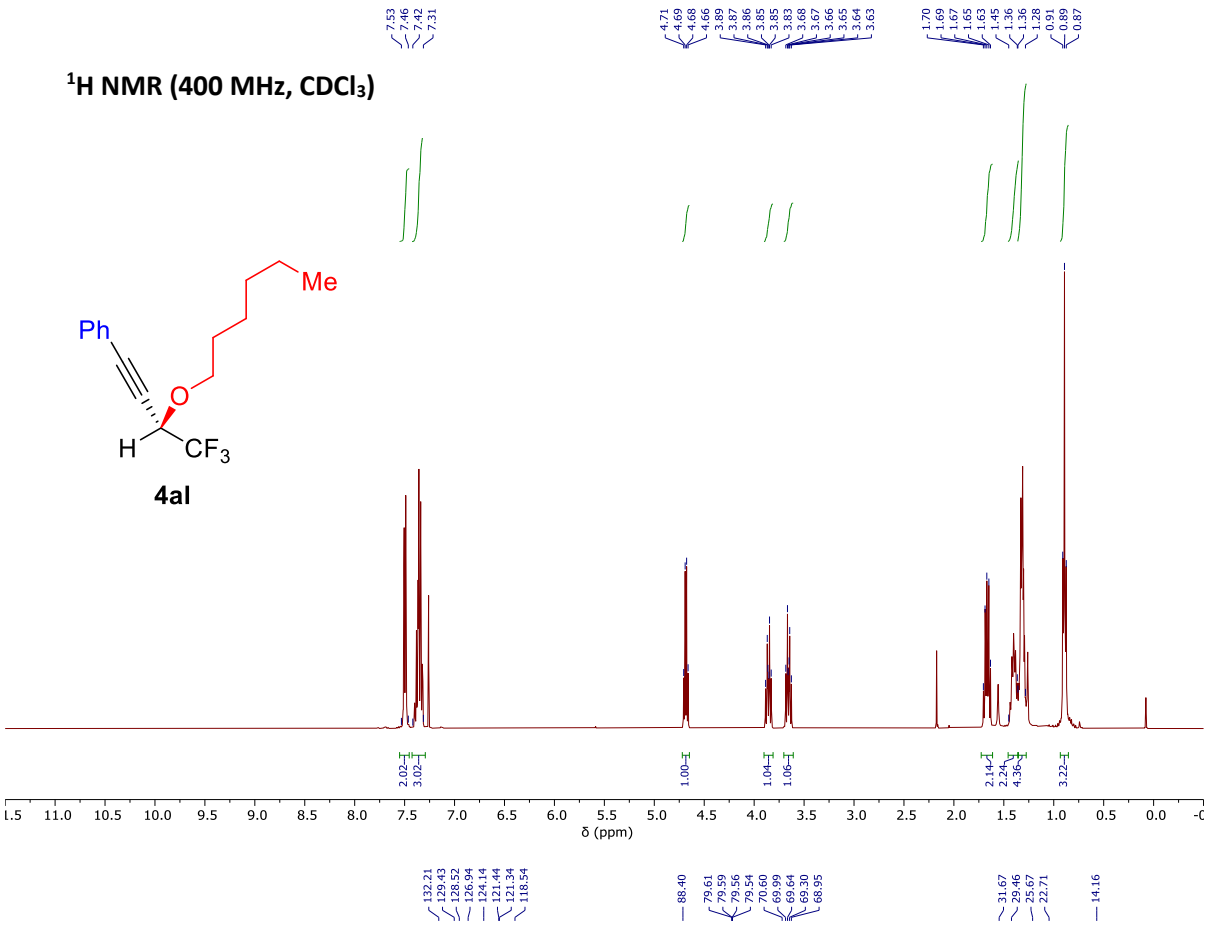
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

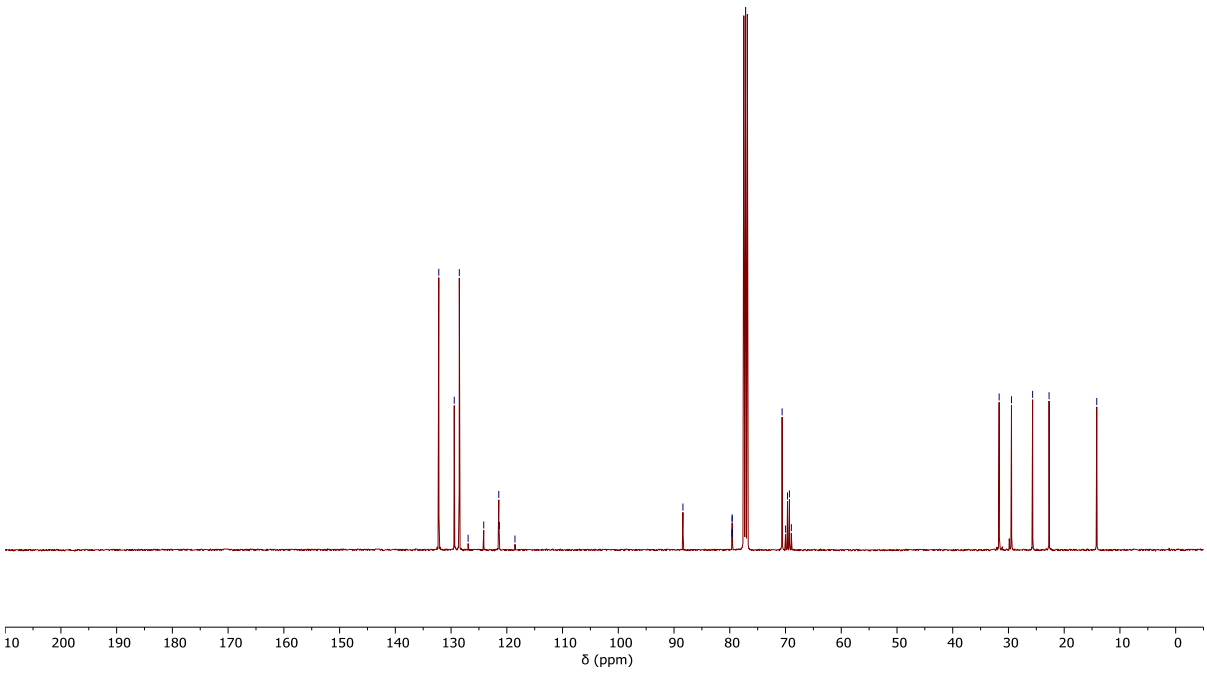


^{1}H NMR (400 MHz, $CDCl_3$)

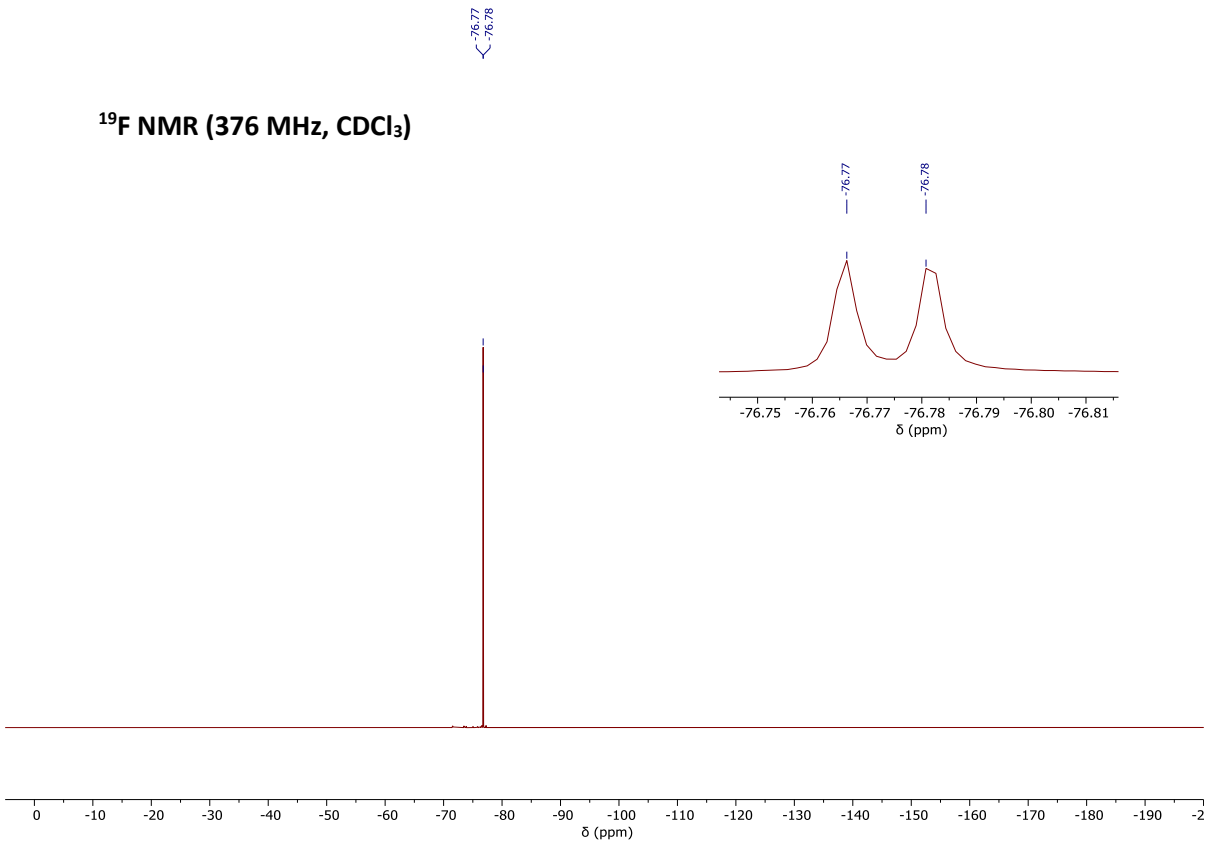


4al

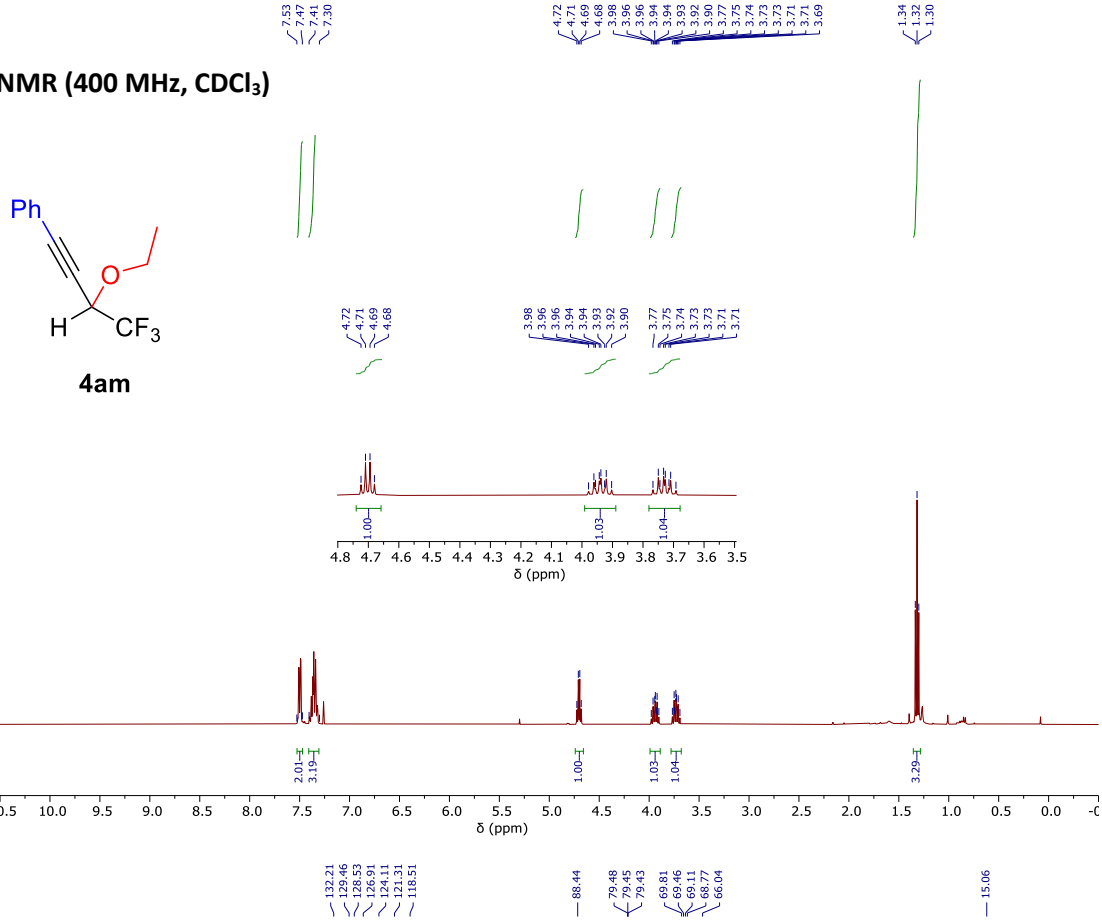
^{13}C NMR (101 MHz, $CDCl_3$)



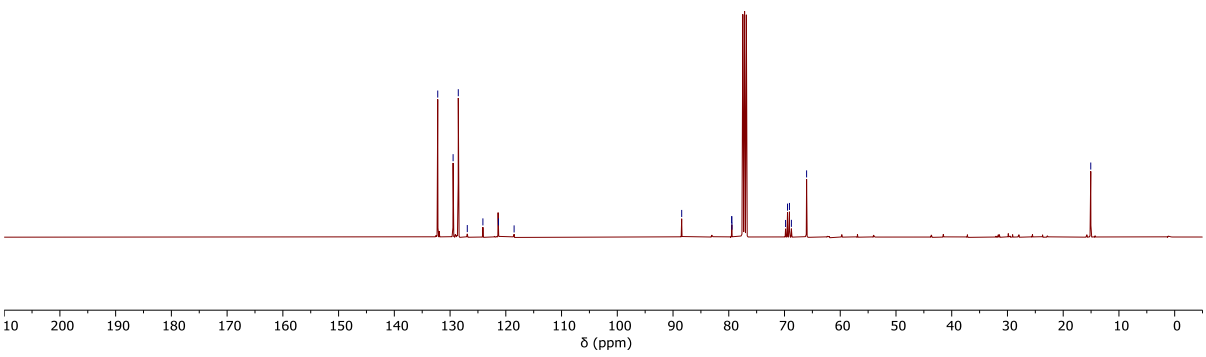
^{19}F NMR (376 MHz, $CDCl_3$)



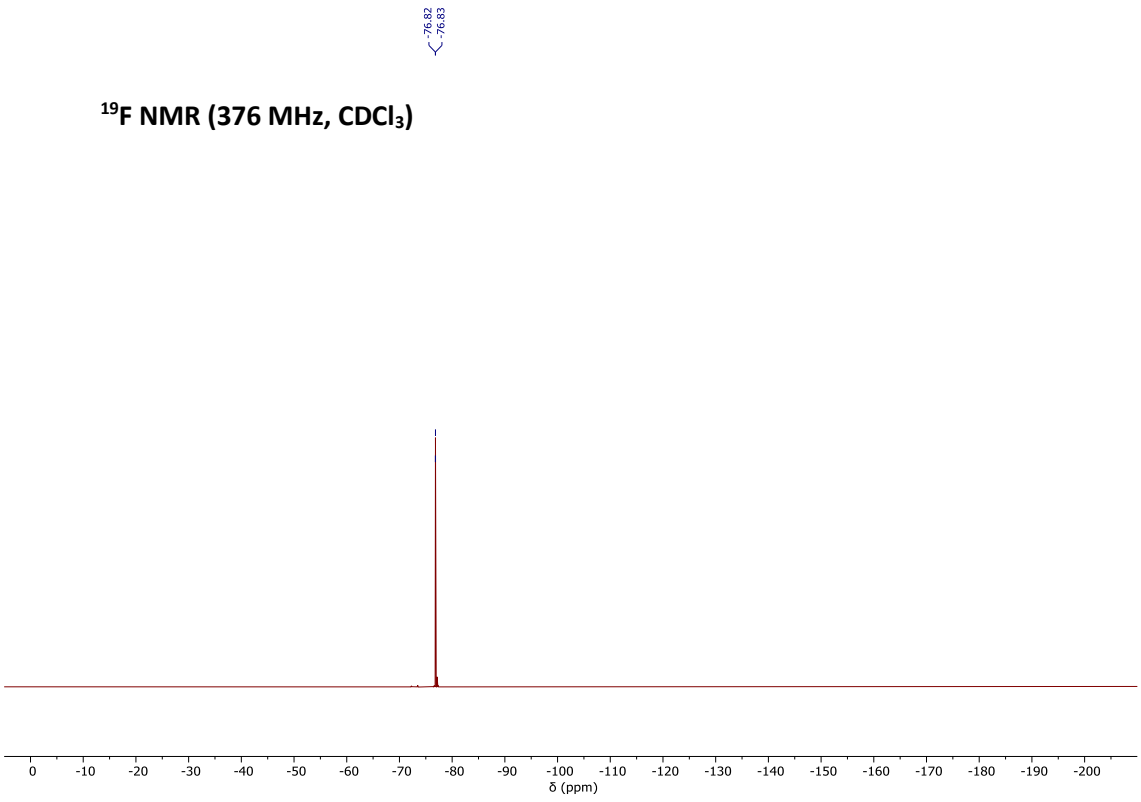
^{1}H NMR (400 MHz, $CDCl_3$)



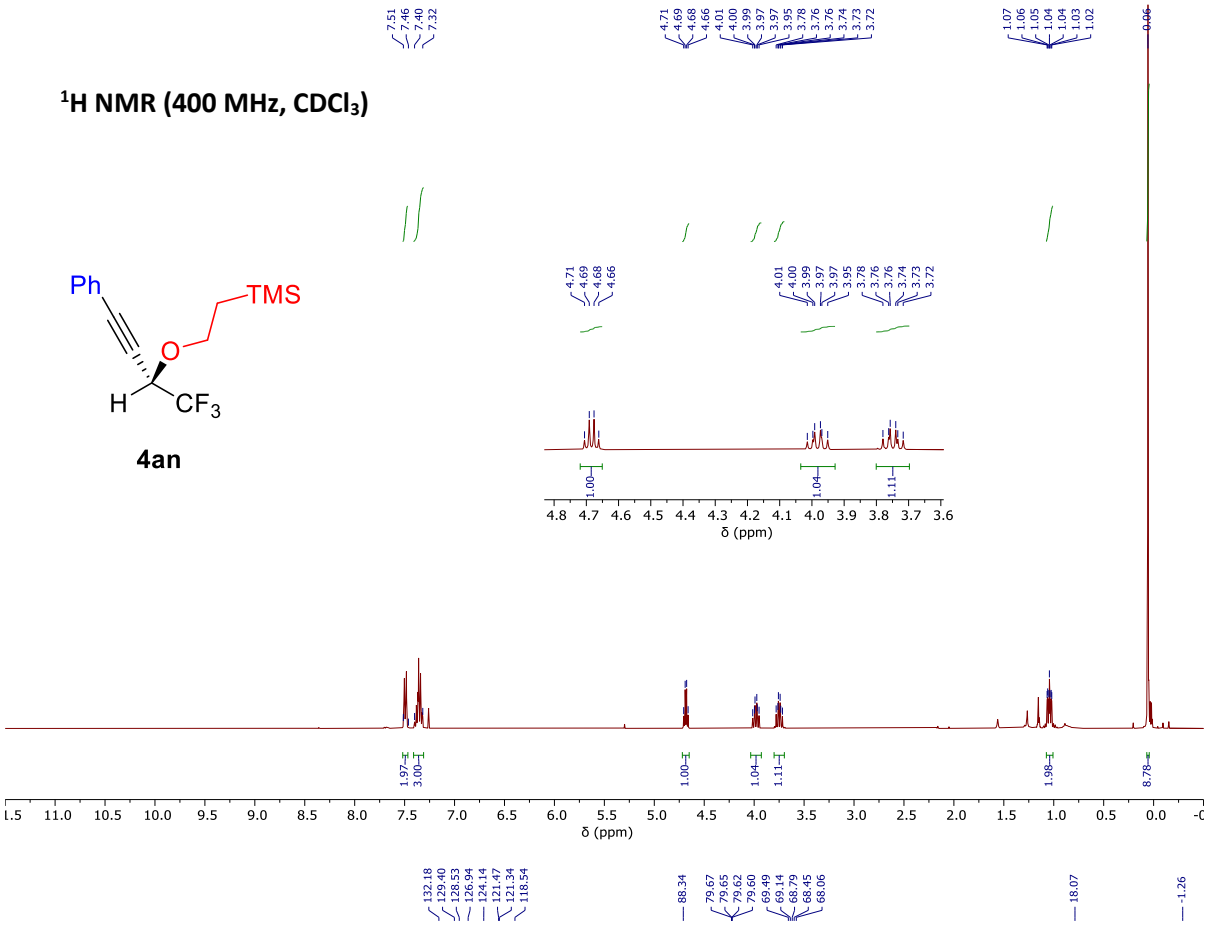
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

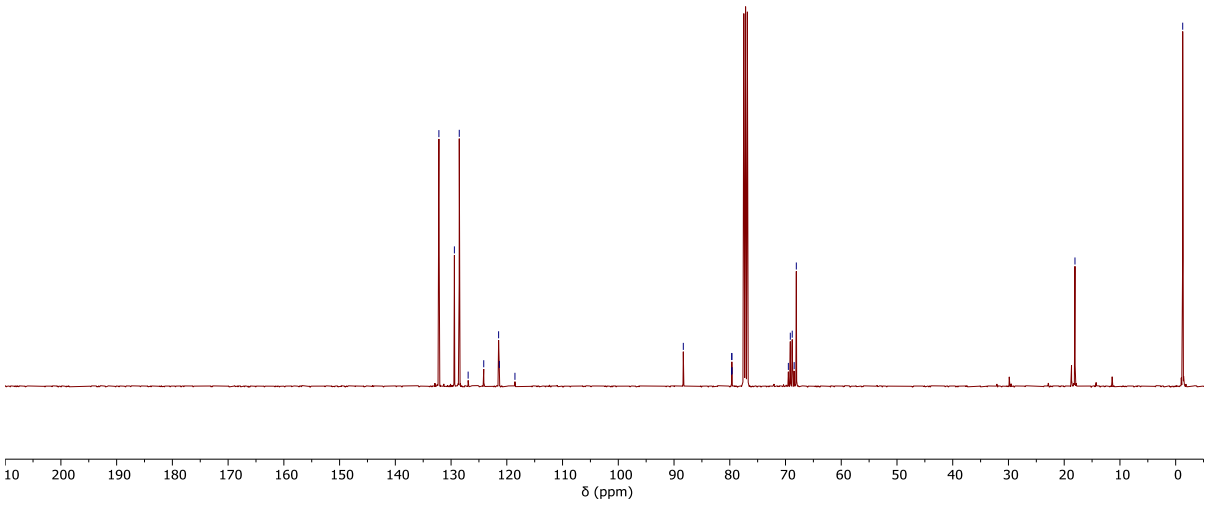


^{1}H NMR (400 MHz, $CDCl_3$)

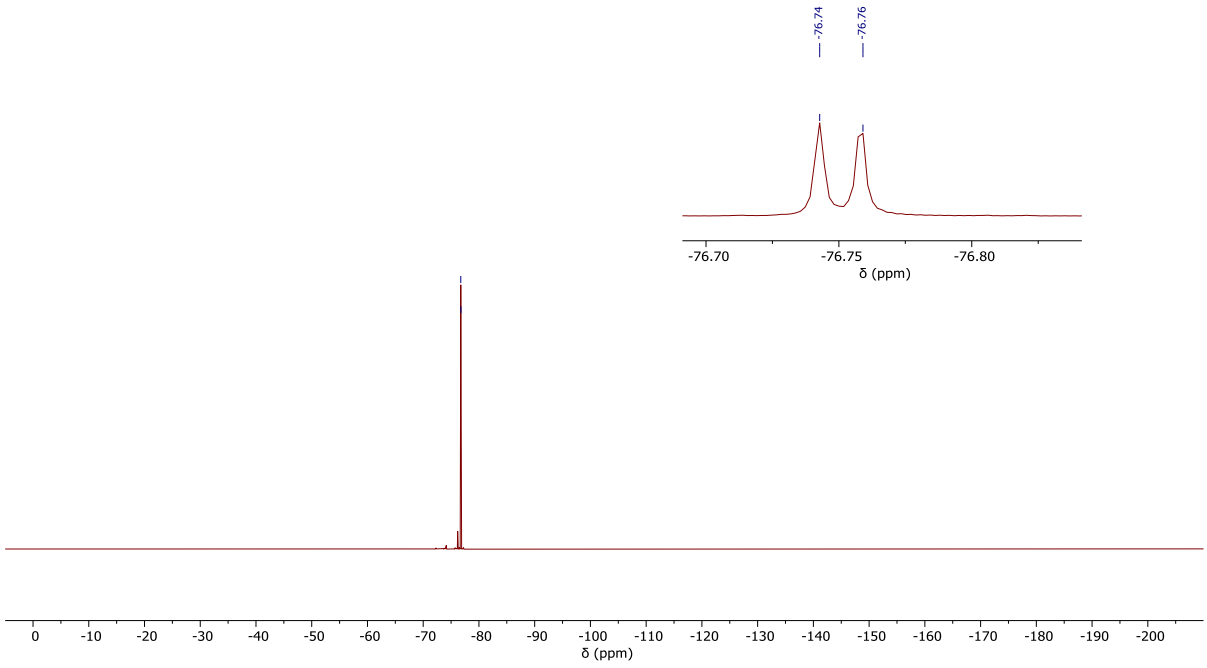


4an

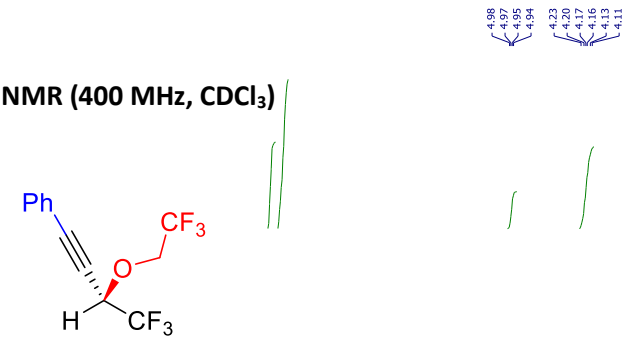
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

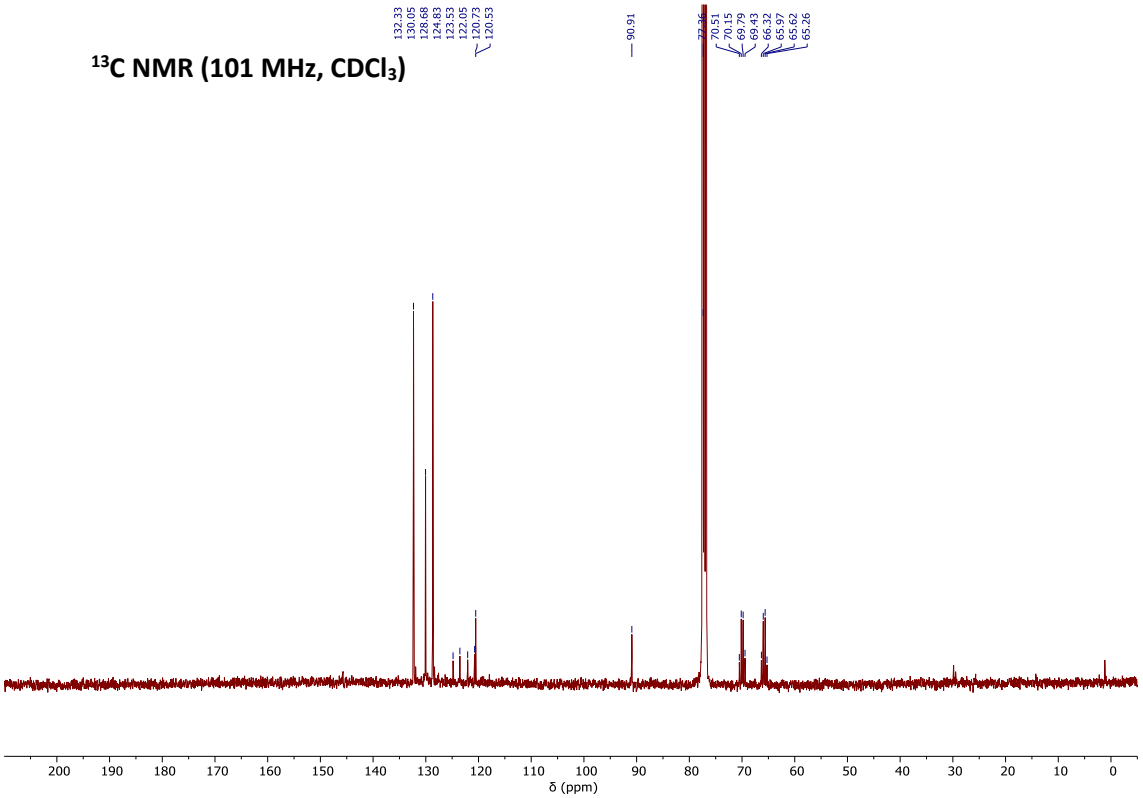


^{1}H NMR (400 MHz, $CDCl_3$)

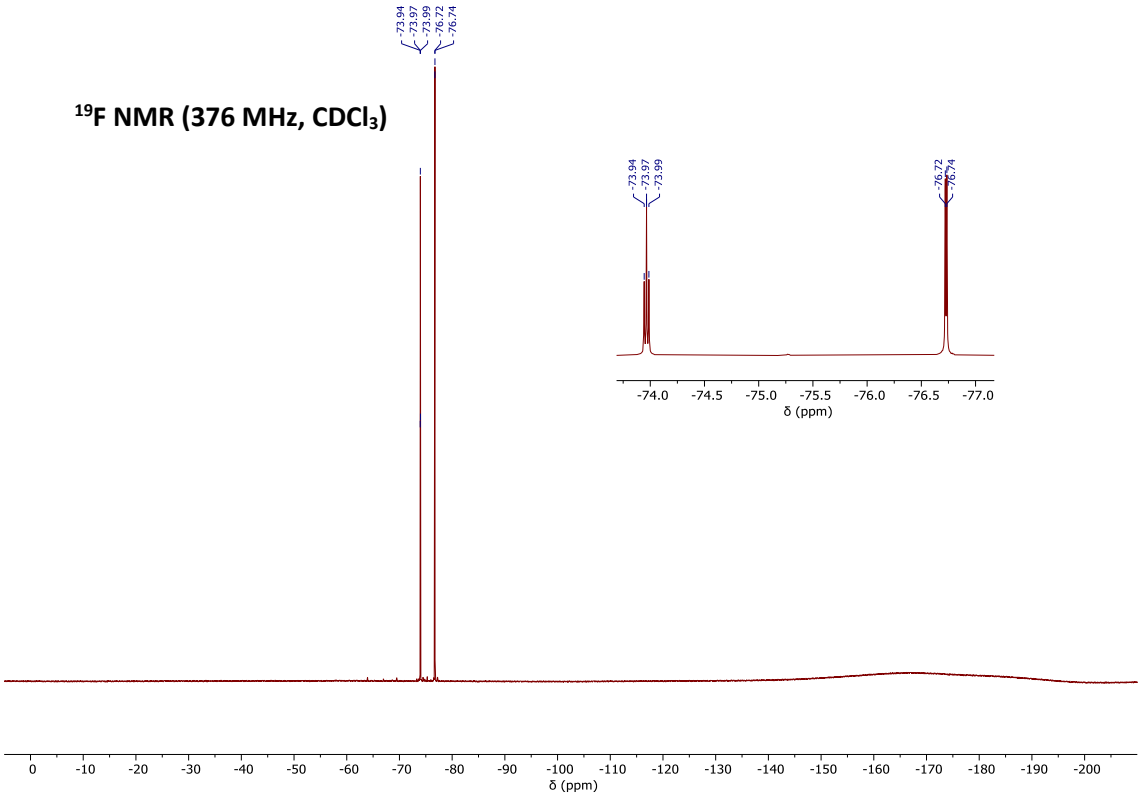


4ao

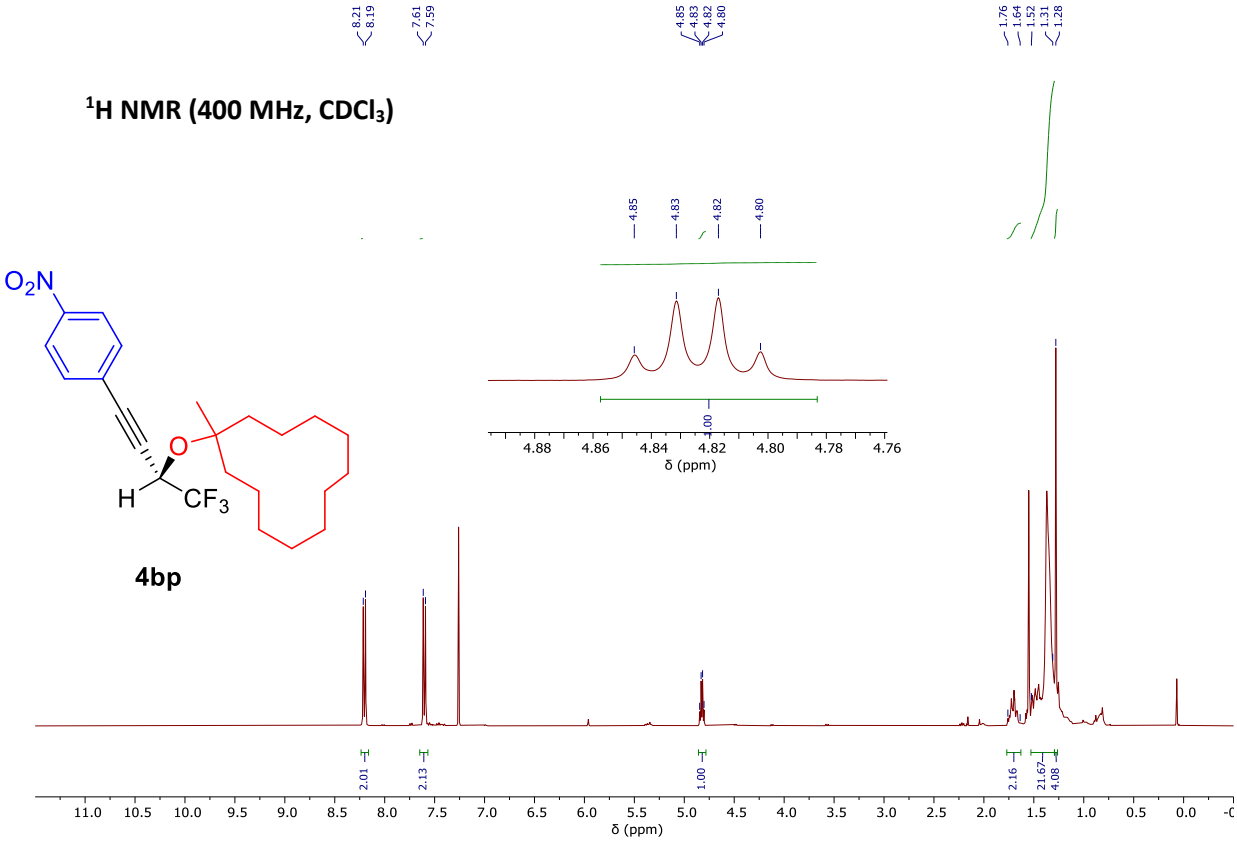
^{13}C NMR (101 MHz, $CDCl_3$)



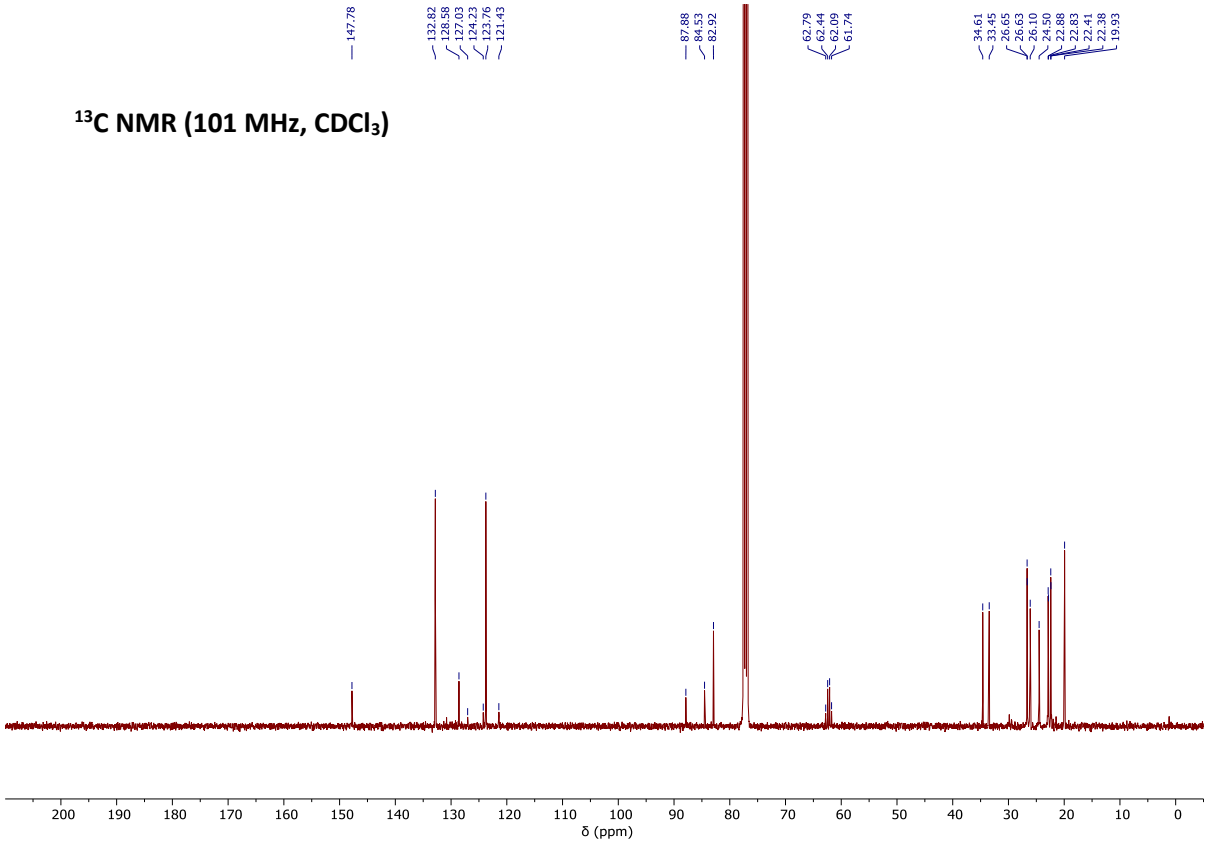
^{19}F NMR (376 MHz, $CDCl_3$)



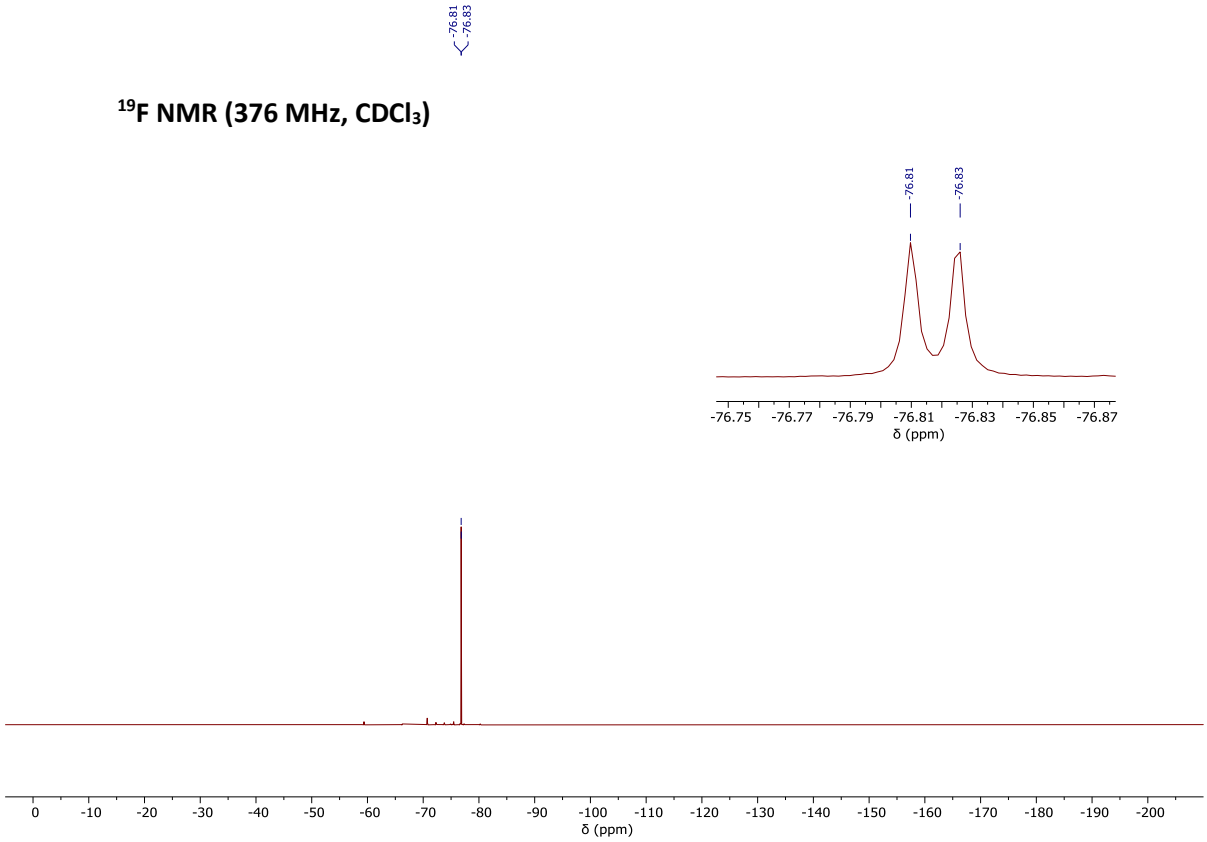
^{1}H NMR (400 MHz, $CDCl_3$)



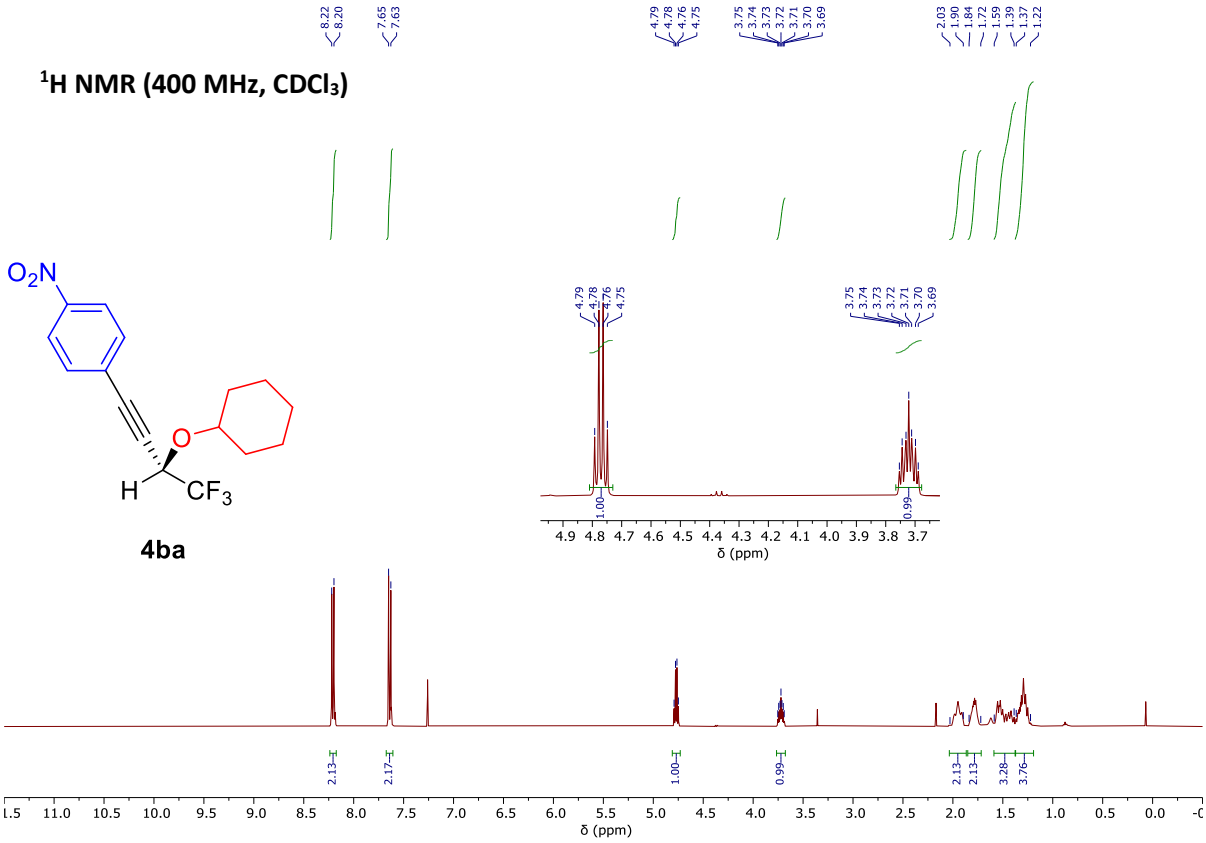
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

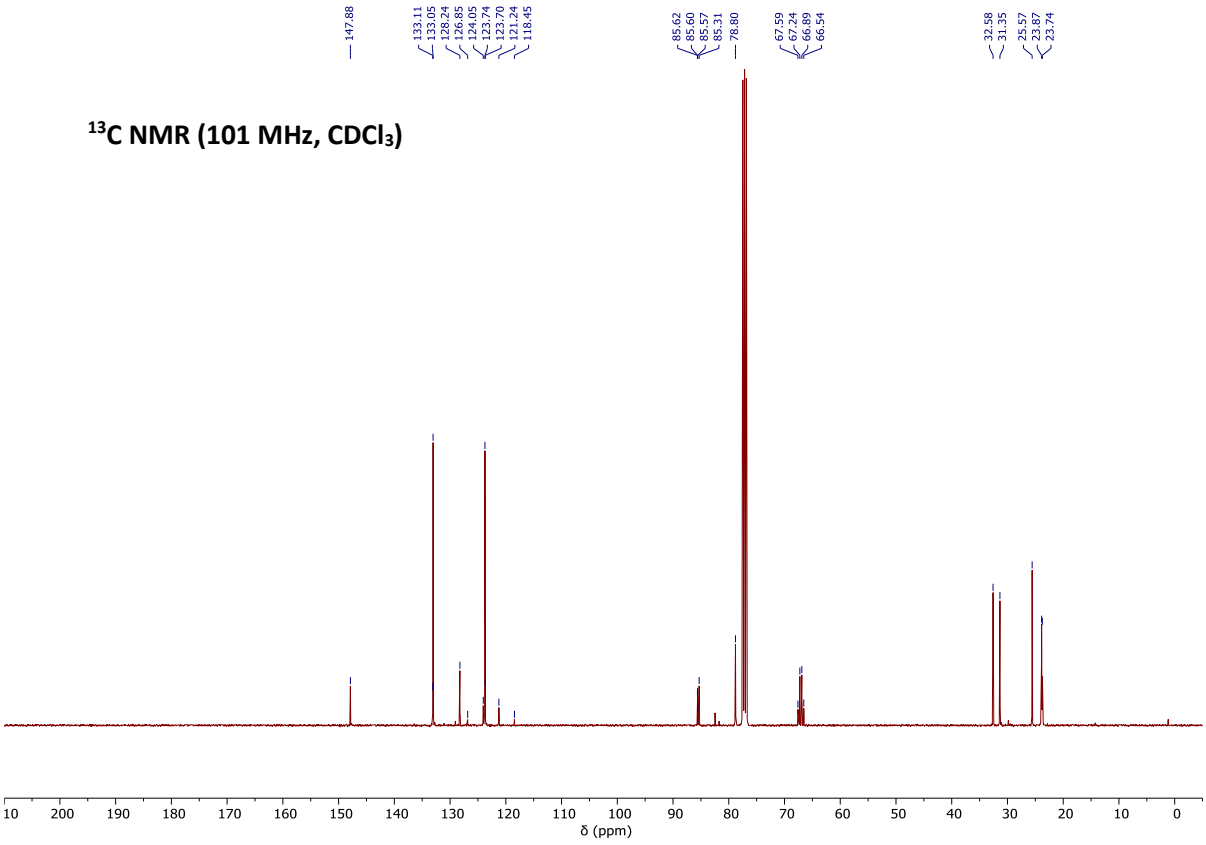


^{1}H NMR (400 MHz, $CDCl_3$)

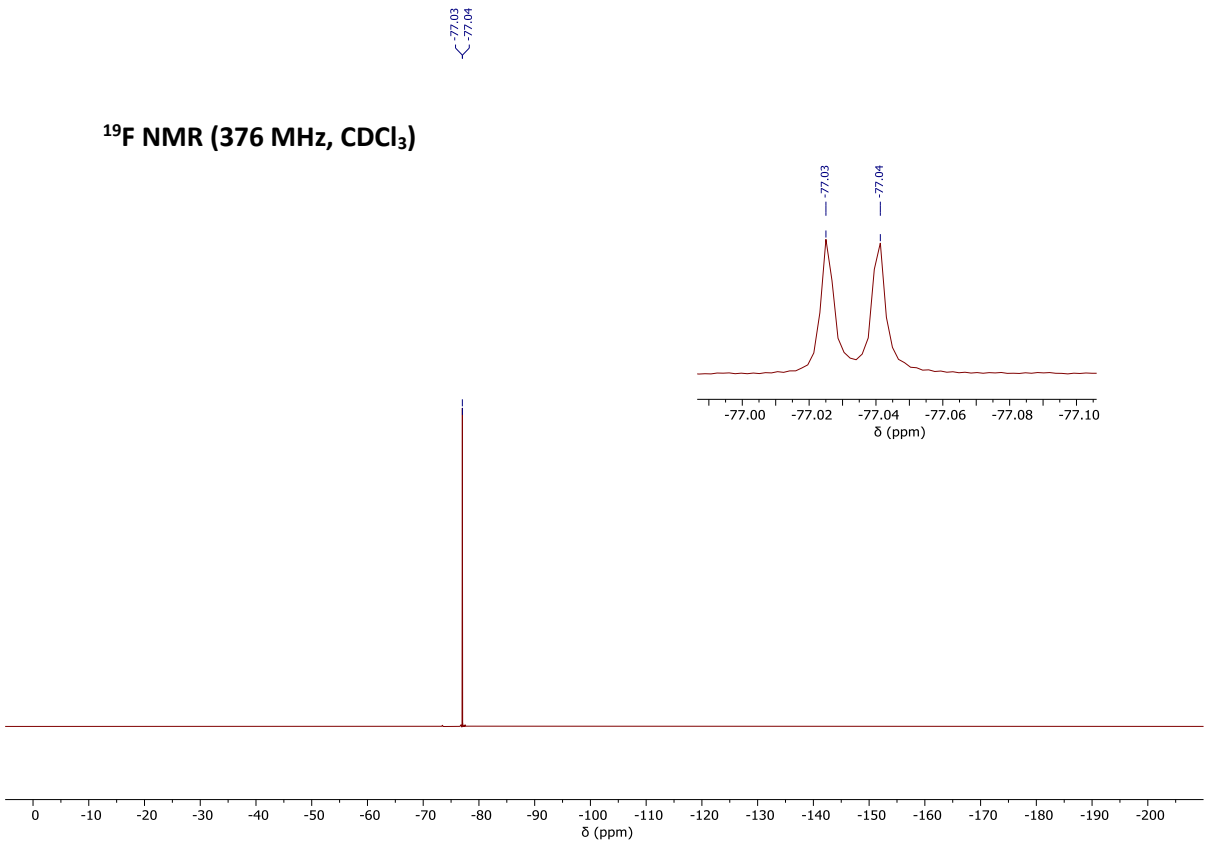


4ba

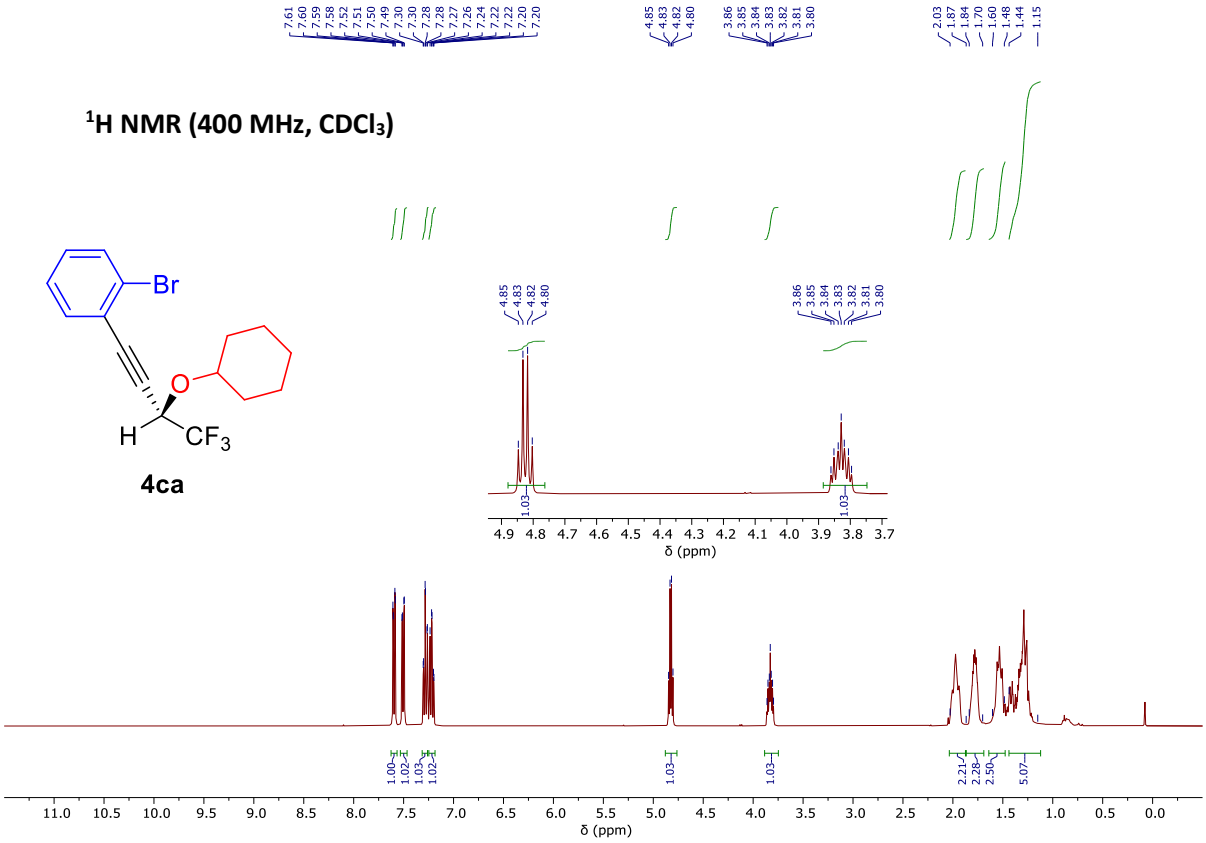
^{13}C NMR (101 MHz, $CDCl_3$)



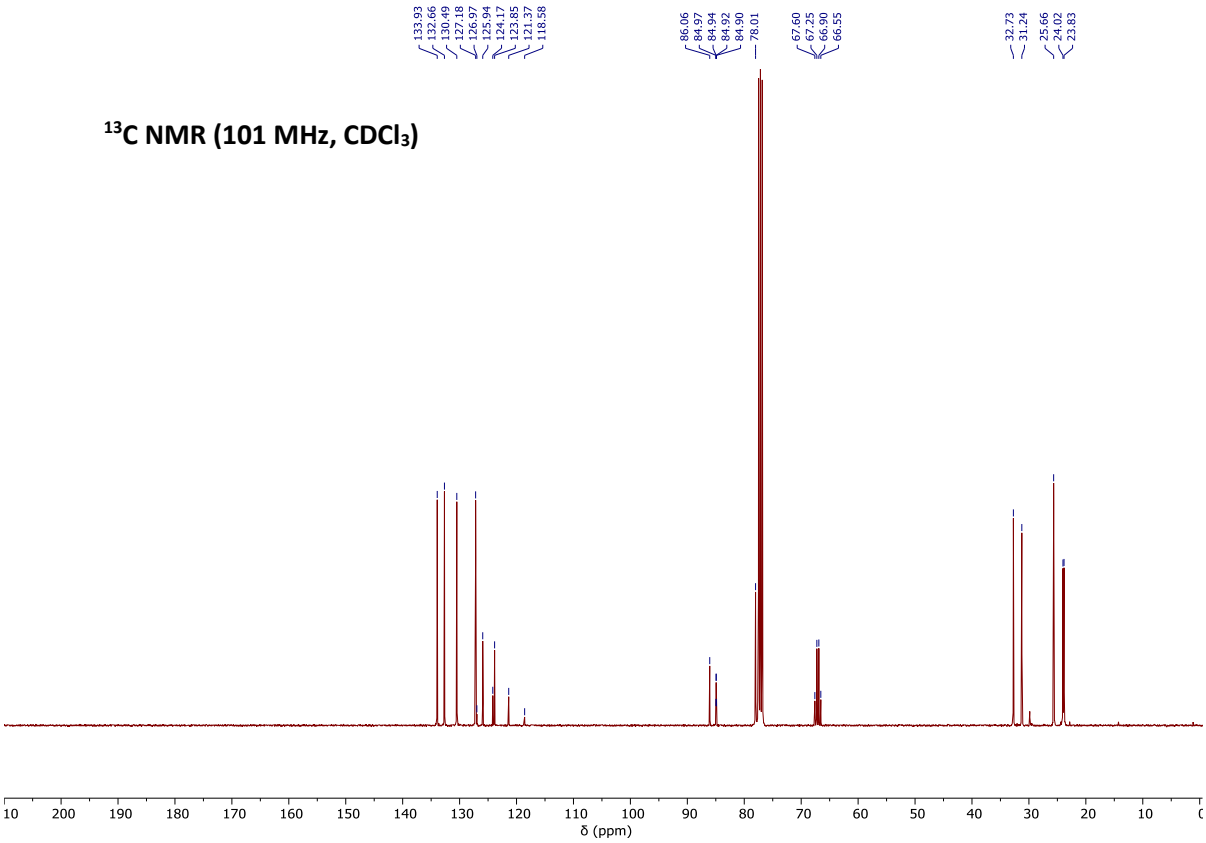
^{19}F NMR (376 MHz, $CDCl_3$)



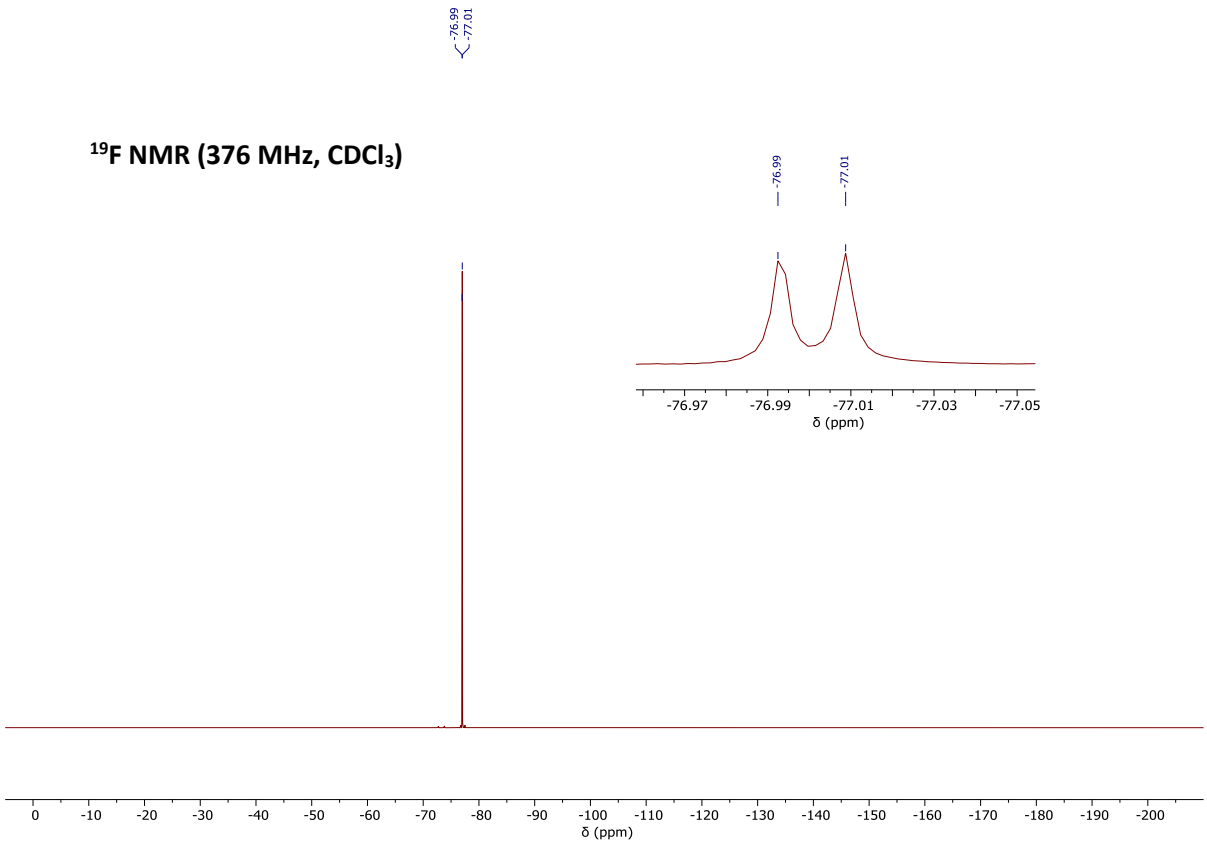
^{1}H NMR (400 MHz, $CDCl_3$)



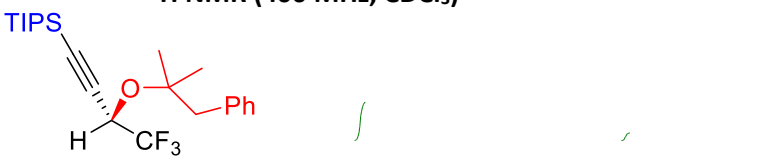
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

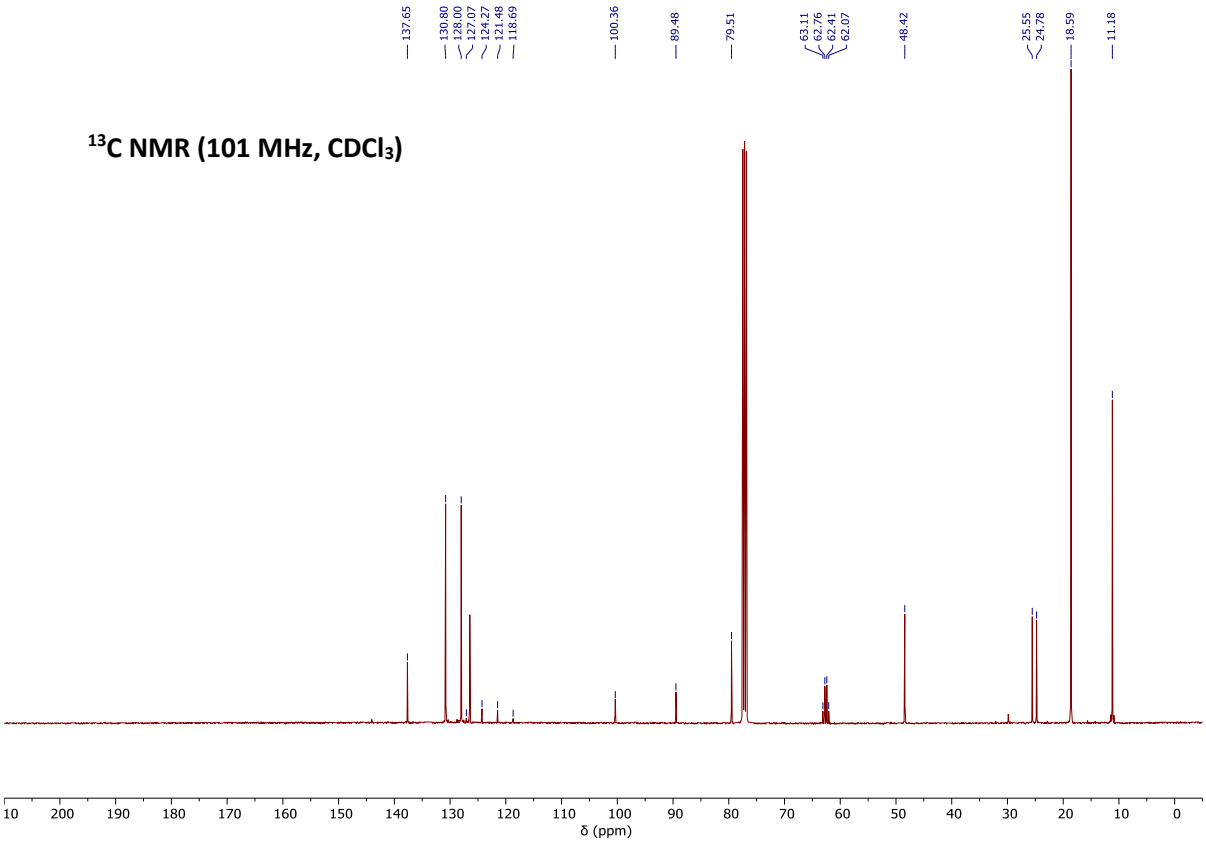


^{1}H NMR (400 MHz, $CDCl_3$)

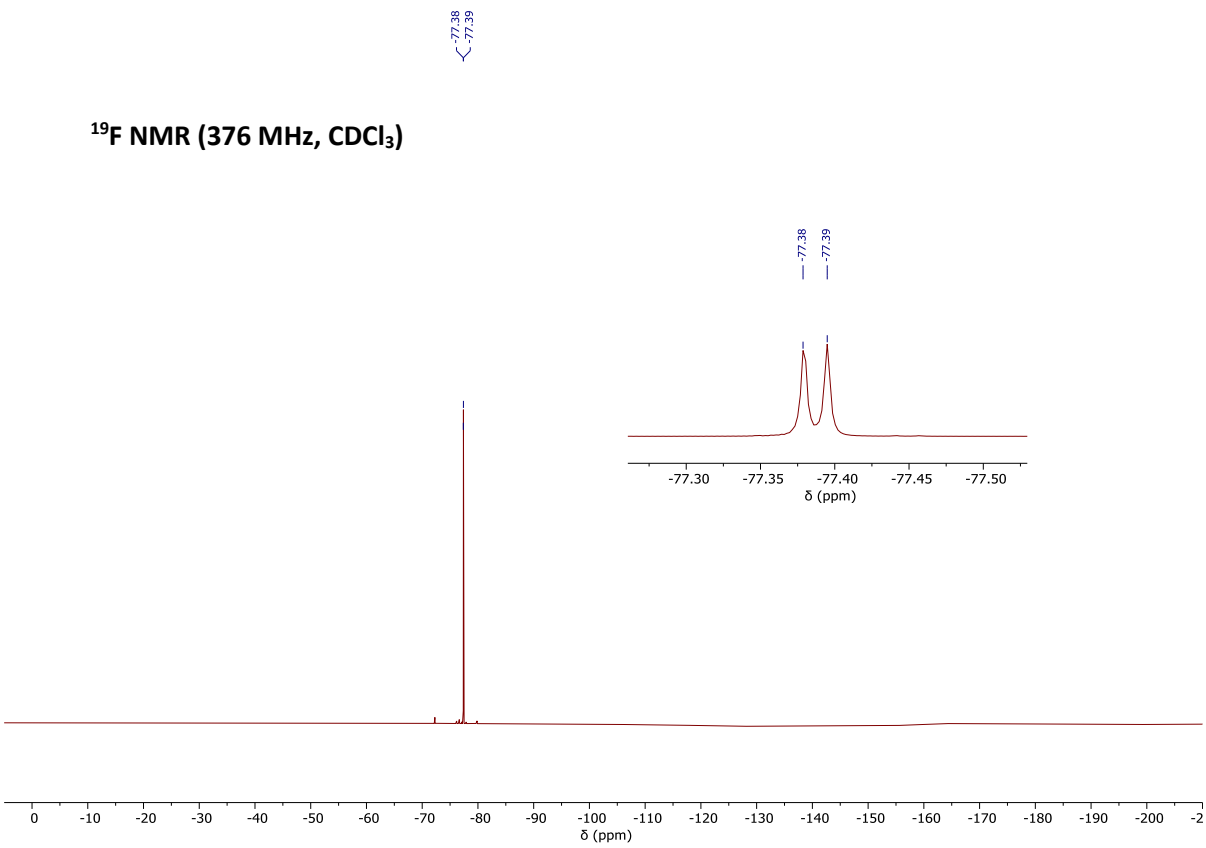


4de

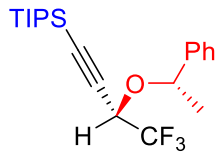
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

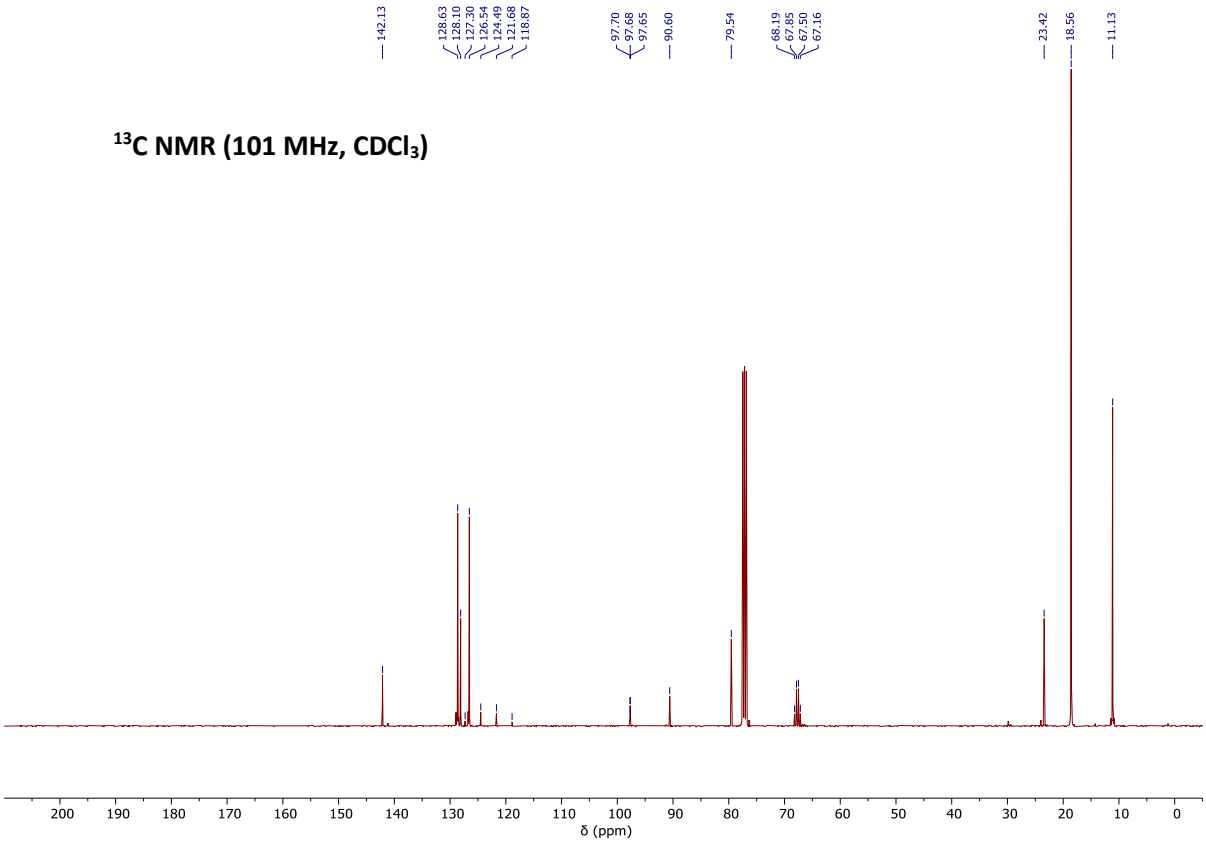


^{1}H NMR (400 MHz, $CDCl_3$)

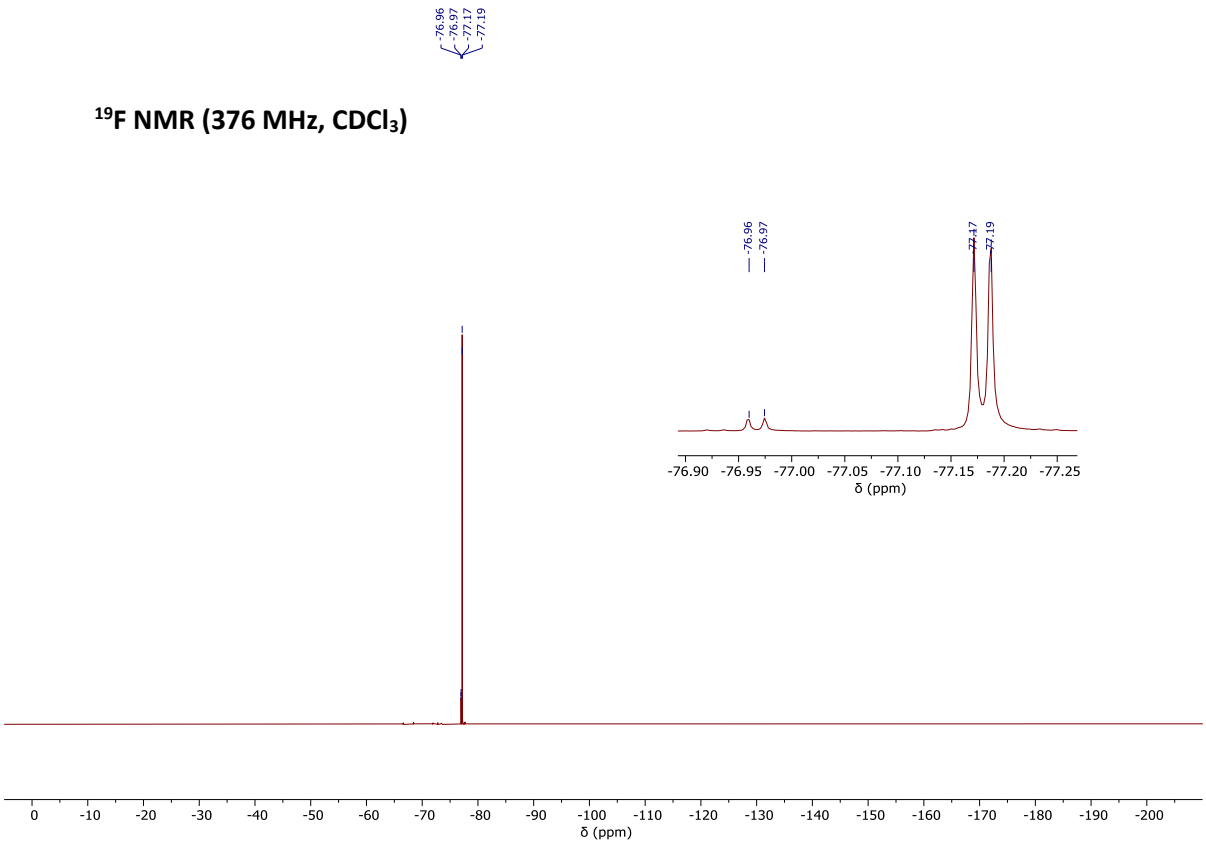


4db

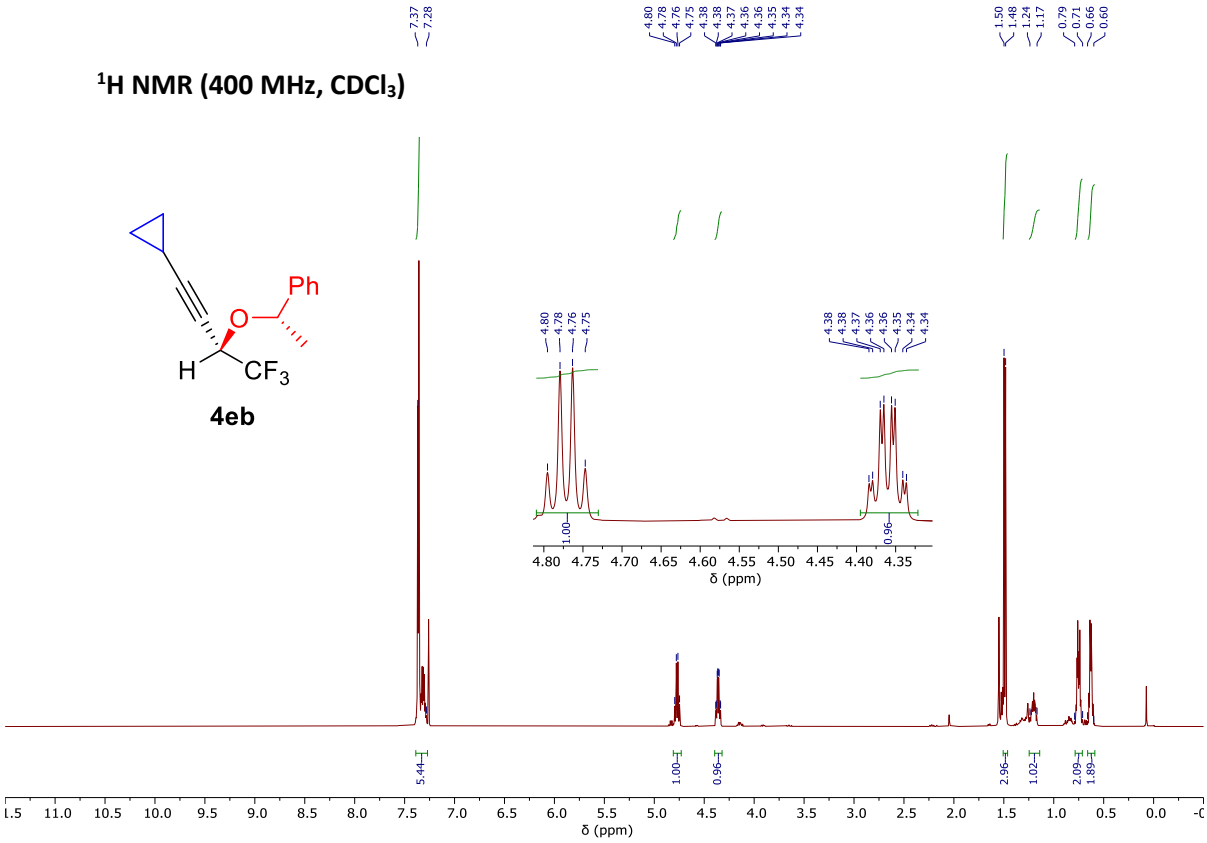
^{13}C NMR (101 MHz, $CDCl_3$)



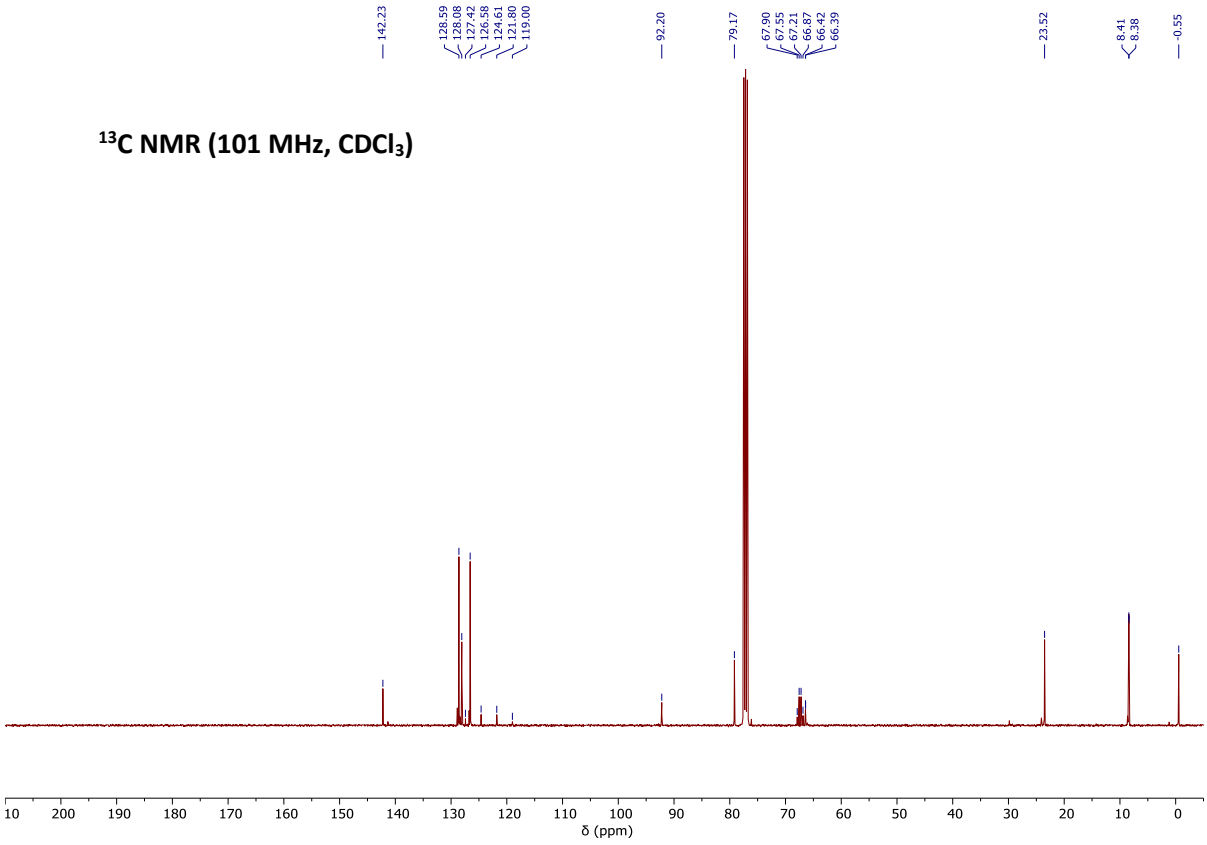
^{19}F NMR (376 MHz, $CDCl_3$)



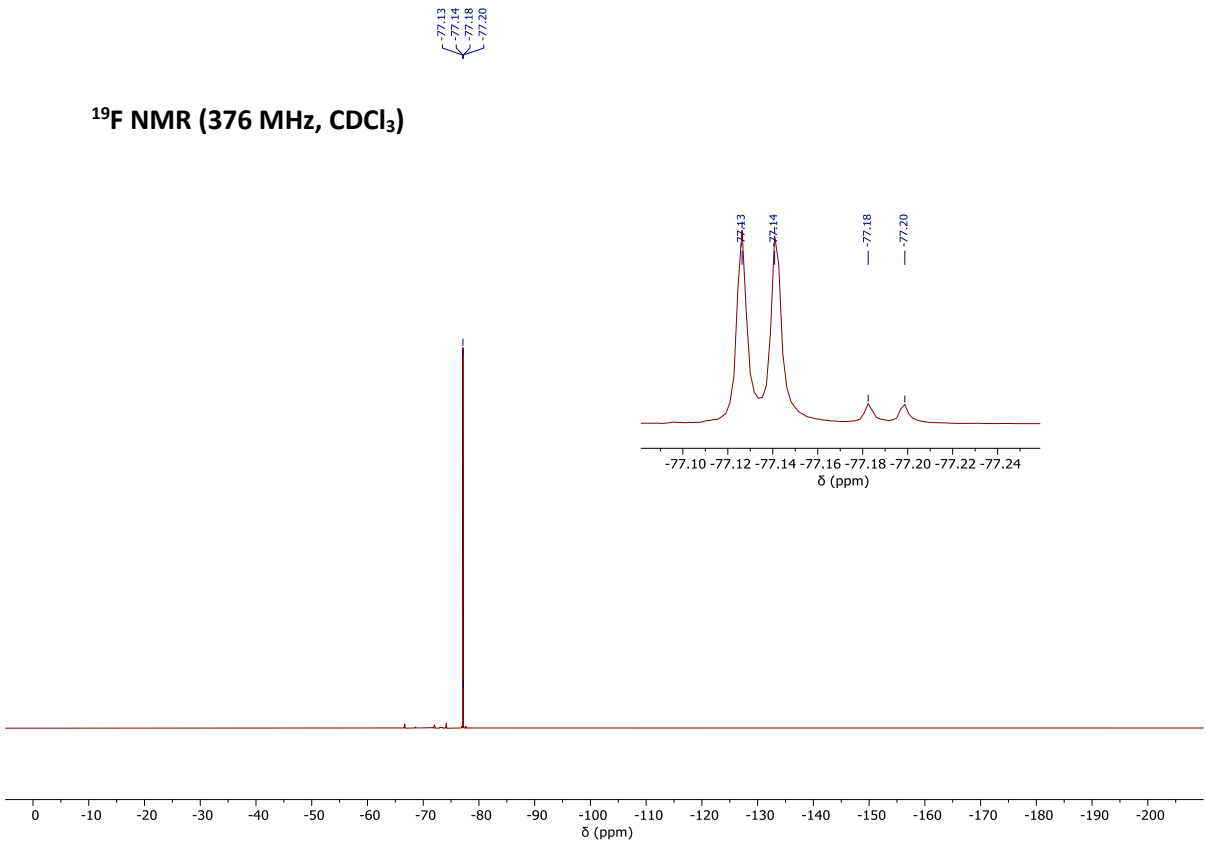
^{1}H NMR (400 MHz, $CDCl_3$)



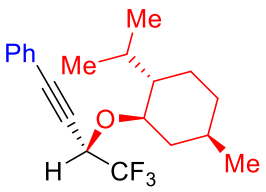
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

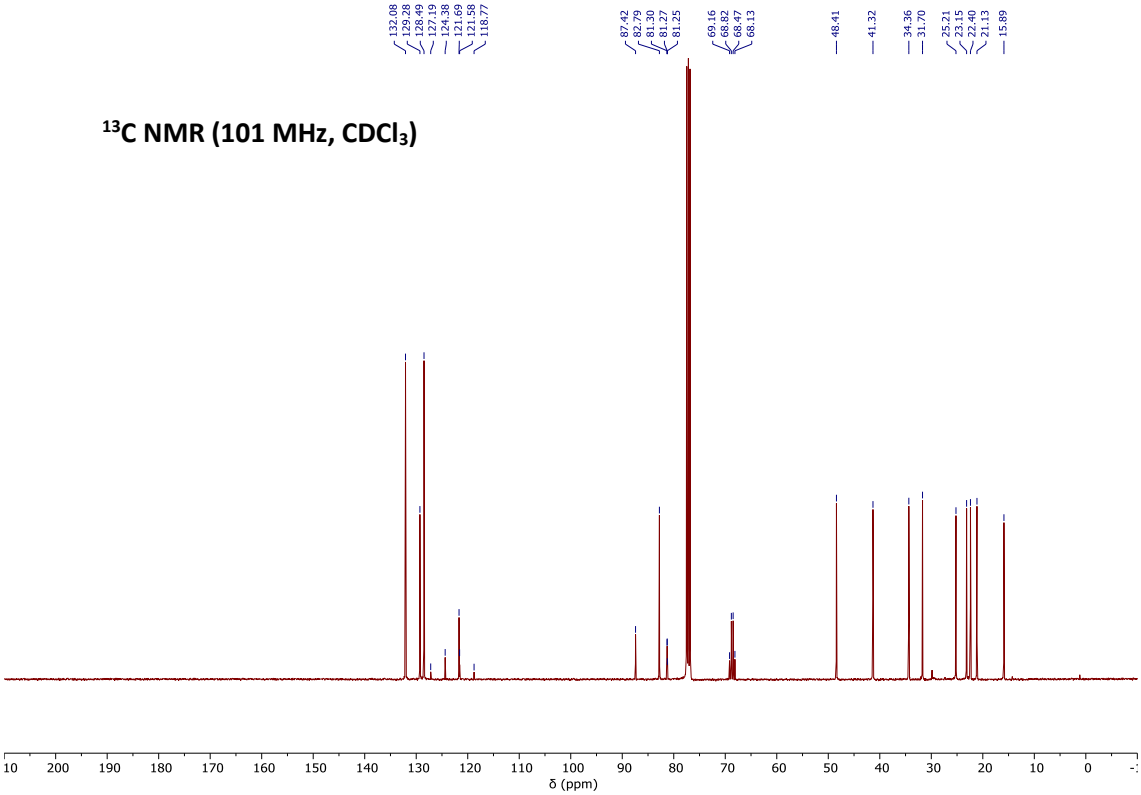


^{1}H NMR (400 MHz, $CDCl_3$)

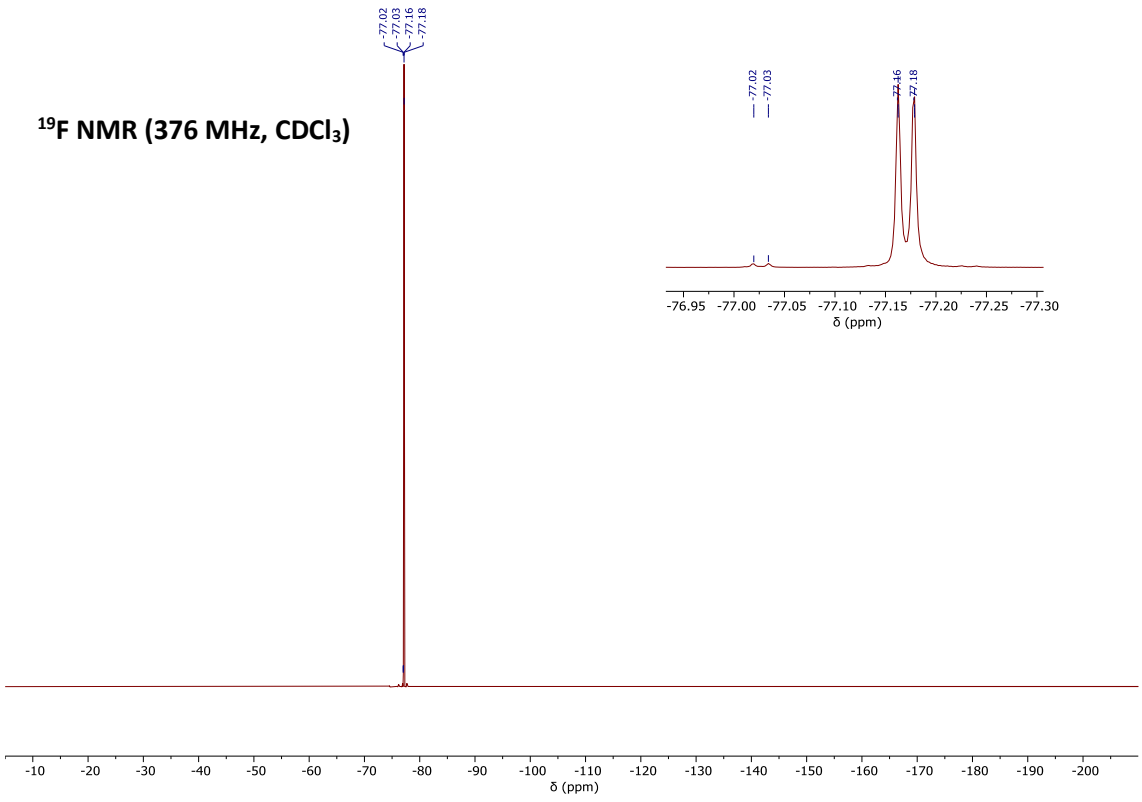


6

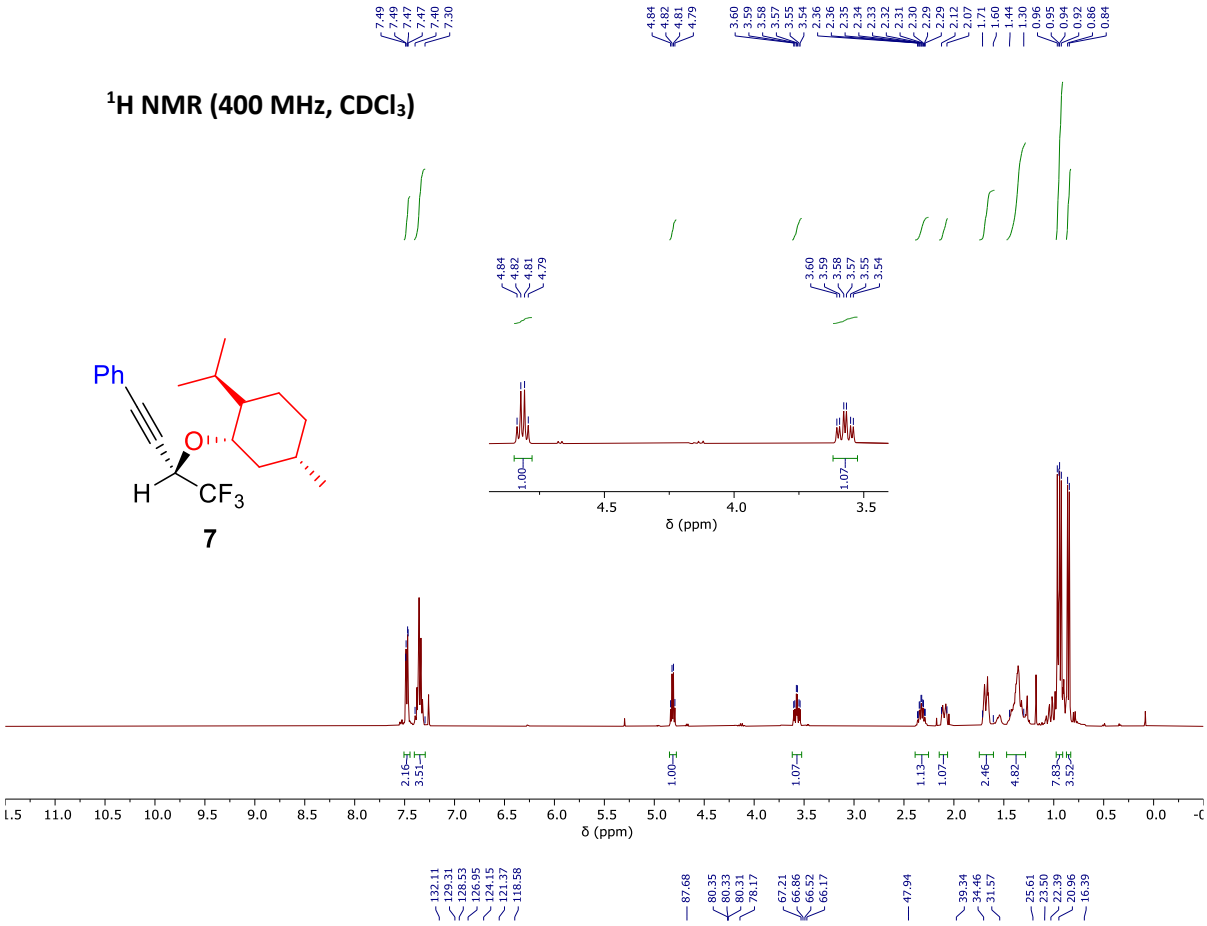
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

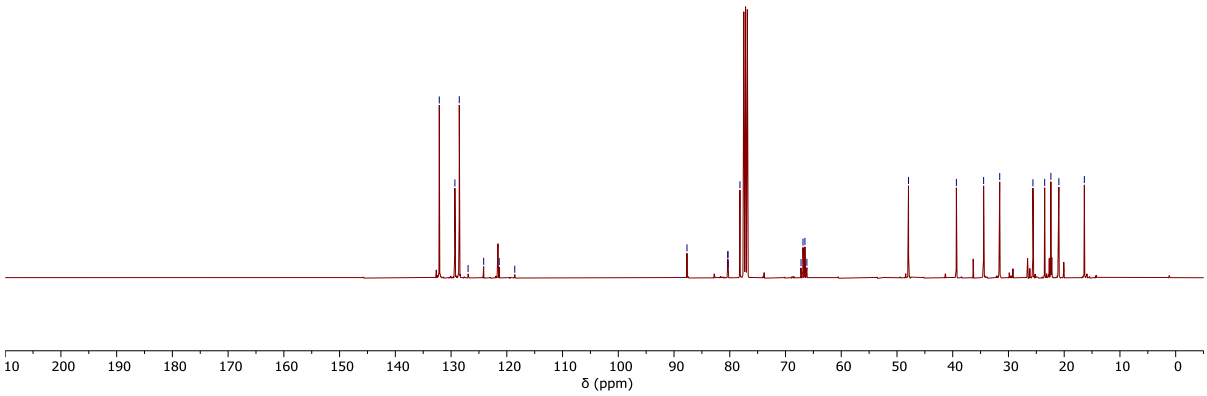


^{1}H NMR (400 MHz, $CDCl_3$)

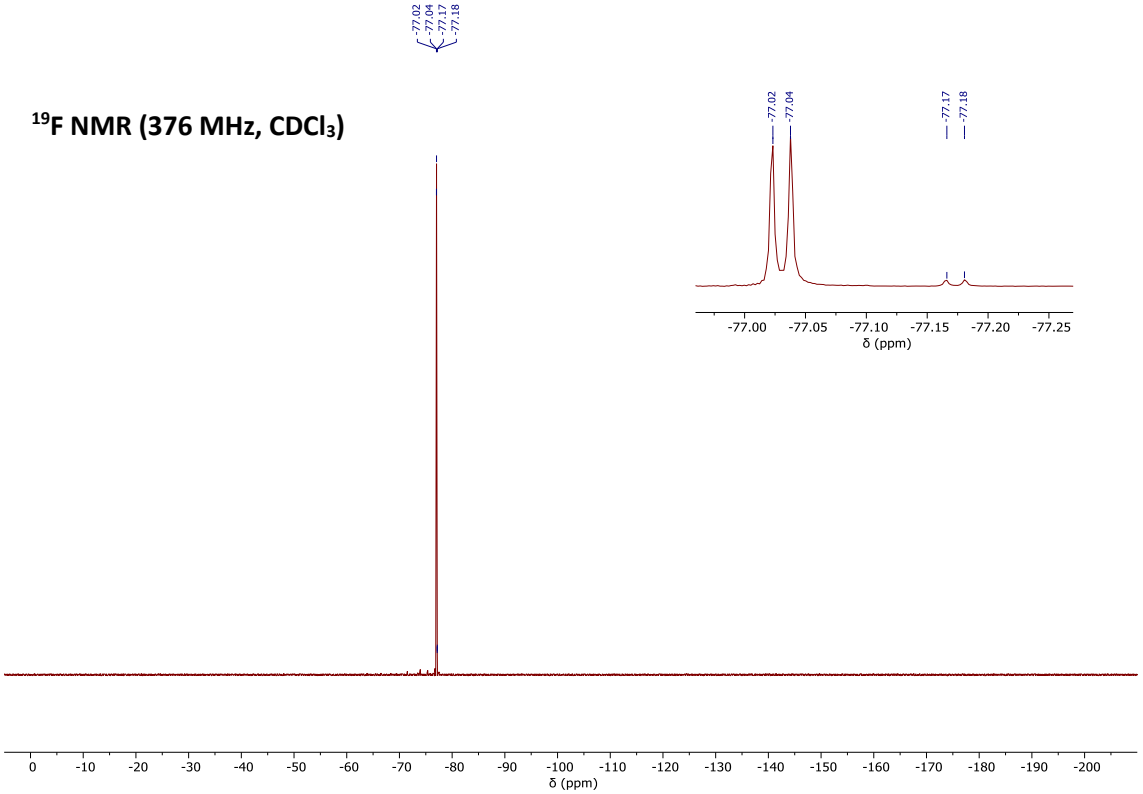


7

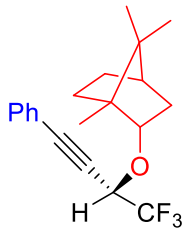
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

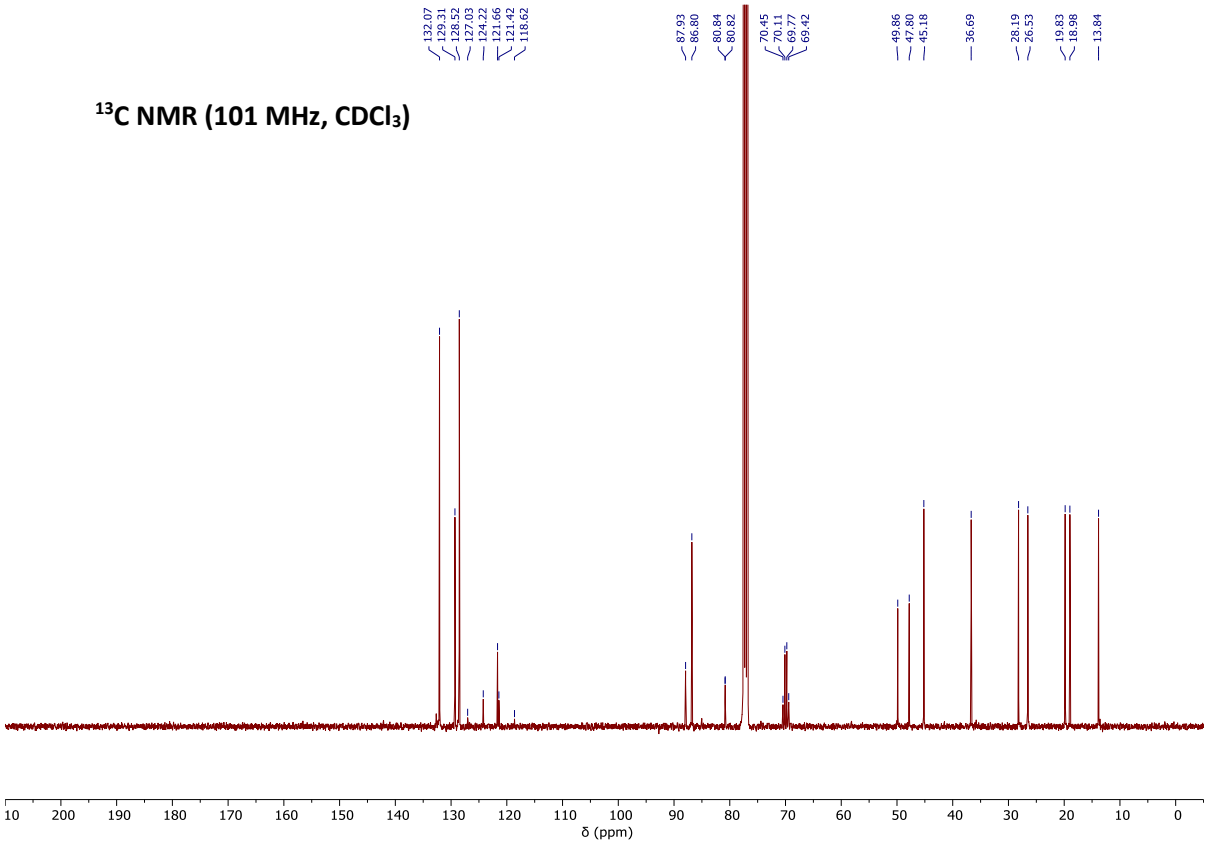


^{1}H NMR (400 MHz, $CDCl_3$)

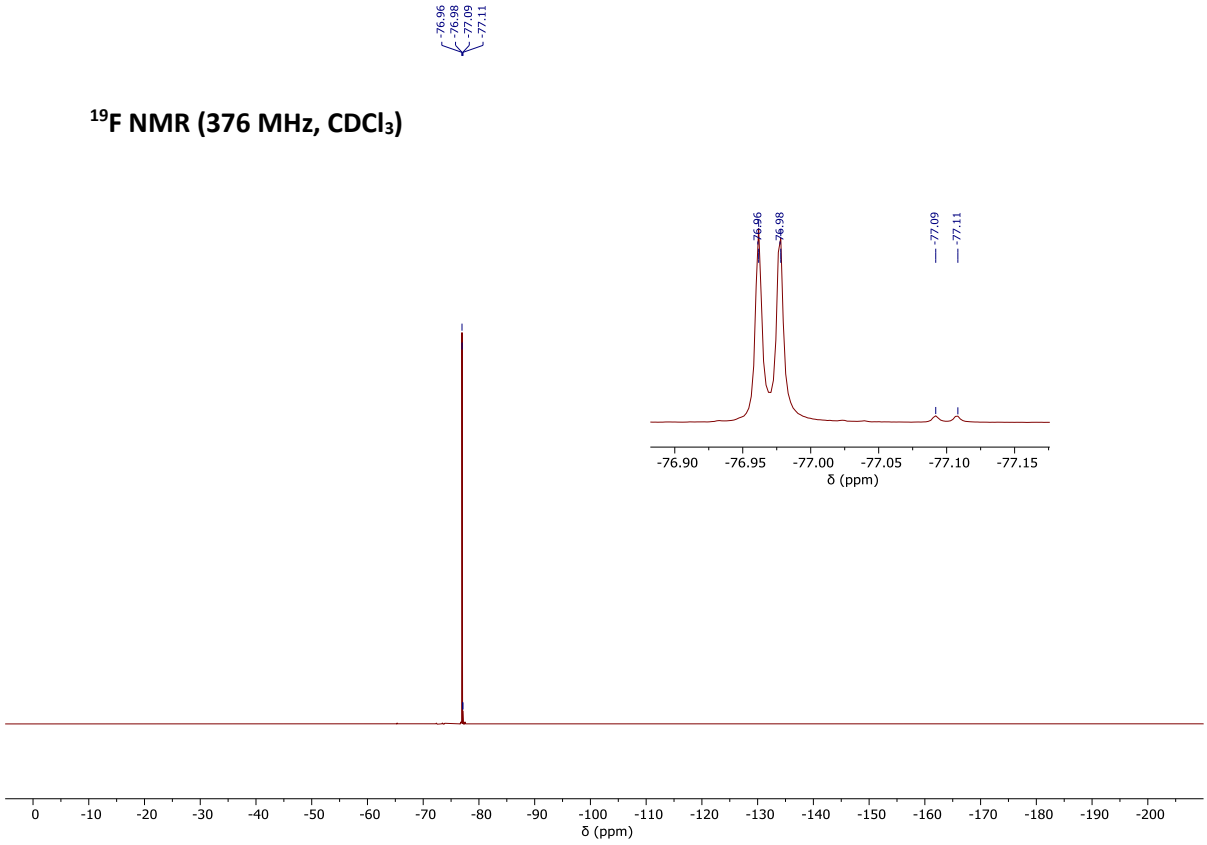


8

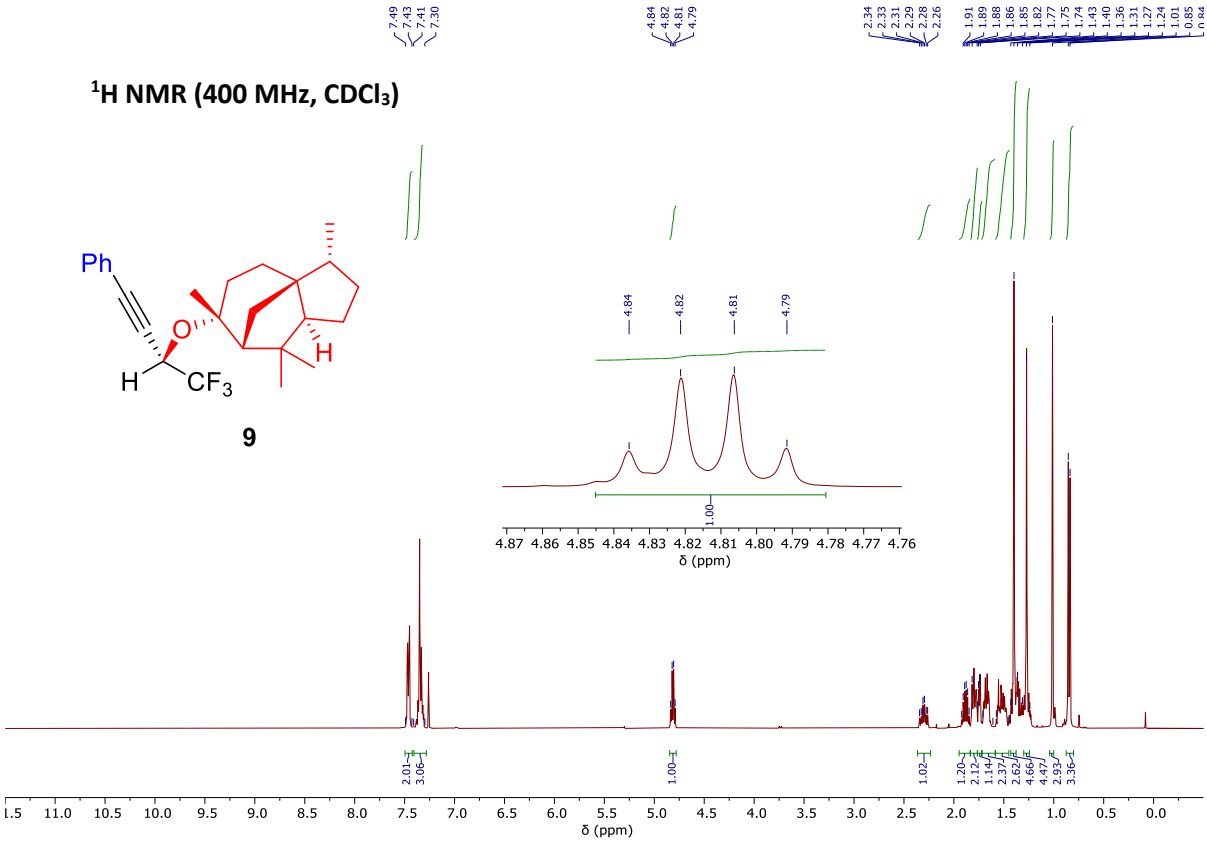
^{13}C NMR (101 MHz, $CDCl_3$)



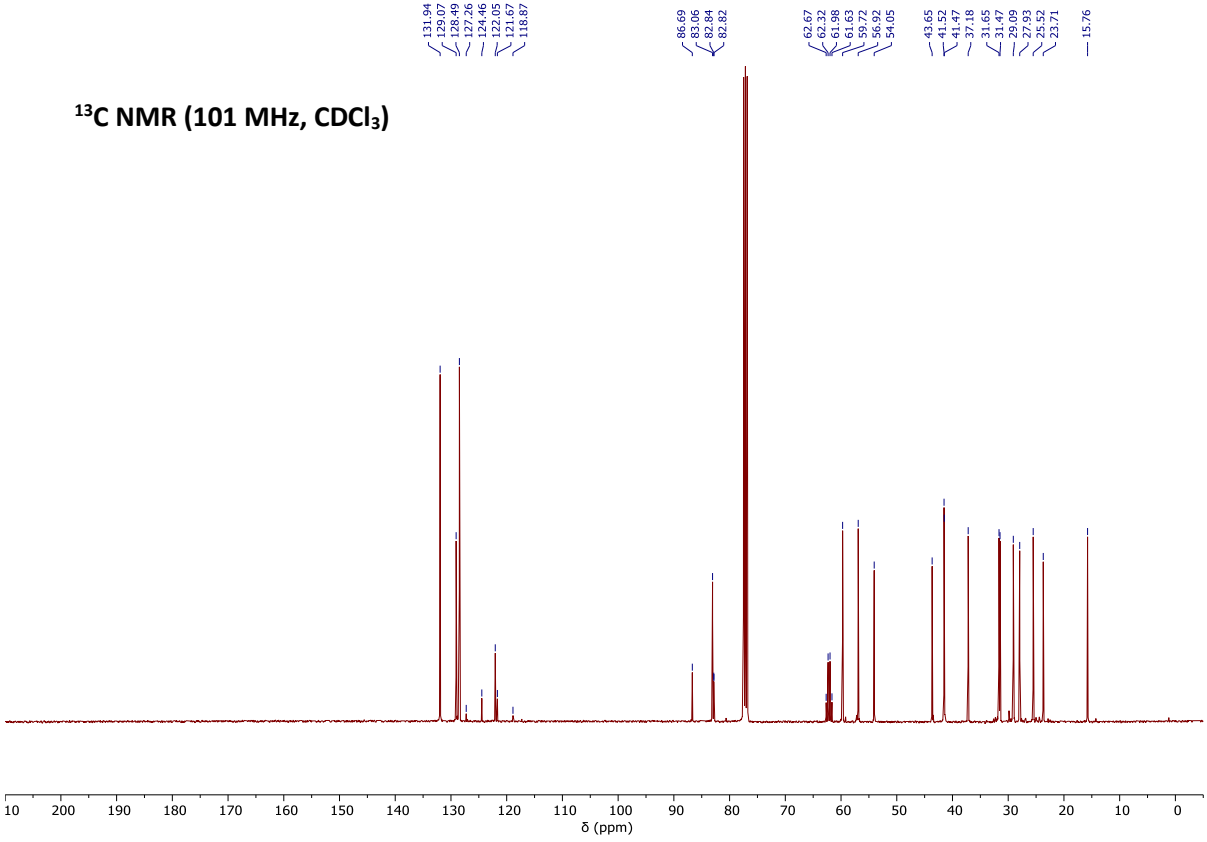
^{19}F NMR (376 MHz, $CDCl_3$)



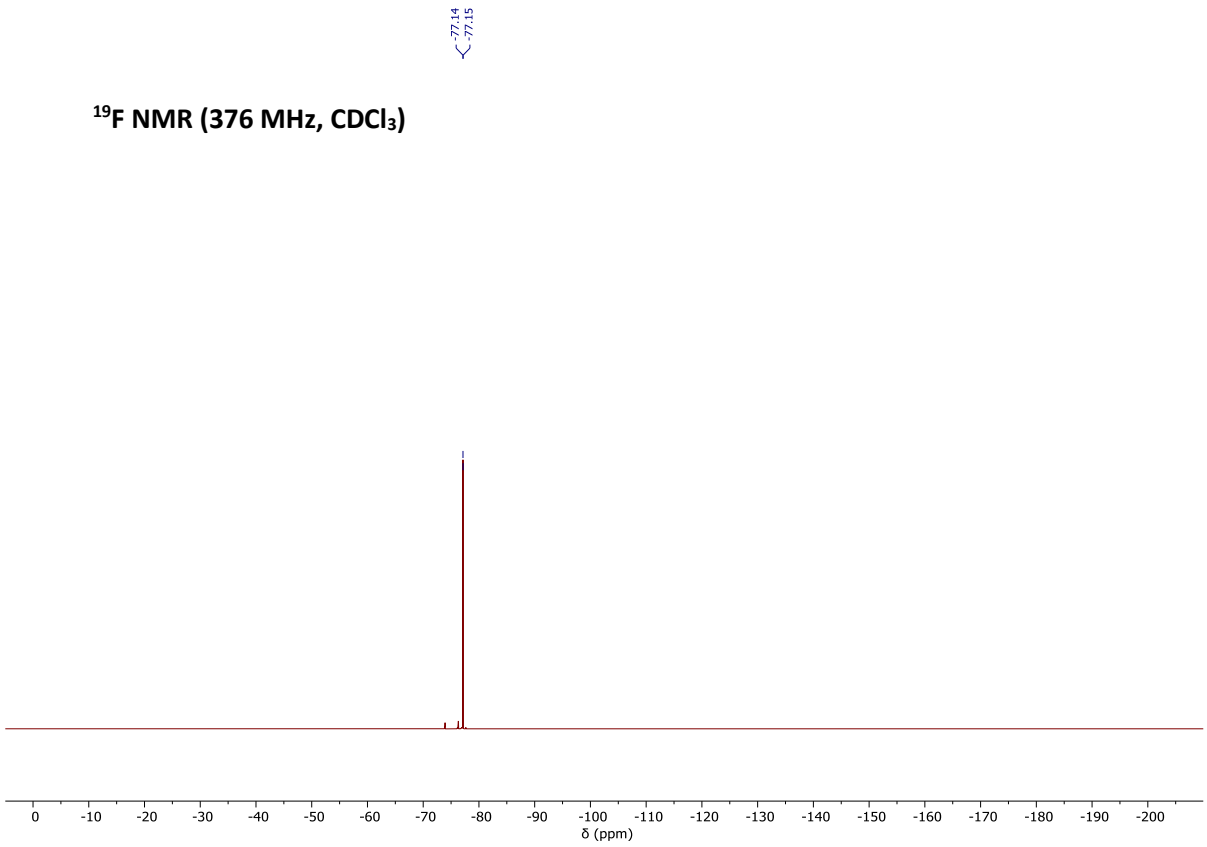
^{1}H NMR (400 MHz, $CDCl_3$)



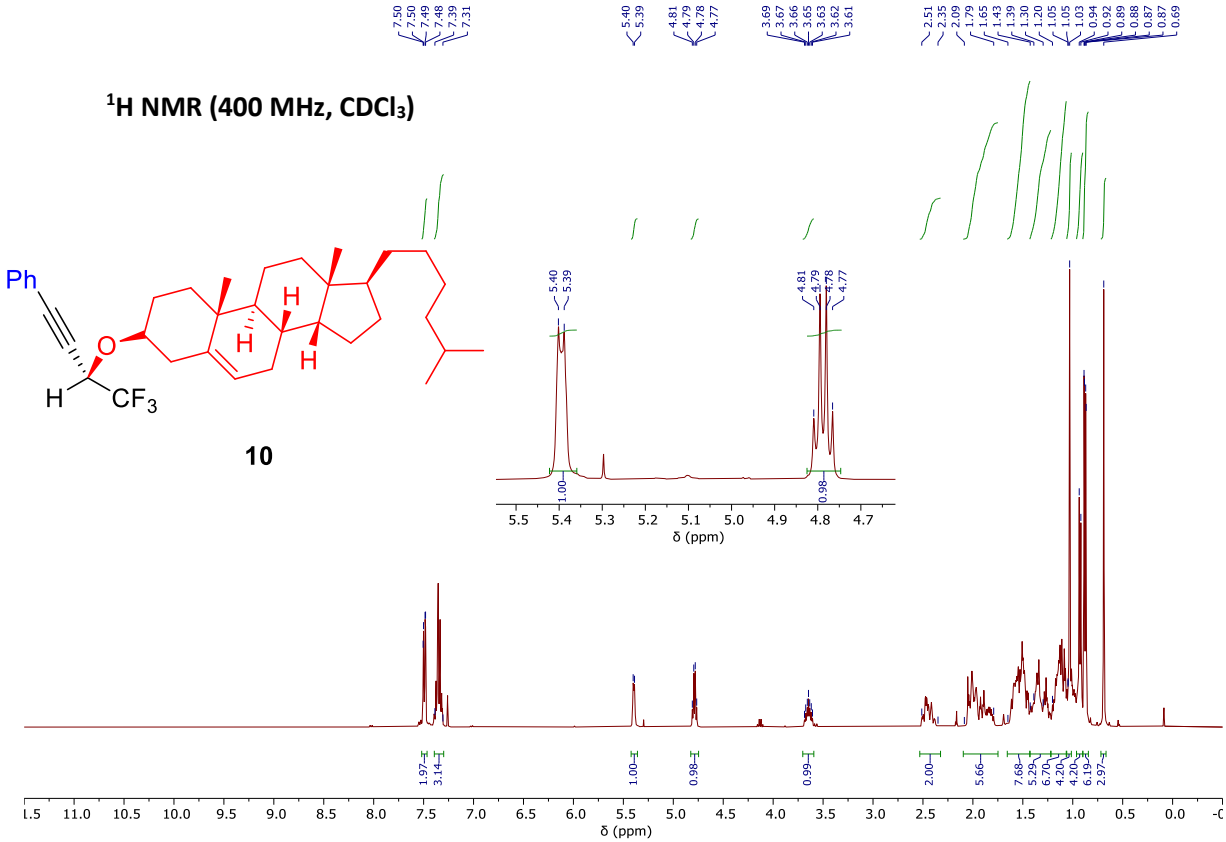
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

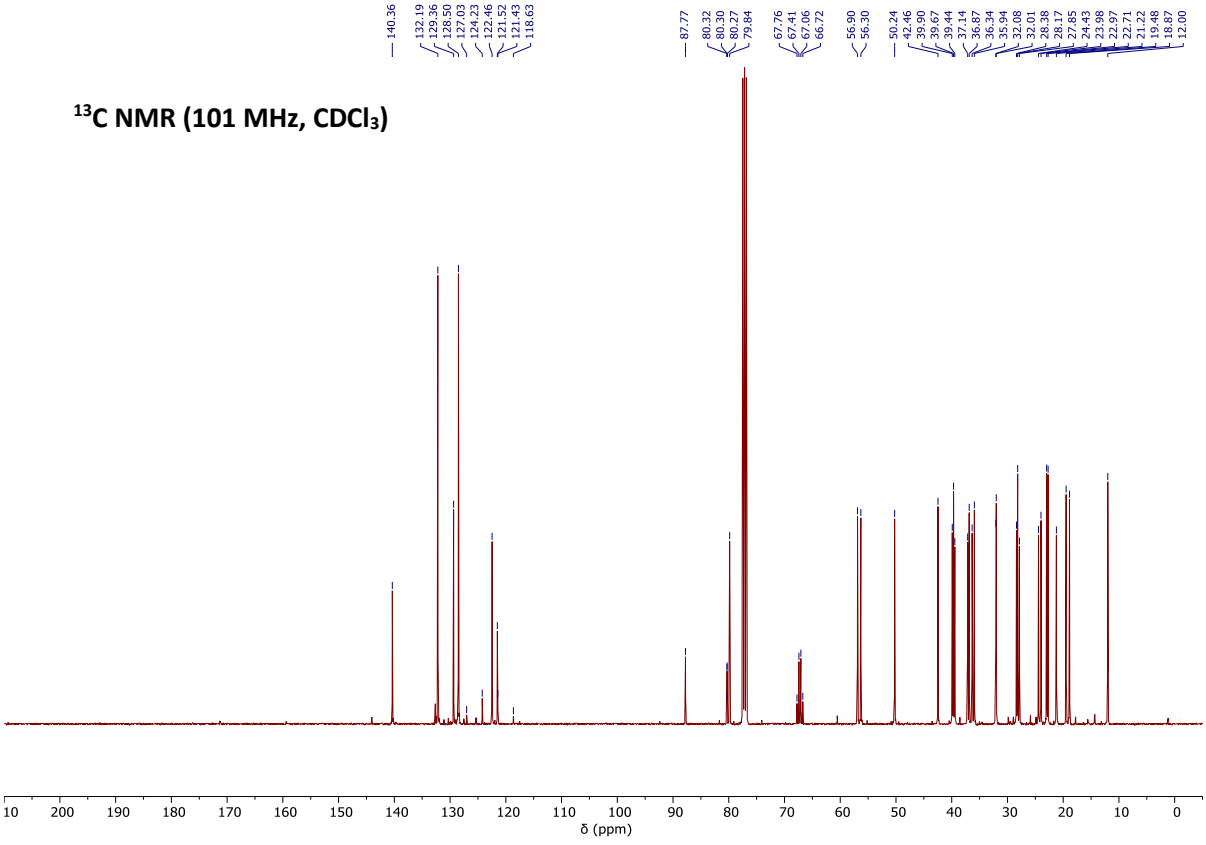


^{1}H NMR (400 MHz, $CDCl_3$)

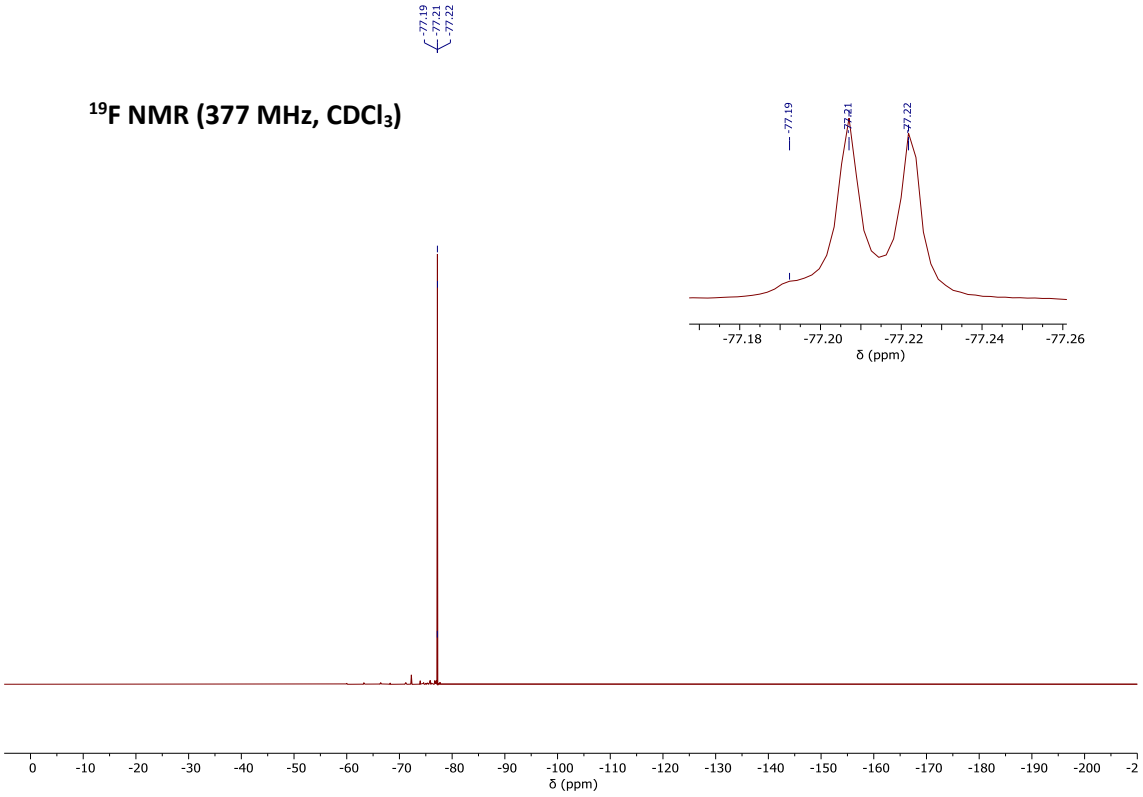


10

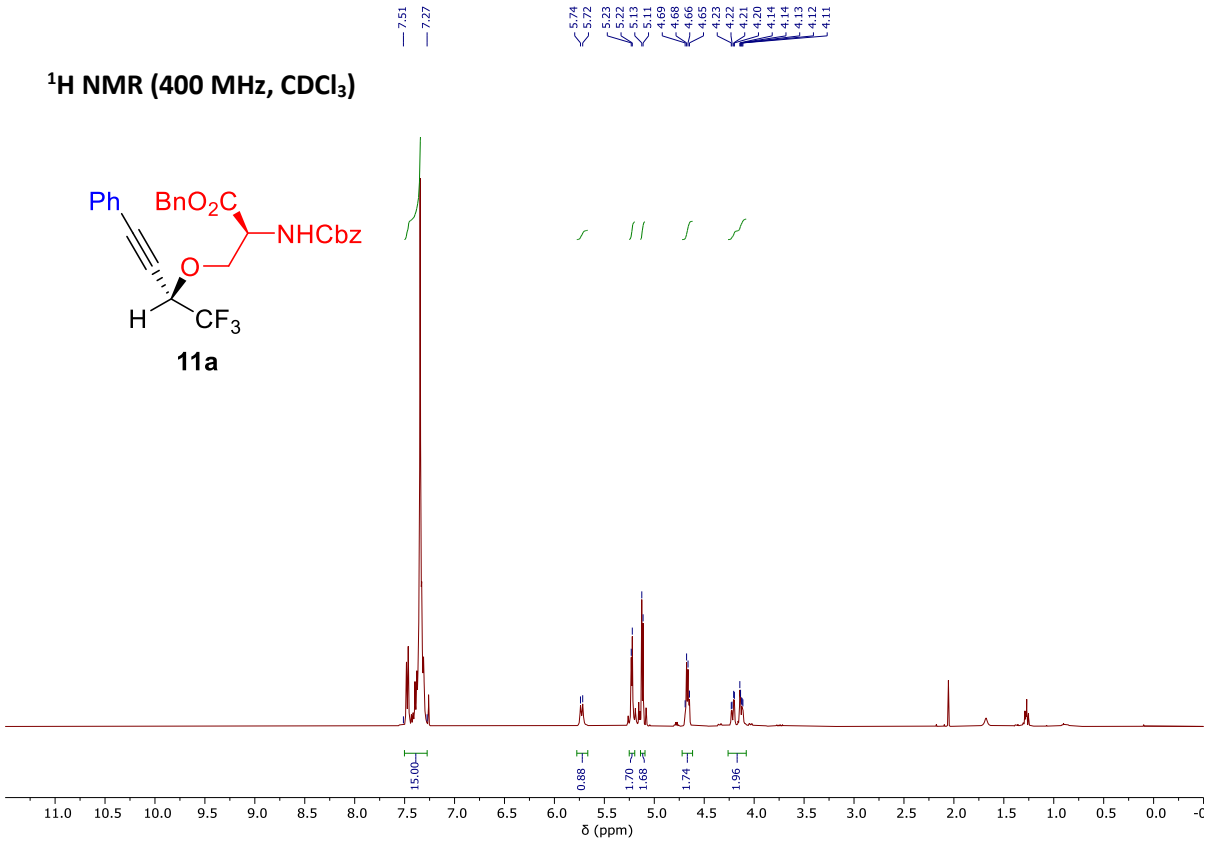
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

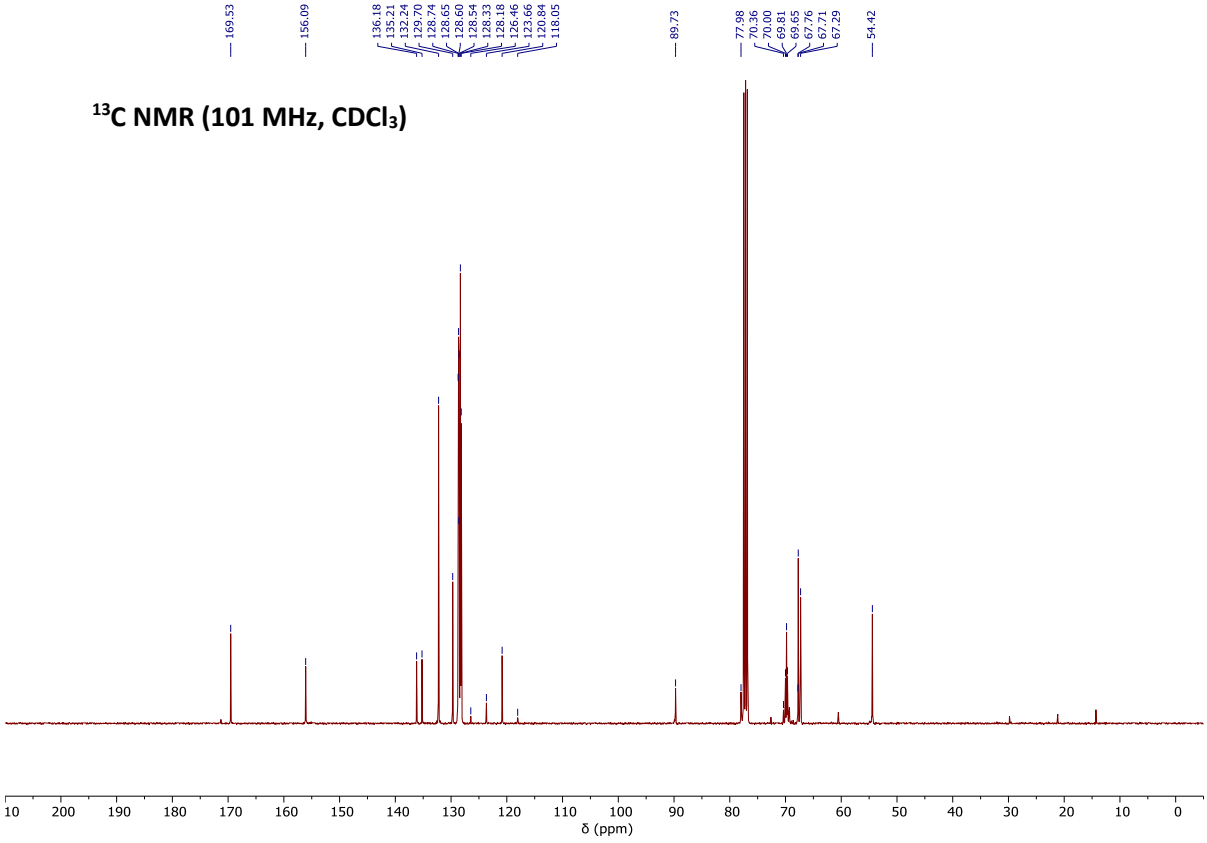


^{1}H NMR (400 MHz, $CDCl_3$)

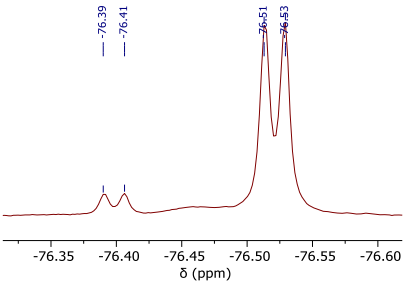


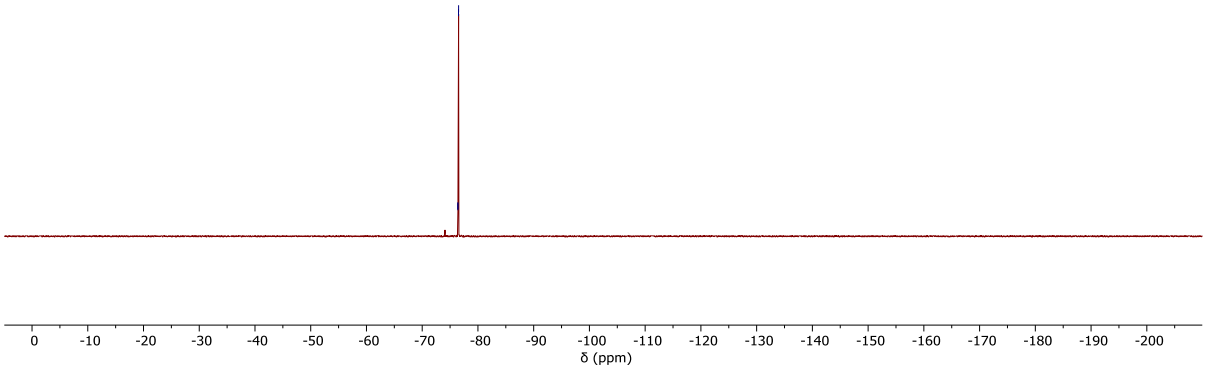
11a

^{13}C NMR (101 MHz, $CDCl_3$)

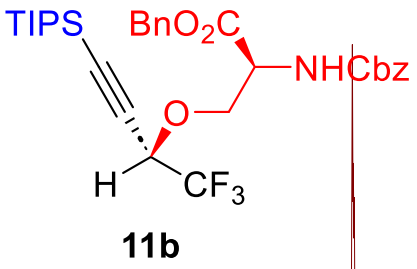


^{19}F NMR (376 MHz, $CDCl_3$)



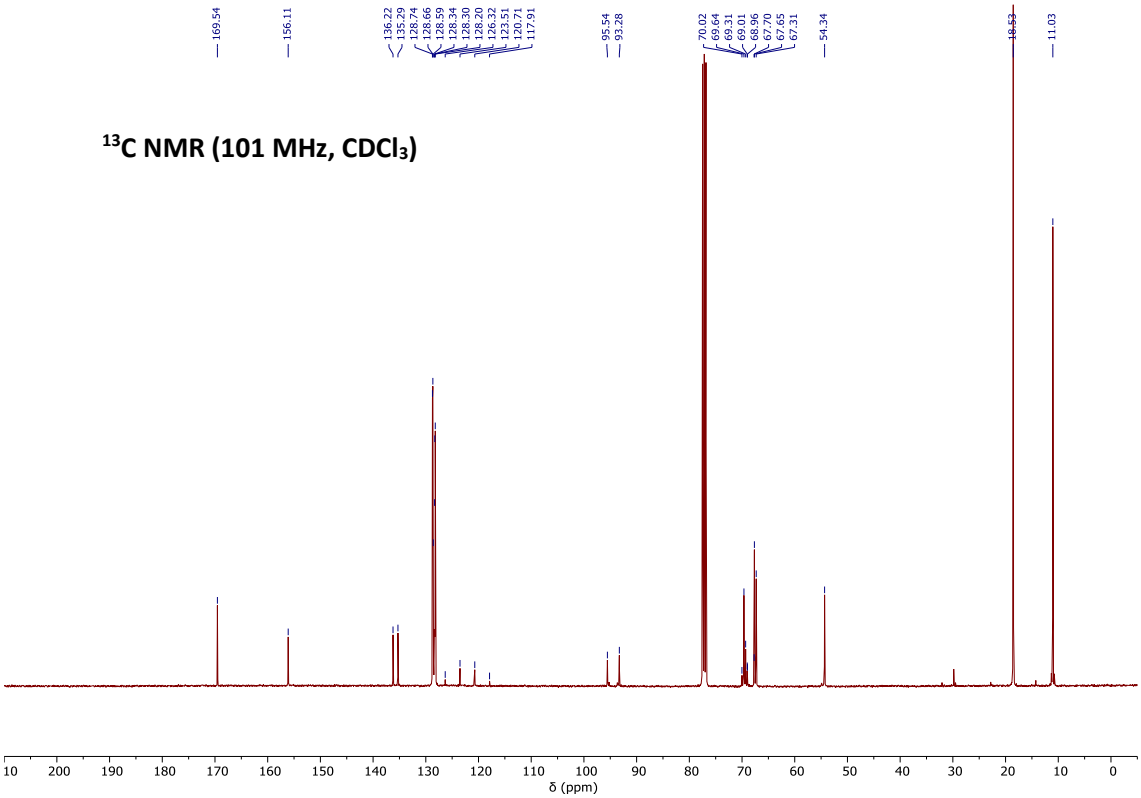


^{1}H NMR (400 MHz, $CDCl_3$)

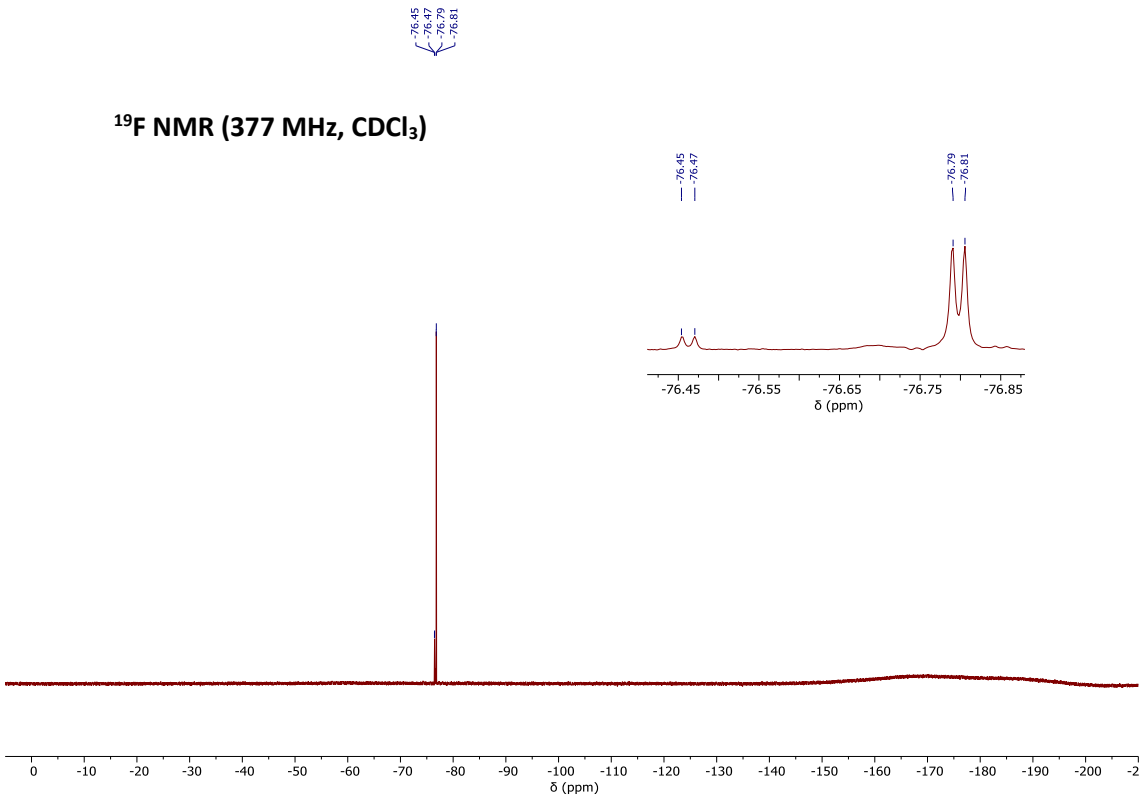


11b

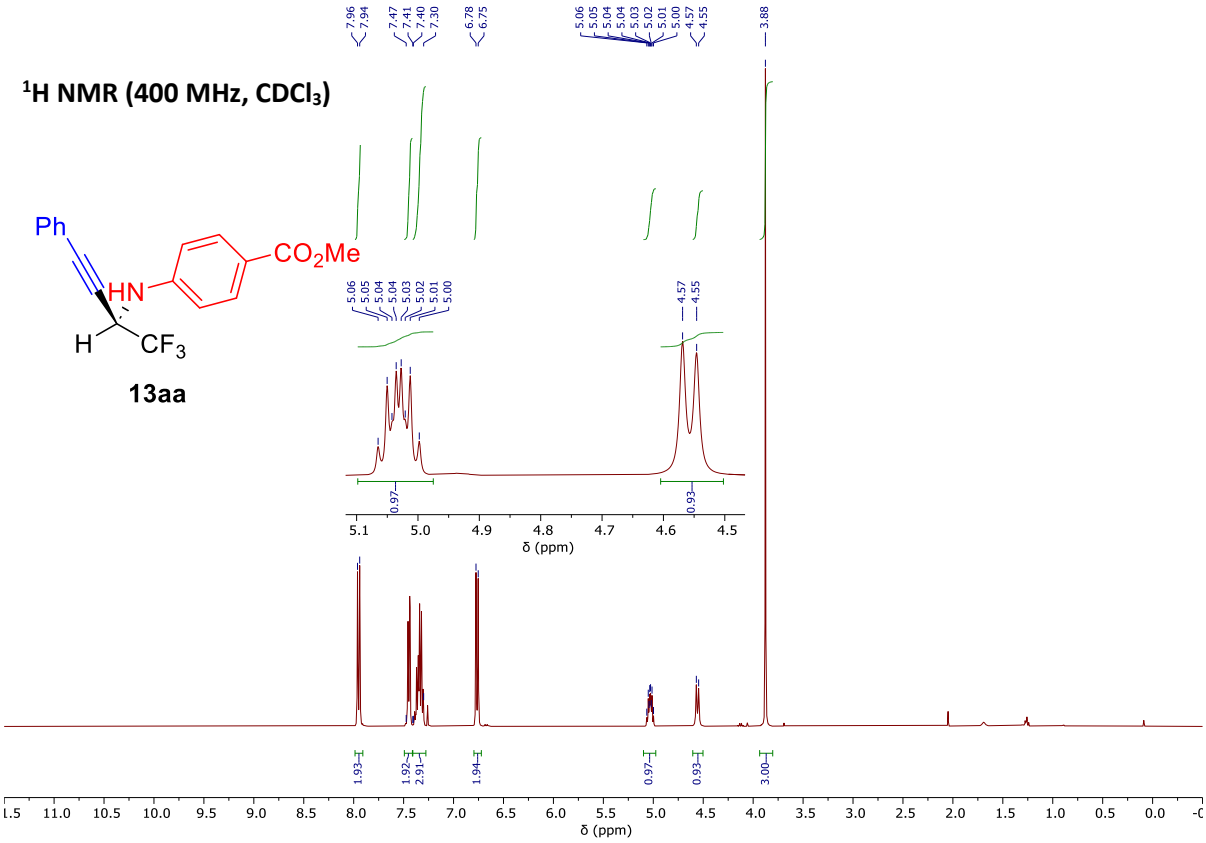
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

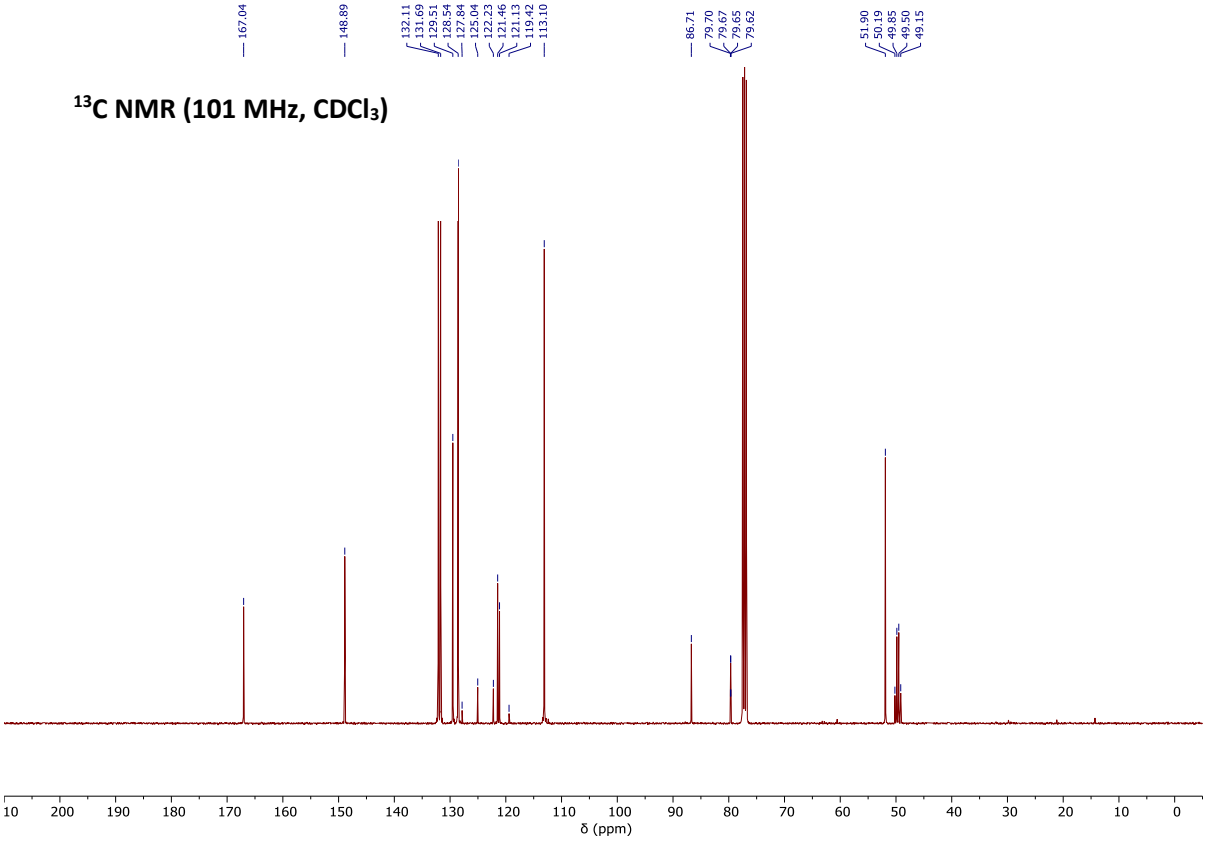


^{1}H NMR (400 MHz, $CDCl_3$)



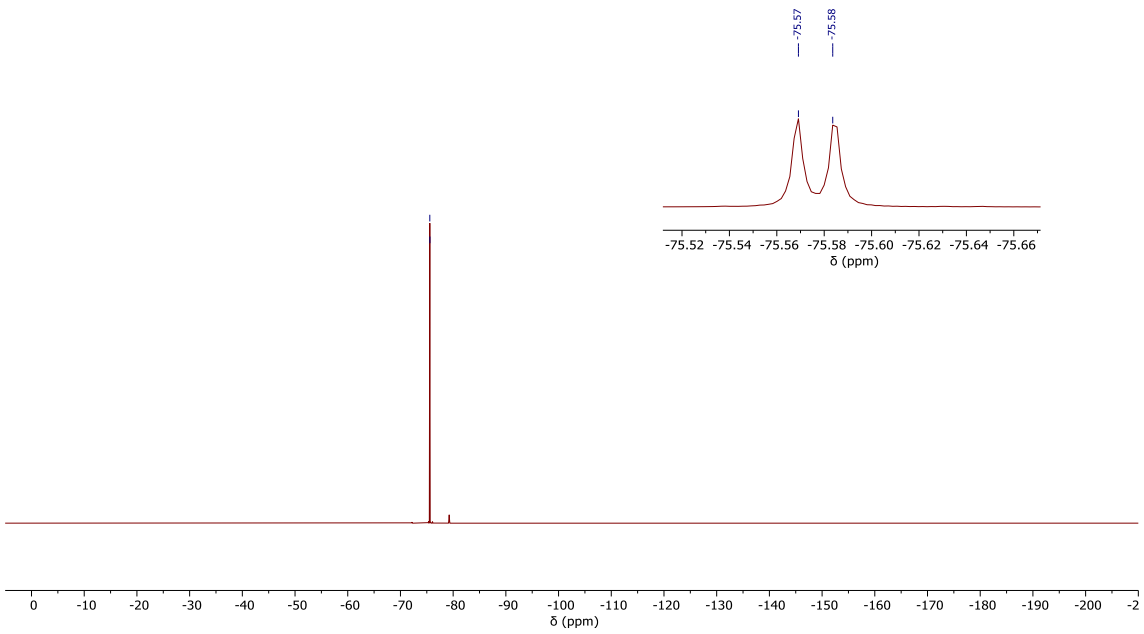
13aa

^{13}C NMR (101 MHz, $CDCl_3$)

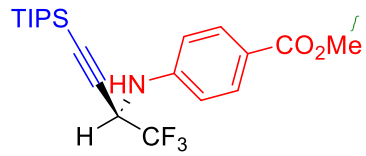


-75.57
-75.58

^{19}F NMR (376 MHz, $CDCl_3$)

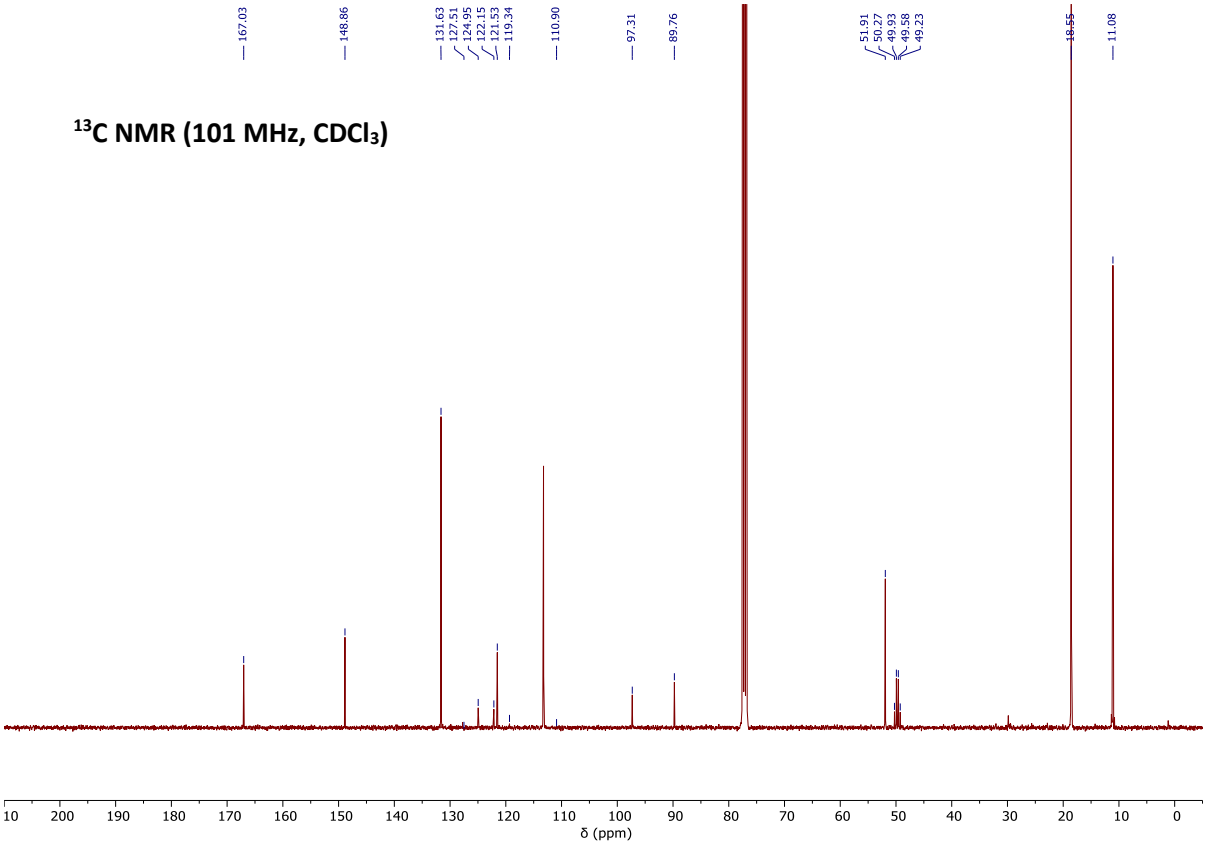


^{1}H NMR (400 MHz, $CDCl_3$)

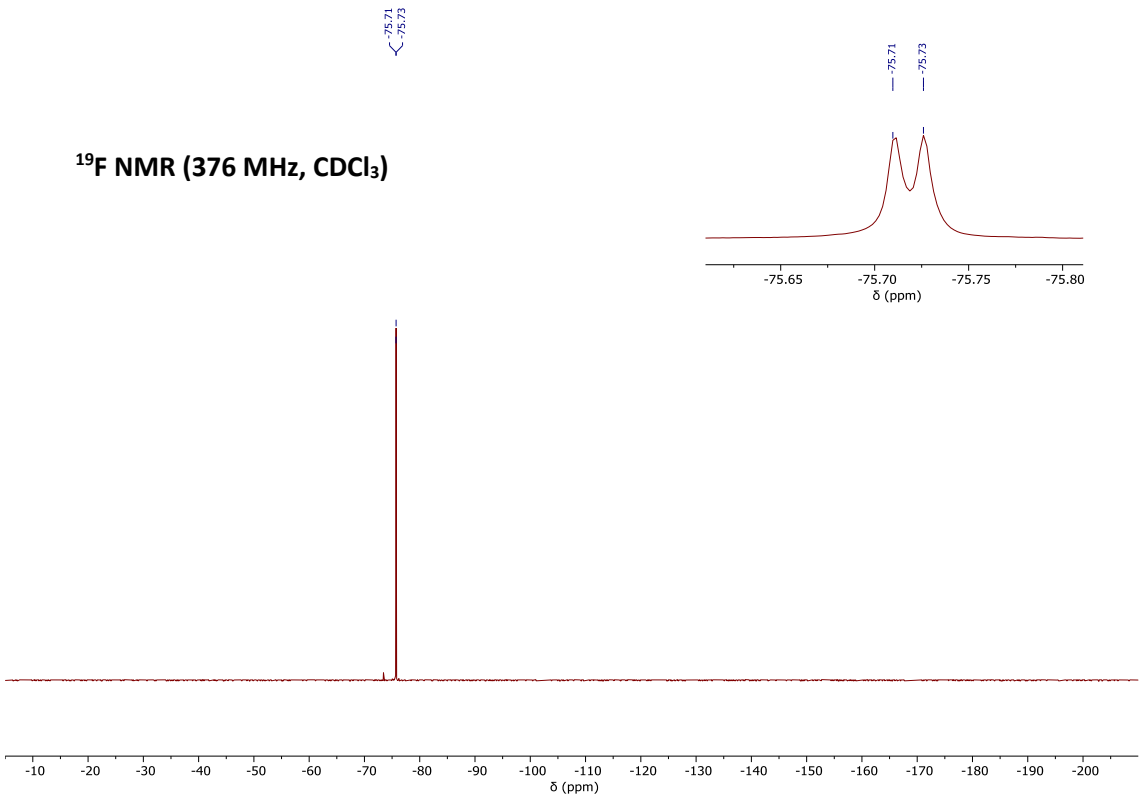


13da

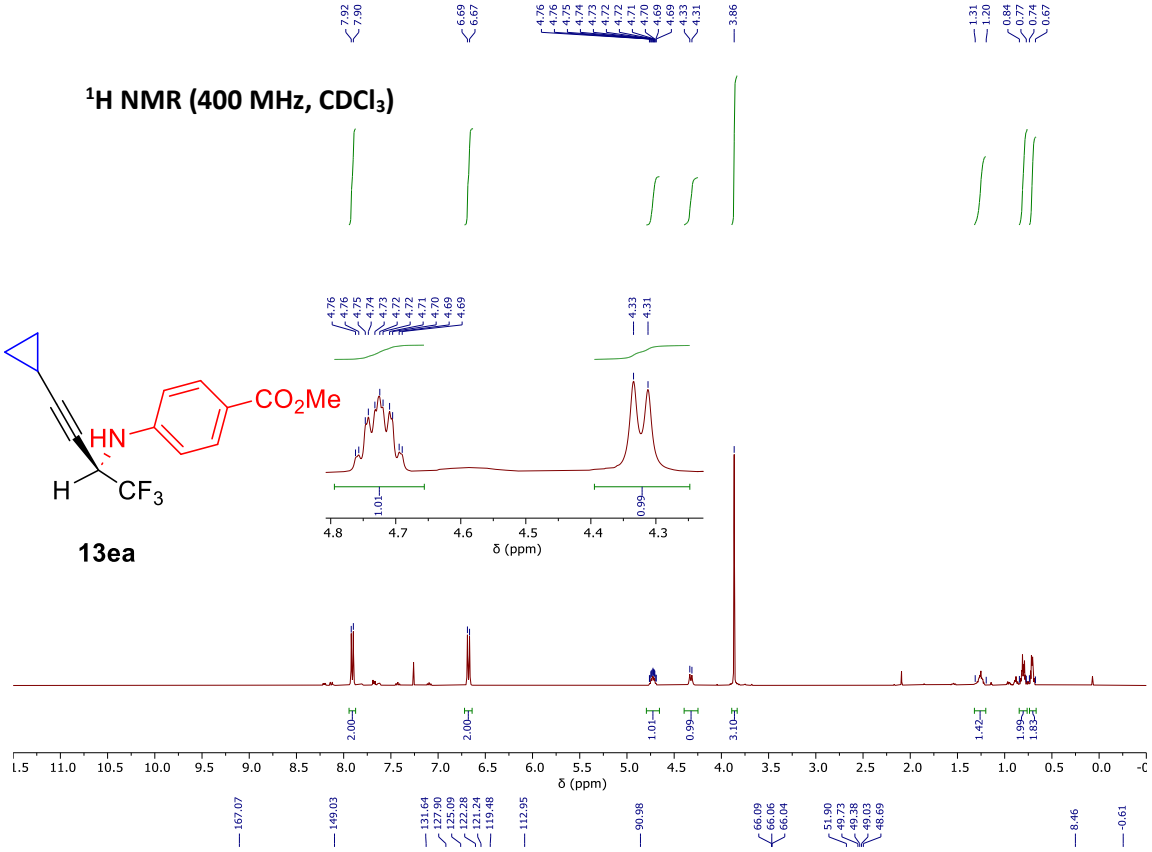
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

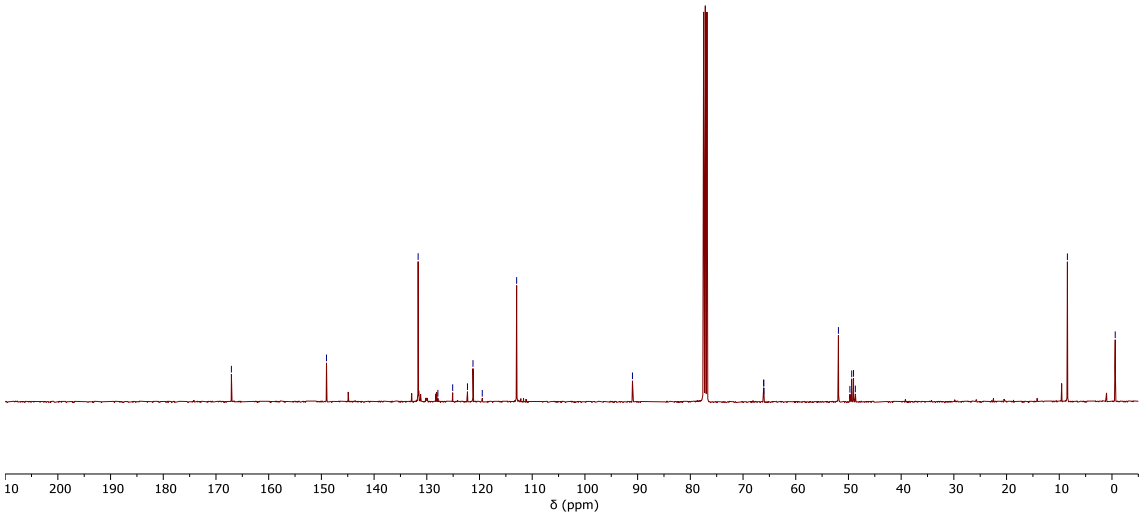


^{1}H NMR (400 MHz, $CDCl_3$)

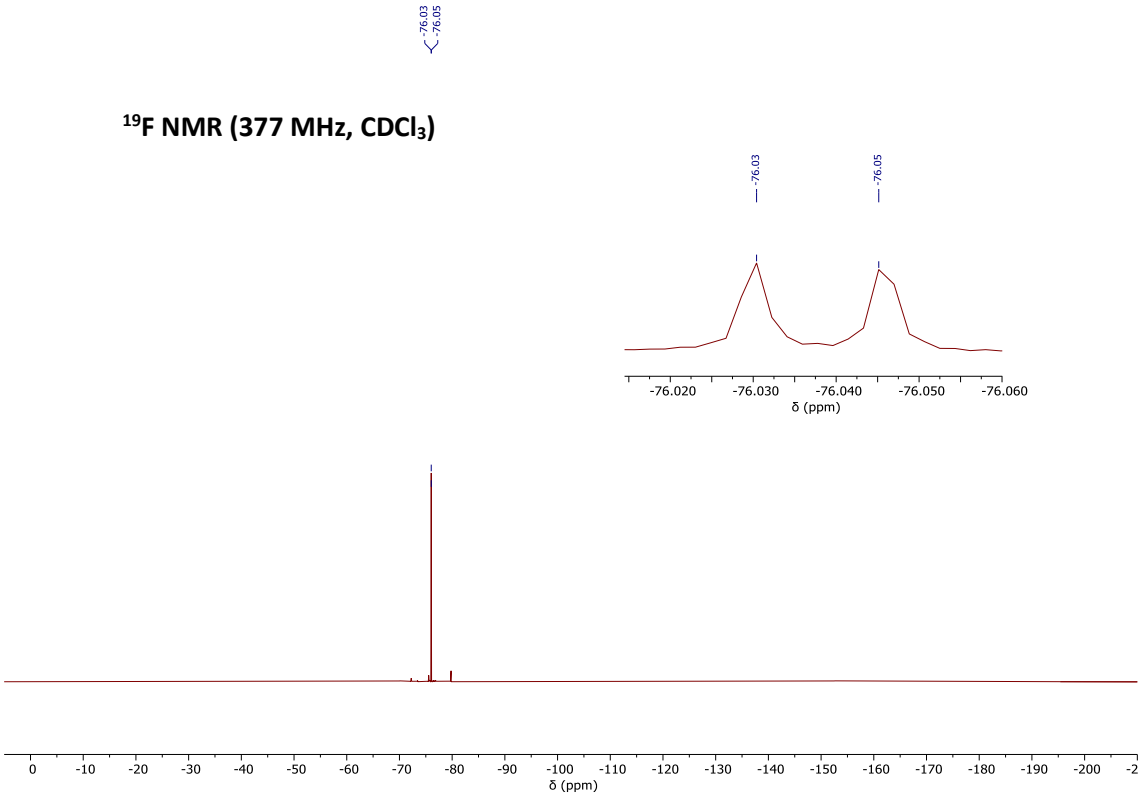


13ea

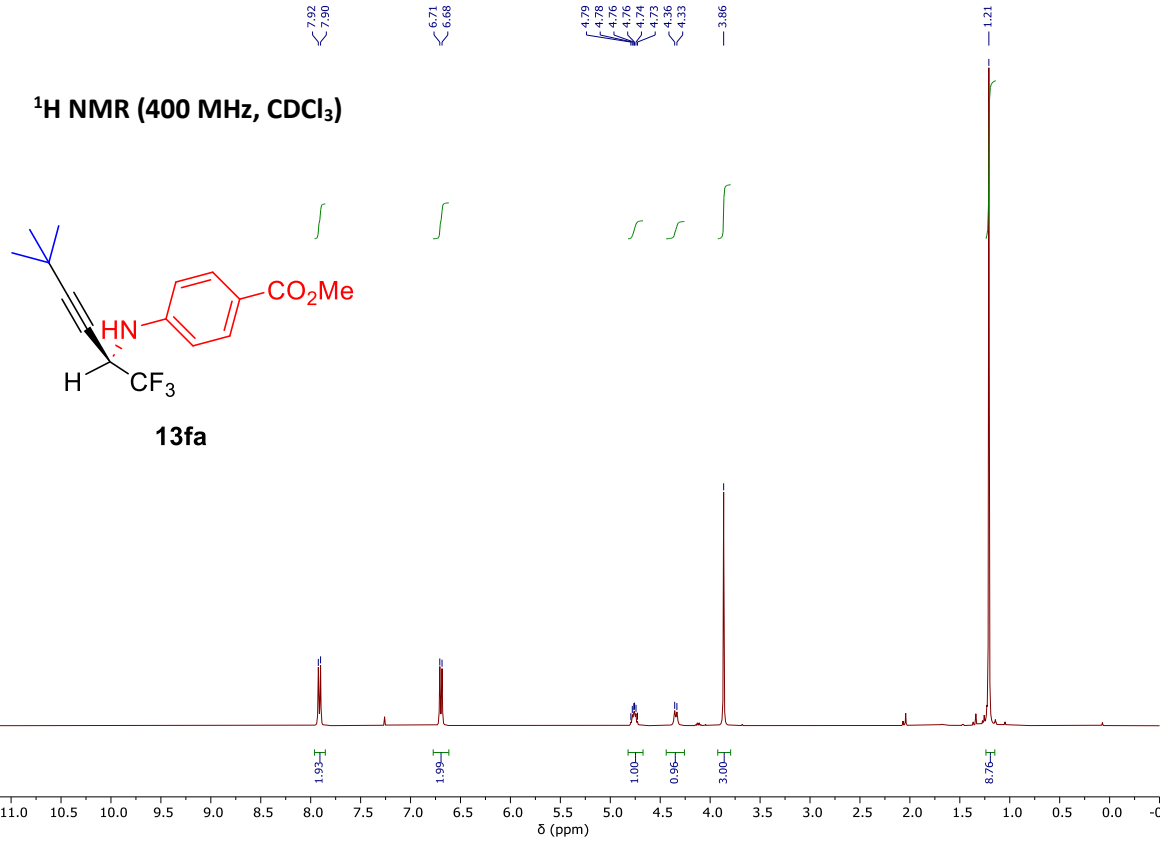
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

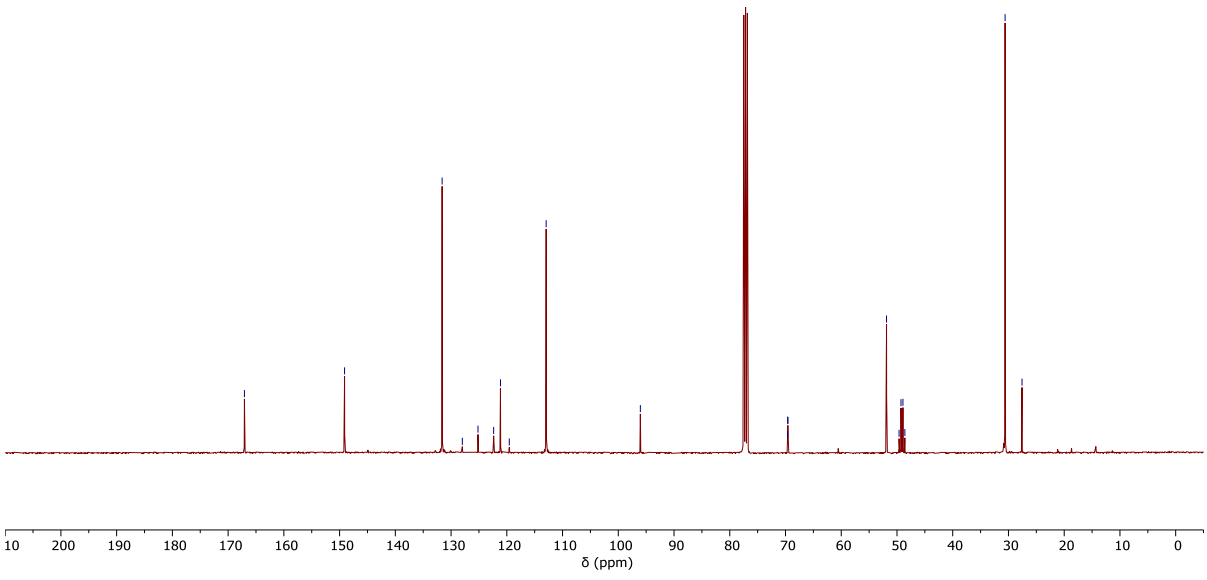


^{1}H NMR (400 MHz, $CDCl_3$)

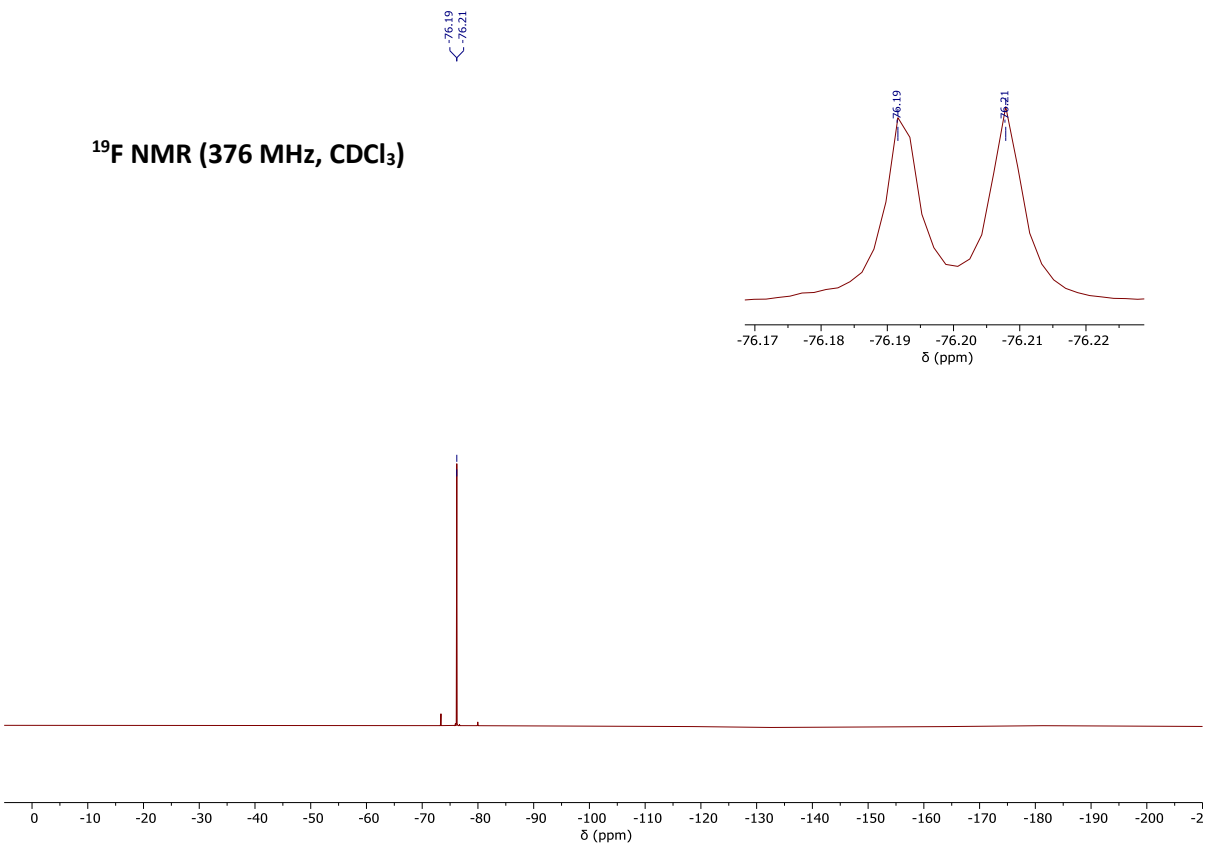


13fa

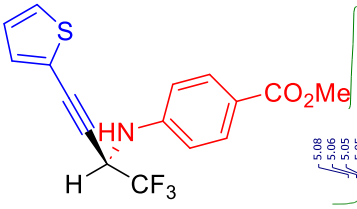
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

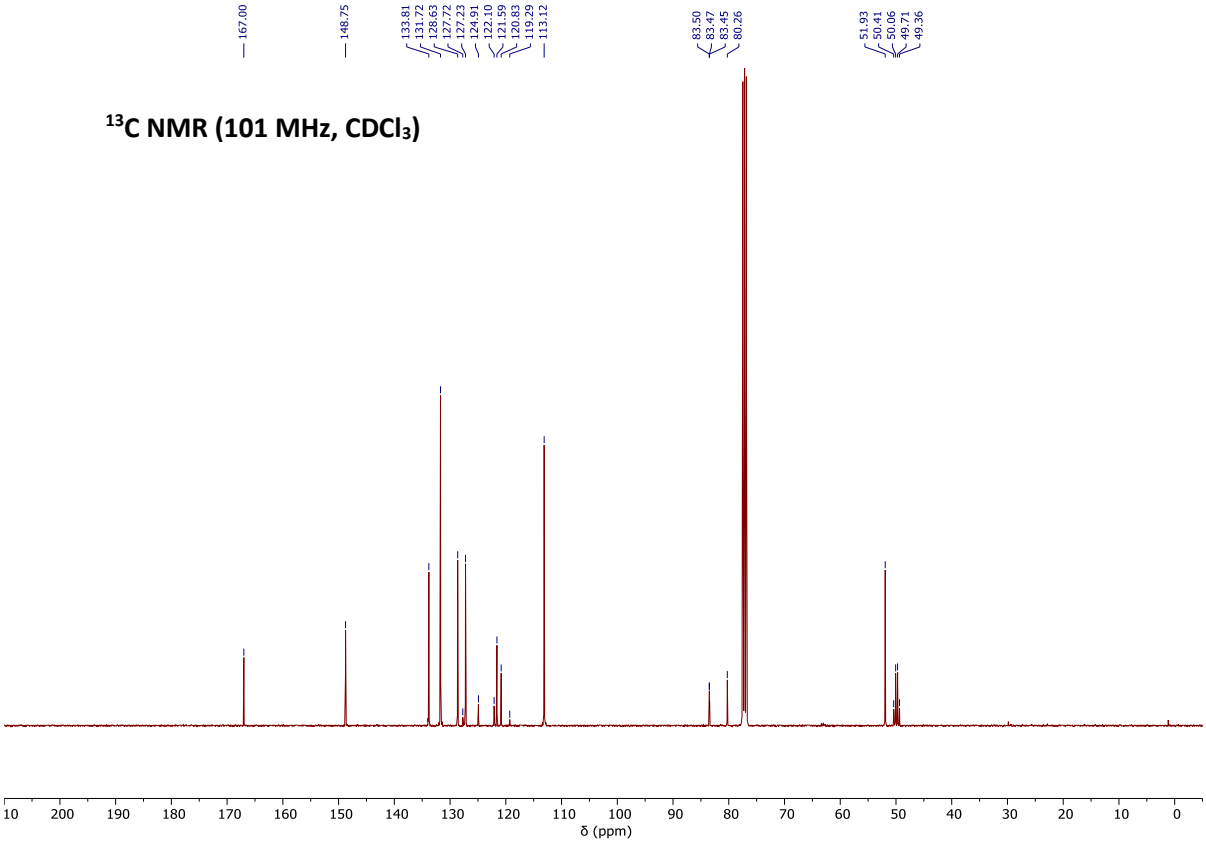


^{1}H NMR (400 MHz, $CDCl_3$)

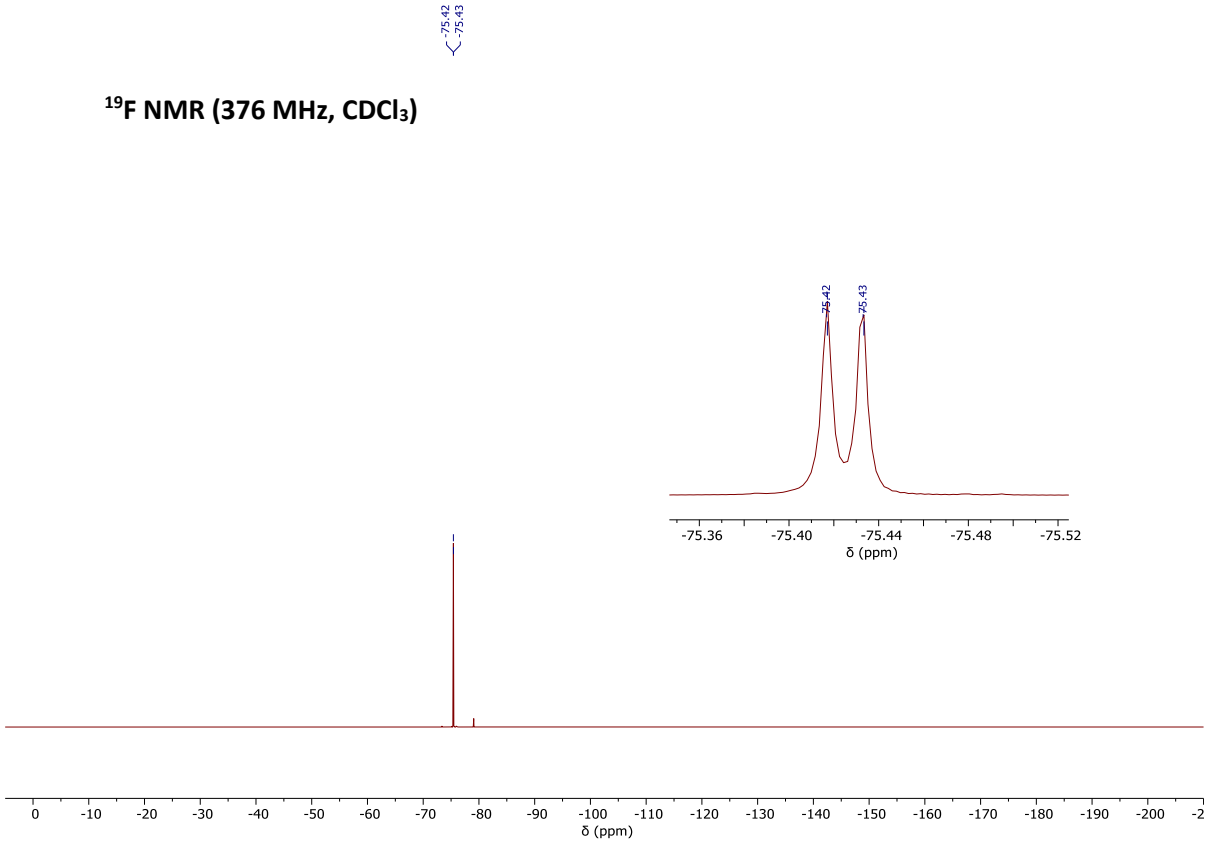


13ga

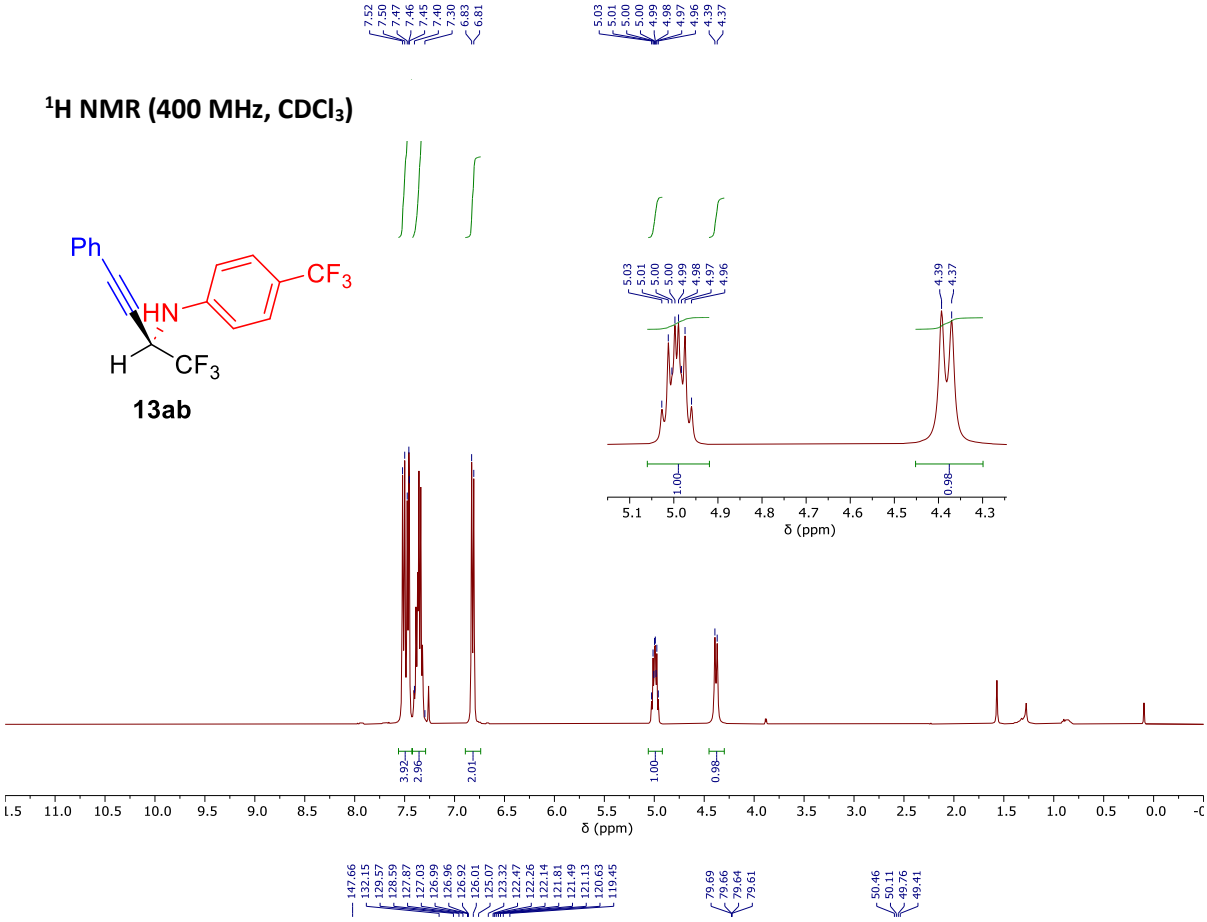
^{13}C NMR (101 MHz, $CDCl_3$)



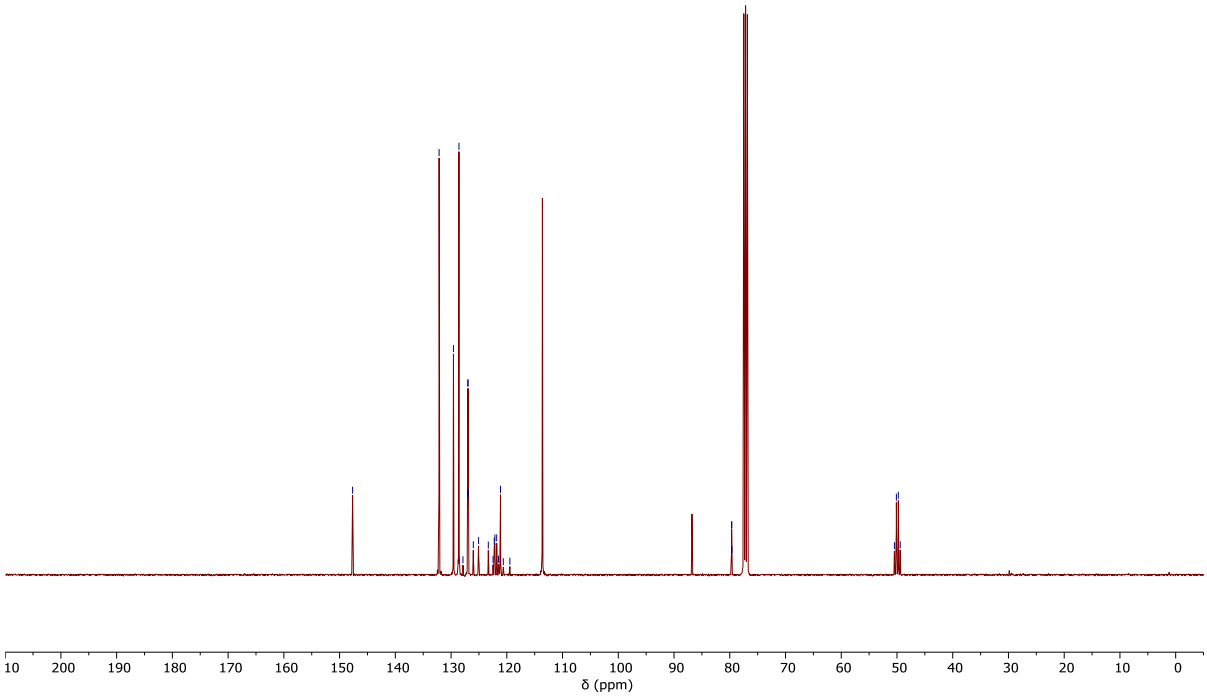
^{19}F NMR (376 MHz, $CDCl_3$)



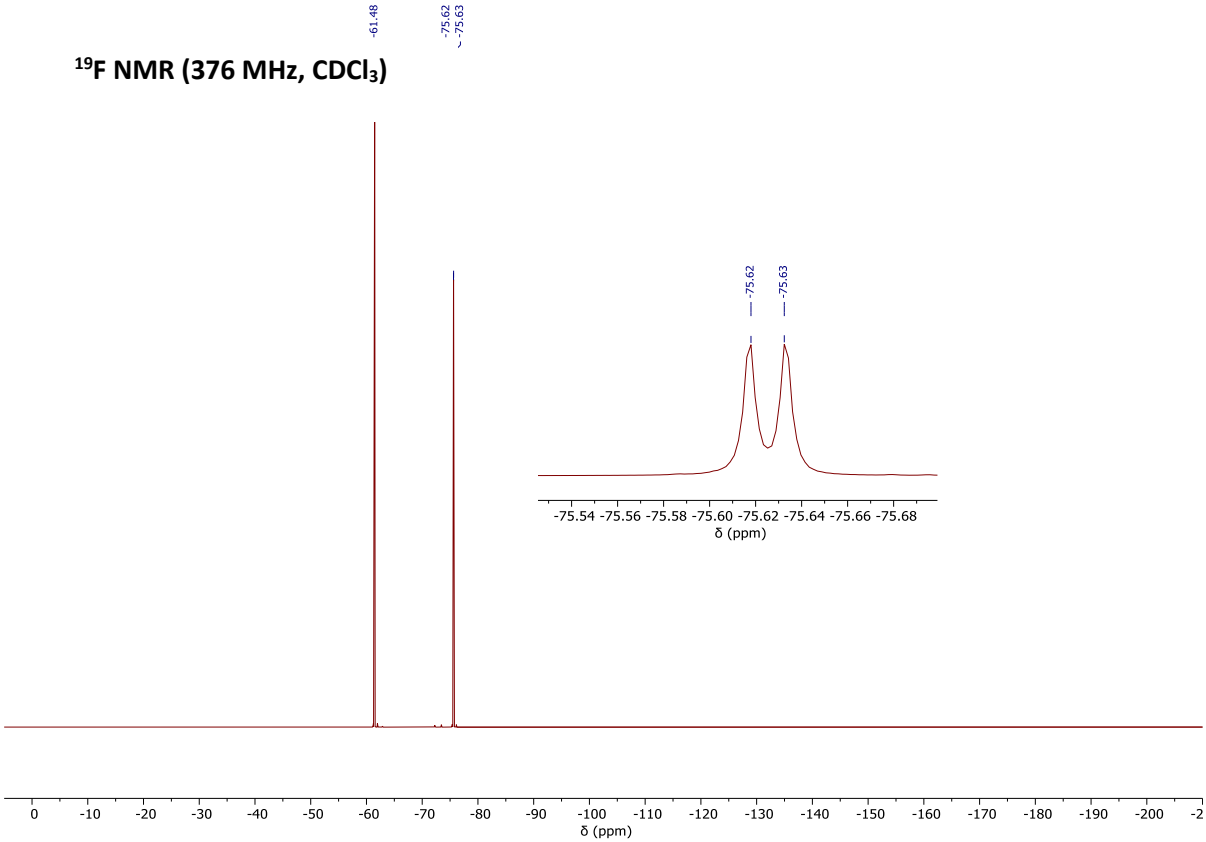
^{1}H NMR (400 MHz, $CDCl_3$)

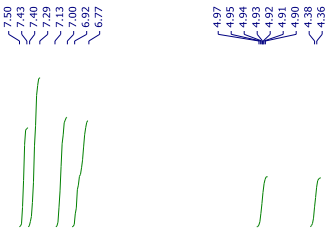


^{13}C NMR (101 MHz, $CDCl_3$)

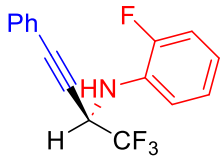


^{19}F NMR (376 MHz, $CDCl_3$)

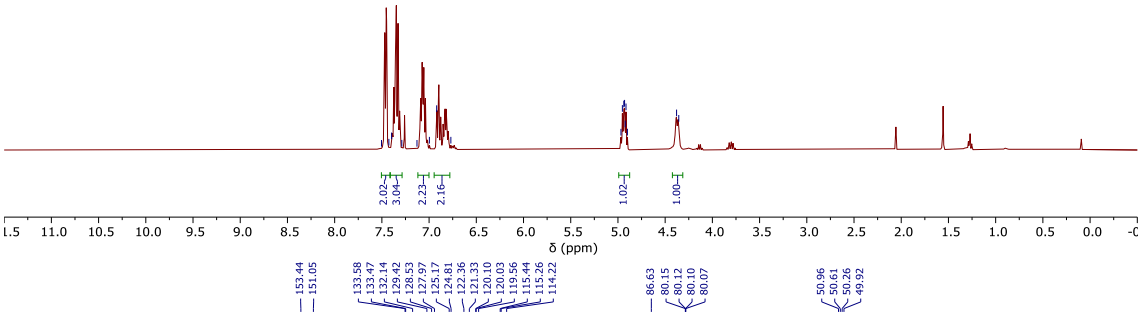




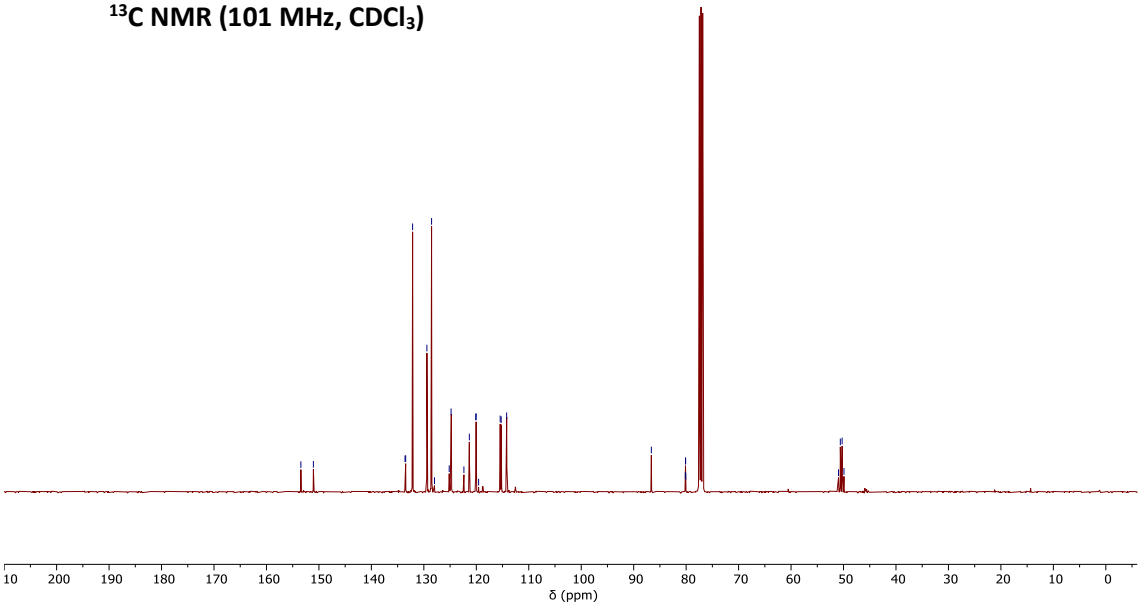
^{1}H NMR (400 MHz, $CDCl_3$)



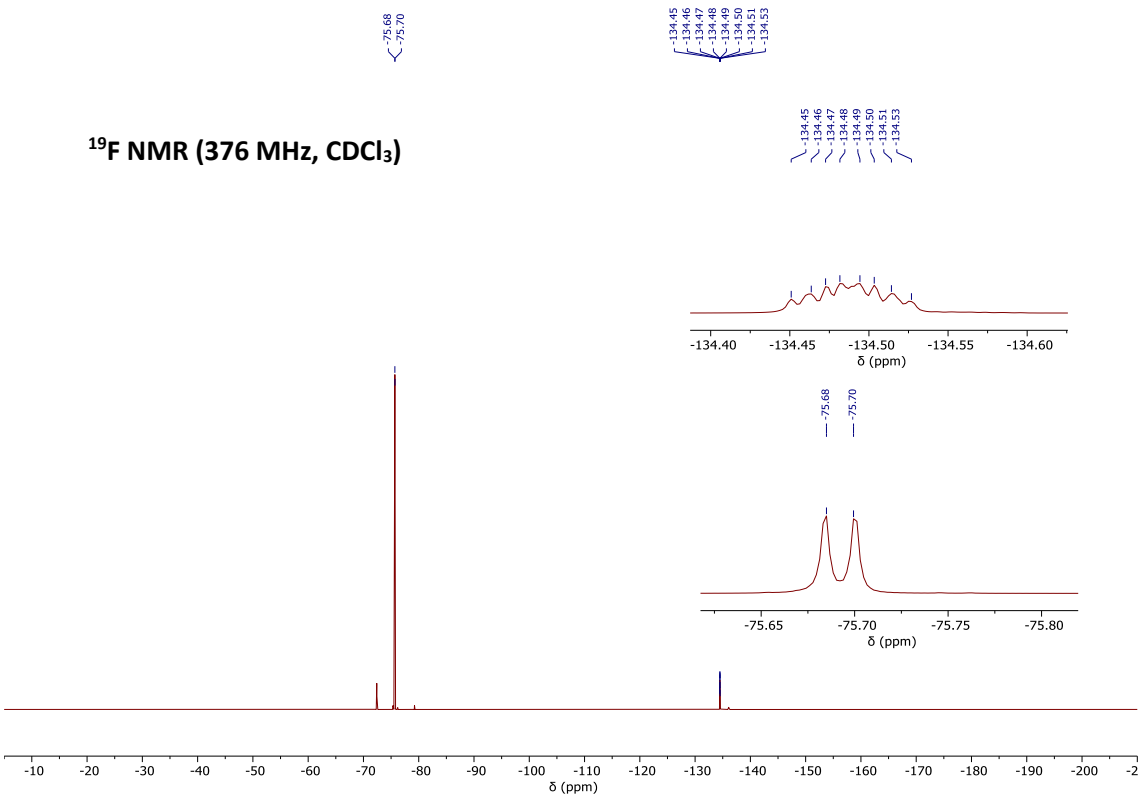
13ac

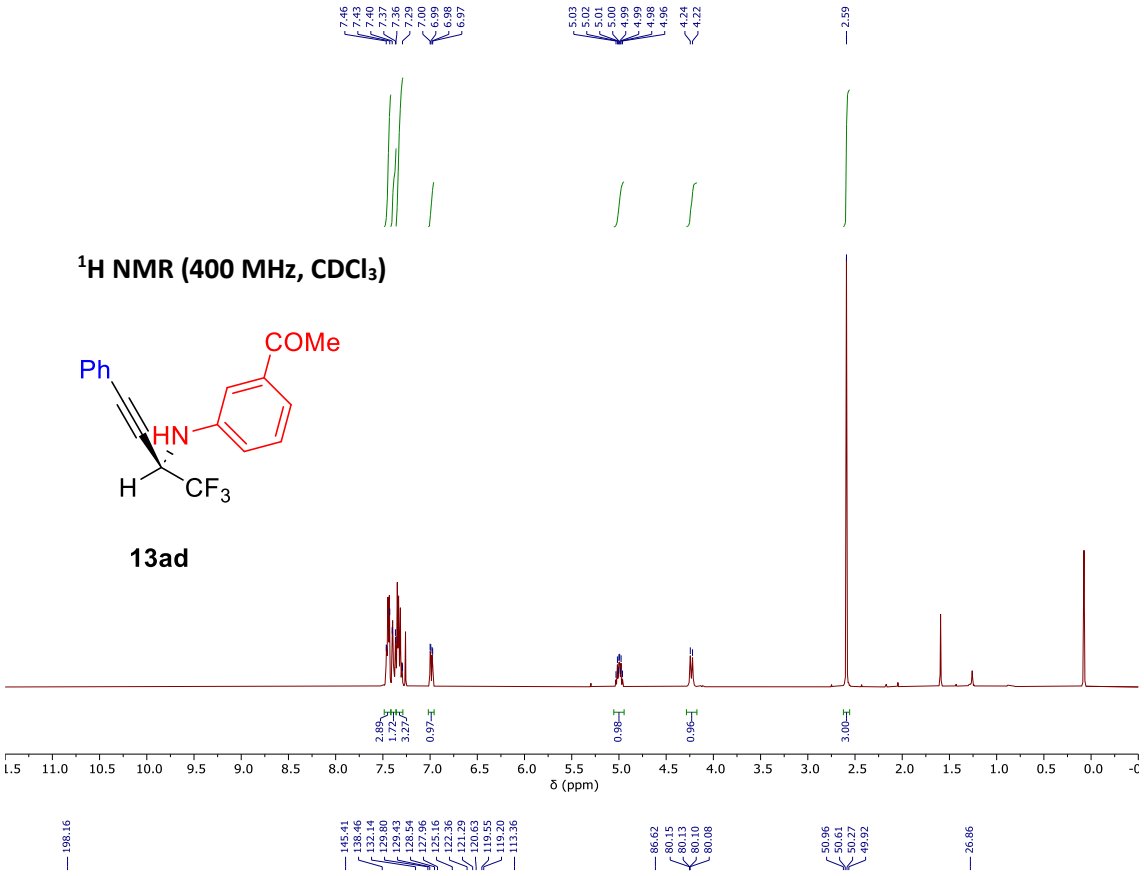


^{13}C NMR (101 MHz, $CDCl_3$)



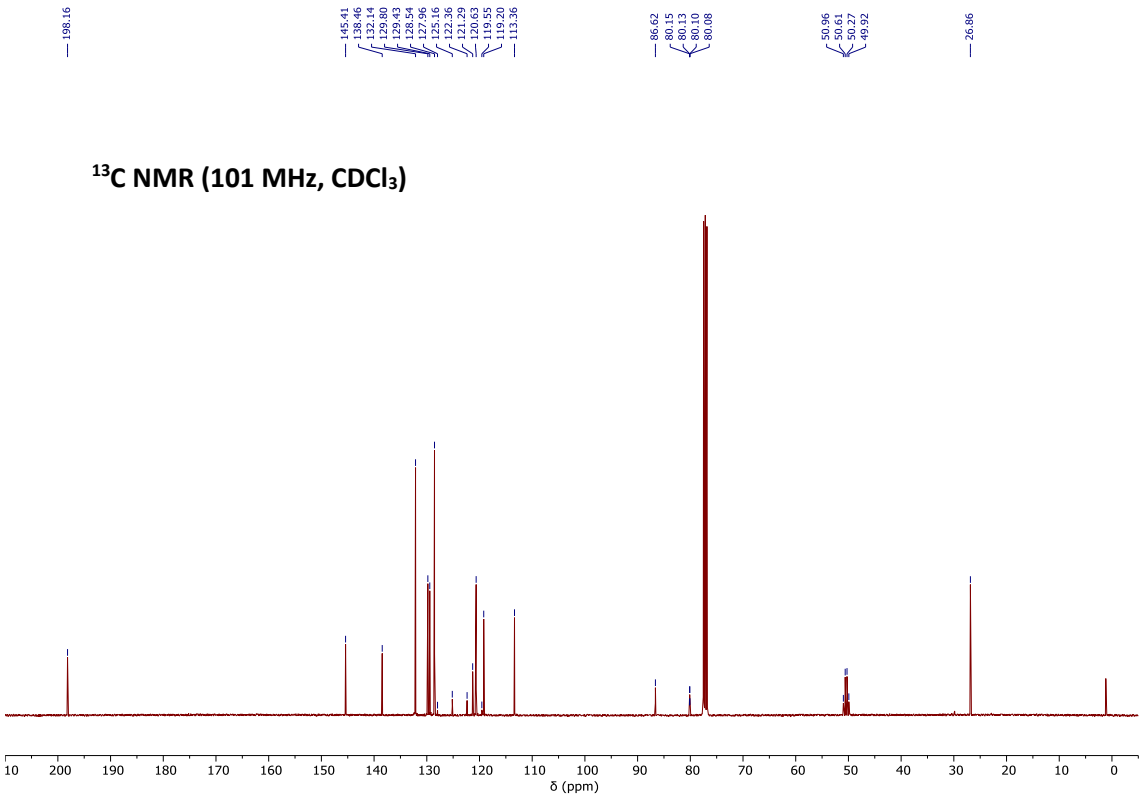
^{19}F NMR (376 MHz, $CDCl_3$)





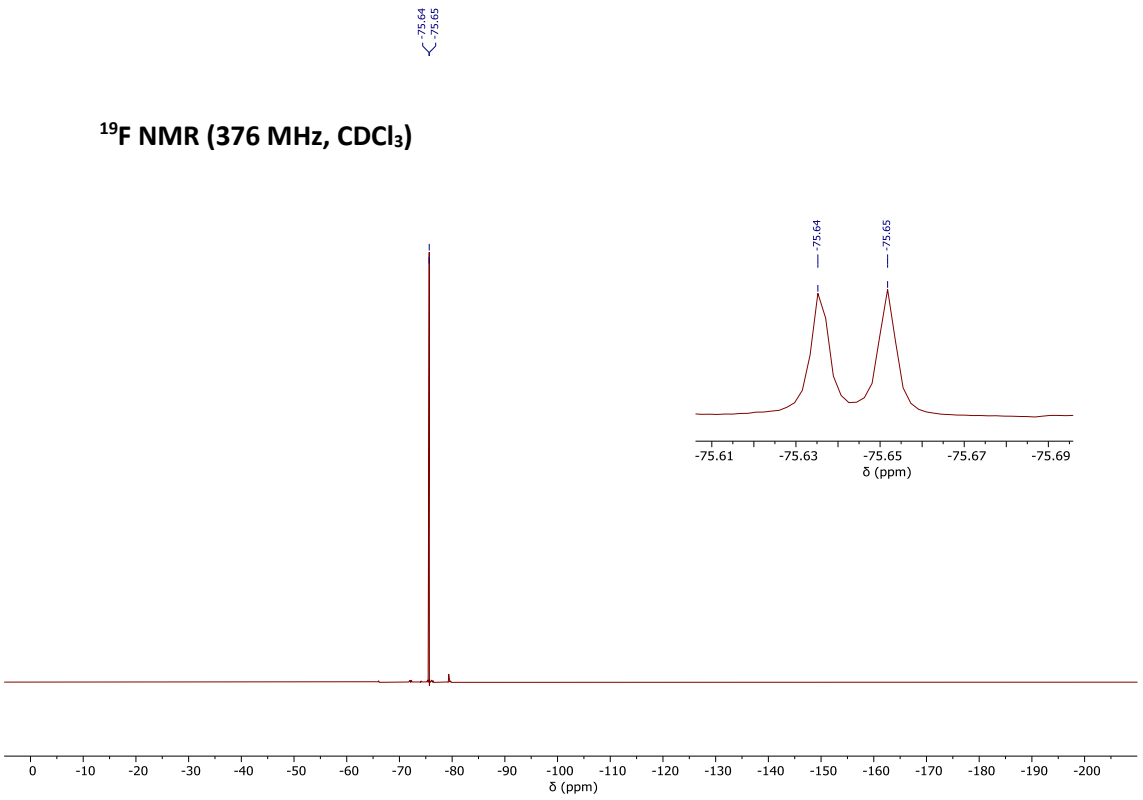
^{1}H NMR (400 MHz, $CDCl_3$)

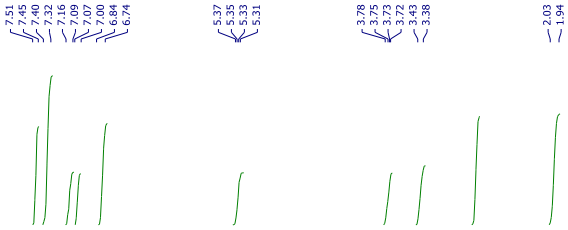
13ad



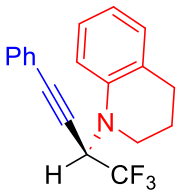
^{13}C NMR (101 MHz, $CDCl_3$)

^{19}F NMR (376 MHz, $CDCl_3$)

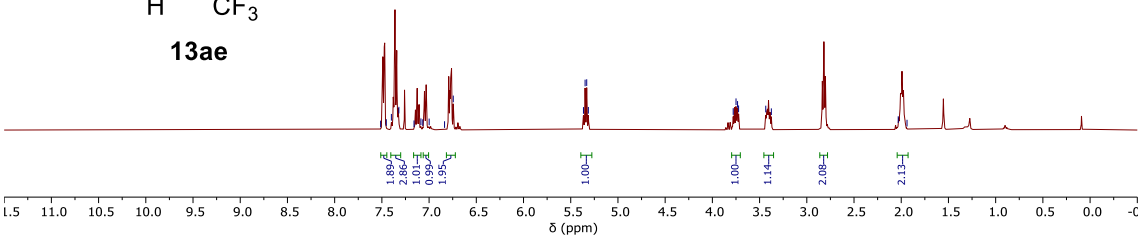




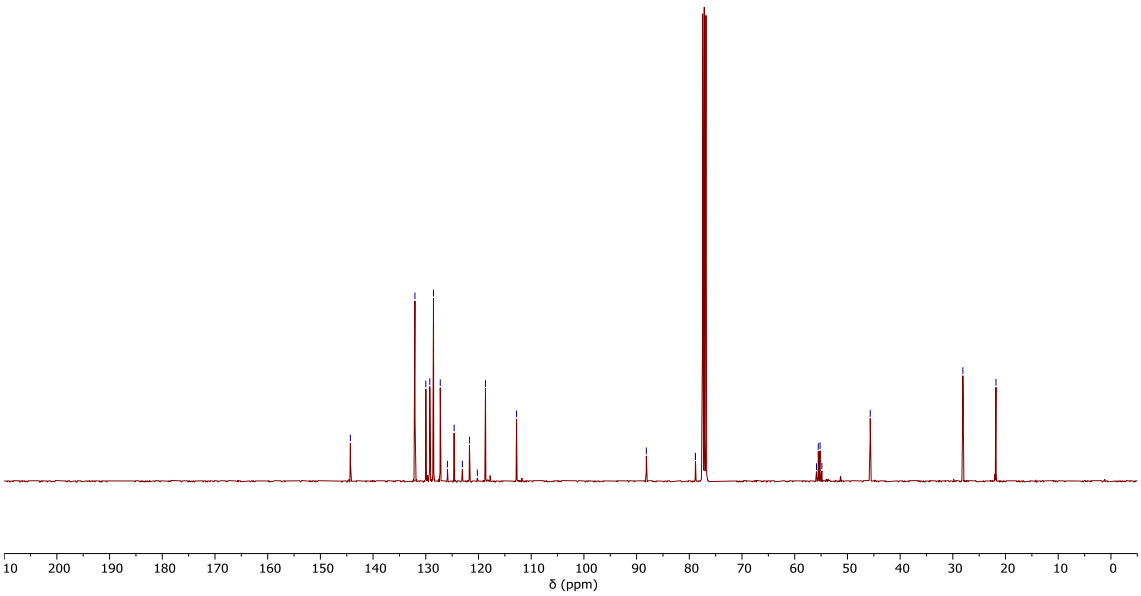
^{1}H NMR (400 MHz, $CDCl_3$)

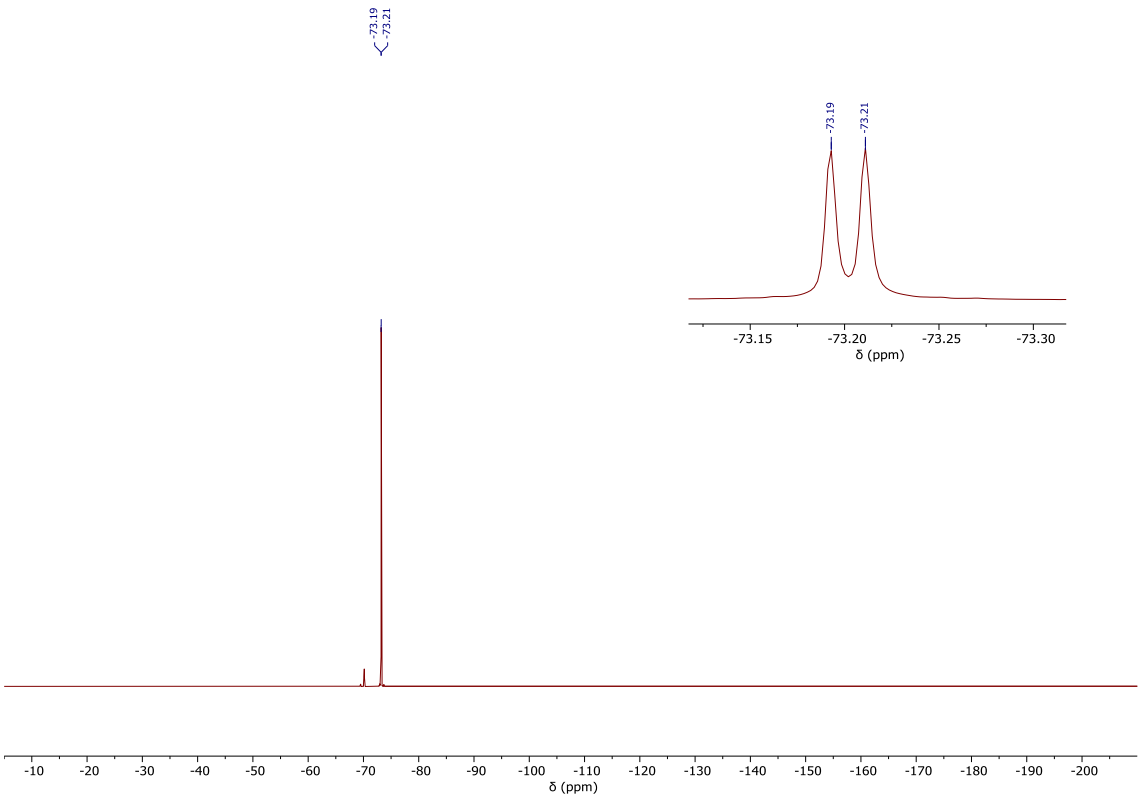


13ae

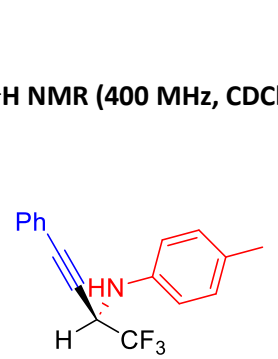


^{13}C NMR (101 MHz, $CDCl_3$)



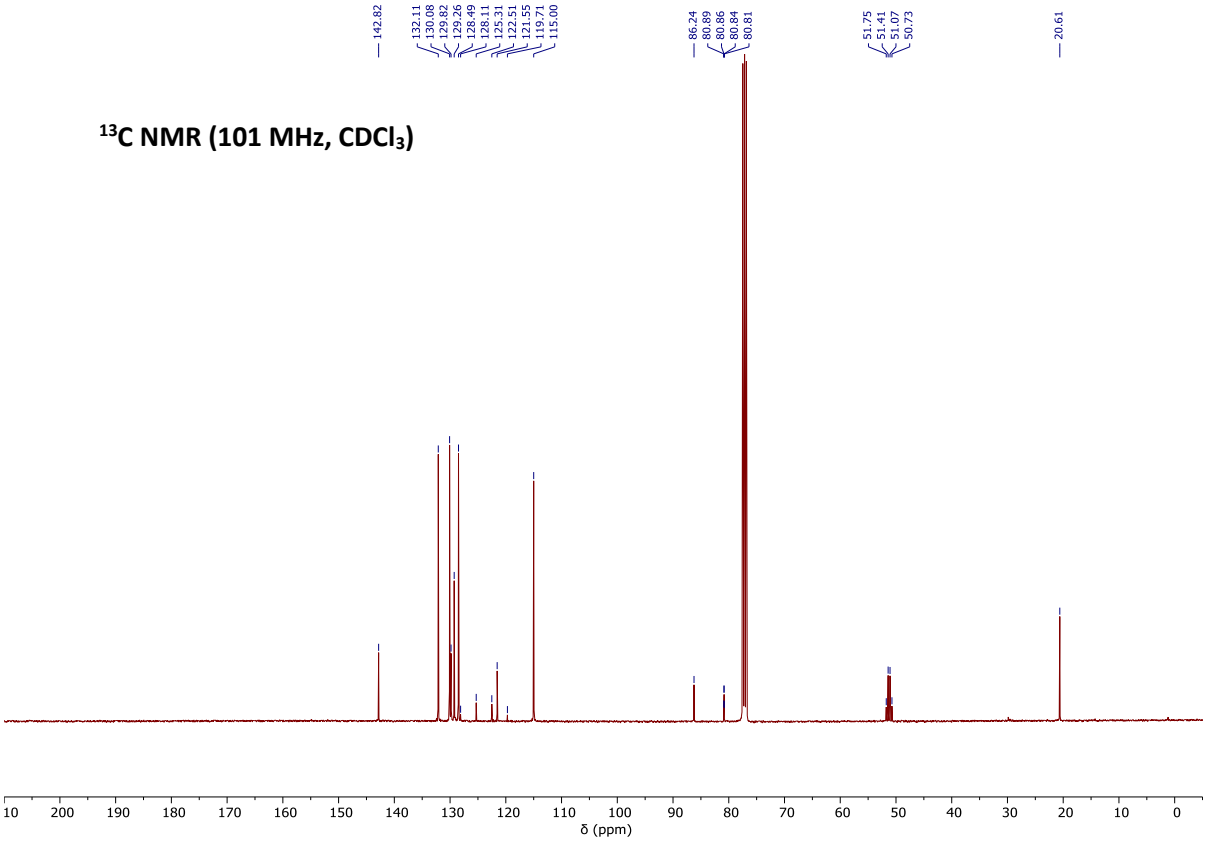

-73.19
-73.21
-73.19
-73.21
-73.15
-73.20
-73.25
-73.30
δ (ppm)
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
δ (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

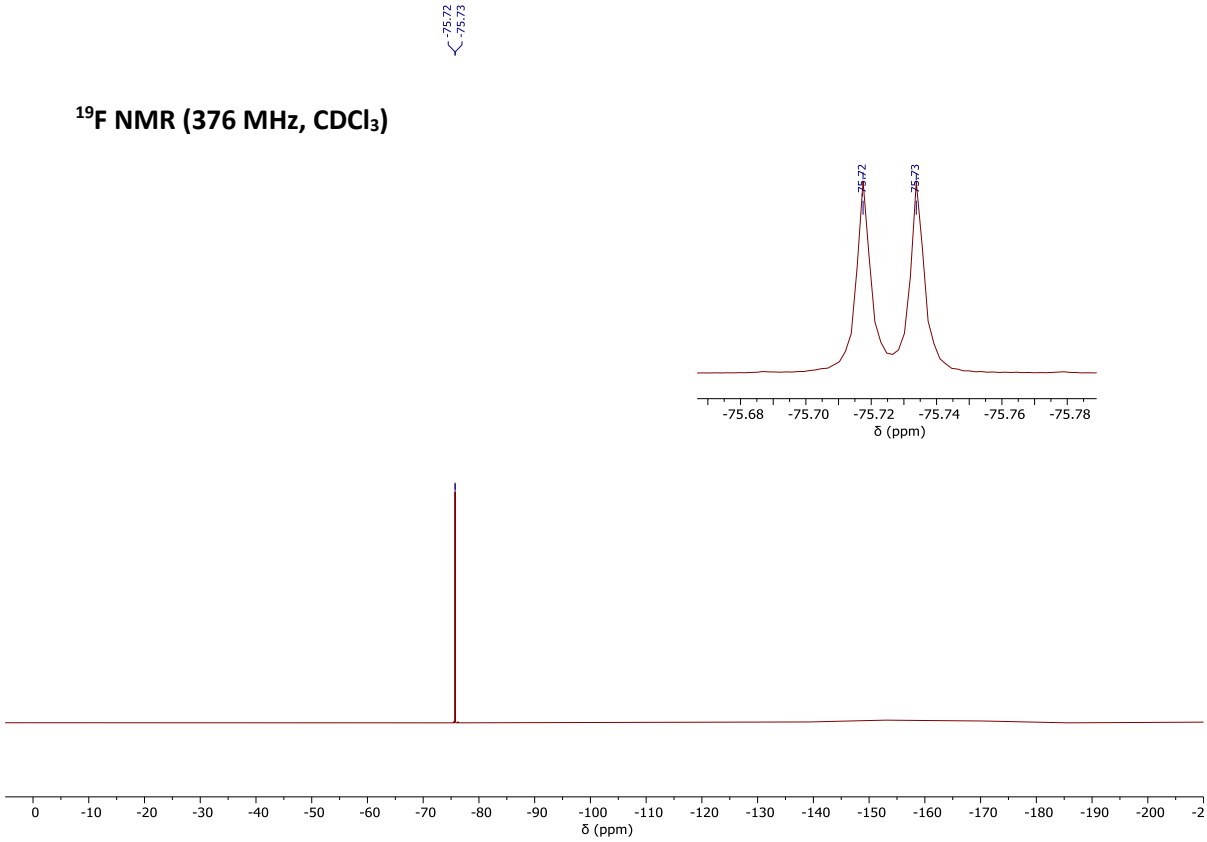


13af

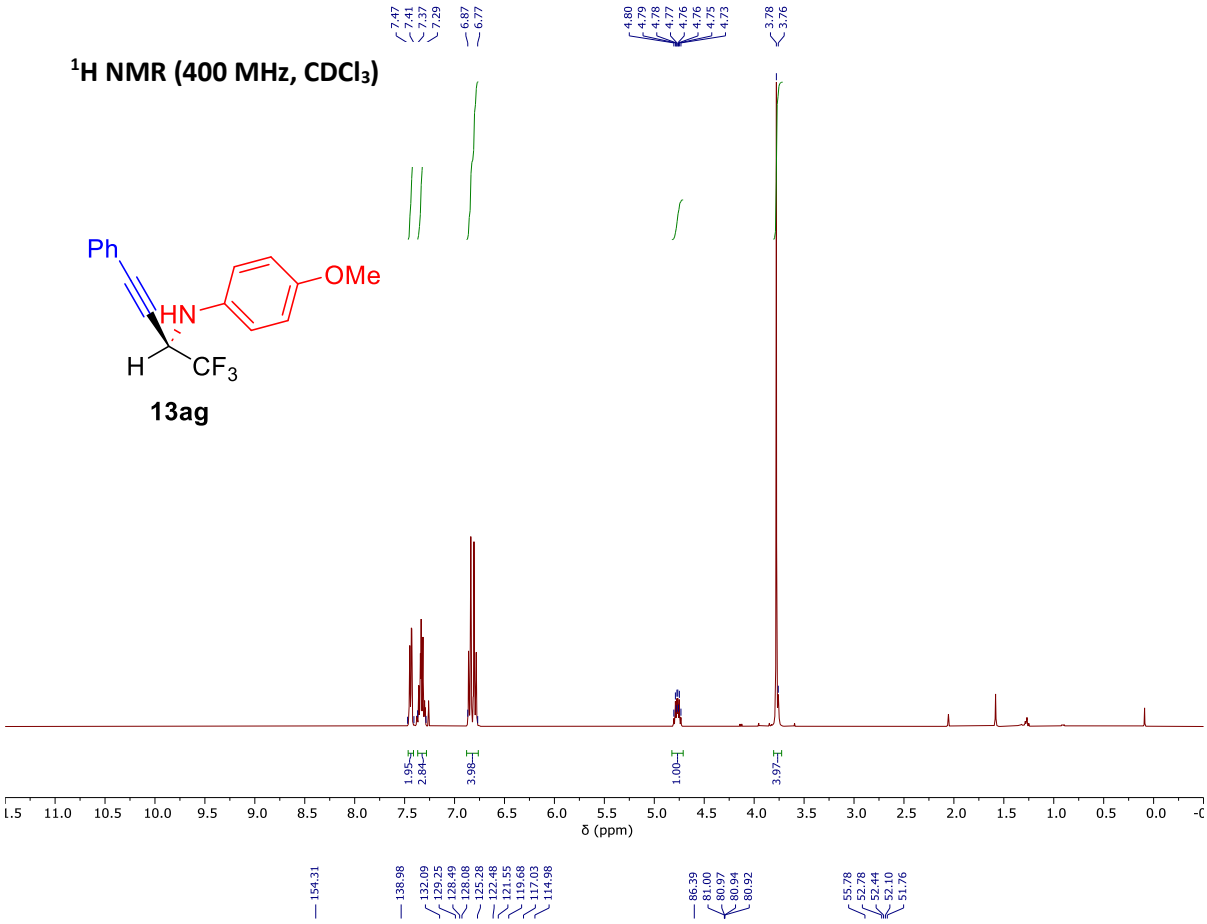
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

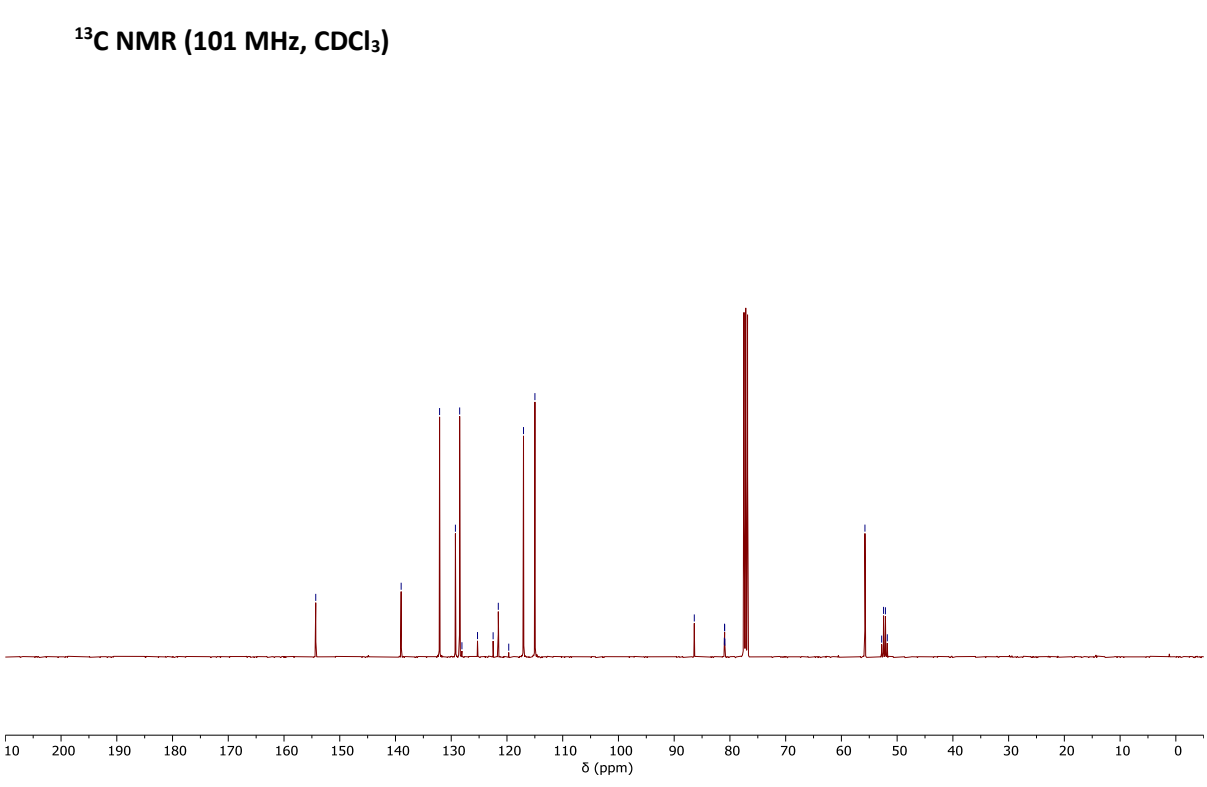


^{1}H NMR (400 MHz, $CDCl_3$)

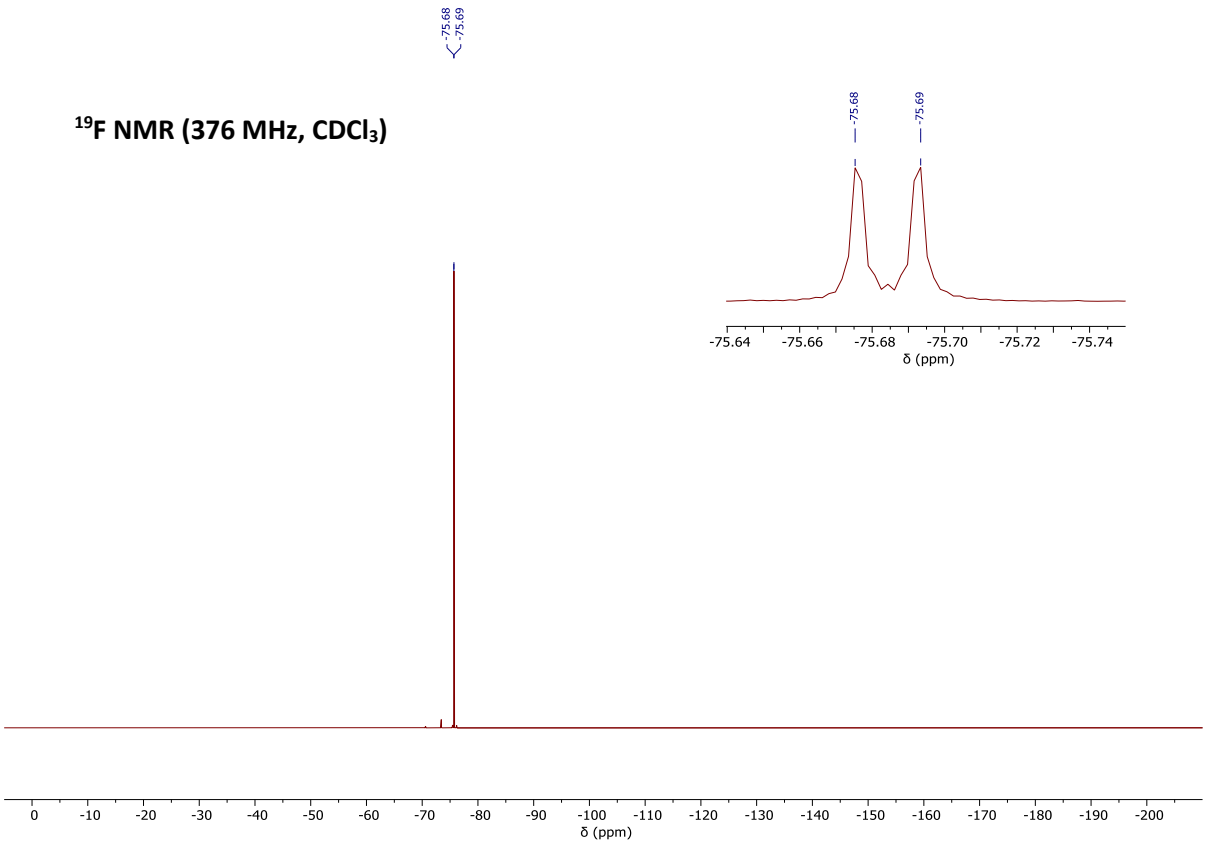


13ag

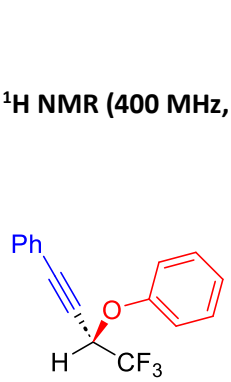
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

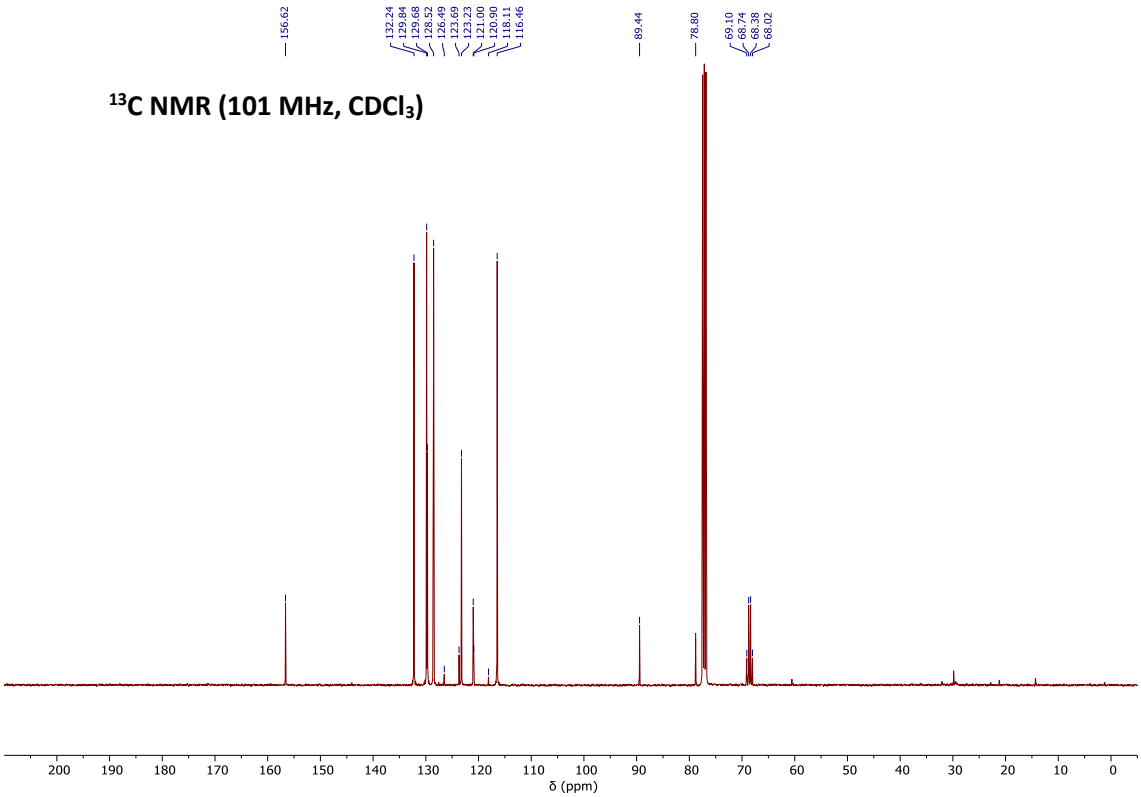


^{1}H NMR (400 MHz, $CDCl_3$)

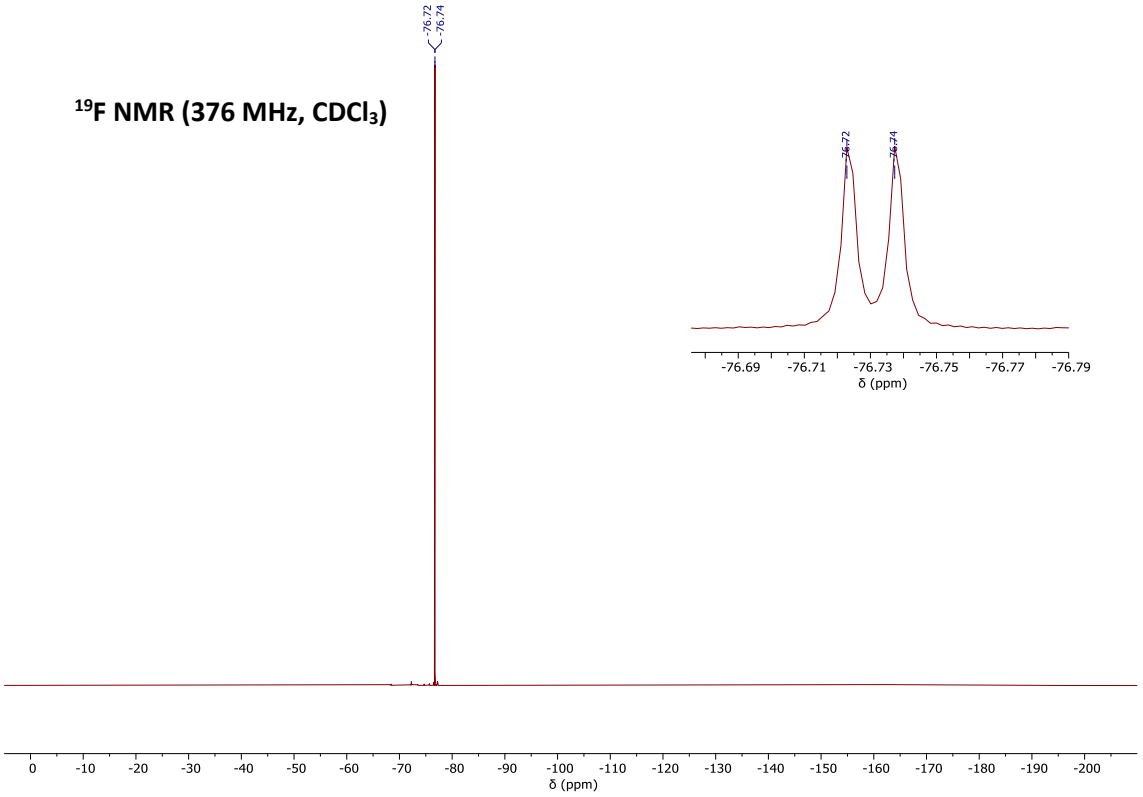


15a

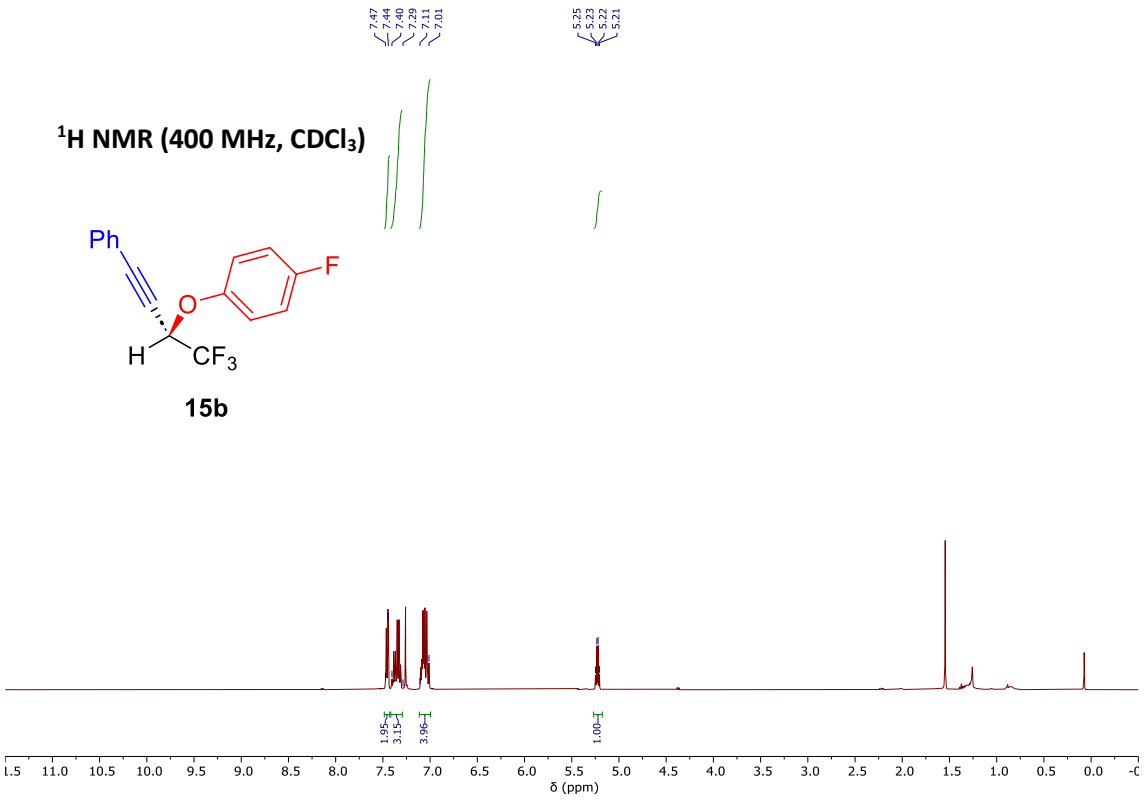
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

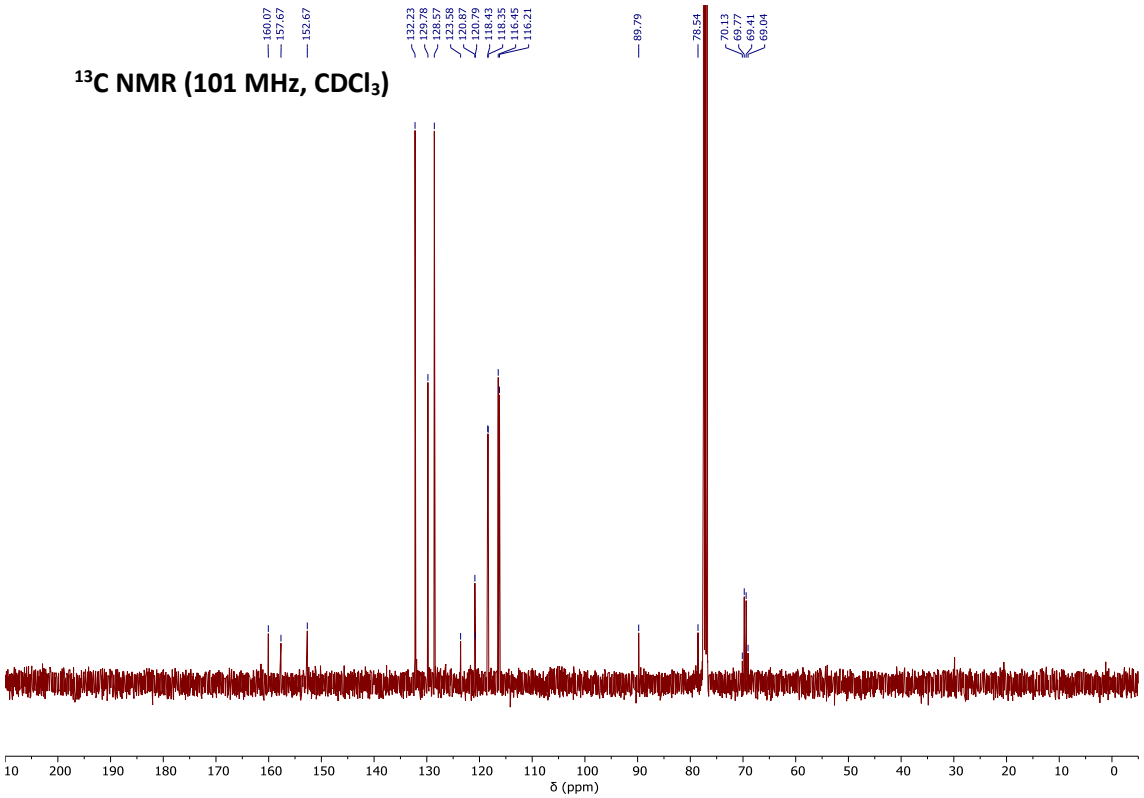


^{1}H NMR (400 MHz, $CDCl_3$)

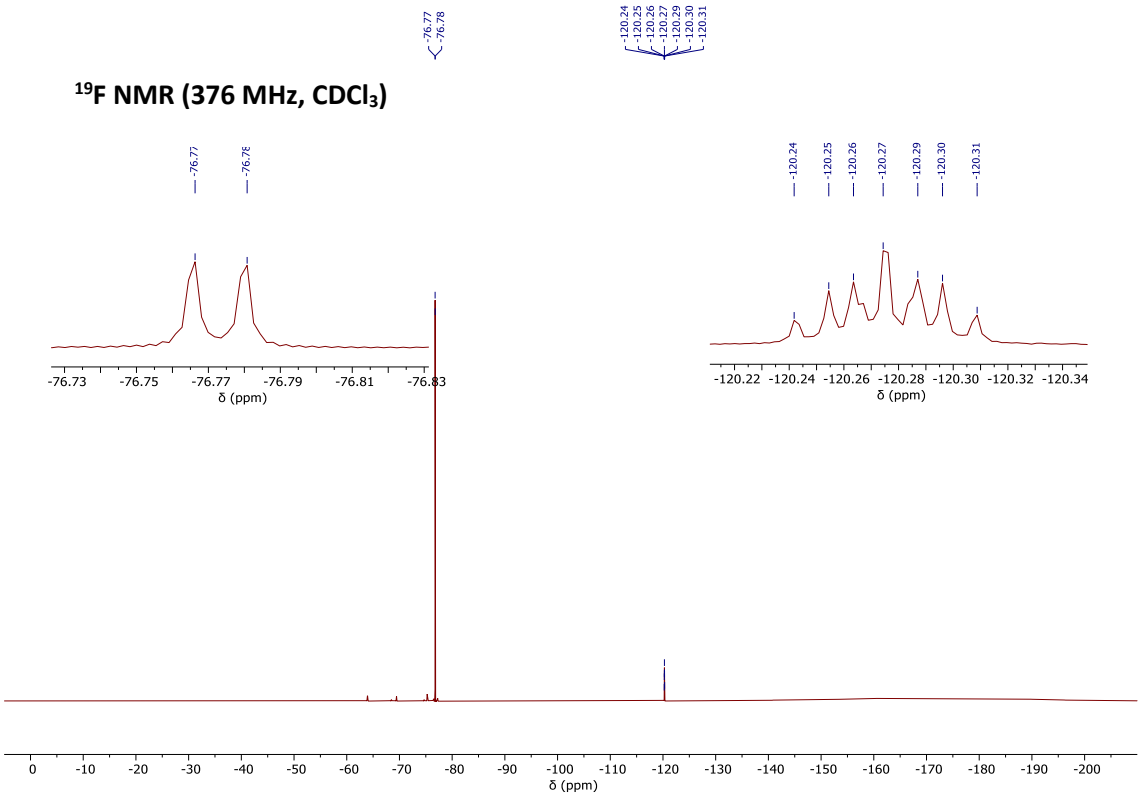


15b

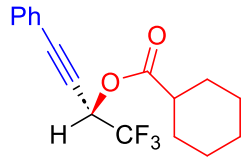
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

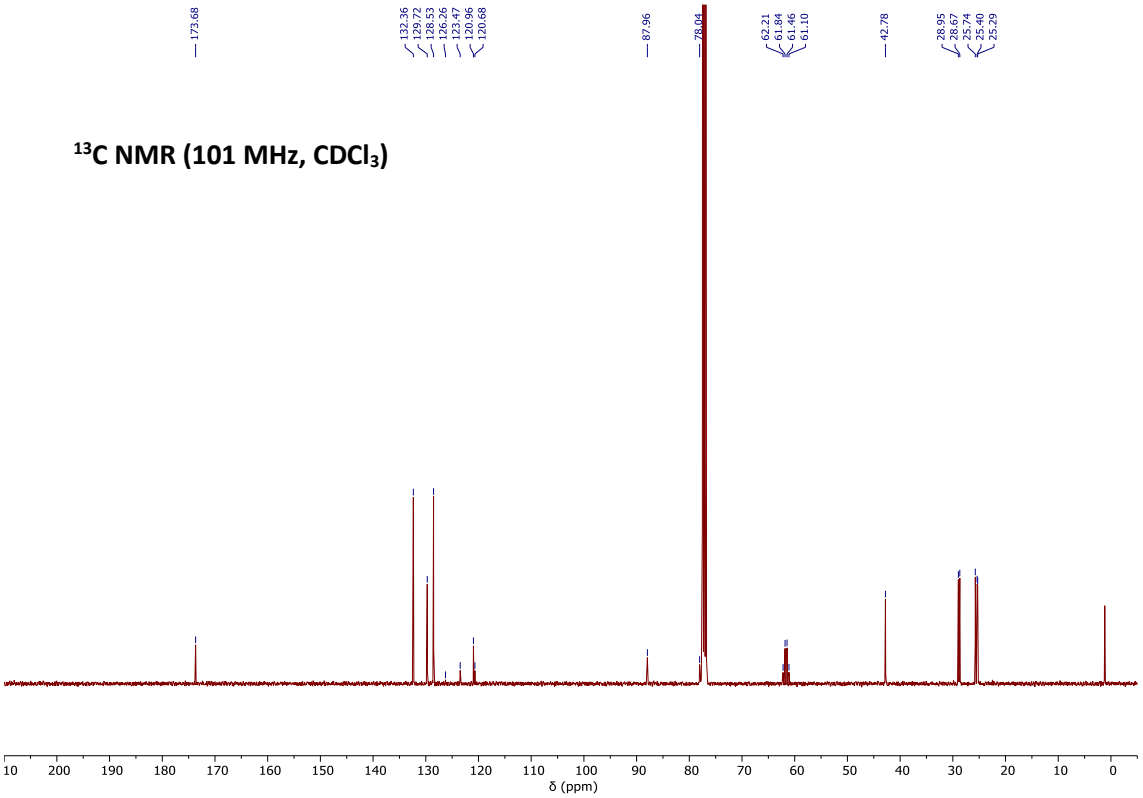


^{1}H NMR (400 MHz, $CDCl_3$)

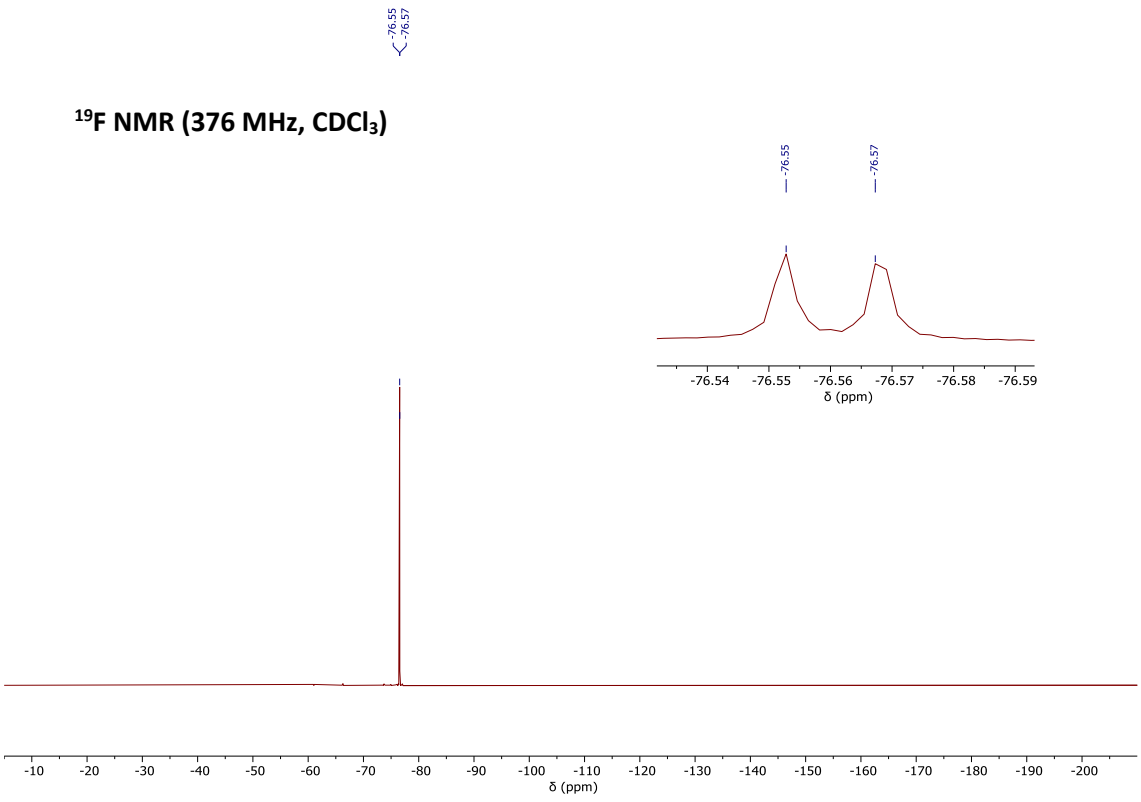


17

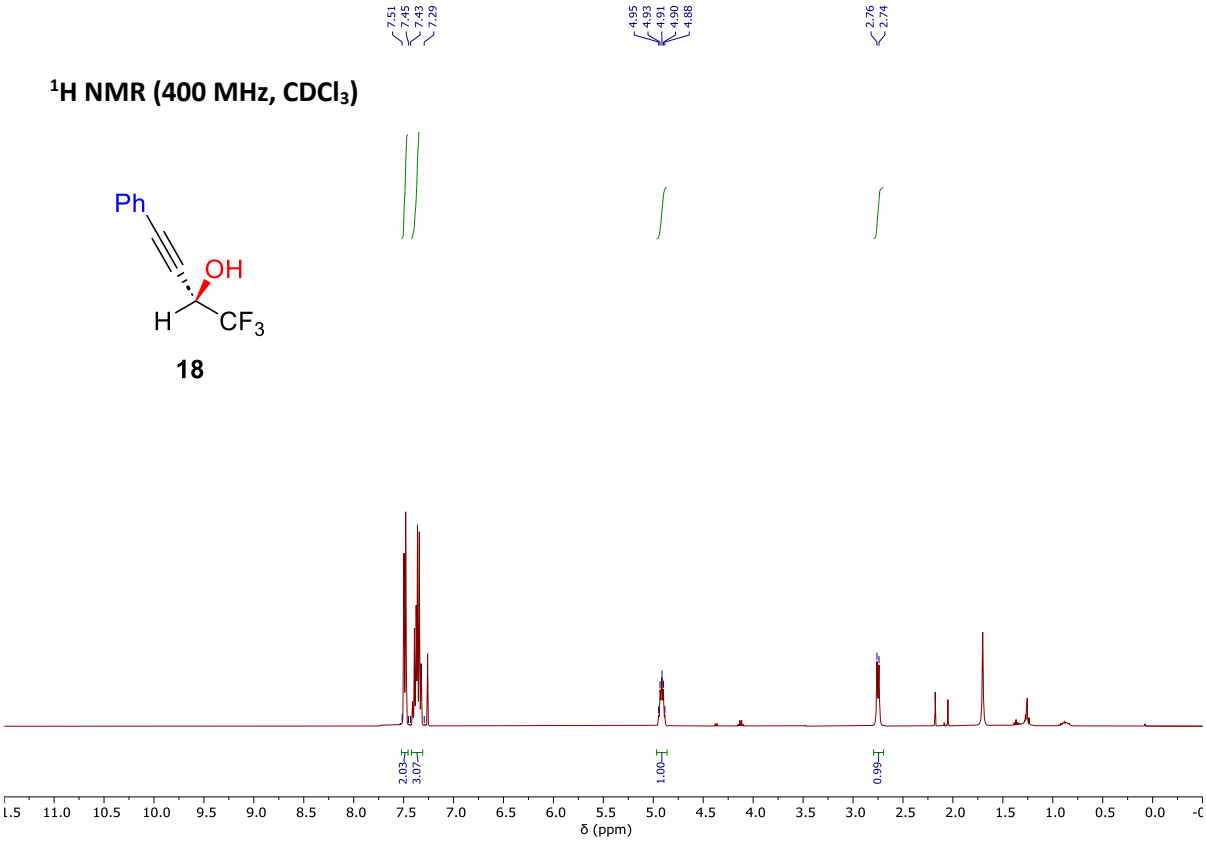
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

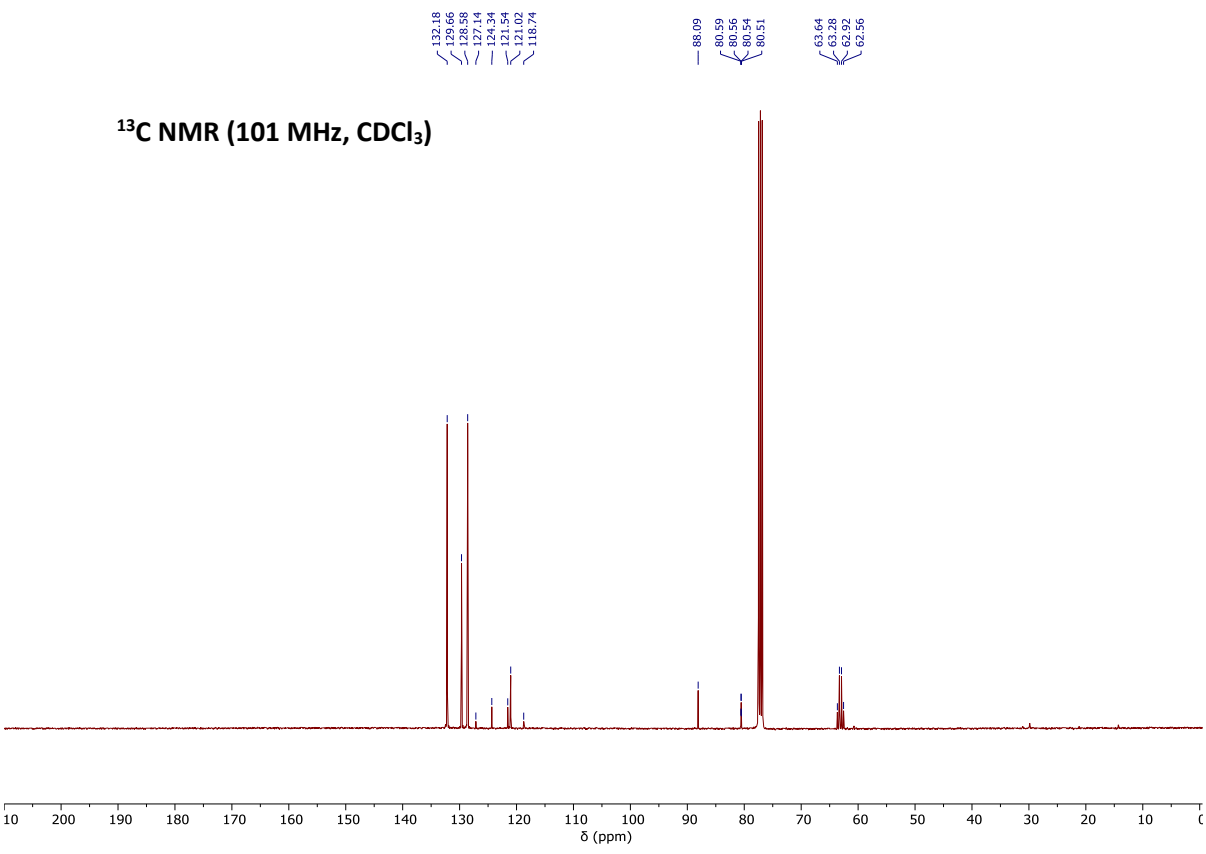


^{1}H NMR (400 MHz, $CDCl_3$)

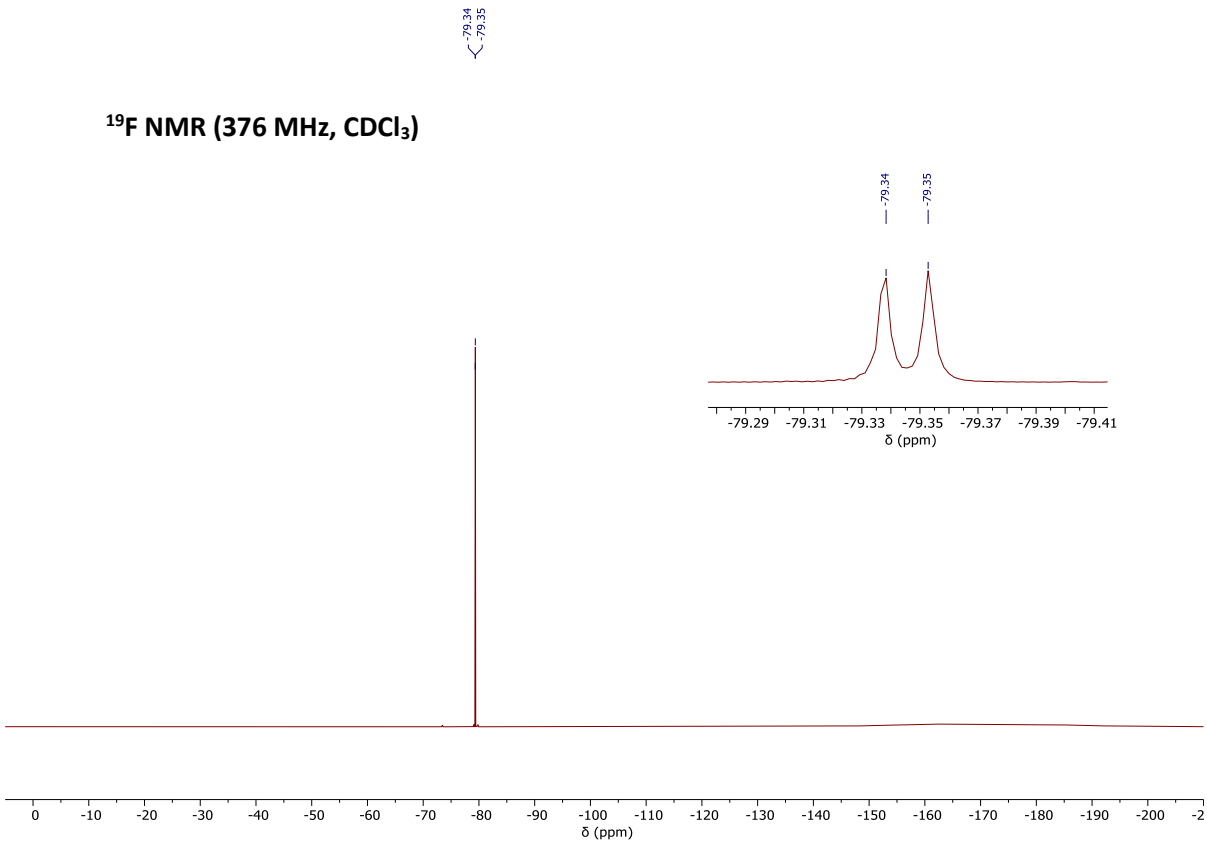


18

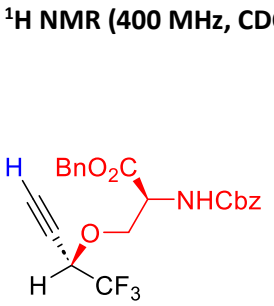
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)

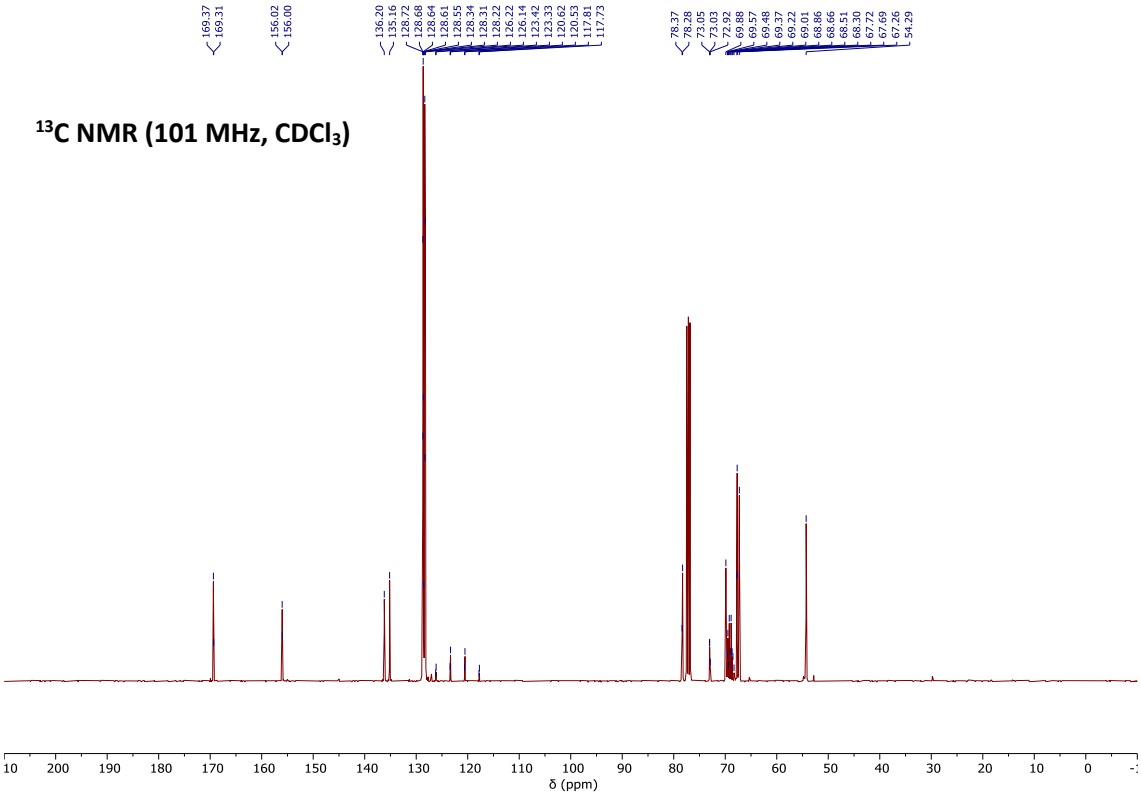


^{1}H NMR (400 MHz, $CDCl_3$)

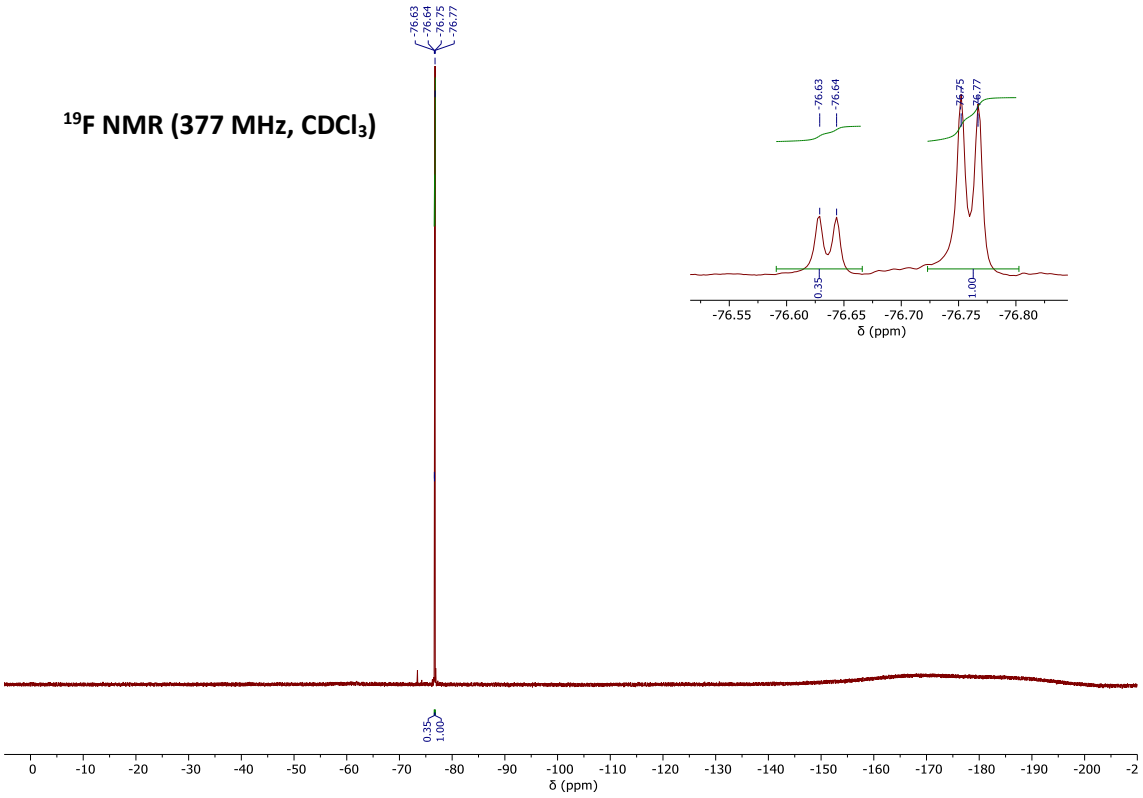


20

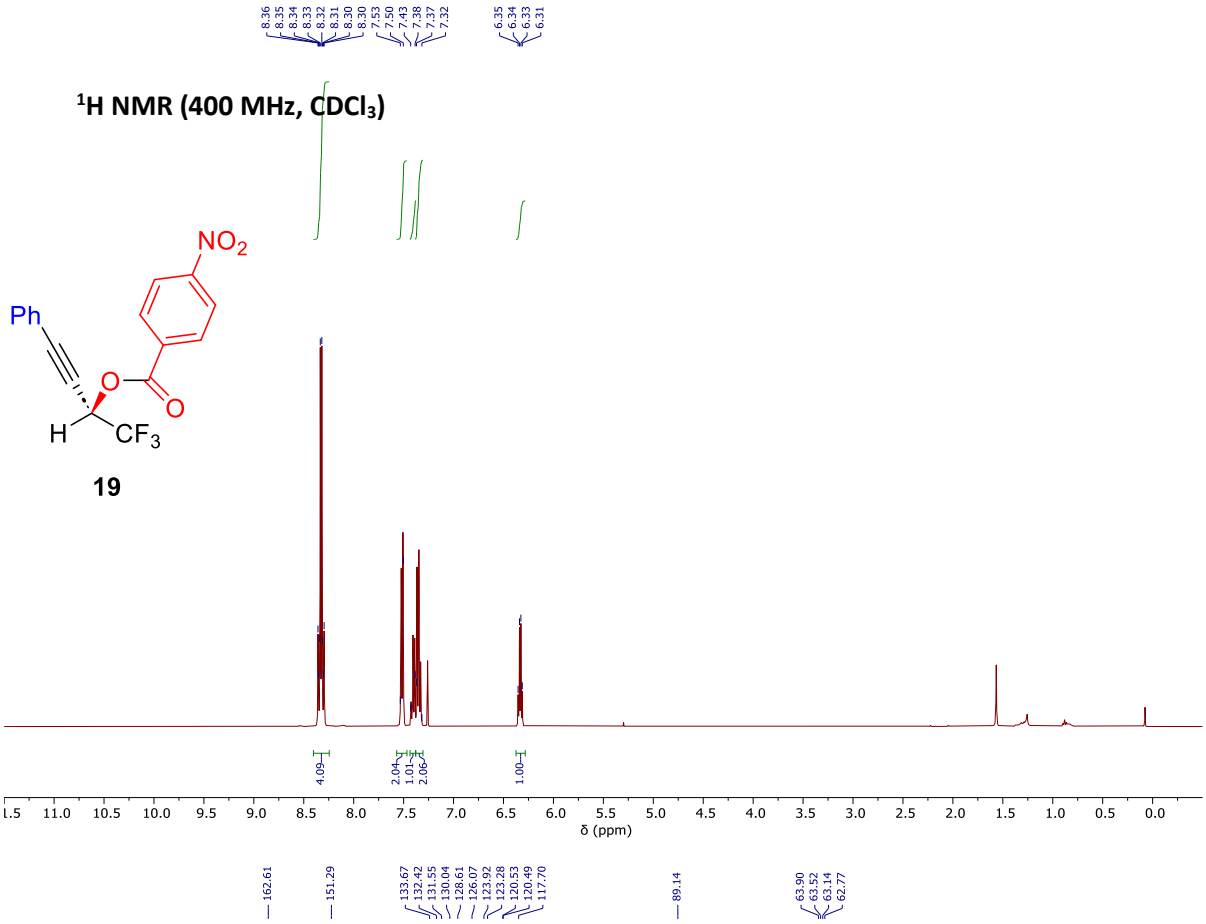
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

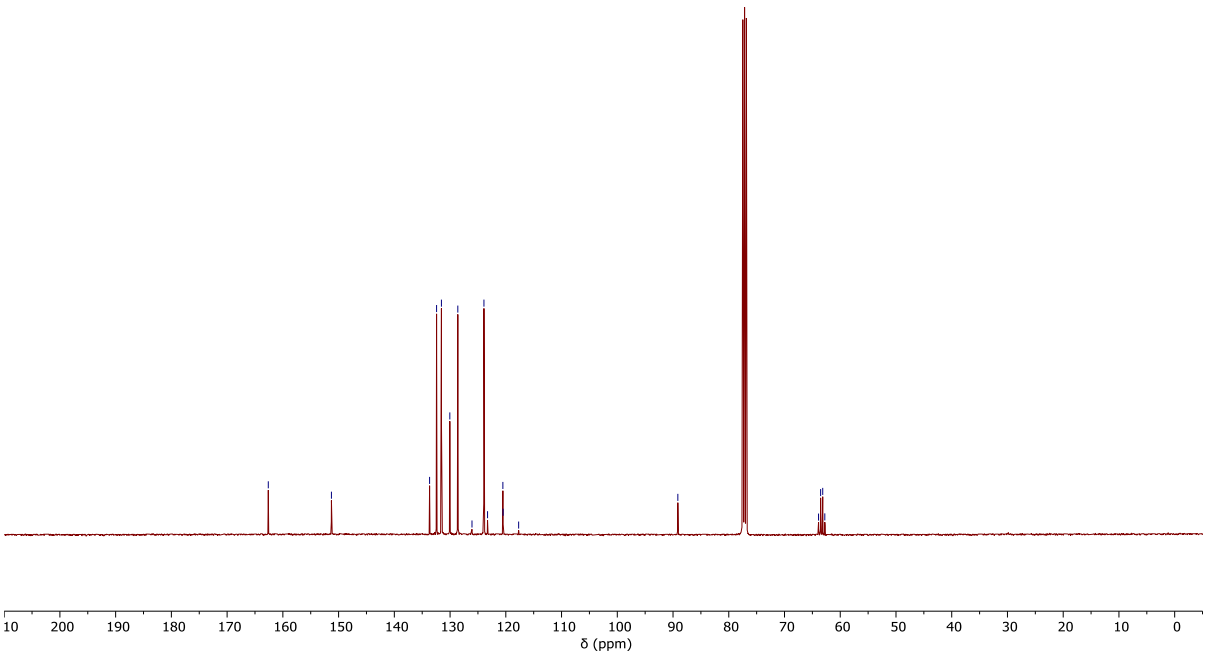


^{1}H NMR (400 MHz, $CDCl_3$)

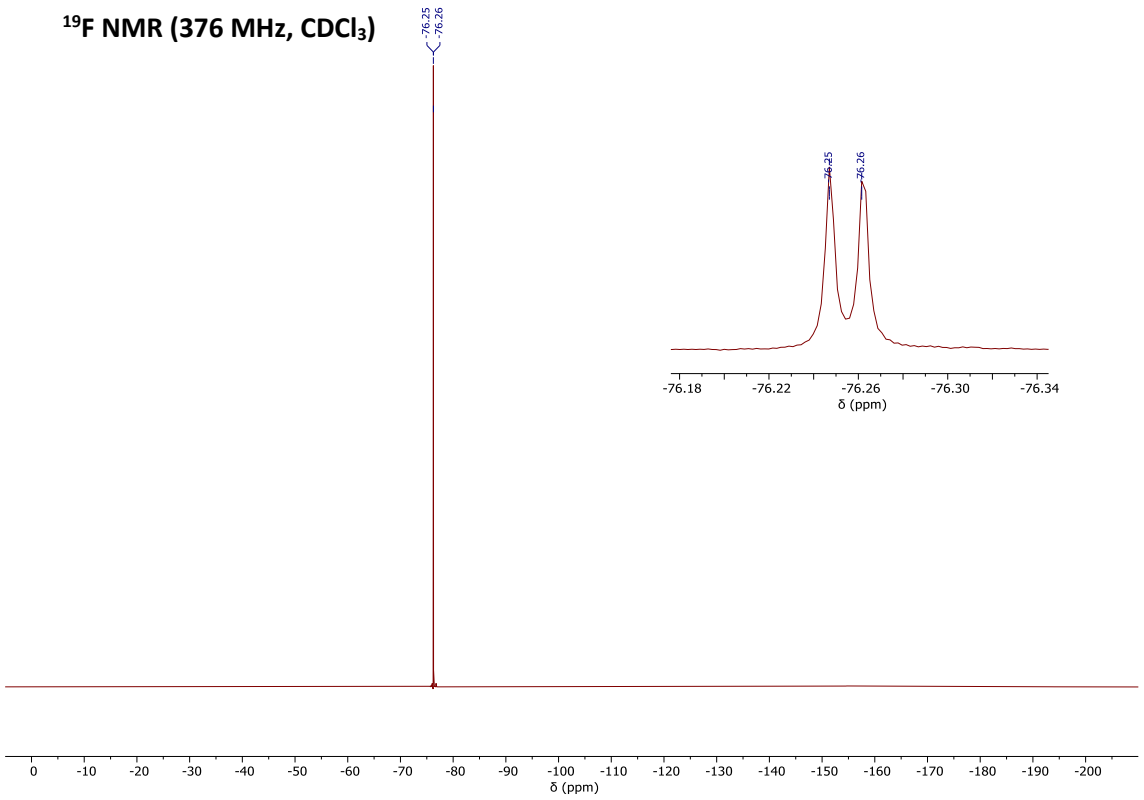


19

^{13}C NMR (101 MHz, $CDCl_3$)



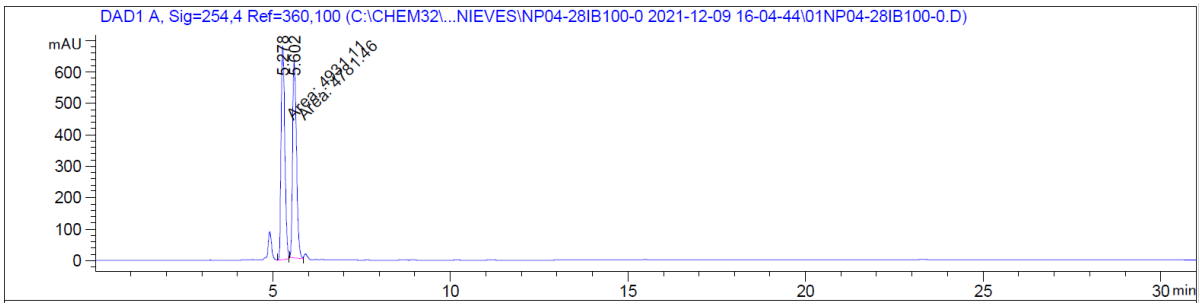
^{19}F NMR (376 MHz, $CDCl_3$)



13. Chiral HPLC traces.

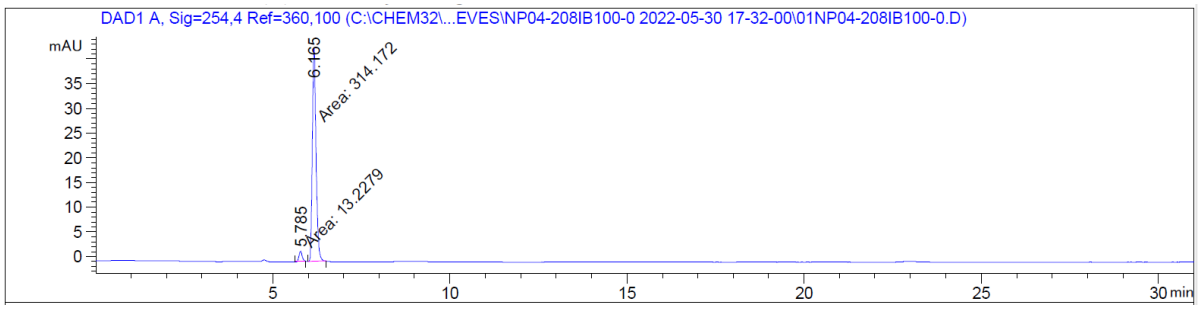
Chiral HPLC traces for compound 4aa.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.278	MM	0.1206	4931.11426	681.46576	50.7704
2	5.602	MM	0.1283	4781.46045	621.32062	49.2296
Totals :				9712.57471	1302.78638	

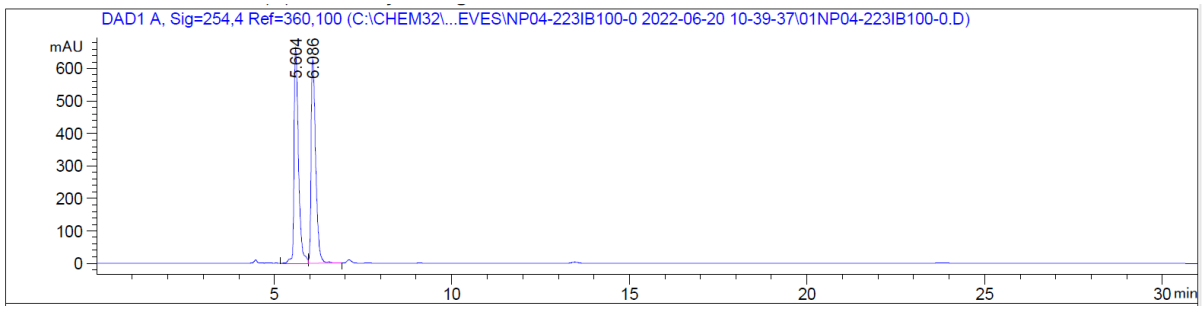


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.785	MM	0.1078	13.22787	2.04507	4.0403
2	6.165	MM	0.1209	314.17172	43.31188	95.9597
Totals :				327.39959	45.35696	

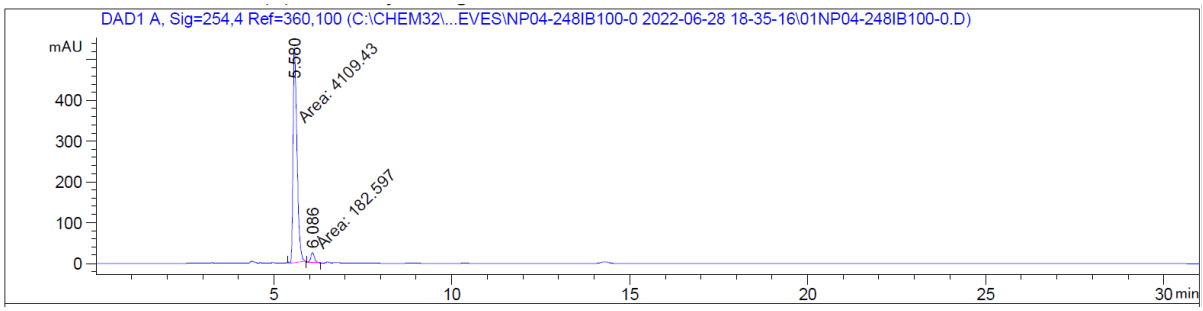
Chiral HPLC traces for compound 4ac.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.604	BV	0.1307	5712.18896	661.55518	50.3754
2	6.086	VV R	0.1362	5627.06055	626.94861	49.6246
Totals :				1.13392e4	1288.50378	

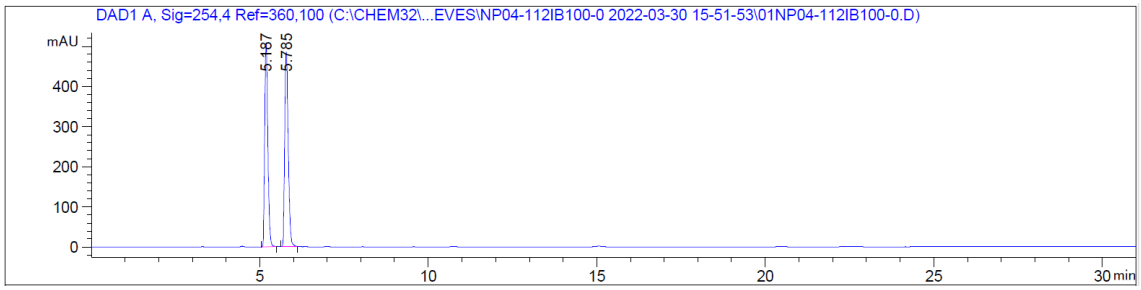


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.580	MM	0.1299	4109.42627	527.07288	95.7457
2	6.086	MM	0.1233	182.59717	24.68895	4.2543
Totals :				4292.02344	551.76183	

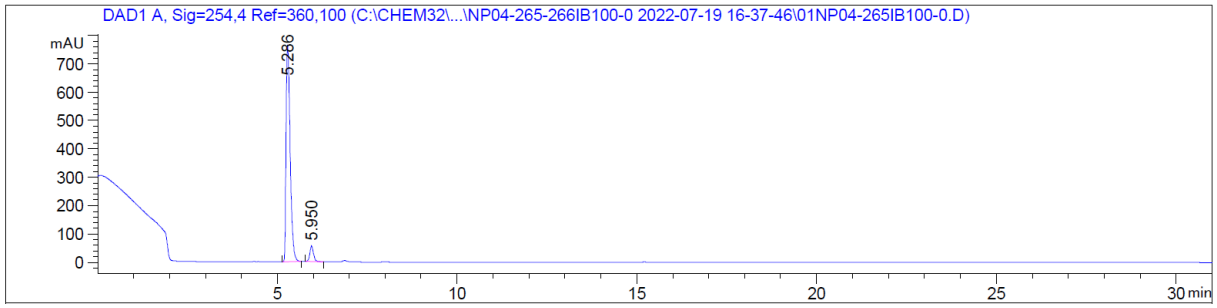
Chiral HPLC traces for compound 4ad.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.187	BB	0.1012	3276.57153	508.18280	48.3940
2	5.785	BB	0.1118	3494.04858	486.31168	51.6060
Totals :				6770.62012	994.49448	

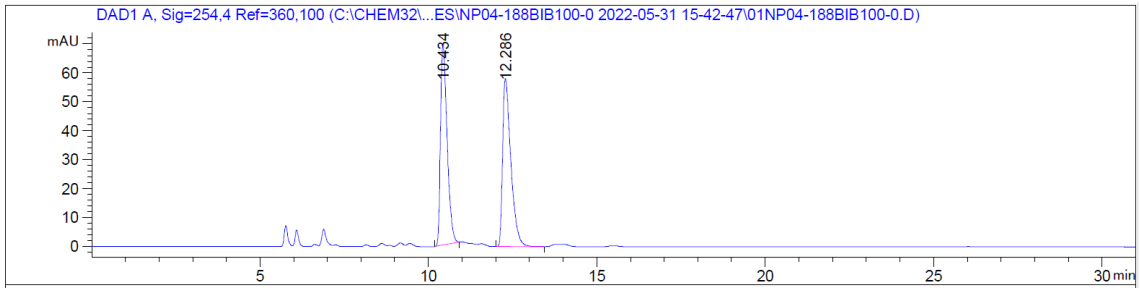


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.286	BB	0.1186	5948.41309	765.71027	93.6132
2	5.950	BB	0.1104	405.83075	56.07053	6.3868
Totals :				6354.24384	821.78080	

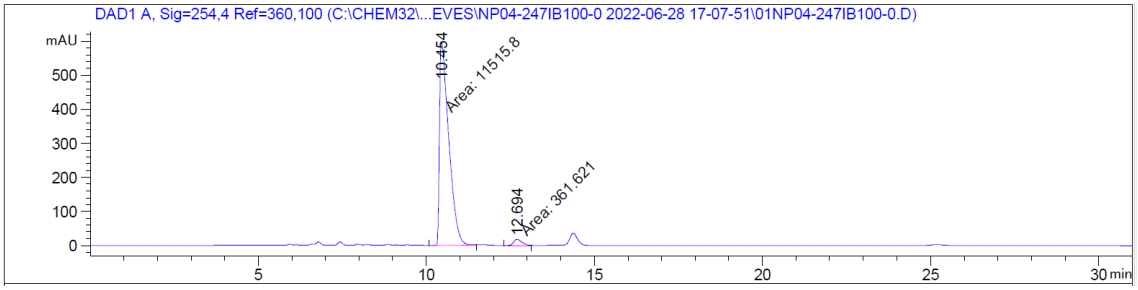
Chiral HPLC traces for compound 4ae.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.434	BB	0.2055	945.10815	70.02354	48.9305
2	12.286	BB	0.2542	986.42297	58.05066	51.0695
Totals :				1931.53113	128.07420	

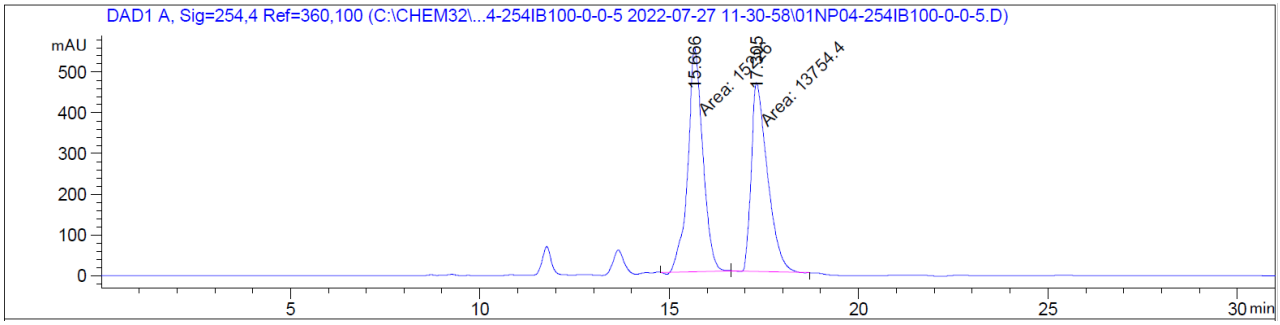


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.454	MM	0.3207	1.15158e4	598.48419	96.9554
2	12.694	MM	0.3138	361.62051	19.20488	3.0446
Totals :				1.18774e4	617.68907	

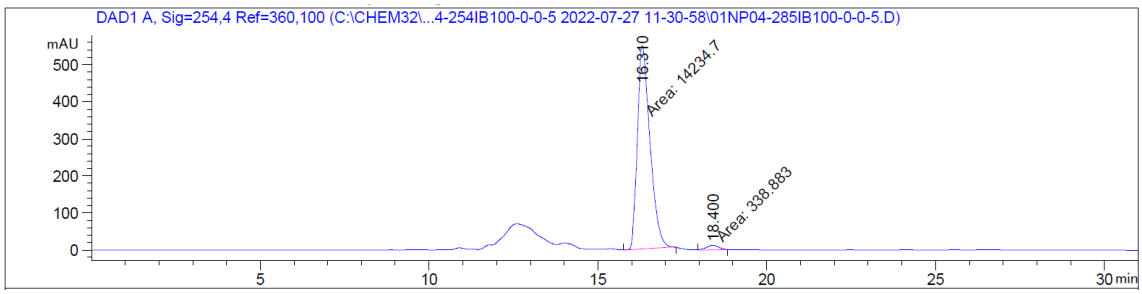
Chiral HPLC traces for compound 4af.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.666	MM	0.4663	1.55159e4	554.54999	52.7421
2	17.305	MM	0.4989	1.39026e4	464.46289	47.2579
Totals :				2.94185e4	1019.01288	

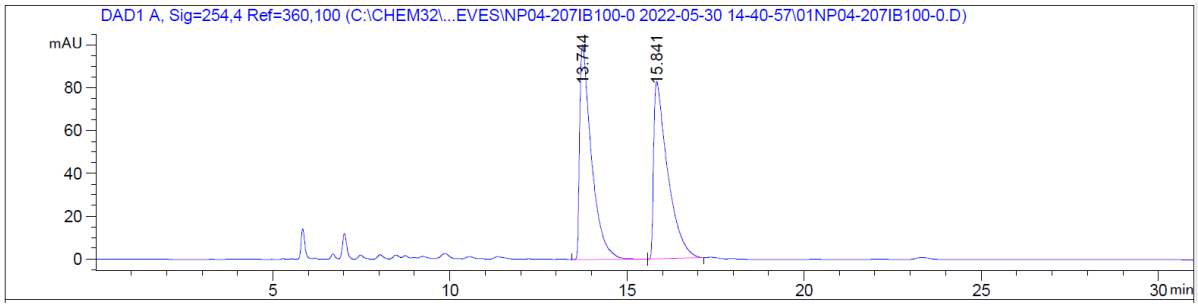


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.310	MM	0.4319	1.42347e4	549.30884	97.6747
2	18.400	MM	0.4337	338.88263	13.02343	2.3253
Totals :				1.45736e4	562.33227	

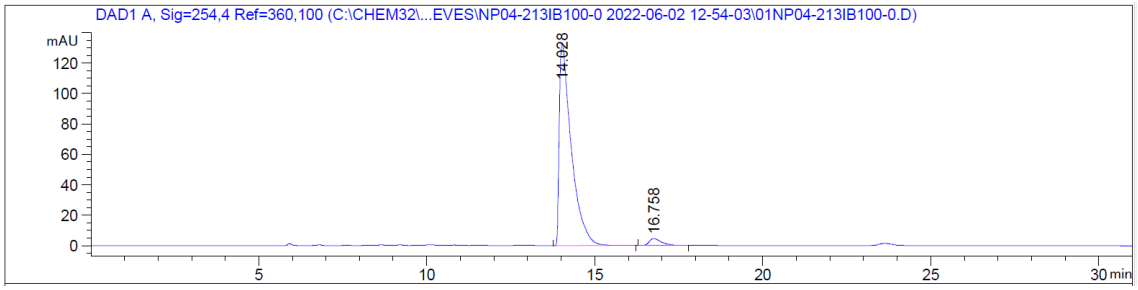
Chiral HPLC traces for compound 4ag.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.744	BB	0.3321	2321.16016	100.26518	50.4277
2	15.841	BB	0.3849	2281.78857	82.95090	49.5723
Totals :				4602.94873	183.21608	

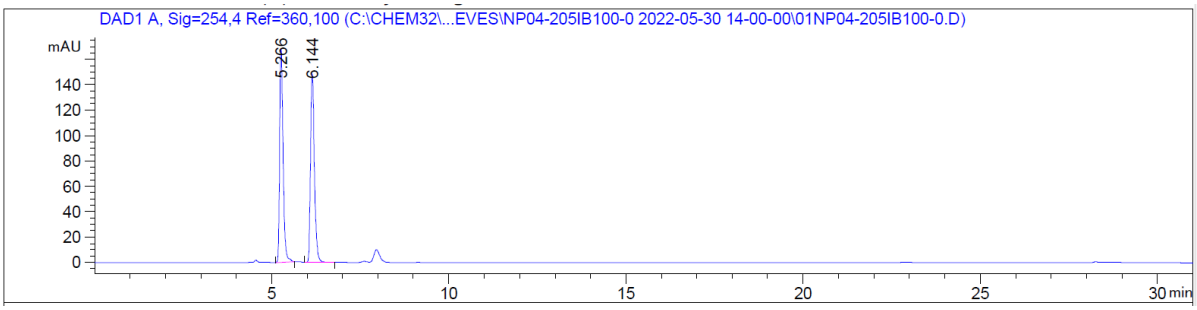


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.028	BB	0.3531	3309.82886	133.56996	96.6543
2	16.758	BB	0.3750	114.57117	4.56236	3.3457
Totals :				3424.40002	138.13232	

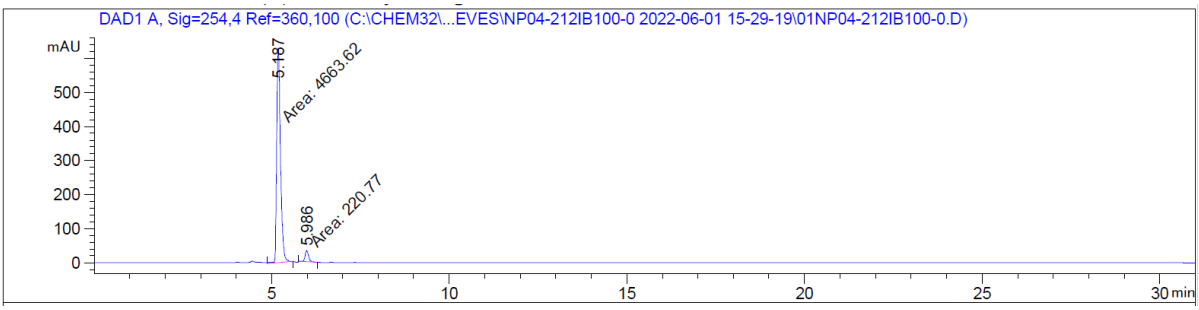
Chiral HPLC traces for compound 4ah.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.266	BB	0.1015	1123.05127	169.03957	50.1307
2	6.144	BB	0.1137	1117.19653	148.55783	49.8693
Totals :				2240.24780	317.59740	

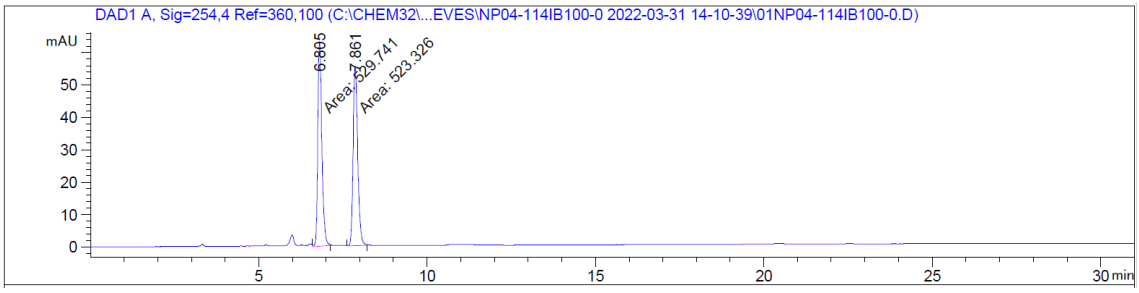


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.187	MM	0.1231	4663.62256	631.56360	95.4801
2	5.986	MM	0.1147	220.77011	32.08010	4.5199
Totals :				4884.39267	663.64370	

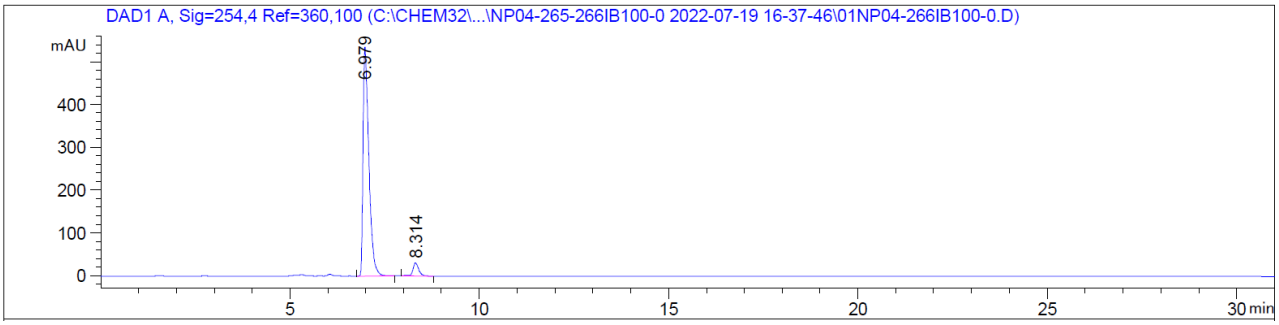
Chiral HPLC traces for compound 4ai.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.805	MM	0.1403	529.74060	62.90982	50.3046
2	7.861	MM	0.1580	523.32556	55.19047	49.6954
Totals :				1053.06616	118.10030	

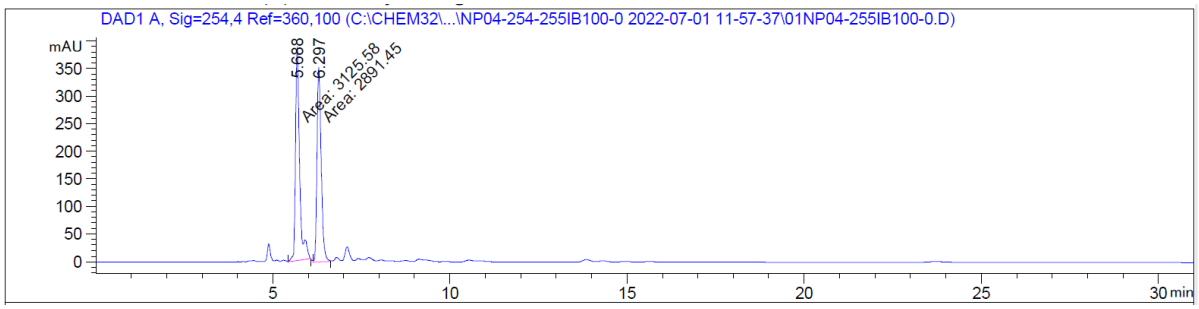


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.979	BB	0.1602	5694.57617	534.82843	94.5344
2	8.314	VB R	0.1591	329.23828	30.40454	5.4656
Totals :				6023.81445	565.23297	

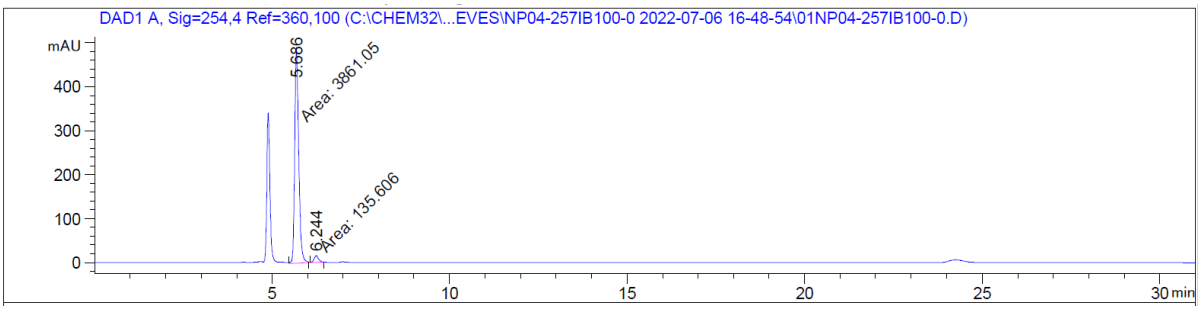
Chiral HPLC traces for compound 4aj.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.688	MM	0.1352	3125.57520	385.36795	51.9455
2	6.297	MM	0.1364	2891.45093	353.32962	48.0545
Totals :				6017.02612	738.69757	

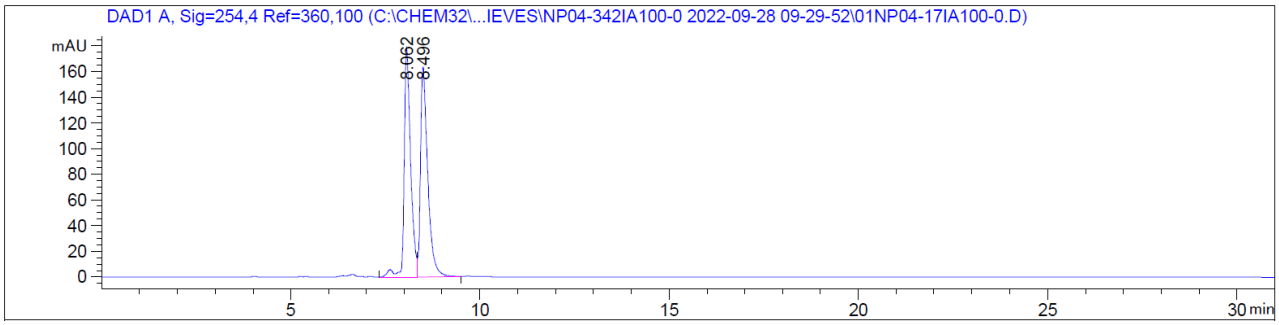


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.686	MM	0.1312	3861.04785	490.50647	96.6070
2	6.244	MM	0.1459	135.60649	15.49576	3.3930
Totals :				3996.65434	506.00223	

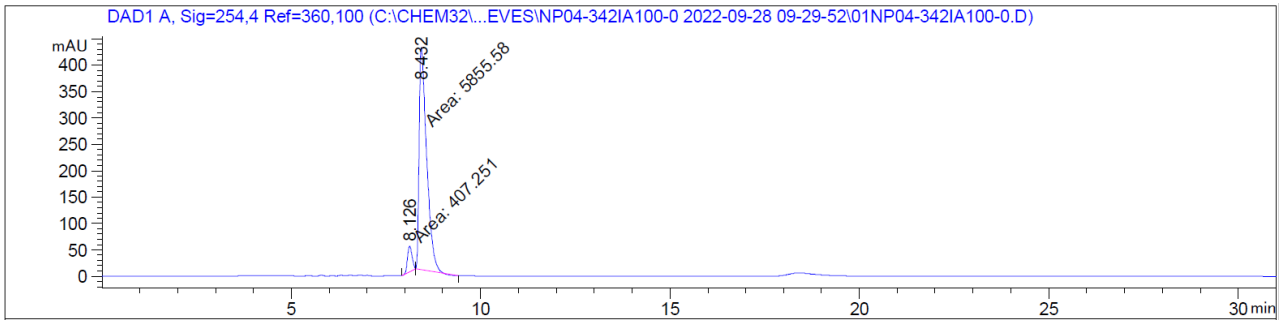
Chiral HPLC traces for compound 4ak.

Conditions: Daicel Chiralpak IB N-5 column: IA 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.062	VV R	0.1744	2134.05518	178.67944	49.6312
2	8.496	VB	0.1964	2165.76782	163.65567	50.3688
Totals :				4299.82300	342.33511	

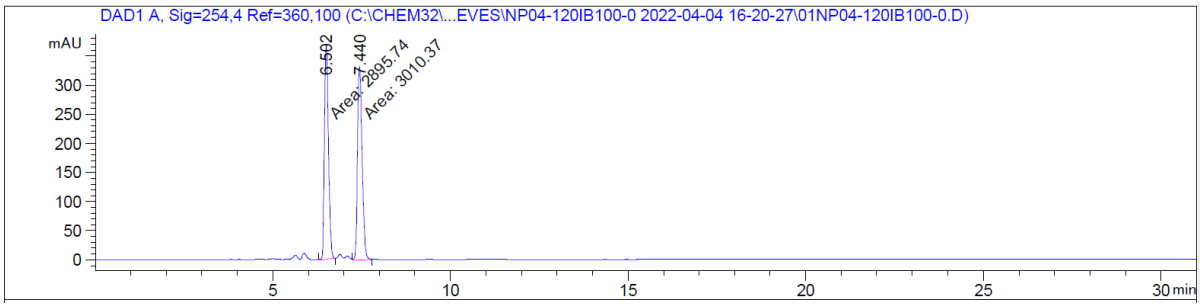


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.126	MM	0.1405	407.25095	48.31989	6.5027
2	8.432	MM	0.2316	5855.58350	421.42700	93.4973
Totals :				6262.83444	469.74689	

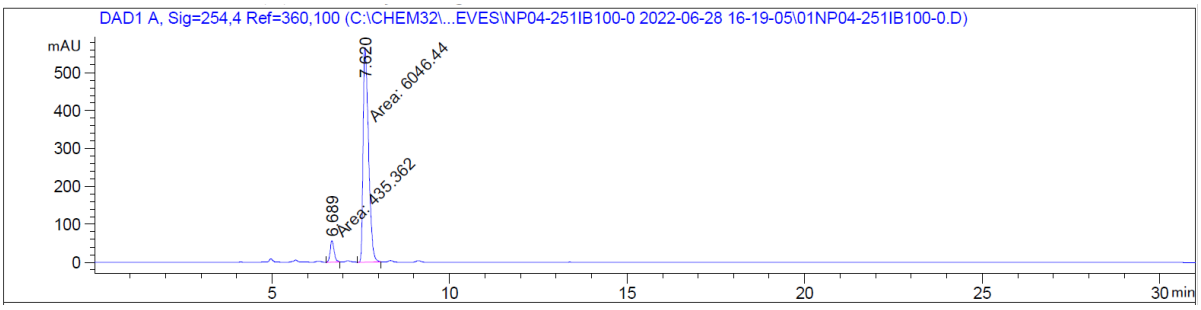
Chiral HPLC traces for compound 4al.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.502	MM	0.1307	2895.74243	369.25925	49.0296
2	7.440	MM	0.1510	3010.36548	332.27228	50.9704
Totals :				5906.10791	701.53152	

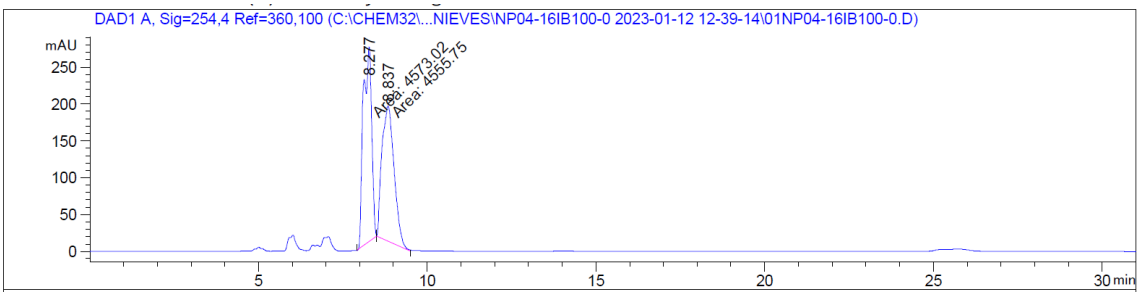


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.689	MM	0.1285	435.36194	56.47586	6.7167
2	7.620	MM	0.1779	6046.44287	566.58496	93.2833
Totals :				6481.80481	623.06082	

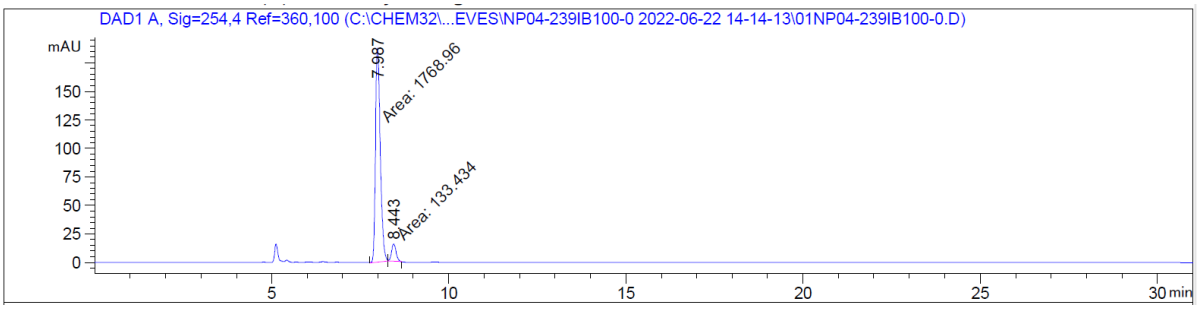
Chiral HPLC traces for compound 4am.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.277	MM	0.2889	4573.02100	263.85651	50.0946
2	8.837	MM	0.4151	4555.75195	182.92178	49.9054
Totals :				9128.77295	446.77829	

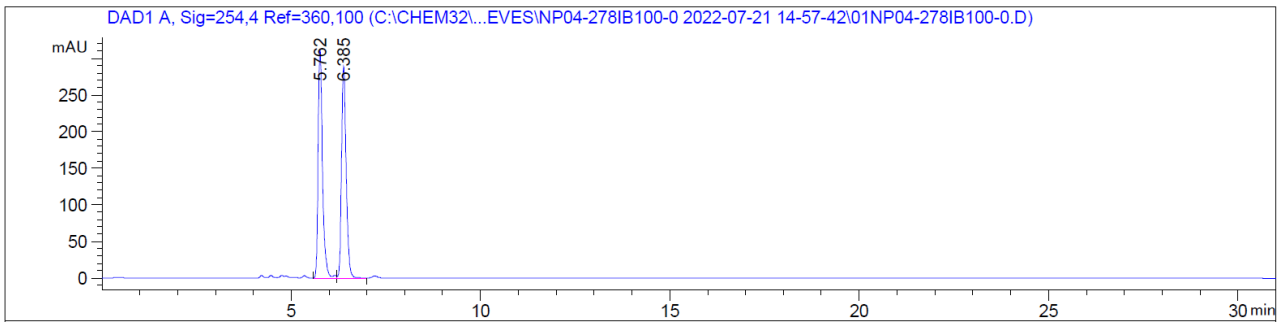


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.987	MM	0.1572	1768.96167	187.58540	92.9860
2	8.443	MM	0.1477	133.43443	15.05945	7.0140
Totals :				1902.39610	202.64486	

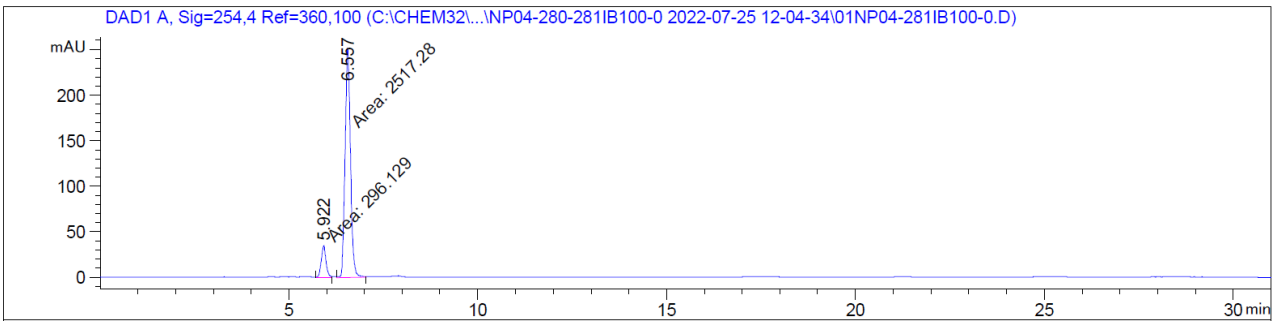
Chiral HPLC traces for compound 4an.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.762	BV R	0.1209	2515.94019	313.30023	50.6584
2	6.385	VB	0.1309	2450.54492	289.07428	49.3416
Totals :				4966.48511	602.37451	

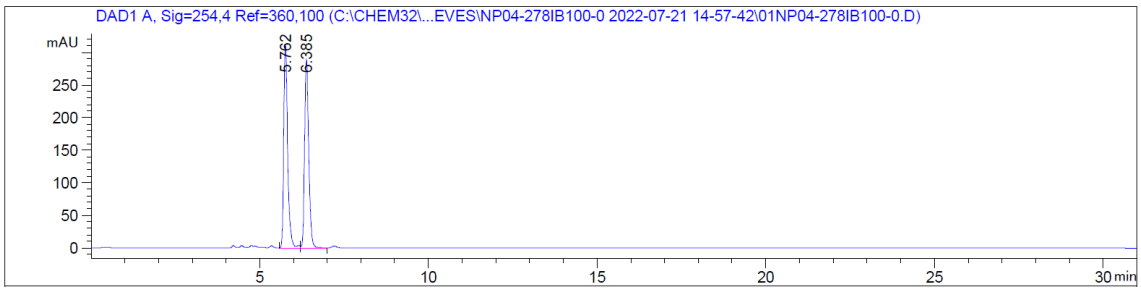


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.922	MM	0.1437	296.12933	34.34717	10.5256
2	6.557	MM	0.1668	2517.28345	251.49266	89.4744
Totals :				2813.41278	285.83983	

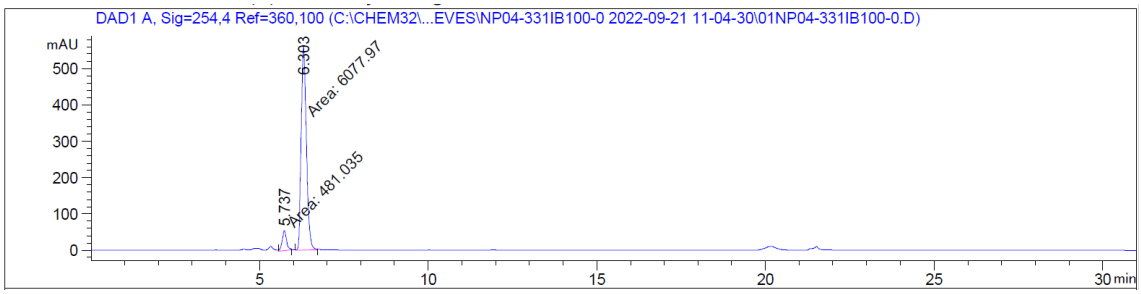
Chiral HPLC traces for compound 4an (1 mmol)

Conditions: **Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.**



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.762	BV R	0.1209	2515.94019	313.30023	50.6584
2	6.385	VB	0.1309	2450.54492	289.07428	49.3416
Totals :				4966.48511	602.37451	

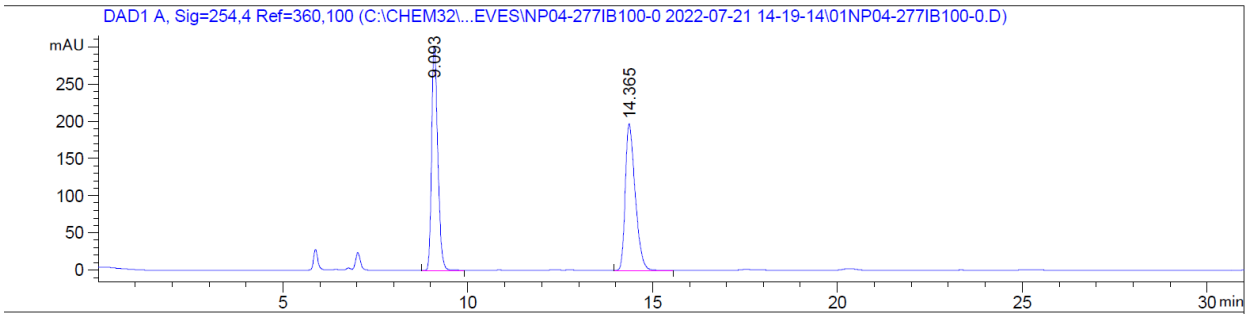


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.737	MM	0.1471	481.03482	54.52038	7.3340
2	6.303	MM	0.1801	6077.96826	562.47162	92.6660
Totals :				6559.00308	616.99200	

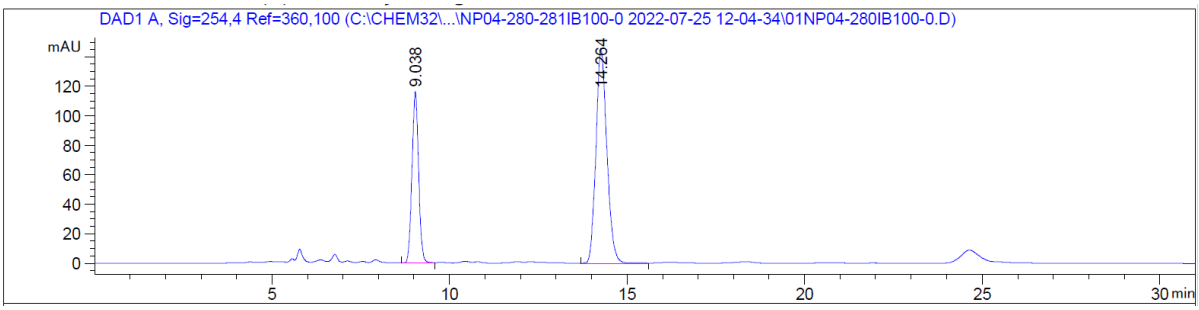
Chiral HPLC traces for compound 4ao.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.093	BB	0.1769	3476.17505	300.53433	48.6883
2	14.365	BB	0.2831	3663.47607	196.89226	51.3117
Totals :				7139.65112	497.42659	

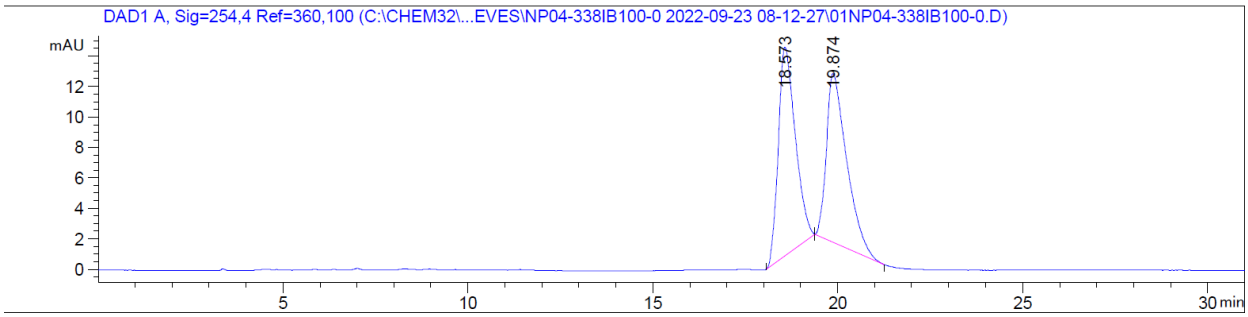


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.038	BB	0.1963	1496.56714	116.16468	32.5344
2	14.264	BB	0.3206	3103.38892	145.63454	67.4656
Totals :				4599.95605	261.79922	

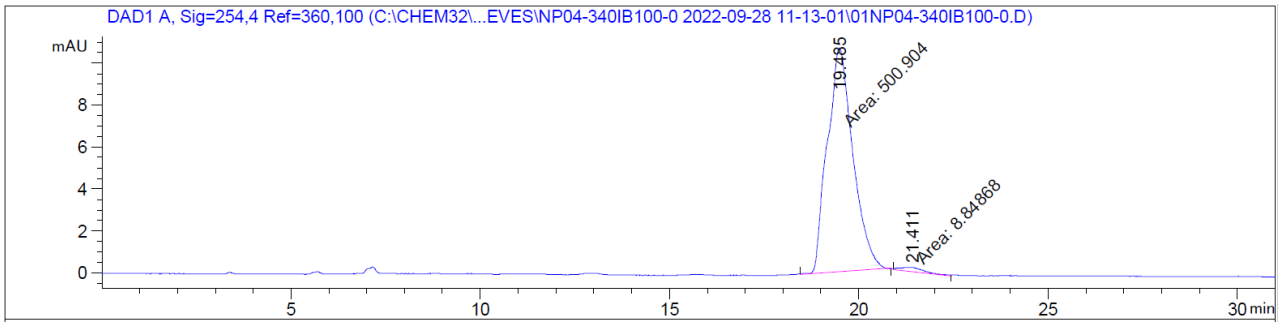
Chiral HPLC traces for compound 4bp.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.573	BB	0.4746	437.50229	13.70035	50.8825
2	19.874	BB	0.5576	422.32590	11.05848	49.1175
Totals :				859.82819	24.75883	

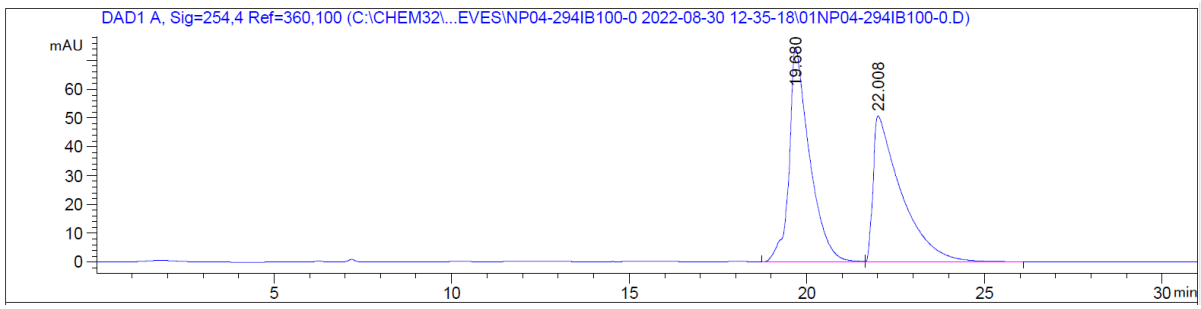


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.485	MM	0.7836	500.90356	10.65432	98.2641
2	21.411	MM	0.7312	8.84868	2.01697e-1	1.7359
Totals :				509.75224	10.85602	

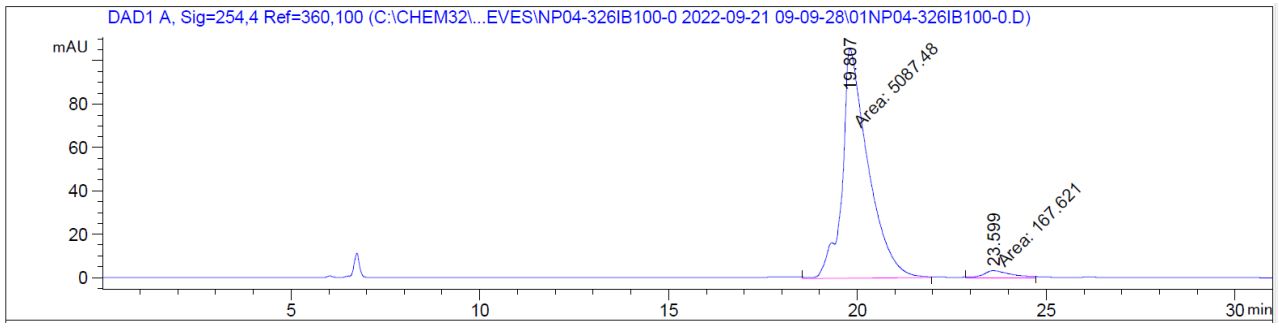
Chiral HPLC traces for compound 4ba.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.680	BV	0.5606	2981.35547	74.55145	51.5466
2	22.008	VB	0.7305	2802.44971	50.72628	48.4534
Totals :				5783.80518	125.27773	

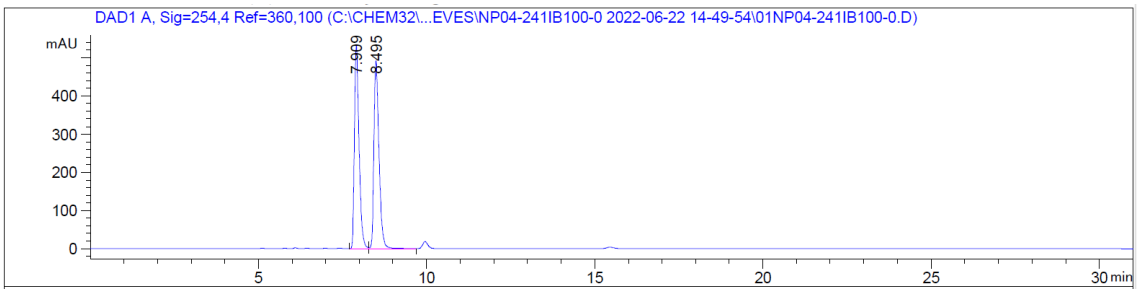


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.807	MM	0.8006	5087.47705	105.90881	96.8103
2	23.599	MM	0.8543	167.62076	3.27003	3.1897
Totals :				5255.09781	109.17884	

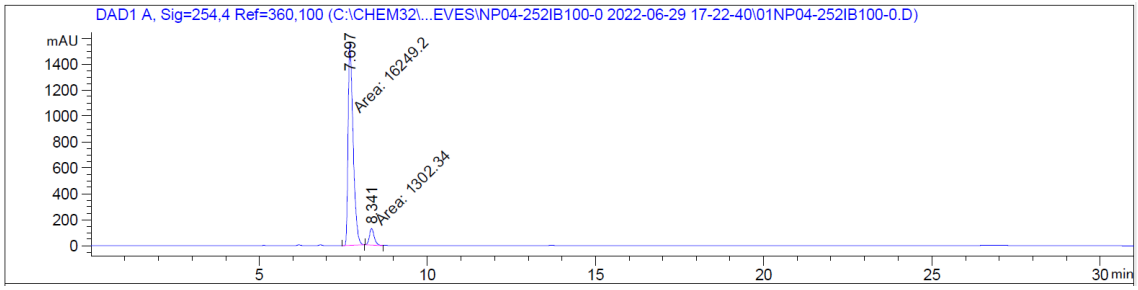
Chiral HPLC traces for compound 4ca.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.909	BV	0.1450	5068.94971	532.73236	49.6663
2	8.495	VB	0.1597	5137.05615	492.35797	50.3337
Totals :				1.02060e4	1025.09033	

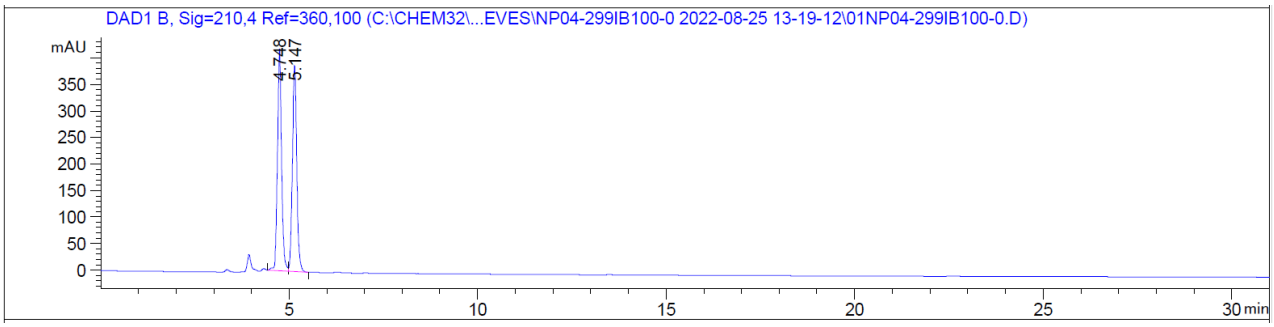


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.697	MM	0.1729	1.62492e4	1566.14905	92.5799
2	8.341	MM	0.1695	1302.34204	128.05785	7.4201
Totals :				1.75516e4	1694.20689	

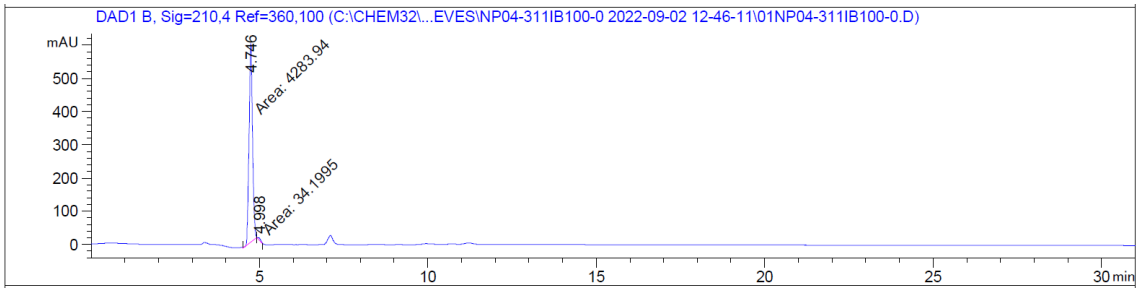
Chiral HPLC traces for compound 4de.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.748	VV R	0.1122	3189.68555	418.96887	50.4971
2	5.147	VB	0.1199	3126.89209	388.69141	49.5029
Totals :				6316.57764	807.66028	

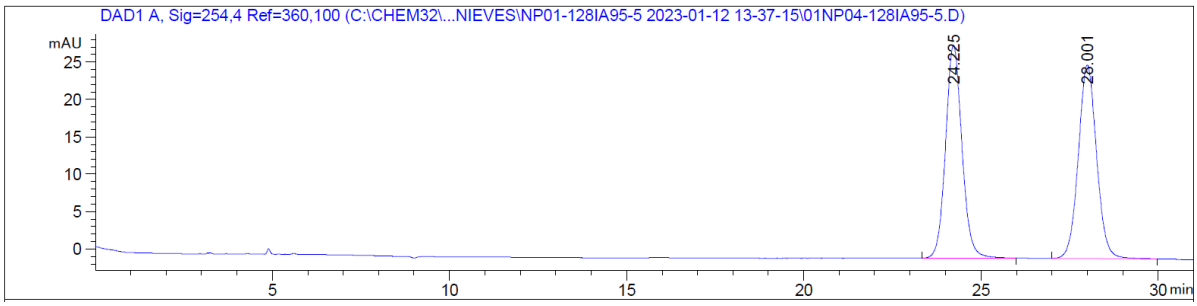


Signal 2: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.746	MM	0.1197	4283.94141	596.66980	99.2080
2	4.998	MM	0.0939	34.19955	6.07304	0.7920
Totals :				4318.14095	602.74284	

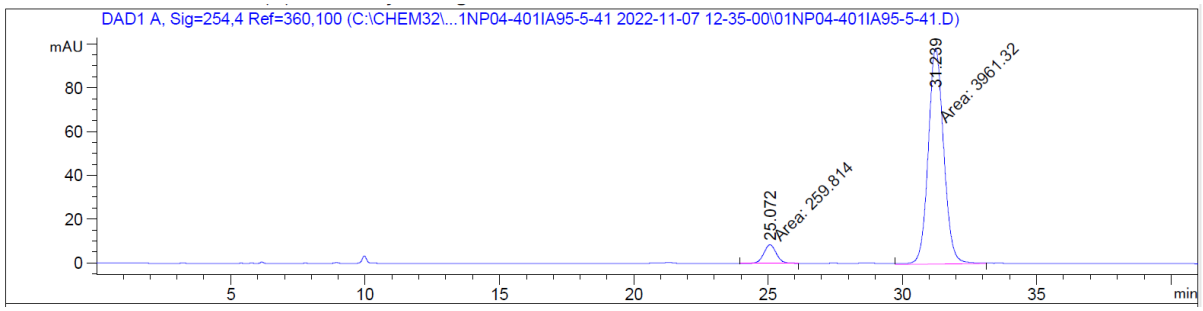
Chiral HPLC traces for compound 13aa.

Conditions: Daicel Chiralpak IA N-5 column: IA 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.225	BB	0.4924	914.58942	28.50194	49.6263
2	28.001	BB	0.5505	928.36426	25.87931	50.3737
Totals :				1842.95367	54.38125	

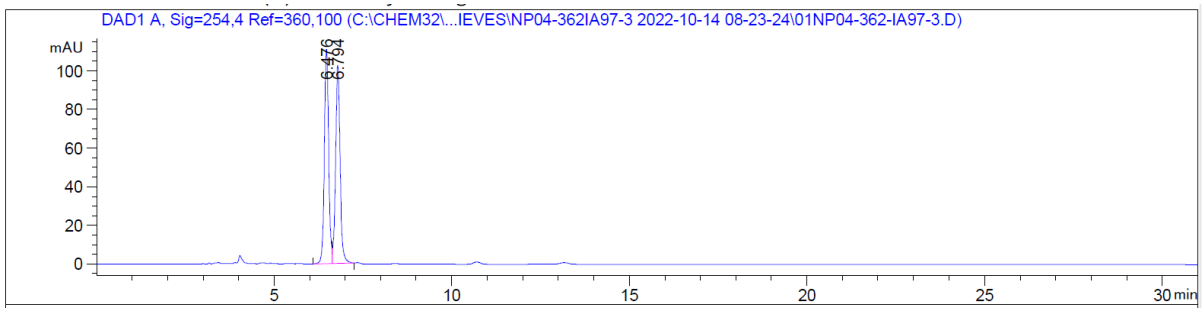


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.072	MM	0.5206	259.81366	8.31850	6.1551
2	31.239	MM	0.6708	3961.32422	98.42547	93.8449
Totals :				4221.13788	106.74397	

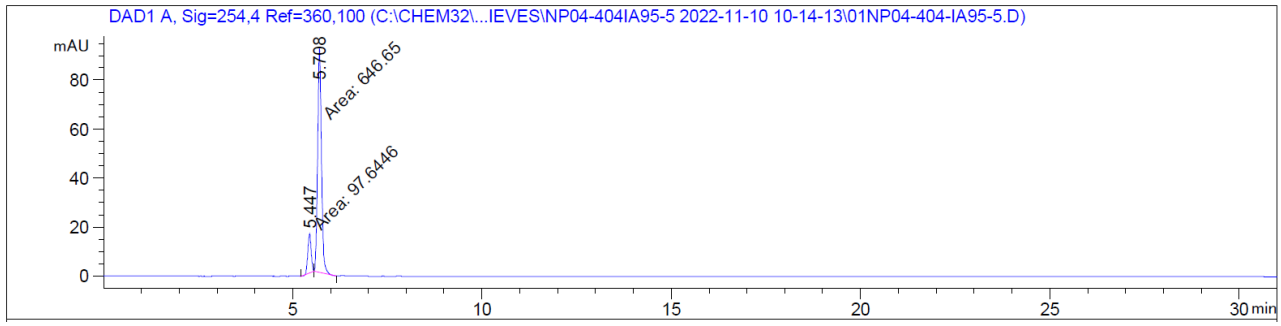
Chiral HPLC traces for compound 13da.

Conditions: Daicel Chiralpak IA N-5 column: IA 97:3 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.476	BV	0.1273	926.11584	111.02064	50.5346
2	6.794	VB	0.1349	906.52118	102.82911	49.4654
Totals :				1832.63702	213.84975	

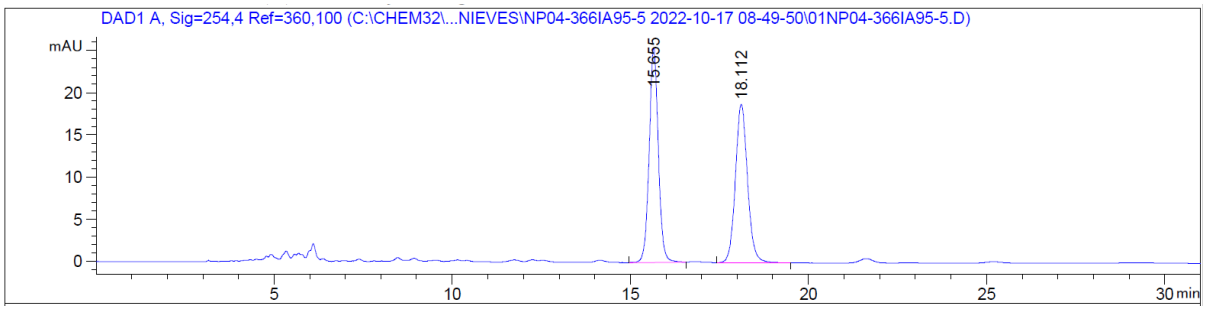


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.447	MM	0.1019	97.64458	15.96888	13.1191
2	5.708	MM	0.1174	646.65021	91.83762	86.8809
Totals :				744.29478	107.80649	

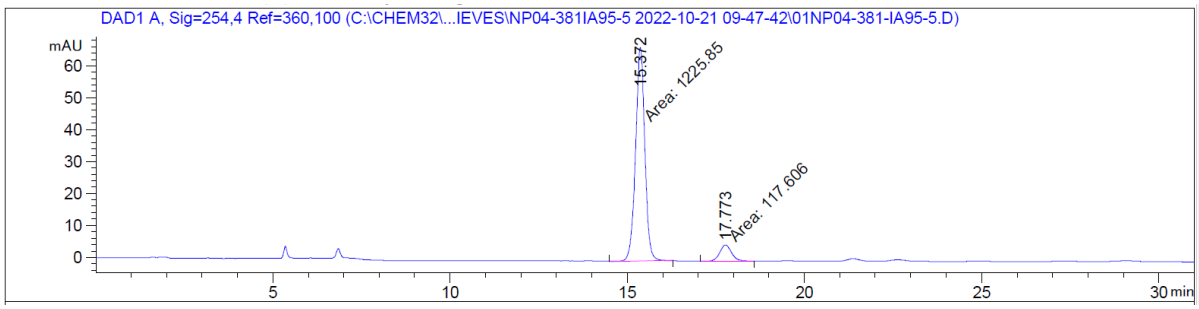
Chiral HPLC traces for compound 13ea.

Conditions: Daicel Chiralpak IA N-5 column: IA 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.655	BB	0.2739	453.16168	25.42892	50.4890
2	18.112	BB	0.3645	444.38327	18.74728	49.5110
Totals :				897.54495	44.17619	

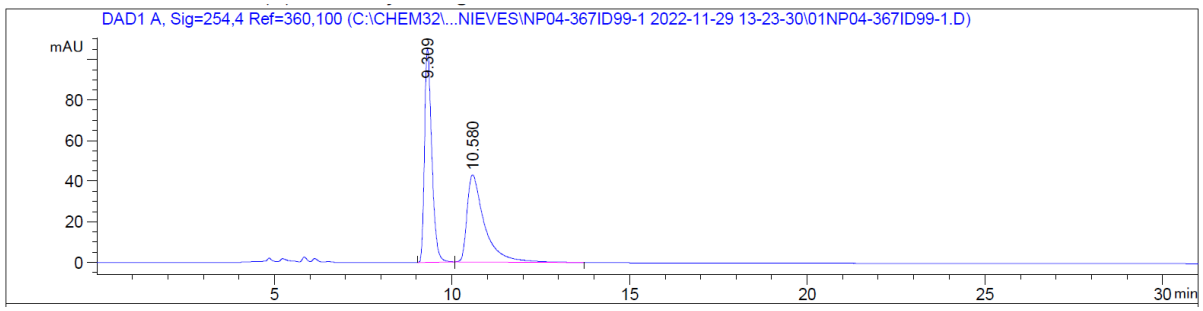


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.372	MM	0.3051	1225.85059	66.96079	91.2460
2	17.773	MM	0.3857	117.60568	5.08213	8.7540
Totals :				1343.45627	72.04292	

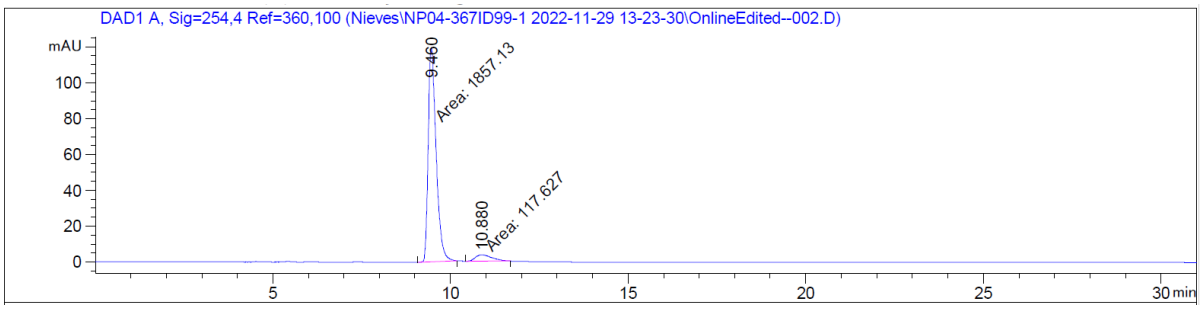
Chiral HPLC traces for compound 13fa.

Conditions: Daicel Chiralpak ID N-5 column: ID 99-1:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.309	BB	0.2179	1497.95154	105.31300	50.6998
2	10.580	BB	0.4940	1456.60144	42.91156	49.3002
Totals :				2954.55298	148.22456	

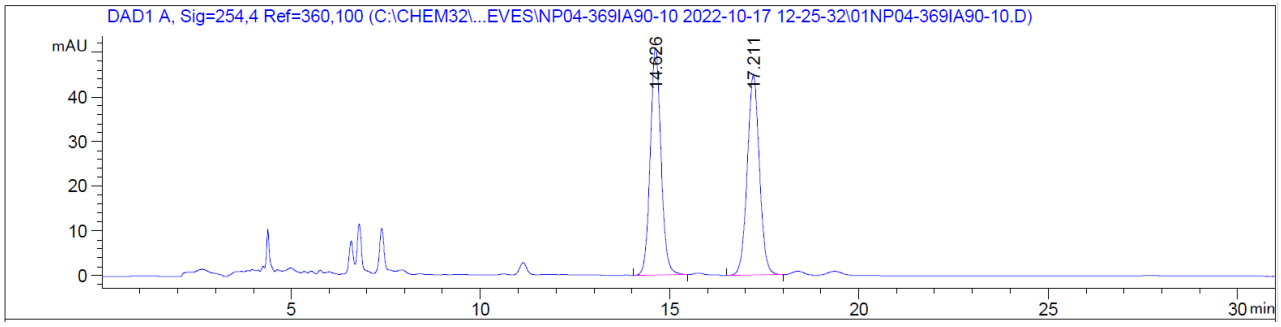


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.460	MM	0.2587	1857.13000	119.64703	94.0435
2	10.880	MM	0.5407	117.62692	3.62590	5.9565
Totals :				1974.75693	123.27294	

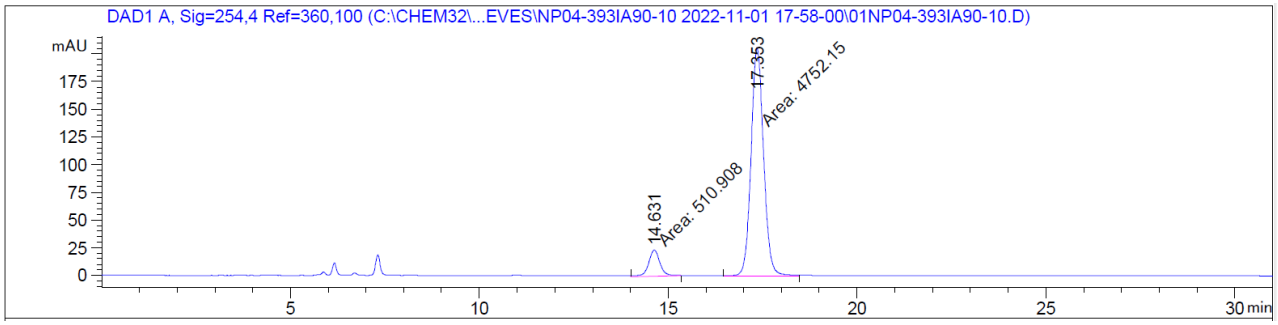
Chiral HPLC traces for compound 13ga.

Conditions: Daicel Chiralpak IA N-5 column: IA 90:10 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.626	BB	0.3020	1002.59393	50.86053	50.0314
2	17.211	BB	0.3461	1001.33539	44.58021	49.9686
Totals :				2003.92932	95.44075	

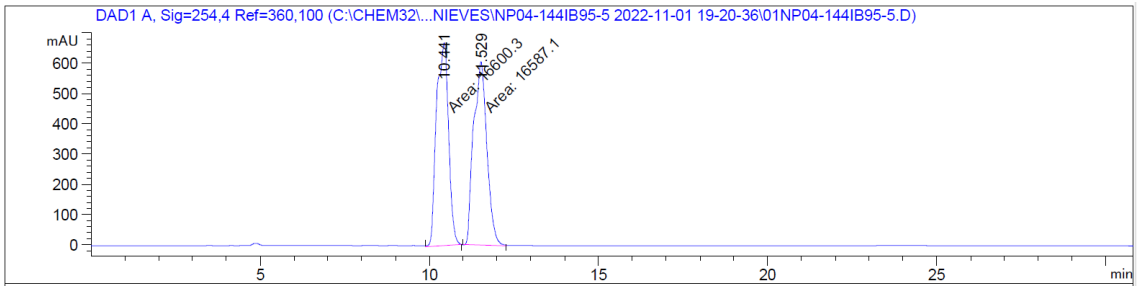


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.631	MM	0.3580	510.90845	23.78626	9.7074
2	17.353	MM	0.3842	4752.14844	206.16560	90.2926
Totals :				5263.05688	229.95186	

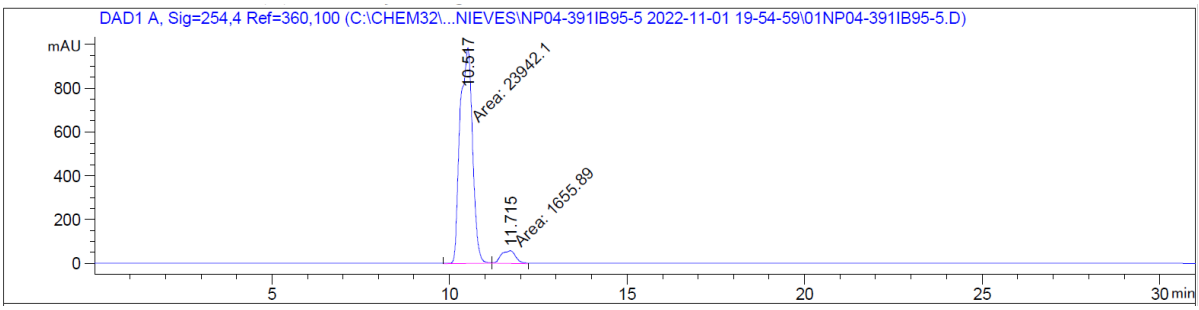
Chiral HPLC traces for compound 13ab.

Conditions: Daicel Chiralpak IB N-5 column: IB 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.441	MM	0.4126	1.66003e4	670.56763	50.0199
2	11.529	MM	0.4555	1.65871e4	606.87750	49.9801
Totals :				3.31874e4	1277.44513	

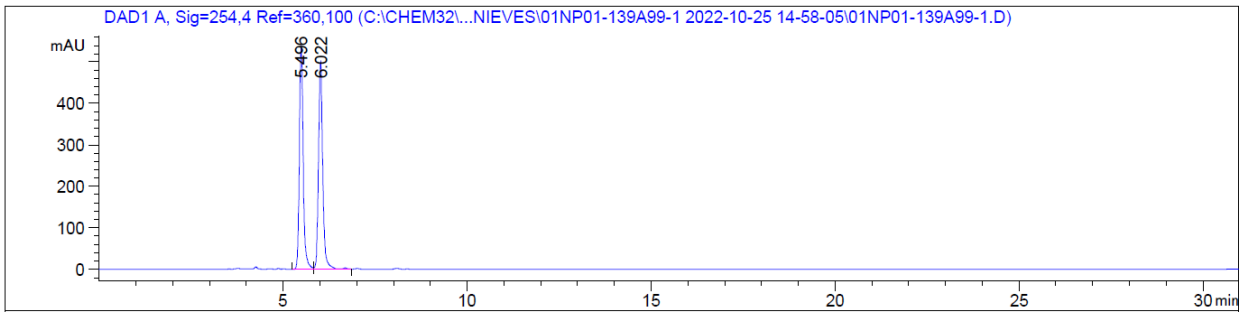


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.517	MM	0.4045	2.39421e4	986.47083	93.5312
2	11.715	MM	0.4734	1655.89099	58.30177	6.4688
Totals :				2.55980e4	1044.77259	

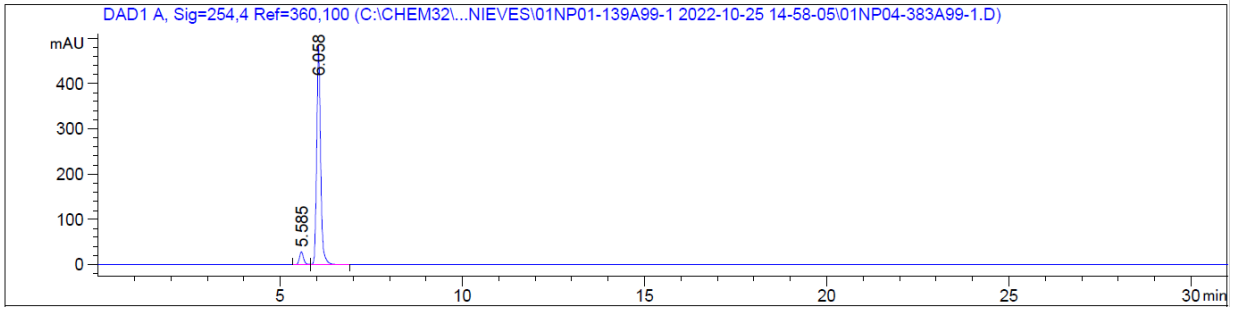
Chiral HPLC traces for compound 13ac.

Conditions: Daicel Chiralpak IA N-5 column: IA 99:1 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.496	BV	0.1113	3918.93604	536.09155	49.4792
2	6.022	VV R	0.1209	4001.42847	499.52161	50.5208
Totals :				7920.36450	1035.61316	

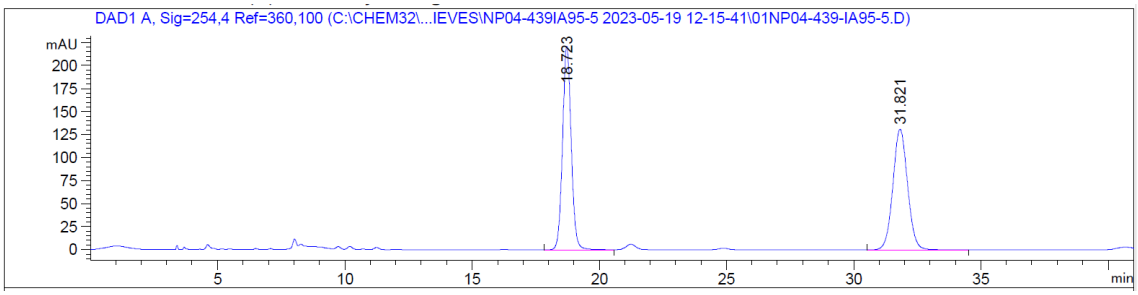


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.585	BV	0.1187	225.07982	28.95849	5.7761
2	6.058	VB	0.1142	3671.63843	485.70844	94.2239
Totals :				3896.71825	514.66693	

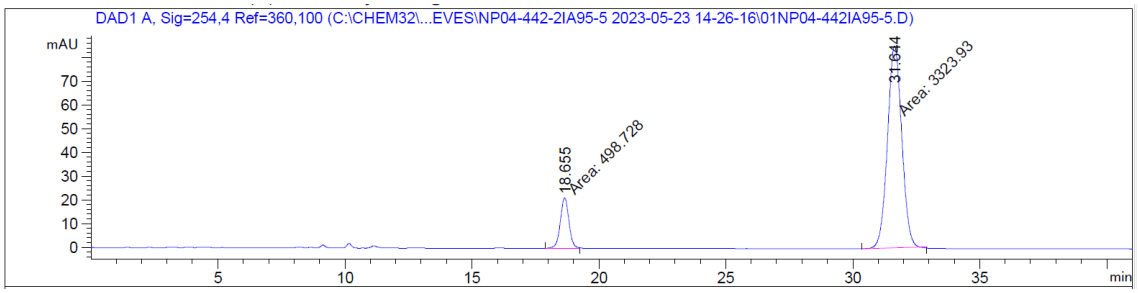
Chiral HPLC traces for compound 13ad.

Conditions: Daicel Chiralpak IB N-5 column: IA 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.723	BB	0.3628	5211.18066	221.20428	49.8027
2	31.821	BB	0.6194	5252.46973	131.10262	50.1973
Totals :				1.04637e4	352.30690	

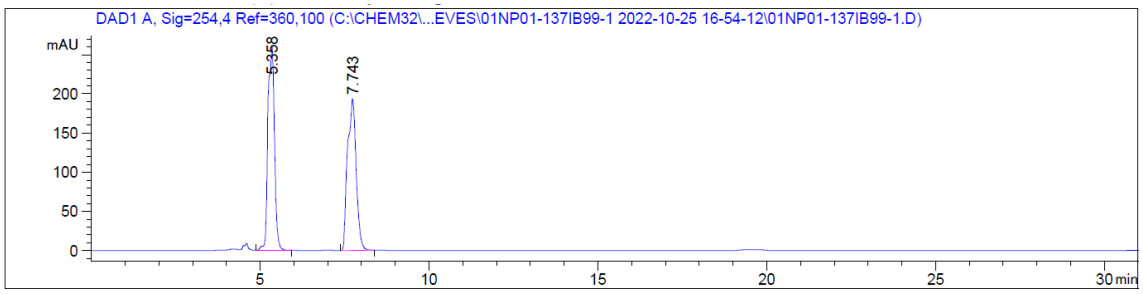


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.655	MM	0.3907	498.72784	21.27726	13.0466
2	31.644	MM	0.6516	3323.92944	85.01898	86.9534
Totals :				3822.65729	106.29625	

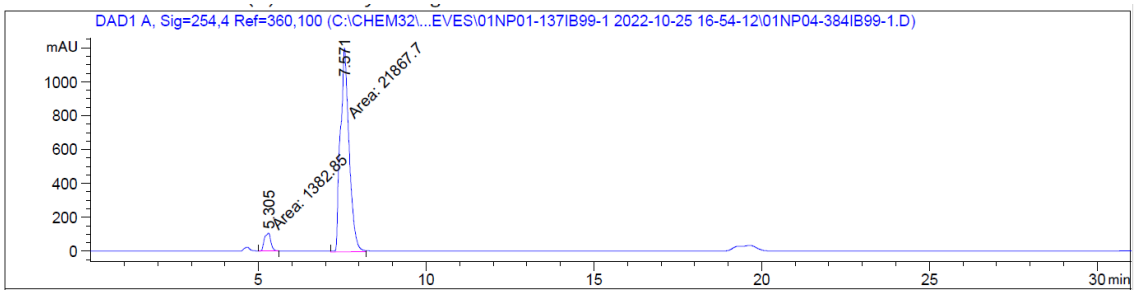
Chiral HPLC traces for compound 13ae.

Conditions: Daicel Chiralpak IB N-5 column: IB 99:1 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.358	BB	0.1830	3503.92358	260.32596	50.5465
2	7.743	BB	0.2428	3428.16113	193.40060	49.4535
Totals :				6932.08472	453.72656	

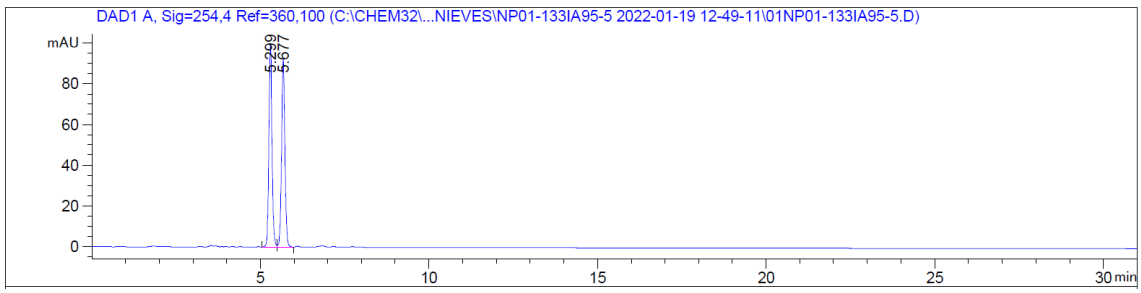


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.305	MM	0.2178	1382.85071	105.83273	5.9476
2	7.571	MM	0.3028	2.18677e4	1203.61890	94.0524
Totals :				2.32506e4	1309.45162	

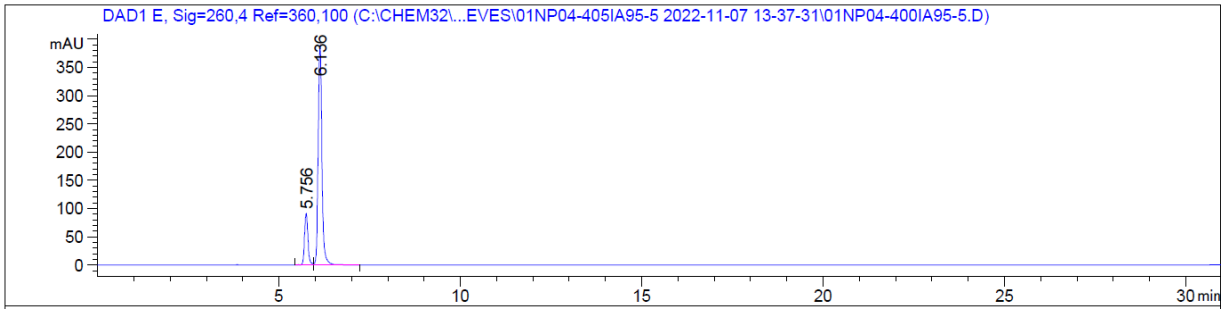
Chiral HPLC traces for compound 13af.

Conditions: Daicel Chiralpak IA N-5 column: IA 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.299	BV	0.0984	637.32288	99.92163	50.0352
2	5.677	VB	0.1033	636.42615	93.59975	49.9648
Totals :				1273.74902	193.52139	

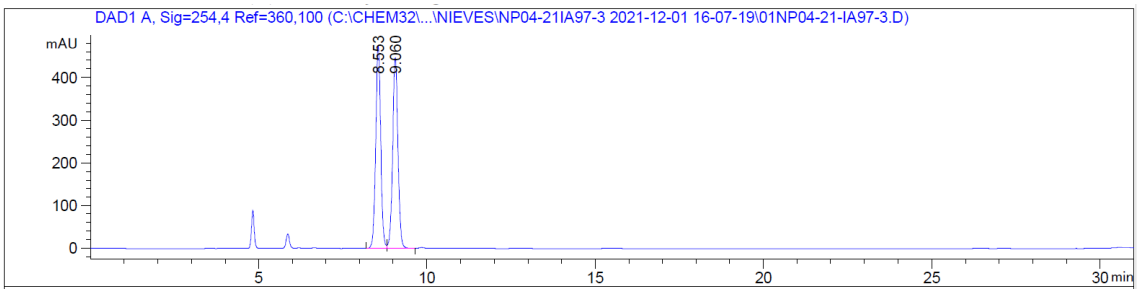


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.756	VV R	0.1005	948.37866	144.54817	17.9447
2	6.136	VB	0.1100	4336.62646	602.22552	82.0553
Totals :				5285.00513	746.77370	

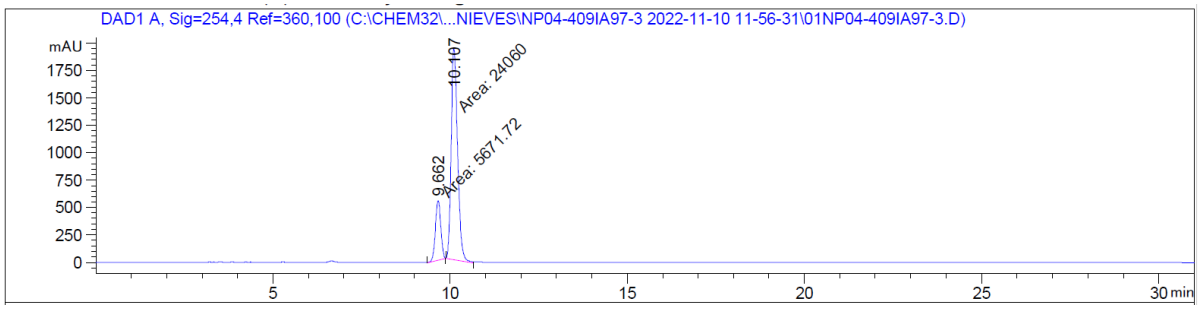
Chiral HPLC traces for compound 13ag.

Conditions: Daicel Chiralpak IA N-5 column: IA 97:3 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.553	BV	0.1576	4860.35986	474.20950	49.9697
2	9.060	VB	0.1675	4866.26270	445.32407	50.0303
Totals :				9726.62256	919.53357	

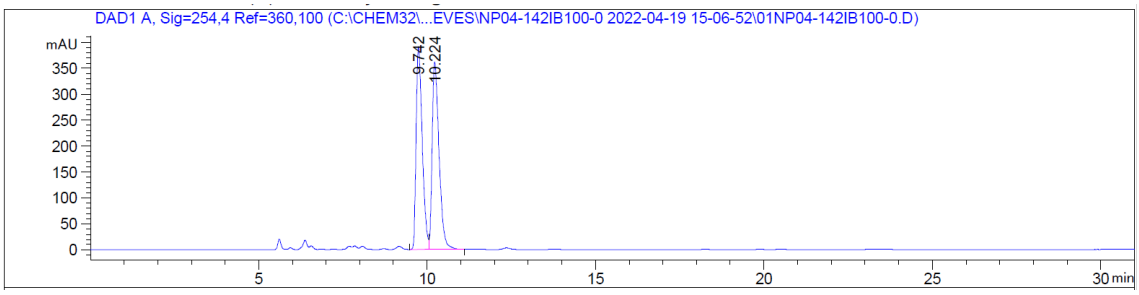


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.662	MM	0.1743	5671.71582	542.39227	19.0763
2	10.107	MM	0.2082	2.40600e4	1925.89502	80.9237
Totals :				2.97318e4	2468.28729	

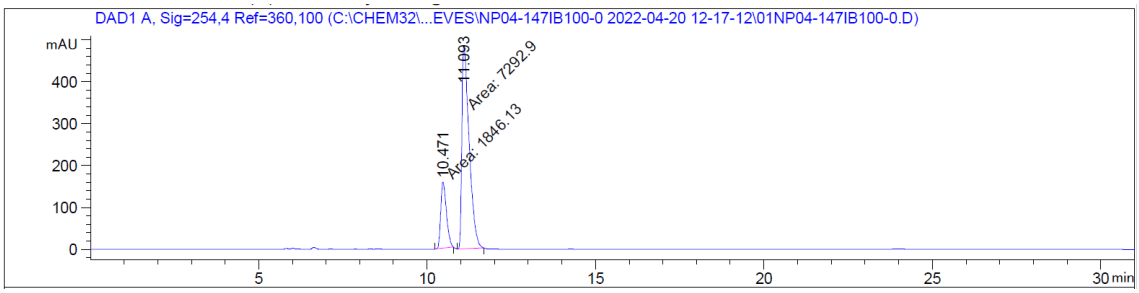
Chiral HPLC traces for compound 15a.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.742	VV	0.1924	4921.39600	392.18802	49.0014
2	10.224	VB	0.2153	5121.98438	361.49240	50.9986
Totals :				1.00434e4	753.68042	

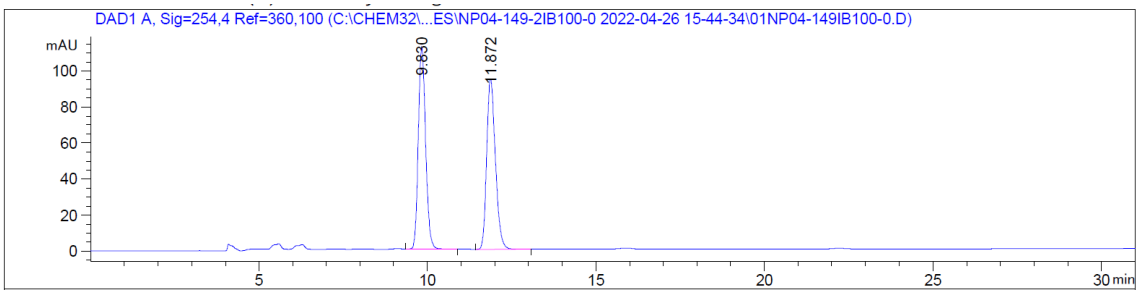


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.471	MM	0.1950	1846.13013	157.77492	20.2005
2	11.093	MM	0.2512	7292.90430	483.91309	79.7995
Totals :				9139.03442	641.68800	

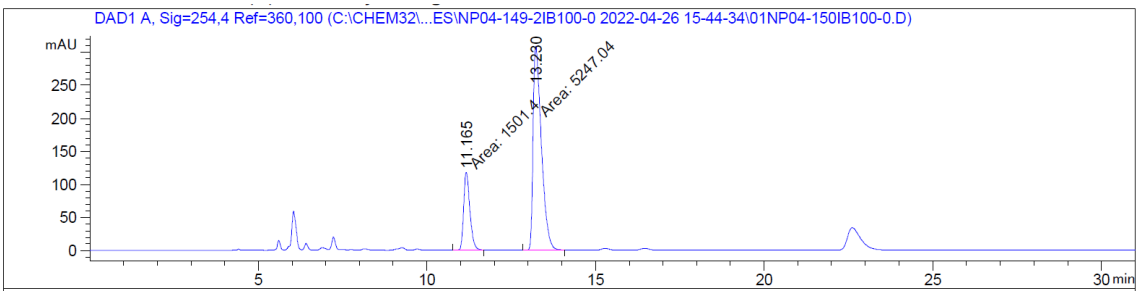
Chiral HPLC traces for compound 15b.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.830	BB	0.2362	1697.42236	112.40637	49.9702
2	11.872	BB	0.2793	1699.44861	94.71603	50.0298
Totals :				3396.87097	207.12240	

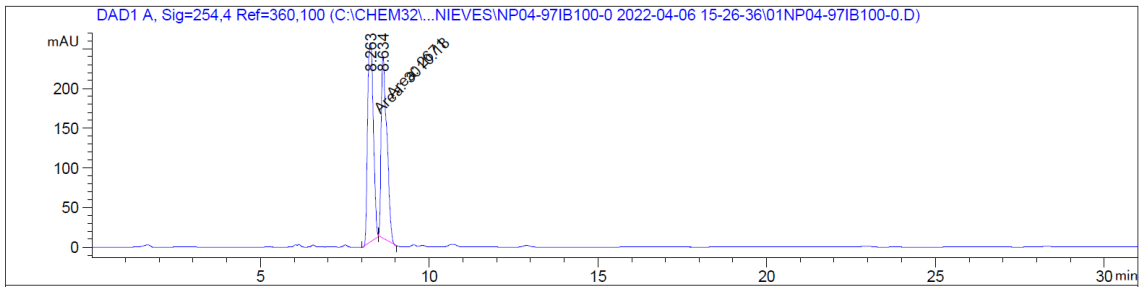


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.165	MM	0.2133	1501.39746	117.29741	22.2481
2	13.230	MM	0.2838	5247.03516	308.11914	77.7519
Totals :				6748.43262	425.41655	

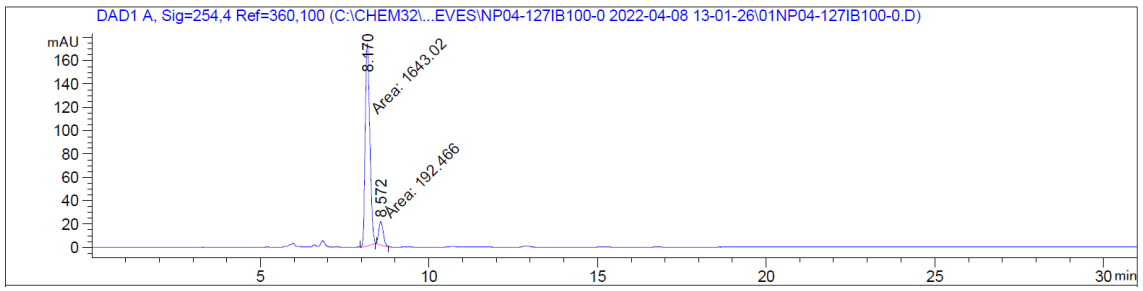
Chiral HPLC traces for compound 17.

Conditions: Daicel Chiralpak IB N-5 column: IB 100:0 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.263	MM	0.2000	3010.18140	250.80333	52.9851
2	8.634	MM	0.1947	2670.99951	228.65280	47.0149
Totals :				5681.18091	479.45613	

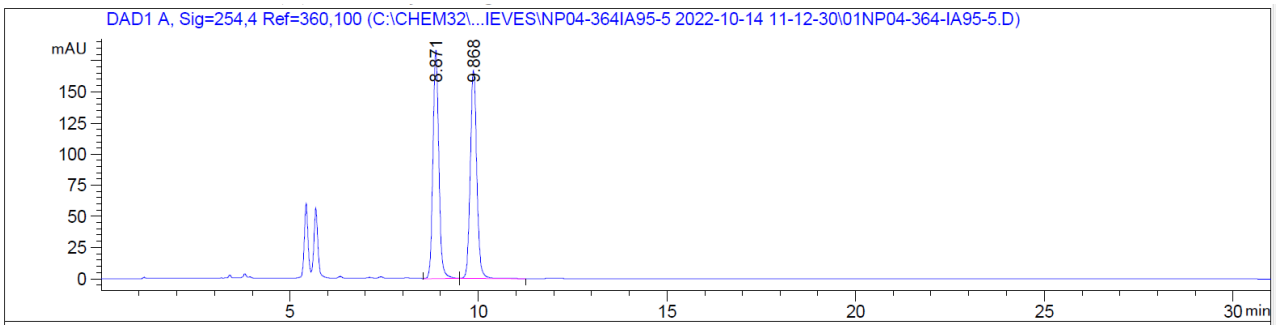


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.170	MM	0.1579	1643.01782	173.37292	89.5142
2	8.572	MM	0.1567	192.46599	20.46877	10.4858
Totals :				1835.48381	193.84169	

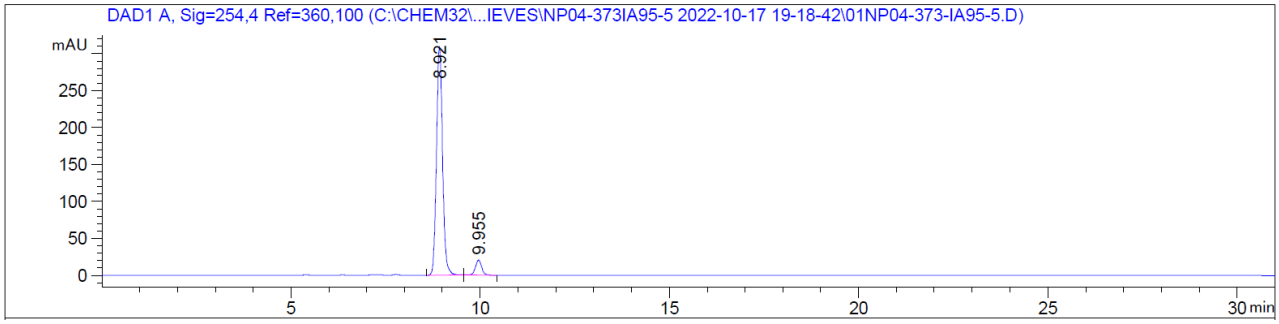
Chiral HPLC traces for compound 18.

Conditions: Daicel Chiralpak IB N-5 column: IA 95:5 hexane/isopropanol, flow rate 1 mL/min, 2 µL sample's injection.



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

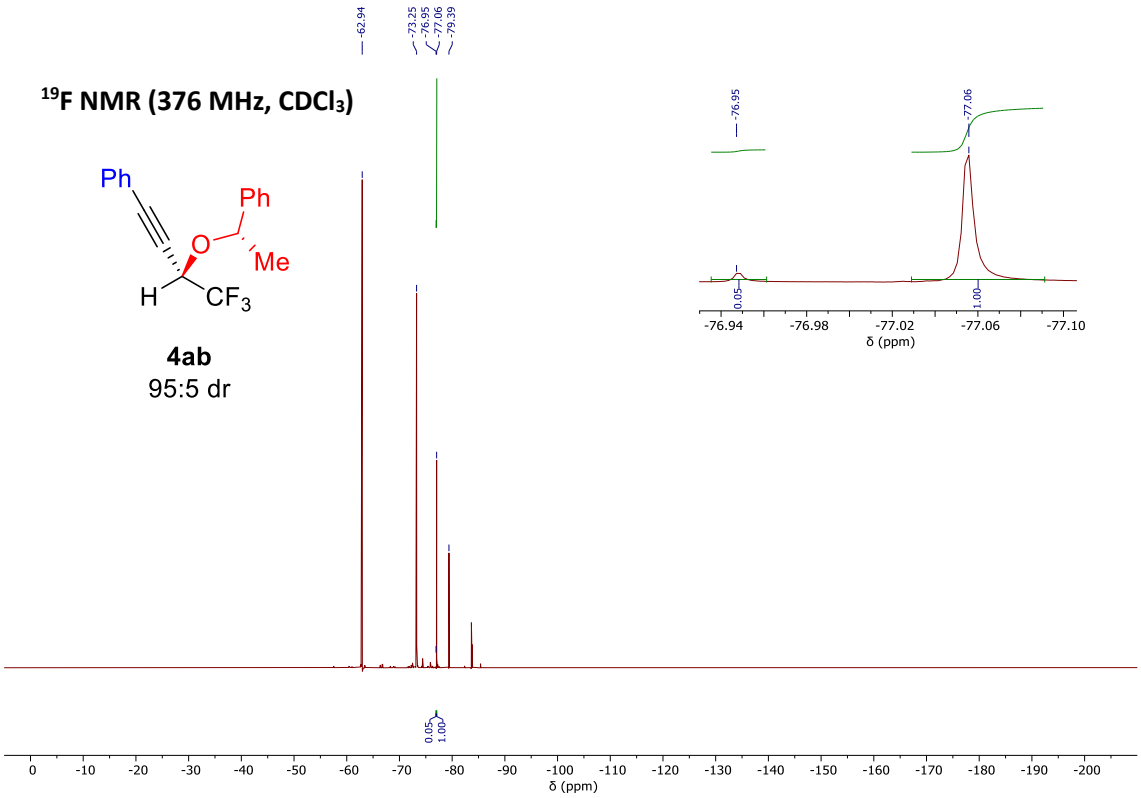
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.670	MM	0.4595	2150.76636	78.01522	50.2528
2	15.842	MM	0.6137	2129.12695	57.82581	49.7472
Totals :				4279.89331	135.84103	

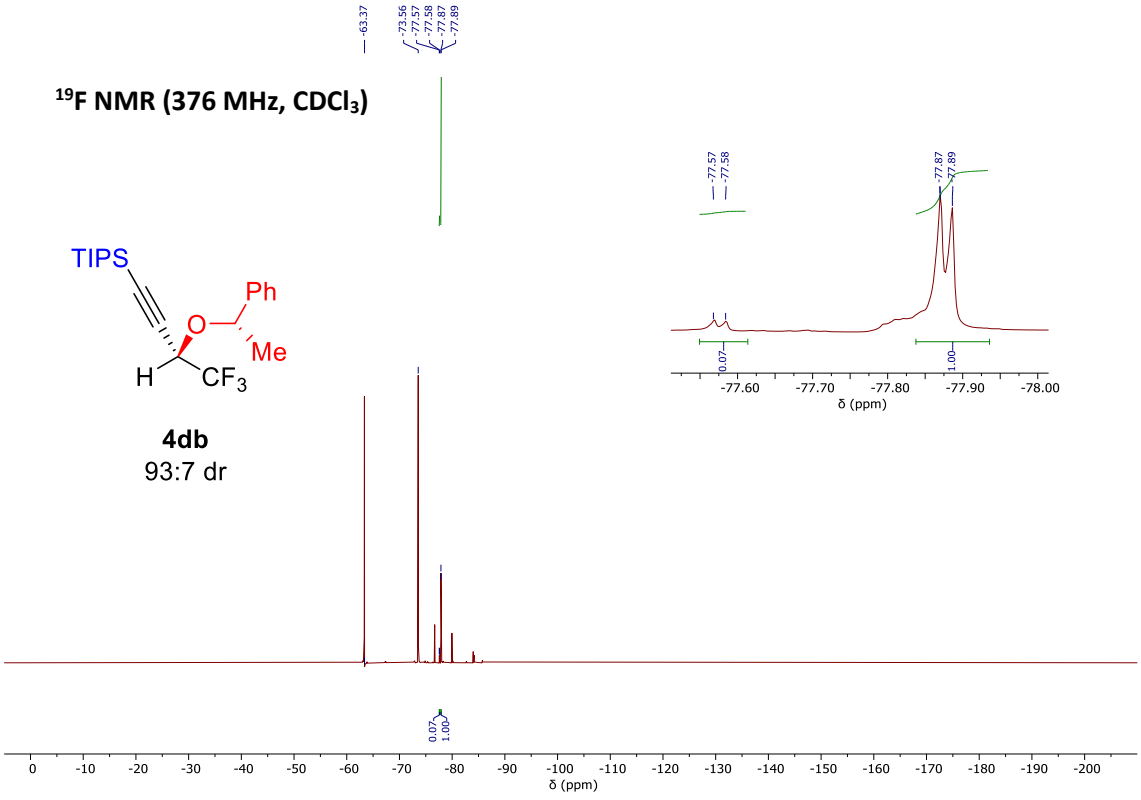


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

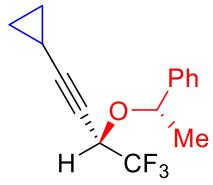
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.921	BB	0.1728	3469.08984	309.40891	93.7306
2	9.955	BB	0.1752	232.03981	20.31787	6.2694
Totals :				3701.12965	329.72678	

14. ^{19}F NMR crude spectra for chiral alcohols to determine the diastereomeric ratio (dr)



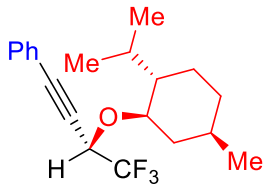


^{19}F NMR (376 MHz, $CDCl_3$)



4eb
92:8 dr

^{19}F NMR (376 MHz, $CDCl_3$)

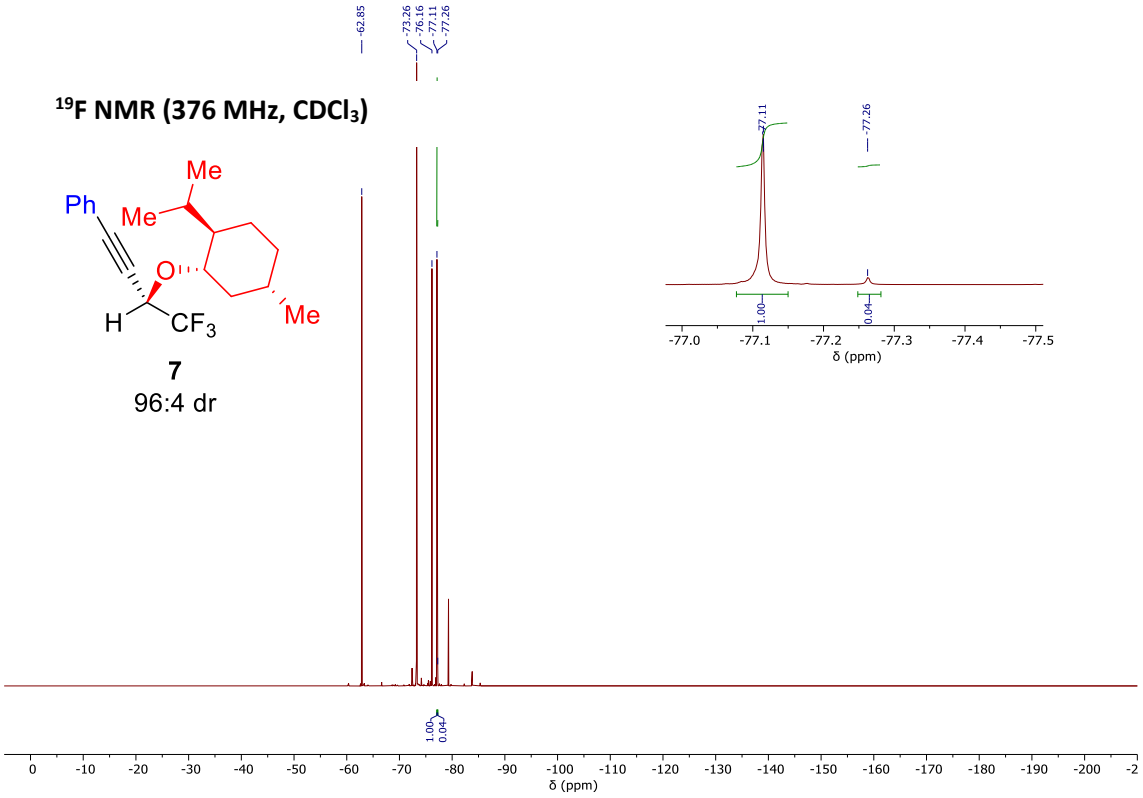


6
98:2 dr

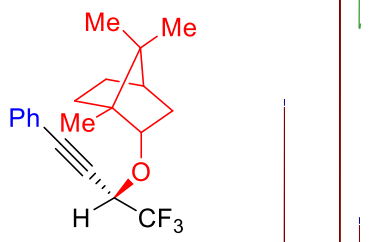
^{19}F NMR (376 MHz, $CDCl_3$)

7

96:4 dr



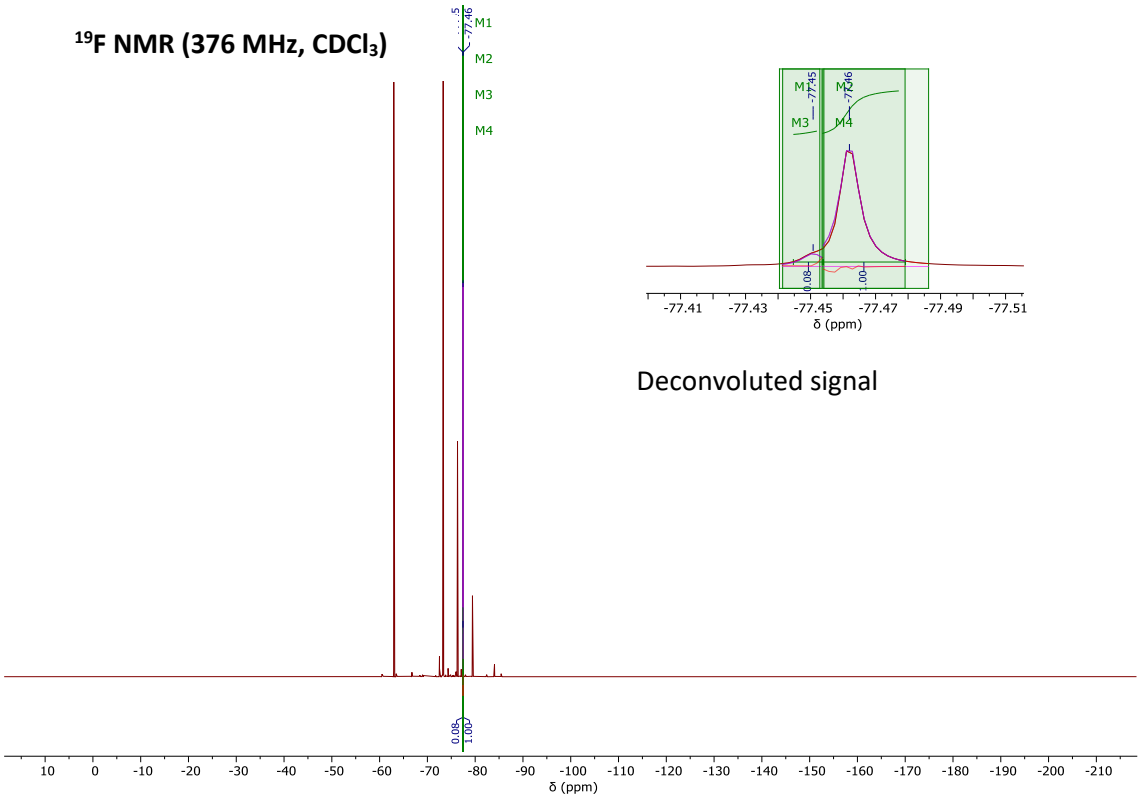
^{19}F NMR (376 MHz, $CDCl_3$)



8

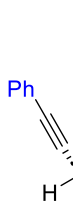
97:3 dr

^{19}F NMR (376 MHz, $CDCl_3$)



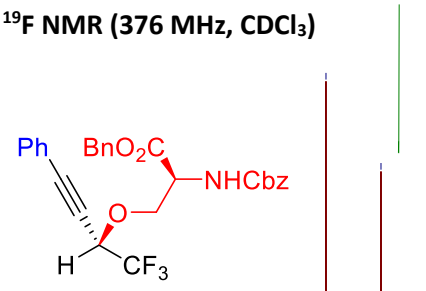
Deconvoluted signal

^{19}F NMR (376 MHz, $CDCl_3$)



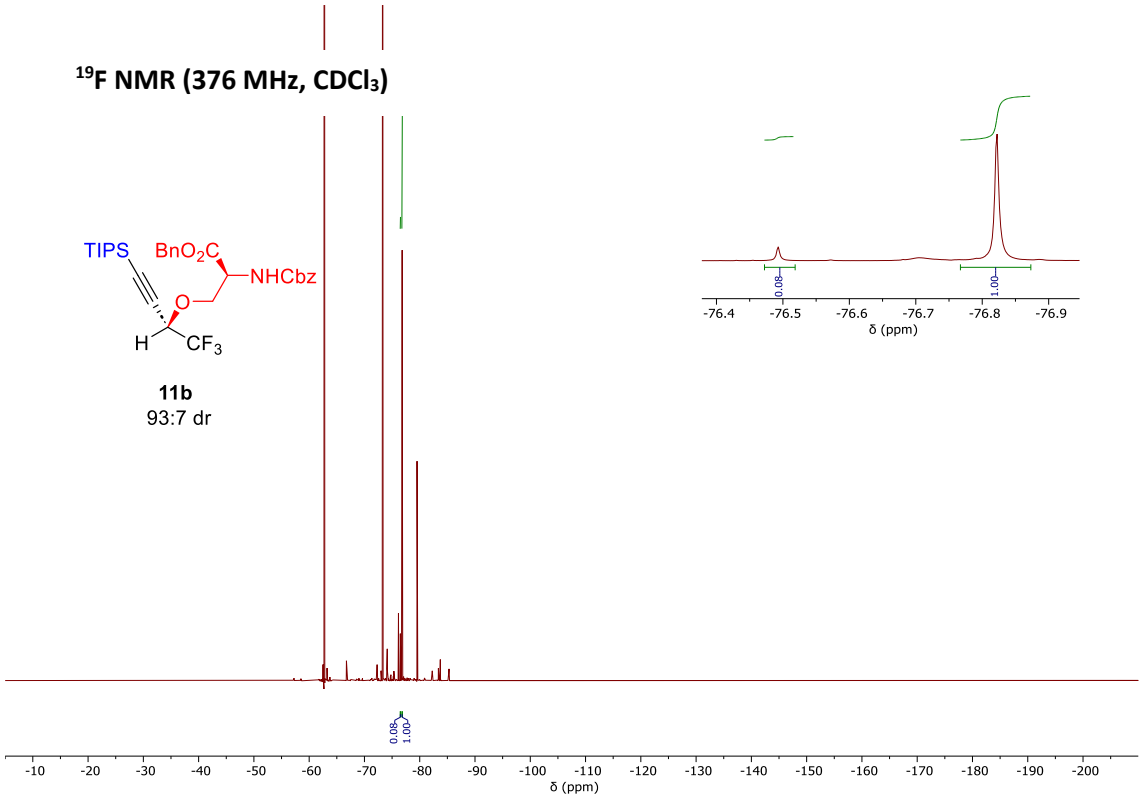
12
85:15 dr

^{19}F NMR (376 MHz, $CDCl_3$)



11a
93:7 dr

^{19}F NMR (376 MHz, $CDCl_3$)



11b
93:7 dr